Occupational/environmental and lifestyle risk factors for Motor Neurone Disease in New Zealand

A thesis with publications presented in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

in

Public Health (epidemiology)

at Massey University, Wellington, New Zealand

Grace Xia Chen

2022

Abstract

Motor Neurone Diseases (MND) are a group of progressive, irreversible, and terminal neurodegenerative diseases, with death usually resulting about three years after first symptoms of weakness. No cure is available. Whilst the aetiology of MND is largely unknown, some occupations, occupational exposures, and lifestyle factors have been associated with elevated risks, but evidence has been mixed.

This thesis describes a case-control study that assessed associations with MND for a range of potentially modifiable risk factors, including specific occupations; occupational exposures (extremely low frequency-magnetic fields (ELF-MF), electric shocks, and a range of chemicals including pesticides); physical and emotional trauma; and leisure sports. A total of 321 cases and 605 population controls participated in the study.

Elevated risks for MND were observed for several horticultural occupations, including field crop and vegetable growers, fruit growers, gardeners and nursery growers, crop and livestock producers. Employment as a builder, electrician, caregiver, forecourt attendant, plant and machine operator and assembler, and telecommunications technician was also positively associated with MND.

Having ever worked in an occupation with potential for electric shocks was positively associated with MND, but no association was observed for occupational exposure to ELF-MF. Occupational exposure to pesticides, in particular insecticides, fungicides, and fumigants was associated with MND, with longer exposure duration associated with

higher risk. Elevated odds for MND were also found for exposure to petrol/diesel fuel, unspecified solvents, disinfectants, and cleaning products.

Having had multiple head injuries with concussion was associated with increased odds of MND; spine injury was not associated with MND. Playing sports throughout childhood and adulthood increased the risk of MND compared to never engaging in sports. Playing football (soccer) for >12 years was also positively associated with MND. Reporting emotionally traumatic events in more than three specific categories of trauma was positively associated with MND, with physical childhood abuse, the only specific emotional trauma category associated with MND risk.

In conclusion, this research identified a range of occupational (pesticides, electric shocks, fumigants, unspecified solvents, cleaning products) and non-occupational (repeated head injury and physical child abuse) risk factors for MND, which provide promising opportunities for interventions to prevent MND.

"Knowledge is a treasure, but practice is the key to it."

— Lao Tzu

"To raise new questions, new possibilities, to regard old problems from a new angle, requires creative imagination and marks real advance in science."

— Albert Einstein

Author's declaration

This thesis was produced according to Massey University's "Thesis with publication" requirements. That is, it is based on research that is published, under review, or submitted for publication. Chapters 3, 4, 5, and 6 have been written as individual research papers, and each of these chapters was written in the style of the journal to which it was submitted. Consequently, there is some repetition (particularly in the methods, and study participants characteristics sections), and there are minor stylistic differences between chapters.

The published and submitted manuscripts include other authors, including my Ph.D. supervisors, colleagues, and collaborators in different institutes in New Zealand, Australia, the United Kingdom, and the Netherlands. While having been provided with assistance and support from my supervisors and co-authors, my input was greatest, as reflected by being the first author on these papers. I have been working as a research assistant on this MND project from 2013 to 2015, and my main responsibilities included the recruitment of study participants and coordination of data collection. I was also involved in the preparation of two ethics amendments for this project. In 2015, I enrolled as a Ph.D. student (part-time) and since then I led the work described in the thesis, including continuing the recruitment of study participants and coordination of data collection, data cleaning, data analyses, and preparation of the first drafts of the manuscripts and subsequent revisions following comments from co-authors and external reviewers. The statements of contribution for each publication/manuscript included in this thesis are provided in Appendix 3.

Acknowledgements

During the course of this research, I have received extensive assistance and encouragement from many people. I am indebted to each and every one, without whom this thesis would not have been possible. I would like to formally acknowledge and thank the following people:

All MND patients who generously shared their time, which was both limited and valuable, and all other study participants, without their kind and invaluable participation, this research work would not have been possible.

The Motor Neurone Disease Association and their wonderful support team: (Grant Diggle - National manager, Beth Watson - President, Moira, Linda, Kate, Lynne, and Lin - specific support fieldworkers, a group of amazing ladies who are kind, warm, and enthusiastic for this research), thank you for your incredible support throughout the recruitment.

The Health Research Council of New Zealand which funded the MND case-control study that formed the basis of the research described in this thesis.

My incredible supervisors. Doctor Dave Mclean, thank you for your advice and support and for your faith in me from the beginning. It was with your encouragement that I decided to undertake this thesis. Professor Andrea ’t Mannetje, thank you for your wonderful help and your patience and advice as I have come to you with many questions over the years, for all your invaluable guidance and for challenging and inspiring me with your superb skills on epidemiology and analysis throughout the PhD process, and for your encouragement and constantly elevating my work, and your creative crafts and sewing ideas which also inspired me to take on some little sewing

project as a hobby for the future. Professor Jeroen Douwes, thank you for offering me a position as a research assistant at the CPHR all those years ago, for your ongoing support and valuable suggestions, and for your ever encouraging and motivating guidance throughout my entire research career to date. Professor Leonard van der Berg, thank you for your time, your valuable inputs, and suggestions throughout this research. It was so important for me to understand the physician's view of this disease.

To Professor Neil Pearce, thank you for your wisdom, invaluable feedback on the manuscripts included in this thesis, I have benefited greatly from your wealth of knowledge on epidemiology. Professor Hans Kromhout, thank you for your support, particularly on JEMs, which were new tools for me to use, and also for your detailed feedback on the manuscripts. Doctor Naomi Brewer, thank you for your help at the beginning of the recruitment and for showing me how to request ethics approval for using NMDS data.

To Shelley, Angela, Heather, Tiz, Leigh, Aly, Lynne, and Deirdre, thank you for helping with the interviews and support during fieldwork. Shelley, thank you so much for your hard work on searching for phone numbers from the White pages for people who had not responded and thank you for helping me track down some of the missing data. Heather, thank you so much for conducting the interviews, which in many cases were logistically and emotionally challenging.

I would also like to thank Soo and Alex. Soo, thank you for setting up the database and helping me with a logical way to do the data cleaning, thank you Soo for your "green fingers" which made my office bloom with cacti (for most of them, I have no idea of their name). Alex, thank you so much for "calling me" for a coffee every morning at 10.00 am in the office, your coffee gives me an everyday booster.

Hilary and Nathalie, thank you for always looking after me, for your generous personal support and kindness, and your excellent administrative assistance for all the field work.

I am grateful to have shared an office with a group of wonderful people. Thank you to Lucy, Hajar, Hana, and Ruth, for your support and kind words, for cookies, chocolates, laughter, and giggles, and for listening to me talk about my precious dog Toto.

Sam and Collin, thank you for your encouragement and invaluable advice on all aspects of doing a PhD, and for your practical advice in doing up houses. Collin, your "PhD progress and complete tick box table" was very helpful to keep my thesis preparation in the right order. Sam, thank you for your creative skills in designing me a range of cooking utensils.

Thank you to all my wonderful colleagues, you have all made me feel incredibly welcome when I came to Wellington, and your kind words and encouragement throughout the whole journey. Thank you for just being nice people and for always being willing to provide help if needed.

To all my friends who live in New Zealand and who live in the Northern Hemisphere. I am so grateful for your patience, friendship, and support. Especially for my old classmates, ex-colleagues, and my childhood friends in Beijing who learned not to ask how the thesis was going and thank you for looking after mum during the pandemic.

My greatest debt is to my family who have encouraged and supported me throughout my life. Dad, you are my hero and my real model in life. Mum, you are a pretty, wise, and caring mum. Thank you both for always encouraging me to do my best and loving me unconditionally. My sister, Li. Thank you for feeding me all the yummy dumplings and buns, and saving me a lot of time for cooking, it would not be the same without you

for the last 2 years. My brother, Bing. Thank you for your sense of humour and loud laughter over the phone, which lights up the room. Emmy, thank you for sharing everything with me and for being a wonderful and caring niece and best friend. I treasure all the weekend's coffee, talks, giggles, shopping, and window shopping. Thank you for dragging me to do "Wellington Round the Bays", not once but twice, I hated running, but I enjoyed the hot dogs very much at the end.

Finally, and most importantly, Bill- my "comrade in arms". Thank you for having always been there for me, always being positive and encouraging, and for sharing your lifetime experience in occupational health with me. The road towards completion would have been a lot more difficult without your support and love. Thank you for listening to my ideas whenever they popped out from my mind, most time after midnight. Thank you for accepting me as a night owl, I know it is hard for a morning lark to do that, so thank you so much, and love you. Toto, thank you for accompanying me for most nights when I was tapping away, your love and affection make you the best dog in my life.

Table of contents

List of tables

Abbreviations

AChE	Acetylcholinesterase Enzyme
ACC	Accident Compensation Corporation
AD	Alzheimer's Disease
ALS	Amyotrophic Lateral Sclerosis
ALS-FTD	Amyotrophic Lateral Sclerosis - Frontotemporal Dementia
ASLoD	ALS Online Genetics Database
BBB	Blood-Brain Barrier
BCB	Blood-Cerebrospinal Fluid Barrier
BMAA	β-N-methylamino-L-alanine
BMI	Body Mass Index
BROHNZ	Building Research in Occupational Health in New Zealand
CI	Confidence Interval
CSF	Cerebrospinal Fluid
CTE	Chronic Traumatic Encephalopathy
C9orF72	The Chromosome 9 open reading frame 72
DDT	Dichlorodiphenyltrichloroethane
ELF-MF	Extremely Low-Frequency Magnetic Fields
EPA	Environmental Protection Authority
FDA	Food and Drug Administration
FTD	Frontotemporal Dementia
FUS	Fused in Sarcoma
GWAS	Genome-wide Association Study
HR	Hazard Ratio
ICD	International Classification of Diseases

IDI	Integrated Data Infrastructure
ISCO88	International Standard Classification of Occupations 1988
IV	Instrumental Variables
JEM	Job Exposure Matrix
LD	Linkage Disequilibrium
MET	Lifetime Metabolic Equivalent of Task
MND	Motor Neurone Disease
MNDANZ	Motor Neurone Disease Association of New Zealand
MoH	Ministry of Health
MOR	Mortality Odds Ratio
MPI	Ministry for Primary Industries
MR	Mendelian Randomisation
NHI	National Health Index
NZDep2006	New Zealand Deprivation Index 2006
NZF	New Zealand Football
NMDS	New Zealand National Minimum Dataset
NZSCO99	New Zealand Standard Classification of Occupations 1999
OCPs	Organochlorine Pesticides
OECD	Organisation for Economic Co-operation and Development
OPs	Organophosphates Pesticides
OR	Odds Ratio
AF	Attributable Fraction
PBP	Progressive Bulbar Palsy
PCBs	Polychlorinated Biphenyls
PD	Parkinson's Disease

PLS	Primary Lateral Sclerosis
PMA	Progressive Muscular Atrophy
PON1	Paraoxonase 1
PPE	Personal Protective Equipment
RR	Risk Ratio
SES	Socioeconomic Status
SIR	Standardized Incidence Ratio
SMR	Standardized Mortality Ratio
SNPs	Single-nucleotide Polymorphisms
SOD1	Superoxide Dismutase 1
SPMR	Standardized Proportionate Mortality Ratio
SRR	Standardized Rate Ratio
TARDBP	Transactive Response DNA binding protein
TBIs	Traumatic brain injuries
TDP-43	Transactive Response DNA binding protein of 43 kDa
2,4-D	2,4-Dichlorophenoxyacetic acid

CHAPTER 1 Introduction

Motor Neurone Disease (MND) is a term that encompasses a group of devastating and terminal neurological disorders, the most prevalent being amyotrophic lateral sclerosis (ALS). MND is characterised by rapidly progressive motor neurone loss in the brain and spinal cord that leads to progressive muscle weakness and wasting. MND may start in different parts of the body and progress in different patterns and rates. The initial presentation of MND is usually muscle weakness of the upper or lower limbs or speech difficulties that progresses to paralysis, swallowing and breathing difficulties, and eventually general respiratory failure.[1-3]

There is no known cure for MND, and death usually results from respiratory failure and other lung complications, on average about three years after the first symptoms of weakness appear.[3-6]Although palliative care has improved, no treatment significantly alters its course.[7 8] Riluzole is the only widely available medicine that is used to slow the progress of the disease and may extend the patient's life expectancy by about 2-3 months.[9 10]

MND is considered a rare disease, and affects over 330,000 of the world's population, and kills over 34,000 people every year.[11] The global incidence is approximately 2/100,000 persons,[12] onset typically occurs in later life, peaking between 70 and 75 years of age, affecting persons of both sexes and all ethnicities.[13]

There is some evidence of increasing incidence and mortality rates of MND among high-income countries over the last two decades,[11 12 14-19] including New Zealand. For example, while mortality rates from MND in New Zealand in the period 1968-1977 were similar to those in England and Wales, during the period 1978-1987, MND mortality in New Zealand significantly ($p<0.01$) increased to more than 30% higher than in England and Wales in the same period.[20] MND mortality in NZ (2.8/100,000) from 2008 to 2013 is also higher than the estimated mean global MND mortality (1.7/100,000).[21] An increase in the incidence of MND from 1.6 to 3.3/100,000 per annum over the period 1985-2006 has also been reported in the Canterbury region.[22] This rate is well beyond the median global incidence rate of MND of 1.68–1.9 per 100,000 per year.[23 24] The reasons for the increased incidence and higher mortality rate in New Zealand remain largely unclear but are likely due to environmental (including occupational) and lifestyle factors since genetic factors vary little over time.[3 25-27]

The majority of MND cases (90-95%) are sporadic and only 5-10% of cases are familial.[28] The familial cases are inherited in an autosomal dominant fashion with few exceptions. The aetiology of sporadic MND is largely unknown. It is considered to be a complex heterogeneous disease likely to result from a combination of genetic susceptibility factors, environmental and occupational exposures, and lifestyle triggers.[29] Several risk factors have been suggested to be associated with MND, but the only established risk factors to date are older age, male sex, and a family history of MND.[28]

Studies on occupational risk factors have reported that farmers, electrical workers, power production plants operators, construction workers, welders, manual heavy

physical labourers, health care workers, hairdressers, and professional football (soccer) players have an increased risk of MND.[3 30-33] Also, previous exposure to heavy metals including lead,[34] pesticides,[35-41] organic solvents,[36 42-44] extremely low-frequency magnetic fields (ELF-MF),[45-47] a history of electric shock,[38 48] and a history of physical trauma/injury,[41-43] have been suggested to play a role. Other suggested risk factors include smoking,[49] and military service.[50] However, results have not always been consistent and the evidence for these risk factors, therefore, remains largely inconclusive.

Because there is no cure or effective treatment for the disease, it is imperative that causes of the disease are identified, so that effective public health interventions can be developed. Moreover, because of the ageing population in New Zealand (the proportion aged 65 years or older has increased from 11.8% to 13.1% during 2000-2015[51] and is expected to reach 26% by 2043[52]) and the increasing incidence as previously mentioned, the number of MND cases in New Zealand is expected to rise significantly.

Population-based studies on risk factors of MND have not previously been conducted in New Zealand, and MND risk factors relevant for the New Zealand population, therefore, remain largely unknown. The research described in this thesis, involving the first population-based MND case-control study conducted in New Zealand aimed to contribute towards the identification of modifiable risk factors for MND. The case-control study, conducted in 2013-2016, assessed information on occupational risk factors, and a range of lifestyle-related risk factors, using questionnaires.

1.1 Aims of the thesis

1. Identify which occupations, and/or industries are associated with an increased risk of MND in New Zealand (Chapter 3)
2. Determine associations between occupational exposure to ELF-MF and electric shocks and the risk of MND (Chapter 4).
3. Identify which specific chemical exposure(s) in the workplace are associated with an increased risk of MND in New Zealand (Chapter 5).
4. Identify whether physical trauma, emotional trauma, and sports are associated with MND in New Zealand (Chapter 6).

1.2 Outline of the thesis

Chapter 1 General introduction

This chapter provides a brief introduction to the thesis, including a general description of MND and a brief description of the main risk factors. The aims of the thesis are presented, followed by an outline of the chapters.

Chapter 2 Literature review

This chapter comprises a review of general information of MND, including the main forms of MND, age at onset, the incidence and prevalence of MND in New Zealand and internationally; and literature on genetic, occupational/environmental, and lifestyle risk factors of MND, including the strengths, weaknesses, and gaps in current knowledge.

Chapter 3 Occupation and motor neurone disease: a New Zealand case-control study *(This chapter has been published - Chen GX, 't Mannetje AM, Douwes J, van den*

Berg LH, Pearce N, Kromhout H, D'Souza W, McConnell M, Glass B, Brewer N, McLean DJ. Occupation and motor neurone disease: a New Zealand case-control study. Occup Environ Med 2019;76(5):309-16. doi: 10.1136/oemed-2018-105605). [published Online First: 2019/03/25].

This chapter describes associations between employment in particular occupations and industries and MND. Associations for the duration of employment in these occupations are also presented.

Chapter 4 Associations of occupational exposures to electric shocks and extremely low-frequency magnetic fields with motor neurone disease *(This chapter has been published - Chen GX, 't Mannetje AM, Douwes J, van den Berg LH, Pearce N, Kromhout H, Glass B, Brewer N, McLean DJ. Associations of Occupational Exposures to Electric Shocks and Extremely Low-Frequency Magnetic Fields with Motor Neurone Disease. Am J Epidemiol 2021;190(3):393-402. doi: 10.1093/aje/kwaa214). [published Online First: 2020/10/10].*

This chapter describes associations between occupational exposure to electric shocks and extremely low-frequency magnetic fields (ELF-MF) and motor neurone disease (MND). Job exposure matrices (JEMs) were used to assess exposure to ELF-MF and the potential for electric shocks. Associations for the duration of exposure and cumulative exposure were also assessed.

Chapter 5 Occupational exposures to pesticides and other chemicals: a New Zealand motor neurone disease case-control study *(This chapter has been published - Chen GX, Douwes J, van den Berg LH, Pearce N, Kromhout H, Glass B, McLean DJ, 't Mannetje AM. Occupational exposures to pesticides and other chemicals: a New*

Zealand motor neuron disease case-control study. Occup Environ Med 2022;79(6):412-20. doi: 10.1136/oemed-2021-108056). [published Online First: 2022/03/24].

This chapter describes the associations with MND for 11 broad categories of occupational exposures (dust, fibres, environmental tobacco smoke, other smoke or fume, gas, fumigants, oils and solvents, acids or alkalis, pesticides, other chemical products, and animals or animal products), as well as more specific exposures within these categories. Associations for exposure duration were also assessed.

Chapter 6 Sports and trauma as risk factors for motor neurone disease: New Zealand case-control study *(This chapter has been accepted for publication - Chen GX, Douwes J, van den Berg LH, Glass B, McLean DJ, 't Mannetje AM. Sports and trauma as risk factors for Motor Neurone Disease: New Zealand case-control study. Acta Neurologica Scandinavica 2022;145(6):770-85. doi: 10.1111/ane.13615). [published Online First: 2022/04/01].*

This chapter describes the associations with MND for sports and physical activities, history of head injury, history of spine injury, and history of emotional trauma.

Chapter 7 General discussion

This chapter discusses the main findings and makes comparisons with the findings of other studies. It also reviews the main strengths and limitations and discusses the implications of the study findings and makes recommendations for future research.

Chapter 8 Conclusions

This chapter summarises the main findings and conclusions of the studies described in this thesis.

Appendices

The thesis does not include a specific methods chapter, as the methods are described in each of the individual results chapters (Chapters 3, 4, 5, and 6). Additional background information related to the study population recruitment and data collection methodology is provided in appendix 1, including a flow chart illustrating the different steps involved in the case and control recruitment, and the study recruitment materials that were used. The questionnaire used in the case-control study is included in appendix 2. The Statements of Contribution Doctorate with Publication/Manuscripts are in appendix 3. The supplementary materials on MND risk with smoking status and alcohol consumption is provided in appendix 4.

Appendix 1: Background information on the study population recruitment and data collection methodology used for the Motor Neurone Disease Study

Appendix 2: Motor Neurone Disease Study Questionnaire

Appendix 3: Statements of Contribution Doctorate with Publication/Manuscripts

Appendix 4: Supplementary tables

CHAPTER 2 Literature Review

2.1 Introduction

Considering the volume and scope of literature on MND and associated risk factors, it is not feasible to provide a complete or comprehensive overview of all aspects of the literature. Instead, this review will focus on issues most relevant to the subsequent chapters of this thesis. In particular, this review will give an overview of:

1. The general characteristics of MND. These will include the main forms of MND; and the epidemiology of MND (the age of onset, incidence, prevalence, and mortality rate).

2. The known risk factors of MND. These will include age; male gender; and genetic factors (the superoxide dismutase 1 (*SOD1*) gene, the transactive response (TAR) DNA binding protein *TDP-43* gene, *C9orF72* gene, and *FUS*).

3. The suspected environmental and lifestyle risk factors of MND. These will include exposure to lead; other heavy metals; solvents; electrical shocks; extremely low frequency-magnetic fields (ELF-MF); pesticides; head injury; physical activity; military service; tobacco smoking; alcohol consumption; body mass index (BMI).

2.2 General characteristics of Motor Neurone Disease

2.2.1 Main forms of Motor Neurone Disease

Motor Neurone Disease (MND) is a group of progressive and terminal neurological disorders that destroy motor neurones, the cells that control essential voluntary muscle activity such as upper and lower limb activities, speech, breathing, and swallowing.[1-3] The majority of MND cases (90-95%) are sporadic and only 5-10% of cases are familial.[28] The familial cases are inherited in an autosomal dominant fashion with few exceptions.

The term "motor neurone disease" was introduced in 1962[53] to group syndromes of four different forms, depending on the pattern of motor neurone involvement and which part of the body the symptoms begin. The four main forms of MND are Amyotrophic Lateral Sclerosis (ALS), Progressive Bulbar Palsy (PBP), Progressive Muscular Atrophy (PMA), and Primary Lateral Sclerosis (PLS).[1]

ALS was first described in 1869 by Jean-Martin Charcot[54] and is now the most common form of MND accounting for about 70% of the total cases.[55] ALS involves the degeneration of both the upper motor neurone of the motor cortex and brainstem and the lower motor neurone of the brainstem and the spinal cord including the connecting tracts.[56 57] Symptoms and signs depend on the part of the body where the muscles are first affected (e.g., arm or leg). The key symptoms of ALS are muscle wasting, weakness, stiffness, and overactive reflexes. The patient gradually loses the ability to walk and move their arms and hands. Over time, as the disease progresses, different areas of the body become involved; difficulties in speech, swallowing, and breathing

normally are last affected.[3] The disease progression varies markedly from person to person and the average life expectancy is between two to five years from the onset of symptoms.[58 59]

Progressive Bulbar Palsy (PBP) is mixed bulbar palsy and pseudo-bulbar palsy,[13] and contributes to 20% of MND cases.[55] PBP involves degeneration of both upper and lower motor neurone in the bulbar region (medulla oblongata).[60] The symptoms of PBP include weakness of the jaw and facial muscles, weakness or stiffness of the tongue, swallowing difficulty, and loss of speech. Limb symptoms develop later during the course of the disease.[2 60] The average life expectancy is between six months and three years from the onset of symptoms.[55 60] Traditionally, PBP was only applied to the symptoms that involve the bulbar muscles, but now, PBP is considered a variant form of ALS i.e. although the terms "bulbar palsy" and "pseudobulbar palsy" are sometimes used as diagnoses, they are considered phenotypes of ALS.[61]

Progressive Muscular Atrophy (PMA) accounts for 4-10% of total MND cases,[55 62] and mainly causes damage to the lower motor neurones. The patient normally first presents with wasting in the arms, weakness, and clumsiness of the hands, progressing to the lower limbs, but bulbar involvement is rare until late in the disease. PMA is typically associated with an earlier onset compared with other types of motor neurone disease.[63 64] Over time the upper motor neurones can be involved and the diagnosis then changes to ALS.[61 64] PMA has a slower rate of progression and longer survival time compared to ALS and Progressive Bulbar Palsy.[55] Most PMA patients live for more than five years after diagnosis.[59]

Primary Lateral Sclerosis (PLS) is a rare form of MND and accounts for approximately 2% of MND cases.[65] PLS affects the upper motor neurones only, with symptoms of spasticity, stiffness, cramping, and hyperreflexia.[63 64] The onset of the disease is gradual and asymmetrical. Patients with PLS generally show weakness in the lower limbs, although some cases may experience clumsiness in the hands or speech problems. Speaking, swallowing, or breathing problems can develop later. The condition progresses more slowly than the other forms of MND. In some cases, PLS can develop into ALS.[13 55] Life expectancy could be normal (>20 years) for individuals who do not progress to ALS,[59 63 64] although disability levels can be high.

Whether PLS and PMA should be regarded as a phenotype of ALS or as a disease in their own right is still being debated.[61] Nevertheless, the term ALS is used interchangeably with MND in the UK and some other countries.[61] ALS is also commonly known as Lou Gehring's Disease in the US, following the famous baseball player who died from the disease.[66] In New Zealand, as with the UK, MND is used as an umbrella term to include all forms of the disease.

MND has recently been recognised as a complex multi-system disorder with considerable extra-motor involvement rather than a disease limited to the motor neurones.[3 67 68] About 50% of ALS patients also develop cognitive and/or behavioural impairment during the course of the disease,[57 61 69] and up to 13% of ALS patients also present with coincident frontotemporal dementia (FTD), so-called ALS-FTD.[57 61 68 70] Similar to PLS and PMA, it is currently unclear whether ALS-FTD should be regarded as a phenotype of ALS or as a separate diagnosis.[61]

2.2.2 Epidemiology of MND

MND is a relatively rare disease. Disease onset typically occurs in mid to later life, with the mean age of onset being 58-63 years for sporadic cases and 40-60 years for familial cases.[3] The incidence increases with age in both men and women.[23 71] MND is rare before the age of 40 years and then increases rapidly after the age of 40 years.[3] The peak of onset globally is between the ages of 60 and 75 years[23 30 72-74] (peak at 70-74 years for men and 65-69 years for women[71]) and declines rapidly after the age of 80 years.[2 71 75-77] The mean age at onset is younger in men than in women, e.g., the median age at onset in Europe is 65 years for men and 67 years for women.[71]

Men have a higher risk of MND than women, leading to a male to female ratio of approximately 1.5. This sex difference was seen in most studies that included all familial and sporadic cases, but not when familiar cases were assessed independently.[78] Sporadic MND has different clinical features in men and women, with men having a greater likelihood of onset in the spinal regions and women in the bulbar region.[59]

MND affects over 330,000 of the world's population.[11] The incidence and prevalence are relatively uniform among Caucasian populations across Western countries,[3 23 24 71 79-81] with a median global incidence and prevalence of 1.68-1.9/100,000[23 24] and 4.48/100,000, respectively.[23] However, the incidence of MND is lower in East Asia (0.83 per 100,000 person-years follow up) and South Asia (0.73 per 100,000 person-years).[24 79] Populations of Hispanic, African[79] and American Indian and Alaska Native origin[57 82] also have lower incidences of MND.

Despite an otherwise reasonably uniform world distribution, a prevalence 50-100 times higher has been reported in the Western Pacific, mainly in Guam, the Kii Peninsula of Honshu Island, Japan, and West New Guinea in the 1950s.[83] In these regions, the disease is either atypically associated with dementia and parkinsonism,[84] or, as in New Guinea, not well documented. The causes of these aggregations remain unknown, but the clustering of high incidences suggest a possible environmental trigger. A role for the cumulative consumption of a neurotoxin BMAA (β-N-methylamino-L-alanine) found in cycad flour in the Guam diet has been proposed,[85] but a recent review concluded that there was no causal relationship between BMAA and neurodegenerative disease.[86] The previously high incidence in these areas is now falling to levels more typical of the rest of the world for reasons that remain unclear.[80 87]

Based on a voluntary national MND register, it is suggested that there are approximately 100 new diagnosed cases in New Zealand each year, and 300 cases at any one time.[88] However, although MND incidence has been studied in the different regions by using neurologists' databases and records, or hospital coding data in New Zealand, the exact national incidence and prevalence of MND in New Zealand are unknown.[22 89 90] An observational study in the greater Wellington region identified 40 MND patients over a 12-month period and estimated a seemingly high prevalence of 8.5/100,000.[89] A prospective study in Canterbury (1985–2006) reported an increasing incidence of MND from 1.5 to 3.0/100,000 per year.[22] MND mortality in New Zealand (1992-2013) was 2.8/100,000, and it has been reported to be higher than the estimated mean global MND mortality (1.7/100,000).[21]

There is some evidence of increasing incidence and mortality rate of MND among developed countries in the last decades.[3 15-17 19 22 91 92] There is also some evidence of increasing incidence and mortality rates of MND in New Zealand. For example, the incidence rate has steadily increased by 3% per year over 20 years in the Canterbury region. Also, while the MND mortality rate in New Zealand in the period 1968-1977 was similar to those in England and Wales, it was more than 30% higher ($p<0.01$) than the rates in England and Wales during the period 1978-1987.[20]

There is no cure or standard treatment for MND, and the survival is variable. Progressive functional deficits lead to an overall loss of independence, and death usually results from respiratory failure and other lung complications, on average about three years after the first symptoms of weakness appear,[41] and only 5-10% of cases survive beyond ten years.[3-6 23 75] Recent studies have also reported that longer survival is associated with male sex,[93] spinal onsets,[75 93-98] younger age at onset,[94 96 99] higher body mass index,[96 99] and weight gain after diagnosis.[100]

Riluzole is the first treatment approved by US Food and Drug Administration (FDA) for ALS in 1995.[101] It is the only effective medicine that is used to slow the progress of ALS and may extend the patient's life expectancy by about 3-6 months.[10 59] It might prove more effective when given to younger patients or at an early stage of the disease,[95 102] and the most recent review reported that Riluzole may extend survival by 6-9 months,[103] but there was no significant difference in functional measures or mortality.[101] Edaravone is the second drug approved by FDA in 2017.[104] It preserves function and delays motor deterioration, specifically when initiated in patients with early disease (i.e., those with functionality retained in most activities of daily living),

but it will not alter the outcome.[101] Although palliative care has improved, no treatment will significantly alter its course.[7 8] So far, Riluzole (trade name "Rilutek") is the only drug funded for the treatment of MND in New Zealand since 2013.[105] A recent diagnosis (within the past five years), and good respiratory function, is necessary for approval for the drug.[106]

2.3 Known risk factors

Little is known about what causes MND, but the most widely accepted risk factors are increasing age, male gender, and a family history of MND.[107]

2.3.1 Age

MND is an age-associated neurodegenerative condition.[56] MND is rare before the age of 40 years and the incidence increases exponentially after age 40[3] for both men and women,[23 71] reaching a peak at 75 years.[23 30 72-74 108] The incidence for those over age 65 years is four times greater than those under 65 years of age.[109] Thus, it is clear that MND risk increases with increasing age, particularly between 65-75 years.[23 109 110] However, the incidence declines rapidly after the age of 80 years.[2 71 75 76 111] It is unclear as to why the incidence declines after 80 years. Some studies suggest that under-ascertainment or under-reporting of MND among the elderly could be the reason, as it could be difficult to diagnose because of comorbidity, or that more rapid and aggressive disease and shorter survival may cause elderly patients to die before the diagnosis.[71 77 111 112]

2.3.2 Gender

Male sex has long been considered a risk factor for ALS.[3 12 41] Both the incidence and prevalence of MND are greater in men than in women.[2] The incidence in the European population is 3.1/100,000 person-years among men and 2.2/100,000 person-years among women.[2 71] The lifetime risk of disease development is estimated at 1 in 472 for women and 1 in 350 for men.[2 81] Prior to the 1990s most clinical studies reported a male to female ratio of 2:1,[113-118] but more recent population-based studies suggested a ratio of approximately 1.5:1 worldwide,[19 20 73 93 95 119-125] except in Africa, where the male to female ratio was reported to be as high as 2.9.[126]

This gender difference in MND could be related to genetic differences, and/or differences in activities and environmental exposures. Males and females have different occupations,[30] different occupational/environmental exposures that potentially cause disease or different responses to those exposures.[78] However, male preponderance in the incidence has declined in recent decades,[41] and some studies have reported a changing trend, with the male to female ratio moving toward one.[94] This suggests that women's exposure to potential risk factors of MND, such as smoking and occupational/ environmental risk factors, has changed over time relative to that of males. It also suggests that non-genetic risk factors likely explain at least part of the observed gender difference.[127]

2.3.3 Genetic risk factors

It is believed that approximately 5-10 % of ALS cases are familial, suggesting that genetic factors play an important role in the pathogenesis of ALS.[56 59] However, ALS is

considered a complex genetic disorder with a Mendelian pattern of inheritance in some cases but with no discernible family history in others.[57 128] Approximately 60–70% of familial ALS and about 11% of sporadic ALS cases are accounted for by known linked genes.[57 129] Moreover, some evidence also suggests the roles of oligogenic inheritance[130] (not inherited as a single-gene, but a phenotypic trait determined by more than one gene) and genetic pleiotropy (with a single gene having multiple phenotypic manifestations) in ALS.[57]

More than 50 potentially causative or disease-modifying genes have been identified as being associated with ALS.[131] Around 30 genes can be grouped functionally into three main pathophysiological processes which are RNA biology, protein turnover, and axonal transport, suggesting that deficits in these pathways may be causally linked to disease development.[9] A description of each MND-related gene is beyond the scope of this thesis, but the interested reader is directed to the following online resource for a complete list: ALS Online Genetics Database (ASLoD)[132 133] http://alsod.iop.kcl.ac.uk.

Among these identified genes, four genes account for up to 70% of familial ALS cases:[57 134] SOD1 (encoding superoxide dismutase), TARDBP (encoding Transactive response DNA binding protein 43, TDP43), C9orf72 (Chromosome 9 open reading frame 72), and FUS (encoding RNA-binding protein FUS). These four genes are key to the normal functioning of motor neurones and other cells.[135]

2.3.3.1 SOD1 (Cu/Zn superoxide dismutase gene)

SOD1 was the first gene that was identified in familial ALS patients in 1993,[136] and SOD1 variants are found in about 20% of familial cases, and 1% of sporadic cases.[137]

Individuals with mutated SOD1 present mostly with limb onset, starting predominantly in the lower limb rather than the upper limb. A few cases also present with bulbar onset. Over a hundred disease-associated variations in SOD1 have been identified, many are missense mutations, but only a small portion of these variations have shown reliable evidence of pathogenicity.[129 138] SOD1 mutant ALS cases can differ significantly in phenotype, age of onset, disease duration, and severity, depending on the variants involved.[128 131] D90A mutation is the most common mutation in SOD1, which is recessive in the Scandinavian population. Patients with the D90A variant can develop respiratory failure after 10 years of onset[139] and generally have a longer life expectancy.[140] The A4V variant in SOD 1 gene is the most frequent variant in the North American population, which can lead to a short survival with death within a year of disease onset.[129 141]

2.3.3.2 TARDBP (TAR DNA-binding protein 43)

Mutations of the TARDBP gene were first reported in familial ALS cases in 2008.[142] To date, around 50 variants in TARDBP have been associated with ALS.[143] Pathogenic missense mutations in the TARDBP gene have been reported in both sporadic and familial cases of ALS and frontotemporal dementia.[144] TARDBP-related ALS patients present an autosomal dominant form of ALS with predominant limb onset,[144] and a wide variation in the age of onset (30–77 years) and disease duration.[128] Mutations in the TARDBP gene account for 4-5% of familial ALS cases and 2% of sporadic ALS cases,[145] but TAR DNA-binding protein 43 (TDP-43) coded by the TARDBP gene has been discovered as a major component of the ubiquitin-positive neuronal inclusions that are the pathological hallmark of both ALS and frontotemporal dementia.[129 146] Even though mutations in TARDBP are a rare cause of ALS,[57] the majority of patients (up to

97%) with sporadic ALS have features of TDP43 positive neuronal inclusions (aggregation of the protein TDP43 in the cytoplasm of affected neurones),[144] suggesting a role for this protein in disease pathogenesis.[147] TDP-43 inclusions are also evident in familial ALS phenotypes linked to multiple gene mutations including the TDP-43 gene (TARDBP) and other unrelated genes (such as C9orf72).[147]

2.3.3.3 C9orf72 (Hexanucleotide repeat expansion)

In 2011 Renton et al.[148] and DeJesus-Hernandez et al.[149] reported that a massive non-coding GGGGCC hexanucleotide repeat expansion in C9ORF72 was the cause of chromosome 9p21 linked ALS and FTD. Typically, between five and ten copies of this hexanucleotide repeat expansion are present in the gene, while in ALS patients, the expansion may have hundreds to thousands of repeats. This repeat expansion can lead to the production of abnormal RNA species that can be identified as nuclear RNA foci and might induce direct RNA toxicity by sequestering RNA-binding proteins.[57] The repeat expansions are also known to disrupt RNA metabolism in other neurodegenerative diseases.[143 150] The GGGGCC hexanucleotide repeat expansion in C9orf72 is a major cause of ALS and frontotemporal dementia and has the highest prevalence in familial ALS (40-65%),[151] and about 4-21% of sporadic ALS cases in Europe and North America.[69 129] It is the most common inherited cause of ALS in those with European ancestry[131] but is less frequent in Asian populations.[152] C9orf72 mutation leads to an adult-onset, autosomal dominant disorder which presents with the symptoms of both familial ALS and frontotemporal dementia.[128] The C9orf72 hexanucleotide repeat expansion also accounts for about 37% of familial frontotemporal dementia and 6% of sporadic frontotemporal dementia cases.[153] Although traditionally ALS and frontotemporal dementia were considered as two separate diseases, it is now thought

that they form a continuum of neurological diseases that share a common pathological background as they have an overlap of clinical symptoms. Clinically, approximately 13% of ALS patients also developed frontotemporal dementia[57 61 70] and up to 50% have cognitive impairment.[69 154]

2.3.3.4 FUS (encoding RNA-binding protein FUS (Fused in Sarcoma))

FUS is an RNA-binding protein that was identified in ALS patients in a previously identified locus in chromosome 16.[155 156] ALS patients with FUS mutations are characterised by a wide range of disease onset from 26–80 years with the mean disease duration around 33 months.[157] Most cases show low motor neurone predominance, without bulbar region involvement[128] and cognitive impairment is rarely seen with ALS caused by FUS mutations.[143] More than 50 FUS mutations have been identified, and FUS gene variants account for around 4% of familial cases[129] and 1% of sporadic cases.[152] FUS variants are associated with early-onset and juvenile ALS.[158 159] FUS variant linked ALS is characterised by pathological FUS aggregation generally reported occurring only in patients with pathogenic variants in the FUS gene.[160] While very few studies have investigated the role of FUS in neuronal development, maintenance, and degeneration, it is suggested that FUS plays a similar role as TDP-43 in RNA transcription, transport, and maintenance of neuritic processes.[143 161 162]

2.4 Occupational/environmental and lifestyle risk factors

Around 90% of cases are sporadic, and the aetiology of sporadic MND is largely unknown,[129 131] but there is evidence of multiple mechanisms including oxidative stress,[163 164] altered mitochondrial dysfunction,[165-167] impaired axonal transport,[131 168]

glutamate-induced excitotoxicity,[169] neurofilament[169 170] and protein aggregation in motor neurones,[166 171] and inflammatory dysfunction[131] may contribute to cell death in MND.[172]

MND has been considered to be a complex heterogeneous disease likely to result from a combination of genetic susceptibility factors, occupational and environmental exposures, and lifestyle triggers, which together cause the disease.[29] Previous epidemiological studies have suggested several occupational/environmental and lifestyle exposures may contribute to the risk of MND. These include exposure to lead, other heavy metals, solvents, electric shocks, extremely low Frequency-magnetic fields (ELF-MF), pesticides, occupations in agriculture, rural living, head trauma, physical activities, military service, tobacco smoking, alcohol consumption, and body mass index (BMI).

2.4.1 Heavy metals

Exposure to heavy metals, such as lead, mercury, manganese, and selenium have long been suspected to be associated with an increased risk of MND. The potential role of heavy metals in the molecular mechanisms that lead to the degeneration of motor neurone has been widely explored in the last two decades.[173] Evidence on the possible association between heavy metals and ALS mainly stems from occupational and ecological studies, as well as from case-control studies in which metal concentration has been evaluated in different biological specimens such as cerebrospinal fluid (CSF), blood, hair, toenail, and urine. Each one of these heavy metals will be discussed below,

with relevant studies summarised in Table 2.1 (lead) and Table 2.2 (mercury, manganese, and other metals).

2.4.1.1 Lead

Lead is a well-known neurotoxin and has been linked to an increased risk of neurodegenerative disorders.[174 175] The biological plausibility of lead exposure in MND aetiology has been studied extensively, with the mechanisms involved in lead neurotoxicity including increased oxidative stress, mitochondrial dysfunction, and excitotoxicity, which are also involved in MND pathogenesis.[34 174 176]

The long-standing hypothesis of a causal association between environmental lead exposure and the risk of MND has been reported in several cases studies in the literature since the 1960s.[177 178] Since then, several case-control studies using standardised questionnaires[34 179-184] have shown statistically significant associations between occupational exposure to lead and subsequent risk of MND. Other case-control studies also observed increased risks but did not reach statistical significance.[185-192] Two case-control studies have used a job-exposure matrix (JEM) to estimate lead exposure. Peters et al.[188] reported an OR of 1.07 (95%CI: 0.85, 1.35) for occupational exposure to lead at least 10 years before diagnosis. Dickerson et al.[193] in a Danish study found that males with exposure to lead at any time 10 years prior to diagnosis increased risk by 33% (OR 1.33; 95%CI: 1.03, 1.72).

Several case-control studies have investigated biomarkers of lead exposure. An increased lead concentration in blood,[34 181 182 194-197] bone,[34 181 182] and CSF[194] among ALS cases compared to controls has been observed in several case-control studies.

However, Vicenti et al.[189] reported no association between blood lead levels or CFS lead levels and the risk of ALS. Other studies reported no difference between cases and controls in lead concentration in urine,[195] hair,[195] and toenails.[198]

A positive association between lead and ALS was also supported by two ecological studies.[199 200] An Australian study[199] found that a one percent increase in lifetime petrol lead exposure increased the MND death rate by about 0.33%, suggesting that lead exposure from leaded petrol is a risk factor for MND mortality. A Spanish study[200] found that higher MND mortality occurred with higher air lead levels in people over the age of 65 years.

Several meta-analyses concluded that occupational exposure to lead (prior to diagnosis) is associated with MND,[201-206] with reported increases in the risk of between 50% and 80% (pooled ORs was between 1.46 to 1.81 in different studies, see Table 2.1). The most recent umbrella review[207] on a wide range of ALS risk factors also concluded that there was convincing evidence that chronic occupational exposure to lead was associated with a higher risk of amyotrophic lateral sclerosis.

Table 2.1. Exposure to lead and the risk of MND

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
Case-control study						
Campbell et al., 1970[190]	UK	Lead	Questionnaires and bone biopsy	74 cases, 74 controls match age and gender	Both	Slight lead exposure was common between cases and control, but severe lead exposure was much higher in cases than controls (15% vs 5.4%), there was no difference in bone lead content between cases and controls.
Pierce-Ruhland & Patten. 1981[191]	USA	Lead	Questionnaire	80 cases, 78 controls	Both	OR 2.03 (95%CI: 0.90, 4.58).
Deapen & Henderson. 1986[185]	USA	Lead, Mercury, Chromium, and Nickel	Questionnaire	518 cases, 518 controls	Both	Exposure to lead: OR 1.1 (95%CI: 0.6, 1.9).
Gresham et al., 1986[186]	USA	Lead	Questionnaire	66 cases, 66 controls	N/A	OR 2.0 (95%CI: 0.63, 7.00).
Armon et al., 1991[179]	USA	Lead	Questionnaire	74 cases, 201 controls	Male only	OR 5.5 (95%CI: 1.44, 21.0) for lifetime exposures of 200 hours or more for males only, as data for females were insufficient.
Gunnarsson et al., 1992[187]	Sweden	Lead, welding	Questionnaire	92 cases, 372 controls	Male only	Occupational exposure to lead: OR 6.0 (95% CI: 0.7, 9.20). Occupational exposure to welding: OR 8.0 (95% CI: 1.1, 13.0).
Chancellor et al., 1993[180]	Scotland	Lead	Questionnaire	103 cases and 103 controls	Both	occupational exposure to lead: OR 5.7 (95% CI: 1.6, 30).
McGuire et al., 1997[36]	USA	Lead	Questionnaires based on self-reported exposure and industry	174 cases, 348 controls match age (±5) and gender	Both	For both sexes combines: OR 1.9 (95%CI: 1.0, 3.6) based on self-reported exposure, OR 1.1 (95%CI: 0.6, 2.1) based on industry hygienists' assessment.

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
			hygienists' assessment.			For males, OR 1.6 (95%CI: 1.04, 2.5) based on self-reported exposure, OR 1.2 (95%CI: 0.7, 2.0) based on industry hygienists' assessment.
Kamel et al., 2002[181] & 2005[34]	USA	Lead	Both lead biomarkers and questionnaire	109 cases, 256 controls. frequency-matched age & gender	Both	OR 1.9 (95%CI: 1.1, 3.3), with a dose-response for lifetime days of lead exposure. OR 1.9 (95% CI: 1.4, 2.6) for each ug/dl increase in blood lead, OR 3.6 (95% CI: 0.6, 20.6) for each unit increase in log-transformed patella lead, and OR 2.3 (95% CI: 0.4, 14.5) for each unit increase in log-transformed tibia lead.
Fang et al., 2010[182]	USA	Lead	Blood lead, bone turnover, ALAD genotype.	184 cases/ 194 controls among US veterans	Both	OR 1.9 (95%CI: 1.3, 2.7, for all types of MND.) OR 1.8 (95%CI: 1.2, 2.5, for ALS) after adjusted age and CTX (C-terminal telopeptides of type 1 collagen) level. Elevated blood lead levels were associated with a higher ALS risk, and the ALAD genotype did not modify the lead-ALS association.
Roos et al., 2013[194]	Norway	Manganese, aluminium, cadmium, cobalt, copper, zinc, lead, vanadium, and uranium	Biomarker of heavy metal antecedent exposure on cerebrospinal fluid (CSF) concentrations	17 cases, 10 controls	Both	Statistically significant higher concentrations of manganese, aluminium, cadmium, cobalt, copper, zinc, lead, vanadium, and uranium were found in ALS CSF compared to control CSF.
Garzillo et al., 2014[196]	Italy	Lead, aluminium	Blood lead, blood aluminium	34 case, 25 controls	Both	Lead concentration in blood was significantly higher in cases than controls.
Bocca et al., 2015[195]	Italy	Lead, aluminium, manganese	Blood, hair, and urine of lead,	34 cases, 30 controls	Both	Lead concentration in blood was significant higher in cases (24.4 μg/L) than controls (20.8 μg/L), (p=0.0026), blood lead positively

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
			aluminium, and manganese			correlated ($p = 0.015$, $\rho = 0.433$) with age of ALS cases. Aluminium concentration in blood was significantly higher in cases than controls ($p=0.045$).
Andrew et al., 2017[183]	USA	Lead	Self-reported job or hobby-related exposures	295 cases/ 225 controls	Male only	Exposure to lead was associated with ALS risk, OR 2.58 (95%CI: 1.13, 6.71) overall, and OR 2.74 (95%CI: 1.31, 6.32) for males. analysis was restricted to males, adjusted age.
Peters et al., 2017[188]	Sweden	Lead	JEM	5020 cases/ 25100 controls in the study. Analysis of occupational exposure based on 2647 cases/13378 controls	Both	Occupational exposure to lead at least 10 years before diagnosis, OR 1.07 (95%CI: 0.85, 1.35).
Vinceti et al., 2017[189]	Italy	Lead, cadmium, mercury	Biomarker of heavy metal antecedent exposure on cerebrospinal fluid (CSF) concentrations	38 cases/38 controls	Both	For the highest tertile of exposure, ALS odds ratio was 1.43 (95% CI: 0.46, 4.41) for lead, 0.24 (95% CI: 0.06, 0.89) for cadmium, and 3.12 (95% CI: 0.51, 19.03) for mercury. No dose-response relation was found.
Dickerson et al., 2019[193]	Demark	Lead	JEM	1639 cases, 15,1974 controls	Both	For males, increased risks for exposures in the 60th percentile or higher during anytime 5 years prior to diagnosis OR 1.35 (95%CI: 1.04,1.76), and in 10 years prior to diagnosis OR 1.33 (95%CI: 1.03, 1.72). For females, OR 1.0 (95%CI: 0.66, 1.53; 5 years prior to diagnosis) OR 0.95 (95%CI: 0.6, 1.49; 10 years prior to diagnosis).

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
Filippini et al., 2020[184]	Italy	Lead, mercury, and selenium	Self-administered questionnaire	95 cases, 135 controls, match age (±5) and gender	Both	Exposure to lead: OR 3.66 (95%CI: 1.63, 9.38). Exposure to mercury: OR 4.87 (95% CI: 0.92, 25.80), Exposure to selenium: OR 2.54 (95% CI: 0.40, 16.22).
Peters et al., 2021[197]	European	Lead, cadmium, zinc	Blood samples and questionnaires	168 cases, 319 controls. (107 cases with blood sample included for analysis)	Both	Exposure to cadmium: OR 2.04 (95%CI: 1.08, 3.87). Exposure to lead: OR 0.89 (95% CI: 0.97, 3.67) suggest associations with increased ALS risk. Zinc was associated with a decreased risk: OR 0.50 (95% CI: 0.27, 0.94).
Mortality study						
Zahran et al., 2017[199]	Australia	Petrol lead exposure	Age standard mortality data and age-specific lifetime petrol lead exposure	10,669 MND deaths	Both	Lifetime petrol lead exposure, one percent increase in lifetime petrol lead exposure increased the MND death rate by about 0.33%.
Meta-analysis & Umbrella reviews						
Wang et al., 2014[201]	Canada	Lead	9 case-control studies	191 out of 1228 cases, and 160 out of 1544 controls had a history of previous exposure to lead.	Both	Individuals with a history of exposure to lead associated with an increased risk of ALS, OR 1.81 (95%CI: 1.39, 2.36).
Belbasis et al., 2016[203]	Greece	Lead	A systematic collection and assessment of multiple systematic reviews and meta-analyses performed on a specific research topic.	16 meta-analyses from 176 articles	Both	Chronic occupational exposure to lead (random-effects OR 1.81(95% CI: 1.39, 2.35)).

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
Gunnarsson et al., 2018[206]	Sweden	Metals, lead	Relevant published articles before Feb 15th 2017	79 studies	Male only	RR 1.51 (95%CI: 0.96-2.36) for lead exposure. RR1.46 (95%CI: 0.95-2.14) for metals other than lead. Overall, RR1.45 (95%CI: 1.07, 1.96) for exposure to metals.
Gunnarsson et al., 2019[204]	Sweden	Metals	Publications with good scientific standards (Armon global score II or III) were used in our meta-analyses.	19 studies were selected based on 66 original publications.	Male only	Lead exposure showed 50% increased ALS risk (RR1.57, 95%CI: 1.11, 2.20) based on 5 studies. The weighted RR for all the non-lead exposures was RR 0.97 (95% CI: 0.88, 1.06). Exposure to a mixture of metals or welding was not associated with increased risk.
Meng et al., 2020[205]	China	Lead	Two authors independently searched for published articles in the PubMed, MEDLINE, Embase, and Science Direct databases up to April 2019.	11 case-control studies out of 583 items were selected.	Both	Environmental/occupational lead exposure was positively proportional to the risk of ALS. Pooled OR 1.46 (95% CI: 1.16, 1.83), after adjusted publication bias OR 1.28 (95% CI: 1.02, 1.63).
Mentis et al., 2021[207]	Greece	Lead	A systematic analysis of umbrella reviews (meta-umbrella) published until 2018	2797 potentially relevant reviews, and 14 umbrella reviews (203 unique meta-analyses).	Both	Chronic occupational exposure to lead was associated with higher risk of amyotrophic lateral sclerosis (class I evidence).

2.4.1.2 Mercury

Mercury neurotoxicity in humans is well documented.[208] Exposure to mercury or mercury compounds can result in toxic effects depending on its chemical form (methylmercury, mercury vapour, and mercury-containing products) as well as the route of exposure. Mercury toxicity is associated with nervous system damage in adults and impaired neurological development in infants and children.[209]

There is evidence suggesting that mercury is toxic to motor neurones from in vitro and in vivo studies.[210-212] Early case-reports[213-216] have supported this view and shown that people developed ALS or ALS-like symptoms after mercury exposure. In addition, a cluster of ALS among long-term residents of the Two Rivers in Wisconsin indicated that dietary consumption of fish with high levels of mercury was associated with ALS.[217] However, case-control studies that investigated the association between occupational mercury exposure and ALS using questionnaires have reported no association[36 43 185-187 218] or only a slightly increased risk[183 219] that did not reach statistical significance.

Most case-control studies that have measured mercury concentration in biological specimens have reported either no difference between cases and controls in mercury concentration in CSF and blood plasma[195 220] or reported a significantly lower concentration of mercury among cases than controls.[189 221] However, Roos et al.[194] reported a slightly elevated mercury concentration in the blood plasma of ALS cases compared to controls. Andrew et al.[222] reported a higher toenail mercury levels in ALS cases than controls and suggested that this association related to methylmercury intake via fish, however, the study did not adjust for Socioeconomic Status (SES), which could

lead to bias. As people are exposed to methylmercury mainly through the diet, especially by the consumption of fish,[223 224] and higher fish consumption was positively associated with higher SES,[225] and higher SES has also been associated with a risk of ALS in some populations.[226] Most recently, Hoffman et al.[225] reported that SES was positively associated with ALS risk, but this association was not linked to mercury intake estimated via fish or seafood consumption patterns. Therefore, the association between dietary mercury and MND is inconsistent and complex.

Currently, only one cohort study has investigated mercury exposure and MND and reported that no ALS case was found in their study.[227] No meta-analysis has examined the association between mercury exposure and ALS. A review indicated that the relation between mercury exposure and ALS was weak, and more systematic investigation is needed.[228]

2.4.1.3 Manganese

Manganese toxicity is known to occur in certain occupational settings through inhalation of manganese-containing dust.[229] Manganese can cross the blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCB) through several carriers and in different oxidation states.[230 231] Manganese exposure can accumulate in the brain and has been associated with dysfunction of the basal ganglia system causing a severe neurological disorder similar to Parkinson's disease.[232] Exposure to manganese has also been implicated in the development of ALS. The first case report from 1939 described a worker employed in batteries and electrical elements manufactory who developed ALS after 15 years of chronic manganese poisoning.[233] However, more recent studies on occupational exposure to manganese and MND have provided conflicting results. Three

case-control studies found no association between manganese exposure and MND,[186 187 198] although one case-control study observed an elevated but not statistically significant risk.[36]

A further nine case-control studies have evaluated the manganese concentration in biological specimens which also provide inconsistent results. Three of them have observed a significantly higher concentration of manganese in the CSF of cases.[194 234 235] Two have reported a significantly lower manganese concentration in blood cells[236] and hair[195] among ALS cases compared to controls. The other four studies have found no association with manganese concentration.[196 198 237 238]

2.4.1.4 Other metals

Exposure to selenium and ALS risk has been investigated since 1977 when a cluster of four ALS cases was reported in a selenium-rich region of South Dakota in the USA.[239] Since then, two Italian studies[240 241] have also observed an association between ALS and consumption of drinking water containing inorganic selenium. However, case-control studies of occupational exposure to selenium have shown either no association[186] or a slight and not statistically significant increase in risk.[184] Further, four case-control studies have evaluated selenium concentrations in biological specimens, one reported no association[198] and two studies observed an inverse association.[221 237] The fourth study from Japan[236] observed a higher selenium concentration in blood cells in cases compared to controls.

A few studies investigated the possible association between ALS and a range of other metals (such as aluminium, cadmium, cobalt, zinc, magnesium, chromium, copper,

nickel, see Table 2.2) which showed inconsistent results.[194 198 242] Among three meta-analyses,[41 206] that evaluated associations with combined heavy metal exposure, two showed that exposure to heavy metals was associated with a 45-70% increased MND risk, whereas another study indicated no increased risk (OR 0.97, 95%CI: 0.88, 1.06).[204]

Overall, of all heavy metals, occupational/environmental exposure to lead has most consistently been associated with the risk of MND.

Table 2.2. Exposure to mercury, manganese and other metals and the risk of MND

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
Case report						
Barber 1978[213]	USA	Mercury	Clinical examination	2 cases	Male only	2 workers in a mercuric oxide manufacturing plant developed ALS-like syndrome after exposure to mercury vapour.
Adams et al., 1983[214]	USA	Mercury	Clinical examination	1 case	Male only	Men developed ALS-like syndrome after a brief but intense exposure to elemental mercury.
Schwarz et al., 1996[215]	Germany	Mercury	Clinical examination	1 case	Female only	A nurse developed ALS after accidental injection of mercury
Praline et al., 2007[216]	France	Mercury	Clinical examination	1 case	Female only	Mercury intoxication after chronic exposure related to pressure therapy (in a bath of containment mercury. Increased blood level and massive urinary excretion of mercury proved mercury intoxication.
Case-control study						
Nagata et al., 1985[236]	Japan	Manganese, selenium	Biological specimens: blood plasma	40 cases, 25 controls	Both	Manganese concentrations in blood cells from ALS patients were significantly lower ($P < 0.01$) than those from the other groups. Selenium concentrations in blood cells from ALS patients were significantly higher ($P < 0.01$) than those from the other two groups.
Deapen & Henderson 1986[185]	USA	Mercury, Chromium, and Nickel	Questionnaire	518 cases, 518 controls	Both	Exposure to Mercury OR 0.6 (95%CI: 0.2, 1.8). Exposure to Chromium OR 1.3 (95%CI: 0.2, 9.1), Exposure to Nickel OR 2.5 (95%CI: 0.4, 26.2).
Gresham et al., 1986[186]	USA	Mercury, aluminium, magnesium, manganese, alkyl, nickel, and selenium	Questionnaire	66 cases, 66 controls	Both	No association was found between any heavy metal exposure and the pathogenesis of ALS.

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
Provinciali et al., 1990[219]	Italy	Mercury	Questionnaire/interview	77 cases, 80 controls	Both	OR 1.9 (95%CI: 0.53, 6.77)
Gunnarsson et al., 1992[187]	Sweden	Aluminium, lead, mercury, manganese	Questionnaire	92 cases, 372 controls	Both	OR 0.9(95%CI: 0.2, 3.9) for aluminium. OR 2.8(95%CI: 0.7, 9.2) for lead. OR 0.4 (95%CI: 0.01, 3.2) for manganese. No exposure to mercury. OR 1.6 (95%CI: 0.7, 3.9) for any heavy metals. OR 8.0 (95%CI: 1.1, 13.0) for welders.
Moriwaka et al., 1993[221]	Japan	Mercury, selenium	Clinical examination, biological specimens (Mercury and selenium levels in plasma and blood cells)	21 cases and 36 controls	Male only	Hg and Se levels in plasma and blood cells of ALS patients were significantly lower in advanced staged ALS patients than controls.
Louwerse et al., 1995[220]	The Netherlands	Mercury	Clinical examination	53 cases, 53 controls	Both	The amount of mercury excreted in urine after DMSA (oral administration of dimercaptosuccinic acid) administration was only slightly higher than the background level and no significant difference was found between cases and controls. The study does not provide evidence that the internal dose of lead and mercury is higher in patients with MND than in controls
Kapaki et al., 1997[234]	Greece	Magnesium	Biological specimens: cerebrospinal fluid (CSF)	28 cases, 38 controls	Both	serum manganese levels were found to be increased in patients (3.59 ± 0.89 SD μg/l) compared to controls (3.03 ± 1.23 SD μg/l).
McGuire et al., 1997[36]	USA	Lead, manganese, mercury, aluminium, cadmium, chromium	Questionnaire with panel assessment	174 cases, 348 controls	Both	OR 1.1 (95%CI: 0.6, 2.1) for lead, OR 4.7 (95%CI: 0.4, 53.3) for manganese, OR 0.5 (95%CI: 0.1, 4.5) for mercury, OR 1.2 (95%CI: 0.5, 2.9) for aluminium, OR 2.0 (95%CI: 0.3, 14.4) for cadmium, OR 2.5 (95%CI: 1.0, 6.7) for chromium.

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
Pamphlet & Waley 1998[218]	Australia	Mercury	Clinical examination	38 cases, 31 adults' controls, 40 infants' controls	Both	Mercury was found in the spinal motor neurones of 36% of adult control cases and 45% of adult SMND cases, with no significant difference between groups
Bergomi et al., 2002[198]	Italy	Cadmium, lead, copper, zinc, manganese, selenium, chromium, cobalt, iron, and aluminium	Biological specimens: toenail	22 cases, 40 controls	Both	No association between ALS risk and toenail content of cadmium, lead, copper, zinc, manganese, selenium, chromium, cobalt, iron, and aluminium. This investigation does not suggest a major role in sporadic ALS aetiology of environmental exposure to these trace elements,
Fang et al., 2009[43]	USA	Lead, mercury	Questionnaire	253 cases, 109 controls	Both	OR 1.0 (95%CI: 0.4, 2.7) for exposure to mercury.
Hozumi et al., 2011[238]	Japan	Magnesium manganese and zinc	Biological specimens: cerebrospinal fluid (CSF)	52 cases, 15 controls	Both	The levels of Mg ($p<0.01$ significant difference), Fe, Cu ($p<0.05$), and Zn ($p<0.10$) in CSF were higher than those in controls.
Roos et al., 2012[235]	Sweden	Manganese	Biological specimens: cerebrospinal fluid (CSF) and blood plasma	17 cases, 19 controls	Both	Manganese CSF concentrations were significantly higher in the case (median 5.67 μg/L) than in controls (median 2.08 μg/L).
Roos et al., 2013[194]	Sweden	Mercury, manganese, aluminium, cadmium, cobalt, copper, zinc, lead, vanadium, and uranium	Biological specimens: cerebrospinal fluid (CSF) and blood plasma	17 cases, 10 controls	Both	Slightly elevated mercury concentrations can be noted in ALS cases (Median 0.827, Maximum 1.623) blood plasma compared to controls (Median 0.510, Maximum 0.914). Statistically significant higher concentrations of manganese, aluminium, cadmium, cobalt, copper, zinc, lead, vanadium, and uranium were found in ALS CSF and compared to control CSF.

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
Garzillo et al., 2014[196]	Italy	Aluminium, manganese, and lead	Biological specimens: blood	34 cases, 25 controls	Both	For aluminium, serum concentrations in patients and controls were similar and lower than those provided by the Italian Society of Reference Values. For manganese, no differences were observed in serum concentrations between cases and controls.
Bocca et al., 2015[195]	Italy	Mercury, Aluminium, Manganese	Questionnaire, biological specimens (blood, hair, and urine samples)	34 cases, 30 controls	Both	For mercury, no association with ALS (no differences in mercury content of blood, hair, and urine of ALS subjects when compared to controls). for Aluminium: in blood, concentrations of Aluminium ($p = 0.045$) were higher in ALS patients than in control subjects. In hair, decreased aluminium ($p = 0.006$) and manganese ($p = 0.032$) concentrations in ALS subjects compared to controls were found. In urine, no significant differences between the groups were found.
Peters et al., 2016[237]	USA	Manganese selenium, zinc, copper	Biological specimens: blood levels of selenium (Se), zinc (Zn), copper (Cu), and manganese (Mn).	163 cases, 229 controls	Both	ALS was inversely associated with both Se (OR0.4, 95% CI: 0.2, 0.8) and Zn (OR 0.4, 95% CI: 0.2, 0.8). For Manganese, no linear trend was evident (OR0.9, 95% CI: 0.6, 1.3, P for trend=0.51).
Andrew et al., 2017[183]	USA	Mercury	Questionnaire	295 cases, 225 controls	Both	OR 1.35 (95%CI: 0.53, 3.77) for overall, OR 1.5 (95%CI: 0.48, 5.62) for male-only.
Vinceti et al., 2017[189]	Italy	Mercury, cadmium, lead	Biological specimens: cerebrospinal fluid (CSF)	38 cases, 38 controls	Both	ALS patients had higher median values for lead (155 vs. 132ng/L) but lower levels for cadmium (36 vs. 72ng/L) and mercury (196 vs. 217ng/L). In the highest exposure group, OR 1.39 (95% CI: 0.48, 4.25) for lead, OR 0.29 (95%CI: 0.08, 1.04) for Cadmium OR 3.03 (95% CI: 0.52, 17.55) mercury.

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
Andrew et al., 2018[222]	USA	Mercury	Biological specimens: toenail	46 cases, 66 controls	Both	ALS patients had higher toenail mercury levels (OR 2.49, 95%CI:1.18, 5.80, P=0.024) compared to controls.
Dickerson et al., 2020[242]	Denmark	Chromium, Iron, and Nickel	JEM	1639 ALS cases and 168,194 controls.	Both	Men exposed to chromium was associated with an increased risk of ALS, (OR1.24, 95% CI: 0.91, 1.69) in the third quartile and (OR 1.19, 95% CI: 0.80, 1.76) in the fourth quartile compared to those with no exposure. women exposed to nickel was associated with an increased risk of ALS (OR 2.21, 95% CI: 1.14, 4.28) in the third quartile but not for the fourth quartile (OR 0.61, 95% CI: 0.23, 1.64).
Filippini et al., 2020[184]	Italy	Lead, mercury, selenium, and cadmium	Questionnaires	95 cases, 135 controls	Both	OR 4.2 (95%CI: 1.63, 8.20) for lead, OR 4.87 (95%CI: 0.92, 25.80) for mercury, OR 2.54 (95%CI: 0.4, 16.22) for selenium, OR 1.79 (95%CI: 0.23, 13.73) for cadmium.
Cohort study						
Moriwaka et al.,1991[227]	Japan	Mercury	Clinical examination	0 cases from 148 controls from mercury mines	Male only	No ALS case was found in 148 ex-mercury workers.

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
Meta-analysis & Review						
Vinceti et al., 2012[228]	Italy	Mercury, cadmium, and lead	N/A	N/A	N/A	The review did not support the association between ALS and exposure to mercury, cadmium, and lead.
Wang et al., 2017[41]	Canada	Heavy metals	A meta-analysis, observation studies for ALS risk factories published before 2016	233cases, 202 controls	Both	OR 1.71 (95%CI: 1.38, 2.11) for exposure to heavy metals (excluded lead)
Gunnarsson et al., 2019[204]	Sweden	Lead, the mixture of metals	Publications with good scientific standards (Armon global score II or III) were used in our meta-analyses.	19 studies were selected based on 66 original publications	Both	RR 0.97 (95%CI: 0.88, 1.06) for exposure to a mixture of metals or welding. Suggested no increased risk.

2.4.2 Solvents

Solvents are volatile chemicals and are used to dissolve or disperse other substances. They are widely used in industrial/commercial and domestic household products, including paints, adhesives, degreasing agents, fillers, cleaning products, lacquers, metal cleaners, inks, resins, rust removers, surface preparation products, dry cleaning products, and fuels.[243-245] Solvents can potentially cross the BBB,[246] and acute exposure is neurotoxic while chronic exposure has also been associated with encephalopathy, memory deficits, and dysmetria.[247-250] Exposure to solvents (such as toluene, xylene) has also been associated with increased oxidative stress,[251 252] which has been implicated in the development of MND.[253 254] Relevant solvent related studies are presented in Table 2.3.

Solvents have been suspected to play a role in ALS since Hawkes[255 256] observed excess mortality from MND in leather industry workers. Many studies have investigated occupational exposures to solvents, with some reporting statistically significant positive associations between overall occupational solvent exposure and ALS[36 44 180 187 257] while others have reported positive, but not statistically significant associations[43 258-260] or no association.[261 262]

However, most of these studies were based on self-reported exposure or workplace hygiene assessment and did not distinguish between specific solvents. Recently, three studies have used JEMs to estimate the association between exposure to specific solvents and ALS. Dickerson et al.[263] examined a range of solvents (benzene, methylene chloride, toluene, trichloroethylene, perchloroethylene, and 1,1,1-trichloroethane) and

observed associations with exposure to benzene (OR 1.20; 95%CI: 1.02, 1.41) and methylene chloride (OR 1.23; 95%CI: 1.07, 1.42; see Table 2.3) in men. They also reported a 25-28% increased risk for exposure to any solvent when applying both a 5-year and 10-year exposure lag-time. Koeman et al.[264] observed a positive but not statistically significant association for exposure to aromatic and chlorinated solvents, whilst Peters et al.[188] found no association with any specific solvent exposure and ALS.

Two meta-analyses have evaluated the role of solvent exposure in ALS. Wang et al.[41] reported a 43% increased risk of previous occupational exposure to solvents, whereas Capozzella et al.[265] reported only a slight increased risk, which was not statistically significant (OR 1.08, 95%CI: 0.91, 1.30). In a systematic review,[35] a slightly increased risk (OR 1.1- OR1.2) associated with overall solvents exposure was found. A five-fold increased risk, although not statistically significant, was found for exposure to benzene and other aromatic hydrocarbons (Table 2.3).

Overall, exposure to solvents as a group has repeatedly been associated with an increased risk of MND. However, most of these previous studies did not distinguish between specific solvents, and some were not able to estimate the lifetime solvent exposure as no lifetime work histories were available. Thus, a detailed lifetime work history with detailed specific solvent exposure assessment is needed to determine which specific solvent(s) are associated with MND and to assess dose-response relationships.

Table 2.3. Solvents and risk of MND

Authors, year	Country	Risk factors	Exposure assessment method	Subjects	Sex	Main findings
Mortality study						
Hawkes et al., 1981[255]	UK	Leatherworkers	Occupation recorded in death certificate in England and Wales from MND among leather workers.	16 MND deaths	Both	16 deaths, 8.70 expected. *P*<0.01, suspected to be related to glue solvents
Hawkes et al., 1989[256]	UK	Leatherworkers	Occupation recorded in death certificate in England and Wales from MND in leather workers.	18 MND deaths	Both	18 deaths, 9.79 expected *P*<0.01.
Park et al., 2005[42]	USA	Solvents in general and benzene	JEM (a continuous ten levels, the lowest level for no exposure, the highest for jobs with high probability and high intensity of exposure.)	6,347 cases among 2,614,346 deaths	Both	Exposure to solvents, in general, showed a slight but significant linear association mortality odds ratios (MOR) of 1.16 (95% CI%:1.01, 1.34). Exposure to benzene, MOR 1.14 (95%CI: 0.97, 1.33).
Case-control study						
Gunnarsson et al., 1989[258]	Sweden	Occupational solvent exposure	Occupation and industry register	1961 cases, 2245 controls	Both	42 ALS cases with known occupational exposure to solvents, 11 had been employed at printing works (OR1.6, 95%CI:0.6, 4.4).
Savettier et al., 1991[259]	Italy	Solvents	Questionnaire	46 cases, no information on controls	Both	Solvents, exposed/non-exposed: cases = 8/38, controls = 8/84, OR 2.14 (95%CI: 0.6-7.2).
Gunnarsson et al., 1992[187]	Sweden	Solvents	Questionnaire	92 cases, 372 controls	Both	Male exposure to solvents: OR 15.6 (95% CI: 2.8, 87.0) with a mean exposure time of 10 years.

Authors, year	Country	Risk factors	Exposure assessment method	Subjects	Sex	Main findings
						For both cases and controls most, solvent exposures were to aromatic hydrocarbons (OR1.7, 95%CI: 0.8, 3.8), volatile hydrocarbons (OR 0.8, 95%CI: 0.4, 1.8), petrol (OR 1.4, 95%CI: 0.7, 3.0), any solvent (OR 1.3, 95%CI: 0.7, 2.5).
Chancellor et al., 1993[180]	UK	Solvent & chemicals	Questionnaire	103 cases, 103 controls	Both	OR 3.0 (95%CI: 1.3, 10) for exposure to solvents.
McGuire et al., 1997[36]	USA	Solvents and metals	Exposure assessment by self-reported questionnaires and also by industrial hygienists panel assessment.	174 cases, 348 controls	Both	Based on the hygienist's assessment, overall exposure to solvents, OR 1.2 (95% CI: 0.8, 1.9) for men and women combined, and separately (Men OR 1.3, 95% CI: 0.7, 2.3; Women OR 1.1, 95% CI: 0.6, 2.2). When specific solvents were examined, an increased risk associated with cleaning solvent and degreaser exposures was found among women (OR 3.6, 95%CI: 1.8, 7.3) but not among men (OR1.2, 95%CI: 0.7, 2.07). Based on self-reported exposure, overall exposure to solvents, OR 1.6, (95% CI: 1.1, 2.5), in particular in women (OR 2.4, 95% CI: 1.3, 4.3), but not in men (OR1.1, 95% CI: 0.6, 2.1). Exposure to alcohols or ketones, OR 2.0 (95%CI: 1.0, 4.0), The association for alcohol and ketones was stronger in men (OR 2.6, 95%CI: 1.1, 6.1) than in women (OR1.2, 95%CI: 0.4, 3.7). Cleaning solvents or degreasers, OR 1.9 (95%CI: 1.1, 3.3)

Authors, year	Country	Risk factors	Exposure assessment method	Subjects	Sex	Main findings
						Exposure to benzene, toluene, and xylene, OR 1.7 (95%CI: 0.9, 1.3). Exposure to Styrene, OR 1.1 (95%CI: 0.1, 12.5).
Gait et al., 2003[260]	UK	Solvents	Exposure assessment by industrial hygienists	22 cases, 206 controls	Male only	OR 1.12 (95% CI: 0.45, 2.78), no duration responses relationship.
Morahan et al., 2006[44]	Australia	Solvents and chemicals	Questionnaire	179 cases, 179 controls	Both	For exposure to solvents, OR 1.92 (95%CI: 1.26, 2.93) overall; OR1.85 (95%CI: 1.12, 3.04) for men, and OR 2.57 (95%CI: 1.05, 6.31) for women.
Qureshi et al., 2006[266]	USA	Solvents	Questionnaire	95 case, 106 controls		15 cases reported exposure to industrial solvents, no difference between cases and controls in industrial solvent exposure (P=0.25).
Fang et al., 2009[43]	USA	Solvents	Questionnaire, self-reported exposure	109 cases, 253 controls	Both	Exposure to solvents OR 2.1 (95%CI: 0.8, 5.5) for all. Specific chemicals related to a > 50% increase in the risk of ALS included aliphatic chlorinated hydrocarbons, glycols, glycol ethers, and hexane.
Malek et al., 2014[261]	USA	Solvents (organic/ chlorinated or aromatic solvents)	Questionnaire, self-reported exposure	66 cases, 66 controls	Both	Exposure to organic/chlorinated solvents, OR 0.75 (95%CI: 0.38, 1.47) Exposure to aromatic solvents, OR1.13 (95%CI: 0.57, 2.27).
Koeman et al., 2017[264]	Netherlands	Occupational exposure to solvents (total solvent, aromatic solvent, and	JEMs, occupational history collected at baseline	136 cases, after 17 years follow up from 4166 subjects.	Both	For total solvent, OR 1.46 (95%CI: 0.81, 2.61) for high exposure. For aromatic solvent, OR 1.99 (95%CI: 0.81, 4.92) for high exposure. For chlorinated solvent, OR 1.23 (95%CI: 0.63, 2.39) for high exposure.

Authors, year	Country	Risk factors	Exposure assessment method	Subjects	Sex	Main findings
		chlorinated solvents)				
Andrew et al., 2017[183]	USA	Solvents	Questionnaire	295 cases, 224 controls	Both	Exposure to solvents was associated with increased risk, OR 2.03 (95%CI: 1.23, 3.44) for overall, OR 1.51 (95%CI: 0.84, 2.79) for males only.
Peters, et al., 2017[188]	Sweden	Solvents (toluene, benzene, trichloroethylene, methylene chloride, perchloroethylene, 1,1,1, -trichloroethane) and formaldehyde.	JEMs, occupational histories from the Swedish censuses in 1970, 1980 and 1990	5020 cases, 25100 controls	Both	Solvents as a group: OR 0.92 (95%CI: 0.77, 1.09) A lower risk of ALS was found for methylene chloride, OR 0.49 (95% CI: 0.26, 0.93). For Trichloroethylene OR 1.10 (95%CI: 0.82, 1.47), Perchloroethylene OR 1.03 (95%CI: 0.66, 1.62), Toluene OR 0.90 (95%CI: 0.44, 1.82), Benzene OR 1.12 (95%CI: 0.61, 2.04), Benzo pyrene OR 0.99 (95%CI: 0.75, 1.31), 1,1,1-Trichloroethane OR 0.89 (95%CI: 0.65, 1.23).
Dickerson et al., 2020[263]	Denmark	Solvents (benzene, methylene chloride, toluene, trichloroethylene, perchloroethylene, and 1,1,1-trichloroethane)	JEM, occupational history from the Danish Pension Fund	1,639 cases and 151,974 controls	Both	OR 1.20 (95% CI: 1.02, 1.41) for men with exposure to benzene OR 1.23 (95% CI: 1.07, 1.42) for men with exposure to methylene chloride. No association for women.
Filippini et al., 2020[184]	Italy	Solvents (thinners, paint removers)	Questionnaire, self-reported exposure	95 cases, 135 controls	Both	Occupational exposure to solvents suggested a positive association, especially for thinners (OR 2.27, 95% CI: 1.14, 4.54) and paint removers (OR 2.01, 95% CI: 0.90, 4.48).

Authors, year	Country	Risk factors	Exposure assessment method	Subjects	Sex	Main findings
Bellavia et al., 2021[257]	Denmark	Solvents	JEMs, occupational history from the Danish Pension Fund	1086 cases, 111,507 controls	Both	Exposure to solvents OR 1.49 (95% CI: 1.17, 1.89) for men, OR 1.02 (95%CI: 0.99, 1.05) for women.
Cohort study						
Weisskopf et al., 2009[262]	USA	Solvents	Questionnaire at baseline	1156 ALS deaths, follow up 987,229 people	Both	RR1.05 (95%CI: 0.86, 1.29) in the full cohort, RR1.04 (95%CI: 0.73, 1.49) in a restricted cohort that excluding individuals reporting exposure to a given chemical class but with no information on duration.
Meta-analysis & Systematic review						
Sutedja et al., 2009[35]	The Netherlands	Organic solvents, occupational potentially exposed to solvents	Systematic review up to March 2007	7 studies dealing with chemicals were included in the study	Both	Risk estimates reported in three studies were slightly increased (OR range between 1.1-1.2). For the subcategory of solvents including benzene and other aromatic hydrocarbons, the risk estimates are in the range of OR between 1.1-6.9, but not significant.
Capozzella et al., 2014[265]	Italy	Solvents, metals, solvents, pesticides, and electromagnetic fields	Cohorts and case-control studies published from 1980 up to April 2013	Only 2 case-control studies have been selected for solvents analysis.	Both	Exposure to solvent was associated with ALS (OR 1.08, 95%CI: 0.91, 1.30), but this is not statistically significant.
Wang et al., 2017[41]	Canada	Solvents	Published papers before February 2016	11 papers were collected, but only 7 papers were included in the analysis.	Both	Exposure to solvents OR 1.43 (95%CI: 1.10, 1.86).

2.4.3 Electric shocks

As early as 1889, Charcot[267] noted that the nervous system could be affected by electrical injury. A hypothesis that accumulative electric injuries may cause MND was first proposed in 1964[268] and the first report of an increased risk of MND among people with electricity and electronics-related occupations was published in 1986.[185] Since then, several case reports have pointed out the possibility of the development of MND after electric injury.[269-271] Table 2.4 illustrates studies that have assessed the association between MND and electric shocks or electrical occupations or ELF-MF.

Over the past three decades, associations between work in "electrical occupations" and the risk of MND have been observed in a number of studies with different study designs. Many studies[116 187 272-274] found a statistically significant increase in risk (OR/RR between 1.2-2.3), whilst others showed elevated RR/ORs but these did not reach statistical significance.[30 43 275 276] This suggests a possible role for electric shocks (electrical accidents) in the development of MND. However, measuring the exposure of the electric shocks and the frequency of the exposure is complex. As a consequence, most studies rely on job titles as a proxy for exposure to electric shocks.

Studies using the job title as a surrogate for exposure observed an increased risk of MND associated with electric shocks, including several case-control studies[185 272 273 277] and cohort studies.[278 279] The relative risk estimates among these studies ranged from 1.2-3.0 (see Table 2.4) However, a Swedish study[187] found that male electricity workers had a more than a 6-fold increased risk of MND (OR 6.7, 95%CI 1.0-32.1; Table 2.4) and a similar result was also reported in a Danish mortality study[280] that reported a ten-fold increase in risk in utility workers (Table 2.4).

Electric shocks JEMs have been developed in the last 10 years. As a result, it is now possible to assess exposure to electric shocks in a more systematic manner. In those studies, in which electric shocks JEMs were used to estimate the exposure, results have been inconsistent. For example, Peters et al.[281] reported an elevated MND risk (OR 1.23, 95%CI: 1.02-1.43; Table 2.4) for ever having had potential exposure above background to electric shocks, while others have observed no association between potential electric shocks and risk of MND.[48 264 282]

2.4.4 Extremely Low Frequency-Magnetic Fields (ELF-MF)

ELF-MF is classified as very low-energy non-ionising radiation, with frequencies below 300 Hz. Occupational exposure to ELF-MF may occur in workplaces where electrical energy is used. An association between ELF-MF and the risk of MND was first suggested by Davanipour et al. in 1991.[283] Since then, exposure to ELF-MF has been considered in a number of MND studies with different study designs, but the findings have been inconsistent.[30 46-48 187 272 273 279-281 284-290] Case-control studies during the 1990s consistently reported an increased MND risk for occupational exposure to ELF-MF (with ORs ranging from 1.2-8.0; see Table 2.4). The majority of these studies estimated the ELF-MF exposure based on job title or self-reported history of ELF-MF exposure, two studies estimated the exposure based on a JEM developed based on occupational hygienist measurements.[272 284] However, studies from 2000-2010 showed inconsistent results. Some studies found a positive association between occupational exposure to ELF-MF and MND based on a JEM,[278 285] some studies observed increased risks associated with electrical occupations but not ELF-MF,[273 279] and other studies found no association using either a JEM[42 291] or job title.[261 292 293] Since 2010, most studies used JEMs to estimate exposure to ELF-MF, but the results were again inconsistent. Six

studies reported a statistically significant elevated risk for occupational exposure to ELF-MF,[42 264 277 281 282 285] two studies observed an increased MND risk for ELF-MF exposure but the results did not reach statistical significance,[45 276] and five studies have found no association (see Table 2.4 which provides detailed ORs).[48 279 290 291 294]

In the last 20 years, several meta-analyses have been carried out to examine the association between occupational exposure to ELF-MF and the risk of MND. Overall, all meta-analyses reported a slightly increased risk of MND with ELF-MF exposure.[46 47 204 206 289 295 296] Gunnarsson et al.[204 206] in their meta-analysis reported an approximately 20% increased risk which was based on exposures estimated using JEMs established by occupational hygienists. Huss et al.[46] also observed elevated risks of MND in those exposed to higher levels of ELF-MF compared to lower levels (RR 1.14, 95%CI: 1.0, 1.3), and for electrical occupations (RR 1.41, 95%CI: 1.05, 1.92; Table 2.4). Jalilian et al.[295] also found a weak but statistically significant association between ELF-MF and risk of MND (RR 1.20, pooled, and RR 1.16 among studies that estimated exposure by JEM or direct measurements; see Table 2.4). The most recent meta-analysis[296] showed a relative risk of 1.14 for MND and occupational exposure to ELF-MF (Table 2.4).

In occupations exposed to ELF-MF, exposure to electric shocks may also occur, and these exposures may therefore act as mutual confounders. Only a few studies investigated both ELF-MF and electric shocks in the same study. These studies, using JEMs to assess exposures, have also provided conflicting findings.[48 264 277 281 282] A US case-control study, using only the main occupation registered on death certificates to assess exposure, found a weak positive association with ELF-MF, while an inverse association with electric shocks was observed.[277] A Swedish population-based case-

control study found no association between exposure to ELF-MF and MND, while an association with electric shocks was observed, but only in people under 65 years of age.[48] Cohort studies from the Netherlands and Switzerland, both with incomplete job histories, showed an increased risk of MND with ELF-MF, but not electric shocks.[264 282] The most recent study, using pooled data from three European case-control studies with lifetime job histories, showed that both ever-exposure to ELF-MF and ever-exposure to the potential for electric shocks above background level were associated with MND.[281]

Table 2.4. Exposure to ELF-MF and electric shocks and the risk of MND

Authors, year	Country	Risk factors	Data collection method	Subjects	Gender	Main findings
Case-control study						
Gawel et al., 1983[116]	USA	Electric shocks	Questionnaire	63 cases, 61 controls	Both	Electric shock was more frequent in cases (13 out of 48) than controls (5 out of 56), $p<0.05$.
Deapen & Henderson. 1986[185]	USA	ELF-MF Electric shocks	Questionnaire, job title	518 cases, 518 controls	Both	OR 3.80 (95%CI:1.4, 13.0) for ELF-MF, OR 2.80 (95%CI:1.00, 9.9) for electric shocks
Gunnarsson et al., 1991[30]	Sweden	Electrical occupation, ELF-MF	Census data, job title	1961 cases, 2245 controls	Both	OR 1.5 (95%CI:0.8, 2.6) for male electrical workers.
Gunnarsson et al., 1992[187]	Sweden	Electrical occupation, ELF-MF	Questionnaire, occupation history	92 cases, 372 controls	Both	Male electricity workers had an increased risk of MND, OR 6.7 (95%CI:1.0, 32.1).
Strickland et al., 1996[275]	USA	ELF-MF	Questionnaire, job title	25 cases, 50 controls	Both	For electric plating job OR 8.0 (95%CI:0.9, 72.0)
Davanipour et al., 1997[284]	USA	ELF-MF	Questionnaire, occupational history, JEM	28 cases, 32 controls	Both	OR 2.3 (95%CI:0.8, 6.6).
Savitz et al., 1998 (a)[272]	USA	ELF-MF, electrical occupations	Job title from death certificate	28 cases 114 cases, 228 controls	Both	OR 1.3 (95%CI:1.06, 1.6) for male electrical workers.
Noonan et al., 2002[273]	USA	ELF-MF	Job title on death certificates, ELF-MF JEM	312 cases, 1248 controls	Male only	RR 2.3 (95%CI:1.29, 4.09) by job title for male electrical workers. RR 0.77(95%CI:0.37, 1.59) by JEM (> 0.3μT).
Park et al., 2005[42]	USA	ELF-MF	JEM	6,347 cases among 2,614,346 deaths	Both	Mortality odds ratio (MOR) was 1.63 (95%CI:1.10, 2.39)

Authors, year	Country	Risk factors	Data collection method	Subjects	Gender	Main findings
Fang et al., 2009[43]	England	Electronic or electrical machinery	Questionnaire, job title	109 cases, 253 controls	Both	OR 1.4 (95%CI: 0.9, 2.3) for self-reported exposure to electrical or electronics machinery, male-only
Malek et al., 2014[261]	USA	ELF-MF	Questionnaire	66 cases, 66 controls	Both	OR 0.41 (95%CI: 0.20, 0.82)
Vergara et al., 2015[277]	USA	ELF-MF, electric shocks	JEMs (ES, ELF-MF) occupation at death certificate	5,886 cases, 57,667 controls	Both	For ELF-MF exposure OR 1.09 (95%CI:1.00, 1.19). for high exposure, OR1.09 (95%CI: 0.96, 1.23) for medium exposure. For electric shocks OR 0.73 (95%CI: 0.67, 0.79), for high and 0.90 (95%CI: 0.84, 0.97) for medium exposure. OR 1.23 (95%CI: 1.03, 1.47) for electrical occupation.
Koeman et al., 2017[264]	The Netherland	ELF-MF, electric shocks	JEMs (ELF-MF, ES)	2092 men and 2074 women, followed up, and ALS deaths (76 men and 60 women).	Both	Occupational exposure to ELF-MF showed a possible association with ALS mortality among men: HR for ever holding a job with high exposure versus background 2.19 (95%CI: 1.02, 4.73) and HR for the highest tertile of cumulative exposure versus background 1.93 (95%CI: 1.05, - 3.55). No increased risk of ALS for subjects with a higher risk of injuries due to electrical shocks in the workplace (HR 1.04, 95%CI:0.57, 1.92).
Peters et al., 2019[281]	Multi-centre (Ireland, Italy, the Netherlands)	ELF-MF, electric shocks	Questionnaire, JEM (ES, ELF-MF)	1,323 cases, 2,704 controls	Both	Exposure to ELF-MF: OR 1.16 (95%CI: 1.01, 1.33) Exposure to electric shocks: OR 1.23 (95%CI: 1.05, 1.43)
Mortality study						
Schulte et al., 1996[274]	USA	Electrical occupation	Occupation from census data	9,435 deaths from 130, 420	Both	Proportionate mortality ratio (PMR) 2.74 (95%CI: 1.18, 5.40) for white male power plant operators

Authors, year	Country	Risk factors	Data collection method	Subjects	Gender	Main findings
				total deaths between 1982-1991		
Johansen & Olsen 1998[280]	Denmark	ELF-MF, electric shocks	Job record from employment data	21,236 men with 303,000 persons follow up, 14 deaths from ALS, when 6.9 deaths would have been expected	Male only	14 deaths from ALS, when 6.9 deaths would have been expected, SMR 2.7 (95%CI: 1.0, 6.0), A highly increased rate of mortality from accidents caused by electricity was also observed, with 10 deaths observed and 0.6 expected. SMR1.12 (95%CI: 1.04, 1.19) for ELF-MF exposure.
Cohort study						
Buckley et al., 1983[115]	UK	Electrical occupation	Job title from death certificates	17 electrical and electronics workers from the 866 cohort	Both	SMR 0.94 (95%CI: 0.55, 1.51) for both sexes.
Savitz et al., 1998(b)[290]	USA	ELF-MF, electrical occupation	Job title from occupational records and JEM (> 1.1μT)	33 cases from 139,905 men cohort in electric utility workers	Both	For electrical occupation: RR 2.4 (95%CI: 0.8, 6.7) For ELF-MF: RR 1.2 (95%CI: 0.5, 3.0) by JEM (> 1.1μT).
Johansen 2000[278]	Denmark	ELF-MF	JEM (> 1.0μT)	20 cases, 30631 persons	Both	RR 1.56 (95%CI: 0.29, 8.53), JEM (> 1.0μT) RR 1.72 (95%CI: 1.05, 2.83) for male electrical workers.
Feychting et al., 2003[279]	Sweden	ELF-MF, electrical occupation	Two censuses, occupation at	1965 cases from	Both	For electrical occupation: RR 1.4 (95%CI:1.1, 1.9). ALS was not associated with the occupations having

Authors, year	Country	Risk factors	Data collection method	Subjects	Gender	Main findings
			censuses, JEM (ELF-MF)	4,812,646 persons		the highest EMF exposure (OR 0.8, 95%CI: 0.6, 1.1 in occupation in 1970s, OR 0.7(95%CI: 0.5, 1.1 in occupations in 1980s).
Hakansson et al., 2003[285]	Sweden	ELF-MF	JEM, occupation at census	97 cases from 537,692 men and 180,529 women.	Both	RR 2.16 (95%CI: 1.01, 4.66) JEM (> 0.53μT), RR 2.06 (95%CI: 0.92, 4.61) for male.
Weisskopf et al., 2005[292]	USA	ELF-MF, electrical occupation	Questionnaire, job title	937 cases from 1,184,561 persons	Both	For electrical occupation: RR 0.96 (95%CI: 0.48, 1.94) for male only For ELF-MF: RR 0.99 (95%CI: 0.49, 1.99), RR 0.96 (95%CI: 0.48, 1.24) for male.
Röösli et al., 2007[291]	Switzerland	ELF-MF	Job title from death certificates, JEM, cumulative lifetime exposure	15 cases from 20,141 Swiss railway persons	Male only	RR 1.31 (95%CI: 0.31, 5.59), RR 2.32 (95%CI: 0.70, 7.73) for male JEM (> 5.7μT-year).
Sorahan & Kheifets 2007[293]	UK	ELF-MF, electrical occupation	Job title from occupational records, cumulative exposure to magnetic fields cumulative year>10 μT by industry assessments.	68 deaths from 21,888 persons	Both	For electricity generation and transmission workers, cumulative exposure to ELF-MF, RR *per10μT-year* 1.04 (95%CI: 0.84, 1.30), For first employed in electricity power stations, cumulative exposure to ELF-MF, RR *per10μT-year*,1.03 (95%CI: 0.80, 1.33). For electrical occupation: SMR0.84 (95%CI: 0.65, 1.08).
Parlett et al., 2011[294]	USA	ELF-MF	JEM	40 MND deaths from 307,012 persons	Both	RR 0.98 (95%CI: 0.39, 2.50), for exposure level>0.27μT.

Authors, year	Country	Risk factors	Data collection method	Subjects	Gender	Main findings
Sorahan & Mohammed 2014[276]	UK	ELF-MF	Job title from occupational records, cumulative exposure to magnetic fields cumulative year>20 μT by industry assessment.	68 cases from 73,051 persons	Both	Occupational cumulative lifetime exposure to MF: RR 2.23 (95%CI: 1.21, 4.09) for 2.5-4.9 μT-year RR 1.41 (95%CI: 0.76, 2.61) for 5.0-9.9 μT-year RR 1.11 (95%CI: 0.55, 2.23) for 10.0-20 μT-year RR 1.30 (95%CI: 0.83, 1.27) for >=20 μT-year No trends.
Fischer et al., 2015[48]	Sweden	ELF-MF, electrical occupation	JEM (ES, ELF-MF), occupation at census	4,709 cases, 28,044 controls	Both	OR 0.99 (95%CI: 0.90, 1.09).
Huss et al., 2015[282]	Switzerland	Electrical occupation, ELF-MF, electric shocks	JEM (ELF-MF), occupation at census	237 cases from 2,167,046 workers	Both	For ELF-MF exposure: HR 1.56 (95% CI: 1.09, 2.25), JEM(≥0.2μT) For electric shocks. HR 0.97 (95%CI: 0.66, 1.42)
Pedersen et al., 2017[45]	Denmark	ELF-MF	JEM (ELF-MF) on occupational history	44 cases from 32,006 Danish electric utility workers cohort	Both	RR 2.65 (95%CI 0.98-7.13) for males only.
Meta-analysis						
Zhou et al., 2012[47]	China	ELF-MF	17 studies from PubMed databases up to April 2012 on the risk of ALS and occupational exposure to EMF.	17 studies	Both	Occupational exposure to ELF-significantly associated with ALS, RR 1.29 (95%CI: 1.02, 1.62) in pooled studies, RR 1.39 (95%CI: 1.05, 1.84) in case-control studies, but not in cohort studies (RR 1.16 95% CI: 0.80, 1.69). Sub-analysis showed a significant association ((OR 1.45 (95%CI: 1.15, 1.84) in pooled studies) when the exposure levels were defined by the job title, but not by the JEM.

Authors, year	Country	Risk factors	Data collection method	Subjects	Gender	Main findings
Vergara et al., 2013[289]	USA	ELF-MF	42 peer-reviewed publications with occupational EMF exposure and Alzheimer's disease (AD) and MND before January 2012	42 peer-reviewed publications	Both	A weak association for occupational exposure to EMF and MND (RR1.26, 95%CI: 1.10, 1.44). MND risk was associated with occupational job title but not with MF level.
Gunnarsson et al., 2018[206]	Sweden	ELF-MF, electric shocks	79 original publications on associations between work and ALS before 15 February 2017.	36 peer-reviewed publications	Both	RR 1.23 (95%CI: 1.04, 1.45) for exposure to ELF-MF, based on JEM, RR 1.16 (95%CI: 1.00, 1.35) for exposure to electric shocks (electrical accidents/trauma) based on job titles and years of work with electricity. The weighted RR for electromagnetic fields or working with electricity was 1.18 (95%CI:1.07, 1.31).
Huss et al., 2018[46]	The Netherlands	ELF-MF	Searched publications (209) in EMBASE and MEDLINE with occupational ELF-MF exposure and MND/ALS	20 peer-reviewed publications	Both	For high level of ELF-MF exposure, RR 1.14 (95%CI: 1.00, 1.30) For electrical occupations, RR 1.41(95%CI: 1.05, 1.92), but with large heterogeneity between studies (I^2>70%). RR 1.09 (95%CI: 0.51, 2.32) for self-reported exposures. RR 1.07 (95%CI: 0.96, 1.21) for occupations from death certificates. An increased risk was observed for the highest-longest exposure versus lowest (RR 1.89, 95%CI: 1.31, 2.73). For studies that had the full occupational histories, RR 1.06 (95%CI: 0.75, 1.57).

Authors, year	Country	Risk factors	Data collection method	Subjects	Gender	Main findings
Gunnarsson et al., 2019[204]	Sweden	ELF-MF	Original publications on associations between exposure to metals, pesticides, and ELF-MF work and neurodegenerative diseases before 2017.	66 peer-reviewed publications	Both	RR for occupational exposure to EMFs was 1.26 (95% CI: 1.07, 1.50).
Jalilian et al., 2020[295]	Iran	ELF, electric shocks	Searched from PubMed, Embase, Web of Science databases up to the end of 2019.	27 studies	Both	Pooled RR 1.20 (95%CI:1.05, 1.38, I^2=66.3%) for occupational exposure to ELF-MF and risk of ALS. Pooled RR 0.97 (95%CI: 0.80, 1.17, I^2=80.5%) for occupational exposure to electrical shocks and risk of ALS. Supported occupational exposure to ELF-MF, but not electric shocks.
Bakken et al., 2021[296]	Germany	ELF	included 10 cohort studies one was analysed as a nested case-control study) and 5 case-control studies. 13 studies based on JEM, 1 study based on measurements and modelling, and 1 study based on industrial hygienist experience. Only 8 studies provided original data.	7,357 cases in 8,230,768 participants in cohort studies. 13,896 cases and 61,651 controls in 5 case-control studies.	Both	A relative risk of ≥1.14 for ALS was associated with occupational exposure to ELF-MF, with a power of more than 80% in a pooled study.

2.4.5 Pesticide exposure, agriculture occupations, and rural living

2.4.5.1 Pesticide exposure

Previous exposure to agricultural chemicals, especially to pesticides, has received increasing attention in relation to MND in the last three decades. Most pesticides are neurotoxins and they are also known to be a risk factor for other neurodegenerative diseases such as Parkinson's and Alzheimer's.[297-299 300] In particular, organophosphates (OP) can induce progressive brain damage[301] and may result in OP-induced delayed neuropathy, a condition akin to ALS.[302] An increased MND risk was also reported for certain polymorphisms of the PON1 gene, which detoxifies organophosphates.[303] Moreover, most of these chemical compounds in pesticides are known for their ability to induce oxidative stress, mitochondrial dysfunction,[167] and neuronal loss,[304] which play an important role in the pathogenesis of MND.[305]

Case reports of MND diagnoses following exposure to pesticides have been reported.[306-308] The association between pesticides exposure and MND has also been evaluated in previous epidemiologic studies. The majority of these studies reported a positive association between pesticides exposures and MND risk,[36 38 44 180 183 185 259 261 262 266 309-313] although not all were statistically significant. All studies with at least five pesticide exposed subjects reported an increased risk of ALS, with ORs ranging from 1.4 to 6.95. Only a few studies reported no association.[113 187] Table 2.5 presents studies that assessed agricultural chemicals and MND risk.

The relationship between pesticides and MND has also been evaluated in six meta-analyses. The first meta-analysis was published in 2012 by Kamel et al.[37] which also reported previously unpublished results from a large agricultural cohort, the agricultural

health study.[314] This meta-analysis showed that occupational exposure to pesticides (not differentiated by the type of pesticides) was associated with a statistically significant two-fold (OR 1.9, 95%CI: 1.1, 3.1) risk for ALS. In the agricultural health study, ALS was not associated with pesticides. In the same year, Malek et al.[39] conducted a meta-analysis on a retrospective cohort study and five case-control studies and reported an approximately two-fold (OR 1.88, 95%CI: 1.36, 2.61) increase in the risk of MND among pesticides exposed men, but not among women. Two years later, Kang et al.[40] carried out a meta-analysis of three cohorts and 19 case-control studies and found a significant positive association between the risk of MND and pesticides exposure (OR 1.44, 95%CI:1.22, 1.70), and this association was stronger for men (OR, 1.96, 95%CI: 95%CI: 1.50, 2.55); a positive association with farming (OR 1.42, 95%CI: 1.17, 1.73) was also reported. They did not, however, find an association between the risk of MND and rural living. Later, Wang et al.[41] reported that pesticides exposure was associated with an approximately 1.5-fold risk of MND, based on 12 case-control studies. Recently, Gunnarsson et al.[204] reported a weighted relative risk of 1.35 for occupational exposure to pesticides based on five studies. Furthermore, several reviews have expressed that exposure to pesticides was a potential risk factor for developing MND.[35] [228] [315] [316] An umbrella review[203] and a meta-umbrella review[207] also illustrated that previous exposure to pesticides was associated with a 1.5 fold risk of developing MND (Table 2.5).

However, most studies investigated the association of MND with pesticides exposure as a group and have not been able to identify the specific pesticide classes (i.e., insecticides, herbicides, fungicides) and specific chemicals involved (i.e., organophosphate (OPs), organochlorines (OCPs)). The few studies that considered

specific pesticides or specific chemicals[36 43 317] showed inconclusive results. Burns et al.[317] in an industry cohort found an increased risk of ALS among workers exposed to the herbicide 2,4-Dichlorophenoxyacetic acid (2,4-D) compared to other company employees (RR 3.45, 95%CI: 1.1, 11.11; see Table 2.5), although this result was based on only three deaths. Similarly, in a case-control study[318] of US military veterans, ALS was positively associated with exposure to herbicides for military purposes, in particular, war-field exposure to Agent Orange increased the risk of ALS nearly 3-fold. One case report[307] has described chronic exposure to organochlorines insecticides and the development of ALS. This association was also supported by McGuire et al.[36] who observed a statistically significant elevated risk of MND for insecticides exposure in men (OR 2.1, 95%CI: 1.1, 3.8). Kamel et al.[37] in the agricultural health cohort of 84,739 private pesticide applicators revealed that ALS risks were associated in particular with organochlorine insecticides (OR 1.6, 95%CI: 0.8, 3.5), pyrethroids (OR 1.4, 95%CI: 0.6, 3.4), herbicides (OR 1.6, 95%CI:0.7, 3.7), and fumigants (OR 1.8, 95%CI: 0.8, 3.9). Although none of the associations with specific agents was statically significant, the risk was consistently elevated for individual organochlorine insecticides including aldrin (OR 2.1, 95%CI: 0.8, 5.1), dieldrin (OR 2.6, 95%CI: 0.9, 7.3), DDT (Dichlorodiphenyltrichloroethane) (OR 2.1, 95%CI: 0.9, 5.0), and toxaphene (OR 2.0, 95%CI: 0.8, 4.9). Furthermore, Su et al.[319] measured the blood level of organochlorine pesticides in ALS cases and controls and reported that ALS was significantly associated with pentachlorobenzene (OR 2.57, 95%CI: 1.31, 5.02), and cis-chlordane (OR 6.51, 95%CI: 2.05, 20.73). Whereas Fang et al.[43] observed no association with MND for exposures to insecticides, herbicides, fungicides, or fumigants.

Table 2.5. Agricultural chemicals and the risk of MND

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
Case-control study						
Deapen & Henderson 1986[185]	USA	Pesticides, living in a rural area for more than 10 years	Questionnaire, self-reported occupational exposure	518 cases, 518 controls	Both	Exposure to pesticides OR 2.0 (95%CI: 0.8, 5.4)
Granieri et al., 1988[113]	Italy	Agricultural chemicals, rural living	Questionnaire, self-reported occupational exposure	70 case, 216 controls	Both	OR 1.8 (95%CI: 1.1, 3.1) for rural residence, OR 1.0 (95%CI: 0.5, 1.9) for exposure to agriculture chemicals.
Savettieri et al., 1991[259]	Italy	Agricultural chemicals	Questionnaire, self-reported occupational exposure	46 cases, 92 controls	Both	Exposure to agriculture chemicals (OR 3.0, 95%CI: 0.4, 20.3)
Gunnarsson et al., 1992[187]	Sweden	Pesticides, insecticides	Self-reported occupational pesticide/insecticides	92 cases, 372 controls	Both	Exposure to pesticides/insecticides was not associated with ALS risk (OR1.1, 95%CI: 0.2, 5.3)
Chancellor et al., 1993[180]	UK	Pesticides	Questionnaire, self-reported occupational exposure	103 cases, 103 controls	Both	OR 1.4 (95%CI: 0.6, 3.1) for pesticides exposure.
McGuire et al., 1997[36]	USA	Agricultural chemicals	Assessment of detailed lifetime job history for exposure to metals, solvents, and agricultural chemicals using questionnaire and in-person interviews. Self-reported exposures with industrial hygienists panel	174 cases, 348 controls.	Both	Self-reported exposure to agricultural chemicals in general, there was an association with ALS in men (OR 2.1, 95%CI: 1.1, 3.8), but not in women (OR 0.8, 95%CI: 0.3, 2.4), with a dose-response (p = 0.02). In men, the comparison between the groups not exposed to low exposure shows OR1.5 (95%CI: 0.6, 4.1), and between non-exposed to high exposure, OR 2.7 (95% CI:1.3, 5.7). Based on the industrial hygienists' panel's assessment, ever exposure to agricultural

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
			assessment on exposure intensity (0-none, 1-low, 2-medium, 3-high).			chemicals was associated with ALS risk (OR 2.0, 95%CI: 1.1, 3.5), this association was observed separately in men (OR 2.4, 95%CI: 1.2–4.8) with the presence of a dose-response (p = 0.03), but not in women (OR 0.9, 95%CI: 0.2, 3.8). Exposure to specific agriculture chemicals: OR 2.3 (95%CI: 1.0, 5.5) for fertilisers; OR 1.7 (95%CI: 0.7, 4.2) for fungicides; OR 3.0 (95%CI: 0.9, 9.6) for herbicides; OR 2.1 (95%CI: 1.1, 4.1) for insecticide.
Morahan & Pamphlett. 2006[44]	Australia	Solvents, chemical substances, herbicides, pesticides	Questionnaire to verify exposure to solvent/chemical substances and herbicides/pesticides	179 cases and 179 controls	Both	Overall herbicides/pesticides: OR 1.57 (95%CI: 1.03, 2.41); Industrial herbicides/pesticides: OR 5.58 (95%CI: 2.07, 15.06). Exposure to herbicides/pesticides shows a dose-response effect.
Qureshi et al., 2006[266]	UAS	Pesticides	Questionnaire	95 cases 106 controls	Both	A significant risk associated with pesticide exposure (p=0.03). no OR and 95%CI provided.
Fang et al., 2009[43]	USA	Insecticides, herbicides, fungicides, fumigants	Questionnaire	109 cases, 253 controls	Both	OR1.1 (95%CI: 0.5, 2.2) for insecticides exposure; OR1.1 (95%CI: 0.3, 4.1) for herbicides exposure; OR 0.2 (95%CI: 0, 1.6) for fungicides exposure; OR 0.9 (95%CI: 0.3, 2.8) for fumigants exposure.
Bonvicini et al., 2010[309]	Italy	Pesticides	Self-reported occupational pesticide exposure>=6month.	41 cases, 82 controls	Both	ALS associated with pesticides OR 3.6 (95%CI:1.2, 10.5).
Furby et al., 2010[310]	France	Agricultural chemicals, rural living	Questionnaire to collect main	108 cases, 122 age, and sex-	Both	OR 3.04 (95%CI:1.19, 7.76) for exposure to agricultural chemicals OR 1.35 (95%CI: 0.79, 2.31) for rural living.

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
			occupation and exposures	matched controls		A strong association was found between agricultural workers and ALS (OR 2.92, p=0.01), while rural residence itself did not influence the risk of the disease.
Das et al., 2012[38]	India	Pesticides, and insecticides	Questionnaire, pesticides, and insecticides	110 cases, 240 controls	Both	Exposures to insecticides or pesticides (OR1.61, 95%CI; 1.27, 1.99), and rural livings (OR 1.99, 95%CI: 1.02, 3.88) were associated with ALS.
Pamphlett 2012[311]	Australia	Herbicides, pesticides	Questionnaire, herbicides/pesticides	614 cases, 778 controls	Both	Males exposed to pesticides or herbicides was associated with significant risk (OR 1.77, 95%CI: 1.30, 2.39), Women who reported exposure to herbicides or pesticides also tended to have an increased risk for (OR 1.43) but this did not reach statistical significance after correction for multiple testing.
Malek et al., 2013[261]	USA	Pesticides	Questionnaire	66 cases, 66 controls	Both	Occupational exposure to pesticides was associated with ALS risk (OR 6.50, 95%CI: 1.78, 23.77).
Yu et al., 2014[312]	USA	Pesticides	Questionnaire,	66 cases, 66 controls	Both	ALS risk was associated with more than 30 years of exposure to pesticides (OR 6.95, 95%CI:1.23, 39.1).
Beard et al., 2016[318]	USA	Agent Orange (in Vietnam war)	Questionnaire	621cases, 958 controls	Male only	Exposure to Agent Orange in the field was associated with ALS risk (OR 2.80, 95%CI: 1.44, 5.44)
Su et al., 2016[319]	USA	OCPs, PCBs (polychlorinated biphenyls), and brominated flame retardants	Questionnaires, lifetime cumulative occupational exposures to pesticides based on JEM, blood samples for measuring	156 cases, 128 controls	Both	Lifetime cumulative exposure to pesticides was significantly associated with ALS, OR 5.09 (95%CI: 1.85, 13.99). Measured persistent environmental pollutants in the blood (representing cumulative occupational and residential exposure) showed

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
			persistent environmental pollutants			increased odds of ALS for pentachlorobenzene (OR 2.57, 95%CI: 1.31, 5.02), and cis chlordane (OR 6.51, 95%CI: 2.05, 20.73).
Andrew et al., 2017[183]	USA	Pesticides	Self-reported job or hobby-related exposures	295 cases, 225 controls	Both	Exposure to pesticides was associated with ALS risk, OR 3.28 (95%CI: 1.36, 9.19)
Beaudin et al., 2020[313]	France	Pesticides	Assessment of exposure through questionnaire	403 cases, 381 controls	Both	Occupational exposure to pesticides OR 2.05 (95%CI: 1.22, 3.54, unadjusted), OR1.53 (95%CI: 0.89, 2.69 adjusted).
Cohort study						
Burns et al., 2001[317]	USA	Herbicide, 2,4-D	JEM used to rank the time-weighted average of occupational exposure to the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D)	3 ALS deaths were observed from 1517 people who were employed by the Dow Chemical Company from 1945 to 1994	Male only	RR of 3.45 (95%CI: 1.1, 11.11).
Weisskopf et al., 2009[262]	USA	Pesticides, herbicides	Assessment of exposure through questionnaire	617 male ALS deaths during 5,473,411 person-years among men; 539 female ALS deaths during 8,104,402 person-years among women from the Cancer	Both	The RR for ALS mortality among individuals exposed to pesticides/herbicides compared with that among unexposed individuals was 1.07 (95%CI: 0.79, 1.44), but somewhat higher after excluding those with a missing duration of pesticides exposure (RR 1.44, 95%CI: 0.89, 2.31).

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
				Prevention Study-II cohort of the American Cancer Society (period 1989–2004).		
Meta-analysis						
#Kamel et al., 2012[37]	USA	Exposure to pesticides as a group and specific pesticides.	Questionnaire, OCs (organochlorines)	Cohort study: 84,739 private pesticides user and spouses to evaluate the risk associated with specific pesticides, using data from the Agricultural Health Study. Meta-analysis: published studies (before 31 Dec 2011) on exposure to pesticides as a group	Both	Meta-analysis: pesticides as a group was associated with ALS (OR1.9, 95%CI: 1.1, 3.1). Cohort: no association with pesticides as a group, but increased risks with organochlorine insecticides (OR 1.6, 95%CI: 0.8, 3.5), pyrethroids (OR1.4, 95%CI: 0.6, 3.4), herbicides (OR1.6, 95%CI: 0.7, 3.7), and fumigants (OR 1.8, 95%CI: 0.8, 3.9). ORs were elevated for ever use of the specific organochlorine insecticides: aldrin (OR2.1, 95%CI: 0.8, 5.1), dieldrin (OR2.6, 95%CI: 0.9, 7.3), DDT (OR2.1, 95%CI: 0.9, 5.0), and toxaphene (OR 2.0, 95%CI: 0.8, 4.9). None of these associations was statistically significant. when analyses were restricted to men, ORs were elevated for organochlorine insecticides as a group (2.0), aldrin (2.4), dieldrin (3.0), DDT (2.4), and toxaphene (2.2) too, confidence interval level did not provide in the study. few female cases had used pesticides to analyse separately.

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
Malek et al., 2012[39]	USA	Pesticides	82 relevant studies were published before May 2011, and 6 peer-reviewed studies were included for meta-analysis.	The meta-analysis of men included 1517 deceased ALS cases from a retrospective cohort, 589 ALS cases from 5 case-control studies. The meta-analysis of women involved a total of 144 ALS cases from three case-control studies.	Both	Exposure to pesticides as a group was associated with ALS risk (OR 1.88, 95%CI: 1.36, 2.61) in male cases. No relationship was found between exposure to pesticides and risk of ALS among female cases compared to controls (OR1.31, 95% CI: 0.69, 2.47).
Capozzella et al., 2014[265]	USA	ELF-MF, solvents, heavy metals, and pesticides.	750 articles published from 1980 up to April 2013, studies that meet both the methodological criteria and those of exposure were included in the meta-analysis.	9 EMF studies, 2 solvents studies, 2 heavy metals studies, and 2 pesticides 2 studies were included in the meta-analysis.	Both	The association between exposure to pesticides and ALS as a whole is weak and not significant (RR 1.09, 95%CI: 0.75, 1.58), but there was an association with ALS in men (OR 2.1, 95%CI: 1.1, 3.8) but not in women (OR 0.8, 95%CI: 0.3, 2.4), with a dose-response relationship (p=0.02).
Kang et al., 2014[40]	Korea	Pesticides, rural residence, farming occupations	A search was performed in OVID MEDLINE and	22 studies (19 case-control studies, 3 cohorts) were	Both	The risk of ALS was significantly increased with pesticide exposure (OR 1.44, 95% CI 1.22, 1.70) and with farmers (OR 1.42, 95% CI

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
			EMBASE up to September 2013.	included for this meta-analysis.		1.17, 1.73), but was not significant with rural residence (OR1.25, 95% CI 0.84, 1.87). Pesticide exposure and ALS indicated a significant positive association with men (OR 1.96, 95%CI: 1.50, 2.55), and in studies using El Escorial criteria for ALS definition (OR, 1.63, 95%CI: 1.24, 2.13) and expert judgment for pesticide exposure (OR 2.04, 95%CI: 1.12, 3.70) as well.
Wang et al., 2017[41]	Canada	Pesticides, agriculture chemicals	Using a designed literature search strategy to search terms for the disease itself, risk factors for the disease, and related terms for publications prior to February 2016. A total of 133 observational studies related to environmental risk factors was identified.	12 case-control studies (10 studies with pesticides exposure, 2 studies with agriculture chemicals)	Both	OR1.48 (95%CI: 1.18, 1.86) for exposure to pesticides; OR 3.08 (95%CI: 1.04, 3.68) for exposure to agriculture chemicals, OR 1.57 (95%CI: 1.25, 1.98) for exposure to pesticides including agriculture chemicals.
Gunnarsson et al., 2018[206] & 2019[204]	Sweden	Agriculture work and or pesticides	Search published articles using bibliographic search engines in PubMed and Embase to the 15th of Feb 2017. Original publications of the good scientific	37 studies in 2018 meta-analysis. 31 studies in 2019 meta-analysis. (5 studies on pesticides in	Both	Weighted RR1.35 (95% CI: 1.02, 1.79) for occupational exposure to pesticides based on 5 studies. Suggested risk of amyotrophic lateral sclerosis was statistically significantly elevated for occupational exposures to pesticides.

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
			epidemiological standard were selected for meta-analysis.	both meta-analyses)		
Review						
Johnson & Atchison 2009[315]	USA	Mercury, lead, and pesticides	n/a	n/a	Both	Exposure to heavy metals and pesticides are potential candidates for MND. Exposure to organophosphate was a risk factor in developing ALS.
Sutedja et al., 2009[35]	USA	Chemical agents and metals	Two systemic reviews (chemical agents and metals) of literature were performed according to the MOOSE guidelines for performing and reporting a meta-analysis or systemic review of observational studies. Screened for case-control and cohort studies. Studies appraised according to Armon's s classification system for ALS risk factor studies, and newly developed classification system	Seven of 37 studies (case-control or cohort studies) concerning exposure to chemical agents and metals.	Both	Pesticides are a potential environmental risk factor for ALS, but additional well-designed studies are needed. a significant association with increased ALS risk was reported for exposure to pesticides.

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
			for exposure assessment.			
Vinceti et al., 2012[228]	Italy	Pesticides, selenium, and heavy metals	n/a	n/a	n/a	The overall evidence is suggestive of an association between increased ALS risk and pesticide exposure.
Tanner et al., 2014[316]	USA	Pesticides, lead, other metals, solvents, formaldehyde	n/a	n/a	n/a	epidemiologic evidence provides good support for an association of pesticides and ALS.
Belbasis et al., 2016[203]	Greece	Farming	Meta-analyses published before August 20th, 2015.	16 meta-analyses of different risk factors and ALS were considered in the review	Both	OR 1.42 (95%CI: 1.17, 1.73) for farming, OR 1.44 (95%CI: 1.22, 1.70) for pesticides exposure assessment, OR 1.25 (95%CI: 0.84, 1.88) for rural living.
Couratier et al., 2016[107]	France	Pesticides, metals, ELF-MF, occupations	n/a	n/a	n/a	An association between pesticides use and ALS was suggested by previous studies, specifically involving organochlorine compounds, pyrethroids, herbicides, and fumigants.
Mentis et al., 2021[207]	Greece	Farming, pesticides among other non-genetic risks	Reviews and meta-analyses on non-genetic risk/protective factors for neurological disorders which were published before Sept 20th, 2018, were selected.	14 umbrella reviews (203 unique meta-analyses) were eligible for this meta-umbrella review.	Both	The meta-umbrella review shows a positive association of exposure to farming (OR 1.42, 95%CI: 1.17, 1.73) and pesticides (OR 1.44, 95%CI: 1.22, 1.70).

[#] The study combines a cohort and a meta-analysis.

2.4.5.2 Agriculture occupations & rural living

The first observation of an increased ALS risk among agricultural workers dates back over three decades,[114] and since then, occupational exposure to pesticides has frequently been suggested as the underlying reason for temporal increases in ALS risk in those occupations.[184 320] As agriculture occupations and rural living can be used as surrogate indices for pesticide exposures, several studies have investigated the correlation between agriculture occupations or living on/near a farm, and the risk of MND. Table 2.6 illustrates the relevant studies that have assessed the associations between MND risk and agriculture occupations, and Table 2.7 presents the relevant studies on rural living and MND.

The majority of these studies[30 38 42 113 310 320-324] reported an increased MND risk among farmers or agriculture workers, with an estimated OR between 1.2 - 2.1 (Table 2.6), but others found no association.[31 43 275 325]

Among studies that investigated the association between rural living and MND risk, seven studies reported inconsistent findings, two early studies observed no association[266 326] and a recent study found that participants who lived less than 100m from an agricultural area were at greater risk of MND (see Table 2.7).[327] Few case-control studies have assessed associations with MND for both rural living and farming occupation in the same study. Granieri et al.[113] observed an increased MND risk (OR 1.8, 95%CI: 1.1, 3.1; Table 2.7) for both agriculture workers and for those who lived in rural areas. Furby et al.[310] reported that market-oriented skilled agricultural workers had an approximately 3-fold increased risk while living in rural areas was not associated with MND. Similarly, Govoni et al.[321] observed more incident ALS cases than expected

(22 vs 6; 95%CI: 13.8, 32.3; Table 2.7) among agricultural workers, but no association with rural residence. Conversely, Das et al.[38] observed that rural living was associated with a 2-fold MND risk, but no association with farming occupations was observed.

In the last 15 years, systematic reviews[35 107 228 315 316] have supported the hypothesis that exposure to pesticides is a potential risk factor for MND. An umbrella-review[203] noted a 1.4 times increased risk of MND with pesticides exposure and farmer occupation, but not with rural living. The most recent meta-umbrella review[207] has also reported a more than 1.4 fold risk for exposure to pesticides and farming occupation (see Table 2.5 under Review section).

Therefore, the evidence from epidemiological studies supports the role of pesticides exposure in the development of ALS. However, as noted before, most studies investigating the association of MND with pesticides exposure as a group have not been able to identify the specific pesticide classes and specific chemicals involved. Similarly, studies that investigated farming occupations have not been able to identify which farming occupations/jobs were associated with MND. Moreover, the majority of studies have assessed either pesticides exposure or occupations in the study but have not been able to assess both in the same study.

Table 2.6. Agricultural occupations and the risk of MND

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
Mortality study						
Park et al., 2005[42]	USA	Farming occupations	Expert judgement	6,347 cases, 2,614,346 controls	Both	MND was significantly elevated for farming occupations of all ages, strongest for farmers Mortality odd ratio (MOR)1.20, 95% CI:1.02–1.41) but with no difference in age.
Incidence study						
Kab et al., 2017[324]	France	Farmers and agricultural workers	Farmers from The Mutualite Sociale Agricole ((MSA), which is the agricultural social mutual organisation in France) members and non-MSA members	8931 incidence cases from MSA member and non-MSA member	Male only	The incidence of MND was similar in MSA compared with non-MSA members (RR 1.04; 95%CI: 0.96, 1.13), but there was a trend towards higher incidence in MSA farmers compared with non-MSA members (RR, 1.08, 95%CI: 0.99, 1.18) and MSA workers (RR 1.13, 95%CI: 0.97, 1.31)
Case-control study						
Granier et al., 1988[113]	Italy	Agricultural workers, rural residence (ever lived in suburban areas and rural farming areas with ≤ 5,000 inhabitants)	Questionnaire	72 cases, 216 controls	Both	OR 1.8 (95%CI:1.0, 3.2) for agriculture workers and OR 1.8 (95%CI: 1.1, 3.1) for people who live in the rural areas.
Chió et al., 1991[320]	Italy	Farmers	Questionnaire	512 cases, 512 controls	Both	Farming was associated with an increased risk (OR 1.6, 95%CI:1.3, 2.0).

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
Gunnarsson et al., 1991[30]	Sweden	Farmworkers	Census records	1375 cases, 1434 controls	Both	Significantly more male cases than expected were found among farmer workers (OR 1.74, 95%CI: 1.28, 2.38)
Kalfakis et al., 1991[325]	Greece	Farmers	Clinical records	316 cases, 360 controls	Both	Farming was associated with an elevated ALS risk (OR 1.17, 95%CI: 0.5, 2.77)
Strickland et al., 1996[275]	USA	Farming occupations	Questionnaires	25 cases, 50 controls	Both	No association with farming occupations (OR 0.2, 95%CI: 0.02, 1.6).
Govoni et al., 2005[321]	Italy	Agricultural workers, rural residence	Questionnaires	91 cases among 68,279 general populations	Both	Based on the occupational pattern, the number of incident cases of ALS whose usual occupation was in agricultural work exceeded the expected number (observed ALS cases = 22, 95%CI: 13.8, 32.3, expected ALS cases 6.0). The rural residence itself does not influence the risk of ALS.
Sutedja et al., 2007[31]	Netherlands	Skilled agricultural and fishery workers	Questionnaires	364 cases, 392 controls	Both	No association was found with skilled agricultural and fishery work (OR 0.9, 95%CI: 0.3, 2.5 for males; OR1.1, 95%CI: 0.1, 8.9 for females).
Fang et al., 2009[43]	USA	Farming, forestry, and fishing occupation	Questionnaires	109 cases, 253 controls	Both	OR 1.0 (95%CI: 0.2, 4.2) for farming, forestry, and fishing occupations.
Furby et al., 2010[310]	France	Agricultural workers	Questionnaire to collect main occupation and exposures	108 cases, 122 age, and sex-matched controls	Both	Market-oriented skilled agricultural workers with OR 2.88 (95%CI:1.27, 6.53)
Das et al., 2012[38]	India	Farming occupation	Questionnaires	110 cases, 240 controls	Both	OR 1.07 (95%CI: 0.62, 1.85) for farming occupations.
Dickerson et al., 2018[323]	Denmark	Agriculture, hunting, forestry, and fishing occupations.	Use Danish Pension Fund to determine occupation history	1,826 cases, 182,600 controls	Male only	OR1.20 (95%CI: 0.99, 1.44) for agriculture and farming; OR 1.25 (95%CI: 0.75, 2.09) for forestry; OR 1.04 (95%CI: 0.65, 1.64) for hunting and fishing, for males only.

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
						Males who worked in agriculture, hunting, forestry, or fishing as a group was associated with ALS risk (OR 1.21(95%CI: 1.02, 1.45).
Filippini et al., 2020[184]	Italy	Agricultural workers	Self-administered questionnaire	95 cases, 135 controls, match age (±5) and gender	Both	Agriculture work showed a risk for ALS OR 2.09 (95%CI: 0.79, 7.54), but it was not significant, however, being employed more than 10 years in agriculture was associated with a significantly increased risk, OR 2.72 (95%CI: 1.02, 7.20).

Table 2.7. Rural residence and the risk of MND

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
Case-control study						
Granieri et al., 1988[113]	Italy	Ever lived in suburban areas and rural farming areas	Questionnaire	72 cases, 216 controls	Both	OR 1.8 (95%CI 1.1, 3.1) for ever lived in suburban areas and rural farming areas with ≤ 5,000 inhabitants
Cruz et al., 1999[326]	USA	Ever resided on a farm or ranch	Questionnaire	174 cases, 238 controls	Both	Ever resided on a farm or ranch was not associated with ALS (OR 0.8, 95%CI: 0.6, 1.3)
Govoni et al., 2005[321]	Italy	Agricultural workers, rural residence	Questionnaires	91 cases among 68,279 general populations	Both	Rural residence was not associated with the risk of ALS. No difference was found between the observed and expected number of ALS cases (observed ALS cases 16, 95%CI: 9.1, 25.9, expected ALS cases 18.3).
Qureshi et al., 2006[266]	USA	Living in the rural area	Questionnaire	95 cases, 106 controls	Both	OR 0.74 (95%CI: 0.28, 1.93) for living in rural areas compared with living in urban areas.
Furby et al., 2010[310]	France	Living in a rural area	Questionnaire	108 cases, 122 controls	Both	OR 1.35 (95%CI 0.79, 2.31) for living in an area with ≤ 8,000 inhabitants for the longest period over their lifetimes.
Das et al., 2012[38]	India	Living in a rural area for more than 10 years	Questionnaire	110 cases, 240 controls	Both	Rural living was associated with ALS (OR 1.99, 95%CI: 1.02, 3.88)
Povedano et al., 2018[327]	Spain	Pesticides, air pollutants	Use the distance between residential addresses to the nearest agricultural areas as a proxy to the exposure of pesticides. Use 142 pollution control and prevention monitoring stations to measure the levels of air pollutants.	383 cases, 383 controls	Male Only	OR 5.48 (95% CI 1.28, 25.23) for those who lived less than 100m from an agricultural area. OR 1.36 (95% CI 0.89, 2.1) for living between 25 and 100 m from the nearest road, suggested that exposure to air pollutants as a result of urban traffic could be associated with the occurrence of ALS.

2.4.6 Head trauma

Head trauma has been repeatedly studied as a potential risk factor for MND.[328] This association is biologically plausible as head trauma is known to disrupt and to cause deterioration to the BBB,[329] which may play a role in MND pathogenesis.[330 331] In ALS animal models, traumatic brain injury can trigger TAR DNA-binding protein 43 (TDP-43) pathology, which is a neuropathological hallmark lesion in the brain of patients with ALS.[332] Head trauma has also been implicated in the development of other neurodegenerative diseases, such as Parkinson's disease[333] and Alzheimer's disease,[334] both of which share some pathological and epidemiologic characteristics with ALS.[335 336]

The link between head trauma and MND risk has been investigated over several decades, with conflicting results. Some studies have suggested that head injury was associated with an increased risk of ALS, although not all were statistically significant,[322 328 337-350] other studies found no association.[74 113 266 320 346 351-354] Table 2.8 provides a summary of relevant studies on head trauma and MND risk.

The studies which observed a positive association also observed different intervals between when the injury occurred and the onset of the disease. Chen et al.[337] in a case-control study found a higher risk of ALS in those who reported more than one head injury (OR 3.1, 95%CI: 1.2, 8.1) and having been injured within 10 years before diagnosis was also associated with an increased risk (OR 3.2, 95%CI: 1.0, 10.2). Schmidt et al.[341] reported a relatively long latency (more than 15 years) between a head injury and the onset of ALS. Binazzi et al.[347] observed that individuals who had their last head injury between the age of 30-40 had an increased risk of ALS (OR 14.2,

90%CI: 1.04, 194.42). However, in two other studies, odds ratios were statistically significantly elevated only in those who had a head injury within 1 year of disease onset,[345 349] suggesting that head injury in this study may have been the result of early signs of disease.[345] In order to reduce the problem of reverse causation in which incipient ALS leads to trauma, several studies have excluded head injuries that take place during either the 3 years or 5 years prior to the index date,[338 340 349] providing inconsistent results. Pupillo et al.[340] showed that elevated risks remained significant when the analysis was limited to injuries that occurred 5 years and 10 years before ALS onset, whereas two large prospective studies,[338 349] in which exposure assessments were based on the medical records of head trauma, found no association between head trauma and ALS when trauma events occurring 3 years/5 years before the diagnosis of ALS were excluded (Table 2.8).

Several meta-analyses have also investigated this association. The first, including nine studies,[337] reported a 1.7-fold increased risk of MND in relation to a head injury (Table 2.8). In 2016, a meta-analysis by Perry et al.[355] including four studies, observed an increased but not a statistically significant risk, whereas Belbasis et al.[203] in an umbrella review observed a statistically significant 1.6 fold increased risk. A year later, Wang et al.[41] conducted a meta-analysis of 15 case-control studies that showed a positive association between previous head trauma and ALS risk (OR 1.27, 95%CI: 1.02, 1.57; Table 2.8). Subsequently, another meta-analysis of 16 studies[356] reported a slightly weaker meta-estimate (OR 1.21, 95% CI: 1.01, 1.46; Table 2.8) for injuries that occurred ≥1 year prior to the first diagnosis and suggested that due to reverse-causation head-injury-oriented risk of ALS has been somewhat overestimated. A recent meta-analysis conducted by Gu et al.[357] demonstrated that head injury was associated with an

approximately 1.51-fold risk of ALS, this association was similar for studies that assessed head trauma based on medical records (OR 1.47, 95%CI: 1.36, 1.59; Table 2.8) and questionnaires (OR 1.56, 95%CI: 1.18, 2.06; Table 2.8). The most recent meta-analysis,[358] which was based on 14 studies also suggested that head trauma was associated with an increased ALS risk (OR 1.38, 95%CI: 1.20, 1.60; Table 2.8), and the association remained when excluding those who had a head injury within 1 year before diagnosis (OR 1.35 for 5-10 years' time lag; OR 1.10 for >10 years' time lag; Table 2.8). A slightly stronger association with ALS was observed for severe head injury (OR 1.69, 95%CI: 1.27, 2.23; Table 2.8) in this meta-analysis.

Overall, these meta-analyses have indicated a 1.3-to-1.7-fold increased risk of MND associated with head trauma. However, it is not clear how particular patterns of head trauma, for example, frequency, severity, or how the timing of injuries (the age when head trauma occurred) contribute to ALS risk.

Table 2.8. Head trauma and risk of MND

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
Case-control study						
Kurtzke et al., 1980[346]	USA	Physical trauma	Medical record	504 cases, 504 controls	Male only	OR 2.49 (95%CI: 1.37, 4.52) for head injury.
Gallagher et al., 1987[350]	USA	Head injury	Questionnaire	135 cases, 85 controls	Both	OR 1.65 (95%CI: 0.81, 3.37) for head/neck injury.
Granieri et al.,1988[113]	Italy	Head injury	Medical file abstraction	72 cases, 216 controls	Male only	Physical traumas considered as a whole was associated with MND (RR 2.1, 95%CI: 1.24, 3.70), but head injury was not associated with ALS (RR 1.0, 95%CI: 0.15, 6.81).
Chiò et al., 1991[320]	Italy	Head injury	Medical record review	512 cases, 512 controls	Both	OR 0.8 (95%CI: 0.2, 1.2) for head injury
Kurtzke et al., 1991[74]	USA	Head injury	Medical records	504 cases, 504 controls	Both	OR1.00 (95%CI: 0.14, 7.12) for head injury.
Strickland et al., 1996[328]	USA	Head, neck and back injuries combined	Questionnaire	25 cases, 50 controls	Both	Cases when compared to the matched controls reported significantly more severe back, neck, and head injury (OR 5.3, 95%CI: 1.7, 17.0).
Qureshi et al., 2006[266]	USA	Head injury	Questionnaire	95 cases, 106 controls	Male only	OR 0.79 (95%CI: 0.37, 1.68) for a history of head injury.
[#]Chen et al., 2007[337]	USA	Head injury	Questionnaire was used to collect information for the case-control study. Meat-analysis based on published studies (8 studies) conducted between 1980 and 2007	109 cases, 255 controls	Both	Results from the case-control study: OR 1.4 (95%CI: 0.8, 2.6) for ever having had a head injury was non-significantly associated with a higher ALS risk. An OR of 3.1 (95%CI: 1.2, 8.1) was found for having had more than one head injury; and OR 3.2 (95%CI: 1.0, 10.2) for participants who had had a head injury during the past 10 years. (For participants who had had multiple head injuries with the latest occurring in

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
						the past 10 years, the risk was elevated more than 11-fold (OR 11.3, 95%CI: 1.1, 114.3). Results from the meta-analysis: OR1.7 (95%CI: 1.3, 2.2).
Binazzi et al., 2009[347]	Italy	Head injury	Questionnaire	77 cases, 185 controls	Both	The head injury that occurred at the age of 30-40 years was associated with ALS, (OR 14.2, 90%CI: 1.04, 194.42) for all ALS cases, OR 17.4 (90%CI: 1.70, 178.5) for bulbar cases. OR 7.13, (90%CI: 1.34, 37.94) for having a head injury less than 30 years among spinal cases. Risk of a period of 11-30 years since the last head injury was found in bulbar cases (OR 3.51, 90%CI: 1.03, 11.95).
Beghi et al., 2010[351]	Europe (Italy, Ireland, and the UK)	Physical activities and trauma	Questionnaire	61 cases, 112 controls	Both	The number of patients reporting traumatic events was similar in the two groups (cases, 47.5%; controls, 52.7%) and no differences were found for the site of trauma, the severity of trauma (including residual disability and hospital admission), and repeated trauma.
Schmidt et al., 2010[341]	USA	Head injury	Questionnaire	241 cases, 597 controls	Both	Head injuries during the last 15 years before the reference date was associated with ALS risk OR 2.33 (95%CI:1.18, 4.61).
Pupillo et al., 2012[340]	Italy	All physical trauma events	Questionnaire	377 cases, 754 controls	Both	Elevate risks for head injury (OR 1.59; 95%CI: 1.02, 2.47), ALS risks were also associated with concussion (OR 1.85; 95%CI: 1.06, 3.24), the OR was 4.77 (95%CI: 1.41, 16.13) for a history of 2+ head injuries. OR 3.07 (95%CI: 1.86, 5.05) for patients reporting 3+ traumatic events and OR 2.44 (95% CI:1.36, 4.40) for severe traumatic events. The

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
						ORs remained significant when the analysis was limited to events that occurred 5+ and 10+ years before ALS onset, to incident ALS, and direct informant.
Peters et al., 2013[349]	Sweden	Head injury	Medical records	4,004casess, 20,020 controls	Both	Association of ALS risk with severe head injury <= 1 year before diagnosis (OR 3.9, 95%CI: 2.6, 6.1). No association for severe head injury > 3 years before ALS diagnosis (OR1.2, 95%CI: 0.9, 1.5), no association with subtypes of head injury or repeated injuries occurring > 3 years before diagnosis.
Seelen et al., 2014[342]	The Netherlands	Head injury	Questionnaire	722 cases, 2268 controls	Both	Head trauma was associated with an increased ALS risk (OR 1.95, 95%CI: 1.11, 3.43).
Pupillo et al., 2014[343]	Europe multicentre (France, Ireland, Italy, United Kingdom, Serbia)	Physical activities and traumatic injuries	Questionnaire	652cases, 1166 controls	Both	An increased risk of ALS was associated with participants who had 2 traumatic events and not practising sports as compared to those with no trauma who were practising sports (OR 2.16, 95%CI: 1.14, 4.07).
Feddermann-Demont et al., 2016[339]	Switzerland	Head injury, physical activities	Questionnaire	92 cases from patients who requested Riluzole treatment on Swiss Federation for Joint Tasks of Health Insurers (SVK)	Both	OR 1.41 (95%CI: 0.52, 3.82) for head injury, 57% of patients have had a mild traumatic brain injury (mTBI), a history of one or more head/neck injuries was associated with younger age at symptom- onset (p=0.013).

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
Seals et al., 2016[338]	Denmark	Head injury	Hospital recorded for a history of trauma diagnoses.	3,650 cases, 365,000 controls	Both	OR 1.51 (95%CI: 1.11, 2.06) for head injury only. When traumas in the 5 years prior to the index date were excluded, OR 0.85 (95%CI: 0.56, 1.30) for head only. There was a borderline significant association between any trauma and ALS (OR 1.09, 95%CI: 0.99, 1.19). The first trauma before age 55 years was associated with ALS (OR1.22, 95%CI: 1.08, 1.37), whereas first traumas at older ages were not (OR 0.97, 95%CI: 0.85, 1.10).
Pupillo et al., 2018[348]	Europe (Italy, France, Ireland)	Trauma	Questionnaire	575 cases, 1150 controls	Both	OR 1.29 (95%CI: 0.84, 1.98) for head trauma, OR 1.16 (95%CI: 0.73,1.83) for having had one head injury, OR 2.62 (95%CI: 0.85, 8.11) for having had more than 2 head trauma. Head trauma leading to functional disability was associated with a two-fold risk of ALS (OR 2.04, 95%CI:1.18, 3.54).
Lian et al., 2019[344]	China	Head injury	Questionnaire	123 cases, 239 controls	Both	Head trauma associated with ALS risk (OR 3.40, 95%CI:1.30, 8.89)
Filippini et al., 2020[322]	Italy	Head injury	Questionnaire	95cases, 135 controls	Both	Head trauma association of ALS risk (OR 2.61, 95%CI: 1.19, 5.72)
Cohort study						
Williams et al., 1991[352]	USA	Head injury	Medical records	1 case from 821 people had suffered a head injury	Male only	SMR 1.05 (95%CI: 0.027, 5.85)
Turner et al., 2010[345]	UK	Head, upper and lower limb trauma	Medical records	281 cases, 618424 controls	Both	OR1.5 (95% CI: 1.1, 2.1) for head injury, but this elevation of risk was only found within the first year after injury and suggested this is most likely

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
						to be a consequence of incipient ALS causing a tendency to fall.
Sagiraju et al., 2020[353]	US	Traumatic brain injury (TBI)	Medical records	226 cases from1,149,620 veterans.	Both	No association with Traumatic head injury (OR 1.0, 95%CI: 0.7, 1.4) among US veterans.
Meta-analysis & Systematic review						
Armon & Nelson 2012[354]	USA	Head trauma	A Medline literature search on epidemiological literature regarding the association between head trauma and ALS for the period between 1980 and October 2010	12 studies	Both	A single instance of head trauma is not a risk factor for ALS.
Perry et al., 2016[355]	USA	Mild traumatic brain injury (TBI)	All studies from January 1995 to February 2012 with reporting TBI as a risk factor.	57 studies were selected, 4 studies were included in the meta-analysis	Both	OR 2.07 (95%CI: 0.94, 4.56) for traumatic brain injury.
Belbasis et al., 2016[203]		Head injury	A systematic collection and assessment of multiple systematic reviews and meta-analyses performed on a specific research topic,	16 meta-analyses from 176 articles	Both	OR 1.65 (95%CI: 1.09, 2.51) for head injury.

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
			which was published before Aug 2015.			
Watanabe et al., 2017[356]	UK	Head injury	Searching in Medline and Web of Science for case-control, cross-sectional, or cohort studies that quantitatively investigated the head-injury-related risk of ALS and were published until 1 December 2016.	15 studies	Both	A positive association between head injury and ALS (OR 1.45, 95%CI: 1.21, 1.74). OR 1.21 (95%CI: 1.01, 1.46) for time lag ≥ 1 year; OR 1.16 (95%CI: 0.84, 1.59) for time lag ≥ 3 years.
Wang et al., 2017[41]	Canada	Physical trauma including head trauma	Searches of systematic reviews/meta-analyses and observational studies for risk factors associated with ALS disease occurrence and progression, relevant articles published up to Feb 16, 2016	15 case-control studies	Both	A positive association between ALS and previous head trauma (OR 1.27, 95%CI: 1.02, 1.57),
Gu et al., 2021[357]	China	Trauma	Literature search for related studies was conducted using PubMed (published	18,390 cases, 6,519,391 controls from 29 studies	Both	OR 1.47 (95%CI: 1.36, 1.59) for head trauma with the exposure assessment methods based on medical records.

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
			on or before April 30, 2020)			OR 1.56 (95%CI: 1.18, 2.06) for head trauma with the exposure assessment methods based on the questionnaire. approximately 1.51–fold risk of ALS. Additionally, in the meta-analysis concerning the number of traumatic events and ALS risk, we found that repeated trauma could slightly increase the risk of ALS, This meta-analysis indicated that trauma could increase ALS risk
Liu et al., 2021[358]	China	Head injury	A systematic search in PubMed for observational studies that quantitatively investigated the association between head injury and ALS risk was published before April 10, 2020.	10,703 cases, 2,159,324 controls from 14 studies (10 case-control, 4 cohort)	Both	Head injury was associated with an increased risk of ALS (OR1.38, 95%CI: 1.20, 1.60) and the association was slightly stronger for severe head injury (OR 1.69, 95%CI: 1.27, 2.23). The association between the number of head injuries was weak (OR 1.23, 95%CI: 1.10, 1.37, for Number = 1; OR 1.29, 95%CI: 0.89, 1.86; for Number ≥ 2). Lag-time analysis: strong association with ALS risk was found in individuals who suffered head injury <1 year (OR 4.05, 95%CI: 2.79, 5.89), and when the time lag was set at 1–5, 5–10, and >10 years, the pooled OR was 1.13, 1.35, and 1.10, respectively. OR 1.30 (95%CI: 1.10, 1.54) when excluding individuals who suffered ALS within 1 year of head injury in a 10 years' time lag.

[#] A case-control study and a meta-analysis

2.4.7 Physical activity

The hypothesis of an association between MND and physical activity has been raised since Lou Gehrig, the American baseball legend died from ALS in 1941. This association is biologically plausible as vigorous exercise increases tissue metabolism, which may induce oxidative stress[359] and glutamate excitotoxicity,[360] two well-established mechanisms for MND.[360] Many studies have reported on the association between physical activity and ALS with conflicting results.[343 361-365] Several studies have evaluated MND risk among professional sportspersons,[41 361-363 366-373] while others have investigated the association between work-related and or leisure-time physical activities among non-professional individuals.[328 339 343 351 364 374-387] A summarised relevant studies on physical activities and MND are presented in Table 2.9.

Among studies that investigated MND risk in sports professionals, increased MND risk was reported for professional football (soccer) players,[361 362 366 367 369 370 372] American football players,[363 388] long-distance cross-country skiers,[371] and athletes[368] in the last three decades. Several studies from Italy[361 362 366 367 372] have observed an increased MND risk among professional football (soccer) players, with high standardised mortality ratios (SMRs) from 2 to 18. Two UK studies also reported elevated risks among professional football (soccer) players (HR 3.66, 95%CI: 2.88, 4.65; HR 4.33, 95%CI: 2.05, 9.15; Table 2.9).[369 370] Additionally, there were some suggestions of earlier onset of the disease among football (soccer) players when playing at midfielder position, and greater excess risk (SMR 10 - 12.2; Table 2.9).[361 362] A dose-response relationship of increasing risk with the increasing number of years spent in professional football (soccer) activity was also found.[361] Several potential explanations have been

suggested for the excess occurrence of ALS in former football (soccer) players, such as head trauma,[41 361] misuses of illegal and toxic substances for improving athletic performance,[361 389] and exposure to herbicides or pesticides on football pitches,[361] but the impact of these factors have yet to be fully determined.

Studies that assessed the association between MND risk and physical activity in non-professional sports have provided inconsistent results. Some studies have observed an increased MND risk with general sports,[351 374 376 379] organised sports[375] and vigorous physical activity,[328 380-382 385] whereas other studies have found no association[339 364 377 378 383 384] or an inverse association.[343]

Few studies have examined the association between work-related physical activities and MND risk, again with conflicting results. Some reported no association,[339 343 375 378 383] but the recent European multi-centre study has reported positive associations between a history of physical activity both in leisure time (OR 1.07, 95%CI: 1.02, 1.12; Table 2.9) and in occupational activities (OR 1.06, 95%CI: 1.03, 1.09; Table 2.9) and risk for the development of ALS.[381]

While two earlier reviews[390 391] indicated that physical activity in the general population is not a risk factor for ALS, several meta-analyses reported that ever participating in professional sports (in particular football (soccer) and American football);[206 373 392] strenuous exercises at professional-level;[393] participating in organised competitive sports;[373] or athletic clubs in high school or college;[85] or heavy physical activities at work[206] were associated with increased risk of ALS (see Table 2.9).

Moreover, a recent cross-sectional study[385] reported that ALS patients who have been engaged in vigorous physical activities at least moderately (three times a week) during early adulthood (before age 35), were more likely to have an ALS diagnosis earlier (before age 60) compared to ALS patients who did not participate in any vigorous physical activities ($p < 0.0001$).

Furthermore, in 2019, Bandres-Ciga et al.[394] used linkage disequilibrium score regression and Mendelian Randomisation (MR) to test genetic correlations and the relationships between phenotypic traits and ALS based on published ALS genome-wide association studies (GWAS), and a number of UK biobank questionnaire items suggested that physical exercise is genetically correlated with ALS phenotypic traits. Bandres-Ciga et al.[394] also reported that phenotypic traits which were related to light physical activity (e.g., walking for pleasure or walking as a mean of transport) were associated with decreased risk of developing ALS, whereas phenotypic traits which were related to heavier activity levels (e.g., duration of moderate activity) were positively associated with ALS.

The MR approach was also used by Julian et al.[387] providing evidence for a positive causal relationship between physical exercise and ALS. Julian and colleagues[387] pointed out that participation with frequent and strenuous leisure-time physical activity is a risk factor for ALS, but did not support a causal role for low-intensity, infrequent exercise. Authors in this study also observed that frequent and high-intensity physical activity is likely to cause motor neurone injury, particularly in the context of certain risk genotypes (C9ORF72 G4C2 repeat expansion). It was, therefore, suggested that

excessive exercise is a risk factor for MND, especially for individuals who carry a genetic predisposition.

Overall, a range of studies using different methodological designs have reported that strenuous physical activities can contribute to an increased risk of MND.

Table 2.9. Physical activities and risk of MND

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
Prevalence study						
Abel, 2007[388]	USA	Professional American football	National foot league database, ALD/MND Association database	8 cases among 3,891 players	Male only	A prevalence of 206 per 100,000, a 40-fold higher prevalence rate than the rate of 5 per 100,000 in the general U.S. population.
Cross-sectional study						
Raymond et al., 2021[385]	USA	Vigorous physical activity (VPA)	USA national ALS Registry (Registry) collects physical activity data from persons with ALS.	5463 LAS patients with VPA history, and 956 ALS patients who never engaged in VPA.	Both	Patients who reported engaging in VPA at least moderately (three times a week) during early adulthood (before age 35), were more likely to have an ALS diagnosis earlier (before age 60) compared to patients who did not ($p < 0.0001$).
Case-control study						
Felmus et al., 1976[374]	UAS	General sports	Questionnaire	25 cases, 50 controls	Male only	More ALS patients (36%) reported participation in athletics than controls (12%) $p<0.001$.
Strickland et al., 1996[328]	USA	Physical activities	Questionnaire	25 cases, 50 controls	Both	OR 1.6 (95%CI: 1.1, 2.4) for frequency of sweating in work; (OR1.6, 95%CI: 1.1, 2.5) for frequency of sweating in leisure activity; OR 3.1 (95%CI: 1.04, 9.3) for having received recognition in organised sports.
Scarmeas et al., 2002[376]	USA	Non-professional general sports, university sports	Medical records	279 cases, 152 controls	Male only	OR 1.70 (95%CI: 1.04, 2.76) for varsity athletics.
Valenti et al., 2005[377]	Italy	Physical activities, sports (non-professional)	Questionnaire	300 cases, 300 controls	Both	OR 0.4 (95%CI: 0.17, 0.86) for practice of football (soccer), OR 0.26 (95%CI: 0.08, 0.73) for competitive sports rather than football (soccer), OR 0.38 (95%CI: 0.45, 0.58) for practice of all sports. No association between the practice of competitive sports and ALS.

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
Veldink et al., 2005[378]	Netherlands	Non-professional general sports	Questionnaire, accurate exposure measurement (MET)	219 cases, 254 controls	Both	Sport at early age: OR 1.0 (95%CI: 0.6, 1.5); adulthood OR 1.3 (95%CI: 0.8, 2.1); intense activity OR 1.2 (95%CI: 0.6, 2.3). No significant association with occupational or leisure-time physical activity was found (all ORs ≤ 1.7). Higher leisure time activities before age of 25 were associated with an earlier age at onset (7 years earlier, p=0.001). Higher leisure time activities during the last 10 years before reference data was associated with an earlier age at onset (3 years earlier, p=0.02).
Okamoto et al., 2009[380]	Japan	Physical activities	Questionnaire, Metabolic equivalents (METs) were calculated for physical activity	153 cases, 306 controls	Both	OR 2.0 (95%CI: 1.0, 4.0) for vigorous physical activities.
Beghi et al., 2010[351]	European (Italy, Ireland, UK)	Physical activities at work and or leisure	Questionnaire	61 cases, 112 controls	Both	OR 1.03 (95% CI: 1.00, 1.05) for the duration of sport-related physical exercise.
Vanacore et al., 2010[368]	USA	Professional general sports	Death certificate	14,628 cases, 58,512 controls	Both	OR1.81(99%CI: 0.69, 4.78) for professional athletes (male only, no female athletes). OR 1.0 (99%CI: 0.82, 1.20) for intense physical activity at work.
Huisman et al., 2013[379]	Netherlands	Non-professional, marathon, triathlon, or ice skating	Questionnaire, using Compendium of Physical Activities metabolic equivalent (MET) score for measuring physical activities	636 cases, 2166 controls	Both	OR 1.24 (95%CI: 0.96, 1.61) for vigorous physical activities, OR 1.15 (95%CI: 0.58, 2.29) for marathon; OR 1.21 (95%CI: 0.29, 4.98) for triathlon. OR 1.08 (95%CI: 1.02, 1.14) for leisure-time physical activity. OR 1.01 (95%CI: 0.96, 1.04) for occupational activities, and OR 1.02 (95%CI: 0.98, 1.06) for total physical activities.

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
Pupillo et al., 2014[343]	Europe (France, Ireland, Italy, United Kingdom, Serbia)	Physical activity, professional & non-professional general sports	Questionnaire and activities metabolic equivalent (MET) score for measuring physical activities	652 cases, 1166 controls	Both	An inverse correlation was observed between ALS and physical/sport activities (OR 0.65, 95%CI: 0.48, 0.89) for overall physical activity; OR 0.56 (95%CI: 0.36, 0.87) for work-related physical activity, and OR 0.49 (95%CI: 0.32, 0.75) for organised sports. An inverse correlation was observed between ALS, the duration of physical activity (p=0.0041). An inverse correlation between ALS and sport was found in women but not in men.
Feddermann-Demont et al., 2016[339]	Switzerland	Physical activities	Questionnaire, Metabolic equivalents (METs) were calculated for physical activity	92 cases from patients who requested Riluzole treatment on Swiss Federation for Joint Tasks of Health Insurers (SVK)	Both	OR 0.70 (95%CI: 0.29, 1.68) for vigorous physical activities. OR 1.75 (95%CI: 0.55, 5.62) for moderate physical activities, and OR 1.04 (95%CI: 0.35, 3.08) low level physical activities.
Visser et al., 2018[381]	European countries (multi-centre)	Physical activities	Metabolic equivalent of task (MET) based on Compendium of Physical Activities	1557 cases, 2922 controls	Both	Lifetime physical activities in leisure time (OR 1.07, 95%CI:1.02, 1.12) and occupational activities. (OR 1.06,95%CI: 1.03,1.09), and all activities combined (OR 1.06,95%CI: 1.04,1.09).
Cohort study						
Longstreth et al., 1998[375]	USA	Physical activities	Questionnaire, with MET calculation	174 cases, 348 controls	Male only	OR1.28 (95%CI: 0.74, 2.21) for workplace vigorous physical activity; OR 1.20 (95%CI: 0.64, 2.23) for leisure-time vigorous physical activity; OR 1.52 (95%CI: 1.03, 2.25) for organised university sports.
Belli et al., 2005[366]	Italy	Professional football (soccer) player	Death certificates were obtained from the Italian Statistics Bureau (ISTAT),	8 ALS deaths from 350 deaths in 24,000	Male only	8 ALS deaths were observed vs 0.69 expected. SPMR 11.58 (95%CI: 6.72, 19.98)

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
			and annual reports of active football (soccer) players from 1960 to 1996 in the three top leagues (A, B, and C).	football(soccer) players		
Chiò et al., 2005[361]	Italy	Professional football (soccer) player	Death certificates were obtained from the Italian Statistics Bureau (ISTAT), archives of the football (soccer) players' pension plan, archives of the major Italian football (soccer) cards publisher.	5 deaths from 7,325 football (soccer) players	Male only	5 ALS deaths observed vs 0.77 expected, SMR 6.5 (95%CI: 2.1, 15.1). A significantly increased risk for ALS onset before 49 years (SMR 7.5, 96%CI: 2.0, 19.2), the mean age of onset was 43.4 years. SMR12.2 (95%CI: 3.3, 31.2) for midfield position. A dose-response relationship between the duration of professional football (soccer) activity and the risk of ALS was found (>5 years, 15.2, 95%CI: 3.1, 4.4; <5 years, 3.5, 95%CI: 0.4, 12.7).
Taioli, 2007[367]	Italy	Professional football (soccer)	Death certificate	4 ALS death, from 5389 players, 204, 125 subject-years of follow-up.	Male only	4 ALS deaths observed vs 0.22 expected, SMR 18.18 (95%CI: 5.0, 46.55).
*Chiò et al., 2009[362]	Italy	Professional football (soccer), basketball, and road cyclist	Death certificates. Archives of the football (soccer) players' pension plan and archives of the major Italian football (soccer) cards publisher. The list of basketball players was obtained from the Italian Basketball Federation (FIB) and the Italian Basketball League. The list of cyclists was	8 ALS death from 7,325 football (soccer) players, 1,973 basketball players, and 1,701 road cyclists.	Male only	For football (soccer) players, 8 ALS deaths were observed vs 1.24 expected, SMR of 6.45 (95% CI: 2.78, 12.70). Mean age of onset, 41.6 years, and the risk of ALS was higher for careers lasting >5 years (SMR 15.6, 95%CI: 5.1, 36.3), for midfielders (SMR 10.5, 95%CI: 3.9, 22.9). No basketball player and no cyclist developed ALS.

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
			obtained from the Historical Yearbook of Italian Professional Cyclists.			
Savica et al., 2012[364]	USA	American football (non-professional)	Death certificate	2 cases from 438 football players, 1 case from 140 non-football players	Male only	HR 0.52 (95%CI% 0.05, 5.68), no significant difference between the observed and population-based expected number of cases for either group: SIR 3.15(95%CI, 0.38, 11.33) in the football players and SIR 6.44 (95%CI: 0.16, 35.7) in the non–football cohort.
Lehman et al., 2012[363]	USA	American football (professional)	Death certificate, national football league players identified by a pension fund database of vested players with at least 5 credited playing seasons between 1959 and 1988.	7 ALS deaths from 3,439 National Football League players	Male only	SMR 4.31 (95%CI: 1.73, 8.87) for ALS mortality. ALS mortality was also observed among players in speed positions compared with players in non-speed positions (SRR 3.88, 95%CI: 0.47, 32.2).
Fang et al., 2016[371]	Sweden	Long-distance cross-country skiers	Data from long-distance cross-country skiing race office	39 ALS cases among 212,246 cross-country skiers and 508,176 general population	Both	HR 4.31(95%CI: 1.78, 10.4) for fastest skiers (100–150 % of winner time) compared to skiers that finished at >180% of winner time. HR 2.08 (95%CI: 1.12, 3.84) for fastest skiers compared to non-skiers. HR 3.13 (95%CI: 1.37, 7.17) for skiers who participated >4 races during this period compared to those who participated in only one race. HR 1.88 (95%CI: 1.05, 3.35) for skiers who participated >4 races during this period compared to non-skiers. HR 0.46 (95%CI: 0.24, 0.87) for those finishing at >180 % of winner time compared to non-skiers.

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
Eaglehouse et al., 2016[382]	USA	Physical activities	Questionnaire	165 cases from 161,809 postmenopausal women	Female only	OR 1.56 (95%CI: 1.02, 2.37) for participants with strenuous physical activities 3 or more days per week compared with no reported strenuous physical activities. This is the first cohort study to report an increased risk for ALS mortality associated with strenuous PA in postmenopausal women.
Gallo et al., 2016[383]	Europe (European Prospective Investigation into Cancer and Nutrition)	Physical activities	Questionnaire, total physical activities was expressed by the Cambridge Physical Activity Index (CPAI)	219 ALS death from 472,100 individuals	Both	HR 0.67 (95%CI: 0.42, 1.06) for physically active individual. Total physical activities was weakly inversely associated with ALS mortality with a borderline statistically significant trend across categories (p = 0.042).
Janssen et al., 2017[384]	USA	Non-professional American football	Use the school's yearbooks and records-linkage system to the medical record of each included individual.	No cases from 486 varsity football players and athletes.	Male only	No ALS case was observed.
Mackay et al., 2019[369]	UK	Professional football (soccer) players	Scottish players databases, death certificate	22 MND deaths from 7,676 professional football (soccer) players and 17 MND deaths from 23,028 controls	Male only	HR 4.33 (95%CI: 2.05, 9.15).
Pupillo et al., 2020[372]	Italy	Professional football (soccer) player	Death certificate, players included in the three Italian professional football (soccer) leagues (A, B, and	34 cases were observed among 23,586 football (soccer) players, 1,001,318	Male only	34 cases observed vs 17.8 expected. SIR 1.91 (95%CI: 1.32, 2.67). SIR 2.37 (95%CI: 1.32, 3.90) for midfielder position. The mean age at diagnosis was 45.0 years, which was 20 years younger than the general population (65.2 years).

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
			C division) between 1959 and 2000.	person-years follow up.		
Russell et al., 2021[370]	UK	Professional football (soccer) players	Scottish Morbidity Record and death certification	7676 former professional football (soccer) players, 23,028 general populations, a total of 1,812,22 person-years of follow up	Both	HR 3.66 (95%CI: 2.88, 4.65) for neurodegenerative disease. HR 3.52 (95%CI: 1.81, 6.88) for MND; HR 3.59 (95%CI: 2.93, 4.39) for Dementia; HR 2.09 (95%CI: 1.20, 3.61) for Parkinson disease. The risk of neurodegenerative disease was highest for defenders (HR, 4.98, 95%CI: 3.18, 7.79) and lowest for goalkeepers (HR1.83, 95%CI: 0.93, 3.60). The risk was highest among former football (soccer) players with professional career lengths longer than 15 years (HR 5.20, 95%CI 3.17, 8.51).
Meta-analysis & Systematic review						
Hamidou et al., 2014[390]		Physical activities	All relevant articles were published up to April 2014.	37 studies (13 cohorts, 21 case-control, 3 case-series reports)	n/a	PA is not a risk factor for ALS in the general population (Level A evidence), but football (soccer) may be a risk factor for ALS, but the impact of confounding factors needs to be better evaluated.
Lacorte et al., 2016[392]	Italy	Physical activities, participation in sports	Relevant literature published up to January 2015 was gathered through structured searches on Medline, The Cochrane Library, and the ISI Web of Science databases	26 studies (19 case-control studies, 7 cohorts)	n/a	Evidence on cumulative measures of PA as a risk factor for ALS remains inconclusive and highlighted limitations of previous studies relating to heterogeneous classification of both physical activity and ALS. However, cohort studies report a significantly higher number of cases of ALS in professional football (soccer) and American football players and a slightly increased risk of ALS in varsity athletes.
Wang et al., 2017[41]	Canada	Participating in professional sports	All relevant articles were published up to Feb 2016.	6 case-control studies	Both	The results showed that participating in recreational sports or other physical activities was not associated with an increased risk of ALS (OR0.90, 95%CI: 0.78, 1.03), in contrast, ever

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
						participating in an organised athletic club in high school or college, or professional sports was likely to be associated with ALS (OR1.35, 95%CI: 1.11, 1.65).
Luna et al., 2017[391]	France	Physical activities	Review	n/a	n/a	Physical Activities in the general population is not a risk factor for ALS. Further research is needed to clarify the association of physical activities in some occupations and some athletic activities (including extreme levels of physical activities).
Gunnarsson et al., 2018[206]	Sweden	Heavy physical activities at work, professional sports	All relevant articles were published up to Feb 2017.	37 studies in total, 7 studies related to physical activities	Both	Heavy physical work was associated with ALS risk (OR 3.98, 95%CI: 2.04, 7.77; from 6 studies), professional sports was also associated with ALS risk (OR 1.45, 95%CI: 1.07, 1.96; from 3 studies). Overall physical activities (OR 1.89 95%CI: 1.27, 2.82) was associated with ALS risk.
Riancho et al., 2018[393]	Spain	Physical activities	Review	n/a	n/a	Strenuous exercise, particularly at a professional level and during the early stages of life was associated with disease onset.
Blecher et al., 2019[373]	USA	Contact sports	Using electronic databases to search studies that meet inclusion criteria and published up to November 22, 2017.	16 studies	Both	Organised competitive sports was associated with an increased risk of ALS compared with controls (pooled RR 1.80, 95%CI: 1.13, 2.88). Professional sports were associated with greater effects (pooled RR 4.07, 95%CI: 1.99, 8.32) compared with nonprofessional sports (pooled RR 1.13, 95%CI: 0.79, 1.62). Professional sports prone to repetitive concussive head and cervical spinal trauma were associated with substantially greater effects (pooled RR 8.52, 95%CI: 5.18, 14.0) compared with (a) non-professional sports prone to repetitive concussive head and cervical spinal trauma (pooled RR 0.60,

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
						95%CI: 0.12, 3.06); (b) professional sports not prone to repetitive head and neck trauma (pooled RR 1.35, 95%CI: 0.67, 2.71); or (c) nonprofessional sports not prone to repetitive concussive head and cervical spinal trauma (pooled RR 1.17, 95%CI 0.79, 1.71).
Mendelian Randomisation (MR) experiments						
Bandres-Ciga et al., 2020[386]	UK	Physical activity, smoking, cognitive performance, education	Linkage disequilibrium (LD) score regression and Mendelian randomisation. Data from genome-wide association studies (GWASes) summary statistics from MR Base and LD-hub.	GWAS data included 20,806 cases and 59,804 controls.	n/a	There was a correlation between genetic liability to physical exercise and ALS. Heavier levels of physical activity (such as duration of moderate activity and performing a job that involves mainly walking or standing) were positively associated with ALS (smallest adjusted p-value = 3.09 × 10–2; regression coefficient = 0.28; 95%CI: –0.36, –0.09), and light levels of physical activity including walking for pleasure, walking as a mean of transport, and light DIY physical activities were associated with decreased risk of ALS (smallest adjusted p-value = 5.19 × 10–4; regression coefficient = –0.403; 95%CI: –0.35, –0.14).
[#]Julian et al., 2021[387]	UK	Physical exercise (frequent and intense, anaerobic, burst activity)	Two-sample Mendelian randomisation (MR) experiments & linkage disequilibrium (LD) score regression testing. Instrumental variables (IV) were derived from publicly available GWAS (genome-wide association studies) data.	SSOE GWAS data included 124,842 cases, 225,650 controls. Specific case-control study: 17 ALS cases with confirmed C9ORF72 pathological	n/a	MR approach suggested a positive causal relationship between ALS and physical exercise (p=0.01, multiplicative random effects by using liberal instrument). The study also suggested that genetic liability to leisure-time physical activity is a risk factor for ALS and C9ORF72-ALS in particular. The results indicate that participation in frequent and strenuous leisure-time physical activity is a risk

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
			Strenuous sports and other exercises (SSOE) were measured via a questionnaire in the UK biobank. Specific(C9ORF72) case-control study data: cases: ALS patients with confirmed C9ORF72 pathological G4C2-repeat expansion was selected as cases. Two controls group: 1. ALS patients without the C9ORF72 G4C2-expansion. 2. Neurologically normal controls.	G4C2-repeat expansion. Controls: 34 ALS without the C9ORF72 G4C2-expansion, and 34 neurologically normal controls.		factor for ALS, particularly in the context of certain risk genotypes. This suggests that intense leisure-time physical exercise is more likely to include strenuous anaerobic activity and might explain why this type of physical activity shows a strong association with ALS. Similarly, the data show that static activity such as heavy DIY is not associated with ALS.

[#]Three cohorts combined into one study

2.4.8 Military service

An association between military service and ALS was first proposed after the Gulf War (1991), as veterans expressed their concern of a higher-than-expected ALS rate among Gulf War veterans.[50 395] Since then, many studies have investigated the association between military service and the risk of ALS. The majority of these studies were conducted in the USA and only a few studies were carried out in other countries. Studies conducted outside of America generally reported no association between Military service and ALS,[31 188 323 396] whereas a study[397] from Denmark observed that military employees overall had an elevated risk of ALS (OR 1.30, 95%CI: 1.1, 1.6). However, most studies conducted in America reported a positive association between military service and ALS,[33 318 353 395 398-400] with only a few studies showing no association.[43 183 401] Increased ALS risks were particularly observed among Gulf War and WWII veterans.[50 402] A meta-analysis[403] based on 11 studies between 1981 and 2016 reported that the risk of ALS was significantly increased in military personnel compared to non-military personnel (OR 1.29, 95%CI: 1.08, 1.54).

Overall, as the Institute of Medicine 2006 report states, there is suggestive evidence of an association between military service and later development of ALS.[404] However, there is no strong evidence on which specific risk factors are responsible for this association. Exposure to herbicides (including Agent Orange) for military purposes and herbicides in the field;[318 405 406] pesticides;[406] certain chemicals (engine exhaust, burning agents);[318] heavy metals;[182] and head trauma[341] all appeared to increase the risk of ALS among military personnel.

2.4.9 Tobacco smoking

The role of cigarette smoking has been studied for its possible impact on the risk of developing MND.[407] Cigarette smoking might contribute to the risk of MND through oxidative stress[408 409] or exposure to neurotoxic chemicals which are abound in cigarette smoke,[49] and so it remains an important candidate for studies of environmental aetiology.

Cigarette smoking was found to increase the risk of MND in many studies,[27 31 410-413] while others found no association,[341 414-416] or the risk was only observed for women.[49 417] The majority of these studies assessed the association by smoking status and only a few studies have explored this association with more detailed smoking parameters. Opie-Martin et al.[415] using a comprehensive smoking index measuring lifetime smoking and ALS risk, found a weak association between current smoking and risk of ALS, but the increase in comprehensive smoking index score did not increase the risk of ALS (OR 0.81), indicating no evidence of a dose-dependent association between smoking and the risk of ALS. However, Gallo et al.[418] found an almost 2-fold increased ALS risk for current smokers at recruitment in comparison with never smokers, a clear duration relationship was also observed between years of smoking and ALS, with a stronger effect of smoking duration than intensity. Conversely, the number of years since quitting smoking was associated with a decreased risk compared with continued smoking. Similar, Peters et al.[412] in a multi-centre study observed that smoking more than 27 pack-years was associated with ALS risk (OR 1.26, 95%CI: 1.03, 1.54) compared with never smokers, but this association was predominantly driven by smoking duration rather than intensity. A clear inverse relation was observed for time since quitting smoking (OR 0.65 for individuals who quit smoking for 33+ years versus

current smokers). The ORs decreased with time since quitting smoking, until about 10 years prior to disease onset, which suggests that smoking may be an early disease trigger.

Wang et al.[419] in a pooled study of 5 cohorts reported a 1.4-fold increased ALS risk for smokers versus never smokers. A clear linear trend for pack-years was also found, with a positive association for both smoking intensity (number of cigarettes smoked per day) and duration, but these findings did not persist when never smokers were excluded. Among smokers, the risk of ALS increased with the earlier age of commencement.

Several recent studies used the Mendelian randomisation (MR) approach to assess the association between smoking and ALS. Zhan et al.[420] based on data from genome-wide associations studies (GWAS) on smoking status (ever vs never), selected 176 single-nucleotide polymorphisms (SNPs) of genome-wide significance as instrumental variables for MR analyses. The study reported that ever smokers were found to have a higher risk for ALS compared to never smokers (OR 1.25, P=0.04). Opie-Martin et al.[416] used GWAS data on lifetime-smoking and ever-smoking, and ALS GWAS data[421] selected 119 SNPs of lifetime-smoking and 353 SNPs of ever-smoking as instrumental variables to assess the relationship between smoking and ALS. This study observed no causal relationship between lifetime smoking and ALS (OR 0.94, p=0.59), whereas ever-smoking (OR1.10, p=0.05) was associated with ALS with borderline significance. As a result, the authors concluded that there was no strong evidence for a causal relationship between ALS and lifetime smoking or ever-smoking.[416] Most recently, a longitudinal, population-based case-control study from the Netherlands[69] also used the MR approach with Bayesian instrumental variable analyses including 107 SNPs

associated with tobacco smoking to assess the causal effect between smoking and ALS. This study reported a positive association between smoking and ALS, and higher amounts of smoking pack-years in both case groups (OR 3.15 (95%CI: 0.36, 5.93) for cases with C9orf72 mutation; OR 3.2 (95%CI: 2.02, 4.39) for cases without C9orf72 mutation) compared with controls, which could be detected decades before symptom onset. An effect of smoking in patients without C9orf72 mutation was also observed, but not for those with C9orf72 mutation, suggestive of an underlying increased genetic vulnerability for substance abuse via tobacco consumption in patients with ALS. The inconsistent findings among MR studies illustrate the complexity of gene-environmental interactions in MND.

The discrepancies in findings among other studies may in part be explained by possible survivor bias or confounding. Some studies identified ALS cases from death certificates, which may over-represent smokers due to a shorter life expectancy,[415] and studies based on prevalent and clinic cohorts could also under-represent smokers because their survival is shorter.[413] Moreover, the majority of these studies that assessed the association between smoking and ALS did adjust for age, gender, education, and alcohol consumption in their analysis, but often did not adjust for occupational risk factors (e.g., exposure to pesticides, metals, electric shocks) or lifestyle factors (e.g., physical activity) which have been discussed in the previous paragraphs as potential risk factors and therefore potential confounders in the association for smoking.

Taken together, multiple studies have reported a weak positive association between smoking and MND, but to what extent other risk factors play a confounding role in this association is not clear.

2.4.10 Alcohol consumption

Compared with tobacco smoking, the association between alcohol consumption and the risk of MND is more controversial. Some studies found no significant association between alcohol consumption and MND,[122 380 410 411 422] others found a protective role of alcohol intake in MND onset,[378 413 423 424] although the most recent study reported a 1.5-fold increased risk with alcohol consumption.[425]

One recent meta-analysis[426] reported that the risk of developing ALS was reduced among those who consume alcohol compared with those who do not consume alcohol (OR 0.57, 95%CI: 0.51, 0.64), suggesting that alcohol drinking has a protective effect on the development of MND. However, this meta-analysis could not assess a dose-response relationship between alcohol intake and ALS as only one study in this meta-analysis had investigated this relationship.

In summary, the association between alcohol intake and ALS is still unclear. This association requires a more detailed examination, including the patterns of alcohol intake, the type of alcohol, the dose/duration-response relationship, and the role of confounders.

2.4.11 Body mass index (BMI)

Clinical evidence shows that ALS patients commonly have raised energy expenditure,[427] and often encounter a loss of weight and a decrease in body mass index (BMI) at the early phase of diagnosis.[2 427-429] Substantial changes in BMI in ALS patients have been identified as an independent prognostic factor and have been linked

to disease progression.[430] It has been observed that rapid reduction of BMI at the initial disease stage is a strong indicator of faster disease progression and shorter survival time.[431 432] Table 2.10 summarise relevant studies on BMI and MND risk.

The association between premorbid BMI and the risk of MND has also been investigated among some epidemiological studies. These have suggested that a low premorbid BMI is associated with a higher risk of ALS.[3 41 108 376 423 433-438] A recent meta-analysis[431] based on 11 studies reported that one unit increase of premorbid BMI can result in about 3.0% risk reduction of ALS. However, this meta-analysis also applied the Mendelian Randomisation approach to investigate the causal relationship between BMI and ALS, and the result did not support a causal role of premorbid BMI and the risk of ALS (Table 2.10). A few studies[430 434] have also shown that BMI may already begin to change 10 years before disease onset, implying that the change of BMI may be an early consequence rather than a risk factor of ALS. A recent study from the Netherlands[69] observed that ALS patients with C9orf72 mutation had a lower BMI during the pre-symptomatic phase of the disease than controls, whereas non C9orf72 mutation patients had a higher BMI (Table 2.10).

Table 2.10. BMI and the risk of MND

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
Case-control study						
Scarmeas et al., 2002[376]	USA	BMI	Questionnaire	207 cases, 139 controls	Both	OR 2.10 (95%CI: 1.08, 4.07) for being always slim.
Sutedja et al., 2011[435]	The Netherlands	Smoking, hypertension, hypercholesterolemia, diabetes, and body mass index	Questionnaire	334cases, 538 controls	Both	Patients had a lower BMI (OR0.9, 95%CI: 0.9, 1.0) compared with controls.
Huisman et al., 2015[423]	The Netherlands	BMI	Questionnaire	674 cases, 2093 controls	Both	OR 0.97 (95%CI: 0.94, 0.99). Pre-symptomatic BMI was significantly lower in patients ((25.7 (4.0%) vs 26.0 (3.7%) P = 0.02).
Mariosa et al., 2017[433]	USA	BMI	Questionnaire	467 cases, 975 controls	Both	OR 0.95 (95%CI: 0.91, 0.98) per 1 unit increase in BMI at age 40 years, but not at age 25 years (OR 0.99 (95%CI: 0.95, 1.03). BMI between ages 25 and 40 years, stable or decreasing BMI was positively associated with ALS risk (OR1.61, 95%CI: 1.20, 2.16).
Peter et al., 2017[430]	Swabia	BMI	Questionnaire	393 cases, 791 controls	Both	In ALS cases, BMI was consistently higher than in controls in the 20-70 years before the interview. OR 1.05 (95%CI: 1.00, 1.11, p = 0.041) per 1 kg/m^2 higher BMI 35-45 years before the interview. However, a sharp decrease was evident in the BMI of ALS cases about 10 years before disease onset.
Westeneng et al. 2021[69]	The Netherlands	BMI, smoking, alcohol, daily energy intake	Questionnaire	143 patients with a C9orf72 mutation 1322patients	Both	Current BMI (C9orf72 mutation group OR -2·01 kg/m^2, 95%CI: -2.73, -1.29, p<0·0001; non-C9orf72 mutation group OR -1.35, 95%CI: -1.64, -1.06, p<0·0001) were lower in both C9orf72

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
				without a C9orf72 mutation, 1322 controls		mutation and non-C9orf72 mutation group compared with controls. Median BMI during the pre-symptomatic phase for the C9orf72 mutation group was lower (OR -0.69 kg/m^2, (95%CI: -1.24, -0.13, p=0·015) compared to controls, whereas the median BMI during the pre-symptomatic phase (0.27 kg/m^2, 95%CI: 0.04, 0.50, p=0·022) were higher in the non-C9orf72 mutation group than controls.
Cohort study						
Doyle et al., 2012[108]	UK	BMI	Questionnaire	752 cases among 1,319,360 follow up	Female only	RR 0.86 (95%CI: 0.76, 0.98) for overweight women (BMI 25-30 kg/m^2) compared with women with normal BMI; Obese women (BMI 30 kg/m2 or more) had a 20% lower risk than women of normal BMI (20 to <25 Kg/m^2) RR 0.78 (95%CI: 0.65, 0.94). This effect persisted after the exclusion of the first three years of follow-up.
Gallo et al., 2013[436]	Europe	BMI	Questionnaire	222 ALS death among 518,108 follow up	Both	In men, a significant linear decrease of risk per unit of body mass index was observed (HR 0.93, 95%CI: 0.86, 0.99). Among women, HR 3.36 (95%CI: 1.61, 7.04) for underweight compared with normal-weight women. Among women, a significant risk reduction increasing the waist/hip ratio was also evident: women in the top quartile had less than half the risk of ALS compared with those in the bottom quartile (HR0.48, 95%CI: 0.25, 0.93) with a borderline significant p-value for trend across quartiles (p = 0.056).

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
O'Reilly et al., 2013[437]	USA	BMI	Questionnaire	1153 ALS cases among 110,0910 follow up	Both	Lower BMI at baseline was associated with ALS, for each 5-unit increase in BMI, ALS rates were 21% lower (OR 0.79, 95%CI: 0.73, 0.86) compared to individuals with healthy BMI. The risk of ALS was significantly lower among the overweight (RR 0.76, 95% CI: 0.62, 0.93) and obese (RR 0.73, 95%CI: 0.55, 0.96) compared to participants who had normal BMI. Among never smokers the association persisted: RR 0.75 (95%CI: 0.65, 0.85) for each 5-unit increase in BMI.
#O'Reilly et al., 2018[438]	USA, Europe, and Australia	Pre-diagnostic BMI	Questionnaire	616 ALS deaths among554,335 follow up	Both	Higher mid-to-late adulthood BMI was associated with lower ALS mortality rates. For 5 kg/m^2 increased BMI, the rate was 15% lower (95%CI:0.05, 0.24; p=0.005). Weight gain during adulthood was strongly associated with lower ALS; for an additional 1kg gain in weight/year, the RR was 0.37 (95%CI: 0.23, 0.59; p<0.001). Associations persisted when adjusted for diabetes at enrolment, restricted to never-smokers, and ALS deaths in the five years after enrolment were excluded
Nakken et al., 2019[434]	Norway	BMI	Questionnaire	2968 ALS cases among 1.5 million after 54 years follow up	Both	HR 0.83 (95%CI: 0.79, 0.88) for 5-unit increase in pre-diagnostic BMI. Those in the quartile with the highest weight gain had lower ALS risk than those in the lowest quartile (HR 0.63, 95%CI: 0.44, 0.89. Pre-diagnostic BMI increased during the first 10 years of follow-up, then decreased almost linearly throughout the observation period after 50 years (HR 0.39, 95%CI: 0.62, 0.77).

Authors, year	Country	Risk factors	Data collection method	Subjects	Sex	Main findings
Meta-analysis						
Wang et al., 2017[41]	Canada	BMI	Using PubMed searching all related published articles before 2015/02/15.	5 studies	Both	Meta-analyses supported the inverse association (OR -0.24 (95%CI: -0.34, -0.14))
[^]Zeng et al., 2019[431]	China	BMI	Using PubMed searching published papers up to 2018/09/30. Instruments study using two-sample Mendelian randomisation approach.	11 studies for meta-analysis. 1,031 instruments from GWAS data sources	Both	The meta-analysis showed that a unit increase of premorbid BMI can result in about 3.0% (95%CI: 2.1, 4.5%) risk reduction of ALS. The Mendelian randomisation instrument study showed that the causal effect of one standard deviation increase of BMI was estimated to be 1.04 (95% CI 0.97, 1.11, p = 0.275) in the European population. This null association between BMI and ALS was also held in the East Asian population. Therefore, no causal association between premorbid BMI and ALS risk.

[#]Cohort (10 cohorts combine)

[^]Meta-analysis and Mendelian randomisation approach to investigate the causal relationship.

2.5 Summary

MND is a complex and multifactorial disease, for which there remains no cure. The causes of the disease are largely unknown, but genetic and occupational/environmental factors are believed to contribute to its aetiology. To date the only established risk factors for MND are older age, male sex, and a family history of MND, none of which are amenable to intervention. A number of genes have been found to play a role in MND, but for most MND patients (about 90%), the disease is sporadic, with no definitive cause. Epidemiologic research in the past few decades has identified several potential additional risk factors, such as exposure to pesticides, solvents, metals, electric shocks, ELF-MF, physical activity, head trauma, and smoking, but the evidence is not sufficiently consistent and specific to consider these as established risk factors for MND. Opportunities for the primary prevention of MND, therefore, remain very limited.

CHAPTER 3 Occupation and Motor Neurone Disease: A New Zealand Case-Control Study

Grace Chen[1], Andrea 't Mannetje[1], Jeroen Douwes[1], Leonard van den Berg[2], Neil Pearce[3], Hans Kromhout[4], Wendyl D´Souza[5], Melanie McConnell[6], Bill Glass[1], Naomi Brewer[1], Dave McLean[1]

[1] Centre for Public Health Research, Massey University, Wellington, New Zealand.

[2] Brain Centre Rudolf Magnus, Department of Neurology, University Medical Centre, Utrecht, The Netherlands.

[3] Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom.

[4] Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands

[5] Department of Medicine, University of Melbourne, Melbourne, Australia.

[6] School of Biological Sciences, Victoria University, Wellington, New Zealand

(Published in Occupational and Environmental Medicine 2019;76(5):309-16)

ABSTRACT

Objectives To assess associations between occupation and motor neuron disease (MND).

Methods We conducted a population-based case-control study with cases (n=321) recruited through the New Zealand Motor Neurone Disease Association and hospital discharge data. Controls (n=605) were recruited from the Electoral Roll. Information on personal and demographic details, lifestyle factors and a full occupational history was collected using questionnaires and interviews. Associations with ever/never employed and employment duration were estimated using logistic regression stratified by sex and adjusted for age, ethnicity, socioeconomic deprivation, education, and smoking.

Results Elevated risks were observed for field crop and vegetable growers (OR 2.93, 95%CI: 1.10, 7.77); fruit growers (OR 2.03, 95%CI: 1.09, 3.78); gardeners and nursery growers (OR 1.96, 95%CI: 1.01, 3.82); crop and livestock producers (OR 3.61, 95%CI: 1.44, 9.02); fishery workers, hunters and trappers (OR 5.62, 95%CI: 1.27, 24.97); builders (OR 2.90, 95%CI: 1.41, 5.96); electricians (OR 3.61, 95%CI: 1.34, 9.74); caregivers (OR 2.65, 95%CI: 1.04, 6.79), forecourt attendants (OR 8.31, 95%CI: 1.79, 38.54); plant and machine operators and assemblers (OR 1.42, 95%CI: 1.01, 2.01); telecommunications technicians (OR 4.2, 95%CI: 1.20, 14.64) and draughting technicians (OR 3.02, 95%CI: 1.07, 8.53). Industries with increased risks were agriculture (particularly horticulture and fruit growing), construction, non-residential care services, motor vehicle retailing, and sport and recreation. Positive associations between employment duration and MND were shown for the occupations fruit growers, gardeners and nursery growers, and crop and livestock producers, and for the horticulture and fruit growing industry.

Conclusions This study suggests associations between MND and occupations in agriculture and several other occupations.

Key Messages

What is already known about this subject?

A number of possible occupational/environmental exposures have been suspected of contributing to the risk of developing MND.

What are the new findings?

- We observed positive associations between the risk of MND and a range of occupations within agriculture in both men and women.
- Positive duration-response associations were also seen in horticultural occupations.
- Positive associations were also found for building trades workers, electricians, telecommunication technicians, and forecourt attendants.

How might this impact on policy or clinical practice in the foreseeable future?

- These results have confirmed previous findings and generated a range of hypotheses for specific occupational risk factors for MND.
- If specific causal exposures can be identified, they may provide important opportunities for the prevention of MND.

3.1 Introduction

Motor Neurone diseases (MND) are progressive and terminal neurodegenerative conditions affecting the motor neurone system, with death usually occurring within 2-5 years after the first symptoms of weakness.[2 3] Amyotrophic lateral sclerosis (ALS) accounts for 70% of cases;[2] other forms include progressive muscular atrophy (PMA), progressive bulbar palsy (PBP) and primary lateral sclerosis (PLS).[2]

There is some evidence of increasing incidence and mortality rates of MND among high-income countries including New Zealand in the last two decades,[3 22] with MND mortality in New Zealand (2.8/100,000) reportedly higher than the estimated mean global mortality (1.7/100,000)[21]. The reasons for the increased incidence remain unclear but are likely due to environmental and lifestyle factors since genetic factors vary little over time and familial MND is relatively uncommon (5-10%).[2 3]

Several studies have reported increased relative risks for certain occupations and occupational exposures,[32 41] suggesting a role for agrichemicals,[35 40] extremely low-frequency magnetic fields (ELF-MFs),[46] electric shocks,[280] some heavy metals,[3] welding fumes,[439] and solvents,[43] although the evidence is equivocal.

We report the findings of the first New Zealand population-based case-control study on modifiable risk factors of MND, with a focus on occupational risk factors.

3.2 Methods

The detailed background information on the study population recruitment and data collection methodology of this population-based case-control study is provided in Appendix 1.

3.2.1 Study population

A national Motor Neurone Disease Registry was not available at the time of study commencement (a national registry has since been established).[440] Incident and prevalent cases (n=295) were invited between 2013-2016 through the Motor Neurone Disease Association of New Zealand (MNDANZ). This was supplemented by records contained in the New Zealand National Minimum Dataset (NMDS), a national collection of public and private hospital discharge information including coded clinical data for inpatients and day patients.[441] Incident cases were defined based on a primary or secondary diagnosis of MND (ICD10 code G122) for the period 2013-2015, and surviving cases (n=103) in the NMDS but not registered with MNDANZ were invited. Two of these were misclassified and excluded, leaving 396 eligible cases. The inclusion criterion for cases was a diagnosis by a neurologist, with all forms of MND included.

Controls were randomly selected from the New Zealand Electoral Roll (2008) with two controls for each case, frequency matched by age (5-year categories, based on the age distribution of the UK MND incidence distribution),[81] and sex. Controls with a neurodegenerative disease were excluded.

Of the 396 eligible cases, 390 responded to invitation letters. Of these 44 were not eligible (27 deceased and 17 in intensive care), 25 (6%) refused to participate, leaving 321 participants equating to a 92% response rate.

Of the 2,400 potential controls, 333 (14%) could not be contacted, 230 (10%) were returned to sender, and 587 (24%) were not eligible. Of the remaining 1,250 controls, 645 declined. Thus, 605 participated in the study, equating to a 48% response rate.

All study participants gave written informed consent and ethical approval was granted by the New Zealand Multi-Region Ethics Committee (ref: MEC/12/01/005).

3.2.2 Data collection

Identical data collection methods were used for cases and controls. These included a face-to-face (59% of cases and 16% of controls), or telephone interview by research nurses (23% of cases and 66% of controls) or a postal questionnaire (18% in cases and 18% in controls). Three cases used a proxy (family member) for the face-to-face interview and six used proxy assistance for reading and writing.

We used a European questionnaire[442] with modifications to adapt it to New Zealand (with particular emphasis on agriculture) to collect information on demographic and personal data, lifestyle factors and lifetime occupational history.

3.2.3 Classification of occupational histories

Participants listed all jobs ever held for 6 months or more, and for each job provided information on job title, employer's name, industry, the year and month in which the job began and ended, and a detailed description of tasks performed, and work processes undertaken.

Each job was classified according to the New Zealand Standard Classification of Occupations (NZSCO99),[443] industries were coded according to the Australian and New Zealand Standard Industrial Classification (ANZSIC96).[444] The occupational coding was based on the full job description, rather than on job title alone. Response outside scope was used for responses, such as "housewife", "pensioner" or "student", which are not covered by NZSCO99. The industry code was based on information provided on the activity of the employer. All coding was done blind to case-control status.

3.2.4 Statistical analyses

Analyses were conducted using SAS v9.3. Differences in general characteristics between cases and controls were tested using Chi-squared tests. Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs), for ever compared to never employed/self-employed in a particular occupation or industry.

Analyses were also stratified by sex because men and women have different occupational profiles. Therefore, the specific occupational risk factors contributing to MND may differ between men and women. Analyses were adjusted for age (5-year

categories), ethnicity (European/Pakeha, Māori, Pacific & others), highest education level (primary school or secondary school, technical or trade school diploma, undergraduate university degree, postgraduate university degree), smoking (never, ex-smokers, current) and for socioeconomic deprivation status using the New Zealand Deprivation Index (NZDep2006).[445] NZDep is census-based with a relative deprivation score assigned to geographical meshblocks based on place of residence recorded on the Electoral Roll (with 1 representing the least and 10 representing the most deprived areas).

In order to establish the role of duration of employment, categorical variables were constructed for each job/industry using cut-points of <2, 2-10, and >10 years. These cut-points, which we have previously used in studies on occupational risk factors and cancer,[446-448] ensured that sufficient numbers of cases and controls were available in each category. These categorical variables were included in the logistic regression using never employed in the occupation/industry as the reference. A test for trend was performed by fitting it as a continuous variable in the model.

Lag-time analyses to take into account potential disease latency were conducted, in which employment 5, 10, 15 and 20 years prior to the interview date was disregarded. Analyses were repeated while adjusting for the mode of interview.

To reduce the number of associations presented, tables 3.2 and 3.3 only include results for broad occupation and industry categories (1-digit codes), irrespective of statistical significance, as well as results for specific occupations and industries (2-5 digits) if the association was statistically significant ($p<0.05$) and based on at least 10 subjects (cases

plus controls). Results for all 2,755 occupations and 3,149 industries are available in supplementary tables (Tables S3.4 & S3.5), as well as results by sex (Tables S3.10 & S3.11).

3.3 Results

3.3.1 Population characteristics

Population characteristics are described in Table 3.1. MND was more common in males (64%) than females (36%), and most cases occurred over 60 years of age. While the 70+ age group was overrepresented in the controls, there was little difference between cases and controls in terms of smoking, ethnicity, and education. However, there was a difference in socioeconomic deprivation status for males, with cases being less deprived compared to controls. There was no difference in the number of occupations held by cases and controls (mean=6.8 for cases and controls). The median and interquartile range (IQR) of age was 64 and 13 for cases and 68 and 15 for controls. There were 225 incident and 96 prevalent cases and the time between diagnosis and interview was 6-18 months (median=238 days, IQR=269 days).

3.3.2 Broad occupation and industry categories

Tables 3.2 and 3.3 present the findings for MND risk associated with occupations and industries overall and by the duration of employment.

Ever-employment in the following broad occupation categories (1-digit, Table 3.2) showed an increased risk: Service and Sales Workers; Agriculture and Fishery Workers; Plant and Machine Operators and Assemblers; and Elementary Occupations. A reduced risk was observed for Clerks.

Statistically significant increased risks for ever-employed in the broad industry categories (1-digit, Table 3.3) were observed for: Agriculture, Forestry and Fishing; Mining; and Construction.

Table 3.1. Characteristics of this study population

Characteristics	Male Cases (N=204)	%	Male Controls (N=332)	%	*p*-Value	Female Cases (N=117)	%	Female Controls (N=273)	%	*p*-Value
Age at interview					0.0002					0.0386
20-49	20	9.80	16	4.82		10	8.55	24	8.79	
50-59	48	23.53	52	15.67		26	22.22	48	17.58	
60-69	79	38.73	112	33.73		45	38.46	76	27.84	
≥70	57	27.94	152	45.78		36	30.77	125	45.79	
Smoking					0.6712					0.4196
Never	103	50.49	155	46.69		62	52.99	164	60.07	
Current	16	7.84	26	7.83		4	3.42	9	3.30	
Ex	85	41.67	151	45.48		51	43.59	100	36.63	
Ethnicity					0.8861					0.1102
European/Pakeha[1]	189	92.65	304	91.56		106	90.60	259	94.87	
Māori[2]	8	3.92	14	4.22		6	5.13	11	4.03	
Pacific & others	7	3.43	14	4.22		5	4.27	3	1.10	
Deprivation Index Quintile					0.0235					0.1386
1-2 (least deprived)	76	37.25	83	25.00		23	19.66	82	30.04	
3-4	51	25.00	83	25.00		28	23.93	60	21.98	
5-6	32	15.69	71	21.39		36	30.77	58	21.24	
7-8	27	13.24	64	19.28		16	13.68	44	16.12	
9-10 (most deprived)	18	8.82	31	9.33		14	11.96	29	10.62	
Highest Education					0.2947					0.2481
Primary school	1	0.49	7	2.11		0	0	6	2.20	
Secondary school (college)	91	44.61	154	46.39		53	45.30	123	45.05	
Technical or trade school diploma	70	34.31	94	28.31		35	29.92	61	22.34	
Undergraduate university degree	28	13.73	45	13.55		18	15.38	53	19.41	
Postgraduate university degree	14	6.86	32	9.64		11	9.40	30	11.00	

[1] Pakeha - a Māori-language term for New Zealanders of European descent.
[2] Māori – indigenous people of New Zealand.

Table 3.2. Odds Ratios (OR) and 95% CIs for Occupation by Duration Categories

Occupation[2]	Ever exposure Cases/Controls (n)	Ever exposure OR (95% CI)[1]	Exposure <2 years Cases/Controls (n)	Exposure <2 years OR (95% CI)[1]	Exposure between 2-10 years Cases/Controls (n)	Exposure between 2-10 years OR (95% CI)[1]	Exposure >10 years Cases/Controls (n)	Exposure >10 years OR (95% CI)[1]	Trend *p*-Value
1-Legislators, Administrators and Managers	84/169	0.83[0.60-1.14]	4/21	0.30[0.10-0.90]*	33/43	1.28[0.78-2.10]	42/98	0.71[0.47-1.07]	0.232
2-Professionals	109/254	0.75[0.54-1.05]	11/19	1.00[0.45-2.19]	25/62	0.69[0.41-1.18]	63/155	0.69[0.47-1.03]	0.050
3-Technicians and Associate Professionals	103/197	0.97[0.72-1.32]	16/26	1.15[0.59-2.24]	27/63	0.78[0.48-1.29]	45/77	1.05[0.70-1.59]	0.877
31141-Telecommunications Technician	8/4	4.20[1.20-14.64]*	0/0	-	2/0	-	2/1	3.15[0.26-38.79]	0.102
3118-Draughting Technicians	9/7	3.02[1.07-8.53]*	2/1	6.17[0.53-72.08]	4/0	-	1/3	0.80[0.08-7.83]	0.122
3342- Education Associate Professionals	2/20	0.23[0.05-1.00]*	1/2	0.92[0.08-10.58]	0/9	-	0/1	-	0.119
4-Clerks	90/238	0.62[0.45-0.86]*	12/36	0.54[0.27-1.08]	31/81	0.61[0.38-0.97]*	29/85	0.61[0.38-0.99]*	0.008
5-Service and Sales Workers	130/205	1.40[1.04-1.90]*	25/41	1.23[0.71-2.12]	46/63	1.65[1.06-2.55]*	42/64	1.49[0.95-2.33]	0.015
51-Personal and Protective Services Workers	89/131	1.46[1.04-2.04]*	23/26	1.84[1.00-3.40]	29/44	1.41[0.84-2.37]	26/38	1.47[0.84-2.55]	0.048
52113-Forecourt Attendant	11/2	8.31[1.79-38.54]*	4/0	-	3/1	4.37[0.44-43.34]	3/0	-	0.030
6-Agriculture and Fishery Workers	106/144	1.66[1.21-2.29]*	17/24	1.50[0.76-2.96]	26/27	1.96[1.09-3.54]*	48/59	1.91[1.23-2.95]*	0.001
61-Market Oriented Agricultural and Fishery Workers	106/144	1.66[1.21-2.29]*	17/24	1.50[0.76-2.96]	26/27	1.96[1.09-3.54]*	48/59	1.91[1.23-2.95]*	0.001
611-Market Farmers and Crop Growers	47/46	2.15[1.37-3.38]*	10/12	1.52[0.62-3.75]	13/15	1.69[0.77-3.72]	17/12	3.50[1.59-7.70]*	0.001
6111-Field Crop and Vegetable Growers	11/8	2.93[1.10-7.77]*	5/3	3.67[0.82-16.38]	3/3	2.38[0.40-14.2]	2/1	3.46[0.30-40.30]	0.063
61112-Market Gardener and Related Worker	8/4	3.98[1.14-13.88]*	4/2	4.15[0.71-24.33]	2/1	4.20[0.35-49.75]	1/0	-	0.042
6112-Fruit Growers	23/24	2.03[1.09-3.78]*	3/7	0.77[0.18-3.22]	4/4	2.01[0.47-8.61]	10/7	3.51[1.26-9.78]*	0.014
61121-Fruit Grower, Worker	20/21	2.07[1.07-4.02]*	2/7	0.49[0.09-2.58]	2/2	2.33[0.30-17.94]	10/6	4.21[1.43-12.35]*	0.012
6113-Gardeners and Nursery Growers	20/19	1.96[1.01-3.82]*	4/5	1.14[0.29-4.42]	7/9	1.32[0.47-3.69]	7/4	4.56[1.28-16.28]*	0.030
61133-Grounds or Green Keeper	12/7	3.01[1.14-7.96]*	4/3	1.92[0.41-8.97]	5/1	8.21[0.91-73.71]	2/2	2.54[0.34-18.88]	0.034
6125-Crop and Livestock Producers	14/10	3.61[1.44-9.02]*	0/4	-	3/1	8.14[0.43-155.80]	6/1	12.50[1.45-107.86]*	0.009
614-Fishery Workers, Hunters and Trappers	7/3	5.62[1.27-24.97]*	2/0	-	3/0	-	2/3	1.79[0.26-12.20]	0.077
7-Trades Workers	93/128	1.28[0.89-1.83]	9/12	1.37[0.55-3.39]	18/28	1.05[0.55-2.02]	45/61	1.21[0.77-1.92]	0.411
71-Building Trades Workers	57/49	2.02[1.30-3.14]*	8/6	2.33[0.78-6.98]	10/10	1.78[0.71-4.47]	28/28	1.61[0.90-2.87]	0.045
711-Building Frame and Related Trades Workers	33/27	1.93[1.10-3.39]*	3/1	4.77[0.46-49.63]	4/5	1.57[0.40-6.15]	20/18	1.66[0.83-3.31]	0.097
7112-Carpenters and Joiners	32/25	1.97[1.11-3.48]*	3/1	4.73[0.45-49.22]	4/5	1.56[0.40-6.13]	19/17	1.59[0.79-3.20]	0.126
71122-Builder (Including Contractor)	23/13	2.90[1.41-5.96]*	1/1	2.49[0.15-42.04]	3/2	2.82[0.44-18.06]	12/10	1.82[0.75-4.38]	0.105
71311-Electrician	14/6	3.61[1.34-9.74]*	4/1	6.64[0.70-62.49]	2/1	2.31[0.20-26.64]	3/3	1.70[0.33-8.79]	0.197
8-Plant and Machine Operators and Assemblers	92/120	1.42[1.01-2.01]*	17/21	1.37[0.69-2.73]	32/39	1.43[0.85-2.41]	28/41	1.32[0.76-2.27]	0.133
9-Elementary Occupations (incl Residuals)	80/111	1.44[1.01-2.04]*	12/24	0.85[0.41-1.78]	32/38	1.62[0.96-2.74]	14/32	0.84[0.43-1.65]	0.561
9151-Labourers	48/55	1.61[1.03-2.52]*	11/8	2.18[0.84-5.70]	16/24	1.10[0.55-2.20]	8/12	1.31[0.50-3.39]	0.397

[1] OR adjusted for age, sex, ethnicity, highest education level, socioeconomic deprivation status and smoking.

[2] Only results for all broad occupation categories (all 1-digit) were included, and for specific occupations (2-5 digits) if the association for ever vs. never employed was statistically significant (p<0.05) and based on at least 10 subjects (cases + controls).

*p<0.05

Table 3.3. Odds Ratios (OR) and 95% CIs for Industry by Duration Categories

Industry[2]	Ever exposure Cases/Controls (n)	Ever exposure OR (95% CI)[1]	Exposure <2 years Cases/Controls (n)	Exposure <2 years OR[1] (95% CI)	Exposure between 2-10 years Cases/Controls (n)	Exposure between 2-10 years OR[1] (95% CI)	Exposure > 10 years Cases/Controls (n)	Exposure > 10 years OR[1] (95% CI)	Trend *p*-Value
A-Agriculture, Forestry and Fishing	101/149	1.42[1.03-1.96]*	12/29	0.84[0.40-1.74]	21/33	1.19[0.66-2.16]	49/58	1.82[1.18-2.82]*	0.011
A01-Agriculture	92/123	1.68[1.20-2.35]*	12/24	1.00[0.47-2.11]	19/24	1.69[0.88-3.25]	44/46	2.19[1.37-3.49]*	0.001
A011-Horticulture and Fruit Growing	36/40	1.93[1.18-3.18]*	7/11	1.15[0.42-3.17]	6/11	1.19[0.42-3.38]	15/10	3.74[1.60-8.75]*	0.004
A0119-Fruit Growing nec	20/13	3.67[1.71-7.89]*	3/5	1.20[0.26-5.61]	2/1	6.07[0.50-72.96]	8/4	5.29[1.44-19.4]*	0.005
B-Mining	16/12	2.26[1.03-4.97]*	6/4	2.51[0.68-9.32]	7/5	2.51[0.77-8.24]	1/3	0.38[0.04-3.83]	0.325
B14-Other Mining	7/4	3.81[1.07-13.59]*	2/3	1.51[0.24-9.45]	2/1	5.86[0.51-67.64]	2/0	-	0.047
C-Manufacturing	131/237	0.99[0.74-1.32]	25/44	0.93[0.54-1.60]	40/62	1.20[0.76-1.89]	47/97	0.81[0.53-1.22]	0.567
C212-Dairy Product Manufacturing	11/5	4.98[1.64-15.06]*	3/2	3.34[0.54-20.80]	3/2	3.77[0.57-25.05]	3/1	6.53[0.62-68.43]	0.021
C2129-Dairy Product Manufacturing nec	8/4	4.10[1.16-14.45]*	2/2	2.21[0.29-16.51]	3/1	7.13[0.66-76.42]	2/1	3.33[0.27-41.17]	0.063
C24-Printing, Publishing and Recorded Media	6/35	0.31[0.13-0.75]*	2/9	0.42[0.09-2.01]	3/12	0.53[0.14-1.98]	1/11	0.12[0.02-0.98]*	0.014
C242-Publishing	2/20	0.20[0.05-0.88]*	0/3	-	2/9	0.43[0.09-2.09]	0/5	-	0.056
E-Construction	83/100	1.50[1.04-2.14]*	15/20	1.37[0.67-2.78]	22/30	1.34[0.73-2.44]	37/42	1.52[0.92-2.52]	0.065
E41-General Construction	53/50	1.81[1.16-2.82]*	12/9	2.18[0.88-5.37]	10/18	1.08[0.47-2.46]	26/19	2.24[1.18-4.24]*	0.014
E412-Non-Building Construction	16/11	2.36[1.05-5.29]*	4/2	3.04[0.53-17.37]	5/4	2.04[0.51-8.12]	7/4	3.08[0.87-10.86]	0.029
E4121-Road and Bridge Construction	12/6	3.00[1.09-8.30]*	2/1	2.19[0.19-25.43]	5/2	4.13[0.76-22.49]	5/3	2.59[0.60-11.20]	0.046
F-Wholesale Trade	32/79	0.66[0.42-1.03]	8/11	1.18[0.46-3.02]	12/30	0.67[0.33-1.36]	6/23	0.42[0.16-1.07]	0.047
F471-Food, Drink and Tobacco Wholesaling	4/20	0.35[0.12-1.06]*	2/3	0.96[0.15-6.13]	2/11	0.33[0.07-1.53]	0/2	-	0.105
G-Retail Trade	110/194	1.09[0.81-1.48]	21/44	0.85[0.48-1.49]	45/63	1.40[0.90-2.16]	29/49	1.29[0.77-2.16]	0.145
G5259-Retailing nec	12/6	3.70[1.33-10.24]*	3/2	2.69[0.42-17.13]	7/3	4.07[1.01-16.35]*	1/0	-	0.011
G53-Motor Vehicle Retailing and Services	47/48	1.78[1.14-2.78]*	9/12	1.38[0.56-3.39]	23/18	2.22[1.16-4.25]*	10/10	2.08[0.80-5.37]	0.006
G531-Motor Vehicle Retailing	18/9	3.73[1.62-8.60]*	5/1	10.00[1.13-88.68]*	8/5	3.04[0.95-9.79]	3/3	1.69[0.32-8.89]	0.027
G5311-Car Retailing	13/9	2.47[1.02-6.00]*	4/1	7.81[0.84-72.67]	6/6	1.68[0.52-5.46]	1/2	0.70[0.06-8.30]	0.315
G5321-Automotive Fuel Retailing	19/9	4.10[1.72-9.78]*	4/3	1.89[0.40-8.95]	8/2	10.83[1.82-64.46]*	5/2	6.10[0.91-40.74]	0.002
I-Transport and Storage	58/88	1.20[0.82-1.76]	8/14	1.11[0.44-2.78]	31/36	1.45[0.86-2.45]	11/31	0.61[0.29-1.26]	0.924
I62-Rail Transport	17/12	2.34[1.09-5.06]*	3/4	1.49[0.32-6.94]	4/2	2.81[0.50-15.94]	5/3	2.49[0.57-10.85]	0.088
I620-Rail Transport	12/6	3.19[1.16-8.79]*	0/3	-	4/0	-	3/1	4.11[0.41-40.84]	0.065
L-Property and Business Services	84/174	0.86[0.62-1.18]	16/39	0.80[0.43-1.49]	30/45	1.21[0.73-2.00]	31/69	0.75[0.47-1.20]	0.430
M-Government Administration and Defence	81/148	1.06[0.77-1.46]	18/28	1.21[0.65-2.27]	23/44	1.05[0.61-1.80]	25/47	1.10[0.65-1.86]	0.655
N-Education	61/160	0.75[0.52-1.10]	7/18	0.61[0.24-1.51]	18/41	0.85[0.46-1.55]	27/80	0.70[0.42-1.16]	0.144
O-Health and Community Services	63/139	0.96[0.66-1.39]	12/19	1.32[0.61-2.85]	29/52	1.15[0.69-1.93]	19/57	0.78[0.44-1.39]	0.736
O8729-Non-Residential Care Services nec	7/6	3.49[1.09-11.22]*	2/1	4.99[0.37-66.65]	2/2	4.24[0.55-32.72]	2/2	2.79[0.37-21.12]	0.077

[1] OR adjusted for age, sex, ethnicity, highest education level, socioeconomic deprivation status and smoking.

[2] Only results for broad industry categories were included (all 1-digit), and for specific industries (2-5 digits) if the association for ever vs. never employed was statistically significant (p<0.05) and based on at least 10 subjects (cases+controls).

*p<0.05

nec: not elsewhere classified

3.3.3 Specific occupations within the broad occupation and industry categories

3.3.3.1 Agriculture and fishery workers

Significantly elevated risks were found for Field Crop and Vegetable Growers; Fruit Growers; Gardeners and Nursery Growers; Crop and Livestock Producers (Table 3.2), with similar risks for both males and females (Supplementary Table S3.10). Positive and statistically significant associations between employment duration and MND were shown for most of these groups (Table 3.2). A significant increased risk was also found for Fishery Workers, Hunters and Trappers although based on small numbers (Table 3.2). By contrast, no increased risk was observed for Livestock Producers, the largest 4-digit group within agricultural workers (Supplementary Table S3.4).

Similar results were observed in analyses by industry category, with significantly elevated risks in Agriculture, in particular, Horticulture and Fruit Growing, with ORs increasing by longer duration (Table 3.3) and with similar risks for both males and females (Supplementary Table S3.11). For Grain, Sheep and Beef Cattle Farming and Dairy Cattle Farming there was no statistically significant risk (Supplementary Table S3.5).

3.3.3.2 Building trades workers

Employment as Building Trades Worker was associated with elevated risk (Table 3.2), particularly for Builders and Electricians. These associations were only found in males as there were very few females in these occupations. Risks did not increase with duration of employment.

Analysis by industry also showed a statistically significant increase in risk for Construction, particularly in General Construction, Non-Building Construction and Road and Bridge Construction (Table 3.3), but notably not in Painting and Decorating Services (Supplementary Table S3.5).

3.3.3.3 Service and sales workers

An increased risk was observed among Service and Sales Workers (Table 3.2). Within this heterogeneous category, women who had ever worked as Caregiver had a statistically significant increased risk (Supplementary Table S3.10), and a similar result was observed for women who had worked in Non-Residential Care Services industry (Supplementary Table S3.11). However, increased risks were not observed for other healthcare related occupations or industries.

A particular high risk was found for working as a Forecourt Attendant (Table 3.2), and similar results were also found for employment in both Car Retailing and Automotive Fuel Retailing industry (Table 3.3). None of the other retail trade sectors was associated with a statistically significant increased risk (Supplementary Table S3.5).

3.3.3.4 Other occupations and industries

Occupations in white-collar categories were generally associated with a lower risk, with a significant inverse association found for Clerks (Table 3.2). While male Finance and Administration Managers showed a decreased risk; in contrast, women in this job showed a significantly elevated risk (Supplementary Table S3.10). However, within white-collar occupations, an elevated risk overall was found for men who worked as

Physical Science and Engineering Technicians (Supplementary Table S3.10). Within this occupation group, Telecommunications Technicians and Draughting Technicians both had increased risks (Table 3.2). An elevated risk was observed for Plant and Machine Operators and Assemblers (Table 3.2), this risk did not increase with duration.

Analyses by industry also showed that men having worked in the Sport and Recreation industry were associated with an increased risk (Supplementary Table S3.11), but not for women. A similar excess was observed in Mining especially Other Mining (Table 3.3).

Neither latency analyses (Supplementary Table S3.6) nor adjustment for mode of interview (Supplementary Table S3.7) made any appreciable difference.

3.4 Discussion

This study found that certain occupations in agriculture and construction were associated with an increased risk of MND, which are consistent with prior studies,[40] thus further supporting that occupation may be an important aetiological factor for MND. This study also identified other occupations associated with increased risk including building trades workers, electricians (electrical occupations), telecommunications technicians, draughting technicians, forecourt attendants, caregivers, and plant and machine operators and assemblers.

3.4.1 Agricultural workers

A major finding was the strong association between agricultural employment and MND, with several horticultural occupations within this group showing increased risks. Similar results were observed for analysis by industry. When the duration of employment was considered, the risk increased monotonically for market farmers and crop growers, fruit growers and gardeners/nursery growers. The presence of an increased risk for multiple non-overlapping occupational groups, the presence of positive duration-response associations, and the presence of increased risks for both men and women in these occupations, strongly suggests these are not chance findings.

We found no significant difference in urban/rural residency between cases and controls (Supplementary Table S3.8), suggesting it is unlikely that risk factors associated with urban/rural residency could be responsible for the observed increased MND risks for agricultural workers. To test whether these associations could be explained by differences in urban/rural residency between participating and non-participating

controls, the geographical meshblock for place of residence for all potential controls were linked to New Zealand geographic concordance files to obtain their urban/rural classification,[449] which was then compared between participants and non-participants (Supplementary Table S3.8). This showed that participating controls were slightly more likely to live rurally (18%) compared to non-participating controls (14%), suggesting that participation bias could not explain the observed increased MND risks for agricultural workers.

Our findings are consistent with prior studies that observed increased MND risk among farmers and agricultural workers,[30 321 323] and workers exposure to herbicides/pesticides.[44 327] Also, several meta-analyses[39 40] have shown that previous exposure to agricultural chemicals, especially to pesticides, is associated with MND. Pesticide exposure is also a plausible explanation for the risk patterns observed in this study, given that risks were mainly elevated for agricultural occupations and industries in fruit and crop growing, while agricultural occupations and industries primarily in livestock production did not show an increased risk.

3.4.2 Construction workers

A strong association was observed with construction workers, particularly building trades workers and general labourers. The analysis by industry category confirmed this and results are also consistent with earlier studies in construction workers,[43 183] heavy labour and blue-collar occupations.[180] Associated exposures to dusts, heavy metals,[3] and repetitive and strenuous work have also previously been shown to be a risk factor. As blue-collar workers have been related to lower socioeconomic deprivation status and

higher smoking rates,[450] these confounders were considered in our study. Although male cases were more deprived on average compared to controls, and there were no differences in education and smoking status between cases and controls in our study, we also adjusted for socioeconomic deprivation status, education, and smoking status. Therefore, the general pattern of increased MND risk for blue-collar occupations is unlikely due to confounding.

This study showed an elevated risk for electricians and telecommunications technicians, which is consistent with previous studies showing associations with electrical occupations.[187 279] Exposure to ELF-MFs or electric shocks have been suggested as an explanation for these findings.[46 264]

3.4.3 Other occupations

An increased risk was observed among forecourt attendants and in the automotive fuel retailing industry. While this association has not previously been reported (possibly due to the absence of a specific code for forecourt attendants in occupational classifications used in other studies), increased risks associated with exposures experienced by forecourt attendants have been shown, in particular exposure to lead, which was used as a fuel additive until 1996 in New Zealand.[451] A Spanish study[200] found that MND mortality was associated with higher air lead levels, and a recent Australian study[199] showed a one percent increase in life-time petrol lead exposure increased the MND death rate by approximately one-third of a percent.

Other significant associations were observed in plant and machine operators and assemblers. This is a heterogeneous occupational group including stationary machine operators as well as vehicle drivers, but none of the specific occupations within this group showed an increased risk. The increased risk may, therefore, be associated with non-specific exposures such as cutting, cooling, or lubricating oils,[43] diesel exhaust emissions[452] and ELF-MFs.[46]

We also observed an elevated risk for women caregivers but not for other healthcare related occupations, although two mortality studies[30 292] showed that female nurses and medical services workers had an increased risk for MND.

3.4.4 Strengths and limitations

Using the MNDANZ national register, the NMDS and the New Zealand Electoral Roll to identify cases and controls was an important strength of this study. In particular, the MNDANZ national register and NMDS provided a reliable source for all MND patients in New Zealand, and the Electoral Roll records virtually all New Zealand citizens and permanent residents in the age of particular relevance to this study (i.e. >40 years).[453] These sources are representative of the general population that generated the cases. Misclassification of disease status was also minimised as cases were diagnosed by a neurologist, and diagnosis details and neurologists' contact details were provided by all cases. The use of both prevalent and incident cases was necessary to achieve an adequate sample size, but as the time between diagnosis and interview (6-18 months) was short and within the normal survival time for all cases, this was considered unlikely to introduce a bias. Additional analyses excluding prevalent cases did not alter our main

findings, apart from wider confidence intervals due to lower numbers. We also ran additional models adjusting for sports and alcohol consumption, but this made little difference to the risk estimates and did not alter our findings. Another important strength of the study was that full occupational histories were collected from all cases and controls without the use of proxies to answer the questionnaire, a particular advantage compared to studies based on mortality and cause of death data. The study is also relatively large in comparison with many other case-control studies focusing on occupation,[180 309] and particularly compared to small clinic-based samples.[189 261]

The limitations include the reliance on self-reporting, which could introduce recall bias. To minimise this, the lifetime work-history questionnaire was provided to every participant a few weeks before the interview to allow sufficient time to recall their work history, and the interviewers were trained to probe for the full occupational history without any gaps. There was no difference in the number of occupations held by cases and controls (mean=6.8) and there was, therefore, no indication of recall bias in the occupational histories (i.e. cases recalling particular jobs more often than controls), although this cannot be fully excluded.

Another limitation was the lower response rate in controls (48%) compared to cases (92%). We assessed whether participation was associated with occupation by comparing the occupation, as recorded on the Electoral Roll, between participating and non-participating controls. The frequency of digit 1 and 2 job codes showed no difference between participating and non-participating controls for the occupations for which we found an increased risk, e.g., 61-Market-Oriented Agricultural and Fishery workers, 4.29% non-participating controls vs 4.63% participating controls (Supplementary Table

S3.9). Although these comparisons were based on one occupation and not the full occupational history, they provide no indication that the increased risks observed in this study are explained by non-response bias.

There were nine cases with proxy, all of whom were proxy-assisted for the interview only. Given that this represents only 2.8% of the total case population, we consider that any bias resulting from this would be negligible.

There were also differences in the interview method used between cases and controls. For cases, it was often difficult to engage in a long telephone interview or to complete the full postal questionnaire. As a result, 62% of cases preferred a face-to-face interview, with only 18% interviewed over the phone and 20% completing a postal questionnaire. In controls, 65% preferred a telephone interview, 17% chose a face-to-face interview and 18% completed a postal questionnaire. To minimise potential bias, the completeness of questionnaires was checked, and follow-up interviews by telephone were made for all cases and controls where there was missing or incomplete data. We also did an additional analysis by repeating all analyses controlling for the interview method in the model, which made little difference and did not alter our findings.

Genetic data was not available as genetic testing is not routinely offered to patients in New Zealand, unless there is a clear family history, and then often only at the request of the patient.[440] However, familial MND only accounts for 5-10% of all MND cases, and genetic differences are therefore unlikely to explain our findings.

The other limitation was that the age distribution between cases and controls was different between men and women. This is likely due to age matching controls using the age distribution of MND incidence in the UK, which may be different from that in New Zealand (equivalent New Zealand data was not available at the time of participant recruitment).

3.5 Conclusions

The findings of this study suggest that MND risks may be associated with certain occupations and industries in New Zealand. In particular, several agricultural occupations were associated with an increased risk. Agriculture also represented the largest occupational group for which an increased risk was observed (i.e., 33% of cases and 24% of controls had worked in agriculture), illustrating that occupational risk factors for MND may have a high prevalence in New Zealand population. If specific causal exposures can be identified, this may provide important opportunities for the prevention of MND. We also observed increased MND risk for other large occupational groups such as building trades workers, plant and machine operators and assemblers, and unspecified labourers, but also for smaller more specific occupational groups including care workers, forecourt attendants, telecommunications technicians, draughting technicians, and electricians. These results have suggested specific occupational risk factors for MND (e.g., agricultural chemicals, organic solvents, metals, ELF-MFs, and electric shocks) that merit further scrutiny in future analyses.

Acknowledgements

We are grateful to the study participants, the Motor Neurone Disease Association New Zealand, and their field staff for their generous support. We would also like to thank Michelle Gray, Di Marshal, Heather Duckett, Deirdre Thurston, Aly Timmings, for their help with conducting interviews.

The study was funded by a grant from the Health Research Council (HRC) of New Zealand (Part of 11/1041 HRC Programme Grant - Building Research in Occupational Health in New Zealand (BROHNZ)).

Declaration of competing financial interests

The authors declare they have no actual or potential competing financial interests.

3.6 Supplementary material

Table S3.4. Supplement Table. Odds Ratios (OR) and 95% CIs for Occupation Categories

Occupation	Number (Cases/Controls)	OR (95%CI)
0-Response Outside Scope	92/210	0.86[0.63-1.19]
00001-student	30/61	0.97[0.59-1.60]
00002-housewife/husband	42/107	0.89[0.57-1.40]
00003-unemployed	14/27	0.93[0.47-1.85]
00004-retired	14/35	0.89[0.46-1.73]
00006-overseas / travelling	13/28	0.80[0.40-1.61]
00008-held various odd jobs, that cannot be coded individually	6/8	1.31[0.44-3.89]
00009-Volunteer	1/9	0.25[0.03-2.04]
1-Legislators, Administrators and Managers	84/169	0.83[0.60-1.14]
11-Legislators and Administrators	5/17	0.52[0.18-1.45]
113-Senior Business Administrators	5/9	0.89[0.28-2.77]
1131-Senior Business Administrators	5/9	0.89[0.28-2.77]
11311-Chief Executive and/or Managing Director	5/9	0.89[0.28-2.77]
12-Corporate Managers	82/158	0.89[0.64-1.23]
121-General Managers	8/19	0.64[0.27-1.52]
1211-General Managers	8/19	0.64[0.27-1.52]
12111-General Manager	8/19	0.64[0.27-1.52]
122-Specialised Managers	79/148	0.94[0.68-1.31]
1221-Production and Operation Managers	23/39	1.04[0.59-1.83]
12211-Senior Education Manager	6/16	0.90[0.34-2.43]
12213-Production Manager (Manufacturing)	6/15	0.61[0.22-1.65]
1222-Finance and Administration Managers	17/35	0.87[0.47-1.60]
12222-Administration Manager	7/18	0.82[0.33-2.04]
12224-Finance Manager	7/15	0.79[0.31-1.99]
1224-Sales and Marketing Managers	12/14	1.35[0.60-3.05]
12241-Sales and/or Marketing Manager	12/14	1.35[0.60-3.05]
1226-Supply and Distribution Managers	32/61	0.99[0.62-1.58]
12263-Retail Manager	10/28	0.72[0.34-1.53]

Occupation	Number (Cases/Controls)	OR (95%CI)
12264-Hotel or Motel Manager	11/16	1.22[0.54-2.75]
12266-Other Lodging Services Manager	4/8	1.04[0.30-3.60]
12267-Other Catering Services Manager	2/9	0.45[0.09-2.17]
1229-Other Specialised Managers	6/19	0.66[0.26-1.70]
12291-Office Manager	6/19	0.66[0.26-1.70]
2-Professionals	109/254	0.75[0.54-1.05]
21-Physical, Mathematical and Engineering Science Professionals	30/47	1.11[0.66-1.85]
211-Physicists, Chemists and Related Professionals	3/7	0.81[0.20-3.27]
213-Computing Professionals	8/14	0.90[0.36-2.22]
2131-Computing Professionals	8/14	0.90[0.36-2.22]
21311-Systems Analyst	4/7	0.87[0.25-3.10]
21313-Systems Manager	2/8	0.36[0.07-1.77]
214-Architects, Engineers and Related Professionals	21/29	1.31[0.71-2.43]
2142-Civil Engineers	8/10	1.21[0.45-3.21]
2145-Mechanical Engineers	4/11	0.65[0.20-2.15]
21455-Other Mechanical Engineer	3/8	0.64[0.16-2.52]
22-Life Science and Health Professionals	25/74	0.70[0.42-1.15]
221-Life Science Professionals	8/17	0.94[0.38-2.31]
2211-Biologists, Botanists, Zoologists and Related Professionals	1/10	0.21[0.03-1.74]
2213-Agricultural and Natural Resource Scientists	5/8	1.21[0.37-3.91]
222-Health Professionals (Except Nursing)	5/13	0.84[0.28-2.52]
223-Nursing and Midwifery Professionals	13/47	0.58[0.30-1.14]
2231-Nursing and Midwifery Professionals	13/47	0.58[0.30-1.14]
22312-Registered Nurse	12/43	0.59[0.29-1.18]
23-Teaching Professionals	34/98	0.76[0.48-1.20]
231-Tertiary Teaching Professionals	9/24	0.77[0.34-1.73]
2311-Tertiary Teaching Professionals	9/24	0.77[0.34-1.73]
23111-University and Higher Education Lecturer and/or Tutor	9/24	0.77[0.34-1.73]
232-Secondary Teaching Professionals	9/41	0.50[0.23-1.07]
2321-Secondary Teaching Professionals	9/41	0.50[0.23-1.07]
23211-Secondary School Teacher	9/41	0.50[0.23-1.07]
233-Primary and Early Childhood Teaching Professionals	20/49	1.00[0.56-1.78]
2331-Primary Teaching Professionals	15/43	0.84[0.44-1.60]
23311-Primary School Teacher	15/43	0.84[0.44-1.60]

Occupation	Number (Cases/Controls)	OR (95%CI)
2332-Early Childhood Teaching Professionals	5/8	1.47[0.46-4.72]
23321-Early Childhood Teacher	5/7	1.66[0.50-5.51]
234-Special Education Teaching Professionals	2/12	0.42[0.09-1.96]
2341-Special Education Teaching Professionals	2/12	0.42[0.09-1.96]
23411-Special Education Teacher	2/9	0.52[0.11-2.51]
24-Other Professionals	33/74	0.84[0.53-1.32]
241-Business Professionals	17/46	0.63[0.35-1.12]
2411-Accountants	8/30	0.46[0.20-1.02]
24111-Accountant	7/26	0.47[0.20-1.12]
2412-Human Resources Professionals	6/4	3.07[0.84-11.26]
2413-Other Business Professionals	5/14	0.55[0.19-1.58]
242-Legal Professionals	3/7	0.83[0.20-3.38]
243-Archivists, Librarians and Related Information Professionals	6/12	1.23[0.44-3.42]
2432-Librarians and Related Information Professionals	6/11	1.31[0.47-3.70]
24321-Librarian	6/11	1.31[0.47-3.70]
244-Social and Related Science Professionals	6/9	1.42[0.48-4.16]
3-Technicians and Associate Professionals	103/197	0.97[0.72-1.32]
31-Physical Science and Engineering Associate Professionals	42/65	1.20[0.78-1.85]
311-Physical Science and Engineering Technicians	28/35	1.69[0.98-2.91]
3111-Physical Science Technicians	3/7	1.21[0.30-4.91]
31111-Physical Science Technician	3/7	1.21[0.30-4.91]
3114-Electronic Engineering Technicians	10/9	2.09[0.81-5.38]
31141-Telecommunications Technician	8/4	4.20[1.20-14.64]
3118-Draughting Technicians	9/7	3.02[1.07-8.53]
31181-Draughting Technician	9/7	3.02[1.07-8.53]
312-Computer Equipment Controllers	7/6	1.77[0.57-5.47]
3121-Computer Equipment Controllers	7/6	1.77[0.57-5.47]
313-Optical and Electronic Equipment Controllers	4/8	0.89[0.26-3.04]
315-Safety and Health Inspectors	2/13	0.24[0.05-1.11]
3151-Safety and Health Inspectors	2/13	0.24[0.05-1.11]
32-Life Science and Health Associate Professionals	14/24	1.11[0.55-2.23]
321-Life Science Technicians and Related Workers	6/11	0.93[0.33-2.60]
3211-Life Science Technicians	2/11	0.30[0.06-1.40]
322-Health Associate Professionals	7/12	1.25[0.47-3.34]

Occupation	Number (Cases/Controls)	OR (95%CI)
33-Other Associate Professionals	61/129	0.88[0.62-1.25]
331-Finance and Sales Associate Professionals	35/53	1.15[0.72-1.84]
3312-Insurance Representative	8/7	2.34[0.81-6.73]
33121-Insurance Representative	8/7	2.34[0.81-6.73]
3313-Real Estate Agents	6/10	1.14[0.40-3.27]
33131-Real Estate Agent/Property Consultant	5/10	0.97[0.32-2.94]
3315-Sales Representatives	15/29	0.83[0.43-1.62]
33152-Technical Representative	5/10	0.94[0.31-2.90]
33153-Sales Representative	11/16	1.03[0.46-2.32]
332-Administrative Associate Professionals	8/19	0.82[0.35-1.92]
3321-Administrative and Related Associate Professionals	4/10	0.73[0.22-2.42]
33211-Administration Officer	3/8	0.70[0.18-2.77]
334-Social Work Associate Professionals	8/32	0.56[0.25-1.28]
3341-Social Work Associate Professionals	6/12	1.20[0.42-3.43]
33411-Social Worker	5/10	1.32[0.42-4.14]
3342-Education Associate Professionals	2/20	0.23[0.05-1.00]
33422-Teacher Aide	2/19	0.24[0.05-1.05]
336-Writers, Artists, Entertainment and Sports Associate Professionals	15/34	0.82[0.43-1.55]
3361-Authors, Journalists and Other Writers	1/12	0.17[0.02-1.36]
3369-Sportspersons and Related Workers	4/7	0.89[0.25-3.13]
4-Clerks	90/238	0.62[0.45-0.86]
41-Office Clerks	82/204	0.70[0.51-0.98]
411-Secretaries and Keyboard Operating Clerks	27/60	1.03[0.61-1.72]
4111-Typists and Word Processor Operators	9/23	1.10[0.48-2.51]
41111-Typist and Word Processor Operator	9/23	1.10[0.48-2.51]
4112-Data Entry Operators	4/6	1.40[0.37-5.23]
41121-Data Entry Operator	4/6	1.40[0.37-5.23]
4114-Secretaries	15/39	0.79[0.41-1.49]
41141-Secretary	15/39	0.79[0.41-1.49]
412-Numerical Clerks	16/31	0.98[0.52-1.85]
4121-Accounting and Bookkeeping Clerks	12/23	1.04[0.50-2.17]
41211-Accounts Clerk	10/17	1.24[0.54-2.83]
4122-Statistical and Finance Clerks	6/8	1.40[0.46-4.24]
41221-Finance Clerk	4/7	1.02[0.28-3.63]

Occupation	Number (Cases/Controls)	OR (95%CI)
413-Material Recording and Transport Clerks	10/22	0.72[0.33-1.58]
4131-Stock Clerks	8/19	0.69[0.29-1.65]
41311-Stock Clerk	3/16	0.29[0.08-1.02]
414-Library, Mail and Related Clerks	52/139	0.67[0.46-0.98]
4142-Mail Carriers and Sorting Clerks	11/11	1.70[0.71-4.05]
4144-Office Clerks	42/129	0.58[0.39-0.86]
41443-General Clerk	33/121	0.48[0.31-0.73]
41445-Human Resources Clerk	3/8	0.75[0.19-3.00]
42-Customer Services Clerks	29/75	0.79[0.49-1.29]
421-Cashiers, Tellers and Related Clerks	14/42	0.65[0.34-1.23]
4211-Cashiers and Ticket Issuers	5/16	0.60[0.21-1.72]
42111-Cashier	4/12	0.64[0.20-2.10]
4212-Bank Officers	10/29	0.68[0.32-1.45]
42121-Bank Officer	10/29	0.68[0.32-1.45]
422-Client Information Clerks	17/39	0.99[0.53-1.85]
4221-Receptionists and Information Clerks	12/23	1.16[0.55-2.46]
42213-Information Clerk and Other Receptionist	10/20	1.19[0.53-2.69]
4222-Telephone Switchboard Operators	6/17	0.84[0.31-2.24]
42221-Telephone Switchboard Operator	6/17	0.84[0.31-2.24]
5-Service and Sales Workers	130/205	1.40[1.04-1.90]
51-Personal and Protective Services Workers	89/131	1.46[1.04-2.04]
512-Housekeeping and Restaurant Services Workers	36/63	1.08[0.68-1.72]
5121-Housekeepers	5/12	0.88[0.29-2.64]
51212-Housekeeper (Not Private)	3/8	0.68[0.17-2.70]
5122-Cooks	9/20	0.86[0.37-1.96]
51222-Cook	7/14	1.07[0.41-2.77]
5123-Waiters and Bartenders	26/44	1.12[0.65-1.91]
51231-Bartender	8/10	1.11[0.42-2.95]
51233-Waiter	9/17	1.17[0.49-2.79]
51234-Catering Counter Assistant	5/11	0.94[0.31-2.83]
51235-Kitchenhand	8/7	2.51[0.87-7.21]
513-Personal Care Workers	18/38	1.06[0.58-1.96]
5131-Personal Care Workers	18/38	1.06[0.58-1.96]
51314-Nurse Aide	4/15	0.67[0.21-2.10]

Occupation	Number (Cases/Controls)	OR (95%CI)
51316-Care Giver	11/13	2.02[0.85-4.77]
514-Other Personal Services Workers	12/17	1.75[0.78-3.92]
5141-Hairdressers, Beauty Therapists and Related Workers	5/6	1.67[0.47-5.92]
5142-Child Care Workers	8/12	1.83[0.70-4.77]
51421-Child Care Worker	8/12	1.83[0.70-4.77]
515-Protective Services Workers	28/33	1.45[0.84-2.50]
5152-Police	7/13	0.93[0.36-2.39]
51522-Police Officer	7/13	0.93[0.36-2.39]
5154-Other Protective Services Workers	6/5	2.07[0.58-7.37]
51542-Security Officer	6/4	2.47[0.63-9.63]
5155-Armed Forces	13/13	1.77[0.79-3.99]
51551-Armed Forces	13/13	1.77[0.79-3.99]
52-Salespersons, Demonstrators and Models	66/110	1.22[0.85-1.77]
521-Salespersons and Demonstrators	62/108	1.17[0.80-1.70]
5211-Salespersons and Demonstrators	62/108	1.17[0.80-1.70]
52111-Sales Assistant	57/106	1.09[0.74-1.60]
52113-Forecourt Attendant	11/2	8.31[1.79-38.54]
6-Agriculture and Fishery Workers	106/144	1.66[1.21-2.29]
61-Market Oriented Agricultural and Fishery Workers	106/144	1.66[1.21-2.29]
611-Market Farmers and Crop Growers	47/46	2.15[1.37-3.38]
6111-Field Crop and Vegetable Growers	11/8	2.93[1.10-7.77]
61112-Market Gardener and Related Worker	8/4	3.98[1.14-13.88]
6112-Fruit Growers	23/24	2.03[1.09-3.78]
61121-Fruit Grower, Worker	20/21	2.07[1.07-4.02]
6113-Gardeners and Nursery Growers	20/19	1.96[1.01-3.82]
61131-Nursery Grower, Nursery Worker	7/8	1.87[0.65-5.39]
61133-Grounds or Green Keeper	12/7	3.01[1.14-7.96]
612-Market Oriented Animal Producers	64/106	1.19[0.82-1.73]
6121-Livestock Producers	42/73	1.10[0.72-1.69]
61211-Dairy Farmer, Dairy Farm Worker	27/45	1.09[0.65-1.84]
61212-Sheep Farmer, Sheep Farm Worker	12/24	0.91[0.44-1.89]
6122-Mixed Livestock Producers	8/21	0.63[0.27-1.49]
61221-Mixed Livestock Farmer, Mixed Livestock Farm Worker	8/21	0.63[0.27-1.49]
6125-Crop and Livestock Producers	14/10	3.61[1.44-9.02]

Occupation	Number (Cases/Controls)	OR (95%CI)
61251-Crop and Livestock Farmer, Worker	14/10	3.61[1.44-9.02]
6126-Other Agriculture Workers	11/16	1.03[0.46-2.33]
613-Forestry and Related Workers	3/8	0.69[0.18-2.75]
6131-Forestry Workers and Loggers	3/8	0.69[0.18-2.75]
614-Fishery Workers, Hunters and Trappers	7/3	5.62[1.27-24.97]
7-Trades Workers	93/128	1.28[0.89-1.83]
71-Building Trades Workers	57/49	2.02[1.30-3.14]
711-Building Frame and Related Trades Workers	33/27	1.93[1.10-3.39]
7112-Carpenters and Joiners	32/25	1.97[1.11-3.48]
71121-Carpenter and/or Joiner	12/12	1.32[0.56-3.09]
71122-Builder (Including Contractor)	23/13	2.90[1.41-5.96]
712-Building Finishers and Related Trades Workers	14/17	1.20[0.57-2.53]
7124-Painters and Paperhangers	8/10	1.13[0.43-2.96]
71241-Painter, Decorator and/or Paperhanger	6/8	1.07[0.36-3.21]
713-Electricians	16/8	3.21[1.32-7.79]
7131-Electricians	16/8	3.21[1.32-7.79]
71311-Electrician	14/6	3.61[1.34-9.74]
72-Metal and Machinery Trades Workers	29/51	0.88[0.52-1.49]
721-Metal Moulders, Sheet-Metal and Related Workers	8/11	1.07[0.41-2.80]
7212-Sheet-Metal Workers	8/11	1.07[0.41-2.80]
72124-Fitter and Welder	8/8	1.44[0.51-4.05]
722-Blacksmiths, Toolmakers and Related Workers	5/7	1.46[0.43-4.93]
723-Machinery Mechanics and Fitters	21/35	0.91[0.50-1.67]
7231-Machinery Mechanics and Fitters	21/35	0.91[0.50-1.67]
72311-Machinery Mechanic	7/18	0.56[0.22-1.42]
72312-Motor Mechanic	12/16	1.03[0.46-2.29]
724-Electrical and Electronic Instrument Mechanics and Fitters	2/8	0.39[0.08-1.90]
73-Precision Trades Workers	6/15	0.67[0.25-1.81]
733-Printing Trades Workers	3/13	0.43[0.12-1.56]
7331-Printing Trades Workers	1/12	0.16[0.02-1.29]
74-Other Craft and Related Trades Workers	7/26	0.49[0.21-1.17]
741-Food and Related Products Processing Trades Workers	1/10	0.15[0.02-1.19]
743-Tailors and Dressmakers	4/13	0.70[0.22-2.22]
8-Plant and Machine Operators and Assemblers	92/120	1.42[1.01-2.01]

Occupation	Number (Cases/Controls)	OR (95%CI)
81-Industrial Plant Operators	20/26	1.19[0.63-2.25]
811-Mining and Mineral Processing Plant Operators	6/7	1.18[0.38-3.65]
8111-Mining Plant Operators	4/6	0.89[0.24-3.30]
812-Metal-Processing Plant Operators	8/11	1.12[0.43-2.94]
814-Wood-Processing and Papermaking Plant Operators	7/5	2.57[0.78-8.43]
82-Stationary Machine Operators and Assemblers	48/64	1.27[0.83-1.94]
821-Metal and Mineral Products Processing Machine Operators	7/4	2.68[0.73-9.82]
826-Textile Products Machine Operators	10/19	1.23[0.53-2.82]
8263-Sewing and Embroidering Machine Operators	4/13	0.75[0.23-2.45]
82631-Sewing Machinist	4/13	0.75[0.23-2.45]
827-Food and Related Products Processing Machine Operators	12/16	1.09[0.49-2.38]
8271-Meat and Fish Processing Machine Operators	6/9	0.93[0.32-2.71]
829-Assemblers	14/20	1.03[0.50-2.12]
8292-Electrical Machinery Assemblers	6/9	1.04[0.35-3.07]
82923-Linesperson	4/7	0.88[0.24-3.23]
8294-Wood and Related Materials Products Assemblers	4/6	0.85[0.23-3.16]
83-Drivers and Mobile Machinery Operators	37/50	1.31[0.80-2.14]
832-Motor Vehicle Drivers	22/32	1.22[0.67-2.23]
8321-Car, Taxi and Light Van Drivers	6/7	1.21[0.39-3.78]
8323-Heavy Truck Drivers	15/24	1.14[0.56-2.33]
83231-Heavy Truck or Tanker Driver	15/24	1.14[0.56-2.33]
833-Agricultural, Earthmoving and Other Materials-Handling Equipment Operators	14/15	1.59[0.72-3.50]
8331-Motorised Farm Machinery Operators	3/7	0.92[0.22-3.91]
8332-Earthmoving and Related Machinery Operators	8/8	1.43[0.51-3.99]
83324-Earthmoving Machine Operator	6/5	1.97[0.58-6.76]
834-Ships' Deck Crews and Related Workers	6/9	1.44[0.47-4.38]
8341-Ships' Deck Crews and Related Workers	6/9	1.44[0.47-4.38]
83411-Deck Rating	4/9	1.03[0.29-3.61]
84-Building and Related Workers	5/6	1.19[0.34-4.12]
841-Building and Related Workers	5/6	1.19[0.34-4.12]
8411-Building and Related Workers	5/5	1.33[0.37-4.84]
9-Elementary Occupations (incl Residuals)	80/111	1.44[1.01-2.04]
91-Labourers and Related Elementary Service Workers	78/110	1.39[0.98-1.98]
911-Building Caretakers and Cleaners	19/35	1.18[0.64-2.18]

Occupation	Number (Cases/Controls)	OR (95%CI)
9111-Caretakers and Cleaners	19/35	1.18[0.64-2.18]
91111-Cleaner	17/28	1.30[0.68-2.51]
91112-Building Caretaker	4/7	1.29[0.35-4.74]
912-Messengers and Doorkeepers	5/12	0.73[0.25-2.18]
9121-Messengers and Doorkeepers	5/12	0.73[0.25-2.18]
91211-Courier and Deliverer	5/11	0.81[0.27-2.43]
914-Packers and Freight Handlers	12/29	0.65[0.32-1.32]
9141-Packers and Freight Handlers	12/29	0.65[0.32-1.32]
91411-Packer	7/13	1.02[0.39-2.67]
91412-Loader and/or Checker	5/16	0.44[0.16-1.25]
915-Labourers	48/55	1.61[1.03-2.52]
9151-Labourers	48/55	1.61[1.03-2.52]
91512-Builder's Labourer	8/5	2.94[0.91-9.49]
91513-Sawmill Labourer	5/6	1.28[0.38-4.38]
91514-General Labourer	39/46	1.49[0.92-2.42]

OR adjusted for Age, Sex, Ethnicity, Highest Education Level, Socioeconomic Deprivation Status and Smoking.
Results were based on at least 10 subjects (cases + controls).
"Response outside scope" was used for responses, such as 'housewife', 'pensioner' or 'student', which are not covered by NZSCO99.

Table S3.5. Supplementary Table. Odds Ratios (OR) and 95% CIs for Industry Categories

Industry	Number (Cases/Controls)	OR (95%CI)
0-Response Outside Scope	91/203	0.90[0.65-1.24]
00001-Student	23/56	0.79[0.46-1.36]
00002-Housewife/husband	42/107	0.89[0.57-1.40]
00003-Unemployed	14/25	1.05[0.53-2.09]
00004-Retired	14/36	0.87[0.45-1.70]
00006-Overseas / travelling	13/27	0.81[0.40-1.64]
00008-Held various odd jobs, that cannot be coded individually	6/10	1.00[0.35-2.83]
A-Agriculture, Forestry and Fishing	101/149	1.42[1.03-1.96]
A01-Agriculture	92/123	1.68[1.20-2.35]
A011-Horticulture and Fruit Growing	36/40	1.93[1.18-3.18]
A0111-Plant Nurseries	5/5	1.66[0.45-6.06]
A0113-Vegetable Growing	8/7	2.62[0.89-7.76]
A0119-Fruit Growing nec	20/13	3.67[1.71-7.89]
A012-Grain, Sheep and Beef Cattle Farming	34/44	1.50[0.91-2.46]
A0123-Sheep-Beef Cattle Farming	21/26	1.59[0.85-2.96]
A0124-Sheep Farming	7/15	0.82[0.32-2.10]
A0125-Beef Cattle Farming	5/6	1.48[0.43-5.11]
A013-Dairy Cattle Farming	29/41	1.40[0.83-2.36]
A0130-Dairy Cattle Farming	29/41	1.40[0.83-2.36]
A015-Other Livestock Farming	12/17	1.18[0.53-2.59]
A0159-Livestock Farming nec	7/13	0.94[0.35-2.52]
A02-Services to Agriculture; Hunting and Trapping	13/26	0.89[0.44-1.81]
A021-Services to Agriculture	13/24	0.95[0.46-1.94]
A0219-Services to Agriculture nec	8/22	0.60[0.26-1.41]
A03-Forestry and Logging	5/10	0.77[0.25-2.37]
A030-Forestry and Logging	5/10	0.77[0.25-2.37]
A04-Commercial Fishing	6/8	1.33[0.44-4.04]
A041-Marine Fishing	6/7	1.55[0.49-4.89]
B-Mining	16/12	2.26[1.03-4.97]
B14-Other Mining	7/4	3.81[1.07-13.59]
C-Manufacturing	131/237	0.99[0.74-1.32]
C21-Food, Beverage and Tobacco	41/67	1.12[0.73-1.71]

Industry	Number (Cases/Controls)	OR (95%CI)
C211-Meat and Meat Product Manufacturing	20/29	1.16[0.63-2.13]
C2111-Meat Processing	20/27	1.26[0.68-2.33]
C212-Dairy Product Manufacturing	11/5	4.98[1.64-15.06]
C2129-Dairy Product Manufacturing nec	8/4	4.10[1.16-14.45]
C217-Other Food Manufacturing	4/20	0.40[0.13-1.21]
C2179-Food Manufacturing nec	3/9	0.63[0.16-2.42]
C218-Beverage and Malt Manufacturing	7/9	1.30[0.47-3.60]
C22-Textile, Clothing, Footwear and Leather Manufacturing	25/57	0.93[0.56-1.56]
C221-Textile Fibre, Yarn and Woven Fabric Manufacturing	9/13	1.25[0.52-3.04]
C2214-Wool Textile Manufacturing	6/10	1.19[0.41-3.42]
C222-Textile Product Manufacturing	4/8	1.12[0.31-4.05]
C224-Clothing Manufacturing	9/23	1.10[0.48-2.54]
C2240-Clothing Manufacturing	5/10	1.20[0.39-3.73]
C225-Footwear Manufacturing	1/10	0.19[0.02-1.54]
C23-Wood and Paper Product Manufacturing	21/34	1.14[0.63-2.04]
C231-Log Sawmilling and Timber Dressing	12/10	2.12[0.87-5.19]
C2311-Log Sawmilling	11/9	1.99[0.79-4.99]
C232-Other Wood Product Manufacturing	3/9	0.59[0.15-2.31]
C233-Paper and Paper Product Manufacturing	8/15	1.05[0.43-2.56]
C2331-Pulp, Paper and Paperboard Manufacturing	6/13	0.88[0.32-2.41]
C24-Printing, Publishing and Recorded Media	6/35	0.31[0.13-0.75]
C241-Printing and Services to Printing	4/15	0.42[0.13-1.31]
C2412-Printing	3/14	0.36[0.10-1.30]
C242-Publishing	2/20	0.20[0.05-0.88]
C2421-Newspaper Printing or Publishing	2/13	0.32[0.07-1.49]
C25-Petroleum, Coal, Chemical and Associated Product Manufacturing	18/34	0.97[0.53-1.78]
C253-Basic Chemical Manufacturing	4/6	1.19[0.32-4.44]
C254-Other Chemical Product Manufacturing	9/15	1.09[0.46-2.59]
C255-Rubber Product Manufacturing	2/8	0.58[0.12-2.84]
C256-Plastic Product Manufacturing	4/6	1.02[0.28-3.78]
C26-Non-Metallic Mineral Product Manufacturing	8/10	1.37[0.52-3.64]
C263-Cement, Lime, Plaster and Concrete Product Manufacturing	6/5	2.11[0.62-7.19]
C27-Metal Product Manufacturing	24/36	1.21[0.69-2.11]
C271-Iron and Steel Manufacturing	7/14	0.85[0.33-2.21]

Industry	Number (Cases/Controls)	OR (95%CI)
C2711-Basic Iron and Steel Manufacturing	4/14	0.48[0.15-1.52]
C274-Structural Metal Product Manufacturing	6/5	1.74[0.51-5.89]
C276-Fabricated Metal Product Manufacturing	9/16	1.16[0.49-2.75]
C2769-Fabricated Metal Product Manufacturing nec	2/12	0.36[0.08-1.69]
C28-Machinery and Equipment Manufacturing	27/47	0.91[0.54-1.53]
C281-Motor Vehicle and Part Manufacturing	8/16	0.77[0.32-1.87]
C2811-Motor Vehicle Manufacturing	6/13	0.74[0.27-2.03]
C282-Other Transport Equipment Manufacturing	7/11	1.14[0.42-3.08]
C2822-Boatbuilding	3/8	0.66[0.17-2.65]
C285-Electrical Equipment and Appliance Manufacturing	3/10	0.59[0.15-2.22]
C286-Industrial Machinery and Equipment Manufacturing	10/15	1.11[0.48-2.60]
C2869-Industrial Machinery and Equipment Manufacturing nec	5/11	0.74[0.24-2.25]
C29-Other Manufacturing	9/17	0.79[0.34-1.85]
C292-Furniture Manufacturing	4/9	0.59[0.18-1.97]
C294-Other Manufacturing	5/8	1.08[0.33-3.52]
D-Electricity, Gas and Water Supply	14/20	1.16[0.57-2.39]
D36-Electricity and Gas Supply	14/20	1.16[0.57-2.39]
D361-Electricity Supply	13/16	1.40[0.65-3.00]
E-Construction	83/100	1.50[1.04-2.14]
E41-General Construction	53/50	1.81[1.16-2.82]
E411-Building Construction	40/43	1.47[0.91-2.38]
E4111-House Construction	31/30	1.59[0.92-2.76]
E4113-Non-Residential Building Construction	7/5	1.98[0.60-6.47]
E412-Non-Building Construction	16/11	2.36[1.05-5.29]
E4121-Road and Bridge Construction	12/6	3.00[1.09-8.30]
E4122-Non-Building Construction nec	4/6	1.06[0.28-3.99]
E42-Construction Trade Services	46/63	1.23[0.80-1.90]
E421-Site Preparation Services	6/5	1.62[0.47-5.55]
E4210-Site Preparation Services	6/5	1.62[0.47-5.55]
E422-Building Structure Services	4/6	1.04[0.27-3.95]
E423-Installation Trade Services	19/20	1.53[0.78-2.98]
E4231-Plumbing Services	6/5	1.86[0.54-6.39]
E4232-Electrical Services	10/10	1.69[0.68-4.24]
E424-Building Completion Services	18/31	1.04[0.56-1.93]

Industry	Number (Cases/Controls)	OR (95%CI)
E4242-Carpentry Services	6/10	1.05[0.36-3.03]
E4244-Painting and Decorating Services	7/13	0.89[0.34-2.29]
E425-Other Construction Services	6/6	1.41[0.43-4.64]
F-Wholesale Trade	32/79	0.66[0.42-1.03]
F45-Basic Material Wholesaling	13/39	0.54[0.28-1.05]
F451-Farm Produce Wholesaling	8/17	0.81[0.33-1.96]
F4519-Farm Produce and Supplies Wholesaling nec	6/10	1.00[0.35-2.90]
F453-Builders Supplies Wholesaling	5/13	0.64[0.22-1.88]
F4539-Building Supplies Wholesaling nec	3/8	0.66[0.17-2.59]
F46-Machinery and Motor Vehicle Wholesaling	8/12	1.03[0.41-2.63]
F461-Machinery and Equipment Wholesaling	6/9	0.98[0.33-2.89]
F47-Personal and Household Good Wholesaling	12/39	0.54[0.27-1.06]
F471-Food, Drink and Tobacco Wholesaling	4/20	0.35[0.12-1.06]
F4719-Grocery Wholesaling nec	3/7	0.84[0.21-3.39]
F479-Other Wholesaling	6/11	0.90[0.32-2.51]
G-Retail Trade	110/194	1.09[0.81-1.48]
G51-Food Retailing	32/66	0.95[0.60-1.52]
G511-Supermarket and Grocery Stores	18/45	0.81[0.45-1.47]
G5110-Supermarket and Grocery Stores	15/41	0.75[0.40-1.41]
G512-Specialised Food Retailing	18/31	1.10[0.59-2.03]
G5124-Bread and Cake Retailing	2/11	0.34[0.07-1.58]
G5125-Takeaway Food Retailing	7/8	1.78[0.61-5.20]
G52-Personal and Household Good Retailing	57/111	0.97[0.67-1.41]
G521-Department Stores	8/26	0.55[0.24-1.27]
G522-Clothing and Soft Good Retailing	17/21	1.93[0.96-3.88]
G5221-Clothing Retailing	9/12	1.79[0.71-4.50]
G523-Furniture, Houseware and Appliance Retailing	13/24	0.92[0.45-1.86]
G5233-Domestic Hardware and Houseware Retailing	3/10	0.43[0.11-1.63]
G5234-Domestic Appliance Retailing	5/7	1.32[0.40-4.29]
G524-Recreational Good Retailing	6/20	0.66[0.25-1.70]
G5243-Newspaper, Book and Stationery Retailing	5/13	0.89[0.30-2.61]
G525-Other Personal and Household Good Retailing	21/28	1.36[0.74-2.50]
G5251-Pharmaceutical, Cosmetic and Toiletry Retailing	6/7	1.32[0.43-4.08]
G5259-Retailing nec	12/6	3.7[1.33-10.24]

Industry	Number (Cases/Controls)	OR (95%CI)
G526-Household Equipment Repair Services	6/6	1.59[0.49-5.18]
G53-Motor Vehicle Retailing and Services	47/48	1.78[1.14-2.78]
G531-Motor Vehicle Retailing	18/9	3.73[1.62-8.60]
G5311-Car Retailing	13/9	2.47[1.02-6.00]
G532-Motor Vehicle Services	37/39	1.62[0.99-2.65]
G5321-Automotive Fuel Retailing	19/9	4.10[1.72-9.78]
G5329-Automotive Repair and Services nec	17/25	1.07[0.55-2.07]
H-Accommodation, Cafes and Restaurants	48/81	1.13[0.75-1.71]
H57-Accommodation, Cafes and Restaurants	48/81	1.13[0.75-1.71]
H571-Accommodation	34/44	1.51[0.92-2.49]
H5710-Accommodation	34/44	1.51[0.92-2.49]
H572-Pubs, Taverns and Bars	6/6	1.55[0.48-5.02]
H573-Cafes and Restaurants	12/38	0.59[0.29-1.17]
H5730-Cafes and Restaurants	8/9	1.68[0.61-4.62]
I-Transport and Storage	58/88	1.20[0.82-1.76]
I61-Road Transport	17/38	0.74[0.39-1.38]
I611-Road Freight Transport	10/31	0.54[0.25-1.16]
I6110-Road Freight Transport	4/9	0.92[0.26-3.30]
I612-Road Passenger Transport	7/11	0.98[0.37-2.63]
I6122-Short Distance Bus Transport (including Tramway)	3/7	0.70[0.17-2.83]
I62-Rail Transport	17/12	2.34[1.09-5.06]
I620-Rail Transport	12/6	3.19[1.16-8.79]
I6200-Rail Transport	9/6	2.27[0.78-6.62]
I63-Water Transport	8/11	1.72[0.64-4.62]
I630-Water Transport	8/11	1.72[0.64-4.62]
I6301-International Sea Transport	3/8	0.87[0.21-3.56]
I64-Air and Space Transport	4/11	0.64[0.20-2.08]
I640-Air and Space Transport	4/9	0.82[0.24-2.74]
I66-Services to Transport	15/20	1.39[0.69-2.81]
I662-Services to Water Transport	4/11	0.71[0.22-2.30]
I664-Other Services to Transport	7/8	1.51[0.52-4.34]
I6641-Travel Agency Services	6/6	1.66[0.51-5.36]
J-Communication Services	33/47	1.43[0.88-2.32]
J71-Communication Services	33/47	1.43[0.88-2.32]

Industry	Number (Cases/Controls)	OR (95%CI)
J711-Postal and Courier Services	25/35	1.47[0.85-2.56]
J7111-Postal Services	19/31	1.25[0.68-2.29]
J712-Telecommunication Services	10/17	1.12[0.49-2.55]
J7120-Telecommunication Services	7/6	2.44[0.78-7.61]
K-Finance and Insurance	32/78	0.79[0.50-1.24]
K73-Finance	20/41	0.97[0.55-1.72]
K732-Deposit Taking Financiers	14/35	0.82[0.42-1.57]
K7321-Banks	14/34	0.85[0.44-1.65]
K74-Insurance	13/27	1.02[0.51-2.05]
K742-Other Insurance	10/27	0.78[0.37-1.67]
K7422-General Insurance	9/27	0.70[0.32-1.54]
K75-Services to Finance and Insurance	8/17	0.80[0.34-1.92]
K751-Services to Finance and Investment	8/11	1.22[0.47-3.15]
K7519-Services to Finance and Investment nec	6/11	0.92[0.33-2.57]
L-Property and Business Services	84/174	0.86[0.62-1.18]
L77-Property Services	16/40	0.70[0.38-1.29]
L771-Property Operators and Developers	8/13	1.08[0.43-2.67]
L7712-Commercial Property Operators and Developers	3/9	0.58[0.15-2.21]
L772-Real Estate Agents	7/20	0.67[0.27-1.62]
L774-Machinery and Equipment Hiring and Leasing	2/9	0.32[0.07-1.51]
L78-Business Services	73/146	0.92[0.66-1.29]
L781-Scientific Research	10/14	1.48[0.62-3.49]
L782-Technical Services	18/31	1.04[0.56-1.92]
L7821-Architectural Services	6/5	2.76[0.80-9.51]
L7823-Consultant Engineering Services	9/15	1.02[0.43-2.41]
L7829-Technical Services nec	3/9	0.51[0.13-2.00]
L783-Computer Services	13/11	2.00[0.86-4.62]
L7834-Computer Consultancy Services	11/8	2.39[0.92-6.15]
L784-Legal and Accounting Services	16/46	0.66[0.36-1.21]
L7841-Legal Services	6/20	0.62[0.24-1.59]
L7842-Accounting Services	10/28	0.65[0.31-1.39]
L785-Marketing and Business Management Services	7/27	0.49[0.21-1.16]
L7851-Advertising Services	2/11	0.34[0.07-1.58]
L7855-Business Management Services	2/11	0.35[0.08-1.64]

Industry	Number (Cases/Controls)	OR (95%CI)
L786-Other Business Services	21/42	1.00[0.56-1.76]
L7861-Employment Placement Services	4/8	1.03[0.30-3.61]
L7864-Security and Investigative Services (except Police)	7/5	2.32[0.70-7.71]
L7866-Cleaning Services	5/14	0.70[0.24-2.07]
L7869-Business Services nec	2/10	0.42[0.09-2.03]
M-Government Administration and Defence	81/148	1.06[0.77-1.46]
M81-Government Administration	61/120	0.99[0.70-1.42]
M811-Government Administration	56/117	0.92[0.64-1.33]
M8111-Central Government Administration	37/73	0.99[0.64-1.54]
M8113-Local Government Administration	17/52	0.61[0.34-1.09]
M82-Defence	25/35	1.36[0.78-2.37]
M820-Defence	25/35	1.36[0.78-2.37]
M8200-Defence	25/35	1.36[0.78-2.37]
N-Education	61/160	0.75[0.52-1.10]
N84-Education	61/160	0.75[0.52-1.10]
N841-Preschool Education	4/8	1.03[0.30-3.58]
N842-School Education	36/102	0.75[0.48-1.16]
N8421-Primary Education	20/52	0.87[0.50-1.54]
N8422-Secondary Education	14/44	0.71[0.37-1.36]
N8423-Combined Primary and Secondary Education	2/17	0.27[0.06-1.19]
N843-Post School Education	23/44	1.11[0.63-1.94]
N8431-Higher Education	13/37	0.72[0.36-1.42]
N8432-Technical and Further Education	9/9	2.17[0.83-5.71]
N844-Other Education	11/45	0.51[0.25-1.02]
N8440-Other Education	5/5	2.56[0.72-9.16]
O-Health and Community Services	63/139	0.96[0.66-1.39]
O86-Health Services	46/108	0.92[0.61-1.39]
O861-Hospitals and Nursing Homes	27/73	0.79[0.48-1.29]
O8611-Hospitals (except Psychiatric Hospitals)	26/69	0.81[0.49-1.33]
O862-Medical and Dental Services	9/32	0.61[0.28-1.33]
O8621-General Practice Medical Services	5/19	0.54[0.19-1.51]
O8623-Dental Services	2/12	0.40[0.09-1.83]
O863-Other Health Services	14/25	1.18[0.59-2.38]
O8639-Health Services nec	12/17	1.67[0.76-3.66]

Industry	Number (Cases/Controls)	OR (95%CI)
O87-Community Services	28/51	1.25[0.74-2.11]
O871-Child Care Services	5/13	0.97[0.33-2.87]
O872-Community Care Services	24/37	1.47[0.83-2.61]
O8721-Accommodation for the Aged	6/18	0.69[0.26-1.81]
O8722-Residential Care Services nec	11/15	1.47[0.64-3.36]
O8729-Non-Residential Care Services nec	7/6	3.49[1.09-11.22]
P-Cultural and Recreational Services	35/56	1.23[0.77-1.95]
P91-Motion Picture, Radio and Television Services	5/7	1.52[0.47-4.97]
P92-Libraries, Museums and the Arts	13/25	1.07[0.53-2.19]
P921-Libraries	6/9	1.95[0.66-5.78]
P924-Arts	5/10	0.92[0.30-2.81]
P9242-Creative Arts	2/9	0.40[0.08-1.90]
P93-Sport and Recreation	19/27	1.25[0.67-2.33]
P931-Sport	11/14	1.32[0.58-3.01]
P9312-Sports Grounds and Facilities nec	5/7	1.24[0.38-4.08]
P933-Other Recreation Services	7/9	1.50[0.53-4.23]
Q-Personal and Other Services	49/68	1.32[0.88-2.00]
Q95-Personal Services	19/30	1.08[0.59-2.00]
Q952-Other Personal Services	19/29	1.13[0.61-2.10]
Q9521-Laundries and Dry-Cleaners	3/9	0.59[0.16-2.26]
Q9525-Gardening Services	6/10	0.88[0.31-2.51]
Q9526-Hairdressing and Beauty Salons	4/9	0.80[0.23-2.76]
Q96-Other Services	29/39	1.37[0.82-2.30]
Q961-Religious Organisations	7/11	1.48[0.55-4.01]
Q962-Interest Groups	13/13	1.92[0.85-4.32]
Q9629-Interest Groups nec	7/6	1.87[0.61-5.78]
Q963-Public Order and Safety Services	11/16	1.04[0.47-2.33]
Q9631-Police Services	7/8	1.58[0.55-4.52]

OR adjusted for Age, Sex, Ethnicity, Highest Education Level, Socioeconomic Deprivation Status and Smoking.
Results were based on at least 10 subjects (cases + controls).
"Response outside scope" was used for responses, such as 'housewife', 'pensioner' or 'student', which are not covered by NZSCO99.

Table S3.6. Supplementary Table. Odds Ratios (OR) and 95% CIs for Occupation Lag Time

Occupation	20 Years Lag -Time		15 Years Lag -Time		10 Years Lag -Time		5 Years Lag -Time		Ever vs. Never	
	Cases/Controls (n)	OR (95%CI)-20y	Cases/Controls (n)	OR (95%CI)-15y	Cases/Controls (n)	OR (95%CI)-10y	Cases/Controls (n)	OR (95%CI)-5y	Cases/Controls (n)	OR (95%CI)
0-Response Outside Scope	73/168	0.91[0.63-1.29]	77/182	0.84[0.60-1.19]	80/192	0.82[0.59-1.15]	85/203	0.82[0.59-1.14]*	92/210	0.86[0.63-1.19]
1-Legislators, Administrators and Managers	60/141	0.72[0.51-1.03]*	67/154	0.73[0.52-1.02]*	75/160	0.79[0.57-1.10]	81/165	0.83[0.60-1.15]	84/169	0.83[0.60-1.14]
2-Professionals	101/228	0.86[0.61-1.20]	103/236	0.80[0.57-1.12]	107/246	0.78[0.56-1.09]	108/252	0.75[0.54-1.05]*	109/254	0.75[0.54-1.05]*
232-Secondary Teaching Professionals	10/36	0.63[0.30-1.33]	10/37	0.60[0.29-1.28]	10/42	0.52[0.25-1.09]*	10/42	0.53[0.25-1.10]*	9/41	0.50[0.23-1.07]*
2411-Accountants	8/25	0.56[0.25-1.28]	8/27	0.52[0.23-1.17]	8/28	0.50[0.22-1.11]*	8/29	0.48[0.21-1.07]*	8/30	0.46[0.20-1.02]*
3-Technicians and Associate Professionals	87/169	0.97[0.71-1.33]	96/178	1.03[0.76-1.40]	99/187	0.99[0.73-1.34]	103/191	1.02[0.76-1.38]	103/197	0.97[0.72-1.32]
311-Physical Science and Engineering Technicians	28/33	1.79[1.03-3.09]**	28/34	1.73[1.00-2.99]**	28/34	1.74[1.01-3.00]**	28/35	1.69[0.98-2.91]*	28/35	1.69[0.98-2.91]*
31141-Telecommunications Technician	8/4	4.21[1.21-14.69]**	8/4	4.21[1.21-14.68]**	8/4	4.22[1.21-14.71]**	8/4	4.21[1.21-14.67]	8/4	4.2[1.20-14.64]**
31181-Draughting Technician	9/7	2.99[1.06-8.46]**	9/7	2.97[1.05-8.39]**	9/7	2.96[1.05-8.37]**	9/7	2.98[1.05-8.40]**	9/7	3.02[1.07-8.53]**
3342-Education Associate Professionals	2/18	0.26[0.06-1.14]*	2/18	0.26[0.06-1.15]*	2/19	0.23[0.05-1.04]*	2/19	0.24[0.05-1.04]*	2/20	0.23[0.05-1.00]**
33422-Teacher Aide	2/17	0.27[0.06-1.22]*	2/17	0.28[0.06-1.23]*	2/18	0.25[0.06-1.10]*	2/18	0.25[0.06-1.10]*	2/19	0.24[0.05-1.05]*
3361-Authors, Journalists and Other Writers	1/11	0.20[0.02-1.57]	1/12	0.17[0.02-1.36]*	1/12	0.17[0.02-1.37]*	1/12	0.17[0.02-1.37]*	1/12	0.17[0.02-1.36]*
4-Clerks	85/218	0.66[0.48-0.92]**	87/227	0.65[0.47-0.90]**	89/231	0.65[0.47-0.90]**	89/234	0.63[0.46-0.88]**	90/238	0.62[0.45-0.86]**
41-Office Clerks	75/189	0.69[0.49-0.97]**	76/196	0.67[0.48-0.94]**	80/198	0.72[0.51-1.00]**	80/200	0.70[0.51-0.98]**	82/204	0.70[0.51-0.98]**
41311-Stock Clerk	3/14	0.35[0.10-1.26]	3/14	0.35[0.10-1.26]	3/14	0.35[0.10-1.26]	3/15	0.32[0.09-1.14]*	3/16	0.29[0.08-1.02]*
414-Library, Mail and Related Clerks	47/128	0.66[0.45-0.97]**	47/134	0.62[0.42-0.91]**	52/136	0.69[0.48-1.01]*	52/137	0.69[0.47-1.00]*	52/139	0.67[0.46-0.98]**
4144-Office Clerks	35/119	0.52[0.34-0.79]**	36/125	0.50[0.33-0.76]**	41/126	0.58[0.39-0.87]**	41/127	0.58[0.39-0.86]**	42/129	0.58[0.39-0.87]**
41443-General Clerk	30/110	0.48[0.31-0.75]**	30/116	0.45[0.29-0.71]**	32/118	0.48[0.31-0.74]**	32/119	0.47[0.31-0.73]**	33/121	0.48[0.31-0.73]**
5-Service and Sales Workers	116/184	1.40[1.03-1.91]**	123/192	1.45[1.07-1.97]**	128/196	1.51[1.11-2.05]**	129/203	1.43[1.05-1.93]**	130/205	1.41[1.04-1.90]**
51-Personal and Protective Services Workers	74/114	1.36[0.96-1.93]*	81/121	1.42[1.01-2.00]**	84/126	1.42[1.01-1.99]**	87/131	1.41[1.01-1.97]**	89/131	1.46[1.05-2.04]**
51235-Kitchenhand	6/6	2.35[0.72-7.61]	7/6	2.71[0.87-8.42]*	8/7	2.58[0.90-7.39]*	8/7	2.60[0.90-7.44]*	8/7	2.51[0.87-7.21]*
52113-Forecourt Attendant	9/1	13.41[1.67-108]**	10/1	14.85[1.87-118.23]**	10/1	14.76[1.85-117.53]**	11/1	17.55[2.22-139.04]**	11/2	8.31[1.79-38.54]**
6-Agriculture and Fishery Workers	97/130	1.71[1.23-2.37]**	102/134	1.77[1.28-2.46]**	102/139	1.66[1.20-2.30]**	105/140	1.72[1.25-2.37]**	106/144	1.66[1.21-2.29]**
61-Market Oriented Agricultural and Fishery Workers	97/130	1.71[1.23-2.37]**	102/134	1.77[1.28-2.46]**	102/139	1.66[1.20-2.30]**	105/140	1.72[1.25-2.37]**	106/144	1.66[1.21-2.29]**
611-Market Farmers and Crop Growers	37/34	2.47[1.48-4.11]**	40/36	2.51[1.53-4.13]**	40/43	2.00[1.25-3.21]**	46/43	2.33[1.47-3.68]**	47/46	2.15[1.37-3.38]**
6111-Field Crop and Vegetable Growers	10/7	3.02[1.07-8.50]**	10/7	3.06[1.09-8.60]**	10/8	2.60[0.96-7.02]*	11/8	3.01[1.13-7.97]**	11/8	2.93[1.10-7.77]**
61112-Market Gardener and Related Worker	8/4	4.06[1.17-14.15]**	8/4	4.11[1.18-14.31]**	8/4	4.11[1.18-14.33]**	8/4	4.13[1.19-14.39]**	8/4	3.98[1.14-13.88]**
6112-Fruit Growers	17/18	2.12[1.04-4.33]**	20/20	2.17[1.12-4.23]**	20/23	1.83[0.96-3.47]*	22/23	2.04[1.09-3.84]**	23/24	2.03[1.09-3.78]**
61121-Fruit Grower, Worker	17/18	2.12[1.04-4.33]**	18/20	1.96[0.99-3.88]*	18/21	1.83[0.93-3.60]*	20/21	2.07[1.07-4.01]**	20/21	2.07[1.07-4.02]**

Occupation	20 Years Lag -Time		15 Years Lag -Time		10 Years Lag -Time		5 Years Lag -Time		Ever vs. Never	
	Cases/Controls (n)	OR (95%CI)-20y	Cases/Controls (n)	OR (95%CI)-15y	Cases/Controls (n)	OR (95%CI)-10y	Cases/Controls (n)	OR (95%CI)-5y	Cases/Controls (n)	OR (95%CI)
6113-Gardeners and Nursery Growers	14/11	2.65[1.15-6.07]**	14/12	2.42[1.08-5.43]**	14/15	1.87[0.87-4.02]	19/16	2.32[1.15-4.69]**	20/19	1.96[1.01-3.82]**
61133-Grounds or Green Keeper	7/3	4.94[1.24-19.75]**	7/4	3.71[1.05-13.12]**	7/5	2.77[0.85-9.05]*	11/5	4.14[1.38-12.39]**	12/7	3.01[1.14-7.96]**
6125-Crop and Livestock Producers	13/9	4.11[1.56-10.83]**	13/9	4.12[1.57-10.83]**	13/9	4.09[1.56-10.77]**	14/10	3.61[1.45-9.02]**	14/10	3.61[1.44-9.02]**
61251-Crop and Livestock Farmer, Worker	13/9	4.11[1.56-10.83]**	13/9	4.12[1.57-10.83]**	13/9	4.09[1.56-10.77]**	14/10	3.61[1.45-9.02]**	14/10	3.61[1.44-9.02]**
614-Fishery Workers, Hunters and Trappers	6/2	-	7/2	-	7/3	5.61[1.26-24.92]**	7/3	5.61[1.26-24.91]**	7/3	5.62[1.27-24.97]**
7-Trades Workers	87/120	1.28[0.89-1.85]	89/122	1.29[0.90-1.86]	93/124	1.35[0.94-1.93]	93/127	1.29[0.90-1.85]	93/128	1.28[0.89-1.83]
71-Building Trades Workers	52/41	2.25[1.41-3.59]**	54/44	2.17[1.37-3.42]**	57/46	2.20[1.40-3.44]**	57/48	2.10[1.34-3.27]**	57/49	2.02[1.30-3.14]**
711-Building Frame and Related Trades Workers	30/23	2.07[1.14-3.74]**	31/25	1.97[1.11-3.52]**	33/25	2.11[1.19-3.73]**	33/27	1.94[1.11-3.40]**	33/27	1.93[1.10-3.39]**
7112-Carpenters and Joiners	30/21	2.20[1.20-4.02]**	31/23	2.09[1.16-3.76]**	32/23	2.16[1.20-3.86]**	32/25	1.98[1.12-3.50]**	32/25	1.97[1.11-3.48]**
71122-Builder (Including Contractor)	22/9	3.98[1.77-8.94]**	22/11	3.31[1.55-7.10]**	23/11	3.45[1.62-7.34]**	23/13	2.92[1.42-5.99]**	23/13	2.90[1.41-5.96]**
713-Electricians	14/6	3.82[1.41-10.34]**	15/6	4.09[1.53-10.95]**	16/8	3.23[1.33-7.84]**	16/8	3.23[1.33-7.84]**	16/8	3.21[1.32-7.79]**
7131-Electricians	14/6	3.82[1.41-10.34]**	15/6	4.09[1.53-10.95]**	16/8	3.23[1.33-7.84]**	16/8	3.23[1.33-7.84]**	16/8	3.21[1.32-7.79]**
71311-Electrician	14/4	5.69[1.81-17.87]**	14/4	5.68[1.81-17.82]**	14/6	3.63[1.34-9.79]**	14/6	3.62[1.34-9.77]**	14/6	3.61[1.34-9.74]**
741-Food and Related Products Processing Trades Workers	1/10	0.15[0.02-1.23]*	1/10	0.15[0.02-1.24]*	1/10	0.15[0.02-1.24]*	1/9	0.15[0.02-1.25]*	1/10	0.15[0.02-1.19]*
8-Plant and Machine Operators and Assemblers	75/107	1.26[0.87-1.81]	81/111	1.34[0.94-1.91]	84/114	1.36[0.95-1.93]*	90/119	1.41[0.99-1.99]*	92/120	1.42[1.01-2.01]**
9-Elementary Occupations (incl Residuals)	69/109	1.21[0.84-1.73]	74/109	1.34[0.94-1.91]	78/110	1.43[1.00-2.03]**	80/110	1.47[1.04-2.08]**	80/111	1.44[1.01-2.04]**
9151-Labourers	42/53	1.46[0.92-2.33]	43/53	1.50[0.94-2.38]*	45/55	1.51[0.96-2.38]*	47/55	1.57[1.00-2.46]**	48/55	1.61[1.03-2.52]**
91512-Builder's Labourer	6/5	2.35[0.68-8.11]	6/5	2.34[0.68-8.07]	8/5	2.94[0.91-9.45]*	8/5	2.93[0.91-9.43]*	8/5	2.94[0.91-9.49]*

OR adjusted for Age, Sex, Ethnicity, Highest Education Level, Socioeconomic Deprivation Status and Smoking.
Results include all broad occupation categories (all 1-digit), and for specific occupations (2-5 digits) if the association for ever vs. never, 5 years lag, 10 years lag, 15years lag and 20years lag employed in the specific occupation was statistically significant (p<0.05) and borderline (p<0.1).
**p<0.05, *p<0.1
Results were based on at least 10 subjects (cases + controls).
"Response outside scope" was used for responses, such as 'housewife', 'pensioner' or 'student', which are not covered by NZSCO99

Table S3.7. Supplementary Table. Odds Ratios (OR) and 95% CIs for Occupations adjusted by interview methods

Occupation	Never/Ever		
	N (Cases/Controls)	OR1 (95%CI)	OR2 (95%CI)
1-Legislators, Administrators and Managers	84/169	0.83[0.60-1.14]	0.78[0.54-1.13]
2-Professionals	109/254	0.75[0.54-1.05]	0.82[0.56-1.21]
3-Technicians and Associate Professionals	103/197	0.97[0.72-1.32]	0.92[0.65-1.30]
31141-Telecommunications Technician	8/4	4.20[1.20-14.64]*	3.75[0.89-15.74]
3118-Draughting Technicians	9/7	3.02[1.07-8.53]*	2.65[0.84-8.38]
3342- Education Associate Professionals	2/20	0.23[0.05-1.00]*	0.26[0.05-1.26]
4-Clerks	90/238	0.62[0.45-0.86]*	0.67[0.46-0.96]*
5-Service and Sales Workers	130/205	1.40[1.04-1.90]*	1.27[0.90-1.79]
51-Personal and Protective Services Workers	89/131	1.46[1.04-2.04]*	1.47[1.00-2.16]
52113-Forecourt Attendant	11/2	8.31[1.79-38.54]*	7.05[1.32-37.61]*
6-Agriculture and Fishery Workers	106/144	1.66[1.21-2.29]*	1.56[1.08-2.26]*
61-Market Oriented Agricultural and Fishery Workers	106/144	1.66[1.21-2.29]*	1.56[1.08-2.26]*
611-Market Farmers and Crop Growers	47/46	2.15[1.37-3.38]*	2.04[1.23-3.39]*
6111-Field Crop and Vegetable Growers	11/8	2.93[1.10-7.77]*	1.98[0.67-5.89]
61112-Market Gardener and Related Worker	8/4	3.98[1.14-13.88]*	2.47[0.60-10.17]
6112-Fruit Growers	23/24	2.03[1.09-3.78]*	2.41[1.19-4.89]*
61121-Fruit Grower, Worker	20/21	2.07[1.07-4.02]*	2.17[1.01-4.66]*
6113-Gardeners and Nursery Growers	20/19	1.96[1.01-3.82]*	1.75[0.84-3.64]
61133-Grounds or Green Keeper	12/7	3.01[1.14-7.96]*	2.70[0.91-7.96]
6125-Crop and Livestock Producers	14/10	3.61[1.44-9.02]*	4.88[1.73-13.78]*
614-Fishery Workers, Hunters and Trappers	7/3	5.62[1.27-24.97]*	3.09[0.52-18.23]
7-Trades Workers	93/128	1.28[0.89-1.83]	1.13[0.75-1.69]
71-Building Trades Workers	57/49	2.02[1.30-3.14]*	2.03[1.21-3.38]*
711-Building Frame and Related Trades Workers	33/27	1.93[1.10-3.39]*	1.68[0.88-3.22]
7112-Carpenters and Joiners	32/25	1.97[1.11-3.48]*	1.82[0.94-3.54]
71122-Builder (Including Contractor)	23/13	2.90[1.41-5.96]*	2.92[1.28-6.68]*
71311-Electrician	14/6	3.61[1.34-9.74]*	3.74[1.16-12.02]*
8-Plant and Machine Operators and Assemblers	92/120	1.42[1.01-2.01]*	1.29[0.87-1.92]
9-Elementary Occupations (incl Residuals)	80/111	1.44[1.01-2.04]*	1.35[0.90-2.02]
9151-Labourers	48/55	1.61[1.03-2.52]*	1.39[0.83-2.34]

OR1 adjusted for Age, Sex, Ethnicity, Highest Education Level, Socioeconomic Deprivation Status and Smoking.

OR2 adjusted for Age, Sex, Ethnicity, Highest Education Level, Socioeconomic Deprivation Status, Smoking and Interview Method.

The table includes results for all broad occupation categories (1-digit), and for specific occupations (2-5 digits) if the association for ever vs. never employed was statistically significant ($p<0.05$).

Results were based on at least 10 subjects (cases + controls). *$p<0.05$

Table S3.8. Supplementary Table. Urban/Rural residence (as recorded on the Electoral Roll) for participants and non-participants

	All study subject					Participants					Non-Participants					Controls				
	Cases (N=396)		Controls (N=2400)		*P*	Cases (N=321)		Controls (N=605)		*P*	Cases (N=75)		Controls (N=1795)		*P*	Participants (N=605)		Non-Participants (N=1795)		*P*
Urban/Rural living	N	%	N	%	0.69	N	%	N	%	0.45	N	%	N	%	0.92	N	%	N	%	0.01
Urban	334	84.34	2043	85.12		269	83.80	495	81.82		65	86.67	1548	86.24		495	81.82	1548	86.24	
Rural	62	15.66	357	14.88		52	16.20	110	18.18		10	13.33	247	13.76		110	18.18	247	13.76	

Urban area including main urban area, secondary urban area, and minor urban area.
Rural area including rural central and rural including offshore islands.
• main urban area – city or major centre with a population of > 30,000.
• secondary urban area – larger regional centres with a population of 10,000-29,999.
• minor urban area – urbanised settlement centred around a smaller town with a population of 1,000 – 9,999.
• rural central – an area outside the urban centres (described above) which does not incorporate coastal areas and off-shore islands.
• rural including offshore islands -an area outside the urban centres (described above) which incorporates coastal areas and off-shore islands.
Geographic definitions by Statistics New Zealand.

Table S3.9. Supplementary Table. Occupation (as recorded on the Electoral Roll) for participating and non-participating Controls

Occupation	Non-Participants Controls		Participants Controls		P
Occupation-1 Digit	**(N=1795)**	**%**	**(N=605)**	**%**	<.0001
0-Response Outside Scope*	874	48.69	246	40.66	
1-Legislators, Administrators and Managers	118	6.57	51	8.43	
2-Professionals	135	7.52	109	18.02	
3-Technicians and Associate Professionals	85	4.74	40	6.61	
4-Clerks	63	3.51	27	4.46	
5-Service and Sales Workers	87	4.85	22	3.64	
6-Agriculture and Fishery Workers	77	4.29	28	4.63	
7-Trades Workers	101	5.63	23	3.80	
8-Plant and Machine Operators and Assemblers	56	3.12	20	3.31	
9-Elementary Occupations (incl Residuals)	199	11.08	39	6.44	
Occupation-2 Digit	**(N=1795)**	**%**	**(N=605)**	**%**	<.0001
00-Response Outside Scope*	874	48.69	246	40.66	
11-Legislators and Administrators	6	0.33	2	0.33	
12-Corporate Managers	112	6.24	49	8.10	
21-Physical, Mathematical and Engineering Science Professionals	42	2.34	23	3.80	
22-Life Science and Health Professionals	21	1.17	19	3.14	
23-Teaching Professionals	29	1.61	37	6.11	
24-Other Professionals	43	2.40	30	4.95	
31-Physical Science and Engineering Associate Professionals	31	1.73	9	1.49	
32-Life Science and Health Associate Professionals	3	0.17	3	0.50	
33-Other Associate Professionals	51	2.84	28	4.63	
41-Office Clerks	53	2.95	23	3.80	
42-Customer Services Clerks	10	0.56	4	0.66	
51-Personal and Protective Services Workers	50	2.79	11	1.82	
52-Salespersons, Demonstrators and Models	37	2.06	11	1.82	
61-Market Oriented Agricultural and Fishery Workers	77	4.29	28	4.63	
71-Building Trades Workers	59	3.29	16	2.64	
72-Metal and Machinery Trades Workers	28	1.56	4	0.66	
73-Precision Trades Workers	3	0.17	1	0.17	
74-Other Craft and Related Trades Workers	11	0.61	2	0.33	
81-Industrial Plant Operators	4	0.22	2	0.33	
82-Stationary Machine Operators and Assemblers	20	1.11	9	1.49	
83-Drivers and Mobile Machinery Operators	27	1.50	7	1.16	
84-Building and Related Workers	5	0.28	2	0.33	
91-Labourers and Related Elementary Service Workers	49	2.73	9	1.49	
97-Response Unidentifiable	22	1.23	0	0	
99-Not Stated	128	7.13	30	4.96	

*Response outside scope was used for responses, such as 'housewife', 'pensioner' or 'student', which are not covered by NZSCO99.

Table S3.10. Supplementary Table. Odds Ratios (OR) and 95% CIs for Occupation Stratified by Gender

Occupational Title	Male (Cases/Controls) (n)	OR (95% CI)	Female (Cases/Controls) (n)	OR (95% CI)
1-Legislators, Administrators and Managers	54/111	0.61[0.40-0.93]*	30/58	1.26[0.73-2.15]
1222-Finance and Administration Managers	9/31	0.44[0.20-0.98]*	8/4	4.98[1.38-17.99]*
2-Professionals	52/120	0.54[0.33-0.88]*	57/134	0.98[0.59-1.63]
2411-Accountants	3/19	0.25[0.07-0.90]*	5/11	0.93[0.30-2.89]
3-Technicians and Associate Professionals	67/105	1.13[0.76-1.67]	36/92	0.77[0.47-1.28]
311-Physical Science and Engineering Technicians	23/25	1.98[1.05-3.77]*	5/10	1.26[0.40-3.95]
4-Clerks	32/83	0.57[0.35-0.91]*	58/155	0.70[0.43-1.12]
41443-General Clerk	14/46	0.49[0.26-0.94]*	19/75	0.44[0.24-0.80]*
5-Service and Sales Workers	67/77	1.52[1.01-2.30]*	63/128	1.26[0.78-2.04]
51316-Care Giver	0/2	-	11/11	2.65[1.04-6.79]*
52113-Forecourt Attendant	9/2	6.21[1.28-30.10]*	2/0	-
6-Agriculture and Fishery Workers	76/96	1.65[1.10-2.47]*	30/48	1.67[0.95-2.96]
61-Market Oriented Agricultural and Fishery Workers	76/96	1.65[1.10-2.47]*	30/48	1.67[0.95-2.96]
611-Market Farmers and Crop Growers	32/23	2.64[1.46-4.78]*	15/23	1.76[0.82-3.77]
6112-Fruit Growers	15/9	2.99[1.24-7.16]*	8/15	1.45[0.55-3.85]
61121-Fruit Grower, Worker	13/9	2.68[1.09-6.58]*	7/12	1.62[0.56-4.70]
7-Trades Workers	84/116	1.19[0.79-1.77]	9/12	1.86[0.73-4.76]
71-Building Trade Workers	53/48	1.85[1.15-2.96]*	4/1	-
71122-Builder (Including Contractor)	21/13	2.65[1.25-5.62]*	2/0	-
71311-Electrician	14/6	3.61[1.31-9.96]*	0/0	-
8-Plant and Machine Operators and Assemblers	78/94	1.50[1.00-2.25]	14/26	1.33[0.63-2.80]
9-Elementary Occupations (incl Residuals)	57/70	1.47[0.95-2.27]	23/41	1.50[0.80-2.82]

OR adjusted for age, ethnicity, highest education level, socioeconomic status (SES) and smoking. To reduce the number of associations presented here, the table only includes results for all broad occupation categories (all 1-digit occupation codes), irrespective of the statistical significance of the association, as well as results for specific occupations (2-5 digits) if the association was statistically significant ($p<0.05$) for either men or women, as well as based on at least 10 subjects (cases+controls). *$p<0.05$

Table S3.11. Supplementary Table. Odds Ratios (OR) and 95% CIs for Industry Stratified by Gender

Industry Title	Male (Cases/Controls) (n)	OR (95% CI)	Female (Cases/Controls) (n)	OR (95% CI)
A-Agriculture, Forestry and Fishing	69/98	1.30[0.87-1.96]	32/51	1.61[0.92-2.81]
A01-Agriculture	61/78	1.56[1.02-2.40]*	31/45	1.89[1.07-3.34]*
A011-Horticulture and Fruit Growing	19/17	2.06[1.02-4.16]*	17/23	2.08[0.99-4.39]
A0119-Fruit Growing nec	10/6	2.95[1.02-8.52]*	10/7	5.87[1.80-19.08]*
B-Mining	15/11	2.43[1.05-5.58]*	/	-
B14-Other Mining	7/3	5.53[1.36-22.51]*	/	-
C-Manufacturing	93/143	1.04[0.72-1.52]	38/94	0.91[0.55-1.51]
E-Construction	74/86	1.51[1.00-2.26]*	9/14	1.84[0.74-4.56]
E41-General Construction	50/47	1.83[1.14-2.94]*	/	-
E412-Non-Building Construction	15/11	2.42[1.04-5.61]*	/	-
E4121-Road and Bridge Construction	11/6	2.93[1.02-8.40]*	/	-
F-Wholesale Trade	23/52	0.58[0.33-1.02]	9/27	0.88[0.39-1.98]
G-Retail Trade	62/94	1.02[0.68-1.53]	47/99	1.07[0.66-1.75]
G53-Motor Vehicle Retailing and Services	34/38	1.54[0.91-2.61]	13/10	3.49[1.35-8.99]*
G531-Motor Vehicle Retailing	12/6	3.60[1.28-10.16]*	/	-
G5321-Automotive Fuel Retailing	13/7	3.07[1.14-8.23]*	/	-
I-Transport and Storage	44/66	1.17[0.74-1.84]	14/21	1.43[0.68-3.03]
L-Property and Business Services	47/87	0.83[0.53-1.27]	37/85	0.89[0.54-1.47]
N-Education	23/54	0.83[0.47-1.48]	38/106	0.74[0.44-1.26]
O-Health and Community Services	15/31	0.77[0.39-1.54]	47/108	1.01[0.63-1.61]
O8729-Non-Residential Care Services nec	1/0	-	5/6	3.76[1.07-13.26]*
P-Cultural and Recreational Services	22/20	1.90[0.98-3.68]	13/36	0.71[0.35-1.46]
P93-Sport and Recreation	14/8	3.01[1.18-7.70]*	5/19	0.44[0.15-1.29]
P931-Sport	10/4	4.30[1.26-14.75]*	1/10	0.20[0.02-1.65]

OR adjusted for Age, Ethnicity, Highest Education Level, Socioeconomic Deprivation Status and Smoking.
The table includes results for all broad industry categories (1-digit), and for specific industries (2-5 digits) if the association for ever vs. never employed was statistically significant ($p<0.05$).
Results are based on at least 10 subjects (cases + controls). *$p<0.05$

CHAPTER 4 Occupational exposure to Electric Shocks and Extremely Low-Frequency Magnetic Fields and Motor Neurone Disease

Grace Chen[1], Andrea 't Mannetje[1], Jeroen Douwes[1], Leonard H. van den Berg[2], Neil Pearce[3], Hans Kromhout[4], Bill Glass[1], Naomi Brewer[1], Dave McLean[1]

[1] Centre for Public Health Research, Massey University, Wellington, New Zealand.

[2] Brain Centre Rudolf Magnus, Department of Neurology, University Medical Centre, Utrecht, The Netherlands.

[3] Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom.

[4] Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands

(Published in American Journal of Epidemiology 2021;190(3):393-402)

ABSTRACT

In a New Zealand population-based case-control study we assessed associations with occupational exposure to electric shocks and extremely low-frequency magnetic fields (ELF-MF) and motor neurone disease (MND) using Job-exposure matrices to assess exposure. Associations with ever/never, duration, and cumulative exposure were assessed using logistic regression adjusted for age, sex, ethnicity, socioeconomic status, education, smoking, alcohol consumption, sports, head or spine injury and solvents, and mutually adjusted for the other exposure. All analyses were repeated stratified by sex. An elevated risk was observed for having ever worked in a job with potential for electric shocks (odds ratio (OR)=1.35, 95% confidence interval (CI): 0.98, 1.86), with the strongest association for the highest level of exposure (OR=2.01, 95%CI: 1.31, 3.09). Analysis by duration suggested a non-linear association: risk was increased for both short-duration (<3 years) (OR= 4.69, 95%CI: 2.25, 9.77) and long-duration in a job with high level of electric shock exposure (>24 years; OR=1.88; 95%CI: 1.05, 3.36), with less pronounced associations for intermediate durations. No association with ELF-MF was found. Our findings provide support for an association between occupational exposure to electric shocks and MND but did not show associations with exposure to work-related ELF-MF.

4.1 Introduction

Motor neurone diseases (MND) are a group of progressive, terminal neurodegenerative conditions for which there is no cure. Amyotrophic Lateral Sclerosis (ALS) is the most common form, accounting for 85% of cases, with other forms including Progressive Muscular Atrophy(PMA), Progressive Bulbar Palsy and Primary Lateral Sclerosis.[454] Several environmental and occupational exposures have been associated with MND, but the only established risk factors to date are older age, male sex, military service, and a family history of MND.[28] An association with work in "electrical occupations" has been observed in a number of studies,[30 36 48 187 279 284] with exposure to both extremely low-frequency magnetic fields (ELF-MF) and electric shocks suggested as risk factors.[185 455-457] Exposure to ELF-MF and electric shocks have been considered in a number of studies with different designs, but findings have been inconsistent, with some showing positive associations with electric shocks,[280 322] whereas no association was found in other studies.[180 187 326] Similarly, occupational exposure to ELF-MF was associated with MND in some studies[47 285 288] but not in others.[273 289]

The few studies that investigated both exposures within the same study, using job-exposure-matrices (JEMs), have also provided conflicting findings.[48 264 277 281 282] In particular, a US case-control study, using only the main occupation registered on death certificates to assess exposure, found a weak positive association with ELF-MF, but an inverse association with electric shocks.[277] In addition, a Swedish population-based case-control study found no association between exposure to ELF-MF and ALS, while an association with electric shocks was observed, but only in people aged <65 years.[48] Also, cohort studies from the Netherlands and Switzerland, both with incomplete job histories, showed an increased risk of ALS with ELF-MF, but not electric shocks.[264 282]

However, the most recent study, using pooled data from three European case-control studies with life-time job histories, showed that both ever exposure to ELF-MF and ever exposure to the potential for electric shocks above background level were associated with ALS.[281]

We have previously reported that both electricians and telecommunication technicians (among other occupations) had elevated risks of MND,[458] and have now assessed associations with occupational exposure to ELF-MF and potential for electric shocks using JEMs applied to lifetime occupational histories.

4.2 Methods

The detailed background information on the study population recruitment and data collection methodology of this population-based case-control study is provided in Appendix 1.

4.2.1 Study population

As reported previously,[458] the study population consisted of 396 incident and prevalent cases with a diagnosis of MND. Cases were recruited primarily through the MND Association (MNDANZ) register over a period of three years (2013-2016), supplemented with searches (2013-2015) of the National Minimum Dataset, which holds records of all hospital outpatients, for individuals with a primary or secondary diagnosis of MND (ICD 10 code-G122).[441] The inclusion criterion for cases was a diagnosis by a neurologist, including all forms of MND. Controls were randomly selected from the New Zealand Electoral Roll (2008), two per case, frequency matched by age (based on the age-distribution of the United Kingdom MND incidence distribution)[81] and sex. Controls with any other neurodegenerative disease such as Parkinson's and Alzheimer's disease were excluded based on their response to the questionnaire, as these diseases can affect memory and cognition, and may also be related to occupational exposure of ELF-MF.[289]

Participation rates were 92% for cases (n=321) and 48% for controls (n=605). All participants gave written informed consent. Ethics approval was provided by the Multi-region Ethics Committee in New Zealand (MEC/12/01/005).

4.2.2 Data collection

Data on demographic and personal characteristics, family history, lifestyle factors, and a lifetime occupational history were collected using questionnaires as described previously.[458] All jobs were assigned a New Zealand Standard Classification of Occupations (NZSCO99) [443] five-digit code and the industry was coded according to the Australian and New Zealand Standard Industrial Classification 1996.[444]

4.2.3 Exposure assessment

We applied JEMs for potential for electric shocks[459] and ELF-MF exposure.[460] The electric shocks JEM was developed by Huss et al.[459] based on pooled national accident registry data from five European countries and reflects the potential for electric injury for each three-digit code of the International Standard Classification of Occupation 1988 (ISCO88). This JEM categorised jobs into low (background), medium and high potential for electric injury.

The ELF-MF JEM was developed in The Netherlands[460] as a modified version of the JEM developed by Bowman et al.[461] based on magnetic fields measurements taken on or near workers from 10 studies in the United States, Sweden, New Zealand, Finland, and Italy. It reflects both intensity and probability of exposure to magnetic flux density for each job (the 4-digit code of ISCO88) on a scale of low (background), medium and high. The median intensity of these magnetic field categories were 0.11μT for background, 0.19 μT for low and 0.52 μT for high exposure.

In order to apply the JEMs, occupations of study participants were re-coded from New Zealand Standard Classification of Occupations 1999 to International Standard Classification of Occupation 1988 using a correspondence table.

Participants who ever had a job with exposure above background level were considered as exposed; those who never worked in an occupation with exposure above background level served as the reference category.

Duration of exposure was defined as the number of years with exposures above background level. Cumulative exposure was expressed as unit-years, which was calculated as the product of the level of exposure (using arbitrary units 0 for background, 1 for medium and 4 for high level/probability of exposure, as used in previous studies[264 281]), and duration in years for each exposed job, summed over the entire job history. The cut-points for categories of duration and cumulative exposure were based on the quartiles of exposure in the controls.[281]

The exposure metrics developed for ELF-MF included: (1) ever/never exposure above background level; (2) level of exposure (background; medium exposure only; ever high exposure); (3) duration of exposure (background; <3 years; 3-8; 9-23; >23 years); and (4) cumulative exposure (background; <4-unit years; 4-12; 13-28; >28-unit years).

The exposure metrics developed for electric shocks included: (1) ever/never exposure above background level; (2) level of exposure (background; medium exposure only; ever high exposure); (3) duration of exposure (background; <3 years; 3-8; 9-24; >24

years); and (4) cumulative exposure (background; <4-unit years; 4-16; 17-52; >52-unit years).

4.2.4 Statistical analyses

Analyses were conducted using SAS version 9.4. Differences in general characteristics between cases and controls were tested using Chi-squared tests, and unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs).

ORs were reported with adjustment for age (5-year categories) and sex. The 'fully adjusted' ORs were also adjusted for ethnicity (European, Māori, Pacific & others); highest achieved education level (primary and secondary school, technical or trade school diploma, undergraduate university degree, postgraduate university degree); smoking status before diagnosis (never, ex, smoker at the time of diagnosis); alcohol consumption before diagnosis (≤once a month,1-2 times/week, 3-5 times/week, daily); sports (never versus ever in adulthood (>18 years); head injury (never/ever); spine injury (never/ever); and socioeconomic status (SES) using the New Zealand Deprivation Index (NZDep2006, quintiles).[445] Models were also adjusted for self-reported occupational exposure (never/ever) to solvents using a detailed questionnaire, and mutually adjusted for ELF-MF or electric shocks. All analyses were repeated separately for males and females.

We also explored the effects of additional adjustments for other self-reported occupational exposures, including fumes, gas, dust, fibers, acids or alkalis, fumigants,

fungicides, insecticides, herbicides or timber preservatives, other chemical products, animals or animal products. Analyses were also stratified by age (<65, ≥65).

Categorical variables for duration of exposure and cumulative exposure were used in regression models, again using background level as the reference. A test for trend was performed by fitting these categorical exposure variables as a continuous variable.

Latency analyses were conducted with employment 5, 10, 20 and 40 years prior to the interview date disregarded. Participants without employment during the lag time were excluded from these analyses.

4.3 Results

4.3.1 Population characteristics

A total of 319 cases and 604 controls were included in the analyses (Table 4.1), two cases and one control without occupational history were excluded. Most cases (67% male and 69% female) were aged >60 years. While the 70+ age group was overrepresented in the controls, there was little difference between cases and controls in terms of tobacco smoking, ethnicity, and education. However, there was a difference in SES for males, with cases less deprived compared to controls. There was no difference in the number of occupations held (mean=6.8 for cases and controls).

Table 4.1. Characteristics of Participants in a Population-Based Case-Control Study of Occupational Exposure to Electric Shocks and Extremely Low-Frequency Magnetic Fields and Motor Neurone Disease, New Zealand, 2013-2016

Characteristics	Male Cases (n=203)		Male Control (n=331)		*p*-value[a]	Female Cases (116)		Female Controls (273)		*p*-value[a]
	No.	%	No.	%		No.	%	No.	%	
Age at interview					0.0002					0.0466
20-49	20	9.85	16	4.83		10	8.62	24	8.79	
50-59	47	23.15	51	15.41		26	22.41	48	17.58	
60-69	79	38.92	112	33.84		44	37.93	76	27.84	
≥70	57	28.08	152	45.92		36	31.04	125	45.79	
Ethnicity					0.9462					0.1222
European/Pakeha[b]	188	92.61	304	91.84		106	91.38	259	94.87	
Māori[c]	8	3.94	14	4.23		5	4.31	11	4.03	
Pacific & others	7	3.45	13	3.93		5	4.31	3	1.10	
Deprivation Index Quintile					0.0237					0.1671
1-2 (least deprived)	76	37.44	83	25.08		23	19.83	82	30.04	
3-4	50	24.63	83	25.08		28	24.14	60	21.98	
5-6	32	15.76	71	21.45		35	30.17	58	21.24	
7-8	27	13.30	64	19.34		16	13.79	44	16.12	
9-10 (most deprived)	18	8.87	30	9.05		14	12.07	29	10.62	
Highest Education					0.4090					0.3952
Primary & secondary school	92	45.32	160	48.34		52	44.83	129	47.25	
Technical or trade school diploma	70	34.48	94	28.40		35	30.17	61	22.34	
Undergraduate university degree	27	13.30	45	13.60		18	15.52	53	19.41	
Postgraduate university degree	14	6.90	32	9.66		11	9.48	30	11.00	
Smoking (prior diagnosis)					0.6966					0.4711
Never	102	50.25	155	46.83		62	53.45	164	60.07	
Smoker at the time of diagnosis	16	7.88	25	7.55		4	3.45	9	3.30	
Ex	85	41.87	151	45.62		50	43.10	100	36.63	

a P-values were calculated using a chi-square test for categorical variables.
b Pakeha (a Māori word) - this is used as a term specifically for New Zealand European people.
c Māori – indigenous people of New Zealand.

4.3.2 Potential exposure to electric shocks

The results on potential exposure to electric shocks are presented in Table 4.2. Among cases, 55% had ever worked in occupations with potential exposure to electric shocks above background level (44% in controls), and 32% had ever worked in an occupation with high potential for exposure to electric shocks (19% in controls). An elevated risk was found for potential exposure to electric shocks above background (OR 1.35, 95% CI: 0.98,1.86) in both males and females (OR males 1.35, 95%CI: 0.87, 2.10; OR females 1.38, 95%CI: 0.80, 2.35; respectively, Supplementary Table S4.5 and S4.6). Similarly, we observed an increased risk for high potential exposure to electric shocks (OR 2.01, 95%CI: 1.31, 3.09), also in both males and females (OR 1.83, 95%CI: 1.11, 3.02 and OR 6.88, 95%CI: 1.13, 42.12, respectively; Supplementary Table S4.5 and S4.6), although for women, employment in a job with high potential for electric shock was rare.

Analysis by duration of employment in a job with potential for electric shocks showed a significantly elevated risk for short durations (<3 years) (OR 1.85, 95%CI: 1.18, 2.90), particularly for those who had a job with high potential for electric shock (OR 4.69, 95%CI: 2.25, 9.77). More than 24 years of duration in jobs with high potential for electric injury was also associated with an increased risk (OR 1.88, 95%CI: 1.05, 3.36).

For cumulative exposure, a similar pattern of elevated risks in the lowest and highest categories was observed, but this did not reach statistical significance when adjusted for all potential confounders. In females, a statistically significant positive trend was observed for cumulative exposure (p-test for trend=0.02), with the highest risk shown

for the 16-52 unit-years exposure category (OR 4.02, 95%CI: 1.25, 12.92; Supplementary Table S4.6).

When we repeated the analyses using 5-, 10-, 20- and 40-years lag, the risk estimates changed only slightly from 5 years (OR=1.45) to 20 years lag time (OR=1.50), with a small drop for the 40 years lag time (OR=1.42) (Table 4.3).

Table 4.2. Risk of Motor Neurone Disease with Occupational Exposure to Electric Shocks in a Population-Based Case-Control Study, New Zealand, 2013-2016

Exposure to Electric Shock	Cases (n=319) NO.	%	Controls (n=604) NO.	%	OR[a]	95%CI	OR[b]	95%CI
Background potential for shocks	143	45	338	56	1.00	Referent	1.00	Referent
Ever exposed above background level	176	55	266	44	1.39	1.04, 1.86	1.35	0.98, 1.86
Exposure level								
Background potential for shocks	143	45	338	56	1.00	Referent	1.00	Referent
Only medium potential for shocks	75	23	154	25	1.06	0.75, 1.50	1.07	0.74, 1.55
Ever high potential for shocks	101	32	112	19	1.99	1.37, 2.90	2.01	1.31, 3.09
Duration of exposure, years								
Background potential for shocks	143	45	338	56	1.00	Referent	1.00	Referent
Exposure <3 years	52	16	62	10	1.80	1.18, 2.75	1.85	1.18, 2.90
Exposure 3-8 years	36	11	72	12	1.05	0.66, 1.65	1.00	0.61, 1.62
Exposure 9-24 years	37	12	64	11	1.21	0.76, 1.94	1.12	0.67, 1.86
Exposure >24 years	51	16	68	11	1.52	0.97, 2.37	1.41	0.86, 2.28
P-value (test for trend)					0.69		0.45	
Background potential for shocks	143	45	338	56	1.00	Referent	1.00	Referent
Medium potential[c] <3 years	24	7	48	8	1.07	0.63, 1.84	1.12	0.64, 1.96
3-8 years	20	6	49	8	0.86	0.49, 1.52	0.85	0.47, 1.52
9-24 years	16	5	28	5	1.25	0.65, 2.40	1.21	0.62, 2.40
>24 years	15	5	29	5	1.22	0.62, 2.41	1.22	0.60, 2.47
Ever high potential[d] <3 years	28	9	14	2	4.42	2.20, 8.87	4.69	2.25, 9.77
3-8 years	16	5	23	4	1.59	0.89, 3.20	1.56	0.74, 3.29
9-24years	21	7	36	6	1.32	0.72, 2.43	1.27	0.65, 2.49
>24 years	36	11	39	6	1.95	1.14, 3.32	1.88	1.05, 3.36
Cumulative exposure, unit-years[e]								
Background potential for shocks	143	45	338	56	1.00	Referent	1.00	Referent
Exposure <4 unit-years	42	13	68	11	1.32	0.85, 2.04	1.34	0.85, 2.13
Exposure 4-16 unit-years	37	12	68	11	1.17	0.74, 1.86	1.17	0.72, 1.90
Exposure 17-52 unit-years	45	14	64	11	1.52	0.96, 2.39	1.45	0.88, 2.39
Exposure >52 unit-years	52	16	66	11	1.63	1.04, 2.56	1.53	0.92, 2.54
P-value (test for trend)					0.33		0.54	

Abbreviation: CI, confidence interval; ELF-MF, extremely low-frequency magnetic fields; OR, odds ratio.

[a] OR adjusted for age and sex.

[b] OR adjusted for age, sex, education, ethnicity, socioeconomic status, smoking status, sports, alcohol, head injury, spine injury, ELF-MF, and solvents.

[c] Duration above background (for those with medium exposure only).

[d] Duration above background (for those with ever high exposure).

[e] Cumulative exposure (unit-years) is the product of duration and level of exposure (background level assigned 0, medium-level exposure assigned 1, high exposure level assigned 4).

Table 4.3. Risk of Motor Neurone Disease with Occupational Exposure to Electric Shocks with Different Lag Times in a Population-Based Case-Control Study, New Zealand, 2013-2016

Exposure to Electric shocks	Case		Controls		OR[a]	95%CI	OR[b]	95%CI
	No.	%	No.	%				
Lag time –Exposure above background								
5 years lag	(319)		(604)					
Background potential for shocks	143	45	340	56	1.00	Referent	1.00	Referent
Ever exposure above background level	176	55	264	44	1.41	1.05, 1.88	1.45	1.04, 2.02
10 years lag	(319)		(602)					
Background potential for shocks	145	45	344	57	1.00	Referent	1.00	Referent
Ever exposure above background level	174	55	258	43	1.44	1.08, 1.93	1.48	1.06, 2.05
20 years lag	(314)		(595)					
Background potential for shocks	147	47	351	59	1.00	Referent	1.00	Referent
Ever exposure above background level	167	53	244	41	1.50	1.12, 2.01	1.50	1.08, 2.09
40 years lag	(238)		(496)					
Background potential for shocks	126	53	314	63	1.00	Referent	1.00	Referent
Ever exposure above background level	112	47	182	37	1.40	1.00, 1.97	1.42	0.97, 2.08
Lag time –Medium and high level exposure								
5 years lag	(319)		(604)					
Background potential for shocks	143	45	340	56	1.00	Referent	1.00	Referent
Only medium potential for shocks	75	23	153	25	1.08	0.76, 1.53	1.14	0.79, 1.66
Ever high potential for shocks	101	32	111	19	2.02	1.39, 2.94	2.22	1.43, 3.43
10 years lag	(319)		(602)					
Background potential for shocks	145	45	344	57	1.00	Referent	1.00	Referent
Only medium potential for shocks	74	23	148	25	1.11	0.79, 1.57	1.17	0.81, 1.70
Ever high potential for shocks	100	32	110	18	2.04	1.40, 2.97	2.19	1.42, 3.39
20 years lag	(314)		(595)					
Background potential for shocks	147	47	351	59	1.00	Referent	1.00	Referent
Only medium potential for shocks	71	23	139	23	1.16	0.81, 1.65	1.19	0.81, 1.73
Ever high potential for shocks	96	30	105	18	2.09	1.43, 3.06	2.23	1.44, 3.46
40 years lag	(238)		(496)					
Background potential for shocks	126	53	314	63	1.00	Referent	1.00	Referent
Only medium potential for shocks	47	20	89	18	1.25	0.82, 1.90	1.25	0.80, 1.96
Ever high potential for shocks	65	27	93	19	1.58	1.03, 2.43	1.70	1.04, 2.79

Abbreviation: CI, confidence interval; ELF-MF, extremely low-frequency magnetic fields; OR, odds ratio.

[a] OR adjusted for age and sex.

[b] OR adjusted for age, sex, education, ethnicity, socioeconomic status, smoking status, sports, alcohol, head injury, spine injury, ELF-MF, and solvents.

4.3.3 Exposure to ELF-MF

The prevalence of occupational exposure to ELF-MF above background was 59% for cases and 62% for controls, and 9% of cases ever had high exposure compared with 8% of controls (Table 4.4). No association between exposure to ELF-MF and MND was observed and ORs did not increase with longer duration or higher cumulative exposure (Table 4.4, Supplementary Table S4.7 and S4.8).

Cumulative exposure to ELF-MF and electric shocks were moderately correlated (Pearson correlation: R=0.32, p<0.0001). The effect of ELF-MF adjustment on the association between potential exposure to electric shocks and MND was small, as was the effect of adjustment for solvent exposure. For example, the OR for ever exposed to the highest level of electric shocks changed from 1.89 to 2.04 when adjusted for ELF-MF, and from 2.04 to 2.01 when also adjusting for solvent exposure (other data not shown).

The effect of adjustment for potential for electric shocks and solvents on the association between exposure to ELF-MF and MND was also small. For example, the OR for ever exposed to the highest level of ELF-MF changed from 0.80 to 0.73 after adjustment for electric shocks and from 0.73 to 0.71 after additional adjustment for solvents (other data not shown). Additional adjustment for other occupational exposures (see methods) did not change the results for both electric shocks and ELF-MF (data not shown).

Analyses stratified by age at interview (<65 versus ≥65 years) showed that potential for electric shocks was associated with MND in both age groups. However, associations

were more pronounced for those <65 years. For example, the OR for exposure to the highest level of electric shocks was 3.32 (95%CI: 1.60, 5.92) in the younger age group, compared to 1.43 (95%CI: 0.73, 2.81) in the older age group (other data not shown).

Table 4.4. Risk of Motor Neurone Disease with Occupational Exposure to Extremely Low-Frequency Magnetic Fields in a Population-Based Case-Control Study, New Zealand, 2013-2016

Exposure to ELF-MF	Cases (n=319)		Controls (n=604)		OR[a]	95%CI	OR[b]	95%CI
	No.	%	No.	%				
Background level	130	41	227	38	1.00	Referent	1.00	Referent
Ever exposed above background level	189	59	377	62	0.87	0.66, 1.15	0.77	0.56, 1.05
Exposure level								
Background level	130	41	227	38	1.00	Referent	1.00	Referent
Medium level only	161	50	326	54	0.87	0.65, 1.16	0.77	0.56, 1.06
Ever exposed at high level	28	9	51	8	0.88	0.52, 1.48	0.71	0.39, 1.28
Duration of exposure, years								
Background level	130	41	227	38	1.00	Referent	1.00	Referent
Exposure <3 years	55	17	99	16	0.95	0.64, 1.42	0.88	0.58, 1.35
Exposure 3-8 years	45	14	93	15	0.82	0.54, 1.25	0.74	0.47, 1.16
Exposure 9-23 years	40	13	92	15	0.78	0.50, 1.21	0.71	0.45, 1.13
Exposure >23 years	49	15	93	16	0.92	0.61, 1.40	0.73	0.46, 1.15
P-value (test for trend)						0.85		0.47
Background level	130	41	227	38	1.00	Referent	1.00	Referent
Medium level[c] <3 years	40	12	77	13	0.91	0.58, 1.43	0.85	0.53, 1.35
3-8 years	41	13	79	13	0.89	0.57, 1.38	0.80	0.50, 1.28
9-23 years	37	12	86	14	0.79	0.50, 1.23	0.72	0.45, 1.16
>23 years	43	13	84	14	0.89	0.58, 1.38	0.71	0.45, 1.14
Ever high level[d] <3 years	15	5	22	4	1.07	0.53, 2.17	0.96	0.45, 2.07
3-8 years	4	1	14	2	0.46	0.15, 1.44	0.35	0.10, 1.21
9-23years	3	1	6	1	0.71	0.17, 2.95	0.50	0.11, 2.27
>23 years	6	2	9	1	1.22	0.41, 3.68	0.76	0.24, 2.41
Cumulative exposure, unit-years[e]								
Background level	130	41	227	38	1.00	Referent	1.00	Referent
Exposure <4 unit-years	52	16	96	16	0.93	0.62, 1.41	0.87	0.57, 1.34
Exposure 4-12 unit-years	47	15	106	17	0.77	0.51, 1.16	0.72	0.46, 1.11
Exposure 13-28 unit-years	43	13	83	14	0.93	0.60, 1.43	0.80	0.50, 1.26
Exposure >28 unit-years	47	15	92	15	0.87	0.57, 1.33	0.67	0.41, 1.07
P-value (test for trend)						0.96		0.42

Abbreviation: CI, confidence interval; ELF-MF, extremely low-frequency magnetic fields; OR, odds ratio.

[a] OR adjusted for age and sex.

[b] OR adjusted for age, sex, education, ethnicity, socioeconomic status, smoking status, sports, alcohol, head injury, spine injury, electric shocks, and solvents.

[c] Duration above background (for those with medium exposure only).

[d] Duration above background (for those with ever high exposure).

[e] Cumulative exposure (unit-years) is the product of duration and level of exposure (background level assigned 0, medium-level exposure assigned 1, high exposure level assigned 4).

4.4 Discussion

In this study, we found a statistically significant increased risk of MND associated with employment in jobs with a high potential for electric shocks. No association was observed for ELF-MF.

The increased risk associated with electric shocks reported here is consistent with earlier studies.[116 185 187 271 280 462 463] A recent study similar to ours, which assessed the potential for electric shocks with lifetime occupational history using JEMs, also reported positive associations.[281] However, other studies that assessed the potential for electric shocks through JEMs,[48 264 277 282] most with access to the only occupation recorded on the census[48 282] or death certificates,[277] showed less consistent results.

We found that MND was associated with employment in occupations with a high potential for electric shocks (OR 2.01; 95%CI: 1.31, 3.09), while in those with medium potential it was not, suggestive of a dose-response association. The association was observed in both men and women and risk estimates did not change after adjusting for other potential risk factors including exposure to ELF-MF and solvents. Confounding is therefore an unlikely explanation of the findings, although confounding by an as yet unidentified occupational risk factor present in electrical occupations cannot be excluded.

We observed a non-linear duration-response association for exposure to potential electric shock, similar to that reported in another case-control study that used the same JEM.[281] This suggests that the potential for electric shock may be higher in short duration jobs (<3 years), during which workers have not yet gained the experience to

prevent such risks,[464] this is consistent with earlier suggestions that young electricians may be more likely to experience electric shocks.[465] The observed increased risk for long (>24 years) employment in jobs with high electric shock potential may be explained by accumulated mild electric injury due to multiple (minor) shocks over longer periods, but also by a higher chance of a single large electric shock when employment duration is longer. To further explore (non-linear) dose-response associations with duration of exposure to electric shocks, we also applied generalised additive modelling with spline smoothing function (GAM in SAS 9.4). Similar to the categorical analyses (Table 4.2), these analyses showed elevated ORs particularly for the short duration of potential exposure to electric shocks (results not presented).

Our latency analyses suggest there may be a long lag, of potentially several decades, between electrical injury and disease onset as, even when disregarding employment periods that occurred up to 20-40 years prior to diagnosis, the association with electric shock potential remained. However, studies into severe electrical injuries (e.g., lightning), where the timing of the one-off injury was known, have suggested a short interval (median 2.25 years) between the electrical injury and disease onset.[465]

A causal mechanism to explain the association between electric shocks and MND has not been established. A recent review[466] suggested that electrical current may hyper-stimulate glutamatergic neurones which can lead to free radical formation through oxidative stress, which may either gradually break down endothelial vascular cells, cutting off blood supply and ending in the death of spinal neurones, or directly damage myelin, gradually leading to a demyelinating neurodegenerative condition without vascular involvement.[467 468] Electric shocks could also result in heat-denatured

proteins[469] leading to protein folding problems, which may form a productive misfolded protein seed that could propagate to non-injured regions.[41]

Thus, while an association between electric injury and MND is plausible and has been observed in multiple studies, the epidemiological evidence remains inconsistent, possibly due to shortcomings in the assessment of exposure to electric shocks. Some studies have relied on self-reports of electric shock, which could result in recall bias and false-positive findings.[465] Most studies, like this study, relied on a JEM, which is less sensitive to recall bias, but cannot indicate if or when an electric injury occurred (as it only estimates the potential for electric shock), resulting in non-differential exposure misclassification and resultant potential attenuation of risk estimates.[470]

We did not observe an association between ever exposed to ELF-MF above background and MND, and ORs did not increase with longer duration or higher cumulative exposure. In additional analyses, we applied another ELF-MF JEM[471] (an enhanced JEM based on the original JEM described by Bowman et al.[461]) developed as part of the INTEROCC study.[471] These resulted in an OR for ELF-MF above background of 1.12 (95%CI: 0.80, 1.57; Supplementary Table S4.9), and ORs did not increase with longer duration or higher cumulative exposure. For females, there was a suggestion of a positive dose-response association, however, this did not reach statistical significance (p-value for trend for duration 0.16 and for cumulative exposure 0.13, Supplementary Table S4.9).

Our findings for ELF-MF are not consistent with a recent systematic review,[46] which reported a meta-estimate of 1.89 (95%CI: 1.31, 2.73) for the category of highest-longest

occupational exposure to ELF-MF based on six studies[45 264 272 276 284 291] that used full occupational histories to assess exposure to ELF-MF via JEM. An MND case-control study[281] published since the 2018 systematic review,[46] which used a full occupational history similar to our study and the modified Bowman JEM,[460] reported a similar OR for ELF-MF above the background level of 1.10 (95%CI: 0.95, 1.28) after adjustment for other exposures, also without a clear dose-response association.

Thus, although a recent systematic review supports the hypothesis that ELF-MF may be a risk factor for MND, our study does not, marking the need for more research in this area.

This study is limited by the relatively small size and some limitations in exposure assessment, as noted above. Another limitation was that the JEMs used in the current study were not based on New Zealand exposure data, although the ELF-MF JEM did use New Zealand specific data for its construction among data from four other countries.[461] The electric shocks JEM was based on data from several European countries, rather than being from any specific country.[459] While there is no indication that New Zealand's occupation-specific exposure levels to ELF-MF and electric shocks are substantially different from those of European countries, we cannot exclude the possibility this has resulted in exposure misclassification. The age distribution also differed between cases and controls, for both men and women. This is likely due to age matching of controls using the age distribution of MND incidence in the United Kingdom, as equivalent New Zealand data was not available at the time of participant recruitment. However, all associations were adjusted for age. Most previous studies assessed associations between ELF-MF or electric shocks with ALS, while in this study

all forms of MND were included (MND subtype specific diagnosis was not recorded), which is a limitation. However, ALS is the most common form of MND accounting for 85% of the total cases, and our case definition is therefore unlikely to differ substantially from those used in other studies on ELF-MF or potential electric shocks.

This study has several strengths, including the use of JEMs combined with full lifetime occupational histories collected without the use of proxies, which is likely to have limited recall bias. Also, cases and controls reported the same number of jobs (mean=6.8), and the number of jobs held by cases and controls was not different by age group (mean=7 for both <60 years of age and 60-70 years age group; mean=6 for 70+ years age group) suggesting that there was no indication of differential recall in occupational history between cases and controls. Furthermore, we were able to adjust the analyses for potential confounders by collecting extensive information on education, SES, smoking, alcohol consumption, and injury, as well as other (self-reported) occupational exposures.

Case ascertainment is a significant challenge when studying the neurodegenerative disease.[472] Our use of the MNDANZ register and the National Minimum Dataset to identify MND cases is a strength, and our association with MNDANZ resulted in a high case participation rate (92%). The participation rate among population controls was lower (48%), but we compared the occupations as recorded on the Electoral Roll between participating and non-participating controls, which showed no difference in frequency of digit 3 job codes for occupations particularly relevant for the exposures of interest, e.g., Building Finishers and Related Trades workers (0.83% in non-participating versus 0.66% in participating controls) and Electricians (0.56% in non-

participating versus 0.50% in participating controls; data not show). It is therefore unlikely that the increased risks observed for potential exposure to electric shocks in this study are explained by non-response bias.

In conclusion, this study supports earlier findings that occupational exposure to electric shocks is associated with an increased risk of MND. Associations were observed in both men and women and were strongest for employment in jobs with the highest potential for electric shock. Occupational exposure to ELF-MF was not associated with the risk of MND in this study.

Acknowledgements

The study was funded by a grant from the Health Research Council (HRC) of New Zealand (Part of 11/1041 HRC Programme Grant - Building Research in Occupational Health in New Zealand (BROHNZ)).

We are grateful to the Motor Neurone Disease Association New Zealand, and their field staff for their generous support. We would also like to express our special thanks to Prof. Hans Kromhout, Dr. Anke Huss and Prof. Roel Vermeulen for making both the ELF-MF and electric shocks JEMs available. We also thank the INTEROCC project for making the ELF-MF JEM available.

The authors have no potential conflicts of interest.

4.5 Supplementary material

Table S4.5. Supplementary Table. Risk of Motor Neurone Disease with Occupational Exposure to Electric Shocks in a Population-Based Case-Control Study, New Zealand, 2013-2016 (Male Participants only)

Exposure to Electric Shock	Male Cases (n=203)		Male Controls (n=331)		OR[a]	95%CI	OR[b]	95%CI
	NO.	%	NO.	%				
Background potential for shocks	67	33	138	42	1.00	Referent	1.00	Referent
Ever exposed above background level	136	67	193	58	1.45	1.00, 2.10	1.35	0.87, 2.10
Exposure level								
Background potential for shocks	67	33	138	42	1.00	Referent	1.00	Referent
Only medium potential for shocks	40	20	83	25	0.95	0.58, 1.55	0.95	0.56, 1.61
Ever high potential for shocks	96	47	110	33	1.84	1.22, 2.77	1.83	1.11, 3.02
Duration of exposure, years								
Background potential for shocks	67	33	138	42	1.00	Referent	1.00	Referent
Exposure <3 years	36	18	26	8	2.86	1.58, 5.20	2.86	1.51, 5.43
Exposure 3-8 years	24	12	50	15	1.00	0.56, 1.79	0.83	0.44, 1.59
Exposure 9-24 years	29	14	52	16	1.13	0.65, 1.96	0.92	0.49, 1.72
Exposure >24 years	47	23	65	19	1.49	0.92, 2.41	1.35	0.77, 2.36
P-value (test for trend)						0.18		0.17
Background potential for shocks	67	33	138	42	1.00	Referent	1.00	Referent
Medium potential[c] <3 years	10	5	14	4	1.40	0.58, 3.38	1.45	0.58, 3.65
3-8 years	10	5	27	8	0.73	0.33, 1.60	0.65	0.28, 1.51
9-24 years	9	4	16	5	1.01	0.42, 2.45	0.89	0.35, 2.25
>24 years	11	5	26	8	0.90	0.42, 1.97	0.98	0.42, 2.26
Ever high potential[d] <3 years	26	13	12	3	4.61	2.16, 9.87	4.88	2.12, 11.22
3-8 years	14	7	23	7	1.37	0.65, 2.87	1.21	0.53, 2.79
9-24years	20	10	36	11	1.19	0.63, 2.23	1.05	0.50, 2.19
>24 years	36	18	39	12	1.86	1.07, 3.22	1.74	0.92, 3.27
Cumulative exposure, unit-years[e]								
Background potential for shocks	67	33	138	42	1.00	Referent	1.00	Referent
Exposure <4 unit-years	24	12	24	7	1.98	1.03, 3.78	1.94	0.97, 3.86
Exposure 4-16 unit-years	25	12	45	14	1.12	0.63, 2.00	1.01	0.54, 1.89
Exposure 17-52 unit-years	36	18	58	17	1.30	0.77, 2.18	1.20	0.66, 2.20
Exposure >52 unit-years	51	25	66	20	1.61	1.00, 2.59	1.44	0.82, 2.54
P-value (test for trend)						0.98		0.89

Abbreviation: CI, confidence interval; ELF-MF, extremely low-frequency magnetic fields; OR, odds ratio. [a] OR adjusted for age. [b] OR adjusted for age, education, ethnicity, socioeconomic status, smoking status, sports, alcohol, head injury, spine injury, ELF-MF, and solvents. [c] Duration above background (for those with medium exposure only). [d] Duration above background (for those with ever high exposure). [e] Cumulative exposure (unit-years) is the product of duration and level of exposure (background level assigned 0, medium-level exposure assigned 1, high exposure level assigned 4).

Table S4.6. Supplementary Table. Risk of Motor Neurone Disease with Occupational Exposure to Electric Shocks in a Population-Based Case-Control Study, New Zealand, 2013-2016 (Female Participants only)

Exposure to Electric Shock	Female Cases (n=116)		Female Controls (n=/273)		OR[a]	95%CI	OR[b]	95%CI
	No.	%	No.	%				
Background potential for shocks	76	66	200	73	1.00	Referent	1.00	Referent
Ever exposed above background level	40	34	73	27	1.34	0.83, 2.15	1.38	0.80, 2.35
Exposure level								
Background potential for shocks	76	66	200	73	1.00	Referent	1.00	Referent
Only medium potential for shocks	35	30	71	26	1.22	0.75, 2.00	1.23	0.70, 2.14
Ever high potential for shocks	5	4	2	1	5.17	0.97, 27.55	6.88	1.13, 42.12
Duration of exposure, years								
Background potential for shocks	76	66	200	73	1.00	Referent	1.00	Referent
Exposure <3 years	16	14	36	13	1.04	0.54, 2.01	1.07	0.52, 2.19
Exposure 3-8 years	12	10	22	8	1.28	0.59, 2.75	1.42	0.61, 3.29
Exposure 9-24 years	8	7	12	5	1.74	0.68, 4.49	1.64	0.58, 4.60
Exposure >24 years	4	3	3	1	3.87	0.83, 18.11	3.57	0.68, 18.67
P-value (test for trend)					0.11		0.18	
Background potential for shocks	76	66	200	73	1.00	Referent	1.00	Referent
Medium potential[c] <3 years	14	12	34	13	0.99	0.50, 1.97	1.04	0.49, 2.19
3-8 years	10	8	22	8	1.08	0.48, 2.41	1.16	0.48, 2.80
9-24 years	7	6	12	4	1.54	0.58, 4.12	1.42	0.49, 4.13
>24 years	4	3	3	1	3.84	0.82, 17.93	3.53	0.66, 18.81
Ever high potential[d] <3 years	2	2	2	1	1.97	0.27, 14.45	1.88	0.20, 17.54
3-8 years	2	2	0	0				
9-24years	1	1	0	0				
>24 years	0	0	0	0				
Cumulative exposure, unit-years[e]								
Background potential for shocks	76	66	200	73	1.00	Referent	1.00	Referent
Exposure <4 unit-years	18	15	44	16	0.97	0.52, 1.82	1.01	0.51, 2.00
Exposure 4-16 unit-years	12	10	23	9	1.27	0.60, 2.71	1.35	0.59, 3.08
Exposure 17-52 unit-years	9	8	6	2	3.96	1.35, 11.64	4.02	1.25, 12.92
Exposure >52 unit-years	1	1	0	0				
P-value (test for trend)					0.02[f]		0.02[f]	

Abbreviation: CI, confidence interval; ELF-MF, extremely low-frequency magnetic fields; OR, odds ratio.

[a] OR adjusted for age. [b] OR adjusted for age, education, ethnicity, socioeconomic status, smoking status, sports, alcohol, head injury, spine injury, ELF-MF, and solvents.

[c] Duration above background (for those with medium exposure only). [d] Duration above background (for those with ever high exposure).

[e] Cumulative exposure (unit-years) is the product of duration and level of exposure (background level assigned 0, medium-level exposure assigned 1, high exposure level assigned 4).

[f] *P*-value (test for trend) <0.05

Table S4.7. Supplementary Table. Risk of Motor Neurone Disease with Occupational Exposure to Extremely Low-Frequency Magnetic Fields in a Population-Based Case-Control Study, New Zealand, 2013-2016 (Male Participants only)

Exposure to ELF-MF	Male Cases (n=203)		Male Controls (n=331)		OR[a]	95%CI	OR[b]	95%CI
	No.	%	No.	%				
Background level	82	40	126	38	1.00	Referent	1.00	Referent
Ever exposed above background level	121	60	205	62	0.88	0.61, 1.27	0.74	0.49, 1.12
Exposure level								
Background level	82	40	126	38	1.00	Referent	1.00	Referent
Medium level only	97	48	169	51	0.86	0.59, 1.26	0.74	0.49, 1.13
Ever exposed at high level	24	12	36	11	0.98	0.54, 1.77	0.73	0.35, 1.51
Duration of exposure, years								
Background level	82	40	126	38	1.00	Referent	1.00	Referent
Exposure <3 years	35	17	46	14	1.08	0.64, 1.84	0.96	0.54, 1.71
Exposure 3-8 years	28	14	47	14	0.86	0.50, 1.50	0.72	0.39, 1.33
Exposure 9-23 years	23	12	45	14	0.78	0.43, 1.40	0.71	0.38, 1.34
Exposure >23 years	35	17	67	20	0.83	0.50, 1.37	0.61	0.35, 1.08
P-value (test for trend)						0.38		0.23
Background level	82	40	126	38	1.00	Referent	1.00	Referent
Medium level[c] <3 years	23	11	34	10	0.99	0.54, 1.82	0.85	0.45, 1.62
3-8 years	24	12	37	11	0.93	0.51, 1.69	0.80	0.42, 1.52
9-23 years	20	10	39	12	0.79	0.43, 1.46	0.75	0.39, 1.45
>23 years	30	15	59	18	0.79	0.47, 1.34	0.62	0.34, 1.11
Ever high level[d] <3 years	12	6	12	4	1.32	0.56, 3.12	1.23	0.46, 3.33
3-8 years	4	2	10	3	0.61	0.18, 2.04	0.44	0.12, 1.67
9-23years	3	1	6	2	0.70	0.17, 2.96	0.48	0.10, 2.36
>23 years	5	3	8	2	1.10	0.34, 3.57	0.56	0.15, 2.05
Cumulative exposure, unit-years[e]								
Background level	82	40	126	38	1.00	Referent	1.00	Referent
Exposure <4 unit-years	32	16	40	12	1.16	0.67, 2.01	0.98	0.55, 1.77
Exposure 4-12 unit-years	25	12	52	16	0.69	0.39, 1.21	0.61	0.33, 1.13
Exposure 13-28 unit-years	26	13	42	13	0.93	0.53, 1.66	0.79	0.42, 1.48
Exposure >28 unit-years	38	19	71	21	0.84	0.51, 1.38	0.61	0.34, 1.08
P-value (test for trend)						0.54		0.28

Abbreviation: CI, confidence interval; ELF-MF, extremely low-frequency magnetic fields; OR, odds ratio.

[a] OR adjusted for age. [b] OR adjusted for age, education, ethnicity, socioeconomic status, smoking status, sports, alcohol, head injury, spine injury, electric shocks, and solvents.

[c] Duration above background (for those with medium exposure only).

[d] Duration above background (for those with ever high exposure).

[e] Cumulative exposure (unit-years) is the product of duration and level of exposure (background level assigned 0, medium-level exposure assigned 1, high exposure level assigned 4).

Table S4.8. Supplementary Table. Risk of Motor Neurone Disease with Occupational Exposure to Extremely Low-Frequency Magnetic Fields in a Population-Based Case-Control Study, New Zealand, 2013-2016 (Females Participants only)

Exposure to ELF-MF	Female Cases (n=116)		Female Controls (n=273)		OR[a]	95%CI	OR[b]	95%CI
	No.	%	No.	%				
Background level	48	41	101	37	1.00	Referent	1.00	Referent
Ever exposed above background level	68	59	172	63	0.85	0.54, 1.33	0.72	0.43, 1.22
Exposure level								
Background level	48	41	101	37	1.00	Referent	1.00	Referent
Medium level only	64	56	157	58	0.88	0.56, 1.38	0.74	0.44, 1.25
Ever exposed at high level	4	3	15	5	0.58	0.18, 1.85	0.47	0.14, 1.66
Duration of exposure, years								
Background level	48	41	101	37	1.00	Referent	1.00	Referent
Exposure <3 years	20	17	53	19	0.81	0.43, 1.50	0.64	0.32, 1.29
Exposure 3-8 years	17	15	46	17	0.76	0.39, 1.48	0.69	0.33, 1.42
Exposure 9-23 years	17	15	47	17	0.78	0.40, 1.51	0.61	0.29, 1.29
Exposure >23 years	14	12	26	10	1.26	0.60, 2.67	1.19	0.48, 2.95
***P*-value (test for trend)**						0.40		0.29
Background level	48	41	101	37	1.00	Referent	1.00	Referent
Medium level[c] <3 years	17	15	43	16	0.84	0.43, 1.64	0.68	0.33, 1.43
3-8 years	17	15	42	15	0.83	0.43, 1.62	0.74	0.36, 1.54
9-23 years	17	15	47	17	0.78	0.40, 1.51	0.60	0.28, 1.27
>23 years	13	11	25	9	1.22	0.57, 2.63	1.26	0.53, 3.01
Ever high level[d] <3 years	3	2	10	4	0.65	0.17, 2.49	0.47	0.11, 1.99
3-8 years	0	0	4	1				
9-23years	0	0	0	0				
>23 years	1	1	1	1	2.23	0.13, 38.20	2.64	0.15, 45.67
Cumulative exposure, unit-years[e]								
Background level	48	41	101	37	1.00	Referent	1.00	Referent
Exposure <4 unit-years	20	17	56	20	0.74	0.40, 1.38	0.64	0.32, 1.28
Exposure 4-12 unit-years	22	19	54	20	0.87	0.47, 1.60	0.74	0.37, 1.47
Exposure 13-28 unit-years	17	15	41	15	0.90	0.46, 1.76	0.67	0.32, 1.42
Exposure >28 unit-years	9	8	21	8	1.02	0.43, 2.43	1.19	0.45, 3.15
***P*-value (test for trend)**						0.49		0.40

Abbreviation: CI, confidence interval; ELF-MF, extremely low-frequency magnetic fields; OR, odds ratio.

[a] OR adjusted for age. [b] OR adjusted for age, education, ethnicity, socioeconomic status, smoking status, sports, alcohol, head injury, spine injury, electric shocks, and solvents.

[c] Duration above background (for those with medium exposure only).

[d] Duration above background (for those with ever high exposure).

[e] Cumulative exposure (unit-years) is the product of duration and level of exposure (background level assigned 0, medium-level exposure assigned 1, high exposure level assigned 4).

Table S4.9. Supplementary Table. Risk of Motor Neurone Disease with Occupational Exposure to Extremely Low-Frequency Magnetic Fields using the enhanced Bowman JEM[471] in a Population-Based Case-Control Study, New Zealand, 2013-2016

Exposure to ELF-MF	All Cases/Controls (319/604)		OR[a] (95%CI)	OR[b] (95%CI)	Male Cases/Controls (203/331)		OR[a] (95%CI)	OR[b] (95%CI)	Female Cases/Controls (116/273)		OR[a] (95%CI)	OR[b] (95%CI)
	No.	%			No.	%			No.	%		
Background level	114/264	(36/44)	1.00	1.00	61/114	(30/34)	1.00	1.00	53/150	(46/55)	1.00	1.00
Ever exposed above background level	205/340	(64/56)	1.26[0.94-1.67]	1.12[0.80-1.57]	142/217	(70/66)	1.19[0.81-1.75]	1.01[0.62-1.63]	63/123	(54/45)	1.35[0.87-2.10]	1.15[0.69-1.92]
Exposure level												
Background level	114/264	(36/44)	1.00	1.00	61/114	(30/34)	1.00	1.00	53/150	(46/55)	1.00	1.00
Medium level only (Medium risk)	168/275	(52/45)	1.28[0.95-1.73]	1.15[0.82-1.62]	115/169	(57/51)	1.24[0.83-1.85]	1.04[0.64-1.70]	53/106	(45/39)	1.33[0.84-2.10]	1.08[0.62-1.87]
Ever exposed at high level (High risk)	37/65	(12/11)	1.14[0.71-1.83]	0.96[0.56-1.64]	27/48	(13/15)	1.02[0.57-1.80]	0.78[0.38-1.58]	10/17	(9/6)	1.50[0.64-3.51]	1.48[0.59-3.76]
Duration of exposure, years												
Background level	114/264	(36/44)	1.00	1.00	61/114	(30/34)	1.00	1.00	53/150	(46/55)	1.00	1.00
Exposure <3 years	51/83	(16/14)	1.26[0.83-1.91]	1.18[0.74-1.86]	32/39	(16/12)	1.35[0.76-2.39]	1.19[0.62-2.28]	19/44	(16/16)	1.13[0.60-2.12]	0.94[0.46-1.91]
Exposure 3-10 years	44/88	(13/14)	1.05[0.68-1.61]	0.98[0.62-1.56]	28/46	(14/14)	1.07[0.60-1.89]	0.92[0.48-1.76]	16/42	(14/16)	0.99[0.51-1.92]	0.98[0.47-2.02]
Exposure 11-27 years	53/90	(17/15)	1.26[0.83-1.91]	1.08[0.68-1.72]	34/62	(17/19)	1.04[0.61-1.76]	0.85[0.46-1.59]	19/28	(16/10)	1.78[0.91-3.49]	1.30[0.06-2.79]
Exposure >27 years	57/79	(18/13)	1.52[0.99-2.33]	1.31[0.82-2.11]	48/70	(23/21)	1.32[0.81-2.17]	1.09[0.60-1.97]	9/9	(8/3)	2.92[1.08-7.89]	2.24[0.76-6.59]
P-value (test for trend)			0.37	0.63			0.95	0.86			0.06	0.16
Background level	114/264	(36/44)	1.00	1.00	61/114	(30/34)	1.00	1.00	53/150	(46/55)	1.00	1.00
Medium level[c] - Exposure <3 years	33/63	(10/10)	1.07[0.66-1.73]	0.99[0.58-1.67]	22/30	(11/9)	1.21[0.64-2.31]	1.08[0.53-2.20]	11/33	(9/12)	0.87[0.41-1.87]	0.62[0.25-1.53]
-Exposure 3-10 years	36/69	(11/12)	1.10[0.69-1.76]	1.03[0.63-1.70]	21/31	(10/9)	1.16[0.61-2.22]	1.01[0.50-2.05]	15/38	(13/14)	1.03[0.52-2.04]	0.96[0.45-2.05]
-Exposure 11-27years	49/75	(15/13)	1.41[0.92-2.17]	1.19[0.74-1.91]	30/49	(15/15)	1.17[0.67-2.05]	0.93[0.49-1.76]	19/26	(16/10)	1.92[0.98-3.79]	1.38[0.63-3.01]
-Exposure >27 years	50/68	(16/11)	1.53[0.98-2.40]	1.30[0.80-2.13]	42/59	(21/18)	1.37[0.82-2.29]	1.13[0.61-2.08]	8/9	(7/3)	2.64[0.95-7.34]	1.84[0.60-5.64]
Ever high level[d] -Exposure <3 years	18/20	(6/3)	1.86[0.93-3.68]	1.64[0.79-3.41]	10/9	(5/3)	1.79[0.68-4.71]	1.44[0.48-4.37]	8/11	(7/4)	1.89[0.71-5.01]	1.79[0.63-5.12]
-Exposure 3-10 years	8/19	(3/3)	0.83[0.35-1.99]	0.70[0.28-1.76]	7/15	(3/5)	0.87[0.33-2.27]	0.67[0.23-1.95]	1/4	(1/1)	0.60[0.07-5.56]	0.72[0.07-7.21]
-Exposure 11-27 years	4/15	(1/2)	0.52[0.16-1.62]	0.40[0.12-1.34]	4/13	(2/4)	0.56[0.17-1.81]	0.47[0.13-1.70]	0/2	(0/1)		
-Exposure >27 years	7/11	(2/2)	1.30[0.48-3.52]	0.98[0.34-2.78]	6/11	(3/3)	1.08[0.37-3.11]	0.73[0.23-2.35]	1/0	(1/0)		
Cumulative exposure, unit-years[e]												
Background level	114/264	(36/44)	1.00	1.00	61/114	(30/34)	1.00	1.00	53/150	(46/55)	1.00	1.00
Exposure <4 unit years	42/87	(13/14)	0.99[0.64-1.54]	0.94[0.59-1.51]	26/39	(13/12)	1.09[0.60-1.99]	0.98[0.50-1.89]	16/48	(14/18)	0.86[0.45-1.66]	0.68[0.32-1.46]
Exposure 4-16 unit years	56/88	(18/15)	1.36[0.91-2.05]	1.23[0.79-1.92]	34/45	(17/14)	1.40[0.80-2.43]	1.13[0.61-2.12]	22/43	(19/16)	1.32[0.72-2.42]	1.28[0.64-2.54]
Exposure 17-35 unit years	56/79	(18/13)	1.51[0.99-2.29]	1.34[0.85-2.11]	35/56	(17/17)	1.14[0.67-1.95]	1.00[0.53-1.88]	21/23	(18/8)	2.52[1.28-4.96]	1.91[0.90-4.03]
Exposure >35 unit years	51/86	(15/14)	1.20[0.77-1.85]	0.99[0.60-1.63]	47/77	(23/23)	1.16[0.71-1.89]	0.93[0.51-1.71]	4/9	(3/3)	1.23[0.36-4.25]	0.82[0.21-3.21]
P-value (test for trend)			0.45	0.83			0.92	0.74			0.05	0.13

Abbreviation: CI, confidence interval; ELF-MF, extremely low-frequency magnetic fields; OR, odds ratio.

[a] OR adjusted for age and sex (or age only in case of sex-stratified analyses).

[b] OR adjusted for age, sex (for analyses combining males and females), education, ethnicity, socioeconomic status, smoking status, sports, alcohol, head injury, spine injury, electric shocks, and solvents.

[c] Duration above background (for those with medium exposure only).

[d] Duration above background (for those with ever high exposure).

[e] cumulative exposure (unit years) is the product of duration and level of exposure (background level assigned 0, medium-level exposure assigned 1, high exposure level assigned 4).

CHAPTER 5 Occupational Exposures to Pesticides and Other Chemicals: a New Zealand Motor Neurone Disease Case-Control Study

Grace Chen[1], Jeroen Douwes[1], Leonard H. van den Berg[2], Neil Pearce[3], Hans Kromhout[4], Bill Glass[1], Dave McLean[1], Andrea 't Mannetje[1]

[1] Research Centre for Hauora and Health (formerly the Centre for Public Health Research), Massey University, Wellington, New Zealand.

[2] Brain Centre Rudolf Magnus, Department of Neurology, University Medical Centre, Utrecht, The Netherlands.

[3] Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom.

[4] Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands

(Published in Occupational and Environmental Medicine 2022;79(6):412-420)

ABSTRACT

Objectives To assess associations between occupational exposures to pesticides and other chemicals and motor neurone disease (MND).

Methods A population-based case-control study that included 319 MND cases (64% male/36% female) recruited through the New Zealand MND Association complemented with hospital discharge data, and 604 controls identified from the Electoral Roll. For each job held, a questionnaire collected information on 11 exposure categories (dust, fibres, tobacco smoke, fumes, gas, fumigants, oils/solvents, acids/alkalis, pesticides, other chemicals, and animals/animal products). Odds Ratios (OR) were estimated using logistic regression adjusting for age, sex, ethnicity, socioeconomic status, education, smoking, alcohol consumption, physical activities, head/spine injury, and other occupational exposures.

Results Two exposure categories were associated with increased MND risks: pesticides (OR 1.70, 95%CI 1.17-2.48) and fumigants (OR 3.98, 95%CI 1.81-8.76), with risks increasing with longer exposure duration ($p<0.01$). Associations were also observed for: methyl bromide (OR 5.28, 95%CI 1.63-17.15), organochlorine insecticides (OR 3.28, 95%CI 1.18-9.07), organophosphate insecticides (OR 3.11, 95%CI 1.40-6.94), pyrethroid insecticides (OR 6.38, 95%CI 1.13-35.96), inorganic (copper) fungicides (OR 4.66, 95%CI 1.53-14.19), petrol/diesel fuel (OR 2.24, 95%CI 1.27-3.93), and unspecified solvents (OR 1.91, 95%CI 1.22-2.99). In women, exposure to textile fibres (OR 2.49, 95%CI 1.13-5.50), disinfectants (OR 9.66, 95%CI 1.29-72.44), and cleaning products (OR 3.53, 95%CI 1.64-7.59) were also associated with MND; this was not observed in men (OR 0.80, 95%CI 0.44-1.48; OR 0.72, 95%CI 0.29-1.84; OR 0.57, 95%CI 0.21-1.56, respectively).

Conclusions This study adds to the evidence that pesticides, especially insecticides, fungicides, and fumigants, are risk factors for MND.

Key Messages

What is already known about this subject?

Several occupational exposures such as pesticides, solvents, and metals have been hypothesised to be associated with Motor Neurone Disease (MND).

What are the new findings?

- In this population-based case-control study with complete lifetime job histories, occupational exposure to pesticides (especially insecticides, fungicides) and fumigants were associated with an increased risk of MND in both men and women.
- Occupational exposure to petrol/diesel fuel and unspecified solvents were also associated with an increased MND risk.

How might this impact on policy or clinical practice in the foreseeable future?

- These results confirm previous findings and support policies to reduce exposures to specific chemicals in the workplace, e.g., by using effective exhaust ventilation, or, where that is not feasible, by using appropriate personal protective equipment (PPE).
- Where feasible, hazardous pesticides should be substituted with less harmful alternatives, and methods of pesticide application need to be improved to reduce exposure and resultant risk of MND.

5.1 Introduction

Motor neurone disease (MND) comprises a group of progressive and fatal neurodegenerative conditions with largely unknown aetiology,[9] although age (with a peak onset between 70-75 years),[11] male sex, and a family history of MND are well-known risk factors.[11 56 61] Amyotrophic Lateral Sclerosis (ALS) is the most common form of MND, accounting for 85% of cases;[61 473 474] other forms include Progressive Bulbar Palsy (PBP), Progressive Muscular Atrophy (PMA), and Primary Lateral Sclerosis (PLS).[11] Despite the growing evidence about the genetics of MND, more than 90% of patients occur sporadically without a clear family history and/or obvious inherited genetic mutations,[39] suggesting an important role for environmental factors, including occupational exposures.[61]

Pesticides exposure has been shown to be associated with an approximately 1.5 to 2.0 fold risk of ALS, as shown in three meta-analyses[37 39 41] and two systematic reviews.[40 203] However, most studies investigated the association of ALS with pesticides exposure as a group, and have not been able to identify the specific pesticide classes involved (i.e. insecticides, herbicides, fungicides). The few that considered specific pesticides showed inconclusive results,[36 43] although a role for organochlorine[39] and organophosphate[302] insecticides has been suggested.

Solvents have also been associated with ALS,[36] with a recent meta-analysis reporting a 40% increased MND risk for solvents exposure as a group,[41] however, results have not always been consistent.[43 264] Some studies reported associations for specific solvents, but results have been mixed.[43 188 263]

Other exposures that have been studied in relation to MND include heavy metals,[36 264] with several studies showing positive associations with blood or bone lead levels[182 197] and systemic reviews reporting an 80% increase in MND risk associated with a history of lead exposure.[201 203]

Although these studies provide support for a role of environmental and occupational chemicals, particularly those known to have neurotoxic properties (i.e., insecticides, solvents, lead), the evidence is currently insufficient to inform effective MND prevention strategies, highlighting the need for more and larger studies, underpinned by detailed exposure assessment.

We have previously reported associations between MND and employment in specific occupations, such as agricultural and construction workers, electricians, forecourt attendants, and plant and machine operators and assemblers,[458] and occupational exposure to electric shocks and extremely low-frequency magnetic fields (ELF-MF).[475] Using data from the same population-based case-control study, we have now assessed associations with specific occupational exposures, based on detailed questionnaire information and full occupational histories.

5.2 Methods

The detailed background information on the study population recruitment and data collection methodology of this population-based case-control study is provided in Appendix 1.

5.2.1 Study population

A New Zealand population-based case-control study was conducted to assess associations between occupational exposures and MND using self-reported lifetime occupational histories with specific information on occupational exposures.[458] Cases were recruited primarily through the New Zealand MND Association register from 2013-2016. This was supplemented with searches for patients with a primary or secondary diagnosis of MND (ICD10 – G122) in the National Minimum Dataset (2013-2015), which holds records of all hospital outpatients in New Zealand. The inclusion criterion for cases was a diagnosis for any form of MND by a neurologist. A total of 396 (275 incident and 121 prevalent) cases with a primary diagnosis of MND were recruited. Controls were randomly selected from the 2008 New Zealand Electoral Roll, frequency matched on the age and sex distribution of the United Kingdom's MND incidence data, as the MND incidence by age and sex was not available for New Zealand at the time of recruitment.[81] We aimed to include two controls for each case and assumed an approximate 50% response rate. In total 2400 potential controls were therefore selected from the Electoral Roll. Controls with any neurodegenerative disease were excluded.

All participants gave written informed consent. Ethics approval was provided by the Multi-region Ethics Committee in New Zealand (MEC/12/01/005).

5.2.2 Questionnaire

Data on demographics, lifestyle factors, injuries, smoking and drinking, and lifetime occupational history were collected by using a questionnaire,[458] which was administered depending on participants' own preference; a face-to-face interview (59% in cases vs 16% in controls); a telephone interview (23% vs 66%); or a postal questionnaire (18% vs 18%). All controls completed the questionnaire themselves, while nine cases used a proxy (three required proxy assistance with a face-to-face interview, and six used proxy assistance for reading and writing only).

5.2.3 Exposures

Participants were asked to complete a full work history (all jobs ever held for ≥6 months) and for each job, information on job title, employer, industry, start and end date, and tasks and work processes was obtained. Participants were asked whether the following 11 exposure categories were present (yes/no) in each job: dust (e.g., coal, metal, wood, grain); fibres (textile fibres, asbestos or insulation material); environmental tobacco smoke (from other workers); other smoke or fume (e.g., combustion products, engine emission, metal fume); gas (e.g., combustion gases, refrigerant); fumigants (e.g., methyl bromide, chloropicrin); oils and solvents (e.g. lubricants, cutting oils, degreasers, thinners); acids or alkalis; pesticides (fungicides, insecticides, herbicides or timber preservatives); other chemical products (e.g., dyes, inks, adhesives, etc.); and animals or animal products (e.g., living animals, meat, faeces). Exposure duration for all 11 exposure categories was determined based on the duration of the job(s) in which the exposure occurred.

For each exposure, participants were asked the name and source of the substance, and how often they were exposed. Based on this free-text information, new variables for occupational exposure sub-categories (yes/no) were constructed, blind to the case-control status of the participant, through automated keywords searches (including alternative spelling and trade names). For each newly created exposure sub-category, the original job descriptions were checked to ensure that the new category captured only participants considered to be truly exposed.

5.2.4 Statistical analyses

Analyses were conducted using SAS version 9.4. Differences in general characteristics between cases and controls were tested using chi-squared tests, and unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs), for ever-exposed to a particular occupational exposure, compared to never being exposed to that particular exposure.

Analyses were adjusted for age (5-year categories); sex; ethnicity (European, Māori (the indigenous population of New Zealand), and other); highest achieved education level (primary and secondary school, technical or trade school diploma, undergraduate university degree, postgraduate university degree); smoking status (never, ex, current smoker; before diagnosis for cases and at the time of the interview for controls); alcohol consumption frequency (average alcohol consumption of the lifetime: ≤once a month, 1-2 times/week, 3-5 times/week, daily; up to diagnosis for cases and up to interview for controls); sports (never versus ever having played sports as an adult (>18 years)); head injury (ever/never); spine injury (ever/never); and socioeconomic status (SES) using the

New Zealand Deprivation Index (NZDep2006, quintiles).[445] Additional analyses were conducted mutually adjusting for all other exposure categories. We checked for multicollinearity by comparing the standard errors for the main effect estimates between the full model, and a minimally adjusted model,[476] there was no evidence of collinearity affecting the study findings. All analyses were repeated separately for males and females. Analyses were also repeated controlling for the questionnaire method, exposure to ELF-MF and electric shocks.

We also assessed associations with exposure duration (for each category) defined as the number of years worked in each exposed job, summed over the entire job history. Exposure duration was categorised based on the quartiles of duration in the controls, specific to each exposure. A test for trend was performed by assigning scores to the categories of the categorical duration variables and fitting them as continuous variables.

5.3 Results

5.3.1 Population characteristics

A total of 321 cases (92% participation) and 605 controls (48% participation) took part in the study. Two cases and one control with missing occupational history were excluded, leaving 319 cases and 604 controls for analyses. The time between diagnosis and interview was 6-18 months (median=238 days, IQR=269 days) for cases.

Table 5.1 summarises the characteristics of the cases (203 (64%) male/116 (36%) female) and controls (331 (55%) male/273 (45%) female). There was little difference between the groups in smoking status, ethnicity, and education. However, the 70+ age group was overrepresented in the controls, and male cases were less deprived compared

to male controls. There was no difference in the number of jobs held by cases and controls (mean=7 for both).

Table 5.1. Characteristics of Participants in a Population-Based Case-Control Study of Occupational Exposures and the Risk of Motor Neurone Disease, New Zealand, 2013-2016

Characteristics	Male Cases (n=203)		Male Control (n=331)		*p*-Value[a]	Female Cases (116)		Female Controls (273)		*p*-Value[a]
	No.	%	No.	%		No.	%	No.	%	
Age at interview					0.001					0.047
20-49	20	9.9	16	4.8		10	8.6	24	8.8	
50-59	47	23.1	51	15.4		26	22.4	48	17.6	
60-69	79	38.9	112	33.8		44	37.9	76	27.8	
≥70	57	28.1	152	46.0		36	31.1	125	45.8	
Ethnicity					0.946					0.122
European/Pakeha[b]	188	92.6	304	91.8		106	91.4	259	94.9	
Māori[c]	8	3.9	14	4.2		5	4.3	11	4.0	
Pacific & others	7	3.5	13	4.0		5	4.3	3	1.1	
Deprivation Index Quintile					0.024					0.167
1-2 (least deprived)	76	37.4	83	25.1		23	19.8	82	30.1	
3-4	50	24.6	83	25.1		28	24.1	60	22.0	
5-6	32	15.8	71	21.4		35	30.2	58	21.2	
7-8	27	13.3	64	19.3		16	13.8	44	16.1	
9-10 (most deprived)	18	8.9	30	9.1		14	12.1	29	10.6	
Highest Education					0.409					0.395
Primary & secondary school	92	45.3	160	48.3		52	44.8	129	47.3	
Technical or trade school diploma	70	34.5	94	28.4		35	30.2	61	22.3	
Undergraduate university degree	27	13.3	45	13.6		18	15.5	53	19.4	
Postgraduate university degree	14	6.9	32	9.7		11	9.5	30	11.0	
Smoking (prior diagnosis)					0.697					0.471
Never	102	50.2	155	46.8		62	53.5	164	60.1	
Smoker at the time of diagnosis	16	7.9	25	7.6		4	3.5	9	3.3	
Ex	85	41.9	151	45.6		50	43.0	100	36.6	
Total jobs [mean (range)]	6.8	(1-22)	6.6	(1-20)	0.533	7.0	(1-23)	7.1	(1-22)	0.686

Chi-square tested the differences in age, ethnicity, education, smoking status, socioeconomic status (SES), and the number of jobs by gender.

[a] p-values were calculated using a chi-square test for categorical variables.

[b] Pakeha (a Māori word) - This is used as a term specifically for New Zealand European people.

[c] Māori – indigenous people of New Zealand.

5.3.2 Exposure categories

Two of the 11 occupational exposure categories were associated with an increased risk of MND after adjustment for all other exposure categories: fumigants (OR 3.98, 95%CI: 1.81, 8.76), and pesticides (OR 1.70, 95%CI: 1.17, 2.48; Table 5.2). Of those reporting exposures to pesticides, half reported having applied the pesticides themselves, while the other half reported being exposed indirectly (Supplementary Table S5.5). An increased risk was observed for those who applied pesticides themselves (OR 2.72, 95%CI: 1.66, 4.44), an occupational activity more common among males than females (13.3% versus 2.6% in controls). This association was stronger in males (OR 2.88, 95%CI:1.61, 5.16 versus OR 2.01, 95%CI: 0.56, 7.24 in females; Supplementary Table S5.5). Of interest, no association was found for those exposed indirectly (Supplementary Table S5.5).

Analyses stratified by sex (Table 5.2) showed stronger or similar findings for males (fumigants: OR 9.69, 95%CI: 3.00, 31.35; pesticides OR 1.72, 95%CI: 1.08, 2.75), whilst for females, an elevated OR of similar magnitude was only found for pesticides, but this did not reach statistical significance (OR 1.82, 95%CI: 0.84, 3.93). For females, exposure to fibres (OR 2.24, 95%CI: 1.09, 4.61) and other chemical products (OR 1.82, 95%CI: 1.03, 3.24) was also associated with an increased risk, which was not observed in males.

A positive association with duration of exposure was observed for: fibres (for females, p test for trend=0.038); fumigants (for males, p test for trend=0.001); oils and solvents (for males, p test for trend =0.004); pesticides (for males, p test for trend= 0.001); and

other chemical products (for females, p test for trend=0.004; Table 5.3). For the other exposure categories, a trend with exposure duration was not observed (Supplementary Table S5.6).

Table 5.2. Risk of Motor Neurone Disease with Self-reported Occupational Exposures in a Population-Based Case-Control Study, New Zealand, 2013-2016

Self-Reported Exposures	All Cases/Controls (319/604) No.	%	OR (95%CI)	OR[1] (95%CI)	Male Cases/ Controls (203/331) No.	%	OR (95%CI)	OR[1] (95%CI)	Female Cases/Controls (116/273) No.	%	OR (95%CI)	OR[1] (95%CI)
Dust	170/287	53.3/47.5	1.00[0.74-1.36]	0.72[0.51-1.03]	133/204	65.5/61.6	1.00[0.67-1.50]	0.68[0.42-1.10]	37/83	31.9/30.4	0.79[0.47-1.33]	0.56[0.30-1.03]
Fibres	91/126	28.5/20.9	1.33[0.95-1.86]	1.26[0.87-1.84]	65/100	32/30.2	1.01[0.67-1.52]	0.92[0.57-1.47]	26/26	22.4/9.5	2.54[1.33-4.86]*	2.24[1.09-4.61]*
Environmental tobacco smoke	166/289	52.0/47.9	1.06[0.79-1.43]	1.00[0.73-1.36]	113/183	55.7/55.3	0.93[0.63-1.36]	0.86[0.57-1.31]	53/106	45.7/38.8	1.23[0.76-2.01]	1.26[0.74-2.15]
Other smoke or Fume	135/193	42.3/32	1.28[0.92-1.76]	1.05[0.72-1.53]	116/158	57.1/47.7	1.39[0.95-2.06]	1.10[0.69-1.76]	19/35	16.4/12.8	0.93[0.48-1.83]	0.72[0.33-1.58]
Gas	51/62	16.0/10.3	1.33[0.88-2.03]	1.06[0.66-1.69]	42/45	20.7/13.6	1.51[0.92-2.46]	1.27[0.73-2.23]	9/17	7.8/6.2	0.81[0.33-2.02]	0.58[0.20-1.64]
Fumigants	26/10	8.2/1.7	4.95[2.29-10.70]*	3.98[1.81-8.76]*	22/4	10.8/1.2	12.32[3.89-39.03]*	9.69[3.00-31.35]*	4/6	3.5/2.2	1.43[0.36-5.61]	1.12[0.27-4.60]
Oils and solvents	133/195	41.7/32.3	1.26[0.91-1.73]	1.09[0.74-1.59]	115/157	56.7/47.4	1.36[0.92-1.99]	1.30[0.82-2.07]	18/38	15.5/13.9	1.09[0.57-2.10]	0.78[0.36-1.72]
Acids or Alkalis	48/72	15.1/11.9	1.02[0.67-1.57]	0.79[0.50-1.26]	41/59	20.2/17.8	1.00[0.62-1.63]	0.80[0.47-1.34]	7/13	6/4.8	1.10[0.40-3.03]	1.00[0.32-3.08]
Pesticides	109/122	34.2/20.2	1.92[1.38-2.67]*	1.70[1.17-2.48]*	87/96	42.9/29	1.95[1.31-2.91]*	1.72[1.08-2.75]*	22/26	19/9.5	2.07[1.07-4.01]*	1.82[0.84-3.93]
Other chemical products	137/193	43/32	1.43[1.07-1.92]*	1.29[0.94-1.78]	90/119	44.3/36	1.28[0.88-1.87]	1.15[0.76-1.74]	47/74	40.5/27.1	1.74[1.06-2.83]*	1.82[1.03-3.24]*
Animals or animal products	105/142	32.9/23.5	1.53[1.11-2.10]*	1.22[0.85-1.77]	73/97	36/29.3	1.45[0.97-2.17]	1.11[0.70-1.78]	32/45	27.6/16.5	1.73[0.99-3.02]	1.51[0.76-2.98]

Abbreviation: CI, confidence interval; OR, odds ratio.
OR adjusted for age and sex (or age only in case of sex-stratified analyses), education, ethnicity, socioeconomic status (SES), smoking status, sports, alcohol, head injury, spine injury.
OR[1] adjusted for age, sex (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking status, sports, alcohol, head injury, spine injury, and for the respective other self-reported exposures.
*P <0.05

Table 5.3. Motor Neurone Disease Risk by Duration of Exposure in a Population-Based Case-Control Study, New Zealand, 2013-2016

	All Cases/Controls (319/604)	OR (95%CI)	Male Cases/Controls (203/331)	OR 95%CI)	Female Cases/Controls (116/273)	OR 95%CI)
Fibres						
Never exposed	228/478	1	138/231	1	90/247	1
Exposed <5 years	28/37	1.34 [0.76-2.35]	15/24	0.85 [0.39-1.84]	13/13	1.83 [0.71-4.72]
Exposed 5-10 years	20/29	1.31 [0.67-2.54]	13/24	0.86 [0.38-1.95]	7/5	3.44 [0.93-12.76]
Exposed 11-29 years	16/29	0.73 [0.35-1.49]	14/23	0.60 [0.26-1.39]	2/6	0.68 [0.11-4.16]
Exposed >29 years	27/31	1.70 [0.92-3.15]	23/29	1.37 [0.68-2.75]	4/2	6.48 [0.93-45.29]
p(trend)		*0.255*		*0.908*		*0.038*
Fumigants						
Never exposed	293/594	1	181/327	1	112/267	
Exposed <4 years	4/4	2.04 [0.48-8.73]	2/1	5.16 [0.31-84.93]	2/3	1.36 [0.19-9.78]
Exposed 4-6 years	5/2	3.97 [0.72-21.92]	3/1	8.06 [0.72-90.11]	2/1	3.17 [0.24-42.26]
Exposed 7-10 years	5/1	9.32 [0.96-90.20]	5/0		0/1	
Exposed >10 years	12/3	4.77 [1.28-17.84]*	12/2	7.54 [1.57-36.19]*	0/1	
p(trend)		*0.001*		*0.001*		*0.691*
Oils and solvents						
Never exposed	186/409	1	88/174	1	98/235	1
Exposed <5 years	22/50	0.73 [0.40-1.34]	15/37	0.63 [0.29-1.38]	7/13	0.88 [0.29-2.66]
Exposed 5-14 years	26/51	0.86 [0.48-1.54]	24/41	0.99 [0.51-1.96]	2/10	0.34 [0.06-1.87]
Exposed 15-31 years	37/47	1.28 [0.72-2.27]	29/37	1.46 [0.74-2.90]	8/10	1.36 [0.39-4.74]
Exposed >31 years	48/47	1.79 [1.04-3.10]*	47/42	2.60 [1.39-4.85]*	1/5	0.41 [0.03-4.99]
p(trend)		*0.056*		*0.004*		*0.633*
Pesticides						
Never exposed	210/482	1	116/235	1	94/247	1
Exposed <5 years	19/32	1.13 [0.59-2.15]	12/28	0.76 [0.34-1.72]	7/4	4.34 [1.03-18.32]*
Exposed 5-15 years	26/33	1.60 [0.87-2.93]	19/25	1.37 [0.64-2.92]	7/8	2.29 [0.69-7.62]
Exposed 16-30 years	27/27	1.89 [1.00-3.54]*	21/19	2.09 [0.96-4.54]	6/8	1.08 [0.30-3.94]
Exposed >30 years	37/30	2.39 [1.32-4.31]*	35/24	3.04 [1.54-5.97]*	2/6	0.52 [0.09-3.17]
p(trend)		*0.001*		*0.001*		*0.659*
Other chemical products						
Never exposed	182/411	1	113/212	1	69/199	1
Exposed <5 years	32/46	1.36 [0.81-2.29]	20/21	1.33 [0.63-2.79]	12/25	1.66 [0.71-3.90]
Exposed 5-11years	34/49	1.12 [0.66-1.88]	26/24	1.28 [0.65-2.53]	8/25	0.58 [0.21-1.63]
Exposed 12-26 years	33/49	1.27 [0.75-2.16]	17/32	0.90 [0.44-1.83]	16/17	3.11 [1.24-7.80]*
Exposed >26 years	38/49	1.41 [0.85-2.35]	27/42	1.13 [0.61-2.10]	11/7	6.27 [1.88-20.95]*
p(trend)		*0.142*		*0.743*		*0.004*

Abbreviation: CI, confidence interval; OR, odds ratio.

OR adjusted for age, sex (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking status, sports, alcohol, head injury, spine injury, and for the respective other self-reported exposures.

*P <0.05

5.3.3 Exposure sub-categories

For exposure categories that showed significant associations with MND, we conducted further analyses on specific exposures within each category (Table 5.4). Among the most frequently reported fibre types, insulation fibre was associated with an increased risk (OR 3.63, 95%CI: 1.59, 8.26), while asbestos was not associated with MND (OR 0.95, 95%CI: 0.59, 1.52). Exposure to textile fibres was associated with an increased risk in women (OR 2.49, 95%CI: 1.13, 5.50) but not in men.

Elevated odds ratios were found for each fumigant sub-category, but this reached statistical significance only for methyl bromide (OR 5.28, 95%CI: 1.63, 17.15). This association was found only in males, as very few females were exposed to methyl bromide.

Among specific exposures within the oils and solvents category, a positive association was observed for non-specified solvents, but only in males (OR 2.72, 95%CI: 1.61, 4.58). A positive association was also observed for exposure to petrol and diesel fuel (OR 2.24, 95%CI: 1.27, 3.93). Most of those reporting exposures to petrol and diesel fuel were exposed before 1996, the year lead was phased out from petrol in New Zealand. The OR was slightly higher for this group (OR 2.20, 95%CI: 1.27, 3.79; Supplementary Table S5.7) compared to that reported for the overall group (Table 5.3) and compared to those exposed to only unleaded fuel oil (after 1996) (OR 1.64, 95%CI: 0.37, 7.18, Supplementary Table S5.7), with the latter risk estimate based on small numbers.

Among the different pesticide groups, statistically significant increased risks were found for insecticides (OR 3.06, 95%CI: 1.90, 4.94) and fungicides (OR 2.40, 95%CI: 1.30, 4.42), for both males and females (Table 5.4). Several specific insecticide sub-categories were also associated with increased risk: organochlorines (OR 3.28, 95%CI: 1.18, 9.07), organophosphates (OR 3.11, 95% CI:1.40, 6.94), and pyrethroids (OR 6.38, 95%CI: 1.13, 35.96). Among fungicides, inorganic (copper) fungicides showed a statistically significant elevated risk (OR 4.66, 95%CI: 1.53, 14.19). Among herbicides, a statistically significant association was found only for non-specified herbicides (OR 2.22, 95%CI: 1.15, 4.30).

Specific exposures most commonly reported under "other chemical products" were dyes, inks, adhesives, disinfectants, and cleaning products, with increased risks observed for disinfectants (OR 9.66, 95%CI:1.29, 72.44) and cleaning products (OR 3.53, 95%CI:1.64, 7.59), but this was found only in females.

Additional adjustment for the interview method (face-to-face/telephone/postal) in these models made little difference and did not alter our findings (data not shown). We previously reported on associations with exposure to ELF-MF and electric shocks assessed through job-exposure matrices for this study population,[475] additional adjustment for these occupational exposures did not alter the findings of the analyses presented here (data not shown).

Table 5.4. Risk of Motor Neurone Disease with Self-reported Occupational Exposure Sub-Categories in a Population-Based Case-Control Study, New Zealand, 2013-2016

	All		Male		Female	
	Cases (319) / Controls (604)	OR (95%CI)	Cases (203) / Controls (331)	OR (95%CI)	Cases (116) / Controls (273)	OR (95%CI)
Fibres						
Asbestos	42/71	0.95 [0.59-1.52]	40/66	0.98 [0.59-1.65]	2/5	0.72 [0.12-4.37]
Insulation fibre#	22/10	3.63 [1.59-8.26]*	20/9	3.82 [1.56-9.34]*	2/1	4.33 [0.29-63.74]
Textile fibre	51/60	1.36 [0.87-2.14]	28/40	0.80 [0.44-1.48]	23/20	2.49 [1.13-5.50]*
Fibreglass	17/16	1.57 [0.72-3.43]	16/14	1.81 [0.76-4.32]	1/2	2.17 [0.15-31.41]
Fumigants						
Methyl bromide	15/4	5.28 [1.63-17.15]*	13/4	5.29 [1.52-18.39]*	2/0	
Formaldehyde	6/3	3.73 [0.85-16.40]	4/0		2/3	1.59 [0.22-11.39]
Chloropicrin	3/1	5.71 [0.53-61.29]	3/1	9.22 [0.83-101.82]	0/0	
Non-specified fumigants	3/3	1.27 [0.23-7.01]	3/0		0/3	
Oils and solvents						
Oils	76/112	1.08 [0.72-1.61]	68/93	1.19 [0.75-1.89]	8/19	0.87 [0.32-2.36]
Cutting Fluid	13/20	0.98 [0.44-2.21]	12/20	0.99 [0.42-2.31]	1/0	
Fuel oil	44/34	2.13 [1.27-3.59]*	40/28	2.56 [1.42-4.63]*	4/6	1.26 [0.28-5.61]
Petrol & Diesel	39/28	2.24 [1.27-3.93]*	35/24	2.45 [1.30-4.60]*	4/4	2.04 [0.37-11.25]
Kerosene	6/9	1.11 [0.37-3.31]	6/7	1.71 [0.52-5.64]	0/2	
Engine oil/Lubricants	40/75	0.65 [0.40-1.05]	34/67	0.56 [0.32-0.97]*	6/8	1.09 [0.31-3.90]
Non-specified oils	3/13	0.53 [0.14-1.99]	2/6	0.54 [0.10-3.00]	1/7	0.41 [0.04-3.78]
Solvents	95/116	1.31 [0.88-1.94]	82/95	1.54 [0.96-2.46]	13/21	1.07 [0.42-2.71]
Chlorinated solvents	29/29	1.37 [0.76-2.46]	22/23	1.22 [0.61-2.46]	7/6	2.53 [0.69-9.23]
Other organic solvents	29/56	0.65 [0.37-1.13]	26/52	0.68 [0.37-1.25]	3/4	1.54 [0.25-9.59]
Non-specified solvents	69/65	1.91 [1.22-2.99]*	62/51	2.72 [1.61-4.58]*	7/14	0.72 [0.28-2.28]
Pesticides						
Herbicides	64/76	1.34 [0.85-2.10]	55/61	1.40 [0.82-2.40]	9/15	1.06 [0.37-3.08]
245T	21/31	1.11 [0.58-2.11]	19/28	1.13 [0.55-2.32]	2/3	1.92 [0.27-13.83]
24D	12/21	0.85 [0.38-1.88]	12/20	0.85 [0.36-2.01]	0/1	
MCPA	4/6	0.85 [0.22-3.25]	4/6	0.91 [0.23-3.56]	0/0	
MCPB	2/2	0.82 [0.11-6.24]	2/2	0.98 [0.12-7.71]	0/0	
Glyphosate	16/17	1.16 [0.54-2.47]	13/12	1.17 [0.47-2.93]	3/5	0.81 [0.16-4.11]
Non-specified herbicides	26/20	2.22 [1.15-4.30]*	22/14	2.57 [1.17-5.69]*	4/6	1.21 [0.25-5.83]
Insecticides	60/38	3.06 [1.90-4.94]*	43/29	2.86 [1.57-5.18]*	17/9	4.24 [1.66-10.78]*
Organochlorines	12/8	3.28 [1.18-9.07]*	10/8	2.27 [0.73-7.07]	2/0	
Organophosphates	22/11	3.11 [1.40-6.94]*	20/6	5.97 [2.16-16.53]*	2/5	0.72 [0.12-4.43]
Pyrethroids	5/2	6.38 [1.13-35.96]*	3/2	2.99 [0.42-21.53]	2/0	
Carbamates	0/2		0/1		0/1	
Non-specified insecticides	25/16	2.42 [1.22-4.78]*	14/13	1.49 [0.62-3.57]	11/3	7.86 [1.85-33.35]*
Fungicides	36/22	2.40 [1.30-4.42]*	28/17	2.24 [1.07-4.69]*	8/5	3.77 [1.08-13.13]*
Aromatic Hydrocarbons	3/0		3/0		0/0	
Phthalimides	5/3	2.87 [0.60-13.76]	4/2	3.62 [0.53-24.91]	1/1	2.25 [0.11-46.04]
Inorganic (Copper)	14/5	4.66 [1.53-14.19]*	10/3	5.13 [1.18-22.21]*	4/2	4.51 [0.70-29.24]
Non-specified fungicides	15/14	1.19 [0.52-2.72]	12/12	0.99 [0.37-2.62]	3/2	3.66 [0.48-27.48]
Sheep/Cattle dip+	20/17	1.90 [0.91-3.94]	18/13	2.27 [0.97-5.30]	2/4	0.59 [0.09-3.95]
Timber treatments	31/25	1.73 [0.94-3.18]	28/22	1.71 [0.87-3.36]	3/3	1.82 [0.28-11.61]
Non-specified pesticides	18/14	1.98 [0.90-4.35]	11/9	1.54 [0.54-4.34]	7/5	2.47 [0.63-9.62]
Other chemical products						
Dyes	27/26	1.55 [0.84-2.88]	14/15	1.16 [0.48-2.76]	13/11	2.44 [0.93-6.40]
Inks	13/18	1.27 [0.58-2.81]	7/10	1.11 [0.36-3.42]	6/8	1.90 [0.57-6.38]
Adhesives	47/71	0.84 [0.53-1.34]	40/54	1.08 [0.61-1.89]	7/17	0.88 [0.30-2.56]
Disinfectants	16/18	1.14 [0.53-2.44]	11/16	0.72 [0.29-1.84]	5/2	9.66 [1.29-72.44]*
Cleaning products	33/35	1.98 [1.13-3.44]*	9/15	0.57 [0.21-1.56]	24/20	3.53 [1.64-7.59]*
Non-specified other chemical products	36/63	0.97 [0.61-1.55]	30/38	1.35 [0.76-2.39]	6/25	0.47 [0.17-1.30]

Abbreviation: CI, confidence interval; OR, odds ratio. *P <0.05 # Insulation fibre: mostly fibreglass. + Sheep/Cattle dip: pesticides, mainly insecticides and fungicides, used to protect cattle and sheep from external parasites.
OR adjusted for age, sex (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking status, sports, alcohol, head injury, spine injury, and for the respective other self-reported exposures.

5.4 Discussion

This study found that several common occupational exposures were associated with an increased risk of MND, including pesticides, fumigants, petrol/diesel fuel, unspecified solvents, textile fibres, and cleaning products.

Exposure to pesticides was associated with a 70% increase in MND risk (OR 1.70; 95%CI: 1.17, 2.48), with very similar relative risk estimates for males and females, and with a lifetime exposure prevalence of 20% among controls (29% males, 9.5% females). Estimating a population attributable fraction (PAF=100*(Px*(OR-1))/(1+(Px*(OR-1))); Px is the exposure prevalence among the controls) based on these numbers suggests that 12.4% of MND cases in our study population may be attributable to pesticide exposure (17.3% for males and 7.2% for females). The associations were strongest for those with the longest exposure duration and for those who had applied pesticides themselves and were, therefore, more likely to have been exposed to higher levels compared to those who were exposed indirectly for whom we found no association. These findings are consistent with three meta-analyses and two recent systematic reviews that reported positive associations between pesticide exposure and ALS.[37 39-41 203] It is also consistent with previous studies showing no associations in people who were indirectly exposed to pesticides.[477 478]

In this study, exposure to insecticides was associated with a three-times greater MND risk, with associations observed for several insecticide classes (organochlorines, organophosphates, and pyrethroids). Other studies focusing on specific pesticide classes have also reported associations for organochlorines,[37 319] including pentachlorobenzene, cis-chlordane,[319] aldrin, dieldrin, DDT, and toxaphene.[37] The role of organochlorines in

MND is biologically plausible, given their known neurotoxicity,[479] but these have largely been discontinued in New Zealand. Consistent with the previous studies[303] we observed increased MND risks for organophosphates, a class of insecticides of continued high use. This is biologically plausible as polymorphisms in paraoxonase 1, an enzyme that detoxifies organophosphates,[480] have been associated with the development of ALS,[481] and high exposure to organophosphates can result in OP-induced delayed neuropathy, a condition akin to ALS.[302] Organophosphates also induce oxidative stress,[482] which plays an important role in the pathogenesis of MND.[408] We observed an elevated MND risk from exposure to pyrethroids insecticides, which is consistent with an earlier case report that presented a patient who developed MND after three years of chronic exposure to pyrethroids.[308] An increased risk for exposure to fungicides, in particular inorganic fungicides, was also found, which is similar to two previous case-control studies that reported an elevated, but not statistically significant risk for occupational fungicides exposure.[36 184]

For fumigants, which are predominantly used as insecticides, we also observed an elevated risk in both men and women, with the greatest risk observed for those with the longest exposure duration. All fumigant sub-categories were positively associated with MND, but only the association with methyl bromide was statistically significant. A meta-analysis reported positive associations with fumigants (OR 1.8) and methyl bromide (OR 1.2), but the findings did not reach statistical significance.[37] An earlier New Zealand report suggested a role for methyl bromide in a cluster of MND cases in port workers,[483] however, a subsequent investigation noted that the evidence was inconclusive.[484] In our study, exposure to methyl bromide predominantly occurred in horticulture where it has been used to sterilise the soil. While this application of methyl

bromide is now discontinued in New Zealand, methyl bromide continues to be used for the fumigation of export logs. Chronic exposure to methyl bromide can damage both the central and peripheral nervous systems,[300] but a specific mechanistic pathway for methyl bromide has not been established.

We observed elevated risks for exposure to petrol/diesel fuel (OR 2.24), which was different from an earlier study that found no association,[43] although another study found an association between diesel motor exhaust and ALS.[485] Lead, a petrol additive until 1996 in New Zealand and a known neurotoxin that can cross the Blood-Brain Barrier and accumulate in neuronal and glial cells,[203] may explain the association with petrol/diesel fuel oil. In particular, several studies have reported positive associations with lead exposure,[36 182 184] including a recent meta-analysis.[201] For the majority of participants, petrol/diesel fuel oil exposure occurred before 1996 when lead was phased out from petrol in New Zealand, hence, we were not able to elucidate whether associations observed in our study were attributable to lead, or other petrol components e.g., benzene.

Solvents have been associated with an increased MND risk,[263] but most studies did not specify the type of solvent. Case-control studies have reported positive associations for alcohols or ketones, cleaning solvents or degreasers,[36] n-hexane,[43] thinners, and paint removers.[184] A recent Danish study, using job exposure matrices (JEM) to estimate cumulative solvent exposure, found associations with methylene chloride and benzene in men.[263] However, a Dutch prospective cohort study, using a JEM to assess occupational exposures to total solvents, chlorinated, and aromatic solvents found no significant association with ALS mortality.[264] In our study, the overall category of

solvents was not associated with MND, although an increased risk for men exposed to non-specified solvents was found (the majority of participants reporting solvent exposure could not recall which specific solvent was used). Organic solvents are known neurotoxins and long-term exposure may cause encephalopathy, cognitive deficits, disrupt motor function,[249] and increase oxidative stress,[486] which play a role in motor neurone degeneration.[408] In addition, exposure to solvents has been associated with other neurodegenerative conditions including Alzheimer's disease, Parkinson's disease, and multiple sclerosis,[249] with which MND shares some underlying biological mechanisms.[487]

We found that several exposures were associated with MND only among women including exposure to textile fibres, despite analyses being based on similar numbers of exposed males and females. Textile and clothing workers have previously been shown to have an increased risk of MND,[488] although another study observed an inverse association between textile work and ALS.[188] The observed increased risk for textile fibres could be the result of exposure to other compounds commonly associated with textiles, such as dyes, solvents, antimicrobial agents, or organophosphorus and organobromine flame retardants.[489]

An increased MND risk was observed for disinfectants and cleaning products, again only among women. In a Danish cohort, an inverse association was found for women employed in the cleaning industry.[323] An association between disinfectants and MND has not been reported previously. The use of disinfectants may also be a marker of exposure to infectious agents, which may play a role in the development of ALS.[490]

This study has several limitations. Exposure was assessed through self-reports, which can be subject to exposure misclassification and recall bias. On average, cases and controls reported the same number of jobs, suggesting no differential recall in lifetime occupational histories between cases and controls. For each job, exposures were initially assessed using tick-boxes for 11 categories, after which participants were asked (for each ticked category) to provide more information on product names, sources, and tasks related to the exposure(s). Self-reported exposures were subsequently compared with job titles and task descriptions to ensure that they were relevant for that job, thus reducing exposure misclassification. This was done blind to the case/control status of participants, thus limiting differential exposure misclassification. However, it cannot be excluded that cases recall their exposures differently from controls, particularly for exposures widely known to adversely impact health. Nevertheless, for our main findings, including the observed increased risks associated with insecticides, fungicides, and petrol/diesel fuel oil, we have previously found corresponding elevated risks for occupational groups where these exposures are most common (e.g., agricultural occupations, forecourt attendant),[458] for which, as noted above, recall bias is less likely. Furthermore, we found positive and statistically significant duration-response associations for these exposures, with exposure duration based on job duration, which is unlikely to be subject to differential recall. Therefore, we consider recall bias to be an unlikely explanation for the observed associations. However, self-reports have clear limitations, particularly when attempting to assess exposures to highly specific agents, as illustrated by the high proportion of participants reporting exposure to non-specified solvents (Table 5.4).

We had no detailed information on personal protective equipment (PPE)-use, but consider that this would have minimal impact on the study results, given that effective PPE such as full protective clothing and respirators have only more recently become available. Moreover, the lack of information on exposure levels is a limitation.

While participation was high among cases (92%), lower participation was achieved for controls (42%), which may contribute to participation bias. We had access to basic information (age, sex, deprivation, address, occupation) from the Electoral Roll for all non-participating controls and compared this with participating controls; this showed no large differences[458] and suggests that participation bias is unlikely to explain our findings. For example, participating controls were slightly more likely to live rurally (18%) compared to non-participating controls (14%), suggesting that participation bias is unlikely to explain the observed increased MND risks for pesticides exposures.

Another limitation is that cases more often opted for a face-to-face interview. To evaluate potential bias, we repeated all analyses controlling for the interview method, which made very little difference and did not alter our findings (data not shown). We also conducted analyses stratified by interview method, which resulted in wider confidence intervals, but largely identified the same exposures as being associated with an elevated risk (Supplementary Table S5.8). This suggests that our main findings are unlikely to be affected by differential information bias due to using different interview methods. Moreover, as both incident and prevalent cases were included, we also conducted stratified analyses to assess whether associations differed by case type (Supplementary Table S5.9). Findings were very similar for the incident and prevalent cases, suggesting that case status did not affect the results.

The age and sex distribution differed between cases and controls. This is due to controls being matched based on the age/sex distribution of MND incidence in the United Kingdom, as equivalent New Zealand data was not available at the time of participant recruitment. However, all associations were adjusted for age and sex, and the main findings are therefore unlikely to be explained by differences in age/sex distribution between cases and controls.

Finally, we had no information on specific MND subtypes (this was not recorded in New Zealand at the time of study recruitment). Analyses could therefore not be restricted to ALS to improve comparability with other studies, the majority of which reported on ALS. However, as ALS is the most common form of MND accounting for 80-90% of the total cases,[474] our case definition is therefore unlikely to differ substantially from those used in other studies.

Our study has several strengths. First, the MND diagnosis was confirmed by neurologists. Second, the study size is relatively large in comparison with many other case-control studies with access to lifetime occupational exposure histories. Third, cases and controls mostly answered the questionnaire without the use of proxies, which is a particular advantage compared to studies based on MND mortality. Fourth, using the MNDANZ national register, the NMDS, and the New Zealand Electoral Roll to identify cases and controls was an important strength of this study. In particular, the MNDANZ national register and NMDS provided a reliable source for all MND patients in New Zealand, and the Electoral Roll records virtually all New Zealand citizens and permanent residents. These sources are therefore representative of the general population that generated the cases. Finally, we were able to adjust analyses for

potential confounders by collecting extensive information on education, SES, smoking, alcohol consumption, and injury, as well as other (self-reported) occupational exposures, ELF-MF, and electric shocks.

5.5 Conclusions

In conclusion, this study shows that several common occupational exposures are associated with MND, including pesticides to which a relatively large proportion of the population continues to be exposed to. Measures to reduce these exposures may contribute to a reduction in MND incidence.

Acknowledgements

We are grateful to the Motor Neurone Disease Association New Zealand, and their field staff for their generous support.

Funding information

The study was funded by a grant from the Health Research Council (HRC) of New Zealand (Part of 11/1041 HRC Programme Grant - Building Research in Occupational Health in New Zealand (BROHNZ)).

Declaration of competing financial interests

The authors declare they have no actual or potential competing financial interests.

5.6 Supplementary material

Table S5.5. Supplementary Table. Risk of Motor Neurone Disease and Self-reported Occupational Exposures to Pesticides by Application Groups in a Population-Based Case-Control Study, New Zealand, 2013-2016

Pesticide exposure	All Cases/Controls (319/604)		OR (95%CI)	OR[1] (95%CI)	Male Cases/Controls (203/331)		OR (95%CI)	OR[1] (95%CI)	Female Cases/Controls (116/273)		OR (95%CI)	OR[1] (95%CI)
	No.	%			No.	%			No.	%		
Not exposed	210/482	65.8/79.8	1	1	116/235	57.1/71	1	1	94/247	81/90.5	1	1
Exposed indirectly	41/71	12.9/11.8	1.23[0.79-1.90]	1.14[0.71-1.82]	25/52	12.3/15.7	1.01[0.57-1.77]	0.98[0.53-1.80]	16/19	13.8/7	2.02[0.95-4.32]	1.75[0.74-4.15]
Applied pesticides	68/51	21.3/8.4	2.99[1.94-4.60]*	2.72[1.66-4.44]*	62/44	30.5/13.3	3.12[1.92-5.06]*	2.88[1.61-5.16]*	6/7	5.2/2.6	2.20[0.67-7.22]	2.01[0.56-7.24]

Abbreviation: CI, confidence interval; OR, odds ratio.
OR adjusted for age and sex (or age only in case of sex-stratified analyses), education, ethnicity, socioeconomic status (SES), smoking status, sports, alcohol, head injury, spine injury.
OR[1] adjusted for age, sex (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking status, sports, alcohol, head injury, spine injury, and for the respective other self-reported exposures.
*P <0.05

Table S5.6. Supplementary Table. Motor Neurone Disease Risk by Duration in a Population-Based Case-Control Study, New Zealand, 2013-2016

Exposures	All Cases/Controls (n) (319/604)	OR (95%CI)	Male Cases/Controls (n) (203/331)	OR (95%CI)	Female Cases/Controls (n) (116/273)	OR (95%CI)
Dust						
Never exposed	149/317	1	70/127	1	79/190	1
Exposed <7 years	42/82	0.70[0.44-1.13]	26/52	0.54[0.28-1.04]	16/30	0.65[0.29-1.46]
Exposed 7-16 years	29/66	0.58[0.33-1.00]	24/44	0.53[0.26-1.06]	5/22	0.33[0.10-1.08]
Exposed 17-34 years	41/68	0.71[0.42-1.20]	29/48	0.62[0.31-1.23]	12/20	0.67[0.26-1.73]
Exposed >34 years	58/71	0.95[0.58-1.57]	54/60	1.06[0.58-1.93]	4/11	0.57[0.15-2.18]
p(trend)		*0.526*		*0.843*		*0.112*
Environmental Tobacco smoke						
Never exposed	153/315	1	90/148	1	63/167	1
Exposed <6 years	44/81	0.90[0.57-1.42]	25/38	0.75[0.39-1.46]	19/43	1.10[0.55-2.21]
Exposed 6-12 years	36/65	1.01[0.62-1.65]	21/37	0.84[0.44-1.64]	15/28	1.57[0.69-3.59]
Exposed 13-30 years	43/70	1.07[0.66-1.74]	30/48	0.87[0.47-1.59]	13/22	1.34[0.56-3.25]
Exposed >30 years	43/73	1.04[0.64-1.68]	37/60	0.96[0.55-1.69]	6/13	1.19[0.36-3.87]
p(trend)		*0.782*		*0.816*		*0.392*
Other smoke or fume						
Never exposed	184/411	1	87/173	1	97/238	1
Exposed <6 years	28/49	0.88[0.51-1.54]	21/35	0.82[0.40-1.68]	7/14	0.80[0.27-2.40]
Exposed 6-15 years	32/51	1.06[0.61-1.83]	24/40	0.98[0.50-1.94]	8/11	0.83[0.27-2.58]
Exposed 16-29 years	35/46	1.11[0.62-1.97]	31/40	1.16[0.60-2.24]	4/6	0.87[0.16-4.63]
Exposed >29 years	40/47	1.22[0.70-2.14]	40/43	1.43[0.77-2.67]	0/4	
p(trend)		*0.466*		*0.244*		*0.251*
Gas						
Never exposed	268/542	1	161/286	1	107/256	1
Exposed <5 years	12/16	0.90[0.38-2.12]	9/8	1.37[0.43-4.37]	3/8	0.41[0.09-1.90]
Exposed 5-16 years	18/16	1.54[0.70-3.37]	16/13	1.75[0.73-4.18]	2/3	0.67[0.07-6.54]
Exposed 17-30 years	11/16	0.96[0.40-2.30]	8/13	0.84[0.30-2.31]	3/3	2.06[0.29-14.8]
Exposed >30 years	10/14	0.83[0.32-2.12]	9/11	1.19[0.40-3.55]	1/3	0.17[0.01-2.39]
p(trend)		*0.974*		*0.607*		*0.399*
Acids or Alkalis						
Never exposed	271/532	1	162/272	1	109/260	1
Exposed <7 years	15/20	0.79[0.37-1.67]	12/15	0.77[0.33-1.81]	3/5	0.98[0.19-5.16]
Exposed 7-16 years	7/17	0.46[0.17-1.24]	5/15	0.33[0.10-1.14]	2/2	2.19[0.20-24.44]
Exposed 17-29 years	14/18	1.00[0.45-2.19]	12/15	0.96[0.39-2.34]	2/3	1.21[0.16-9.38]
Exposed >29 years	12/17	0.94[0.41-2.15]	12/14	1.16[0.48-2.80]	0/3	
p(trend)		*0.561*		*0.774*		*0.778*
Animal and Animal products						
Never exposed	214/462	1	130/234	1	84/228	1
Exposed <4 years	23/38	1.03[0.57-1.85]	13/24	0.86[0.39-1.89]	10/14	1.58[0.58-4.31]
Exposed 4-10 years	21/33	1.05[0.56-2.00]	15/22	1.00[0.45-2.26]	6/11	1.24[0.37-4.20]
Exposed 11-22 years	24/38	1.09[0.59-2.00]	13/27	0.76[0.33-1.73]	11/11	2.19[0.79-6.10]
Exposed >22 years	37/33	1.90[1.07-3.40]*	32/24	2.00[0.99-4.04]	5/9	0.87[0.24-3.24]
p(trend)		*0.080*		*0.213*		*0.408*

Abbreviation: CI, confidence interval; OR, odds ratio.

OR adjusted for age, sex (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking status, sports, alcohol, head injury, spine injury, and for the respective other self-reported exposures.

*P <0.05

Table S5.7. Supplementary Table. Risk of Motor Neurone Disease with Self-reported Occupational Exposures to Leaded Fuel Oil in a Population-Based Case-Control Study, New Zealand, 2013-2016

Fuel exposure	All				Male				Female			
	Cases/Controls (319/604)		OR (95%CI)	OR[1] (95%CI)	Cases/Controls (203/331)		OR (95%CI)	OR[1] (95%CI)	Cases/Controls (116/273)		OR (95%CI)	OR[1] (95%CI)
	No.	%			No.	%			No.	%		
Exposure to Fuel oils												
Never exposed	275/570	86.2/94.4	1	1	163/303	80.3/91.5	1	1	112/267	96.6/97.8	1	1
Exposed to Leaded fuel oil	40/30	12.5/5.0	2.41[1.43-4.06]*	2.20[1.27-3.79]*	36/24	17.7/7.3	2.81[1.57-5.05]*	2.63[1.41-4.91]*	4/6	3.4/2.2	1.57[0.41-6.11]	1.26[0.28-5.61]
Exposed to Unleaded fuel oil only	4/4	1.3/0.6	1.49[0.35-6.32]	1.64[0.37-7.18]	4/4	2.0/1.2	1.63[0.36-7.39]	2.09[0.44-9.96]	0/0			
Duration of exposure to leaded fuel oil												
Never exposed	279/574	87.5/95.0	1	1	167/307	82.3/92.8	1	1	112/267	96.6/97.8	1	1
Exposed <3 years	8/9	2.5/1.5	1.47[0.54-3.97]	1.59[0.58-4.35]	6/7	3.0/2.1	1.41[0.45-4.44]	1.75[0.54-5.65]	2/2	1.7/0.7	1.67[0.21-13.19]	1.18[0.14-10.26]
Exposed 3-8 years	13/6	4.1/1.0	3.17[1.14-8.77]	2.28[0.76-6.84]	13/4	6.4/1.2	4.52[1.38-14.78]	2.67[0.73-9.73]	0/2	0/0.7		
Exposed 9-29 years	14/8	4.4/1.3	3.66[1.46-9.18]	3.45[1.35-8.81]	12/7	5.9/2.1	4.04[1.49-10.96]	4.12[1.48-11.52]	2/1	1.7/0.4	6.12[0.49-77.26]	4.39[0.24-81.48]
Exposed >29 years	5/7	1.6/1.2	1.53[0.46-5.10]	1.43[0.41-4.93]	5/6	2.4/1.8	1.85[0.52-6.60]	1.84[0.50-6.81]	0/1	0/0.4		
p(trend)			*0.002*	*0.008*			*0.001*	*0.004*			*0.524*	*0.673*

Abbreviation: CI, confidence interval; OR, odds ratio.

OR adjusted for age and sex (or age only in case of sex-stratified analyses), education, ethnicity, socioeconomic status (SES), smoking status, sports, alcohol, head injury, spine injury.

OR[1] adjusted for age, sex (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking status, sports, alcohol, head injury, spine injury, and for the respective other self-reported exposures.

*P <0.05

Table S5.8. Supplementary Table. Risk of Motor Neurone Disease with Self-reported Occupational Exposures stratified by Interview Methods in a Population-Based Case-Control Study, New Zealand, 2013-2016

Self-Reported Exposures	Telephone Cases/Controls (73/401)		OR (95%CI)	OR[1] (95%CI)	Face to Face Cases/Controls (187/97)		OR (95%CI)	OR[1] (95%CI)	Post Cases/Controls (59/106)		OR (95%CI)	OR[1] (95%CI)
	No.	%			No.	%			No.	%		
Dust	41/193	56.2/48.1	0.97[0.55-1.73]	0.74[0.38-1.42]	109/63	58.3/65	0.71[0.39-1.31]	0.57[0.29-1.12]	20/31	33.9/29.3	1.60[0.67-3.84]	1.29[0.42-3.96]
Fibres	17/82	23.3/20.5	0.87[0.45-1.70]	0.73[0.35-1.54]	64/32	34.2/33	1.08[0.61-1.93]	1.18[0.61-2.28]	10/12	17/11.3	1.73[0.58-5.10]	1.88[0.53-6.61]
Environmental tobacco smoke	41/194	56.2/48.4	1.19[0.67-2.09]	1.20[0.66-2.19]	106/58	56.7/59.8	0.86[0.49-1.51]	0.86[0.47-1.57]	19/37	32.2/34.9	0.83[0.38-1.82]	0.88[0.36-2.15]
Other smoke or Fumes	31/127	42.5/31.7	1.10[0.60-2.00]	1.01[0.52-1.95]	91/44	48.7/45.4	1.21[0.65-2.24]	1.19[0.58-2.43]	13/22	22/20.8	1.23[0.48-3.13]	0.66[0.17-2.62]
Gas	8/44	11/11	0.93[0.39-2.23]	0.87[0.34-2.22]	38/13	20.3/13.4	1.60[0.74-3.45]	1.41[0.60-3.30]	5/5	8.5/4.7	2.25[0.52-9.81]	2.74[0.44-17.1]
Fumigants	0/4	0/1			22/4	11.8/4.1	3.46[1.06-11.28]*	2.94[0.85-10.13]	4/2	6.8/1.9	2.91[0.47-18.09]	2.82[0.40-19.75]
Oils and solvents	33/126	45.2/31.4	1.60[0.88-2.91]	1.89[0.97-3.69]	86/44	46/45.4	1.02[0.56-1.85]	0.91[0.43-1.91]	14/25	23.7/23.6	1.00[0.42-2.39]	0.83[0.23-3.05]
Acids or Alkalis	5/42	6.9/10.5	0.48[0.17-1.34]	0.40[0.14-1.18]	37/18	19.8/18.6	1.08[0.53-2.20]	1.01[0.48-2.14]	6/12	10.2/11.3	0.76[0.21-2.75]	0.30[0.05-1.65]
Pesticides	22/85	30.1/21.2	1.34[0.72-2.48]	1.21[0.60-2.46]	69/27	36.9/27.8	1.72[0.93-3.18]	1.75[0.89-3.46]	18/10	30.5/9.4	4.91[1.76-13.69]*	5.12[1.45-18.15]*
Other chemical products	30/123	41.1/30.7	1.40[0.80-2.43]	1.46[0.80-2.64]	94/43	50.3/44.3	1.04[0.60-1.82]	1.05[0.57-1.93]	13/27	22/25.5	0.80[0.33-1.92]	0.64[0.20-1.99]
Animals or animal products	26/90	36.5/22.4	1.84[1.03-3.29]*	1.83[0.94-3.53]	64/36	34.2/37.1	1.04[0.58-1.84]	0.86[0.45-1.66]	15/16	25.4/15.1	2.08[0.82-5.28]	1.86[0.56-6.22]

Abbreviation: CI, confidence interval; OR, odds ratio.
OR adjusted for age and sex (or age only in case of sex-stratified analyses), education, ethnicity, socioeconomic status (SES), smoking status, sports, alcohol, head injury, spine injury.
OR[1] adjusted for age, sex (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking status, sports, alcohol, head injury, spine injury, and for the respective other self-reported exposures.
*P <0.05

Table S5.9. Supplementary Table. Risk of Motor Neurone Disease with Self-reported Occupational Exposures by Case Status in a Population-Based Case-Control Study, New Zealand, 2013-2016

Self-Reported Exposures	Incident Cases/Controls (223/604)		OR (95%CI)	OR[1] (95%CI)	Prevalent Cases/Controls (96/604)		OR (95%CI)	OR[1] (95%CI)
	No.	%			No.	%		
Dust	118/287	52.9/47.5	0.99[0.70-1.40]	0.75[0.50-1.13]	52/287	54.2/47.5	1.05[0.65-1.69]	0.70[0.39-1.24]
Fibres	66/126	29.6/20.9	1.39[0.96-2.03]	1.40[0.96-2.04]	25/126	26/20.9	1.18[0.69-2.03]	1.00[0.54-1.85]
Environmental tobacco smoke	117/289	52.5/47.9	1.06[0.76-1.48]	1.02[0.72-1.45]	49/289	51/47.9	1.06[0.67-1.68]	0.89[0.54-1.47]
Other smoke or Fumes	88/193	39.5/32	1.13[0.79-1.63]	0.92[0.60-1.41]	47/193	49/32	1.77[1.06-2.95]*	1.56[0.86-2.84]
Gas	30/62	13.5/10.3	1.06[0.65-1.74]	0.87[0.50-1.51]	21/62	21.7/10.3	2.04[1.14-3.65]*	1.61[0.81-3.19]
Fumigants	15/10	6.7/1.7	3.84[1.62-9.09]*	3.29[1.37-7.90]*	11/10	11.5/1.7	7.77[3.03-19.92]*	5.39[1.97-14.78]*
Oils and solvents	93/195	41.7/32.3	1.28[0.89-1.85]	1.19[0.78-1.83]	40/195	41.7/32.3	1.19[0.72-1.94]	0.87[0.48-1.58]
Acids or Alkalis	32/72	14.4/11.9	1.00[0.62-1.62]	0.79[0.47-1.34]	16/72	16.7/11.9	1.07[0.56-2.05]	0.72[0.35-1.48]
Pesticides	74/122	33.2/20.2	1.82[1.26-2.63]*	1.55[1.02-2.37]*	35/122	36.5/20.2	2.03[1.23-3.34]*	1.87[1.04-3.37]*
Other chemical products	90/193	40.4/32	1.29[0.93-1.80]	1.13[0.78-1.63]	47/193	49/32	1.87[1.19-2.94]*	1.80[1.10-2.96]*
Animals or animal products	77/142	34.5/23.5	1.64[1.15-2.34]*	1.44[0.96-2.17]	28/142	29.2/23.5	1.23[0.74-2.04]	0.82[0.45-1.48]

Abbreviation: CI, confidence interval; OR, odds ratio.
OR adjusted for age and sex (or age only in case of sex-stratified analyses), education, ethnicity, socioeconomic status (SES), smoking status, sports, alcohol, head injury, spine injury.
OR[1] adjusted for age, sex (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking status, sports, alcohol, head injury, spine injury, and for the respective other self-reported exposures.
*P <0.05

CHAPTER 6 Sports and trauma as risk factors for Motor Neurone Disease: New Zealand case-control study

Grace Chen[1], Jeroen Douwes[1], Leonard H. van den Berg[2], Bill Glass[1], David McLean[1], Andrea 't Mannetje[1]

[1] Research Centre for Hauora and Health, Massey University, Wellington, New Zealand

[2] Brain Centre Rudolf Magnus, Department of Neurology, University Medical Centre, Utrecht, The Netherlands.

(Published in Acta Neurologica Scandinavica. 2022 145(6):770-785)

ABSTRACT

Objectives To assess whether sports, physical trauma and emotional trauma are associated with motor neurone disease (MND) in a New Zealand case-control study (2013-2016).

Methods In total 321 MND cases and 605 population-controls were interviewed collecting information on lifetime-histories of playing sports, physical trauma (head injury with concussion, spine injury), and emotional trauma (14 categories). ORs were estimated using logistic regression adjusting for age, sex, ethnicity, socioeconomic status, education, smoking status, alcohol consumption and mutually adjusting for all other exposures.

Results Head injury with concussion ≥3 years before diagnosis was associated with MND (OR 1.51,95%CI:1.09-2.09), with strongest associations for two (OR 4.01,95%CI:1.82-8.86), and three or more (OR 2.34,95%CI:1.00-5.45) head injuries. Spine injury was not associated with MND (OR 0.81,95%CI:0.48-1.36). Compared to never playing sports, engaging in sports throughout childhood and adulthood increased MND risk (OR 1.81,95%CI:1.01-3.25), as was more than 12-years playing football/soccer (OR 2.35,95%CI:1.19-4.65). Reporting emotionally traumatic events in more than three categories was associated with MND (OR 1.88,95%CI:1.17-3.03), with physical childhood abuse the only specific emotional trauma associated with MND (OR 1.82,95%CI:1.14-2.90), particularly for those reporting longer abuse duration ($OR_{(5\text{-}8\ years)}$ 2.26,95%CI:1.14-4.49; $OR_{(>8\ years)}$ 3.01,95%CI:1.18-7.70). For females, having witnessed another person being killed, seriously injured or assaulted also increased MND risk (OR 2.68, 95%CI:1.06-6.76).

Conclusions This study adds to the evidence that repeated head injury with concussion, playing sports in general, and playing football (soccer) in particular, are associated with

an increased risk of MND. Emotional trauma, i.e. physical abuse in childhood, may also play a role.

6.1 Introduction

Motor Neurone diseases (MND) are a group of relatively rare, progressive, and terminal neurodegenerative conditions (with Amyotrophic Lateral Sclerosis (ALS) being the most common) characterised by the degeneration of upper and lower motor neurones leading to motor and extra-motor symptoms.[57] The aetiology of MND is believed to involve complex interactions of environmental, lifestyle and genetic factors,[56 491] but few conclusive risk factors have been established.

There is growing interest in the role of contact sports (football (or soccer in the US), American football, and rugby) following MND diagnoses in several high-profile professional athletes.[373] Several studies have since assessed the association between professional sports and MND. An Italian cohort study, comparing professional football (soccer) players with the general population,[361] reported a standardised morbidity ratio (SMR) of 6.5 (95%CI: 2.1, 15.1) (5 ALS cases observed, 0.77 expected); a longer career in professional football (soccer) was associated with a greater risk and earlier onset. A recent update[372] reported a two-fold risk of ALS for professional football (soccer) players (34 ALS cases observed, 17.8 expected) and 20-year earlier disease onset. Similar findings were reported for a Scottish cohort of professional football (soccer) players[369] for which an MND hazard ratio of 4.33 (95%CI: 2.05, 9.15) was observed.

Professional athletes in sports other than football (soccer) have been less studied. In a US cohort of National (American) Football League players,[363] ALS mortality was increased (SMR 4.31, 95%CI: 1.73, 8.87) with a higher risk for players in speed positions compared to non-speed positions. A Swedish study among cross-country

skiers[371] showed an increased risk for elite skiers (OR 4.31 95%CI: 1.78, 10.4) but not for recreational skiers. A clinic-based observational study[492] showed that triathletes were over-represented in a population of patients with ALS (OR 16.15, 95%CI: 5.82, 36.38) and also had earlier disease onset.

Association with professional sports may be due to high strenuous physical exertion and/or more frequent traumatic brain injury, although evidence is mixed. Several case-control studies reported an increased MND risk among people who engage in strenuous physical activities,[351 375 379 380] but other case-control studies reported no[378] or inverse associations.[343 377] A prospective cohort study among postmenopausal women showed that strenuous physical activities were associated with an increased risk of MND,[382] in contrast, another cohort study in European Prospective Investigation into Cancer and Nutrition showed a slightly reduced risk of dying from ALS in those with high levels of total physical activity at enrolment.[383] A recent Mendelian randomisation study suggested a positive association between physical exercise and ALS in those with a specific risk-genotype.[387]

Several studies have shown an increased risk[337-340] with traumatic brain injury, while others found no association.[345 351 352] Meta-analyses[41 337 357 358] have indicated a 1.3-1.7-fold increased risk of MND in relation to a head injury. However, another meta-analysis found that the association was weaker and suggested that due to reverse-causation, head-injury-associated-risk of ALS has been somewhat overestimated.[356]

Emotional trauma has also been proposed as a risk factor for MND (and other neurodegenerative diseases), possibly due to increased oxidative stress,[493] but the

evidence is limited. A Japanese case-control study[380] showed that self-reported stress was associated with an increased risk of ALS (OR 1.8, 95%CI: 1.3, 2.7) while a UK study[494] reported a 1.5-fold increased MND risk for a former diagnosis of depression. However, a recent Australian study[495] found no difference in exposures to potentially stressful life events between ALS cases and controls.

Thus, while studies have provided intriguing leads about the role of physical activity, traumatic brain injury, and emotional trauma, the evidence remains largely inconclusive. As part of a New Zealand MND case-control study, we assessed the association between sports, physical trauma (head injury, spine injury), emotional trauma, and the risk of MND.

6.2 Methods

The detailed background information on the study population recruitment and data collection methodology of this population-based case-control study is provided in Appendix 1.

6.2.1 Study population

Cases were recruited primarily through the Motor Neurone Disease Association of New Zealand (MNDANZ) over a period of three years (2013-2016). This was supplemented with searches for all hospital outpatients with a primary or secondary diagnosis of MND (ICD 10 code-G122) from the National Minimum Dataset (2013-2015).[441] The inclusion criterion for cases was a diagnosis by a neurologist, with all forms of MND included. A total of 2400 controls (two per case) were randomly selected from the New Zealand Electoral Roll (2008), frequency matched by age (based on the age-distribution of the Unite Kingdom MND incidence distribution, as New Zealand MND incidence age distribution was not available)[81] and sex. Controls with any neurodegenerative disease were excluded.

All participants gave written informed consent. Ethical approval was obtained by the Multi-region Ethics Committee in New Zealand (ref: MEC/12/01/005).

6.2.2 Data collection

Depending on the preference of the participants, a face-to-face (59% in cases vs 16% in controls) or a telephone interview (23% vs 66%), or a postal questionnaire (18% vs 18%) was used to collect information on demographic and personal characteristics,

family history, physical trauma/injury, emotional trauma (life events) physical activities (sports), smoking, alcohol, and a lifetime occupational history as described previously.[458] All controls completed the questionnaire themselves, while nine cases used a proxy (three required proxy assistance with a face-to-face interview, and six used proxy assistance for reading and writing only).

6.2.3 Exposure assessment

6.2.3.1 Physical trauma

All participants were asked whether they had ever had an injury that required medical care. If they answered yes, information for each injury was collected including injury type (head injury with a concussion, fracture, contusion, sprain, strain, other); circumstances of the injury (work, sport, leisure other than sport, traffic accident, other); age at which the injury occurred; body location of the injury (head, arms, chest, abdomen, legs, spine); and the severity of the injury (mild, moderate, severe). The number of times the specific injury occurred was calculated for: (1) head injury with concussion; and (2) spine injury.

6.2.3.2 Sports

Participants were asked to complete a lifetime sports history. For each sport listed, information on year of start and cessation, and hours per week was obtained. A question on strenuous physical exertion was also included (“Have you ever engaged in a sport that required great physical effort, for instance running a marathon?”).

6.2.3.3 Emotional trauma (life events)

Participants were asked whether life events had occurred in any of the following 14 emotional trauma categories at any point in their life, including life-threatening illness; life-threatening accident; been physically forced in a robbery; threatened by a weapon (a knife or gun); experienced a close relation die of an accident, homicide or suicide; miscarriage (for women only); been physically forced to have sex; sexual harassment; been physically beaten/harmed by a family member or caregiver as a child; been physically beaten/harmed as an adult; been bullied by a family member; witnessed another person being killed or seriously injured; life in danger (living in military combat or a war zone); extremely frightening or horrifying situation. For each of these events, follow-up questions included how often and at what age the event occurred. Those who answered yes to 'physically beaten/harmed as a child' were also asked to describe the force/nature (the name and source of the force) used against them.

6.2.4 Statistical analyses

Statistical analyses were conducted using SAS version 9.4. Differences in general characteristics between cases and controls were tested using Chi-squared tests, and unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs), for ever-exposed to a particular event (sports, head injury, spine injury, emotional traumas), compared to never being exposed to that particular event.

Analyses were adjusted for age (5-year categories); sex; ethnicity (European; Māori, the indigenous population of New Zealand; other); highest achieved education level

(primary and secondary school, technical or trade school diploma, undergraduate university degree, postgraduate university degree); smoking status (never, ex, current smoker (smoker at the time of diagnosis for cases)); alcohol consumption before diagnosis (≤once a month,1-2 times/week, 3-5 times/week, daily); and socioeconomic status (SES) using the New Zealand Deprivation Index (NZDep2006, quintiles). All analyses were repeated separately for males and females. Additional analyses were conducted mutually adjusting for all other exposures (sports, head injury, spine injury, and emotional trauma). We checked for multicollinearity by comparing the standard errors for the main effect estimates between the full model, and a minimally adjusted model,[476] this showed no evidence of collinearity. Analyses were also repeated while controlling for the interview method.

We also assessed associations with the lifetime number of years played in a particular sport (for each sport separately). Duration was categorised based on quartiles in the controls, specific to each sport. A test for trend was performed by assigning scores to the categories of the categorical duration variables, which were subsequently fitted as continuous variables.

As it cannot be excluded that accidents and injuries may be an early manifestation of MND, even before diagnosis,[345] analyses were repeated excluding all injuries that occurred within 3 years before the index date (diagnosis date for cases, interview date for controls).

6.3 Results

6.3.1 Population characteristics

A total of 321 cases and 605 controls were included in the analyses. Of the cases, 63% were male versus 55% in controls. The majority of cases (68%) were aged >60 years. While the 70+ age group was overrepresented in the controls, there was little difference between cases and controls in ethnicity, socioeconomic status (SES), education, tobacco smoking, and alcohol consumption (Table 6.1).

Table 6.1. Characteristics of Participants in a Population-Based Case-Control Study of Sports, Physical Trauma, Emotional Trauma and Motor Neurone Disease, New Zealand, 2013-2016

	Cases (n=321)		Controls (n=605)		p-Value
	No.	%	No.	%	
Gender					0.0142
Male	203	63.24	332	54.88	
Female	118	36.76	273	45.12	
Age at interview					<.0001
20-59	103	32.09	140	23.14	
60-69	125	38.94	188	31.07	
≥70	93	28.97	277	45.79	
Ethnicity					0.7284
European/Pakeha [a]	295	91.90	563	93.06	
Māori [b]	14	4.36	25	4.13	
Pacific & others	12	3.74	17	2.81	
Deprivation Index Quintile					0.4665
1-2 (least deprived)	99	30.84	165	27.27	
3-4	79	24.61	143	23.64	
5-6	68	21.81	129	21.32	
7-8	43	13.40	108	17.85	
9-10	32	9.97	60	9.92	
Highest Education					0.1157
Secondary school (college)	145	45.17	290	47.93	
Technical or trade school diploma	105	32.71	155	25.62	
Undergraduate university degree	46	14.33	98	16.20	
Postgraduate university degree	25	7.79	62	10.25	
Alcohol consumption					0.1925
Never or less than once a month	75	23.36	166	27.44	
1-2 times a week	116	36.14	188	31.07	
3-5 times a week	76	23.67	129	21.32	
Daily	54	16.82	122	20.17	
Smoking (prior to diagnosis)					0.9142
Never	165	51.40	319	52.73	
Ex	20	6.23	35	5.78	
Current	136	42.37	251	41.49	

p-Values were calculated using a chi-square test for categorical variables.
[a] Pakeha (a Māori word) - This is used as a term specifically for New Zealand European people.
[b] Māori – indigenous people of New Zealand.

6.3.2 Head injury with concussion and spine injury

Among cases, 33% reported having ever had a head injury with a concussion, compared to 22% among controls (OR 1.49, 95%CI: 1.09, 2.05; Table 6.2). This difference remained after excluding all brain injuries that occurred within 3 years prior to diagnosis (OR 1.51, 95%CI: 1.09, 2.09). Reporting only one head injury with a concussion was not associated with an increased risk (OR 1.16, 95%CI: 0.80, 1.69), while statistically significant increased risks were observed for reporting two (OR 4.01, 95%CI: 1.82, 8.86; based on 22 cases and 10 controls), and 3 or more (OR 2.34, 95%CI: 1.00, 5.45; based on 14 cases and 11controls) head injuries. Elevated risks were observed for self-reported mild, moderate, and severe head injuries, but this reached statistical significance only for moderate injury (OR 1.77, 95%CI: 1.14, 2.77).

When considering the age at which head injury occurred (childhood only, adulthood only, or both childhood and adulthood), the highest risk was observed for having had head injuries in both childhood and adulthood (OR 1.87, 95%CI: 1.09, 3.21). While more males reported head injuries with concussion than females (28% of male and 16% of female controls), the observed pattern of an increased risk associated with multiple head injuries was similar for males and females. Head injuries in two or more different circumstances (work-related, sport-related, leisure-related, traffic accident, other accidents, and multiple circumstances) was associated with an almost 2.5-fold increased risk (OR 2.46, 95%CI: 1.11, 5.44; Table 6.3). When the number of head injuries in each circumstance was considered, elevated risks were observed for having had more than one sport-related head injury (OR 3.05, 95%CI: 1.06, 8.77), and more than one leisure-related head injury (OR 6.89, 95%CI: 1.18, 40.3). Having had one work-related head

injury was also associated with an increased risk (OR 2.48, 95%CI: 1.01, 6.09; Table 6.3).

Having ever had a spine injury (9% for cases and controls), repeated spine injury, the severity of the injury, and the age at the injury, were not associated with the risk of MND (Supplemental Table S6.7).

Table 6.2. Risk of Motor Neurone Disease with Head Injuries in a Population-Based Case-Control Study, New Zealand, 2013-2016

Exposure	All Cases/Controls (321/605) No	%	OR	95%CI	OR[1]	95%CI	Male Cases/Controls (203/332) No	%	OR	95%CI	OR[1]	95%CI	Female Cases/Controls (118/273) No	%	OR	95%CI	OR[1]	95%CI
Head Injury with concussion																		
Never	216/469	(67/78)	1	referent	1	referent	130/239	(64/72)	1	referent	1	referent	86/230	(73/84)	1	referent	1	referent
Ever	105/136	(33/22)	1.54	1.13, 2.11*	1.49	1.09, 2.05*	73/93	(36/28)	1.37	0.93, 2.03	1.32	0.89, 1.97	32/43	(27/16)	1.95	1.12, 3.38*	1.87	1.07, 3.27*
Head injury with concussion (>3 years before diagnosis)[a]																		
Never	224/483	(70/80)	1	referent	1	referent	134/248	(66/75)	1	referent	1	referent	90/235	(76/86)	1	referent	1	referent
Ever	97/122	(30/20)	1.57	1.13, 2.16*	1.51	1.09, 2.09*	69/84	(34/25)	1.45	0.97, 2.16	1.38	0.92, 2.08	28/38	(24/14)	1.82	1.02, 3.26*	1.76	0.98, 3.17
Frequency of head injury[a]																		
Never	224/483	(70/80)	1	referent	1	referent	134/248	(66/75)	1	referent	1	referent	90/235	(76/86)	1	referent	1	referent
Once	61/101	(19/17)	1.21	0.84, 1.74	1.16	0.80, 1.69	43/67	(21/20)	1.16	0.74, 1.83	1.12	0.71, 1.79	18/34	(15/12)	1.27	0.65, 2.46	1.20	0.61, 2.36
twice	22/10	(7/1)	4.17	1.90, 9.15*	4.01	1.82, 8.86*	14/9	(7/3)	2.50	1.01, 6.20*	2.34	0.94, 5.83	8/1	(7/1)	23.36	2.74, 199*	24.19	2.81, 208*
≥3 times	14/11	(4/2)	2.48	1.07, 5.74*	2.34	1.00, 5.45*	12/8	(6/2)	2.59	0.98, 6.83	2.39	0.90, 6.37	2/3	(2/1)	1.48	0.21, 10.3	1.45	0.20, 10.50
Severity of the head injury[a]																		
Never	224/483	(70/80)	1	referent	1	referent	134/248	(66/75)	1	referent	1	referent	90/235	(76/86)	1	referent	1	referent
Mild	21/29	(6/5)	1.52	0.83, 2.77	1.41	0.77, 2.59	15/20	(7/6)	1.41	0.68, 2.95	1.31	0.62, 2.77	6/9	(5/3)	1.64	0.53, 5.06	1.47	0.47, 4.58
Moderate	48/53	(15/9)	1.78	1.14, 2.76*	1.77	1.14, 2.77*	34/36	(17/11)	1.56	0.91, 2.70	1.55	0.89, 2.68	14/17	(12/6)	2.01	0.91, 4.43	2.03	0.91, 4.52
Severe	28/40	(9/6)	1.33	0.79, 2.25	1.25	0.73, 2.12	20/28	(10/8)	1.32	0.69, 2.51	1.21	0.63, 2.33	8/12	(7/5)	1.68	0.64, 4.44	1.61	0.60, 4.29
Age of head injury[a]																		
Never had a head injury	224/483	(70/80)	1	referent	1	referent	134/248	(6/75)	1	referent	1	referent	90/235	(76/86)	1	referent	1	referent
Childhood[b] only	18/30	(5/5)	1.18	0.63, 2.19	1.17	0.62, 2.18	11/21	(6/6)	0.93	0.42, 2.06	0.94	0.42, 2.10	7/9	(6/3)	1.87	0.64, 5.44	1.76	0.60, 5.17
Adulthood[c] only	47/61	(15/10)	1.57	1.02, 2.41*	1.49	0.96, 2.29	35/43	(17/13)	1.49	0.89, 2.51	1.39	0.82, 2.38	12/18	(10/7)	1.82	0.81, 4.08	1.75	0.77, 3.96
Childhood and adulthood	32/31	(10/5)	1.93	1.13, 3.30*	1.87	1.09, 3.21*	23/20	(11/6)	1.89	0.96, 3.71	1.81	0.92, 3.56	9/11	(8/4)	1.79	0.68, 4.73	1.78	0.67, 4.75

Abbreviation: CI, confidence interval; OR, odds ratio.
OR adjusted age, gender (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking, alcohol consumption.
OR[1]: adjusted age, gender (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking, alcohol consumption, sport, spine injury & emotional trauma.
[a] excluding head injuries that occurred within 3 years before diagnosis (for cases) and within 3 years before the interview (for controls).
[b] head injury occurred at age <=18 years
[c] head injury occurred at age >19 years
*P <0.05

Table 6.3. Risk of Motor Neurone Disease with Head Injuries in Different Circumstances in a Population-Based Case-Control Study, New Zealand, 2013-2016

Exposure	All Cases/Controls (321/605)		OR	95%CI	OR[1]	95%CI	Male Cases/Controls (203/332)		OR	95%CI	OR[1]	95%CI	Female Cases/Controls (118/273)		OR	95%CI	OR[1]	95%CI
	No	%					No	%					No	%				
Circumstances of head injury																		
Never	224/483	(70/80)	1	referent	1	referent	134/248	(66/75)	1	referent	1	referent	90/235	(76/86)	1	referent	1	referent
Work-related	14/11	(4/2)	2.25	0.98, 5.14	2.22	0.96, 5.12	12/9	(6/3)	2.46	0.97, 6.23	2.39	0.93, 6.10	2/2	(2/1)	1.81	0.22, 15.0	2.07	0.25, 17.4
Sport-related	29/37	(9/6)	1.48	0.87, 2.52	1.39	0.81, 2.38	22/30	(11/9)	1.27	0.68, 2.36	1.18	0.63, 2.21	7/7	(6/3)	2.47	0.78, 7.88	2.34	0.73, 7.53
Leisure-related	14/21	(4/3)	1.48	0.72, 3.03	1.50	0.73, 3.07	7/12	(3/4)	1.10	0.40, 3.06	1.13	0.40, 3.19	7/9	(6/3)	1.91	0.65, 5.65	1.83	0.61, 5.51
Traffic accident-related	17/27	(5/4)	1.34	0.70, 2.57	1.30	0.67, 2.50	10/15	(5/5)	1.30	0.54, 3.12	1.28	0.53, 3.11	7/12	(6/4)	1.55	0.57, 4.21	1.47	0.54, 4.04
Other accidents	6/14	(2/2)	0.85	0.32, 2.31	0.85	0.31, 2.30	3/8	(1/2)	0.63	0.16, 2.48	0.61	0.15, 2.42	3/6	(3/2)	1.09	0.25, 4.84	1.09	0.24, 4.92
Multiple events[a]	17/12	(5/2)	2.65	1.21,5.83*	2.46	1.11, 5.44*	15/10	(7/3)	2.32	0.98, 5.50	2.15	0.90, 5.14	2/2	(2/1)	3.44	0.42, 28.1	3.30	0.39, 27.9
Frequency of head injury in different circumstances																		
Never	224/483	(70/80)	1	referent	1	referent	134/248	(66/75)	1	referent	1	referent	90/235	(76/86)	1	referent	1	referent
Work-related																		
once only	13/9	(4/1)	2.55	1.05, 6.21*	2.48	1.01, 6.09*	11/8	(5/2)	2.50	0.94, 6.64	2.39	0.89, 6.43	2/1	(2/0)	3.92	0.30, 52.0	4.46	0.33, 59.6
>1	1/2	(0/0)	0.85	0.08, 9.60	0.95	0.08, 10.66	1/1	(0/0)	2.02	0.12, 34.2	2.14	0.13, 35.86	0/1	(0/0)	-	-	-	
Sport-related																		
once only	18/31	(6/5)	1.13	0.60, 2.11	1.06	0.56, 1.98	14/25	(7/8)	1.04	0.51, 2.14	0.98	0.47, 2.02	4/6	(3/2)	1.53	0.38, 6.11	1.33	0.33, 5.40
>1	11/6	(3/1)	3.24	1.14, 9.22*	3.05	1.06, 8.77*	8/5	(4/2)	2.32	0.69, 7.82	2.07	0.61, 7.05	3/1	(3/0)	7.57	0.72, 79.2	8.52	0.80, 90.9
Leisure-related																		
once only	10/19	(3/3)	1.09	0.49, 2.43	1.08	0.48, 2.42	5/11	(2/3)	0.75	0.24, 2.39	0.77	0.24, 2.47	5/8	(4/3)	1.40	0.41, 4.80	1.29	0.37, 4.48
>1	4/2	(1/0)	6.28	1.08,36.6*	6.89	1.18, 40.3*	2/1	(1/0)	6.66	0.55, 80.4	7.32	0.59, 90.9	2/1	(2/0)	5.05	0.41, 62.7	5.27	0.42, 65.5
Traffic accident-related																		
once only	14/25	(4/4)	1.16	0.58, 2.33	1.13	0.56, 2.27	9/13	(4/4)	1.25	0.50, 3.16	1.22	0.48, 3.12	5/12	(4/4)	1.06	0.35, 3.21	1.01	0.33, 3.09
>1	3/2	(1/0)	3.73	0.59, 23.8	3.49	0.54, 22.4	1/2	(0/1)	1.65	0.14, 20.1	1.64	0.13, 20.2	2/0	(2/0)	-	-	-	-
Other circumstances																		
once only	5/14	(2/2)	0.70	0.24, 2.03	0.70	0.24, 2.03	3/8	(1/2)	0.62	0.16, 2.44	0.6	0.15, 2.39	2/6	(2/2)	0.76	0.14, 4.14	0.76	0.14, 4.23
>1	1/0	(0/0)	-	-	-	-	0/0	(0/0)	-	-	-	-	1/0	(1/0)	-	-	-	-
Multiple circumstances[a]																		
>1	17/12	(5/2)	2.69	1.22, 5.92*	2.48	1.12, 5.50*	15/10	(7/3)	2.32	0.98, 5.52	2.15	0.90, 5.14	2/2	(2/1)	3.67	0.45, 29.8	3.43	0.41, 29.0

Abbreviation: CI, confidence interval; OR, odds ratio.

OR adjusted age, gender (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking, alcohol consumption.

OR[1] adjusted age, gender (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking, alcohol consumption, sport, spine injury & emotional trauma.

[a] Multiple events: participants who had more than one type of circumstance of head injury.

*P <0.05

6.3.3 Sports

None of the participants reported having been professional athletes. The majority of study participants participated in leisure sports throughout childhood and adulthood (73% of male and 64% of female controls), which was associated with an almost doubling of the MND risk (OR 1.81, 95%CI: 1.01, 3.25, Table 6.4).

Analysis by type of sports did not reveal statistically significant associations for any specific sport, although elevated ORs were observed for several common sports including football (soccer) (OR 1.40, 95%CI: 0.95, 2.06), running (OR 1.48, 95%CI: 0.92, 2.38), golf (OR 1.38, 95%CI: 0.88, 2.16), and rugby (OR 1.26, 95%CI: 0.86, 1.83). Analysis by duration for these sports revealed a positive association with longer duration of playing football (soccer) (p for trend=0.04), with playing football (soccer) for >12 years associated with a more than two-fold MND risk (OR 2.35, 95%CI: 1.19, 4.65; Supplemental Table S6.8). For rugby, running, and golf, a trend with duration was not observed. For rugby and golf, only the shortest duration category was associated with a statistically significant increased risk (Supplemental Table S6.8).

Table 6.4. Risk of Motor Neurone Disease with Physical Activities in a Population-Based Case-Control Study, New Zealand, 2013-2016

Exposure	All Cases/Controls (321/605) N	%	OR	95%CI	OR[1]	95%CI	Male Cases/Controls (203/332) N	%	OR	95%CI	OR[1]	95%CI	Female Cases/Controls (118/273) N	%	OR	95%CI	OR[1]	95%CI
Playing sports																		
Never	17/58	(5/10)	1	referent	1	referent	11/28	(5/8)	1	referent	1	referent	6/30	(5/11)	1	referent	1	referent
Ever	304/547	(95/90)	1.84	1.04, 3.28	1.74	0.98, 3.11	192/304	(95/92)	1.71	0.80, 3.68	1.63	0.76, 3.51	112/243	(95/89)	2.48	0.98, 6.28	2.38	0.93, 6.09
Playing sports at different age																		
Never	17/58	(5/10)	1	referent	1	referent	11/28	(5/8)	1	referent	1	referent	6/30	(5/11)	1	referent	1	referent
Childhood only	53/109	(17/18)	1.56	0.81, 2.99	1.49	0.77, 2.86	29/51	(14/15)	1.39	0.57, 3.35	1.33	0.55, 3.21	24/58	(20/21)	2.20	0.78, 6.20	2.15	0.76, 6.11
Adulthood only	11/20	(3/3)	1.91	0.75, 4.91	1.79	0.69, 4.63	5/9	(2/3)	1.78	0.45, 7.00	1.64	0.41, 6.51	6/11	(5/4)	3.54	0.88, 14.2	3.42	0.84, 14.0
Childhood and adulthood	240/418	(75/69)	1.92	1.07, 3.43*	1.81	1.01, 3.25*	158/244	(78/73)	1.79	0.83, 3.87	1.70	0.79, 3.69	82/174	(69/64)	2.52	0.99, 6.44	2.40	0.93, 6.21
Type of sports[a]																		
Rugby	140/204	(41/34)	1.35	0.93, 1.95	1.26	0.86, 1.83	137/201	(67/61)	1.29	0.88, 1.90	1.23	0.83, 1.83	3/3	(3/1)	1.92	0.36, 10.2	1.67	0.30, 9.13
Football (Soccer)	66/82	(21/14)	1.43	0.97, 2.10	1.40	0.95, 2.06	57/73	(28/22)	1.35	0.88, 2.07	1.33	0.87, 2.04	9/9	(8/3)	2.43	0.87, 6.79	2.25	0.79, 6.38
Cricket	52/103	(16/17)	0.88	0.60, 1.30	0.83	0.56, 1.23	46/88	(23/27)	0.88	0.58, 1.36	0.85	0.55, 1.31	6/15	(5/5)	0.81	0.29, 2.26	0.72	0.25, 2.03
Basketball/Netball	80/176	(25/29)	0.96	0.66, 1.40	0.98	0.67, 1.43	15/22	(7/7)	1.02	0.49, 2.11	1.03	0.49, 2.16	65/154	(55/56)	0.90	0.57, 1.44	0.93	0.58, 1.49
Cycling	27/37	(8/6)	1.38	0.81, 2.36	1.32	0.77, 2.25	18/22	(9/7)	1.38	0.69, 2.74	1.33	0.67, 2.66	9/15	(8/5)	1.20	0.48, 3.00	1.10	0.44, 2.76
Running	38/49	(12/8)	1.45	0.91, 2.33	1.48	0.92, 2.38	28/31	(14/9)	1.52	0.85, 2.71	1.57	0.87, 2.83	10/18	(8/7)	1.25	0.52, 3.01	1.14	0.46, 2.83
Athletetics	31/46	(10/8)	1.12	0.68, 1.83	1.08	0.66, 1.78	19/28	(9/8)	0.93	0.49, 1.76	0.87	0.46, 1.67	12/18	(10/7)	1.43	0.62, 3.29	1.56	0.67, 3.63
Tennis	92/193	(29/32)	0.96	0.70, 1.32	0.94	0.69, 1.30	56/94	(28/28)	0.97	0.63, 1.47	0.92	0.60, 1.42	36/99	(31/36)	0.91	0.55, 1.51	0.95	0.57, 1.59
Swimming	41/73	(13/12)	1.09	0.71, 1.67	1.05	0.68, 1.62	21/29	(10/9)	1.03	0.55, 1.92	1.00	0.53, 1.88	20/44	(17/16)	1.11	0.60, 2.05	1.06	0.57, 1.98
Hockey	47/96	(15/16)	1.03	0.69, 1.54	1.03	0.68, 1.54	19/28	(9/8)	1.23	0.64, 2.36	1.24	0.65, 2.39	28/68	(24/25)	0.90	0.53, 1.52	0.88	0.51, 1.50
Volleyball	7/15	(2/2)	0.71	0.27, 1.84	0.62	0.24, 1.62	4/4	(2/1)	1.22	0.27, 5.40	1.11	0.25, 4.90	3/11	(3/4)	0.36	0.08, 1.64	0.30	0.07, 1.35
Badminton	24/50	(7/8)	1.03	0.61, 1.74	1.02	0.60, 1.74	11/17	(5/5)	1.23	0.54, 2.82	1.19	0.52, 2.75	13/33	(11/12)	0.91	0.45, 1.87	0.94	0.45, 1.96
Table tennis	11/22	(3/4)	1.16	0.54, 2.50	1.10	0.51, 2.36	6/14	(3/4)	0.88	0.32, 2.43	0.87	0.31, 2.39	5/8	(4/3)	1.67	0.51, 5.40	1.44	0.44, 4.74
Lawn Bowl	14/36	(4/6)	0.85	0.44, 1.63	0.83	0.43, 1.61	7/21	(3/6)	0.71	0.28, 1.79	0.69	0.28, 1.73	7/15	(6/5)	1.09	0.41, 2.89	1.16	0.43, 3.10
Boxing	6/8	(2/1)	1.53	0.50, 4.65	1.46	0.48, 4.45	6/7	(3/2)	1.93	0.59, 6.29	1.89	0.58, 6.16	0/1	(0/0)	-	-	-	-
Golf	39/59	(12/10)	1.36	0.87, 2.13	1.38	0.88, 2.16	29/40	(14/12)	1.33	0.78, 2.29	1.33	0.77, 2.29	10/19	(8/7)	1.49	0.63, 3.50	1.61	0.68, 3.82
Gymnastics	16/29	(5/5)	1.06	0.55, 2.04	0.99	0.51, 1.92	7/9	(3/3)	1.51	0.53, 4.34	1.53	0.52, 4.46	9/20	(8/7)	1.00	0.41, 2.45	0.87	0.35, 2.17
Horse riding	7/10	(2/2)	1.57	0.57, 4.31	1.42	0.51, 3.93	3/3	(1/1)	1.87	0.35, 10.2	1.80	0.33, 9.96	4/7	(3/3)	1.53	0.41, 5.69	1.30	0.34, 4.98
Walking	12/22	(4/4)	1.18	0.56, 2.48	1.17	0.55, 2.48	2/7	(1/2)	0.52	0.10, 2.79	0.45	0.08, 2.44	10/15	(8/5)	1.53	0.62, 3.75	1.74	0.70, 4.33
Tramping	13/20	(4/3)	1.37	0.65, 2.89	1.45	0.68, 3.07	7/12	(3/4)	1.17	0.43, 3.20	1.22	0.44, 3.36	6/8	(5/3)	2.16	0.68, 6.84	2.20	0.69, 7.08
Softball	22/39	(7/6)	0.99	0.56, 1.75	0.98	0.55, 1.73	11/15	(5/5)	1.04	0.44, 2.45	1.04	0.44, 2.45	11/24	(9/9)	1.04	0.47, 2.29	0.98	0.44, 2.21
Surfing	8/10	(2/2)	1.21	0.46, 3.20	1.12	0.42, 2.97	6/8	(3/2)	0.94	0.30, 2.91	0.91	0.29, 2.85	2/2	(2/1)	2.25	0.29, 17.6	1.54	0.20, 12.2
Yachting	4/16	(1/3)	0.40	0.13, 1.25	0.40	0.13, 1.25	3/15	(1/5)	0.27	0.07, 1.00	0.27	0.07, 1.01	1/1	(1/0)	1.69	0.08, 37.6	2.05	0.09, 47.0
Rowing	8/23	(2/4)	0.50	0.22, 1.17	0.49	0.21, 1.14	7/20	(3/6)	0.53	0.21, 1.30	0.52	0.21, 1.29	1/3	(1/1)	0.73	0.07, 7.48	0.66	0.06, 7.07
Diving	4/8	(1/1)	0.78	0.22, 2.70	0.78	0.22, 2.74	4/7	(2/2)	0.86	0.23, 3.13	0.89	0.24, 3.31	0/1	(0/0)	-	-	-	-
Skiing	10/18	(3/3)	1.00	0.44, 2.27	0.96	0.42, 2.21	8/10	(4/3)	0.97	0.36, 2.62	0.96	0.35, 2.62	2/8	(2/3)	0.77	0.15, 4.00	0.64	0.12, 3.58
Endurance sports activities[b]	61/71	(19/12)	1.57	1.06,2.33*	1.50	1.01, 2.22*	45/47	(22/14)	1.52	0.94, 2.46	1.46	0.90, 2.37	16/24	(14/9)	1.52	0.72, 3.17	1.43	0.67, 3.03
Types of Endurance sports activities																		
Marathons[c]	46/58	(14/10)	1.36	0.88, 2.11	1.30	0.83, 2.01	35/39	(17/12)	1.31	0.77, 2.22	1.25	0.73, 2.13	11/19	(9/7)	1.24	0.53, 2.91	1.19	0.50, 2.84
Full Marathons only	29/30	(9/5)	1.66	0.95, 2.88	1.63	0.93, 2.84	23/22	(11/7)	1.49	0.78, 2.87	1.47	0.76, 2.84	6/8	(5/3)	1.74	0.56, 5.49	1.70	0.53, 5.44
Other running	9/8	(3/1)	2.06	0.77, 5.51	2.05	0.77, 5.49	6/4	(3/1)	2.16	0.58, 8.08	2.15	0.58, 8.01	3/4	(3/1)	1.71	0.36, 8.18	1.70	0.35, 8.28
Cycling[d]	6/12	(2/2)	0.96	0.35, 2.65	0.87	0.31, 2.40	3/9	(1/3)	0.64	0.16, 2.49	0.57	0.14, 2.26	3/3	(3/1)	2.08	0.38, 11.50	1.86	0.33, 10.4
Others	3/2	(1/0)	1.72	0.28, 0.72	1.71	0.27, 11.0	3/2	(1/1)	1.75	0.27, 11.4	1.80	0.27, 11.9	1/0	(1/0)	-	-	-	-

Abbreviation: CI, confidence interval; OR, odds ratio. *P <0.05.

[a] Analyses of never/ever of different types of sports was based on cases + controls >=10 participants. [b] Sports with great physical effort ("Have you ever engaged in a sport that required great physical effort, for instance running a marathon?") [c] Marathons included a full marathon, full ironman, triathlon, half marathon & half ironman. [d] Cycling includes both mountain biking and road biking, but the majority was road biking.

OR adjusted age, gender (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking, alcohol consumption.

OR[1]: adjusted age, gender (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking, alcohol consumption, head injury, spine injury & emotional trauma.

6.3.4 Emotional trauma

The majority of cases (76%) and controls (72%) reported a traumatic life event within at least one of the 14 categories (Table 6.5), but this was not associated with MND (OR 1.17, 95%CI: 0.84, 1.63). Multiple traumatic life events in different categories were associated with elevated risks, with the highest risk observed for reporting traumatic life events in ≥4 categories (OR 1.88, 95%CI: 1.17, 3.03); elevated ORs were observed in both males (OR 1.76, 95%CI: 0.92, 2.34) and females (OR 2.30, 95%CI: 1.06, 5.00).

Results for the individual emotional trauma categories, mutually adjusted for life events in the other emotional trauma categories, showed that having been beaten by a family member or a carer during childhood was associated with an increased risk for MND (OR 1.82, 95%CI: 1.14, 2.90), with similar ORs for males (OR 2.10, 95%CI: 1.16, 3.83) and females (OR 2.06, 95%CI: 0.88, 4.82). For females who witnessed another person being killed or seriously injured, an increased risk was also observed (OR 2.68, 95%CI: 1.06, 6.76; Table 6.5). For females, having been bullied by a close relation was also associated with an increased risk, but this did not reach statistical significance (OR1.81, 95%CI: 0.87, 3.38; Table 6.5).

More detailed analyses on the association between self-reported childhood physical abuse and MND are presented in Table 6.6. Increased risks were observed independent of the age at which the physical abuse first occurred (before the age of 7 or after). Reporting multiple episodes of physical abuse was associated with an increased risk, being statistically significant for having experienced physical abuse as a child 2-4 times (OR 5.72, 95%CI: 1.41, 23.24), and more than 10 times (OR 2.04, 95%CI: 1.13, 3.66).

The pattern of elevated ORs for the higher frequency categories was observed for both males and females but reached statistical significance only in males.
Analyses by duration of childhood physical abuse suggested that longer duration was associated with a higher risk, i.e., physical abuse lasting 5-8 years was associated with a two-fold risk (OR 2.26, 95%CI: 1.14, 4.49) and physical abuse lasting >8 years with a three-fold risk (OR 3.01, 95%CI: 1.18, 7.70).

Of those reporting childhood physical abuse, half reported that this resulted in physical injury. While similar ORs were observed for physical abuse with (OR 1.73) and without (OR 1.89) physical injury, statistical significance was reached only for physical abuse without physical injury (OR 1.89; 95%CI: 1.06, 3.38).

When considering the type of force used (fist, belt, stick, smacking on the hands, combined fist/belt/stick, other non-specific types), the use of fist, belt and stick were all associated with a more than two-fold MND risk, reaching statistical significance for the use of a stick (OR 2.57, 95%CI: 1.10, 5.97), with a particularly high risk observed for females (OR 6.35, 95%CI: 1.31, 30.82; Table 6.6).

Table 6.5. Risk of Motor Neurone Disease with Emotional Trauma in a Population-Based Case-Control Study, New Zealand, 2013-2016

Exposure	All Cases/Controls (321/605) N	%	OR	95%CI	OR[1]	95%CI	Male Cases/Controls (203/332) N	%	OR	95%CI	OR[1]	95%CI	Female Cases/Controls (118/273) N	%	OR	95%CI	OR[1]	95%CI
Emotional Trauma (life events)																		
Never	77/169	(24/28)	1	Referent	1	Referent	56/102	(28/31)	1	Referent	1	Referent	21/67	(18/25)	1	Referent	1	Referent
Ever	244/436	(76/72)	1.23	0.89, 1.71	1.17	0.84, 1.63	147/230	(72/69)	1.14	0.76, 1.71	1.11	0.74, 1.69	97/206	(82/75)	1.41	0.79, 2.49	1.27	0.71, 2.28
Number of different categories of life events reported																		
None	77/169	(24/28)	1	Referent	1	Referent	56/102	(28/31)	1	Referent	1	Referent	21/67	(18/25)	1	Referent	1	Referent
One	68/194	(21/32)	0.78	0.53, 1.17	0.77	0.52, 1.15	42/101	(21/31)	0.71	0.43, 1.18	0.71	0.42, 1.19	26/90	(22/33)	0.87	0.44, 1.72	0.82	0.41, 1.64
Two	76/114	(24/19)	1.55	1.02, 2.34*	1.51	1.00, 2.29*	51/54	(25/16)	1.8	1.06, 3.06*	1.84	1.08, 3.15*	25/60	(21/22)	1.22	0.60, 2.49	1.11	0.54, 2.29
Three	36/57	(11/9)	1.28	0.77, 2.15	1.23	0.73, 2.07	21/38	(10/11)	0.89	0.46, 1.72	0.84	0.43, 1.63	15/19	(13/7)	2.31	0.95, 5.62	2.37	0.96, 5.82
four or more	64/71	(20/12)	2.06	1.30, 3.26*	1.88	1.17, 3.03*	33/34	(16/10)	1.81	0.97, 3.39	1.76	0.92, 3.34	31/37	(26/14)	2.79	1.32, 5.88*	2.30	1.06, 5.00 *
Life event categories																		
Life-threatening illness	113/183	(35/30)	1.34	1.00, 1.81*	1.26	0.92, 1.71	69/109	(34/33)	1.16	0.79, 1.71	1.12	0.74, 1.68	44/74	(37/27)	1.58	0.97, 2.56	1.37	0.81, 2.31
Life-threatening accident	62/99	(19/16)	1.10	0.76, 1.60	0.88	0.59, 1.30	47/66	(23/20)	1.09	0.70, 1.72	0.94	0.58, 1.53	15/33	(13/12)	1.34	0.67, 2.69	1.03	0.47, 2.27
Physically forced in a robbery	22/20	(7/3)	2.04	1.06, 3.91*	1.90	0.95, 3.80	16/17	(8/5)	1.67	0.79, 3.53	1.65	0.73, 3.73	6/3	(5/1)	5.22	1.18, 23.11*	4.44	0.87, 22.71
Loss of close relation to accident/homicide/suicide	81/113	(25/19)	1.46	1.04, 2.05*	1.39	0.98, 1.98	48/60	(24/18)	1.50	0.95, 2.35	1.32	0.81, 2.13	33/53	(28/19)	1.51	0.89, 2.55	1.64	0.92, 2.92
Miscarriage (women only)													44/75	(37/27)	1.65	1.01, 2.70*	1.58	0.92, 2.72
Physically forced to have sex	14/28	(4/5)	1.01	0.50, 2.02	0.77	0.36, 1.64	3/4	(1/1)	1.26	0.27, 5.97	1.53	0.27, 8.63	11/24	(9/9)	1.10	0.49, 2.49	0.58	0.22, 1.55
Sexual harassment	24/46	(7/8)	1.08	0.63, 1.85	0.80	0.45, 1.43	6/10	(3/3)	1.07	0.37, 3.14	0.86	0.26, 2.79	18/36	(15/13)	1.10	0.58, 2.12	0.74	0.35, 1.55
Been beaten in childhood	57/52	(18/9)	2.13	1.40, 3.25*	1.82	1.14, 2.90*	36/31	(18/9)	2.13	1.22, 3.71*	2.10	1.16, 3.83*	21/21	(18/8)	2.61	1.30, 5.24*	2.06	0.88, 4.82
Been beaten in adulthood	37/44	(12/7)	1.48	0.91, 2.41	1.04	0.61, 1.77	23/20	(11/6)	1.82	0.94, 3.53	1.43	0.71, 2.91	14/24	(12/9)	1.04	0.47, 2.26	0.53	0.20, 1.40
Bullied by a close relation	49/59	(15/10)	1.73	1.13, 2.65*	1.44	0.88, 2.34	20/23	(9/7)	1.31	0.68, 2.53	1.10	0.54, 2.25	29/36	(25/13)	2.09	1.16, 3.77*	1.81	0.87, 3.78
Threatened with a weapon	30/54	(9/9)	0.93	0.57, 1.53	0.64	0.37, 1.10	18/36	(9/11)	0.66	0.35, 1.25	0.42	0.21, 0.87	12/18	(10/7)	1.64	0.71, 3.79	1.15	0.43, 3.12
Witness of killing/serious injury/assault	60/69	(19/11)	1.64	1.11, 2.44*	1.40	0.91, 2.16	43/53	(21/16)	1.44	0.89, 2.31	1.32	0.79, 2.22	17/16	(14/6)	2.94	1.35, 6.42*	2.68	1.06, 6.76*
Seriously injured or life was in danger	22/37	(7/6)	1.15	0.65, 2.03	1.06	0.58, 1.95	16/23	(8/7)	1.21	0.60, 2.43	1.29	0.60, 2.77	6/14	(5/5)	0.90	0.31, 2.60	0.40	0.11, 1.43
Extremely frightening situation	48/61	(15/10)	1.47	0.97, 2.23	1.21	0.77, 1.92	28/36	(14/11)	1.17	0.67, 2.03	0.92	0.50, 1.69	20/25	(17/9)	1.90	0.97, 3.70	1.43	0.66, 3.13

Abbreviation: CI, confidence interval; OR, odds ratio.

OR adjusted age, gender (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking, alcohol consumption.

OR1 adjusted age, gender (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking, alcohol consumption, sport, head injury, spine injury, and mutually adjusted for other emotional traumas (for analyses on specific life event categories only).

*P <0.05

Table 6.6. Risk of Motor Neurone Disease with Childhood Physical Abuse in a Population-Based Case-Control Study, New Zealand, 2013-2016

Exposure	All Cases/Controls (321/605) N	%	OR	95%CI	OR[1]	95%CI	Male Cases/Controls (203/332) N	%	OR	95%CI	OR[1]	95%CI	Female Cases/Controls (118/273) N	%	OR	95%CI	OR[1]	95%CI
Age when been beaten																		
Never	264/553	(82/91)	1	Referent	1	Referent	167/301	(82/91)	1	Referent	1	Referent	97/252	(82/92)	1	Referent	1	Referent
Age <7	30/28	(10/5)	2.04	1.17, 3.58*	1.83	0.99, 3.37	18/13	(9/4)	2.39	1.10, 5.21*	2.41	1.06, 5.52*	12/15	(10/6)	2.17	0.93, 5.06	1.61	0.58, 4.46
Age 7+	27/24	(8/4)	2.23	1.24, 4.03*	1.81	0.97, 3.39	18/18	(9/5)	1.93	0.93, 4.00	1.88	0.87, 4.08	9/6	(8/2)	3.65	1.18, 11.23*	3.13	0.87, 11.21
Frequency																		
Never	264/553	(82/91)	1	Referent	1	Referent	167/301	(82/91)	1	Referent	1	Referent	97/252	(82/92)	1	Referent	1	Referent
Once	2/8	(1/1)	0.51	0.10, 2.52	0.42	0.08, 2.08	1/4	(0/1)	0.42	0.04, 3.92	0.42	0.04, 4.10	1/4	(1/1)	0.78	0.08, 7.62	0.47	0.04, 5.49
2-4 times	8/3	(2/1)	6.84	1.74, 26.9*	5.72	1.41, 23.24*	6/1	(3/0)	14.73	1.69, 128.65*	12.07	1.36, 107.25*	2/2	(2/1)	3.05	0.37, 25.18	3.02	0.33, 27.49
5-10 times	11/11	(3/2)	1.68	0.70, 4.03	1.44	0.58, 3.58	8/9	(4/3)	1.58	0.57, 4.40	1.44	0.50, 4.15	3/2	(3/1)	3.65	0.54, 24.90	4.14	0.51, 33.68
>10 times	36/30	(11/5)	2.32	1.36, 3.95*	2.04	1.13, 3.66*	21/17	(10/5)	2.23	1.08, 4.62*	2.39	1.09, 5.26*	15/13	(13/5)	2.89	1.27, 6.60*	2.15	0.78, 5.93
Duration																		
Never	264/553	(82/91)	1	Referent	1	Referent	167/301	(82/91)	1	Referent	1	Referent	97/252	(82/92)	1	Referent	1	Referent
<6 months	7/9	(2/1)	1.42	0.50, 3.99	1.36	0.47, 3.89	6/5	(3/2)	1.79	0.53, 6.11	1.96	0.55, 6.95	1/4	1/1	0.79	0.08, 7.64	0.75	0.07, 7.93
6 month-2 years	6/4	(2/1)	3.04	0.81, 11.45	2.71	0.70, 10.42	5/3	(2/1)	3.26	0.70, 15.28	3.08	0.63, 15.01	1/1	1/0	2.67	0.13, 54.01	2.55	0.13, 48.43
3-4 years	4/11	(1/2)	0.66	0.20, 2.15	0.44	0.13, 1.52	1/9	(0/3)	0.22	0.03, 1.82	0.17	0.02, 1.46	3/2	3/1	3.57	0.52, 24.56	3.31	0.37, 29.64
5-8 years	24/19	(7/3)	2.59	1.36, 4.94*	2.26	1.14, 4.49*	16/11	(8/3)	2.78	1.20, 6.45*	2.82	1.16, 6.84*	8/8	7/3	2.92	1.03, 8.27*	2.08	0.60, 7.14
>8 years	16/9	(5/2)	3.30	1.40, 7.82*	3.01	1.18, 7.70*	8/3	(4/1)	4.64	1.14, 18.99*	4.78	1.07, 21.3*	8/6	7/2	2.96	0.92, 9.49	2.30	0.59, 8.99
Reported injury																		
Never	264/553	(82/91)	1	Referent	1	Referent	167/301	(82/91)	1	Referent	1	Referent	97/252	(82/92)	1	Referent	1	Referent
Injured	25/25	(8/4)	2.07	1.12, 3.81*	1.73	0.88, 3.40	12/12	(6/4)	2.04	0.83, 5.04	2.01	0.77, 5.27	13/13	(11/5)	2.66	1.09, 6.51*	2.10	0.70, 6.30
Not injured	32/27	(10/4)	2.18	1.26, 3.78*	1.89	1.06, 3.38*	24/19	(12/6)	2.18	1.13, 4.21*	2.16	1.07, 4.35*	18/8	(7/3)	2.53	0.88, 7.28	2.01	0.63, 6.46
Method																		
Never	264/553	(82/91)	1	Referent	1	Referent	167/301	(82/91)	1	Referent	1	Referent	97/252	(82/92)	1	Referent	1	Referent
Fist	8/6	(2/1)	3.01	0.98, 9.31	3.09	0.95, 10.05	5/4	(2/1)	2.93	0.70, 12.37	3.21	0.69, 14.99	3/2	(3/1)	4.79	0.71, 32.55	5.27	0.63, 44.10
Belt	16/14	(5/2)	2.22	1.03, 4.77*	2.03	0.91, 4.53	9/9	(4/3)	1.58	0.59, 4.28	1.85	0.66, 5.20	7/5	(6/2)	3.61	1.04, 12.57*	2.90	0.69, 12.20
Stick	16/11	(5/2)	3.08	1.37, 6.91*	2.57	1.10, 5.97*	9/8	(4/2)	2.35	0.83, 6.63	2.22	0.75, 6.57	7/3	(6/1)	7.01	1.68, 29.19*	6.35	1.31, 30.82*
Other	4/5	(1/1)	1.38	0.36, 5.35	1.09	0.25, 4.76	3/2	(1/1)	3.13	0.50, 19.59	2.50	0.32, 19.46	1/3	(1/1)	0.67	0.06, 7.12	0.80	0.07, 9.87
Smacking on the hands	3/9	(1/1)	0.59	0.15, 2.28	0.47	0.12, 1.91	3/5	(1/2)	1.02	0.23, 4.61	0.85	0.18, 4.07	0/4	(0/1)				
Combine (fist, belt, stick)	10/7	(3/1)	2.55	0.92, 7.08	1.76	0.60, 5.13	7/3	(3/1)	4.02	0.94, 17.14	3.84	0.87, 17.02	3/4	(3/1)	1.42	0.28, 7.29	0.45	0.07, 3.00

Abbreviation: CI, confidence interval; OR, odds ratio.

OR adjusted age, gender (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking, alcohol consumption.

OR1 adjusted age, gender (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking, alcohol consumption, sport, head injury, spine injury, and mutually adjusted for other emotional traumas.

*P <0.05

6.4 Discussion

We found significantly increased risks of MND with having experienced multiple head injuries with concussion, participating in leisure sports in general and playing football (soccer) in particular, and having experienced multiple emotionally traumatic life events. In addition, this is the first study to show an association with having experienced physical abuse as a child.

This study has several limitations. All exposure information was self-reported, potentially resulting in recall bias. To minimise this, questions on physical activity focussed on sports played rather than more subjective self-reported physical activity levels. Questions on head trauma specified a head injury with a concussion, to reduce recall bias that may be associated with using open questions on any head trauma. The questions on emotional trauma included highly sensitive and personal questions. False-positive associations due to reporting bias may occur if cases were more likely to report sensitive events as they may put more value on the study and the importance of being open when answering these questions. However, we did not observe a pattern of more positive answers to sensitive questions in cases. For example, equal proportions of cases and controls reported having experienced sexual assault, which was among the most sensitive questions.

We did not have access to MND subtype-specific diagnosis (this was not recorded in New Zealand at the time of study recruitment), and analyses could therefore not be restricted to the ALS case group to improve comparability with other studies, which predominantly reported on ALS. However, ALS is the most common form of MND

accounting for 85% of the total cases, and our case definition is therefore unlikely to differ substantially from those used in other studies.

The participation rate among population controls (48%) was lower than among cases (92%). To evaluate the potential for participation bias we compared the occupations recorded on the Electoral Roll between participating and non-participating controls,[458] which showed no significant difference suggesting that responders and non-responders are comparable (at least in terms of occupation and therefore likely socioeconomic position), making it less likely that the observed increased risks are explained by non-response bias.

There were differences in the interview method used between cases and controls, with cases more likely to opt for a face-to-face interview than controls. We therefore repeated all analyses controlling for the interview method. This did not alter our main findings, suggesting that interview methods did not bias the results.

Smoking and alcohol consumption have also been studied as risk factors for MND in several studies; however, results have been inconsistent.[69 407] In this study population, neither smoking nor alcohol consumption was associated with MND (data not shown). Nonetheless, smoking status and alcohol consumption have been adjusted for in all analyses, and this did not alter our findings.

6.4.1 Head injury

Having had multiple head injuries with concussion was associated with a two-fold risk of MND. These findings are consistent with several meta-analyses[41 356-358] reporting

increased MND risk for head injury, and particularly for repeated head injuries.[357] It has been argued that this may, at least in part, be due to reverse causation[345] as accidents and injuries may be an early manifestation of MND. Our findings did not change after excluding head injuries that occurred 3 years before the index date, suggesting that reverse causation is unlikely to explain our findings.

A recent meta-analysis[358] showed that severe head injury was associated with a higher risk of MND. We did not observe a clear association with injury severity, although misclassification due to the self-reported nature of the injury severity may have contributed to this. However, several reports have suggested that repetitive mild traumatic brain injuries alone could be sufficient to trigger the physiological changes required to increase the risk of MND.[348 496 497] Head trauma is known to disrupt and deteriorate the BBB,[329] which may play a role in MND pathogenesis.[330 331] In ALS animal models, traumatic brain injury has been found to trigger TAR DNA-binding protein 43 (TDP-43) associated pathology, which is a neuropathological hallmark lesion in the brain of patients with ALS.[332] TDP-43 pathology has also been shown in the brains of athletes that experienced a repetitive head injury.[496]

In this study population, head injury with a concussion most commonly occurred as part of leisure sports (9% of male and 3% of female controls reported at least one sport-related head injury) and having more than one sport-related head injury was associated with a three-fold MND risk. This identifies leisure sports as an important setting of preventable head injury that may be contributing to MND risk.

6.4.2 Sports

In this study participating in sports throughout childhood and adulthood was associated with an increased risk for MND, which is consistent with several previous studies.[69 351 376 379 381] The association between physical activities and the risk of MND is biologically plausible as vigorous exercise may induce oxidative stress and glutamate excitotoxicity, two well-established mechanisms for MND.[360]

MND risk differed by the type of sport played. For many individual sports, we did not observe an increase in MND risk, including cricket, basketball/netball, tennis, swimming, hockey, volleyball, badminton, lawn bowl, yachting, rowing, diving, and skiing. Taking part in endurance sports (when considered collectively) was associated with an increased MND risk, but when considering specific endurance sports separately, none of the associations reached statistical significance. A number of common sports in New Zealand were associated with elevated ORs that did not reach statistical significance, including rugby, football (soccer), running, and golf.

Only for playing football (soccer), we observed a statistically significant positive association with duration, with a two-fold MND risk for those who played football (soccer) >12 years. This is of interest, as several studies[361 362 366 367] have reported an increased MND risk for professional football (soccer) players. This study adds to this body of evidence and suggests that non-professional football (soccer) may also increase the risk of MND.

The association observed for football (soccer) may be mediated through strenuous physical activities and/or head injury.[41 361] As our analyses were adjusted for head injury

with a concussion, diagnosed concussions are unlikely to explain the observed association. Therefore, with football (soccer) being the only sport in which players purposefully use the head to deflect the ball, and it emerging as the only specific sport associated with an increased risk in our study, a role for sub-concussive impacts to the head in football (soccer) players cannot be excluded,[361 384 498] and merits further study.

6.4.3 Emotional trauma

In the current study, elevated risks were associated with having experienced more than two different types of traumatic life events, with an almost two-fold risk associated with having experienced four or more types of traumatic life events. An Australian ALS case-control study,[495] which used a checklist for potentially stressful life events as part of an anonymous online questionnaire, found no difference in life events inventory scores between cases and controls, but results for specific traumatic life events were not presented. We are not aware of other studies that evaluated the association between traumatic life events and MND. Our findings show some parallels with a Japanese study,[380] which found that self-reported stress and type A behaviour pattern (related to emotional distress and to more keenly perceived life stress) were associated with an increased ALS risk. Emotional trauma has also been proposed as a risk factor for other neurodegenerative diseases, including Alzheimer's disease[499] and Parkinson's disease,[500] and mechanistic studies have demonstrated that psychological stress is associated with increased oxidative stress,[493 501] which plays an important role in the pathology of neurodegenerative diseases including MND.[502]

It cannot be fully excluded that self-reports of traumatic events may systematically differ between cases and controls, either because of differences in recall, or because of

possible differences in personality type and the perception of life stress between cases and controls, as suggested by the Japanese study.[380] Our relative risk estimates for specific categories of traumatic events, which identified childhood physical abuse as a risk factor for MND, are, however, less likely to be affected by this, as these were adjusted for the report of all other categories of traumatic events.

It is possible that physical trauma, including head injury, may play a role in the observed associations for emotionally traumatic events and MND, as several of the emotional trauma categories relate to physical violence that may result in physical trauma. In particular, we observed a two-fold MND risk for having experienced physical abuse as a child. This association was consistently observed for both males and females, and risks increased for higher frequency, as well as longer duration of child abuse. While this association was adjusted for self-reported head injuries with concussion, physical child abuse may result in undiagnosed and unreported physical trauma that could not be taken into account in this study. A role for emotional trauma cannot be excluded either, as similar ORs were observed for physical child abuse with and without physical injury. Whilst the underlying contributing factors could not be identified, this new finding warrants further research.

6.5 Conclusions

This study supports earlier findings that repeated head injury with concussion and playing leisure sports in general and football (soccer) in particular are associated with an increased risk of MND, and suggests, for the first time, a possible role for physical child abuse in the development of MND. The observed associations are complex and inter-connected because both sports and emotional trauma may also involve physical trauma including head injury. These findings merit further scrutiny in future studies, as they may provide important opportunities for MND prevention and add to our understanding of the aetiological mechanisms involved in MND.

Acknowledgements

We are grateful to the Motor Neurone Disease Association New Zealand, and their field staff for their generous support. We would also like to thank Michelle Gray, Di Marshal, Heather Duckett, Deirdre Thurston, Aly Timmings, for their help with conducting interviews.

The study was funded by a grant from the Health Research Council (HRC) of New Zealand (Part of 11/1041 HRC Programme Grant - Building Research in Occupational Health in New Zealand.

6.6 Supplementary material

Table S6.7. Supplementary Table. Risk of Motor Neurone Disease with Spine Injuries in a Population-Based Case-Control Study, New Zealand, 2013-2016

Exposure	All Cases/Controls (321/605)		OR	95%CI	OR[1]	95%CI	Male Cases/Controls (203/332)		OR	95%CI	OR[1]	95%CI	Female Cases/Controls (118/273)		OR	95%CI	OR[1]	95%CI
	N	%					N	%					N	%				
Ever had a spine Injury																		
Never	291/553	(91/91)	1	referent	1	referent	182/302	(90/91)	1	referent	1	referent	109/251	(92/92)	1	referent	1	referent
Ever	30/52	(9/9)	0.93	0.57, 1.52	0.93	0.56, 1.52	21/30	(10/9)	0.84	0.45, 1.56	0.84	0.45, 1.58	9/22	(8/8)	0.95	0.40, 2.23	0.91	0.38, 2.18
Spine Injury (>3 years before diagnosis) [a]																		
Never	295/557	(92/92)	1	referent	1	referent	184/302	(91/91)	1	referent	1	referent	111/255	(94/93)	1	referent	1	referent
Ever	26/48	(8/8)	0.81	0.48, 1.36	0.81	0.48, 1.36	19/30	(9/9)	0.72	0.38, 1.37	0.73	0.38, 1.38	7/18	(6/7)	0.86	0.33, 2.21	0.81	0.31, 2.12
Frequency of spine injury [a]																		
Never	295/557	(92/92)	1	referent	1	referent	184/302	(91/91)	1	referent	1	referent	111/255	(94/93)	1	referent	1	referent
Once	18/41	(6/7)	0.65	0.36, 1.17	0.65	0.36, 1.19	15/26	(7/8)	0.66	0.33, 1.33	0.67	0.38, 1.38	3/15	(3/5)	0.40	0.11, 1.46	0.38	0.10, 1.41
≥twice	8/7	(2/1)	1.76	0.61, 5.10	1.72	0.59, 5.01	4/4	(2/1)	1.09	0.26, 4.68	1.09	0.25, 4.77	4/3	(3/1)	4.07	0.81, 20.46	3.78	0.74, 19.43
Severity of spine injury [a]																		
Never	295/557	(92/92)	1	referent	1	referent	184/302	(91/91)	1	referent	1	referent	111/255	(94/93)	1	referent	1	referent
Mild	5/5	(2/1)	1.53	0.42, 5.52	1.79	0.50, 6.47	5/2	(2/1)	3.06	0.55, 16.97	3.41	0.62, 18.95	0/3	(0/1)				
Moderate	12/26	(4/4)	0.64	0.31, 1.32	0.62	0.30, 1.30	10/15	(5/5)	0.70	0.29, 1.66	0.70	0.29, 1.68	2/11	(2/4)	0.36	0.07, 1.70	0.30	0.06, 1.48
Severe	9/17	(3/3)	0.87	0.37, 2.06	0.84	0.35, 1.98	4/13	(2/4)	0.37	0.11, 1.24	0.36	0.11, 1.20	5/4	(4/1)	3.55	0.89, 14.21	3.32	0.82, 13.38
Age of Spine Injury [a]																		
never	295/557	(92/92)	1	referent	1	referent	184/302	(91/91)	1	referent	1	referent	111/255	(94/92)	1	referent	1	referent
only in childhood[b]	2/6	(1/1)	0.36	0.07, 1.85	0.39	0.08, 2.01	2/5	(1/2)	0.34	0.06, 1.93	0.37	0.07, 2.05	0/1	(0/0)				
only in adulthood[c]	20/35	(6/6)	0.86	0.48, 1.57	0.89	0.49, 1.61	15/23	(7/7)	0.75	0.37, 1.54	0.75	0.37, 1.55	5/12	(4/4)	0.93	0.3, 2.89	1.05	0.34, 3.28
both childhood and adulthood	4/7	(1/1)	1.00	0.28, 3.58	0.84	0.23, 3.04	2/2	(1/1)	1.53	0.19, 12.11	1.55	0.19, 12.46	2/5	(2/2)	0.89	0.16, 4.90	0.54	0.09, 3.18

Abbreviation: CI, confidence interval; OR, odds ratio.

OR adjusted age, gender (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking, alcohol consumption.

OR1: adjusted age, gender (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking, alcohol consumption, sport, head injury & emotional trauma.

a excluding spine injuries that occurred within 3 years before diagnosis (for cases) and within 3 years before the interview (for controls).

b <=18 years old

c >18 years old

Table S6.8. Supplementary Table. Risk of Motor Neurone Disease with Duration of Selected Sports in a Population-Based Case-Control Study, New Zealand, 2013-2016

Exposure	All Cases/Controls (321/605)		OR	95%CI	OR[1]	95%CI	Male Cases/Controls (203/332)		OR	95%CI	OR[1]	95%CI	Female Cases/Controls (118/273)		OR	95%CI	OR[1]	95%CI
	N	%					N	%					N	%				
Rugby																		
Never	181/401	(56/66)	1	referent	1	referent	66/131	(33/39)	1	referent	1	referent	115/270	(97/99)	1	referent	1	referent
Duration <8 years	50/5	(16/9)	1.80	1.11, 2.93*	1.68	1.03, 2.75*	47/53	(23/16)	1.72	1.03, 2.87*	1.66	0.99, 2.80	3/2	(3/1)	2.79	0.43, 18.02	2.33	0.35, 15.40
Duration 8-10 years	21/53	(7/9)	0.80	0.44, 1.46	0.76	0.42, 1.39	21/53	(10/16)	0.77	0.42, 1.43	0.75	0.41, 1.39	0/0	(0/0)				
Duration 10-15 years	27/46	(8/8)	1.14	0.64, 2.04	1.05	0.59, 1.89	27/46	(13/14)	1.10	0.60, 1.99	1.04	0.57, 1.90	0/0	(0/0)				
Duration >15 years	42/50	(13/8)	1.52	0.91, 2.55	1.42	0.84, 2.39	42/49	(21/15)	1.52	0.89, 2.61	1.45	0.85, 2.50	0/1	(0/0)				
p-value (test for trend)			0.32		0.50				0.37		0.50				0.99		0.94	
Football (Soccer)																		
Never	255/523	(79/86)	1	referent	1	referent	146/259	(72/78)	1	referent	1	referent	109/264	(92/97)	1	referent	1	referent
Duration <6 years	22/28	(7/5)	1.30	0.71, 2.38	1.28	0.69, 2.35	19/24	(9/7)	1.27	0.65, 2.49	1.26	0.64, 2.48	3/4	(3/1)	2.11	0.41, 10.78	1.74	0.33, 9.05
Duration 6-8 years	12/16	(4/3)	1.28	0.58, 2.85	1.24	0.56, 2.77	10/15	(5/5)	1.07	0.45, 2.56	1.06	0.44, 2.54	2/1	(2/0)	2.51	0.21, 29.33	2.15	0.18, 25.67
Duration 8-12 years	11/20	(3/3)	0.98	0.44, 2.16	0.91	0.41, 2.03	9/19	(4/6)	0.79	0.33, 1.92	0.75	0.31, 1.82	2/1	(2/0)	5.66	0.45, 71.66	6.34	0.45, 88.79
Duration >12 years	21/18	(7/3)	2.31	1.17, 4.54*	2.35	1.19, 4.65*	19/15	(9/5)	2.52	1.19, 5.33*	2.55	1.20, 5.43*	2/3	(2/1)	1.72	0.26, 11.56	1.78	0.26, 12.26
p-value (test for trend)			0.04*		0.04*				0.08		0.09				0.14		0.15	
Running																		
Never	283/556	(88/92)	1	referent	1	referent	175/301	(86/91)	1	referent	1	referent	108/255	(92/93)	1	referent	1	referent
Duration <8 years	13/15	(4/2)	1.58	0.72, 3.45	1.59	0.72, 3.50	10/9	(5/3)	1.95	0.75, 5.10	2.02	0.76, 5.32	3/6	(3/2)	0.85	0.19, 3.85	0.75	0.16, 3.52
Duration 8-10 years	9/11	(3/2)	1.57	0.62, 3.98	1.62	0.64, 4.14	4/7	(2/2)	0.94	0.26, 3.44	0.98	0.27, 3.58	5/4	(4/1)	3.20	0.78, 13.08	3.20	0.76, 13.44
Duration 10-24 years	9/11	(3/2)	1.76	0.69, 4.51	1.80	0.70, 4.65	8/7	(4/2)	2.11	0.69, 6.46	2.18	0.70, 6.77	1/4	(1/1)	0.73	0.07, 7.26	0.64	0.06, 6.79
Duration >24 years	7/12	(2/2)	0.97	0.37, 2.55	0.99	0.37, 2.62	6/8	(3/2)	1.09	0.36, 3.35	1.14	0.37, 3.52	1/4	(1/1)	0.54	0.05, 5.34	0.44	0.04, 4.60
p-value (test for trend)			0.29		0.26				0.32		0.28				0.84		0.99	
Golf																		
Never	282/546	(88/90)	1	referent	1	referent	174/292	(86/88)	1	referent	1	referent	108/254	(92/93)	1	referent	1	referent
Duration <20 years	17/16	(5/3)	2.51	1.21, 5.22*	2.51	1.21, 5.23*	9/12	(4/4)	1.52	0.60, 3.88	1.49	0.59, 3.80	8/4	(7/1)	6.18	1.69, 22.58*	6.62	1.81, 24.2*
Duration 20-31 years	4/14	(1/2)	0.46	0.15, 1.47	0.45	0.14, 1.44	4/9	(2/3)	0.68	0.19, 2.39	0.64	0.18, 2.29	0/5	(0/2)				
Duration 31-46 years	8/16	(2/3)	1.01	0.41, 2.44	1.07	0.44, 2.63	7/8	(3/2)	1.41	0.48, 4.15	1.46	0.49, 4.33	1/8	(1/3)	0.31	0.04, 2.63	0.37	0.04, 3.24
Duration >46 years	10/13	(3/2)	1.62	0.68, 3.87	1.60	0.67, 3.83	9/11	(4/3)	1.67	0.65, 4.32	1.70	0.66, 4.40	1/2	(1/1)	1.69	0.14, 20.26	1.25	0.10, 15.96
p-value (test for trend)			0.41		0.39				0.28		0.27				0.76		0.82	

Abbreviation: CI, confidence interval; OR, odds ratio.

OR adjusted age, gender (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking, alcohol consumption.

OR1: adjusted age, gender (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking, alcohol consumption, head injury, spine injury & emotional trauma.

*P <0.05

CHAPTER 7 General discussion

7.1 Introduction

The work presented in this thesis investigated a range of potentially modifiable risk factors for MND, with a focus on occupational factors, as well as several lifestyle-related factors. The thesis was based on the first MND case-control study conducted in New Zealand, and one of relatively few that have been conducted in the Southern hemisphere. Among the identified risk factors for MND, several are consistent with earlier findings, such as the observed increased MND risks for horticultural occupations, electricians, occupational exposure to pesticides, occupational exposure to electric shocks, head injury, and sports. Occupational exposure to ELF-MF, on the other hand, was not associated with MND in this study, contrary to other studies. The work presented in this thesis also identified new risk factors for MND that have not previously been reported. In particular, having experienced multiple traumatic life events, and especially childhood physical abuse was associated with an elevated risk for MND. Also, the observed elevated MND risk for employment in automotive fuel retailing had not previously been reported.

Collectively, the findings presented in this thesis contribute towards a better understanding of modifiable risk factors for MND. The main findings of this thesis are outlined below, followed by a discussion of specific results, the strengths and limitations of the research, and recommendations for future research.

The main study findings are as follows:

- Occupations in horticulture and crop growing are associated with an increased risk of MND, in both men and women, and risk increased with longer employment duration in these occupations (Chapter 3).
- Other occupations associated with an increased risk include electricians, telecommunication technicians, building trades workers, forecourt attendants, and caregivers (Chapter 3).
- Having worked in occupations with potential exposure to electric shocks was associated with an increased risk of MND (Chapter 4)
- Having worked in occupations with potential exposure to ELF-MF was not associated with MND (Chapter 4).
- Occupational exposure to pesticides (especially insecticides, fungicides) and fumigants was associated with an increased risk of MND, in both men and women, and risk increased with longer duration of exposure (Chapter 5).
- Occupational exposure to petrol/diesel fuel, unspecified solvents, cleaning products, and disinfectants were also found to increase the risk of MND (Chapter 5).
- Head injuries, especially multiple head injuries, were associated with an increased risk of MND (Chapter 6).
- Playing sports throughout childhood and adulthood was associated with an increased risk of MND when compared to not playing sports (Chapter 6).
- Playing football (soccer) >12 years was also found to increase the risk of MND (Chapter 6).
- Individuals who reported to have experienced multiple types of traumatic life events had an increased risk of MND (Chapter 6).

- Childhood physical abuse was associated with an increased risk of MND in both men and women, and risk increased with longer duration of physical abuse (Chapter 6).

7.2 Discussion of specific findings

7.2.1 Agricultural occupations and associated exposures

Among the wide range of agricultural occupations, several horticultural occupations were associated with a more than 2-fold increased risk of MND, with similar risks found for males and females. The risk increased with longer employment in these occupations (Chapter 3). The specific occupations associated with an increased risk (e.g., vegetable growers, fruit growers, gardeners, and nursery growers) are typically associated with higher pesticide-use compared to other agricultural occupations for which an increased risk was not observed (i.e., livestock farmers), strongly suggesting that exposure to pesticides may play a role. This is further supported by the findings described in Chapter 5, in which pesticide exposure was associated with an increased MND risk, with strongest associations for those with the longest pesticide exposure duration and for those who had applied pesticides themselves and were, therefore, more likely to have been exposed to higher levels compared to those who were exposed only indirectly. Thus, the presence of an increased risk for multiple non-overlapping horticultural occupational groups and multiple insecticides classes, the presence of positive duration-response associations, and the presence of increased risks for both men and women, strongly suggest that occupational exposure to pesticides is a risk factor for MND in New Zealand.

Previous studies have shown that exposure to pesticides as a group is associated with MND risk (Chapter 2) but identifying which specific pesticides are associated with MND has been difficult because agricultural workers have typically been exposed to a wide range of different pesticides over their working life. This was also the case in this study, but some differences in risk between pesticide groups were observed. In particular, while increased risks were observed for multiple categories of pesticides, the association was particularly strong and consistent for insecticides (Chapter 5). The role of insecticides in MND aetiology is biologically plausible, given their known neurotoxicity to either the central or peripheral nervous system or both.[479 503] Insecticides primarily target the nervous system, and similarities between the insect and human nervous systems often lead to cross-toxicity.[300] Different classes of insecticides have been used over time, including OCPs, OPs and pyrethroids, all of which were associated with an increased MND risk (Chapter 5). OCPs such as DDT was widely used but have largely been banned in high-income countries including New Zealand during the 1970s and 1980s. OPs continue to be widely used and constituted the insecticide class with the highest exposure prevalence in the study population (Chapter 5). OPs inhibit the acetylcholinesterase enzyme (AChE) resulting in acetylcholine (a neurotransmitter) accumulation and subsequent overstimulation of nerves and muscles.[503 504] High exposure to OPs can result in OP-induced delayed neuropathy, a condition akin to ALS.[302] Furthermore, polymorphisms in paraoxonase 1, an enzyme that detoxifies OPs,[480] have been associated with the development of ALS.[481] OPs also induce oxidative stress,[164 482 505] which plays an important role in the pathogenesis of MND.[305]

In addition to insecticides, exposure to inorganic (copper) fungicides and methyl bromide fumigants were also associated with elevated risk. In this study, methyl bromide was predominantly used to sterilise the soil in horticulture (Chapter 5), which is no longer permitted in New Zealand.[506] However, methyl bromide continues to be used for cargo fumigation in international sea transport,[507] thus potentially contributing to an increased risk of MND in container handlers and/or fumigators.

Taken together, these findings support earlier findings of increased MND risks for certain agricultural occupations and occupational exposure to pesticides,[30 36 37 39-41 44 183 203 261 309 321 323 327 508] and provide further evidence that specifically insecticides are associated with an increased risk of MND.

7.2.2 Electricians, telecommunication technicians, and associated exposures

Another group of occupations of interest is those involved in electrical work, as several overseas studies[116 187 272-274] and this New Zealand study (Chapter 3) report an increased MND risk for these workers. Elevated risks were found for electricians and telecommunications technicians (Chapter 3), but these risks did not increase with the duration of employment. In these occupations, exposure to ELF-MFs or electric shocks have been proposed as possible explanations and these exposures were therefore investigated in more detail in this thesis (Chapter 4).

A two-fold MND risk was observed for having ever worked in occupations with a high potential for electric shocks. The risk did not increase with a longer duration of employment, and elevated risks were observed in those with both the shortest (< 3

years) and longest (>24 years) exposure durations (Chapter 4). The elevated risk for a short duration of employment may be explained by earlier findings that showed that young (and less experienced) electricians may be more likely to experience electric shocks at work.[465 509-511] An overseas study also showed that the highest risk of injury (OR 7.95) was among those being apprentices for 19-24 months. On the other hand, the observed increased risk for occupational duration <3 years may also be explained by the "healthy worker effect" involving workers who experience electric shocks during their early career leaving this occupation. This has been observed with electricians in an overseas study,[512] and the "healthy worker effect" has also previously been reported to be strongest at the beginning of employment.[513]

The observed increased risk for more than 24 years of employment in jobs with high potential for electric shocks may be explained by accumulated mild electric injury due to multiple (minor) shocks over a longer period, but also by a higher chance of a single large electric shock when employment duration is longer.

A causal mechanism has not been established. However, a recent review[466] on neurological consequences of electric injury suggested that electrical current may hyper-stimulate glutamatergic neurones that can lead to free radical formation through oxidative stress, which may either gradually break down endothelial vascular cells, thus cutting off blood supply and ending in the death of spinal neurones, or directly damage myelin, gradually leading to a demyelinating neurodegenerative condition without vascular involvement.[467 468] Electric shocks could also result in heat-denatured proteins[469] leading to protein folding problems, which may potentially form a productive misfolded protein seed that could propagate to non-injured regions.[41]

The elevated risk of MND observed for electricians has also been suggested to be the result of ELF-MF exposure. In this thesis, exposure to ELF-MF was not associated with MND (Chapter 4), which is consistent with previous residential exposure studies,[514-516] but is different from some other occupational exposure studies in which ELF-MF was shown to be a risk factor for MND.[264 282 284 296] This discrepancy may be explained by the possible confounding effect by exposure to electric shocks. The absence of an association for ELF-MF observed in the study described in this thesis suggests that the increased MND risk observed for electricians and telecommunication technicians may be due to electric shocks rather than ELF-MF.

7.2.3 Forecourt attendants and associated exposures

In this thesis, an increased risk of MND was observed for individuals who worked as forecourt attendants (i.e., pumping petrol), and for employment in Automotive Fuel Retailing (Chapter 3). Possible exposures that may explain this association include engine emissions, automotive fuels, associated solvents including benzene, and tetraethyl-lead (TEL), a petrol-fuel additive mixed with gasoline from the 1920s, which was removed from petrol in most western countries by the 1980s, although this did not happen in New Zealand until 1996.[451]

Interestingly, in the occupational exposure study (Chapter 5), exposure to petrol/diesel fuel was associated with a more than two-fold increase in MND risk. Most of those reporting exposures to petrol and diesel fuel were exposed before 1996, the year lead was phased out from petrol in New Zealand, thus suggesting a role for lead exposure. Additionally, exposure to solvents was also associated with a 1.9-fold increased risk,

even though most participants reporting solvent exposure could not recall which specific solvent was used. Thus, exposure to lead and/or solvents are the most plausible exposures to explain the observed increased risk for forecourt attendants and those that worked in the automotive fuel retailing industry, although a role for other exposures such as engine emissions, or other petrol components such as benzene cannot be excluded.

The biological plausibility of lead exposure in MND aetiology has been studied extensively. The proposed mechanisms include increased oxidative stress, mitochondrial dysfunction, and excitotoxicity, which are also involved in MND pathogenesis.[34 174 176] Organic solvents are known neurotoxins and long-term exposure may cause encephalopathy[250] and cognitive deficits,[517] disrupt motor function and increase oxidative stress,[486] which play a role in motor neurone degeneration.[408] In addition, exposure to solvents has been associated with other neurodegenerative conditions including Alzheimer's disease,[518] Parkinson's disease,[519] and multiple sclerosis,[520] with which MND shares some underlying biological mechanisms.[487]

In the past few decades, exposures of forecourt attendants have changed substantially with the introduction of self-serviced petrol stations and the phase out of lead from petrol. The observed increased risk may therefore be largely due to historical exposures.

7.2.4 Caregivers and associated exposures

In Chapter 3, an elevated MND risk was observed for female caregivers. Interestingly, there was no increased risk for other healthcare-related occupations. In previous studies

employment in healthcare has generally not been associated with MND, although two mortality studies[30 292] showed that female nurses and medical services workers had an increased risk for MND. Among women in this study, exposure to disinfectants and cleaning products was associated with MND (Chapter 5), although an association between disinfectants and MND has not been reported previously. The use of disinfectants may also be a marker of exposure to infectious agents, which may play a role in the development of ALS.[490] Many cleaning products contain solvents, and exposure to non-specified solvents was also associated with MND risk (Chapter 5). However, these putative exposures are not specific to caregivers, and can also occur in other healthcare-related occupations for which this research did not observe an increase in MND risk. Therefore, based on current evidence, it remains unclear what may explain the association with female caregivers.

7.2.5 Building trades workers, plant and machine operators and assemblers and associated exposures

A positive association with MND was observed for two other groups of occupations: construction workers, in particular, building trades workers; and plant and machine operators and assemblers (Chapter 3).

For building trade workers, especially builders (including contractors), an increased risk was observed for males only as there were very few females in these occupations, and the risks did not increase with the duration of employment. This is consistent with several studies that reported an increased MND risk for construction workers.[43 183 323 521 522] Building trade workers represent a diversity of occupations exposed to dust (e.g., lead dust),[523] fibres, fumes (diesel exhaust), and solvents.[323] Exposure to lead,[3] diesel

exhaust[229], and solvents[263] have also previously been shown to be a risk factor for MND. In this thesis, occupational exposure to dust and fumes was not associated with MND, but an elevated risk was observed for men who were exposed to non-specific solvents (Chapter 5), which suggests that exposure to solvents may play a role for this group of workers. However, other unidentified occupational risk factors cannot be excluded.

The group of plant and machine operators and assemblers is heterogeneous and included stationary machine operators, electrical machinery assemblers as well as vehicle drivers. Several earlier studies have reported that workers employed as stationary machine operators, mobile plant operators, truck drivers,[524] and power-production plant operators[32] had an increased risk of MND. In this study, an elevated MND risk was observed for males who worked as plant and machine operators and assemblers. However, the risks did not increase with the duration of employment and no statistically significant increased risks were observed for the specific occupations within this group (Chapter 3).

Plant and machine operators and assemblers can be exposed to a number of exposures such as cutting, cooling, or lubricating oils,[43] gas,[525] diesel exhaust fumes,[452 524] ELF-MF,[46] electric shocks,[459] and solvents.[263] However, exposure to cutting fluid, lubricating oils, fumes, gas, and ELF-MF were not associated with MND (Chapter 5); instead the increased risk may be associated with potential exposure to electric shocks or non-specific solvents, or a combination of both. Nevertheless, a role for other unidentified occupational risk factors in these occupations cannot be excluded and further studies

using JEMs for exposures that are specific to certain tasks in each of these occupations are needed.

7.2.6 Head injury

An increased MND risk was associated with multiple head injuries with concussion (Chapter 6). These findings were consistent with several meta-analyses[41 356-358] reporting increased MND risk for head injury, and particularly for repeated head injuries.[357] An important issue to consider is reverse causation as accidents and injuries may be an early manifestation of MND.[345] However, after excluding head injuries that occurred within the 3 years prior to the index date (diagnosis date), the association remained the same, indicating that reverse causation is unlikely to explain the association. Head trauma is known to disrupt and deteriorate the blood-brain-barrier (BBB),[329] which has been proposed to play a role in MND pathogenesis.[330 331] A complex interplay of pathological mechanisms including neuroinflammation, glutamate excitotoxicity, oxidative stress,[526] and mitochondrial dysfunction[527-529] have been suggested to follow traumatic brain injuries.

Head injury can occur in a range of settings and circumstances. In this study, head injury with concussion most commonly occurred as part of leisure sports (9% of male and 3% of female controls reported at least one sport-related head injury) and having more than one sport-related head injury was associated with a three-fold MND risk. This identifies leisure sports as an important target for interventions to prevent head injuries and associated risks.

7.2.7 Sports

Physical activity has previously been shown to be a risk factor for MND, but results have been mixed (Chapter 2). In this thesis, the association between physical activity and MND risk was assessed by lifetime participation in sports (Chapter 6). None of the participants reported having been a professional athlete, and most participants participated in leisure sports throughout childhood and adulthood. When compared to those never playing sports, this group was found to have a higher MND risk (Chapter 6). This finding is consistent with several overseas studies[351 376 379] that reported a positive association between ALS risk and leisure physical activities, although not all studies found associations with leisure sports.[372]

Elevated ORs were observed for several common sports in New Zealand (rugby, football (soccer), running, and golf) although none reached statistical significance. A positive association was also observed for those who participated in strenuous sports (Chapter 6), which was consistent with a European multi-centre study that reported a linear association between physical activities and risk of ALS based on a lifetime metabolic equivalent of task (MET) scores, supporting the hypothesis that vigorous physical activities increase the risk of ALS.[381] Elevated ORs were observed for several strenuous sports in this thesis (e.g., full marathon, ironman, triathlon, other running) but these associations did not reach statistical significance as the number of people involved was small resulting in a lack of study power (Chapter 6). These results were similar to a Dutch study[379] that also observed a non-significant elevated risk for vigorous physical activities, marathons, and triathlons.

Football (soccer) was the only sport played by the study participants in this thesis for which the MND risk increased with longer duration of playing the sport. The association was statistically significant only for those who played football (soccer) for more than 12 years (Chapter 6). This is consistent with several studies[361 362 366 367] that have reported an increased MND risk for professional football (soccer) players. Thus, this thesis adds to this body of evidence and suggests that playing football (soccer) in a non-professional setting may also increase the risk of MND. It is noteworthy that among all sports, particularly football (soccer) was associated with MND. Besides physical exertion, this may suggest a potential role for repeated low-level head trauma associated with head impacts through heading the ball.[361 370 498] Thus, more studies are needed to assess whether MND is associated with repeated, low-intensity head injury in sports, particularly football (soccer) at both the professional and non-professional levels.

7.2.8 Childhood physical abuse

Only a few studies have investigated the association between MND and emotional trauma. Chapter 6 of this thesis reports an increased MND risk associated with having experienced traumatic life events in multiple categories. In particular, having been beaten by a family member or a carer during childhood was associated with an increased risk for MND in both males and females. Risks increased with higher frequency, as well as longer duration of child abuse (Chapter 6). Given that head injuries with concussions have repeatedly been associated with MND, including in this study population, a role for head injuries in the association between physical child abuse and MND needs to be considered. As the association remained after adjusting for self-

reported head injuries with concussion, it is less likely that diagnosed concussions are responsible for the observed association. However, a role for undiagnosed and unreported head trauma that may be associated with physical child abuse cannot be excluded, as these could not be taken into account in this study. Similar ORs (1.73 vs 1.89) were observed for physical child abuse with and without physical injury. It can therefore not be excluded that emotional trauma plays an independent role in this association. Psychological stress is associated with increased oxidative stress,[493 501] which plays an important role in the pathology of neurodegenerative diseases including MND.[502]

Whilst the underlying contributing factors could not be identified, this new finding suggests a role for physical child abuse in MND and further illustrates the enduring and far-reaching impact child abuse may have on health.

7.2.9 Confounding factors in the observed associations

A number of potential confounding factors were considered in the here reported associations, including age, gender, education, SES, ethnicity, smoking and alcohol consumption. How these factors are associated with MND in this study population, and how adjustment for these factors affected the odds ratios is considered in more detail below.

As summarised in Chapter 2, both age and gender are established risk factors for MND and are therefore potential confounders in the studied associations. In this study, age

and gender were therefore used to frequency-match controls to cases and all associations were adjusted for these variables.

MND has also been associated with both education and SES. Several studies have reported that higher levels of education were associated with a decreased risk of ALS,[41 394] whereas other studies indicated that higher educational attainment was associated with a higher rate of ALS.[530] Inconsistent associations have also been observed for SES, with some studies reporting higher MND risk associated with higher SES,[225] while others have shown no association.[530] In this study population there was little difference between cases and controls in terms of education, although cases had a higher SES compared to controls (Table 3.1).

Smoking and alcohol consumption have also been investigated as risk factors for MND in several studies, however, the results have been inconsistent.[69 407 425] In this study population, neither smoking nor alcohol consumption was associated with MND (Supplementary Tables ST1 and ST2 provided in Appendix 4).

Although MND affects people of all races and ethnicities, the incidence rates differ between European and non-European populations (Asian, African) and a potential role for ethnicity cannot be excluded.[24] In this study population, there was little difference between cases and controls in terms of ethnicity (Table 3.1).

While the role of education, SES, smoking, alcohol consumption and ethnicity in MND remains unclear, these are all factors that may be associated with occupational exposures and lifestyle factors and are therefore potential confounders in the studied

associations. The effect that adjustment for these potential confounders had on the estimated Odds Ratios for selected main findings of this thesis is presented in Table 7.1. This shows that there was no appreciable difference in effect estimates following adjustment for education, SES, alcohol consumption, smoking or ethnicity (Table 7.1). This is not surprising, given that these potential confounders were not found to be strong risk factors for MND in this study population.

Overall, these findings strongly indicate that it is unlikely that any of the observed associations can be explained by residual confounding by age, gender, education, SES, alcohol consumption, smoking or ethnicity.

Table 7.1. The effect of confounders on the ORs for selected MND risk factors identified in this thesis

Exposure	Cases /Controls (319/604) N	%	OR [95%CI]	OR1 [95%CI]	OR2 [95%CI]	OR3 [95%CI]	OR4 [95%CI]	OR5 [95%CI]
Exposure to pesticides	109/122	(35/20)	1.70[1.17-2.48]	1.65[1.13-2.39]	1.69[1.16-2.45]	1.68[1.15-2.44]	1.70[1.17-2.47]	1.70[1.17-2.48]
Ever exposed at high level of electric shocks	101/112	(32/19)	2.01[1.31-3.09]	2.10[1.38-3.22]	1.97[1.28-3.01]	2.01[1.31-3.08]	2.02[1.32-3.09]	2.04[1.33-3.13]
Ever had head injury with concussion (>3 years before diagnosis)	97/122	(30/20)	1.51[1.09-2.09]	1.49[1.08-2.06]	1.50[1.08-2.08]	1.51[1.09-2.09]	1.51[1.09-2.09]	1.50[1.08-2.08]
Physical child abuse	57/52	(18/9)	1.82[1.14-2.90]	1.85[1.17-2.95]	1.81[1.14-2.88]	1.83[1.15-2.91]	1.81[1.14-2.88]	1.81[1.14-2.89]

OR: adjusted for age, gender, education, ethnicity, SES, smoking status, sports, alcohol consumption, head injury, spine injury& other self-reported exposures
OR1: As OR, but not adjusted for education.
OR2: As OR, but not adjusted for ethnicity.
OR3: As OR, but not adjusted for SES.
OR4: As OR, but not adjusted for smoking status.
OR5: As OR, but not adjusted for alcohol consumption.

7.2.10 Fraction of MND cases attributable to specific risk factors

The work presented in this thesis has identified several occupational risk factors for MND, as well as several non-occupational risk factors. The calculation of attributable fractions (AFs) can help illustrate the importance of each of these, as it can quantify the fraction of cases that could be prevented if the risk factor were to be reduced or eliminated by an intervention. In case-control studies, AFs can be calculated by using the ORs as an estimate of the risk ratio and the prevalence of the exposure among the controls as an estimate of the exposure prevalence in the population (i.e. $AF = 100\% * (P(OR-1)\ )/(1+P(OR-1))$, where P is the prevalence exposure among the controls). This approach requires the rare-disease assumption,[531] which applies to MND. The definition of AFs used here reflects the proportion of MND cases in the study population that is attributable to the given risk factor, assuming that the association is causal.

Table 7.2 provides the calculations of AFs for the main findings presented in this thesis. AFs are calculated for the whole study population (both genders) only for associations that were statistically significant ($p<0.05$). To enable the comparison of AFs between males and females, gender-specific AFs are also calculated based on elevated ORs that in many cases did not reach statistical significance. In those instances, the OR and AF are given in parentheses.

Table 7.2. Attributable Fractions (AF) for the main MND risk factors observed in this thesis

	All (males & females)			Males			Females		
Identified risk factor	OR	Prevalence in controls	AF	OR	Prevalence in controls	AF	OR	Prevalence in controls	AF
Agriculture occupations & associated exposures									
Agriculture industry (Chapter 3)	1.68	20.4%	12%	1.56	23.6%	12%	1.89	16.5%	13%
Occupation in 611 market farmers and crop growers (Chapter 3)	2.15	7.6%	8%	2.64	6.9%	10%	(1.76)	8.4%	(6%)
Occupation in 6125 crop and livestock (Chapter3)	3.61	1.7%	4%	(2.70)	2.4%	(4%)	-	-	-
Exposed to insecticides (Chapter 5)	3.06	6.3%	12%	2.86	8.8%	14%	4.24	3.3%	10%
Exposed to fumigants (Chapter 5)	3.98	1.7%	5%	9.69	1.2%	10%	(1.12)	2.2%	(0.3%)
Applied pesticides (Chapter 5)	2.99	8.4%	14%	3.12	13.3%	22%	(2.20)	2.6%	(3%)
Forecourt attendants & associated exposures									
Automotive fuel retailing industry (Chapter 3)	4.10	1.5%	4%	3.07	2.1%	4%	-	-	-
occupation in 52113 forecourt attendants (Chapter 3)	8.31	0.3%	2%	6.21	0.6%	3%	-	-	-
exposure to petrol and diesel (Chapter 4)	2.13	4.6%	5%	2.45	7.3%	10%	(2.04)	1.5%	(2%)
Electrician, telecommunication technicians, & associated exposures									
occupation in 71311 electricians (Chapter 3)	3.61	1.0%	3%	3.61	1.8%	5%	-	-	-
occupation in 71122 builders (Chapter 3)	2.90	2.2%	4%	2.65	3.9%	6%	-	-	-
ever in occupation with high potential for electric shock (Chapter 2)	2.01	18.5%	15%	1.84	33.2%	21%	6.88	0.7%	4%
Head injury									
head injury ever (Chapter 6)	1.51	20.2%	9%	(1.38)	25.3%	(9%)	(1.76)	13.9%	(10%)
work related head injury (Chapter 6)	2.48	1.5%	2%	(2.39)	2.4%	(3%)	(4.46)	0.4%	(1%)
sports related head injury (>1) (Chapter 6)	3.05	1.0%	2%	(2.07)	1.5%	(2%)	(8.52)	0.4%	(3%)
leisure-related head injury (>1) (Chapter 6)	6.89	0.3%	2%	(7.32)	0.3%	(2%)	(5.27)	0.4%	(2%)
Sports									
played sports in childhood and adulthood (Chapter 6)	1.81	69.1%	36%	(1.70)	73.5%	(34%)	(2.40)	63.7%	(47%)
played football (soccer) >12 years (Chapter 6)	2.35	3.0%	4%	2.55	4.5%	7%	(1.78)	1.1%	(1%)
participated in strenuous sports (Chapter 6)	1.50	11.7%	6%	(1.76)	10.2%	(7%)	(1.43)	8.8%	(4%)
Childhood physical abuse & life events related									
reported being beaten as child (Chapter 6)	1.82	8.6%	7%	2.13	9.3%	10%	(2.06)	7.7%	(7%)
reported four or more life event categories (Chapter 6)	1.88	11.7%	9%	(1.76)	10.2%	(7%)	2.30	13.6%	15%
Other									
occupation in 9151 labourers (Chapter 3)	1.61	9.1%	5%	(1.59)	14.2%	(8%)	(2.54)	2.9%	(4%)
exposure to non-specified solvents (Chapter 5)	1.91	10.8%	9%	2.72	15.4%	21%	-	-	-
exposure to cleaning products (Chapter 5)	1.98	5.8%	5%	-	-	-	3.53	7.3%	16%

Parentheses symbol () indicates the OR did not reach statistical significance.

Among the identified occupational MND risk factors, the highest AFs were observed for pesticides and electric shocks (Table 7.2). The proportion of MND in the study population that could be attributed to employment in agriculture and the application of insecticides was estimated to be 12%. AF estimates were very similar for males and females (12% and 13% respectively). A high potential of electric shocks at work was associated with an AF of 15%, with a higher AF for males (21%) compared to females (4%) due to the much lower prevalence of occupational electric shocks exposure for females.

Among non-occupational MND risk factors identified in this research, a particularly high AF was estimated for playing sports in childhood and adulthood, due to its very high prevalence. However, as discussed in more detail below, reducing physical activity is not an option for intervention because of the many health benefits of physical activity and the AF is therefore not a particularly useful indicator in this instance. However, this high AF does emphasise the need for more research into which specific aspects of physical activity impact on MND risk, as it is possible that engaging in physical activities in a different way rather than reducing overall physical activity levels may reduce MND risk. Head injuries were associated with an AF of 9%, with very similar estimates for males and females (9% and 10%, respectively). The proportion of MND in the study population that could be attributed to physical child abuse was estimated to be 7%, with a slightly higher AF for males (10%) compared to females (7%).

Although the AFs are a useful illustration of the relative importance of these identified risk factors, the many limitations of AFs need to be considered. Firstly, AFs can be biased in the presence of confounding even if the adjusted ORs are used in the

calculation.[532] Secondly, AFs assume causality of the association, but for many risk factors causality has not been fully established. Finally, AFs are not valid if the elimination of the risk factor affects the distribution of other risk factors.[531-533]

Notwithstanding these limitations, the estimated AFs suggest that a substantial proportion of MND cases may be attributable to occupational exposure to pesticides and electric shocks, with smaller proportions attributable to other occupational exposure such as petrol and diesel fuel and solvents. This identifies the workplace as an important target for interventions to reduce the burden of MND and gives an approximate indication of the potential impact such interventions may have. These results also suggest that the reduction of head injuries may have a substantial impact on the burden of MND.

7.2.11 Common aetiological mechanisms

The MND risk factors identified in this research are highly diverse, in terms of the different settings in which they can occur (the home, the workplace, leisure sports), the different periods in life they can occur (childhood through to adulthood), and the different types of exposures they encompass (chemicals, electric shocks, head injury, physical exercise, trauma including child abuse). These diverse risk factors have nonetheless certain commonalities that link them to MND. Specifically, all have been associated with neurological damage, which is highly relevant for MND, a disease with motor neurone degeneration and motor neurone death as its defining hallmark.

Neurological damage can occur through a wide range of mechanisms. Several occupational MND risk factors were identified in this research that have neurotoxic properties. Pesticides, in particular insecticides, are known for their neurotoxicity and target either the central or peripheral nervous system or both.[300] The neurotoxic effects of solvents are also well described, with exposure to solvents causing cognitive deficits but also peripheral neuropathy, encephalopathy, and disruption of motor function.[249] Electric shocks can result in neurological complications, involving both peripheral and central nervous systems.[534] Head injury is the most frequent cause of nervous tissue damage in developed countries.[348] Furthermore, these occupational/environmental and lifestyle risk factors are all involved in complex pathological mechanisms including neuroinflammation,[535 536] glutamate excitotoxicity,[535] oxidative stress,[526] and mitochondrial dysfunction[527-529] which have been suggested as important factors in the pathogenesis of MND.

It is important to highlight that an individual can be affected by multiple risk factors throughout their life and the aetiology of MND is also believed to be multifactorial in which complex occupational/environmental, lifestyle, and genetic factors interact.[56 491] Recently, a hypothesis has been suggested by Al-Chalabi et al.[537] that MND is a multistep process which has been confirmed by several studies.[538-540] The theory of this hypothesis was based on a mathematical modelling approach originally applied to cancer epidemiology, which demonstrated that the relationship between incidence and age follows a power law connected to the number of underlying steps, and, therefore, that logs of incidence and age of onset would show a linear relationship.[541] This multistep hypothesis suggested that MND is caused by a sequence of six different risk factors over a lifetime, one of these factors (steps) is thought to be the genetic risk, but

other factors (steps) could be occupational, environmental and lifestyle factors. This illustrates the need for more epidemiological studies that focus on multiple (modifiable) risk factors simultaneously. This could lead to preventive strategies to reduce MND risk for the entire population, and particularly those carrying genetic variations that are predisposed to MND.

7.3 Strengths and limitations

The study design (population-based case-control study) and the methods used to assess occupational/environmental and lifestyle exposures (questionnaire and JEMs) have considerable strengths, but also some limitations. These are discussed below.

7.3.1 Strengths

First, using the MNDANZ national register, the NMDS, and the New Zealand Electoral Roll to identify cases and controls was a significant strength. Case ascertainment has been reported to be a significant challenge when studying neurodegenerative diseases.[472] This is also the case for New Zealand, for which an established and nationwide mandatory registry for MND is not available. To ascertain MND cases, the study relied on records of MND patients maintained by MNDANZ, and the national collection of public and private hospital discharge data known as the NMDS. As MNDANZ is the only organisation in New Zealand that focuses on MND support, and their specialist support team members help link almost every person with MND to appropriate health care professionals, MNDANZ records provide a reliable way to identify MND cases in New Zealand. The NMDS records nationwide hospital discharge information, including clinical information, for inpatients and day patients, and all

records must have a valid National Health Index (NHI) number. MND cases were defined based on a primary or secondary diagnosis of MND using ICD10 code G122 from NMDS, providing an additional identification of MND cases that have been hospitalised. The majority of cases (74%) was recruited through the MNDA and the other 26% was identified from NMDS records (Appendix 2), as there were only 103 cases identified in the NMDS records that were not registered with MNDANZ over three years (around 30 cases every year). Thus, the use of both MNDA and NMDS enabled the inclusion of 225 incident cases and 96 prevalent cases with a primary diagnosis of MND that participated in the study. The 225 incident cases covered an estimated 75% of New Zealand's incident MND cases between 2013-2016, as there are around 100 new MND cases each year.

Second, misclassification of disease status was minimised as for all cases the MND diagnosis was confirmed by a neurologist. Not all cases had a diagnosis letter from their neurologist, in which case we used the neurologists' (and GPs') contact details (provided by cases on the consent form) to contact the neurologist to obtain the diagnosis information. As a result, the disease status was confirmed for all cases. However, while the MND diagnosis could be confirmed by the neurologist, diagnosis details such as subtype of MND were not available for the majority of the cases.

Third, the controls were selected from The Electoral Roll, which records virtually all New Zealand citizens and permanent residents aged over 18 years,[453] and is therefore highly representative of the general population that generated the cases. The Electoral Roll is almost 100% complete in the age range of particular relevance to this study (i.e., >50 years). Moreover, the address as recorded on the Electoral Roll is reasonably up to

date as it is updated in each election cycle, which is three years in New Zealand. Based on this address, all potential controls were sent a letter detailing the objectives and information about the study. Non-responders' addresses were then linked to the white pages to obtain a phone number. This proved to be a practical and useful tool for this study, as for people aged >50 years, many still have a landline. As a result, only 14% of potential controls (Appendix 1) could not be contacted through mail or phone. Another particular advantage of using the Electoral Roll is that basic information such as age, gender, occupation and NZDep is available, providing an opportunity to investigate participation bias by comparing these characteristics between participants and non-participants, which is important as the participation rate among controls was considerably lower than that of cases.

As many agricultural occupations were associated with an increased risk of MND, a check was conducted to assess whether controls in agricultural occupations (as registered on the electoral roll) were somehow less likely to participate in the study. The results showed that this was not the case, and there was no difference between participating and non-participating controls for the occupations for which an increased risk was found (Chapter 3). In addition, to test whether these associations could be explained by differences in urban/rural residency between participating and non-participating controls, the geographical mesh-block for addresses for all potential controls (recorded on the electoral roll) were linked to New Zealand geographic concordance files to obtain their urban/rural classification,[542] which was then compared between participants and non-participants. The results showed participating controls were slightly more likely to live rurally (18%) compared to non-participating controls

(14%), suggesting that participation bias was an unlikely explanation for the observed association between agricultural occupations and MND risks.

Fourth, the vast majority of cases and controls answered the questionnaire without the use of proxies, as opposed to other studies with much higher proxy rates.[343 433 543] In this study, proxies were used for nine cases, all of whom were proxy-assisted for the interview only (helping to read and write). Given that this represents only 2.8% of the total case population, it is considered that any bias resulting from this is negligible. Several of the findings observed were for risk factors that typically can only be recalled by the participant themselves. These include for example the full occupational history, head injuries that occurred during childhood, and physical abuse as a child. Studies highly reliant on proxy interviews would therefore be less likely to be able to detect associations for these risk factors.

Fifth, comprehensive data were collected from the study questionnaires, which on average took 1.5 hours to complete. This included comprehensive data on potential confounders (age, gender, education, ethnicity, SES, smoking status, and alcohol consumption), all of which were adjusted for in the analyses. Detailed information on occupations, occupational exposure, and lifestyle factors were collected, which proved to be important as certain risk factors were associated with others (e.g., sports and head injury, occupational exposure to pesticides and rural residence, etc.). Furthermore, the full lifetime occupational history was collected, which is a particular advantage over, for example, occupational mortality studies, and studies based on census data, which typically only have one occupation available for analysis (occupation recorded on the death certificate, and occupation recorded on the census, respectively). The results of

this thesis also indicate that having a full lifetime occupational history is important as latency analyses indicated that some occupations or occupational exposures that occurred early in their professional lives may be particularly relevant. Having a detailed full occupational history also provides the opportunity to code the occupation information and then apply it to available JEMs, which allows the assessment of associations with more specific exposures.

7.3.2 Limitations

First, exposure to most potential risk factors was assessed through self-report, which can be subject to exposure misclassification and recall bias. In the design of the questionnaire and training of the interviewers, every effort was made to minimise recall bias. For example, the questionnaire collected information on exposures through standardised interviews and structured questionnaires. The questionnaire used in the studies was comprehensive, including 16 sections with demographic and personal data, lifestyle factors, and lifetime occupational history. The sections of the lifetime work history questionnaire were provided to every participant a few weeks before the interview to allow sufficient time to recall their work history.

Recall bias can result in false-positive findings if cases, compared to controls, have thought more about potential causes of their diagnosis, thus potentially improving recall of past events/exposures, or overemphasising particular events/exposures they believe may explain their diagnosis. For this reason, exposure to electric shocks was assessed through a JEM, rather than through self-report. However, for most occupational exposures the possible link with MND is not widely known, reducing the risk of recall

bias and subsequent bias. The fact that only some of the assessed exposures were associated with MND, adds weight to the assumption that these associations were unlikely to be based entirely on recall bias. For example, statistically significant associations were observed for exposure to OPs insecticides, but not for 245T or 2-4D herbicides, which are all well-known and commonly used pesticides (Chapter 6).

Recall bias can also result in false-negative findings or inverse associations when the disease impacts an individual's memory or cognitive function, which may result in poorer recall among cases. There is increasing recognition that in some cases, people with ALS can experience cognitive changes when disease conditions deteriorate, in particular, some ALS patients (13%) may also develop frontotemporal dementia.[69] However, cases at the late stage of the disease process (e.g., in intensive care not being able to manage with the interview, 16 cases), and diagnosed with FTD (1 case), were not eligible for the study. Also, among cases, no signs of obvious cognitive impairments were noticed by the research nurses during the interview, which indicated that recall bias due to memory loss from cases is unlikely to have played a major role.

Another aspect impacting recall is that some specific exposures are very difficult to recall because people are not aware of that exposure. This is most relevant for invisible exposures, such as ELF-MF. For this reason, a JEM was used to assess this exposure. Exposure assessment through JEMs is based on job titles, which are generally easy and accurately recalled.

To aid recall precision, exposures included in the questionnaire were assessed using multiple questions. For the study on occupations (Chapter 3), the occupational code was

not only based on job title, but also the job/task descriptions, and employer description, to ensure that the job code was representative of that job. For the study on occupational exposures (Chapter 5), self-reported exposures were subsequently compared with job titles and task descriptions to ensure that they were relevant for that job, thus reducing exposure misclassification. These exposure checks were done blind to the case/control status of participants, thus limiting differential exposure misclassification. For the selected lifestyle factors (Chapter 6), exposures again were assessed using multiple questions. Moreover, questions used on head trauma specified a head injury with a concussion, to reduce recall bias that may be associated with using open questions on any head trauma.

However, it cannot be excluded that cases recall their exposures differently from controls, particularly for exposures widely known to adversely impact health. Nevertheless, on average, cases and controls reported the same number of jobs, suggesting no differential recall in lifetime occupational histories between cases and controls. Furthermore, positive duration-response associations were observed for most risk factors identified, which argues against recall bias as an explanation for some of the associations observed. In addition, no difference was observed between cases and controls in terms of their response to the more sensitive questions. For example, equal proportions of cases and controls reported having experienced sexual assault, which was among the most sensitive questions. Thus, for the main findings, as discussed before (Chapter 3-6), recall bias is not considered to be a likely explanation for the observed associations. Nevertheless, the reliance on self-reported exposures has limitations, particularly when attempting to assess exposures to highly specific agents, as illustrated

by the high proportion of participants reporting exposure to solvents without being able to specify the specific solvent they had been exposed to (Chapter 5).

Second, the participation rate among population controls (48%) was lower than among cases (92%), which, as noted above, may contribute to participation bias. To evaluate the potential for participation bias, the age, gender, urban/rural living, and occupations[458] were compared as recorded on the Electoral Roll between participating and non-participating controls (Supplementary Tables ST3 and ST4 provided in Appendix 4; Supplementary Table S3.8 in Chapter 3, respectively). These showed no significant differences between participating and non-participating controls, making it less likely that the observed increased risks were explained by non-response bias.

Third, there were also differences in the interview method used between cases and controls, with cases more likely to opt for a face-to-face interview than controls. There are clear reasons for this. For cases with breathing and speech difficulty, an interview over the phone for an hour is not an option. For cases with weakness of upper limbs and loss of the ability to write, a self-completed postal questionnaire is not an option. Fatigue is very common in MND patients,[544] which, in combination with immobility and other physical limitations for many cases, makes a face-to-face interview with the flexibility of a follow-up telephone conversation for missing questions, the best option. To evaluate whether the different interview methods could have impacted the results, additional analyses were conducted controlling for the interview method in the models. These additional adjustments made very little difference and did not alter the findings. In addition, analyses stratified by the interview methods were applied to the 11 main

occupational exposures categories based on Chapter 5 and did not change the results for the main findings (Supplementary Table S5.8, Chapter 5).

Fourth, most previous studies assessed associations with ALS, while in this thesis all forms of MND were included (MND subtype-specific diagnosis was not recorded in New Zealand at the time of study recruitment), and analyses could therefore not be restricted to the ALS case group to improve comparability with other studies on this topic. However, ALS is the most common form of MND accounting for 80-90% of the total cases,[474] and the case definition in this thesis is therefore unlikely to differ substantially from those used in other studies on potential risk factors.

Finally, while this study included over three hundred cases, study power was still limited, particularly for less common occupations and exposures. For example, work as a forecourt attendant was associated with an increased MND risk, but this was based on small numbers (Chapter 3). Elevated risks were also observed for formaldehyde and chloropicrin fumigant (Chapter 5), but as this was based on small numbers, it is unclear whether this is real or just a chance finding. Larger-sized studies are needed to assess the associations for such rare occupations and exposures.

7.4 Implications

This is the first study in New Zealand examining a wide range of potentially modifiable risk factors for MND. Based on the findings of the studies described in this thesis, and other recent relevant international publications, there are several recommendations that follow from this work.

The sections below will first discuss what the study implications are with regards to opportunities for MND prevention, followed by a discussion of remaining research gaps and recommendations for further research.

7.4.1 Opportunities for MND prevention

While MND has been regarded as a disease with very few opportunities for prevention, this thesis has indicated that certain occupations and occupational exposures play a role in the development of MND in New Zealand, which provides several opportunities for the prevention of MND.

7.4.1.1 Reducing occupational exposure to pesticides

The associations with MND were particularly strong and consistent for multiple agriculture/horticulture occupations and exposure to pesticides (insecticides, fungicides, fumigants). Agriculture represented the largest occupational group for which an increased risk was observed in this thesis (i.e., 33% of cases and 24% of controls had worked in agriculture, Chapter 3), and the estimated AF suggests that 14% of MND cases in the study population may be attributable to pesticide exposure, thus reducing pesticide exposure may potentially have an appreciable impact on the MND burden in New Zealand.

The agriculture sector is New Zealand's leading primary industry that employed >83,000 people in 2020,[545] and within the agriculture sector, horticulture has steadily increased in economic value by more than 60% in the last 10 years, with a trend of continued increase in the future. There are >60,000 people who work in the horticulture

industry, not including seasonal, temporary, and council green workers.[546] In New Zealand, more than 3,000 tonnes of pesticide active ingredients are applied in agriculture each year and more than 300 pesticides have been approved for use in fruit and vegetable production. In the work presented in this thesis, exposure to insecticides was associated with a three-times greater MND risk, with associations observed for several insecticide classes (organochlorines, organophosphates, and pyrethroids). The most common types of insecticides, such as organophosphates and pyrethroids that were associated with MND, are still widely used in commercial and domestic activities in New Zealand. Therefore, interventions to reduce the reliance on and exposures to pesticides may reduce the risk of MND.

The hierarchy of control is a step-by-step approach to eliminating or reducing risks in the workplace, based on practical and well-established principles.[547] Highest in the hierarchy of control is the elimination of the harmful agent. Over time certain classes of pesticides have been eliminated, such as OCPs. The book Silent Spring[548] increased public awareness of the ecological damage resulting from the use of OCPs in 1962. OCPs were banned for use in most high-income countries during the 1970s and 1980s, and worldwide after 2001, due to their environmental persistence, bioaccumulation, adverse effects on wildlife and off-target species, and potential negative impact on human health.[549 550] Other major insecticide classes, such as OPs, continue to be widely used, even though these are also associated with negative health and ecological impacts. However, the decision to ban harmful chemicals is not a quick and easy process for policymakers, for instance, the Environmental Protection Authority (EPA) is currently calling for submissions on an application to reassess the expiry dates of the approvals for three organophosphate insecticides (diazinon, fenamiphos, and methamidophos),

which initially were planned to be phased out from 2023 (fenamiphos and methamidophos) and 2028 (diazinon). It is important to note that these three insecticides have already been banned in the EU (diazinon in 2006,[551] fenamiphos in 2021,[552] and methamidophos in 2008[553]).

Second in the hierarchy of control is the substitution of more hazardous chemicals by less hazardous alternative chemicals. However, care must be taken to ensure that the new chemical does not result in new and more severe risks.

Third in the hierarchy of control are engineering controls that are designed to protect workers from hazardous conditions by placing a barrier between the worker and the hazard or by removing a hazardous substance through air ventilation. The use of filtered ventilation in tractor cabins while applying pesticides is an example of this. Other new technologies and innovative ideas are being developed in agriculture in New Zealand, such as “robotic apple pickers”,[554] and “robotic sprayers” for applying pesticides.

Fourth in the hierarchy of controls are administrative controls, which reduce exposure by changing the way people work, for example by reducing the exposure time in the work shift; reducing the frequency of the exposure by limiting the work shifts to 3 or 4 days a week if possible. This approach could apply to for example cleaning chemicals, solvents, or methyl bromide fumigation at the workplace. However, as the use of pesticides is highly seasonal and weather dependent, this leaves little opportunity for such administrative controls.

Fifth in the hierarchy of controls is PPE. This can include protective clothing, including gloves, and respiratory protective equipment. This requires regular cleaning, replacement, and test for fitting of PPE. Adherence to consistent PPE-use also highly depends on comfort, which can be a challenge in physical jobs such as pesticide spraying under often hot weather conditions. Another important issue that needs to be considered is that most PPE is not specifically designed for females and may therefore not be as effective for women.

Finally, for any of these interventions to be effective, adequate work safety education is important, for both employers and employees. Updating regulations according to the most recent scientific evidence, and adherence to these, are also crucial. In 2013, the EPA placed tighter controls on acephate, chlorpyrifos, and other organophosphate pesticides based on international evidence about their toxicity.[555] However, according to the 2019 Ministry for Primary Industries (MPI) report, some agricultural chemical suppliers and growers remained unaware of these changes and required reminders.[556]

To ensure that these approaches are effective, more strict enforcement of workplace exposure standards within the priority industries (e.g., fruit and vegetable growing) is needed. Also, regular health monitoring, both specific (biomarker) and in general is critical. Routine monitoring of how pesticides are used, stored, and disposed of is also important. The EPA reported that little was known about New Zealand's chemical landscape or the impact it has on human and environmental health, and they are currently developing a "chemical map" with information about what is used and where, and evidence of harm.[557] For example, as the EPA is responsible for approving pesticides and setting controls on their use, all pesticides used on fruits and vegetables

must also be registered with the MPI, and growers must keep records of pesticide use. However, according to New Zealand Consumer, regulators do not routinely monitor the volume of pesticides applied to crops.[558] As a result, detailed data on pesticide use in New Zealand is lacking, making it more difficult to target interventions.

The results of this research suggest that interventions should focus on individuals who apply pesticides themselves, as the increase in risk was particularly observed for this occupational group. Moreover, among the different pesticide groups, insecticides were associated with three times greater MND risk, including several specific insecticide sub-categories: organochlorines (OR 3.28), organophosphates (OR 3.11), and pyrethroids (OR 6.38). As discussed before, most organochlorines have been banned from the market, but organophosphates and pyrethroids are still widely used in commercial and domestic activities in New Zealand. In addition to MND, many of these pesticides (insecticides, herbicides, fungicides) have been linked to increased risk of other neurodegenerative diseases[559 560] (e.g. Parkinson's and Alzheimer's diseases) and other serious diseases such as Non-Hodgkin's lymphoma,[447] leukemia,[561] and prostate cancer,[562] in particular among pesticides applicators and agricultural workers.[563] The current evidence that pesticides may also be a risk factor for MND provides an important additional reason to reduce occupational pesticide exposure.

7.4.1.2 Prevention of electric shocks

Potential exposure to electric shocks was associated with a two-fold increased MND, and the estimated AF suggests that 15% of MND cases in this study population may be attributable to electric shocks at work, and 3% of MND cases were estimated to be attributable to occupations as electricians (Table 7.1). This suggests that preventing

electric shocks at workplaces may provide another opportunity to reduce MND prevalence. In 2020, WorkSafe reported that over the period 2016-2020 about 50% of electrical accidents involved electrical workers and the highest cause of electrical accidents (24%) was the failure to follow safe work procedures.[564] WorkSafe has also noted that the threshold for the electrical notifiable accident was raised, resulting in a smaller number of electrical accidents qualifying as "notifiable accidents", now only including accidents resulting in death or injury that need hospital admission or receiving medical treatment from a medical practitioner.

The risk of injury from electricity is strongly linked to where and how it is used. Electrical hazards need to be identified before the work starts, labelling the hazards clearly, so anybody can easily recognise them. All electrical cords should be thoroughly inspected before use for signs of damage. Equipment needs to be kept away from energy sources, and only equipment specifically made for the job should be used, while wearing proper protective clothing and using insulated tools when around electrical hazards. The potential electric shock risk may also differ between workplaces of different sizes; between different types of equipment/tools, between company employees and subcontractors. Therefore, the method and practices of identifying, eliminating, or minimising the potential electric injury risk require tailored approaches.

In this thesis, increased MND risks were associated both with job duration less than 3 years and job duration of more than 24 years. This supports previous findings that young electricians may be more likely to experience electric shocks at work,[465 509-511] and suggest good apprenticeship training and on-the-job safety training are essential. Good apprenticeship training does not only include teaching the right skills for future

work and being able to carry out the electrical work safely and legally but should also focus on good behaviour and attitude towards health and safety. An overseas report[565] showed that more than a third of apprentice electricians accepted electric shocks and burns as part and parcel of their work, which has raised concern that a mentality of acceptance of electric shocks exists in the industry and is putting lives at risk. Furthermore, apprentices often do not have the understanding of risk that comes from experience on the job. Effective supervision will allow apprentices to develop the knowledge and skills they need to competently perform the work in a safe working environment and prevent them from electric shocks. Moreover, supervisor(s) or employers must carry out monitoring to ensure that safety procedures are properly followed and be models for their apprentices to follow safe practices at work.

Overall, the high prevalence of electric injury that continues to occur in the workplace indicates there is still ample opportunity for prevention. The prevention of electric shocks will not only prevent their acute effects (injury and death) but may also contribute towards the prevention of severe long-term health effects such as MND. While MND is a very rare outcome, the severity of the disease may nonetheless provide additional motivation for the prevention of electric shocks at the workplace through safer work practices.

7.4.1.3 Reducing workplace exposure to lead

As summarised in Chapter 2, lead exposure has repeatedly been associated with MND, and it is possible that the observed increase in MND risk for forecourt attendants (Chapter 3) is the result of exposure to lead. Several interventions to reduce exposure to lead have already taken place (e.g., removal of lead from paint and petrol), which over

the last 36 years has resulted in a 90% reduction in blood lead levels in the New Zealand population.[566] Historical lead exposure will, however, continue to impact on the MND burden. Once lead has entered the body it is stored in tissue[567] and bones for years.[568] Bone-stored lead forms a continual source of internal lead exposure[567] when remobilised back into the bloodstream.[567-569] This is particularly relevant for those with osteoporosis,[570 571] and women undergoing menopause.[572] Thus, while occupational lead exposure has reduced substantially among for example automotive fuel retail workers, the internal exposure still exists and may continue to impact on the MND burden. Blood lead notifications in New Zealand indicate that high lead exposures continue to occur in some occupations, in particular painters involved in the removal of leaded paint,[573] indicating that opportunities for reducing lead exposure in the workplace remain.

7.4.1.4 Preventing head injury

This thesis also indicates that MND risks are associated with multiple head injuries with concussion, a finding supported by several other studies. The attributable fraction estimates suggest that 2% of MND cases could be attributed to work-related head injury, 2% to sport-related head injury; and 2% to leisure-related head injury.

Traumatic brain injuries (TBIs) are extremely common in New Zealand, with around 100 cases every day (35,000 people every year) ranging from mild concussion to the more severe.[574] According to Accident Compensation Corporation (ACC), 95% of these individuals are considered to be mild TBIs,[575] and men are twice as likely to suffer mild TBI than women.[574] Over half of ACC's serious injury claims are related to TBIs.[575] A study on the incidence of TBIs in New Zealand[576] indicated that TBI incidence (790

total cases; 749 mild TBIs cases per 100,000 people per year) was substantially greater than in Europe and North America (47-618 cases per 100,00 per year).[577-579] Of interest, according to Feigin et al.[576] TBIs among the general population are significantly under-reported in New Zealand because people with mild TBIs do not always seek medical treatment. The New Zealand Treasury has also identified that TBIs are second only to stroke for their impacts on employment and income.[580]

The most common causes of TBIs in New Zealand are recreation or sports, motor vehicle accidents, assault, falls and using machinery. Of these, recreation or playing sports accounts for around 30% of the total TBIs.[575] Also, in the study population discussed in this thesis, head injury with concussion most commonly occurred during leisure and sports. Having had more than one sport-related head injury was associated with a three-fold MND risk and more than one leisure-related head injury with an approximately 7-fold increased MND risk (Chapter 6).

In general, different prevention strategies apply to the different causes of head injury. To prevent head injuries in the workplace, such as falls or due to using specific machinery, enforcement of workplace safety, regular workplace hazard identification, workplace safety education and training, workplace practices monitoring, and periodic workplace safety reviews all play a crucial role.

Playing sports increases an individual's risk of falls and collisions with objects or other players, such as a helmet-to-helmet tackle in American football; heading a ball when playing football (soccer); falls during biking; skateboarding wipe-outs; collisions between skiers or snowboarders, all of which could cause head injury with concussion.

In many of these situations wearing the correct protective headgear, other protective equipment, and certain adjustments of and adherence to the rules of the game can reduce the risk of brain injury.

Some recreation/sports activities have already introduced the mandatory wearing of headgear in New Zealand. This policy exists in boxing, equestrian sports, cricket, cycling, and mountain biking, with no mandatory but highly recommended helmet wearing for skiing and snowboarding. For rugby and rugby league, some players wear a scrum cap which is a form of headgear used to protect the ears in the scrum, but research has shown it offers no significant protection against head injury and concussions.[581-583] Concern about head injuries in rugby has resulted in the development of hi-tech head protection gear, and a field trial is currently being conducted by Canterbury University looking into head collisions in junior rugby and the potential of World Rugby sanctioned headgear to reduce impacts.[584]

Although most headgear policies are mandatory for professional sports and professional players during the match/competitions and training, they are not for leisure sports. For example, elite skiers have to wear a helmet for competition, whereas for leisure skiers wearing a helmet is strongly recommended but is not mandatory and difficult to enforce.[585] However, an Australian report showed that after 2013 when Michael Schumacher suffered a skiing accident, the percentage of people wearing a helmet in Australian ski resorts increased from 57.4% in 2013 to 80.8% in 2018,[586] and a similar trend was also found in New Zealand (from 42% in 2010 to 84% in 2015).[587]

In New Zealand, most of these policies tend to be more focused on team sports rather than individual sports in leisure/recreational settings. More safety policies are needed for leisure sports, especially for children and young adults, as head injury is among the most common reasons for children, adolescents, and young adults to present to emergency departments.[588] A recent study on TBIs in children (between age 5-18) among 10 Emergency Departments in Australia and New Zealand reported that 36% of these head injuries were sports-related, and children involved in recreational sports such as bicycle riding, skateboarding, and horse riding were more likely to suffer serious head injuries (clinically important TBI (ciTBI)) than children who play team sports.[589] In this thesis, an increased MND risk was observed for individuals who had a head injury in childhood, and an 80% increase in risk was reported for individuals who had a head injury in both childhood and adulthood (Chapter 6). This indicates that having head injuries in childhood may play a role in the later development of MND, illustrating the importance of preventing head injury starting in childhood.

Education on the awareness of understanding the function of protective headgear and risk-taking behaviours is another important part of preventing head injury in leisure or sports activities. A study among UK rugby union players indicated that some players who wear headgear have a false sense of security thereby increasing the risk of reckless play, and were not aware that headgear is designed only to prevent superficial head injuries.[583] A study on ski-related accidents in New Zealand showed that even though the percentage of people who wear a helmet had increased, head injuries with a concussion in ski and snowboarding had not reduced. In contrast, concussions had increased by 29% over 5 years, likely due to those wearing helmets overestimating the

protective capacity of the helmet and taking greater risks with speed and/or jump height than those not wearing a helmet.[587]

Technological advances have played a role in sports to prevent head injuries, such as the move from leather headgear to a "Revolution Speed-Flex" helmet which was based on impact protection for concussion in American football, and the move from the leather shell football (soccer) ball to a synthetic shell football (soccer) ball, to reduce the weight of the ball during the play under wet conditions (a leather shell football (soccer) ball can absorb rain easily and become very heavy to play, especially when heading the ball). However, more new technology and innovative ideas, such as lightweight high-impact materials and 3D design are needed in the development of new headgear to prevent head injury more effectively in leisure and professional sports. Making protective gear comfortable to wear and fit most people is another technological challenge.

As well as preventing head injury, it is also important to minimise the risk of repeated head injury and prevent the second-impact syndrome, where a second injury to the brain occurs before the first is fully recovered. According to ACC, about 20% of concussions in sports were missed,[575] and persistent post-concussive symptoms affect more than a third of people who had TBIs.[590] Therefore, seeking treatment on time, taking a break from sports, letting the brain heal completely, and avoiding repeat concussions, will help prevent long-term problems.

As noted in Chapter 6, the only specific sport associated with MND risk ($p<0.05$) was playing football (soccer) for more than 12 years. Football (soccer) distinguishes itself from other sports by allowing the ball to be played with the head. On average, a player

might head the ball 6 to 12 times during one game, but during practice, it's common for players to gently head a ball repeatedly. However, in a competitive setting, they usually head the ball with more impact. Even though concussion is not common in football (soccer), over time, repeated head injuries can accumulate and result in more serious damage such as chronic traumatic encephalopathy (CTE). This is consistent with the literature that suggests that repetitive mild TBIs alone could be sufficient to trigger physiological changes that may also increase the risk of MND.[348 496 497]

As the most popular sport in the world, football (soccer) is played by people of all ages, including both professionals and amateurs. In New Zealand, according to the Active New Zealand 2018 survey, 19% of young people participated in football (soccer) (28% male, 10% female), and football (soccer) is the most popular team sport among young people.[591] As a result of the increased concern regarding the high prevalence of neurodegenerative diseases (MND, Parkinson's disease, and dementia)[369] among football (soccer) players in the UK, new guidance on the heading limits has been released this year for professional and amateur players in both training and matches.[592] This heading guidance is applied across all players, at all levels of the game. The guidance limits "higher-force" headers in training to ten for professional players,[593] amateur adult and adolescent (14-18) football (soccer) players are limited to 10 headers a week,[594] children aged 12 and 13 are limited to 5 headers a week, and heading is not permitted for children under age 12.[595]

In New Zealand, the concussion and head injury policy provides guidelines on the identification and management of concussions to all those involved in football (soccer). However, NZF (New Zealand Football) "do not believe that there is any need to ban

heading or alter the laws of the game", although NZF is aware of the heading rule changes in the UK.[596] Thus, there is further room for developments on the policy for heading in football (soccer) in New Zealand.

The above indicates that many opportunities remain for the prevention of head injury. Preventing head injuries will not only reduce their acute impacts but may also impact on a wide range of longer-term outcomes, including headaches, dizziness, fatigue, depression, irritability memory problems,[597] and reduce their impacts on employment and income.[580] The results presented in this thesis indicate that the prevention of head injuries may also reduce the risk of MND, in line with previous MND research as well as research on other neurodegenerative diseases, such as Alzheimer's disease[598] and Parkinson's disease.[599] The results presented here also indicate that to reduce MND risk prevention should not only focus on severe TBI but also repetitive mild TBIs.

Independent of head injury, the results presented in this thesis identified that those who played sports throughout life had a higher MND risk compared to those who did not. A recommendation of discouraging sports should, however, not be made based on these findings. A recent study from the UK indicated that high-intensity physical activity is likely to contribute to motor neurone injury in individuals who had a predisposing genetic profile (a risk-genotype),[387] but the authors strongly emphasised that this finding does not mean that they advise against exercise. Playing sports and being active has been demonstrated to be protective against many diseases[600] (e.g., cardiovascular disease, diabetes, and a variety of cancers). The benefit of reducing the risk of these common conditions outweighs the increased risk of a relatively rare disease such as MND. Reducing physical activity by itself is therefore not a good candidate for

intervention, but the prevention of head injury in football (soccer) and other sports may provide opportunities for MND prevention, as discussed before.

7.4.1.5 Preventing child abuse

This thesis identified a two-fold MND risk for having experienced physical abuse as a child (Chapter 6). This association was consistently observed for both males and females, and these risks increased for a higher frequency, as well as longer duration of child abuse. This is the first study that observed this risk factor for MND, meriting further scrutiny in future studies among other populations, which will provide more insight on whether physical trauma or emotional trauma or both contribute to the observed risk. While this study provides the first indication that preventing child abuse may contribute to the prevention of MND, there are many other reasons why physical child abuse needs to be prevented.

Family violence, particularly violent behaviour towards children, is a major public health issue in New Zealand.[601] Among other high-income countries, New Zealand has the 10th highest rate of assault mortality (1.2 per 100,000). New Zealand's rate is above the OECD (Organisation for Economic Co-operation and Development) median (0.9 per 100,000) and is also higher than that of Australia (0.8 per 100,000) and the United Kingdom (0.3 per 100,000).[602] In 2016, the rate of child deaths due to assault in New Zealand was 1.6 per 100,000 for children under 5 years[602] and New Zealand's child assault deaths level was 4-6 times higher than the average for other leading countries.[603]

In 2007, in an effort to improve child health outcomes in New Zealand, the Government introduced anti-smacking legislation that prohibited the physical punishment of

children.[604] However, a 2016 report[605] found that not a single social indicator relating to the abuse of children had shown significant or sustained improvement in the seven years since the passing of the law. In a recent New Zealand cohort,[606] childhood physical punishment remained a common form of child discipline, despite both changing perceptions towards physical abuse of children and the 2007 legislation, with over 40% of parents still using physical punishment on their children in 2017, 10 years after the legislation came into force. Severe punishment (hitting a child with a belt, stick, or other hard objects; hitting a child with the fist or kicking) was reported for 4% of children in the cohort.[606]

Although a clear downward trend in parental reported use of physical punishment has been observed (from 77% to 42%) and the frequency of physical violence has decreased, a large number of New Zealand parents are continuing to use physical punishment when disciplining their children.[606] This indicates that other strategies are required besides law enforcement. This may include public education on reducing physical violence, ongoing monitoring of parental use of physical abuse toward children, providing alternative approaches for managing child behaviours, and educating parents and caregivers on how to manage their own emotional stress. Interventions may have to particularly focus on high-risk groups, such as individuals who were themselves raised in abusive households, or experienced physical violence in the household as an adult.[601]

Thus, the available data indicate that physical child abuse remains an important public health issue. By providing the first indication that child abuse may increase MND risk, the research presented in this thesis adds to the evidence that child abuse may have

long-lasting impacts on physical health, further highlighting the importance of increasing efforts to reduce physical child abuse.

7.4.2 Recommendations for future research

The following sections will discuss the implications of the work presented in this thesis in the context of recommendations for future research. Recommendations will be categorised as: (1) recommendations for future MND studies; (2) recommendations for the further use of the case-control study; and (3) recommendations to facilitate further MND research in New Zealand.

7.4.2.1 Recommendations for future MND studies

The work presented in this thesis identified several modifiable risk factors associated with MND. Some occupational exposures were associated with MND risk, but more research is needed to identify the specific chemicals involved. For example, it is not clear which specific solvents, or which specific cleaning products are associated with MND. Although pesticides as a group were associated with MND, and certain specific insecticides classes (OPs, OCPs, pyrethroids) were identified, more work is needed to more comprehensively identify the specific chemicals involved. A positive association was also observed for electric shocks, but the exposure was assessed through a JEM and not based on individual information on electric shocks, and information on the severity and number of electric shocks was not available. Therefore, more work is needed to identify which aspects of electric shocks (e.g., a big single shock or cumulated mild small shocks) contribute to MND risk. Exposure to petrol and diesel fuel was associated with MND, but it remains unclear whether the risk observed in this study was

attributable solely to lead, or that other petrol components e.g., benzene may play a role also. Physical child abuse was observed as a risk factor for MND, but which aspect of child abuse (physical or emotional) plays a role is not clear and findings require a confirmation from other studies.

Although the MND case-control study was based on a reasonably large number of cases, it nonetheless had limited study power to assess associations for less common exposures. Data linkage studies based on administrative data (e.g., mortality, hospitalisations) could provide a low-cost way to include a larger number of MND cases, thus increasing study power. Large mortality studies would be an appropriate approximation of incidence studies, as MND is a rare and fatal disease with a short life expectancy and no cure. MND mortality studies can be conducted by linking routinely collected mortality data from the Ministry of Health (MoH) and occupation can be identified from the death notification. This way the association between occupation and the risk of MND can be studied in a large sample size, which will also provide the opportunity to see whether the findings from this thesis can be replicated. As noted before, the limitation of mortality studies is that only one occupation is recorded on the death certificate. However, for certain occupations, such as agricultural occupations and electricians, individuals who worked in these occupations tend to not change their occupations often. To address this limitation, other routinely collected data that contain occupational information could be linked to the mortality data, such as Electoral Roll and Census Data, providing occupational information for multiple time points. If the mortality study is repeated over time, this approach can also be used to track trends over time. For example, it will be of interest to explore whether agricultural occupations continue to be associated with MND given the changes in pesticide use over time and

whether occupation as a forecourt attendant continues to be associated with MND, given the phase-out of lead from petrol. Occupational mortality studies would also provide the opportunity to apply a range of JEMs so that besides MND risk for occupation, MND risk for specific exposures can also be assessed.

Data linkage studies could also be used to further clarify the association between head injury and MND risk, by linking routinely collected MND mortality data to ACC injury claims. As the electronic ACC injury claims data (work and non-work) is covered from 1994, this approach would enable analyses into the role of older injuries, recent injuries, and repeated injuries, as well as the circumstances of the injury (e.g., sport-related, work-related).

Data linkage studies may also be able to elucidate the association between childhood abuse and MND, by using routinely collected MND mortality data linked to Child, Youth, and Family data from Oranga Tamariki on instances of neglect or abuse. This approach has the advantage that it will overcome the recall bias that can occur in questionnaire-based case-control studies.

New Zealand has the advantage that the infrastructure for data linkage studies is already available through the Integrated Data Infrastructure (IDI), a longitudinal meta-dataset linking social, health, and economic data from different Government agencies managed by Statistics New Zealand.[607] The IDI has been primarily used by government agencies but is increasingly used by researchers throughout New Zealand. Mortality studies making use of the IDI infrastructure, therefore, present a low-cost way to study risk

factors for MND, as well as other neurodegenerative diseases, such as Parkinson's disease and dementia.

Associations between certain exposures and MND can also be further explored through gene-environment interaction studies. To date, more than 30 genes have been associated with sporadic MND. Different genotypes can be associated with varying effects of environmental or occupational exposure, making the study of gene-environment interactions valuable in the identification of causal exposures. For example, as discussed in Chapter 6, exposure to organophosphates was associated with a 3-fold MND risk. Other research suggests that this risk differs for different genotypes related to the enzyme paraoxonase 1 (PON1). Polymorphisms in the PON1 gene are associated with variations in the breakdown of organophosphates,[481] which will impact on neurotoxicity. Overseas studies have suggested that certain PON1 promoter polymorphisms may predispose to sporadic ALS, possibly by making motor neurones more susceptible to organophosphates.[303 608]

The gene-environment interaction between MND risk genes and physical activities has also been studied recently, suggesting that strenuous exercise is likely to cause motor neurone injury only in patients with a risk-genotype.[69 387] Further gene-environment interaction studies are likely to help elucidate which exposures are causally associated with MND and will also help identify the specific mechanism through which the exposure may cause MND. A better understanding of these mechanisms may facilitate the development of therapies as well as preventive strategies.

7.4.2.2 Recommendations for further use of the case-control study

The rich data collected as part of the case-control study provides additional opportunities to further investigate MND risk factors. In this thesis, JEMs were used to assess exposure for two specific agents: electric shocks and ELF-MF. The full occupational histories collected and coded as part of the case-control study provides the opportunity to apply JEMs for other exposures. This could be particularly useful for exposures that can typically not be accurately recalled by study participants. For example, in this thesis most participants that reported exposure to solvents, could not recall, or did not know, the specific solvent they were exposed to. A JEM for specific solvents could help to identify which solvents may be responsible for the overall increased risk observed for solvents. Other occupational exposures of interest that may be assessed through JEMs are physical exertion at work, exposure to specific metals, and exposure to diesel engine exhaust.

In this research, potential risk factors for MND were investigated one at a time, treating other potential risk factors as confounders in the association. While this is the best way to investigate individual risk factors, in reality individuals are likely exposed to multiple risk factors throughout their lives, potentially compounding the risk. MND is recognised as a multifactorial disease, with the degenerative process in MND considered to be the consequence of a combination of genetic and environmental/occupational factors, and it has been proposed that the process leading to MND needs on average 6 steps for MND patients without genetic mutations and fewer steps (2-4 steps) for MND patients with genetic mutations.[537 539] As the information on a wide range of potential risk factors was collected in this thesis, covering the whole lifetime, the collected data of the case-control study could be used to further test the "multiple-step hypothesis" for MND, by

investigating the role of combined exposures including pesticides, solvents, electric shocks, head injury, childhood physical abuse.

The data from the case-control study also provide an opportunity to join an international consortium of MND case-control studies. This would allow for pooled analyses of data that will increase statistical power due to the large sample size leading to more precise risk estimates and allowing the investigation of consistency of findings. This current research is already part of a collaboration with the New Zealand Brain Research Centre on a study to investigate the MND disease-specific signatures associated with BBB leakage, as perivascular cells - brain/spinal cord pericytes have been shown to contribute to MND by making blood vessels leaky.[609] As part of this collaboration, blood samples from 30 cases and 30 controls from the current research were used to determine whether blood vessels are leaky in patients with MND by measuring molecules that have previously been shown to correlate with BBB leakage.

7.4.2.3 Recommendations to facilitate further MND research in New Zealand

The New Zealand MND Research Network has been instrumental in providing a platform for the communication of MND research, promoting collaboration between different research areas (clinical, biomedical, epidemiological), stimulating discussion of the latest advances in research, and research translation. The findings from this thesis have been contributing to the MND research network in New Zealand.[610] However, it has been noted that there are many gaps in the epidemiology, aetiology, diagnosis, and clinical management of MND in New Zealand. As stated in the MNDA New Zealand 2019-2022 research strategy, “Motor neurone disease research in New Zealand is still in its relative infancy.”[611]

An important aspect hampering MND research in New Zealand is the absence of a national MND registry. The implementation of a national MND registry, similar to for example the New Zealand cancer registry, would provide an invaluable source of information on MND that is currently not available. It would be a reliable source to determine New Zealand's MND incidence over time, provide better descriptive epidemiological data on MND in New Zealand in terms of age, gender, and ethnicity distributions, and will provide more reliable projections for MND health care needs. The availability of an MND registry would also enable research into other aspects of MND, such as how to improve the care and management of MND patients and to better understand the patients' needs within the New Zealand context.

Future MND research in New Zealand would also greatly benefit from having the specific MND subtype recorded for every MND patient. Different MND subtypes may differ in their underlying aetiology and causal exposures,[2] which can only be assessed if the MND subtype is available. Different MND subtypes also have different disease progression and prognosis, and better information on MND subtypes will help facilitate timely planning of the care that is essential to maximising quality of life.[473] Additionally, formally recorded disease subtypes can also assist for clinical trial enrolment and other research focussing on specific MND subtypes.

It would also be beneficial if the MND Registry had occupations recorded. This thesis has indicated that occupational risk factors play an important role in MND, and the recording of occupation for MND cases would facilitate further research to update the current findings on occupations and MND risk as well as enable the assessment and timely identification of any occupational MND clusters.

Given its many advantages, it is therefore highly recommended to implement a national and mandatory MND Registry in New Zealand.

CHAPTER 8 Conclusions

Results from the research described in this thesis indicate that both occupational and non-occupational factors contribute to the development of MND and provide support for the following conclusions, which directly relate to the aims of this thesis (Chapter 1):

- A range of occupations and industries are associated with MND in New Zealand, including horticultural occupations, building trades workers, plant and machine operators and assemblers, unspecified labourers, care workers, forecourt attendants, telecommunications technicians, draughting technicians, and electricians. (Aim 1).

- Occupational exposure to electric shocks is associated with MND. Exposure to ELF-MF is not associated with the risk of MND in New Zealand (Aim 2).

- Several common occupational exposures are associated with an increased risk of MND, including pesticides, fumigants, petrol/diesel fuel, unspecified solvents, and cleaning products. For pesticides, and in particular insecticides, MND risk increases with longer duration of exposure (Aim 3).

- Both physical and emotional trauma and playing leisure sports are associated with MND, with strongest associations for head injury with concussion, playing football (soccer) for a longer duration, and experiencing physical abuse as a child (Aim 4).

Taken together, this research represents the first comprehensive investigation on modifiable risk factors of MND in New Zealand and illustrates the importance of occupational and non-occupational exposures in the aetiology of the disease. The MND risk factors identified through this research represent important opportunities to reduce the future burden of MND through feasible interventions, such as preventing electric shocks, preventing head injuries, and reducing pesticide exposure. Considerable gaps in current knowledge remain, and more work is needed to identify the specific exposures involved (e.g., it remains unclear which specific solvents or cleaning products are associated with MND), and to clarify how physical exertion and traumatic experiences such as child abuse may contribute to MND. This will further our understanding of the modifiable risk factors of MND and will allow the development of effective interventions to reduce the incidence of MND in New Zealand and internationally.

References

1. Motor Neuron Disease Fact Sheet. National Institute of Neurological Disorders and Stroke: NIH Neurological Institute, Bethesda, MD20824; 2012 [20 May 2016]. Available from: https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Motor-Neuron-Diseases-Fact-Sheet accessed April 2015.
2. Kiernan MC, Vucic S, Cheah BC, et al. Amyotrophic lateral sclerosis. *The Lancet* 2011;377(9769):942-55. doi: https://doi.org/10.1016/S0140-6736(10)61156-7
3. Ingre C, Roos PM, Piehl F, et al. Risk factors for amyotrophic lateral sclerosis. *Clin Epidemiol* 2015;7:181-93. doi: 10.2147/clep.S37505 [published Online First: 2015/02/25]
4. Soriani MH, Desnuelle C. [Epidemiology of amyotrophic lateral sclerosis]. *Rev Neurol (Paris)* 2009;165(8-9):627-40. doi: 10.1016/j.neurol.2009.04.004 [published Online First: 2009/06/16]
5. Kihira T, Yoshida S, Okamoto K, et al. Survival rate of patients with amyotrophic lateral sclerosis in Wakayama Prefecture, Japan, 1966 to 2005. *J Neurol Sci* 2008;268(1-2):95-101. doi: 10.1016/j.jns.2007.11.011 [published Online First: 2008/01/01]
6. Talbot K. Motor neuron disease: the bare essentials. *Practical neurology* 2009;9(5):303-9. doi: 10.1136/jnnp.2009.188151 [published Online First: 2009/09/19]
7. Logroscino G, Armon C. Amyotrophic lateral sclerosis: a global threat with a possible difference in risk across ethnicities. *Neurology* 2007;68(13):E17. doi: 10.1212/01.wnl.0000260229.42772.a6
8. Leigh PN, Abrahams S, Al-Chalabi A, et al. The management of motor neurone disease. *J Neurol Neurosurg Psychiatry* 2003;74 Suppl 4(Suppl 4):iv32-iv47. doi: 10.1136/jnnp.74.suppl_4.iv32 [published Online First: 2003/12/03]
9. van Es MA, Hardiman O, Chio A, et al. Amyotrophic lateral sclerosis. *Lancet (London, England)* 2017;390(10107):2084-98. doi: 10.1016/S0140-6736(17)31287-4 [published Online First: 2017/05/30]
10. Miller RG, Mitchell JD, Lyon M, et al. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). *Amyotroph Lateral Scler Other Motor Neuron Disord* 2003;4(3):191-206. [published Online First: 2003/09/18]
11. Logroscino G, Piccininni M, Marin B, et al. Global, regional, and national burden of motor neuron diseases 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology* 2018;17(12):1083-97. doi: https://doi.org/10.1016/S1474-4422(18)30404-6
12. Longinetti E, Fang F. Epidemiology of amyotrophic lateral sclerosis: an update of recent literature. *Current Opinion in Neurology* 2019;32(5):771-76. doi: 10.1097/wco.0000000000000730
13. Facts about MND. MNDA. Auckland, New Zealand: Motor Neurone Disease New Zeland; 2021 [Available from: https://mnd.org.nz/about-mnd/ accessed 9th Sept 2021.
14. Maasilta P, Jokelainen M, Löytönen M, et al. Mortality from amyotrophic lateral sclerosis in Finland, 1986–1995. *Acta Neurologica Scandinavica* 2002;104(4):232-35. doi: 10.1034/j.1600-0404.2001.00361.x
15. Seljeseth YM, Vollset SE, Tysnes OB. Increasing mortality from amyotrophic lateral sclerosis in Norway? *Neurology* 2000;55(9):1262-6. doi: 10.1212/WNL.55.9.1262 [published Online First: 2000/11/23]
16. Neilson S, Robinson I, Alperovitch A. Rising amyotrophic lateral sclerosis mortality in France 1968-1990: increased life expectancy and inter-disease competition as an explanation. *J Neurol* 1994;241(7):448-55. doi: 10.1007/BF00900964 [published Online First: 1994/06/01]
17. Riggs JE. Longitudinal Gompertzian analysis of amyotrophic lateral sclerosis mortality in the U.S., 1977-1986: evidence for an inherently susceptible population subset.

Mechanisms of ageing and development 1990;55(3):207-20. doi: 10.1016/0047-6374(90)90149-A [published Online First: 1990/09/01]
18. Cima V, Logroscino G, D'Ascenzo C, et al. Epidemiology of ALS in Padova district, Italy, from 1992 to 2005. *European journal of neurology* 2009;16(8):920-4. doi: 10.1111/j.1468-1331.2009.02623.x [published Online First: 2009/05/29]
19. Fang F, Valdimarsdottir U, Bellocco R, et al. Amyotrophic lateral sclerosis in Sweden, 1991-2005. *Archives of neurology* 2009;66(4):515-9. doi: 10.1001/archneurol.2009.13 [published Online First: 2009/04/15]
20. Dean G, Elian M. Motor neuron disease and multiple sclerosis mortality in Australia, New Zealand and South Africa compared with England and Wales. *J Neurol Neurosurg Psychiatry* 1993;56(6):633-7.
21. Cao MC, Chancellor A, Charleston A, et al. Motor neuron disease mortality rates in New Zealand 1992–2013. *Amyotroph Lateral Scler Frontotemporal Degener* 2018;19(3-4):285-93. doi: 10.1080/21678421.2018.1432660
22. Murphy M, Quinn S, Young J, et al. Increasing incidence of ALS in Canterbury, New Zealand: a 22-year study. *Neurology* 2008;71(23):1889-95. doi: 10.1212/01.wnl.0000336653.65605.ac
23. Chiò A, Logroscino G, Traynor BJ, et al. Global epidemiology of amyotrophic lateral sclerosis: a systematic review of the published literature. *Neuroepidemiology* 2013;41(2):118-30. doi: 10.1159/000351153 [published Online First: 2013/07/19]
24. Marin B, Boumédiene F, Logroscino G, et al. Variation in worldwide incidence of amyotrophic lateral sclerosis: a meta-analysis. *International journal of epidemiology* 2017;46(1):57-74. doi: 10.1093/ije/dyw061 [published Online First: 2016/05/18]
25. Plato CC, Garruto RM, Galasko D, et al. Amyotrophic lateral sclerosis and parkinsonism-dementia complex of Guam: changing incidence rates during the past 60 years. *Am J Epidemiol* 2003;157(2):149-57. doi: 10.1093/aje/kwf175 [published Online First: 2003/01/11]
26. Pablo J, Banack SA, Cox PA, et al. Cyanobacterial neurotoxin BMAA in ALS and Alzheimer's disease. *Acta Neurol Scand* 2009;120(4):216-25. doi: 10.1111/j.1600-0404.2008.01150.x [published Online First: 2009/03/04]
27. Armon C. Smoking may be considered an established risk factor for sporadic ALS. *Neurology* 2009;73(20):1693-8. doi: 10.1212/WNL.0b013e3181c1df48 [published Online First: 2009/11/18]
28. Armon C. An Evidence-Based Medicine Approach to the Evaluation of the Role of Exogenous Risk Factors in Sporadic Amyotrophic Lateral Sclerosis. *Neuroepidemiology* 2003;22(4):217-28. doi: 10.1159/000070562
29. O'Toole O. Motor neuron disease in Ireland: epidmiology, risk factors and prognostic indicators. Royal College of Surgeons in Ireland, 2011.
30. Gunnarsson LG, Lindberg G, Soderfeldt B, et al. Amyotrophic lateral sclerosis in Sweden in relation to occupation. *Acta Neurol Scand* 1991;83(6):394-8. doi: 10.1111/j.1600-0404.1991.tb03970.x [published Online First: 1991/06/01]
31. Sutedja NA, Veldink JH, Fischer K, et al. Lifetime occupation, education, smoking, and risk of ALS. *Neurology* 2007;69(15):1508-14. doi: 10.1212/01.wnl.0000277463.87361.8c
32. Sutedja NA, Fischer K, Veldink JH, et al. What we truly know about occupation as a risk factor for ALS: a critical and systematic review. *Amyotroph Lateral Scler* 2009;10(5-6):295-301. doi: 10.3109/17482960802430799 [published Online First: 2009/11/20]
33. Weisskopf MG, O'Reilly EJ, McCullough ML, et al. Prospective study of military service and mortality from ALS. *Neurology* 2005;64(1):32-7. doi: 10.1212/01.WNL.0000148649.17706.D9
34. Kamel F, Umbach DM, Hu H, et al. Lead exposure as a risk factor for amyotrophic lateral sclerosis. *Neurodegener Dis* 2005;2(3-4):195-201. doi: 10.1159/000089625 [published Online First: 2006/08/16]

35. Sutedja NA, Veldink JH, Fischer K, et al. Exposure to chemicals and metals and risk of amyotrophic lateral sclerosis: a systematic review. *Amyotroph Lateral Scler* 2009;10(5-6):302-9. doi: 10.3109/17482960802455416
36. McGuire V, Longstreth WT, Jr., Nelson LM, et al. Occupational exposures and amyotrophic lateral sclerosis. A population-based case-control study. *Am J Epidemiol* 1997;145(12):1076-88. doi: 10.1093/oxfordjournals.aje.a009070
37. Kamel F, Umbach DM, Bedlack RS, et al. Pesticide exposure and amyotrophic lateral sclerosis. *Neurotoxicology* 2012;33(3):457-62. doi: 10.1016/j.neuro.2012.04.001 [published Online First: 2012/04/24]
38. Das K, Nag C, Ghosh M. Familial, environmental, and occupational risk factors in development of amyotrophic lateral sclerosis. *North American Journal of Medical Sciences* 2012;4(8):350-55. doi: 10.4103/1947-2714.99517
39. Malek AM, Barchowsky A, Bowser R, et al. Pesticide exposure as a risk factor for amyotrophic lateral sclerosis: a meta-analysis of epidemiological studies: pesticide exposure as a risk factor for ALS. *Environ Res* 2012;117:112-9. doi: 10.1016/j.envres.2012.06.007 [published Online First: 2012/07/24]
40. Kang H, Cha ES, Choi GJ, et al. Amyotrophic lateral sclerosis and agricultural environments: a systematic review. *J Korean Med Sci* 2014;29(12):1610-7. doi: 10.3346/jkms.2014.29.12.1610 [published Online First: 2014/12/04]
41. Wang MD, Little J, Gomes J, et al. Identification of risk factors associated with onset and progression of amyotrophic lateral sclerosis using systematic review and meta-analysis. *Neurotoxicology* 2017;61:101-30. doi: 10.1016/j.neuro.2016.06.015 [published Online First: 2016/07/06]
42. Park RM, Schulte PA, Bowman JD, et al. Potential occupational risks for neurodegenerative diseases. *American Journal of Industrial Medicine* 2005;48(1):63-77. doi: 10.1002/ajim.20178
43. Fang F, Quinlan P, Ye W, et al. Workplace exposures and the risk of amyotrophic lateral sclerosis. *Environ Health Perspect* 2009;117(9):1387-92. doi: 10.1289/ehp.0900580
44. Morahan JM, Pamphlett R. Amyotrophic lateral sclerosis and exposure to environmental toxins: an Australian case-control study. *Neuroepidemiology* 2006;27(3):130-5. doi: 10.1159/000095552 [published Online First: 2006/09/02]
45. Pedersen C, Poulsen AH, Rod NH, et al. Occupational exposure to extremely low-frequency magnetic fields and risk for central nervous system disease: an update of a Danish cohort study among utility workers. *International Archives of Occupational and Environmental Health* 2017;90(7):619-28. doi: 10.1007/s00420-017-1224-0
46. Huss A, Peters S, Vermeulen R. Occupational exposure to extremely low-frequency magnetic fields and the risk of ALS: A systematic review and meta-analysis. *Bioelectromagnetics* 2018;39(2):156-63. doi: 10.1002/bem.22104 [published Online First: 2018/01/20]
47. Zhou H, Chen G, Chen C, et al. Association between extremely low-frequency electromagnetic fields occupations and amyotrophic lateral sclerosis: a meta-analysis. *PLoS One* 2012;7(11):e48354. doi: 10.1371/journal.pone.0048354 [published Online First: 2012/11/29]
48. Fischer H, Kheifets L, Huss A, et al. Occupational exposure to electric shocks and magnetic fields and amyotrophic lateral sclerosis in Sweden. *Epidemiology* 2015;26(6):824-30. doi: 10.1097/EDE.0000000000000365
49. Alonso A, Logroscino G, Hernán MA. Smoking and the risk of amyotrophic lateral sclerosis: a systematic review and meta-analysis. *Journal of Neurology, Neurosurgery & Psychiatry* 2010;81(11):1249-52. doi: 10.1136/jnnp.2009.180232
50. Beard JD, Kamel F. Military service, deployments, and exposures in relation to amyotrophic lateral sclerosis etiology and survival. *Epidemiol Rev* 2015;37(1):55-70. doi: 10.1093/epirev/mxu001 [published Online First: 2014/11/05]

51. Statistics. National population estimates: June 2010 quarter. Wellington: Statistics New Zealand,2010.
52. Stats. National population projections: 2016(base)–2068. 19 October, 2016 ed. Wellington, New Zealand: Stats New Zealand, 2016.
53. Brain WR. Disease of the nervous system. 6th ed. Oxford: Oxford University Press 1962.
54. Charcot JM, Joffroy, A. Deux cas d'atrophie musculaire progressive avec lésions de la substance grise et des faisceaux antérolatéraux de la moelle épinière. *Arch Physiol Norm Pathol* 1869(2):744-54.
55. Different types of MND. The Leeds Teaching Hospitals: National Health Service, United Kingdom; [cited 2021 4th March]. Available from: https://www.leedsth.nhs.uk/a-z-of-services/leeds-motor-neurone-disease-mnd-care-centre/your-condition-and-treatment/different-types-of-mnd/ accessed 2 November, 2021 2021.
56. Al-Chalabi A, Hardiman O. The epidemiology of ALS: a conspiracy of genes, environment and time. *Nature Reviews Neurology* 2013;9:617. doi: 10.1038/nrneurol.2013.203
57. Hardiman O, Al-Chalabi A, Chio A, et al. Amyotrophic lateral sclerosis. *Nature reviews Disease primers* 2017;3:17071. doi: 10.1038/nrdp.2017.71 [published Online First: 2017/10/06]
58. Different types of MND. Dublin: Irish Motor Neurone Disease Association; [cited 2021 11th Sept]. Available from: https://imnda.ie/about-mnd/different-types-of-mnd/.
59. Hardiman O, van den Berg LH, Kiernan MC. Clinical diagnosis and management of amyotrophic lateral sclerosis. *Nature reviews Neurology* 2011;7(11):639-49. doi: 10.1038/nrneurol.2011.153 [published Online First: 2011/10/13]
60. Karam C, Scelsa SN, MacGowan DJL. The clinical course of progressive bulbar palsy. *Amyotrophic Lateral Sclerosis* 2010;11(4):364-68. doi: 10.3109/17482960903513159
61. Al-Chalabi A, Hardiman O, Kiernan MC, et al. Amyotrophic lateral sclerosis: moving towards a new classification system. *Lancet Neurol* 2016;15(11):1182-94. doi: 10.1016/s1474-4422(16)30199-5 [published Online First: 2016/09/21]
62. Wijesekera LC, Mathers S, Talman P, et al. Natural history and clinical features of the flail arm and flail leg ALS variants. *Neurology* 2009;72(12):1087-94. doi: 10.1212/01.wnl.0000345041.83406.a2
63. Brashear A, Elovic E. Spasticity: diagnosis and management2016.
64. Morris J. Amyotrophic Lateral Sclerosis (ALS) and Related Motor Neuron Diseases: An Overview. *The Neurodiagnostic Journal* 2015;55(3):180-94. doi: 10.1080/21646821.2015.1075181
65. Singer MA, Kojan S, Barohn RJ, et al. Primary Lateral Sclerosis: Clinical and Laboratory Features in 25 Patients. *Journal of Clinical Neuromuscular Disease* 2005;7(1):1-9. doi: 10.1097/01.cnd.0000176974.61136.45
66. Amyotrophic Lateral Sclerosis (ALS) Fact Sheet. NIH. NIH Neurological Institute: National Institute of Neurological Disorders and Stroke, US; 2021 [updated 15/11/2021; cited 2021 12 December]. Available from: https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Amyotrophic-Lateral-Sclerosis-ALS-Fact-Sheet accessed 12 December 2021.
67. Silani V, Ludolph A, Fornai F. The emerging picture of ALS: a multisystem, not only a "motor neuron disease. *Arch Ital Biol* 2017;155(4):99-109. doi: 10.12871/00039829201741 [published Online First: 2018/02/07]
68. Christidi F, Karavasilis E, Rentzos M, et al. Clinical and Radiological Markers of Extra-Motor Deficits in Amyotrophic Lateral Sclerosis. *Frontiers in neurology* 2018;9:1005-05. doi: 10.3389/fneur.2018.01005
69. Westeneng HJ, van Veenhuijzen K, van der Spek RA, et al. Associations between lifestyle and amyotrophic lateral sclerosis stratified by C9orf72 genotype: a longitudinal, population-based, case-control study. *Lancet Neurol* 2021;20(5):373-84. doi: 10.1016/s1474-4422(21)00042-9 [published Online First: 2021/04/25]

70. Phukan J, Elamin M, Bede P, et al. The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population-based study. *J Neurol Neurosurg Psychiatry* 2012;83(1):102-8. doi: 10.1136/jnnp-2011-300188 [published Online First: 2011/08/13]
71. Logroscino G, Traynor BJ, Hardiman O, et al. Incidence of amyotrophic lateral sclerosis in Europe. *J Neurol Neurosurg Psychiatry* 2010;81(4):385-90. doi: 10.1136/jnnp.2009.183525 [published Online First: 2009/08/28]
72. Worms PM. The epidemiology of motor neuron diseases: a review of recent studies. *J Neurol Sci* 2001;191(1-2):3-9. doi: 10.1016/s0022-510x(01)00630-x [published Online First: 2001/10/26]
73. Chancellor AM, Warlow CP. Adult onset motor neuron disease: worldwide mortality, incidence and distribution since 1950. *J Neurol Neurosurg Psychiatry* 1992;55(12):1106-15.
74. Kurtzke JF. Risk factors in amyotrophic lateral sclerosis. *Advances in neurology* 1991;56:245-70. [published Online First: 1991/01/01]
75. Chiò A, Mora G, Calvo A, et al. Epidemiology of ALS in Italy: a 10-year prospective population-based study. *Neurology* 2009;72(8):725-31. doi: 10.1212/01.wnl.0000343008.26874.d1 [published Online First: 2009/02/25]
76. O'Toole O, Traynor BJ, Brennan P, et al. Epidemiology and clinical features of amyotrophic lateral sclerosis in Ireland between 1995 and 2004. *J Neurol Neurosurg Psychiatry* 2008;79(1):30-2. doi: 10.1136/jnnp.2007.117788 [published Online First: 2007/07/20]
77. Beghi E, Millul A, Micheli A, et al. Incidence of ALS in Lombardy, Italy. *Neurology* 2007;68(2):141-5. doi: 10.1212/01.wnl.0000250339.14392.bb [published Online First: 2007/01/11]
78. McCombe PA, Henderson RD. Effects of gender in amyotrophic lateral sclerosis. *Gender medicine* 2010;7(6):557-70. doi: 10.1016/j.genm.2010.11.010 [published Online First: 2011/01/05]
79. Cronin S, Hardiman O, Traynor BJ. Ethnic variation in the incidence of ALS A systematic review. *Neurology* 2007;68:6.
80. Plato CC, Garruto RM, Galasko D, et al. Amyotrophic Lateral Sclerosis and Parkinsonism-Dementia Complex of Guam: Changing Incidence Rates during the Past 60 Years. *American Journal of Epidemiology* 2003;157(2):149-57. doi: 10.1093/aje/kwf175
81. Alonso A, Logroscino G, Jick SS, et al. Incidence and lifetime risk of motor neuron disease in the United Kingdom: a population-based study. *European journal of neurology* 2009;16(6):745-51. [published Online First: 2009/05/29]
82. Gordon PH, Mehal JM, Holman RC, et al. Incidence of amyotrophic lateral sclerosis among American Indians and Alaska natives. *JAMA Neurol* 2013;70(4):476-80. doi: 10.1001/jamaneurol.2013.929 [published Online First: 2013/02/27]
83. Kurland LT, Mulder DW. Epidemiologic investigations of amyotrophic lateral sclerosis. I. Preliminary report on geographic distribution, with special reference to the Mariana Islands, including clinical and pathologic observations. *Neurology* 1954;4(5):355-78. doi: 10.1212/wnl.4.5.355 [published Online First: 1954/05/01]
84. McGeer PL, Steele JC. The ALS/PDC syndrome of Guam: potential biomarkers for an enigmatic disorder. *Progress in neurobiology* 2011;95(4):663-9. doi: 10.1016/j.pneurobio.2011.04.001 [published Online First: 2011/04/30]
85. Ra D, Sa B, Sl B, et al. Is Exposure to BMAA a Risk Factor for Neurodegenerative Diseases? A Response to a Critical Review of the BMAA Hypothesis. *Neurotoxicity Research* 2021;39(1):81-106. doi: 10.1007/s12640-020-00302-0
86. Chernoff N, Hill DJ, Diggs DL, et al. A critical review of the postulated role of the non-essential amino acid, β-N-methylamino-L-alanine, in neurodegenerative disease in humans. *J Toxicol Environ Health B Crit Rev* 2017;20(4):1-47. doi: 10.1080/10937404.2017.1297592 [published Online First: 2017/06/10]

87. Kuzuhara S, Kokubo Y, Sasaki R, et al. Familial amyotrophic lateral sclerosis and parkinsonism-dementia complex of the Kii peninsula of Japan: Clinical and neuropathological study and tau analysis. *Annals of Neurology* 2001;49(4):501-11. doi: 10.1002/ana.100
88. Motor Neurone Disease/ALS. MNDNZ. Auckland, New Zealand: MND New Zealand; 2019 [Available from: https://neurological.org.nz/what-we-do/awareness-and-education/brain-disorders-and-support/motor-neuron-disease-als/?gclid=EAIaIQobChMIq-_G18r48wIVT1RgCh0J3wRLEAAYASAAEgIwsfD_BwE accessed 2 November 2021.
89. Dayal V, Rosemergy I, Turnbull J. Motor neurone disease in the greater Wellington region: an observational study. *The New Zealand medical journal* 2015;128(1409):29-34. [published Online First: 2015/02/28]
90. Baker PC. Incidence of motor neurone disease in Hawke's Bay and Gisborne/East Coast. *The New Zealand medical journal* 2015;128(1413):79-80. [published Online First: 2015/06/24]
91. de Jongh AD, van Eijk RPA, Peters SM, et al. Incidence, Prevalence, and Geographical Clustering of Motor Neuron Disease in the Netherlands. *Neurology* 2021;96(8):e1227-e36. doi: 10.1212/wnl.0000000000011467
92. Gowland A, Opie-Martin S, Scott KM, et al. Predicting the future of ALS: the impact of demographic change and potential new treatments on the prevalence of ALS in the United Kingdom, 2020-2116. *Amyotrophic lateral sclerosis & frontotemporal degeneration* 2019;20(3-4):264-74. doi: 10.1080/21678421.2019.1587629 [published Online First: 2019/04/09]
93. Leighton DJ, Newton J, Stephenson LJ, et al. Changing epidemiology of motor neurone disease in Scotland. *J Neurol* 2019;266(4):817-25. doi: 10.1007/s00415-019-09190-7 [published Online First: 2019/02/26]
94. Longinetti E, Regodón Wallin A, Samuelsson K, et al. The Swedish motor neuron disease quality registry. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* 2018;19(7-8):528-37. doi: 10.1080/21678421.2018.1497065
95. Benjaminsen E, Alstadhaug KB, Gulsvik M, et al. Amyotrophic lateral sclerosis in Nordland county, Norway, 2000-2015: prevalence, incidence, and clinical features. *Amyotroph Lateral Scler Frontotemporal Degener* 2018;19(7-8):522-27. doi: 10.1080/21678421.2018.1513534 [published Online First: 2018/09/29]
96. Dorst J, Chen L, Rosenbohm A, et al. Prognostic factors in ALS: a comparison between Germany and China. *J Neurol* 2019;266(6):1516-25. doi: 10.1007/s00415-019-09290-4 [published Online First: 2019/03/30]
97. Goutman SA, Boss J, Patterson A, et al. High plasma concentrations of organic pollutants negatively impact survival in amyotrophic lateral sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry* 2019;90(8):907-12. doi: 10.1136/jnnp-2018-319785
98. Korner S, Kammeyer J, Zapf A, et al. Influence of Environment and Lifestyle on Incidence and Progress of Amyotrophic Lateral Sclerosis in A German ALS Population. *Aging Dis* 2019;10(2):205-16. doi: 10.14336/AD.2018.0327
99. Karanevich AG, Weisbrod LJ, Jawdat O, et al. Using automated electronic medical record data extraction to model ALS survival and progression. *BMC Neurol* 2018;18(1):205. doi: 10.1186/s12883-018-1208-z [published Online First: 2018/12/15]
100. Shimizu T, Nakayama Y, Matsuda C, et al. Prognostic significance of body weight variation after diagnosis in ALS: a single-centre prospective cohort study. *J Neurol* 2019;266(6):1412-20. doi: 10.1007/s00415-019-09276-2 [published Online First: 2019/03/15]
101. Chen JJ. Overview of current and emerging therapies for amytrophic lateral sclerosis. *Am J Manag Care* 2020;26(9 Suppl):S191-s97. doi: 10.37765/ajmc.2020.88483 [published Online First: 2020/08/26]

102. Lacomblez L, Bensimon G, Leigh PN, et al. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis/Riluzole Study Group II. *Lancet (London, England)* 1996;347(9013):1425-31. doi: 10.1016/s0140-6736(96)91680-3 [published Online First: 1996/05/25]
103. Andrews JA, Jackson CE, Heiman-Patterson TD, et al. Real-world evidence of riluzole effectiveness in treating amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener* 2020;21(7-8):509-18. doi: 10.1080/21678421.2020.1771734 [published Online First: 2020/06/24]
104. FDA approves drug to treat ALS. FDA. UA: US Food and Drug Administration; [cited 2021 14th September]. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-drug-treat-als.
105. PHARMAC. First funded treatment for motor neurone disease. Wellington, New Zealand: PHARMAC, 2013 [updated 30 September 2014. Available from: https://pharmac.govt.nz/news-and-resources/news/first-funded-treatment-for-motor-neurone-disease/.
106. PHARMAC. Approval of proposal to fund riluzole for amyotrophic lateral sclerosis (motor neurone disease). Wellington, New Zealand: PHARMAC, 2013 [updated 11 September. Available from: https://pharmac.govt.nz/news-and-resources/consultations-and-decisions/approval-of-proposal-to-fund-riluzole-for-amyotrophic-lateral-sclerosis-motor-neurone-disease/.
107. Couratier P, Corcia P, Lautrette G, et al. Epidemiology of amyotrophic lateral sclerosis: A review of literature. *Revue Neurologique* 2016;172(1):37-45. doi: https://doi.org/10.1016/j.neurol.2015.11.002
108. Doyle P, Brown A, Beral V, et al. Incidence of and risk factors for motor neurone disease in UK women: a prospective study. *BMC Neurol* 2012;12:25. doi: 10.1186/1471-2377-12-25 [published Online First: 2012/05/09]
109. Chancellor AM, Hendry A, Caird FI, et al. Motor neuron disease: a disease of old age. *Scott Med J* 1993;38(6):178-82. doi: 10.1177/003693309303800606 [published Online First: 1993/12/01]
110. Forbes R, Colville S, Swingler R. The epidemiology of amyotrophic lateral sclerosis (ALS/MND) in people aged 80 or over. *Age and ageing* 2004;33:131-4. doi: 10.1093/ageing/afh013
111. Logroscino G, Traynor BJ, Hardiman O, et al. Descriptive epidemiology of amyotrophic lateral sclerosis: new evidence and unsolved issues. *J Neurol Neurosurg Psychiatry* 2008;79(1):6-11. doi: 10.1136/jnnp.2006.104828 [published Online First: 2007/12/15]
112. Forbes RB, Colville S, Cran GW, et al. Unexpected decline in survival from amyotrophic lateral sclerosis/motor neurone disease. *J Neurol Neurosurg Psychiatry* 2004;75(12):1753-5. doi: 10.1136/jnnp.2003.024364 [published Online First: 2004/11/19]
113. Granieri E, Carreras M, Tola R, et al. Motor neuron disease in the province of Ferrara, Italy, in 1964-1982. *Neurology* 1988;38(10):1604-8. doi: 10.1212/wnl.38.10.1604 [published Online First: 1988/10/01]
114. Rosati G, Pinna L, Granieri E, et al. Studies on epidemiological, clinical, and etiological aspects of ALS disease in Sardinia, Southern Italy. *Acta Neurol Scand* 1977;55(3):231-44. doi: 10.1111/j.1600-0404.1977.tb05642.x [published Online First: 1977/03/01]
115. Buckley J, Warlow C, Smith P, et al. Motor neuron disease in England and Wales, 1959-1979. *J Neurol Neurosurg Psychiatry* 1983;46(3):197-205. [published Online First: 1983/03/01]
116. Gawel M, Zaiwalla Z, Rose F. Antecedent events in motor neuron disease. J Neurol Neurosurg Psychiatry. *Journal of Neurology, Neurosurgery, and Psychiatry* 1983;46:1041-43.

117. Durrleman S, Alperovitch A. Increasing trend of ALS in France and elsewhere: are the changes real? *Neurology* 1989;39(6):768-73. [published Online First: 1989/06/01]
118. Fong KY, Yu YL, Chan YW, et al. Motor neuron disease in Hong Kong Chinese: epidemiology and clinical picture. *Neuroepidemiology* 1996;15(5):239-45.
119. Jun KY, Park J, Oh KW, et al. Epidemiology of ALS in Korea using nationwide big data. *J Neurol Neurosurg Psychiatry* 2019;90(4):395-403. doi: 10.1136/jnnp-2018-318974 [published Online First: 2018/11/10]
120. Turgut N, Varol SaraÇoglu G, Kat S, et al. An epidemiologic investigation of amyotrophic lateral sclerosis in Thrace, Turkey, 2006-2010. *Amyotroph Lateral Scler Frontotemporal Degener* 2019;20(1-2):100-06. doi: 10.1080/21678421.2018.1525403 [published Online First: 2018/11/24]
121. Zhou S, Zhou Y, Qian S, et al. Amyotrophic lateral sclerosis in Beijing: Epidemiologic features and prognosis from 2010 to 2015. *Brain Behav* 2018;8(11):e01131. doi: 10.1002/brb3.1131 [published Online First: 2018/10/20]
122. D'Ovidio F, Rooney JPK, Visser AE, et al. Association between alcohol exposure and the risk of amyotrophic lateral sclerosis in the Euro-MOTOR study. *Journal of Neurology, Neurosurgery & Psychiatry* 2019;90(1):11-19. doi: 10.1136/jnnp-2018-318559
123. Mehta P, Kaye W, Raymond J, et al. Prevalence of Amyotrophic Lateral Sclerosis - United States, 2014. *MMWR Morb Mortal Wkly Rep* 2018;67(7):216-18. doi: 10.15585/mmwr.mm6707a3 [published Online First: 2018/02/23]
124. Nakken O, Lindstrøm JC, Tysnes OB, et al. Assessing amyotrophic lateral sclerosis prevalence in Norway from 2009 to 2015 from compulsory nationwide health registers. *Amyotroph Lateral Scler Frontotemporal Degener* 2018;19(3-4):303-10. doi: 10.1080/21678421.2017.1418004 [published Online First: 2017/12/23]
125. Kim JM, Park JH, Kim HS, et al. Epidemiology and diagnostic process of amyotrophic lateral sclerosis as distinct from myelopathy: 5-year cohort study of whole-population in South Korea. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* 2018;19(7-8):547-54. doi: 10.1080/21678421.2018.1491600
126. Luna J, Diagana M, Ait Aissa L, et al. Clinical features and prognosis of amyotrophic lateral sclerosis in Africa: the TROPALS study. *J Neurol Neurosurg Psychiatry* 2019;90(1):20-29. doi: 10.1136/jnnp-2018-318469 [published Online First: 2018/09/23]
127. Gordon PH, Artaud F, Aouba A, et al. Changing mortality for motor neuron disease in France (1968-2007): an age-period-cohort analysis. *Eur J Epidemiol* 2011;26(9):729-37. doi: 10.1007/s10654-011-9595-0 [published Online First: 2011/06/16]
128. Chen S, Sayana P, Zhang X, et al. Genetics of amyotrophic lateral sclerosis: an update. *Mol Neurodegener* 2013;8:28. doi: 10.1186/1750-1326-8-28
129. Renton AE, Chio A, Traynor BJ. State of play in amyotrophic lateral sclerosis genetics. *Nature neuroscience* 2014;17(1):17-23. doi: 10.1038/nn.3584 [published Online First: 2013/12/27]
130. van Blitterswijk M, van Es MA, Hennekam EA, et al. Evidence for an oligogenic basis of amyotrophic lateral sclerosis. *Hum Mol Genet* 2012;21(17):3776-84. doi: 10.1093/hmg/dds199 [published Online First: 2012/05/31]
131. Mejzini R, Flynn LL, Pitout IL, et al. ALS Genetics, Mechanisms, and Therapeutics: Where Are We Now? *Frontiers in Neuroscience* 2019;13(1310) doi: 10.3389/fnins.2019.01310
132. Abel O, Powell JF, Andersen PM, et al. ALSoD: A user-friendly online bioinformatics tool for amyotrophic lateral sclerosis genetics. *Hum Mutat* 2012;33(9):1345-51. doi: 10.1002/humu.22157 [published Online First: 2012/07/04]
133. Wroe R, Wai-Ling Butler A, Andersen PM, et al. ALSOD: the Amyotrophic Lateral Sclerosis Online Database. *Amyotroph Lateral Scler* 2008;9(4):249-50. doi: 10.1080/17482960802146106 [published Online First: 2008/07/09]
134. Boylan K. Familial Amyotrophic Lateral Sclerosis. *Neurologic clinics* 2015;33(4):807-30. doi: 10.1016/j.ncl.2015.07.001 [published Online First: 2015/09/08]

135. Andersen PM, Al-Chalabi A. Clinical genetics of amyotrophic lateral sclerosis: what do we really know? *Nature reviews Neurology* 2011;7(11):603-15. doi: 10.1038/nrneurol.2011.150 [published Online First: 2011/10/13]
136. Rosen DR, Siddique T, Patterson D, et al. Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. *Nature* 1993;362(6415):59-62. doi: 10.1038/362059a0 [published Online First: 1993/03/04]
137. Chio A, Traynor BJ, Lombardo F, et al. Prevalence of SOD1 mutations in the Italian ALS population. *Neurology* 2008;70(7):533-7. doi: 10.1212/01.wnl.0000299187.90432.3f [published Online First: 2008/02/13]
138. Andersen PM, Sims KB, Xin WW, et al. Sixteen novel mutations in the Cu/Zn superoxide dismutase gene in amyotrophic lateral sclerosis: a decade of discoveries, defects and disputes. *Amyotrophic lateral sclerosis and other motor neuron disorders: official publication of the World Federation of Neurology, Research Group on Motor Neuron Diseases* 2003;4(2):62-73. doi: 10.1080/14660820310011700
139. Andersen PM, Forsgren L, Binzer M, et al. Autosomal recessive adult-onset amyotrophic lateral sclerosis associated with homozygosity for Asp90Ala CuZn-superoxide dismutase mutation. A clinical and genealogical study of 36 patients. *Brain* 1996;119 (Pt 4):1153-72. doi: 10.1093/brain/119.4.1153 [published Online First: 1996/08/01]
140. Yamashita S, Ando Y. Genotype-phenotype relationship in hereditary amyotrophic lateral sclerosis. *Translational neurodegeneration* 2015;4:13-13. doi: 10.1186/s40035-015-0036-y
141. Cudkowicz ME, McKenna-Yasek D, Sapp PE, et al. Epidemiology of mutations in superoxide dismutase in amyotrophic lateral sclerosis. *Ann Neurol* 1997;41(2):210-21. doi: 10.1002/ana.410410212 [published Online First: 1997/02/01]
142. Sreedharan J, Blair IP, Tripathi VB, et al. TDP-43 mutations in familial and sporadic amyotrophic lateral sclerosis. *Science* 2008;319(5870):1668-72. doi: 10.1126/science.1154584 [published Online First: 2008/03/01]
143. Lattante S, Rouleau GA, Kabashi E. TARDBP and FUS mutations associated with amyotrophic lateral sclerosis: summary and update. *Hum Mutat* 2013;34(6):812-26. doi: 10.1002/humu.22319 [published Online First: 2013/04/06]
144. Chiò A, Mazzini L, Mora G. Disease-modifying therapies in amyotrophic lateral sclerosis. *Neuropharmacology* 2020;167:107986. doi: 10.1016/j.neuropharm.2020.107986 [published Online First: 2020/02/18]
145. Chiò A, Calvo A, Mazzini L, et al. Extensive genetics of ALS: a population-based study in Italy. *Neurology* 2012;79(19):1983-9. doi: 10.1212/WNL.0b013e3182735d36 [published Online First: 2012/10/27]
146. Neumann M, Sampathu DM, Kwong LK, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science* 2006;314(5796):130-3. doi: 10.1126/science.1134108 [published Online First: 2006/10/07]
147. de Boer EMJ, Orie VK, Williams T, et al. TDP-43 proteinopathies: a new wave of neurodegenerative diseases. *J Neurol Neurosurg Psychiatry* 2020;92(1):86-95. doi: 10.1136/jnnp-2020-322983 [published Online First: 2020/11/13]
148. Renton AE, Majounie E, Waite A, et al. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. *Neuron* 2011;72(2):257-68. doi: 10.1016/j.neuron.2011.09.010 [published Online First: 2011/09/29]
149. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. *Neuron* 2011;72(2):245-56. doi: 10.1016/j.neuron.2011.09.011 [published Online First: 2011/09/29]
150. Schipper LJ, Raaphorst J, Aronica E, et al. Prevalence of brain and spinal cord inclusions, including dipeptide repeat proteins, in patients with the C9ORF72 hexanucleotide

repeat expansion: a systematic neuropathological review. *Neuropathol Appl Neurobiol* 2016;42(6):547-60. doi: 10.1111/nan.12284 [published Online First: 2015/09/17]
151. Majounie E, Renton AE, Mok K, et al. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. *Lancet Neurol* 2012;11(4):323-30. doi: 10.1016/s1474-4422(12)70043-1 [published Online First: 2012/03/13]
152. Zou ZY, Zhou ZR, Che CH, et al. Genetic epidemiology of amyotrophic lateral sclerosis: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2017;88(7):540-49. doi: 10.1136/jnnp-2016-315018 [published Online First: 2017/01/07]
153. López-Cáceres A, Velasco-Rueda M, Garcia-Cifuentes E, et al. Analysis of Heritability Across the Clinical Phenotypes of Frontotemporal Dementia and the Frequency of the C9ORF72 in a Colombian Population. *Frontiers in Neurology* 2021;12(1272) doi: 10.3389/fneur.2021.681595
154. Ringholz GM, Appel SH, Bradshaw M, et al. Prevalence and patterns of cognitive impairment in sporadic ALS. *Neurology* 2005;65(4):586-90. doi: 10.1212/01.wnl.0000172911.39167.b6 [published Online First: 2005/08/24]
155. Kwiatkowski TJ, Jr., Bosco DA, Leclerc AL, et al. Mutations in the FUS/TLS gene on chromosome 16 cause familial amyotrophic lateral sclerosis. *Science* 2009;323(5918):1205-8. doi: 10.1126/science.1166066 [published Online First: 2009/03/03]
156. Vance C, Rogelj B, Hortobágyi T, et al. Mutations in FUS, an RNA processing protein, cause familial amyotrophic lateral sclerosis type 6. *Science* 2009;323(5918):1208-11. doi: 10.1126/science.1165942 [published Online First: 2009/03/03]
157. Czaplinski A, Yen AA, Simpson EP, et al. Slower Disease Progression and Prolonged Survival in Contemporary Patients With Amyotrophic Lateral Sclerosis: Is the Natural History of Amyotrophic Lateral Sclerosis Changing? *Archives of neurology* 2006;63(8):1139-43. doi: 10.1001/archneur.63.8.1139
158. Zou ZY, Cui LY, Sun Q, et al. De novo FUS gene mutations are associated with juvenile-onset sporadic amyotrophic lateral sclerosis in China. *Neurobiology of aging* 2013;34(4):1312.e1-8. doi: 10.1016/j.neurobiolaging.2012.09.005 [published Online First: 2012/10/11]
159. Gromicho M, Oliveira Santos M, Pinto A, et al. Young-onset rapidly progressive ALS associated with heterozygous FUS mutation. *Amyotroph Lateral Scler Frontotemporal Degener* 2017;18(5-6):451-53. doi: 10.1080/21678421.2017.1299762 [published Online First: 2017/03/16]
160. Lagier-Tourenne C, Cleveland DW. Rethinking ALS: the FUS about TDP-43. *Cell* 2009;136(6):1001-4. doi: 10.1016/j.cell.2009.03.006 [published Online First: 2009/03/24]
161. Colombrita C, Zennaro E, Fallini C, et al. TDP-43 is recruited to stress granules in conditions of oxidative insult. *J Neurochem* 2009;111(4):1051-61. doi: 10.1111/j.1471-4159.2009.06383.x [published Online First: 2009/09/22]
162. Wang IF, Wu LS, Chang HY, et al. TDP-43, the signature protein of FTLD-U, is a neuronal activity-responsive factor. *J Neurochem* 2008;105(3):797-806. doi: 10.1111/j.1471-4159.2007.05190.x [published Online First: 2007/12/20]
163. Barber SC, Shaw PJ. Oxidative stress in ALS: Key role in motor neuron injury and therapeutic target. *Free Radical Biology and Medicine* 2010;48(5):629-41. doi: https://doi.org/10.1016/j.freeradbiomed.2009.11.018
164. Cunha-Oliveira T, Montezinho L, Mendes C, et al. Oxidative Stress in Amyotrophic Lateral Sclerosis: Pathophysiology and Opportunities for Pharmacological Intervention. *Oxidative Medicine and Cellular Longevity* 2020:5021694. doi: 10.1155/2020/5021694

165. Jaiswal MK. Calcium, mitochondria, and the pathogenesis of ALS: the good, the bad, and the ugly. *Frontiers in cellular neuroscience* 2013;7:199-99. doi: 10.3389/fncel.2013.00199
166. Ferraiuolo L, Kirby J, Grierson AJ, et al. Molecular pathways of motor neuron injury in amyotrophic lateral sclerosis. *Nature Reviews Neurology* 2011;7(11):616-30. doi: 10.1038/nrneurol.2011.152
167. Smith EF, Shaw PJ, De Vos KJ. The role of mitochondria in amyotrophic lateral sclerosis. *Neuroscience Letters* 2019;710:132933. doi: https://doi.org/10.1016/j.neulet.2017.06.052
168. De Vos KJ, Hafezparast M. Neurobiology of axonal transport defects in motor neuron diseases: Opportunities for translational research? *Neurobiology of disease* 2017;105:283-99. doi: 10.1016/j.nbd.2017.02.004 [published Online First: 2017/02/22]
169. Cluskey S, Ramsden DB. Mechanisms of neurodegeneration in amyotrophic lateral sclerosis. *Mol Pathol* 2001;54(6):386-92.
170. Benatar M, Zhang L, Wang L, et al. Validation of serum neurofilaments as prognostic and potential pharmacodynamic biomarkers for ALS. *Neurology* 2020;95(1):e59-e69. doi: 10.1212/wnl.0000000000009559
171. Blokhuis AM, Groen EJ, Koppers M, et al. Protein aggregation in amyotrophic lateral sclerosis. *Acta Neuropathol* 2013;125(6):777-94. doi: 10.1007/s00401-013-1125-6 [published Online First: 2013/05/16]
172. Shaw PJ. Molecular and cellular pathways of neurodegeneration in motor neurone disease. *Journal of Neurology, Neurosurgery & Psychiatry* 2005;76(8):1046-57. doi: 10.1136/jnnp.2004.048652
173. Trojsi F, Monsurrò MR, Tedeschi G. Exposure to environmental toxicants and pathogenesis of amyotrophic lateral sclerosis: state of the art and research perspectives. *International journal of molecular sciences* 2013;14(8):15286-311. doi: 10.3390/ijms140815286
174. Sanders T, Liu Y, Buchner V, et al. Neurotoxic effects and biomarkers of lead exposure: a review. *Reviews on environmental health* 2009;24(1):15-45. doi: 10.1515/reveh.2009.24.1.15
175. Weuve J, Korrick SA, Weisskopf MG, et al. Cumulative exposure to lead in relation to cognitive function in older women. *Environ Health Perspect* 2009;117(4):574-80. doi: 10.1289/ehp.11846 [published Online First: 2009/05/15]
176. Fang F, Peters TL, Beard JD, et al. Blood Lead, Bone Turnover, and Survival in Amyotrophic Lateral Sclerosis. *American Journal of Epidemiology* 2017;186(9):1057-64. doi: 10.1093/aje/kwx176
177. Boothby JA, DeJesus PV, Rowland LP. Reversible forms of motor neuron disease. Lead "neuritis". *Archives of neurology* 1974;31(1):18-23. doi: 10.1001/archneur.1974.00490370044005 [published Online First: 1974/07/01]
178. Livesley B, Sissons CE. Chronic lead intoxication mimicking motor neurone disease. *British medical journal* 1968;4(5627):387-88. doi: 10.1136/bmj.4.5627.387-d
179. Armon C, Kurland LT, Daube JR, et al. Epidemiologic correlates of sporadic amyotrophic lateral sclerosis. *Neurology* 1991;41(7):1077-84.
180. Chancellor AM, Slattery JM, Fraser H, et al. Risk factors for motor neuron disease: a case-control study based on patients from the Scottish Motor Neuron Disease Register. *J Neurol Neurosurg Psychiatry* 1993;56(11):1200-6. doi: 10.1136/jnnp.56.11.1200 [published Online First: 1993/11/01]
181. Kamel F, Umbach DM, Munsat TL, et al. Lead exposure and amyotrophic lateral sclerosis. *Epidemiology* 2002;13(3):311-9.
182. Fang F, Kwee LC, Allen KD, et al. Association between blood lead and the risk of amyotrophic lateral sclerosis. *Am J Epidemiol* 2010;171(10):1126-33. doi: 10.1093/aje/kwq063 [published Online First: 2010/04/22]

183. Andrew AS, Caller TA, Tandan R, et al. Environmental and occupational exposures and amyotrophic lateral sclerosis (ALS) in New England. *Neurodegener Dis* 2017;17(2-3):110-16. doi: 10.1159/000453359
184. Filippini T, Tesauro M, Fiore M, et al. Environmental and Occupational Risk Factors of Amyotrophic Lateral Sclerosis: A Population-Based Case-Control Study. *Int J Environ Res Public Health* 2020;17(8) doi: 10.3390/ijerph17082882 [published Online First: 2020/04/26]
185. Deapen DM, Henderson BE. A case-control study of amyotrophic lateral sclerosis. *Am J Epidemiol* 1986;123(5):790-9. doi: 10.1093/oxfordjournals.aje.a114308
186. Gresham LS, Molgaard CA, Golbeck AL, et al. Amyotrophic lateral sclerosis and occupational heavy metal exposure: a case-control study. *Neuroepidemiology* 1986;5(1):29-38. doi: 10.1159/000110810 [published Online First: 1986/01/01]
187. Gunnarsson LG, Bodin L, Soderfeldt B, et al. A case-control study of motor neurone disease: its relation to heritability, and occupational exposures, particularly to solvents. *Br J Ind Med* 1992;49(11):791-8.
188. Peters TL, Kamel F, Lundholm C, et al. Occupational exposures and the risk of amyotrophic lateral sclerosis. *Occup Environ Med* 2017;74(2):87-92. doi: 10.1136/oemed-2016-103700 [published Online First: 2016/07/16]
189. Vinceti M, Filippini T, Mandrioli J, et al. Lead, cadmium and mercury in cerebrospinal fluid and risk of amyotrophic lateral sclerosis: A case-control study. *J Trace Elem Med Biol* 2017 doi: 10.1016/j.jtemb.2016.12.012
190. Campbell AM, Williams ER, Barltrop D. Motor neurone disease and exposure to lead. *Journal of neurology, neurosurgery, and psychiatry* 1970;33(6):877-85. doi: 10.1136/jnnp.33.6.877
191. Pierce-Ruhland R, Patten BM. Repeat study of antecedent events in motor neuron disease. *Ann Clin Res* 1981;13(2):102-7. [published Online First: 1981/04/01]
192. Bertke SJ, Lehman EJ, Wurzelbacher SJ, et al. Mortality of lead smelter workers: A follow-up study with exposure assessment. *American Journal of Industrial Medicine* 2016;59(11):979-86. doi: https://doi.org/10.1002/ajim.22618
193. Dickerson AS, Hansen J, Specht AJ, et al. Population-based study of amyotrophic lateral sclerosis and occupational lead exposure in Denmark. *Occupational and Environmental Medicine* 2019;76(4):208-14. doi: 10.1136/oemed-2018-105469
194. Roos PM, Vesterberg O, Syversen T, et al. Metal concentrations in cerebrospinal fluid and blood plasma from patients with amyotrophic lateral sclerosis. *Biol Trace Elem Res* 2013;151(2):159-70. doi: 10.1007/s12011-012-9547-x [published Online First: 2012/12/12]
195. Bocca B, Forte G, Oggiano R, et al. Level of neurotoxic metals in amyotrophic lateral sclerosis: A population-based case-control study. *J Neurol Sci* 2015;359(1-2):11-7. doi: 10.1016/j.jns.2015.10.023 [published Online First: 2015/12/17]
196. Garzillo EM, Lamberti M, Genovese G, et al. Blood Lead, Manganese, and Aluminum Levels in a Regional Italian Cohort of ALS Patients: Does Aluminum Have an Influence? *Journal of Occupational and Environmental Medicine* 2014;56(10)
197. Peters S, Broberg K, Gallo V, et al. Blood Metal Levels and Amyotrophic Lateral Sclerosis Risk: A Prospective Cohort. *Annals of Neurology* 2021;89(1):125-33. doi: https://doi.org/10.1002/ana.25932
198. Bergomi M, Vinceti M, Nacci G, et al. Environmental exposure to trace elements and risk of amyotrophic lateral sclerosis: a population-based case-control study. *Environ Res* 2002;89(2):116-23. doi: 10.1006/enrs.2002.4361 [published Online First: 2002/07/19]
199. Zahran S, Laidlaw MA, Rowe DB, et al. Motor neuron disease mortality and lifetime petrol lead exposure: evidence from national age-specific and state-level age-standardized death rates in Australia. *Environ Res* 2017;153:181-90. doi: 10.1016/j.envres.2016.11.023 [published Online First: 2016/12/20]

200. Santurtun A, Villar A, Delgado-Alvarado M, et al. Trends in motor neuron disease: association with latitude and air lead levels in Spain. *Neurol Sci* 2016;37(8):1271-5. doi: 10.1007/s10072-016-2581-2 [published Online First: 2016/04/22]
201. Wang M-D, Gomes J, Cashman NR, et al. A meta-analysis of observational studies of the association between chronic occupational exposure to lead and amyotrophic lateral sclerosis. *Journal of occupational and environmental medicine* 2014;56(12):1235-42. doi: 10.1097/JOM.0000000000000323
202. Farace C, Fenu G, Lintas S, et al. Amyotrophic lateral sclerosis and lead: A systematic update. *Neurotoxicology* 2020 doi: 10.1016/j.neuro.2020.09.003 [published Online First: 2020/09/18]
203. Belbasis L, Bellou V, Evangelou E. Environmental Risk Factors and Amyotrophic Lateral Sclerosis: An Umbrella Review and Critical Assessment of Current Evidence from Systematic Reviews and Meta-Analyses of Observational Studies. *Neuroepidemiology* 2016;46(2):96-105. doi: 10.1159/000443146 [published Online First: 2016/01/06]
204. Gunnarsson LG, Bodin L. Occupational Exposures and Neurodegenerative Diseases-A Systematic Literature Review and Meta-Analyses. *Int J Environ Res Public Health* 2019;16(3) doi: 10.3390/ijerph16030337 [published Online First: 2019/01/30]
205. Meng E, Mao Y, Yao Q, et al. Population-based study of environmental/occupational lead exposure and amyotrophic lateral sclerosis: a systematic review and meta-analysis. *Neurol Sci* 2020;41(1):35-40. doi: 10.1007/s10072-019-04067-z [published Online First: 2019/10/04]
206. Gunnarsson LG, Bodin L. Amyotrophic Lateral Sclerosis and Occupational Exposures: A Systematic Literature Review and Meta-Analyses. *International Journal of Environmental Research and Public Health, Vol 15, Iss 11, p 2371 (2018)* 2018(11):2371. doi: 10.3390/ijerph15112371
207. Mentis A-FA, Dardiotis E, Efthymiou V, et al. Non-genetic risk and protective factors and biomarkers for neurological disorders: a meta-umbrella systematic review of umbrella reviews. *BMC Medicine* 2021;19(1):6. doi: 10.1186/s12916-020-01873-7
208. Bernhoft RA. Mercury Toxicity and Treatment: A Review of the Literature. *Journal of Environmental and Public Health* 2012;2012:460508. doi: 10.1155/2012/460508
209. Rice KM, Walker EM, Jr., Wu M, et al. Environmental mercury and its toxic effects. *J Prev Med Public Health* 2014;47(2):74-83. doi: 10.3961/jpmph.2014.47.2.74 [published Online First: 2014/03/31]
210. Pamphlett R, Kum Jew S. Heavy metals in locus ceruleus and motor neurons in motor neuron disease. *Acta Neuropathologica Communications* 2013;1(1):81. doi: 10.1186/2051-5960-1-81
211. Arvidson B. Inorganic mercury is transported from muscular nerve terminals to spinal and brainstem motoneurons. *Muscle Nerve* 1992;15(10):1089-94. doi: 10.1002/mus.880151006 [published Online First: 1992/10/01]
212. Chuu JJ, Liu SH, Lin-Shiau SY. Differential neurotoxic effects of methylmercury and mercuric sulfide in rats. *Toxicol Lett* 2007;169(2):109-20. doi: 10.1016/j.toxlet.2006.12.006 [published Online First: 2007/02/13]
213. Barber TE. Inorganic mercury intoxication reminiscent of amyotrophic lateral sclerosis. *J Occup Med* 1978;20(10):667-9.
214. Adams CR, Ziegler DK, Lin JT. Mercury intoxication simulating amyotrophic lateral sclerosis. *Jama* 1983;250(5):642-3. [published Online First: 1983/08/05]
215. Schwarz S, Husstedt I, Bertram HP, et al. Amyotrophic lateral sclerosis after accidental injection of mercury. *Journal of neurology, neurosurgery, and psychiatry* 1996;60(6):698-98. doi: 10.1136/jnnp.60.6.698
216. Praline J, Guennoc AM, Limousin N, et al. ALS and mercury intoxication: a relationship? *Clin Neurol Neurosurg* 2007;109(10):880-3. doi: 10.1016/j.clineuro.2007.07.008

217. Sienko DG, Davis JP, Taylor JA, et al. Amyotrophic lateral sclerosis. A case-control study following detection of a cluster in a small Wisconsin community. *Archives of neurology* 1990;47(1):38-41. doi: 10.1001/archneur.1990.00530010046017 [published Online First: 1990/01/01]
218. Pamphlett R, Waley P. Mercury in human spinal motor neurons. *Acta Neuropathol* 1998;96(5):515-9. doi: 10.1007/s004010050927 [published Online First: 1998/11/26]
219. Provinciali L, Giovagnoli AR. Antecedent events in amyotrophic lateral sclerosis: do they influence clinical onset and progression? *Neuroepidemiology* 1990;9(5):255-62. doi: 10.1159/000110782 [published Online First: 1990/01/01]
220. Louwerse ES, Buchet J-P, Van Dijk MA, et al. Urinary excretion of lead and mercury after oral administration ofmeso-2,3-dimercaptosuccinic acid in patients with motor neurone disease. *International Archives of Occupational and Environmental Health* 1995;67(2):135-38. doi: 10.1007/BF00572238
221. Moriwaka F, Satoh H, Ejima A, et al. Mercury and selenium contents in amyotrophic lateral sclerosis in Hokkaido, the northernmost island of Japan. *J Neurol Sci* 1993;118(1):38-42. doi: 10.1016/0022-510x(93)90243-r [published Online First: 1993/08/01]
222. Andrew AS, Chen CY, Caller TA, et al. Toenail mercury Levels are associated with amyotrophic lateral sclerosis risk. *Muscle & nerve* 2018:10.1002/mus.26055. doi: 10.1002/mus.26055
223. Kazantzis G. Mercury exposure and early effects: An overview. *La Medicina del lavoro* 2001;93:139-47.
224. Kim N-S, Lee B-K. Blood total mercury and fish consumption in the Korean general population in KNHANES III, 2005. *Science of The Total Environment* 2010;408(20):4841-47. doi: https://doi.org/10.1016/j.scitotenv.2010.06.026
225. Hoffman HI, Bradley WG, Chen CY, et al. Amyotrophic Lateral Sclerosis Risk, Family Income, and Fish Consumption Estimates of Mercury and Omega-3 PUFAs in the United States. *Int J Environ Res Public Health* 2021;18(9) doi: 10.3390/ijerph18094528 [published Online First: 2021/05/01]
226. Beard JD, Steege AL, Ju J, et al. Mortality from Amyotrophic Lateral Sclerosis and Parkinson's Disease Among Different Occupation Groups - United States, 1985-2011. *MMWR Morb Mortal Wkly Rep* 2017;66(27):718-22. doi: 10.15585/mmwr.mm6627a2 [published Online First: 2017/07/14]
227. Moriwaka F, Tashiro K, Doi R, et al. [A clinical evaluation of the inorganic mercurialism--its pathogenic relation to amyotrophic lateral sclerosis]. *Rinsho Shinkeigaku* 1991;31(8):885-7. [published Online First: 1991/08/01]
228. Vinceti M, Bottecchi I, Fan A, et al. Are environmental exposures to selenium, heavy metals, and pesticides risk factors for amyotrophic lateral sclerosis? *Rev Environ Health* 2012;27(1):19-41. doi: 10.1515/reveh-2012-0002 [published Online First: 2012/07/05]
229. Dobson AW, Erikson KM, Aschner M. Manganese Neurotoxicity. *Annals of the New York Academy of Sciences* 2004;1012(1):115-28. doi: https://doi.org/10.1196/annals.1306.009
230. Bowman AB, Kwakye GF, Herrero Hernández E, et al. Role of manganese in neurodegenerative diseases. *Journal of trace elements in medicine and biology: organ of the Society for Minerals and Trace Elements (GMS)* 2011;25(4):191-203. doi: 10.1016/j.jtemb.2011.08.144 [published Online First: 2011/10/01]
231. Bornhorst J, Wehe CA, Hüwel S, et al. Impact of manganese on and transfer across blood-brain and blood-cerebrospinal fluid barrier in vitro. *The Journal of biological chemistry* 2012;287(21):17140-51. doi: 10.1074/jbc.M112.344093 [published Online First: 2012/03/28]

232. Aschner M, Guilarte TR, Schneider JS, et al. Manganese: recent advances in understanding its transport and neurotoxicity. *Toxicol Appl Pharmacol* 2007;221(2):131-47. doi: 10.1016/j.taap.2007.03.001 [published Online First: 2007/05/01]
233. Voss H. Progressive Bulbar Paralysis and Amyotrophic Lateral Sclerosis Following Chronic Manganese Poisoning. *Arch f Gewerbepath u Gewerbehyg* 1939;9:464-76.
234. Kapaki E, Zournas C, Kanias G, et al. Essential trace element alterations in amyotrophic lateral sclerosis. *Journal of the Neurological Sciences* 1997;147(2):171-75. doi: https://doi.org/10.1016/S0022-510X(96)05334-8
235. Roos PM, Lierhagen S, Flaten TP, et al. Manganese in cerebrospinal fluid and blood plasma of patients with amyotrophic lateral sclerosis. *Experimental Biology and Medicine* 2012;237(7):803-10. doi: 10.1258/ebm.2012.011396
236. Nagata H, Miyata S, Nakamura S, et al. Heavy metal concentrations in blood cells in patients with amyotrophic lateral sclerosis. *J Neurol Sci* 1985;67(2):173-8. doi: 10.1016/0022-510x(85)90113-3 [published Online First: 1985/02/01]
237. Peters TL, Beard JD, Umbach DM, et al. Blood levels of trace metals and amyotrophic lateral sclerosis. *Neurotoxicology* 2016;54:119-26. doi: 10.1016/j.neuro.2016.03.022 [published Online First: 2016/04/18]
238. Hozumi I, Hasegawa T, Honda A, et al. Patterns of levels of biological metals in CSF differ among neurodegenerative diseases. *J Neurol Sci* 2011;303(1-2):95-9. doi: 10.1016/j.jns.2011.01.003 [published Online First: 2011/02/05]
239. Kilness AW, Hichberg FH. Amyotrophic lateral sclerosis in a high selenium environment. *Jama* 1977;237(26):2843-4. [published Online First: 1977/06/27]
240. Vinceti M, Guidetti D, Pinotti M, et al. Amyotrophic lateral sclerosis after long-term exposure to drinking water with high selenium content. *Epidemiology* 1996;7(5):529-32. [published Online First: 1996/09/01]
241. Vinceti M, Bonvicini F, Rothman KJ, et al. The relation between amyotrophic lateral sclerosis and inorganic selenium in drinking water: a population-based case-control study. *Environ Health* 2010;9:77. doi: 10.1186/1476-069x-9-77 [published Online First: 2010/12/08]
242. Dickerson AS, Hansen J, Gredal O, et al. Study of Occupational Chromium, Iron, and Nickel Exposure and Amyotrophic Lateral Sclerosis in Denmark. *Int J Environ Res Public Health* 2020;17(21) doi: 10.3390/ijerph17218086 [published Online First: 2020/11/06]
243. Boyes WK. Information resources in toxicology. 4th Edition ed. San Diego: Academic Press 2009.
244. Steber J. Handbook for cleaning/decontamination of surfaces. Amsterdam: Elsevier 2007:721-746.
245. Worksafe. Reducing harm when working with organic solvents. Wellington: Worksafe, New Zealand Government,2019:What is an organic solvent?
246. Benke G, Turner MC, Fleming S, et al. Occupational solvent exposure and risk of glioma in the INTEROCC study. *British Journal of Cancer* 2017;117(8):1246-54. doi: 10.1038/bjc.2017.285
247. Sabbath EL, Gutierrez L-A, Okechukwu CA, et al. Time may not fully attenuate solvent-associated cognitive deficits in highly exposed workers. *Neurology* 2014;82(19):1716-23. doi: 10.1212/WNL.0000000000000413
248. Letellier N, Choron G, Artaud F, et al. Association between occupational solvent exposure and cognitive performance in the French CONSTANCES study. *Occupational and environmental medicine* 2020;77(4):223-30. doi: 10.1136/oemed-2019-106132
249. Dick FD. Solvent neurotoxicity. *Occup Environ Med* 2006;63(3):221-6, 179. doi: 10.1136/oem.2005.022400 [published Online First: 2006/02/25]
250. Sainio MA, Sr. Neurotoxicity of solvents. *Handb Clin Neurol* 2015;131:93-110. doi: 10.1016/b978-0-444-62627-1.00007-x [published Online First: 2015/11/14]

251. Mattia CJ, Ali SF, Bondy SC. Toluene-induced oxidative stress in several brain regions and other organs. *Mol Chem Neuropathol* 1993;18(3):313-28. doi: 10.1007/bf03160122 [published Online First: 1993/04/01]
252. Revilla AS, Pestana CR, Pardo-Andreu GL, et al. Potential toxicity of toluene and xylene evoked by mitochondrial uncoupling. *Toxicol In Vitro* 2007;21(5):782-8. doi: 10.1016/j.tiv.2007.01.012 [published Online First: 2007/02/27]
253. Braconi D, Bernardini G, Santucci A. Linking protein oxidation to environmental pollutants: redox proteomic approaches. *J Proteomics* 2011;74(11):2324-37. doi: 10.1016/j.jprot.2011.06.029 [published Online First: 2011/07/20]
254. Pollari E, Goldsteins G, Bart G, et al. The role of oxidative stress in degeneration of the neuromuscular junction in amyotrophic lateral sclerosis. *Frontiers in cellular neuroscience* 2014;8:131-31. doi: 10.3389/fncel.2014.00131
255. Hawkes CH, Fox AJ. Motor neurone disease in leather workers. *Lancet (London, England)* 1981;1(8218):507. [published Online First: 1981/02/28]
256. Hawkes CH, Cavanagh JB, Fox AJ. Motoneuron disease: a disorder secondary to solvent exposure? *Lancet (London, England)* 1989;1(8629):73-6. doi: 10.1016/s0140-6736(89)91430-x [published Online First: 1989/01/14]
257. Bellavia A, Dickerson AS, Rotem RS, et al. Joint and interactive effects between health comorbidities and environmental exposures in predicting amyotrophic lateral sclerosis. *International journal of hygiene and environmental health* 2021;231:113655. doi: 10.1016/j.ijheh.2020.113655 [published Online First: 2020/11/02]
258. Gunnarsson LG, Lindberg G. Amyotrophic lateral sclerosis in Sweden 1970-83 and solvent exposure. *Lancet (London, England)* 1989;1(8644):958. [published Online First: 1989/04/29]
259. Savettieri G, Salemi G, Arcara A, et al. A case-control study of amyotrophic lateral sclerosis. *Neuroepidemiology* 1991;10(5-6):242-5. [published Online First: 1991/01/01]
260. Gait R, Maginnis C, Lewis S, et al. Occupational exposure to metals and solvents and the risk of motor neuron disease. A case-control study. *Neuroepidemiology* 2003;22(6):353-6. doi: 72925 [published Online First: 2003/10/15]
261. Malek AM, Barchowsky A, Bowser R, et al. Environmental and occupational risk factors for amyotrophic lateral sclerosis: a case-control study. *Neurodegener Dis* 2013;14(1):31-8. doi: 10.1159/000355344 [published Online First: 2013/11/20]
262. Weisskopf MG, Morozova N, O'Reilly EJ, et al. Prospective study of chemical exposures and amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 2009;80(5):558-61. doi: 10.1136/jnnp.2008.156976 [published Online First: 2009/04/18]
263. Dickerson AS, Hansen J, Thompson S, et al. A mixtures approach to solvent exposures and amyotrophic lateral sclerosis: a population-based study in Denmark. *Eur J Epidemiol* 2020;35(3):241-49. doi: 10.1007/s10654-020-00624-5 [published Online First: 2020/03/21]
264. Koeman T, Slottje P, Schouten LJ, et al. Occupational exposure and amyotrophic lateral sclerosis in a prospective cohort. *Occup Environ Med* 2017;74(8):578-85. doi: 10.1136/oemed-2016-103780 [published Online First: 2017/03/31]
265. Capozzella A, Sacco C, Chighine A, et al. Work related etiology of amyotrophic lateral sclerosis (ALS): a meta-analysis. *Annali di igiene : medicina preventiva e di comunita* 2014;26(5):456-72. doi: 10.7416/ai.2014.2005 [published Online First: 2014/11/19]
266. Qureshi MM, Douglas H, Urbinelli L, et al. Analysis of factors that modify susceptibility and rate of progression in amyotrophic lateral sclerosis (ALS). *Amyotrophic Lateral Sclerosis* 2006;7(3):173-82. doi: 10.1080/14660820600640596
267. Charcot JM. Des accidents nerveux provoqués par la foudre. Bulletin Medical de la Societé des Hôspitaux de Paris1889:4.
268. Haynal A, Regli F. Amyotrophic Lateral Sclerosis Associated With Accumulated Electric Injury. *Confinia neurologica* 1964;24:189-98. [published Online First: 1964/01/01]

269. Gallagher JP, Talbert OR. Motor neuron syndrome after electric shock. *Acta Neurol Scand* 1991;83(2):79-82. doi: 10.1111/j.1600-0404.1991.tb04653.x [published Online First: 1991/02/01]
270. Sirdofsky MD, Hawley RJ, Manz H. Progressive motor neuron disease associated with electrical injury. *Muscle Nerve* 1991;14(10):977-80. doi: 10.1002/mus.880141008 [published Online First: 1991/10/01]
271. Jafari H, Couratier P, Camu W. Motor neuron disease after electric injury. *Journal of Neurology, Neurosurgery & Psychiatry* 2001;71(2):265-67. doi: 10.1136/jnnp.71.2.265
272. Savitz DA, Loomis DP, Tse CK. Electrical occupations and neurodegenerative disease: analysis of U.S. mortality data. *Archives of Environmental Health* 1998;53(1):71.
273. Noonan CW, Reif JS, Yost M, et al. Occupational exposure to magnetic fields in case-referent studies of neurodegenerative diseases. *Scandinavian journal of work, environment & health* 2002;28(1):42-8. [published Online First: 2002/03/02]
274. Schulte PA, Burnett CA, Boeniger MF, et al. Neurodegenerative diseases: occupational occurrence and potential risk factors, 1982 through 1991. *Am J Public Health* 1996;86(9):1281-8. doi: 10.2105/ajph.86.9.1281 [published Online First: 1996/09/01]
275. Strickland D, Smith SA, Dolliff G, et al. Amyotrophic lateral sclerosis and occupational history. A pilot case-control study. *Archives of neurology* 1996;53(8):730-3.
276. Sorahan T, Mohammed N. Neurodegenerative disease and magnetic field exposure in UK electricity supply workers. *Occup Med (Lond)* 2014;64(6):454-60. doi: 10.1093/occmed/kqu105 [published Online First: 2014/08/12]
277. Vergara X, Mezei G, Kheifets L. Case-control study of occupational exposure to electric shocks and magnetic fields and mortality from amyotrophic lateral sclerosis in the US, 1991-1999. *Journal of exposure science & environmental epidemiology* 2015;25(1):65-71. doi: 10.1038/jes.2014.39 [published Online First: 2014/06/12]
278. Johansen C. Exposure to electromagnetic fields and risk of central nervous system disease in utility workers. *Epidemiology* 2000;11(5):539-43. doi: 10.1097/00001648-200009000-00009 [published Online First: 2000/08/24]
279. Feychting M, Jonsson F, Pedersen NL, et al. Occupational magnetic field exposure and neurodegenerative disease. *Epidemiology* 2003;14(4):413-9; discussion 27-8. doi: 10.1097/01.EDE.0000071409.23291.7b [published Online First: 2003/07/05]
280. Johansen C, Olsen J. Mortality from amyotrophic lateral sclerosis, other chronic disorders, and electric shocks among utility workers. *Am J Epidemiol* 1998;148(4):362-8. doi: 10.1093/oxfordjournals.aje.a009654
281. Peters S, Visser AE, D'Ovidio F, et al. Associations of Electric Shock and Extremely Low-Frequency Magnetic Field Exposure With the Risk of Amyotrophic Lateral Sclerosis. *Am J Epidemiol* 2019;188(4):796-805. doi: 10.1093/aje/kwy287 [published Online First: 2019/01/17]
282. Huss A, Spoerri A, Egger M, et al. Occupational exposure to magnetic fields and electric shocks and risk of ALS: the Swiss National Cohort. *Amyotroph Lateral Scler Frontotemporal Degener* 2015;16(1-2):80-5. doi: 10.3109/21678421.2014.954588 [published Online First: 2014/09/18]
283. Davanipour Z, Sobel E, Vu H, et al. Electromagnetic field exposure and amyotrophic lateral sclerosis. *Neuroepidemiology* 1991;10(5-6):308. doi: 10.1159/000110288 [published Online First: 1991/01/01]
284. Davanipour Z, Sobel E, Bowman JD, et al. Amyotrophic lateral sclerosis and occupational exposure to electromagnetic fields. *Bioelectromagnetics* 1997;18(1):28-35. [published Online First: 1997/01/01]
285. Hakansson N, Gustavsson P, Johansen C, et al. Neurodegenerative diseases in welders and other workers exposed to high levels of magnetic fields. *Epidemiology* 2003;14(4):420-6; discussion 27-8. doi: 10.1097/01.EDE.0000078446.76859.c9 [published Online First: 2003/07/05]

286. Hug K, Röösli M, Rapp R. Magnetic field exposure and neurodegenerative diseases – recent epidemiological studies. *International Journal of Public Health* 2006;51(4):210.
287. Su L, Jin Y, Lou H, et al. Re: "Associations of Electric Shock and Extremely Low-Frequency Magnetic Field Exposure With the Risk of Amyotrophic Lateral Sclerosis: The Euro-MOTOR Project". *Am J Epidemiol* 2019 doi: 10.1093/aje/kwz122 [published Online First: 2019/06/01]
288. Li CY, Sung FC. Association between occupational exposure to power frequency electromagnetic fields and amyotrophic lateral sclerosis: a review. *Am J Ind Med* 2003;43(2):212-20. doi: 10.1002/ajim.10148 [published Online First: 2003/01/24]
289. Vergara X, Kheifets L, Greenland S, et al. Occupational exposure to extremely low-frequency magnetic fields and neurodegenerative disease: a meta-analysis. *J Occup Environ Med* 2013;55(2):135-46. doi: 10.1097/JOM.0b013e31827f37f8
290. Savitz DA, Checkoway H, Loomis DP. Magnetic field exposure and neurodegenerative disease mortality among electric utility workers. *Epidemiology* 1998;9(4):398-404. [published Online First: 1998/07/02]
291. Roosli M, Lortscher M, Egger M, et al. Mortality from neurodegenerative disease and exposure to extremely low-frequency magnetic fields: 31 years of observations on Swiss railway employees. *Neuroepidemiology* 2007;28(4):197-206. doi: 10.1159/000108111 [published Online First: 2007/09/14]
292. Weisskopf MG, McCullough ML, Morozova N, et al. Prospective study of occupation and amyotrophic lateral sclerosis mortality. *Am J Epidemiol* 2005;162(12):1146-52. doi: 10.1093/aje/kwi343
293. Sorahan T, Kheifets L. Mortality from Alzheimer's, motor neuron and Parkinson's disease in relation to magnetic field exposure: findings from the study of UK electricity generation and transmission workers, 1973-2004. *Occup Environ Med* 2007;64(12):820-6. doi: 10.1136/oem.2006.031559 [published Online First: 2007/07/13]
294. Parlett LE, Bowman JD, van Wijngaarden E. Evaluation of occupational exposure to magnetic fields and motor neuron disease mortality in a population-based cohort. *J Occup Environ Med* 2011;53(12):1447-51. doi: 10.1097/JOM.0b013e318237a1d0
295. Jalilian H, Najafi K, Khosravi Y, et al. Amyotrophic lateral sclerosis, occupational exposure to extremely low frequency magnetic fields and electric shocks: a systematic review and meta-analysis. *Rev Environ Health* 2021;36(1):129-42. doi: 10.1515/reveh-2020-0041 [published Online First: 2020/09/19]
296. Baaken D, Dechent D, Blettner M, et al. Occupational Exposure to Extremely Low-Frequency Magnetic Fields and Risk of Amyotrophic Lateral Sclerosis: Results of a Feasibility Study for a Pooled Analysis of Original Data. *Bioelectromagnetics* 2021 doi: 10.1002/bem.22335 [published Online First: 2021/03/26]
297. Parrón T, Requena M, Hernández AF, et al. Association between environmental exposure to pesticides and neurodegenerative diseases. *Toxicology and Applied Pharmacology* 2011;256(3):379-85. doi: https://doi.org/10.1016/j.taap.2011.05.006
298. Elbaz A, Dufouil C, Alpérovitch A. Interaction between genes and environment in neurodegenerative diseases. *Comptes Rendus Biologies* 2007;330(4):318-28. doi: https://doi.org/10.1016/j.crvi.2007.02.018
299. Stozická Z, Zilka N, Novák M. Risk and protective factors for sporadic Alzheimer's disease. *Acta Virol* 2007;51(4):205-22. [published Online First: 2008/01/17]
300. Keifer MC, Firestone J. Neurotoxicity of pesticides. *J Agromedicine* 2007;12(1):17-25. doi: 10.1300/J096v12n01_03 [published Online First: 2007/11/23]
301. Chen Y. Organophosphate-induced brain damage: mechanisms, neuropsychiatric and neurological consequences, and potential therapeutic strategies. *Neurotoxicology* 2012;33(3):391-400. doi: 10.1016/j.neuro.2012.03.011 [published Online First: 2012/04/14]

302. Merwin SJ, Obis T, Nunez Y, et al. Organophosphate neurotoxicity to the voluntary motor system on the trail of environment-caused amyotrophic lateral sclerosis: the known, the misknown, and the unknown. *Arch Toxicol* 2017;91(8):2939-52. doi: 10.1007/s00204-016-1926-1 [published Online First: 2017/01/11]
303. Morahan JM, Yu B, Trent RJ, et al. A gene–environment study of the paraoxonase 1 gene and pesticides in amyotrophic lateral sclerosis. *NeuroToxicology* 2007;28(3):532-40. doi: https://doi.org/10.1016/j.neuro.2006.11.007
304. Bozzoni V, Pansarasa O, Diamanti L, et al. Amyotrophic lateral sclerosis and environmental factors. *Functional neurology* 2016;31(1):7-19. doi: 10.11138/fneur/2016.31.1.007
305. Cookson MR, Shaw PJ. Oxidative stress and motor neurone disease. *Brain Pathol* 1999;9(1):165-86. doi: 10.1111/j.1750-3639.1999.tb00217.x [published Online First: 1999/02/16]
306. Pall HS, Williams AC, Waring R, et al. Motoneurone disease as manifestation of pesticide toxicity. *Lancet (London, England)* 1987;2(8560):685. doi: 10.1016/s0140-6736(87)92468-8 [published Online First: 1987/09/19]
307. Fonseca RG, Resende LA, Silva MD, et al. Chronic motor neuron disease possibly related to intoxication with organochlorine insecticides. *Acta Neurol Scand* 1993;88(1):56-8. doi: 10.1111/j.1600-0404.1993.tb04187.x [published Online First: 1993/07/01]
308. Doi H, Kikuchi H, Murai H, et al. Motor neuron disorder simulating ALS induced by chronic inhalation of pyrethroid insecticides. *Neurology* 2006;67(10):1894-5. doi: http://10.1212/01.wnl.0000244489.65670.9f
309. Bonvicini F, Marcello N, Mandrioli J, et al. Exposure to pesticides and risk of amyotrophic lateral sclerosis: a population-based case-control study. *Ann Ist Super Sanita* 2010;46(3):284-7. doi: 10.4415/ann_10_03_10 [published Online First: 2010/09/18]
310. Furby A, Beauvais K, Kolev I, et al. Rural environment and risk factors of amyotrophic lateral sclerosis: a case-control study. *J Neurol* 2010;257(5):792-8. doi: 10.1007/s00415-009-5419-5 [published Online First: 2009/12/17]
311. Pamphlett R. Exposure to environmental toxins and the risk of sporadic motor neuron disease: an expanded Australian case-control study. *European journal of neurology* 2012;19(10):1343-8. doi: 10.1111/j.1468-1331.2012.03769.x [published Online First: 2012/05/31]
312. Yu Y, Su FC, Callaghan BC, et al. Environmental risk factors and amyotrophic lateral sclerosis (ALS): a case-control study of ALS in Michigan. *PLoS One* 2014;9(6):e101186. doi: 10.1371/journal.pone.0101186
313. Beaudin M, Trudelle A-M, Lamarre M-S, et al. Occupational Exposition to Pesticides and Amyotrophic Lateral Sclerosis in Quebec and France (2119). *Neurology* 2020;94(15 Supplement):2119.
314. Alavanja MC, Sandler DP, McMaster SB, et al. The Agricultural Health Study. *Environ Health Perspect* 1996;104(4):362-9. doi: 10.1289/ehp.96104362 [published Online First: 1996/04/01]
315. Johnson FO, Atchison WD. The role of environmental mercury, lead and pesticide exposure in development of amyotrophic lateral sclerosis. *Neurotoxicology* 2009;30(5):761-5. doi: 10.1016/j.neuro.2009.07.010 [published Online First: 2009/07/28]
316. Tanner CM, Goldman SM, Ross GW, et al. The disease intersection of susceptibility and exposure: Chemical exposures and neurodegenerative disease risk. *Alzheimer's & Dementia* 2014;10(3, Supplement):S213-S25. doi: https://doi.org/10.1016/j.jalz.2014.04.014
317. Burns CJ, Beard KK, Cartmill JB. Mortality in chemical workers potentially exposed to 2,4-dichlorophenoxyacetic acid (2,4-D) 1945-94: an update. *Occup Environ Med* 2001;58(1):24-30. doi: 10.1136/oem.58.1.24 [published Online First: 2000/12/19]

318. Beard JD, Engel LS, Richardson DB, et al. Military service, deployments, and exposures in relation to amyotrophic lateral sclerosis etiology. *Environ Int* 2016;91:104-15. doi: 10.1016/j.envint.2016.02.014
319. Su FC, Goutman SA, Chernyak S, et al. Association of Environmental Toxins With Amyotrophic Lateral Sclerosis. *JAMA Neurol* 2016;73(7):803-11. doi: 10.1001/jamaneurol.2016.0594
320. Chió A, Meineri P, Tribolo A, et al. Risk factors in motor neuron disease: a case-control study. *Neuroepidemiology* 1991;10(4):174-84. doi: 10.1159/000110267 [published Online First: 1991/01/01]
321. Govoni V, Granieri E, Fallica E, et al. Amyotrophic lateral sclerosis, rural environment and agricultural work in the Local Health District of Ferrara, Italy, in the years 1964-1998. *J Neurol* 2005;252(11):1322-7. doi: 10.1007/s00415-005-0859-z [published Online First: 2005/07/05]
322. Filippini T, Fiore M, Tesauro M, et al. Clinical and Lifestyle Factors and Risk of Amyotrophic Lateral Sclerosis: A Population-Based Case-Control Study. *International journal of environmental research and public health* 2020;17(3):857. doi: 10.3390/ijerph17030857
323. Dickerson AS, Hansen J, Kioumourtzoglou MA, et al. Study of occupation and amyotrophic lateral sclerosis in a Danish cohort. *Occup Environ Med* 2018;75(9):630-38. doi: 10.1136/oemed-2018-105110 [published Online First: 2018/06/27]
324. Kab S, Moisan F, Elbaz A. Farming and incidence of motor neuron disease: French nationwide study. *European journal of neurology* 2017:n/a-n/a. doi: 10.1111/ene.13353
325. Kalfakis N, Vassilopoulos D, Voumvourakis C, et al. Amyotrophic lateral sclerosis in southern Greece: an epidemiologic study. *Neuroepidemiology* 1991;10(4):170-3. doi: 10.1159/000110266 [published Online First: 1991/01/01]
326. Cruz DC, Nelson LM, McGuire V, et al. Physical trauma and family history of neurodegenerative diseases in amyotrophic lateral sclerosis: a population-based case-control study. *Neuroepidemiology* 1999;18(2):101-10. doi: 10.1159/000069413 [published Online First: 1999/02/19]
327. Povedano M, Saez M, Martinez-Matos JA, et al. Spatial assessment of the association between long-term exposure to environmental factors and the occurrence of amyotrophic lateral sclerosis in Catalonia, Spain: a population-based nested case-control study. *Neuroepidemiology* 2018;51(1-2):33-49. doi: 10.1159/000489664 [published Online First: 2018/06/01]
328. Strickland D, Smith SA, Dolliff G, et al. Physical activity, trauma, and ALS: a case-control study. *Acta Neurologica Scandinavica* 1996;94(1):45-50. doi: https://doi.org/10.1111/j.1600-0404.1996.tb00038.x
329. Wu Y, Wu H, Guo X, et al. Blood–Brain Barrier Dysfunction in Mild Traumatic Brain Injury: Evidence From Preclinical Murine Models. *Frontiers in Physiology* 2020;11(1030) doi: 10.3389/fphys.2020.01030
330. Shlosberg D, Benifla M, Kaufer D, et al. Blood-brain barrier breakdown as a therapeutic target in traumatic brain injury. *Nature reviews Neurology* 2010;6(7):393-403. doi: 10.1038/nrneurol.2010.74 [published Online First: 2010/06/17]
331. Zlokovic BV. The blood-brain barrier in health and chronic neurodegenerative disorders. *Neuron* 2008;57(2):178-201. doi: 10.1016/j.neuron.2008.01.003 [published Online First: 2008/01/25]
332. Wiesner D, Tar L, Linkus B, et al. Reversible induction of TDP-43 granules in cortical neurons after traumatic injury. *Exp Neurol* 2018;299(Pt A):15-25. doi: 10.1016/j.expneurol.2017.09.011 [published Online First: 2017/09/25]

333. Goldman SM, Tanner CM, Oakes D, et al. Head injury and Parkinson's disease risk in twins. *Ann Neurol* 2006;60(1):65-72. doi: 10.1002/ana.20882 [published Online First: 2006/05/24]
334. Szczygielski J, Mautes A, Steudel WI, et al. Traumatic brain injury: cause or risk of Alzheimer's disease? A review of experimental studies. *J Neural Transm (Vienna)* 2005;112(11):1547-64. doi: 10.1007/s00702-005-0326-0 [published Online First: 2005/06/17]
335. Cavaleri F. Review of Amyotrophic Lateral Sclerosis, Parkinson's and Alzheimer's diseases helps further define pathology of the novel paradigm for Alzheimer's with heavy metals as primary disease cause. *Med Hypotheses* 2015;85(6):779-90. doi: 10.1016/j.mehy.2015.10.009 [published Online First: 2015/11/26]
336. Eisen A, Calne D. Amyotrophic lateral sclerosis, Parkinson's disease and Alzheimer's disease: phylogenetic disorders of the human neocortex sharing many characteristics. *Can J Neurol Sci* 1992;19(1 Suppl):117-23. [published Online First: 1992/02/01]
337. Chen H, Richard M, Sandler DP, et al. Head injury and amyotrophic lateral sclerosis. *Am J Epidemiol* 2007;166(7):810-6. doi: 10.1093/aje/kwm153
338. Seals RM, Hansen J, Gredal O, et al. Physical Trauma and Amyotrophic Lateral Sclerosis: A Population-Based Study Using Danish National Registries. *Am J Epidemiol* 2016;183(4):294-301. doi: 10.1093/aje/kwv169
339. Feddermann-Demont N, Junge A, Weber KP, et al. Prevalence of potential sports-associated risk factors in Swiss amyotrophic lateral sclerosis patients. *Brain and behavior* 2017;7(4):e00630-e30. doi: 10.1002/brb3.630
340. Pupillo E, Messina P, Logroscino G, et al. Trauma and amyotrophic lateral sclerosis: a case-control study from a population-based registry. *European journal of neurology* 2012;19(12):1509-17. doi: 10.1111/j.1468-1331.2012.03723.x [published Online First: 2012/04/28]
341. Schmidt S, Kwee LC, Allen KD, et al. Association of ALS with head injury, cigarette smoking and APOE genotypes. *J Neurol Sci* 2010;291(1-2):22-9. doi: 10.1016/j.jns.2010.01.011 [published Online First: 2010/02/05]
342. Seelen M, van Doormaal PT, Visser AE, et al. Prior medical conditions and the risk of amyotrophic lateral sclerosis. *J Neurol* 2014;261(10):1949-56. doi: 10.1007/s00415-014-7445-1 [published Online First: 2014/07/26]
343. Pupillo E, Messina P, Giussani G, et al. Physical activity and amyotrophic lateral sclerosis: a European population-based case-control study. *Ann Neurol* 2014;75(5):708-16. doi: 10.1002/ana.24150 [published Online First: 2014/04/08]
344. Lian L, Liu M, Cui L, et al. Environmental risk factors and amyotrophic lateral sclerosis (ALS): A case-control study of ALS in China. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia* 2019;66:12-18. doi: 10.1016/j.jocn.2019.05.036 [published Online First: 2019/06/04]
345. Turner MR, Abisgold J, Yeates DG, et al. Head and other physical trauma requiring hospitalisation is not a significant risk factor in the development of ALS. *J Neurol Sci* 2010;288(1-2):45-8. doi: 10.1016/j.jns.2009.10.010 [published Online First: 2009/11/03]
346. Kurtzke JF, Beebe GW. Epidemiology of amyotrophic lateral sclerosis: 1. A case-control comparison based on ALS deaths. *Neurology* 1980;30(5):453-62. doi: 10.1212/wnl.30.5.453 [published Online First: 1980/05/01]
347. Binazzi A, Belli S, Uccelli R, et al. An exploratory case-control study on spinal and bulbar forms of amyotrophic lateral sclerosis in the province of Rome. *Amyotrophic Lateral Sclerosis* 2009;10(5-6):361-69. doi: 10.3109/17482960802382313
348. Pupillo E, Poloni M, Bianchi E, et al. Trauma and amyotrophic lateral sclerosis: a European population-based case-control study from the EURALS consortium. *Amyotrophic*

Lateral Sclerosis and Frontotemporal Degeneration 2018;19(1-2):118-25. doi: 10.1080/21678421.2017.1386687
349. Peters TL, Fang F, Weibull CE, et al. Severe head injury and amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener* 2013;14(4):267-72. doi: 10.3109/21678421.2012.754043 [published Online First: 2013/01/05]
350. Gallagher JP, Sanders M. Trauma and amyotrophic lateral sclerosis: a report of 78 patients. *Acta Neurol Scand* 1987;75(2):145-50. doi: 10.1111/j.1600-0404.1987.tb07909.x [published Online First: 1987/02/01]
351. Beghi E, Logroscino G, Chio A, et al. Amyotrophic lateral sclerosis, physical exercise, trauma and sports: results of a population-based pilot case-control study. *Amyotroph Lateral Scler* 2010;11(3):289-92. doi: 10.3109/17482960903384283 [published Online First: 2010/05/04]
352. Williams DB, Annegers JF, Kokmen E, et al. Brain injury and neurologic sequelae: a cohort study of dementia, parkinsonism, and amyotrophic lateral sclerosis. *Neurology* 1991;41(10):1554-7. doi: 10.1212/wnl.41.10.1554 [published Online First: 1991/10/01]
353. Sagiraju HKR, Živković S, VanCott AC, et al. Amyotrophic Lateral Sclerosis Among Veterans Deployed in Support of Post-9/11 U.S. Conflicts. *Mil Med* 2020;185(3-4):e501-e09. doi: 10.1093/milmed/usz350 [published Online First: 2019/10/24]
354. Armon C, Nelson LM. Is head trauma a risk factor for amyotrophic lateral sclerosis? An evidence based review. *Amyotroph Lateral Scler* 2012;13(4):351-6. doi: 10.3109/17482968.2012.660954 [published Online First: 2012/03/20]
355. Perry DC, Sturm VE, Peterson MJ, et al. Association of traumatic brain injury with subsequent neurological and psychiatric disease: a meta-analysis. *J Neurosurg* 2016;124(2):511-26. doi: 10.3171/2015.2.Jns14503 [published Online First: 2015/09/01]
356. Watanabe Y, Watanabe T. Meta-analytic evaluation of the association between head injury and risk of amyotrophic lateral sclerosis. *Eur J Epidemiol* 2017;32(10):867-79. doi: 10.1007/s10654-017-0327-y [published Online First: 2017/10/29]
357. Gu D, Ou S, Tang M, et al. Trauma and amyotrophic lateral sclerosis: a systematic review and meta-analysis. *Amyotroph Lateral Scler Frontotemporal Degener* 2021;22(3-4):170-85. doi: 10.1080/21678421.2020.1861024 [published Online First: 2021/01/12]
358. Liu G, Ou S, Cui H, et al. Head Injury and Amyotrophic Lateral Sclerosis: A Meta-Analysis. *Neuroepidemiology* 2021:1-9. doi: 10.1159/000510987 [published Online First: 2021/02/24]
359. Sjödin B, Hellsten Westing Y, Apple FS. Biochemical mechanisms for oxygen free radical formation during exercise. *Sports Med* 1990;10(4):236-54. doi: 10.2165/00007256-199010040-00003 [published Online First: 1990/10/01]
360. Harwood CA, McDermott CJ, Shaw PJ. Physical activity as an exogenous risk factor in motor neuron disease (MND): A review of the evidence. *Amyotrophic Lateral Sclerosis* 2009;10(4):191-204. doi: 10.1080/17482960802549739
361. Chio A, Benzi G, Dossena M, et al. Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players. *Brain* 2005;128(Pt 3):472-6. doi: 10.1093/brain/awh373 [published Online First: 2005/01/07]
362. Chio A, Calvo A, Dossena M, et al. ALS in Italian professional soccer players: the risk is still present and could be soccer-specific. *Amyotroph Lateral Scler* 2009;10(4):205-9. doi: 10.1080/17482960902721634 [published Online First: 2009/03/10]
363. Lehman EJ, Hein MJ, Baron SL, et al. Neurodegenerative causes of death among retired National Football League players. *Neurology* 2012;79(19):1970-4. doi: 10.1212/WNL.0b013e31826daf50
364. Savica R, Parisi JE, Wold LE, et al. High school football and risk of neurodegeneration: a community-based study. *Mayo Clin Proc* 2012;87(4):335-40. doi: 10.1016/j.mayocp.2011.12.016

365. Maugeri G, D'Agata V. Effects of Physical Activity on Amyotrophic Lateral Sclerosis. *J Funct Morphol Kinesiol* 2020;5(2):29. doi: 10.3390/jfmk5020029
366. Belli S, Vanacore N. Proportionate mortality of Italian soccer players: is amyotrophic lateral sclerosis an occupational disease? *Europen Journal of Epidemiology* 2005;20(3):237-42. [published Online First: 2005/06/01]
367. Taioli E. All causes mortality in male professional soccer players. *European Journal of Public Health* 2007;17(6):600-04. doi: 10.1093/eurpub/ckm035
368. Vanacore N, Cocco P, Fadda D, et al. Job strain, hypoxia and risk of amyotrophic lateral sclerosis: Results from a death certificate study. *Amyotroph Lateral Scler* 2010;11(5):430-4. doi: 10.3109/17482961003605796 [published Online First: 2010/08/12]
369. Mackay DF, Russell ER, Stewart K, et al. Neurodegenerative Disease Mortality among Former Professional Soccer Players. *N Engl J Med* 2019;381(19):1801-08. doi: 10.1056/NEJMoa1908483 [published Online First: 2019/10/22]
370. Russell ER, Mackay DF, Stewart K, et al. Association of Field Position and Career Length With Risk of Neurodegenerative Disease in Male Former Professional Soccer Players. *JAMA Neurology* 2021 doi: 10.1001/jamaneurol.2021.2403
371. Fang F, Hållmarker U, James S, et al. Amyotrophic lateral sclerosis among cross-country skiers in Sweden. *European Journal of Epidemiology* 2016;31(3):247-53. doi: 10.1007/s10654-015-0077-7
372. Pupillo E, Bianchi E, Vanacore N, et al. Increased risk and early onset of ALS in professional players from Italian Soccer Teams. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* 2020;21(5-6):403-09. doi: 10.1080/21678421.2020.1752250
373. Blecher R, Elliott MA, Yilmaz E, et al. Contact Sports as a Risk Factor for Amyotrophic Lateral Sclerosis: A Systematic Review. *Global Spine J* 2019;9(1):104-18. doi: 10.1177/2192568218813916 [published Online First: 2019/01/31]
374. Felmus MT, Patten BM, Swanke L. Antecedent events in amyotrophic lateral sclerosis. *Neurology* 1976;26(2):167-72. doi: 10.1212/wnl.26.2.167 [published Online First: 1976/02/01]
375. Longstreth WT, Jr, McGuire V, Koepsell TD, et al. Risk of Amyotrophic Lateral Sclerosis and History of Physical Activity: A Population-Based Case-Control Study. *Archives of neurology* 1998;55(2):201-06. doi: 10.1001/archneur.55.2.201
376. Scarmeas N, Shih T, Stern Y, et al. Premorbid weight, body mass, and varsity athletics in ALS. *Neurology* 2002;59(5):773-75. doi: 10.1212/wnl.59.5.773
377. Valenti M, Pontieri FE, Conti F, et al. Amyotrophic lateral sclerosis and sports: a case-control study. *European journal of neurology* 2005;12(3):223-5. doi: 10.1111/j.1468-1331.2004.00978.x [published Online First: 2005/02/08]
378. Veldink JH, Kalmijn S, Groeneveld GJ, et al. Physical activity and the association with sporadic ALS. *Neurology* 2005;64(2):241-5. doi: 10.1212/01.Wnl.0000149513.82332.5c [published Online First: 2005/01/26]
379. Huisman MHB, Seelen M, de Jong SW, et al. Lifetime physical activity and the risk of amyotrophic lateral sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry* 2013;84(9):976-81. doi: 10.1136/jnnp-2012-304724
380. Okamoto K, Kihira T, Kondo T, et al. Lifestyle Factors and Risk of Amyotrophic Lateral Sclerosis: A Case-Control Study in Japan. *Annals of Epidemiology* 2009;19(6):359-64. doi: https://doi.org/10.1016/j.annepidem.2009.01.015
381. Visser AE, Rooney JPK, D'Ovidio F, et al. Multicentre, cross-cultural, population-based, case-control study of physical activity as risk factor for amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 2018 doi: 10.1136/jnnp-2017-317724 [published Online First: 2018/04/25]

382. Eaglehouse YL, Talbott EO, Chang Y, et al. Participation in Physical Activity and Risk for Amyotrophic Lateral Sclerosis Mortality Among Postmenopausal Women. *JAMA Neurology* 2016;73(3):329-36. doi: 10.1001/jamaneurol.2015.4487
383. Gallo V, Vanacore N, Bueno-de-Mesquita HB, et al. Physical activity and risk of Amyotrophic Lateral Sclerosis in a prospective cohort study. *Eur J Epidemiol* 2016;31(3):255-66. doi: 10.1007/s10654-016-0119-9
384. Janssen PH, Mandrekar J, Mielke MM, et al. High School Football and Late-Life Risk of Neurodegenerative Syndromes, 1956-1970. *Mayo Clin Proc* 2017;92(1):66-71. doi: 10.1016/j.mayocp.2016.09.004 [published Online First: 2016/12/17]
385. Raymond J, Mehta P, Larson T, et al. History of vigorous leisure-time physical activity and early onset amyotrophic lateral sclerosis (ALS), data from the national ALS registry: 2010–2018. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* 2021:1-10. doi: 10.1080/21678421.2021.1910308
386. Bandres-Ciga S, Noyce AJ, Hemani G, et al. Shared polygenic risk and causal inferences in amyotrophic lateral sclerosis. *Annals of Neurology* 2020;87(6):991-92. doi: https://doi.org/10.1002/ana.25431
387. Julian TH, Glascow N, Barry ADF, et al. Physical exercise is a risk factor for amyotrophic lateral sclerosis: Convergent evidence from Mendelian randomisation, transcriptomics and risk genotypes. *EBioMedicine* 2021;68:103397. doi: https://doi.org/10.1016/j.ebiom.2021.103397
388. Abel EL. Football increases the risk for Lou Gehrig's disease, amyotrophic lateral sclerosis. *Percept Mot Skills* 2007;104(3 Pt 2):1251-4. doi: 10.2466/pms.104.4.1251-1254 [published Online First: 2007/09/21]
389. Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med* 2000;343(25):1833-8. doi: 10.1056/nejm200012213432502 [published Online First: 2000/12/16]
390. Hamidou B, Couratier P, Besançon C, et al. Epidemiological evidence that physical activity is not a risk factor for ALS. *European Journal of Epidemiology* 2014;29(7):459-75. doi: 10.1007/s10654-014-9923-2
391. Luna J, Logroscino G, Couratier P, et al. Current issues in ALS epidemiology: Variation of ALS occurrence between populations and physical activity as a risk factor. *Revue Neurologique* 2017;173(5):244-53. doi: https://doi.org/10.1016/j.neurol.2017.03.035
392. Lacorte E, Ferrigno L, Leoncini E, et al. Physical activity, and physical activity related to sports, leisure and occupational activity as risk factors for ALS: A systematic review. *Neurosci Biobehav Rev* 2016;66:61-79. doi: 10.1016/j.neubiorev.2016.04.007 [published Online First: 2016/04/25]
393. Riancho J, Bosque-Varela P, Perez-Pereda S, et al. The increasing importance of environmental conditions in amyotrophic lateral sclerosis. *International Journal of Biometeorology* 2018;62(8):1361-74. doi: 10.1007/s00484-018-1550-2
394. Bandres-Ciga S, Noyce AJ, Hemani G, et al. Shared polygenic risk and causal inferences in amyotrophic lateral sclerosis. *Ann Neurol* 2019;85(4):470-81. doi: 10.1002/ana.25431 [published Online First: 2019/02/07]
395. Horner RD, Feussner JR, Kasarskis EJ. Prospective study of military service and mortality from ALS. *Neurology* 2005;65(1):180-1; author reply 80-1.
396. Drouet A, Desjeux G, Balaire C, et al. [Retrospective study of ALS in French military personnel]. *Rev Neurol (Paris)* 2010;166(6-7):621-9. doi: 10.1016/j.neurol.2010.01.004
397. Seals RM, Kioumourtzoglou MA, Hansen J, et al. Amyotrophic Lateral Sclerosis and the Military: A Population-based Study in the Danish Registries. *Epidemiology* 2016;27(2):188-93. doi: 10.1097/ede.0000000000000417 [published Online First: 2015/11/20]

398. Weisskopf MG, Cudkowicz ME, Johnson N. Military Service and Amyotrophic Lateral Sclerosis in a Population-based Cohort. *Epidemiology* 2015;26(6):831-8. doi: 10.1097/EDE.0000000000000376
399. Haley RW. Excess incidence of ALS in young Gulf War veterans. *Neurology* 2003;61(6):750-6.
400. Horner RD, Kamins KG, Feussner JR, et al. Occurrence of amyotrophic lateral sclerosis among Gulf War veterans. *Neurology* 2003;61(6):742-9. [published Online First: 2003/09/25]
401. Barth SK, Kang HK, Bullman TA, et al. Neurological mortality among U.S. veterans of the Persian Gulf War: 13-year follow-up. *Am J Ind Med* 2009;52(9):663-70. doi: 10.1002/ajim.20718
402. McKay KA, Smith KA, Smertinaite L, et al. Military service and related risk factors for amyotrophic lateral sclerosis. *Acta Neurol Scand* 2021;143(1):39-50. doi: 10.1111/ane.13345 [published Online First: 2020/09/10]
403. Tai H, Cui L, Shen D, et al. Military service and the risk of amyotrophic lateral sclerosis: A meta-analysis. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia* 2017;45:337-42. doi: 10.1016/j.jocn.2017.08.035 [published Online First: 2017/09/03]
404. Academies IoMotN. Amyotrophic Lateral Sclerosis in Veterans: Review of the Scientific Literature. Washington, DC: Institute of Medicine of the National Academies,2006.
405. Schmidt S, Allen KD, Loiacono VT, et al. Genes and Environmental Exposures in Veterans with Amyotrophic Lateral Sclerosis: the GENEVA study. Rationale, study design and demographic characteristics. *Neuroepidemiology* 2008;30(3):191-204. doi: 10.1159/000126911 [published Online First: 2008/04/18]
406. Yi SW, Hong JS, Ohrr H, et al. Agent Orange exposure and disease prevalence in Korean Vietnam veterans: the Korean veterans health study. *Environ Res* 2014;133:56-65. doi: 10.1016/j.envres.2014.04.027 [published Online First: 2014/06/07]
407. Cucovici A, Fontana A, Ivashynka A, et al. The Impact of Lifetime Alcohol and Cigarette Smoking Loads on Amyotrophic Lateral Sclerosis Progression: A Cross-Sectional Study. *Life (Basel)* 2021;11(4) doi: 10.3390/life11040352 [published Online First: 2021/05/01]
408. D'Amico E, Factor-Litvak P, Santella RM, et al. Clinical perspective on oxidative stress in sporadic amyotrophic lateral sclerosis. *Free Radic Biol Med* 2013;65:509-27. doi: 10.1016/j.freeradbiomed.2013.06.029 [published Online First: 2013/06/26]
409. Keon M, Musrie B, Dinger M, et al. Destination Amyotrophic Lateral Sclerosis. *Frontiers in Neurology* 2021;12(392) doi: 10.3389/fneur.2021.596006
410. Kamel F, Umbach DM, Munsat TL, et al. Association of cigarette smoking with amyotrophic lateral sclerosis. *Neuroepidemiology* 1999;18(4):194-202. doi: 10.1159/000026211 [published Online First: 1999/06/12]
411. Nelson LM, McGuire V, Longstreth WT, Jr., et al. Population-based case-control study of amyotrophic lateral sclerosis in western Washington State. I. Cigarette smoking and alcohol consumption. *Am J Epidemiol* 2000;151(2):156-63. doi: 10.1093/oxfordjournals.aje.a010183 [published Online First: 2000/01/25]
412. Peters S, Visser AE, D'Ovidio F, et al. Effect modification of the association between total cigarette smoking and ALS risk by intensity, duration and time-since-quitting: Euro-MOTOR. *J Neurol Neurosurg Psychiatry* 2020;91(1):33-39. doi: 10.1136/jnnp-2019-320986 [published Online First: 2019/08/23]
413. de Jong SW, Huisman MH, Sutedja NA, et al. Smoking, alcohol consumption, and the risk of amyotrophic lateral sclerosis: a population-based study. *Am J Epidemiol* 2012;176(3):233-9. doi: 10.1093/aje/kws015 [published Online First: 2012/07/14]
414. Fang F, Bellocco R, Hernan MA, et al. Smoking, snuff dipping and the risk of amyotrophic lateral sclerosis--a prospective cohort study. *Neuroepidemiology* 2006;27(4):217-21. doi: 10.1159/000096956 [published Online First: 2006/11/16]

415. Opie-Martin S, Jones A, Iacoangeli A, et al. UK case control study of smoking and risk of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener* 2020:1-6. doi: 10.1080/21678421.2019.1706580 [published Online First: 2020/04/18]
416. Opie-Martin S, Wootton RE, Budu-Aggrey A, et al. Relationship between smoking and ALS: Mendelian randomisation interrogation of causality. *Journal of neurology, neurosurgery, and psychiatry* 2020;91(12):1312-15. doi: 10.1136/jnnp-2020-323316
417. Weisskopf MG, McCullough ML, Calle EE, et al. Prospective study of cigarette smoking and amyotrophic lateral sclerosis. *Am J Epidemiol* 2004;160(1):26-33. doi: 10.1093/aje/kwh179
418. Gallo V, Bueno-De-Mesquita HB, Vermeulen R, et al. Smoking and risk for amyotrophic lateral sclerosis: Analysis of the EPIC cohort. *Annals of Neurology* 2009;65(4):378-85. doi: 10.1002/ana.21653
419. Wang H, O'Reilly ÉJ, Weisskopf MG, et al. Smoking and Risk of Amyotrophic Lateral Sclerosis: A Pooled Analysis of 5 Prospective Cohorts. *Archives of neurology* 2011;68(2):207-13. doi: 10.1001/archneurol.2010.367
420. Zhan Y, Fang F. Smoking and amyotrophic lateral sclerosis: A mendelian randomization study. *Ann Neurol* 2019;85(4):482-84. doi: 10.1002/ana.25443 [published Online First: 2019/02/21]
421. Nicolas A, Kenna KP, Renton AE, et al. Genome-wide Analyses Identify KIF5A as a Novel ALS Gene. *Neuron* 2018;97(6):1268-83.e6. doi: 10.1016/j.neuron.2018.02.027 [published Online First: 2018/03/24]
422. Peng B, Yang Q, R BJ, et al. Role of Alcohol Drinking in Alzheimer's Disease, Parkinson's Disease, and Amyotrophic Lateral Sclerosis. *Int J Mol Sci* 2020;21(7) doi: 10.3390/ijms21072316 [published Online First: 2020/04/02]
423. Huisman MH, Seelen M, van Doormaal PT, et al. Effect of Presymptomatic Body Mass Index and Consumption of Fat and Alcohol on Amyotrophic Lateral Sclerosis. *JAMA Neurol* 2015;72(10):1155-62. doi: 10.1001/jamaneurol.2015.1584 [published Online First: 2015/08/19]
424. Ji J, Sundquist J, Sundquist K. Association of alcohol use disorders with amyotrophic lateral sclerosis: a Swedish national cohort study. *European journal of neurology* 2016;23(2):270-5. doi: 10.1111/ene.12667 [published Online First: 2015/02/03]
425. Yu X, Wang T, Chen Y, et al. Alcohol Drinking and Amyotrophic Lateral Sclerosis: An Instrumental Variable Causal Inference. *Ann Neurol* 2020;88(1):195-98. doi: 10.1002/ana.25721 [published Online First: 2020/03/21]
426. Meng E, Yu S, Dou J, et al. Association between alcohol consumption and amyotrophic lateral sclerosis: a meta-analysis of five observational studies. *Neurol Sci* 2016;37(8):1203-8. doi: 10.1007/s10072-016-2575-0 [published Online First: 2016/04/23]
427. Dupuis L, Pradat PF, Ludolph AC, et al. Energy metabolism in amyotrophic lateral sclerosis. *Lancet Neurol* 2011;10(1):75-82. doi: 10.1016/s1474-4422(10)70224-6 [published Online First: 2010/11/03]
428. Ioannides ZA, Ngo ST, Henderson RD, et al. Altered Metabolic Homeostasis in Amyotrophic Lateral Sclerosis: Mechanisms of Energy Imbalance and Contribution to Disease Progression. *Neurodegener Dis* 2016;16(5-6):382-97. doi: 10.1159/000446502 [published Online First: 2016/07/12]
429. Nelson LM, Matkin C, Longstreth WT, Jr., et al. Population-based case-control study of amyotrophic lateral sclerosis in western Washington State. II. Diet. *Am J Epidemiol* 2000;151(2):164-73. doi: 10.1093/oxfordjournals.aje.a010184 [published Online First: 2000/01/25]
430. Peter RS, Rosenbohm A, Dupuis L, et al. Life course body mass index and risk and prognosis of amyotrophic lateral sclerosis: results from the ALS registry Swabia. *Eur J*

Epidemiol 2017;32(10):901-08. doi: 10.1007/s10654-017-0318-z [published Online First: 2017/10/05]
431. Zeng P, Yu X, Xu H. Association Between Premorbid Body Mass Index and Amyotrophic Lateral Sclerosis: Causal Inference Through Genetic Approaches. *Frontiers in Neurology* 2019;10(543) doi: 10.3389/fneur.2019.00543
432. Dardiotis E, Siokas V, Sokratous M, et al. Body mass index and survival from amyotrophic lateral sclerosis: A meta-analysis. *Neurol Clin Pract* 2018;8(5):437-44. doi: 10.1212/cpj.0000000000000521 [published Online First: 2018/12/20]
433. Mariosa D, Beard JD, Umbach DM, et al. Body Mass Index and Amyotrophic Lateral Sclerosis: A Study of US Military Veterans. *American Journal of Epidemiology* 2017;185(5):362-71. doi: 10.1093/aje/kww140
434. Nakken O, Meyer HE, Stigum H, et al. High BMI is associated with low ALS risk. *A population-based study* 2019;93(5):e424-e32. doi: 10.1212/wnl.0000000000007861
435. Sutedja NA, van der Schouw YT, Fischer K, et al. Beneficial vascular risk profile is associated with amyotrophic lateral sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry* 2011;82(6):638-42. doi: 10.1136/jnnp.2010.236752
436. Gallo V, Wark PA, Jenab M, et al. Prediagnostic body fat and risk of death from amyotrophic lateral sclerosis: the EPIC cohort. *Neurology* 2013;80(9):829-38. doi: 10.1212/WNL.0b013e3182840689 [published Online First: 2013/02/08]
437. O'Reilly EJ, Wang H, Weisskopf MG, et al. Premorbid body mass index and risk of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener* 2013;14(3):205-11. doi: 10.3109/21678421.2012.735240 [published Online First: 2012/11/09]
438. O'Reilly É J, Wang M, Adami HO, et al. Prediagnostic body size and risk of amyotrophic lateral sclerosis death in 10 studies. *Amyotroph Lateral Scler Frontotemporal Degener* 2018;19(5-6):396-406. doi: 10.1080/21678421.2018.1452944 [published Online First: 2018/04/17]
439. Sjogren B, Iregren A, Frech W, et al. Effects on the nervous system among welders exposed to aluminium and manganese. *Occup Environ Med* 1996;53(1):32-40. doi: 10.1136/oem.53.1.32
440. Walker KL, Rodrigues MJ, Watson B, et al. Establishment and 12-month progress of the New Zealand Motor Neurone Disease Registry. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia* 2019;60:7-11. doi: 10.1016/j.jocn.2018.11.034 [published Online First: 2018/11/27]
441. National Minimum Dataset (hospital events). Wellington, New Zealand: Ministry of Health, New Zealand; 1999 [updated July 1, 2017. Available from: https://www.health.govt.nz/nz-health-statistics/national-collections-and-surveys/collections/national-minimum-dataset-hospital-events accessed September 18, 2019.
442. Euro-Motor Questionnaire version 1.0. Utrecht, Netherlands: Department of Neurology, University Medical Center Utrecht,2011.
443. New Zealand Standard Classification of Occupations 1999. Wellington, New Zealand: Stats New Zealand; 2001 [updated August 3, 2015. Available from: http://archive.stats.govt.nz/methods/classifications-and-standards/classification-related-stats-standards/download-the-classification-coding-system.aspx#gsc.tab=0 accessed September 18, 2019.
444. Australian and New Zealand Standard Industrial Classification (New Zealand Use Version) 1996. Version 4.1. Wellington, New Zealand: Stats New Zealand; 2002 [updated July 16, 2002. Available from: http://archive.stats.govt.nz/methods/classifications-and-standards/classification-related-stats-standards/industrial-classification-1996.aspx#gsc.tab=0 accessed September 18, 2019.

445. Salmond C, Crampton P, Atkinson J. NZDep2006 Index of Deprivation. University of Otago, Wellington, New Zealand: Department of Public Health, 2007.
446. Corbin M, McLean D, Mannetje A, et al. Lung cancer and occupation: A New Zealand cancer registry-based case-control study. *Am J Ind Med* 2011;54(2):89-101. doi: 10.1002/ajim.20906 [published Online First: 2010/10/20]
447. t Mannetje A, Dryson E, Walls C, et al. High risk occupations for non-Hodgkin's lymphoma in New Zealand: case-control study. *Occup Environ Med* 2008;65(5):354-63. doi: 10.1136/oem.2007.035014 [published Online First: 2007/11/23]
448. McLean D, Mannetje A, Dryson E, et al. Leukaemia and occupation: a New Zealand Cancer Registry-based case-control Study. *International journal of epidemiology* 2009;38(2):594-606. doi: 10.1093/ije/dyn220 [published Online First: 2008/10/28]
449. Statistics New Zealand. ANZLIC Metadata Template Core metadata elements for a geographic dataset. Wellington, New Zealand: Statistics New Zealand; 2013 [
450. Ham DC, Przybeck T, Strickland JR, et al. Occupation and workplace policies predict smoking behaviors: analysis of national data from the current population survey. *J Occup Environ Med* 2011;53(11):1337-45. doi: 10.1097/JOM.0b013e3182337778
451. Fuel quality regulations. NZTA. New Zealand Transport Agency1996 [Available from: https://www.nzta.govt.nz/roads-and-rail/highways-information-portal/technical-disciplines/air-quality-climate/vehicles/fuel-quality-regulations/ accessed May 2016.
452. Dickerson AS, Hansen J, Gredal O, et al. Amyotrophic lateral sclerosis and exposure to diesel exhaust in a Danish cohort. *Am J Epidemiol* 2018 doi: 10.1093/aje/kwy069 [published Online First: 2018/03/29]
453. Dean J. Inquiry into the 2014 General Election - Report of the Justice and Electoral Committee. Wellington, New Zealand: House of Representatives,2016.
454. What is Amyotrophic lateral sclerosis (ALS)? . CDC. National Amyotrophic Lateral Sclerosis (ALS) Registry, Centers for Disease Control and Prevention, US Department of Health & Human Services; 2018 [updated April 6, 2018; cited 2019 December 10]. Available from: https://www.cdc.gov/als/WhatisAmyotrophiclateralsclerosis.html accessed December 10, 2019.
455. Kheifets L, Bowman JD, Checkoway H, et al. Future needs of occupational epidemiology of extremely low frequency electric and magnetic fields: review and recommendations. *Occup Environ Med* 2009;66(2):72-80. doi: 10.1136/oem.2007.037994 [published Online First: 2008/09/23]
456. Farrell DF, Starr A. Delayed neurological sequelae of electrical injuries. *Neurology* 1968;18(6):601-6. doi: 10.1212/wnl.18.6.601 [published Online First: 1968/06/01]
457. Grell K, Meersohn A, Schüz J, et al. Risk of neurological diseases among survivors of electric shocks: A nationwide cohort study, Denmark, 1968–2008. *Bioelectromagnetics* 2012;33(6):459-65. doi: 10.1002/bem.21705
458. Chen GX, t Mannetje AM, Douwes J, et al. Occupation and motor neuron disease: a New Zealand case-control study. *Occup Environ Med* 2019;76(5):309-16. doi: 10.1136/oemed-2018-105605 [published Online First: 2019/03/25]
459. Huss A, Vermeulen R, Bowman JD, et al. Electric shocks at work in Europe: development of a job exposure matrix. *Occupational & Environmental Medicine* 2013;70(4):261-7.
460. Koeman T, Slottje P, Kromhout H, et al. Occupational exposure to extremely low-frequency magnetic fields and cardiovascular disease mortality in a prospective cohort study. *Occup Environ Med* 2013;70(6):402-7. doi: 10.1136/oemed-2012-100889
461. Bowman JD, Touchstone JA, Yost MG. A population-based job exposure matrix for power-frequency magnetic fields. *Journal of occupational and environmental hygiene* 2007;4(9):715-28. doi: 10.1080/15459620701528001 [published Online First: 2007/07/27]

462. Huynh W, Lam A, Vucic S, et al. Corticospinal tract dysfunction and development of amyotrophic lateral sclerosis following electrical injury. *Muscle Nerve* 2010;42(2):288-92. doi: 10.1002/mus.21681 [published Online First: 2010/07/01]
463. Zoccolella S, Masi G, Mezzapesa D, et al. Motoneuron disease after electric injury: a case report. *Neurol Sci* 2008;29(1):47-9. doi: 10.1007/s10072-008-0860-2 [published Online First: 2008/04/02]
464. Vergara XP, Kheifets L, Silva M, et al. New electric-shock job exposure matrix. *Am J Ind Med* 2012;55(3):232-40. doi: 10.1002/ajim.21027 [published Online First: 2011/11/10]
465. Abhinav K, Al-Chalabi A, Hortobagyi T, et al. Electrical injury and amyotrophic lateral sclerosis: a systematic review of the literature. *Journal of Neurology, Neurosurgery, and Psychiatry* 2007;78(5):450-53. doi: 10.1136/jnnp.2006.104414
466. Andrews CJ, Reisner AD. Neurological and neuropsychological consequences of electrical and lightning shock: review and theories of causation. *Neural Regen Res* 2017;12(5):677-86. doi: 10.4103/1673-5374.206636 [published Online First: 2017/06/16]
467. Reisner AD. Possible mechanisms for delayed neurological damage in lightning and electrical injury. *Brain Inj* 2013;27(5):565-9. doi: 10.3109/02699052.2013.766928 [published Online First: 2013/03/12]
468. Reisner AD. Delayed neural damage induced by lightning and electrical injury: neural death, vascular necrosis and demyelination? *Neural Regen Res* 2014;9(9):907-8. doi: 10.4103/1673-5374.133130 [published Online First: 2014/09/11]
469. Tsong TY, Su Z-D. Biological Effects of Electric Shock and Heat Denaturation and Oxidation of Molecules, Membranes, and Cellular Functions. *Annals of the New York Academy of Sciences* 1999;888(1):211-32. doi: 10.1111/j.1749-6632.1999.tb07958.x
470. Armstrong BG. Effect of measurement error on epidemiological studies of environmental and occupational exposures. *Occup Environ Med* 1998;55(10):651-6. doi: 10.1136/oem.55.10.651 [published Online First: 1999/02/04]
471. Turner MC, Benke G, Bowman JD, et al. Occupational Exposure to Extremely Low-Frequency Magnetic Fields and Brain Tumor Risks in the INTEROCC Study. *Cancer Epidemiology Biomarkers & Prevention* 2014;23(9):1863-72. doi: 10.1158/1055-9965.Epi-14-0102
472. Pearce N, Kromhout H. Neurodegenerative disease: the next occupational disease epidemic? *Occup Environ Med* 2014;71(9):594-5. doi: 10.1136/oemed-2013-101943 [published Online First: 2014/07/19]
473. Turner MR, Talbot K. Mimics and chameleons in motor neurone disease. *Practical neurology* 2013;13(3):153-64. doi: 10.1136/practneurol-2013-000557
474. Rojas P, Ramírez AI, Fernández-Albarral JA, et al. Amyotrophic Lateral Sclerosis: A Neurodegenerative Motor Neuron Disease With Ocular Involvement. *Frontiers in Neuroscience* 2020;14(976) doi: 10.3389/fnins.2020.566858
475. Chen GX, 't Mannetje AM, Douwes J, et al. Associations of Occupational Exposures to Electric Shocks and Extremely Low-Frequency Magnetic Fields With Motor Neurone Disease. *Am J Epidemiol* 2021;190(3):393-402. doi: 10.1093/aje/kwaa214 [published Online First: 2020/10/10]
476. Greenland S, Daniel R, Pearce N. Outcome modelling strategies in epidemiology: traditional methods and basic alternatives. *International journal of epidemiology* 2016;45(2):565-75. doi: 10.1093/ije/dyw040 [published Online First: 2016/04/22]
477. Vinceti M, Filippini T, Violi F, et al. Pesticide exposure assessed through agricultural crop proximity and risk of amyotrophic lateral sclerosis. *Environ Health* 2017;16(1):91. doi: 10.1186/s12940-017-0297-2 [published Online First: 2017/08/31]
478. Bermudo Fuenmayor S, Serrano Castro PJ, Quiroga Subirana P, et al. Environmental exposure to pesticides and Amyotrophic Lateral Sclerosis in the South of Spain.

Neurologia (Engl Ed) 2021 doi: 10.1016/j.nrl.2021.01.013 [published Online First: 2021/03/28]
479. Costa LG. Handbook of Clinical Neurology. In: Lotti M, Bleecker ML, eds. Handbook of Clinical Neurology: Elsevier 2015:135-48.
480. van Blitterswijk M, Blokhuis A, van Es MA, et al. Rare and common paraoxonase gene variants in amyotrophic lateral sclerosis patients. *Neurobiology of aging* 2012;33(8):1845.e1-3. doi: 10.1016/j.neurobiolaging.2012.01.007 [published Online First: 2012/02/15]
481. Verde F, Tiloca C, Morelli C, et al. PON1 is a disease modifier gene in amyotrophic lateral sclerosis: association of the Q192R polymorphism with bulbar onset and reduced survival. *Neurological Sciences* 2019;40(7):1469-73. doi: 10.1007/s10072-019-03834-2
482. Ledda C, Cannizzaro E, Cinà D, et al. Oxidative stress and DNA damage in agricultural workers after exposure to pesticides. *Journal of Occupational Medicine and Toxicology* 2021;16(1):1. doi: 10.1186/s12995-020-00290-z
483. Shaw I. Motor neurone disease - a methyl bromide exposure cluster points to a causal mechanism. *Hum Exp Toxicol* 2010;29(3):241-2. doi: 10.1177/0960327109359462
484. Kiddle E. Cluster Investigation into Motor Neurone Disease Nelson. Nelson: Nelson Marlborough District Health Board, New Zealand,2005.
485. Visser AE, D'Ovidio F, Peters S, et al. Multicentre, population-based, case-control study of particulates, combustion products and amyotrophic lateral sclerosis risk. *J Neurol Neurosurg Psychiatry* 2019;90(8):854-60. doi: 10.1136/jnnp-2018-319779 [published Online First: 2019/03/10]
486. Ratner MH, Jabre JF, Ewing WM, et al. Amyotrophic lateral sclerosis-A case report and mechanistic review of the association with toluene and other volatile organic compounds. *Am J Ind Med* 2018;61(3):251-60. doi: 10.1002/ajim.22791 [published Online First: 2017/11/11]
487. Lee D-H, Gold R, Linker RA. Mechanisms of Oxidative Damage in Multiple Sclerosis and Neurodegenerative Diseases: Therapeutic Modulation via Fumaric Acid Esters. *International Journal of Molecular Sciences* 2012;13(9):11783-803.
488. Abarbanel JM, Herishanu YO, Osimani A, et al. Motor neuron disease in textile factory workers. *Acta Neurol Scand* 1989;79(4):347-9. doi: 10.1111/j.1600-0404.1989.tb03796.x [published Online First: 1989/04/01]
489. Singh Z, Chadha P. Textile industry and occupational cancer. *Journal of Occupational Medicine and Toxicology* 2016;11(1):39. doi: 10.1186/s12995-016-0128-3
490. Castanedo-Vazquez D, Bosque-Varela P, Sainz-Pelayo A, et al. Infectious agents and amyotrophic lateral sclerosis: another piece of the puzzle of motor neuron degeneration. *Journal of Neurology* 2019;266(1):27-36. doi: 10.1007/s00415-018-8919-3
491. Oskarsson B, Horton DK, Mitsumoto H. Potential Environmental Factors in Amyotrophic Lateral Sclerosis. *Neurologic clinics* 2015;33(4):877-88. doi: 10.1016/j.ncl.2015.07.009
492. Gotkine M, Friedlander Y, Hochner H. Triathletes are over-represented in a population of patients with ALS. *Amyotroph Lateral Scler Frontotemporal Degener* 2014;15(7-8):534-6. doi: 10.3109/21678421.2014.932383 [published Online First: 2014/07/11]
493. Møller P, Wallin H, Knudsen LE. Oxidative stress associated with exercise, psychological stress and life-style factors. *Chem Biol Interact* 1996;102(1):17-36. doi: 10.1016/0009-2797(96)03729-5 [published Online First: 1996/09/27]
494. Turner MR, Goldacre R, Talbot K, et al. Psychiatric disorders prior to amyotrophic lateral sclerosis. *Ann Neurol* 2016;80(6):935-38. doi: 10.1002/ana.24801
495. Parkin Kullmann JA, Hayes S, Pamphlett R. Is psychological stress a predisposing factor for amyotrophic lateral sclerosis (ALS)? An online international case-control study of premorbid life events, occupational stress, resilience and anxiety. *PLOS ONE* 2018;13(9):e0204424. doi: 10.1371/journal.pone.0204424

496. McKee AC, Gavett BE, Stern RA, et al. TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy. *J Neuropathol Exp Neurol* 2010;69(9):918-29. doi: 10.1097/NEN.0b013e3181ee7d85 [published Online First: 2010/08/20]
497. VanItallie TB. Traumatic brain injury (TBI) in collision sports: Possible mechanisms of transformation into chronic traumatic encephalopathy (CTE). *Metabolism* 2019;100s:153943. doi: 10.1016/j.metabol.2019.07.007 [published Online First: 2019/10/16]
498. Pearce N, Gallo V, McElvenny D. Sports-related head trauma and neurodegenerative disease. *The Lancet Neurology* 2014;13(10):969-70. doi: https://doi.org/10.1016/S1474-4422(14)70146-2
499. Song H, Sieurin J, Wirdefeldt K, et al. Association of Stress-Related Disorders With Subsequent Neurodegenerative Diseases. *JAMA Neurol* 2020;77(6):700-09. doi: 10.1001/jamaneurol.2020.0117 [published Online First: 2020/03/10]
500. Artemiadis AK, Anagnostouli MC, Alexopoulos EC. Stress as a risk factor for multiple sclerosis onset or relapse: a systematic review. *Neuroepidemiology* 2011;36(2):109-20. doi: 10.1159/000323953 [published Online First: 2011/02/22]
501. Black CN, Bot M, Révész D, et al. The association between three major physiological stress systems and oxidative DNA and lipid damage. *Psychoneuroendocrinology* 2017;80:56-66. doi: 10.1016/j.psyneuen.2017.03.003 [published Online First: 2017/03/21]
502. Shaw CE, al-Chalabi A, Leigh N. Progress in the pathogenesis of amyotrophic lateral sclerosis. *Curr Neurol Neurosci Rep* 2001;1(1):69-76. doi: 10.1007/s11910-001-0078-7 [published Online First: 2002/03/20]
503. Abreu-Villaça Y, Levin ED. Developmental neurotoxicity of succeeding generations of insecticides. *Environment international* 2017;99:55-77. doi: 10.1016/j.envint.2016.11.019 [published Online First: 2016/11/28]
504. Sánchez-Santed F, Colomina MT, Herrero Hernández E. Organophosphate pesticide exposure and neurodegeneration. *Cortex; a journal devoted to the study of the nervous system and behavior* 2016;74:417-26. doi: 10.1016/j.cortex.2015.10.003 [published Online First: 2015/12/22]
505. López O, Hernández AF, Rodrigo L, et al. Changes in antioxidant enzymes in humans with long-term exposure to pesticides. *Toxicology Letters* 2007;171(3):146-53. doi: 10.1016/j.toxlet.2007.05.004
506. Authority ERM. Environmental Risk Management Authority Decision Wellington, New Zealand: Environmental Risk Management Authority,2010:Methyl Bromide Reassessment — Summary of Decision
507. Decision: modified reassessment of methyl bromide Wellington, New Zealand: Environmental Protection Authority,2021.
508. Andrew A, Zhou J, Gui J, et al. Pesticides applied to crops and amyotrophic lateral sclerosis risk in the U.S. *NeuroToxicology* 2021;87:128-35. doi: https://doi.org/10.1016/j.neuro.2021.09.004
509. Shih JG, Shahrokhi S, Jeschke MG. Review of Adult Electrical Burn Injury Outcomes Worldwide: An Analysis of Low-Voltage vs High-Voltage Electrical Injury. *J Burn Care Res* 2017;38(1):e293-e98. doi: 10.1097/BCR.0000000000000373
510. Biering K, Kærgaard A, Carstensen O, et al. Incidence and immediate consequences of electrical shocks among Danish electricians: a cohort study. *BMJ open* 2021;11(8):e046584-e84. doi: 10.1136/bmjopen-2020-046584
511. Vergara XP, Fischer HJ, Yost M, et al. Job exposure matrix for electric shock risks with their uncertainties. *International journal of environmental research and public health* 2015;12(4):3889-902. doi: 10.3390/ijerph120403889
512. Thygesen LC, Hvidtfeldt UA, Mikkelsen S, et al. Quantification of the healthy worker effect: a nationwide cohort study among electricians in Denmark. *BMC Public Health* 2011;11(1):571. doi: 10.1186/1471-2458-11-571

513. Choi BC. Definition, sources, magnitude, effect modifiers, and strategies of reduction of the healthy worker effect. *J Occup Med* 1992;34(10):979-88. [published Online First: 1992/10/01]
514. Frei P, Poulsen AH, Mezei G, et al. Residential distance to high-voltage power lines and risk of neurodegenerative diseases: a Danish population-based case-control study. *Am J Epidemiol* 2013;177(9):970-8. doi: 10.1093/aje/kws334 [published Online First: 2013/04/11]
515. Huss A, Spoerri A, Egger M, et al. Residence near power lines and mortality from neurodegenerative diseases: longitudinal study of the Swiss population. *Am J Epidemiol* 2009;169(2):167-75. doi: 10.1093/aje/kwn297 [published Online First: 2008/11/08]
516. Marcilio I, Gouveia N, Pereira Filho ML, et al. Adult mortality from leukemia, brain cancer, amyotrophic lateral sclerosis and magnetic fields from power lines: a case-control study in Brazil. *Rev Bras Epidemiol* 2011;14(4):580-8. doi: 10.1590/s1415-790x2011000400005 [published Online First: 2012/01/06]
517. White RF, Proctor SP. Solvents and neurotoxicity. *Lancet (London, England)* 1997;349(9060):1239-43. doi: 10.1016/S0140-6736(96)07218-2 [published Online First: 1997/04/26]
518. Kukull WA, Larson EB, Bowen JD, et al. Solvent exposure as a risk factor for Alzheimer's disease: a case-control study. *Am J Epidemiol* 1995;141(11):1059-71; discussion 72-9. doi: 10.1093/oxfordjournals.aje.a117370 [published Online First: 1995/06/01]
519. Goldman SM, Quinlan PJ, Ross GW, et al. Solvent exposures and Parkinson disease risk in twins. *Annals of neurology* 2012;71(6):776-84. doi: 10.1002/ana.22629 [published Online First: 2011/11/14]
520. Landtblom AM, Kristoffersson A, Boström I. Organic solvent exposure as a risk factor for multiple sclerosis: An updated review. *Revue Neurologique* 2019;175(10):625-30. doi: https://doi.org/10.1016/j.neurol.2019.07.014
521. Farrugia Wismayer M, Borg R, Farrugia Wismayer A, et al. Occupation and amyotrophic lateral sclerosis risk: a case-control study in the isolated island population of Malta. *Amyotroph Lateral Scler Frontotemporal Degener* 2021;22(7-8):528-34. doi: 10.1080/21678421.2021.1905847 [published Online First: 2021/04/07]
522. Andrew AS, Bradley WG, Peipert D, et al. Risk factors for amyotrophic lateral sclerosis: A regional United States case-control study. *Muscle & Nerve* 2021;63(1):52-59. doi: https://doi.org/10.1002/mus.27085
523. Guidelines for the Management of Lead-based Paint. Wellington: Ministry of Health and Ministry of Business, Innovation and Employment,2013.
524. Pamphlett R, Rikard-Bell A. Different occupations associated with amyotrophic lateral sclerosis: Is diesel exhaust the link? *PLoS ONE* 2013;8(11):e80993. doi: 10.1371/journal.pone.0080993
525. Eng A, 'T Mannetje A, Cheng S, et al. The New Zealand Workforce Survey I: Self-Reported Occupational Exposures. *The Annals of Occupational Hygiene* 2010;54(2):144-53. doi: 10.1093/annhyg/mep097
526. Katz PS, Sulzer JK, Impastato RA, et al. Endocannabinoid degradation inhibition improves neurobehavioral function, blood-brain barrier integrity, and neuroinflammation following mild traumatic brain injury. *J Neurotrauma* 2015;32(5):297-306. doi: 10.1089/neu.2014.3508 [published Online First: 2014/08/29]
527. Mazzeo AT, Beat A, Singh A, et al. The role of mitochondrial transition pore, and its modulation, in traumatic brain injury and delayed neurodegeneration after TBI. *Exp Neurol* 2009;218(2):363-70. doi: 10.1016/j.expneurol.2009.05.026 [published Online First: 2009/06/02]
528. Lenzlinger PM, Hans VH, Jöller-Jemelka HI, et al. Markers for cell-mediated immune response are elevated in cerebrospinal fluid and serum after severe traumatic brain

injury in humans. *J Neurotrauma* 2001;18(5):479-89. doi: 10.1089/089771501300227288 [published Online First: 2001/06/08]
529. Arundine M, Tymianski M. Molecular mechanisms of glutamate-dependent neurodegeneration in ischemia and traumatic brain injury. *Cell Mol Life Sci* 2004;61(6):657-68. doi: 10.1007/s00018-003-3319-x [published Online First: 2004/03/31]
530. Roberts AL, Johnson NJ, Chen JT, et al. Race/ethnicity, socioeconomic status, and ALS mortality in the United States. *Neurology* 2016;87(22):2300-08. doi: 10.1212/WNL.0000000000003298 [published Online First: 2016/10/14]
531. Lovsai G. Adjusted Attributable Fractions. Department of Epidemiology, Columbia University Mailman School of Public Health: Columbia University, 2021.
532. Khosravi A, Nazemipour M, Shinozaki T, et al. Population attributable fraction in textbooks: Time to revise. *Global Epidemiology* 2021;3:100062. doi: https://doi.org/10.1016/j.gloepi.2021.100062
533. Levine B. What does the population attributable fraction mean? *Prev Chronic Dis* 2007;4(1):A14-A14. [published Online First: 2006/12/15]
534. Kim HM, Ko Y-A, Kim JS, et al. Neurological complication after low-voltage electric injury: a case report. *Annals of rehabilitation medicine* 2014;38(2):277-81. doi: 10.5535/arm.2014.38.2.277 [published Online First: 2014/04/29]
535. Bonafede R, Mariotti R. ALS Pathogenesis and Therapeutic Approaches: The Role of Mesenchymal Stem Cells and Extracellular Vesicles. *Frontiers in cellular neuroscience* 2017;11:80-80. doi: 10.3389/fncel.2017.00080
536. Swash M. Chitinases, neuroinflammation and biomarkers in ALS. *J Neurol Neurosurg Psychiatry* 2020;91(4):338. doi: 10.1136/jnnp-2019-322520 [published Online First: 2020/01/16]
537. Al-Chalabi A, Calvo A, Chio A, et al. Analysis of amyotrophic lateral sclerosis as a multistep process: a population-based modelling study. *The Lancet Neurology* 2014;13(11):1108-13. doi: 10.1016/s1474-4422(14)70219-4
538. Vucic S, Westeneng H-J, Al-Chalabi A, et al. Amyotrophic lateral sclerosis as a multi-step process: an Australia population study. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* 2019;20(7-8):532-37. doi: 10.1080/21678421.2018.1556697
539. Chiò A, Mazzini L, D'Alfonso S, et al. The multistep hypothesis of ALS revisited: The role of genetic mutations. *Neurology* 2018;91(7):e635-e42. doi: 10.1212/WNL.0000000000005996 [published Online First: 2018/07/25]
540. ALS is a Multistep Process in South Korean, Japanese, and Australian Patients. *Neurology* 2021;97(3):151-51. doi: 10.1212/wnl.0000000000010323
541. Armitage P, Doll R. The age distribution of cancer and a multi-stage theory of carcinogenesis. *British journal of cancer* 1954;8(1):1-12. doi: 10.1038/bjc.1954.1
542. Stats. New Zealand: An Urban/Rural Profile. Wellington, New Zealand: Statistics New Zealand,2004.
543. Schischlevskij P, Cordts I, Günther R, et al. Informal Caregiving in Amyotrophic Lateral Sclerosis (ALS): A High Caregiver Burden and Drastic Consequences on Caregivers' Lives. *Brain sciences* 2021;11(6):748. doi: 10.3390/brainsci11060748
544. Gibbons CJ, Thornton EW, Young CA. The patient experience of fatigue in motor neurone disease. *Frontiers in psychology* 2013;4:788-88. doi: 10.3389/fpsyg.2013.00788
545. Stats. Business enterprises and employees by detailed industry 2000-2020. Wellington, New Zealand: Stats New Zealand.
546. About the horticulture industry in New Zealand. Wellington, New Zealand: Horticulture New Zealand; [cited 2020 10 October]. Available from: https://www.hortnz.co.nz/about-us/ accessed 10 October 2020.

547. The hierarchy of control. Australia: WorkSafe Victoria; 2021 [updated 12/07/2021. Available from: https://www.worksafe.vic.gov.au/hierarchy-control accessed 18 January 2022 2022.
548. Carson R. Silent Spring. Boston: Boston: Houghton Mifflin; Cambridge: The Riverside Press 1962.
549. Mostafalou S, Abdollahi M. Pesticides: an update of human exposure and toxicity. *Archives of Toxicology* 2017;91(2):549-99. doi: 10.1007/s00204-016-1849-x
550. Zhang Y, Qi S, Xing X, et al. Chapter 21 - Legacies of Organochlorine Pesticides (OCPs) in Soil of China—A Review, and Cases in Southwest and Southeast China. In: De Vivo B, Belkin HE, Lima A, eds. Environmental Geochemistry (Second Edition): Elsevier 2018:543-65.
551. What substances are banned and authorised in the EU market ? London, UK: Pan Europe; [updated 15 October 2021; cited 2021 20 October]. Pan Europe pesticides action network Europe:[Available from: https://www.pan-europe.info/old/Archive/About%20pesticides/Banned%20and%20authorised.htm accessed 20 October 2021.
552. Von Der Leyen U. Commission Implementing Regulation (EU) 2020/1246. Brussels: Official Journal of the European Union.
553. Food and fairness briefing No 1: Food and Which Pesticides are Banned in Europe. 2008: Pesticides action network UK; 2008 [updated 15 Oct 2021; cited 2021 20 October]. Available from: https://www.pan-europe.info/old/Resources/Links/Banned_in_the_EU.pdf accessed 20 October 2021.
554. Vegetables GF. NZ apple orchard uses world's first commercial robot picker. Queensland, Australia: Good Fruit & Vegetables, Australian Community Media, 2019 [updated 27 March. Available from: https://www.goodfruitandvegetables.com.au/story/5978042/nz-orchard-says-domo-arigato-mr-roboto/.
555. Application for the Reassessment of a Group of Hazardous Substances: Decision. Wellington, New Zealand: Environmental Protection Authority,2013.
556. 2017-2019 Plant based foods survey interim report covering 2017-2018. Wellington: Ministry for Primary Industries,2019.
557. Annual report for the year ended 2019. Wellington: Environmental Protection Authority 2019.
558. Castles B. Pesticides in fruit and vege. Consumer. Wellington: Consumer NZ, 2020.
559. Baltazar MT, Dinis-Oliveira RJ, de Lourdes Bastos M, et al. Pesticides exposure as etiological factors of Parkinson's disease and other neurodegenerative diseases—A mechanistic approach. *Toxicology Letters* 2014;230(2):85-103. doi: https://doi.org/10.1016/j.toxlet.2014.01.039
560. Yan D, Zhang Y, Liu L, et al. Pesticide exposure and risk of Alzheimer's disease: a systematic review and meta-analysis. *Scientific Reports* 2016;6(1):32222. doi: 10.1038/srep32222
561. Pearce NE, Sheppard RA, Howard JK, et al. Leukemia among New Zealand agricultural workers. A cancer registry-based study. *Am J Epidemiol* 1986;124(3):402-9. doi: 10.1093/oxfordjournals.aje.a114410 [published Online First: 1986/09/01]
562. Lewis-Mikhael A-M, Bueno-Cavanillas A, Ofir Guiron T, et al. Occupational exposure to pesticides and prostate cancer: a systematic review and meta-analysis. *Occupational and Environmental Medicine* 2016;73(2):134-44. doi: 10.1136/oemed-2014-102692
563. Alavanja MC, Ross MK, Bonner MR. Increased cancer burden among pesticide applicators and others due to pesticide exposure. *CA Cancer J Clin* 2013;63(2):120-42. doi: 10.3322/caac.21170 [published Online First: 2013/01/17]
564. WorkSafe. Electrical and Gas accidents Annual Report 2020. Wellington,2020.

565. Warning over apprentices' tolerance of electric shocks. UK: Safety and Health Practitioner 2013 [updated 2013. Available from: https://www.shponline.co.uk/culture-and-behaviours/warning-over-apprentices-tolerance-of-electric-shocks/.
566. Mannetje A, Coakley J, Douwes J. Where are we at with lead? Current levels, time trend, and determinants of blood lead in New Zealand children and adults. *International journal of hygiene and environmental health* 2020;225:113468. doi: 10.1016/j.ijheh.2020.113468 [published Online First: 2020/02/03]
567. Gulson BL, Mahaffey KR, Mizon KJ, et al. Contribution of tissue lead to blood lead in adult female subjects based on stable lead isotope methods. *J Lab Clin Med* 1995;125(6):703-12. [published Online First: 1995/06/01]
568. Abadin H, Ashizawa A, Stevens YW, et al. Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles. Toxicological Profile for Lead. Atlanta (GA): Agency for Toxic Substances and Disease Registry (US) 2007.
569. Vig EK, Hu H. Lead Toxicity in Older Adults. *Journal of the American Geriatrics Society* 2000;48(11):1501-06. doi: https://doi.org/10.1111/jgs.2000.48.11.1501
570. Akbal A, Tutkun E, Yılmaz H. Lead exposure is a risk for worsening bone mineral density in middle-aged male workers. *Aging Male* 2014;17(3):189-93. doi: 10.3109/13685538.2013.836482 [published Online First: 2013/10/05]
571. Meyers AL, Woodbury MP, Nelson RA. Orthopedic Manifestations of Lead Toxicity. *Orthopedics* 2020;43(4):e202-e07. doi: 10.3928/01477447-20200415-06 [published Online First: 2020/04/24]
572. Potula V, Kaye W. The impact of menopause and lifestyle factors on blood and bone lead levels among female former smelter workers: the Bunker Hill Study. *Am J Ind Med* 2006;49(3):143-52. doi: 10.1002/ajim.20262 [published Online First: 2006/02/14]
573. Lead absorption notifications. Wellington, New Zealand: Environmental Health Indicators New Zealand, Massry University,2019.
574. Traumatic Brain Injury. Foundation N. Auckland, New Zealand: Neurological Foundation; [Available from: https://neurological.org.nz/what-we-do/awareness-and-education/brain-disorders-and-support/traumatic-brain-injury/.
575. ACC. Traumatic brain injury Strategy and Action Plan (2017-2021). Wellington, New Zealand: ACC,2017.
576. Feigin VL, Theadom A, Barker-Collo S, et al. Incidence of traumatic brain injury in New Zealand: a population-based study. *Lancet Neurol* 2013;12(1):53-64. doi: 10.1016/s1474-4422(12)70262-4 [published Online First: 2012/11/28]
577. Brazinova A, Rehorcikova V, Taylor MS, et al. Epidemiology of Traumatic Brain Injury in Europe: A Living Systematic Review. *J Neurotrauma* 2021;38(10):1411-40. doi: 10.1089/neu.2015.4126 [published Online First: 2015/11/06]
578. Tagliaferri F, Compagnone C, Korsic M, et al. A systematic review of brain injury epidemiology in Europe. *Acta Neurochir (Wien)* 2006;148(3):255-68; discussion 68. doi: 10.1007/s00701-005-0651-y [published Online First: 2005/11/29]
579. Leibson CL, Brown AW, Ransom JE, et al. Incidence of traumatic brain injury across the full disease spectrum: a population-based medical record review study. *Epidemiology* 2011;22(6):836-44. doi: 10.1097/EDE.0b013e318231d535 [published Online First: 2011/10/05]
580. Dixon S. The Employment and Income Effects of Eight Chronic and Acute Health Conditions. New Zealand Treasury Working Paper 15/15. Wellington, New Zealand: New Zealand Government,2015.
581. Marshall SW, Loomis DP, Waller AE, et al. Evaluation of protective equipment for prevention of injuries in rugby union. *International journal of epidemiology* 2005;34(1):113-8. doi: 10.1093/ije/dyh346 [published Online First: 2004/11/25]

582. McIntosh AS, McCrory P, Finch CF, et al. Does padded headgear prevent head injury in rugby union football? *Med Sci Sports Exerc* 2009;41(2):306-13. doi: 10.1249/MSS.0b013e3181864bee [published Online First: 2009/01/08]
583. Barnes A, Rumbold JL, Olusoga P. Attitudes towards protective headgear in UK rugby union players. *BMJ Open Sport Exerc Med* 2017;3(1):e000255. doi: 10.1136/bmjsem-2017-000255 [published Online First: 2017/10/31]
584. Canterbury study tackles head collision risks for junior rugby players. University of Canterbury, Christchurch, New Zealand: University of Canterbury Communications Team, 2021 [updated 21/07/2021. Available from: https://www.canterbury.ac.nz/news/2021/canterbury-study-tackles-head-collision-risks-for-junior-rugby-players.html.
585. Price M. Helmets on ski-fields 'difficult to enforce'. *New Zealand Herald* 2012 03/08/2012.
586. Australian Skier Visitation Statistics. Australia: Australian Ski Areas Association,2018.
587. Costa-Scorse B, Hopkins W, Cronin J, et al. New Zealand Snow Sports Injury Trends Over Five Winter Seasons 2010–2014. 2017:17-28. doi: 10.1007/978-3-319-52755-0_2
588. Byrne B. Australia and New Zealand-specific child head injury guidelines created. Victoria, Australia: Murdoch Children's Research Institute (MCRI) 2021.
589. Eapen N, Davis GA, Borland ML, et al. Clinically important sport-related traumatic brain injuries in children. *Medical Journal of Australia* 2019;211(8):365-66. doi: https://doi.org/10.5694/mja2.50311
590. McMahon P, Hricik A, Yue JK, et al. Symptomatology and functional outcome in mild traumatic brain injury: results from the prospective TRACK-TBI study. *J Neurotrauma* 2014;31(1):26-33. doi: 10.1089/neu.2013.2984 [published Online First: 2013/08/21]
591. Active NZ: The New Zealand Participation Survey 2018. Wellington, New Zealand: Sport New Zealand,2018.
592. English football introduces new guidance for heading ahead of 2021-2022 season. London, United Kingdom: English Football Association, 2021 [updated 28/07/2021. Available from: https://www.thefa.com/news/2021/jul/28/20210728-new-heading-guidance-published.
593. Assoication EF. Heading Guidance: Professional Football Heading in Training Guidance. London, United Kingdom, 2021 [updated July 2021. Available from: https://www.thefa.com/news/2021/jul/28/20210728-new-heading-guidance-published.
594. Heading Guidance: Adult Amateur Heading Guidance. London, United Kingdom: England Football Association, 2021 [updated August 2021. Available from: https://www.thefa.com/news/2021/jul/28/20210728-new-heading-guidance-published.
595. Heading Guidance: Youth heading guidance chart. London, United Kingdom: England Football Association, 2021 [updated 22/06/2021. Available from: https://www.thefa.com/news/2021/jul/28/20210728-new-heading-guidance-published.
596. Fulcher M. Concussion & Heading in Football, What does the Evidence Say? New Zealand Football: Fit 4 Football,2020.
597. Gravel J, D'Angelo A, Carrière B, et al. Interventions provided in the acute phase for mild traumatic brain injury: a systematic review. *Systematic reviews* 2013;2:63. doi: 10.1186/2046-4053-2-63
598. Marras C, Hincapié CA, Kristman VL, et al. Systematic Review of the Risk of Parkinson's Disease After Mild Traumatic Brain Injury: Results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Archives of Physical Medicine and Rehabilitation* 2014;95(3, Supplement):S238-S44. doi: https://doi.org/10.1016/j.apmr.2013.08.298

599. Graham NS, Sharp DJ. Understanding neurodegeneration after traumatic brain injury: from mechanisms to clinical trials in dementia. *Journal of Neurology, Neurosurgery & Psychiatry* 2019;90(11):1221-33. doi: 10.1136/jnnp-2017-317557
600. Durstine JL, Gordon B, Wang Z, et al. Chronic disease and the link to physical activity. *Journal of Sport and Health Science* 2013;2(1):3-11. doi: https://doi.org/10.1016/j.jshs.2012.07.009
601. Woodward LJ, Fergusson DM, Chesney A, et al. Punitive parenting practices of contemporary young parents. *The New Zealand medical journal* 2007;120(1267):U2866. [published Online First: 2007/12/25]
602. MSD. The Social Report 2016. Wellington, New Zealand: Ministry of Social Development,2016.
603. UNICEF. A League Table of Child Maltreatment Deaths in Rich Nations. Innocenti Report Card, Issue No.5. 2003 [updated 18 September. Available from: https://www.unicef-irc.org/files/documents/d-3119-Child-Abuse-Leads-to-3-50.pdf.
604. Crimes (Substituted Section 59) Amendment Act 2007. Public Act 2007 No 18. Public Act 2007 No 18 Wellington, New Zealand: Parliamentary Counsel Office,2007.
605. McCoskerie B. Defying Human Nature: An analysis of New Zealand's 2007 Anti-Smacking Law. Manukau City, New Zealand,2016.
606. McLeod GF, Horwood J, Boden JM, et al. Parental use of physical punishment in a birth cohort. *The New Zealand medical journal* 2021;134(1534):17-30. [published Online First: 2021/05/01]
607. Statistics New Zealand. Integrated Data Infrastructure Wellington, New Zealand: Statistics New Zealand; 2020 [Available from: https://www.stats.govt.nz/integrated-data/integrated-data-infrastructure/.
608. Diekstra FP, Beleza-Meireles A, Leigh NP, et al. Interaction between PON1 and population density in amyotrophic lateral sclerosis. *NeuroReport* 2009;20(2):186-90. doi: 10.1097/WNR.0b013e32831af220
609. Winkler EA, Sengillo JD, Sullivan JS, et al. Blood-spinal cord barrier breakdown and pericyte reductions in amyotrophic lateral sclerosis. *Acta Neuropathol* 2013;125(1):111-20. doi: 10.1007/s00401-012-1039-8 [published Online First: 2012/09/04]
610. MND Research in New Zealand. MNDA. MND Research Network; [4 December 2021]. Available from: https://www.mndresearch.auckland.ac.nz/research/ accessed 2 December 2021.
611. Research Strategy 2019-2021. MNDA. Auckland, New Zealand: The Motor Neurone Disease Association New Zealand; 2019 [cited 2021 23 November]. Available from: https://mnd.org.nz/wp-content/uploads/Research-Strategy-2019-22-FINAL.pdf.

Appendix

Appendix 1: Background information on the study population recruitment and data collection methodology used for the Motor Neurone Disease Study

All results presented in this thesis are based on the first New Zealand population-based MND case-control study. The study methods are described in each of the individual results chapters (Chapters 3, 4, 5, and 6), and published in peer-reviewed journals. This appendix provides additional background information related to the study population recruitment and data collection methodology that was applied for this study. The flow chart illustrates the different steps involved in the case and control recruitment. The study recruitment materials are also included (i.e., study pamphlet, study invitation letter, case interview request form, control interview request form, case consent form, and control consent form).

Case recruitment

MND cases were recruited primarily through the Motor Neurone Disease Association (MNDA) of New Zealand over three years (2013-2016). This was supplemented with searches (2013-2015) of hospital discharges for MND, which, in New Zealand, are recorded in the National Minimum Dataset (NMDS).

Motor Neurone Disease Association (MNDA)

Cases were primarily recruited between 2013 and 2016 through the MNDA of New Zealand, which is a voluntary MND patient support organisation. Three recruitment methods were used.

The first method was to obtain referrals of cases through MNDA field workers. MNDA field workers are a group of nurses who visit the patients several times a year to assist them with the appropriate health care (such as speech therapists, and physiotherapists) as well as to assist patients and their families to obtain government subsidies to modify their bathrooms and facilitate wheelchair access. However, it became apparent early in the recruitment phase that this approach was not effective because field workers were too busy to take on additional tasks. For this reason, this approach was discontinued and only 5% of the cases were recruited through this method. An alternative approach was developed to reduce the field workers' workload associated with the study as much as possible.

For this second method, an MND study pack was developed that included a study pamphlet, a study invitation letter, an interview request form, a consent form (attached at the end of this appendix), and a returning envelope. MNDA field workers included the MND study pack into their new patients' welcome pack, which they provided to the patients on their first visited. This method allowed patients to read through the study information provided and then respond directly to the study researcher if they wished to participate. Some cases signed the consent form and participated directly. Other cases contacted the researchers via email or the study 0800 number to discuss the study and its interview procedures and then decided to participate later. This method proved successful and about 65% of the cases were recruited using this approach.

A third method consisted of raising awareness of the study among MND patients and their family members through the MNDA's regular newsletters, annual meetings, and various fundraising activities such as auctions, movie nights, round-the-bay runs,

walking 2'D feet MND and a fund-raising activity at the Wellington train station. This method encouraged MND patients who had not participated before to take part in the study. Approximately 15% of cases were recruited through this method.

Each case completed a consent form (attached at the end of this appendix) before participating in the study. When the signed consent form from a case was received, the field worker was contacted to make sure that the case was able to cope with the study procedures. After confirming this with the field worker, this information was then passed to the interview nurses to arrange a face-to-face interview or telephone interview depending on the case's preference. A pre-questionnaire on lifetime work history was then sent to all participating cases before the interview, and a full questionnaire was sent to those participating cases who preferred self-complete the questionnaire.

Collectively, these methods proved successful primarily due to the ongoing support from the MNDA and their field workers. A total of 295 cases (225 incident cases and 49 prevalent cases) on the MNDA records over a period of three years (2013-2016) were identified and invited to participate.

The National Minimum Dataset (NMDS)

Patient affiliation with the MNDA is voluntary, and although this study has received excellent cooperation and support from the MNDA, the voluntary nature of the MNDA has meant that not all MND cases were registered with the MNDA. In order to capture all of the diagnosed MND cases in New Zealand, this study also obtained approval to recruit MND cases indirectly through hospital discharge data from the National Minimum Dataset (NMDS).[441]

All individuals with a hospital discharge with a primary or secondary diagnosis of MND (ICD10 code G122) over the period of 2013-2015 were identified from the NMDS including their National Health Index (NHI) number. The identified MND cases' NHI numbers were then linked with the NHI dataset to obtain information on their full name, date of birth, date of death (if applicable), residential address, and contact phone number.

Deceased cases were excluded from the study. All other MND cases identified from the hospitalisation records (NMDS) were compared to the list of cases identified through the MNDA. There was approximately 70% overlap between the MNDA records and NMDS hospitalisation data. The MND cases who appeared in the NMDS and not on the MNDA records were then invited to participate in the study. A total of 103 surviving prevalent cases in the NMDS, but not registered with the MNDA, were identified this way; of these, two cases were misclassified, and excluded from the study, which left 101 prevalent cases invited to participate. Approximately 15% of participating cases were recruited through hospitalisation data.

Diagnosis verification

The inclusion criterion for cases was a diagnosis with MND confirmed by a neurologist, with all forms of MND being included in the study. For each participating case, details of diagnosis and participants' neurologist contact details were provided in the consent form. When the signed consent form from a case was received, the first step was to contact the case to obtain a copy of the diagnosis letter if available. If not, the case's neurologist or general practitioner was contacted to confirm the diagnosis. For two cases who completed a consent form, the MND diagnosis could not be confirmed and

were excluded from the study. MND subtype-specific diagnoses were not recorded in New Zealand at the time of study recruitment and the diagnosis letters from the neurologists therefore typically did not include a subtype-specific diagnosis. While the MND subtypes were listed as a tick box in the case consent form (consent form included at the end of this appendix), this could not be completed for the majority of cases. As a result, analyses by MND subtype could not be performed.

Case response rate

A total of 396 cases (295 from MNDA and 101 from NMDS) were invited to participate. Of these, 390 responded (6 cases identified from hospital records (NMDS) did not reply after 3 invitation letters and had no contact phone number available), of which 44 were not eligible (27 deceased (all from NMDS), 16 in intensive care (10 from MNDA and 6 from NMDS), and 1 case from MNDA was diagnosed with MND-Frontotemporal Dementia). Of the 346 (89%) remaining cases, 25 (6%) declined to participate (10 from MNDA and 15 from NMDS), leaving a total of 321 cases (274 from MNDA and 47 from NMDS) in the study, equating to a 92% response rate. Among these 321 participated cases, 225 were incident cases (from MNDA) and 96 were prevalent cases (49 from MNDA and 47 from NMDS). Most cases identified through the MNDA were incident cases; cases on the MNDA records and diagnosed prior to 2013 were also invited to participate in the study and defined as prevalent cases. All cases recruited from the NMDS were defined as prevalent cases, as hospitalisation data were typically available in the NMDS with a 10–12-month lag. However, for all cases, the time between diagnosis and interview was typically short, between 6-18 months, with a median time of 238 days.

Control recruitment

Controls were randomly selected from the New Zealand Electoral Roll (2008). The Electoral Roll includes information on age, occupation, ethnicity, and residential address, and is approximately 95% complete. The Electoral Roll includes virtually all New Zealand citizens and permanent residents in the age range of relevance to this study (i.e., > 50 years); it is therefore the best sample frame available for the research described in this thesis. Controls were frequency matched to cases by age and gender (5-year age categories, based on the age distribution of the United Kingdom MND incidence distribution[81] as equivalent New Zealand data was not available at the time of participant recruitment). For study power purposes, it was aimed to achieve a case-to-control ratio of 1:2.

Potential controls were sent an invitation letter (attached at the end of this appendix) detailing the objectives of the study and information about the interview. Non-responders were contacted by phone (where a phone number was available) or mailed with up to three reminders.

Invitation letters were sent to 2,400 potential controls. Of these, 333 (14%) could not be contacted as no reply after three invitation letters was received and no contact phone number was available, 230 (10%) were returned to sender as they were no longer living at the address recorded on the Electoral Roll, and 587 (24%) were either deceased or diagnosed with a neurodegenerative disease. Of the remaining 1,250 potential controls, 645 declined and 605 took part in the study, equating to a 48% response rate.

All controls completed a consent form (attached at the end of this appendix) before participating in the study. Controls who reported (on the control interview request form which is included at the end of this appendix) to have any other neurodegenerative disease such as Parkinson's Disease or Alzheimer's disease were excluded from the study, as these diseases can affect memory and cognition and may also be related to occupational and non-occupational risk factors assessed in the research described in this thesis.

Data collection

Identical data collection methods were used for cases and controls. These included, depending on participants' preference, a face-to-face interview (59% of cases and 16% of controls opted for this option), a telephone interview by research nurses (23% of cases and 66% of controls), or a postal questionnaire (18% in cases and 18% in controls).

A pre-questionnaire on lifetime work history was provided to participants two to four weeks prior to the interview by post or email, which allowed participants to think through their lifetime work history and obtain as much information as possible before the interview. All controls completed the questionnaire themselves. Nine cases used a proxy (usually a partner or other family member) to complete their consent forms, three used proxy assistance for the face-to-face interview, and six used proxy assistance for reading and writing only.

Interviews

The interviews were carried out during the period 2013-2017. In recognition of the physical and emotional distress of the cases due to their MND diagnosis, we were guided by the MNDA field workers on the cases' ability to communicate and cooperate with the study procedures without adding further stress. As a result, the state of physical ability and emotional state of the participated cases were discussed with MNDA field workers for cases recruited through MNDA. For cases recruited through the NMDS, we discussed this issue with their family members. The information on the state of the physical and emotional ability of each case was obtained before the interviews, and the interview nurses were aware of these before the interviews.

Six interview nurses worked on the study. The interview nurses had previously been involved in earlier studies for many years in our research centre. They were trained and experienced in obtaining information in a consistent and objective manner for both cases and controls.

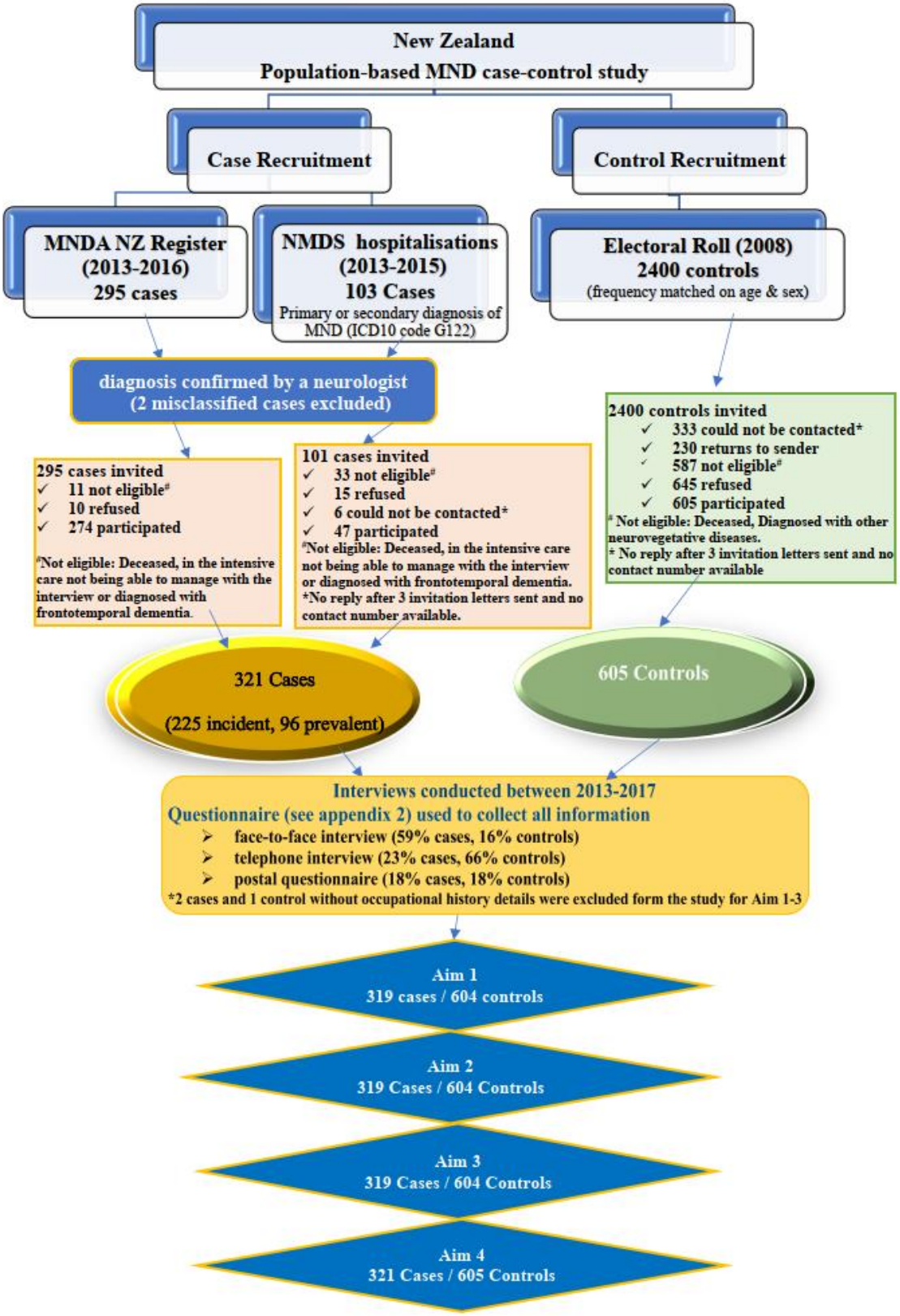
Several briefings with the interview nurses took place prior to the interviews. During these briefings, all interview nurses read the questionnaire and were familiar with and understood each question. For questions on traumatic life events, which were the most sensitive questions, each interview nurse was fully aware of the sensitivity of these questions before the interview. Their approach was both empathetic and understanding, in particular concerning the sensitive parts of the questionnaire. At the end of each interview, the interview nurse would normally make an offer to the study participants to see if they would like to discuss any issues related to the study or questionnaire.

The interview would on average take one and a half hours. In situations where a case could not complete the interview during the visit, the interview nurses were able to return for a second or third visit, and 51 cases (16%) requested a second visit, and 13 cases (4%) needed a third visit. After each interview, an in-depth discussion with the interview nurse took place to allow them to raise any issues or concerns that arose during the interview.

Questionnaire

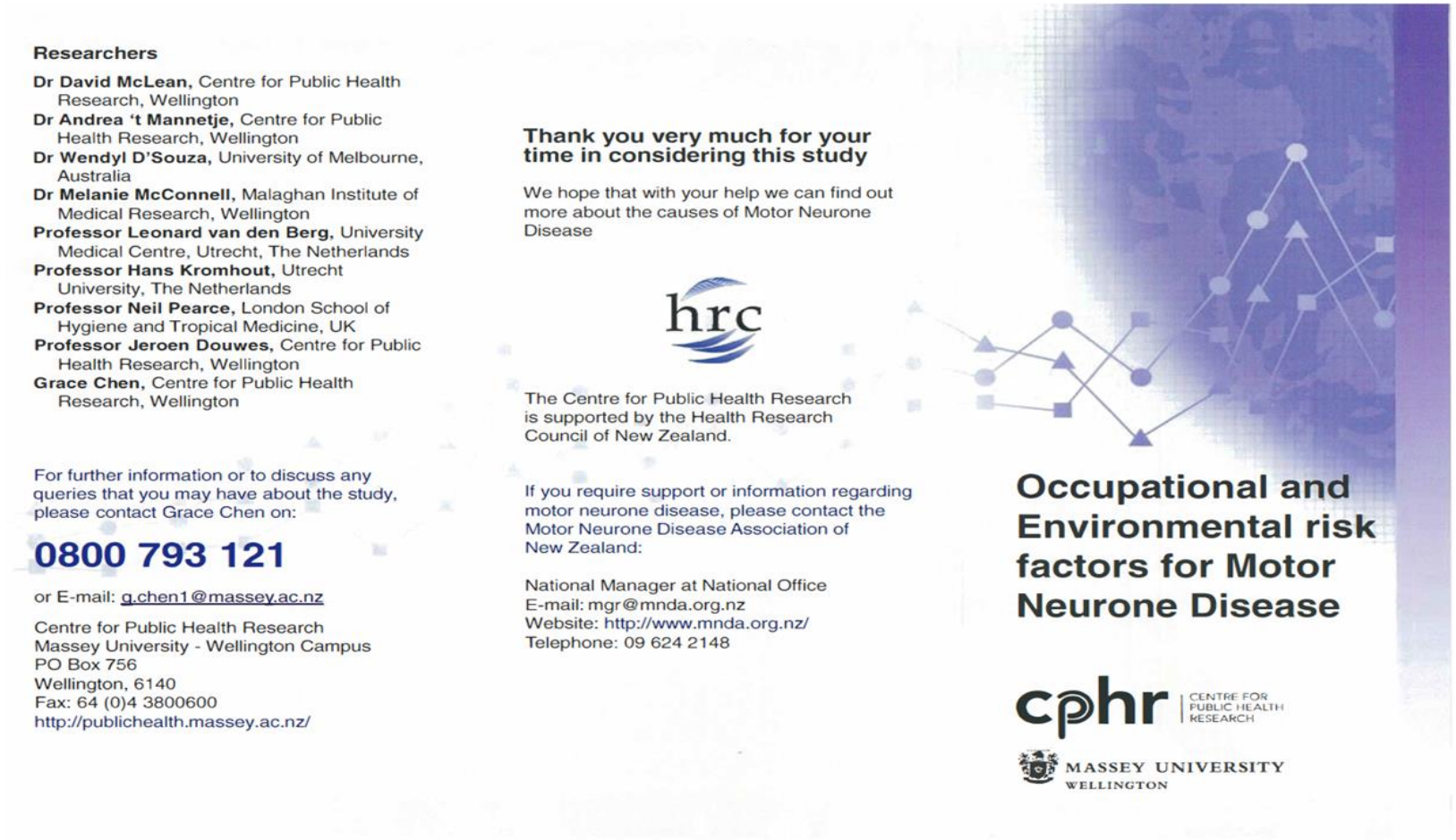
The study questionnaire was based on a European questionnaire[442] with modifications to adapt it to the New Zealand situation, in particular questions for detailed specific occupational exposures were added to the questionnaire. The questionnaire collected comprehensive information on demographic and personal data, family history, residential history, lifestyle factors, dietary, smoking and drinking habits, medical history, use of drugs, injury, and a lifetime occupational history with detailed occupational exposures. The questionnaire used in this population-based case-control study is included in appendix 2.

Case-control study recruitment flow chart



The study recruitment materials

MND study pamphlet



Researchers

Dr David McLean, Centre for Public Health Research, Wellington
Dr Andrea 't Mannetje, Centre for Public Health Research, Wellington
Dr Wendyl D'Souza, University of Melbourne, Australia
Dr Melanie McConnell, Malaghan Institute of Medical Research, Wellington
Professor Leonard van den Berg, University Medical Centre, Utrecht, The Netherlands
Professor Hans Kromhout, Utrecht University, The Netherlands
Professor Neil Pearce, London School of Hygiene and Tropical Medicine, UK
Professor Jeroen Douwes, Centre for Public Health Research, Wellington
Grace Chen, Centre for Public Health Research, Wellington

For further information or to discuss any queries that you may have about the study, please contact Grace Chen on:

0800 793 121

or E-mail: g.chen1@massey.ac.nz

Centre for Public Health Research
Massey University - Wellington Campus
PO Box 756
Wellington, 6140
Fax: 64 (0)4 3800600
http://publichealth.massey.ac.nz/

Thank you very much for your time in considering this study

We hope that with your help we can find out more about the causes of Motor Neurone Disease

hrc

The Centre for Public Health Research is supported by the Health Research Council of New Zealand.

If you require support or information regarding motor neurone disease, please contact the Motor Neurone Disease Association of New Zealand:

National Manager at National Office
E-mail: mgr@mnda.org.nz
Website: http://www.mnda.org.nz/
Telephone: 09 624 2148

Occupational and Environmental risk factors for Motor Neurone Disease

cphr | CENTRE FOR PUBLIC HEALTH RESEARCH

MASSEY UNIVERSITY WELLINGTON

What is Motor Neurone Disease?

Motor Neurone Disease (MND) is the name given to a group of diseases in which the nerve cells - neurones - controlling the muscles that enable us to move, speak, breathe and swallow undergo degeneration and die. With no nerves to activate them, muscles gradually weaken and waste away, causing increasing loss of mobility in the limbs, and difficulties with speech, swallowing and breathing. The patterns of weakness vary from person to person.

What is this study about?

Very little is known about the causes of MND. This study aims to investigate the relationship between MND in New Zealand and a range of known or suspected occupational and environmental exposures. To do this we are inviting up to 400 people who have been diagnosed with MND, as well as 800 people randomly chosen from the Electoral Roll, who do not have MND, to take part in this study. This study is looking at ways in which people with MND and people without MND differ.

Why was I chosen to take part?

You may have been chosen to take part in the study because you do not have MND and your name was selected randomly from the Electoral Roll. The general population controls are vital to this research. Their information on occupational and environmental exposures will be compared with that of those with MND.

Any differences in the exposures of the cases and the controls provide important clues as to what could cause MND.

Or you may have been chosen to take part because you have been diagnosed with MND. The Motor Neurone Disease Association supports this research and will send everyone on their Register some information about our study asking them to take part in it.

What do I have to do?

Questionnaire

The study will involve a face to face or telephone interview with a trained interviewer or completion of a questionnaire by you. We will ask questions about your occupation, education and medical history, about lifestyle factors such as smoking and alcohol use, your residential history, your ethnicity, and your hobbies. The questionnaire takes about one and a half hours to complete. If you agree to take part, we will contact you to discuss the different options for completing the questionnaire and to answer any questions that you may have.

Blood Sample

Once you have completed the questionnaire, we will be inviting a small number of study participants to provide a blood sample. We will take three 10 milliliter tube of blood from your arm, and use this to examine the presence of substances which indicate a breakdown of the protective blood brain barrier and inflammation of neural cells. Blood collection may be slightly uncomfortable, and may result in a temporary bruise.

If you wish to participate please read through this information pamphlet, and complete and return the enclosed consent form. Participants with advanced motor disability may nominate a proxy to sign the consent form on their behalf. **If you do not wish to take part in this study please state this on the consent form and return it to us in the enclosed freepost envelope.**

What happens to the information?

All of the information that you give us is confidential. Each questionnaire will be entered into a database using ID numbers. When all the interviews have taken place we will analyse the information and **no individual information or names will be published.**

The questionnaires will only be seen by the researchers, and when the study is finished all of the questionnaires will be securely locked away in filing cabinets, which will be the responsibility of the Director of the Centre for Public Health Research.

It is also possible that we may try to contact you in the future to invite you to take part in a follow-up to this study. You are under no obligation to do so.

This project has received ethical approval from the Multi-region Ethics Committee, Application MEC/12/01/005. If you have any concerns about the conduct of this research, please contact the Committee on 0800 4 ETHICS.

Study invitation letter

MASSEY UNIVERSITY
WELLINGTON

BROHNZ Building Research in Occupational Health in New Zealand

Occupational and Environmental risk factors for Motor Neurone Disease

Dear Sir/Madam

We are inviting you to take part in a study examining the relationship between Motor Neurone Disease (MND) in New Zealand and a range of known or suspected occupational and environmental exposures.

In order for us to learn more about the risk factors for the development of MND, we are inviting people who have been diagnosed with MND, and people randomly chosen from the electoral roll, to take part in the study. This will involve a postal questionnaire, or a face-to-face or telephone interview with a research nurse.

If you wish to take part in this study, please read through the included information pamphlet, and then complete and sign the enclosed Interview Request Form and return the form to us in the pre-paid envelope.

All of the information that you supply is confidential and no individual information or names will be published in any reports resulting from this study. However, we will store the information so that we can look at the data again if any more questions arise in the future about MND. If you would like us to, we will send you a copy of the results when this research project has finished.

- You have the right to:
  - ◆ decline to participate
  - ◆ refuse to answer any particular questions
  - ◆ withdraw from the study at any time

Please contact us at the Centre for Public Health Research if you have any queries about the study. Free phone: 0800 793 121

Thank you very much for your time.

Yours sincerely

Dr David McLean
Centre for Public Health Research

Centre for Public Health Research

Massey University – Wellington Campus
PO Box 756
Wellington, 6140
New Zealand

Administration
+64 (0)4 380 0602

Direct Fax
+64 (0)4 380 0600

Courier Address
Block 3, Level D, Entrance B,
Wallance Street,
Wellington 6021
New Zealand

Internet
www.massey.ac.nz

Free number:
0800 793 121

David McLean

Telephone
+64 (0)4 801-5799

Extension
63372

Email
d.j.mclean@massey.ac.nz

Grace Chen

Telephone
+64 (0)4 801-5799

Extension
63121

Email
g.chen1@massey.ac.nz

Case interview request form

MASSEY UNIVERSITY
WELLINGTON

BROHNZ Building Research in Occupational Health in New Zealand

Occupational and Environmental risk factors for Motor Neurone Disease

Interview Request Form

- I wish / do not wish to participate in the study (please delete one)
- I have read the Information brochure, and I understand that I may ask questions at any time.

I would like to complete a postal questionnaire ☐

OR

I would like to be interviewed face-to-face (at my home, or another location of my choice) ☐

OR

I would like to be interviewed on the telephone ☐

Signed:.....

Name:.....

Date: .....

Telephone number:.....

Address: .....

Email address:.....

Suggested time and date for the interview (if you have chosen to be interviewed):

....

A research nurse will contact you to arrange your interview or you will be sent a questionnaire if this is what you have chosen.

Please contact us at the Centre for Public Health Research to discuss any queries or concerns about the study.

Thank you very much for your time in considering this study.

We hope that with your help we can find out more about the causes of Motor Neurone Disease.

Case consent form

MASSEY UNIVERSITY
WELLINGTON

BROHNZ Building Research in Occupational Health in New Zealand

Occupational and Environmental risk factors for Motor Neurone Disease
Consent Form

Request for interpreter:

English	I wish to have an interpreter	Yes	No
Deaf	I wish to have a NZ sign language interpreter	Yes	No
Māori	E hiahia ana ahau ki tetahi kaiwhaka Māori/kaiwhaka pakeha korero	Ae	Kao
Cook Island Māori	Ka inangaro au i tetai tangata uri reo	Ae	Kare
Fijian	Au gadreva me dua e vakadewa vosa vei au	Io	Sega
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu	E	Nakai
Sāmoan	Ou te mana'o ia i ai se fa'amatala upu	Ioe	Leai
Tokelauan	Ko au e fofou ki he tino ke fakaliliu te gagana Peletania ki na gagana o na motu o te Pahefika	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea	Io	Ikai

Venue of study:

Centre for Public Health Research

Massey University – Wellington Campus
PO Box 756
Wellington, 6140
New Zealand

Administration
+64 (0)4 380 0602

Direct Fax
+64 (0)4 380 0600

Courier Address
Block 3, Level D,
Entrance B,
Wallance Street,
Wellington, 6021
New Zealand

Internet
www.massey.ac.nz

David McLean

Telephone
+64 (0)4 801-5799

Extension
63372

Email
d.j.mclean@massey.ac.nz

Grace Chen

Telephone
+64 (0)4 801-5799

Extension
63121

Email
g.chen1@massey.ac.nz

Principal Investigators:

Dr. David McLean, Senior Research Fellow, Centre for Public Health Research (CPHR), Massey University, Wellington.
Dr. Andrea 't Mannetje, Senior Research Fellow, CPHR, Massey University, Wellington.
Dr. Wendyl D'Souza, Neurologist, St Vincent's Hospital, University of Melbourne, Melbourne, Australia.
Dr Melanie McConnell, Cell Survival Research Group Leader, Malaghan Institute of Medical Research, Victoria University, Wellington.
Professor Leonard van den Berg, Professor of Neurology, University Medical Centre, Utrecht, The Netherlands.
Professor Hans Kromhout, Institute for Risk Assessment Sciences, Utrecht University, The Netherlands.
Professor Neil Pearce, Professor of Epidemiology and Biostatistics, London School of Hygiene and Tropical Medicine, London, UK
Professor Jeroen Douwes, Director, CPHR, Massey University, Wellington.

- I have read and I understand the Information Sheet dated 01 February 2012 for volunteers taking part in the study about the causes of Motor Neurone Disease. I have had the opportunity to discuss this study and I am satisfied with the answers I have been given.
- I have had the opportunity to use whānau support or a friend to help me ask questions and understand the study.
- I understand that taking part in this study is voluntary (my choice), and that I may withdraw from the study at any time and decline to answer any particular questions.
- I agree to provide information to the researchers on the understanding that my participation in this study is confidential, and that no material that could identify me will be used in any reports on this study.
- I agree to participate in this study under the conditions set out in the Information Sheet.
- I understand that the researchers may try to contact me in the future and invite me to take part in a follow-up to this study, and that I am under no obligation to do so.

I _____ (print full name) hereby consent to take part in this study.

Proxy consent: ☐ yes ☐ no

If yes, relationship to case: _____

Date:	
Signature:	
Address:	
Email:	
Phone number:	

I would like to be sent a summary of the study results: ☐ yes ☐ no

Full names of researchers:	
Contact phone number for researchers:	
Project explained by:	
Role in project:	
Signature of researcher:	
Date:	

MASSEY UNIVERSITY
WELLINGTON

BROHNZ Building Research in Occupational Health in New Zealand

Occupational and Environmental risk factors for Motor Neurone Disease

Further Consent/Information Sheet

Subject ID #: **MND** **DH** | | | | |

We would like to ask you some questions about your diagnosis of motor neurone disease and then confirm them with your General Practitioner and/or Specialist.

If you have a copy of the letter that you received explaining the diagnosis to you, and you would be prepared for us to read the letter, it would be very helpful to us.

Details of your diagnosis

I was diagnosed with:

- Spinal amyotrophic lateral sclerosis ☐
- Bulbar amyotrophic lateral sclerosis ☐
- Not sure which type, but amyotrophic lateral sclerosis ☐
- Primary lateral sclerosis ☐
- Progressive bulbar palsy ☐
- Progressive muscular atrophy ☐

On what date was your diagnosis made (please give approximate month and year if you cannot remember the exact date):

_____

I _____ (full name) hereby consent/do not consent (please delete as appropriate) to the research team contacting my General Practitioner and/or Specialist to confirm the details of my diagnosis of motor neurone disease.

Proxy consent: ☐ yes ☐ no

If yes, relationship to case: _____

Date:	
Signature:	

Name and address of General Practitioner:	

Contact phone number for General Practitioner:	

Name and address of Specialist:	

Contact phone number for Specialist:	

Please contact us at the Centre for Public Health Research to discuss any queries or concerns about the study.

Thank you very much for your time in considering this study.

We hope that with your help we can find out more about the causes of Motor Neurone Disease.

Control interview request form

MASSEY UNIVERSITY
WELLINGTON

BROHNZ Building Research in Occupational Health in New Zealand

Occupational and Environmental risk factors for Motor Neurone Disease

Interview Request Form

- I wish / do not wish to participate in the study (please delete one)
- I have read the Information brochure, and I understand that I may ask questions at any time.

I would like to complete a postal questionnaire ☐

OR

I would like to be interviewed face-to-face (at my home, or another location of my choice) ☐

OR

I would like to be interviewed on the telephone ☐

Signed:.....

Name:.....

Date: .....

Telephone number:.....

Address: .....

Email address:.....

Suggested time and date for the interview (if you have chosen to be interviewed):

.....

Have you been diagnosed with: Parkinson's Disease ☐ Alzheimer's disease☐ Dementia ☐

A research nurse will contact you to arrange your interview or you will be sent a questionnaire if this is what you have chosen.

Please contact us at the Centre for Public Health Research to discuss any queries or concerns about the study.

Thank you very much for your time in considering this study.

We hope that with your help we can find out more about the causes of Motor Neurone Disease.

Control consent form

MASSEY UNIVERSITY
WELLINGTON

BROHNZ Building Research in Occupational Health in New Zealand

Occupational and Environmental risk factors for Motor Neurone Disease
Consent Form

Request for interpreter:

English	I wish to have an interpreter	Yes	No
Deaf	I wish to have a NZ sign language interpreter	Yes	No
Māori	E hiahia ana ahau ki tetahi kaiwhaka Māori/kaiwhaka pakeha korero	Ae	Kao
Cook Island Māori	Ka inangaro au i tetai tangata uri reo	Ae	Kare
Fijian	Au gadreva me dua e vakadewa vosa vei au	Io	Sega
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu	E	Nakai
Sāmoan	Ou te mana'o ia i ai se fa'amatala upu	Ioe	Leai
Tokelauan	Ko au e fofou ki he tino ke fakaliliu te gagana Peletania ki na gagana o na motu o te Pahefika	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea	Io	Ikai

Venue of study:

Centre for Public Health Research

Massey University – Wellington Campus
PO Box 756
Wellington, 6140
New Zealand

Administration
+64 (0)4 380 0602

Direct Fax
+64 (0)4 380 0600

Courier Address
Block 3, Level D,
Entrance B,
Wallance Street,
Wellington, 6021
New Zealand

Internet
www.massey.ac.nz

David McLean

Telephone
+64 (0)4 801-5799

Extension
63372

Email
d.j.mclean@massey.ac.nz

Grace Chen

Telephone
+64 (0)4 801-5799

Extension
63121

Email
g.chen1@massey.ac.nz

Principal Investigators:

Dr. David McLean, Senior Research Fellow, Centre for Public Health Research (CPHR), Massey University, Wellington.
Dr. Andrea 't Mannetje, Senior Research Fellow, CPHR, Massey University, Wellington.
Dr. Wendyl D'Souza, Neurologist, St Vincent's Hospital, University of Melbourne, Melbourne, Australia.
Dr Melanie McConnell, Cell Survival Research Group Leader, Malaghan Institute of Medical Research, Victoria University, Wellington.
Professor Leonard van den Berg, Professor of Neurology, University Medical Centre, Utrecht, The Netherlands.
Professor Hans Kromhout, Institute for Risk Assessment Sciences, Utrecht University, The Netherlands.
Professor Neil Pearce, Professor of Epidemiology and Biostatistics, London School of Hygiene and Tropical Medicine, London, UK
Professor Jeroen Douwes, Director, CPHR, Massey University, Wellington.

- I have read and I understand the Information Brochure for volunteers taking part in the study about the causes of Motor Neurone Disease. I have had the opportunity to discuss this study and I am satisfied with the answers I have been given.
- I have had the opportunity to use whānau support or a friend to help me ask questions and understand the study.
- I understand that taking part in this study is voluntary (my choice), and that I may withdraw from the study at any time and decline to answer any particular questions.
- I agree to provide information to the researchers on the understanding that my participation in this study is confidential, and that no material that could identify me will be used in any reports on this study.
- I agree to participate in this study under the conditions set out in the Information Brochure.
- I understand that the researchers may try to contact me in the future and invite me to take part in a follow-up to this study, and that I am under no obligation to do so.

I _____ (print full name) hereby consent to take part in this study.

Proxy consent: ☐ yes ☐ no

If yes, relationship to case: _____

Date:	
Signature:	
Address:	
Email:	
Phone number:	

I would like to be sent a summary of the study results: ☐ yes ☐ no

Appendix 2: Motor Neurone Disease Study Questionnaire

Motor Neurone Disease Study Questionnaire

Subject ID #: **MND** DH ☐☐☐☐ **Today's date** ☐☐ Day ☐☐ Month ☐☐ Year

Part 1: Demographics and Education

Name of Interviewer: ☐

Name of person being interviewed: ☐

Person answering question is a: Patient/control ☐
Proxy of patient/control ☐

Gender: Male ☐ Female ☐

Date of Birth: ☐☐ Day ☐☐ Month ☐☐ Year

To which ethnic group or groups do you belong?

European/ Pakeha ☐ Māori ☐ Pacific Island ☐ Other ☐

Specify: ☐

Highest level of education received:

Primary school	Secondary school (college)	Technical or trade school diploma	Undergraduate university degree	Postgraduate university degree	None
☐	☐	☐	☐	☐	☐

1

Part 2: Biometrics

1. Current weight (kg) (self reported, whole numbers): _____
2. Current height (cm) (self reported, whole numbers): _____
3. Waist circumference (cm) (measured at the level of the navel, whole numbers): _____
4. Apart from when you were young, have you ever been more than 5 kilo's heavier or lighter than your current weight?

   Yes ☐ No ☐

5. What did you approximately weigh at the following ages?

   a. 20 years: _____kg
   b. 30 years: _____kg
   c. 40 years: _____kg
   d. 50 years: _____kg
   e. 60 years: _____kg
   f. 70 years: _____kg

6. BMI (automatically calculated): _____

Part 3: Ancestry

7. What is your country of origin: _____
8. What is your province/region/county of origin: _____
9. What is the country of origin of your biological father: _____
10. What is the country of origin of your biological mother: _____
11. What is the country of origin of your grandfather (paternal): _____
12. What is the country of origin of your grandmother (paternal): _____
13. What is the country of origin of your grandfather (maternal): _____
14. What is the country of origin of your grandmother (maternal): _____

Part 4: Residential history

15. What is your current address: (will be filled in, but not stored, and converted to geocode)

GEOCODE (provided by database): _____

16. Have you always lived here Yes ☐ No ☐

17. If no, from _____ (age) to _____ (age)

Please list ALL previous residential addresses starting with the most recent

	Home address until current	Address (*will be filled in not stored and converted to geocode)*	From (age)	To (age)
A	First			
B	Second			
C	Third			
D	Fourth			
E	Fifth			
F	Sixth			
G	Seventh			

	Home address until current	Address (*will be filled in not stored and converted to geocode)*	From (age)	To (age)
H	Eighth			
I	Ninth			
J	Tenth			
K	Eleventh			
L	Twelfth			
M	Thirteenth			
N	Fourteenth			

Please continue below if necessary.

Part 5: Medical history

18. Have you ever been diagnosed with diabetes? Yes ☐ No ☐ *(If No, go to Question 20)*

19. If yes, in which year was this diagnosis made? _____

20. Do you have raised cholesterol? Yes ☐ No ☐ *(If No, go to Question 26)*

21. If yes, in which year was this first established? _____

22. Are you **currently** using medication(s) for raised cholesterol? Yes ☐ No ☐

23. If yes, what is the name and in which year did you start taking it/them?

_____(name), _____(Year)

_____(name), _____(Year)

_____(name), _____(Year)

24. Have you ever used any other medication for raised cholesterol? Yes ☐ No ☐

25. If yes, what was the name of the drug, and in which year did you start using it?

_____(name), _____(Year started) - _____(Year stopped)

_____(name), _____(Year started) - _____(Year stopped)

_____(name), _____(Year started) - _____(Year stopped)

26. Have you ever had high blood pressure (except during pregnancy)?

Yes ☐ No ☐ *(If No, go to Question 32)*

27. If yes, in which year was this first found: _____

28. If yes, are you **currently** using medication(s) for high blood pressure?

Yes ☐ No ☐

29. If yes, what is the name and in which year did you start and stop taking the medication(s)?

_____(name), _____(Year started) - _____(Year stopped)

_____(name), _____(Year started) - _____(Year stopped)

_____(name), _____(Year started) - _____(Year stopped)

30. Have you ever taken other medications for high blood pressure?

Yes ☐ No ☐

31. If yes, what is the name and in which year did you start and stop taking the medication(s)?

_____(name), _____(Year started) - _____(Year stopped)

_____(name), _____(Year started) - _____(Year stopped)

_____(name), _____(Year started) - _____(Year stopped)

32. Have you ever had heart problems? Yes ☐ No ☐ *(If No, go to Question 37)*

33. Did you visit a GP/doctor or hospital with these heart problems? Yes ☐ No ☐

34. Have you ever had angina pectoris? Yes ☐ No ☐

35. Have you ever had a heart attack? Yes ☐ No ☐

36. If yes, when? _____

37. Have you ever been told that you have narrowing of one or both carotid arteries?

Yes ☐ No ☐

38. Have you ever had a "TIA"? Yes ☐ No ☐

39. Have you ever had a stroke? Yes ☐ No ☐ *(If No, go to Question 41)*

40. If yes, in which year did you have the (first) stroke? _____

41. Have you ever undergone one of the following procedures?

a: Heart bypass: Yes ☐ No ☐

If yes, in which year? _____

b: Bypass operation in the legs: Yes ☐ No ☐

If yes, in which year? _____

c: Balloon catheter dilatation (angioplasty) in the legs: Yes ☐ No ☐

If yes, in which year? _____

d: Balloon catheter dilatation (angioplasty) in the heart: Yes ☐ No ☐

If yes, in which year? _____

42. Have you ever had cancer? Yes ☐ No ☐ *(If No, go to Question 46)*

43. What type of cancer did you have? _____

44. In which year was your cancer diagnosed? _____

45. What kind of treatment did you receive (more than one answer possible)?

- ☐ 1=> Radiation therapy
- ☐ 2=> Surgery
- ☐ 3=> Chemotherapy
- ☐ 4=> Other, namely: _____

46. Did you have all of the childhood vaccinations that were recommended by the vaccination programme of your country of birth?

Yes ☐ No ☐ I don't know ☐

47. Have you ever had inflammatory bowel disease (e.g. Crohn's Disease)

Yes ☐ No ☐ I don't know ☐

48. Have you ever had an X-ray taken of your skull?

Yes ☐ No ☐ I don't know ☐

If yes, how many? _____

If yes, in which year(s)? _____

49. Have you ever had an X-ray taken of your neck?

Yes ☐ No ☐ I don't know ☐

If yes, how many? _____

If yes, in which year(s)? _____

50. Have you ever had an X-ray taken of your teeth?

Yes ☐ No ☐ I don't know ☐

If yes, how many? _____

If yes, in which year(s)? _____

51. Have you ever had a CT scan taken of your brain?

Yes ☐ No ☐ I don't know ☐

If yes, how many? _____

If yes, in which year(s)? _____

52. Have you ever had a CT scan taken of your neck?

Yes ☐ No ☐ I don't know ☐

If yes, how many? _____

If yes, in which year(s)? _____

53. Have you ever had an MRI taken? Yes ☐ No ☐ I don't know ☐

If yes, how many? _____

If yes, in which year(s)? _____

Part 6: Hormones (women only)

Menstruation/pregnancy

54. At what age did you have your first period: _____

55. How regular were your periods when you were about 25 years of age (do not include periods of using the pill, hormone-containing coils, pregnancies and breast-feeding):

☐ 1=>every 24 days or less

☐ 2=>every 25 or 26 days

☐ 3=>every 27, 28 or 29 days

☐ 4=>every 30 or 31 days

☐ 5=>every 32 or more

☐ 6=>irregular

☐ 7=>I no longer know

56. Has there ever been a time when your cycle was irregular?

Yes ☐ No ☐ Can't remember ☐

If yes, when: _____year - _____year

57. Has there ever been a period when you stopped menstruating for more than a year (with the exception of pregnancies)?

Yes ☐ No ☐ Can't remember ☐

58. Have your periods stopped permanently? Yes ☐ No ☐

If yes, at what age: _____

59. How often have you been pregnant? _____

60. How many live births have you had? _____

61. Did you breastfeed your children? Yes ☐ No ☐

If yes, how many children did you breastfeed: _____

62. If you breastfed, per child, for how many months did you breastfeed them:

Child 1: _____

Child 2: _____

Child 3: _____

Child 4: _____

Hormones

63. Are you currently using hormonal contraceptives or have you ever done so?

Yes ☐ No ☐

If you used/are using the pill please answer questions 64-67, if not, please go to question 68:

64. If yes, what form:

☐ 1=>Pill

☐ 2=>Subcutaneous implant

☐ 3=>Injection

☐ 4=>Other _____

65. Have you stopped taking the pill: Yes ☐ No ☐

If yes, at what age: _____

66. How old were you when you started taking the pill: _____

67. How long have you been using the pill?

☐ 1=>never

☐ 2=>less than 1 year

☐ 3=>1-4 years

☐ 4=>5-9 years

☐ 5=>10-14 years

☐ 6=>15-19 years

☐ 7=>20 years or more

What are the name(s) of the pill you used:

68. Are you using or have you ever used hormone replacement therapy (HRT)?

Yes ☐ No ☐

If you used/are using hormone replacement therapy please answer questions 69-72, if not, please go to Part 7:

69. How old were you when you started: _____

70. For how many years did you use hormone replacement therapy: _____

71. What form did you use?

☐ 1=>Pill
☐ 2=>Estrogen plaster
☐ 3=>Subcutaneous implant
☐ 4=>Injection
☐ 5=>Cream

What were the name(s) of these hormones:

72. Have you stopped taking hormone replacement therapy? Yes ☐ No ☐

If yes, at what age: _____

Part 7: Operations (women only)

73. Have you had a hysterectomy? Yes ☐ No ☐ *(If No, go to Question 75)*

74. If yes, at what age? _____

75. Have you had your ovaries removed?

☐ 1=>No
☐ 2=>Yes, one site
☐ 3=>Yes, both sites
☐ 4=>I don't know

If yes, at what age? _____

Part 8: Trauma/Injury

76. Have you ever had an injury that required medical care? Yes ☐ No ☐ *(If No, go to Part 9)*

If yes, please fill in the table below:

	Injury type? 1=>Head injury with concussion 2=>Fracture 3=>Contusion 4=>Sprain 5=>Strain 6=>Other, namely:	At what age did the injury occur?	Circumstances? 1=>Work 2=>Sport 3=>Leisure (other than sport) 4=>Traffic accident 5=> Other, namely:	Did the injury cause disability? 1=>Yes 2=>No	The injury was? 1=>Temporary 2=>Permanent	Where was the injury? 1=>Head 2=>Arms 3=>Chest 4=>Abdomen 5=>Legs 6=>Spine	Severity of the injury? 1=>Mild 2=>Moderate 3=>Severe
A							
B							
C							
D							
E							
F							
G							

Part 9: Life events

The items listed below refer to events that may have taken place at any point in your entire life, including early childhood. **If an event or ongoing situation occurred more than once, please record all pertinent information about additional events on the last page of this questionnaire.** (Please print or write neatly).

The interviewer should determine if the respondent is reporting the same incident in multiple questions, and should record it in the most appropriate category.

77. Have you ever had a life-threatening illness? Yes ☐ No ☐

If yes, at what age? _____

Duration of Illness _____

Describe specific illness _____

78. Were you ever in a life-threatening accident? Yes ☐ No ☐

If yes, at what age? _____

Describe accident_____

Did anyone die? ____ Who? (Relationship to you)_____

What physical injuries did you receive? _____

Were you hospitalized overnight? Yes ☐ No ☐

79. Was physical force or a weapon ever used against you in a robbery or mugging?

Yes ☐ No ☐

If yes, at what age? _____

How many perpetrators?_____

Describe physical force (e.g., restrained, shoved) or weapon used against you.

_____

Did anyone die? Yes ☐ No ☐

Who?_____

What injuries did you receive? _____

Was your life in danger? _____

80. Has an immediate family member, romantic partner, or very close friend died because of accident, homicide, or suicide?

Yes ☐ No ☐

If yes, how old were you? _____

How did this person die? _____

Relationship to person lost _____

In the year before this person died, how often did you see/have contact with him/her?

_____

81. (**For women only**) Have you had a miscarriage? Yes ☐ No ☐

If yes, at what age?_____

82. At any time, has anyone (parent, other family member, romantic partner, stranger or someone else) ever physically forced you to have intercourse, or to have oral or anal sex against your wishes, or when you were helpless, such as being asleep or intoxicated? Yes ☐ No ☐

If yes, at what age? _____

If yes, how many times?

☐ 1
☐ 2-4
☐ 5-10
☐ more than 10

If repeated, over what period?

☐ 6 mo. or less
☐ 7 mos.-2 yrs
☐ more than 2 yrs. but less than 5 yrs. _____
☐ 5 yrs. or more _____

Who did this? (Specify stranger, parent, etc.) _____

Has anyone **else** ever done this to you? Yes ☐ No ☐

83. Other than experiences mentioned in earlier questions, has anyone ever touched private parts of your body, made you touch their body, or tried to make you to have sex against your wishes? Yes ☐ No ☐

If yes, at what age? _____

If yes, how many times?

☐ 1
☐ 2-4
☐ 5-10
☐ more than 10

If repeated, over what period?

☐ 6 mo. or less
☐ 7 mos.-2 yrs
☐ more than 2 yrs. but less than 5 yrs. _____
☐ 5 yrs. or more _____

Who did this? (Specify sibling, date, etc.) _____

Has anyone **else** ever done this to you? Yes ☐ No ☐

84. When you were a child, did a parent, caregiver or other person ever slap you repeatedly, beat you, or otherwise attack or harm you?

Yes ☐ No ☐

If yes, at what age? _____

If yes, how many times?

- ☐ 1
- ☐ 2-4
- ☐ 5-10
- ☐ more than 10

If repeated, over what period?

- ☐ 6 mo. or less
- ☐ 7 mos.-2 yrs
- ☐ more than 2 yrs. but less than 5 yrs. _____
- ☐ 5 yrs. or more _____

Describe force used against you (e.g., fist, belt) _____

Were you ever injured? _____ If yes, describe _____

Who did this? (Relationship to you) _____

Has anyone **else** ever done this to you? Yes ☐ No ☐

85. As an adult, have you ever been kicked, beaten, slapped around or otherwise physically harmed by a romantic partner, date, family member, stranger, or someone else?

Yes ☐ No ☐

If yes, at what age? _____

If yes, how many times?

- ☐ 1
- ☐ 2-4
- ☐ 5-10
- ☐ more than 10

If repeated, over what period?

- ☐ 6 mo. or less
- ☐ 7 mos.-2 yrs
- ☐ more than 2 yrs. but less than 5 yrs. _____
- ☐ 5 yrs. or more _____

Describe force used against you (e.g., fist, belt) _____

Were you ever injured?_____ If yes, describe_____

Who did this? (Relationship to you) _____

If sibling, what age was he/she_____

Has anyone **else** ever done this to you? Yes ☐ No ☐

86. Has a parent, romantic partner, or family member repeatedly ridiculed you, put you down, ignored you, or told you you were no good?

Yes ☐ No ☐

If yes, at what age? _____

If yes, how many times?

- ☐ 1
- ☐ 2-4
- ☐ 5-10
- ☐ more than 10

If repeated, over what period?

- ☐ 6 mo. or less
- ☐ 7 mos.-2 yrs
- ☐ more than 2 yrs. but less than 5 yrs. _____
- ☐ 5 yrs. or more _____

Who did this? (Relationship to you) _____

If sibling, what age was he/she_____

Has anyone **else** ever done this to you? Yes ☐ No ☐

87. Other than the experiences already covered, has anyone ever threatened you with a weapon like a knife or gun?

Yes ☐ No ☐

If yes, at what age? _____

If yes, how many times?

☐ 1
☐ 2-4
☐ 5-10
☐ more than 10

If repeated, over what period?

☐ 6 mo. or less
☐ 7 mos.-2 yrs
☐ more than 2 yrs. but less than 5 yrs. _____
☐ 5 yrs. or more _____

Describe nature of threat _____

Who did this? (Relationship to you) _____

Has anyone **else** ever done this to you? Yes ☐ No ☐

88. Have you ever been present when another person was killed? Seriously injured? Sexually or physically assaulted?

Yes ☐ No ☐

If yes, at what age? _____

Please describe what you witnessed _____

Was your own life in danger? _____

89. Have you ever been in any other situation where you were seriously injured or your life was in danger (e.g., involved in military combat or living in a war zone)?

Yes ☐ No ☐

If yes, at what age? _____

Please describe. _____

_____

90. Have you ever been in any other situation that was extremely frightening or horrifying, or one in which you felt extremely helpless, that you haven't reported?

Yes ☐ No ☐

If yes, at what age? _____

Please describe. _____

_____

Part 10: Food

91. Do you eat cheese (1 portion = 1/8 of a camembert = 30 g)?

- ☐ No
- ☐ Less than 2 portions a week
- ☐ 3 to 6 portions a week
- ☐ 1 portion a day
- ☐ 2 portions a day
- ☐ 3 or more portions a day

92. Do you eat red meat (apart from poultry) or variety meats (liver, kidneys…)?

- ☐ No
- ☐ Less than 3 times a week
- ☐ 3 to 6 times a week
- ☐ 7 or more times a week

93. Do you eat fresh or canned fish (such as canned sardines or tuna)?

- ☐ No
- ☐ Less than once a week
- ☐ Once a week
- ☐ 2 to 3 times a week
- ☐ 4 or more times a week

94. Do you eat food from the delicatessen (including sausages, cassoulet, gherkins) except lean ham?

- ☐ No
- ☐ Less than twice a week
- ☐ 2 to 3 times a week
- ☐ 4 to 6 times a week
- ☐ 7 or more times a week

95. Do you eat commercial (not homemade) pies, pizzas, rolls or sandwiches?

- ☐ No
- ☐ Less than twice a week
- ☐ 2 to 3 times a week
- ☐ 4 or more times a week

96. Do you eat French fries?

☐ No

Frequency: per week (<1= less than once a week, 1=once a week, 2=twice a week, etc)

☐ Homemade French fries cooked with vegetable oil, kind of oil:……..

☐ Homemade French fries cooked with solid fat

☐ Oven cooked frozen French fries

☐ Restaurants or fast food French fries

97. Do you eat cakes and pastries (including croissants, pain au chocolat)?

☐ No

☐ Less than twice a week

☐ 2 to 4 times a week

☐ 5 or more times a week

98. Do you eat fruit or drink fruit juice (1 portion = 1 average fruit = 1 glass of 200 ml fruit juice)?

☐ No

☐ Less than 3 portions a week

☐ 3 to 6 portions a week

☐ 7 to 13 portions a week (at least 1 fruit a day)

☐ 14 or more portions a week (at least 2 fruits a day)

99. At present, do you eat nuts?

☐ No

☐ Yes, daily consumption:……

100. Do you eat cooked vegetables or vegetable soup (1 portion = 1 plate or 1 bowl)?

☐ No

☐ Less than 3 portions a week

☐ 3 to 7 portions a week

☐ 8 or more portions a week

101. Do you eat raw vegetables or salads?

☐ No

☐ Less than 3 portions a week

☐ 3 to 7 portions a week

☐ 8 or more portions a week

102. Do you eat butter and cream (1 portion = 1 individual block of 10 to 15 g)?

- ☐ Never
- ☐ Raw, 1 portion a day
- ☐ Raw, 2 portions a day
- ☐ Raw, 3 portions a day
- ☐ Raw and used for cooking (that is to say more than 3 portions a day)

103. Apart from butter, do you use other kinds of fat (like margarine)?

- ☐ No
- ☐ To spread, to season your cooked dishes?

Yes, kind of fat:.....

1. 1 meal a day (that is 1 individual block)
2. 2 meals a day (that is 2 individual blocks)
3. 3 or more portions a day (more than 3 individual blocks)

For cooking?

- ☐ No
- ☐ Yes, kind of fat:.....

1. 1 meal a day (that is 1 individual block)
2. 2 meals a day (that is 2 individual blocks)

104. Do you eat oil?

For cooking?

- ☐ No
- ☐ Yes, kind of oil:.....

1. 1 meal a day (about 1 tablespoon)
2. 2 meals a day (about 2 tablespoons)

For salad dressing?

- ☐ No
- ☐ Yes, kind of oil:.....

1. Once a day (about 1 tablespoon)
2. Twice a day (about 2 tablespoons)
3. 3 or more times a day (more than 2 tablespoons)

Part 11: Alcohol

105. Do you sometimes drink alcohol or have you ever done so?

Yes ☐ No ☐ *(If No, go to Part 12)*

If yes, year started: _____

106. Have you stopped drinking alcohol? Yes ☐ No ☐

If yes, year stopped: _____

107. If no, has there been a period when you did not drink alcohol? Yes ☐ No ☐

If yes, for how many years: _____

108. Throughout your life to date, **on average** how often have you consumed alcohol?

☐ Never ☐ Less than once a month ☐ 1-2 times a week ☐ 3-5 times a week ☐ Daily

109. How many of the following alcoholic drinks would you have consumed over a normal working week?

☐ Bottles of beer *(number)*
☐ Glasses of wine *(number)*
☐ How many of these would have been red wine *(number)*?
☐ Small glasses of spirits *(number)*

110. How often do you **currently** consume alcohol?

☐ Never ☐ Less than once a month ☐ 1-2 times a week ☐ 3-5 times a week ☐ Daily

Part 12: Smoking

111. Have you ever smoked tobacco (the equivalent of more than 5 packets of cigarettes in your whole life)?

Yes ☐ No ☐ *(If No, go to Question 118)*

112. What did you smoke? _____

113. How old were you when you started smoking?: _____ years old

114. Do you still smoke now?: Yes ☐ *(Go to Question 116)* No ☐

115. How old were you when you stopped smoking? _____ years old

116. How many did/do you smoke per day? _____

117. Beginning with when you started to smoke regularly please indicate any changes in your smoking consumption of at least 5 cigarettes per day. (Finish with either the present age or the age at which cigarettes were given up completely)

	From (age)	To (age)	Number of cigarettes (or pipes, cigars) per day	Favourite brand	Type*
1					
2					
3					
4					
5					
6					
7					
8					

Notes for interviewer:
** Type: 1=filter;2=nonfilter;3=rolled*

When more than one tobacco product is smoked (e.g. cigarettes and cigars) fill in separate smoking periods for each product. The age periods can overlap.
If the smoking period refers to a tobacco product other than cigarettes, make sure that the type of tobacco product (e.g. pipe, cigar, marijuana) is specified in the 'brand' box. For cigarettes, specify the most used brand.

For never smokers only

118. Have you ever lived with a smoker for 1 year or more?

Yes ☐ No ☐ *(Go to Part 13)*

If yes, during what period did you live with a smoker? From year _____ to year _____

Part 13: Physical activities

119. Did you ever play sport when you were young (before your 18th birthday)?

Yes ☐ No ☐

120. Do you/did you play sport as an adult? Yes ☐ No ☐

If yes, what is/was your sport (both when you were younger and older)?

	Sport	Hours per week	START (year)	STOP (year)
A				
B				
C				
D				
E				
F				
G				

121. In addition to the sports that you may have mentioned, do/did you have any hobbies?

Yes ☐ No ☐ *(Go to Question 122)*

	Hobby	Hours per week	START (year)	STOP (year)
A				
B				
C				
D				
E				
F				
G				

122. Have you ever engaged in sport that required great physical effort, for instance running a marathon?

Yes ☐ No ☐ *(Go to Part 14)*

	STRENUOUS PHYSICAL EXERTION	When? (years)
1		
2		
3		
4		

Part 14: Use of drugs/substances

Drugs in sport

123. Have you ever used any of the following drugs, and if so, please indicate the age when you started and stopped taking them?

Oral

Name of the drug:	Used: Yes or No	Age started:	Age stopped:
Creatine			
Anabolic Androgenic Steroids			
Clenbuterol, tibolone, zeranol, zilpaterol			
Amphetamines			
Adrenaline			
Heroin, fentanyl hydromorphone/ Hydromorfine, methadone, morphine, oxycodone, oxymorphone/ oxymorfine, pentazocine, pethidine			

Intramuscular performance enhancing agents

Name of the drug:	Used: Yes or No	Age started:	Age stopped:
Erythropoietin (EPO), dEPO, CERA or hematide			
Chorionic Gonadotrophin (CG)			
Luteinizing Hormone (LH)			
Growth Hormone (GH)			
Insulin-like Growth Factor-1 (IGF-1)			
Mechano Growth Factors (MGFs)			
Platelet-Derived Growth Factor (PDGF)			
Fibroblast Growth Factors (FGFs)			
Vascular-Endothelial Growth Factor (VEGF)			
Hepatocyte Growth Factor (HGF)			

Anti-depressants and anti-psychotics

124. Have you ever been prescribed any of the following drugs and if so, please indicate the age when you started and stopped taking them

Anti-anxiety / Anti-depressants

Name of the drug:	Used: Yes or No	Age started:	Age stopped:
Diazepam (Valium)			
Duloxetine (Cymbalata)			
Venlafaxine (Efexor)			
Escitalopram (Lexapro)			
Sertraline (Lustral)			
Fluoxetine (Prozac)			
Citalopram (Cipramil)			
Sodium Valproate (Epilim)			
Lamotrigine (Lamictal)			
Lofepramine (Gamanil)			
Mirtazepine (Zispin)			
Trazodone			
Paroxetine (Seroxat)			
Lithium (Priadel)			
Dothiepin (Prothiaden)			
Trimipramine (Surmontil)			
Buproprion			
OTHER			

Anti-psychotics

Name of the drug:	Used: Yes or No	Age started:	Age stopped:
Trifluoperazine (Stelazine)			
Arpiprazole (Abilify)			
Chlorpromazine (Largactil)			
Clozapine (Clozaril)			
Flupenthizol (Depixol)			
Sulpiride (Dolmatil)			
Ziprasidone (Geodon)			
Haloperidol (Haldol, Serenase)			
Fluphenazine			
Risperidone			
Quetiapine (Seroquel)			
Olanzepine (Zyprexa)			
Thioridazine (Melleril)			
OTHER			

Part 15: Family history

The following questions are about your father, your mother, your grandfather and grandmother on your father's (F) side, and your grandfather and grandmother on your mother's side (M).

Parents

125. What is your father's date of birth? _____

126. If applicable, how old was he when he died? _____ (age in years)

127. If applicable, what was the cause of death? _____

128. What is your mother's date of birth? _____

129. If applicable, how old was she when she died? _____ (age in years)

130. If applicable, what was the cause of death? _____

Siblings

131. How many brothers do/did you have? _____

132. If you have/had any brothers, what are/were their dates of birth?
If you only know the year, fill in: 01-01-year of birth.
If applicable, please also fill in age at death and cause of death.

Brother	Date of birth (dd-mm-yyyy)	Age at death (in years)	Cause of Death
1			
2			
3			
4			
5			
6			
7			
8			

133. How many sisters do/did you have? _____

134. If you have/had any sisters, what are/were their dates of birth?
If you only know the year, fill in: 01-01-year of birth.
If applicable, please also fill in age at death and cause of death.

Sister	Date of birth	Age at death (in years)	Cause of Death
1			
2			
3			
4			
5			
6			
7			
8			

Twins

135. Do you have a twin brother or sister? Yes ☐ No ☐ ***(Go to Question 140)***

If yes, what type of twin are you?

☐ 1=> Identical

☐ 2=> Non-identical

☐ 3=> Unknown

If unknown:

a: When you were children, did you and your twin brother or sister look identical or was there only the usual family resemblance?

☐ 1=> Identical

☐ 2=> Normal family resemblance

b: When you were children, did your parents/brothers/sisters/teachers have trouble telling you apart?

Yes ☐ No ☐

136. What is the gender of your twin?

☐ 1=> Male

☐ 2=>Female

137. Which disorder(s) has/have been found in your twin brother or sister? (more than one answer possible)

- ☐ 1=> ALS
- ☐ 2=> Polyneuropathy
- ☐ 3=> PLS
- ☐ 4=> PSMA
- ☐ 5=> Parkinson disease
- ☐ 6=> Dementia
- ☐ 7=> Other, namely: _____
- ☐ 8=> None of the above

138. Has your twin brother or sister died? Yes ☐ No ☐

If yes, when did he/she die? _____ (year)

139. If applicable, what was the cause of death? _____

140. **What were the main occupations held by your:**

Mother _____

Father _____

Below are questions about your family history

The diseases that we are interested in are across the top and the family members are along the side.(*Please note, the questions only relate to your direct family and not to relations through marriage (in-laws).)*

- If a relative has (had) ALS, Parkinson's disease or dementia, you can indicate this by colouring the "YES" square black (or ticking it) beside the relevant family member.
- If a **female** relative has had a heart attack or a stroke before her **65**th birthday, you can indicate this by colouring the "YES" square black (or ticking it) beside the relevant family member.
- If a **male** relative has had a heart attack or a stroke before his **55**th birthday, you can indicate this by colouring the "YES" square black (or ticking it) beside the relevant family member.
- If a relative has not had the disease, you can indicate this by colouring the "NO" square black (or ticking it) beside the relevant family member.
- If you are not sure whether a relative has (had) the disease, you can indicate this by colouring the "?" square black (or ticking it) beside the relevant family member.

If you do not have a particular relative (they are listed in case you DO have them), leave the squares empty.

Parents and grandparents

	ALS	PLS	PSMA	Polyneuropathy	Parkinson's disease	Dementia	Stroke, brain infarction, brain haemorrhage	Depression	Alcoholism	Suicide	Heart attack	None of these
Father	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐
Mother	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐
Grand-father (F)	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐
Grand-mother (F)	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐
Grand-father (M)	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐
Grand-mother (M)	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐

ALS: Amyotrophic Lateral Sclerosis (a type of motor neurone disease)
PLS: Primary Lateral Sclerosis (a type of motor neurone disease)
PSMA: progressive spinal muscular atrophy (a type of motor neurone disease)

Brothers

	ALS	PLS	PSMA	Polyneuropathy	Parkinson's disease	Dementia	Stroke, brain infarction, brain haemorrhage	Depression	Alcoholism	Suicide	Heart attack	None of these
Brother 1	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐
Brother 2	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐
Brother 3	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐
Brother 4	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐
Brother 5	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐
Brother 6	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐

ALS: Amyotrophic Lateral Sclerosis (a type of motor neurone disease)
PLS: Primary Lateral Sclerosis (a type of motor neurone disease)
PSMA: progressive spinal muscular atrophy (a type of motor neurone disease)

Sisters

	ALS	PLS	PSMA	Polyneuropathy	Parkinson's disease	Dementia	Stroke, brain infarction, brain haemorrhage	Depression	Alcoholism	Suicide	Heart attack	None of these
Sister 1	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐
Sister 2	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐
Sister 3	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐
Sister 4	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐
Sister 5	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐
Sister 6	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐ No ☐ Yes ☐ ?	☐

ALS: Amyotrophic Lateral Sclerosis (a type of motor neurone disease)
PLS: Primary Lateral Sclerosis (a type of motor neurone disease)
PSMA: progressive spinal muscular atrophy (a type of motor neurone disease)

Part 16: Lifetime Work History

141. Please tell me all the jobs you have held in order from the first job you ever held to the most recent job ever held.

Interviewer:
Please include all jobs that lasted at least 6 months in total. Please start with the first job after leaving school and end with the most recent.
The list should be without gaps, meaning that also e.g. unemployed periods or periods taking care of children should be reported here.
The last year in the work history should be the year of interview. If the person has served in the military, please include which of the armed forces they served with, whether they were ever deployed, and, if so, where.

Job Number	Who was your **employer**? (Name and Location)	Over what **period** did you work for this employer?	What was the **main activity** of the **company** or **organisation** you worked for? *(For example: sheep farming, selling shoes, making clothes)*	What **department** did you work in, and what was your **job title**?
1.	Name …… Location ……	From: …… *(year)* To: …… *(year)* Total time employed: …… *years*		Department: …… Job title: ……
2.	Name …… Location ……	From: …… *(year)* To: …… *(year)* Total time employed: …… *years*		Department: …… Job title: ……
3.	Name …… Location ……	From: …… *(year)* To: …… *(year)* Total time employed: …… *years*		Department: …… Job title: ……
4.	Name …… Location ……	From: …… *(year)* To: …… *(year)* Total time employed: …… *years*		Department: …… Job title: ……

	Who was your **employer**? (Name and Location)	Over what **period** did you work for this employer?	What was the **main activity** of the company or organisation you worked for?	What **department** did you work in, and what was your **job title**?
5.	Name …… Location ……	From: …… *(year)* To: …… *(year)* Total time employed: …… *years*		Department: …… Job title: ……
6.	Name …… Location ……	From: …… *(year)* To: …… *(year)* Total time employed: …… *years*		Department: …… Job title: ……
7.	Name …… Location ……	From: …… *(year)* To: …… *(year)* Total time employed: …… *years*		Department: …… Job title: ……
8.	Name …… Location ……	From: …… *(year)* To: …… *(year)* Total time employed: …… *years*		Department: …… Job title: ……
9.	Name …… Location ……	From: …… *(year)* To: …… *(year)* Total time employed: …… *years*		Department: …… Job title: ……
10.	Name …… Location ……	From: …… *(year)* To: …… *(year)* Total time employed: …… *years*		Department: …… Job title: …… *Interviewer: use add-in if more than 10 jobs*

Work History Questionnaire

Please complete questions 142-152 **for each job** that you held for more than 6 months in total or a seasonal job held for more than one season. (You will need to copy the two pages on which this part of the questionnaire is written for each job that you held for more than 6 months.)

142. Job Number (from lifetime work history): _____

143. Period of Employment:
From (mm yyyy):.....

To (mm yyyy):.....

144. Number of hours worked per week (on average) _____

145. Number of days worked per week (on average): _____

146. What was the main activity of the company or organisation?

.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....

147. What **department** did you work in?

.....

148. What was **your job title?**

.....

149. Please describe your **specific job** in detail

What did you do?

How did you do it?

What **materials** did you use?

What **tools** or **machinery** did you use?

Did you use any **personal protective equipment**?

What type of **process** was it?

.....

.....

.....

.....

.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....

150. Have you ever worked shiftwork?

.....

If yes, what hours

.....

151. In the environment where you worked, were any of the following present?

Note for interviewer: Always go through the whole list and name all the listed examples.

If you tick any one of these boxes, please complete question 152, else go to next section.

Dust: e.g. coal, metal, wood, grain	☐1
Fibres: textile fibres, asbestos or insulation material	☐2
Environmental tobacco smoke: from people smoking in your workplace	☐3
Other **Smoke** or **fume:** e.g. combustion products, engine emission, metal fume	☐4
Gas: e.g. combustion gases, refrigerant	☐5
Fumigants: e.g. methyl bromide, chloropicrin	☐6
Oils and **solvents:** e.g. lubricants, cutting oils, degreasers, thinners	☐7
Acids or **alkalis**	☐8
Fungicides, Insecticides, Herbicides or **Timber Preservatives**	☐9
Other chemical products e.g. dyes, inks, adhesives etc.	☐10
Animals or animal products : e.g. living animals, meat, faeces	☐11

152. If you ticked any of the boxes in Q.151, please write the names of the substances you were exposed to and complete the table below.

Name/s of Substance	Weeks per year exposed	Hours per day exposed	Source of Substance
☐ *(Please specify number)*			
☐			
☐			
☐			

Name/s of Substance Con't	Weeks per year exposed	Hours per day exposed	Source of Substance
☐			
☐			
☐			
☐			
☐			
☐			
☐			
☐			
☐			
☐			

Part 16a: Specialized questionnaire for agriculture

Please only complete these farming questions if you have lived or worked on a farm

153. Please indicate the type of agricultural production on the farm you worked or lived on *(more than 1 answer possible)*. Please also indicate the size:

Crop

- ☐ Plant nursery _____ hectares
- ☐ Flower growing _____ hectares
- ☐ Vegetable growing _____ hectares
- ☐ Grape growing _____ hectares
- ☐ Apple and pear growing _____ hectares
- ☐ Stone fruit growing _____ hectares
- ☐ Kiwi fruit growing _____ hectares
- ☐ Berry fruit growing _____ hectares
- ☐ Other (avocado) _____ hectares
- ☐ Grain growing _____ hectares
- ☐ Other crop: _____ _____ hectares

Livestock

- ☐ Sheep farming _____ animals
- ☐ Beef cattle farming _____ animals
- ☐ Dairy cattle farming _____ animals
- ☐ Poultry farming (eggs) _____ animals
- ☐ Poultry farming (meat) _____ animals
- ☐ Pig farming _____ animals
- ☐ Horse farming _____ animals
- ☐ Deer farming _____ animals
- ☐ Other livestock _____ _____ animals
- ☐ No livestock **GO TO Q 157**

154. If livestock, were you involved in feeding the animals?

- ☐ Yes
- ☐ No
- ☐ Don't remember

If **YES**, how often did you feed the animals?

155. If livestock, were you involved in treating the animals for parasites?

- ☐ Yes
- ☐ No
- ☐ Don't remember

If **YES**, what did you use to treat the animals, and how often did you treat the animals?

Treatment: _____

How often: _____

156. If livestock, were you involved in disinfecting the stables?

- ☐ Yes
- ☐ No
- ☐ No, no stables
- ☐ Don't remember

If **YES**, what did you use to disinfect the stables and how often did you disinfect the stables?

Disinfecting agent: _____

How often: _____

157. If crop, were there any pesticides used on the crop?

- ☐ Yes
- ☐ No
- ☐ Don't know

If **YES**, can you specify the type of pesticide and mode and reason of application of the pesticide?

Type, name: _____

Mode of application: _____

Reason for application: _____

Number of times applied (in this period): _____

Type, name: _____

Mode of application: _____

Reason for application: _____

Number of times applied (in this period): _____

Type, name: _____

Mode of application: _____

Reason for application: _____

Number of times applied (in this period): _____

If **YES**, were you yourself involved in applying these pesticides?

☐ Yes
☐ No
☐ Don't know

If **YES**, did you use any protective equipment or clothes when applying pesticides?

☐ Yes: _____
☐ No
☐ Don't know

If **YES**, did you mix the pesticides yourself?

☐ Yes
☐ No
☐ Don't know

If **YES**, did you clean equipment or the tools used for the pesticide treatments?

☐ Yes
☐ No
☐ Don't know

158. Did you enter the field after the crop was treated?

☐ Yes
☐ No
☐ Don't know

If **YES**, how often and for what reason?

How often: _____

Reason for field entry: _____

If **YES**, did you use any protective equipment or clothes when entering the field?

- ☐ Yes: _____
- ☐ No
- ☐ Don't know

159. On the farm, were there any herbicides used to fight obnoxious weeds such as gorse or blackberry?

- ☐ Yes
- ☐ No
- ☐ Don't know

If **YES**, can you specify the type and mode of application of the herbicide?

Type, name: _____
Mode of application: _____
Number of times applied (in this period): _____

Type, name: _____
Mode of application: _____
Number of times applied (in this period): _____

Type, name: _____
Mode of application: _____
Number of times applied (in this period): _____

If **YES**, were you yourself involved in applying these herbicides?

- ☐ Yes
- ☐ No
- ☐ Don't know

If **YES**, did you use any protective equipment or clothes when applying these herbicides?

- ☐ Yes: _____
- ☐ No
- ☐ Don't know

If **YES**, did you mix the herbicides yourself?

- ☐ Yes
- ☐ No
- ☐ Don't know

If **YES**, did you clean equipment or the tools used for the herbicide treatments?

- ☐ Yes
- ☐ No
- ☐ Don't know

160. Were pesticides stored in your house?

- ☐ Yes
- ☐ No
- ☐ Don't know

161. Did you apply any wood preservatives to fences?

- ☐ Yes
- ☐ No
- ☐ Don't know

162. Did you wash the working clothes of other workers on the farm?

- ☐ Yes
- ☐ No
- ☐ Don't know

Appendix 3: Statements of Contribution Doctorate with Publication/Manuscripts

DRC 16

MASSEY UNIVERSITY
TE KUNENGA KI PŪREHUROA
UNIVERSITY OF NEW ZEALAND

GRADUATE RESEARCH SCHOOL

STATEMENT OF CONTRIBUTION
DOCTORATE WITH PUBLICATIONS/MANUSCRIPTS

We, the candidate and the candidate's Primary Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated below in the *Statement of Originality*.

Name of candidate:	Grace Xia Chen
Name/title of Primary Supervisor:	Prof. Andrea 't Mannetje
In which chapter is the manuscript /published work:	Chapter 3

Please select one of the following three options:

(●) The manuscript/published work is published or in press

- Please provide the full reference of the Research Output:

Chen GX, 't Mannetje AM, Douwes J, van den Berg LH, Pearce N, Kromhout H, D'Souza W, McConnell M, Glass B, Brewer N, McLean DJ. Occupation and motor neuron disease: a New Zealand case-control study. Occup Environ Med 2019;76(5):309-16

( ) The manuscript is currently under review for publication – please indicate:

- The name of the journal:

- The percentage of the manuscript/published work that was contributed by the candidate: 90%

- Describe the contribution that the candidate has made to the manuscript/published work:

Formulated the concept, supervised and contributed to conducting the fieldwork to collect the data, conducted all statistical analyses of the collected data, and prepared the manuscript.

( ) It is intended that the manuscript will be published, but it has not yet been submitted to a journal

Candidate's Signature:	Grace X Chen
Date:	15-Dec-2021
Primary Supervisor's Signature:	Andrea 't Mannetje
Date:	15-Dec-2021

This form should appear at the end of each thesis chapter/section/appendix submitted as a manuscript/ publication or collected as an appendix at the end of the thesis.

GRS Version 5 – 13 December 2019
DRC 19/09/10

MASSEY UNIVERSITY
TE KUNENGA KI PŪREHUROA
UNIVERSITY OF NEW ZEALAND

GRADUATE RESEARCH SCHOOL

STATEMENT OF CONTRIBUTION
DOCTORATE WITH PUBLICATIONS/MANUSCRIPTS

We, the candidate and the candidate's Primary Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated below in the *Statement of Originality*.

Name of candidate:	Grace Xia Chen
Name/title of Primary Supervisor:	Prof. Andrea 't Mannetje
In which chapter is the manuscript /published work:	Chapter 4

Please select one of the following three options:

(●) The manuscript/published work is published or in press

- Please provide the full reference of the Research Output:

Chen GX, 't Mannetje AM, Douwes J, van den Berg LH, Pearce N, Kromhout H, Glass B, Brewer N, McLean DJ. Associations of Occupational Exposures to Electric Shocks and Extremely Low-Frequency Magnetic Fields with Motor Neurone Disease. Am J Epidemiol 2021;190(3):393-402

( ) The manuscript is currently under review for publication – please indicate:

- The name of the journal:

- The percentage of the manuscript/published work that was contributed by the candidate: 90%

- Describe the contribution that the candidate has made to the manuscript/published work:

Formulated the concept, supervised and contributed to conducting the fieldwork to collect the data, conducted all statistical analyses of the collected data, and prepared the manuscript.

( ) It is intended that the manuscript will be published, but it has not yet been submitted to a journal

Candidate's Signature:	Grace X Chen Digitally signed by Grace X Chen DN: cn=Grace X Chen, c=NZ, o=Massey University, ou=Research Centre for Hauora and Health, email=g.chen1@massey.ac.nz Reason: I am the author of this document Date: 2021.12.15 17:23:18 +13'00'
Date:	15-Dec-2021
Primary Supervisor's Signature:	Andrea 't Mannetje Digitally signed by Andrea 't Mannetje DN: cn=Andrea 't Mannetje, c=NZ, o=Massey University, ou=Centre for Public Health Research, email=a.mannetje@massey.ac.nz Date: 2021.12.15 16:32:32 +13'00'
Date:	15-Dec-2021

This form should appear at the end of each thesis chapter/section/appendix submitted as a manuscript/ publication or collected as an appendix at the end of the thesis.

MASSEY UNIVERSITY
TE KUNENGA KI PŪREHUROA
UNIVERSITY OF NEW ZEALAND

GRADUATE RESEARCH SCHOOL

STATEMENT OF CONTRIBUTION
DOCTORATE WITH PUBLICATIONS/MANUSCRIPTS

We, the candidate and the candidate's Primary Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated below in the *Statement of Originality*.

Name of candidate:	Grace Xia Chen
Name/title of Primary Supervisor:	Prof. Andrea 't Mannetje
In which chapter is the manuscript /published work:	Chapter 5

Please select one of the following three options:

(●) The manuscript/published work is published or in press

- Please provide the full reference of the Research Output:

Chen GX, Douwes J, van den Berg LH, Pearce N, Kromhout H, Glass B, McLean DJ, t Mannetje AM. Occupational exposures to pesticides and other chemicals: a New Zealand motor neuron disease case-control study. Occupational and Environmental Medicine 2022:oemed-2021-108056.

( ) The manuscript is currently under review for publication – please indicate:

- The name of the journal:

- The percentage of the manuscript/published work that was contributed by the candidate: 90%

- Describe the contribution that the candidate has made to the manuscript/published work:

Formulated the concept, supervised and contributed to conducting the fieldwork to collect the data, conducted all statistical analyses of the collected data, and prepared the manuscript.

( ) It is intended that the manuscript will be published, but it has not yet been submitted to a journal

Candidate's Signature:	Grace X Chen
Date:	23-Mar-2022
Primary Supervisor's Signature:	Andrea 't Mannetje
Date:	24-Mar-2022

This form should appear at the end of each thesis chapter/section/appendix submitted as a manuscript/ publication or collected as an appendix at the end of the thesis.

MASSEY UNIVERSITY
TE KUNENGA KI PŪREHUROA
UNIVERSITY OF NEW ZEALAND

GRADUATE RESEARCH SCHOOL

STATEMENT OF CONTRIBUTION
DOCTORATE WITH PUBLICATIONS/MANUSCRIPTS

We, the candidate and the candidate's Primary Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated below in the *Statement of Originality*.

Name of candidate:	Grace Xia Chen
Name/title of Primary Supervisor:	Prof. Andrea 't Mannetje
In which chapter is the manuscript /published work:	Chapter 6

Please select one of the following three options:

(●) The manuscript/published work is published or in press

- Please provide the full reference of the Research Output:

Chen GX, Douwes J, van den Berg LH, Glass B, McLean DJ, 't Mannetje AM. Sports and trauma as risk factors for motor neurone disease: New Zealand case-control study. Acta Neurologica Scandinavica 2022;145(6):770-85. doi: 10.1111/ane.13615). [published Online First: 2022/04/01].

( ) The manuscript is currently under review for publication – please indicate:

- The name of the journal:

- The percentage of the manuscript/published work that was contributed by the candidate: 90%

- Describe the contribution that the candidate has made to the manuscript/published work:

Formulated the concept, supervised and contributed to conducting the fieldwork to collect the data, conducted all statistical analyses of the collected data, and prepared the manuscript.

( ) It is intended that the manuscript will be published, but it has not yet been submitted to a journal

Candidate's Signature:	Grace X Chen
Date:	17-Aug-2022
Primary Supervisor's Signature:	Andrea 't Mannetje
Date:	17-Aug-2022

This form should appear at the end of each thesis chapter/section/appendix submitted as a manuscript/ publication or collected as an appendix at the end of the thesis.

Appendix 4: Supplementary materials

Supplementary Table ST1. Risk of Motor Neurone Disease and Smoking Status in a Population-Based Case-Control Study, New Zealand, 2013- 2016

Exposure	All Cases/Controls (321/605) No.	%	OR	95%CI	OR[1]	95%CI	Male Cases/Controls (203/332) No.	%	OR	95%CI	OR[1]	95%CI	Female Cases/Controls (118/273) No.	%	OR	95%CI	OR[1]	95%CI
Smoking Status																		
Never	165/319	(51/53)	1		1		102/155	(50/47)	1		1		63/164	(53/60)	1		1	
Ever	156/286	(49/47)	1.02	0.77, 1.34	1.03	0.77, 1.38	101/177	(50/53)	0.96	0.67, 1.37	1.00	0.68, 1.47	55/109	(47/40)	1.18	0.76, 1.85	1.28	0.79, 2.08
Smoking Status																		
Never	165/319	(51/53)	1		1		102/155	(50/47)	1		1		63/164	(53/60)	1			
Current	20/35	(6/6)	0.87	0.48, 1.57	0.90	0.48, 1.67	16/26	(8/8)	0.80	0.40, 1.58	0.96	0.46, 1.98	4/9	(4/3)	0.98	0.29, 3.35	1.00	0.27, 3.68
Ex-smoker	136/251	(43/41)	1.04	0.78, 1.39	1.05	0.78, 1.42	85/151	(42/45)	0.99	0.68, 1.45	1.01	0.68, 1.51	51/100	(43/37)	1.20	0.76, 1.90	1.30	0.79, 2.14

Abbreviation: CI, confidence interval; OR, odds ratio.

OR adjusted age, sex (for analyses combining males and females)

OR[1]: adjusted age, sex (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), alcohol consumption, head injury, spine injury & emotional trauma.

Supplementary Table ST2: Risk of Motor Neurone Disease and Alcohol Consumption in a Population-Based Case-Control Study, New Zealand, 2013- 2016

Exposure	All Cases/Controls (321/605) No. %		OR	95%CI	OR[1]	95% CI	Male Cases/Controls (203/332) No. %		OR	95%CI	OR[1]	95%CI	Female Cases/Controls (118/273) No. %		OR	95%CI	OR[1]	95%CI
Alcohol consumption frequency																		
Never	19/58	(6/10)	1		1		6/16	(3/5)	1		1		13/42	(11/15)	1		1	
At least once a month	302/547	(94/90)	1.30	0.75, 2.26	1.26	0.70, 2.24	197/316	(97/95)	1.36	0.51, 3.63	1.24	0.45, 3.43	105/231	(89/85)	1.29	0.66, 2.54	1.24	0.58, 2.65
Alcohol consumption frequency (5 categories)																		
Never	19/58	(6/10)	1		1		6/16	(3/5)	1		1		13/42	(11/15)	1		1	
Once a month	56/108	(17/18)	1.33	0.71, 2.48	1.30	0.68, 2.45	26/40	(13/12)	1.37	0.46, 4.05	1.34	0.44, 4.07	30/68	(25/25)	1.33	0.62, 2.85	1.22	0.53, 2.80
1-2 time per week	116/188	(36/31)	1.41	0.79, 2.54	1.36	0.73, 2.50	76/106	(37/32)	1.56	0.57, 4.25	1.42	0.50, 4.05	40/82	(34/30)	1.33	0.63, 2.80	1.27	0.55, 2.92
3-5 times per week	76/129	(24/21)	1.32	0.71, 2.43	1.26	0.66, 2.39	55/84	(27/25)	1.43	0.52, 3.98	1.16	0.40, 3.37	21/45	(18/17)	1.29	0.56, 2.94	1.35	0.54, 3.33
Daily	54/122	(17/20)	1.03	0.55, 1.94	1.00	0.51, 1.94	40/86	(20/26)	1.05	0.38, 2.96	1.02	0.35, 2.99	14/36	(12/13)	1.15	0.47, 2.79	1.11	0.42, 2.98
Alcohol consumption frequency (4 categories)																		
Never/once a month	75/166	(23/28)	1		1		32/56	(16/17)	1		1		43/110	(36/40)	1		1	
1-2 time per week	116/188	(36/31)	1.15	0.80, 1.67	1.12	0.76, 1.65	76/106	(37/32)	1.22	0.71, 2.09	1.13	0.65, 1.99	40/82	(34/30)	1.10	0.65, 1.87	1.10	0.62, 1.96
3-5 times per week	76/129	(24/21)	1.07	0.71, 1.62	1.04	0.68, 1.60	55/84	(27/25)	1.12	0.64, 1.98	0.93	0.51, 1.69	21/45	(18/17)	1.06	0.56, 2.02	1.17	0.59, 2.31
Daily	54/122	(17/20)	0.84	0.54, 1.31	0.82	0.52, 1.30	40/86	(20/26)	0.83	0.46, 1.49	0.81	0.44, 1.50	14/36	(12/13)	0.95	0.46, 1.96	0.97	0.45, 2.09

For cases the alcohol consumption frequency refers to before diagnosis, for controls to the time of interview.
Abbreviation: CI, confidence interval; OR, odds ratio.
OR adjusted age, sex (for analyses combining males and females)
OR[1]: adjusted age, sex (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking status, head injury, spine injury & emotional trauma.

Supplementary Table ST3: The Difference between Participant Controls and Non-Participant Controls in Sex in a Population-Based Case-Control Study, New Zealand, 2013- 2016

	Non-Participants Control		Participant Controls		*P*
	No.	%	No.	%	
Male	1028	57.27	332	54.88	0.3041
Female	767	42.73	273	45.12	

Supplementary Table ST4: The Difference between Participant Controls and Non-Participant Controls in Age Group in a Population-Based Case-Control Study, New Zealand, 2013- 2016

Age Group	Non-Participants Controls (%)	Participants Controls (%)	*P*
20-49	10.37	7.44	0.001
50-59	14.04	16.53	
60+	75.59	76.03	