The Neuropsychological Sequelae of Long-COVID in a New Zealand Sample

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ABSTRACT

There is an increasing concern globally that COVID-19 infections may result in lasting neuropsychological sequelae. This Case-Control study aimed to explore whether the neuropsychological sequelae associated with long-COVID internationally were also evident in Aotearoa New Zealand. The adult sample was recruited through social media, with median age of 41 to 50. While a total of 114 participants were recruited, the study groups consisted of 31 participants with long-COVID (Cases), and 31 demographically matched healthy participants (Controls). The neuropsychological sequelae of long-COVID were divided into three constituent components; symptomology, impacts on quality of life, and changes in cognitive performance. These were all assessed with computerised versions of the following measures. Symptomology was assessed with the De-Paul Symptom Questionnaire-Short Form, and a newly authored long-COVID symptom questionnaire based on the work of Davis et al., (2021). Quality of Life (QoL) was measured with the NeuroQoL Cognition-Short Form and a newly authored long-COVID QoL measure based on the work of Fontera et al., (2021). Cognitive performance was assessed with a Cognitive Battery, comprising of Immediate and Delayed Word Recall, Digit Span, the Stroop task, and the Trail Making A and B tasks. Data was analysed using independent samples *t*-tests. Results showed that Cases had significantly more severe and frequent symptomology, poorer quality of life, and slower reaction times than Controls. Results also showed insignificant differences between Cases and Controls cognitive performance on the Delayed Word Recall, Digit Span and Trail Making tasks. The study's small sample size resulting from case-control matching may have impacted the significance of these findings. However, these findings do establish a precedent for further study on long-COVID's neuropsychological sequelae in Aotearoa New Zealand

and have important clinical implications for the neuropsychological assessment of long-COVID using symptomology questionnaires, QoL and Cognitive Batteries.

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"The worst thing you can do is nothing."

Terry Pratchett

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CHAPTER ONE

Introduction

The COVID-19 pandemic was a significant global event that resulted in widespread change at all levels of society. In the wake of this pandemic follows what has been termed a silent pandemic, where an increasing number of people are found to be experiencing long-term signs and symptoms of COVID-19 to a debilitating extent. This condition is called long-COVID and is known to involve neuropsychological sequelae which have been associated with poor quality of life, and impaired cognitive performance. [1] While there is a growing body of international literature on this topic, there is a substantial gap surrounding the incidence of long-COVID's neuropsychological sequelae in a New Zealand population.

With the present study, I address this gap in the literature, and explore the incidence of long-COVID's neuropsychological sequalae and associated changes to quality of life and cognition, in a New Zealand population. This study is the first known study to address this topic in Aotearoa New Zealand. To establish the context for exploring this topic, in Chapter Two, I locate this study within the pandemic setting and highlight factors which have shaped current understandings of long-COVID and its neuropsychological sequelae. In this chapter I also review the historical and empirical evidence pointing to potential societal and individual factors that might predict the development of long-COVID at its neuropsychological sequelae.

In Chapter Three I undertake an in-depth review of the international literature detailing the complexity of long-COVID's neuropsychological sequelae, and associated

[1] Sequelae is a term used to refer to the chronic complications or long-term effects of an acute or short-term disease (Horberg et al., 2022). Neuropsychology is the study of the relationship between behaviour, emotion, cognition and brain function (American Psychological Association, 2022). Neuropsychological sequelae then refers to the long-term behavioural, emotional, and cognitive impacts relating to altered brain function following an acute illness, which in this case, COVID-19 (Buonsenso et al., 2022; C. Chen et al., 2021).

changes in quality of life and cognition. I also outline a bio-psycho-social model of disease as a potential theoretical framework, which might explain some of the complexity observed in this topic. In Chapter Four, I provide the rationale for this study, and establish the precedent for using online recruitment and data collection methods for long-COVID research, in a New Zealand context. The chapter ends with a set of exploratory research questions which guided this work.

In Chapter Five I report on this study's methodology which includes a discussion of the study's sample, providing rationale for the measures used, and outlining the procedural mechanisms that enabled this study to be delivered online. The results of this study are discussed in Chapter Six, in which I outline data scoring, data collation, testing assumptions of normalcy, and the preliminary analyses used to determine whether parametric or non-parametric statistical analyses would be required. I then unpack the key significant and non-significant results for Research Questions One, Two and Three, and explain why the sample is unable to support analyses required for Research Questions Four and Five.

Finally, in Chapter Seven, I give a summary of the study's key findings, I then unpack in greater detail how significant and non-significant results might be explained by the international literature surrounding long-COVID's neuropsychological sequelae and associated changes on quality of life and cognition. Following this, I discuss some of this study's limitations, and draw attention to certain issues relating to conducting neuropsychological research online that are not mentioned in the international research. I end this chapter by briefly touching on this study's implications for future research and clinical practice.

CHAPTER TWO

Contextualising the Present Study: Long-COVID the Silent Pandemic

The purpose of this chapter is to locate this study within the pandemic and highlight some of the contextual factors that have shaped our current understandings of long-COVID and its neuropsychological sequelae. I begin by outlining some of the issues with recognising and defining long-COVID in the wake of the COVID-19 pandemic. Following this, I explore the evidence from past-pandemics that corroborate the incidence of neuropsychological sequelae following viral infections. After acknowledging those factors impacting the validation of long-COVID and its neuropsychological sequelae, I highlight key societal and individual risk factors that may pre-dispose individuals to the development of long-COVID and its neuropsychological sequelae.

The COVID-19 Pandemic

The first SARS-CoV-2 virus case was detected in Wuhan, Hubei province, China in late December 2019 (World Health Organisation, 2022a, 2022b). By 11 March 2020 the increasing hospitalisation and mortality rates illustrated that the disease was a significant risk to humanity, and the World Health Organisation (WHO) declared a global pandemic (World Health Organisation, 2022a, 2022b). By August 2022, there were 581.8 million confirmed cases, with 6.4 million deaths reported globally (World Health Organisation, 2022b). In response to the harms posed by COVID-19, most countries introduced a range of public health measures to slow transmission rates including the use of face masks and hand sanitiser in public to curb the water-born spread of the virus (Wang et al., 2022; World Health Organisation, 2022a). New Zealand became known globally for its unique COVID-19 response (Ministry of Health, 2022b). Unlike many countries overseas, the Government was quick to impose strict public health measures to slow the rate of infection (Ministry of Health,

2022b). This protected the population whilst vaccines were developed (Russell et al., 2022). Only once the majority of the population were vaccinated, were the public health restrictions eased (Ministry of Health, 2022a; Russell et al., 2022). Post-vaccination, the numbers of infection then began to rise quickly, soon infection rates seen in other countries, though without the rates of death seen elsewhere (Ministry of Health, 2022a; Russell et al., 2022).

Long-COVID

In early 2021, researchers began publishing studies on long-COVID or the post-acute sequelae of COVID-19. While understandings of long-COVID depicted in these studies were quite generalised, this work drew attention to the growing numbers of people experiencing lasting and debilitating signs and symptoms of COVID-19. Long-COVID is now understood to have international prevalence rates of 10% to 30% of non-hospitalised cases; 50% to 70% of hospitalised cases; and 10% to 12% of vaccinated cases (Davis et al., 2023). Long-COVID prevalence rates in New Zealand have been estimated between 12% and 20% (Ministry of Health, 2022b; Radio New Zealand, 2021, 2022; Russell et al., 2022; Wolters, 2020). It is possible that New Zealand's strict public health measures, including mandatory vaccination of 89.3% of the population, has helped keep hospitalisation rates down, and protected against the development of long-COVID (Ministry of Health, 2022a). In addition to different public health measures, certain contextual factors make it difficult to accurately gauge the prevalence of long-COVID. Other such factors include the lack of consistent diagnostic criteria and confusing number of names for the condition, as well as the huge breadth of symptomology to recognise and diagnose the condition by. Each of these factors will now be discussed in turn.

Issues with Recognition and Definition

In New Zealand, the Ministry of Health's (MOH) long-COVID information page for the public offers WHO, Centre for Disease Control in the United States (CDC) and the United

Kingdoms's National Institute for Health and Care Excellence (NICE) definitions in place of their own (Ministry of Health, 2022b). As illustrated in Appendix A, these definitions are similar and have points of similarity, the recourse to all of them introduces a degree of confusion as to what long-COVID certainly is, and certainly is not. In addition to the lack of a singular and inclusive definition, the MoH have codified long-COVID under two different names ongoing symptomatic COVID-19, and Post COVID-19 syndrome (MoH, 2022b, 2022c). The numerous diagnostic and naming protocols from New Zealand (echoing those observed overseas) confuse and dilute understandings of long-COVID, and limit researchers', patients' and clinicians' ability to recognise, understand, diagnose and treat the condition.

One issue surrounding these definitions is the supplanting of the term long-COVID which was given to the condition by those experiencing it, for numerous complex biomedical terms. It has been argued by some long-hauler academics and doctors that the shift to biomedical language reflects a shift of long-COVID research to focus more on the disease than the people it affects.

An issue with many of long-COVID's numerous diagnostic and sub-diagnostics categories is the dependence on delineating a timeline of disease, counting the number of weeks or months from acute COVID-19 infection to the present moment (Nalbandian et al., 2021). For many people living with long-COVID, self-described as long-haulers, delineating a timeline of disease is difficult (Baird, 2020; Kingstone et al., 2020; Mercer & Salit, 2021; UK Government, 2020). For individuals who were infected with SARS-CoV-2 at the beginning or end of the pandemic there was limited availability of PCR and RAT tests to confirm when this first day of infection might be (Baird, 2020; Kingstone et al., 2020; Mercer & Salit, 2021; UK Government, 2020). Alternatively, people who had asymptomatic COVID-19 may never have tested, not knowing they were ill in the first place, but still go on to develop long-COVID (Baird, 2020; Kingstone et al., 2020; Mercer & Salit, 2021; UK

Government, 2020). In addition, peoples' access to testing was also limited by circumstances such as material wellbeing, socio-economic status, and social mobility (Bonsaksen et al., 2022). It is likely that people who were time poor, or experiencing material hardship would have encountered more barriers to access a test than those of higher socioeconomic status.

Establishing a timeline is also complicated when long-haulers are experience fluctuating symptoms. Indeed, anecdotal and empirical evidence also supports the fact that long-COVID symptoms can fluctuate, sometimes completely remitting for a period of days to weeks, before coming back – how should people establish a timeline of symptom prevalence in such cases (Davis et al., 2021; Lu, 2022)? Consequently, it is not unlikely that these issues with establishing a timeline of disease and testing access have substantially impacted peoples' ability to recognise and diagnosis long-COVID (Au et al., 2022). It would not be surprising then if present long-COVID prevalence rates underestimate reality (Au et al., 2022; Russell et al., 2022).

Such issues with defining and recognising long-COVID also lead to further questions; who are these definitions and sub-diagnoses most useful for, and is time a sufficient way of qualifying and quantifying the burden of disease? It is likely that in the years to come these definitions will become clearer and our understanding of the disease more precise. This does not however detract from the symbolism of these definitions. For many, the removal of long-hauler established term 'long-COVID', the dependence on positive COVID-19 testing, and the need to establish a timeline of disease reflects how research can in-validate and de-value the lived experience that patients have of their own disease, de-centring people to focus more intently on a disease.

Neuropsychological Sequelae from Past-Pandemics

It has been argued that the de-centring people from the study of disease is one of the factors that has kept post-viral neuropsychological sequelae hidden from the public for the last 100 years (Au et al., 2022, 2022; Islam et al., 2020). In fact, there is a body of historical evidence of long-term neuropsychological sequelae following the Russian (1889,1892) and Spanish (1918-1919) Flu Pandemics, the AIDS/HIV pandemic (1981-present), and SARS pandemic (2003) (Chen, 2020; Honigsbaum & Krishnan, 2020; Islam et al., 2020). Indeed, the insights that past-pandemic have afforded us are now being put in a new light in the wake of the COVID-19 pandemic (Islam et al., 2020). Following each of these viral infections there is evidence of neuropsychological sequelae where patients have reported lingering symptoms like fatigue, nerve pain, headache, poor memory and concentration, and systemic inflammation (Chen, 2020; Honigsbaum & Krishnan, 2020; Islam et al., 2020).

Investigation into the long-term neuropsychological sequelae following the AIDS/HIV and SARS pandemics highlighted suspicions that viral bodies could enter and permanently damage the nervous system (Clifford & Ances, 2013; Islam et al., 2020; Zayyad & Spudich, 2015). There is a strong body of literature documenting HIV neuro-invasion where the virus is detected in cerebrospinal fluid (CSF) 8 days following infection (Clifford & Ances, 2013). HIV-associated neurocognitive disorder (HAND) is a mild-form of cognitive impairment involving difficulties with concentration, memory, planning, organising, and decision making (Clifford & Ances, 2013; Kemp et al., 2021; Vance et al., 2013). While the neuropathogenic nature of HIV requires further study, it is generally accepted that the virus directly or indirectly causes neuronal damage or dysfunction which is known to manifest as HAND (Zayyad & Spudich, 2015). Animal studies have shown that macaques infected with simian immunodeficiency virus causes viral encephalitis, neuronal apoptosis (death) and severe HAND (Adle-Biassette et al., 1995; F. Gray et al., 2001; Matsuda et al., 2014). HAND is

characterised, as with other dementias, by memory loss, speech and motor dysfunction, slow cognitive processes, inattention, and behavioural changes (Kimani, 2018).

Similarly, viral SARS particles have been found in the brain tissue of individuals who died from the virus in the 2003 outbreak (J. Xu et al., 2005). The neuro-invasion caused increased numbers of glial cells, neuronal cell death and abnormally high numbers of immune cells (J. Xu et al., 2005). Transgenic mice models of disease found that infection of CNS invasion was more fatal than lung infection, with neuronal death in the brain regions key for breathing, and correlated increased CNS viral load with increased mortality (Netland et al., 2008). SARS survivors experience ongoing fatigue and un-restful sleep, significantly impacting their ability to function normally and stay in work, up to 8 years following acute infection (Moldofsky & Patcai, 2011).

This characteristic pattern of post-viral neuropsychological sequelae involving nervous, cognitive, and psychological symptoms has also been studied following non-pandemic viruses including Ebola, Ross River, Epstein-Barr, and Dengue Fever infections (Ficenec et al., 2022; Keita et al., 2017; Tiffany et al., 2016). Post-Ebola virus sequelae overlap with those seen after COVID-19, Influenza, SARS and HIV. Most common symptoms are arthralgia (77.7%), fatigue (69.8%), abdominal pain (54.2%), headache (52.4%), anaemia (50%), skin disorders (48.8%) and eye complications (56.7%) (Tiffany et al., 2016). Possible neuro-invasion has been theorised in people experiencing bilateral hearing loss following infection, with symptoms of the middle or inner ear ($p < .001$), eye ($p = .005$), psychiatric ($p = .0019$) and nervous system ($p = .037$) increasing the likelihood of hearing loss (Ficenec et al., 2022). Psychological changes have also been observed; as with other post-viral infectious sequelae, people can experience anxiety, depression, PTSD and hallucinations following Ebola infection (Keita et al., 2017). As with COVID-19, Ebola is a multi-system

disease, where pathologies in multiple organs may converge to cause neuropsychological symptoms (Islam et al., 2020).

A commonality among different post-infective conditions is the co-presentation of fatigue and neuropsychological changes (Islam et al., 2020). Chronic Fatigue Syndrome or Myalgic Encephalomyelitis (CFS/ME) and its cause has been a highly contested disease; from the 1980s to the 2010s many health professionals and biomedical researchers insisted on its non-existence (Aly & Saber, 2021; Islam et al., 2020; Jason et al., 2021). However, given CFS/ME similarities to PVF and long-COVID, recent theorisations argue they are all examples of a systemic post-infective fatigue syndrome (Aly & Saber, 2021; Islam et al., 2020; Jason et al., 2021). CFS/ME is typified by highly debilitating fatigue, from which few recover, and most experience a poor quality of life. Psychological and cognitive impairments are often co-morbid with CFS/ME (Chu et al., 2018; Cockshell & Mathias, 2010; Cook et al., 2017; Daly et al., 2001; DeLuca et al., 1997; Rayhan & Baraniuk, 2021). And despite the push-back, CFS/ME researchers have found evidence to link abnormal stress hormone levels, mitochondrial dysfunction, glial cell damage, and increased levels of oxidative free radicals (toxic stress in the brain) with CFS/ME, furthering the idea that PVF is linked to significant neuro-pathology (Anderson & Maes, 2020; Herbert Renz-Polster et al., 2022; Hickie et al., 2006; VanElzakker et al., 2020; Washington et al., 2020).

While some evidence suggests that SARS-CoV-2 vaccination may protect and, in some instances, alleviate long-COVID symptomology, we need to be prepared for the reality of subsequent neuro-COVID associated conditions, like dementia, or language processing issues in adulthood; for which we will need a range of neuropsychological assessments and interventions to help us understand individuals' specific long-COVID related needs, highlighting functional strengths just as much as weaknesses (Ayoubkhani et al., 2022; Islam et al., 2020; Notarte et al., 2022).

Societal Factors Associated with Long-COVID's Neuropsychological Sequelae

There are several pandemic related societal measures that have been linked to long-COVID and associated neuropsychological sequelae. Such factors include public health measures like vaccination and social isolation, as well as hospitalisation, health care access and medical gaslighting.

Vaccination. There is evidence to suggest that vaccination against COVID-19 may help reduce long-COVID symptomology (Ayoubkhani et al., 2022; Byambasuren et al., 2023; Tran et al., 2023). One cohort study followed up on participants' long-COVID sequelae after first and second doses of the vaccine, and found that the first does of the vaccine was associated with a 12% decrease in symptomology 141 days post-vaccination (Ayoubkhani et al., 2022). Another study assessing the efficacy of the vaccine in reducing long-COVID sequelae, measured individuals 120 days after vaccination found a remission rate of 16.6% (Tran et al., 2023). Neither of these studies however specify what symptoms or sequelae were measured (Ayoubkhani et al., 2022; Tran et al., 2023). These findings are consistent with a systematic review that looked at the efficacy of the vaccine in reducing symptomology across 16 observational studies, and 614,392 participants (Byambasuren et al., 2023). While neuropsychological sequelae (fatigue, loss of smell, loss of taste, headache, difficulty sleeping, difficulty concentrating, worry, anxiety, memory loss and confusion) were found to be the most common in the studies included, the extent that these sequelae were those in which significant reductions were observed is not clarified (Byambasuren et al., 2023). Moreover, the extent that such studies control or adjust for potential confounders such as changes in protective behaviours or missing data is seemingly lacking (Ayoubkhani et al., 2022; Byambasuren et al., 2023; Tran et al., 2023). While there is evidence associating neuropsychological sequelae with reductions in long-COVID symptoms following

vaccination, the extent that neuropsychological sequelae are included in these reductions is not yet established.

Social Isolation. It is possible that the prolonged isolation that many adults experienced during the covid lockdowns may have long term neuropsychological effects. Marked differences in cognition have been linked to increased time in lock-down, where increased opportunity for social interaction with a greater variation of people were linked with improved performance on attention, decision making, time-estimation and learning tasks (Ingram et al., 2021). Isolation was also linked with changes in adults' cognitive ability to perceive stressful or crisis events without anxious or traumatic emotional responses (C. Xu et al., 2020). Moreover, cognitive reappraisal negatively moderated the relationship with perceived stress and anxiety symptoms (C. Xu et al., 2020). It has been theorised that social isolation may impact individuals' health and risk for developing long-COVID and neuropsychological sequelae in two ways. Firstly social isolation for many meant greater exposure to stressful familial or interpersonal settings, with little respite, working to fatigue ones' body and mind concurrently (Ingram et al., 2021; Manca et al., 2020). Secondly, social isolation can prevent sick individuals from accessing the support systems and care they require to make a good recovery (Ingram et al., 2021; Manca et al., 2020; Ortona & Malorni, 2022). This can potentially expose them to longer and more arduous course of sickness, adding to the risk of long-COVID development, and reduces exposure to protective factors such as positive social engagements (Ingram et al., 2021; Manca et al., 2020; Ortona & Malorni, 2022).

Hospitalisation. There is substantial evidence associating hospitalisation with long-COVID and neuropsychological sequelae (Batty et al., 2020; Braga et al., 2022; Frontera, Lewis, et al., 2021). One study compared the incidence of neuropsychological symptoms (anxiety, confusion or memory loss) in two groups of hospitalised participants, those who had

long-COVID, and those who were hospitalised with another illness (Rivera-Izquierdo et al., 2022). There was a similar frequency of symptomology at 12 months after discharge for both groups. However, neuropsychological sequelae were found with higher prevalence in those long-COVID participants who had been hospitalised with COVID-19 (Rivera-Izquierdo et al., 2022). While there is consistent evidence associating hospitalisation with more severe neuropsychological sequelae in long-COVID, the mechanism explaining this relationship is not yet clear (Frontera, Lewis, et al., 2021).

Denying the Diagnosis. There is also evidence suggesting that a form of medical gaslighting occurs at the systemic level during the pandemic (Au et al., 2022). It is argued that clinicians intentional or unintentional dismissal of long-haulers' symptoms has cast doubt on the legitimacy of long-hauler's experience at an institutional (medical institutions, government agencies) and societal level (public perception) (Au et al., 2022; Sebring, 2021). For long-haulers the additional psychological strain invoked by medical gaslighting can cause further harm by exacerbating long-COVID symptomology like anxiety, cognitive and attentional impairment, fatigue and depression (Au et al., 2022; Houben-Wilke et al., 2022). A qualitative study has found that even long-hauler doctors, as institutional insiders, found it difficult having their symptoms believed by fellow GPs (Taylor et al., 2021). Importantly, these long-hauler doctors reflected that the most successful way to prove their complaints were legitimate was to ask for tests that could demonstrate functional impairment (Taylor et al., 2021). These findings highlight that even with 'insider' experience, escaping the harms of medical gaslighting is difficult (Roberts, 2005; Roth & Gadebusch-Bondio, 2022).

Individual Risk Factors Associated with Long-COVID's Neuropsychological Sequelae

Gender. A growing body of literature indicates that male and female populations are affected by the virus and the pandemic in different ways (Bai et al., 2022; Binns et al., 2022;

Ortona & Malorni, 2022). Results from the Asia-Pacific region indicate that clinical case rates are approximately 10% higher in females than males, but the number of deaths is greater in males than females (Binns et al., 2022). Studies on long-COVID and cognitive impairment often have higher incidence of female than male participants (Au et al., 2022; Bai et al., 2022; Binns et al., 2022; Bucciarelli et al., 2022; Mezzatesta et al., 2022; Ortona & Malorni, 2022; Peng, 2023; Tanzi & Hawkins, 2023). One cross-sectional study comparing the extent of cognitive impairment in hospitalised and non-hospitalised people with long-COVID found that both groups had similar levels of cognitive impairment when adjusted for age and time since acute illness (Miskowiak et al., 2021, 2023). However, participants in the cognitively impaired group were more likely to be female, older, hospitalised, with a higher BMI and asthma (Miskowiak et al., 2021, 2023). Broadly speaking it appears that females experience less severe short-term illness (acute COVID-19), but worse long-term illness (long-COVID) that includes higher rates of depression, reduced physical activity, and worsening lifestyle habits (Bucciarelli et al., 2022).

Factors which might explain the higher rates of long-COVID incidence in females (and thus long-COVID associated cognitive impairment) include a bio-psycho-social model (Bai et al., 2022; Peng, 2023; Sacks-Zimmerman et al., 2023; Thurner & Stengel, 2023). It is hypothesised that in addition to managing their own illness (COVID-19), women still carried much of the burden of running house-holds, minding children and sick relatives, whilst continuing to work during their own illness throughout the pandemic (Aghaei et al., 2022; Scholz et al., 2023). It is possible that these cumulative, mutually exacerbating, and long-lasting burdens expose females to higher levels of biological and psychological stress for prolonged periods, making them more vulnerable to infection and less able to get the rest necessary to recover well (Belz et al., 2021; Ortona & Malorni, 2022). It is has been theorised that these concomitant bio-psycho-social factors converge to put females at greater risk for

developing long-COVID and its neuropsychological sequelae than males (Aghaei et al., 2022; Bai et al., 2022; Belz et al., 2021; Ortona & Malorni, 2022).

Age. Age has been identified as a significant risk factor for the neuropsychological sequelae associated with long-COVID (Peng, 2023). One study analysed and stratified 1,487,712 electronic health records by age for the 2-year cognitive impairment risk trajectories following COVID-19 infection (Taquet et al., 2022). The risk of long-term cognitive deficit was greater among older adults aged 65+ years (1.4), than younger adults aged 18-64 years (1.35) and children aged 0-18 years (1.22) (Taquet et al., 2022).

It is worth noting that while children (people 18 years and younger) were not included in the present study, there is 3.92% incidence of cognitive deficits among children (Taquet et al., 2022). It has been predicted that there will be an emergent cohort of younger individuals exhibiting new and idiosyncratic cognitive impairments to presently unidentified long-term impacts of COVID-19 infection on the body and nervous system, due to the lack of research on this age group (Calvano et al., 2022; Peng, 2023; Widmann et al., 2023; Zheng et al., 2023).

Age is now a well-established risk factor for both long-COVID and its neuropsychological sequelae (Asadi-Pooya et al., 2021; Fernández-de-las-Peñas et al., 2022). Older adults (50 years and older) have been found to have more significant loss of brain tissue than younger adults in post-mortem and neuroimaging case studies (Abdel-Mannan et al., 2020; Douaud et al., 2022; Matschke et al., 2020; Remmelink et al., 2020). They have also been found to have poorer cognitive performance than younger adults (Davis et al., 2021; Douaud et al., 2022; Guo, Ballesteros, et al., 2022). However, this view may be biased by the fact that many early studies on the neuropsychological sequelae were conducted with hospitalised samples (Batty et al., 2020; Braga et al., 2022; Frontera, Yang, et al., 2021). Indeed, because older and elderly adults were more likely to be hospitalised due to the risk of

fatal COVID-19 infections compared to younger adults, it has been questioned whether this has skewed data from hospitalised samples towards an older age (Batty et al., 2020; Braga et al., 2022; Frontera, Yang, et al., 2021).

Another factor potentially giving rise to the older samples seen in this literature investigating long-COVID's neuropsychological sequelae is that much of the research on this topic is conducted in Western countries with ageing populations (Batty et al., 2020; Frontera, Lewis, et al., 2021; Frontera, Yang, et al., 2021; Stephens & Breheny, 2022). One theory for this is that elderly individuals who would not usually have cause to interact with the health system, have because of COVID-19. And when they receive care for COVID-19, are having other signs and symptoms picked up, including neuropsychological sequelae that may or may not be resulting from COVID-19 or long-COVID.

It is also possible that the mode of research delivery, online via surveys or video calls, has skewed the age of long-COVID and neuropsychological sequelae samples (Peng, 2023; Van de Vyver et al., 2021). It may be that 41-50 years olds are at the peak of being able to enjoy their free-time, unencumbered by young children, but still earning decent income and able to access online technology (Peng, 2023; Van de Vyver et al., 2021). This compares to younger adults, aged 18-39 who are busy studying, working, and starting families; and those aged 51-66+ who are leaving the workforce, and are less familiar or adapted to the technologies of the time (Peng, 2023; Van de Vyver et al., 2021). Taken together these factors suggest adults in their forties and fifties are those most available and best suited to participate in long-COVID neuropsychological research conducted online, compared to other age groups (Peng, 2023; Van de Vyver et al., 2021).

Summary

In this chapter, I introduced the long-COVID and the pandemic context. Then highlighted the historical evidence from past-pandemics for the incidence and prevalence of

long-COVID's neuropsychological sequelae seen today. Finally, I discussed those societal and individual factors which might increase the risk for developing long-COVID and its lasting neuropsychological effects.

CHAPTER THREE

Literature Review: Long-COVID's Neuropsychological Sequelae

In this chapter I conduct an in-depth review of the numerous and complex neuropsychological sequelae, symptomology and cognitive changes associated with long-COVID. I begin with a concise introduction to some idiosyncrasies surrounding the term 'neuropsychological sequelae' as it is applied in the long-COVID literature. This is followed by a brief overview of long-COVID's neuropsychological sequelae. Possible neurobiological mechanisms thought to underlie long-COVID's neuropsychological sequelae like changes in inflammation, functional neural networks, cerebrovascular lesions, and tissue loss are then described. A detailed review of the extant literature on long-COVID's broader neuropsychological sequelae such as loss of taste and smell, sensorimotor changes, brain fog, fatigue, and mood and mental health changes is undertaken. This is followed by a closer look at the specific neurocognitive symptoms implicated in long-COVID, such as memory, language, attention, and processing speed, and highlight possible impairments of quality of life. The chapter ends with a summary of a bio-psycho-social model of disease, wherein the changes to individuals' neurobiology, cognition and daily-life might interact through a multitude of pathways, to culminate in the unique set of challenges faced by long-haulers.

Introduction

In long-COVID research, the term 'neuropsychological sequelae' has been used to cover all manner of functional (behaviour, cognition, affect, sensation, and perception) and structural (neurotropism, neurotoxin accumulation, altered excitation) changes seen in relation to the nervous system following confirmed and presumed COVID-19 infection (Ahmed et al., 2022; Arenivas et al., 2020; Ariza et al., 2022; Baslet et al., 2022; Braga et al., 2022; Douaud et al., 2022; Guo, Benito Ballesteros, et al., 2022; Stefano, 2021). In any other field of

research this would be a stretch of the meaning ‘neuropsychological’, which typically refers to cognitive, behavioural, sensory and emotional factors or features (American Psychological Association, 2022). Moreover, while sequelae are different to symptoms, these terms have also been used relatively interchangeably in long-COVID literature (Sevryugina & Dicks, 2022).[2] It is suggested this apparent confusion in terminology may be a result of the pandemic context, where the urgent need to understand long-COVID resulted in studies that were published simultaneously, without any prior information available (Sevryugina & Dicks, 2022). It may also be due to the lack of agreement whether the observed signs are latent impacts of acute COVID-19 (sequelae), or new signs related to new onset of long-COVID (symptoms). This matter has not yet been resolved in the literature, subsequently, in this study the terms sequelae and symptoms are used interchangeably.

An Overview of long-COVID’s Neuropsychological Symptoms and Sequelae

There is now substantial evidence associating functional and structural neuropsychological sequelae in post-acute COVID-19 and long-COVID (Achar & Ghosh, 2020; Cecchetti et al., 2022; Çinar et al., 2020; Cockshell & Mathias, 2010; Desforges et al., 2020; Douaud et al., 2022; Hellgren et al., 2022; Meinhardt et al., 2021; Shi et al., 2021). For example, reductions in functional network activity, global brain size, reduced grey matter thickness and density, as well as tissue damage in regions functionally connected to the olfactory cortex have been associated with fatigue, slowed reaction times, poor cognitive performance and higher levels of psychological distress (Douaud et al., 2022; Kapoor et al., 2022; Verger et al., 2022).

[2] Sequelae refers to the ongoing complications of an acute illness, and symptoms refers to a feature (mental or physical) which indicates a condition, illness or disease (C. Chen et al., 2021; Jason et al., 2021; Oxford University Press, 2023). For the most part, the terms symptom and sequelae are used interchangeably in long-COVID research; however the difference between the terms is that sequelae are the result of a prior disease, whereas symptoms are indicative of a current disease (C. Chen et al., 2021; Jason et al., 2021; Oxford University Press, 2023).

There is also a large body of evidence that suggests COVID-19 has significant long-term effects on the nervous system. Indeed, several studies have reported that the risk of neuropsychological sequelae is higher in COVID-19 compared to other infectious diseases (Agarwal et al., 2022; Bucciarelli et al., 2022; Denke et al., 2018; Fernández-de-las-Peñas et al., 2022; Horn et al., 2021; Islam et al., 2020; Jason et al., 2021; Peng, 2023; Taquet et al., 2021, 2022). There is also a growing understanding that timing is also a key factor in long-COVID's neuropsychological sequelae, with many studies showing that somatic symptoms begin to alleviate over a period of six to seven months following acute infection while neuropsychological ones persist (Agarwal et al., 2022; Cecchetti et al., 2022; Davis et al., 2021; Emecen et al., 2022; Horn et al., 2021; Tarantino et al., 2022).

An international cohort study (N = 3762) analysing the prevalence of long-COVID sequelae over seven months, found that there were up to 203 sequelae relating to 10 different organ systems, reported by long-COVID participants (Davis et al., 2021). Neuropsychological sequelae were highly prevalent, with 83 discrete sequelae observed, that were then clustered into nine groups. These groups and prevalence rates were: Taste and Smell at 57.60%, Sensorimotor Changes at 91.44%, Hallucinations at 15.42%, Sleep and Fatigue at 78.58%, Headaches at 76.74%, Emotion and Mood at 88.25%, Cognitive Function at 85.43%, Memory at 77.81, and Speech and Language at 48.62%, (Davis et al., 2021). To illustrate the breadth of long-COVID's neuropsychological impacts, these 83 neuropsychological sequelae are listed in Appendix B.

Long-COVID's Neurobiological Mechanisms

The following research derives from literature on post-acute-COVID-19, and long-COVID; given the uncertainty surrounding the difference of these terms, they are used interchangeably in this chapter. Several possible pathogenic biological mechanisms have been implicated in long-COVID (Bhandari et al., 2020; Bougakov et al., 2021; Desforges et al.,

2020; Francistiová et al., 2021a; Meinhardt et al., 2021; Peters et al., 2021). These include the persistence of viral RNA, proteins and responsive inflammatory reactions in organs throughout the body including the heart, lungs, brain and vasculature (Bhandari et al., 2020; Kumari et al., 2021; Yachou et al., 2020). It has been suggested that such changes may cause of thrombosis, micro and macro nervous and vascular changes, and long-term damage to somatic and neurological tissues observed in long-COVID (Bhandari et al., 2020; Kumari et al., 2021; Yachou et al., 2020). Given the long-term systemic sequelae seen in CFS/ME, SARS and AIDS there are growing concerns that metabolic, immune, autoimmune and inflammatory changes seen with long-COVID may be permanent with potentially fatal consequences (Lucas, 2021; Robertson et al., 2007; VanElzakker et al., 2020).

It has been suggested that sustained neurocognitive impairments after acute-COVID-19 could be related to pathological mechanisms such as dysregulation of renin-angiotensin-aldosterone and Hypothalamic-Pituitary-Adrenal pathways resulting in abnormal immune, stress and blood pressure levels (Elizalde-Díaz et al., 2022; Füzesi et al., 2016; Klein et al., 2022; Peters et al., 2021). Indeed, animal studies have provided substantial evidence for peripheral cytokines crossing the blood-brain-barrier, to negatively modulate neurological immune and inflammatory processes and cause impaired cognitive function (Keita et al., 2017; Netland et al., 2008; Neufeld-Cohen et al., 2010; J. Xu et al., 2005). In humans, high levels of C-reactive protein and interleukin-6 have been linked with decreases in spatial reasoning, short-term memory, verbal ability, learning, memory, executive function, and changes to brain white and grey matter volume, including the surface area of the hippocampus (responsible for memory, spatial processing) and the cerebral cortices (Marsland et al., 2015).

Long-term neuropsychological conditions associated with long-COVID may also involve functional neuronal networks, encephalopathies and cerebrovascular lesions, and neuropathy (neuronal cell death) (Akbarialiabad et al., 2021; Anand et al., 2020; Cecchetti et

al., 2022; Elizalde-Díaz et al., 2022; Francistiová et al., 2021a; Hellgren et al., 2022; Idrees & Kumar, 2021; Kapoor et al., 2022; Meinhardt et al., 2021; Peters et al., 2021). These changes may be caused by direct binding and damage due to the SARS-CoV-2 viral particles in the brain; they may also be the result of abnormal respiratory and cardiovascular changes occurring in acute-COVID-19 (Anand et al., 2020; Jung et al., 2022; Kumari et al., 2021; Netland et al., 2008; Yachou et al., 2020). Each of these biological mechanisms are unpacked in greater detail.

Inflammation

There is evidence that SARS-CoV-2 viral particles can infect the brain via retrograde axonal transport, and blood circulation to cause neuro-inflammation (Yachou et al., 2020). Once in CNS tissue, the virus causes mitochondrial distress, aberrant glial cell over-activation, impaired removal of oxidative stress – causing downstream nerve cell apoptosis (Baslet et al., 2022; Crunfli et al., 2022; Desforges et al., 2020; Klein et al., 2022; Peña-Bautista et al., 2020; Qiao et al., 2020; Vollmer-Conna et al., 2008; Yachou et al., 2020). There is evidence to suggest that SARS-CoV-2 can lie dormant in neural tissue, only to be re-activated by stress and up-regulated immune responses (Kumari et al., 2021). If SARS-CoV-2 can lie dormant in the brain, this poses questions as to whether neuropsychological changes seen in long-covid are the result of long-term damage caused during acute infection, or if they are indicative of a re-emergent inflammatory response in the brain as seen with HAND, and potentially CFS/ME (Borsche et al., 2021; Elizalde-Díaz et al., 2022; Lucas, 2021; Whiteside et al., 2022; Zayyad & Spudich, 2015).

Functional Neurological Networks

One study using fMRI has shown that long-COVID is also associated with significant changes in functional neural networks with links to those functional neuropsychological

sequelae (Kapoor et al., 2022).[3] Specifically, reduced activity was seen in long-COVID participants in the medial frontal cortex (attention, executive control, decision-making), default mode network (the brain activity at rest), salience network (co-ordinates functional response to important stimuli), sensorimotor network (processes sensory and motor functions), dorsal attention network (coordinates visual motor control during attention) (Kapoor et al., 2022). Fatigue (91% prevalence) was associated with overactivity in the lateral right posterior parietal node (integrates sensory and interoceptive information for sustained attention) (Kapoor et al., 2022). Post-traumatic stress (80% prevalence) was characterised by overexcitation of visual network and the cerebellum ((Kapoor et al., 2022). Anosognosia was characterised by overactivity in the basal ganglia (Kapoor et al., 2022).[4]

Cerebrovascular Lesions and Lost Function

Haemorrhagic lesions have been noted in diverse brain anatomies of patients known to die from COVID-19, including the medial temporal lobe, hippocampus, orbitofrontal cortex, thalamus, and sub-insular regions (Le Guennec et al., 2020; Meinhardt et al., 2021; Moriguchi et al., 2020; Poyiadji et al., 2020). Respectively, these areas are responsible for language processes, memory, decision making, attention, sleep regulation and respiration – thus it has been suggested that significant structural damage to the brain underlies the functional deficits seen in long-COVID (Le Guennec et al., 2020; Meinhardt et al., 2021; Moriguchi et al., 2020; Poyiadji et al., 2020).

Tissue Loss

Autopsy, histological and neuroimaging studies have found evidence of encephalitis, widespread neurodegeneration and decreased neuronal functioning linked to cognitive decline (Bougakov et al., 2021; Douaud et al., 2022; Mehta, 2011). A neuro-imaging study compared

[3] fMRI stands for Functional Magnetic Resonance Imaging, and can show the levels and changes of brain activity (Kapoor et al., 2022).
[4] Anosognosia is the inability to perceive ones' own neurological, psychological or neuropsychological deficits (American Psychological Association, 2023).

magnetic resonance images (MRI) between 401 COVID-19 positive participants and 384 controls (non-COVID infected) from two separate occasions, an average of 141 days apart (Douaud et al., 2022). Participants who had SARS-CoV-2 showed greater cognitive decline between the first and second MRIs (Douaud et al., 2022). Moreover, when comparing COVID-19 participants to controls, it was also found that the COVID-19 group had reduced grey matter thickness in the orbitofrontal cortex and para-hippocampal gyrus; greater changes in markers of tissue damage in regions functionally linked with the olfactory cortex; and a marked reduction in global brain size of participants with SARS-CoV-2 (Douaud et al., 2022). Tissue loss localised to left hemisphere cingulate cortex and right hemisphere amygdala has been linked with neurological deficits such as language impairments (typically associated with the left-hemisphere) observed in people with long-COVID (Bougakov et al., 2021). Once brain tissue has died, the functions associated with those brain regions can be irreparably lost too. Cortical atrophy and neural tissue loss may explain the extent of neuropsychological changes seen in long-COVID, and why in some people, such changes are resistant to recovery.

Summary

Given the broad range of potential biological mechanisms underlying the neuropsychological sequelae of long-COVID, there is a need for delineating possible different phenotypes of long-COVID over time, in which a multi-disciplinary approach will be vital. Importantly, this short review of the biological mechanisms associated with long-COVID's neuropsychological sequelae exemplifies that long-COVID is a highly complex condition that is likely the result of numerous biological, psychological and social factors and their interactions over time (Davis et al., 2021; Guo, Benito Ballesteros, et al., 2022; Levine et al., 2020).

Broad Neuropsychological Sequelae

Many early studies on long-COVID and its neuropsychological sequelae were conducted with convenience samples – often of hospitalised or discharged individuals – and relied of patients' self-reported survey data. Because of these limitations, rates of cognitive impairment vary greatly, and the neuropsychological sequelae reported are quite broad. These neuropsychological sequelae have been clustered into four broad groups: loss of taste and smell, other sensorimotor changes including hallucination, brain fog, and sleep problems and fatigue.

Loss of taste and smell

Loss of taste or smell, anosmia and dysgeusia are some of the first symptoms of acute COVID-19, and most common symptoms of long-COVID (Lechien et al., 2020). Loss of taste and smell have also been linked with self-rated poor memory and cognitive performance (Damiano et al., 2022). Interestingly participants who had concomitant loss of taste and smell during acute COVID-19 were significantly ($p = .006$) more likely to experience episodic memory impairments than controls (Damiano et al., 2022). Some evidence suggests there may be a link between functional and structural neuropsychological sequelae highlighted by this loss of taste or smell (Douaud et al., 2022; Lechien et al., 2020; Meinhardt et al., 2021). One possible explanation is that the SARS-CoV-2 virus infects the olfactory nerve, and travels via this nerve to the olfactory cortex in the middle of the brain, escaping the defence mechanisms of the blood brain barrier, before spreading to other regions (Douaud et al., 2022; Lechien et al., 2020; Meinhardt et al., 2021). The virus in the brain is then thought to damage brain structures to the extent that resulting functions are also impaired (Douaud et al., 2022; Lechien et al., 2020; Meinhardt et al., 2021).

Other Sensorimotor Changes and Hallucination

Alongside changes in taste and smell, sensorimotor symptoms like dizziness or changed balance, neuralgia, myalgia, auditory and visual hallucinations, migraine and headaches have all been reported in association with cognitive changes seen in long-COVID (C. Chen et al., 2021; Davis et al., 2021). While some symptoms such as myalgia and neuralgia are common in conditions like post-viral fatigue, and CFS/ME, just because they are sensorimotor changes does not mean they are caused by the same pathology underlying sequelae such as psychosis or hallucination, nor that underlying dizziness or change in balance (Davis et al., 2021; Guo, Benito Ballesteros, et al., 2022; Monje & Iwasaki, 2022; Stefano, 2021). It is possible that the neuralgia, myalgia, headaches, migraine and vertigo may all be the result abnormal sensing and perception following SARS-CoV-2 damage to underlying neurological structures (Damiano et al., 2022; Monje & Iwasaki, 2022; Yachou et al., 2020).

Indeed, given that SARS-CoV-2 particles found in damaged nasal tissue and the olfactory cortex, loss of taste and smell has been attributed to damage to those cellular structures underlying that function (Lechien et al., 2020; Meinhardt et al., 2021). Similarly, changes in balance or dizziness may result in damage to the nerves and inner ear structures underlying that function (Kumari et al., 2021; Yachou et al., 2020). Subsequently, it is not certain that the dizziness or loss of smell are causally related to those cognitive changes seen in long-COVID (Monje & Iwasaki, 2022). Rather, both these sensorimotor and processing changes as well as cognition may be associated because they are all be caused by the same underlying pathology, and thus often co-present (Monje & Iwasaki, 2022).

Brain Fog

‘Brain fog’ is a symptom which is increasingly reported on, particularly in relation to its impact on individuals’ quality of life, and ability to function in day-to-day (Jennings et al.,

2022a). The term ‘brain fog’ broadly refers to clouded cognitive capacity, though a strict definition has not been agreed upon in the literature (Nordvig et al., 2023; Nouraeinejad, 2023). Given this lack of definition, and that this term is often used by participants in self-reporting of their long-COVID symptomology, it is possible that the term describes generalised impairment to one’s neuropsychological performance (Bonsaksen et al., 2022; Orfei et al., 2022; C. M. Thompson et al., 2022). Indeed, an Irish study investigated 108 participants’ self-reported experiences of ‘brain fog’ with computer based cognitive assessments; 65.7% reported brain fog (Jennings et al., 2022a). Those with self-reported ‘brain fog’ also experienced a higher frequency of memory impairment, word-finding difficulties, dizziness, visual and hearing problems, anosmia, pins and needles, and higher scores on fatigue, depression and PTSD scales, slower gait speed and strength (Jennings et al., 2022a). Regression analysis however, found that fatigue, memory impairment, and myalgia had the best, independent associations with brain fog (Jennings et al., 2022a).

Some evidence suggests that brain fog is worse in individuals who had more severe respiratory problems, or had be admitted to the ICU during acute COVID-19 (Asadi-Pooya et al., 2022; Nordvig et al., 2023). One year after acute infection, brain fog was significantly associated with sleep disturbances, shortness of breath, weakness, dysosmia and dysgeusia, activity limitations, social isolation and higher rates of disability leave (Nordvig et al., 2023). It was found that brain fog had 30% prevalence rates among long-COVID participants, one year after acute infection (Nordvig et al., 2023).

One study investigated self-reported brain fog as concomitant concentration and memory issues (Rabaiotti et al., 2023). The Montreal Cognitive Assessment (MoCA) assessed cognitive function of long-COVID participants (N=56) at admission and discharge from a rehabilitation program (Rabaiotti et al., 2023). At admission 12% had normal cognitive function, but this significantly improved following psychological treatment, with 43% of the

cohort having normal cognition (Rabaiotti et al., 2023). Improvements were observed in attention, abstract reasoning, language repetition, memory recall, orientation and visuospatial abilities (Rabaiotti et al., 2023). At discharge, 4.7% of participants had residual cognitive impairment, however this study suggests that multidisciplinary treatment can be enhanced with neuropsychological therapies to improve brain fog in long-COVID (Rabaiotti et al., 2023).

Given its potential to signal a broad range of concomitant cognitive and neuropsychological features, it has been suggested that patients presenting with brain fog should have comprehension neuropsychological assessments (Berger et al., 2021; Nordvig et al., 2023; Nouraeinejad, 2023; Rabaiotti et al., 2023).

Sleep and Fatigue

Via an underlying component of brain fog, and in its own right, fatigue has been closely associated with poor cognitive performance in long-COVID. For instance, one study looking at blood markers, neuropsychological testing, and MRI imaging at 30 weeks following acute infection found that hospitalised long-COVID participants performed worse on global cognition, logical reasoning, and verbal memory processing than non-hospitalised long-COVID participants (Bungenberg et al., 2022). In both groups, reduced performance on attention and psychomotor tasks was associated with fatigue severity ($p < .05$) and reduced quality of life ($p < .001$) (Bungenberg et al., 2022).

High levels of neuropsychological fatigue are often associated with physical exhaustion, and high symptom loads in long-COVID (Van Herck et al., 2021; Ziauddeen et al., 2022). Indeed there is evidence patients, who experienced multiple symptoms during acute COVID-19 were more likely to experience psychological distress, fatigue, and long-term symptoms 9 months after acute infection (Righi et al., 2022).

Indeed, while there is evidence that respiratory and cardiovascular symptom severity and frequency can lessen, and in some cases fully recover, in the first seven months after acute infection, fatigue along with brain fog and cognitive impairments are more-likely to persist (Davis et al., 2021; Ziauddeen et al., 2022). Interestingly, for some long-COVID survivors, the experience of physical exertion and exhaustion, disordered sleep were likely to trigger other symptoms (Ziauddeen et al., 2022). Often fatigue and symptomatic burden began to impair individuals' ability to function independently about six weeks following acute infection (Ziauddeen et al., 2022).

There are two possible explanations for these sequelae that are being explored in the literature. The first theory suggests that the fatigue observed stems from body-wide fatigue and mitochondrial exhaustion, as seen in other cases of post-viral fatigue and CFS/ME (Anderson & Maes, 2020; Hickie et al., 2006; Islam et al., 2020). The second theory suggests that this fatigue stems from excessive neuropsychological strain (Cook et al., 2017; Kumari et al., 2021; Yachou et al., 2020). In this instance, the brain simply cannot cope with the burden of neuroplastic recovery in the wake of SARS-CoV-2 neuroinvasion on top of needing to complete the numerous cognitive tasks necessary for daily life (Bungenberg et al., 2022; Hawke et al., 2022; Widmann et al., 2023). Of course, it is also possible that both mechanisms interact to produce the degree of fatigue observed in long-COVID.

Mood and Mental Health

Changes in mood and emotion have been frequently associated with the cognitive changes seen in long-COVID (Davis et al., 2021; Garjani et al., 2021; Guo, Benito Ballesteros, et al., 2022; Houben-Wilke et al., 2022; Rudenstine et al., 2022). A cross-sectional study (N=199) using The Impact of Event Scale – Revised (IES-R) and The Depression, Anxiety and Stress Scale (DASS-21) found that severe psychological distress

(28.5%), severe depression (26.05%) and severe stress (31.09%) was significantly associated with long-COVID symptoms (Bautista-Rodriguez et al., 2023). Having lost a loved one, being a female, married, having children or caring for someone with disease all increased participants vulnerability to depression, stress, and anxiety (Bautista-Rodriguez et al., 2023). Interestingly, anxiety is likely a predictive factor for the development of long-COVID, where greater pre-COVID disability and anxiety were associated with the persistence of long-COVID symptomology 12 weeks following the end of acute COVID-19 (Garjani et al., 2021). A study with a hospitalised cohort (N = 45) approximately 200 days follow acute infection found that long-haulers who had moderate to mild acute-COVID-19 had poorer emotion recognition and greater stress, anxiety and depression than individual with severe acute-COVID-19 (Voruz, Allali, Benzakour, Nuber-Champier, Thomasson, Alcântara, et al., 2022). However, long-haulers who had severe acute-COVID-19 performed more poorly on a comprehensive neuropsychological battery, particularly in long-term memory (Voruz, Allali, Benzakour, Nuber-Champier, Thomasson, Alcântara, et al., 2022).[5] [6]

Continued psychopathological burden at one and three months after acute-COVID infection was also found by Mazza et al., in a different out-patient long-COVID cohort (N = 226, Mean age 58) (2021). Like Fumagalli et al., this study did not compare differences in long-COVID performance to a control group (2022; Mazza et al., 2021). Participants were cognitively assessed by psychiatrists one- and three-months following hospital discharge with unstructured psychiatric interviews with reference to the DSM-5 and psychometrically

[5] The neuropsychological battery included Grober & Buschke (RL/RI 16), Rey Osterith Figure, MEM III, WAIS IV, Stroop, TAP, Trail Making Task A, Verbal fluency, BECLA, Evaluation of ideomotor praxis, VOSP, Emotion recognition (GERT) (Voruz, Allali, Benzakour, Nuber-Champier, Thomasson, Alcântara, et al., 2022).

[6] Cognitive Battery, and Neuropsychological Battery are terms used interchangeably to describe a series of tests administered to assess a particular cognition function or domain, namely attention, executive function, learning and memory, language, sensorimotor control and perception, and social cognition (Harvey, 2019).

validated self-report measures including the Impact of Event Scale -Revised (cut off scores >33); PTSD Checklist for DSM-5 (cut off scores > 33); the Zung Self-Rating Depression Scale (cut off scores > 50); the BDI-13 (cut off score >9); State-Trait Anxiety Inventory f(cut off scores > 40); Women's Health Initiative Insomnia Rating Scale (cut off scores > 9); and the Obsessive Compulsive Inventory (cut off scores > 21). A sub-sample of 133 patients had cognitive functions assessed through the Brief Assessment of Cognition in Schizophrenia, and a cognitive battery using verbal memory, verbal fluency, digit sequence (working memory), symbol coding (selective attention and processing speed), token motor (psychomotor coordination) and the Tower of London (executive function) tasks. Authors state that only 25 patients (19% of the sample) showed equivalent scores within the normal range across all cognitive domains - however they do not clarify whether these scores are from the sub-sample of patients assessed with the cognitive battery, or from the whole study sample using the self-report measures noted above. As with Fumagalli et al., the generalisability, relevance and reliability of this study's findings are limited by the lack of a control sample. It is also unusual to take a sub-sample through a full cognitive battery, and not relate these findings to the outcomes in the total sample. The authors do not explain why this sub-sample was chosen but state that any patients over 70 years of age were excluded. If this exclusion criteria was applied, why not simply use the smaller-sub-sample as the sample for this study. Either way, this sub-sampling is problematic in that by excluding the whole sample in the cognitive battery, the results may be skewed toward a younger, more cognitively capable patient sample, thus the findings (although already unable to be generalised to the general population) are also unable to be generalised to those in the study who had been hospitalised with possibly more severe cognitive impairments.

A separate cohort study compared cognitive and psychological status from two different condition groups, Major Depressive Disorder (MDD; N= 165) and long-COVID

(N=92), to a healthy control group (165) (Poletti et al., 2021). Unlike Fumagalli et al., this study assessed cognitive and psychological symptomology with reliable and valid psychometric tests (Zung Self Rating Depression Scale, EuroQol-5, Tower of London Test, and the Brief Assessment of Cognition in Schizophrenia) alongside a clinician administered DSM-5 Unstructured Diagnostic Interview (2022; Poletti et al., 2021). Depressive symptomology was found to significantly impact cognitive performance at one-, three-, and six-months post-hospital discharge in both condition groups (Poletti et al., 2021). Long-COVID participants had cognitive impairments at one, three, and six months after discharge compared to MDD and control groups (Poletti et al., 2021). Poor performance associated with long-covid was seen across cognitive domains, specifically, verbal memory, working memory, psychomotor coordination, verbal fluency, slower information processing, and executive function (Poletti et al., 2021). Interestingly however, COVID-19 survivors performed as well as healthy controls and significantly better than MDD participants on working memory (digit sequence; $p < .001$) and verbal memory ($p < .001$) (Poletti et al., 2021).

A more neuropsychologically rigorous assessment of cognitive function in 53 outpatients (mean age of 50) 6 months following acute infection investigated performance validity, attention/working memory, processing speed, language, visuospatial processing, executive function, motor and emotional function (Whiteside et al., 2022). Despite using the Test of Memory Malingering, Wechsler Adult Intelligence Scale IV, Reliable Digit Span, Hopkins Verbal learning Test-Revised, Boston Diagnostic Aphasic Examination, Verbal Fluency Tests, Grooved Pegboard Test, Trail Making Tests and the Beck Depression Inventory (BDI) no significant effect sizes were observed across any measure (Whiteside et al., 2022). A lack of statistically significant date may have been attributable to the hospitalised sampling frame and lack of control participants, or whether or not baseline

cognitive measures were available for that hospitalised sample (Price et al., 2017; Whiteside et al., 2022). The study's findings did however indicate worsened cognition and depression six months following acute COVID-19 infection, with 73.5% of participants scoring over the BDI cut-off score for depression at raw scores of >14. Anxiety was similarly elevated, with 65.3% scoring above the raw-score cut-off of 8 (Whiteside et al., 2022). At this point however, it is not clear, whether changes in mood and mental health are associated with poorer cognitive outcomes is due to a shared pathology; or they arise from those circumstances brought about by long-COVID like reduced social connection, inability to exercise well, and poor quality of life (Widmann et al., 2023).

Summary

A review of the nascent literature on those broad, yet characteristic neuropsychological sequelae of long-COVID highlights that the poor neurocognitive performance observed cannot be explained solely by biological mechanisms, but numerous psychological and situational factors must also be considered. Some of this early research was conducted with hospitalised samples, where studies using neuropsychological batteries did not always have a control cohort, or studies using self-reported data did not always use psychometrically validated measures. Subsequently, while some research is beginning to control for pre-morbid factors like cognitive ability, personality traits, and concomitant psychological conditions, the impact of pre-morbid factors on long-COVID's neuropsychological sequelae is yet to be fully realised. In conclusion, such findings remind us that long-COVID, unlike acute-COVID-19, cannot be diagnosed with lab tests, subsequently, recording and testing individuals own self-reported symptoms and their temporal associations may be an essential first step in making an assessment and diagnosis.

Neurocognitive Symptoms and Associated Quality of Life

The extant research highlights that there is a growing understanding that the cognitive changes associated with long-COVID may be subtle, varied, and apparent in individuals who had asymptomatic acute-COVID-19. For example, a Belgian study used an online survey to assess the factors moderating the long-term impacts of COVID-19 in 639 individuals over 65, (average age 73) (De Pue et al., 2021). Over three quarters of participants reported a decrease in wellbeing (76%), with 8% experiencing generalised change in cognition (De Pue et al., 2021). There were also self-perceived changes in memory (85%), concentration (12%), multitasking (6%), recall (10%), and forgetfulness (10%) (De Pue et al., 2021). Again, psychological changes and increased depression was linked with decreased physical activity, quality sleep, wellbeing, and cognitive function (De Pue et al., 2021). While this study was seeking to compare mental wellbeing in the elderly before and after the pandemic, the study lacked both a control group, or baseline measures to compare pandemic measures of wellbeing to. This study was also limited by the lack of a timeline, not recording at what time point participants were assessed (in reference to having acute-COVID-19) means this data could be confounded by participants who are currently ill with COVID-19 or other severe conditions. It is also worth questioning how valid, generalisable, and clinically relevant such self-report data is when it comes from a non-controlled sample, who are already at greater risk for poor cognitive performance.

Memory

There is evidence that memory is significantly impacted in long-COVID (Davis et al., 2021; Guo, Ballesteros, et al., 2022; Llana et al., 2023). The COVCOG2 study from the United Kingdom found substantial associations between long-COVID symptom severity and

worsening memory performance (Guo, Ballesteros, et al., 2022). Long-haulers' (N=181) and healthy controls' (N=185) were administered a Cognitive Battery consisting of the Word List Recognition Memory Test, the Pictorial Associative Memory Test, the Category Fluency Test, the Mental Rotation Test, the Wisconsin Card Sorting Test, the Number Counting Test, and the Relational Reasoning Test (Guo, Ballesteros, et al., 2022). Long-COVID participants performed significantly worse than healthy controls on the Word Recall Test, moreover their self-reported cognitive symptoms were predictive of their performance on objective memory tests (Guo, Ballesteros, et al., 2022). This study also found that the presence of fatigue among mixed symptoms during acute-COVID-19 in addition to ongoing neurological symptoms predicted poorer cognitive performance in long-COVID (Guo, Ballesteros, et al., 2022).

One large cohort study gathered self-reported symptom incidence and prevalence rates seven months after acute COVID-19 from 3762 participants, of whom 1020 had tested positive for COVID-19, and 2742 had suspected (untested) COVID-19 (Davis et al., 2021). All participants were presumed to have long-COVID, and no healthy controls were recruited (Davis et al., 2021). In this cohort, the three most debilitating symptoms were fatigue (n=2652), breathing issues (n=2242), and cognitive dysfunction (n=1274). Of those experiencing cognitive dysfunction (n=3212), 2739 experienced memory issues (Davis et al., 2021). Individuals aged 40 to 49 were more likely to experience memory issues, specifically in the domains of short-term memory loss, long-term memory loss, inability to make new memories, and trouble remembering how to do routine tasks (Davis et al., 2021). Self-reported memory and cognitive dysfunction with mild to severe impacts, substantially impaired individuals' ability to complete day-to-day tasks (Davis et al., 2021). Areas of life disrupted for 50% or more of participants included work (~86%), making serious decisions (~74%), communicating one's thoughts (~69%), conversing with others (~62%), driving (~61%), remembering medication (~54%), and following simple instructions (~53%) (Davis

et al., 2021). Those aged 18 to 29 were most likely to experience cognitive and memory dysfunction impacting their ability to work (Davis et al., 2021). Interestingly, cognitive dysfunction (attention, thinking, executive functioning, problem solving, and slowed thoughts), but not memory changes, were more prevalent in ages 18 to 49, compared to those 50 and older (Davis et al., 2021).

Davis et al., were especially interested in mapping the severity of cognitive and memory changes over the first seven months that participants had long-COVID (Davis et al., 2021). Memory, brain fog, and speech and language issues rose in severity 0 to 10 weeks post-acute-COVID-19, to then plateau in severity around 15 weeks, and show little signs of decline for the remainder of the seven months (Davis et al., 2021). Interestingly, sensorimotor neuropsychological sequelae (dizziness, hallucinations, headache, insomnia, slurring speech) peaked in severity within the first 5 weeks post-acute-COVID-19, and then began to decline over the remainder of the seven months (Davis et al., 2021). These findings suggest that the pathological mechanisms underlying those sensorimotor sequelae are distinct from neurocognitive ones; and highlights that there may be numerous neuropsychological long-COVID phenotypes, identifiable by time and symptom prevalence (Davis et al., 2021).

Unfortunately, this study did not recruit healthy controls, nor did it utilise objective neuropsychological measures to compare participants' self-reported results to (Davis et al., 2021). While this study's findings are illuminating, they are difficult to relate to a wider population. Moreover, while it is clear that those with long-COVID are no-longer able to complete the tasks necessary for daily-life due to these memory and cognitive changes, there is no measure used (like a Quality of Life measure) to substantiate such findings.

Another study comparing memory in 42 long-COVID participants with 30 controls found that consolidation of procedural and declarative memories were more impaired than the

acquisition of new memories in those with long-COVID (Llana et al., 2022). Participants' objective memory performance was assessed with the Paired Associate Learning test (verbal declarative memory), the Mirror Tracing Test (procedural memory), the Montreal Cognitive Assessment (general cognitive function), and the Digital Symbol Substitution Test (psychomotor speed and incidental learning) (Llana et al., 2022). The long-term retention of the Paired Associate Learning and Mirror Tracing tests was assessed a second time, 24 hours following initial acquisition (Llana et al., 2022). Long-COVID participants had poorer levels of general cognition, psychomotor speed and attention compared to controls. Interestingly, long-COVID participants with anosmia (loss of smell; n=17) had poorer cue-guided learning and free recall compared to controls, with no difference between controls and non-anosmia (n=25) long-COVID participants (Llana et al., 2022). Participants with anosmia also had slower procedural times, and long-term memory that non-anosmia and control participants (Llana et al., 2022). These findings show that while those with long-COVID have significantly impaired memory compared to health controls, individuals with loss of smell are especially impacted (Llana et al., 2022).

Interestingly, when long-COVID results were grouped based on duration of illness (less than six months; seven to 12 months; 13 to 18 months; and 19 months or longer) no significant differences were observed in participants cognitive or memory performance (Llana et al., 2022). The findings of Llana et al., (2022), potentially conflict with Davis et al., (2021); where the prior study suggests that time does not impact severity of memory and cognitive performance in long-COVID; whereas the latter do. Given the embryonic state of the literature on this matter, further research may help resolve whether time elapsed and anosmia are significant predictive and diagnostic factors for the cognitive, memory and functional impairments seen in long-COVID (Davis et al., 2021; Llana et al., 2022).

Language

Numerous changes to language production and comprehension have been reported in associated with long-COVID, including word finding difficulties, stuttering, and trouble engaging in conversation (Davis et al., 2021; Furlanis et al., 2023; Guo, Ballesteros, et al., 2022; Jason et al., 2021). Indeed, following brain fog, and memory, issues with language are the most commonly reported cognitive symptoms of long-COVID (Davis et al., 2021). The pathogenic mechanism underlying these changes is not known, however, low arterial oxygen partial pressure has been positively correlated with verbal memory performance, and ARDS was associated with worse verbal memory performance (Ferrucci et al., 2021). In this Italian study 38 participants (age range 22 to 74) with post-acute-COVID-19 found that 42.1% of participants had processing speed deficits, 23.6% had delayed verbal recall deficits, and 21 % had processing speed and verbal memory deficits (Ferrucci et al., 2021).

A case study has reported the two incidences of neurogenic stuttering following acute-COVID-19 (Furlanis et al., 2023). Both individuals were also reported to have impaired attention, word finding, and memory consolidation following neuropsychological assessment; and electroencephalography found slowed brain activity (Furlanis et al., 2023). Unlike the brain fog, memory and attention impairments which can last well over seven months, these language difficulties gradually improved in the four to five months post-acute-COVID-19 (Davis et al., 2021; Furlanis et al., 2023; Jason et al., 2021).

Many studies report language impairments in association with long-COVID's neuropsychological and cognitive sequelae (Barnden et al., 2023; Furlanis et al., 2023; Guo, Ballesteros, et al., 2022; Jennings et al., 2022a; Kelly et al., 2022; Saucier et al., 2023; Voruz, Allali, Benzakour, Nuber-Champier, Thomasson, Alcântara, et al., 2022). Self-reported language impairments have been associated with brain fog, fatigue, and memory impairment

(Guo, Ballesteros, et al., 2022; Jennings et al., 2022a). However, very few studies have worked to specifically investigate these language difficulties in long-COVID (Guo, Ballesteros, et al., 2022; Jennings et al., 2022a). The most common modes of language assessment in this field is via Cognitive or Neuropsychological Batteries, in Word Finding, Word Recall, and Verbal Fluency tests (Égerházi et al., 2007; Guo, Ballesteros, et al., 2022; Jason et al., 2021). Each of these tests assess language in association with another cognitive domains (in these instances, cognitive processing and consolidated or long-term memory), detailing language processes in association with long-COVID seldom occurs (Guo, Ballesteros, et al., 2022; Jennings et al., 2022a).

For example, in the COVCOG studies, language (category fluency and word finding) was assessed in conjunction with memory (Guo, Ballesteros, et al., 2022; Guo, Benito Ballesteros, et al., 2022). In the COVCOG study, no difference was seen in category fluency while those with long-COVID had significantly longer word finding times, which might suggest impaired memory, or language production (Guo, Ballesteros, et al., 2022; Guo, Benito Ballesteros, et al., 2022). Further assessments to discriminate between long-term memory and word production were not conducted, which may have otherwise clarified these findings (Guo, Ballesteros, et al., 2022; Guo, Benito Ballesteros, et al., 2022). While memory is an essential component of language production and comprehension, such findings cloud which specific aspects of language production and comprehension are implicated in long-COVID (Guo, Ballesteros, et al., 2022; Guo, Benito Ballesteros, et al., 2022).

Indeed, those studies which report slurring of speech, and ongoing language production issues in long-COVID tend to rely solely on participants self-reporting measures, where additional assessment with Verbal Word Recall, Category Fluency, Reading Comprehension, and Word Production tasks might highlight whether language production or

comprehension are more impacted in long-COVID (Davis et al., 2021; Islam et al., 2020; Kirchberger et al., 2023).

There is a similar degree of ambiguity surrounding language impairment in studies assessing the prevalence of long-COVID's neuropsychological sequelae (Davis et al., 2021). While speech and language issues (difficulty word finding, communicating verbally, processing written text, comprehending speech, difficulty writing, slurring words, and speaking non-words) have ~9% to ~49% prevalence in a long-COVID population, the extent that language difficulties are incorporated or included in the measurements of constructs like slowed thoughts is not clarified (Davis et al., 2021). While the existing long-COVID literature suggests that language production and comprehension are implicated within the conditions neuropsychological sequelae, we do not yet know to what degree language capabilities are impaired, how long for, nor in which age groups.

Attention and Processing Speed

Approximately 80% of those with long-COVID report attention difficulties in the first seven months of their condition (Davis et al., 2021). Attentional deficits in long-COVID have been commonly associated with decreased psychomotor speed tasks, and increased levels of fatigue, brain fog and hospitalisation for acute-COVID-19 (Bungenberg et al., 2022). These changes in attention associated with long-COVID have been assessed with self-reporting, Neuropsychological Battery tests, and psychometric measures (Bungenberg et al., 2022; Davis et al., 2021; Guo, Ballesteros, et al., 2022; Houben-Wilke et al., 2022; Jason et al., 2021; Voruz, Allali, Benzakour, Nuber-Champier, Thomasson, Alcântara, et al., 2022).

A British cohort study of 81,337 outpatients of individuals, aged 40 and older, undertook a Cognitive Battery which included Digit Span, Rare Word Definition, Analogical Reasoning, Target Detection, 2D Mental Rotations, Spatial Span, Block Rearranging, Tower

of London, and Face Emotional Discrimination tasks (Hampshire et al., 2021). Cognitive performance was compared to self-reported COVID-19 symptomology (Hampshire et al., 2021). People who had COVID and long-COVID showed significant cognitive deficits compared to healthy controls. Specifically, mean response times were worse on target detection and face discrimination tasks, and major psychological comorbidities were anxiety and depression (Hampshire et al., 2021).

One study (N=100) compared self-reported stress and anxiety (Perceived Stress Scale and the Mood and Anxiety Questionnaire), depression (Beck Depression Inventory-II) and anhedonia with results on the Attention Network Test (ANT) between long-COVID participants and healthy controls (Lamontagne et al., 2021). Attention was measured with reaction times as participants responded to changing commands in the ANT (Lamontagne et al., 2021). Reaction times were significantly slower for participants with long-COVID than controls in response to congruent, incongruent and neutral stimuli (Lamontagne et al., 2021). Interestingly, there were no significant correlations between severity of long-COVID symptoms and self-reported measures of mood, implying that long-COVID may be unrelated to heightened depressive or anxious symptoms.

Attentional changes in long-COVID have been investigated as a component of executive function and processing speed (Guo, Ballesteros, et al., 2022; Guo, Benito Ballesteros, et al., 2022; Kirchberger et al., 2023; Lauria et al., 2023; Maiorana et al., 2023; Park & Schott, 2022; Resch et al., 2023; Varela et al., 2022). In particular, a cross-sectional study from Texas (N=72; age 22 to 65) used the Trail Making Test (assessing executive function, specifically, cognitive flexibility), the Digit Symbol Substitution Test (assessing attention and processing speed), the Stroop Test (executive function, specifically, response inhibition), and the List Learning Test (assessing immediate and delayed verbal memory) to assess cognitive function in post-acute-COVID-19 (Henneghan et al., 2022; Scarpina &

Tagini, 2017). Symptom burden was associated with lower levels of self-reported cognitive function; and moderately severe acute-COVID-19 was associated with significant attention and processing speed impairment in post-acute-COVID-19 (Arbuthnott & Frank, 2000; Baykara et al., 2022; Henneghan et al., 2022; Moore et al., 2016; Moscardini & Tucker, 2023). Attention and processing speed was more impaired in males, younger participants, and belonging to an ethnic minority group (Henneghan et al., 2022).

One longitudinal cohort study assessed working memory, attention, reasoning, and motor control in healthy controls and those with long-COVID at a two-year intervals (Cheetham et al., 2023). While these discrete neuropsychological functions were outlined within the study's measures; they are combined and discussed throughout the rest of the paper as "cognitive deficits" (Cheetham et al., 2023). It was found that cognitive deficits are significantly worse in those with long-COVID, both immediately after acute-COVID-19 and two years later. Cognitive performance in participants with long-COVID, two years following infection, was comparable to that both at hospitalisation, or to the cognitive performance of those 10 years older (Cheetham et al., 2023). These findings have led some to hypothesise that the neuropsychological impairment seen in long-COVID may result in pre-mature aging of the brain (Cheetham et al., 2023). While these findings are pertinent to comprehending the long-term impacts and outcomes associated with long-COVID's neuropsychological sequalae, they do not explain whether specific aspect of cognition are implicated more than others.

Quality of Life

Prevalence, pattern, and severity of long-COVID sequelae, including neuropsychological sequelae, have been associated with decreased ability to work, and quality of life (Graham et al., 2021; Hopkins et al., 2011; Líška et al., 2022; Malesevic et al., 2023; Miskowiak et al., 2023; Poletti et al., 2021; Samper-Pardo et al., 2023; Scholz et al., 2023;

Shanbehzadeh et al., 2023; Umakanthan et al., 2023). In one study, 197 sex, age, and education matched long-COVID and healthy participants were recruited via a long-COVID clinic to complete a quality of life questionnaires and cognitive screen (Miskowiak et al., 2023). Clinically relevant cognitive impairments were seen in 44.53% of long-COVID participants (Miskowiak et al., 2023). Substantial impairments were evidence in global cognition, working memory and executive functioning, and moderate impairments were seen in verbal fluency, verbal learning and memory of the long-COVID group compared to controls (Miskowiak et al., 2023). Such findings highlight that individuals who were more cognitively impaired were more likely to be older, hospitalised, and have lower quality of health, quality of life, and greater impairment at work (Cox et al., 2023; Genecand et al., 2023; Miskowiak et al., 2023; Spektor & Poluektov, 2022; Umakanthan et al., 2023).

Decreased quality of life has also been associated with brain fog, headache, numbness or tingling, dysgeusia, anosmia, fatigue and myalgia (Graham et al., 2021). While the number and severity of symptoms are well evidenced to predict long-haulers' quality of life, there is less evidence associating the length of time that participants have had symptoms with quality of life (Graham et al., 2021; Líška et al., 2022; Miskowiak et al., 2023; Poletti et al., 2021; Shanbehzadeh et al., 2023). One study however comparing cognition and quality of life between long-haulers and healthy controls investigated cognition and quality of life levels at one month, three months, and six months following acute-COVID-19 (Poletti et al., 2021). No significant differences in cognition, nor quality of life were observed at one, three or six months following acute-COVID-19 (Poletti et al., 2021). These results suggest that the cognitive impairment associated with long-COVID affects quality of life for at least six-months following acute infection (Poletti et al., 2021).

One study looked at the association between long-COVID, cognition and quality of life in older adults, 60 to 90 years of age (Shanbehzadeh et al., 2023). Quality of life and

functional activity were assessed with the Fatigue Severity Scale, Physical Activity Elderly, the SF12, the Post-COVID-19 functional status scale, and the COVID-19 Yorkshire rehabilitation screening scale (Shanbehzadeh et al., 2023). To work within social isolation mandates during the pandemic, participants were assessed via phone interview (Shanbehzadeh et al., 2023). Cognitive and communication problems, fatigue, physical activity, worsening pain, and difficulties in activities of daily living were predictive of physical health (Shanbehzadeh et al., 2023).

Using methods other than in-person assessment was implemented successfully by Liska et al., (2022). This study used an anonymous online questionnaire as the mode of measurement delivery which meant participants could complete the study from their own homes (Líška et al., 2022). Long-COVID participants were health-clinic patients (mean age 41) and control participants were all college students (mean age 24). Long-COVID participants'(n=469) scores on the SF-36 were compared to those of healthy controls (n=338; Líška et al., 2022). Long-COVID participants had significantly poorer physical functionality, and poorer self-reported quality of life (Líška et al., 2022).

Taken together, findings from Poletti et al,. (2021), Shanbehzadeh et al., (2023), and Líška et al., (2022), these findings suggest that across the life-span, fatigue, cognitive impairment, physical and mental wellbeing are all factors contributing to long-haulers' quality of life. These findings also highlight possible alternatives to in-person participation; where studies are able to maintain good respondent rates and return significant results through delivery modes such as phone-interviews or anonymised online surveys (Cox et al., 2023; Davis et al., 2021; Jason et al., 2021; C. M. Thompson et al., 2022; E. J. Thompson et al., 2022). A review of the extant literature however, highlights that the links between specific neuropsychological sequelae or symptoms and quality of life in relation to long-COVID are not yet well established.

Burden of Disease

We are still in the early years following the pandemic and are only getting a glimpse of the many long-term neuropsychological impacts of the disease. Already, evidence suggests that long-covid is associated with increased mental health conditions, cerebrovascular damage and incident, encephalopathies, early onset cognitive decline (memory issues, language impairment, slower processing speed) (Aghaei et al., 2022; Malesevic et al., 2023; Ngasa et al., 2021; Scholz et al., 2023; Van de Vyver et al., 2021). Such conditions bring with them extra medical costs, greater need for in-home care, and remove able bodies from an already strained global workforce. Current estimates suggest the US will spend an extra $9000 USD per person annually on medical costs alone in the months and years following a COVID-19 infection (Cutler & Summers, 2020). Total cost to the US public is estimated to sit around $2.7 trillion a year; however, national spending on health-care in the US differs significantly to countries like Australia and New Zealand which are publicly and not privately funded (Cutler, 2022; Cutler & Summers, 2020). The New Zealand Ministry of Health is yet to release estimates of health-care costs related to long-covid. However, it should be noted that current theorisations about the long-term burden of long-covid on the brain are based on the similarity of the signs and symptoms of COVID-19 to other conditions – but it is likely there will be long-term neuropsychological impacts of COVID-19 and long-covid that we cannot predict or anticipate.

Summary

Throughout this section, it has been made evident that long-COVID's broad neuropsychological sequelae, and specific neurocognitive symptoms impact individuals of all ages' quality of life. Moreover, it has been suggested that long-COVID is not only a great

burden to the individuals who suffer from the condition but may also pose a significant burden to society.

A Bio-Psycho-Social Model of Disease

In this section, a theoretical psycho-bio-social model of disease is described, to tease out the complex and multi-directional interactions of biological, psychological and social factors that are hypothesised to underpin the cognitive impairments observed in long-COVID (Monje & Iwasaki, 2022). This model is illustrated in Figure 1.

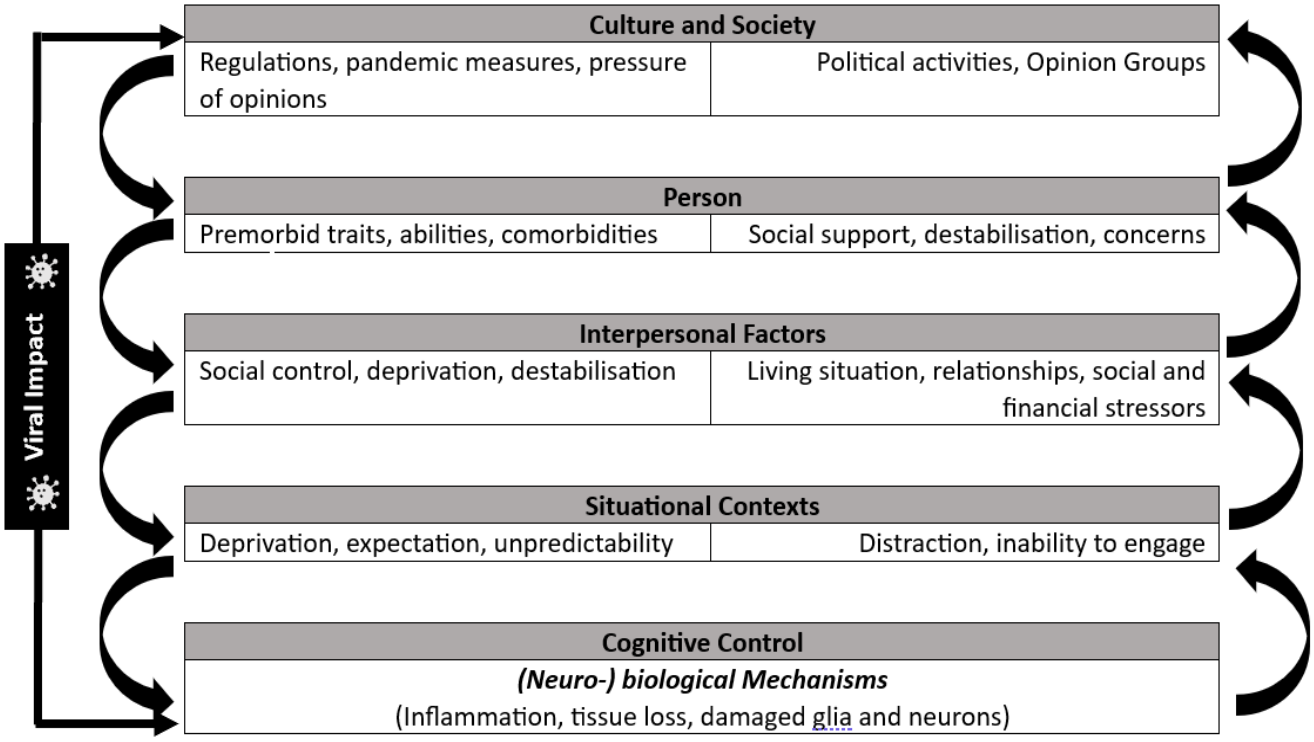
There is a growing evidence base giving increasing credibility to a bio-psycho-social model of long-COVID (Aghaei et al., 2022; Ares et al., 2021; Diana et al., 2023; Monje & Iwasaki, 2022; Ngasa et al., 2021). This theoretical model stems out of research on hospitalised patients with and without long-COVID (Braga et al., 2022; Every-Palmer et al., 2020; Hellgren et al., 2022; Hugon, 2022; Klinkhammer et al., 2021; Taquet et al., 2022). To explain, a large proportion of the early research on long-COVID's neuropsychological sequelae were conducted with hospitalised samples, as those populations were easiest to identify and access for researchers during the pandemic (Braga et al., 2022; Hellgren et al., 2022; Hugon, 2022; Klinkhammer et al., 2021). It was initially theorised that the neuropsychological sequelae of long-COVID were thought to primarily occur in hospitalised patients due to the extreme physical stress and psychological trauma of being hospitalised or staying in ICU in the height of the pandemic (Braga et al., 2022; Hellgren et al., 2022; Hugon, 2022; Klinkhammer et al., 2021; Ngasa et al., 2021; Nordvig et al., 2023).

However, as more long-COVID research has been published (especially large cross-sectional national studies like COVCOG and Biobank series from the United Kingdom) it is becoming clearer that neuropsychological symptoms are prevalent among those living with long-COVID, regardless of hospitalisation or ICU stays (Douaud et al., 2022; Guo,

Ballesteros, et al., 2022; Guo, Benito Ballesteros, et al., 2022; Saucier et al., 2023). Indeed, numerous correlational and cohort studies associating neurological imaging with Cognitive

Figure 1

A Bio-Psycho-Social Model of Long-COVID's Disease[7]



Note. This theoretical model has been adapted from (Monje & Iwasaki, 2022), and describes the interactions between numerous bio-psycho-social factors and their route of influence on cognition in long-COVID. The arrows on the left of the diagram represent top-down influences, which determine how factors at lower levels must change and adapt depending on

[7] Based on the Work of Monje & Iwasaki, (2022) and Peper et al., (2016)

that higher order context. The arrows on the right represent bottom-up influences, which might explain how factors at lower levels determine higher order contexts.

Battery performance have found that medial prefrontal cortex, and olfactory bulb tissue loss is associated with the loss of taste and smell, lower mood and poorer cognitive function, or ‘brain-fog’, characteristic of long-COVID (Douaud et al., 2022; R. Gray, 2006; Guo, Ballesteros, et al., 2022; Guo, Benito Ballesteros, et al., 2022; Hugon, 2022; Jennings et al., 2022a; Tassignon et al., 2023).

These findings, alongside post-mortem neuro-histological and immunological long-COVID research have given rise to the hypothesis that COVID-19 viral particles can invade, damage, and ultimately kill nervous system cells, disrupting the functions those cells are responsible for (Elizalde-Díaz et al., 2022; Francistiová et al., 2021b; Matschke et al., 2020; Ortona & Malorni, 2022; Remmelink et al., 2020). In this neurobiological model of long-COVID, the lasting or chronicity of symptomology and cognitive impairment seen in the disease is hypothesised to be the result of organs, including the brain, that have been damaged (in some cases irreparably so) by the COVID-19 virus (Barnden et al., 2023; Bungenberg et al., 2022; Cecchetti et al., 2022; Ferrucci et al., 2021; Hellgren et al., 2022; Tian et al., 2022).

Current evidence suggests that it is a complex interplay between psychological and neurocognitive factors that contribute to people with long-COVID’s diminished QoL and cognitive functioning (Miskowiak et al., 2023; Scholz et al., 2023). Some studies have shown that greater symptom burden is associated with poorer QoL, reduced mobility and ability to carry out the tasks required of daily life (Cox et al., 2023; Genecand et al., 2023; Miskowiak et al., 2023; Spektor & Poluektov, 2022; Umakanthan et al., 2023). It is suggested that greater symptom burden negatively impacts healthy sleep, disrupts circadian rhythms, and causes

heightened sensitivity to pain, and increases negative affect (Cox et al., 2023; Genecand et al., 2023; Miskowiak et al., 2023; Spektor & Poluektov, 2022; Umakanthan et al., 2023). These symptom loads can be very difficult to manage which, in conjunction with low mood, can contribute to feelings of extreme social isolation, and hopelessness (Cox et al., 2023; Genecand et al., 2023; Miskowiak et al., 2023; Spektor & Poluektov, 2022; Umakanthan et al., 2023). Indeed, social isolation and poor sleep have independently been identified as significant mediating factors in experiences of anxiety, depression, and mental distress (Aghaei et al., 2022; Malesevic et al., 2023; Ngasa et al., 2021; Scholz et al., 2023; Van de Vyver et al., 2021).

It has been suggested that these biological and psychological impacts of long-COVID may also be exacerbated by societal factors such as the uncertainty (economic, housing, environmental, and health-related) and unpredictability arising from the pandemic (Aghaei et al., 2022; Every-Palmer et al., 2020; Faulkner et al., 2022; Hanna et al., 2022; Hawke et al., 2022; Van de Vyver et al., 2021; Van Herck et al., 2021). Many people have experienced worsening familial and interpersonal relationships, including higher rates of domestic and familial violence, some of which is hypothesised to result from the societal shifts brought about by the pandemic (Aghaei et al., 2022; Atilla et al., 2023; Every-Palmer et al., 2020; Van de Vyver et al., 2021). It has also been suggested that the proliferation of anti-vaccination sentiment, distrust in governments, and disbelief in news media led during the pandemic led to new levels of anxiety and hypervigilance for people across all of society and impacting population's general sense of wellbeing (Calvano et al., 2022; Gasteiger et al., 2021; Swami et al., 2017; Van de Vyver et al., 2021).

Summary

This theoretical model of disease highlights that it will be important to understand how sequalae and experience of long-COVID might be intensified by the uncertainty and unpredictability relating to the pandemic, individuals' own illness, and society's general lack of comprehension and acknowledgement of these points.

CHAPTER FOUR

Rationale for the Current Study

This chapter assesses the empirical evidence supporting the utility of online recruitment and data collection methods for conducting neuropsychological tests with long-haulers, and vulnerable populations. The rationale for the current study will then be established, and research questions discussed.

Long-COVID in New Zealand

While there is anecdotal evidence of long-COVID in the New Zealand, there is no empirical evidence yet published on the topic. As such, it has been assumed that this study will be the first investigating long-COVID's neuropsychological sequelae in the New Zealand context.

Using Online Cognitive Tests with Vulnerable Populations

A commonality among many studies of long-COVID's neuropsychological sequelae was using online surveys and social medias as a means to gather information from individuals who might otherwise not be able to access or participate in such a study. While there are seemingly no studies from New Zealand on long-COVID and cognition, it seems that some studies did however investigate changes in wellbeing among New Zealanders more broadly during the pandemic and relied on online forums for data collection.

From this New Zealand based research, vulnerable groups highlighted by studies utilising social media for recruitment, and survey websites for data collection included pregnant and breast-feeding women, the elderly, people with low socio-economic status (SES), and Māori and Pasifika peoples (Cheung et al., 2022; Faulkner et al., 2022; Freeman et al., 2022; Gasteiger et al., 2021; Muthc, 2021; Officer et al., 2022; Serlachius et al., 2021;

Stephens & Breheny, 2022; Wiki et al., 2021). In the context of mandatory lockdowns, online recruitment and data collection methods helped people participate in studies from the confines of their own homes, improving accessibility for some vulnerable people like pregnant women, elderly people, and adolescents with mental health concerns (Cheung et al., 2022; Faulkner et al., 2022; Freeman et al., 2022; Gasteiger et al., 2021; Muthc, 2021; Officer et al., 2022; Serlachius et al., 2021; Stephens & Breheny, 2022; Wiki et al., 2021). Nonetheless, there is also evidence to suggest that these methods (however unintentionally) exclude people with lower SES, lower technological competency, those who live more rurally, and lack internet connection or computer to participate (Cheung et al., 2022; Faulkner et al., 2022; Freeman et al., 2022; Gasteiger et al., 2021; Muthc, 2021; Officer et al., 2022; Serlachius et al., 2021; Stephens & Breheny, 2022; Wiki et al., 2021). Indeed, the majority of research investigating cognition in long-COVID populations is dependent on online methods because it brings studies into the homes of people who are unable to leave the house due to their illness (Day, 2022; Jason et al., 2021; Ziauddeen et al., 2022).

Māori and Pasifika are key vulnerable populations who are likely to be less well represented among online-sampling due to the accessibility issues outlined above. What is more, Māori and Pasifika people are also more likely to be significantly impacted by COVID-19 (MOH, 2020). Indeed, regression analyses have found that Māori with COVID-19 are 2.5 times as likely to be hospitalised that non-Māori and non-Pasifika people with COVID-19 (Steyn et al., 2020, 2021). Infection fatality rates (IFR) have also been modelled to be around 50% higher for Māori than non-Māori (Steyn et al., 2020, 2021). However, when the IFR is calculated assuming that individuals have concomitant health conditions, Māori are estimated to be 2.5 more likely IFR than non-Māori (Steyn et al., 2020, 2021). The challenge remains, if the easiest way for long-haulers to access and participate in research is via the use of online

tools – how can these tools be made more accessible to vulnerable people, especially Māori and Pasifika in New Zealand.

A key advantage available to us now, that was not available to researchers investigating mental health changes during pandemic lockdowns, is that because we are no longer in lockdown, recruitment of participants is not restricted to occur only in online spaces. To compromise, the current study consisted of an online survey and cognitive test that was accessible through a link, and which self-saved so it could be completed over several days, and different computers if necessary. To access a broader sample of New Zealanders, and to achieve ethical representation of vulnerable peoples in this study's groups, this study was advertised both online on social-media support groups, and in real community spaces like libraries, community centres, and local health clinics around New Zealand's Wellington and Lower Hutt regions.

The Current Study

This study aims to specify which cognitive domains are impacted by long-COVID, and whether cognitive changes are correlated with decreased quality of life in a New Zealand sample. Unlike the pandemic related cohort studies already conducted with New Zealand samples (and unlike many of the long-COVID and cognition studies conducted overseas) this study seeks to draw differences by comparing long-hauler performance to that of a control group, on the same measures.

As Chapters Two and Three have established, the historical and empirical literature convincingly highlights a pattern of altered neuropsychological functioning following viral infections. The case for long-term neuropsychological impacts following viral infections would have largely been ignored if not for the scale of the COVID-19 pandemic and the sheer number of people suffering the long-term effects of COVID bringing this narrative to light.

However, factors contributing to the development of long-COVID vary widely due to country-specific factors like timeline of COVID variant outbreak, vaccination availability, and access to health care. What is more, many long-COVID studies adopt a cohort design, yet lack adequate normative or control data, or objective measures to compare long-haulers cognitive performance or quality of life to. At present, the New Zealand-specific research on the topic is lacking, and thus the impacts of long-covid on cognition and quality of life remain unknown.

While some evidence suggests significant cognitive impairment amongst long-haulers, much of this research stems from convenience sampling of hospitalised populations who lack demographically matched healthy controls. During the pandemic, (especially during lockdowns) it can be assumed that individuals accessing the same hospital were living in the same geographical location, and thus were exposed to similar if not the same geopolitical and socioeconomic burdens including national COVID responses, vaccination status, and access to health care. Subsequently, neuropsychological data stemming from groups recruited from the same hospitals stands to be highly influenced by confounding variables, which could be matched away if there had been data from randomly sampled controls to compare it to. As such, there is little in the way of New Zealand based research to highlight whether differences in national COVID-19 responses, access to hospital care, and other socio-economic factors have any bearing on cognition outcomes associated with long-COVID. Indeed, these international cohort studies provide little in the way of sub-group vulnerabilities amongst long-haulers – a nuance which will have been significantly influenced by studies' dependence on severely ill and hospitalised participants and a lack of healthy controls to compare them with.

Finally, at present the majority of long-COVID and cognition research seeks to associate symptomology with pathology to delineate possible biochemical sites for

pharmacological intervention and treatment. In contrast, the current study takes a special interest in assessing the relationship between quality of life and neuropsychological changes, because this is seldom explored in the long-COVID literature yet provides an alternate route to identifying sites for intervention and treatment.

Rationale for Research Questions

This study poses a series of exploratory questions to investigate whether the neuropsychological sequelae of long-COVID observed internationally occur in a New Zealand context. The neuropsychological sequelae have been broken into its constituent components of neuropsychological symptomology, quality of life, and cognitive performance. As this study is the first of its kind to investigate the presence of these phenomena in Aotearoa, a secondary goal is to investigate those demographic aspects highlighted as risk factors for the neuropsychological sequelae of long-COVID overseas within a New Zealand based-sample.

Research Questions

1. Were symptoms worse (more frequent and severe) in people with long-COVID (Cases) than healthy participants (Controls)?
2. Were quality of life (QoL) scores worse in those with long-COVID (Cases) than healthy participants (Controls)?
3. Were Cognitive Battery scores worse in those with long-COVID (Cases) than health participants (Controls)?
4. Did QoL mediate those with long-COVID (Cases) Cognitive Battery performance?
5. Did demographic factors (age, gender and ethnicity) moderate neuropsychological symptom severity and frequency, and neuropsychological performance?

CHAPTER FIVE

Methods

Data Source

The current study uses a case-control cohort study design, with data gathered in the field from demographically matched case (long-COVID) and control (healthy, non-long-COVID) participants.

Participants

Recruitment

Given the nature of long-COVID, and the isolation periods associated with the COVID pandemic, the study information sheet, consent form and supplementary documentation was distributed in health clinics and online to the New Zealand long-COVID support group on Facebook. Participants could volunteer to be either in the long-COVID case study group, or in the healthy control group. Volunteers with long-COVID were asked to find demographically similar individuals from their own lives to be matched healthy controls if possible. This approach is common in long-COVID research (Clerici et al., 2017; Henneghan et al., 2021; Kirchberger et al., 2023; Moscardini & Tucker, 2023; Spanakis et al., 2019).

The Inclusion Criteria

Participants were included in the study if they were over the age of 18, and did not currently have COVID-19, or an un-managed health condition. Participants were automatically directed out of the survey if they selected the age group 18 or younger; or selected (a) that they had underlying health conditions, *and* (b) that these health conditions were not managed. Those directed out of the survey were thanked for their time and willingness to participate. Participants were included in the long-COVID Case group if they

had been experiencing symptoms associated with COVID-19 for three months or longer following initial infection, at the time of recruitment.

Sample Characteristics

A total of 114 participants were recruited into the study and were sorted into a healthy Control group (N=31) and long-COVID Case group (N= 83) based on whether they did or did not have long-COVID. The study had a matched-case-controls design to ensure that the groups were demographically matched, controlling for age and ethnicity as confounding factors. To match group sizes, several options were explored, including statistical manipulation such as bootlegging, to increase both group's sizes to 120 participants (Price et al., 2017). However, given the substantial attrition of response rates across the cognitive battery results for both groups, using a technique like bootlegging to multiply the control sample size from 30 to 83 also risked increasing error rates within the sample (Price et al., 2017). A simpler option, which was implemented in this study, involved matching control-group participants by demographic similarity as closely as possible with case group participants. In doing this, the case sample size was reduced from 83 to 31 to match the controls case size. Age, then gender, then ethnicity were prioritised based on their evidenced impact on long-COVID severity and cognitive function as confounding variables (Asadi-Pooya et al., 2021; Bai et al., 2022).

The resulting sample, whose data was used for data analysis consisted of 31 long-COVID participants (Cases), and 31 healthy participants (Controls). This sample's demographic characteristics are set out in Table 1. Many more participants with long-COVID joined the study than those without. Even following the application of exclusion and inclusion criteria, the long-COVID group (N=83) was much larger than the Control group (N=31). While this study utilised case-control matching to ensure even distribution of demographic

Table 1

Demographic Distribution Across Groups

	Frequency			Valid %		
	Controls	Un-Matched Cases	Matched Cases	Controls	Un-Matched Cases	Matched Cases
Age						
18-25	1	3	1	3.2	3.6	3.2
26-30	4	7	4	12.9	8.4	12.9
31-40	7	23	5	22.6	27.7	16.1
41-50	9	26	10 [a]	29.0	31.3	32.3
51-60	5	14	5	16.1	16.9	16.1
61-65	3	6	3	9.7	7.2	9.7
66+	2	4	3	6.5	4.8	9.7
Total	31	83	31	100	100	100
Gender						
Female	25	72	25	80.6	86.7	80.6
Male	4	6	4	12.9	7.2	12.9
Gender Diverse	2	4	2	6.5	4.8	6.5
Prefer not to say	-	1	-	-	1.2	-
Total	31	83	31	100	100	100
Ethnicity						
Māori	1	2	1	3.2	2.4	3.2
Pacific Islander	-	1	-	-	1.2	-
Asian	1	2	2	3.2	2.4	6.5
Pakeha	25	59	22	80.6	71.1	71.0
Māori, Pakeha	2	5	2	6.5	6.0	6.5
Māori, Pacific Islander	-	1	1	-	1.2	3.2
Other [b]	2	10	1	6.5	12.0	9.7
Total	31	83	31	100	100	100

Note. This table illustrates the demographic make up of this study's sample. Controls refer to the study's Control Group participants (N=31). Un-Matched Cases refer to the study's long-COVID participant group, Cases (N=83), before they were matched with Controls. Matched Cases (N=31) refers to the study's long-COVID participant group after they were matched to Controls.

[a] Matching by age was first preference, but not always possible as seen here.

[b] Participants could write as many options for ethnicity as they wished, or no option at all, so the total number of optional 'Other' ethnicities written by participants does not necessarily match the number of those who selected 'Other'. These ethnicities included British (*n*=4); Danish (*n*=1); Euro/Indian/Pacific (*n*=1); European (*n*=2); Irish (*n*=1); Israeli (*n*=1); Latin American (*n*=1).

features across groups, the inclusion of Matched Cases and Un-Matched Cases illustrates consistent distribution of demographic factors across groups in both instances.

Statistical Power

The statistical power of a study is calculated based on the significance level and sample size and represents the likelihood of getting statistically significant results on the condition of a specific and assumed effect size (Allana & Clark, 2018; Bernard, 2013; Price et al., 2017). The power calculation for the present study was conducted *a priori and* calculated by G*Power 3.1 (Erdfelder et al., 2007, 2009). With a two tailed alpha set at .05, desired power at 80% and Cohen's d = 0.5, sufficient sample size was calculated to be 64 participants in each group. These power analyses suggested that the sample size needed to reach at least 60 participants per group to undertake this study. While these sample sizes were reached for the Case group, numbers had to be reduced to match the smaller recruitment frame from the Control sample (N=31). This restriction on account of the inadequate numbers of control participants meant the total sample size for the study was (N=62) half of that indicated by power calculations.

A second power calculation was conducted to determine the statistical power that was likely to be found with this smaller sample size. This power calculation was conducted *post hoc* (after collection of data, but prior to statistical analyses) and calculated by G*Power

(Erdfelder et al., 2007, 2009). With a two tailed alpha set at 0.5, Cohen's d = 0.5, and total sample size at 62, power was calculated to be 0.99. Desired power is usually accepted to be around 0.80, however a power of 0.99 suggests that there is a 99% probability that the researcher will not commit type II error (Erdfelder et al., 2007, 2009).

Measures

Online Survey

All symptom and quality of life measures were administered via a single online survey that required an anonymised ID to access, and can be viewed in its entirety in Appendix C. The survey was designed by the researcher and built on Qualtrics by Massey University's School of Psychology's IT Analyst. The survey began with the study's information sheet, and consent sheet. After providing consent, participants were automatically redirected to the start of the survey.

The survey opens with basic demographic questions (age, ethnicity, gender and employment) and then screening questions which were used to sort participants into study groups or direct them out of the survey. These screening questions asked participants whether they currently had long-COVID, COVID-19 or other health conditions; when they tested COVID-19 positive; and whether their other (non-long-COVID) health conditions were managed. Participants were excluded from the study if they had COVID-19 or un-managed health conditions at the time of participation. Participants were sorted into the long-COVID case group if they had long-COVID and had tested positive for COVID-19 three or more months earlier in alignment with the long-COVID definitions accepted by the Ministry of Health (MoH, 2021). Participants were sorted into the healthy control group if they had managed health-conditions, did not have COVID-19, or long-COVID.

The survey contained a total of four measures, delivered in the following order: the Long-COVID Symptom Questionnaire (LCSQ), the Long-COVID Quality of Life Screen (LCQoL), the De Paul Symptom Questionnaire Short Form (DSQ), the NeuroQoL Cognition-Short Form Version 2.0 (NeuroQoL). Both the DSQ and the Neuro-QoL are open source and available for free use, with the provision that they are cited, and re-produced with the appropriate copyrights (Appendix C).The use of psychometrically validated measures in the survey helped affirm the reliability of participants self-reported symptomology (National Institute for Neurological Disorders and Stroke [NINDS], 2021; Sunnquist et al., 2019). As identified in Chapter Three, many long-COVID studies failed to corroborate and validate participants self-identified sequelae with psychometrically validated and diagnostically relevant measures (Bonsaksen et al., 2022; Bungenberg et al., 2022; Kirchberger et al., 2023; Roth & Gadebusch-Bondio, 2022)s. It was hoped that by using both types of measures (self-identified, and psychometrically validated), in this study findings might have had improved face and construct validity, whilst also offering greater credence for the experiences of long-COVID participants represented in this work.

The Long-COVID Symptom Questionnaire. The Long-COVID Symptom Questionnaire (LCSQ) was written because while DSQ covered a significant portion of those characteristic sequelae of long-COVID, it did not include those neuropsychological that have found to be associated with long-COVID and poorer cognitive domain function in the international literature (Davis et al., 2021; Jason et al., 2021). The LCSQ asked participants to rate the severity and frequency of 17 neuropsychological sequelae specific to long-COVID and evidenced to be associated with the cognitive and neurological changes associated with the disease (Davis et al., 2021; Jason et al., 2021).

The symptoms chosen for the LCSQ were identified by Davis et al., as being highly prevalent among long-COVID populations and included: *dry cough, tightness of chest, new*

allergies or anaphylaxis, hearing changes or tinnitus, runny nose or nasal congestion, sinus issues, hallucinations, neuralgia or nerve pain, vibrating sensations, acute confusion, brain fog, slurring of words, and *speech and language issues* (2021). Severity and Frequency scoring and response options were modelled off the DSQ (Sunnquist et al., 2019). For each symptom participants rated severity on a 5-point Likert *scale, 0 = symptom not present, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe*. Symptom frequency was rated on a 5-point Likert scale*, 0 = none of the time, 2 = about half the time, 3 = most of the time, and 4 = all of the time.*

To compare the severity and frequency of neuropsychological symptoms with other symptoms, all 17 sequelae were clustered into two domains, a Neurocognitive Symptom Domain, and a Somatic Symptom Domain. This clustering was informed by those neuropsychological sequelae that have been highlighted in the literature as experienced as primarily somatically or sensorimotor, and those that were primarily neurocognitive (Almeria et al., 2020; Ariza et al., 2022; Davis et al., 2021; Llana et al., 2023).

The Somatic Symptom Domain included seven symptoms: *dry cough, breathing difficulties, tight chest, new allergies, shortness of breath, runny nose or congestion,* and *sinus issues*. A domain score was the sum of each symptom score (either severity or frequency); with a possible score out of four for each symptom, the total possible somatic domain raw score was 28. Scores were standardised to a scale of 100, by multiplying total domain scores by 3.57. This method of scoring each domain was repeated for severity scores and frequency scores independently. Standardised severity and frequency scores were used for statistical analysis.

The Neuropsychological Symptom Domain included ten symptoms: *loss of taste, loss of smell, hearing changes or tinnitus, hallucinations, nerve pain or neuralgia, vibrating*

sensations, acute confusion, brain fog, slurring of words, and *speech or language issues.* A domain score was the sum of each symptom score, with a possible score out of four for each symptom. The total possible domain score was 40 and were standardised to a scale of 100 by multiplying total domain scores by 2.5. This method of scoring each domain was repeated for severity scores and frequency scores independently. Standardised severity and frequency scores were used for statistical analysis. The LCSQ was found to have excellent internal consistency (Chronbach's $\alpha = 0.90$).

Long-COVID Quality of Life. The Long-COVID Quality of Life measure (LCQoL) was written specifically for this study, with the intent to assess those aspects of life possibly impacted by long-COVID but not commonly assessed in long-COVID quality of life literature (Horgan et al., 2022; Líška et al., 2022; Malesevic et al., 2023). Indeed, most studies investigating quality of life in long-COVID use pre-existing measures that tend to be interested in one aspects of an individuals' life such as returning to work, ability to exercise, or physical health (Ariyo et al., 2021; Genecand et al., 2023; Horgan et al., 2022; Líška et al., 2022; Malesevic et al., 2023). Because long-haulers experience such a diverse range of presentations consisting of any number of symptoms, there is reason to believe that how this condition impacts quality of life may be as equally diverse. It is possible then, that quality of life measures focusing on one aspect of life may miss the impacts that long-COVID has across the breadth of long-haulers lives. For this reason, it is hoped that a quality of life measure written specifically for long-COVID may better illuminate how this condition affects individuals in all aspects of their lives. However, to ensure construct validity – that this measure was accurately assessing quality of life in a population experiencing cognitive changes – the NeuroQoL was also used (NINDS, 2021).

Participants were asked to rate how "in the past months have your symptoms impacted your ability to:

1. complete work to your previous standard
2. engage familiarly (hold conversations with those you live with)
3. engage socially (hold conversations and spend time with people you do not live with)
4. engage with a daily routine (for example, dress, brush teeth, prepare meals)
5. engage with hobbies (reading, watch TV, attend sports meets or spiritual/religious worship)
6. feel positively toward yourself (show compassion, appreciation or respect for yourself)
7. feel positive about tomorrow or your future.

These items were scored on a 6-point Likert scale, *0 = not at all, 1=up to one day a week, 2 = 2-3 days a week, 3 = 3-4 days a week, 4 = 5 days a week,* and *5 = daily/every day*. Scoring for the LCQoL was modelled of the NeuroQoL. The score of each item was summed to give a total raw score, from which z and t-scores were calculated to ensure normalcy of the data. Raw scores were used for statistical analysis. The LCQoL had excellent internal consistency (Chronbach's $\alpha = 0.91$).

De Paul Symptom Questionnaire-Short Form. The De Paul Symptom Questionnaire-Short Form (DSQ) is a 14-item measure that reliably assesses Chronic Fatigue Symptom severity and frequency in individuals and can be scored to diagnose chronic fatigue in those individuals (Sunnquist et al., 2019). The DSQ has been validated for use in those with chronic fatigue syndrome, as well as those with long-COVID (Jason et al., 2021; Sunnquist et al., 2019).

The DSQ asked participants how much symptom severity and frequency bothered them in the past six months, across 14 symptoms. Symptoms included *fatigue, next day soreness after everyday activities, tired after minimum exercise, feeling unrefreshed after*

waking in the morning, aching muscles, bloating, problems remembering, difficulty paying attention for long periods, irritable bowel problems, feeling unsteady on your feet, cold limbs, feeling hot or cold for no reason, flu-like symptoms, and *some smells, chemicals, medications or foods inducing nausea.* Frequency is scored as: 0 = *none of the time,* 1 = *a little of the time,* 2 = *about half of the time,* 3 = *most of the time,* and 4 = *all of the time*. Severity scores are defined as: 0 = *symptom not present,* 1 = *mild,* 2 = *moderate,* 3 = *severe,* 4 = *very severe*. To compare the severity and frequency of neuropsychological symptoms with other symptoms, all 14 symptoms were clustered into four domains, *a Fatigue Domain, a Pain Domain, a Neuropsychological Domain,* and a *Somatic Domain.*

The Fatigue Domain contained three symptoms: *fatigue, minimum energy after exercise,* and *feeling unrefreshed after waking*. A domain score was the sum of each symptom score (either severity or frequency); with a possible score out of four for each symptom, the total possible fatigue domain raw score was 12. Scores were standardised to a scale of 100, by multiplying total domain scores by 8.33 recurring.

The Pain Domain consisted of the symptoms of *next day soreness* and *painful or aching muscles,* with a total possible domain score of 8. Scores were standardised to a scale of 100 by multiplying total domain scores by 12.5.

The Neuropsychological Symptom Domain contained the symptoms of *problems remembering, difficulties sustaining attention, feeling unsteady on ones' feet,* and *being nauseated by smells or tastes,* with a total possible domain score of 16. Scores were standardised to a scale of 100 by multiplying total domain scores by 6.25.

The Somatic Symptom Domain contained the symptoms of *bloating, irritable bowl symptoms, feeling too hot or too cold for no reason, cold limbs,* and *flu-like symptoms*, with a

total possible domain score of 20. Scores were standardised to a scale of 100 by multiplying total domain scores by 5.

This method of scoring each domain was repeated for severity scores and frequency scores independently. Standardised severity and frequency scores were used for statistical analysis. The measure had excellent internal consistency (Chronbach's $\alpha = 0.92$).

Neurological Quality of Life-Cognition Short Form Version 2.0. The Neurological Quality of Life Measures assess the impacts of different neurological conditions on individual's quality of life; these measures have been validated for use to assess levels of health-related quality of life in clinical and research settings (Bai et al., 2022; Bode et al., 2010; Gudesblatt et al., 2016; NINDS, 2021). The Neurological Quality of Life-Cognition Short Form (NeuroQoL) assesses quality of life in relation to cognitive impairment and has recently been used to screen impaired quality of life in individuals after having COVID-19 (Frontera et al., 2022; Frontera, Lewis, et al., 2021; Frontera, Yang, et al., 2021).

The Neurological Quality of Life-Cognition Short Form measure (NeuroQoL) assesses an individuals' ability to function across eight cognitive domains related to participating well in daily life over the previous seven days (NINDS, 2021). The domains read as follows:

In the past 7 days …

1. I had to read something several times to understand it…
2. My thinking was slow …
3. I had to work really hard to pay attention or I would make a mistake …
4. I had trouble concentrating …

How much DIFFICULTY do you currently have …

5. Reading and following complex instructions …
6. Planning for and keeping appointments that are not part of your weekly routine …
7. Managing your time to do most of your daily activities …
8. Learning new tasks or instructions …

Domains 1 to 4 were scored on a 5-point Likert scale: *5 =Never, 4 = rarely/once, 3 = sometimes (2-3 times), 2 = often (once a day), 1 = very often (several times a da*y). Domains 5 to 8 were scored on a different 5-point Likert scale. This scale included the following, *5=None, 4=A little, 3 = Somewhat, 2 = A lot, 1 = Cannot do*. To score the NeuroQol, the numerical value for each domain is added to give a total raw score. These raw scores are transformed into t-scores using a score chart provided by the measure's authors. In line with author's recommendations, numerical t-scores were used for statistical analyses, including calculating mean responses for each group. The lower the score the poorer the quality of life. The NeuroQoL had excellent internal consistency (Cronbach's $\alpha = 0.91$).

Cognitive Battery

Following the symptom and quality of life measures participants completed an online Cognitive Battery, hosted by Massey University's School of Psychology's online lab space. The Cognitive Battery was selected by the researcher and modelled off Cognitive Batteries or Neuropsychological Batteries successfully administered in participants with long-COVID to assess their cognitive performance (Égerházi et al., 2007; Frontera, Lewis, et al., 2021; Guo, Benito Ballesteros, et al., 2022).[8] The cognitive battery was limited in the specific tests that it could include, due to what was available without cost, and its compatibility with the online

[8] As explained earlier, Cognitive Battery and Neuropsychological Battery are terms used interchangeably to describe a series of tests administered to assess a particular cognition function or domain, namely attention, executive function, learning and memory, language, sensorimotor control and perception, and social cognition (Harvey, 2019).

mechanism of delivery. Tests that required participants to draw or respond verbally like the Word List Recognition or Rey Osterith Drawing task could not be included (Ariza et al., 2022; Guo, Benito Ballesteros, et al., 2022; Henneghan et al., 2021; Kirchberger et al., 2023; Tassignon et al., 2023).

In line with studies successfully assessing cognitive performance in long-COVID, this Cognitive Battery consisted of four cognitive tests, namely the Word Recall, Digit Span, Stroop and Trail Making tasks (Ariza et al., 2022; Guo, Ballesteros, et al., 2022; Henneghan et al., 2021; Voruz, Allali, Benzakour, Nuber-Champier, Thomasson, Jacot de Alcântara, et al., 2022). Each of these tasks assesses a different component of neuropsychological functioning.

Immediate and Delayed Word Recall. The Word Recall task assesses working memory and learning. Many variations of the Word Recall task exist, with alternatives for verbal delivery, list length (ranging five to 15 words), different time delays, with and without task interference between the immediate and delayed trials psychometrically validated for use in those with mild cognitive impairment and dementia, adults with and without concussion (aged 18 to 70) and in those with long-COVID (Clerici et al., 2017; Guo, Ballesteros, et al., 2022; McElhiney et al., 2014; Meyer & Arnett, 2015; Mormont et al., 2012; Shankle et al., 2009).

In this cognitive task, scores were based on the number of words presented in sequence that were correctly recalled. Participants were exposed to three trials. The first trial exposed participants to a subset of the 15 words from the word list, and allowed them to practice being presented with words, and entering the list in the correct order as best as they could remember. Trial two exposed participants to the full set of 15 words; immediately after being presented with this list, they had to type in as many of these words as possible (order of

presentation did not matter). The third trial involved delayed recall. After completing all of the other cognitive tasks in this battery, the delayed recall trial began. Participants were asked to type in as many of the 15 words as they could remember. A score was generated for each trial, with the highest possible score of 15. Raw scores were used for statistical analysis. As applied in this study, the Word Recall task had good internal consistency (Chronbach's $\alpha = 0.81$).

Digit Span. The Digit Span task is often used in cognitive batteries to assess memory span. Similar to Word Recall, there a many variations of the Digit Span task, and it has been validated for verbal and sign-language delivery, in those with Alzheimer's disease, traumatic brain injury, mild cognitive impairment, and those with COVID-19 (Gignac et al., 2018; Greve et al., 2010; Heinly et al., 2005; Kirchberger et al., 2023; Resch et al., 2023; Schroeder et al., 2012; Varela et al., 2022). The Digit Span assesses learning and working memory by exposing participants to a sequence of numbers, after which they must recall as many as they can in the correct order. In some trials participants are asked to recall the numbers in the order they were presented (forward span), or in reverse (reverse span).

In the present study, participants experienced a total of eight trials. The first two trials were practice trials, in which a shorter sequence of numbers was presented so participants could practice recalling and entering said numbers. In the practice trials participants would receive feedback to know whether numbers had been entered correctly. Practice trials were followed by test trials. In test trials, a sequence of up to ten numbers (of any number between 1 to 10). The first three trials were forward span trials. The last three trials were reverse span trials. Participants did not receive feedback in test trials. Participants were scored out of ten for each of their total forward and reverse span trials. In the context of this study, the Digit Span had good internal consistency (Chronbach's $\alpha = 0.81$).

The Stroop Test. The Stroop test assesses attention and processing speed and is used in research and clinical settings to investigate individuals' ability to switch between cognitive tasks (Scarpina & Tagini, 2017). The Stroop effect is the delayed reaction time between correctly identifying congruent and non-congruent stimuli (Scarpina & Tagini, 2017). Typically, this stimulus is the difference in word colour, and the words for colour (Scarpina & Tagini, 2017). The Stroop test has been validated for delivery by computers and smartphones, in adults of all ages (18 to 80) and in those with long-COVID, alcohol dependence and older adults with cognitive complaints (Barnden et al., 2023; Clerici et al., 2017; Kirchberger et al., 2023; Pinnock et al., 2022; Spanakis et al., 2019; Voruz, Allali, Benzakour, Nuber-Champier, Thomasson, Jacot de Alcântara, et al., 2022).

For the present study's Stroop Test, participants were presented with a series of colour words, either Red, Blue or Green. The actual colour of the word itself was also either red, blue or green. However, the colour of the word was not necessarily the same as the word itself. That is, the word Red could have been presented in the colour blue. Participants were required to identify as quickly as possible the colour of the word, not the word text. The Stroop test consisted of 72 trials, (eight blocks with nine words each). Participants' reaction times were recorded in milli-seconds, and the correct number of recalled congruent and non-congruent colour words was counted. In this instance, congruent stimulus was when the word's colour and word spelt matched. The non-congruent stimulus was when the word was a different colour to the colour it spelt. In the context of this study, the Stroop test had very low internal consistency (Chronbach's $\alpha = 0.16$). However, this is likely because internal consistency measures the extent that all items on a test assess the same latent variable. And those discrete units for reaction time (milliseconds) and correctly identified stimulus assess very different aspects of the same variable.

Trail Making Test. The Trail Making Test (TMT) comprises two components, called Trail Making Test A (TMT-A) and Trail Making Test B (TMT-B). The fundamental components of TMT-A and TMT-B are very similar; however, each test assesses different components of cognition (Sanchez-Cubillo et al., 2009).

The task requires participants to connect 25 consecutive items with a line, either on a piece of paper or computer screen. In TMT-A the items are numbers, from 1 to 25. In TMT-B the items alternate between a number (from 1 to 13) and letters (A to L); in other words, participants must draw the line from 1-A-2-B-3-C, and so on. TMT-A assesses visuo-spatial processing speed, and TMT-B assesses task switching as a component of executive function, and working memory (Arbuthnott & Frank, 2000; Christidi et al., 2015; Sanchez-Cubillo et al., 2009). The TMT has been validated for tablet and computerised delivery, in all ages from 11 to 74, including in those with dementia, traumatic brain injury, Alzheimer's disease and mild-cognitive impairment (Arbuthnott & Frank, 2000; Baykara et al., 2022; Christidi et al., 2015; R. Gray, 2006; Park & Schott, 2022; Whiteside et al., 2019).

For the present study, participants were given a shortened practice trial in the format of TMT-A but with fewer items to connect. TMT-A was then delivered followed by TMT-B**.** There was no practice trial for TMT-B. Number of errors made, and total time spent in task, in milliseconds, were scored. As applied in the present study, the Stroop test had very low internal consistency (Chronbach's $\alpha = 0.36$). As outlined above, this low value might be explained by the degree of difference in the metrics used number of correct moves, versus time in milliseconds.

Procedure

This study's survey and Cognitive Battery were fully automated, and delivered in full online. The survey was designed to be completed online to reduce the impact of participating on

respondents' wellbeing, especially those in the long-COVID group. Participants accessed the study's online information and consent sheets via a link or QR code. Participants had to provide consent to participate before being directed to the survey. When participants began the survey, they were automatically attributed a random and anonymised four-digit ID. The survey was designed to be self-saving so participants could take as many rests as they needed, using their ID numbers to regain access to the survey.

Twenty-four hours following the completion of the survey, participants were emailed a second link that would take them to the Cognitive Battery, which they could access using their participant ID. The Cognitive Battery was fully automated, with participants being able to skip tasks if they were becoming fatigued or tired. Upon completing the Cognitive Battery, participants were given the option of entering a koha pool to win one of ten $100 supermarket vouchers, and to be emailed the study's findings.[9] After selecting either or both of these options, participants were thanked for their time and directed out of the survey site.

Ethics

A number of ethical issues arising in this study needed to be addressed and carefully managed to gain ethics approval from Massey University's institutional Ethics Committee. The central ethical issue stemmed from the very nature of working with participants with precarious health.

There was the potential issue of violating ethical precepts of non-maleficence and beneficence in that the mental, psychological and physical exertion required to participate could cause harm to participants by exacerbating their long-COVID symptomology. To mitigate these ethical risks, the online survey and Cognitive Battery were designed such that participants could take as many breaks as they needed to complete it. Participants were also

[9] Koha is a custom in Aotearoa New Zealand, of making a small offering in thanks for someone's contributions.

able to skip as many survey and Cognitive Battery components as they wished. These freedoms were highlighted in the study's information sheet and reinforced intermittently throughout the survey and the Cognitive Battery.

An issue of privacy and confidentiality was also encountered, as the nature of conducting this study online meant the sharing and gathering of personal health data in a manner that was potentially vulnerable to hacking, or computer malware attacks. To mitigate potential sharing or losing participants' private and confidential health data, extra safeguards were required to ensure participants' anonymity, and the confidentiality of their health-related information. While participants were recruited via an online Long-COVID support group, the researcher did not have personal access to this platform. The calls for participation were posted by the support groups' administrator who acted as an intermediary, and in doing so kept group members' identities private from the researcher. As soon as participants gave consent in the survey platform, they were given randomised and anonymised computer-generated IDs. Participants' survey and Cognitive Battery results were saved under these ID numbers, adding a further layer of privacy and anonymisation to participant's confidential data. A participant's completion of the online survey and Cognitive Battery would generate two separate files which were then stored securely in Massey's Data Cloud. These documents were backed-up fortnightly on a secure detachable, password protected and encrypted hard-drive.

Another ethical concern was ensuring that cultural contexts of the study's prospective participants were treated with sensitivity. Given the post-colonial context of Aotearoa New Zealand, it was important that the researcher was informed about the cultural, historical and personal impacts that neuropsychology as a scientific and clinical discipline has had on indigenous and vulnerable people. This was achieved through consultation with cultural advisors, engaging with relevant literature, and using research practices to make the study as

accessible as possible to those from different cultural and socio-economic backgrounds. In addition, the researcher adopted a phenomenological perspective to be aware of and minimise the impact that her cultural and personal values may have on participants, and interactions with their data.

This project was reviewed and approved by the Massey University Human Ethics Committee: Southern A, Application 22/27.

CHAPTER SIX

Results

Overview

The results of this study are split into five sections; Data Collation, Testing Assumptions of Normalcy, followed by Research Questions One, Two and Three. First the scoring and collation of data are discussed, followed by a brief discussion of testing assumptions of normalcy in the study groups. Preliminary analyses determined whether parametric or non-parametric statistical analysis would be required for Research Questions One, Two and Three.

Quantitative variables are described with means, standard error of the mean, and standard deviations. Independent samples, two-tailed, *t*-tests were conducted to compare Case and Control scores on the LCSQ, DSQ, LCQoL, NeuroQoL, and the Cognitive Battery tests. Given the attrition and variation in response rates seen across all study measures (Table 6.1), equal variance was not assumed for all *t*-tests, and the assumption of homoscedacity was rejected. These factors meant the sample was not viable for completing multiple regression and moderation analyses necessary to satisfy Research Questions Four and Five respectively. All data analyses were conducted using IBM SPSS Statistics version 22 for Windows 11.

Data Collation

Data was collated and scored and in SPSS, using the standardised procedures in test manuals (Jason et al., 2021; NINDS, 2021; Sunnquist et al., 2019). Scores were aggregated across participants in each study group to give a mean score for each test domain. Privacy and anonymity of individual participants was further protected by grouping data for analyses. Data collation highlighted substantial attrition in participants response rates across all measures and is displayed in Table 6.1. Because of this attrition, a two-tailed independent

Table 2

Available responses for comparison across measures

	LCSQ	LCQoL	DSQ	Neuro QoL	Word Recall	Digit Span	Stroop	Trail A	Trail B	Delayed Word Recall
Cases	31	31	30	31	23	18	14	14	14	13
Controls	30	29	28	28	18	14	13	13	13	12
Total	61	60	58	41	41	32	27	27	27	25

Note. Cases refers to the available responses from the long-COVID group for statistical analysis. Controls refers to the available responses from the health control group for statistical analysis. Total refers to the total number of responses per measure available for statistical analysis.

samples *t*-test was conducted to ensure that any differences in response rates between groups would not have a statistically significant effect on further statistical analyses. The difference in response rates between Cases (M = 21.9, *SD* = 8.14) and Controls (M = 19.8, *SD* = 7.89) was insignificant *t*(.59), *p* = .57), and the data was deemed appropriate for further analysis.

Collated data was then double-checked by the author and cross-checked by their supervisor. Errors were referred back to the author, ensuring that data were scored and entered correctly, minimising possibility for human error in the scoring procedure.

Testing Assumptions of Normalcy

Age, ethnicity and gender have been associated as potential confounding or influencing variables on long-COVID incidence and severity (Asadi-Pooya et al., 2021; Fernández-de-las-Peñas et al., 2022). In this study, case-control matching was used to help

manage the potential error introduced by these confounders into the sample (Tenny et al., 2023). Gender and ethnicity as categorical variables cannot be used to ascertain the normalcy of a sample; age group however, as an ordinal variable can, and consequently was selected as the subjective variable of interest to infer normalcy in both case and control groups (Goodwin, 2017; Price et al., 2017). Descriptive analysis was used to investigate the normalcy of the samples.

Descriptive analysis of age in the Cases group showed skewness of .22, indicating the distribution was slightly right-skewed (or older). The kurtosis of age for Cases was found to be -.39, which means the distribution is slightly flatter or less varied than a normal distribution curve. Descriptive analysis of age in the Control group showed skewness of .17, indicating that the distribution was slightly right skewed (or older). Kurtosis was found to be -.15, which means the distribution was slightly flatter or less varied than a normal distribution.

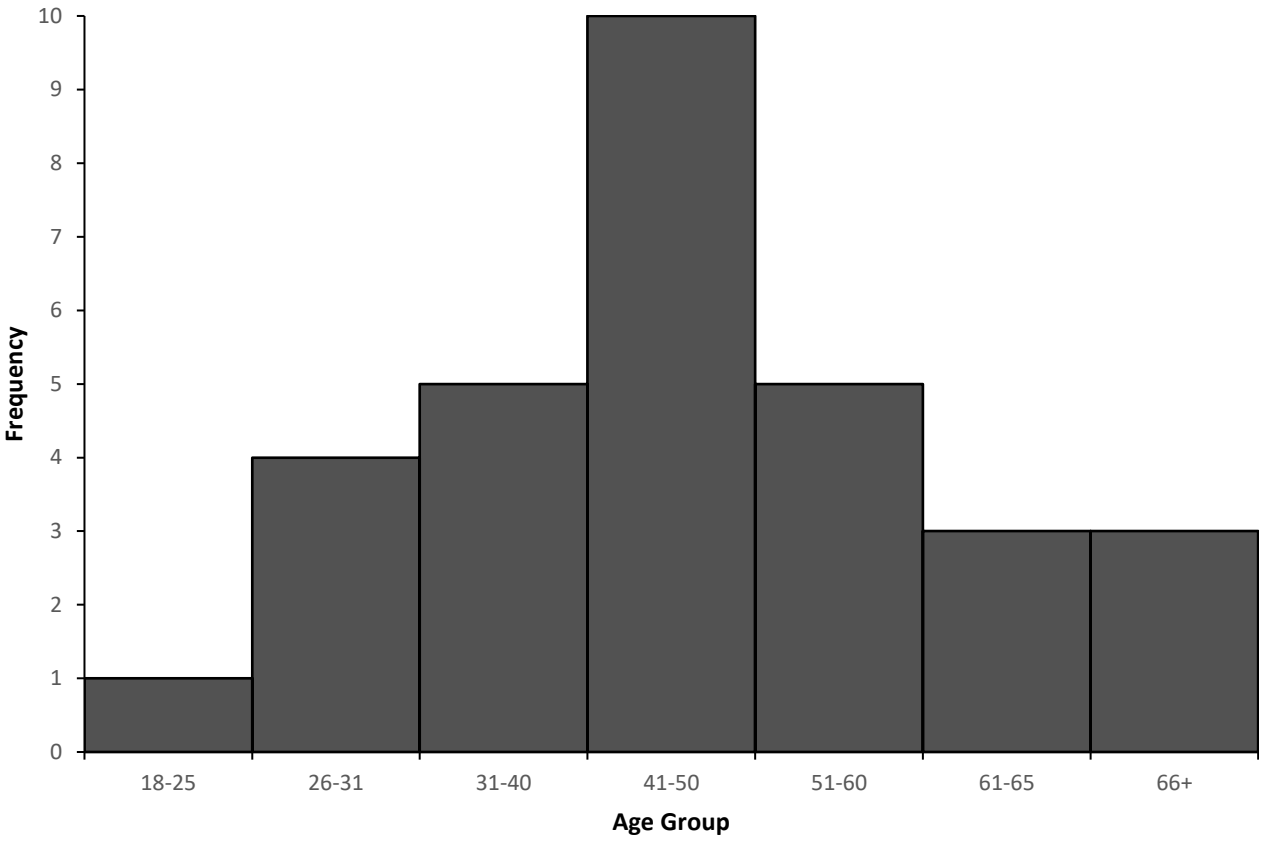
A visual inspection of the sample's graphical data was also conducted to affirm this acceptance of the assumption of normalcy (Goodwin, 2017; Price et al., 2017). The age distribution for the long-COVID Cases group (N=31) is seen in Figure 2. The distribution of age-group in the Cases group has a bell-shape and is symmetrically clustered horizontally around the median (*N=10,* in the 41-50 age group), indicating a kurtosis near, or equal to 0. Values are not clustered either to the right or to the left of the median, suggesting the sample's age is not drastically positively or negatively skewed, but normally distributed (Goodwin, 2017; Price et al., 2017).

Likewise, the age distribution in the Control group, as seen in Figure 3, is symmetrically clustered horizontally around the median *(N*=9, 41-50 age group), indicating a kurtosis near, or equal to 0. The shape of the graph illustrates that the majority of values lie

neither to the left or the right of the median (41-50), which suggests the sample is not skewed positively or negatively but is normally distributed (Goodwin, 2017; Price et al., 2017).

Figure 2

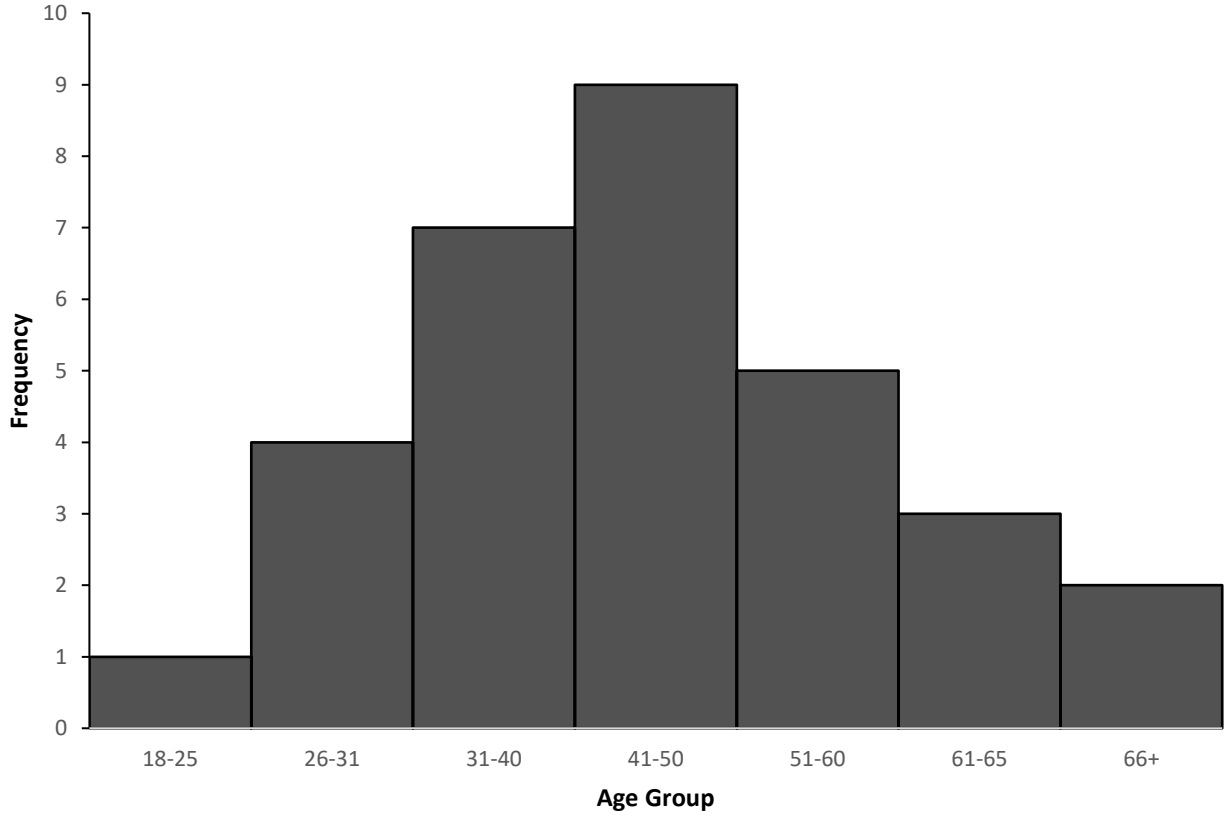
Frequency Distribution for Age in the Case (Long-COVID) Group



Note. Figure 2 shows the age distribution in the Cases Group. Ages were clustered into eight groups and ranged from 18 years to over 65. Frequency indicates the number of participants who fell within each age group. Median age group was 41-50 years old, with a frequency of ten participants.

Figure 3

Frequency Distribution for Age in the (healthy) Control Group



Note. Figure 3 shows the age distribution in the Control Group. Ages were clustered into eight groups and ranged from 18 years and older. Frequency indicates the number of participants who fell within each age group. Median age group was 41-50 years old, with a frequency of nine participants.

As the sample appears to be normally distributed, parametric analyses were applied as they were best suited the variable types and available data for each research question (Verma & Abdel-Salam, 2019).

Research Question One: **Independent Samples, Two-Tailed, *T*-Test**

Were symptoms worse (more frequent and severe) in those with long-COVID (Cases) than healthy participants (Controls)?

LCSQ

Mean, standard deviation (SD), and standard error of the mean (SEM) statistics for the frequency and severity of symptom scores on the LCSQ are displayed in Table 3.

Table 3

LCSQ Descriptive Statistics in Cases and Controls (N = 62)

	Cases			Controls		
	N	M *(SD)*	SEM	*N*	M *(SD)*	SEM
Somatic Symptom Frequency	31	29.37 (20.92)	3.76	29	23.52 (18.81)	3.50
Somatic Symptom Severity	30	28.69 (16.50)	3.01	28	22.31 (15.72)	2.97
Neuropsychological Symptom Frequency	30	31.83 (15.71)	2.87	30	15.92 (14.61)	2.67
Neuropsychological Symptom Severity	31	25.73 (13.23)	2.38	30	14.91 (11.94)	2.18

Descriptive analysis of the LCSQ shows that Cases (M=29.37, *SD*=20.92) had larger means on the Somatic Symptom Frequency scale than in Controls (M= 23.52, *SD* =18.81). This difference of 5.85, 95% CI [-4.41, 16.12] in Case and Control means this result was not statistically significant, *t*(1.14), *p* = .26, Cohen's d = 0.29 (small effect).

Cases (M= 28.69, *SD* =16.50) also had larger means than Controls (M =23.52, *SD* =18.81) on the Somatic Symptom Severity scale. This 5.17 difference in means, 95% CI [-2.12, 14.86], was not statistically significant, *t*(1.51), *p*= .14, Cohen's d = 0.34 (small effect).

Cases (M=31.83, *SD* = 15.71) had higher means than Controls (M= 15.92, *SD* = 14.61) on the Neuropsychological Symptom Frequency scale. This 15.91 difference, in group means, 95% CI [8.07, 23.76], was statistically significant, *t*(4.06), *p*< .001, Cohen's d = 1.05 (large effect size).

Similarly, Cases (M= 25.73, *SD* =13.23) had higher means than Controls (M=14.91 *SD*= 11.94) on the Neuropsychological Symptom Severity scale. The 10.84 difference in group means, 95% CI [4.35, 17.27], was statistically significant, *t*(3.35), *p* = .001, Cohen's d = 0.86 (large effect size).

DSQ

Descriptive analysis of the DSQ found that mean Symptom Frequency and Severity scale mean scores were higher in Cases than in Controls across all four symptom domains. Mean and standard deviation statistics for the frequency and severity of symptom scores on the DSQ are displayed in Table 4.

Cases (M= 78.61, *SD* =19.16) had higher means than Controls (M= 54.31, *SD* =30.10) on the Fatigue Symptom Frequency scale. This 24.3 difference in means, 95% CI [11.04, 37.56], was statistically significant, *t*(3.69), *p*< .001, CI, Cohen's d = 0.97 (large effect size). Cases (M = 62.91, *SD* =14.53) also had higher mean scores than Controls (M = 48.75, *SD* = 21.88) on the Fatigue Symptom Severity scale. This 14.16 difference in means, 95% CI [4.09, 24.23], was statistically significant, *t*(2.83), *p* = .007, Cohen's d = 0.77 (medium effect size).

Cases (M = 61.66, *SD* = 26.86) had higher mean scores than Controls (M = 42.67, *SD* = 33.66) on the Pain Symptom Frequency scale. This 18.99 difference in means, 95% CI [3.06 -34.92], was statistically significant, *t*(2.39), *p* = .02, CI, Cohen's d = 0.62 (medium effect size). Cases (M = 56.47, *SD* = 14.53) had higher mean scores than Controls (M = *9.81, SD* = 25.49) on the Pain Symptom Severity scale. This 46.66 difference in means, 95% CI [3.42, 29.89], was statistically significant, *t*(2.52), *p* = .015, Cohen's d = 0.68 (medium effect size).

Table 4

DSQ Descriptive Statistics in Cases and Controls (N = 62)

	Cases			Controls		
	N	M *(SD)*	SEM	*N*	M *(SD)*	SEM
Fatigue Symptom Frequency	30	78.61 *(19.16)*	3.50	29	54.31 *(30.10)*	5.59
Fatigue Symptom Severity	29	62.91 *(14.53)*	2.70	27	48.75 *(21.88)*	4.21
Pain Symptom Frequency	30	61.66 *(26.86)*	4.90	29	42.67 *(33.66)*	6.25
Pain Symptom Severity	29	56.47 *(14.53)*	2.70	27	*9.81(25.49)*	4.90
Neuropsychological Symptom Frequency	30	48.96 *(19.08)*	3.48	27	30.32 *(21.56)*	4.15
Neuropsychological Symptom Severity	29	44.83 *(19.84)*	3.68	24	31.77 *(20.43)*	4.17
Somatic Symptom Frequency	29	33.45 *(18.86)*	3.50	27	24.07 *(23.49)*	4.52
Somatic Symptom Severity	28	31.61 *(16.72)*	3.16	24	26.88 *(21.96)*	4.48

Neuropsychological Symptom Frequency score means were higher in Cases (M = 48.96, *SD* =19.08) than in Controls (M = 30.32, *SD* =21.56). This 18.69 difference in means, 95% CI [7.77 – 29.50], was statistically significant, *t*(3.44), *p* = .001, CI Cohen's d = 0.92 (large effect size). Neuropsychological Symptoms Severity score means were also higher in Cases (M = 44.83, *SD* =19.84) than in Controls (M = 31.77, *SD* =20.43). This 13.06 difference in means, 95% CI [1.87, 24.24], was statistically significant *t*(2.35), *p*= .023, Cohen's d = 0.65 (medium effect size).

Somatic Symptom Frequency mean scores were higher for Cases (M =33.45, *SD* =18.86) than in Controls (M = 19.26, *SD* =18.76). This 14.59 difference in means, 95% CI [-2.11, 20.86], was not statistically significant, *t*(1.64), *p* = .11, Cohen's d = 0.44 (small effect size). Somatic Symptom Severity mean scores were also higher for Cases (M = 31.61, *SD* =16.72) than in Controls (M = 26.88, *SD* = 21.96). This 4.73 difference in means, 95% CI [-6.33, 15.80], was not statistically significant, *t*(.86), *p* = .39, Cohen's d = 0.25 (small effect size).

Research Question Two: **Independent Samples, Two-Tailed, *T*-Tests**

Were quality of life scores worse in those with long-COVID (Cases) than healthy participants (Controls)?

LCQoL

Mean Raw Scores for the LCQoL were higher for Cases (M = 23.19, *SD* = 1.5) than Controls (M = 12.55, *SD* = 2.19). This 10.64 difference in means, 95% CI [5.31, 15.97], was statistically significant, *t*(4.06), *p* < .001, Cohen's d = 1.05 (large effect size).

NeuroQoL

NeuroQoL mean Raw Scores were lower for Cases (M = 21.26, *SD* = 6.22) than Controls (M = 24.59, *SD* = 9.35). This 3.33 difference in means, 95% CI [-7.61, .96], was not statistically significant, *t*(-1.60), *p* = .13, Cohen's d = 0.42 (medium effect size). NeuroQoL mean t-scores were also lower for Cases (M = 36.37, *SD* = 7.5) than Controls (M = 40.34, *SD* = 12.14). This 3.97 difference in means, 95% CI [-9.77, .83], was not statistically significant, *t*(-1.69), *p* = .10, Cohen's d = -0 .45 (medium effect size).

Research Question Three: **Independent Samples, Two-Tailed, *T*-Tests**

Were Cognitive Battery scores worse in those with long-COVID (Cases) than healthy participants (Controls)?

Cognitive Battery

Descriptive statistics (Mean, SD, and SEM) for Case and Control scores on all Cognitive Battery tests are displayed in Table 5.

Immediate and Delayed Word Recall. The mean number of Words Correctly Recalled immediately in Trial A was about the same in Cases (M = 5.38, *SD* = 2.46) and Controls (M = 5.17, *SD* = 0.56). This .21 difference in means, 95% CI [-1.36, 1.79], was not statistically significant, *t*(0.276), *p* = 0.78, Cohen's d = 0.09 (small effect size).

The mean number of Words Correctly Recalled immediately in Trial B was slightly less in Cases (M = 9.10, *SD* = 2.96) than Controls (M = 9.78, *SD* = 2.67). This - .68 difference in means, 95% CI [-2.51, 1.15], was not statistically significant, *t*(- .75), *p* = .46, Cohen's d = -0.24 (small effect size).

The mean number of Words Correctly Recalled in the Delayed Trial was less in Cases (M = 6.21, *SD* = 2.89) and Controls (M = 8.25, *SD* = 3.82). This -2.04 difference in means,

95% CI [-4.84, .44], was not statistically significant, *t*(-1.51), *p* = .15), Cohen's d = -0.61 (medium effect size).

Digit Span. The mean Forward Digit Span for the Forward Trial (numbers correctly recalled in sequence) was about the same in Cases (M = 5.25, *SD* = 1.98) and Controls (M = 5.21, *SD* = 1.81). This .04 difference in means, 95% CI [-1.38, 1.45], was not statistically significant, *t*(.052), *p* = .96, Cohen's d = 0.02 (small effect size).

The mean Reverse Digit Span for the Reverse Trial (numbers correctly recalled in reverse sequence) was slightly lower for Cases (M = 3.81, *SD* = 1.68) than Controls (M = 4.57, *SD* = 1.99). This -.76 difference in means, 95% CI [-2.15, .64], was not statistically significant, *t*(-1.12), *p*= .27, Cohen's d = -0.42 (small effect size).

Stroop Test. The mean Congruent Accuracy was very similar in Cases (M = .99, *SD* = .03) and Controls (M = .99, *SD* = .01). There was no statistical difference in group means, 95% CI [-.03, .02], *t*(- .35), *p* = .73, Cohen's d = -0.13 (small effect size).

Mean number of Correctly Identified Congruent Items were very similar in Cases (M = 26.97, *SD* = 1.13) and Controls (M = 27.23, *SD* = 1.48). The -.036 difference in means, 95% CI [-1.41, 0.68], were not statistically significant, *t*(- .74), *p* = .48, Cohen's d = 1.3 (large effect size).

Mean Congruent Reaction Times (in milliseconds) were longer in Cases (M = 1359.47, *SD* = 423.78) than Controls (M = 969.90, *SD* = 331.37). This 425.57ms difference in means, 95% CI [131.71, 719,43], was statistically significant, *t*(2.98), *p*= 0.006, Cohen's d = 1.12 (large effect size).

The mean Non-Congruent Accuracy was slightly lower in Cases (M = .94, *SD* = .07) than Controls (M = .97, *SD* = .02). This -.03 difference in means, 95% CI [- .07, .01], was not statistically significant, *t*(-1.60), *p*= .13, Cohen's d = -0.6 (medium effect size).

Table 5

Descriptive Statistics for Case and Control Cognitive Battery Score

	Case			Control		
	n	**M *(SD)***	**SEM**	***n***	**M *(SD)***	**SEM**
Word Recall						
Trial A Correct	21	5.38 (2.46)	0.54	18	5.17 (2.38)	0.56
Trial B Correct	21	9.10 (2.96)	0.65	18	9.78 (2.67)	0.63
Delayed Correct	14	6.21 (2.89)	0.77	12	8.25 (3.82)	1.10
Digit Span						
Forward Digit Span (Score)	16	5.25 (1.98)	0.50	14	5.21 (1.81)	0.48
Reverse Digit Span (Score)	16	3.81 (1.68)	0.42	14	4.57 (1.99)	0.53
Stroop						
Congruent Accuracy	15	0.99 (0.03)	0.01	13	0.99 (031)	0.01
Congruent Correct	15	26.97 (1.13)	0.29	13	27.23 (1.48)	0.41
Congruent Reaction Time (ms)	15	1395.47 (423.78)	109.42	13	969.90 (331.37)	91.9
Non-Congruent Accuracy	15	0.94 (0.07)	0.02	13	0.97 (0.02)	0.01
Non-Congruent Correct	15	51.27 (4.50)	1.61	13	53.46 (2.72)	0.76
Non-Congruent Reaction Time (ms)	15	2197.92 (2046.6)	528.43	13	1066.08 (367.73)	101.99
Trail Making						
Trail A Completion Time	15	45237.47 (37012.88)	9556.68	13	32447.38 (13560.15)	3760.91
Trail A Errors	15	0.47 (0.83)	0.215	13	0.31 (0.75)	0.21
Trail B Completion Time	15	64304.80 (17970.15)	4639.87	13	59366.62 (29194.42)	8097.07
Trail B Errors	15	2 (3.16)	0.82	13	0.69 (1.18)	0.33

The mean number of Correctly Identified Non-Congruent Items was slightly lower in Cases (M = 51.27, *SD* = 4.50) than Controls (M = 53.46, *SD* = 2.72). This -2.19 difference in means, 95% CI [-5.06, .67], was not statistically significant, *t*(-1.58), *p* = .13, Cohen's d = -0.58 (medium effect size

Mean Non-Congruent Reaction Times (in milliseconds) were longer in Cases (M = 64304.80, *SD* = 17970.15) than Controls (M = 59366.62, *SD* = 29194.42). This 1131.84ms difference in means, 95% CI [-15.02, 2278.70], was statistically significant *t*(2.1), *p = 0.05*, Cohen's d = 0.73 (medium effect size).

Trail Making Task. Mean task Completion Time (in milliseconds) to complete Trail Making Task A was longer for Cases (M = 45,237.47, *SD* = 37,012.88) than Controls (M = 32,447.38, *SD* = 13,560.15). The 12,789.09ms difference in means, 95% CI [-8,772.62, 34,352.78], was not statistically significant, *t*(1.25), *p* = .23, CI Cohen's d = .45 (medium effect size).

The mean number of Errors Made in Trail A were slightly higher for Cases (M = .47, *SD* = .83) than Controls (M = .31, *SD* = .75). This difference of .16 in means, 95% CI [-.46, .78], was not statistically significant, *t*(.527), *p* = .6, Cohen's d = 0.2 (small effect size).

Mean Completion Time (in milliseconds) to complete Trail Making Task B was longer for Cases (M = 64,304.80, *SD* = 17,970.15) than Controls (M = 59,366, *SD* = 29,194.42). This 4,938.18ms difference in means, 95% CI [-14,568.35, 24,444.72], was not statistically significant, *t*(.53), *p* = 0.60, Cohen's d = -0.54 (medium effect size).

The mean number of errors made in Trail B were higher for Cases (M = 2, *SD* = 3.16) than Controls (M = .69, *SD* = 1.18). This 1.31 difference in means, 95% CI [- .54, 3.15], was not statistically significant, *t*(1.49), *p* = .154, Cohen's d = 0.53 (medium effect size)

CHAPTER SEVEN

Discussion

The present study explored whether neuropsychological symptomology and impaired neuropsychological performance was more common in people with long-COVID than healthy individuals. While there is a considerable amount of international research on the neuropsychological impacts of long-COVID, this present study fills an important gap in the literature by providing what we believe may be one of the first New Zealand based findings on the topic. Because this research is likely the first on this topic to be conducted in New Zealand it has retained an exploratory focus, identifying any difference in neuropsychological symptoms and cognitive function between people who had long-COVID and those who did not. The results of this study suggest that the neuropsychological factors associated with long-COVID observed in international samples are also present in the New Zealand populus. This chapter opens with a summary of the key findings which is then followed by an in-depth discussion of each of these findings in relation to the international literature. The study's limitations are then unpacked, which is then followed by a brief discussion of this study's implications for future research and clinical practice.

Key Findings

Key findings from this study include a combination of significant and insignificant results. Firstly, as measured by the LCSQ and DSQ neuropsychological symptoms, including fatigue and pain, were experienced to be significantly more frequent and severely by long-haulers compared to health individuals. In contrast, differences in somatic symptoms between groups was found to be insignificant. It was also found that quality of life was significantly poorer for long-haulers as measured by the LCQoL, but not by the NeuroQoL. Long-haulers were not found to have poorer cognitive performance than healthy controls in the majority of

cognitive domains assessed (short term memory, learning, working memory, attention, and decision making) except for processing speed. In other words, language comprehension and processing speed were found to be significantly slower in participants with long-COVID than healthy controls. The implications of these findings, and how they relate to existing long-COVID research are discussed in more detail below.

Neuropsychological Sequelae Including Pain and Fatigue

The findings of this study showed that long-haulers experienced more frequent and severe neuropsychological sequelae, including fatigue and pain, than healthy individuals (Davis et al., 2021, 2023; Douaud et al., 2022; Jason et al., 2021). While there is little published research in New Zealand on this topic, the international literature highlighted that such outcomes were possible (Guo, Ballesteros, et al., 2022; Guo, Benito Ballesteros, et al., 2022; Jason et al., 2021; Radio New Zealand, 2020, 2022; Wolters, 2020). As measured by both the LCSQ and the DSQ, it was found that long-haulers experienced significantly more severe and more frequent neuropsychological long-COVID symptoms than healthy participants. Of the long-COVID sequelae commonly associated with CFS/ME, symptoms of fatigue and pain were also significantly more frequent and severe in long-haulers than in healthy individuals. Interestingly however, and in contrast to some international studies, neither the LCSQ or the DSQ found significant differences in somatic symptomology (both severity and frequency) between long-haulers and healthy controls (Davis et al., 2021, 2023; Douaud et al., 2022; Jason et al., 2021).

Evidence for a Bio-Psycho-Social Model of Disease?

The Bio-Pscyho-Social Model of long-COVID (outlined in Chapter Three) might also explain the significant pain and fatigue symptomology and insignificant somatic symptomology observed in this study. It is possible that the pain experienced by those with

long-COVID is related to peripheral or central nervous system disruptions caused by the neuro-invasive properties of the SARS-CoV-2 virus (Achar & Ghosh, 2020; Bougakov et al., 2021; Desforges et al., 2020; Meinhardt et al., 2021; Shi et al., 2021). It is also possible, and not a mutually exclusive possibility, that this pain is due to the damage and disruption of organs around the body (Achar & Ghosh, 2020; Bougakov et al., 2021; Desforges et al., 2020; Meinhardt et al., 2021; Monje & Iwasaki, 2022; Shi et al., 2021).

Undoubtedly however, exposure to constant and fluctuating pain is exhausting on both one's' body and psychology, so it is unsurprising that fatigue, feeling tired after minimal exercise, and feeling unrefreshed upon waking were elevated in association with elevated levels of next day soreness and painful muscles in the present study (Çinar et al., 2020; Cockshell & Mathias, 2010). It is well established in pain literature, that cognitive fatigue can make the experience of pain more intense which then becomes an increasingly salient and exhausting stimulus, also potentially contributing to the chronicity and severity consistently observed in long-COVID sequelae internationally, and now in New Zealand too (Agarwal et al., 2022; Asadi-Pooya et al., 2021; Guo, Ballesteros, et al., 2022; Ngasa et al., 2021; Peng, 2023).

Somatic Symptoms

It was surprising that levels of somatic symptoms were found to be insignificant in the present cohort considering that these symptoms have been commonly found at high levels in those with long-COVID compared to controls (Agarwal et al., 2022; X. (1 Chen 2) et al., 2021; Davis et al., 2021; Denke et al., 2018; Horn et al., 2021; Peng, 2023). The Bio-Psycho-Social model of disease, which considers the interaction between biological factors (such as time-elapsed since infection and rate of recovery), psychological factors (such as excessive stress, anxiety and fatigue), and social factors (like public health factors influencing which

viral strain infects the public) might also provide an explanation for the lack of significance in these results (Cornish & Stelson, 2023; Laher et al., 2021; Sacks-Zimmerman et al., 2023; Thurner & Stengel, 2023).

Biological and Psychological Factors

Timing is a likely factor underscoring long-COVID's biological outcomes which is evidenced by findings that show how somatic symptoms begin to alleviate over a period of six to seven months following acute infection while neuropsychological ones persist (Agarwal et al., 2022; Cecchetti et al., 2022; Davis et al., 2021; Emecen et al., 2022; Horn et al., 2021; Tarantino et al., 2022). In the context of the present study, it is possible that the time-elapsed since participants' acute COVID-19 infection was greater than this six-to-seven-month period, and somatic symptoms had begun to remit due to healing in somatic tissue (Agarwal et al., 2022; Cecchetti et al., 2022; Davis et al., 2021; Emecen et al., 2022; Horn et al., 2021; Tarantino et al., 2022).

In general terms, even though SARS-CoV-2 viral packages may have entered and damaged or ablated somatic cells in the body's organs, these cells can and do heal and replenish (Bhandari et al., 2020; Bougakov et al., 2021; Desforges et al., 2020; Francistiová et al., 2021a; Meinhardt et al., 2021; Peters et al., 2021). Neural tissue is not the same. As seen in dementia, Alzheimer's disease, and HIV Associated Neurodegenerative Disease (HAND) damaged neurons and glia might heal depending on the presence and health of surrounding glia (Bouhrara et al., 2018; Clifford & Ances, 2013; Elizalde-Díaz et al., 2022; Idrees & Kumar, 2021; Islam et al., 2020).[10] Moreover, high levels of psychological stress are known to impair the brain's immune system, and its ability to heal (Peña-Bautista et al., 2020). In this

[10] Glia are nerve cells which remove toxins from the brain, and support and replenish neurons. Neurons are the tissue necessary for the conductance of information.

bio-psycho-social model of long-COVID's neuropsychological sequelae, it is possible that the increased levels of psychological stress observed in association with the pandemic and the experience of long-COVID further influenced the brain's ability to recover . Unfortunately, and concerningly for those living with long-COVID's neuropsychological sequelae, when neural tissue dies, there is very little chance it replenishes (Bouhrara et al., 2018; Clifford & Ances, 2013; Elizalde-Díaz et al., 2022; Idrees & Kumar, 2021; Islam et al., 2020). It is possible that after this six-to-seven-month mark, the cellular damage in the body has begun to heal, thus the somatic symptoms drop off in severity and frequency (Borsche et al., 2021; Davis et al., 2021; Monje & Iwasaki, 2022; Whiteside et al., 2022). The neuropsychological symptoms however, persist and show less indications of improving because the tissue responsible for the lost or altered function may be irreparably damaged and unable to be restored (Borsche et al., 2021; Davis et al., 2021; Monje & Iwasaki, 2022; Whiteside et al., 2022). While there is a substantial body of work interrogating the persistence of long-COVID's neuropsychological sequelae, new studies could investigate why it is that those neuropsychological sequelae persist when somatic symptoms abate.

Societal Factors: Exposure to Viral Strains

Another possible explanation for these findings has to do with a potential association between long-COVID sequelae and viral strain. As this is the first study investigating long-COVID's neuropsychological sequelae in Aotearoa New Zealand, there is no prior research in which a possible explanation for these results might be found. It has been suggested internationally however that neuropsychological sequelae experienced in long-COVID is in-part determined by which variant of the SARS-CoV-2 virus individuals were infected by (Asadi-Pooya et al., 2021; Jung et al., 2022).

Long-COVID research happening earlier in the pandemic was likely conducted with participants who were infected with one of these earlier strains of COVID-19. Indeed, a lot of the international literature on long-COVID's neuropsychological sequelae was conducted in the first two years of the pandemic (2020 and 2021) in which the alpha, beta, and gamma strains were dominant (Akbarialiabad et al., 2021). Importantly, during these years, alpha, beta, gamma viral strains were, for the most part, kept out of the New Zealand population by rigorous public health measures (MoH, 2023, 2020). It was not until the more contagious delta and omicron variants reached New Zealand at the end of 2021 and became established in the community in early 2022, that acute-COVID-19 and long-COVID case numbers began to rise (MoH, 2021). Subsequently, if viral strains impact what long-COVID sequelae are experience, this difference in time-frames means earlier long-COVID research compared to the present study might be capturing long-COVID caused by different viral strains, and thus have different experiences sequelae including somatic symptoms (Jung et al., 2022; Ministry of Health, 2023). To clarify this point, further research could explore the extent that COVID-19 variants are risk factors for the development of long-COVID's neuropsychological sequelae. This will become more important over time as the virus continuous to mutate, resulting in different acute symptomology, and by extension, long-COVID sequelae.

Quality of Life

Quality of life was found to be significantly worse for long-COVID individuals compared to healthy controls as measured by the LCQoL, but not by the NeuroQoL. These findings are interesting because they contradict research investigating quality of life in long-COVID, including research using the NeuroQoL, that has found that long-haulers have significantly poorer quality of life than other individuals (Ariyo et al., 2021; Cox et al., 2023; Frontera, Yang, et al., 2021; Genecand et al., 2023; Lerer et al., 2022; Tabacof et al., 2022).

The LCQoL and the NeuroQoL assess different areas of functioning in daily life. Where the LCQoL probes individuals capacity to engage with key aspects of life (working, familiarly, socially, hobbies, routine) in relation to esteeming themselves and their lives. The NeuroQoL on the other hand probes aspects of cognition as they relate to daily life (ability to read, think, pay attention and concentrate; and difficulty following instructions, planning and keeping dates, managing time, and learning). That long-COVID participants' quality of life was significantly impaired in relation to key aspects of living rather than the daily demands of cognition could be explained by the possibility that the decreased quality of life is not associated with objective decrements in cognitive function. While these findings were surprising because they contradict a growing body of international research, they would corroborate the lack of significant Cognitive Battery results observed in this study (Genecand et al., 2023; Hopkins et al., 2011; Malesevic et al., 2023; Miskowiak et al., 2023; Samper-Pardo et al., 2023; Scholz et al., 2023; Umakanthan et al., 2023). There are also however contextual psychological and societal factors that, while they may not have directly impacted this study's findings, have been highlighted in the literature as likely moderating variables on long-COVID, its neuropsychological sequelae, and associated quality of life.

Psychological Factors. It is possible that these significant quality of life results could be explained by the inclusion of two probes for depression, anxiety and mental distress: feeling positively about themselves, and feeling positively about the future (American Psychiatric Association, 2013). Indeed, several studies have now shown that long-haulers with histories of psychological distress and diagnoses may be more vulnerable to cognitive fatigue and decreased QoL (Diana et al., 2023; Every-Palmer et al., 2020; Taquet et al., 2022). Thus, in the context of the present study it is possible that the significant LCQoL results stem from picking up these concomitant levels of psychological distress associated with long-COVID's neuropsychological sequelae, in a way that the NeuroQoL was not sensitive to.

Given this small yet convergent body of literature on the topic, it would be unsurprising that these concomitant psychogenic factors commonly experienced in long-COVID are associated with the significant decrement in QoL seen in this study (Genecand et al., 2023; Malesevic et al., 2023; Nordvig et al., 2023; Scholz et al., 2023).

Societal Factors. Long-haulers' significant decrement in quality of life seen in this study (as measured by the LCQoL) might be explained by the fact that the LCQoL was written to assess how long-COVID's symptoms impacted individuals' work, family, social, spiritual, interpersonal, and internal lives. Some examples of these peripheral, yet influencing factors, include the uncertainty (economic, housing, environmental, and health-related) and unpredictability arising from the pandemic (Aghaei et al., 2022; Every-Palmer et al., 2020; Faulkner et al., 2022; Hanna et al., 2022; Hawke et al., 2022; Van de Vyver et al., 2021; Van Herck et al., 2021). Increased uptake of anti-vaccination sentiment, distrust in governments, and disbelief in news media during the pandemic has been linked to increased anxiety and hypervigilance across society, significantly impacting the general wellbeing in the population (Calvano et al., 2022; Gasteiger et al., 2021; Swami et al., 2017; Van de Vyver et al., 2021).

Indeed, worsened familial and interpersonal relationships as well as increased rates of domestic and familial violence and abuse have been hypothesised to result from such societal shifts (Aghaei et al., 2022; Atilla et al., 2023; Every-Palmer et al., 2020; Van de Vyver et al., 2021).

It is possible that respondents inadvertently confused the incidence of their long-COVID symptomology with these changes to their work, family, socialising, daily routines, and spiritual and recreational activities that were actually caused by the sorts of societal factors associated with the pandemic outlined above.

Cognition

The Cognitive Implications of Fluctuating Symptomology

Some of the most remarkable findings of this study are that those with long-COVID had significantly slower reaction times on the Stroop task, despite all assessments of all other cognitive domains returning non-significant results. Specifically, Cases took longer to identify whether the stimulus was both congruent or non-congruent. Such findings were surprising given a substantial amount of the international literature on the topic shows that participants with long-COVID perform significantly worse than healthy participants on Word Recall, Digit Span, Stroop and Trail Making tasks (Guo, Ballesteros, et al., 2022; Guo, Benito Ballesteros, et al., 2022; Maiorana et al., 2023; Park & Schott, 2022; Resch et al., 2023; Varela et al., 2022).

However, in such studies it has been similarly found that the most significant results are that those with long-COVID have slower reaction times than healthy controls (Guo, Benito Ballesteros, et al., 2022; Kirchberger et al., 2023; Lauria et al., 2023). Given the high levels of non-completion in the Cognitive Battery, it seems highly likely that this low response rates meant the sample size was too small for any calculations of difference between groups to have sufficient statistical power to return significant results (Boniface, 2019; Erdfelder et al., 2007).

Another explanation for these results is that these non-significant Cognitive Battery findings are not a null-result, so much as a pattern of cognitive performance idiopathic to long-COVID (Daitch et al., 2022; Widmann et al., 2023). Long-COVID, like CFS/ME and other chronic illnesses is known to have fluctuating symptomology which can be exacerbated by both mental, psychological and physical exertion (Cockshell & Mathias, 2010; Islam et al., 2020; Jason et al., 2021). In such instances, it is important to understand the range of participants' abilities, as on some days they will have to contend with greater physical, mental

and psychological demands than others. Conducting cognitive assessments for those with long-COVID in rested and worked states may be of benefit; not only in highlighting the upper and lower bounds of individuals' cognitive functioning but also highlighting the extent that cognition might be dependent on other physical, mental and psychological loads. For that matter, it is also likely that cross-sectional study designs are not able to catch all chronically unwell participants having a bad symptom day at the same time. In these instances, artificially stressing participants by exposing them to cognitively fatiguing stimuli may better work to elucidate the cognitive difficulties of interest to a fuller extent. It is possible that these factors explain or contribute to the statistically insignificant results from this study's Cognitive Battery.

Slowed Reaction Times

Slowed reaction times have been well documented across many different cognitive and physiological measures in those with long-COVID, but especially on the Stroop test and the Trail Making Test (Barnden et al., 2023; Guo, Ballesteros, et al., 2022; Kelly et al., 2022; Kirchberger et al., 2023; Lauria et al., 2023; Maiorana et al., 2023; Saucier et al., 2023; Scarpina & Tagini, 2017). Subsequently, it is surprising that in the present study only the reaction times in the Stroop task were significant, and not the Trail Making tasks which also measured reaction times.

One possible explanation for significant reaction times on the Stroop task, but not the Trial Making Tasks is that each test has been designed to use reaction time as a measure for slightly different cognitive functions. The Stroop task interrogates decision making time taken to inhibit cognitive interference (Arbuthnott & Frank, 2000; Baykara et al., 2022; Moore et

al., 2016; Moscardini & Tucker, 2023; Scarpina & Tagini, 2017).[11] In contrast, the Trail Making Task interrogates visual attention, or rather visual search speed, and processing speed as time taken to switch tasks (the time in between trail points) (Arbuthnott & Frank, 2000; Baykara et al., 2022). Moreover, while at the high-level both the Stroop and Trail Making Tasks are considered as assessments of the executive function cognitive domain, the mechanisms by which these tasks do so differs; the Stroop by measuring cognitive interference and stimulus inhibition and the Trail Making Task via measuring task switching processing speed (Lauria et al., 2023; Scarpina & Tagini, 2017).

The results from this study's Cognitive Battery then may reflect, quite simply, that cognitive interference and stimulus inhibition are more significantly more impacted in long-COVID than task switching or cognitive flexibility. Such findings would corroborate the theorisation that the brain fog and the neuropsychological sequelae seen in long-COVID reflects a mild cognitive impairment across cognitive domains (Asadi-Pooya et al., 2022; Jennings et al., 2022b). In this paradigm, it is highly likely that constantly working to supress distracting stimulus like in the Stroop test is more taxing and detrimental to global cognitive function than simply attending to, and switching between salient stimuli like in the Trail Making Test (Baykara et al., 2022; R. Gray, 2006; Orfei et al., 2022; Scarpina & Tagini, 2017). It will be interesting to see in the future research, whether there is a correlation between Stroop performance and severity of brain fog.

Research Questions Four and Five

Current evidence suggests that that age, gender, and ethnicity may be key moderating variables impacting and potentially predicting the severity long-COVID (Aghaei et al., 2022;

[11] Cognitive interference broadly speaking, is recognised as the attention and decision making required to supress unwanted or intrusive thoughts or stimuli (Sarason et al., 2009).

Guo, Ballesteros, et al., 2022; Ortona & Malorni, 2022; Peng, 2023). To investigate this matter further, the present study had intended to investigate whether age, gender or ethnicity moderated neuropsychological symptoms and performance in the long-COVID (Case) group; several moderation analyses had been planned. However, the present study's small sample size and declining response rate across measures ultimately meant that the planned moderation analyses could not be performed. It is therefore not possible to comment further whether, in this sample, that neuropsychological performance and symptomology is worse in participants based on factors of gender, age or ethnicity.

Limitations

Ethics and Safety Requirements

A significant risk identified through ethics procedures was the likelihood that participation in this study (completing a long set of cognitive tests online) could exacerbate or worsen symptomology for long-COVID participants. The Ethics Committee requested that special measures were implemented to help protect participants from this risk. Subsequently, a 24-hour break was implemented between when participants completed the survey, and when they would be able to access and complete the Cognitive Battery. One possible explanation for the substantial drop in respondent rate between the survey and Cognitive Battery, is that this 24-hour break in between discouraged participants from completing the Cognitive Battery. Participants may have failed to complete all test measures for numerous reasons such as a loss of interest, becoming too fatigued, or simply forgetting about the study. A particular likelihood for those long-COVID participants with memory impairments. Moreover, these outcomes highlight substantial gaps in the way that online psychological studies are conducted. Despite this online method of delivery being utilised by many studies investigating long-COVID and cognition, few elucidate the mechanisms through which these

issues of respondent burden and response rates are managed (Davis et al., 2021; Guo, Benito Ballesteros, et al., 2022; Jason et al., 2021; Van Herck et al., 2021; Ziauddeen et al., 2022). Future research on this topic, or seeking to utilise an online mode of delivery, may look to carefully consider how to ensure participants finish the study in a safe and manageable way.

Sampling Frame

Recruitment. A characteristic impact of long-COVID is that it impairs individuals' ability to function to the extent that many struggle to leave their homes let alone participate in research (Cox et al., 2023). To overcome this challenge, and the lack of patient (long-hauler) registries, many studies (including this study) adapted to the pandemic situation and used social media and support group forums to access and recruit their target populations (Davis et al., 2021; Jason et al., 2021; C. M. Thompson et al., 2022; E. J. Thompson et al., 2022). However, there are potential biases introduced to these samples because of this recruitment method that may have flow-on impacts in terms of that sample's demographic breakdown. For instance, not all those who have long-COVID will have access either to the internet, or to web-browsing devices (Hawke et al., 2022). And those with more severe impairments may be less likely to participate in these forums or engage with the internet as primary mode of interacting with others. It is possible that much of the research into long-COVID, the present study included, may not include those who experience significant material hardship in their samples. The danger of this sampling frame is that it may be unintentionally excluding the very people and families who long-COVID could be impacting most. While efforts were made to put up study advertisements in local health clinics to recruit a greater variety of participants into the sample, the anonymity of participants meant it was impossible to know which platform – social media, or health clinic bulletin boards – participants accessed the study through.

A key learning from conducting this research is that while education level and employment status, as proxy indicators for SES, are known to impact rates of mental distress, lifestyle disease, long-COVID, and cognitive difficulties, accurately representing these factors in academic research as they exist in the real world poses a unique set of difficulties (Berger et al., 2021; Hopkins et al., 2011). Based on these learnings it is hoped that researchers and clinicians are better positioned to recognise that long-COVID and its neuropsychological sequelae likely impact individuals from all walks of life and socio-economic backgrounds, and it is our collective duty, as a profession, to better understand how this might be.

Inclusion Criteria. One challenge faced in the design of this study was deciding on the inclusion and exclusion criteria; whether those with underlying health conditions should be included in either the Case or Control group. It was decided that those with underlying and un-managed health conditions should not be included in the study groups given the risk that their experience of pain and poor quality of life or cognitive performance could be due to those pre-existing conditions rather than long-COVID. Moreover, notable risk factors for the incidence and persistence of long-COVID include pre-existing mental health conditions, and co-morbid life-style diseases (chronic heart failure, diabetes, and chronic obstructive pulmonary disease) (Asadi-Pooya et al., 2022; MoH, 2020; Peng, 2023). On that note, New Zealand has some of the highest rates of mental distress and non-communicable life-style disease in the OECD, and there are growing concerns about how this might pre-dispose New Zealanders to the complications of long-COVID (MoH, 2021). It is possible that by excluding those with prior health conditions from the study sample, we have excluded individuals who are at greater risk for long-COVID and its cognitive impacts from the study.

Procedure and a Non-Controlled Environment

Unlike studies that require in-person participation, this study actively enabled participants to complete the study from anywhere (provided they had computer and internet access) at any time. This freedom surrounding participation meant that not only was it impossible to supervise and encourage participants to complete all of the study's measures, but it also was also impossible to ensure that participation was occurring in a replicable and controlled environment. Moreover, it was hoped that if participants could control what environment they were participating from, this might help reduce the burden of completing the study. However, by not controlling study settings it is possible that participants were actually exposed to a range of settings, being just as likely to participate in peace and quiet, as they were being distracted by familial obligations. It is possible that this procedure and the non-controlled test environments contributed to the drop in response rates across the study's measures.

Insufficient Statistical Power

Finally, this study's non-significant results might also be explained by this study's small sample size, and the attrition of response rates. Both of these factors may have meant that the difference in long-COVID participants and healthy participants did not have sufficient statistical power to return significant results (Price et al., 2017). To address these potential confounding issues, future research may clarify whether excessive burden in a particular domain (quality of life, or cognitive function), or generalised burden distributed across many domains that are more strongly associated with long-COVID.

Practical and Clinical Implications

The present study is, to date, the only known work that focuses on the link between long-COVID and cognitive function in a New Zealand population. Some results from this work are in line with findings from the fast-growing body of international literature on the

topic of long-COVID and its neuropsychological sequelae. It also has important implications for understanding how to better support and care for those living with long-COVID in the future.

Neuropsychological assessments such as the Cognitive Battery administered in this study do not demand the same degree of sustained attention as required by the many tasks of daily life (Miskowiak et al., 2023; Resch et al., 2023; Scholz et al., 2023). Compared to the single-cognitive domain tasks in this study's Cognitive Battery, real-life situations often involve several cognitive functions simultaneously and the ability to shift between different tasks and stimuli (Miskowiak et al., 2023; Resch et al., 2023; Scholz et al., 2023). Notably, Stroop reaction times are a measure of cognitive flexibility, or the ease and speed with which someone can switch between tasks and cognitive functions (Miskowiak et al., 2023; Resch et al., 2023; Scholz et al., 2023). It is plausible that the significantly slower reaction times in the Stroop task reflect higher ecological validity of the measure than other Cognitive Battery tests. Subsequently, when interpreting neurocognitive results, it will be important to integrate cognitive assessment findings with evaluations of fatigue, symptomology and self-reports of daily functioning or quality of life (Miskowiak et al., 2023; Resch et al., 2023; Scholz et al., 2023).

Conclusion

In the three years since the SARS-CoV-2 triggered a global pandemic, the disease continues to cause illness, impairment, and distress in national and international populations. This research represents the first Case-Control study exploring the presence and impacts of long-COVID and its neuropsychological sequelae on people in Aotearoa New Zealand. This study had an interesting combination of significant and insignificant results; some of which were predicted based on the international literature and a bio-psycho-social model of disease,

and some of which were not. It was not surprising that long-haulers had significantly more frequent and severe experiences of the neuropsychological, pain and fatigue sequelae characteristic of long-COVID. It was surprising however that somatic symptoms were not significantly different between groups as this contrasts with previous research on the matter. While potential explanation for these results were explored, it will be interesting to see whether future research on long-COVID in Aotearoa finds insignificant prevalence of somatic symptomology.

It was also found that quality of life was significantly impaired for long-haulers when it considered the impact that symptomology had on socialising, family, work, recreation, spirituality and a sense of hope and wellbeing. Taking these significant findings alongside the substantive body of literature supporting the idea that cognitive performance and quality of life are impaired in long-COVID, it was then surprising that quality of life relating to cognition was not significantly worse for long-haulers. While these surprising insignificant results were explored, further work could be done to unpack the extent that symptomatic burden is distinct from cognitive impairment and whether this is significantly correlated with quality of life.

Some of this study's least expected and subsequently most interesting findings were that cognitive performance was not impaired on all cognitive domains assessed, except for in the domain of cognitive interference and stimulus inhibition. The implications of such findings were explored. Especially in relation to the need for cognitive assessments to be appropriately tailored to the unique demands of long-haulers sequelae, such as exposing them to sufficiently taxing cognitive tasks to better replicate the demands of daily life in which characteristic long-COVID symptoms like brain fog become apparent.

A reflection on this study's methodology, procedure and limitations also highlighted that there are many unexplored facets of conducting neuropsychological research online which could substantially impact the quality of results. In this study, key factors which may have impacted outcomes were the uncontrolled test environment and inability to support participants to complete the study. Such factors were a result of conducting the study online and were highly likely to have contributed to the low response rates observed.

Because of these poor response rates, a planned in-depth analysis of the socio-demographic factors impacting long-COVID's neuropsychological sequelae could not be conducted. As such, further work is needed to determine which socio-demographic factors unique to Aotearoa, and if any, can highlight who is at risk of developing long-COVID and its lasting neuropsychological sequelae.

In sum, the findings from this study highlight that future administration of cognitive and quality of life assessments whether in research or clinical practice, may better pick up a truer picture of impairment across long-COVID when the circumstances of test administration better replicate the numerous concurrent tasks (especially cognitive tasks) required of daily life.

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APPENDIX A

Variation in Long-COVID names and definitions from international health authorities

Institution	Term/Name	Definition
WHO (2021)	Post-COVID-19 condition	"Occurs in individuals with a history of probable or confirmed Sars-CoV-2 infection, usually three months from the onset of COVID-19 with symptoms that last for at least two months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others which generally have an impact of everyday functioning. Symptoms may be new onset, following initial recovery from an acute COVID-19 episode, or persistent from the initial illness. Symptoms may also fluctuate or relapse over time. A separate definition may be applicable to children."
CDC (2022)	Post-COVID conditions	"A wide range of new, returning, or ongoing health problems people can experience four or more weeks after first being infected with the virus that causes COVID-19"
NICE (2021b)	Ongoing symptomatic COVID-19	"Signs and Symptoms of COVID-19 from 4 weeks up to 12 weeks"
NICE (2021b)	Post-COVID-19 syndrome	"Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks, and are not explained by an alternative diagnosis. It usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body."
NICE (2021b)	Long-COVID	"The term 'long-COVID' is commonly used to describe signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4-12 weeks) and post-COVID-19 syndrome (12 weeks or more)."
MoH (2022b, 2022c)	Ongoing Symptomatic COVID	"Signs and symptoms of COVID-19 from 4 weeks up to 12 weeks"
MoH (2022b, 2022c)	Post-COVID-19 Syndrome	"Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis"

APPENDIX B

A List of Long-COVID's Neuropsychological Sequelae from Davis et al., 2021

Emotion and Mood Sequelae

1) Anxiety
2) Irritability
3) Depression
4) Mood lability
5) Tearfulness
6) Apathy
7) Sense of doom
8) Derealisation/depersonalisation
9) Anger
10) Impulsivity
11) Suicidality
12) Aggression
13) Euphoria
14) Hypomania
15) Delusions
16) Mania
17) Other

Sensorimotor Sequelae

18) Dizziness
19) Tingling
20) Tremors
21) Numbness
22) Sensitivity to noise
23) Tinnitus
24) Sensation of brain pressure
25) Neuralgia
26) Vibrating sensations
27) Electrical zaps
28) One-sided numbness
29) Sensation of brain warmth/fire
30) Inability to yawn
31) Inability to cry

Sleep Sequelae

32) Insomnia
33) Waking up several times at night
34) Difficulty falling asleep
35) Awakened by feeling inability to breathe
36) Vivid dreams
37) Nightmares
38) Waking up early in the morning
39) Restless leg syndrome
40) Lucid dreams
41) Sleep Apnoea

Cognitive Functioning

42) Brain fog
43) Poor attention
44) Difficulty thinking
45) Difficulty problem-solving
46) Slowed thoughts
47) Acute (sudden) confusion
48) Thoughts moving too quickly
49) Agnosia
50) Other

Memory Sequelae

51) Short-term memory loss
52) Long-term memory loss
53) Forgetting how to do routine tasks
54) Inability to make new memories
55) Other

Headaches

56) Headaches, behind the eyes
57) Headaches, diffuse
58) Headaches, in the temples
59) Headaches, at the base of the skull
60) Headaches/pain after mental exertion
61) Migraines
62) Other

Taste and Smell

63) Loss of smell
64) Loss of taste
65) Altered sense of taste
66) Phantom smells
67) Altered sense of small
68) Phantom taste
69) Heightened sense of smell
70) Heightened sense of taste

Speech and Language

71) Difficulty finding the right words

72) Difficulty communicating verbally
73) Changes to non-primary language
74) Difficulty processing written text
75) Difficulty comprehending speech
76) Difficulty communicating in writing
77) Slurry words/speech
78) Speaking unrecognisable words
79) Other

Hallucinations

80) Visual hallucinations
81) Auditory hallucinations
82) Tactile Hallucinations
83) Other

APPENDIX C

The Online Survey

MASSEY UNIVERSITY
TE KUNENGA KI PŪREHUROA
UNIVERSITY OF NEW ZEALAND

School of Psychology

Information Page

MASSEY UNIVERSITY
TE KUNENGA KI PŪREHUROA
UNIVERSITY OF NEW ZEALAND

COLLEGE OF HUMANITIES AND SOCIAL SCIENCES
TE KURA PŪKENGA TANGATA

Long Covid and Cognition

Information Sheet

Researcher Introduction

This study wants to collect information from people with and without long-covid about their cognitive test performance, health symptoms they might have, and their quality of life. The aim of this research is to look at which aspects of thought, memory, and attention people with long-covid have difficulties with, and to highlight the daily impacts these challenges have. The researcher, Zoe, is completing this project as part of a MSc in Psychology.

What is long-covid?

The Ministry of Health outlines that long-covid is a condition involving ongoing or new COVID-19 symptoms, or those that go away but come back again, and that last three months or longer after first getting COVID-19.

Project Description

This study will compare the results from people who have long-covid to those who do not. If you agree to take part in this study, you will be asked to complete two tasks online. The first task will ask you some questions about yourself, what symptoms of long-covid you experience and how they affect your daily life. The second task asks you to complete some tests that measure your attention, memory along with other mental abilities (like language and number processing). These measures will be compared to your long-covid symptom ratings to understand how long-covid impacts your life and different brain functions.

Who Can Join?

Those With Long-Covid (Long-Covid Group)

If you are over 18 and have long-covid you are invited to join this study.

If you decide to join this study and know someone who is a similar age, sex, and ethnicity to you but does not have COVID-19 or long-covid, we encourage you to see if they would also like to join this study as a control group participant. This is not a requirement of the

study, however, and you are welcome to join the study whether you do this or not.

Those Without Long-Covid (Control Group)
If you are over 18 and do not have COVID-19 or long-covid but would like to support those who are affected by these illnesses by participating in this study, we also invite you to join this study.

Study Benefits
Participation in this study will provide information that will help us understand long-covid. As a sign of appreciation for your participation, everyone who joins this study can enter a koha-pool to win a $150 super-market voucher.

Study Risks
Some of the most common symptoms of long-covid are fatigue and brain-fog (difficulty thinking). It is possible that the energy and effort required to complete the two online tasks in the study may make underlying thinking, memory, attention, or fatigue difficulties you might be experiencing worse. To reduce the chance of that happening, we strongly encourage you to use good self-care.

If involvement in this study causes any distress we encourage you to see your GP.

Self-care
We encourage you to take breaks as you need while completing the online tasks and remind you of the right to withdraw from the study at any time until you have clicked "Submit" at the end of the cognitive tasks.

What Does Participation Involve?
If you decide to join this study, you will need to sign the consent form at the link provided. This will automatically enrol you in the study and take you to a survey asking about your long-covid symptoms. This survey takes approximately 15 minutes. You will then have a 24-hour wait before you will be emailed a link to task two, where you will complete some cognitive (thinking skills) tests. Task two takes about 30 minutes to complete. Remember, you can take as many breaks as you need to while completing task one and task two. When you finish task two, a screen will ask you to "Submit" your responses. Once you click "Submit" your participation is complete!

> NOTE: *Remember you cannot withdraw yourself or your data from the study once you click "Submit"*

Data Management

You will be assigned private, anonymous, and randomised ID numbers that your results will be automatically stored under. These results will be stored securely in the Massey University Cloud and backed up in a detachable hard-drive in password protected files. Data will be held for five years in secure locations, after which it will be destroyed.

Participants' Rights
You are under no obligation to accept this invitation. If you decide to participate you have the right to:

- Decline to answer any particular question;
- Withdraw from the study at any point until you have clicked "Submit" and finished the online tasks.

If you tell us that you want to be notified about the study's findings, you will be emailed a summary of the project findings when it is finished. However, because you will be completing the tasks anonymously, we will not be able to provide your personal data, nor how you did compared to the rest of the group.

Your right to withdraw:

- You have until the 31st of October to complete this study, however,
- Once you have clicked "Submit", to finish the cognitive-tests you will no longer be able to withdraw from the study.
- By leaving the survey or thinking tests unfinished you are automatically withdrawn from study.

Let's Talk!
If you have any questions about this study that you would like answered before you agree to take part, please do not hesitate to email me at longcovidandcognition@gmail.com.
Nga Mihi!

Project Contacts
If you have any questions or queries regarding this project, please don't hesitate to contact the following:

Primary Researcher:
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Alternatively, you can contact my research supervisors:

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This project has been reviewed and approved by the Massey University Human Ethics Committee: Southern A, Application 22/27.
If you have any concerns about the conduct of this research, please contact Dr Negar Partow, Chair, Massey University Human Ethics Committee: Southern A, telephone 04 801 5799 x 63363, email humanethicsoutha@massey.ac.nz

Consent

Participant Consent Form

I have read I understood the Information Sheet.

Any questions I had have been answered to my satisfaction, and I understand that I may ask further questions at any time.

I have been given enough time to consider whether to participate in this study. I understand that participation is voluntary, and I can withdraw from this study at any time until I finish the online tasks, by clicking “Submit” to submit my responses.

I agree to participate in this study under the conditions set out in the Study Information Page.

By answering 'yes' to the below you are giving consent to participate in this study.

Disclosure:
If you decide to share your email to enter the koha draw or be emailed the study's findings, please be aware that we will store this confidential information in a location separate to your questionnaire and cognitive test results to protect your privacy.

I have read and understood the information sheet for this study and consent to collection of my responses.
(Please click on the 'Yes' choice if you wish to proceed.)

- ○ Yes
- ○ No

Demographics

Demographics

What is your age group?

- ○ 17 or younger
- ○ 18-25
- ○ 26-30
- ○ 31-40
- ○ 41-50
- ○ 51-60
- ○ 61-65
- ○ 66+

What is your sex?

- ○ Male
- ○ Female
- ○ Gender diverse
- ○ _____ Other
- ○ Prefer not to say

To which of the following ethnicities do you belong?

- ☐ New Zealand Māori
- ☐ Pacific Islander
- ☐ New Zealand European/ Pākehā
- ☐ Asian
- ☐ _____ Other (please specify)

What is your iwi?

_____

What is your marae?

_____

What is your hapu?

_____

What is your current employment status?

- ○ Employed full-time
- ○ Employed part-time
- ○ Not currently employed
- ○ Under-graduate student
- ○ Graduate/post-graduate student
- ○ Retired
- ○ Rather not say

Covid-19 details

Have you tested positive with Covid 19?

- ○ Yes
- ○ No

If yes, what year and month did you test positive?

Year

Month

Have you been diagnosed with long-covid?

- ○ Yes
- ○ No

Who diagnosed you with Long-Covid?

- ○ Medical doctor/practioner
- ○ Alternative Practitioner
- ○ Self-diagnosed

For how many weeks have you had long-covid?

- ○ Less that 4 weeks
- ○ 4-12 weeks
- ○ 3 months
- ○ 6 to 12 Months
- ○ 12 months or more

Do you have any other chronic or long-term health conditions, such as diabetes, high blood pressure, migraines, heart failure? If yes, please specify.

Are your health conditions managed?

- ○ Yes
- ○ No

Symptoms

Symptoms

For the following set of questions, we would like to know **how often you have had each symptom** and then **how much each symptom has bothered you over the last 6 months**.

Frequency:

Throughout the **past 6 months**, **how often** have you had any of the following symptoms?

	None of the time	A little of the time	About half the time	Most of the time	All of the time
Dry cough	○	○	○	○	○
Loss of taste	○	○	○	○	○
Loss of smell	○	○	○	○	○
Breath/ breathing difficulty	○	○	○	○	○

Severity:

Throughout the **past 6 months**, how **much** has each of the following symptoms bothered you?

	Symptom not present	Mild	Moderate	Severe	Very severe
Dry cough	○	○	○	○	○
Loss of taste	○	○	○	○	○
Loss of smell	○	○	○	○	○
Breath/ breathing difficulty	○	○	○	○	○

Frequency:

Throughout the **past 6 months**, **how often** have you had any of the following symptoms?

	None of the time	A little of the time	About half the time	Most of the time	All of the time
Shortness of breath	○	○	○	○	○
Tightness of chest	○	○	○	○	○
New allergies / anaphylaxis	○	○	○	○	○
Hearing changes / tinnitus	○	○	○	○	○

Severity:

Throughout the **past 6 months**, how **much** has each of the following symptoms bothered you?

	Symptom not present	Mild	Moderate	Severe	Very severe
Shortness of breath	○	○	○	○	○
Tightness of chest	○	○	○	○	○
New allergies / anaphylaxis	○	○	○	○	○
Hearing changes / tinnitus	○	○	○	○	○

Frequency:

Throughout the **past 6 months**, **how often** have you had any of the following symptoms?

	None of the time	A little of the time	About half the time	Most of the time	All of the time
Runny nose/ nasal congestion	○	○	○	○	○
Sinus issues	○	○	○	○	○
Hallucinations	○	○	○	○	○
Neuralgia (nerve pain)	○	○	○	○	○

Severity:

Throughout the **past 6 months**, how **much** has each of the following symptoms bothered you?

	Symptom not present	Mild	Moderate	Severe	Very severe
Runny nose/ nasal congestion	○	○	○	○	○
Sinus issues	○	○	○	○	○
Hallucinations (seeing hearing or hearing things that other people can't see or hear)	○	○	○	○	○
Neuralgia (nerve pain)	○	○	○	○	○

Frequency:

Throughout the **past 6 months**, **how often** have you had any of the following symptoms?

	None of the time	A little of the time	About half the time	Most of the time	All of the time
Vibrating sensations	○	○	○	○	○
Acute confusion	○	○	○	○	○
Brain fog	○	○	○	○	○
Slurring of words	○	○	○	○	○
Speech and language issues	○	○	○	○	○

Severity:

Throughout the **past 6 months**, how **much** has each of the following symptoms bothered you?

	Symptom not present	Mild	Moderate	Severe	Very severe
Vibrating sensations	○	○	○	○	○
Acute confusion	○	○	○	○	○
Brain fog	○	○	○	○	○
Slurring of words	○	○	○	○	○
Speech and language issues	○	○	○	○	○

This question is about symptom impact on your daily functioning and quality of life.

In the past month, have your symptoms impacted your ability to:

	not at all	up to 1 day a week	2-3 days a week	3-4 days a week	5 days a week	daily/every day
Engage in, or complete work to your previous standard?	○	○	○	○	○	○
Engage familiarly (hold conversation with those living with you)?	○	○	○	○	○	○
Engage socially (hold conversations, spend time with friends or family outside of your home)?	○	○	○	○	○	○
Engage with a daily routine (dress, brush teeth, prepare meals)?	○	○	○	○	○	○
	not at all	up to 1 day a week	2-3 days a week	3-4 days a week	5 days a week	daily/every day
Engage with hobbies, or normal past times (reading, watch TV, attend sports meets, or groups, spiritual/ religious worship)?	○	○	○	○	○	○
Feel positively toward yourself (show compassion, appreciation, respect for your-self)?	○	○	○	○	○	○
Feel positive or hopeful about tomorrow/ your future?	○	○	○	○	○	○

DePaul Symptom Questionnaire – DSQ – SF

For each symptom below, please select one option for frequency and one option for severity:
Please complete the chart from left to right.

Frequency:
Throughout the **past 6 months**, **how often** have you had this symptom?
Severity:

Throughout the **past 6 months**, **how much** has this symptom bothered you?

	Frequency	Severity
Fatigue/extreme tiredness		
Next day soreness or fatigue after non-strenuous, everyday activities		
Minimum exercise makes you physically tired		
Feeling unrefreshed after you wake up in the morning		
Pain or aching in your muscles		
Bloating		
Problems remembering things		

For each symptom below, please select one option for frequency and one option for severity:
Please complete the chart from left to right.

Frequency:
Throughout the **past 6 months**, **how often** have you had this symptom?
Severity:
Throughout the **past 6 months**, **how much** has this symptom bothered you?

	Frequency	Severity
Difficulty paying attention for a long period of time		
Irritable bowel problems		
Feeling unsteady on your feet, like you might fall		
Cold limbs (e.g. arms, legs, hands)		
Feeling hot or cold for no reason		
Flu-like symptoms		
Some smells, foods, medications, or chemicals make you feel sick		

Neuro_QOL Cognitive

Please respond to each question or statement by marking one box per row.

In the past 7 days…

	Never	Rarely (once)	Sometimes (2-3 times)	Often (once a day)	Very often (several times a day)
I had to read something several times to understand it	○	○	○	○	○
My thinking was slow	○	○	○	○	○
I had to work really hard to pay attention or I would make a mistake	○	○	○	○	○
I had trouble concentrating	○	○	○	○	○

Please respond to each question or statement by marking one box per row.

How much DIFFICULTY do you currently have…

	None	A little	Somewhat	A lot	Cannot do
reading and following complex instructions (e.g., directions for a new medication)?	○	○	○	○	○
planning for and keeping appointments that are not part of your weekly routine, (e.g., a therapy or doctor appointment, or a social gathering with friends and family)?	○	○	○	○	○
managing your time to do most of your daily activities?	○	○	○	○	○
learning new tasks or instructions?	○	○	○	○	○

Thanks

This section of the research survey is now complete.

In order to collect contact details so that we can send you the access details for the second part of the data collection, you will be transferred to a separate survey for this process. Your name and email address will not be part of the data set of your responses entered in the previous questions.

Please click on the **Submit** button below to close the survey and be transferred to the collection of your contact details.

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