Investigating the relationships between body fat distribution, metabolic biomarkers and endocrine regulators in Pacific and New Zealand European women

A thesis presented in partial fulfilment of the

requirements for the degree of

Master of Science
in
Nutrition and Dietetics

Massey University, Albany

New Zealand

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2019

Abstract

Background: The burden of overweight and obesity continues to rise throughout the world, including New Zealand (NZ). Obesity prevalence differs among ethnic groups in NZ and this is associated with considerable health inequities. For example, Pacific peoples living in NZ have higher rates of obesity-related health issues, compared to NZ Europeans. Understanding the link between body composition and metabolic health is essential for the development of more effective preventative and intervention strategies for different population groups, who may have different metabolic disease risk profiles.

Aims: This research aims to, firstly investigate metabolic biomarkers and endocrine regulators in two distinct groups of women with different body fat profiles (normal and obese) and of high metabolic disease risk (Pacific women) or moderate metabolic disease risk (NZ European women); and secondly, to compare different approaches of assessing body composition and fat distribution and their relationship with metabolic and endocrine profiles.

Design: A cross-sectional study conducted in 304 Pacific and NZ European women aged 18-45 years. Anthropometry, a range of body composition and fat distribution measurement approaches, metabolic biomarkers (including lipids, markers of glucose metabolism and inflammation markers) and endocrine regulators (insulin and leptin) will be investigated.

Outcomes: Total body fat percentage (BF%) measured by bioelectrical impedance analysis (BIA) correlated strongly with BF% measured by dual X-ray absorptiometry (DXA). Waist-to-hip ratio (WHR) had weak associations with android fat percentage and BF% measured by DXA, whereas waist circumference (WC) and waist-to-height ratio (WHtR) performed better in this respect. Anthropometric measurements had similar correlations with total body fat percentage and regional fat depots for both ethnic groups. For each ethnicity, women in the high body mass index (BMI) group had higher circulating concentrations of fasting insulin, fasting glucose, glycosylated haemoglobin (HbA1c), triglycerides and total cholesterol to high-density lipoprotein (TC/HDL) ratios, and lower circulating HDL cholesterol concentrations in comparison with the normal BMI group. Gynoid fat percentage had weak associations with circulating cardio-metabolic risk factors, including low-density lipoprotein cholesterol (LDL-C), triglycerides, HbA1c, fasting insulin and fasting glucose concentrations. On the other hand, android and visceral fat percentages had stronger, positive associations with these cardio-metabolic risk factors. Furthermore, BF% measured by DXA and BMI explained a similar amount (57.1% and 49.7% respectively) of the variance in leptin concentrations.

Conclusion: Our findings suggest that in a New Zealand population with markedly different body fat profiles, assessment of WC, WHtR and BMI are effective tools for assessing adiposity and the associated cardio-metabolic disease risk factors in a clinical setting, whereas WHR does not appear to be a useful tool. This thesis research provides strong evidence that these clinically important and effective tools should continue to be used in

dietetic practice, across different population groups with different metabolic disease risks and different body fat profiles.

Acknowledgements

I would like to express my gratitude to all who were involved in the planning and implementation of the PROMISE study. To my main academic supervisor, Prof Bernhard Breier, for guiding me to the completion of this thesis. A/Prof Rozanne Kruger for your support during this time, and Dr Marilize Richter for your guidance with the statistical analysis. I would also like to thank Sophie Kindleysides, Jo Slater and Nikki Renall for supporting me when I needed it. Thank you also to all who participated in this study, without whom this research would not have been possible.

A special thanks to my friends, classmates and family, for their support and encouragement during this time. Mia, Rebecca and Emily, your daily support and friendship made the final stretch a lot more bearable. Emma, Rachel and Dani, thank you for your encouragement and help with everything. To my wonderful parents, thank you for always believing in me.

Finally, to my number one supporter, Zheran. I appreciate your constant encouragement and patience over the last few years. Thank you for always being with me through the highs and the lows. This journey would have been a lot harder without you.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

BF	Body Fat
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
CRP	C-reactive Protein
CVD	Cardiovascular Disease
DXA	Dual-energy X-ray Absorptiometry
FFA	Free Fatty Acids
HbA1c	Glycosylated Haemoglobin
HC	Hip Circumference
HDL-C	High Density Lipoprotein Cholesterol
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
LDL-C	Low Density Lipoprotein Cholesterol
NCD	Non-communicable Disease
NEFA	Non-esterified Fatty Acids
NZ	New Zealand
NZDep	NZ Index of Deprivation
T2D	Type 2 Diabetes
TC	Total Cholesterol
TG	Triglycerides
TNF-α	Tumour Necrosis Factor Alpha
WC	Waist Circumference
WHtR	Waist-to-height ratio
WHR	Waist-to-hip ratio

Chapter 1: Introduction

1.1 Background

1.1.1 Introduction

Overweight and obesity has become a major public health issue, and its prevalence and impact on health continues to rise globally (The GBD 2015 Obesity Collaborators, 2017). Obesity is a systemic disease characterised by excessive accumulation of adipose tissue arising from an energy imbalance due to numerous genetic, physiological, environmental and lifestyle factors (Abdelaal, le Roux, & Docherty, 2017; Schwartz et al., 2017; Silventoinen, Rokholm, Kaprio, & Sørensen, 2009). Some of these factors include altered gene expression, changes to energy homeostasis, low socioeconomic status, high availability of energy-dense, nutrient-poor foods, and sedentary lifestyles (Engin, 2017; Pigeyre, Yazdi, Kaur, & Meyre, 2016; Schwartz et al., 2017). Obesity has been associated with undesirable long-term health outcomes and lifestyle implications (Slagter et al., 2015).

1.1.2 Current Situation in New Zealand

New Zealand (NZ) has one of the highest obesity rates, ranking third in the Organisation for Economic Co-operation and Development (OECD) countries (OECD, 2017). There has been a significant increase in obesity in NZ between 2011 and 2018 (Ministry of Health, 2018). Notably, women are more likely to develop obesity than men, and between the 2011/12 and 2017/18 New Zealand Health Surveys, obesity rates only significantly increased in women (**Figure 1.1**) (Ministry of Health, 2018). Obesity is also associated with ethnic and socio-economic inequities, with Maori and Pacific peoples being more likely to develop obesity than other ethnic groups living in NZ (Ministry of Health, 2018). Maori and Pacific women have the highest obesity rates, with 49.5% of Maori and 69.1% of Pacific women falling into the obese category, compared to 32.4% of European/other and 13.3% of Asian women (Ministry of Health, 2018). While all-cause mortality has been decreasing in NZ over the last three decades, this decline has been slowest in Pacific peoples; another example of the health inequity experienced by the NZ Pacific population (Disney, Teng, Atkinson,

Wilson, & Blakely, 2017). Additionally, people living in the most deprived areas are more likely to develop obesity than those living in the least deprived areas (Ministry of Health, 2018). Previous research has shown that Pacific peoples living in NZ tend to have a lower socioeconomic status, which has been linked to poorer health outcomes (Lotoala, Breheny, Alpass, & Henricksen, 2014). When people have lower incomes, less employment opportunities, lower levels of education, poorer housing and poorer access to health care and social support, this leads to health inequities, including obesity and higher disease risk (Signal, 2008). One pathway connecting these factors to obesity is reduced diet quality that can be associated with financial strain and the food environment in which people live (Swinburn et al., 2013).

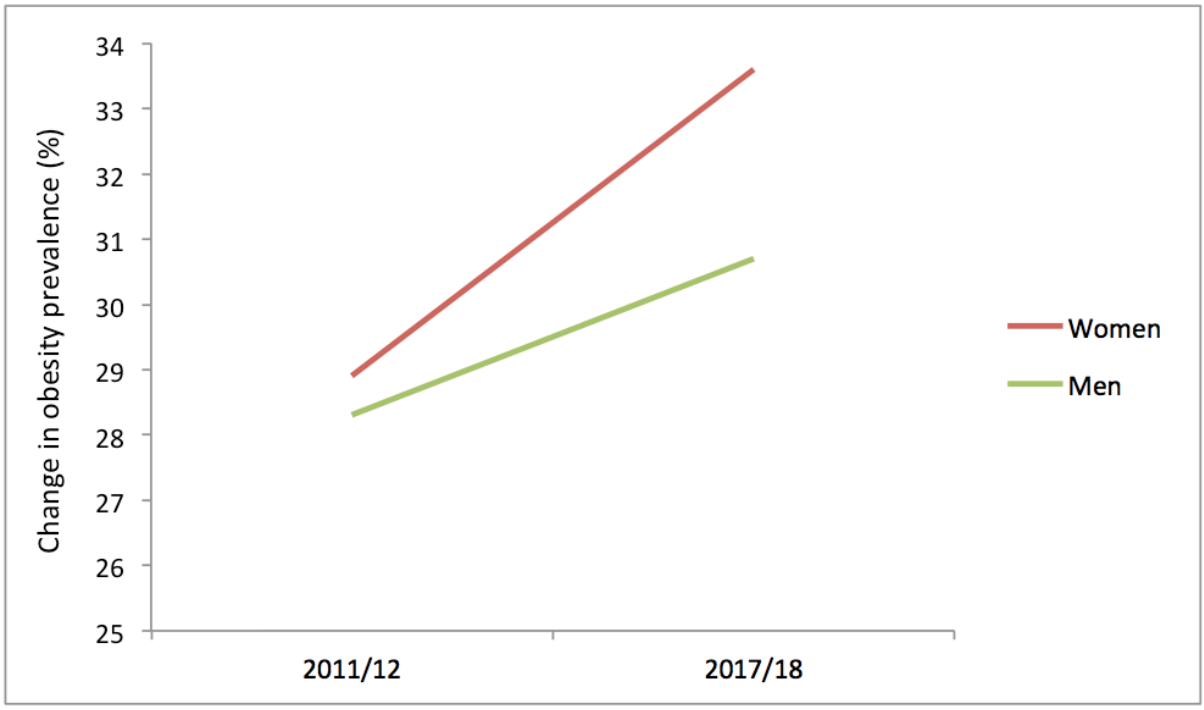


Figure 1.1: Change in the prevalence of obesity (%) in New Zealand overtime

Data from the 2011/12 and 2017/18 New Zealand Health Surveys (Ministry of Health, 2018). Change is significant for women (*p* 0.00) but not for men (*p* 0.06).

1.1.3 Metabolic Health Biomarkers

Biomarkers in the blood can be used to identify disruptions to the metabolic processes underlying increased adiposity. Some of these changes include insulin resistance, glucose

intolerance, dyslipidaemia and changes to liver function (G. A. Bray, 2004). It is important to detect these abnormalities early, as they can lead to disease states such as type 2 diabetes (T2D), cardiovascular disease (CVD), fatty liver disease and some cancers (G. A. Bray et al., 2018).

Leptin is a hormone central to energy balance regulation, through its role in hunger inhibition (Schwartz et al., 2017). Leptin is released from adipocytes, thus higher circulating levels are observed in those with higher amounts of adipose tissue (Schwartz et al., 2017). While changes in the function of leptin during obesity development remain unclear, it is possible that leptin resistance may play a role (Schwartz et al., 2017). Another hormone involved in energy balance is insulin. Insulin is secreted from the pancreatic beta cells in response to an increase in blood glucose levels (Koeppen & Stanton, 2018). Insulin enables the storage of glucose, the body's main energy source, in liver and skeletal muscle cells as glycogen and in adipose tissue as triglycerides (Koeppen & Stanton, 2018). Insulin resistance can occur in the obese state, where cells become less sensitive to insulin signalling, resulting in higher fasting insulin and glucose levels, eventually leading to T2D (B. C. Lee & Lee, 2014). Fasting insulin concentrations are determined by insulin secretion and insulin clearance, and can be used as an indicator of the insulin sensitivity of cells (Goodarzi et al., 2011). Other tests that are useful for detecting alterations to glucose handling include the oral glucose tolerance test (OGTT), fasting glucose concentrations and glycosylated haemoglobin (HbA1c) levels, which are commonly measured to detect and monitor pre-diabetes and T2D (Diabetes, 2011; Karakaya, Akin, Karagaoglu, & Gurlek, 2014). HbA1c is a measure of the average blood glucose concentration over the past 2-3 months, and can predict the risk of diabetes-related complications caused by damage to the blood vessels, such as retinopathy, nephropathy, neuropathy and CVD (NZSSD, 2011).

Low-grade inflammation is a common feature of obesity, and is also present in the metabolic syndrome, T2D, CVD and non-alcoholic fatty liver disease (NAFLD) (Minihane et al., 2015). Inflammation is thought to be a result of obesity, rather than a cause of obesity (Schwartz et al., 2017), and is also linked with pancreatic beta cell dysfunction in diabetes

development, and plaque formation in the early stages of atherosclerosis (Ebrahimi et al., 2016; Golia et al., 2014). Inflammation can be measured by markers in the blood, including tumour necrosis factor alpha (TNF-α) and high sensitivity C-reactive protein (hs-CRP) (Golia et al., 2014). TNF- α is a pro-inflammatory cytokine that is shown to be elevated in obesity and positively correlates with insulin resistance (Nakamura, Fuster, & Walsh, 2014). Also elevated in obesity, CRP is released from the liver in response to pro-inflammatory cytokines (J. Choi, Joseph, & Pilote, 2013). Levels of TNF-α and hs-CRP can be measured to identify metabolic disease risk (D. J. Freeman et al., 2002; Golia et al., 2014; Ridker, Hennekens, Buring, & Rifai, 2000).

Lipids are essential for building lipid membranes, transportation and energy storage (Marieb & Hoehn, 2016). The main role of low-density lipoprotein cholesterol (LDL-C) is to deliver cholesterol to body tissues (Marieb & Hoehn, 2016). On the other hand, high-density lipoprotein cholesterol (HDL-C) removes excess cholesterol from tissues and the blood, to be excreted or recycled by the liver (Marieb & Hoehn, 2016). Triglycerides are the body's main form of stored energy, held in adipocytes to be broken down when required, releasing non-esterified fatty acids (NEFA), also known as free fatty acids (Marieb & Hoehn, 2016). NEFA levels tend to be higher in those with obesity due to fatty acid release from adipose tissue and reduced NEFA clearance (Klop, Elte, & Cabezas, 2013). One of the mechanisms causing increased NEFA concentrations in obesity involves insulin resistance, which affects the release of NEFA from adipocytes (Van Gaal, Mertens, & De Block, 2006). The blood lipid profile continues to be an important consideration for CVD risk. Lipid tests such as total cholesterol, triglycerides, LDL-C, HDL-C and NEFA are used to detect CVD risk (Van Gaal et al., 2006). A lipid profile characteristic of obesity includes raised total cholesterol, LDL-C and triglycerides, and low HDL-C concentrations (Van Gaal et al., 2006).

1.1.4 Anthropometric and Body Composition Measurements

Body proportions can be measured by many different direct and indirect techniques. The most common identifier of body fatness is body mass index (BMI) (Ministry of Health, 2015). BMI is a calculation based on a person's weight and height, giving a measure of body mass in the unit kg/m^2. This number is used to identify underweight, healthy weight, overweight

or obesity, with three categories for the degree of obesity (Ministry of Health, 2015). BMI is frequently used for monitoring obesity in populations, and is also used at the individual level by health professionals (G. A. Bray et al., 2018). While BMI is easy to use and correlates with total body fat mass, it also has limitations affecting its accuracy in some situations (Romero-Corral et al., 2008). Firstly, BMI is an indirect measure of body mass that cannot distinguish lean mass from fat mass (Ministry of Health, 2015). This is problematic for individuals who have a higher than average amount of muscle mass, incorrectly categorising them as overweight or obese. This can lead to inappropriate weight loss recommendations, as lean mass is not associated with the same metabolic disturbances as fat mass (Bastien, Poirier, Lemieux, & Despres, 2014). BMI also does not describe body fat distribution, which is an important factor to consider in cardio-metabolic disease risk assessment (S. W. Lee et al., 2018; Ministry of Health, 2015). There may also be differences in body composition and fat distribution associated with ethnicity, age and gender, which BMI cannot account for (Ministry of Health, 2015; Wen, Rush, & Plank, 2010).

Other common anthropometric measurements include waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR) and sagittal height. These indirect measurements can give some idea of body composition and fat distribution, and are used to identify obesity-related disease risk, including CVD and T2D risk (G. A. Bray et al., 2018). HC is one technique used to measure gluteofemoral fat, but this can also be measured using thigh circumference or leg adipose tissue mass (Manolopoulos, Karpe, & Frayn, 2010). WC is a common anthropometric measurement used to estimate abdominal fat (World Health Organization, 2008). WHR is a measurement reflective of fat distribution, as it takes into account both WC and HC (World Health Organization, 2008). WHtR, on the other hand, is used as a measurement reflecting abdominal adiposity, by adjusting WC for the height of the individual (World Health Organization, 2008).

Dual-energy X-ray absorptiometry (DXA) and bioelectrical impedance analysis (BIA) are direct methods of measuring body composition. DXA scans give an accurate measure of bone mineral density, body fat and lean tissue mass, and identifies the location of these

tissues (Beechy, Galpern, Petrone, & Das, 2012; S. Y. Lee & Gallagher, 2008; Panotopoulos, Charles Ruiz, Guy-Grand, & Basdevant, 2001). DXA is often used as the gold standard for body composition analysis in research studies (Bazzocchi et al., 2014; Day et al., 2018; Ramírez-Vélez et al., 2016). DXA can measure android and gynoid fat distribution profiles, as well as visceral adipose tissue, which are each associated with different levels of cardio-metabolic disease risk (Vasan et al., 2018). While not as precise as DXA, BIA is more easily accessible, less costly, involves a quicker procedure and is simpler to carry out (Day et al., 2018; Gaba, Kapus, Cuberek, & Botek, 2015). Some studies have found good agreement between BIA and DXA measurements of fat mass and fat free mass, while others have found that BIA overestimates fat mass and underestimates fat free mass (Achamrah et al., 2018; Bedogni et al., 2013; Tewari, Awad, Macdonald, & Lobo, 2018). Additionally, some research suggests that the accuracy of BIA may be altered when measuring individuals at the extremities of the BMI scale (Bedogni et al., 2013; Deurenberg, 1996; S. Y. Lee & Gallagher, 2008).

1.1.5 Body Fat Distribution and Metabolic Disease Risk

Fat distribution has a clear and important impact on metabolic health (G. A. Bray et al., 2018; Karpe & Pinnick, 2015; Piche, Poirier, Lemieux, & Despres, 2018). Interestingly, a gynoid fat distribution (fat held predominantly around the hips) tends to be protective of metabolic health, while an android fat distribution (fat held predominantly around the waist) has been associated with CVD risk factors (Piche et al., 2018; Vasan et al., 2018). The excessive accumulation of visceral and ectopic fat around key organs has been associated with cardio-metabolic disease risk factors, with implications that can lead to the development of T2D (Levelt et al., 2016; Okamura et al., 2018; Vasan et al., 2018) and CVD (Mathieu, Boulanger, & Despres, 2014; Piche et al., 2018). Increased subcutaneous and visceral adipose tissue can alter the normal metabolic functions in the body, including changes to lipid metabolism, glucose metabolism, hormone regulation and inflammatory responses (G. A. Bray et al., 2018). This can result in dyslipidaemia, high blood pressure, insulin resistance and chronic inflammation (G. A. Bray et al., 2018). Further progression of these abnormalities can lead to comorbid diseases such as CVD and T2DM (Abdelaal et al., 2017; G. A. Bray et al., 2018; The GBD 2015 Obesity Collaborators, 2017).

1.1.6 Purpose of the Study

Excessive adiposity in women of child-bearing age is associated with a higher risk to the mother and fetus during pregnancy, as well as on-going adverse health outcomes including the perpetuation of increased obesity risk for the next generation (Eriksson, Sandboge, Salonen, Kajantie, & Osmond, 2014). Further exploration of the link between body composition and metabolic biomarkers is necessary to advance our understanding of how the location of adipose tissue can impact on metabolic profiles. The comparison of Pacific and NZ European women is useful in the NZ setting, as the Pacific population is growing, and it is already known that Pacific women may have different body fat proportions than NZ European women.

Previous research has shown that Pacific women had a lower thigh fat mass than NZ European women, and a higher abdominal fat percentage (Rush, Freitas, & Plank, 2009). It is possible that this contributes to the higher cardio-metabolic disease risk seen in Pacific women. Total fat percentage has also been found to be lower in Pacific women at a given BMI when compared to women of other ethnicities, including NZ European women (Rush et al., 2009; Rush et al., 2007; Swinburn, Ley, Carmichael, & Plank, 1999). From these findings, it was proposed that there should be ethnic-specific BMI cut-offs introduced. This idea was opposed with evidence showing that the same BMI and WC cut-offs similarly predict cardiovascular risk for Maori as they did for Europeans, which is likely to extend to the Pacific population as well (Taylor et al., 2010).

With the clear health inequities between Pacific and NZ European groups living in NZ, health interventions may need tailoring for each ethnic group. The mechanisms underlying why Pacific women have a higher metabolic disease risk than NZ European women is unclear and little research has been done in this area. Investigating the ethnic differences in metabolic biomarkers and endocrine regulators associated with fat distribution may shed some light on the mechanisms that lead to this metabolic disease risk. In this study, two different body fat profile groups were recruited (normal and high BMI) to obtain the greatest range in body weight. NZ European and Pacific women vary greatly in terms of physical, ethnic-cultural

and socio-economic characteristics, allowing effect modification by these factors to be assessed. This study involves the assessment of anthropometry, body composition, fat distribution, and circulating concentrations of metabolic biomarkers and endocrine regulators in the blood.

1.2 Hypotheses

This study is designed to test the primary hypothesis that an abdominal fat distribution is linked with an unhealthy profile of metabolic biomarkers. A secondary hypothesis is that the nature of the relationship between body fat distribution and metabolic profiles differ markedly in two populations with different metabolic disease risk (Pacific and European women).

1.3 Aims and Objectives

1.3.1 Study Aims

- To investigate the metabolic biomarkers and endocrine regulators in two distinct groups of women with different body fat profiles (normal and obese).
- To investigate the metabolic biomarkers and endocrine regulators in two distinct groups of women of high metabolic disease risk (Pacific women) or moderate metabolic disease risk (NZ European women).
- To compare different approaches of assessing body composition and fat distribution and their relationship with metabolic and endocrine profiles.

1.3.2 Specific Objectives

1. Investigate and compare different approaches of anthropometric and body composition assessment**.**
2. Describe metabolic biomarkers and endocrine regulators in the study population.

3. Investigate the relationship of body fat profiles and fat distribution with metabolic biomarkers and endocrine regulators.

1.4 Research Questions

- Which measures of anthropometry and body composition best describe body fat distribution and most closely correlate with metabolic health profiles?
- What is the link between body fat distribution and metabolic health profiles in two populations with markedly different metabolic disease risk (Pacific and European women) and does the nature of this relationship differ between these two population groups?

1.5 Structure of the Thesis

This thesis consists of four chapters. Chapter one is an introduction outlining the rationale for the study, including its aims and objectives. Chapter two is a narrative literature review of the relevant research surrounding the topic of the thesis. It covers the aetiology and pathophysiology of obesity, health inequities in New Zealand, measurements of body composition and adiposity, body fat distribution and the relationship with metabolic disease risk, and finally discusses the current strategies to curb obesity. Chapter three is the research study manuscript, consisting of an abstract, introduction, methodology and presentation of the results of this study, followed by the discussion of these findings and conclusions. Chapter four is a conclusion of the findings from this research, the strengths and limitations of the study, and suggestions for future research.

1.6 Contributors to the research

Table 1.1: Contributors to the research

Contributor	Role in the Study
Laura Mickleson	Assisted in data collection and data entry for the wider PROMISE study; data and statistical analysis; interpretation of results; author of the thesis.
Prof Bernhard Breier	Main thesis supervisor; lead investigator of the PROMISE study; concept and research design; ethics application; interpretation of results; revision and approval of the thesis.
A/Prof Rozanne Kruger	Thesis co-supervisor; co-investigator of the PROMISE study; concept and research design; interpretation of results.
Dr Marilize Richter	Thesis co-supervisor; advisor for statistical analysis; interpretation of results.
Niamh Brennan, Moana Manukia, Sherina Holland, Owen Mugridge, Sophie Kindleysides, Jo Slater, Nikki Renall, Rozanne Kruger and Marilize Richter	Recruitment, screening and execution of the PROMISE study; phlebotomy, data collection: anthropometry, body composition; data entry.
Elizabeth Cullen, Bronte Anscombe, Beatrice Drury and Ashleigh Jackson	Data collection and entry.
The Liggins Institute (Chris Keven and Eric Thorstensen)	Measuring metabolic biomarkers (total cholesterol, LDL-C, HDL-C, triglycerides, NEFA, glucose, HbA1c, CRP).
The New Zealand Institute for Plant and Food Research (Dr John Ingram)	Measuring insulin, leptin and TNF-α.

Chapter 2: Literature Review

Narrative literature review of obesity, body fat distribution and the associated cardio-metabolic disease risk

2.1 Introduction

Obesity is a widely researched phenomenon that has been recognised for its impact on health for over 2000 years (G. A. Bray, 2004; Haslam, 2007). Historically, food shortage has been more predominant than an over-supply of food, thus the pandemic of obesity is a relatively recent issue (Eknoyan, 2006). Food has become more easily accessible as technology and agriculture has developed, enabling a higher energy intake (Swinburn et al., 2011). Despite the increasing prevalence of obesity, world hunger statistics are still high, with around 815 million people chronically undernourished in 2016 (FAO, IFAD, UNICEF, WFP, & WHO, 2017), in contrast to the 2.1 billion with an overweight or obese body mass index (BMI) in 2013 (Ng et al., 2014). Both overnutrition and undernutrition can have serious health consequences, and these can both exist within the same population group simultaneously, and in the same individual at different points in their life (World Health Organization, 2017). This is known as the double burden of malnutrition (World Health Organization, 2017).

Obesity has been following an upward trend over the past few decades in most countries, including both developed and developing countries (Ng et al., 2014). The number of individuals with overweight or obesity increased from 921 million in 1980 to over 1.9 billion in 2016 (Ng et al., 2014; World Health Organization, 2018). Despite numerous public health strategies and individual-level interventions, no country has managed to see a decline in their obesity prevalence, although, some have been successful in reducing the rate of its incline (Ng et al., 2014; Roberto et al., 2015). In light of this, the World Health Organization, in their most recent Global Action Plan for the Prevention and Control of NCDs, has set a goal to prevent the incline of obesity prevalence from the year 2013 to 2020 (World Health Organization, 2013). With the current rate at which obesity is increasing, this will require major action from governments and public health sectors (Roberto et al., 2015).

New Zealand (NZ) is one of the many countries experiencing the upward trend in the prevalence of obesity (Ng et al., 2014). NZ continues to have one of the highest obesity rates within the Organisation for Economic Co-operation and Development (OECD) member countries, currently ranking third (OECD, 2017). Within the major population groups in NZ, Maori and Pacific peoples have the highest rates of obesity, while Asian and NZ European groups have the lowest (Ministry of Health, 2018). Health initiatives aimed at reducing obesity have been implemented in NZ since the 2000s (Swinburn & Wood, 2013). Some of these have generated modest success, however, the overall effect on obesity at a population level is yet to be seen (Swinburn & Wood, 2013).

Obesity is commonly defined by using the measurement of BMI. A BMI of 18.5 to 24.9kg/m^2 is considered a normal weight, 25.0 to 29.9kg/m^2 is considered overweight, and a BMI over 30.0 is considered obese (Ministry of Health, 2015). There are three different classifications of obesity; 30.0-34.9kg/m^2 is class I (moderate) obesity, 35.0-39.9kg/m^2 is class II (severe) obesity, and above 40kg/m^2 is class III (very severe) obesity (Ministry of Health, 2015). Obesity has been associated with several comorbid conditions, such as type 2 diabetes (T2D), cardiovascular disease (CVD), osteoarthritis, sleep apnoea and some forms of cancer (Seidell & Halberstadt, 2015). Obesity is also associated with a reduction in quality of life and life span (Seidell & Halberstadt, 2015). With increasing BMI, the risk for these comorbidities also increases, demonstrated by a J-shaped relationship between BMI and all-cause mortality observed by the Global Burden of Disease Project (The Global BMI Mortality Collaboration et al., 2016). Their meta-analysis of 239 prospective studies showed that having a BMI of 20-25kg/m^2 was associated with the lowest mortality, whereas a BMI above or below this range was associated with increased all-cause mortality.

Understanding the complexity of obesity as a multifactorial condition is progressing, as the extent of the research points towards environmental, physiological, genetic and endocrinological contributors, and is steering away from the simplistic and false notion that

obesity predominantly arises from personal lifestyle choices (Schwartz et al., 2017). This narrative literature review describes health inequities in NZ, the aetiology and pathophysiology of obesity, measurements of body composition and adiposity, body fat distribution and the relationship with metabolic disease risk, and finally, discusses current strategies to curb obesity. Key words used in the literature searches include obesity, body fat distribution, metabolic syndrome, insulin, glucose, HOMA-IR, dyslipidaemia, free fatty acids, non-esterified fatty acids, liver function, diabetes, cardiovascular disease, inflammation, adipose tissue, abdominal adiposity, gluteofemoral fat, android obesity, gynoid obesity, ethnic, New Zealand European, Pacific and Polynesian. Databases were searched between June 2017 and January 2019, and included PubMed, Discover, Web of Science and Google Scholar. Search criteria excluded literature that was not written in English.

2.2 Health Inequities and the Deprivation Index

Health inequities are prevalent in NZ, including obesity and its associated comorbidities. Pacific populations have the highest rates of obesity and T2D in NZ, whilst NZ European populations tend to achieve the best health outcomes (Ministry of Health, 2017). Proposed contributors to these inequities include lower levels of education, lower socioeconomic status, individual and institutional racism and incompatibility of the environment with the cultural diversity in NZ (Stoner, Matheson, Hamlin, & Skidmore, 2016). Education level has been linked to health outcomes through its association with health literacy and health-promoting behaviours, as well as occupation and income, which can enable or inhibit access to healthcare and healthy lifestyle opportunities (Cohen, Rai, Rehkopf, & Abrams, 2013). People living in the most deprived areas have a higher risk of obesity than those living in the least deprived areas, as well as a higher risk of CVD and T2D, after adjustment for age, sex and ethnic group (Ministry of Health, 2018).

The NZ Index of Deprivation (NZDep) is an index of socioeconomic deprivation configured from variables taken from the NZ census, including communication, employment, income,

living space, home ownership, qualifications, support and transport (Atkinson, Salmond, & Crampton, 2014). The NZDep2013 is the most recent index, measured on an ordinal scale from 1-10, with 1 representing the least deprived areas, and 10 representing the most deprived areas (Atkinson et al., 2014). The NZDep is useful for identifying groups of people that may be more susceptible to poorer health, who may need additional health funding and support (Exeter, Zhao, Crengle, Lee, & Browne, 2017).

2.3 The Aetiology of Obesity

Obesity is a complex, multi-factorial condition with numerous contributing risk factors. These factors include the physical environment, the social environment, genetics, diet and lifestyle, economic elements and developmental factors (Egger & Dixon, 2014; Schwartz et al., 2017). Ultimately, the interplay of these factors can lead to a positive energy balance, resulting in the excessive accumulation of adipose tissue (Schwartz et al., 2017). While this explains the accumulation of total fat, the distribution of fat is determined by other hormonal and genetic factors (G. A. Bray, 1999; Frank, de Souza Santos, Palmer, & Clegg, 2018). Obesity is also a highly heritable trait, and differences in genetics may leave some people more vulnerable to the environmental influences than others (O'Rahilly, 2009).

2.3.1 The Obesogenic Environment

As the understanding of obesity has developed over the years, the effect of the obesogenic environment has become more widely recognised. An obesogenic environment refers to the environment in which people live, that is set up in such a way that it is very easy to access and consume energy-dense foods, and difficult to expend this excess energy (Swinburn et al., 2019). Contributors to this environment include the increasing number of fast food chains, busy lifestyles driving the demand for convenience foods, affordability of nutrient-poor, high-sugar and fat foods, food advertising, and technological advances leading to less labour-intensive jobs and sedentary lifestyles (Levitsky & Pacanowski, 2012; New Zealand Medical Association, 2014; Swinburn et al., 2011).

Levitsky and Pacanowski (2012) argue that the rise in obesity is largely due to an increase in energy intake, mainly influenced by increasing portion sizes in restaurants and at home, a greater variety of foods available, higher fat content in foods and food advertising that encourages increased consumption. They report that the rise in obesity coincides with the rise in estimated energy intake in America, based on food production data. This trend has accelerated since the 1980s and a similar pattern continues today in most countries (Levitsky & Pacanowski, 2012; Ng et al., 2014).

The obesogenic environment is emerging as the largest determinant of obesity development, and will require focussed government action to reverse its detrimental effects. Swinburn et al. (2011) suggest policies aimed at changing the food environment: reducing the availability of energy-dense, nutrient-poor foods, increasing the opportunities for physical activity, and creating systemic changes that will aid populations to make healthier choices. Such policies and regulations could target unhealthy food advertising, clearer nutrition labelling on packaged foods, food policies in schools and workplaces, and a tax on energy-dense processed foods that are high in sugar and saturated fat (Swinburn et al., 2015).

2.3.2 Developmental, genetic and hormonal factors

Obesity during pregnancy is of particular concern, as it is associated with a higher risk of several complications for the mother, as well as the baby. This includes gestational diabetes, gestational hypertension, large-for-gestational-age (LGA) babies and higher likelihood of Caesarean section birth (S. Zhang et al., 2011). LGA babies have a higher likelihood of developing obesity not only in childhood, but also in adolescence and adulthood (S. Zhang et al., 2011). Pre-pregnancy obesity has been suggested to cause epigenetic changes to the embryo, enhancing fat storage in early life (S. Zhang et al., 2011). Therefore, women of child-bearing age are in a particularly important situation, as obesity in future generations is partially affected by maternal obesity and is a predictor of future CVD and T2D (Eriksson et al., 2014). Hence, the increase in overweight and obesity in NZ women of child-bearing age is concerning for the health of future generations (Ministry of Health, 2017).

Inheritance of genetic factors that have an impact on biological processes can predispose people to obesity (O'Rahilly & Farooqi, 2009). Studies in twins and adopted children indicate that 25-50% of the risk for obesity can be attributed to genetic inheritance (Schwartz et al., 2017). The effect of genetic factors to protect fat mass and create a positive energy balance can be enhanced by the environment (Schwartz et al., 2017). Some adipokine gene polymorphisms may be associated with obesity (Yu et al., 2012). Yu et al. (2012) in their systematic review and meta-analysis concluded that polymorphisms in ADIPOQ, IL-1β, IL-6, and TNF-α adipokine genes increased the risk of obesity. There are multiple classifications of genetic-related obesity, however, many of the specific genes involved in the pathophysiology are yet to be identified (Pigeyre et al., 2016).

Some hormones can cause changes to fat storage and energy balance. Leptin is a hormone released from adipocytes, and thus circulating concentrations of leptin are higher in individuals with more adipose tissue (Schwartz et al., 2017). The absence of leptin leads to hyperphagia and subsequent obesity (Schwartz et al., 2017). Leptin deficiency, or deficiency of the leptin receptor, can therefore lead to obesity (Schwartz et al., 2017). However, this is a very rare condition and leptin resistance is more likely to be contributing to the epidemic of obesity we see today (Schwartz et al., 2017).

2.4 Adipose Tissue Function

Adipose tissue is a functional organ composed of adipocytes, fibroblasts, endothelial cells and immune cells (Huh, Park, Ham, & Kim, 2014). Adipose tissue not only stores and releases energy, it also synthesises and secretes adipokines and hormones (Heymsfield & Wadden, 2017). Aside from its role in energy homeostasis, adipose tissue is important for immunity, thermoregulation and physical cushioning (Thomou, Tchkonia, & Kirkland, 2010).

Adipose tissue has multiple functions, and promotes good health when it is present at normal physiological amounts. Adipocytes hold triglycerides, the body's main form of stored energy, and also helps to protect vital organs and insulate the body (Ahmadian, Duncan, Jaworski, Sarkadi-Nagy, & Sul, 2007; Huh et al., 2014; Koeppen & Stanton, 2018). Triglycerides are also found in skeletal muscle tissue and in the liver, which are organs that regulate the storage and release of fatty acids from the triglycerides (Frayn, Arner, & Yki-Jarvinen, 2006; Koeppen & Stanton, 2018). A certain level of fat stores are preferred by the body as a reservoir for times of prolonged energy deficit and starvation (Wells, 2012), where the body will break down the fatty acids from the adipose tissue to use as energy (Marieb & Hoehn, 2016). Women have a naturally higher proportion of adipose tissue than men (Lassek & Gaulin, 2008), as these fat stores are of particular physiological importance during pregnancy and breast feeding (Wells, 2012). If a woman's fat stores drop too low, this may cause amenorrhoea and infertility (Sharma, Biedenharn, Fedor, & Agarwal, 2013). On the contrary, when fat stores become excessive, fertility may also be hindered, in men and women (Grodstein, Goldman, & Cramer, 1994; Sharma et al., 2013).

Adipose tissue also has a role in glucose homeostasis, as does muscle tissue and the liver (B. C. Lee & Lee, 2014). Although adipose tissue only takes up a small amount of glucose in response to insulin, its endocrine functions have a significant effect on glucose balance (Rosen & Spiegelman, 2006). As an endocrine organ, adipose tissue releases adipokines, signalling to other tissues and organs in the body (Romacho, Elsen, Rohrborn, & Eckel, 2014). Adipose tissue also regulates its own function through autocrine and paracrine signalling (Romacho et al., 2014). There are many adipokines with different functions, including the widely studied leptin, and others such as adiponectin, cytokines, chemokines and regulators of lipoprotein metabolism (Romacho et al., 2014). Leptin was discovered in 1994 and has transformed our understanding of the role of adipose tissue and potential therapeutic targets for obesity (G. A. Bray et al., 2018). Leptin concentrations increase proportionally as adiposity increases, and has an essential role in controlling hunger and normal body weight (G. A. Bray et al., 2018). Treatment with leptin is only effective for controlling obesity in people with leptin deficiency (G. A. Bray et al., 2018). This is a very

rare condition, hence leptin therapy is only useful in a small group of patients with obesity (G. A. Bray et al., 2018).

In summary, adipose tissue plays an important role in reproductive health, development, growth, immunity and cell signalling (Wells, 2012). However, when adipose tissue accumulates in excess, it can disrupt metabolic pathways, leading to the common cardio-metabolic diseases often associated with obesity (Schwartz et al., 2017).

2.5 The Normal Biological Roles of Metabolic Health Biomarkers

Metabolism and energy balance involve a complex interplay of many hormones and biological molecules. Humans have the ability to store ingested energy, enabling survival during prolonged periods of fasting, where the body utilises these energy stores (McNamara & Huber, 2018). Energy is stored as glycogen in the liver and muscles, and as triglycerides in adipocytes (Dashty, 2013). Amino acids from muscles are the least preferred energy source, and are usually only drawn from in situations of extreme starvation when other energy stores are depleted (Marieb & Hoehn, 2016). Proteins have major physiological functions in the body, including essential roles in movement, transportation, storage, structure and enzymatic reactions (Simon, Dickey, Reece, Hogan, & Campbell, 2016). Triglycerides are the major form of stored energy in the body and are held within adipocytes (Marieb & Hoehn, 2016). Adipose tissue mass makes up around 18% of a person's total body weight, holding far more energy than glycogen stores (Marieb & Hoehn, 2016).

Cholesterol in the blood is derived from either the diet or produced in the liver. Dietary lipids are broken down into free fatty acids (FFA) and monoglycerides, which are resynthesised into triglycerides, and transported through the bloodstream in chylomicrons to be delivered to the body's cells (Koeppen & Stanton, 2018). The liver produces high-density lipoprotein cholesterol (HDL-C) and very-low-density lipoprotein cholesterol (VLDL-C) (Marieb & Hoehn, 2016). VLDL-C transports triglycerides mainly to adipose tissue, and is

then converted to LDL-C (Marieb & Hoehn, 2016). The role of LDL-C is to transport cholesterol to tissues, which is vital for hormone production and for cell membrane integrity (Marieb & Hoehn, 2016). In contrast, HDL-C is responsible for removing excess cholesterol from cells and the bloodstream, and transporting it back to the liver to be either excreted or recycled (Marieb & Hoehn, 2016). In the fasting state, FFA, also known as non-esterified fatty acids (NEFA), are released from the triglycerides in adipocytes, into the blood to be used for energy (Elliott & Elliott, 2009).

Dietary carbohydrates are broken down into glucose, to be used as the main source of energy in the body (Marieb & Hoehn, 2016). Glucose levels in the blood are maintained to ensure the brain has sufficient fuel, with remaining glucose stored as glycogen in the liver and muscle cells, or as triglycerides in adipocytes (Marieb & Hoehn, 2016). The entry of glucose into liver, fat and muscle cells is enabled through the action of insulin, where glycogen is synthesised in a process called glycogenesis (Dashty, 2013). Some of the glucose molecules remaining in the blood will attach to haemoglobin in proportion to the total amount of glucose in the blood, creating a complex known as glycosylated haemoglobin (HbA1c) (V. S. Freeman, 2014). HbA1c is measured clinically in patients with T2D to assess blood glucose management, and it is also used as a diagnostic tool to screen for T2D along with fasting glucose or glucose tolerance tests (NZSSD, 2011). Uncontrolled HbA1c in diabetes is a predictor of microvascular complications, including retinopathy, nephropathy and neuropathy, and macrovascular complications such as heart disease (Chawla, Chawla, & Jaggi, 2016).

2.6 The Pathophysiology of Obesity

Metabolic changes occur in the pathophysiology of obesity, including disrupted glucose and lipid metabolism, and the development of chronic, low-grade inflammation (Abdelaal et al., 2017; G. A. Bray et al., 2018). These metabolic disturbances can lead to the development of T2D and CVD (G. A. Bray et al., 2018).

The liver is an organ that is central to metabolism and influences metabolic health in many ways. Fat accumulation around the liver can cause increased glucose production, increased VLDL-C production, and can reduce degradation of insulin and Apolipoprotein B (Bastien et al., 2014). Obesity is also a major risk factor for non-alcoholic fatty liver disease (NAFLD), with increased visceral adipose tissue associated with the highest risk (Milić, Lulić, & Štimac, 2014). Liver function tests such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) can indicate liver damage (Neuman, Cohen, & Nanau, 2014) however, these tend to be raised with obesity and thus may not be sensitive markers (Milić et al., 2014). Alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) are also raised in NAFLD and do not appear to be associated with BMI (Milić et al., 2014).

Insulin resistance is one of the consequences that can arise when an excessive amount of adipose tissue is accumulated. In obesity, higher amounts of ectopic lipids, circulating FFA and pro-inflammatory cytokines can impair insulin signalling (Heymsfield & Wadden, 2017). This results in the β-cells of the pancreatic islets to release more insulin, and thus a hyperinsulinaemic state is brought about (B. C. Lee & Lee, 2014). In an insulin resistant state, the function of the liver, muscle and adipose tissue are compromised (B. C. Lee & Lee, 2014). When the hepatocytes of the liver are unable to respond to insulin, the liver will continue to produce and release glucose through gluconeogenesis and glycogenolysis even when plasma glucose levels are high (B. C. Lee & Lee, 2014). The cells of muscle tissue and adipose tissue, myocytes and adipocytes, are less responsive to insulin signalling in a relative insulin resistant state, and thus glucose storage is hindered (B. C. Lee & Lee, 2014). Prolonged insulin resistance can lead to the β-cells becoming fatigued and eventually failing to produce enough insulin to effectively handle the blood glucose (B. C. Lee & Lee, 2014). The progression of this leads to hyperglycaemia and T2D (G. A. Bray et al., 2018; B. C. Lee & Lee, 2014).

The over-accumulation of adipose tissue can also cause disruptions to the blood lipid profile, leading to dyslipidaemia (Heymsfield & Wadden, 2017). Adipose tissue breaks down the triglycerides within the adipocytes, releasing FFA that enter the bloodstream (Heymsfield &

Wadden, 2017). The development of obesity is associated with elevated levels of FFA, triglycerides and LDL-C, and lower HDL-C levels (G. A. Bray et al., 2018; Van Gaal et al., 2006). Excess abdominal and visceral adipose tissue in particular have been linked to dyslipidaemia (Huang et al., 2015; Tchkonia et al., 2013). Elevated triglyceride levels are associated with excess visceral fat, a risk factor for CVD (Despres, 2012; Huang et al., 2015).

Inflammation is part of the normal response to injury or infection, that initiates a process to bring about repair of the tissue (Rhoades & Bell, 2013). A prolonged state of inflammation is known as chronic inflammation (Rhoades & Bell, 2013). A high level of adiposity has been associated with chronic, low-grade inflammation (Schwartz et al., 2017). In healthy adipose tissue, immune cells within the tissue release anti-inflammatory cytokines that keep the tissue sensitive to insulin (Huh et al., 2014). Obesity can lead to an increase in pro-inflammatory immune cells and a decrease in anti-inflammatory immune cells, which can contribute to the development of insulin resistance (Huh et al., 2014; Mraz & Haluzik, 2014). Tumour necrosis factor alpha (TNF-α) and high sensitivity C-reactive protein (hs-CRP) are markers of inflammation and can be helpful in identifying metabolic disease risk (D. J. Freeman et al., 2002; Golia et al., 2014; Ridker et al., 2000). TNF-α is a pro-inflammatory cytokine that has been found to be elevated with obesity and can disrupt insulin signalling, leading to insulin resistance (Nakamura et al., 2014). CRP is an acute phase reactant synthesised predominantly in the liver in response to tissue damage or inflammation, and plays a role in innate immunity (C. Bray et al., 2016). CRP is also elevated in obesity, marking the presence of inflammation and thus a greater CVD risk (J. Choi et al., 2013).

The prevalence of hypertension increases with increasing BMI (Landsberg et al., 2013). Weight loss has been shown to reduce blood pressure and is an effective treatment for hypertension in participants with overweight or obesity (Neter, Stam, Kok, Grobbee, & Geleijnse, 2003). The mechanisms underlying the development of hypertension in obesity involve the effects of increased adiposity on insulin and leptin levels, and activation of the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) (Landsberg et al., 2013). Insulin and leptin can stimulate the SNS, which may be a link

between obesity and increased blood pressure (Landsberg et al., 2013). Insulin can also stimulate the kidneys to retain sodium, another way in which hyperinsulinaemia may increase blood pressure (Landsberg et al., 2013). Excess adipose tissue surrounding the kidneys can also contribute to fluid retention, causing increased blood pressure (Rocchini, 2002).

2.7 Anthropometric and Body Composition Assessment Methods

2.7.1 Body Mass Index

BMI is a measure of a persons weight in kilograms in proportion to their height, yielding a description of body mass in the unit kg/m^2. This measure has been used for many years as a way to predict morbidity and mortality risk, and is effective in doing so at the population level (G. A. Bray et al., 2018). However, there has been some controversy around the use of BMI to predict mortality, as overweight may be associated with lower mortality than normal weight, as defined by BMI (Flegal, Kit, Orpana, & Graubard, 2013). However, a large meta-analysis of prospective cohort studies has provided evidence contrary to this (The Global BMI Mortality Collaboration et al., 2016). Additionally, mortality risk has been shown to increase with increasing body fat percentage, as well as decreasing BMI (Padwal, Leslie, Lix, & Majumdar, 2016). Keys, Fidanza, Karvonen, Kimura, and Taylor (1972) compared weight-to-height indexes and concluded that BMI had the best correlation with body fat percentage as measured by skinfold thickness and underwater weighing. However, BMI has some limitations and is not considered as an accurate measure of adiposity, although it does prove to be useful for screening and monitoring obesity prevalence in populations over time (G. A. Bray et al., 2018).

The important limitations of a BMI measurement include that it is unable to determine body composition (fat and lean mass) and it gives no indication of fat location (G. A. Bray et al., 2018). Fat and muscle mass both have different metabolic roles, and while muscle mass has many health benefits (Argiles, Campos, Lopez-Pedrosa, Rueda, & Rodriguez-Manas, 2016;

Bayol, Bruce, & Wadley, 2014), excessive fat mass is known for its detriment to health (G. A. Bray et al., 2018). With a measure such as BMI, calculated from only weight and height, it is impossible to determine what proportion of the body is fat or lean mass (Prentice & Jebb, 2001). This can result in a false categorisation of someone as overweight or obese when they have a high proportion of muscle mass, and can also define someone as having a normal weight, who in fact has a high proportion of fat mass, and is relatively unhealthy from a metabolic perspective. A study conducted in 2409 women compared BMI with total body fat percentage measured by bioelectrical impedance analysis (BIA), finding that BMI was ineffective at identifying those with a high proportion of body fat (Gába & Přidalová, 2015). In addition to the total amount of fat mass, the location of adipose tissue has metabolic implications, something BMI cannot measure (G. A. Bray et al., 2018).

There are also concerns about the BMI cut-offs being inappropriate for different ethnicities (Rush et al., 2009; Wen et al., 2010). BMI cut-off values were developed based on Western populations, and there is some research to suggest these are not appropriate for all ethnic groups (Rush et al., 2009; Wen et al., 2010). Asian populations, including Asian Indian, have been found to have a higher body fat percentage at the same BMI as European groups, suggesting that the cut-offs for overweight and obesity should be lower (Rush et al., 2009; Wen et al., 2010). Conversely, Pacific populations have been found to have a lower body fat percentage at the same BMI as Europeans, indicating that higher cut-offs would be more appropriate for these groups (Rush et al., 2009). However, a study by Taylor et al. (2010) compared Maori and European men and women, finding that BMI, waist circumference and waist-to-height ratio performed similarly in both ethnic groups and accurately predicted individuals with and without insulin resistance or the metabolic syndrome. They are opposed to higher cut-offs for Maori and other groups of Polynesian decent, as their findings suggest that this would result in ineffective disease risk identification (Taylor et al., 2010).

2.7.2 Anthropometric Tools

At the individual level, anthropometric measurements can be used to estimate adiposity, fat distribution and the associated disease risk (G. A. Bray et al., 2018). These include waist

circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR) and sagittal height. WC is an indirect measure of abdominal or android adiposity (Bosy-Westphal et al., 2010) and is similar to BMI in its ability to predict T2D and CVD risk (G. A. Bray et al., 2008; Gearon, Tanamas, Stevenson, Loh, & Peeters, 2018). While Freedman et al. (2013) found that WC was a slightly better predictor of disease risk than BMI, they observed a high correlation between WC and BMI. Seo, Choe, and Torabi (2017) found that WC was more effective at predicting diabetes development than BMI, however, these two measures had a similar ability to predict hypertension development. WC is unable to distinguish between visceral and subcutaneous fat, although it correlates well with both (Barreira et al., 2012). Visceral fat is of particular importance when considering disease risk, as it is a predictor of the metabolic syndrome, T2D, CVD and total mortality (G. A. Bray et al., 2018). Considering fat distribution is important, as studies have shown that normal weight participants with central obesity had poorer long-term survival than those without central obesity, despite BMI (Cerhan et al., 2014; Sahakyan et al., 2015). Because of this, some researchers have suggested the inclusion of WC measurements alongside BMI for cardio-metabolic disease risk assessment (G. A. Bray et al., 2018; Cerhan et al., 2014). It is acknowledged that BMI and WC may not align for all individuals, as someone can be classified with obesity using one measure, but not necessarily with the other (Gearon et al., 2018).

Gluteofemoral fat refers to the adipose tissue located in the buttock and thigh regions, and is reflected by the HC measurement (Manolopoulos et al., 2010). While HC correlates with cardio-metabolic risk factors, including fasting glucose, triglycerides, HOMA-IR and mean arterial blood pressure, DXA-measured gynoid fat has a stronger relationship with these risk factors, as it more accurately quantifies the adipose tissue mass (Vasan et al., 2018). WHR is used as a measure of abdominal adiposity and fat distribution (World Health Organization, 2008), however studies have indicated that WHR does not perform as well as BMI, WC or WHtR for measuring total body fat, visceral fat mass and subcutaneous abdominal adipose tissue (Swainson, Batterham, Tsakirides, Rutherford, & Hind, 2017). G. A. Bray et al. (2008) found that BMI, WC, WHR and visceral adipose tissue measured by CT scan were all effective in predicting diabetes development. However, Cheong et al. (2015) found that WC

and BMI were better discriminators of metabolic syndrome than WHR. In contrast, a prospective cohort study found that WHR was a better predictor of mortality and CVD outcomes than body fat percentage or BMI (Myint, Kwok, Luben, Wareham, & Khaw, 2014). WHtR may be a suitable substitute for BMI and WC, as it correlates well with both total body fat percentage and visceral adipose tissue (Swainson et al., 2017). A systematic review and meta-analysis by C. M. Lee, Huxley, Wildman, and Woodward (2008) concluded that WHtR, WC and WHR were better discriminators of T2D risk compared to BMI, however these anthropometric measures performed similarly for risk of hypertension and dyslipidaemia. As the differences between BMI and these other anthropometric measurements are relatively small, the authors do question the practical relevance of this, suggesting that BMI could be just as effective in clinical settings. Additionally, Rost et al. (2018) reported that, in women, WC and WHR were better predictors of all-cause and cardiovascular mortality compared to WHtR. Thus, there is some disagreement in the literature regarding the best anthropometric tools for assessing cardio-metabolic disease risk.

2.7.3 Body Composition Assessment Tools

As anthropometric measurements are unable to accurately measure body composition constituents such as adipose tissue and lean mass, or identify the location of adipose tissue in terms of visceral and subcutaneous fat, advanced body composition methods are used to give more detailed information about this, as well as the overall mass of these tissues (Seabolt, Welch, & Silver, 2015). Dual-energy x-ray absorptiometry (DXA) is an accurate method to assess body composition, as verified by comparison with the four-compartment method (Seabolt et al., 2015); it measures bone mineral density, non-bone lean mass, and fat mass (S. Y. Lee & Gallagher, 2008). DXA scanning is a relatively simple procedure that is performed with the participant lying on the scanning bed (S. Y. Lee & Gallagher, 2008). Limitations of DXA include that it is unsuitable during pregnancy due to a low dose of radiation emitted during the scan (Seabolt et al., 2015), and it has width and weight restrictions, hence some individuals require two half-body scans (S. Y. Lee & Gallagher, 2008; Rothney, Brychta, Schaefer, Chen, & Skarulis, 2009). DXA is often used as the gold standard for comparisons, particularly with anthropometric and BIA measurements (Bazzocchi et al., 2014; Day et al., 2018; Ramírez-Vélez et al., 2016), and is an important tool

for the assessment of total and regional body fat in clinical research (Andreoli, Scalzo, Masala, Tarantino, & Guglielmi, 2009).

BIA is generally a more accessible tool than DXA; it is easier to use, less expensive, portable and time-effective (Day et al., 2018). Multi-frequency BIA provides measurements of total and segmental fat mass and fat free mass (Shafer, Siders, Johnson, & Lukaski, 2009). Some research indicates that BIA may overestimate fat-free mass and underestimate fat mass (Day et al., 2018), or underestimate fat free mass (Tewari et al., 2018). BIA may also be less accurate in participants with a BMI above 30kg/m^2 (Bedogni et al., 2013; Shafer et al., 2009). On the other hand, some studies have found that BIA performs well when compared to DXA, even in participants with a BMI above 30kg/m^2 (Anderson, Erceg, & Schroeder, 2012; Thomson, Brinkworth, Buckley, Noakes, & Clifton, 2007; von Hurst et al., 2016). While there can be variability in the accuracy of different BIA devices, BIA is generally accepted as a useful tool for body composition assessment (Andreoli et al., 2002; Day et al., 2018).

2.8 Fat Distribution and the Associated Cardio-metabolic Risk

Total body fat may not be the best indicator of cardio-metabolic disease risk, as the location of adipose tissue has significant metabolic implications (G. A. Bray et al., 2018). Two body fat distribution profiles are commonly differentiated; the android distribution, which describes adiposity held in the upper-body or abdominal region, and the gynoid fat distribution, which describes adiposity held in the lower-body or hip region (Hocking, Samocha-Bonet, Milner, Greenfield, & Chisholm, 2013). Studies have explored whether there is a difference in cardio-metabolic risk associated with different fat distribution profiles. A recent cross-sectional study investigated total and regional adiposity and the associations with risk factors for T2D and CVD, including impaired fasting glucose, hypertension, hypertriglyceridaemia and insulin resistance (Vasan et al., 2018). They found that gynoid fat and leg fat were protective against these metabolic disease risk factors for T2D and CVD, after adjustment for total adiposity. They also observed an increased metabolic disease risk associated with upper-body fat, however the subcutaneous

component of android adipose tissue was found to be protective against all T2D and CVD risk factors. In agreement with this, a cross-sectional study by Fox et al. (2007) observed that visceral adipose tissue had stronger associations with cardio-metabolic risk factors compared to subcutaneous adipose tissue. These risk factors included fasting triglycerides, HDL-C, total cholesterol, systolic and diastolic blood pressure, and fasting plasma glucose. Furthermore, other studies also support the inverse association of a lower-body fat distribution with cardio-metabolic disease risk (Aasen, Fagertun, & Halse, 2008; S. I. Choi et al., 2017; Sakai et al., 2005; Wiklund et al., 2008; X. Zhang, Hu, Wu, Malik, & Sun, 2013).

Tchkonia et al. (2013) reviewed the potential mechanisms underlying the metabolic differences observed between visceral fat, and lower and upper-body subcutaneous fat depots. They report that there are regional differences in pre-adipocytes, which can explain the differences in function of adipose tissue in different regions of the body. Also, it has been observed that femoral subcutaneous adipocytes have a greater tendency towards hyperplasia, whereas abdominal subcutaneous adipocytes tend to exhibit hypertrophy (Tchkonia et al., 2013; Tchoukalova et al., 2010). Additionally, upper-body adipose tissue releases more FFA in the post-prandial state than lower-body adipose tissue, which can lead to lipotoxicity, dyslipidaemia and impaired insulin signalling (Heymsfield & Wadden, 2017; Tchkonia et al., 2013). Studies have shown that individuals with overweight or obesity displaying predominant visceral and ectopic fat stores have a higher risk for CVD development (Abraham, Pedley, Massaro, Hoffmann, & Fox, 2015; Despres, 2012; Liu et al., 2010; Piche et al., 2018). Excessive visceral fat accumulation is more likely to lead to metabolic disturbances than subcutaneous fat, because visceral fat is more lipolytic and lipogenic, releasing FFA into the portal circulation, which can increase triglyceride synthesis in the liver and cause insulin resistance (Matsuzawa et al., 1995). These alterations can lead to hyperlipidaemia, glucose intolerance and hypertension (Matsuzawa et al., 1995).

2.9 Metabolically Healthy Obesity

An observation that some individuals with obesity do not have the clinical signs of metabolic disease risk that commonly accompanies obesity lead to the idea of metabolically healthy obesity (MHO) (G. A. Bray et al., 2018). Heinonen et al. (2014) investigated differences in twins, observing that adipocyte hyperplasia was associated with a metabolically healthy phenotype, whereas adipocyte hypertrophy was associated with a metabolically unhealthy phenotype.

Individuals with MHO tend to have normal insulin sensitivity, blood pressure and lipid profiles, appearing to have a lower cardio-metabolic disease risk (Primeau et al., 2011). However, MHO appears to be an unstable state that progresses to metabolically unhealthy obesity (MUHO) over time (Bell et al., 2015; G. A. Bray et al., 2018; Mongraw-Chaffin et al., 2018) and thus the risk for mortality in these individuals may not be reduced (Primeau et al., 2011). A meta-analysis of prospective cohort studies found that although metabolic profiles were normal, individuals with MHO showed a four-times higher risk of T2D than metabolically healthy normal weight (MHNW) individuals (Bell, Kivimaki, & Hamer, 2014). Individuals with MHO also have a higher risk of cardiovascular events than MHNW individuals (Eckel, Meidtner, Kalle-Uhlmann, Stefan, & Schulze, 2016). Data from the 2007-2008 and 2009-2010 National Health and Nutrition Examination Surveys (NHANES) showed that individuals with MHO in the United States had better dietary intakes (in relation to nutrition guidelines) than individuals with MUHO (Camhi, Whitney Evans, Hayman, Lichtenstein, & Must, 2015) which may highlight the protective effect of a balanced diet. Physical activity is an important factor in reducing the risk of developing an unhealthy metabolic profile and all-cause mortality (G. A. Bray et al., 2018) and it is suggested that lifestyle interventions should be offered to all individuals with obesity (Primeau et al., 2011). Furthermore, it is possible to reduce mortality risk by adopting healthy lifestyle habits, regardless of BMI (Matheson, King, & Everett, 2012).

2.10 Current Strategies to Curb Obesity

While many strategies to prevent and treat obesity are in place at the individual, community and global levels, no country has yet been successful in reducing their prevalence of obesity (Ng et al., 2014). Diets for weight loss are largely ineffective over the long-term, and often result in weight re-gain (McEvedy, Sullivan-Mort, McLean, Pascoe, & Paxton, 2017). Strategies that the individual can adopt into their lifestyle are more likely to result in long-lasting changes (McEvedy et al., 2017). However, the obesogenic environment is a major barrier that is not easily overcome; there is a need for government action to change the food environment, targeting food advertising, regulations regarding food sold in schools and work places, and nutrition policies (Swinburn et al., 2015). These changes are by no means simple, and will require the support of the community, government and industry. Making the healthy choice the easy choice is a goal that should be adopted by governments and the food industry globally to start the change in the food environment that is needed to support individuals to make healthier food choices (Swinburn et al., 2011). Urgent action is required to eliminate the structural and societal inequities that result in some population groups having higher metabolic disease risk and obesity prevalence (Swinburn et al., 2011).

Identifying fat distributions that are associated with higher disease risks can guide the use of anthropometric and body composition analysis in clinical practice. This will ensure individuals and population groups with increased metabolic disease risk are identified to allow appropriate intervention options to be offered, to reduce the development of obesity in these groups.

2.11 Summary

This narrative literature review describes the current knowledge of the aetiology of obesity and the pathophysiology associated with excess adipose tissue and its distribution. Obesity rates are climbing globally, largely the result of an obesogenic environment. Systemic change is required to improve the food environment and enable healthy choices to be made by consumers. Differences in obesity prevalence and cardio-metabolic disease risk exist

between ethnic groups in New Zealand, illustrating the inequities that are present. The increasing prevalence of obesity in NZ women is particularly concerning, as maternal obesity is a risk factor for obesity and related comorbidities in the subsequent generations. A range of anthropometric and body composition assessment tools are used to screen for overweight and obesity, and to identify those who may have a higher metabolic disease risk. BMI is the most common tool for this purpose and is widely used to define obesity. Waist circumference and its ratio with hip circumference (WHR) and height (WHtR) are suggested as useful tools in the clinical setting to assess adiposity and cardio-metabolic disease risk. Measurements that reflect regional fat depots are useful when addressing cardio-metabolic disease risk; visceral fat is known to be more metabolically active than subcutaneous fat, and thus has different metabolic implications. An upper-body (android) fat distribution profile has been linked to a greater metabolic disease risk than a lower-body (gynoid) fat distribution profile. Identifying anthropometric and body composition assessment tools that best reflect the android and gynoid fat distributions and the association of these fat distribution profiles with cardio-metabolic disease risk factors will help to define which tools are most useful in the clinical setting. Little research has been done in this area within New Zealand population groups. This is of utmost importance considering the health inequities that are observed, and the vast differences in metabolic disease risks observed between ethnic groups such as NZ European and Pacific peoples.

Acknowledgements

This study gratefully acknowledges support from the Health Research Council of New Zealand (HRC). HRC Project grant #15/273 “The gut microbiome: a new pathway to obesity prevention and metabolic health”.

Conflicts of Interest

None.

Chapter 3: Manuscript

Investigating the relationships between body fat distribution, metabolic biomarkers and endocrine regulators in Pacific and New Zealand European women

3.1 Abstract

Background: The burden of overweight and obesity continues to rise throughout the world, including New Zealand (NZ). Obesity prevalence differs among ethnic groups in NZ and this is associated with considerable health inequities. For example, Pacific peoples living in NZ have higher rates of obesity-related health issues, compared to NZ Europeans. Understanding the link between body composition and metabolic health is essential for the development of more effective preventative and intervention strategies for different population groups, who may have different metabolic disease risk profiles.
Aims: This research aims to investigate the metabolic biomarkers and endocrine regulators in two distinct groups of women with different body fat profiles (normal and obese); to investigate the metabolic biomarkers and endocrine regulators in two distinct groups of women of high metabolic disease risk (Pacific women) or moderate metabolic disease risk (NZ European women); and to compare different approaches of assessing body composition and fat distribution and their relationship with metabolic and endocrine profiles.
Design: A cross-sectional study conducted in 304 Pacific and NZ European women aged 18-45 years. Anthropometry, a range of body composition and fat distribution measurement approaches, metabolic biomarkers (including lipids, markers of glucose metabolism and inflammation markers) and endocrine regulators (insulin and leptin) will be investigated.
Outcomes: Total body fat percentage (BF%) measured by bioelectrical impedance analysis (BIA) correlated strongly with BF% measured by dual X-ray absorptiometry (DXA). Waist-to-hip ratio (WHR) had weak associations with android fat percentage and BF% measured by DXA, whereas waist circumference (WC) and waist-to-height ratio (WHtR) performed better in this respect. Anthropometric measurements had similar correlations with total body fat percentage and regional fat depots for both ethnic groups. For each ethnicity, women in the high body mass index (BMI) group had higher circulating concentrations of fasting insulin, fasting glucose, glycosylated haemoglobin (HbA1c), triglycerides and total cholesterol to high-density lipoprotein (TC/HDL) ratios, and lower circulating HDL cholesterol concentrations in comparison with the normal BMI group. Gynoid fat percentage had weak associations with circulating cardio-metabolic risk factors, including low-density lipoprotein cholesterol (LDL-C), triglycerides, HbA1c, fasting insulin and fasting glucose concentrations. On the other hand, android and visceral fat percentages had stronger, positive associations with these cardio-metabolic risk factors. Furthermore, BF% measured by DXA and BMI explained a similar amount (57.1% and 49.7% respectively) of the variance in leptin concentrations.
Conclusion: Our findings suggest that in a New Zealand population with markedly different

body fat profiles, assessment of WC, WHtR and BMI are effective tools for assessing adiposity and the associated cardio-metabolic disease risk factors in a clinical setting, whereas WHR does not appear to be a useful tool. This thesis research provides strong evidence that these clinically important and effective tools should continue to be used in dietetic practice, across different population groups with different metabolic disease risks and different body fat profiles.

3.2 Introduction

The prevalence of obesity has been increasing significantly over the past few decades along with its associated disease burden (The GBD 2015 Obesity Collaborators, 2017). The effects of obesity on cardio-metabolic health have been studied for many years, with findings suggesting that excessive accumulation of fat is detrimental to health (G. A. Bray, 2004). Mounting research also highlights the importance of fat distribution, rather than the total amount of fat itself, in cardio-metabolic disease risk assessment (G. A. Bray et al., 2018; Piche et al., 2018). Implications arising from obesity include the disruption to metabolic profiles, low-grade inflammation, a higher risk for some diseases such as cardiovascular disease (CVD), hypertension, type 2 diabetes (T2D) and some forms of cancer, and mechanical consequences such as osteoarthritis (G. A. Bray et al., 2018). There are multiple factors contributing to the likelihood of an individual developing obesity, which is beginning to be understood as a disease of environmental exposures (Schwartz et al., 2017; Swinburn et al., 2011). Understanding the pathway to obesity development requires consideration of the environmental, genetic and metabolic influences.

New Zealand (NZ) has a high prevalence of obesity, ranking third highest in the Organisation for Economic Co-operation and Development (OECD) member countries, with approximately one third of adults categorised with an obese body mass index (BMI) (Ministry of Health, 2018; OECD, 2017). Worldwide, women are more susceptible to obesity than men, and this is also true for NZ (Ministry of Health, 2018; The GBD 2015 Obesity Collaborators, 2017). Of the major ethnic groups in NZ, Pacific peoples have the highest prevalence of obesity, and are 2.27 times more likely to develop obesity than other ethnic groups (Ministry of Health, 2018). This health inequity also extends to obesity-related comorbidities, with Pacific peoples having the highest rates of T2D and CVD (Ministry of Health, 2017).

Adiposity and its associated disease risk can be assessed in dietetic practice by a number of anthropometric measurements, including BMI, waist circumference (WC), hip circumference

(HC), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR) and sagittal height. These are indirect measurements of body composition. BMI estimates overall body fat to categorise an individual as underweight, normal weight, overweight or obese, adjusted for height (Ministry of Health, 2015). WC, WHR, WHtR and sagittal height estimate abdominal fat and fat distribution, while HC estimates gluteofemoral fat (World Health Organization, 2008). Direct measures of adiposity such as dual-energy X-ray absorptiometry (DXA) and bioelectrical impedance analysis (BIA) provide more accurate estimates of body composition, measuring the amount of total lean and fat mass, as well as the distribution of body fat (Beechy et al., 2012). Together with metabolic health biomarkers, these measures are used to assess disease risk, based on the known association between excess adiposity, particularly abdominal obesity, and long-term metabolic disease outcomes (G. A. Bray et al., 2018; Manolopoulos et al., 2010).

Increasing evidence suggests that body fat distribution is an important contributor to metabolic disease risk, and should be considered in addition to BMI, a tool that is commonly used at the individual and population levels (G. A. Bray et al., 2018). Excessive amounts of adipose tissue in visceral and upper-body fat depots tend to be associated with an increased metabolic disease risk, whereas lower-body fat depots appear to have a protective effect on general metabolic health (G. A. Bray et al., 2018; Vasan et al., 2018). The present study will firstly investigate metabolic biomarkers and endocrine regulators in two distinct groups of women with different body fat profiles (normal and obese) and of high metabolic disease risk (Pacific women) or moderate metabolic disease risk (NZ European women); and secondly, compare different approaches of assessing body composition and fat distribution and their relationship with metabolic and endocrine profiles. To pursue these aims, we conducted a cross-sectional study in 304 Pacific and NZ European women aged 18-45 years. A range of anthropometric, body composition and body fat distribution measurements, as well as metabolic biomarkers (including lipids, markers of glucose metabolism and inflammation markers) and endocrine regulators (insulin and leptin) will be investigated.

3.3 Materials and Methods

3.3.1 Study Design

This study is a sub-study of the PROMISE Study (PRedictors linking Obesity and gut MIcrobiomE), a single-centre cross-sectional study conducted at the Massey University Human Nutrition Research Unit in Auckland, NZ, between July 2016 and September 2017.

All eligible participants attended the research unit on two occasions, 11-14 days apart, where they completed a series of scheduled tasks. Inclusion criteria for the women were: age 18-45 years, being post-menarche and pre-menopausal (as defined by a regular menstrual cycle for the last year), ethnicity (self-identified as NZ European ethnicity and having lived in NZ for a minimum of five years, or self-identified Pacific ethnicity and having at least one parent of Pacific ethnicity), written informed consent, willingness to comply with study requirements and generally healthy. Exclusion criteria for the participants were: BMI outside of the pre-defined normal or obese BMI ranges, pregnant and/or lactating, presence of any diagnosed chronic illness (e.g. T2D, CVD), prior bariatric surgery, severe food allergies, medication that could interfere with appetite or the immune system, current smoker, severe dietary restrictions or avoidances (e.g. vegan) and antibiotic use during the last month. The study population is presented in **Figure 3.1**.

3.3.2 Recruitment Methods

The PROMISE study team recruited Pacific and NZ European women, living in the Auckland region, using a range of recruitment strategies. A partnership was developed with the Fono, a Pacific primary healthcare and social services organisation based in Auckland, to integrate culturally appropriate recruitment and research procedures. This included the appointment of a senior Pacific nurse who liaised within her community networks, and led much of the recruitment, booking and management of the study involving Pacific women. Pacific women were commonly recruited in-person or by phone, and were provided with transport to and from the research unit to reduce barriers that may prevent participation in the study. NZ

European women were recruited more commonly via the online advertisements and self-directed screening system. A number of Facebook community pages, work/university email lists and other social media sources were used to share details of our study for recruitment purposes. Participants were provided with a gift voucher upon study completion.

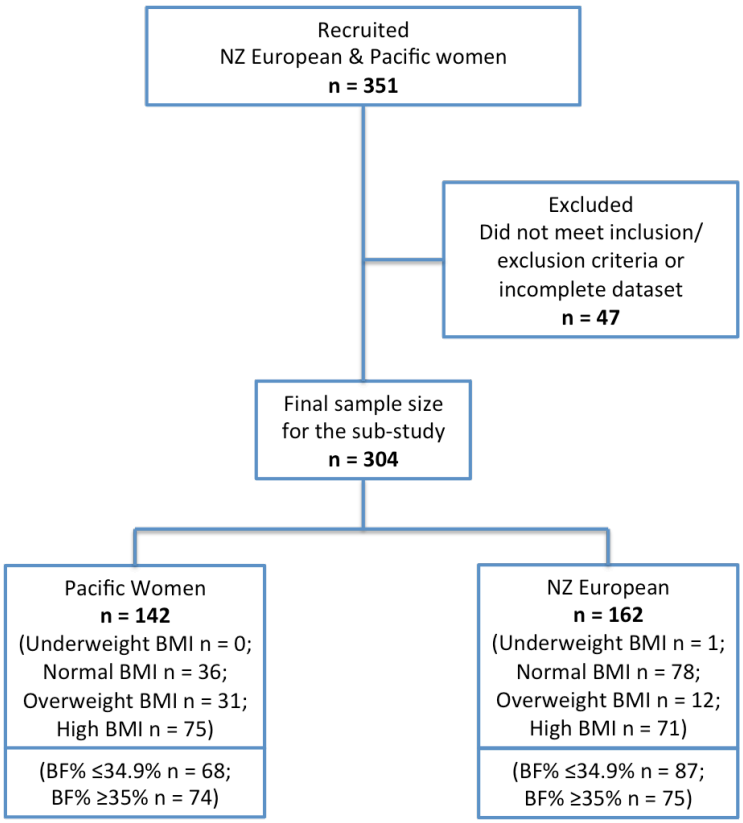


Figure 3.1: Study sample size and participant classification

3.3.3 Study Procedures

Participants each attended two visits. At visit 1, participants were welcomed, asked to carefully read and sign a consent form, and had the opportunity to ask questions prior to commencing the study. Each participant was then allocated a unique study identification number. Participants completed a one-on-one interview with a research staff member to obtain a range of demographic and health information.

3.3.4 Measurement of Metabolic Biomarkers and Endocrine Regulators

Total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), non-esterified fatty acids (NEFA), glucose, glycosylated haemoglobin (HbA1c) and c-reactive protein (CRP) were measured at the Liggins Institute, the University of Auckland, by Chris Keven and Eric Thorstensen using an auto analyser (Roche Cobas e411) and appropriately validated test kits.

Insulin, leptin and tumour-necrosis factor alpha (TNF-α) were measured with the use of a MILLIPLEX MAP Human Metabolic Hormone Magnetic Bead Panel 96-Well Metabolism Multiplex Assay (Millipore, USA, Cat # HMHEMAG-34K). Assay procedures were thoroughly validated and the analyses were performed in the laboratory of Dr John Ingram at the New Zealand Institute for Plant and Food Research.

All analyses were performed in accordance with internationally recognised standards. The methodological details of the procedures are beyond this thesis research project.

3.3.5 Anthropometric Measurements

At visit 1, anthropometric measurements included stretched height and fasting weight measurements. All anthropometric measurements were conducted using the International Society for the Advancement of Kinanthropometry (ISAK) protocol (Marfell-Jones, Stewart, & De Ridder, 2011). All research staff conducting these measurements were Level 1 ISAK trained. BMI was calculated using the Quetelet index (weight / height^2). At visit 2, waist and hip circumferences were measured with a Lufkin W600PM flexible steel tape with the participant in a relaxed standing position with their arms folded across their chest. Sagittal abdominal diameter (sagittal height) was measured at the umbilicus level using the Holtain-Kahn Abdominal Caliper (Holtain Ltd, Crymych, UK) and assessed in a supine position. Bioelectrical Impedance Analysis (BIA) (InBody230, Biospace Co. Ltd, Seoul) was used to assess body composition at visit 1. Body composition measurements were performed using

Dual-energy X-ray Absorptiometry (DXA) (Hologic QDR Discovery A, Hologic Inc, Bedford, MA with APEX V. 3.2 software) at visit 2 to accurately assess body composition profiles in terms of total and regional fat mass. Prior to DXA scanning, participants were asked to remove jewellery, and asked if they were pregnant, had a pacemaker or any metal implants. All staff who conducted DXA scanning procedures had Australian and NZ Bone Mineral Society (ANZBMS) clinical densitometry accreditation.

3.3.6 Data Management

Participants were allocated unique identification numbers, which were printed on each data form, questionnaire, laboratory samples and other data. This number was the only form of identification for the participants to ensure privacy was maintained. Electronic data on computers and servers were password-protected, and this data was routinely backed up on an additional database. Participant contact details and enrolment data were stored separately. Access to all data is restricted to the immediate research team.

3.3.7 Ethics Approval

This study was approved by the Southern Health and Disability Ethics Committee (16/STH/32). This study was registered at anzctr.org.au (ACTRN12618000432213).

3.3.8 Statistical Methods

Data were analysed using IBM SPSS statistics package version 25 (IBM corporation, New York, USA). Power calculations for the sample size were originally determined for the wider PROMISE Study, as specified in the Health Research Council funding grant, to provide adequate statistical power for analysis of ethnic groups separately to detect differences in the gut microbiome.

The central limit theorem was applied due to the sample size being greater than 30 (Field, 2009) and thus the data were treated as parametric for all analyses. Data were reported as mean and standard deviation for continuous variables and number and percentage for categorical variables. A *p* value of less than 0.05 was considered to be significant.

Two-way analysis of variance (ANOVA) was used to analyse interaction effects and differences between ethnicities and BMI groups against each dependent variable, and post hoc tests with Bonferroni adjustment were used to identify which groups had significant differences. In the case of post hoc tests with Bonferroni adjustment, a *p* value of less than 0.013 was considered significant to ensure the cumulative Type 1 error was less than 0.05 (Field, 2009). Pearson's correlation coefficients were used to evaluate the strength of the linear relationships between metabolic biomarkers, endocrine regulators and body composition measurements. Four hierarchical multiple linear regression analysis (enter method) (Field, 2009) was used to investigate predictors of body fat distribution and predictors of metabolic biomarkers and endocrine regulators. The first model was a simple model only including one predictor variable, the second additionally controlled for age, the third additionally controlled for deprivation index, and the fourth fully adjusted model also controlled for ethnicity.

3.4 Results

Key findings from this study are presented in accordance with the objectives set in Chapter 1 of the thesis, section 1.5: Investigate and compare different approaches of anthropometric and body composition assessment; describe metabolic profiles and endocrine regulators in the study population; and investigate the relationship between body fat profiles and fat distribution with metabolic biomarkers and endocrine regulators.

First, participant characteristics are described using number and percentage of participants belonging to the different BMI and body fat percentage classification groups. Demographic, anthropometric and body composition characteristics are then analysed and described using two-way ANOVA and post hoc tests with Bonferroni adjustment. Following this, Pearson's correlations are used to compare anthropometric and body composition measurements with DXA-measured total, android, gynoid and visceral fat percentage, which have been used as the gold standard reference method for comparisons. To describe metabolic profiles and endocrine regulation, two-way ANOVA and post hoc tests with Bonferroni adjustment was used to analyse metabolic biomarkers and endocrine regulators. Finally, to investigate the relationship between body fat profiles and fat distribution with metabolic biomarkers and endocrine regulators, Pearson's correlations were used to compare important metabolic biomarkers and endocrine regulators with DXA-measured total, android, gynoid and visceral fat percentage. Multiple linear regression analysis was then used to further analyse some of the most important relationships identified by the Pearson's correlations.

3.4.1 Participant Characteristics

A total of 304 women were eligible for inclusion in the data analysis, and were classified by either body mass index (BMI) or total body fat percentage (BF%) measured by dual-energy X-ray absorptiometry (DXA). This is displayed in **Table 3.1**.

Table 3.1: Body mass index and total body fat percentage classifications per ethnicity

	Ethnicity	
	Pacific (n = 142)	NZ European (n = 162)
BMI Categories:	n (%)	n (%)
Underweight BMI <18.5kg/m^2)	0 (0%)	1 (0.6%)
Normal BMI (18.5-24.9kg/m^2)	36 (25.4%)	78 (48.2%)
Overweight BMI (25-29.9 kg/m^2)	31 (21.8%)	12 (7.4%)
High BMI (≥30kg/m^2)	75 (52.8%)	71 (43.8%)
Body Fat Percentage Groups:	n (%)	n (%)
Normal BF% (≤34.9%)	68 (47.9%)	87 (53.7%)
High BF% (≥35%)	74 (52.1%)	75 (46.3%)

Values presented are number of participants (percentage within each ethnic group).
Total BF% was measured by DXA.
Abbreviations: BMI body mass index; BF% body fat percentage; DXA dual-energy X-ray absorptiometry.

The demographic and body mass characteristics and differences in participants, classified according to ethnicity and BMI, are presented in **Table 3.2**. Statistically significant differences between ethnicities were observed; the mean age for Pacific women was lower than NZ European women in both the normal and high BMI groups. The important data and key differences observed in this cross sectional study includes statistically significant effects of ethnicity and BMI group for deprivation index. Statistically significant differences between ethnicities were observed; deprivation index was higher for Pacific women in both BMI groups. Statistically significant effects of ethnicity and BMI group were observed for weight (kg), BMI, muscle mass and fat mass measured by BIA (kg), and lean mass measured by DXA (kg). Statistically significant differences between ethnicities were observed within the high BMI group; Pacific women had a higher mean muscle mass (kg) measured by BIA, however, weight (kg) was also higher. There was no statistically significant difference in body fat mass (kg) between Pacific and NZ European women in either of the BMI groups.

Table 3.2: Characteristics and differences in participant demographics and body mass, grouped by ethnicity and BMI

Variable	n	Pacific High BMI§	Pacific Normal BMI§	NZ European High BMI§	NZ European Normal BMI§	Significance^ Ethnicity	BMI group	Ethnicity x BMI group
Age (years)	260	25.4 (±6.1)[a]	23.5 (±5.5)[a]	33.7 (±7.0)[b]	29.9 (±6.5)[c]	0.000	0.001	0.276
NZ Dep Index	257	7.8 (±1.9)[a]	7.2 (±2.5)[a]	4.6 (±2.2)[b]	3.9 (±2.6)[b]	0.000	0.035	0.811
Height (cm)	260	167.70 (±6.75)[a]	169.58 (±7.16)[a]	167.51 (±7.07)[a]	167.17 (±5.55)[a]	0.103	0.366	0.196
Weight (kg)	260	103.40 (±18.00)[a]	66.25 (±7.66)[b]	96.29 (±11.43)[c]	61.76 (±5.47)[b]	0.000	0.000	0.404
BMI (kg/m^2)	260	36.68 (±5.46)[a]	22.97 (±1.60)[b]	34.26 (±3.01)[c]	22.09 (±1.39)[b]	0.000	0.000	0.092
Muscle Mass (kg) (BIA)	259	32.44 (±4.52)[a]	26.37 (±3.95)[b]	29.95 (±3.77)[c]	25.38 (±2.75)[b]	0.000	0.000	0.129
Body Fat Mass (kg) (BIA)	259	46.03 (±12.51)[a]	18.56 (±4.46)[b]	42.64 (±7.82)[a]	15.64 (±3.79)[b]	0.004	0.000	0.828
Lean Mass (kg) (DXA)	260	62.04 (±8.42)[a]	47.20 (±6.01)[b]	56.43 (±6.51)[c]	44.85 (±4.47)[b]	0.000	0.000	0.058
Body Fat mass (kg) (DXA)	260	41.24 (±10.95)[a]	19.37 (±3.64)[b]	39.86 (±6.92)[a]	17.35 (±3.53)[b]	0.075	0.000	0.733

Values are unadjusted means (± standard deviations)

Differences between groups were measured by two-way ANOVA and post hoc tests with Bonferroni adjustment were performed. Means in the same row with different superscript (abcd) indicate a significant difference ($p < 0.013$) between groups.

^Two way ANOVA was used to test effects of Ethnicity and BMI group with demographic and anthropometric variables.

§BMI groups are 18.5-24.9kg/m^2 (normal) and ≥30kg/m^2 (high). Participants that do not belong to these BMI groups were excluded for this analysis.

Abbreviations: BMI body mass index; BIA bioelectric impedance analysis; DXA dual-energy X-ray absorptiometry.

3.4.2 Investigate and Compare Different Approaches of Anthropometric and Body Composition Assessment

Characteristics and differences in anthropometry and body composition are presented in **Table 3.3**. Statistically significant effects of BMI group were observed for total body fat percentage measured by BIA and DXA, as well as statistically significant interactions between the effects of ethnicity and BMI group. Statistically significant differences between BMI groups were observed; women with a high BMI had a higher mean total body fat percentage measured by both BIA and DXA, however this was consistent for both ethnicities, with no statistically significant difference in total body fat percentage seen between Pacific and NZ European women of each BMI group. The means of WC, HC, WHR, WHtR, lean mass percentage (BIA and DXA), gynoid and android fat percentage and visceral fat percentage also showed no statistically significant differences between the two ethnic groups, however statistically significant differences were observed between the two BMI groups, where all means except lean mass percentage were higher for the high BMI group. Statistically significant interactions were seen between the effects of ethnicity and BMI group for sagittal height, lean mass percentage (DXA), android fat percentage, gynoid fat percentage and visceral fat percentage.

Table 3.3: Characteristics and differences in anthropometry and body composition, grouped by ethnicity and BMI

						Significance^		
Variable	**n**	**Pacific High BMI[§]**	**Pacific Normal BMI[§]**	**NZ European High BMI[§]**	**NZ European Normal BMI[§]**	**Ethnicity**	**BMI group**	**Ethnicity x BMI group**
WC (cm)	260	100.51 (±11.31)[a]	74.32 (±4.26)[b]	99.19 (±8.90)[a]	72.62 (±4.82)[b]	0.162	0.000	0.858
HC (cm)	260	123.24 (±11.11)[a]	100.59 (±5.62)[b]	121.52 (±7.51)[a]	97.13 (±5.78)[b]	0.015	0.000	0.410
WHR	260	0.82 (±0.06)[a]	0.74 (±0.04)[b]	0.82 (±0.06)[a]	0.75 (±0.05)[b]	0.388	0.000	0.514
WHtR	260	0.60 (±0.07)[a]	0.44 (±0.03)[b]	0.59 (±0.05)[a]	0.44 (±0.03)[b]	0.405	0.000	0.824
Sagittal Height (cm)	259	25.31 (±3.15)[a]	17.54 (±1.14)[b]	23.47 (±2.20)[c]	17.24 (±1.45)[b]	0.000	0.000	0.009
Body fat % (BIA)	259	43.89 (±5.24)[a]	27.94 (±5.67)[b]	44.10 (±4.54)[a]	25.22 (±5.20)[b]	0.061	0.000	0.029
Lean Mass % (DXA)	260	60.54 (±4.48)[a]	70.93 (±3.93)[b]	58.74 (±3.84)[a]	72.20 (±4.61)[b]	0.635	0.000	0.006
Total Body Fat % (DXA)	260	39.46 (±4.48)[a]	29.07 (±3.93)[b]	41.26 (±3.84)[a]	27.80 (±4.61)[b]	0.644	0.000	0.006
Android Fat % (DXA)	260	41.61 (±5.64)[a]	27.83 (±5.39)[b]	41.75 (±4.63)[a]	24.81 (±5.64)[b]	0.040	0.000	0.025
Gynoid Fat % (DXA)	260	40.77 (±4.53)[a]	35.01 (±4.16)[b]	42.47 (±4.26)[a]	33.36 (±4.29)[b]	0.964	0.000	0.003
Visceral fat % (DXA)	260	39.69 (±5.95)[a]	25.61 (±5.93)[b]	39.87 (±4.87)[a]	22.25 (±6.44)[b]	0.037	0.000	0.021

Values are unadjusted means (± standard deviations)

Differences between groups were measured by two-way ANOVA and post hoc tests with Bonferroni adjustment were performed. Means in the same row with different superscript (abcd) indicate a significant difference ($p < 0.013$) between groups.

^Two way ANOVA was used to test effects of Ethnicity and BMI group with anthropometric and body composition variables.

[§]BMI groups are 18.5-24.9kg/m^2 (normal) and ≥30kg/m^2 (high). Participants that do not belong to these BMI groups were excluded for this analysis.

Abbreviations: BMI body mass index; WC waist circumference; HC hip circumference; WHR waist-to-hip ratio; WHtR waist-to-height ratio; BF% body fat percentage; BIA bioelectric impedance analysis; DXA dual-energy X-ray absorptiometry.

Pearson's correlations were used to compare different approaches of assessing anthropometry and body composition, to assess their accuracy against DXA-measured total and regional body fat percentages as the gold standard reference method for the evaluation of body fat mass (**Table 3.4**). BIA-measured total body fat percentage correlated most strongly with DXA-measured total body fat percentage and all other DXA-measured regional fat depots. Following this, BMI and HC had the next strongest correlations with DXA-measured total body fat percentage. WHtR, WC and sagittal height also had strong correlations with DXA total body fat percentage. WHR correlated least strongly with DXA-measured total body fat percentage and regional fat depots. After BIA-measured total body fat percentage, WHtR, BMI and WC correlated most strongly with android fat percentage. Following BIA-measured total body fat percentage, HC and BMI most strongly correlated with gynoid fat percentage. After BIA-measured total body fat percentage, WHtR, BMI and WC had the strongest correlation with visceral fat percentage. These tools had similar relationships with adiposity for both ethnic groups (**Supplementary table 1**). Important relationships between common anthropometric and body composition measurements used in clinical settings for assessment of adiposity, with the associated fat percentage measurement by DXA, are displayed in **Figure 3.2** (total body fat percentage), **Figure 3.3** (gynoid fat percentage) and **Figure 3.4** (android fat percentage). Android and gynoid fat percentage were assessed against total body fat percentage, revealing a similar relationships between these measurements in both ethnic groups (**Figure 3.5**).

Table 3.4: Pearson's correlation coefficients for anthropometry and body composition measurements compared with total and regional body fat percentage measured by DXA, in the total study population

	n	Total BF% DXA	Android Fat % DXA	Gynoid Fat % DXA	Visceral Fat % DXA
BMI	304	0.841 (0.000)	0.844 (0.000)	0.658 (0.000)	0.824 (0.000)
WC	304	0.811 (0.000)	0.840 (0.000)	0.599 (0.000)	0.822 (0.000)
HC	304	0.839 (0.000)	0.819 (0.000)	0.706 (0.000)	0.807 (0.000)
WHR	304	0.422 (0.000)	0.529 (0.000)	0.205 (0.000)	0.511 (0.000)
WHtR	304	0.819 (0.000)	0.850 (0.000)	0.613 (0.000)	0.827 (0.000)
Sagittal Height	303	0.809 (0.000)	0.829 (0.000)	0.614 (0.000)	0.813 (0.000)
BF% BIA	303	0.937 (0.000)	0.916 (0.000)	0.810 (0.000)	0.903 (0.000)

Values presented are *r* (*p*-value).
All correlations are Pearson's Correlation Coefficients using original variables, with missing values excluded pairwise.
$p < 0.05$ is considered significant.
Abbreviations: BMI body mass index; WC waist circumference; HC hip circumference; WHR waist-to-hip ratio; WHtR waist-to-height ratio; BF% body fat percentage; BIA bioelectric impedance analysis; DXA dual-energy X-ray absorptiometry

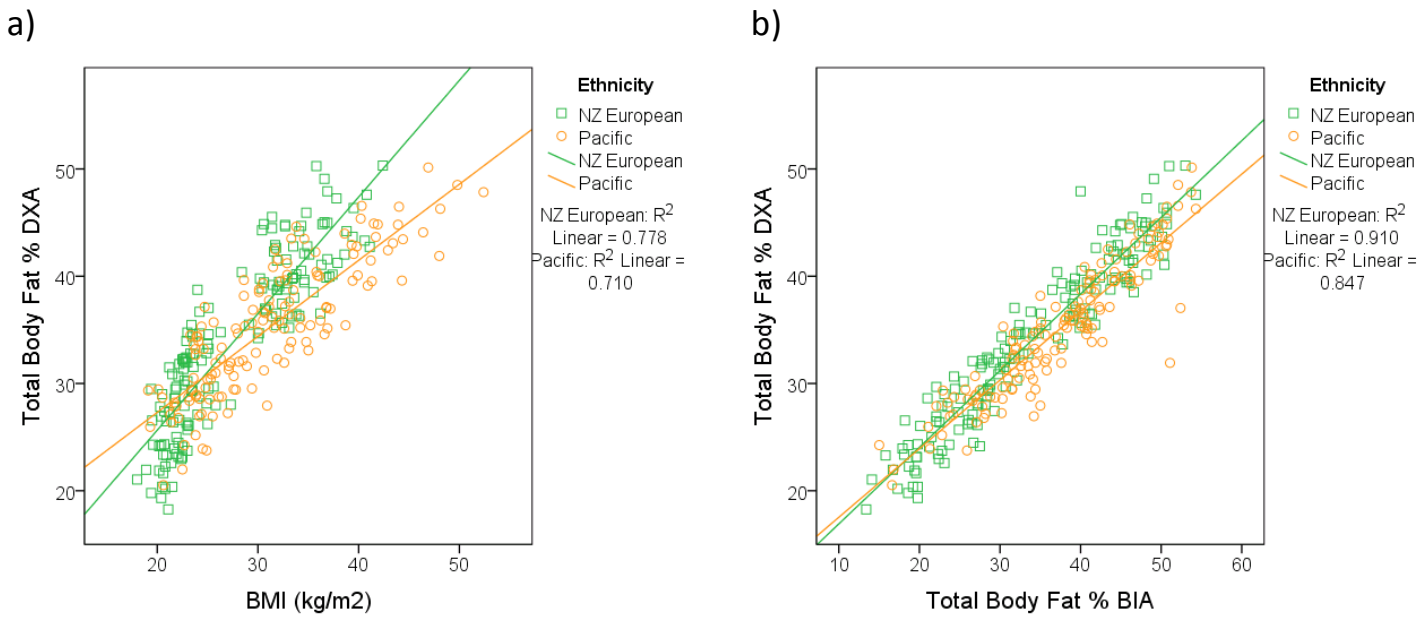


Figure 3.2: Relationship between total body fat % measured by DXA and BMI (kg/m^2) (**a**) and total body fat % measured by BIA (**b**) by ethnicity, in the total study population.

a) n = 304; b) n = 303

Abbreviations: BMI body mass index; BIA bioelectric impedance analysis; DXA dual-energy X-ray absorptiometry

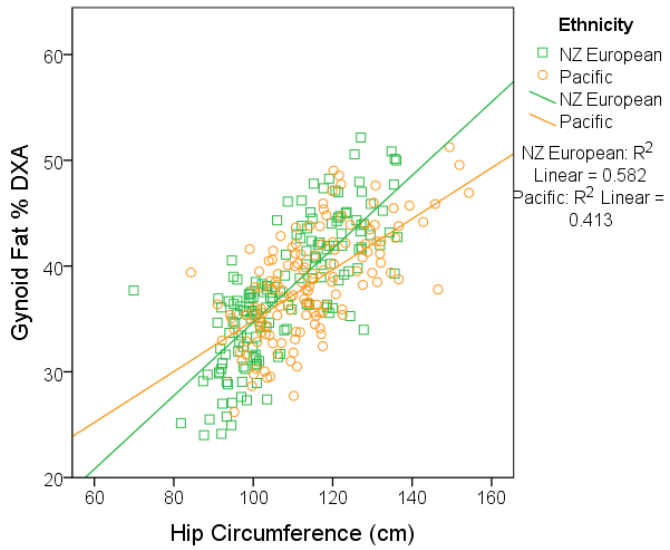


Figure 3.3: Relationship between gynoid fat % measured by DXA and hip circumference (cm) by ethnicity, in the total study population.

n = 304

Abbreviations: BMI body mass index; DXA dual-energy X-ray absorptiometry.

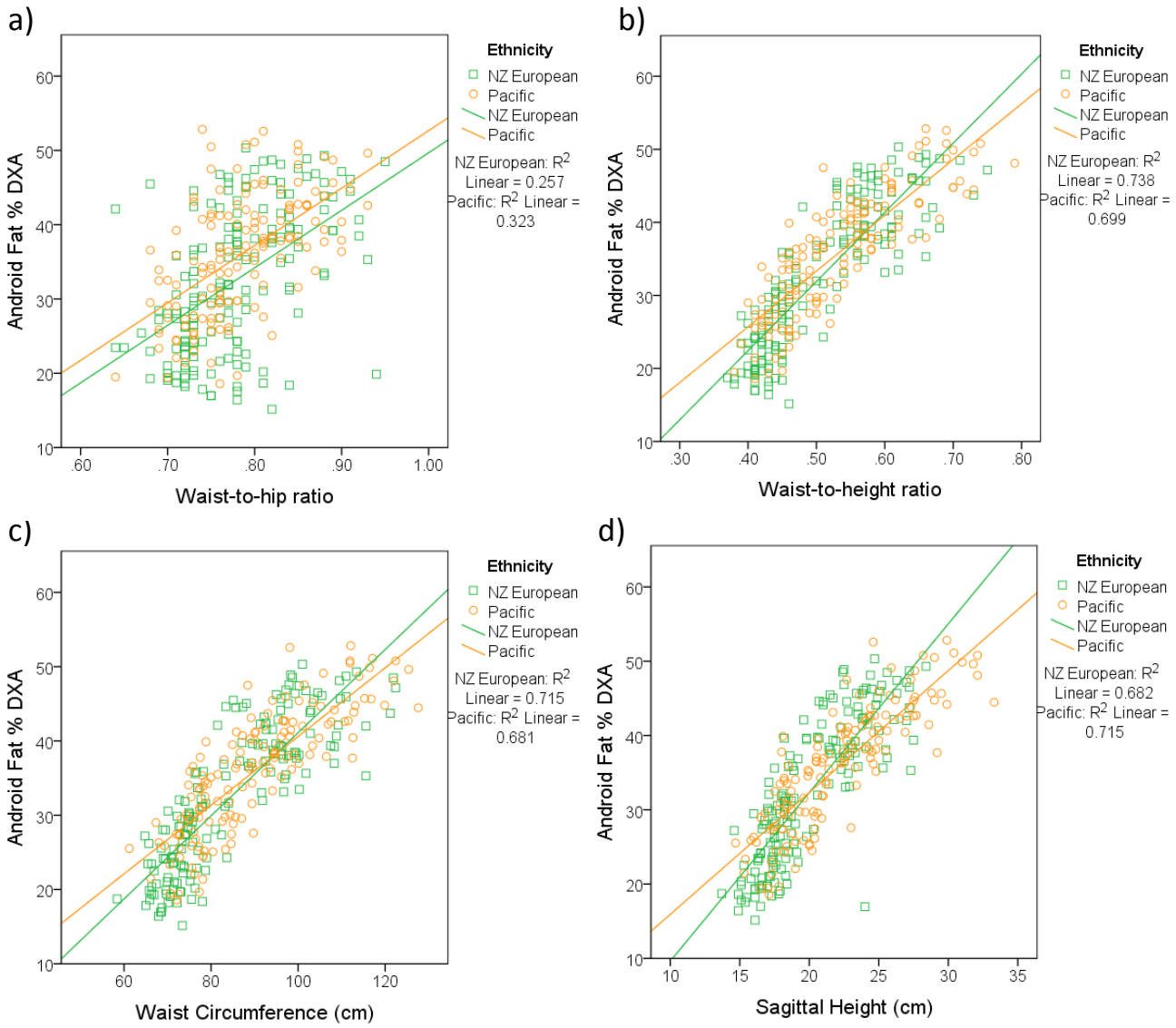
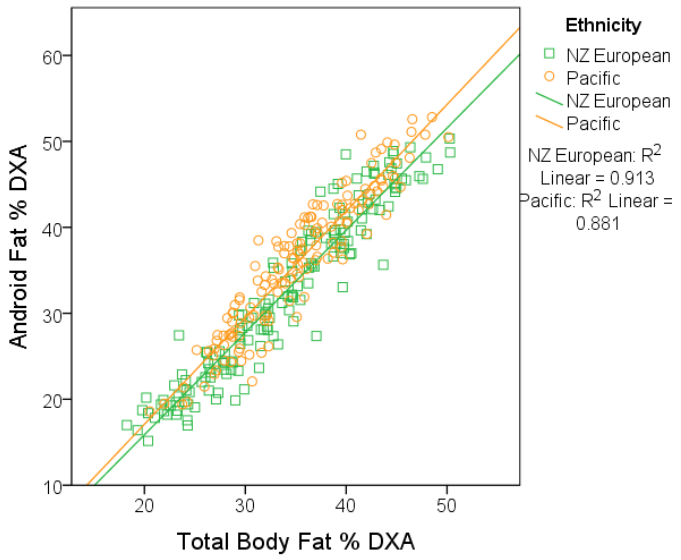


Figure 3.4: Relationship between android fat % measured by DXA and waist-to-hip ratio (a), waist-to-height ratio (b), waist circumference (cm) (c) and sagittal height (cm) (d) by ethnicity, in the total study population. a-c) n = 304; b) n = 303. Abbreviations: BMI body mass index; BIA bioelectric impedance analysis; DXA dual-energy X-ray absorptiometry

a)



b)

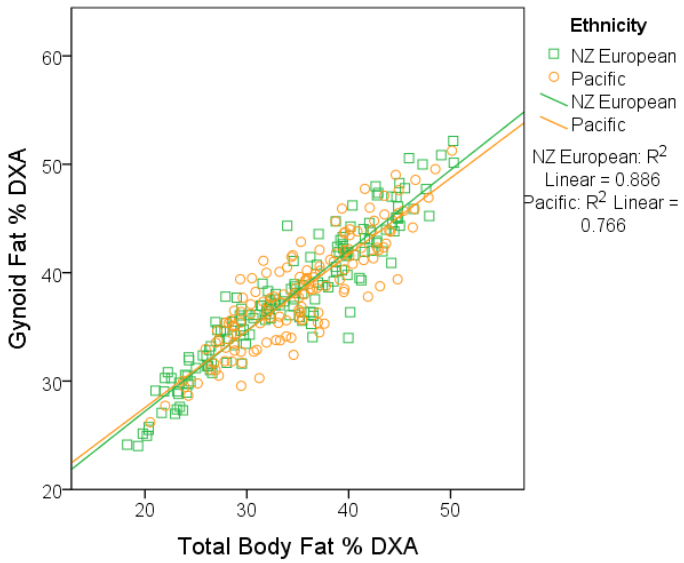


Figure 3.5: Relationship between total body fat % and android fat % (**a**) and gynoid fat % measured by DXA (**b**) by ethnicity, in the total study population.

a) n = 304; **b)** n = 303.
Abbreviations: DXA dual-energy X-ray absorptiometry.

3.4.3 Describe Metabolic Biomarkers and Endocrine Regulators in the Study Population

Metabolic biomarkers and endocrine regulators were analysed by two-way ANOVA and post hoc tests with Bonferroni adjustment, to assess the characteristics and differences relating to the underlying physiological pathways associated with ethnicity and BMI classification (**Table 3.5**). Statistically significant interactions were found between the effects of ethnicity and BMI group for insulin and HOMA-IR. Mean insulin and HOMA-IR showed statistically significant differences, with higher values observed for high BMI Pacific women. Statistically significant effects of ethnicity were observed for TC, LDL-C and HDL-C. Statistically significant differences were also seen between ethnicities for HbA1c, with Pacific women having a higher mean HbA1c within both BMI groups.

Table 3.5: Characteristics and differences of metabolic biomarkers and endocrine regulators in ethnicities and BMI groups

						Significance^		
Variable	**n**	**Pacific High BMI[§]**	**Pacific Normal BMI[§]**	**NZ European High BMI[§]**	**NZ European Normal BMI[§]**	**Ethnicity**	**BMI group**	**Ethnicity x BMI group**
TC (mmol/L)	259	4.68 (±0.77)[a]	4.38 (±0.64)[a]	5.51 (±1.18)[b]	4.83 (±0.80)[a]	0.000	0.000	0.108
LDL-C (mmol/L)	259	2.99 (±0.72)[a]	2.58 (±0.61)[a]	3.63 (±1.15)[b]	2.81 (±0.77)[a]	0.000	0.000	0.071
HDL-C (mmol/L)	259	1.35 (±0.31)[a]	1.63 (±0.32)[bc]	1.51 (±0.32)[ac]	1.83 (±0.37)[b]	0.000	0.000	0.686
TC/HDL ratio	259	3.59 (±0.81)[a]	2.76 (±0.61)[b]	3.78 (±1.10)[a]	2.73 (±0.63)[b]	0.471	0.000	0.302
Triglycerides (mmol/L)	259	1.22 (±0.63)[a]	0.83 (±0.25)[b]	1.20 (±0.50)[a]	0.80 (±0.33)[b]	0.740	0.000	0.927
NEFA (mmol/L)	259	0.76 (±0.38)[a]	0.71 (±0.30)[a]	0.75 (±0.28)[a]	0.69 (±0.41)[a]	0.723	0.252	0.906
Glucose (mmol/L)	259	5.55 (±0.53)[a]	5.26 (±0.40)[bc]	5.51 (±0.47)[ac]	5.10 (±0.33)[b]	0.087	0.000	0.265
HbA1c (mmol/mol)	258	34.38 (±3.22)[a]	31.99 (±1.56)[b]	31.85 (±2.71)[b]	30.33 (±2.25)[c]	0.000	0.000	0.208
Insulin (uU/ml)	259	28.38 (±20.43)[a]	12.05 (±5.90)[bc]	14.94 (±8.17)[b]	7.65 (±3.73)[c]	0.000	0.000	0.005
HOMA-IR	259	7.29 (±6.11)[a]	2.87 (±1.58)[bc]	3.72 (±2.25)[b]	1.75 (±0.91)[c]	0.000	0.000	0.009
Leptin (pg/ml)	255	22893 (±11060)[a]	8265 (±7597)[b]	24393 (±13349)[a]	5682 (±3560)[b]	0.675	0.000	0.115
CRP (mg/L)	259	2.27 (±2.56)[ab]	0.76 (±1.38)[a]	3.63 (±3.15)[b]	1.75 (±3.10)[a]	0.001	0.000	0.617
TNF-α (pg/mL)	255	3.51 (±1.79)[a]	2.87 (±0.91)[a]	3.56 (±1.25)[a]	3.53 (±0.2.31)[a]	0.122	0.147	0.188

Values are unadjusted means (± standard deviations)

Differences between groups were measured by two-way ANOVA and post hoc tests with Bonferroni adjustment were performed. Means in the same row with different superscript (abcd) indicate significant difference ($p < 0.013$) between groups.

^Two way ANOVA was used to test effects of Ethnicity and BMI group with all body composition and metabolic and endocrine variables.

[§]BMI groups are 18.5-24.9kg/m^2 (normal) and ≥30kg/m^2 (high). Participants that do not belong to these BMI groups were excluded for this table.

Abbreviations: BMI body mass index; TC total cholesterol; LDL-C low density lipoprotein cholesterol; HDL-C high density lipoprotein cholesterol; NEFA non-esterified fatty acids; HbA1c haemoglobin A1c; HOMA-IR homeostatic model assessment of insulin resistance; CRP c-reactive protein; TNFα tumour necrosis factor alpha

3.4.4 Investigate the Relationship of Body Fat Profiles and Fat Distribution with Metabolic Biomarkers and Endocrine Regulators

Metabolic biomarkers and endocrine regulators were compared with total and regional body fat percentages measured by DXA, to assess the relationships between these markers and body fat distribution (**Table 3.6**). Pearson's correlations were used to assess the linear relationships between cardio-metabolic risk factors and fat distribution to provide insights into the underlying physiological processes associated with different fat depots. Strong correlation effects (r ±0.7) were found between leptin and the DXA measurements. Moderate correlation effects (r ±0.5) were found for HDL-C, TC/HDL ratio and insulin with the DXA measurements. Weak correlation effects (r ±0.3) were found for LDL-C, triglycerides, glucose, HbA1c, HOMA-IR and CRP with the DXA measurements.

Leptin had the strongest correlations with DXA-measured total body fat percentage, as well as all DXA-measured regional fat depots. Following this, insulin and TC/HDL ratio correlated most strongly with DXA-measured total body fat percentage. LDL-C and TC correlated least strongly with DXA-measured total body fat percentage. After leptin, insulin, HDL-C and TC/HDL ratio correlated most strongly with android fat. CRP, LDL-C and TC correlated least strongly with android fat percentage. Following leptin, HDL-C, CRP and insulin correlated most strongly with gynoid fat percentage, although these were weak correlations. Glucose and LDL-C correlated least strongly with gynoid fat percentage. After leptin, the next strongest correlations for visceral fat percentage were with HDL-C, insulin and TC/HDL ratio. CRP and LDL-C correlated least strongly with visceral fat percentage. NEFA and TNF-α did not correlate significantly with total or regional body fat percentages. Android and gynoid fat percentages showed contrasting correlations with many of the metabolic biomarkers and endocrine regulators, with weaker correlations seen with gynoid fat percentage. The above-mentioned relationships with total body fat percentage, android fat percentage and gynoid fat percentage are displayed for leptin (**Figure 3.6**), insulin (**Figure 3.7**) and HDL-C (**Figure 3.8**) for each ethnic group.

Table 3.6: Pearson's correlation coefficients for metabolic biomarkers and endocrine regulators with total and regional body fat percentages measured by DXA in the total study population

	n	BF% DXA	Android Fat % DXA	Gynoid Fat % DXA	Visceral Fat % DXA
TC	303	0.128 (0.026)	0.123 (0.032)	0.068 (0.241)	0.113 (0.050)
LDL-C	303	0.205 (0.000)	0.221 (0.000)	0.122 (0.033)	0.212 (0.000)
HDL-C	303	-0.367 (0.000)	-0.435 (0.000)	-0.260 (0.000)	-0.434 (0.000)
TC/HDL ratio	303	0.382 (0.000)	0.435 (0.000)	0.236 (0.000)	0.424 (0.000)
Triglycerides	303	0.336 (0.000)	0.387 (0.000)	0.213 (0.000)	0.375 (0.000)
NEFA	303	0.109 (0.059)	0.104 (0.072)	0.098 (0.088)	0.099 (0.084)
Glucose	303	0.307 (0.000)	0.332 (0.000)	0.187 (0.001)	0.321 (0.000)
HbA1c	301	0.242 (0.000)	0.345 (0.000)	0.112 (0.052)	0.337 (0.000)
Insulin	303	0.384 (0.000)	0.441 (0.000)	0.243 (0.000)	0.430 (0.000)
HOMA-IR	303	0.351 (0.000)	0.408 (0.000)	0.218 (0.000)	0.396 (0.000)
Leptin	299	0.751 (0.000)	0.716 (0.000)	0.655 (0.000)	0.709 (0.000)
CRP	303	0.337 (0.000)	0.316 (0.000)	0.249 (0.000)	0.309 (0.000)
TNF-α	299	0.050 (0.393)	0.011 (0.851)	0.037 (0.523)	0.016 (0.781)

All correlations are Pearson's Correlation Coefficients, with missing values excluded pairwise. $P < 0.05$ is considered significant.
All study participants were included in this analysis.
Abbreviations: BF% body fat percentage; DXA dual-energy X-ray absorptiometry; TC total cholesterol; LDL-C low density lipoprotein cholesterol; HDL-C high density lipoprotein cholesterol; NEFA non-esterified fatty acids; HbA1c Haemoglobin A1c; HOMA-IR homeostatic model assessment of insulin resistance; CRP c-reactive protein; TNF-α tumour necrosis factor alpha.

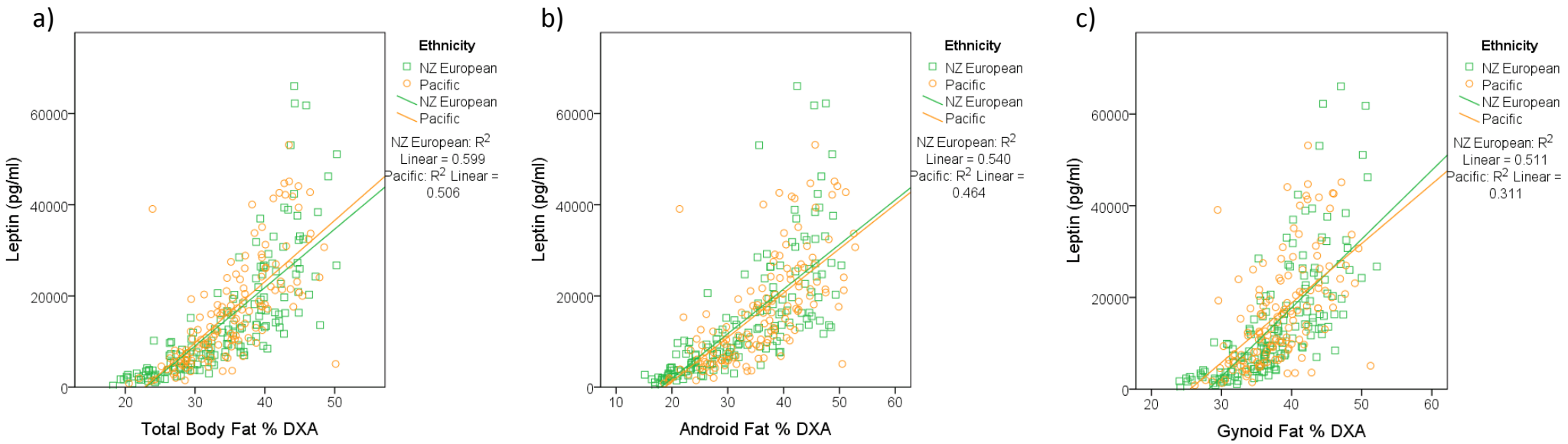


Figure 3.6: Relationship between leptin (pg/ml) and total body fat % (a), android fat % (b), and gynoid fat % measured by DXA (c) by ethnicity, in the total study population.
n = 299.
Abbreviations: DXA dual-energy X-ray absorptiometry.

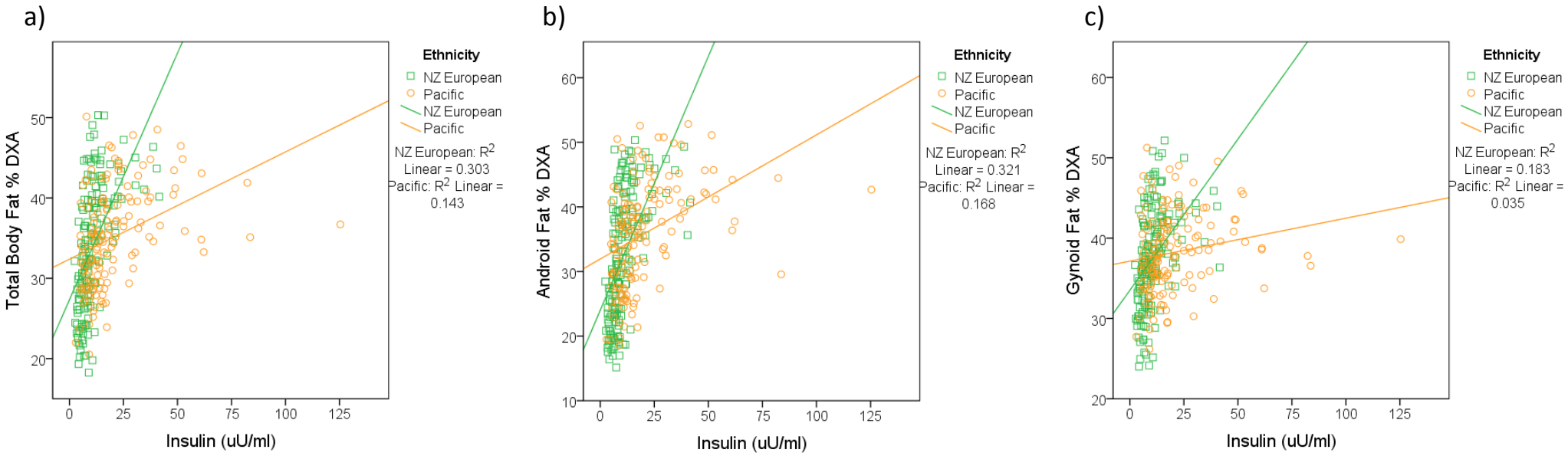


Figure 3.7: Relationship between insulin (uU/ml) and total body fat % (a), android fat % (b), and gynoid fat % measured by DXA (c) by ethnicity, in the total study population.

n = 303.

Abbreviations: DXA dual-energy X-ray absorptiometry.

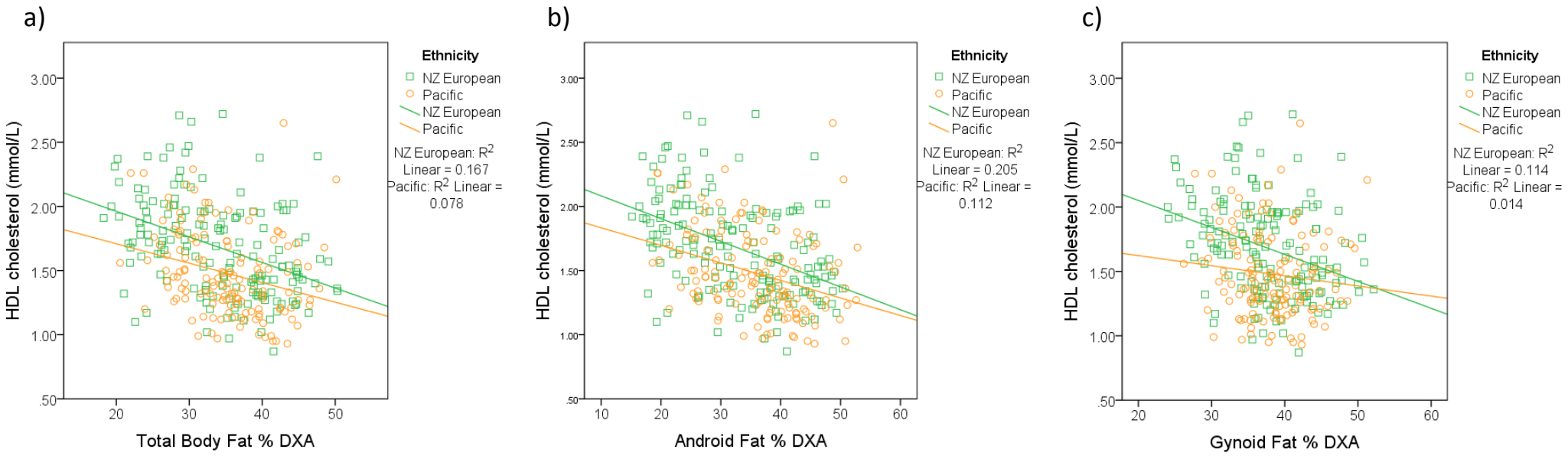


Figure 3.8: Relationship between HDL-C and total body fat % (a), android fat % measured by DXA (b), and gynoid fat % measured by DXA (c) by ethnicity, in the total study population.

n = 303.

Abbreviations: DXA dual-energy X-ray absorptiometry; HDL high-density lipoprotein.

3.4.5 Investigation of Total Body Fat and Regional Fat Percentages with Leptin and Insulin Concentrations

Because circulating leptin and insulin concentrations were found to correlate most strongly with total body fat percentage and regional fat percentages, and have well-documented roles in metabolism and energy homeostasis (McNamara & Huber, 2018; Schwartz et al., 2017), these relationships were further analysed using multiple linear regression analysis. As leptin is produced and released by adipocytes, the relationship with body fat was analysed to discover potential differences in associations with total body fat percentage and different regional fat depots. Circulating insulin was analysed as a predictor of total body fat percentage and body fat distribution due to its role in energy storage and lipogenesis. BMI correlated strongly with DXA-measured total and regional fat percentages in the total study population (**Table 3.4**) and is a common tool used in clinical practice. Thus, the relationship of BMI with circulating leptin and insulin concentrations was also analysed using multiple linear regression analysis, to enable a comparison between DXA measurements and BMI. This comparison was used to assess the efficacy of BMI as a predictor of circulating leptin concentrations, and of circulating insulin concentrations as a predictor of BMI. Each model contains the predictor variable of interest, as well as age, deprivation index and ethnicity, to control for and assess the contribution these variables have to the relationships.

To assess the contribution of total body fat percentage and different regional fat depots to circulating leptin concentrations, multiple linear regression analysis was used. Total body fat percentage (**Table 3.7**), android fat percentage (**Table 3.8**), gynoid fat percentage (**Table 3.9**) and visceral fat percentage (**Table 3.10**) were found to be statistically significant predictors of leptin concentrations. To compare BMI with the aforementioned DXA measurements, BMI was also analysed as a predictor of leptin concentrations (**Table 3.11**). Total body fat percentage explained the largest variance in leptin concentrations (57.1%), followed by android fat percentage (52.3%), visceral fat percentage (51.6%) and BMI (49.7%), with gynoid fat percentage explaining the least variance (45.1%). Age contributed significantly to the analyses for gynoid fat percentage and visceral fat percentage, however

deprivation index and ethnicity did not contribute significantly to any of the analyses for predictors of circulating leptin.

To explore differences associated with energy storage in regional fat depots driven by circulating insulin concentrations, multiple linear regression analysis was used. Circulating insulin was used as a predictor variable to assess its relationship with total body fat percentage (**Table 3.12**), android fat percentage (**Table 3.13**), gynoid fat percentage (**Table 3.14**), visceral fat percentage (**Table 3.15**) and BMI (**Table 3.16**). Circulating insulin explained the largest variance in BMI (34.5%), followed by android fat percentage (23.6%), visceral fat percentage (22.1%) and total body fat percentage (20.6%). Circulating insulin explained the least variance in gynoid fat percentage (9.2%). Age and deprivation index contributed significantly to the analyses, however ethnicity did not.

Table 3.7: Total body fat % as a predictor of circulating leptin concentrations

Predictor	Coefficient (B)	Standard error B	95% CI B	Standardised B	R^2	P-value
					0.571*	0.000
Intercept	-34400	3621	-41527, -27273			
BF% DXA	1287	69.0	1152, 1423	0.737		0.000
Age	100	73.6	-44.8, 245	0.059		0.175
Deprivation Index	174	209	-238, 585	0.041		0.407
Ethnicity	1007	1232	-1418, 3433	0.040		0.414

Multiple linear regression (Enter method) was used. *F (4, 295) = 96.7
Ethnicity was NZ European compared with Pacific. All study participants were included in this analysis, with missing cases excluded listwise (n = 296).
BF% was measured by DXA.
Abbreviations: BF% total body fat percentage; DXA dual-energy X-ray absorptiometry.

Table 3.8: Android fat % as a predictor of circulating leptin concentrations

Predictor	Coefficient (B)	Standard error B	95% CI B	Standardised B	R^2	P-value
					0.523*	0.000
Intercept	-22013	3543	-28986, -15040			
Android Fat % DXA	958	56.8	846, 1070	0.707		0.000
Age	150	77.3	-1.80, 302	0.089		0.053
Deprivation Index	308	219	-123, 740	0.072		0.160
Ethnicity	-905	1307	-3477, 1667	-0.036		0.489

Multiple linear regression (Enter method) was used. *F (4, 295) = 79.8
Ethnicity was NZ European compared with Pacific. All study participants were included in this analysis, with missing cases excluded listwise (n = 296).
Android fat % was measured by DXA.
Abbreviations: DXA dual-energy X-ray absorptiometry.

Table 3.9: Gynoid fat % as a predictor of circulating leptin concentrations

Predictor	Coefficient (B)	Standard error B	95% CI B	Standardised B	R^2	P-value
					0.451*	0.000
Intercept	-47610	4805	-57066, -38154			
Gynoid Fat % DXA	1405	97.1	1213, 1596	0.639		0.000
Age	193	82.7	30.0, 355	0.114		0.020
Deprivation Index	355	235	-108, 817	0.083		0.132
Ethnicity	1508	1393	-1234, 4249	0.061		0.280

Multiple linear regression (Enter method) was used. *F (4, 295) = 59.8
Ethnicity was NZ European compared with Pacific. All study participants were included in this analysis, with missing cases excluded listwise (n = 296).
Gynoid fat % was measured by DXA.
Abbreviations: DXA dual-energy X-ray absorptiometry.

Table 3.10: Visceral fat % as a predictor of circulating leptin concentrations

Predictor	Coefficient (B)	Standard error B	95% CI B	Standardised B	R^2	P-value
					0.516*	0.000
Intercept	-19089	351	-26008, -12171			
Visceral Fat % DXA	899	54.1	793, 1006	0.701		0.000
Age	178	77.7	25.2, 331	0.106		0.023
Deprivation Index	325	221	-109, 759	0.076		0.142
Ethnicity	-817	1316	-3408, 1774	-0.033		0.536

Multiple linear regression (Enter method) was used. *F (4, 295) = 77.5
Ethnicity was NZ European compared with Pacific. All study participants were included in this analysis, with missing cases excluded listwise (n = 296).
Visceral fat % was measured by DXA.
Abbreviations: DXA dual-energy X-ray absorptiometry.

Table 3.11: BMI as a predictor of circulating leptin concentrations

Predictor	Coefficient (B)	Standard error B	95% CI B	Standardised B	R^2	P-value
					0.497 *	0.000
Intercept	-19730	3602	-26820, -12640			0.000
BMI	1280	80.2	1123, 1438	0.713		0.000
Age	5.92	81.0	-154, 165	0.004		0.942
Deprivation Index	189	226	-257, 635	0.044		0.405
Ethnicity	-2481	1357	-5152, 191	-0.100		0.069

Multiple linear regression (Enter method) was used. *F (4, 295) = 71.9
Ethnicity was NZ European compared with Pacific. All study participants were included in this analysis, with missing cases excluded listwise (n = 296).
Abbreviations: BMI body mass index (kg/m^2).

Table 3.12: Circulating insulin concentrations as a predictor of total body fat %

Predictor	Coefficient (B)	Standard error B	95% CI B	Standardised B	R^2	P-value
					0.206*	0.000
Intercept	24.4	2.42	19.7, 29.2			
Insulin	0.214	0.029	0.158, 0.270	0.417		0.000
Age	0.203	0.056	0.093, 0.314	0.212		0.000
Deprivation Index	0.495	0.159	0.182, 0.808	0.203		0.002
Ethnicity	-1.26	0.977	-3.18, 0.665	-0.089		0.199

Multiple linear regression (Enter method) was used. *F (4, 299) = 19.1
Ethnicity was NZ European compared with Pacific. All study participants were included in this analysis, with missing cases excluded listwise (n = 300).
BF% was measured by DXA.
Abbreviations: BF% total body fat percentage; DXA dual-energy X-ray absorptiometry.

Table 3.13: Circulating insulin concentrations as a predictor of android fat %

Predictor	Coefficient (B)	Standard error B	95% CI B	Standardised B	R^2	P-value
					0.236*	0.000
Intercept	19.8	3.07	13.8, 25.9			
Insulin	0.291	0.036	0.220, 0.363	0.439		0.000
Age	0.223	0.071	0.083, 0.362	0.179		0.002
Deprivation Index	0.525	0.201	0.129, 0.922	0.166		0.010
Ethnicity	0.305	1.24	-2.13, 2.74	0.017		0.805

Multiple linear regression (Enter method) was used. *F (4, 299) = 22.8
Ethnicity was NZ European compared with Pacific. All study participants were included in this analysis, with missing cases excluded listwise (n = 300).
Android fat % was measured by DXA.
Abbreviations: DXA dual-energy X-ray absorptiometry.

Table 3.14: Circulating insulin concentrations as a predictor of gynoid fat %

Predictor	Coefficient (B)	Standard error B	95% CI B	Standardised B	R^2	P-value
					0.092*	0.000
Intercept	32.5	2.05	28.5, 36.6			
Insulin	0.107	0.024	0.059, 0.154	0.262		0.000
Age	0.105	0.048	0.011, 0.198	0.138		0.028
Deprivation Index	0.343	0.135	0.078, 0.608	0.177		0.011
Ethnicity	-0.862	0.828	-2.49, 0.77	-0.077		0.299

Multiple linear regression (Enter method) was used. *F (4, 299) = 7.46
Ethnicity was NZ European compared with Pacific. All study participants were included in this analysis, with missing cases excluded listwise (n = 300).
Gynoid fat % was measured by DXA.
Abbreviations: DXA dual-energy X-ray absorptiometry.

Table 3.15: Circulating insulin concentrations as a predictor of visceral fat %

Predictor	Coefficient (B)	Standard error B	95% CI B	Standardised B	R^2	P-value
					0.221*	0.000
Intercept	18.0	3.27	11.6, 24.5			
Insulin	0.296	0.039	0.220, 0.372	0.423		0.000
Age	0.203	0.076	0.054, 0.352	0.155		0.008
Deprivation Index	0.544	0.215	0.122, 0.967	0.164		0.012
Ethnicity	0.313	1.32	-2.28, 2.91	0.016		0.813

Multiple linear regression (Enter method) was used. *F (4, 299) = 20.9
Ethnicity was NZ European compared with Pacific. All study participants were included in this analysis, with missing cases excluded listwise (n = 300).
Visceral fat % was measured by DXA.
Abbreviations: DXA dual-energy X-ray absorptiometry.

Table 3.16: Circulating insulin concentrations as a predictor of BMI

Predictor	Coefficient (B)	Standard error B	95% CI B	Standardised B	R^2	P-value
					0.354*	0.000
Intercept	12.7	2.16	8.39, 16.9			0.000
Insulin	0.254	0.025	0.204, 0.305	0.501		0.000
Age	0.288	0.050	0.189, 0.386	0.303		0.000
Deprivation Index	0.465	0.142	0.186, 0.744	0.193		0.001
Ethnicity	1.28	0.871	-0.439, 2.99	0.091		0.144

Multiple linear regression (Enter method) was used. *F (4, 299) = 40.4
Ethnicity was NZ European compared with Pacific. All study participants were included in this analysis, with missing cases excluded listwise (n = 300).
Abbreviations: BMI body mass index (kg/m^2).

3.5 Discussion

The physiological role and function of adipose tissue is essential to survival as it plays a primary role in metabolism and energy homeostasis. Adipose tissue and its distribution are important to consider when assessing metabolic disease risk, as different fat depots contribute to different metabolic outcomes (Despres, 2012). The aim of this study was firstly, to investigate the metabolic biomarkers and endocrine regulators in two distinct groups of women with different body fat profiles (normal and high BMI) and with high metabolic disease risk (Pacific women) or moderate metabolic disease risk (NZ European women); and secondly, to compare different approaches of assessing body composition and fat distribution and their relationship with metabolic and endocrine profiles.

3.5.1 Anthropometric and Body Composition Assessment

The key findings from this cross-sectional study show some differences and similarities in anthropometry, body composition and fat distribution between ethnic groups and BMI groups. Within the same BMI group, Pacific and NZ European women had the same total body fat percentage and the same body fat mass in kg (measured by DXA and BIA). This contrasts with previous research that has found Pacific women tend to have a lower body fat mass at a given BMI when compared with NZ European women (Rush et al., 2009; Rush et al., 2007; Swinburn et al., 1999). There were also no differences between ethnic groups in android, gynoid or visceral fat percentage measured by DXA in either the normal or high BMI group in our study. The high BMI group had higher fat percentages for total, android, gynoid and visceral fat in both ethnic groups. A previous study reported that Pacific women had a higher abdominal fat mass percentage and a lower thigh fat mass percentage, however this is not in agreement with our results (Rush et al., 2009). These differences may be influenced by age; there is a large age difference between the Pacific women in our study and with that of Rush et al. (2009), with the mean (±SD) for age being 25 (±6) and 42 (±14), respectively. Changes in body fat percentage and distribution may occur during aging (Kuk, Saunders, Davidson, & Ross, 2009), and may explain the differences observed between these studies. Waist circumference has been found to increase with increasing age, however

visceral fat may contribute more to this than the subcutaneous component, which tends to decrease with age (Kuk et al., 2009; Sugihara et al., 2011).

BMI had a strong, but not perfect (r = 0.841; p = 0.000), positive correlation with body fat percentage measured by DXA, a finding that is supported by other studies (Goonasegaran, Nabila, & Shuhada, 2012; Hunma et al., 2016; Rush et al., 2009; Rush et al., 2007). This is expected, as BMI is commonly used as a measure of total body mass, which does not distinguish between fat and lean mass. Similar to previous research, WC, HC and WHtR correlated nearly as strongly with total body fat percentage as BMI (Phan, Maresca, Hossain, & Datto, 2012). WHR has previously been described as a measure of abdominal adiposity and fat distribution, and has been recommended as standard practice for clinicians (Egger, 1992; World Health Organization, 2008). The present study showed that WHR was not a good measure of adiposity, and a simple WC measurement or WHtR was more accurate at discerning total body fat percentage and android fat percentage. Supporting this, a cross-sectional descriptive study by Weerarathna, Lekamwasam, and Rodrigo (2008) found that WHR did not have a significant association with total body fat mass in a group of pre-menopausal women. Although Weerarathna et al. (2008) reported correlations with total body fat mass in kg, with the present study focussed on percentage, our findings of BMI and WC having strong correlations with total body fat are in agreement. Findings from Swainson et al. (2017) also support the notion that WHR is a poor predictor of total body fat percentage, and rather, recommend the use of WHtR. They found WHtR was a stronger predictor of total body fat percentage than BMI, WC or WHR, however, the present study observed strong correlations of BMI and WC, as well as WHtR, with total body fat percentage. Barreira et al. (2012) also found that BMI, WC and WHtR were strongly correlated with body fat percentage, total fat mass and subcutaneous abdominal adipose tissue, with the weakest correlation observed for WHR.

Studies have also looked at the relationship between WHR and health outcomes. A standardised case-control study of myocardial infarction with 27,098 participants from 52 countries found that WHR was a stronger predictor of myocardial infarction than BMI, WC

or HC (Yusuf et al., 2005). They found that BMI was the weakest predictor, and was inconsistent across different ethnic groups. A review of the literature by Huxley, Mendis, Zheleznyakov, Reddy, and Chan (2010) found some evidence that WC and WHR had a stronger association with T2D prevalence compared to BMI, however this was inconclusive. They also found that the associations were similar for BMI, WC and WHR with hypertension and dyslipidaemia prevalence. A prospective cohort study in 15,062 participants was also in agreement, concluding that WHR was a better predictor of mortality and CVD than body fat percentage or BMI (Myint et al., 2014). In contrast to this, Cheong et al. (2015) report that BMI and WC are more effective than WHR at predicting cardio-metabolic disease risk factors described in the metabolic syndrome. Another prospective cohort study by Rost et al. (2018) found a linear increase in risk of all-cause mortality with WHR. Considering this, it appears that while WHR correlates poorly with total body fat, it may still predict cardio-metabolic disease outcomes and could therefore remain an important tool in the clinical context.

Body fat percentage measured by BIA had a very strong correlation with that of DXA, indicating that BIA may be a useful alternative in a setting that does not allow access to DXA measurements. Previous studies have found variability in the accuracy of BIA at the extremes of BMI. Bedogni et al. (2013) found that BIA was not interchangeable with DXA in women with morbid obesity. However, Andreoli et al. (2002) reported strong correlations of fat mass and fat free mass measured by BIA with that of DXA, although, they did observe a difference between BIA devices, with one device in their comparison underestimating fat free mass. Rockamann, Dalton, Arabas, Jorn, and Mayhew (2017) observed a weaker correlation between BIA and DXA total body fat percentage in women, compared to men. Their study concluded that single-frequency BIA devices are unreliable at determining body fat percentage, with DXA used as the gold standard. The present study observed that the strength of the correlations between the BIA and DXA measures of total body fat percentage in Pacific and NZ European groups were strong for both groups (r = 0.921 and 0.954; p = 0.000)) (**Supplementary table 1**). Additionally, we observed a very strong correlation between total body fat percentage measured by BIA with that of DXA, in our total study population of women from two different ethnic groups and body fat profiles. Considering that BIA is quicker, less costly, and easier to use compared with DXA, it is a tool

that can be very useful in many settings where DXA is unavailable (S. Y. Lee & Gallagher, 2008).

3.5.2 Metabolic Profiles and Endocrine Regulators

The present study compared circulating concentrations of metabolic biomarkers and endocrine regulators, by ethnic group (Pacific and NZ European) and by BMI group (normal and high BMI). For each ethnic group, women in the high BMI group had higher circulating concentrations of fasting insulin, fasting glucose, HbA1c, triglycerides, TC/HDL ratios and leptin, and lower HDL-C levels. While our study population of women are defined as generally healthy and without chronic disease, the metabolic profile we observed in our high BMI groups has previously been associated with greater cardio-metabolic disease risk (Despres, 2012). A cross-sectional survey of NZ adults, including Maori, Pacific peoples and others (mostly NZ Europeans), Pacific peoples were found to have lower HDL-C, higher TC/HDL ratio, and higher triglyceride levels (Gentles et al., 2007). However, these differences were associated with overweight, obesity, smoking and physical activity. In contrast, the present study did not include participants who were current smokers, and we compared the metabolic profiles of the two ethnic groups by BMI group (normal and high), controlling for major differences caused by different levels of adiposity. We did not observe differences between Pacific and NZ European women per BMI group in HDL-C, TC/HDL ratio or triglycerides, however, high BMI NZ European women had higher levels of TC. A significant difference was also observed between high BMI Pacific women and normal BMI NZ European women, where HDL-C was lower in high BMI Pacific women. Conversely, there was no significant difference observed between normal BMI Pacific women and high BMI NZ European women. CRP was also highest in the high BMI NZ European group compared to other groups. This may be related to age being significantly higher in this group, as age is associated with an increase in inflammation markers (Singh & Newman, 2011).

Interestingly, fasting insulin concentrations were higher for Pacific women compared to NZ European women, within the high BMI group. The interaction effect observed describes an

amplification of higher circulating insulin with high BMI in Pacific women that was not seen for NZ European women. However, there was no difference in fasting glucose concentrations between ethnic groups within the normal or high BMI group, with the only significant difference seen between high BMI Pacific women and normal BMI NZ European women, where high BMI Pacific women had significantly higher fasting glucose concentrations. HbA1c was higher for Pacific women compared to NZ European women in both the normal and high BMI groups. This may suggest that increased adiposity in the Pacific women in our study could be a result of hyperinsulinaemia driving fat storage. Alternatively, hyper-insulin secretion in these Pacific women, compared to NZ European women, may be required to achieve euglycaemia. This can be a result of prolonged over-consumption of energy-dense foods (Yip, Sequeira, Plank, & Poppitt, 2017), which is often seen in groups with a lower socio-economic status who have less money to spend on food (Swinburn et al., 2019). This may be a reflection of the higher deprivation index observed for the Pacific women in our study. While the hyperinsulinaemia in Pacific women in our study could suggest increased fat storage driven by insulin in this group (Templeman, Skovso, Page, Lim, & Johnson, 2017), no differences in total body fat percentage between ethnic groups were observed. In the wider NZ population, Pacific peoples do experience higher rates of obesity (Ministry of Health, 2018), which could suggest an effect of hyperinsulinaemia at the population level. However, previous research has found that compared to NZ Europeans, Pacific peoples are not hyperinsulinaemic (Simmons, Thompson, & Volklander, 2001). Alternatively, the hyperinsulinaemia in high BMI Pacific women may at least partially explain the higher lean mass (kg) seen in this group, due to the role of insulin in muscle protein synthesis (Fujita, Rasmussen, Cadenas, Grady, & Volpi, 2006).

3.5.3 Relationships between Body Fat Profiles and Fat Distribution with Metabolic Biomarkers and Endocrine Regulators

The relationship of total and regional body fat measures (percentages of total body fat, android fat, gynoid fat and visceral fat measured by DXA) with metabolic biomarkers and endocrine regulators was investigated. Gynoid fat percentage correlated least strongly with

all metabolic biomarkers. This supports previous findings that a gynoid fat distribution is associated with a profile of metabolic biomarkers reflecting low cardio-metabolic risk (Manolopoulos et al., 2010). Schorr et al. (2018) reported negative correlations between lower-body fat depots and cardio-metabolic risk factors in women, including 2-hour glucose, fasting insulin, fasting glucose, HOMA-IR and triglycerides, after controlling for age and BMI. Additionally, the present study also found that android fat percentage, closely followed by visceral fat percentage, had the strongest positive correlations with LDL-C, TC/HDL ratio, triglycerides, glucose, insulin, HOMA-IR and HbA1c compared to total body fat percentage or gynoid fat percentage. Android and visceral fat percentages also had the strongest negative correlations with HDL-C. This describes a metabolic profile reflecting a higher metabolic disease risk, which been associated with android and visceral fat in the literature (G. A. Bray et al., 2018). In agreement with the present study, a cross-sectional study in the United States found that android fat percentage was associated with increases in total cholesterol, LDL-C and triglycerides, and decreases in HDL-C (Min & Min, 2015). They also found that in women, gynoid fat was positively associated with HDL-C, and negatively associated with triglycerides. Furthermore, a prospective cohort study by Rost et al. (2018) reported a strong association between central obesity and CVD mortality, and that this was particularly evident in women.

Leptin and insulin were identified as having strong associations with body fat distribution, thus these relationships were investigated further, using multiple linear regression analysis. As expected, total body fat percentage explained more of the variance in leptin than android, gynoid or visceral fat percentage. Interestingly, gynoid fat percentage explained the least variance in leptin, suggesting that gluteofemoral adipocytes may be less responsible for circulating leptin concentrations than abdominal or visceral fat depots. Previous research has found leptin levels correlate more strongly with subcutaneous fat area, compared to BMI and intra-abdominal (visceral) fat area (Cnop et al., 2002) and leptin mRNA is more prevalent in subcutaneous adipocytes (Manolopoulos et al., 2010). Staiger et al. (2003) observed a similar strength in correlation between leptin and both waist and hip circumferences, reflecting abdominal and gluteofemoral fat depots, which may contrast our findings.

Circulating insulin concentrations predicted android and visceral fat percentage better than the other fat depots, especially gynoid fat percentage. Lower-body fat depots have been found to have an inverse association with fasting insulin levels (Manolopoulos et al., 2010). It is established that visceral fat is a better predictor of insulin resistance than total body fat (G. A. Bray et al., 2018). Removal of visceral fat in humans was found to improve metabolic profiles and reduce insulin resistance (Thorne, Lonnqvist, Apelman, Hellers, & Arner, 2002), however, liposuction of abdominal subcutaneous adipose tissue was not associated with these same improvements (Klein et al., 2004). In the present study, insulin explained a larger amount of the variance in BMI, a finding that reflects the role of insulin in both lipogenesis and muscle synthesis (Fujita et al., 2006; Kersten, 2001).

3.5.4 Strengths and Limitations

A major strength of this study is the recruitment method, selecting women of two ethnicities with different levels of metabolic disease risk, within two BMI categories associated with markedly different metabolic disease risk. This provided a wide range of body fat profiles, to enable the analysis of the relationships between metabolic biomarkers and endocrine regulators with varying proportions of total and regional body fat mass. Investigating two of the main ethnic groups in New Zealand allows comparisons to be made which have importance to public health practices in New Zealand. The large sample size of Pacific women (n = 142) and NZ European women (n = 162) is another strength of this study, allowing greater statistical power for analyses (Field, 2009). Another strength is the large number of metabolic biomarkers and body composition measurements, including DXA measurements, which enabled the exploration of different aspects of metabolism and the associations with adiposity. The use of DXA measurements for comparisons is a strength of this study, as DXA has previously been considered the gold standard for body composition analysis (Bazzocchi et al., 2014; Ramírez-Vélez et al., 2016). A limitation of the cross-sectional design of this study is that causality cannot be inferred, and only associations can be found. The results presented from this study may not be representative of the entire population of Pacific and NZ European women living in NZ, due to potential biases in

recruitment, and recruiting only from the Auckland region. Another limitation is that this study measured markers of metabolic health in a group of healthy women at one point in time, which does not necessarily predict future health outcomes. Longitudinal research in Pacific and NZ European women would be useful to investigate the long-term health outcomes associated with different body fat distributions.

3.6 Conclusions

This cross-sectional study in a sample of healthy women found differences in the associations between metabolic biomarkers and endocrine regulators and adiposity, dependent on where the adipose tissue was located. Gynoid fat percentage had weak correlations with cardio-metabolic risk factors, including LDL-C, TC/HDL ratio, triglycerides, glucose, insulin, HOMA-IR and HbA1c, and a weak negative correlation with HDL-C. On the other hand, android and visceral fat percentages had stronger, positive correlations with these cardio-metabolic risk factors. Circulating insulin explained less of the variance in gynoid fat percentage than other fat depots. Additionally, gynoid fat percentage explained less of the variance in circulating leptin, suggesting adipose tissue in the lower-body region may contribute less to the production and release of leptin compared to upper-body adipose tissue. For each ethnicity, women in the high BMI group had higher levels of fasting insulin, fasting glucose, HbA1c, triglycerides and TC/HDL ratios, and lower HDL-C.

BMI was found to correlate strongly with total body fat percentage measured by DXA. In addition, BMI explained a similar amount of the variance in leptin concentrations as total body fat percentage did, reflecting the ability of BMI to identify individuals with higher amounts of adipose tissue. Waist-to-hip ratio had weak correlations with android fat percentage and total body fat percentage, whereas waist circumference and waist-to-height ratio performed better in this respect. BIA-measured body fat percentage also had strong, positive correlations with total body fat percentage measured by DXA, however the use of BIA may not always be possible. Our findings suggest that in the New Zealand setting, waist circumference, waist-to-height ratio and BMI are useful tools for assessing adiposity and the

associated cardio-metabolic disease risk factors, whereas waist-to-hip ratio was not. This research provides strong evidence that these clinically important and effective tools should continue to be used in dietetic practice, across different population groups with different metabolic disease risk and different body fat profiles.

Acknowledgements

This study gratefully acknowledges support from the Health Research Council of New Zealand (HRC). HRC Project grant #15/273 “The gut microbiome: a new pathway to obesity prevention and metabolic health”. We also thank all of the participants involved in this study, and all of the investigators, staff and students who conducted the study. Metabolic biomarkers and endocrine regulators were measured by the Liggins Institute and the New Zealand Institute for Plant and Food Research.

Conflicts of Interest

None.

Chapter 4: Conclusions and Recommendations

4.1 Aim of the Research

The aims of this research were to investigate the metabolic biomarkers and endocrine regulators in two distinct groups of women with different body fat profiles (normal and obese); to investigate the metabolic biomarkers and endocrine regulators in two distinct groups of women of high metabolic disease risk (Pacific women) or moderate metabolic disease risk (NZ European women); and to compare different approaches of assessing body composition and fat distribution and their relationship with metabolic and endocrine profiles. The specific objectives of this study were to 1) investigate and compare different approaches of anthropometric and body composition assessment; 2) describe metabolic biomarkers and endocrine regulators in the study population; 3) investigate the relationship of body fat profiles and fat distribution with metabolic biomarkers and endocrine regulators. Investigating the relationships and differences in body fat distribution, metabolic biomarkers and endocrine regulators between Pacific and NZ European women will advance our understanding of the mechanisms that lead to the health inequities in NZ. New knowledge in this area may guide future longitudinal studies or intervention studies and may support strategies to prevent or treat obesity.

4.2 Main Findings of the Research

The main findings are presented in accordance with the objectives set in Chapter 1 of the thesis.

4.2.1 Investigate and Compare Different Approaches of Anthropometric and Body Composition Assessment

Anthropometric and body composition assessment tools were compared between two different ethnic groups (Pacific and NZ European) and two BMI groups (normal and high) in our study population of women living in NZ. Pacific and NZ European women within the same BMI group had the same total body fat percentage, android fat percentage, gynoid fat

percentage and visceral fat percentage measured by Dual-energy X-ray Absorptiometry (DXA), and differences were only seen between BMI groups. Women in the high BMI group had higher percentages for all of the aforementioned body fat percentages, regardless of ethnicity. Previous research assessing fat distribution in Pacific and NZ European women is not in agreement with these findings, as they observed a higher abdominal fat mass percentage and lower thigh fat mass percentage in Pacific women compared to NZ European women (Rush et al., 2009). However, the Pacific women included in the research by Rush et al. (2009) were older than that of the present study, with the mean (±SD) for age in the studies being 42 (±14) and 25 (±6), respectively. This may contribute to the differences between their research and the present study, as body composition and fat distribution is known to change with aging (Kuk et al., 2009; Sugihara et al., 2011).

Another key finding from this study is that BMI correlated strongly with total body fat percentage measured by DXA, supporting the use of BMI for the estimation of adiposity in a routine clinical setting. Waist circumference (WC) and waist-to-height ratio (WHtR) correlated more strongly with android fat percentage, visceral fat percentage and total body fat percentage than waist-to-hip ratio (WHR). This suggests that WHR is not a good measure of overall adiposity, and WC or WHtR are more representative of body fat percentage. This is supported by previous studies (Barreira et al., 2012; Swainson et al., 2017; Weerarathna et al., 2008). No major differences in correlation strengths between anthropometric measurements and DXA-measured fat percentage were seen between the two ethnic groups in our study, suggesting that these anthropometric tools are equally effective in both Pacific and NZ European women.

Body fat percentage measured by bioelectrical impedance analysis (BIA) had a very strong correlation with body fat percentage measured by DXA, suggesting that the BIA device used in our study (InBody230) may be a useful substitute for DXA to measure total body fat content under field conditions. Previous studies have found that the accuracy of BIA can vary between devices and individuals, so it is important to validate each device against a gold standard such as DXA (Andreoli et al., 2002).

4.2.2 Describe Metabolic Biomarkers and Endocrine Regulators in the Study Population

A range of metabolic biomarkers and endocrine regulators were analysed in this study. These were total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, non-esterified fatty acids (NEFA), glucose, glycosylated haemoglobin (HbA1c), insulin, homeostatic model assessment of insulin resistance (HOMA-IR), leptin, c-reactive protein (CRP) and tumour necrosis factor alpha (TNFα). Pacific and NZ European women in the high BMI group had higher circulating concentrations of fasting insulin, fasting glucose, HbA1c, triglycerides, TC/HDL ratios and leptin, and lower HDL-C levels. This reflects the metabolic consequences that can be caused by excessive adiposity, which is commonly reported in the literature (Despres, 2012; Heymsfield & Wadden, 2017). Pacific women within the high BMI group had higher circulating insulin concentrations compared to NZ European women. HbA1c was also higher for Pacific women compared to NZ European women; however, no difference between ethnic groups was observed for glucose concentrations. This suggests that increased adiposity in the Pacific women in our study may be a consequence of hyperinsulinemia and hyper-insulin secretion compared to NZ European women, where a higher circulating concentration of insulin may drive increased adiposity in a euglycemic setting. Alternatively, hyperinsulinaemia could represent and early sign of reduced glucose tolerance where increased insulin concentrations may be required to achieve euglycaemia. Glucose intolerance and insulin resistance can arise from over-consumption of energy-dense foods over long periods of time. Due to their high deprivation index, the Pacific women in our study may not have access to a high quality diet. Increased energy storage in adipocytes may be expected as a result of hyperinsulinaemia, however no differences in body fat percentage were seen between Pacific and NZ European women in either BMI group. Pacific women did have a higher body weight (kg) and lean mass (kg), which may reflect the additional role of insulin in muscle synthesis (Fujita et al., 2006).

4.2.3 Investigate the Relationship of Body Fat Profiles and Fat Distribution with Metabolic Biomarkers and Endocrine Regulators

This objective was achieved by investigating the relationship between each metabolic biomarker and endocrine regulator with the various fat depots: total body fat percentage, android fat percentage, gynoid fat percentage and visceral fat percentage. Gynoid fat percentage correlated least strongly with all metabolic biomarkers and endocrine regulators. Android fat percentage, closely followed by visceral fat percentage, showed the strongest positive correlations with LDL-C, TC/HDL ratio, triglycerides, glucose, insulin, HOMA-IR and HbA1c, and the strongest negative correlations with HDL-C.

The relationship between the different fat depots and circulating leptin concentrations was explored further, to assess any potential differences in the contribution to circulating leptin concentrations by specific adipose tissue depots. While total body fat percentage explained the most variance in circulating leptin levels, an interesting finding was that gynoid fat percentage explained the least variance in circulating leptin concentrations. This might suggest that adipose tissue in the lower-body region has a lesser role in leptin production and release, compared to upper-body and visceral adipose tissue. This observation did not differ between ethnic groups in our study of Pacific and NZ European women. The relationship between circulating insulin concentrations and different fat depots was also explored further, to assess any potential differences in energy storage in adipose tissue of different locations, driven by insulin. We observed that circulating insulin concentrations explained the least variance in gynoid fat percentage, contrasting with android and visceral fat percentage, of which circulating insulin explained a greater amount of the variance. These findings align with the underlying pathophysiology associated with excess adiposity; upper-body adiposity is associated with a greater metabolic disease risk than lower-body adiposity, which has shown a “protective effect” on metabolic health outcomes (Despres, 2012; Manolopoulos et al., 2010). Our findings show that this effect appears to be present in Pacific and NZ European women living in NZ.

4.3 Strengths of the Study

The study population is a strength of this study, where women with a high metabolic disease risk (Pacific women) and women with a moderate metabolic disease risk (NZ European women) were included. This allowed comparisons to be made regarding circulating metabolic biomarkers and endocrine regulators, enabling the underlying physiology to be explored. Including two ethnic groups of considerable differences in metabolic disease risk also meant that our findings could be reflective of a wider population, and could reveal differences between two major ethnic groups living in NZ, giving greater relevance for public health practices. Having two distinct body fat profile groups (normal BMI and high BMI) meant that the effect of greater adiposity could be explored, in relation to circulating concentrations of the metabolic biomarkers and endocrine regulators. The wide range of anthropometric and body composition variables is another strength, allowing comparisons to be made between indirect and direct measures of adiposity, as well as being able to assess the effectiveness of these in both ethnic groups. Additionally, using DXA measurements provided a well-established gold standard for our comparisons (Bazzocchi et al., 2014; Ramírez-Vélez et al., 2016). The wide range of metabolic biomarkers and endocrine regulators is also a strength, providing a large scope for investigating aspects of metabolic health. Another strength is the large sample size, which provided greater statistical power for analyses (Field, 2009). A total of 304 participants were included in this study: 142 Pacific women and 162 NZ European women.

Being cross-sectional in design, findings from this study can also form the basis for further research in particular areas. Such as, the findings from the present study have identified body fat depots that have stronger associations with metabolic biomarkers and endocrine regulators. This can form hypotheses regarding the underlying physiological pathways associated with different fat depots, and thus provide valuable direction for future research. Furthermore, a cross-sectional study design is a highly efficient method to compare different approaches of assessing body composition and fat distribution and their relationship with metabolic and endocrine profiles. Recruiting healthy women without any chronic diseases also meant that our findings relating to the metabolic biomarkers and

endocrine regulators were not influenced by metabolic disease states, and were therefore more likely to be associated with different levels of adiposity and the distribution of adipose tissue.

A significant difference in age was identified in our study, with Pacific women being younger, which may be a confounder. However, all women were pre-menopausal and within the ages of 18-45 years. This would limit the effect of menopausal and age-related changes on body composition and metabolic profiles (Dmitruk, Czeczelewski, Czeczelewska, Golach, & Parnicka, 2018; Pu, Tan, Yu, & Wu, 2017). Age was adjusted for in the multiple linear regression models, however future research could further investigate the contribution of age on body fat profiles and metabolic disease risk in Pacific and NZ European women.

4.4 Limitations of the Study

The cross-sectional design of this study has limitations, as our findings cannot infer causality. When data are taken from one point in time, it is unclear what is cause and what is the effect. Potential biases during recruitment may also be a limitation, as participants were volunteers that were taken from the Auckland region only. Therefore, our findings may not be representative of the wider NZ population of Pacific and NZ European women. Another limitation of this study was that markers of metabolic disease risk were measured at one point in time, in a group of healthy women, which may not directly relate to long-term health outcomes. A longitudinal study as a follow-on from this project could provide more in-depth exploration of the relationships identified between fat distribution and metabolic profiles. However this is beyond the scope of the thesis.

4.5 Recommendations for Future Research

This cross-sectional study has identified some areas for further research. The relationship between different anthropometric measurements and cardio-metabolic risk factors could be further investigated, as the present study only assessed correlations between the

anthropometric measurements and body fat depots, to then explore the relationship between these fat depots with metabolic biomarkers and endocrine regulators. Additionally, the relationship between anthropometric measurements and disease outcomes could be investigated in longitudinal research in a population of Pacific and NZ European women, as abnormal levels of metabolic biomarkers do not always lead to disease states.

This study investigated metabolic profiles of healthy women. This minimised the likelihood of participants having levels of metabolic biomarkers outside of the clinical reference ranges. Future research could explore the effects of fat distribution on cardio-metabolic disease risk factors in Pacific and NZ European women with abnormal levels of metabolic biomarkers, to investigate the extent of the effect that different body fat profiles have on metabolic profiles. This may reveal patterns of metabolic disturbance occurring with different body fat distributions, to expand our understanding of the roles each body fat depot has on cardio-metabolic disease risk. Longitudinal research would be useful to observe the changes in cardio-metabolic disease risk factors associated with different body fat distributions occurring over time. This would enable causal relationships to be examined to provide more robust evidence expanding on the effects we observed between different fat depots and the metabolic biomarkers and endocrine regulators.

Similar research could also include participants from the other major ethnic groups in NZ, including Maori and Asian ethnic groups. Considering the lower prevalence of cardio-metabolic disease in Asian populations (Ministry of Health, 2017), future research can investigate the factors contributing to this, which may provide useful insights for public health strategies to reduce the health inequities in NZ. Similar to Pacific peoples, Maori also experience a higher prevalence of obesity and associated comorbidities; further research in this group is also necessary. When considering the most useful anthropometric tools in clinical practice, it is also important to consider the acceptance of these tools by the participants or patients. Therefore, studies exploring the attitudes of Pacific and NZ

European women towards body composition assessment tools are also important, as this may differ between ethnic groups.

4.6 Conclusion

This cross-sectional study found that fat distribution had a significant effect on metabolic profiles in a group of Pacific and NZ European women. Higher android and visceral fat percentages were more adversely associated with cardio-metabolic risk factors. This was shown by the strong, positive correlations of android and visceral fat percentages with LDL-C, TC/HDL ratio, triglycerides, glucose, insulin, HOMA-IR and HbA1c, and a negative correlation with HDL-C. In contrast to this, gynoid fat percentage had weaker correlations with these cardio-metabolic risk factors. Fasting insulin concentrations explained less of the variance in gynoid fat percentage than android, visceral or total body fat percentages, suggesting preferential energy storage in upper-body fat depots, driven by insulin, in both Pacific and NZ European women. Similarly, gynoid fat percentage also explained less of the variance in circulating leptin concentrations, which may indicate that lower-body fat depots contribute less to the production and release of leptin. This is an area for future research.

While BMI has been attributed with some limitations, the present study found a strong correlation between BMI and total body fat percentage in our population of Pacific and NZ European women. BMI was also a significant predictor of circulating leptin concentrations, providing validity for its use in detecting different levels of adiposity in individuals. This is a useful finding to support the ongoing use of BMI in clinical dietetic practice. While it should be acknowledged that BMI does not distinguish between fat mass and lean mass, our research supports its use for identifying individuals who are likely to have a higher total body fat percentage. BIA could be a useful tool for measuring total body fat percentage in clinical settings, demonstrated by its strong correlation with total body fat percentage measured by DXA. WC and WHtR correlated more strongly with android fat percentage and total body fat percentage than WHR, suggesting that WHR is less useful for identifying adiposity. Thus, our findings support the use of WC or WHtR for identifying general or

abdominal adiposity in Pacific and NZ European women, in a clinical dietetic setting. This is relevant for cardio-metabolic disease risk assessment, as our findings also support the established link between visceral adiposity and an android fat distribution with a metabolic profile reflecting greater metabolic disease risk. In summary, this research provides strong evidence for the use of WC, WHtR and BMI in New Zealand dietetic practice for assessing adiposity and the associated cardio-metabolic disease risk.

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Appendices

Appendix A: Supplementary Results

Supplementary table 1: Pearson's correlation coefficients for anthropometric and body composition measurements compared with total and regional body fat percentages measured by DXA, grouped by ethnicity

	Pacific					NZ European				
	n	BF% DXA	Android Fat % DXA	Gynoid Fat % DXA	Visceral Fat % DXA	n	BF% DXA	Android Fat % DXA	Gynoid Fat % DXA	Visceral Fat % DXA
BMI	142	0.843 (0.000)	0.821 (0.000)	0.581 (0.000)	0.798 (0.000)	162	0.882 (0.000)	0.871 (0.000)	0.752 (0.000)	0.855 (0.000)
WC	142	0.809 (0.000)	0.825 (0.000)	0.524 (0.000)	0.806 (0.000)	162	0.823 (0.000)	0.845 (0.000)	0.656 (0.000)	0.828 (0.000)
HC	142	0.832 (0.000)	0.783 (0.000)	0.624 (0.000)	0.769 (0.000)	162	0.859 (0.000)	0.837 (0.000)	0.763 (0.000)	0.826 (0.000)
WHR	142	0.455 (0.000)	0.568 (0.000)	0.145 (0.086)	0.549 (0.000)	162	0.433 (0.000)	0.507 (0.000)	0.242 (0.002)	0.490 (0.000)
WHtR	142	0.812 (0.000)	0.836 (0.000)	0.537 (0.000)	0.813 (0.000)	162	0.834 (0.000)	0.859 (0.000)	0.672 (0.000)	0.837 (0.000)
Sagittal Height	142	0.843 (0.000)	0.846 (0.000)	0.563 (0.000)	0.826 (0.000)	162	0.830 (0.000)	0.826 (0.000)	0.691 (0.000)	0.812 (0.000)
BF% BIA	141	0.921 (0.000)	0.886 (0.000)	0.736 (0.000)	0.869 (0.000)	161	0.954 (0.000)	0.930 (0.000)	0.861 (0.000)	0.918 (0.000)

Values presented are *r* (*p*-value).
All correlations are Pearson's Correlation Coefficients using original variables, with missing values excluded pairwise.
p <0.05 is considered significant.
Abbreviations: BF% body fat percentage; WC waist circumference; HC hip circumference; WHR waist-to-hip ratio; WHtR waist-to-height ratio; BIA bioelectric impedance analysis; DXA dual-energy X-ray absorptiometry.