Exploring body composition and metabolic health amongst NZ European, Pacific Island and Māori women participating in the women's EXPLORE study

Amanda Whitford

2017

A thesis completed as part of the requirements for
Master of Science in Nutrition and Dietetics
at Massey University, Albany Campus
Auckland, New Zealand

Abstract

Background: In New Zealand, 31.6% of adults are obese. Significant ethnic health inequalities exist; Pacific Islanders and Māori have the highest rates.

Objectives: To investigate the body composition and metabolic health profiles of healthy NZ European, Pacific and Māori women participating in the women's EXPLORE study.

Methods/Design: Cross sectional design investigating 233 European, 91 Pacific and 84 Māori women. Different body mass index (BMI) and body fat % (BF%) defined body composition profiles were analysed for anthropometric measurements, body fat location, and metabolic biomarkers.

Results: Obese (BF%) Māori women had higher android fat mass than obese (BF%) Europeans (2.53kg vs 2.23kg) with no difference in waist circumference (WC). Non-obese (BMI) Māori had higher WC than non-obese (BMI) NZ Europeans (78cm vs 73.5cm) with android fat differences. Regardless of body composition grouping, no ethnic differences were found for BF%. Obese Pacific women had higher HOMA-IR (5.12-5.45) and insulin (24.28-23.28mU/L) than obese Europeans (2.10-2.61 and 10.07-11.24mU/L respectively), as did obese Māori (3.64-4.35 and 16.76-19.41mU/L respectively). Body composition measures with highest sensitivity across all biomarkers assessed were BF% ≥30 for Europeans, both BF% ≥30 and BMI ≥25 for Pacific, and BMI ≥25 for Māori.

Conclusion: Māori and Pacific women had significantly higher glucose metabolism markers than NZ Europeans despite no differences in BF%. When comparing Māori to NZ Europeans, a higher WC was not always related to a higher android fat mass or vice versa, suggesting that WC may not be an accurate representation of abdominal fat for Māori. In spite of ethnic differences, BF% ≥30 and BMI ≥25 appear most sensitive to detect high biomarkers compared to abdominal measurements.

Acknowledgements

First and foremost, I would like to thank Massey University, and Rozanne Kruger in particular, for the opportunity to be a part of the EXPLORE study to complete my thesis. I would also like to thank Rozanne and Marilize Richter for their ongoing advice, guidance and support throughout this process, especially during the difficult times. Although it has been a challenging journey, I have learned so much from each of them and for this I will always be grateful.

I would also like to thank all of those who were involved with the recruitment, screening, data collection, and data handling for this study.

Finally I would like to thank my family, friends, and Justin for supporting and encouraging me, reminding me to take study breaks, and helping me through the highs and lows along the way.

Table of Contents

List of Tables

List of Figures

Abbreviations

AG android gynoid

ASMM appendicular skeletal muscle mass

ATM adipose tissue macrophage

BF body fat

BIA bioelectrical impedance analysis

BMD bone mineral density

BMI body mass index

BP blood pressure

Chol/HDL cholesterol to high density lipoprotein ratio

CRP c-reactive protein

CVD cardiovascular disease

DXA dual-energy x-ray absorptiometry

FFA free fatty acids

FM fat mass

FFM fat free mass

HbA1c glycated haemoglobin

HC hip circumference

HDL high density lipoprotein

HH high BMI, high body fat %

HOMA-IR homeostasis model of insulin resistance

IFG impaired fasting glucose

IGT impaired glucose tolerance

IL interleukin

IR insulin resistance

LBM lean body mass

LDL low density lipoprotein

MCP- 1 monocyte chemotactic protein 1

MHO metabolically healthy obese

NH normal BMI, high body fat %

NN normal BMI, normal body fat %

NWO normal weight obesity

NZE New Zealand European

OGTT oral glucose tolerance test

VLDL very low density lipoprotein

SAT subcutaneous adipose tissue

Se sensitivity

Sp specificity

SNS sympathetic nervous system

TC total cholesterol

T2D Type II diabetes

TG triglycerides

TLR-4 Toll like receptor 4

TNF-α tumor necrosis factor

VAT visceral adipose tissue

WC waist circumference

WHO world health organisation

WtHR waist to height ratio

WHR waist to hip ratio

Chapter 1: Introduction

1.1 Background

Obesity, which is an excessive accumulation of body fat, is a major health problem in New Zealand. (Oliveros *et al.*, 2014; Ministry of Health, 2015) Excess body fat has been associated with increased risk of several adverse metabolic health outcomes including insulin resistance, type 2 diabetes (T2D), chronic inflammation, and cardiovascular disease (CVD). (Ozenoglu *et al.*, 2010; Patel and Abate, 2013) These factors can all contribute to considerable reductions in quality of life, increased mortality, and substantial economic burden through high health care costs. (Campfield and Smith, 1999; Lal *et al.*, 2012) The worldwide prevalence of obesity has increased rapidly over recent decades in both developed and developing countries with an estimated increase from 5% to 10% for men, and from 8- 14% for women between 1980 and 2013. (Ng *et al.*, 2014) In New Zealand, obesity rates are high and have mirrored the worldwide increasing pattern with a rise in adult obesity from 27% to 32% between 2006/2007 and 2015/2016. (Ministry of Health, 2016) When looking at individual ethnic groups, Māori and Pacific Island populations have much higher obesity rates of 47.1% and 66.9 % respectively, compared to 29.5% of Europeans. When those that are overweight and obese are combined into one group then 77.7% of Māori, 88.7% of Pacific Island and 65.9% European adults are affected. These alarming statistics highlight the severity and the ethnic inequality of obesity in New Zealand.

Currently, body mass index (BMI) is the commonly used measure to define overweight and obesity. (Romero-Corral *et al.*, 2008; Gomez-Ambrosi *et al.*, 2012) This index, BMI= weight (kg)/height (m^2), is based on a formula using body weight and height to classify into one of several categories (see table 1.1). (World Health Organisation, 2000)

Weight Category	BMI definition
Underweight	<18.5 kg/m²
Normal weight	≥18.5 - <25 kg/m²
Overweight	≥25 - <30 kg/m²
Obese	≥30 kg/m²

Table 1.1 World Health Organisation BMI classifications.
Adapted from: (World Health Organisation, 2000).

While a high BMI often correlates with increased metabolic dysfunction, there are several limitations that affect its ability to accurately predict this. (Huxley *et al.*, 2010; Ozenoglu *et al.*, 2010; Gomez-Ambrosi *et al.*, 2012) These limitations include a lack of information regarding the actual body fat percentage (BF%), lean body mass (LBM), and regional fat location, along with no consideration of ethnic differences in body composition components such as lean body mass and bone density that may affect body weight and metabolic state. (Lear *et al.*, 2007; Ozenoglu *et al.*, 2010; Gomez-Ambrosi *et al.*, 2012)

Differences in proportions of lean body mass (LBM) and body fat (BF) can have vast differences in weight and metabolic outcomes. (Romero-Corral *et al.*, 2008; Oliveros *et al.*, 2014) A person with high LBM and low BF could be misclassified as obese, and a person with reduced LBM and high BF could be considered to be in the healthy range when using BMI cut offs. (Romero-Corral *et al.*, 2008; Hsieh *et al.*, 2010; Jung and Choi, 2014) Additionally, at a given BMI level, body fat percent can differ for difference ethnic groups. (Rush *et al.*, 2007; Rush *et al.*, 2009; Taylor *et al.*, 2010) Pacific Island and Māori ethnic groups tend to have a lower BF % compared to NZ Europeans (NZE) at the same BMI, sparking suggestions that a higher threshold should be used to define obesity for these groups. (Swinburn *et al.*, 1999; Rush *et al.*, 2009) Despite these compositional differences, when metabolic profiles were assessed the evidence did not support the use of separate BMI thresholds. (Taylor *et al.*, 2010)

There are several alternative body fat indices that can be used to assess body composition including BF%, and abdominal obesity measures like waist to height ratio, waist to hip ratio, and waist circumference.

While BF% may provide a more accurate measure of body fatness compared to BMI, (Romero-Corral *et al.*, 2008; Gomez-Ambrosi *et al.*, 2012) it can be difficult and expensive to get accurate measures of this. Although there is no clear consensus on how to define obesity in terms of BF% (Gallagher *et al.*, 2000; Oliveros *et al.*, 2014), accepted ranges are between 20-27% for men and 30-38% for women, (Marques-Vidal *et al.*, 2008a; Oliveros *et al.*, 2014) with obesity for women often defined as 35% of body fat. (Romero-Corral *et al.*, 2008; Gomez-Ambrosi *et al.*, 2012; Shea *et al.*, 2012; Gaba and Pridalova, 2016) Central adiposity measures such as waist circumference (WC), waist to height ratio (WtHR), and waist to hip ratio (WHR) are simple measurements requiring little time and equipment, however there is conflicting evidence to support the idea that either of these is superior to BMI when identifying metabolic risk profiles, particularly insulin resistance and dyslipidaemia. (Lee *et al.*, 2008; Hsieh *et al.*, 2010; Sahakyan *et al.*, 2015) Although these measurements focus solely on abdominal fat accumulation, some may argue that this is the most important measurement as abdominal fat, particularly visceral fat, is associated with worse metabolic outcomes than that located in other parts of the body, particularly the gynoid region. (Smith *et al.*, 2001; Fox *et al.*, 2007)
The uncertainty and disagreement over the best way to identify excess adiposity and associated metabolic disruption indicates a clear need to assess these body fat measurements together to allow for direct comparison of their sensitivities to the various indicators of metabolic health.

Obesity is associated with a range of metabolic disturbances that may predispose to metabolic diseases such as T2D and CVD. (Bray, 1999; Kahn *et al.*, 2006; Van Gaal, 2010) These disturbances include chronic inflammation, (Bullo *et al.*, 2003; McArdle *et al.*, 2013) insulin

resistance, (Kahn *et al.*, 2006; McArdle *et al.*, 2013) dyslipidaemia, (Abbasi *et al.*, 2013) and high blood pressure. (Landsberg *et al.*, 2013)

Chronic inflammation has a strong association with obesity and is a common factor in various states of metabolic disease. (Bullo *et al.*, 2003) Excessive adipose tissue results in an increased release of pro-inflammatory cytokines from the adipose tissue, including tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), and an increased infiltration of macrophages which also contribute to cytokine production and release. (Bullo *et al.*, 2003; Roth *et al.*, 2004; Jung and Choi, 2014; Laforest *et al.*, 2015) Circulating TNF-α and IL-6 levels tend to correlate with levels of C-reactive protein (CRP), an acute phase protein that increases in relation to inflammation and is used as an inflammatory biomarker. (Pannacciulli *et al.*, 2001)

This inflammation and macrophage infiltration, along with an increase in circulating free fatty acids, are contributing factors to the relationship between obesity and insulin resistance. (Roth *et al.*, 2004; McArdle *et al.*, 2013; Jung and Choi, 2014) Insulin resistance occurs when the ability of cells to respond to the insulin reduces and the pancreas has to produce more insulin than usual to keep blood glucose at normal levels. (Kahn *et al.*, 2006) When the response to or the production of insulin declines to a point where blood glucose cannot be maintained within normal physiological range, this is referred to as diabetes. (Franz, 2000) The relationship between body weight and insulin resistance is well established, and weight loss is a key part of treatment. (Stolic *et al.*, 2002; Kloeting *et al.*, 2010) Insulin resistance is also one of the risk factors for development of CVD, along with hypertension and dyslipidaemia. (Landsberg *et al.*, 2013; Jung and Choi, 2014) Obesity can promote hypertension via various mechanisms, putting pressure on the heart and blood vessels and predisposing to the development of CVD. (Landsberg *et al.*, 2013) Additionally, dyslipidaemia, characterised by changes including increased triglycerides, small dense low density lipoprotein (LDL) particles, and reduced high density lipoprotein (HDL), is a risk factor for CVD and has been linked to obesity with the

increased release of free fatty acids from obese adipose tissue thought to play an important role in disrupting lipid metabolism in the liver. (Chapman and Sposito, 2008; Bays *et al.*, 2013; Jung and Choi, 2014)

These various elements of metabolic dysregulation are interlinked and often people present with a combination of the above rather than isolated changes in one area. (Lean, 2000) The ability to detect those who have a body composition that is associated with an altered metabolic profile could help to target those who would benefit from testing for these indicative biomarkers. This would provide an opportunity for awareness, prevention or reversal of negative metabolic changes.

The obesity profile has become more complex with the discovery of a population subgroup of obesity with a normal BMI but a high percentage of body fat, often termed 'Normal Weight Obesity' (NWO). (De Lorenzo *et al.*, 2006; Romero-Corral *et al.*, 2010) This 'hidden fat' profile is associated with metabolic disturbances similar to those seen with traditional obesity. (De Lorenzo *et al.*, 2006; De Lorenzo *et al.*, 2007; Romero-Corral *et al.*, 2010) Although, the percentage of body fat has been found to increase with age, particularly for women, (Marques-Vidal *et al.*, 2008b; Kuk *et al.*, 2009) much of the research looking at this profile used wide age ranges between 18- 80years old. (Marques-Vidal *et al.*, 2008b; Gomez-Ambrosi *et al.*, 2011; Gomez-Ambrosi *et al.*, 2012; Shea *et al.*, 2012) The few studies looking at young age groups found signs of early inflammation and oxidative stress (De Lorenzo *et al.*, 2007; Di Renzo *et al.*, 2010). While the pilot study for this research indicated the presence of NWO in young NZE women, it is not yet known whether it also exists in Māori and Pacific women. (Kruger *et al.*, 2015) This profile provides an example where using BMI as a sole measure of body fatness could result in missed opportunities for identification of those who would benefit for further screening and efforts to prevent development of metabolic disease.

Despite the high prevalence and ethnic inequality of obesity seen in New Zealand, there is little research investigating differences in body composition between NZE, Pacific and Māori women and how this relates to metabolic health. While previous research in this area tended to concentrate on two or three measures of body composition, this study takes a more holistic approach, using multiple means of measurement including BMI, BF%, WC, WtHR and WHR and body fat location to assess various body fat profiles of New Zealand women. This study uses profile groupings of normal BMI and BF%, normal BMI and high BF%, and high BMI and high BF%, along with groupings of obese or not obese defined by both BMI and BF%. The various groups have been analysed in relation to selected biomarkers of metabolic health including blood lipids, markers of glucose metabolism, inflammatory markers, and metabolic hormones. The separation of the ethnic groups allows investigation and comparison of the groups to explore whether there are cultural patterns or differences in relation to body composition and metabolic health. Given the elevated obesity rates in both Māori and Pacific adults, it is important to gain a better understanding of their body composition and how this affects their metabolic health.

1.2 Aims and objectives

Aim:

This research aims to explore the body composition profiles and metabolic health profiles of healthy New Zealand women aged 16-45.

Objectives:

- To use BMI and body fat percent thresholds to investigate different body composition profiles of healthy NZ European, Māori and Pacific women in terms of anthropometry and body fat location.
- To examine the metabolic profiles of these women as indicated by biochemical markers of metabolic health
- To identify ethnic specific patterns between body composition profiles and markers of metabolic health

1.3 Contributors to the research

Contributor	Contribution to Thesis:
Amanda Whitford	Data entry and analysis, statistical analysis, interpretation of results, author of the thesis
A/Prof Rozanne Kruger	Main thesis supervisor, concept and research design of the EXPLORE study, ethical application, execution of the study, interpretation of results, revision and approval of thesis
Dr Marilize Richter	Thesis co-supervisor, advisor for statistical analysis and interpretation of results, revision of thesis
Prof Bernhard Breier	Thesis co-supervisor, revision of thesis
Shakeela Jayasinghe, Wendy O'Brien	Recruitment, screening and testing of participants
Pam von Hurst, Cathryn Conlon, Kathryn Beck, Richard Swift, Owen Mugridge, Maria Casale, Andrea Fenner, Jenna Schrijvers, Adrianna Hepburn, Zara Houston, Sarah Philipsen, Carmel Trubuhovich, Rozanne Kruger	Facilitation of participant testing: screening questionnaire, blood pressure, blood sample, BODPOD and DEXA scanning.

1.4 Structure of the thesis

This thesis has been structured into four chapters and three appendix sections. Chapter 1 provides an introduction, the scope of the research, and the justification for conducting the study. Chapter 2 is a narrative literature review manuscript for submission to Nutrition Reviews Journal covering obesity aetiology and prevalence, adipose tissue, body fat location, metabolic consequences of obesity, assessment of body fat, and body fat profile groups. To complete this review key words were identified and used alone and in combination to find relevant articles. Searches were ordered by relevance to key words. Databases searched were web of science, discover, and google scholar. Key words included: obesity, metabolic health, diabetes, cardiovascular disease, inflammation, adipose tissue, android obesity, gynoid obesity, obesity aetiology, free fatty acids, macrophages, insulin, dyslipidaemia, metabolic syndrome, ethnic, Pacific, Polynesian, and Maori. This chapter has been prepared according to the author guidelines for the journal. Chapter 3 presents the results in a manuscript formatted for submission to Asia Pacific Journal of Clinical Nutrition. This manuscript contains an abstract, introduction, methods, results, discussion, and conclusion. This chapter has also been prepared according to the author guidelines for the journal. Chapter 4 provides an overview and final conclusions of the research, along with strengths, limitations and recommendations for future research. Appendix A contains supplementary methods information that was unable to fit in the manuscript. Appendix B contains supplementary results tables and analyses that were not included in the manuscript, and Appendix C contains additional questionnaires and protocols used in conducting the research, and the author guidelines for the journals chosen for literature review and manuscript. Rather than using the two recommended referencing styles for the literature review and manuscript, a thesis style format using Harvard referencing throughout has been used for presentation and consistency.

1.5 References

Abbasi, F., Blasey, C. & Reaven, G. M. 2013. Cardiometabolic risk factors and obesity: does it matter whether BMI or waist circumference is the index of obesity? *American Journal of Clinical Nutrition,* 98(3)**,** 637-640. Available: DOI 10.3945/ajcn.112.047506.

Bays, H. E., Toth, P. P., Kris-Etherton, P. M., Abate, N., Aronne, L. J., Brown, W. V., Gonzalez-Campoy, J. M., Jones, S. R., Kumar, R., La Forge, R. & Samuel, V. T. 2013. Obesity, adiposity, and dyslipidemia: A consensus statement from the National Lipid Association. *Journal of Clinical Lipidology,* 7(4)**,** 304-383. Available: DOI 10.1016/j.jacl.2013.04.001.

Bray, G. A. 1999. Etiology and pathogenesis of obesity. *Clinical Cornerstone,* 2(3)**,** 1-15. Available: DOI 10.1016/s1098-3597(99)90001-7.

Bullo, M., Garcia-Lorda, P., Megias, I. & Salas-Salvado, J. 2003. Systemic inflammation, adipose tissue tumor necrosis factor, and leptin expression. *Obesity Research,* 11(4)**,** 525-531. Available: DOI 10.1038/oby.2003.74.

Campfield, L. A. & Smith, F. J. 1999. The pathogenesis of obesity. *Best Practice & Research Clinical Endocrinology & Metabolism,* 13(1)**,** 13-30. Available: DOI 10.1053/beem.1999.0004.

Chapman, M. J. & Sposito, A. C. 2008. Hypertension and dyslipidaemia in obesity and insulin resistance: Pathophysiology, impact on atherosclerotic disease and pharmacotherapy. *Pharmacology & Therapeutics,* 117(3)**,** 354-373. Available: DOI 10.1016/j.pharmthera.2007.10.004.

De Lorenzo, A., Del Gobbo, V., Premrov, M. G., Bigioni, M., Galvano, F. & Di Renzo, L. 2007. Normal-weight obese syndrome: early inflammation? *American Journal of Clinical Nutrition,* 85(1)**,** 40-45.

De Lorenzo, A., Martinoli, R., Vaia, F. & Di Renzo, L. 2006. Normal weight obese (NWO) women: an evaluation of a candidate new syndrome. *Nutrition, Metabolism, and Cardiovascular Diseases* 16(8)**,** 513-23. Available: DOI 10.1016/j.numecd.2005.10.010.

Di Renzo, L., Galvano, F., Orlandi, C., Bianchi, A., Di Giacomo, C., La Fauci, L., Acquaviva, R. & De Lorenzo, A. 2010. Oxidative Stress in Normal-Weight Obese Syndrome. *Obesity,* 18(11)**,** 2125-2130. Available: DOI 10.1038/oby.2010.50.

Fox, C. S., Massaro, J. M., Hoffmann, U., Pou, K. M., Maurovich-Horvat, P., Liu, C. Y., Vasan, R. S., Murabito, J. M., Meigs, J. B., Cupples, L. A., D'Agostino, R. B. & O'Donnell, C. J. 2007. Abdominal visceral and subcutaneous adipose tissue compartments -association with metabolic risk factors in the Framingham Heart Study. *Circulation,* 116(1)**,** 39-48. Available: DOI 10.1161/circulationaha.106.675355.

Franz, M. J. 2000. Medical nutrition therapy for diabetes mellitus and hypoglycemia of nondiabetic origin. *In:* Mahan, L. K., Escott-Stump, S. (ed.) *Krause's food, nutrition, & diet therapy.* 10 ed. Philadelphia, Pennsylvania: W.B. Saunders Company.

Gaba, A. & Pridalova, M. 2016. Diagnostic performance of body mass index to identify adiposity in women. *European Journal of Clinical Nutrition,* 70(8)**,** 898-903. Available: DOI 10.1038/ejcn.2015.211.

Gallagher, D., Heymsfield, S. B., Heo, M., Jebb, S. A., Murgatroyd, P. R. & Sakamoto, Y. 2000. Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. *American Journal of Clinical Nutrition,* 72(3)**,** 694-701.

Gomez-Ambrosi, J., Silva, C., Galofre, J. C., Escalada, J., Santos, S., Gil, M. J., Valenti, V., Rotellar, F., Ramirez, B., Salvador, J. & Fruhbeck, G. 2011. Body adiposity and type 2 diabetes: increased risk with a high body fat percentage even having a normal BMI. *Obesity,* 19(7)**,** 1439-1444. Available: DOI 10.1038/oby.2011.36.

Gomez-Ambrosi, J., Silva, C., Galofre, J. C., Escalada, J., Santos, S., Millan, D., Vila, N., Ibanez, P., Gil, M. J., Valenti, V., Rotellar, F., Ramirez, B., Salvador, J. & Fruhbeck, G. 2012. Body mass index classification misses subjects with increased cardiometabolic risk factors related to elevated adiposity. *International Journal of Obesity,* 36(2)**,** 286-294. Available: DOI 10.1038/ijo.2011.100.

Hsieh, S. D., Ashwell, M., Muto, T., Tsuji, H., Arase, Y. & Murase, T. 2010. Urgency of reassessment of role of obesity indices for metabolic risks. *Metabolism-Clinical and Experimental,* 59(6)**,** 834-840. Available: DOI 10.1016/j.metabol.2009.09.032.

Huxley, R., Mendis, S., Zheleznyakov, E., Reddy, S. & Chan, J. 2010. Body mass index, waist circumference and waist: hip ratio as predictors of cardiovascular risk-a review of the literature. *European Journal of Clinical Nutrition,* 64(1)**,** 16-22. Available: DOI 10.1038/ejcn.2009.68.

Jung, U. J. & Choi, M. S. 2014. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance,

dyslipidemia and nonalcoholic fatty liver disease. *International Journal of Molecular Sciences,* 15(4)**,** 6184-6223. Available: DOI 10.3390/ijms15046184.

Kahn, S. E., Hull, R. L. & Utzschneider, K. M. 2006. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature,* 444(7121)**,** 840-846. Available: DOI 10.1038/nature05482.

Kloeting, N., Fasshauer, M., Dietrich, A., Kovacs, P., Schoen, M. R., Kern, M., Stumvoll, M. & Blueher, M. 2010. Insulin-sensitive obesity. *American Journal of Physiology-Endocrinology and Metabolism,* 299(3)**,** E506-E515. Available: DOI 10.1152/ajpendo.00586.2009.

Kruger, R., Shultz, S. P., McNaughton, S. A., Russell, A. P., Firestone, R. T., George, L., Beck, K. L., Conlon, C. A., von Hurst, P. R. & Breier, B. 2015. Predictors and risks of body fat profiles in young New Zealand European, Māori and Pacific women: study protocol for the women's EXPLORE study. *SpringerPlus,* 4(1)**,** 128.

Kuk, J. L., Saunders, T. J., Davidson, L. E. & Ross, R. 2009. Age-related changes in total and regional fat distribution. *Ageing Research Reviews,* 8(4)**,** 339-348. Available: DOI 10.1016/j.arr.2009.06.001.

Laforest, S., Labrecque, J., Michaud, A., Cianflone, K. & Tchernof, A. 2015. Adipocyte size as a determinant of metabolic disease and adipose tissue dysfunction. *Critical Reviews in Clinical Laboratory Sciences,* 52(6). Available: DOI 10.3109/10408363.2015.1041582.

Lal, A., Moodie, M., Ashton, T., Siahpush, M. & Swinburn, B. 2012. Health care and lost productivity costs of overweight and obesity in New Zealand. *Australian and New Zealand Journal of Public Health,* 36(6)**,** 550-556. Available: DOI 10.1111/j.1753-6405.2012.00931.x.

Landsberg, L., Aronne, L. J., Beilin, L. J., Burke, V., Igel, L. I., Lloyd-Jones, D. & Sowers, J. 2013. Obesity-related hypertension: pathogenesis, cardiovascular risk, and treatment a position paper of the obesity society and the american society of hypertension. *Journal of Clinical Hypertension,* 15(1)**,** 14-33. Available: DOI 10.1111/jch.12049.

Lean, M. E. J. 2000. Pathophysiology of obesity. *Proceedings of the Nutrition Society,* 59(3)**,** 331-336. Available: DOI 10.1017/s0029665100000379.

Lear, S. A., Humphries, K. H., Kohli, S., Chockalingam, A., Frohlich, J. J. & Birmingham, C. L. 2007. Visceral adipose tissue accumulation differs according to ethnic background: results of the Multicultural Community Health Assessment Trial (M-CHAT). *American Journal of Clinical Nutrition,* 86(2)**,** 353-359.

Lee, C. M. Y., Huxley, R. R., Wildman, R. P. & Woodward, M. 2008. Indices of abdominal obesity are better discriminators of cardiovascular risk factors than BMI: a meta-analysis. *Journal of Clinical Epidemiology,* 61(7)**,** 646-653. Available: DOI 10.1016/j.jclinepi.2007.08.012.

Marques-Vidal, P., Chiolero, A. & Paccaud, F. 2008a. Large differences in the prevalence of normal weight obesity using various cut-offs for excess body fat. *e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism,* 3(4)**,** e159-e162.

Marques-Vidal, P., Pecoud, A., Hayoz, D., Paccaud, F., Mooser, V., Waeber, G. & Vollenweider, P. 2008b. Prevalence of normal weight obesity in Switzerland: effect of various definitions. *European Journal of Nutrition,* 47(5)**,** 251-257. Available: DOI 10.1007/s00394-008-0719-6.

McArdle, M. A., Finucane, O. M., Connaughton, R. M., McMorrow, A. M. & Roche, H. M. 2013. Mechanisms of obesity-induced inflammation and insulin resistance: insights into the emerging role of nutritional strategies. *Frontiers in Endocrinology,* 4**,** 52-52. Available: DOI 10.3389/fendo.2013.00052.

Ministry of Health. 2015. *Annual update of key results 2014/15, New Zealand health survey*. Wellington: Ministry of Health. Retrieved from http://www.health.govt.nz/system/files/documents/publications/annual-update-key-results-2014-15-nzhs-dec15-1.pdf

Ministry of Health. 2016. *Annual Update of Key Results 2015/16: New Zealand health survey*. Wellington: Ministry of Health. Retrieved from http://www.health.govt.nz/publication/annual-update-key-results-2015-16-new-zealand-health-survey

Ng, M., Fleming, T. & Robinson, M. 2014. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013 (vol 384, pg 766, 2014). *Lancet,* 384(9945)**,** 746-746.

Oliveros, E., Somers, V. K., Sochor, O., Goel, K. & Lopez-Jimenez, F. 2014. The concept of normal weight obesity. *Progress in Cardiovascular Diseases,* 56(4)**,** 426-433. Available: DOI 10.1016/j.pcad.2013.10.003.

Ozenoglu, A., Ugurlu, S., Can, G., Sarkis, C. & Demirel, Y. 2010. Differences in the body composition and biochemistry in women grouped as normal-weight, overweight and obese according to body mass index and their relation with cardiometabolic risk.

Central European Journal of Medicine, 5(6)**,** 724-732. Available: DOI 10.2478/s11536-009-0137-z.

Pannacciulli, N., Cantatore, F. P., Minenna, A., Bellacicco, M., Giorgino, R. & De Pergola, G. 2001. C-reactive protein is independently associated with total body fat, central fat, and insulin resistance in adult women. *International Journal of Obesity,* 25(10)**,** 1416-1420. Available: DOI 10.1038/sj.ijo.0801719.

Patel, P. & Abate, N. 2013. Body fat distribution and insulin resistance. *Nutrients,* 5(6)**,** 2019-2027. Available: DOI 10.3390/nu5062019.

Romero-Corral, A., Somers, V. K., Sierra-Johnson, J., Korenfeld, Y., Boarin, S., Korinek, J., Jensen, M. D., Parati, G. & Lopez-Jimenez, F. 2010. Normal weight obesity: a risk factor for cardiometabolic dysregulation and cardiovascular mortality. *European Heart Journal,* 31(6)**,** 737-746. Available: DOI 10.1093/eurheartj/ehp487.

Romero-Corral, A., Somers, V. K., Sierra-Johnson, J., Thomas, R. J., Collazo-Clavell, M. L., Korinek, J., Allison, T. G., Batsis, J. A., Sert-Kuniyoshi, F. H. & Lopez-Jimenez, F. 2008. Accuracy of body mass index in diagnosing obesity in the adult general population. *International Journal of Obesity,* 32(6)**,** 959-966. Available: DOI 10.1038/ijo.2008.11.

Roth, J., Qiang, X. L., Marban, S. L., Redelt, H. & Lowell, B. C. 2004. The obesity pandemic: Where have we been and where are we going? *Obesity Research,* 12**,** 88S-101S. Available: DOI 10.1038/oby.2004.273.

Rush, E. C., Freitas, I. & Plank, L. D. 2009. Body size, body composition and fat distribution: comparative analysis of European, Māori, Pacific Island and Asian Indian adults. *British Journal of Nutrition,* 102(4)**,** 632-641. Available: DOI 10.1017/s0007114508207221.

Rush, E. C., Goedecke, J. H., Jennings, C., Micklesfield, L., Dugas, L., Lambert, E. V. & Plank, L. D. 2007. BMI, fat and muscle differences in urban women of five ethnicities from two countries. *International Journal of Obesity,* 31(8)**,** 1232-1239. Available: DOI 10.1038/sj.ijo.0803576.

Sahakyan, K. R., Somers, V. K., Rodriguez-Escudero, J. P., Hodge, D. O., Carter, R. E., Sochor, O., Coutinho, T., Jensen, M. D., Roger, V. L., Singh, P. & Lopez-Jimenez, F. 2015. Normal-weight central obesity: implications for total and cardiovascular mortality. *Annals of Internal Medicine,* 163(11). Available: DOI 10.7326/m14-2525.

Shea, J. L., King, M. T. C., Yi, Y., Gulliver, W. & Sun, G. 2012. Body fat percentage is associated with cardiometabolic dysregulation in BMI-defined normal weight

subjects. *Nutrition Metabolism and Cardiovascular Diseases,* 22(9)**,** 741-747. Available: DOI 10.1016/j.numecd.2010.11.009.

Smith, S. R., Lovejoy, J. C., Greenway, F., Ryan, D., deJonge, L., de la Bretonne, J., Volafova, J. & Bray, G. A. 2001. Contributions of total body fat, abdominal subcutaneous adipose tissue compartments, and visceral adipose tissue to the metabolic complications of obesity. *Metabolism-Clinical and Experimental,* 50(4)**,** 425-435. Available: DOI 10.1053/meta.2001.21693.

Stolic, M., Russell, A., Hutley, L., Fielding, G., Hay, J., MacDonald, G., Whitehead, J. & Prins, J. 2002. Glucose uptake and insulin action in human adipose tissue - influence of BMI, anatomical depot and body fat distribution. *International Journal of Obesity,* 26(1)**,** 17-23. Available: DOI 10.1038/sj.ijo.0801850.

Swinburn, B. A., Ley, S. J., Carmichael, H. E. & Planck, L. D. 1999. Body size and composition in Polynesians. *International Journal of Obesity,* 23(11)**,** 1178-1183. Available: DOI 10.1038/sj.ijo.0801053.

Taylor, R. W., Brooking, L., Williams, S. M., Manning, P. J., Sutherland, W. H., Coppell, K. J., Tipene-Leach, D., Dale, K. S., McAuley, K. A. & Mann, J. I. 2010. Body mass index and waist circumference cutoffs to define obesity in indigenous New Zealanders. *American Journal of Clinical Nutrition,* 92(2)**,** 390-397. Available: DOI 10.3945/ajcn.2010.29317.

Van Gaal, L. F. 2010. Mechanisms linking obesity with cardiovascular disease. *Diabetes Obesity & Metabolism,* 12**,** 21-21.

World Health Organisation. 2000. *Obesity: preventing and managing the global epidemic. WHO technical report series No. 894* (0512-3054). Geneva: World Health Organisation. Retrieved from http://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/

Chapter 2: Literature Review

2.1 Introduction

Obesity, the accumulation of excessive body fat, involves various interactions of genetic, metabolic, environmental, and hormonal processes that negatively impact health by predisposing to a host of diseases, increasing mortality, and reducing quality of life. (Campfield and Smith, 1999) Additionally, negative metabolic impacts, (Kearns *et al.*, 2014) and increased risk of chronic disease, (Lal *et al.*, 2012) have been seen below the widely used threshold for defining obesity (body mass index (BMI) ≥30kg/m²) when people fall into the overweight category rather than obese. The relative risk and prevalence of chronic disease for the overweight tend to be between those that are normal weight and those that are obese suggesting a graded risk increase from normal weight, to overweight to obese. (Lal *et al.*, 2012; Kearns *et al.*, 2014) It has been proposed that even a small population wide decrease in BMI of 1kg/m² could result in a significant reduction in prevalence of chronic disease, with an estimated twenty-eight fewer cases of chronic disease per thousand people. (Kearns *et al.*, 2014) The relationship between body size and chronic disease risk is not straight forward and can be affected by various factors including ethnicity, lean body mass versus fat mass, and fat location. This narrative review investigates the published literature on obesity, body composition and the relationship with metabolic health. The topics covered include: the prevalence and aetiology of obesity, adipose tissue function, the metabolic consequences of obesity, body fat distribution, and assessment of body composition.

2.2 The global prevalence of obesity

Obesity is considered an epidemic affecting millions of people worldwide. (Popkin *et al.*, 2012; Ng *et al.*, 2014) A large longitudinal study has investigated the worldwide prevalence and trends of overweight and obesity using BMI cut off points in order to establish the

changes that have taken place between 1980 and 2013. (Ng *et al.*, 2014) Over this period, worldwide overweight and obesity increased by just under 30% in adults and by 47% in children. When looking at obesity only, the increases were estimated to be from 5% to 10% for men, and from 8- 14% for women. (Ng *et al.*, 2014) This pattern of increase was seen in both developed and developing countries. When looking at the pattern of growth over time, they found that the rate was highest between 1992 -2002, slowing down over the following 10 years. This reduced rate of increase was more associated with developed countries than developing. (Ng *et al.*, 2014) While this may indicate obesity rate trends are heading in a promising direction for developed countries, there is currently no evidence of a reduction in prevalence. In 2014, the World Health Organisation (WHO) estimated that around 39% and 13% of the world's adult population were overweight and obese respectively. (World Health Organization, 2014) In the United States of America, a country considered one of the most affected by obesity, the prevalence was over 35% for both men and women in 2010. (Flegal *et al.*, 2012) Data from the WHO European Region suggests that around 23% of women from these countries are obese and over 50% are overweight. (World Health Organization Regional Office for Europe, 2008) While South East Asia has been shown to have a lower incidence of obesity, at around 5% in 2014, there has been a pattern of rising prevalence across many countries in this region including India (from 2.2-3.4%) and Bangladesh (from 0.5-1.4%) between 1996 and 2006. (World Health Organization, 2011)

2.3 Obesity in New Zealand

In New Zealand, the prevalence of obesity has followed the increasing worldwide trend. (Ministry of Health, 2015) In 1989, obesity affected ~11% of the New Zealand population. By 1997 this had increased to 17%, (Ministry of Health, 1999) and in 2015/2016 prevalence was 31.6% of adults. (Ministry of Health, 2016) These latest results are similar to those a few years earlier and may indicate a slowing of obesity growth rates, but it is too early to say this

with certainty. (Ministry of Health, 2015) New Zealand is a country of cultural diversity, with significant parts of the population comprising Māori (~15%) and Pacific Island (~7%) ethnicities. (Statistics New Zealand, 2015) When stratifying for ethnicity, large inequalities in obesity prevalence can be seen where Pacific Islanders and Māori have the highest rates in the country. (Ministry of Health, 2016) According to the 2015/2016 New Zealand Health survey, 66.9% of Pacific Island and 47.1% of Māori adults are obese, compared to 29.5% of Europeans. (Ministry of Health, 2016) When statistics for overweight and obesity are combined, 88.7% of Pacific Island, 77.7% of Māori, and 65.9% of European adults are affected. This is just one of the health related inequalities that these ethnic groups face. They also have poorer overall health, higher incidence of metabolic diseases such as Type II diabetes (T2D) and stroke, and lower life expectancy compared to NZ Europeans. (Simmons *et al.*, 2001; Ministry of Health, 2002; Defay *et al.*, 2007; Tobias *et al.*, 2009) These alarming statistics highlight the need to consider the ethnic groups separately to work towards reducing obesity and the surrounding health inequality currently seen in New Zealand.

2.4 The aetiology of obesity

The aetiology of obesity is complicated as multiple factors can influence the process of fat accumulation. In most cases, energy balance is central to this, however, weight is also affected by other factors such as hormones, genetics, and the environment. (Bray, 1999; Campfield and Smith, 1999; Spiegelman and Flier, 2001)

Energy for vital functions and movements is provided by the breakdown of fat, carbohydrate and protein. (Ogden *et al.*, 2007) The body metabolises these nutrients from food to provide the energy it needs, then any excess is then converted to triglycerides and stored in adipose tissue. (Bray, 1999; Spiegelman and Flier, 2001; Ogden *et al.*, 2007) While carbohydrate and protein can be stored in the body, the reserves to be used solely as energy are low compared to fat. (Ogden *et al.*, 2007) When food supply is lower than energy needs,

these stores are broken down to provide the additional energy needed. (Ogden *et al.*, 2007) Thus, the primary driver of fat accumulation is an imbalance between dietary intake and energy expenditure. (Bray, 1999; Jung and Choi, 2014)

Genetics also play a role; although it is not entirely understood, adoption and twin studies have shown that there is a strong genetic component in relation to body weight. (Roth *et al.*, 2004) Monozygotic twins have more similar body weights than dizygotic twins, and the body fat of adopted children more closely resembles their birth parents than their adoptive parents. (Stunkard *et al.*, 1990) Additionally, several single gene mutations that cause obesity have been identified, but these are rare in humans. (Walley *et al.*, 2006) Although there is evidence that genetics can influence body weight, this is only part of the picture.

Obesity prevalence is rising far too rapidly to hold genetics solely responsible, suggesting that environmental change is playing a causative role in the growth of this disease. (Spiegelman and Flier, 2001; Caterson and Gill, 2002) Modernisation has seen a transition from active to sedentary workplaces, and reduced physical activity for activities of daily living. This in combination with a rapidly rising availability of high energy, highly palatable convenience foods is thought to play an important role in the aetiology of obesity. (Bray, 1999; Campfield and Smith, 1999; Spiegelman and Flier, 2001; Abbade and Dewes, 2015)

2.5 The function of adipose tissue

Adipose tissue is composed of several cell types including adipocytes, pre-adipocytes, immune cells and endothelial cells. (McArdle *et al.*, 2013) When energy is stored in adipocytes, there is either an increase in size (hypertrophy), or an increase in number (hyperplasia). (Spalding *et al.*, 2008; Jung and Choi, 2014) It was found that hyperplasia occurs during the earlier developmental years, and that adult weight gain is mostly by hypertrophy. (Spalding *et al.*, 2008) Alongside its energy storage role, adipose tissue acts as an endocrine organ releasing a range of hormones and signalling molecules affecting

metabolism and other parts of the body. (Roth *et al.*, 2004; McArdle *et al.*, 2013) Leptin, a hormone involved in energy balance, is secreted in approximate proportion to body fat mass. (Park and Ahima, 2015) When body fat is high, leptin levels increase and work via the hypothalamus to decrease appetite and increase energy output, thus trying to correct energy balance. (Pan *et al.*, 2014) Other adipokines produced include: pro-inflammatory tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and monocyte chemotactic protein 1 (MCP-1), (Jung and Choi, 2014) and anti- inflammatory adiponectin and interleukin 10 (IL-10). (Guilherme *et al.*, 2008; McArdle *et al.*, 2013) Additionally, various immune cells reside in adipose tissue, including macrophages. (McArdle *et al.*, 2013; Jung and Choi, 2014) Macrophages have been described as having two main phenotypes that they can switch between depending on environmental triggers. (Lumeng *et al.*, 2007; Perez de Heredia *et al.*, 2012; McArdle *et al.*, 2013) The M1 form is pro-inflammatory, secreting cytokines such as TNF-α and IL-6 as part of their inflammatory response. (Perez de Heredia *et al.*, 2012) Conversely, the M2 form secretes anti-inflammatory molecules such as IL-10 and is associated with resuming homeostasis and cell repair. (Perez de Heredia *et al.*, 2012; Patel *et al.*, 2013) Excessive adipose tissue and dysfunctional adipocytes can lead to changes in immune cell number and function, (Weisberg *et al.*, 2003; Perez de Heredia *et al.*, 2012) pro-inflammatory changes to adipose tissue secretory products, (Fantuzzi, 2005; Eguchi and Manabe, 2014) and changes to lipid metabolism resulting in increased release of free fatty acids (FFA). (Shah *et al.*, 2003; Shi *et al.*, 2006) It is these changes that have been implicated in the development of the metabolic disturbances associated with obesity.

2.6 The metabolic consequences of obesity

Obesity is an important risk factor in the development of metabolic diseases like T2D and CVD , and research into the mechanisms linking these has identified inflammation and insulin resistance (IR) as important contributing factors. (Kahn *et al.*, 2006; Van Gaal, 2010;

McArdle *et al.*, 2013) A schematic diagram for this relationship is shown in Figure 2.1. Chronic low grade inflammation is associated with a range of metabolic conditions including obesity, (Forouhi *et al.*, 2001; Pannacciulli *et al.*, 2001; Bullo *et al.*, 2003) IR, (Pannacciulli *et al.*, 2001; McArdle *et al.*, 2013) and atherosclerosis (Cancello and Clement, 2006) and is thought to be an important linking factor. (Bullo *et al.*, 2003; McArdle *et al.*, 2013)

Inflammatory markers such as C-reactive protein (CRP), and to a lesser extent TNF-α and IL-6 are measured to detect inflammation. TNF-α and IL-6 are pro- inflammatory cytokines, expressed by adipose tissue, that can stimulate production of CRP, an acute phase protein that increases in response to inflammation in the body. (Pannacciulli *et al.*, 2001) In obese women, a strong relationship was found between adipose cytokines TNF-α, and IL-6 and circulating CRP further supporting the link between the two. (Maachi *et al.*, 2004) A summary of studies assessing these markers with measures of body composition can be seen in Table 2.1. Several studies have reported higher levels of CRP associated with higher measures of body composition, including BMI, (Festa *et al.*, 2001; Forouhi *et al.*, 2001; Bullo *et al.*, 2003; Panagiotakos *et al.*, 2005) and measures of central body fat. (Forouhi *et al.*, 2001; Panagiotakos *et al.*, 2005) Analysis of TNF-α and IL-6 is less common, however, studies looking at both found raised levels associated with obesity by BMI, (Panagiotakos *et al.*, 2005; Bahceci *et al.*, 2007) and with central fat. (Panagiotakos *et al.*, 2005)

Obesity is also associated with changes to anti-inflammatory adipokine expression. (Katsareli and Dedoussis, 2014) Adiponectin levels tend to decrease with increasing body fat and fat cell size. (Laforest *et al.*, 2015) Higher adiponectin levels are associated with lower TNF-α and improved insulin sensitivity, (Jung and Choi, 2014) and weight loss has resulted in elevated adiponectin, reduced TNF-α and CRP levels, and improved insulin sensitivity. (Shin *et al.*, 2006; Petelin *et al.*, 2014)

Interleukin 10 (IL-10), another anti-inflammatory cytokine produced by adipocytes and

immune cells including macrophages, appears to be affected by obesity. It has been shown to have increased expression in obese adipose tissue, (Juge-Aubry *et al.*, 2005) while other research found that circulating levels decreased, but only with android obesity. (Manigrasso *et al.*, 2005) IL-10 can reduce the inflammatory action of IL-6 and reduce the associated defects in insulin signalling and action, thus low levels may be an important risk factor for IR. (Kim *et al.*, 2004)

Although the relationship between obesity and inflammation is not completely understood, research has unfolded several potential mechanisms linking the two conditions including alterations to immune cell numbers and profiles, (Lumeng *et al.*, 2007; McArdle *et al.*, 2013) and the increased release of FFA into circulation. (Eguchi and Manabe, 2014) The reasons for the above changes are debated, with supported mechanisms including hypertrophied adipocytes, (Bahceci *et al.*, 2007; Spalding *et al.*, 2008; McArdle *et al.*, 2013) hypoxia resulting from adipocyte expansion, (Wood *et al.*, 2009; Ye, 2009) and oxidative or endoplasmic reticulum stress. (Bluher, 2009)

Excess body weight has been associated with changes in immune cells including alterations to the type of T cells present in the adipose tissue and altered macrophage number and function. (McArdle *et al.*, 2013) In 2003, two studies using mice demonstrated that adipose tissue macrophage (ATM) numbers are increased in obese tissue stimulating further research into the effect of this. (Weisberg *et al.*, 2003; Xu *et al.*, 2003) These ATMs have been shown to release a significant amount of the TNF-α and IL-6 from adipose tissue contributing to the inflammatory state associated with obesity. (Weisberg *et al.*, 2003) Lumeng *et al.* (2007) proposed that obesity is associated with a switch from anti-inflammatory to pro-inflammatory macrophage phenotypes. While this displays a plausible mechanism for the increased inflammation seen with obesity, not all research has found the M1 phenotype to be higher (Fjeldborg *et al.*, 2014). Furthermore, evidence of M2

macrophage remodelling, (Shaul *et al.*, 2010) and the ability of the M2 phenotype to release pro-inflammatory cytokines in adipose tissue, (Zeyda *et al.*, 2007) has also been found, suggesting that there may be various ATM phenotypes. Although it is not yet clear what triggers these macrophage changes, there are several potential contributing factors that have been proposed. Increased pro-inflammatory adipocyte secretions, such as MCP-1, have been shown to attract macrophages and may influence their phenotype. (Roth *et al.*, 2004; Lumeng *et al.*, 2007; Bluher, 2009) Additionally, the attraction of macrophages to areas of hypoxia and/or endoplasmic stress, (Perez de Heredia *et al.*, 2012) or attraction due to the increased FFA release, (Patel *et al.*, 2013) may also contribute to their increased numbers. Weight loss has been shown to reduce macrophage infiltration into adipose tissue and decrease the expression of pro-inflammatory genes, supporting the notion that body fat is a key driver in these pathways to inflammation. (Cancello and Clement, 2006; Aron-Wisnewsky *et al.*, 2009)

Excessive stores of body fat promote the release of FFA from adipocytes into the circulation, which has been implicated in the link between obesity and inflammation. (Roth *et al.*, 2004; Jung and Choi, 2014) Excess circulatory FFA may contribute to inflammation via the stimulation of toll-like receptor 4 (TLR4) and toll-like receptor 2 (TLR2); receptors involved in innate immunity. (Shi *et al.*, 2006; Nguyen *et al.*, 2007; Eguchi and Manabe, 2014) Their actions include activating macrophages, (Nguyen *et al.*, 2007) promotion of pro-inflammatory pathways and stimulating release of cytokines. (Shi *et al.*, 2006) Experimental research has shown that this inflammatory activation by FFAs is inhibited if there is noTLR4, providing support for the relationship between the two. (Shi *et al.*, 2006)

Inflammation and FFA also have a role in the relationship between obesity and the disruption of glucose metabolism, particularly IR and progression to T2D. (Kahn *et al.*, 2006;

Jung and Choi, 2014) Insulin is the main energy storage hormone, signalling for cells to take up excess glucose from circulation for storage. (Ferrannini *et al.*, 1999) The major insulin responsive tissues are adipose tissue, muscle and liver, and when IR occurs there is a reduced sensitivity of these tissues to circulating insulin. (Roth *et al.*, 2004) Excessive body weight is a known risk factor in the development of IR, (Kloeting *et al.*, 2010) and increased adipocyte size has been associated with the development of diabetes. (Weyer *et al.*, 2000; Lonn *et al.*, 2010) Adipose tissue inflammation and the increased release of FFA are implicated in this relationship. Hyperinsulinaemia and insulin sensitivity have both been associated with circulating CRP levels, (Festa *et al.*, 2001; Pradhan *et al.*, 2003) while cross sectional research looking at the predictors of high CRP levels found that total body fat, central body fat, IR and age were the top predictors. (Pannacciulli *et al.*, 2001) Obesity related changes to adiponectin may influence insulin sensitivity supported by weight loss studies resulting in elevated adiponectin, reduced TNF-α and CRP levels, and improved insulin sensitivity. (Shin *et al.*, 2006; Petelin *et al.*, 2014) TNF-α can antagonise insulin in adipose tissue by reducing glucose uptake, and can promote pro-inflammatory changes in adipose tissue. (Suganami *et al.*, 2005; Gregor and Hotamisligil, 2011) Adipose tissue inflammation can reduce these cells' ability to respond to insulin, resulting in a continued release of FFA into the circulation. (Guilherme *et al.*, 2008; Ye and Keller, 2010) This can promote IR in other areas including the liver and skeletal muscle. (Boden, 2001; Shah *et al.*, 2003) One mechanism for this is that high levels of FFA result in intracellular lipid accumulation which interferes with the intracellular insulin signalling pathway. (Boden, 2001; Jung and Choi, 2014) In skeletal muscle this can reduce translocation of GLUT4, inhibiting the uptake of glucose into the cell. (Dresner *et al.*, 1999) Experiments using lipid infusion to mimic elevated FFA levels seen with obesity and T2D, found that this can induce IR in the liver and muscle resulting in reduced glucose uptake into the muscle and reduced suppression of glucose production by the

liver. (Shah *et al.*, 2003; Belfort *et al.*, 2005) Both of these factors contribute to a sustained rise in blood glucose levels, a known risk factor for development of T2D. Although it has been reported that adipocyte inflammation is a contributing factor to IR, (McArdle *et al.*, 2013) IR can also exacerbate inflammation, (Patel and Abate, 2013), suggesting a negative cycle that predisposes to metabolic disease. Measurement of IR is usually done by glucose clamp, however, this is time consuming and expensive. Thus a surrogate measure homeostasis model assessment of insulin resistance (HOMA-IR) is often used, based on a formula using fasting glucose and insulin, and shown to be a reliable measure of IR when compared to the clamp technique. (Bonora *et al.*, 2000)

Both inflammation and IR, along with hypertension and dyslipidaemia, are known risk factors in the development of cardiovascular disease (CVD), another chronic health condition linked to obesity. (DeFronzo, 2010; Van Gaal, 2010; Eguchi and Manabe, 2014) Obesity is a strong contributor to the development of hypertension, and together these conditions can significantly increase the risk of CVD. (Landsberg *et al.*, 2013) Both the presence of IR and elevated leptin, often concurrent with obesity, can stimulate the sympathetic nervous system (SNS) which can increase blood pressure. (Landsberg *et al.*, 2013) The increased release of FFA with obesity has been linked to hypertension by experiments showing raised circulating FFA results with raised blood pressure, (Stojiljkovic *et al.*, 2001; Lopes *et al.*, 2003) and by epidemiological associations of high FFA and hypertension. (Sarafidis and Bakris, 2007)

Dyslipidaemia, referring to an abnormal blood lipid profile, is often seen alongside hypertension, and is characterised by raised levels of triglycerides (TG) and FFA, altered composition of LDL, and reduced HDL. (Chapman and Sposito, 2008; Jung and Choi, 2014) The release of FFA can contribute to dyslipidaemia as uptake of these from the liver results in overproduction of VLDL, which can lead to changes in lipid metabolism that promote

hypertriglyceridemia. (Van Gaal, 2010; Klop *et al.*, 2013; Jung and Choi, 2014) Additionally, high FFA in the circulation can further promote hypertriglyceridemia by reducing the production or the action of lipoprotein lipase in the muscle or adipose cells, resulting in less TG breakdown. (Klop *et al.*, 2013; Jung and Choi, 2014) High levels of circulating triglycerides can result in LDL and HDL with a high TG content, and when hydrolysis of these TG occurs, small dense LDL and HDL particles are formed. (Packard *et al.*, 2000; Van Gaal, 2010; Klop *et al.*, 2013) The presence of small dense LDL particles has been shown to be a stronger predictor of CVD risk than total LDL content suggesting that the quality of LDL cholesterol is another consideration when establishing metabolic risk. (Packard *et al.*, 2000; Alabakovska *et al.*, 2002; Zeljkovic *et al.*, 2008) High circulating TG's above a threshold of 1.5mmol/L promotes the formation of this LDL profile, (Packard *et al.*, 2000) however, the analysis of particle size requires LDL sub-fraction testing, which is not currently part of standard testing in New Zealand.

In summary, obesity results in hypertrophied adipocytes and changes that include promotion of a pro-inflammatory profile, disrupted lipid metabolism including increased release of FFA, and insulin resistant adipocytes. These factors contribute to systematic changes including IR in the liver and muscle, dyslipidaemia, and chronic inflammation that can predispose to diseases like T2D and atherosclerosis (Figure 2.2).

2.7 Body fat content and distribution

In addition to the amount of fat present in the body, the location can have a considerable impact on the likelihood of adverse health outcomes. (Jensen, 2008) Upper body fat can be referred to in terms of subcutaneous, visceral and ectopic adipose tissue, although some categorise visceral as a type of ectopic fat. (Jensen, 2008; Mathieu *et al.*, 2014) Subcutaneous adipose tissue (SAT) is defined as fat that is just beneath the skin; visceral adipose tissue (VAT) is fat found deeper in the abdominal cavity; ectopic fat refers to fat stored outside of

the adipose tissue, usually in or around organs or skeletal muscle. (Arsenault *et al.*, 2012; Lim and Meigs, 2013) As SAT stores become full and hypertrophied, hypoxia can occur, resulting in increased macrophage infiltration, dysfunction of the cell, and a release of FFA into the circulation which can then accumulate in visceral and ectopic tissues. (Arsenault *et al.*, 2012; Patel and Abate, 2013) Fat in the lower body or gynoid region refers to that in the legs and gluteal areas, often termed gluteo-femoral fat. (Jensen, 2008; Manolopoulos *et al.*, 2010) Fat found in the upper body, particularly the android region, has been related to disruption of metabolic markers of glucose and lipid metabolism, (Smith *et al.*, 2001; von Eyben *et al.*, 2003) while it appears that fat located in the gynoid region may actually be protective against metabolic disease. (Manolopoulos *et al.*, 2010) Part of this is attributed to a lower rate of FFA release into the circulation along with higher insulin sensitivity in the gynoid region compared to android region. (Manolopoulos *et al.*, 2010; Shay *et al.*, 2011) Age is an important contributor to body composition, particularly for women following menopause which promotes the accumulation of abdominal fat and may increase risk of mortality and morbidity. (Francucci *et al.*, 2005; Kuk *et al.*, 2009)

Increased levels of VAT have been independently associated with metabolic syndrome risk, cardio-vascular disease (CVD) risk, IR, and all-cause mortality. (Despres, 2006; Fox *et al.*, 2007; Pou *et al.*, 2009) Proposed mechanisms for its pathogenic reputation come from a high level of metabolic activity and its close proximity and drainage of secretory products into the hepatic portal system. (Fox *et al.*, 2007)

When compared to SAT, VAT has a greater lipolytic activity and a lower insulin sensitivity resulting in a lack of control between lipolysis and fatty acid uptake. (Bluher, 2009; Arsenault *et al.*, 2012) Visceral cells are unable to divide so excessive removal of lipids from circulation results in hypertrophied cells. This cell hypertrophy leads to functional changes,

including increased release of pro-inflammatory cytokines and FFA into the circulation. (Despres, 2006; Arsenault *et al.*, 2012) Interestingly, visceral fat has been shown to contribute to just a small amount of circulating FFA, with subcutaneous fat actually releasing the bulk of these, but it is likely the location of VAT, in close proximity to the liver, that results in the adverse effects seen. (Despres, 2006)

2.8 Assessment of body composition

Due to the potential serious consequences associated with excess body fat, it is important to identify those who are at risk. Well validated measures of body composition include air displacement plethysmography (BodPod), which can provide information on fat mass, fat free mass and BF%, (Wingfield *et al.*, 2014) and hydrostatic weighing or dual-energy x-ray absorptiometry (DXA), which can measure whole body and regional composition. (Glickman *et al.*, 2004) While these techniques tend to have high accuracy, they can be time consuming and require both expensive equipment and skilled operators. (Caterson and Gill, 2002; Lowry and Tomiyama, 2015) For this reason, alternative measures tend to be used as an indirect indication of body fatness. (Caterson and Gill, 2002; Rothman, 2008)

The most common indicator of body composition is BMI which is an index based on calculating a person's weight in kilograms divided by their height in meters squared. (Khaodhiar and Blackburn, 2001) Currently, the WHO BMI cut off points are used globally to diagnose overweight (25kg/m²) and obesity (30kg/m²), which are based on statistics of life expectancy and associated disease risk in a European population. (Lean, 2000; World Health Organisation, 2000; Khaodhiar and Blackburn, 2001) While BMI is a widely accepted method of determining obesity and thus predicting associated metabolic risk, it is not without its critics. The publicised drawbacks include its inability to differentiate between lean body mass (LBM) and fat mass, (Khaodhiar and Blackburn, 2001; Rothman, 2008; Gomez-Ambrosi *et al.*, 2012) its lack of consideration regarding the location of body fat and the

related metabolic consequences, (Pou *et al.*, 2009; Mooney *et al.*, 2013) and its debated level of sensitivity for use with different ethnic groups. (Rush *et al.*, 2009; Taylor *et al.*, 2010) BMI does not provide information about the amount of lean mass or fat in the body which can have a significant effect on body weight and metabolic outcomes, (Hsieh *et al.*, 2010) and may lead to the misclassification of someone with a high muscle mass as obese, or the misclassification of an individual with low lean body mass and a high fat mass as normal. This is important as muscle is more metabolically active than fat mass, and a low level of muscle mass has been associated with metabolic dysfunction. (Jung and Choi, 2014) Lean body mass reduction can occur naturally with ageing, and often this is alongside fat accumulation. (Kuk *et al.*, 2009) The use of BMI alone to gauge body composition is unlikely to pick up this kind of compositional change that could predispose to metabolic illness. (Rothman, 2008)

It is important to consider ethnicity when assessing the best way to measure body fatness, as ethnic differences exist in frame size, lean body mass, and body fat percentage at a given BMI. (Rush *et al.*, 2007; Rush *et al.*, 2009; Taylor *et al.*, 2010; Lesser *et al.*, 2013) Table 2.4 displays results found from several studies comparing body compositional and metabolic indicators for various ethnic groups. Studies comparing Asian ethnicities with Europeans found that they tend to have a smaller frame size, a lower BMI, but more body fat, particularly abdominal, and higher metabolic risk at a given BMI. (Lear *et al.*, 2007; Chiu *et al.*, 2011; Lesser *et al.*, 2013) On the other hand Māori and Pacific Islanders tend to have larger frame sizes, more muscle mass and thus, lower body fat % (BF%) than Europeans at the same BMI, so it has been debated whether the use of current BMI cut offs to identify metabolic risk is suitable for these ethnicities. (Swinburn *et al.*, 1999; Rush *et al.*, 2009) Recently a study was conducted looking at BMI, BF% measures of glucose tolerance, and blood lipids to see whether different BMI cut offs are justified for the Māori population.

(Taylor *et al.*, 2010) They found that the higher cut off had a lower sensitivity, meaning there was a reduced ability to identify those that were at risk of metabolic disease. The results of this study supported the use of the 25 kg/m² BMI cut-off for overweight rather than a higher level to determine metabolic risk. At this stage it is unclear whether there are alternative body fat measures that would better predict metabolic risk for these ethnicities. This information would be extremely valuable given the high obesity levels in these populations.

2.9 Body fat profile groups

Traditionally, BMI has defined people into three main body weight categories and seemingly obvious metabolic risk profiles as shown in Table 2.2. However, there are subsets of individuals who do not conform to the expected outcomes in terms of metabolic health. (Gomez-Ambrosi *et al.*, 2011; Roberson *et al.*, 2014) Two in particular have received a lot of recent attention, as they both indicate a need to further refine metabolic risk profiles. (Aung *et al.*, 2014) One profile is often referred to as 'normal weight obesity' (NWO) with a normal BMI but a high BF% and varying degrees of metabolic dysregulation. (Marques-Vidal *et al.*, 2008b; Marques-Vidal *et al.*, 2010; Romero-Corral *et al.*, 2010; Gomez-Ambrosi *et al.*, 2011) The other is the 'metabolically healthy obese' who have a high BMI and high BF% but do not appear to have the adverse metabolic outcomes associated excess body fat. (Karelis *et al.*, 2004; Roberson *et al.*, 2014)

The NWO group has been characterised by a normal body weight when measured by BMI but a high level of fat or 'hidden fat' when actual body fat content is measured, generally using a cut-off between 30-38%. (Marques-Vidal *et al.*, 2008a; Jean *et al.*, 2014; Oliveros *et al.*, 2014) Table 2.3 shows studies investigating the NWO in terms of body composition and metabolic outcomes. This profile has been associated with increased glucose metabolism markers, (Gomez-Ambrosi *et al.*, 2011; Kosmala *et al.*, 2012; Shea *et al.*, 2012; Kim *et al.*, 2013) dyslipidaemia, (Marques-Vidal *et al.*, 2010; Okorodudu *et al.*, 2010;

Kosmala *et al.*, 2012) and CRP. (Gomez-Ambrosi *et al.*, 2011; Kosmala *et al.*, 2012; Shea *et al.*, 2012) Age may be an important factor for the metabolic outcomes of this profile as BF% has been found to increase with age, particularly for women. (Marques-Vidal *et al.*, 2008b) Although the prevalence of NWO has also been shown to increase with age, (Marques-Vidal *et al.*, 2008a) much of the research looking at this profile used wide age ranges between 18-80 years old. (Marques-Vidal *et al.*, 2008b; Gomez-Ambrosi *et al.*, 2011; Gomez-Ambrosi *et al.*, 2012; Shea *et al.*, 2012) Only two of the studies concentrated on young age groups, and they found signs of early inflammation, including raised TNF-α and IL-6, and oxidative stress, although CRP was not raised. (De Lorenzo *et al.*, 2007; Di Renzo *et al.*, 2010) NWO individuals also appear to be at heightened risk of T2D and CVD when looking at research into risk factors and incidence. (Marques-Vidal *et al.*, 2008b; Romero-Corral *et al.*, 2010; Aung *et al.*, 2014) This profile indicates a group where using BMI to identify those who would benefit from further screening could lead to lost opportunities to correct metabolic abnormalities that predispose to future disease.

Metabolically healthy obesity (MHO) is used to describe a subset of 'apparent fat' obese individuals that meet the international classification for obesity without presenting with the expected metabolic disturbances. (Roberson *et al.*, 2014) This group have good insulin sensitivity and lack the abnormal blood pressure, lipid and hormonal profiles, and inflammatory patterns expected with obesity. (Karelis *et al.*, 2004; Velho *et al.*, 2010) Although the prevalence of this subtype varies with the method used to define obesity and the criteria for assessing parameters of metabolic health, a range of studies have reported somewhere between 10-40 % of obese participants may fit into this category. (Karelis *et al.*, 2004; Velho *et al.*, 2010; Roberson *et al.*, 2014) Discrepancies in defining this sub group have caused considerable controversy surrounding not only the prevalence, but also the

stability of this phenotype. Longitudinal research found that 44.5% of the baseline MHO group (defined as having less than two metabolic abnormalities) were classified as unhealthy obese at follow up. (Hamer *et al.*, 2015) Compared to the healthy normal weight group, the MHO group were four times more likely to become metabolically unhealthy. While the reason for this transition is unclear, an increased waist circumference was reported for this group, so it is possible that an increase in android and/or visceral fat may be a contributing factor to the metabolic changes. (Hamer *et al.*, 2015) Similar research by Aung *et al.* (2014) found an increased risk for both CVD and diabetes after 7 years for those with the MHO profile. Other research has reported that MHO may be a transient state with reports of ~30-44% of MHO individuals transitioning to a metabolically unhealthy state over time. (Appleton *et al.*, 2013; Hamer *et al.*, 2015) Guo and Garvey (2016) aimed to address the controversy with defining MHO by suggesting that MHO be defined as a complete absence of metabolic risk factors for blood pressure, blood glucose, and blood lipids, as opposed to many previous studies that have allowed one or two in their definitions. Using data from two large cohort studies, they found that only 260 (1.7%) of the participants (n=14,685) fit the MHO category and that only a small percentage of this group developed one or two risk factors over the 10 years, while the rest maintained their MHO status. These findings suggest that even the presence of one or two metabolic disturbances may predispose to further problems over time. In addition to recognising these subgroups, investigating the potential reasons for the metabolic differences is another important part of understanding the disease. Appleton *et al.* (2013) found that those that maintained MHO status tended to be younger and have higher leg fat, and lower waist circumference that those that were metabolically unhealthy indicating that regional fat location may be an important determinant in the stability of this profile.

2.10 Alternative body composition measures

It has been proposed that BF% is a superior indicator of body composition and metabolic dysfunction than BMI. (Gomez-Ambrosi *et al.*, 2012; Oliveros *et al.*, 2014) This finding is supported by a study comparing the BMI and BF% of 13,000 subjects, where BMI had a sensitivity of only 43%, indicating that a large portion of those with high BF% were not identified by the BMI measure. (Romero-Corral *et al.*, 2008) While BMI and BF% often correlate, where a high body fat is associated with a high BMI and vice versa, the two measures can give very different results when classifying obesity, particularly for people in the overweight BMI range (25-29.99kg/m^2). (Gomez-Ambrosi *et al.*, 2012; Jean *et al.*, 2014; Oliveros *et al.*, 2014) In this middle range, BMI may fail to detect a number of cases with a high BF%. (Romero-Corral *et al.*, 2008) One issue with BF% as a measure is the lack of consensus on reference ranges to define minimal, adequate and excess body fat or obesity. (Gallagher *et al.*, 2000) While it is agreed that different percentages are needed for men and women, the percentages used to define obesity differ between studies. For women obesity is usually defined as ≥30-38% body fat. (Romero-Corral *et al.*, 2008; Okorodudu *et al.*, 2010; Jean *et al.*, 2014; Oliveros *et al.*, 2014) It is likely that the metabolic dysfunction occurs on a continuum with increasing body fat, thus more research is needed looking into defining cut offs in association with metabolic risk. (Romero-Corral *et al.*, 2010)

Central obesity refers to excessive body fat in the abdominal cavity, and is typically measured by either waist circumference (WC), waist to height ratio (WtHR). (Jean *et al.*, 2014) These measures have been shown to predict cardiovascular disease risk with similar or higher accuracy than BMI. (Lee *et al.*, 2008; Sahakyan *et al.*, 2015) One particular study highlighted the importance of central adiposity when it was found that normal BMI and central obesity was associated with higher mortality than obesity by BMI alone. (Sahakyan *et*

al., 2015) It is not clear whether the same cut offs will relate to the same degree of metabolic risk in those with traditional obesity and those with the NWO 'hidden fat' profile.

While WC provides a simple measure of abdominal obesity, it does not take height into account which may reduce its sensitivity, as BF% may differ between people with different heights despite similar waist measurements. (Hsieh and Yoshinaga, 1999; Lee *et al.*, 2008) In fact, given a similar waist circumference, short people are at higher metabolic risk than those that are tall. (Hsieh and Yoshinaga, 1999) For this reason, it has been suggested that WtHR is a better indicator than WC for abdominal obesity. (Ashwell and Hsieh, 2005; Lee *et al.*, 2008) A longitudinal hypertension study found greater predictive power when WC was corrected for height, (Fuchs *et al.*, 2005) and a review looking at metabolic risk factors found WtHR had higher sensitivity and specificity than WC and BMI, (Hsieh *et al.*, 2010) while conversely, several studies have indicated similar sensitivities, (Balkau *et al.*, 2006; Huxley *et al.*, 2010) and predictive power, (Mooney *et al.*, 2013) of these measurements. Ashwell and Hsieh (2005) have proposed that WtHR be used as a universal indicator of obesity with a boundary value of 0.5 for both men and women. Their justification for this is that men tend to be both taller and have larger waists than women so this ratio will be similar. Waist to hip ratio (WHR) is another measure of central obesity, where a threshold of ≥0.8 has been used to indicate those that may be at metabolic disease risk. (World Health Organisation, 2000; Huxley *et al.*, 2010) While WHR and WtHR may be helpful indicators of obesity related metabolic outcomes, they have not been shown to be consistently superior to BMI at predicting abnormal metabolic biomarkers. (Balkau *et al.*, 2006; Huxley *et al.*, 2010; Mooney *et al.*, 2013)

Overall, there appears to be an absence of research looking at the range of aforementioned body composition measures on one participant group, and much of the

available research is contradictory, possibly due to differing ethnicities and cut-off points used. Interestingly, a study comparing WC, BF% and WtHR found that no one measure was the strongest predictor for all metabolic risk factors. (Mooney *et al.*, 2013) WC and WtHR were better at predicting fasting glucose, one of the biomarkers used to identify IR, while BMI was more strongly related to blood pressure, an indicator of CVD risk, and there was little difference between the measures for predicting cholesterol. (Mooney *et al.*, 2013) This suggests that these measurements may be more useful in combination to provide a more accurate picture of body composition and the various elements of metabolic risk.

2.11 Summary

This narrative review describes obesity, its aetiology and prevalence, along with the associations between obesity and metabolic health outcomes including inflammation, IR, T2D and CVD. Various measures of obesity are discussed in terms of identifying those that have high body fat and risk of metabolic dysfunction, and the limitations that these measures may have. Obesity is a major problem in New Zealand, and there are clear ethnic disparities that exist in obesity prevalence and related metabolic diseases. While a small amount of research has identified some ethnic differences in body composition between NZ European, Pacific Island, and Māori people, there is little research investigating and comparing the body composition of these groups in terms of metabolic health. Understanding the body compositional and metabolic similarities and differences between these ethnic groups is an important part of being able to correctly identify those that are at highest risk, and where intervention is needed.

2.12 Acknowledgements

This research was supported by funding from the Netherlands-based Nutricia Research Foundation and New Zealand Lottery Health Research.

2.13 Conflicts of interest

None

2.14 References

Abbade, E. B. & Dewes, H. 2015. Behavioral and societal drivers of an obesogenic environment worldwide. *Nutrition & Food Science,* 45(2). Available: DOI 10.1108/nfs-04-2014-0036.

Alabakovska, S. B., Labudovic, D. D., Tosheska, K. N. & Todorova, B. B. 2002. Low density lipoprotein particle size phenotyping in healthy persons and patients with myocardial infarction. *Croatian Medical Journal,* 43(3)**,** 290-295.

Appleton, S. L., Seaborn, C. J., Visvanathan, R., Hill, C. L., Gill, T. K., Taylor, A. W., Adams, R. J. & North West Adelaide Health Study Team 2013. Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype. *Diabetes Care,* 36(8)**,** 2388-2394. Available: DOI 10.2337/dc12-1971.

Aron-Wisnewsky, J., Tordjman, J., Poitou, C., Darakhshan, F., Hugol, D., Basdevant, A., Aissat, A., Guerre-Millo, M. & Clement, K. 2009. Human adipose tissue macrophages: M1 and M2 cell surface markers in subcutaneous and omental depots and after weight loss. *Journal of Clinical Endocrinology & Metabolism,* 94(11)**,** 4619-4623. Available: DOI 10.1210/jc.2009-0925.

Arsenault, B. J., Beaumont, E. P., Despres, J.-P. & Larose, E. 2012. Mapping body fat distribution: a key step towards the identification of the vulnerable patient? *Annals of Medicine,* 44(8)**,** 758-772. Available: DOI 10.3109/07853890.2011.605387.

Ashwell, M. & Hsieh, S. D. 2005. Six reasons why the waist-to-height ratio is a rapid and effective global indicator for health risks of obesity and how its use could simplify the international public health message on obesity. *International Journal of Food Sciences and Nutrition,* 56(5)**,** 303-307. Available: DOI 10.1080/09637480500195066.

Aung, K., Lorenzo, C., Hinojosa, M. A. & Haffner, S. M. 2014. Risk of developing diabetes and cardiovascular disease in metabolically unhealthy normal-weight and metabolically healthy obese individuals. *Journal of Clinical Endocrinology & Metabolism,* 99(2)**,** 462-468. Available: DOI 10.1210/jc.2013-2832.

Bahceci, M., Gokalp, D., Bahceci, S., Tuzcu, A., Atmaca, S. & Arikan, S. 2007. The correlation between adiposity and adiponectin, tumor necrosis factor α, interleukin-6 and high sensitivity C-reactive protein levels. Is adipocyte size associated with inflammation in adults? *Journal of Endocrinological Investigation,* 30(3)**,** 210-214.

552 Balkau, B., Sapinho, D., Petrella, A., Mhamdi, L., Cailleau, M., Arondel, D., Charles, M. A.
553 & D.E.S.I.R Study Group 2006. Prescreening tools for diabetes and obesity associated
554 dyslipidaemia: comparing BMI, waist and waist hip ratio. The DESIR Study.
555 *European Journal of Clinical Nutrition,* 60(3)**,** 295-304. Available: DOI
556 10.1038/sj.ejcn.1602308.
557 Belfort, R., Mandarino, L., Kashyap, S., Wirfel, K., Pratipanawatr, T., Berria, R., DeFronzo,
558 R. A. & Cusi, K. 2005. Dose-response effect of elevated plasma free fatty acid on
559 insulin signaling. *Diabetes,* 54(6)**,** 1640-1648. Available: DOI
560 10.2337/diabetes.54.6.1640.
561 Bluher, M. 2009. Adipose tissue dysfunction in obesity. *Experimental and Clinical*
562 *Endocrinology & Diabetes,* 117(6)**,** 241-250. Available: DOI 10.1055/s-0029-
563 1192044.
564 Boden, G. 2001. Free fatty acids-the link between obesity and insulin resistance. *Endocrine*
565 *Practice : Official Journal of the American College of Endocrinology and the*
566 *American Association of Clinical Endocrinologists,* 7(1)**,** 44-51.
567 Bonora, E., Saggiani, F., Targher, G., Zenere, M. B., Alberiche, M., Monauni, T.,
568 Bonadonna, R. C. & Muggeo, M. 2000. Homeostasis model assessment closely
569 mirrors the glucose clamp technique in the assessment of insulin sensitivity - studies
570 in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes*
571 *Care,* 23(1)**,** 57-63. Available: DOI 10.2337/diacare.23.1.57.
572 Bray, G. A. 1999. Etiology and pathogenesis of obesity. *Clinical Cornerstone,* 2(3)**,** 1-15.
573 Available: DOI 10.1016/s1098-3597(99)90001-7.
574 Bullo, M., Garcia-Lorda, P., Megias, I. & Salas-Salvado, J. 2003. Systemic inflammation,
575 adipose tissue tumor necrosis factor, and leptin expression. *Obesity Research,* 11(4)**,**
576 525-531. Available: DOI 10.1038/oby.2003.74.
577 Campfield, L. A. & Smith, F. J. 1999. The pathogenesis of obesity. *Best Practice & Research*
578 *Clinical Endocrinology & Metabolism,* 13(1)**,** 13-30. Available: DOI
579 10.1053/beem.1999.0004.
580 Cancello, R. & Clement, K. 2006. Is obesity an inflammatory illness? Role of low-grade
581 inflammation and macrophage infiltration in human white adipose tissue. *Bjog-an*
582 *International Journal of Obstetrics and Gynaecology,* 113(10)**,** 1141-1147. Available:
583 DOI 10.1111/j.1471-0528.2006.01004.x.

584 Caterson, I. D. & Gill, T. P. 2002. Obesity: epidemiology and possible prevention. *Best*
585 *Practice & Research Clinical Endocrinology & Metabolism,* 16(4)**,** 595-610.
586 Available: DOI 10.1053/beem.2002.0228.
587 Chapman, M. J. & Sposito, A. C. 2008. Hypertension and dyslipidaemia in obesity and
588 insulin resistance: Pathophysiology, impact on atherosclerotic disease and
589 pharmacotherapy. *Pharmacology & Therapeutics,* 117(3)**,** 354-373. Available: DOI
590 10.1016/j.pharmthera.2007.10.004.
591 Chiu, M., Austin, P. C., Manuel, D. G., Shah, B. R. & Tu, J. V. 2011. Deriving ethnic-
592 specific BMI cutoff points for assessing diabetes risk. *Diabetes Care,* 34(8)**,** 1741-
593 1748. Available: DOI 10.2337/dc10-2300.
594 De Lorenzo, A., Del Gobbo, V., Premrov, M. G., Bigioni, M., Galvano, F. & Di Renzo, L.
595 2007. Normal-weight obese syndrome: early inflammation? *American Journal of*
596 *Clinical Nutrition,* 85(1)**,** 40-45.
597 Defay, R., Jaussent, I., Lacroux, A. & Fontbonne, A. 2007. Relationships between glycaemic
598 abnormalities, obesity and insulin resistance in nondiabetic Polynesians of New
599 Caledonia. *International Journal of Obesity,* 31(1)**,** 109-113.
600 DeFronzo, R. A. 2010. Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the
601 missing links. The Claude Bernard Lecture 2009. *Diabetologia,* 53(7)**,** 1270-1287.
602 Available: DOI 10.1007/s00125-010-1684-1.
603 Despres, J. P. 2006. Is visceral obesity the cause of the metabolic syndrome? *Annals of*
604 *Medicine,* 38(1)**,** 52-63. Available: DOI 10.1080/07853890500383895.
605 Di Renzo, L., Galvano, F., Orlandi, C., Bianchi, A., Di Giacomo, C., La Fauci, L.,
606 Acquaviva, R. & De Lorenzo, A. 2010. Oxidative Stress in Normal-Weight Obese
607 Syndrome. *Obesity,* 18(11)**,** 2125-2130. Available: DOI 10.1038/oby.2010.50.
608 Dresner, A., Laurent, D., Marcucci, M., Griffin, M. E., Dufour, S., Cline, G. W., Slezak, L.
609 A., Andersen, D. K., Hundal, R. S., Rothman, D. L., Petersen, K. F. & Shulman, G. I.
610 1999. Effects of free fatty acids on glucose transport and IRS-1-associated
611 phosphatidylinositol 3-kinase activity. *Journal of Clinical Investigation,* 103(2)**,** 253-
612 259. Available: DOI 10.1172/jci5001.
613 Eguchi, K. & Manabe, I. 2014. Toll-like receptor, lipotoxicity and chronic inflammation: the
614 pathological link between obesity and cardiometabolic disease. *Journal of*
615 *Atherosclerosis and Thrombosis,* 21(7)**,** 629-639.
616 Fantuzzi, G. 2005. Adipose tissue, adipokines, and inflammation. *Journal of Allergy and*
617 *Clinical Immunology,* 115(5)**,** 911-919. Available: DOI 10.1016/j.jaci.2005.02.023.

Ferrannini, E., Galvan, A. Q., Gastaldelli, A., Camastra, S., Sironi, A. M., Toschi, E., Baldi, S., Frascerra, S., Monzani, F., Antonelli, A., Nannipieri, M., Mari, A., Seghieri, G. & Natali, A. 1999. Insulin: new roles for an ancient hormone. *European Journal of Clinical Investigation,* 29(10)**,** 842-852.

Festa, A., D'Agostino, R., Williams, K., Karter, A. J., Mayer-Davis, E. J., Tracy, R. P. & Haffner, S. M. 2001. The relation of body fat mass and distribution to markers of chronic inflammation. *International Journal of Obesity,* 25(10)**,** 1407-1415. Available: DOI 10.1038/sj.ijo.0801792.

Fjeldborg, K., Pedersen, S. B., Moller, H. J., Christiansen, T., Bennetzen, M. & Richelsen, B. 2014. Human adipose tissue macrophages are enhanced but changed to an anti-inflammatory profile in obesity. *Journal of Immunology Research.* Available: DOI 10.1155/2014/309548.

Flegal, K. M., Carroll, M. D., Kit, B. K. & Ogden, C. L. 2012. Prevalence of Obesity and Trends in the Distribution of Body Mass Index Among US Adults, 1999-2010. *Jama-Journal of the American Medical Association,* 307(5)**,** 491-497. Available: DOI 10.1001/jama.2012.39.

Forouhi, N. G., Sattar, N. & McKeigue, P. M. 2001. Relation of C-reactive protein to body fat distribution and features of the metabolic syndrome in Europeans and South Asians. *International Journal of Obesity,* 25(9)**,** 1327-1331. Available: DOI 10.1038/sj.ijo.0801723.

Fox, C. S., Massaro, J. M., Hoffmann, U., Pou, K. M., Maurovich-Horvat, P., Liu, C. Y., Vasan, R. S., Murabito, J. M., Meigs, J. B., Cupples, L. A., D'Agostino, R. B. & O'Donnell, C. J. 2007. Abdominal visceral and subcutaneous adipose tissue compartments -association with metabolic risk factors in the Framingham Heart Study. *Circulation,* 116(1)**,** 39-48. Available: DOI 10.1161/circulationaha.106.675355.

Francucci, C. M., Pantaleo, D., Iori, N., Camilletti, A., Massi, F. & Boscaro, M. 2005. Effects of raloxifene on body fat distribution and lipid profile in healthy post-menopausal women. *Journal of Endocrinological Investigation,* 28(7)**,** 623-631.

Fuchs, F. D., Gus, M., Moreira, L. B., Moraes, R. S., Wiehe, M., Pereira, G. M. & Fuchs, S. C. 2005. Anthropometric indices and the incidence of hypertension: a comparative analysis. *Obesity Research,* 13(9)**,** 1515-1517. Available: DOI 10.1038/oby.2005.184.

650 Gallagher, D., Heymsfield, S. B., Heo, M., Jebb, S. A., Murgatroyd, P. R. & Sakamoto, Y.
651 2000. Healthy percentage body fat ranges: an approach for developing guidelines
652 based on body mass index. *American Journal of Clinical Nutrition,* 72(3)**,** 694-701.
653 Glickman, S. G., Marn, C. S., Supiano, M. A. & Dengel, D. R. 2004. Validity and reliability
654 of dual-energy X-ray absorptiometry for the assessment of abdominal adiposity.
655 *Journal of Applied Physiology,* 97(2)**,** 509-514. Available: DOI
656 10.1152/japplphysiol.01234.2003.
657 Gomez-Ambrosi, J., Silva, C., Galofre, J. C., Escalada, J., Santos, S., Gil, M. J., Valenti, V.,
658 Rotellar, F., Ramirez, B., Salvador, J. & Fruhbeck, G. 2011. Body adiposity and type
659 2 diabetes: increased risk with a high body fat percentage even having a normal BMI.
660 *Obesity,* 19(7)**,** 1439-1444. Available: DOI 10.1038/oby.2011.36.
661 Gomez-Ambrosi, J., Silva, C., Galofre, J. C., Escalada, J., Santos, S., Millan, D., Vila, N.,
662 Ibanez, P., Gil, M. J., Valenti, V., Rotellar, F., Ramirez, B., Salvador, J. & Fruhbeck,
663 G. 2012. Body mass index classification misses subjects with increased
664 cardiometabolic risk factors related to elevated adiposity. *International Journal of*
665 *Obesity,* 36(2)**,** 286-294. Available: DOI 10.1038/ijo.2011.100.
666 Gregor, M. F. & Hotamisligil, G. S. 2011. Inflammatory mechanisms in obesity. *In:* Paul, W.
667 E., Littman, D. R. & Yokoyama, W. M. (eds.) *Annual Review of Immunology, Vol 29.*
668 Available: DOI 10.1146/annurev-immunol-031210-101322.
669 Guilherme, A., Virbasius, J. V., Puri, V. & Czech, M. P. 2008. Adipocyte dysfunctions
670 linking obesity to insulin resistance and type 2 diabetes. *Nature Reviews Molecular*
671 *Cell Biology,* 9(5)**,** 367-377. Available: DOI 10.1038/nrm2391.
672 Guo, F. & Garvey, W. T. 2016. Cardiometabolic disease risk in metabolically healthy and
673 unhealthy obesity: stability of metabolic health status in adults. *Obesity,* 24(2)**,** 516-
674 525. Available: DOI 10.1002/oby.21344.
675 Hamer, M., Bell, J. A., Sabia, S., Batty, G. D. & Kivimaeki, M. 2015. Stability of
676 metabolically healthy obesity over 8 years: the English longitudinal study of ageing.
677 *European Journal of Endocrinology,* 173(5)**,** 703-708. Available: DOI 10.1530/eje-
678 15-0449.
679 Hsieh, S. D., Ashwell, M., Muto, T., Tsuji, H., Arase, Y. & Murase, T. 2010. Urgency of
680 reassessment of role of obesity indices for metabolic risks. *Metabolism-Clinical and*
681 *Experimental,* 59(6)**,** 834-840. Available: DOI 10.1016/j.metabol.2009.09.032.

Hsieh, S. D. & Yoshinaga, H. 1999. Do people with similar waist circumference share similar health risks irrespective of height? *Tohoku Journal of Experimental Medicine,* 188(1)**,** 55-60. Available: DOI 10.1620/tjem.188.55.

Huxley, R., Mendis, S., Zheleznyakov, E., Reddy, S. & Chan, J. 2010. Body mass index, waist circumference and waist: hip ratio as predictors of cardiovascular risk-a review of the literature. *European Journal of Clinical Nutrition,* 64(1)**,** 16-22. Available: DOI 10.1038/ejcn.2009.68.

Jean, N., Somers, V. K., Sochor, O., Medina-Inojosa, J., Llano, E. M. & Lopez-Jimenez, F. 2014. Normal-weight obesity: implications for cardiovascular health. *Current Atherosclerosis Reports,* 16(12). Available: DOI 10.1007/s11883-014-0464-7.

Jensen, M. D. 2008. Role of body fat distribution and the metabolic complications of obesity. *Journal of Clinical Endocrinology & Metabolism,* 93(11)**,** S57-S63. Available: DOI 10.1210/jc.2008-1585.

Juge-Aubry, C. E., Somm, E., Pernin, A., Alizadeh, N., Giusti, V., Dayer, J. M. & Meier, C. A. 2005. Adipose tissue is a regulated source of interleukin-10. *Cytokine,* 29(6)**,** 270-274. Available: DOI 10.1016/j.cyto.2004.10.017.

Jung, U. J. & Choi, M. S. 2014. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. *International Journal of Molecular Sciences,* 15(4)**,** 6184-6223. Available: DOI 10.3390/ijms15046184.

Kahn, S. E., Hull, R. L. & Utzschneider, K. M. 2006. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature,* 444(7121)**,** 840-846. Available: DOI 10.1038/nature05482.

Karelis, A. D., St-Pierre, D. H., Conus, F., Rabasa-Lhoret, R. & Poehlman, E. T. 2004. Metabolic and body composition factors in subgroups of obesity: What do we know? *Journal of Clinical Endocrinology & Metabolism,* 89(6)**,** 2569-2575. Available: DOI 10.1210/jc.2004-0165.

Katsareli, E. A. & Dedoussis, G. V. 2014. Biomarkers in the field of obesity and its related comorbidities. *Expert Opinion on Therapeutic Targets,* 18(4)**,** 385-401. Available: DOI 10.1517/14728222.2014.882321.

Kearns, K., Dee, A., Fitzgerald, A. P., Doherty, E. & Perry, I. J. 2014. Chronic disease burden associated with overweight and obesity in Ireland: the effects of a small BMI reduction at population level. *Bmc Public Health,* 14. Available: DOI 10.1186/1471-2458-14-143.

716 Khaodhiar, L. & Blackburn, G. L. 2001. Obesity assessment. *American Heart Journal,* 142**,**
717 1095-1101.
718 Kim, H. J., Higashimori, T., Park, S. Y., Choi, H., Dong, J. Y., Kim, Y. J., Noh, H. L., Cho,
719 Y. R., Cline, G., Kim, Y. B. & Kim, J. K. 2004. Differential effects of interleukin-6
720 and-10 on skeletal muscle and liver insulin action in vivo. *Diabetes,* 53(4)**,** 1060-
721 1067. Available: DOI 10.2337/diabetes.53.4.1060.
722 Kim, J. Y., Han, S. H. & Yang, B. M. 2013. Implication of high-body-fat percentage on
723 cardiometabolic risk in middle-aged, healthy, normal-weight adults. *Obesity,* 21(8)**,**
724 1571-1577. Available: DOI 10.1002/oby.20020.
725 Kloeting, N., Fasshauer, M., Dietrich, A., Kovacs, P., Schoen, M. R., Kern, M., Stumvoll, M.
726 & Blueher, M. 2010. Insulin-sensitive obesity. *American Journal of Physiology-*
727 *Endocrinology and Metabolism,* 299(3)**,** E506-E515. Available: DOI
728 10.1152/ajpendo.00586.2009.
729 Klop, B., Elte, J. W. F. & Cabezas, M. C. 2013. Dyslipidemia in obesity: mechanisms and
730 potential targets. *Nutrients,* 5(4)**,** 1218-1240.
731 Kosmala, W., Jedrzejuk, D., Derzhko, R., Przewlocka-Kosmala, M., Mysiak, A. & Bednarek-
732 Tupikowska, G. 2012. Left ventricular function impairment in patients with normal-
733 weight obesity contribution of abdominal fat deposition, profibrotic state, reduced
734 insulin sensitivity, and proinflammatory activation. *Circulation-Cardiovascular*
735 *Imaging,* 5(3)**,** 349-356. Available: DOI 10.1161/circimaging.111.969956.
736 Kuk, J. L., Saunders, T. J., Davidson, L. E. & Ross, R. 2009. Age-related changes in total and
737 regional fat distribution. *Ageing Research Reviews,* 8(4)**,** 339-348. Available: DOI
738 10.1016/j.arr.2009.06.001.
739 Laforest, S., Labrecque, J., Michaud, A., Cianflone, K. & Tchernof, A. 2015. Adipocyte size
740 as a determinant of metabolic disease and adipose tissue dysfunction. *Critical Reviews*
741 *in Clinical Laboratory Sciences,* 52(6)**,** 301-13. Available: DOI
742 10.3109/10408363.2015.1041582.
743 Lal, A., Moodie, M., Ashton, T., Siahpush, M. & Swinburn, B. 2012. Health care and lost
744 productivity costs of overweight and obesity in New Zealand. *Australian and New*
745 *Zealand Journal of Public Health,* 36(6)**,** 550-556. Available: DOI 10.1111/j.1753-
746 6405.2012.00931.x.
747 Landsberg, L., Aronne, L. J., Beilin, L. J., Burke, V., Igel, L. I., Lloyd-Jones, D. & Sowers, J.
748 2013. Obesity-related hypertension: pathogenesis, cardiovascular risk, and treatment a

749 position paper of the obesity society and the american society of hypertension.
750 *Journal of Clinical Hypertension,* 15(1)**,** 14-33. Available: DOI 10.1111/jch.12049.
751 Lean, M. E. J. 2000. Pathophysiology of obesity. *Proceedings of the Nutrition Society,* 59(3)**,**
752 331-336. Available: DOI 10.1017/s0029665100000379.
753 Lear, S. A., Humphries, K. H., Kohli, S., Chockalingam, A., Frohlich, J. J. & Birmingham, C.
754 L. 2007. Visceral adipose tissue accumulation differs according to ethnic background:
755 results of the Multicultural Community Health Assessment Trial (M-CHAT).
756 *American Journal of Clinical Nutrition,* 86(2)**,** 353-359.
757 Lee, C. M. Y., Huxley, R. R., Wildman, R. P. & Woodward, M. 2008. Indices of abdominal
758 obesity are better discriminators of cardiovascular risk factors than BMI: a meta-
759 analysis. *Journal of Clinical Epidemiology,* 61(7)**,** 646-653. Available: DOI
760 10.1016/j.jclinepi.2007.08.012.
761 Lesser, I. A., Gasevic, D. & Lear, S. A. 2013. The effect of body fat distribution on ethnic
762 differences in cardiometabolic risk factors of Chinese and Europeans. *Applied*
763 *Physiology Nutrition and Metabolism,* 38(7)**,** 701-706. Available: DOI 10.1139/apnm-
764 2012-0125.
765 Lim, S. & Meigs, J. B. 2013. Ectopic fat and cardiometabolic and vascular risk. *International*
766 *Journal of Cardiology,* 169(3)**,** 166-176. Available: DOI
767 10.1016/j.ijcard.2013.08.077.
768 Lonn, M., Mehlig, K., Bengtsson, C. & Lissner, L. 2010. Adipocyte size predicts incidence of
769 type 2 diabetes in women. *Faseb Journal,* 24(1)**,** 326-331. Available: DOI
770 10.1096/fj.09-133058.
771 Lopes, H. F., Martin, K. L., Nashar, K., Morrow, J. D., Goodfriend, T. L. & Egan, B. M.
772 2003. DASH diet lowers blood pressure and lipid-induced oxidative stress in obesity.
773 *Hypertension,* 41(3)**,** 422-430. Available: DOI 10.1161/01.hyp.0000053450.19998.11.
774 Lowry, D. W. & Tomiyama, A. J. 2015. Air displacement plethysmography versus dual-
775 energy X-ray absorptiometry in underweight, normal-weight, and overweight/obese
776 individuals. *Plos One,* 10(1). Available: DOI 10.1371/journal.pone.0115086.
777 Lumeng, C. N., Bodzin, J. L. & Saltiel, A. R. 2007. Obesity induces a phenotypic switch in
778 adipose tissue macrophage polarization. *The Journal of Clinical Investigation,* 117(1)**,**
779 175-184.
780 Maachi, M., Pieroni, L., Bruckert, E., Jardel, C., Fellahi, S., Hainque, B., Capeau, J. &
781 Bastard, J. P. 2004. Systemic low-grade inflammation is related to both circulating

and adipose tissue TNF alpha, leptin and IL-6 levels in obese women. *International Journal of Obesity,* 28(8)**,** 993-997. Available: DOI 10.1038/sj.ijo.0802718.

Manigrasso, M. R., Ferroni, P., Santilli, F., Taraborelli, T., Guagnano, M. T., Michetti, N. & Davi, G. 2005. Association between circulating adiponectin and interleukin-10 levels in android obesity: Effects of weight loss. *Journal of Clinical Endocrinology & Metabolism,* 90(10)**,** 5876-5879. Available: DOI 10.1210/jc.2005-0281.

Manolopoulos, K. N., Karpe, F. & Frayn, K. N. 2010. Gluteofemoral body fat as a determinant of metabolic health. *International Journal of Obesity,* 34(6)**,** 949-959. Available: DOI 10.1038/ijo.2009.286.

Marques-Vidal, P., Chiolero, A. & Paccaud, F. 2008a. Large differences in the prevalence of normal weight obesity using various cut-offs for excess body fat. *e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism,* 3(4)**,** e159-e162.

Marques-Vidal, P., Pecoud, A., Hayoz, D., Paccaud, F., Mooser, V., Waeber, G. & Vollenweider, P. 2008b. Prevalence of normal weight obesity in Switzerland: effect of various definitions. *European Journal of Nutrition,* 47(5)**,** 251-257. Available: DOI 10.1007/s00394-008-0719-6.

Marques-Vidal, P., Pecoud, A., Hayoz, D., Paccaud, F., Mooser, V., Waeber, G. & Vollenweider, P. 2010. Normal weight obesity: relationship with lipids, glycaemic status, liver enzymes and inflammation. *Nutrition Metabolism and Cardiovascular Diseases,* 20(9)**,** 669-675. Available: DOI 10.1016/j.numecd.2009.06.001.

Mathieu, P., Boulanger, M.-C. & Despres, J.-P. 2014. Ectopic visceral fat: A clinical and molecular perspective on the cardiometabolic risk. *Reviews in Endocrine & Metabolic Disorders,* 15(4)**,** 289-298. Available: DOI 10.1007/s11154-014-9299-3.

McArdle, M. A., Finucane, O. M., Connaughton, R. M., McMorrow, A. M. & Roche, H. M. 2013. Mechanisms of obesity-induced inflammation and insulin resistance: insights into the emerging role of nutritional strategies. *Frontiers in Endocrinology,* 4**,** 52-52. Available: DOI 10.3389/fendo.2013.00052.

Ministry of Health. 1999. *Taking the pulse- the 1996-97 New Zealand health survey*. Wellington: Ministry of Health. Retrieved from http://www.moh.govt.nz/notebook/nbbooks.nsf/0/b5deda9a12dace3b4c25677d00720599/$FILE/ttp1.pdf

Ministry of Health. 2002. *Reducing inequalities in health*. Wellington: New Zealand: Ministry of Health. Retrieved from http://www.health.govt.nz/system/files/documents/publications/reducineqal.pdf

Ministry of Health. 2015. *Annual update of key results 2014/15, New Zealand health survey*. Wellington: Ministry of Health. Retrieved from http://www.health.govt.nz/system/files/documents/publications/annual-update-key-results-2014-15-nzhs-dec15-1.pdf

Ministry of Health. 2016. *Annual Update of Key Results 2015/16: New Zealand health survey*. Wellington: Ministry of Health. Retrieved from http://www.health.govt.nz/publication/annual-update-key-results-2015-16-new-zealand-health-survey

Mooney, S. J., Baecker, A. & Rundle, A. G. 2013. Comparison of anthropometric and body composition measures as predictors of components of the metabolic syndrome in a clinical setting. *Obesity Research & Clinical Practice,* 7(1)**,** E55-E66. Available: DOI 10.1016/j.orcp.2012.10.004.

Ng, M., Fleming, T. & Robinson, M. 2014. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013 (vol 384, pg 766, 2014). *Lancet,* 384(9945)**,** 746-746.

Nguyen, M. T. A., Favelyukis, S., Nguyen, A.-K., Reichart, D., Scott, P. A., Jenn, A., Liu-Bryan, R., Glass, C. K., Neels, J. G. & Olefsky, J. M. 2007. A subpopulation of macrophages infiltrates hypertrophic adipose tissue and is activated by free fatty acids via toll-like receptors 2 and 4 and JNK-dependent pathways. *Journal of Biological Chemistry,* 282(48)**,** 35279-35292. Available: DOI 10.1074/jbc.M706762200.

Ogden, C. L., Yanovski, S. Z., Carroll, M. D. & Flegal, K. M. 2007. The epidemiology of obesity. *Gastroenterology,* 132(6)**,** 2087-2102. Available: DOI 10.1053/j.gastro.2007.03.052.

Okorodudu, D. O., Jumean, M. F., Montori, V. M., Romero-Corral, A., Somers, V. K., Erwin, P. J. & Lopez-Jimenez, F. 2010. Diagnostic performance of body mass index to identify obesity as defined by body adiposity: a systematic review and meta-analysis. *International Journal of Obesity,* 34(5)**,** 791-799. Available: DOI 10.1038/ijo.2010.5.

Oliveros, E., Somers, V. K., Sochor, O., Goel, K. & Lopez-Jimenez, F. 2014. The concept of normal weight obesity. *Progress in Cardiovascular Diseases,* 56(4)**,** 426-433. Available: DOI 10.1016/j.pcad.2013.10.003.

Packard, C., Caslake, M. & Shepherd, J. 2000. The role of small, dense low density lipoprotein (LDL): a new look. *International Journal of Cardiology,* 74**,** S17-S22. Available: DOI 10.1016/s0167-5273(99)00107-2.

Pan, H. T., Guo, J. & Su, Z. Q. 2014. Advances in understanding the interrelations between leptin resistance and obesity. *Physiology & Behavior,* 130**,** 157-169. Available: DOI 10.1016/j.physbeh.2014.04.003.

Panagiotakos, D. B., Pitsavos, C., Yannakoulia, M., Chrysohoou, C. & Stefanadis, C. 2005. The implication of obesity and central fat on markers of chronic inflammation: The ATTICA study. *Atherosclerosis,* 183(2)**,** 308-315. Available: DOI 10.1016/j.atherosclerosis.2005.03.010.

Pannacciulli, N., Cantatore, F. P., Minenna, A., Bellacicco, M., Giorgino, R. & De Pergola, G. 2001. C-reactive protein is independently associated with total body fat, central fat, and insulin resistance in adult women. *International Journal of Obesity,* 25(10)**,** 1416-1420. Available: DOI 10.1038/sj.ijo.0801719.

Park, H.-K. & Ahima, R. S. 2015. Physiology of leptin: energy homeostasis, neuroendocrine function and metabolism. *Metabolism-Clinical and Experimental,* 64(1)**,** 24-34. Available: DOI 10.1016/j.metabol.2014.08.004.

Patel, P. & Abate, N. 2013. Body fat distribution and insulin resistance. *Nutrients,* 5(6)**,** 2019-2027. Available: DOI 10.3390/nu5062019.

Patel, P. S., Buras, E. D. & Balasubramanyam, A. 2013. The role of the immune system in obesity and insulin resistance. *Journal of obesity,* 2013. Available: DOI 10.1155/2013/616193.

Perez de Heredia, F., Gomez-Martinez, S. & Marcos, A. 2012. Obesity, inflammation and the immune system. *Proceedings of the Nutrition Society,* 71(2)**,** 332-338. Available: DOI 10.1017/s0029665112000092.

Petelin, A., Bizjak, M., Cernelic-Bizjak, M., Jurdana, M., Jakus, T. & Jenko-Praznikar, Z. 2014. Low-grade inflammation in overweight and obese adults is affected by weight loss program. *Journal of Endocrinological Investigation,* 37(8)**,** 745-755. Available: DOI 10.1007/s40618-014-0102-9.

Popkin, B. M., Adair, L. S. & Ng, S. W. 2012. Global nutrition transition and the pandemic of obesity in developing countries. *Nutrition Reviews,* 70(1)**,** 3-21. Available: DOI 10.1111/j.1753-4887.2011.00456.x.

Pou, K. M., Massaro, J. M., Hoffmann, U., Lieb, K., Vasan, R. S., O'Donnell, C. J. & Fox, C. S. 2009. Patterns of abdominal fat distribution: the framingham heart s. *Diabetes Care,* 32(3)**,** 481-485. Available: DOI 10.2337/dc08-1359.

Pradhan, A. D., Cook, N. R., Buring, J. E., Manson, J. E. & Ridker, P. M. 2003. C-reactive protein is independently associated with fasting insulin in nondiabetic women. *Arteriosclerosis Thrombosis and Vascular Biology,* 23(4)**,** 650-655. Available: DOI 10.1161/01.atv.0000065636.15310.9c.

Roberson, L. L., Aneni, E. C., Maziak, W., Agatston, A., Feldman, T., Rouseff, M., Tran, T., Blaha, M. J., Santos, R. D., Sposito, A., Al-Mallah, M. H., Blankstein, R., Budoff, M. J. & Nasir, K. 2014. Beyond BMI: The "Metabolically healthy obese" phenotype & its association with clinical/subclinical cardiovascular disease and all-cause mortality - a systematic review. *BMC Public Health,* 14. Available: DOI 10.1186/1471-2458-14-14.

Romero-Corral, A., Somers, V. K., Sierra-Johnson, J., Korenfeld, Y., Boarin, S., Korinek, J., Jensen, M. D., Parati, G. & Lopez-Jimenez, F. 2010. Normal weight obesity: a risk factor for cardiometabolic dysregulation and cardiovascular mortality. *European Heart Journal,* 31(6)**,** 737-746. Available: DOI 10.1093/eurheartj/ehp487.

Romero-Corral, A., Somers, V. K., Sierra-Johnson, J., Thomas, R. J., Collazo-Clavell, M. L., Korinek, J., Allison, T. G., Batsis, J. A., Sert-Kuniyoshi, F. H. & Lopez-Jimenez, F. 2008. Accuracy of body mass index in diagnosing obesity in the adult general population. *International Journal of Obesity,* 32(6)**,** 959-966. Available: DOI 10.1038/ijo.2008.11.

Roth, J., Qiang, X. L., Marban, S. L., Redelt, H. & Lowell, B. C. 2004. The obesity pandemic: Where have we been and where are we going? *Obesity Research,* 12**,** 88S-101S. Available: DOI 10.1038/oby.2004.273.

Rothman, K. J. 2008. BMI-related errors in the measurement of obesity. *International Journal of Obesity,* 32**,** S56-S59. Available: DOI 10.1038/ijo.2008.87.

Rush, E. C., Freitas, I. & Plank, L. D. 2009. Body size, body composition and fat distribution: comparative analysis of European, Māori, Pacific Island and Asian Indian adults. *British Journal of Nutrition,* 102(4)**,** 632-641. Available: DOI 10.1017/s0007114508207221.

Rush, E. C., Goedecke, J. H., Jennings, C., Micklesfield, L., Dugas, L., Lambert, E. V. & Plank, L. D. 2007. BMI, fat and muscle differences in urban women of five ethnicities

913 from two countries. *International Journal of Obesity,* 31(8)**,** 1232-1239. Available:
914 DOI 10.1038/sj.ijo.0803576.
915 Sahakyan, K. R., Somers, V. K., Rodriguez-Escudero, J. P., Hodge, D. O., Carter, R. E.,
916 Sochor, O., Coutinho, T., Jensen, M. D., Roger, V. L., Singh, P. & Lopez-Jimenez, F.
917 2015. Normal-weight central obesity: implications for total and cardiovascular
918 mortality. *Annals of Internal Medicine,* 163(11). Available: DOI 10.7326/m14-2525.
919 Sarafidis, P. A. & Bakris, G. L. 2007. Non-esterified fatty acids and blood pressure elevation:
920 a mechanism for hypertension in subjects with obesity/insulin resistance? *Journal of*
921 *Human Hypertension,* 21(1)**,** 12-19. Available: DOI 10.1038/sj.jhh.1002103.
922 Shah, P., Vella, A., Basu, A., Basu, R., Adkins, A., Schwenk, W. F., Johnson, C. M., Nair, K.
923 S., Jensen, M. D. & Rizza, R. A. 2003. Elevated free fatty acids impair glucose
924 metabolism in women - decreased stimulation of muscle glucose uptake and
925 suppression of splanchnic glucose production during combined hyperinsulinemia and
926 hyperglycemia. *Diabetes,* 52(1)**,** 38-42. Available: DOI 10.2337/diabetes.52.1.38.
927 Shaul, M. E., Bennett, G., Strissel, K. J., Greenberg, A. S. & Obin, M. S. 2010. Dynamic,
928 M2-like remodeling phenotypes of CD11c+adipose tissue macrophages during high-
929 fat diet-induced obesity in mice. *Diabetes,* 59(5)**,** 1171-1181. Available: DOI
930 10.2337/db09-1402.
931 Shay, C. M., Carnethon, M. R., Church, T. R., Hankinson, A. L., Chan, C. L., Jacobs, D. R.,
932 Lewis, C. E., Schreiner, P. J., Sternfeld, B. & Sidney, S. 2011. Lower extremity fat
933 sass is associated with insulin resistance in overweight and obese individuals: the
934 CARDIA study. *Obesity,* 19(11)**,** 2248-2253. Available: DOI 10.1038/oby.2011.113.
935 Shea, J. L., King, M. T. C., Yi, Y., Gulliver, W. & Sun, G. 2012. Body fat percentage is
936 associated with cardiometabolic dysregulation in BMI-defined normal weight
937 subjects. *Nutrition Metabolism and Cardiovascular Diseases,* 22(9)**,** 741-747.
938 Available: DOI 10.1016/j.numecd.2010.11.009.
939 Shi, H., Kokoeva, M. V., Inouye, K., Tzameli, I., Yin, H. & Flier, J. S. 2006. TLR4 links
940 innate immunity and fatty acid-induced insulin resistance. *Journal of Clinical*
941 *Investigation,* 116(11)**,** 3015-3025. Available: DOI 10.1172/jci28898.
942 Shin, M. J., Kim, O. Y., Koh, S. J., Chae, J. S., Kim, J. Y., Jang, Y. & Lee, J. H. 2006.
943 Modest weight loss does not increase plasma adiponectin levels: effects of weight loss
944 on C-reactive protein and DNA damage. *Nutrition Research,* 26(8)**,** 391-396.
945 Available: DOI 10.1016/j.nutres.2006.06.021.

946 Simmons, D., Thompson, C. F. & Volklander, D. 2001. Polynesians: prone to obesity and
947 Type 2 diabetes mellitus but not hyperinsulinaemia. *Diabetic Medicine,* 18(3)**,** 193-
948 198. Available: DOI 10.1046/j.1464-5491.2001.00435.x.
949 Smith, S. R., Lovejoy, J. C., Greenway, F., Ryan, D., deJonge, L., de la Bretonne, J.,
950 Volafova, J. & Bray, G. A. 2001. Contributions of total body fat, abdominal
951 subcutaneous adipose tissue compartments, and visceral adipose tissue to the
952 metabolic complications of obesity. *Metabolism-Clinical and Experimental,* 50(4)**,**
953 425-435. Available: DOI 10.1053/meta.2001.21693.
954 Spalding, K. L., Arner, E., Westermark, P. O., Bernard, S., Buchholz, B. A., Bergmann, O.,
955 Blomqvist, L., Hoffstedt, J., Naslund, E., Britton, T., Concha, H., Hassan, M., Ryden,
956 M., Frisen, J. & Arner, P. 2008. Dynamics of fat cell turnover in humans. *Nature,*
957 453(7196)**,** 783-787. Available: DOI 10.1038/nature06902.
958 Spiegelman, B. M. & Flier, J. S. 2001. Obesity and the regulation of energy balance. *Cell,*
959 104(4)**,** 531-543.
960 Statistics New Zealand 2015. 2013 census - major ethnic groups in New Zealand.
961 Stojiljkovic, M. P., Zhang, D. A., Lopes, H. F., Lee, C. G., Goodfriend, T. L. & Egan, B. M.
962 2001. Hemodynamic effects of lipids in humans. *American Journal of Physiology-*
963 *Regulatory Integrative and Comparative Physiology,* 280(6)**,** R1674-R1679.
964 Stunkard, A. J., Harris, J. R., Pedersen, N. L. & McClearn, G. E. 1990. The body mass index
965 of twins who have been reared apart. *New England Journal of Medicine,* 322(21)**,**
966 1483-1487. Available: DOI 10.1056/nejm199005243222102.
967 Suganami, T., Nishida, J. & Ogawa, Y. 2005. A paracrine loop between adipocytes and
968 macrophages aggravates inflammatory changes - Role of free fatty acids and tumor
969 necrosis factor alpha. *Arteriosclerosis Thrombosis and Vascular Biology,* 25(10)**,**
970 2062-2068. Available: DOI 10.1161/01.atv.0000183883.72263.13.
971 Swinburn, B. A., Ley, S. J., Carmichael, H. E. & Planck, L. D. 1999. Body size and
972 composition in Polynesians. *International Journal of Obesity,* 23(11)**,** 1178-1183.
973 Available: DOI 10.1038/sj.ijo.0801053.
974 Taylor, R. W., Brooking, L., Williams, S. M., Manning, P. J., Sutherland, W. H., Coppell, K.
975 J., Tipene-Leach, D., Dale, K. S., McAuley, K. A. & Mann, J. I. 2010. Body mass
976 index and waist circumference cutoffs to define obesity in indigenous New
977 Zealanders. *American Journal of Clinical Nutrition,* 92(2)**,** 390-397. Available: DOI
978 10.3945/ajcn.2010.29317.

Tobias, M., Blakely, T., Matheson, D., Rasanathan, K. & Atkinson, J. 2009. Changing trends in indigenous inequalities in mortality: lessons from New Zealand. *International Journal of Epidemiology,* 38(6)**,** 1711-1722. Available: DOI 10.1093/ije/dyp156.

Van Gaal, L. F. 2010. Mechanisms linking obesity with cardiovascular disease. *Diabetes Obesity & Metabolism,* 12**,** 21-21.

Velho, S., Paccaud, F., Waeber, G., Vollenweider, P. & Marques-Vidal, P. 2010. Metabolically healthy obesity: different prevalences using different criteria. *European Journal of Clinical Nutrition,* 64(10)**,** 1043-1051. Available: DOI 10.1038/ejcn.2010.114.

von Eyben, F. E., Mouritsen, E., Holm, J., Montvilas, P., Dimcevski, G., Suciu, G., Helleberg, I., Kristensen, L. & von Eyben, R. 2003. Intra-abdominal obesity and metabolic risk factors: a study of young adults. *International Journal of Obesity,* 27(8)**,** 941-949. Available: DOI 10.1038/sj.ijo.0802309.

Walley, A. J., Blakemore, A. I. F. & Froguel, P. 2006. Genetics of obesity and the prediction of risk for health. *Human Molecular Genetics,* 15**,** R124-R130. Available: DOI 10.1093/hmg/ddl215.

Weisberg, S. P., McCann, D., Desai, M., Rosenbaum, M., Leibel, R. L. & Ferrante, A. W. 2003. Obesity is associated with macrophage accumulation in adipose tissue. *Journal of Clinical Investigation,* 112(12)**,** 1796-1808. Available: DOI 10.1172/jci200319246.

Weyer, C., Foley, J. E., Bogardus, C., Tataranni, P. A. & Pratley, R. E. 2000. Enlarged subcutaneous abdominal adipocyte size, but not obesity itself, predicts Type II diabetes independent of insulin resistance. *Diabetologia,* 43(12)**,** 1498-1506. Available: DOI 10.1007/s001250051560.

Wingfield, H. L., Smith-Ryan, A. E., Woessner, M. N., Melvin, M. N., Fultz, S. N. & Graff, R. M. 2014. Body composition assessment in overweight women: validation of air displacement plethysmography. *Clinical Physiology and Functional Imaging,* 34(1)**,** 72-76.

Wood, I. S., de Heredia, F. P., Wang, B. H. & Trayhurn, P. 2009. Cellular hypoxia and adipose tissue dysfunction in obesity. *Proceedings of the Nutrition Society,* 68(4)**,** 370-377. Available: DOI 10.1017/s0029665109990206.

World Health Organisation. 2000. *Obesity: preventing and managing the global epidemic. WHO technical report series No. 894* (0512-3054). Geneva: World Health Organisation. Retrieved from http://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/

World Health Organization. 2011. *Non-communicable diseases in the South East Asia region*. Geneva: World Health Organisation. Retrieved from http://www.searo.who.int/nepal/mediacentre/2011_non_communicable_diseases_in_the_south_east_asia_region.pdf

World Health Organization. 2014. *Obesity and overweight (fact sheet)*. Geneva: World Health Organisation. Retrieved from http://www.who.int/mediacentre/factsheets/fs311/en/

World Health Organization Regional Office for Europe. 2008. *Data and statistics. The challenge of obesity - quick statistics*. Geneva: World Health Organisation. Retrieved from http://www.euro.who.int/en/health-topics/noncommunicable-diseases/obesity/data-and-statistics

Xu, H., Barnes, G. T., Yang, Q., Tan, G., Yang, D., Chou, C. J., Sole, J., Nichols, A., Ross, J. S. & Tartaglia, L. A. 2003. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *The Journal of Clinical Investigation,* 112(12)**,** 1821-1830.

Ye, J. 2009. Emerging role of adipose tissue hypoxia in obesity and insulin resistance. *International Journal of Obesity,* 33(1)**,** 54-66. Available: DOI 10.1038/ijo.2008.229.

Ye, J. P. & Keller, J. N. 2010. Regulation of energy metabolism by inflammation: A feedback response in obesity and calorie restriction. *Aging (Albany NY),* 2(6)**,** 361-368.

Zeljkovic, A., Spasojevic-Kalimanovska, V., Vekic, J., Jelic-Ivanovic, Z., Topic, A., Bogavac-Stanojevic, N., Spasic, S., Vujovic, A. & Kalimanovska-Ostric, D. 2008. Does simultaneous determination of LDL and HDL particle size improve prediction of coronary artery disease risk? *Clinical and Experimental Medicine,* 8(2)**,** 109-116. Available: DOI 10.1007/s10238-008-0165-z.

Zeyda, M., Farmer, D., Todoric, J., Aszmann, O., Speiser, M., Gyori, G., Zlabinger, G. J. & Stulnig, T. M. 2007. Human adipose tissue macrophages are of an anti-inflammatory phenotype but capable of excessive pro-inflammatory mediator production. *International Journal of Obesity,* 31(9)**,** 1420-1428. Available: DOI 10.1038/sj.ijo.0803632.

Table 2.1 A summary of cross sectional studies investigating inflammatory markers and body composition

Author	Year	n	Gender	Ethnicity	Inflammatory markers assessed	Body Composition Measures	Outcomes
Forouhi et al. (2001)	Engl and	113	Both	South Asian, European	CRP	WC, BMI, BF%, visceral fat	Significant association between body fat measures and CRP. For South Asian the association was stronger for WC and visceral fat, while for Europeans it was stronger for BF% and BMI.
Pannaciulli et al. (2001) (Italy)	Italy	201	Women	European	CRP	BMI, WC, Fat Mass, Fat free Mass	CRP was correlated with all body composition measures. WC and total body fat mass maintained their relationship with CRP after multivariate analysis.
Bullo et al. (Spain)	2003	91	Women	Spanish	Serum CRP, Leptin, IL-6, Subcutaneous adipose tissue TNF-α and leptin mRNA	BMI, BF%, WC	BMI and CRP positively associated. Adipose TNF-α was higher in higher CRP tertiles. BMI was a significant predictor for CRP levels.
Festa et al. (USA)	2001	1625	Both	Non-hispanic whites, African-Americans, Mexican-Americans	CRP	BMI, BF%, WC, WtHR, adipose body mass (kg)	After adjusting for IR, CRP was strongly related to waist for men, and to BMI, BF%, adipose tissue mass and WC in women.
Panagiotakos et al. (Greece)	2005	3042	Both	Greek	CRP, TNF-α, IL-6	BMI, WC, WTH	Obese (by BMI) had higher inflammatory markers than non-obese. Central fat distribution was associated with higher CRP, TNF-α and IL-6 compared to normal body fat distribution.
Bahceci et al. (Turkey)	2007	100	Both	European	CRP, TNF-α, IL-6	BMI, adipocyte cell size	CRP, TNF-α and IL-6 were significantly higher in obese compared to control. Higher inflammatory markers were seen with higher adipocyte size.

Abbreviations: BMI body mass index; BF% body fat %; CRP c-reactive protein; WC waist circumference; IR insulin resistance; kg kilograms; IL-6 interleukin 6; TNF-α tumor necrosis factor alpha; WtHR waist to height ratio; WHR waist to hip ratio

Table 2.2 Traditional and alternative body composition and metabolic profiles

Body Composition Profiles	BMI	Body Fat Status	Metabolic Profile
Traditional:			
Normal Weight	<25kg/m²	Assumed normal	Assumed normal
Overweight	25-≤30kg/m²	Assumed slightly high	Assumed slightly disrupted
Obese	≥30kg/m²	Assumed high	Assumed disrupted
Alternative Profiles			
Normal Weight Obesity	<25kg/m²	High	Disrupted
Metabolically Healthy Obese	≥30kg/m²	Assumed high	Normal

Abbreviations: BMI body mass index; kg kilograms; m metres

Table 2.3 Summary of studies investigating the normal BMI and high body fat % profile, and related body composition/metabolic outcomes.

Author	Country	Participant number (n)	Gender	Age	Ethnicity	BMI and BF% cut offs used	Body composition/metabolic outcome
Gomez- Ambrossi et al. (2012)	Spain	6123	Both	18-80	Caucasian	Overweight: BMI≥25, BF% ≥20% (Men) ≥30% (Women). Obesity: BMI ≥30, BF% ≥25% (Men) ≥35% (women)	29% lean and 80% overweight, were obese by BF%. Normal BMI, obese by BF% group had higher glucose, insulin, lipids, and CRP than normal BMI, normal BF%.
Gomez-Ambrossi et al. (2011)	Spain	4828	Both	18-80	Caucasian	Overweight: BMI≥25, BF% ≥20% (Men) ≥30% (Women). Obesity: BMI ≥30, BF% ≥25% (Men) ≥35% (women)	Higher BF% in women and men with normal BMI that had pre-diabetes and T2D.
Marques- Vidal et al. (2010) (Switzerland)	Switzerland	6125	Both	35-75	Caucasian	BMI≤ 25, BF 26% (men), 38% (women)	NWO: higher BP, LDL, TG than lean. Prevalence of dyslipidaemia, hyperglycaemia higher in NWO than lean.
Romero- Corral et al. (2010)	USA	6171	Both	>20	Non-Hispanic whites, Non-Hispanic blacks, Mexican American, other	BMI≤ 25, BF >23.1% (men), >33.3% (women)	Metabolic syndrome higher in NWO in both sexes. Higher prevalence of dyslipidaemia and hypertension, in men, and CVD in women with NWO compared to lean.
Marques- Vidal et al. (2008a) (Portugal)	Portugal	1523	Both	38± 17	Portuguese	BMI≤ 25, BF% ≥30%. Sex Specific BF% cut offs: 29.1% (men), 37.2% (women)	For women NWO increased with age; using sex specific cut offs resulted in lower NWO prevalence in women
Kosmala et al. (2011) (Poland)	Poland	168	Both	>20	Not available	BMI ≥18.5-<25 and BF% for men and women respectively: 20 to 39 years, >19% and >32%; 40 to 59 years, >21% and >33%; and 60 to 79 years, >24% and >35%	WC, WtHR, android and gynoid fat, AG ratio were higher in NWO compared to lean. Higher LDL, TG, lower HDL, higher insulin, HOMA-IR, and CRP in NWO compared to lean

Shea et al. (2012)	Canada	977	Both	20-79	Canadian	BMI ≥18.5-<25, and medium BF 15.3- 20.7% (men), 29.8-34.9% (women), and high BF >20.8% (men), <35.0% (women)	Increased BF% (medium and high) increases risk of cardio-metabolic abnormality (≥2 of high TG, glucose CRP, IR, hypertension, or decreased HDL) compared to normal BF%
Kim et al. (2013)	Korea	12386	Both	30-49	Korean	BMI ≥18.5-<25, and BF ≥25% (men), ≥30% (women)	Normal BMI & high BF% had higher prevalence of dyslipidaemia and hyperglycaemia compared to lower BF% group
De Lorenzo et al. (2007)	Italy	60	women	20-35	White Italian	BMI≤ 25, BF% ≥30%	NWO: higher inflammatory markers than non-obese (IL-1α, IL-1β, IL-6, IL-8, IL-10, TNF-α), no difference in CRP
Di Renzo et al. (2010)	Italy	60	Women	20-35	White Italian	BMI≤ 25, BF% ≥30%	NWO: BF% higher than lean, but not different to obese, and in a state of early inflammation & oxidative stress

Abbreviations: BMI body mass index; BF% body fat percent; T2D type II diabetes; NWO normal weight obesity; IL interleukin; TNF-α tumor necrosis factor alpha; CRP c-reactive protein; BP blood pressure; LDL low density lipoprotein; TG triglycerides; CVD cardiovascular disease; HDL high density lipoprotein; HOMA-IR homeostatic model assessment of insulin resistance; AG android/gynoid.

Table 2.4 Summary of ethnic comparisons of body composition measures with or without metabolic biomarkers

Author	Country	n	Gender	Age	Ethnicities	Study design	Measures assessed	Outcome
Swinburn et al. (1999)	New Zealand	615	Both	20-70	Polynesian- Māori + Samoan (374), NZ European (241)	Cross sectional	Height, weight, skinfold, BIA, DXA	Polynesians leaner than NZ Europeans at higher BMI. Suggest BMI 32kg/m² for obesity cut off.
Simmons et al. (2001)	New Zealand	464	Both	40-79	Māori (122), Pacific Island (179), NZ European (163)	Cross sectional	WC, BMI, fasting insulin, glucose, HOMA-IR, OGTT.	Obesity (≥31kg/m²) highest in Pacific, then Māori then NZ European. Pacific and Māori had higher risk of diabetes, but were not hyperinsulinaemic or insulin resistant after adjustment for obesity level.
Defay et al. (2006)	New Caledonia	392	Both	30-59	Europeans (57), Melanesians (287), Polynesians (48)	Cross sectional	BMI, WHR, fasting glucose and insulin, OGTT.	Polynesians had highest BMI, WHR, fasting glucose, IFG or IGT and lowest insulin secretory capacity. No ethnic differences in fasting insulin.
Lear et al. (2007)	Canada	822	Both	30-65	Aboriginal (195), European (201), Chinese (219), South Asian (207)	Cross sectional	BMI, total adipose tissues, VAT, SAT, total body fat mass	VAT was underestimated by BMI in all ethnic groups except European. Chinese and South Asians have more abdominal fat than NZ Europeans, particularly VAT
Rush et al. (2007)	New Zealand and South Africa	721	Women	18-60	South Africa (SA): European (94), Black (201); NZ: European (173), Māori (76), Pacific (84), Asian Indian (93)	Cross sectional	WC, body fat: total, central, peripheral, BMD, ASMM	At BMI 30 NZ European had highest body fat %, and decreased from Pacific to Māori to Asian Indian. Same pattern for SA European and black women. Central fat and muscle mass differences may explain some of this difference

Rush et al. (2009)	New Zealand	933	Both	17-80	European (124), Māori (109), Pacific (104), Asian Indian (117)	Cross sectional	Total and % body fat, leg length, abdominal fat, leg fat	For a given BF%, South Asian had a lower BMI, and Māori and Pacific had a higher BMI than European. Asian Indians had more fat and less LBM, bone mass than the other ethnicities. Asian & Pacific women had longer leg length.
Taylor et al. (2010)	New Zealand	1539	Both	≥17	Māori (47%), NZ European (53%	Cross sectional	Sensitivity and specificity of BMI, WC, WtHR to fasting insulin, glucose and lipids.	No evidence to support different ethnic cut offs for the measures for metabolic risk
Chiu et al. (2011)	Canada	59824	Both	≥30	White (57210), South Asian (1001), Chinese (866), Black (747)	Cohort	BMI and diabetes risk	South Asian, Chinese and Black at risk of diabetes at lower BMI, and younger age than white
Lesser et al. (2013)	Canada	418	Both	35-60	European (201), Chinese (217)	Cross sectional	BMI, WC, HC, total abdominal fat and VAT from CT, SAT. HDL, TC, TG, glucose, insulin, HOMA-IR	At the same BMI or WC, Chinese males had higher TG, insulin, HOMA, glucose and females had higher glucose than Europeans with VAT accounting for some but not all ethnic differences.

Abbreviations: BIA bioelectrical impedance analysis; DXA dual-energy x-ray absorptiometry; BMI body mass index; LBM lean body mass; WC waist circumference; HOMA-IR homeostatic model assessment of insulin resistance; OGTT oral glucose tolerance test; WHR waist to hip ratio; IFG impaired fasting glucose; IGT impaired glucose tolerance; VAT visceral adipose tissue; SAT subcutaneous adipose tissue; BMD bone mineral density; ASMM appendicular skeletal muscle mass; LBM lean body mass; WtHR waist to height ratio; TG triglycerides.

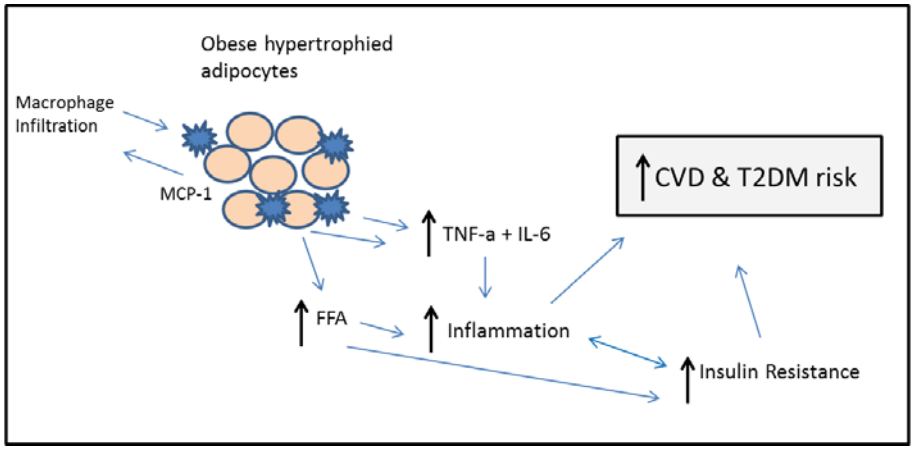


Figure 2.1 Obesity related disturbances in adipose tissue and how they relate to inflammation and insulin resistance**.** Adapted from: (McArdle et al. 2013)

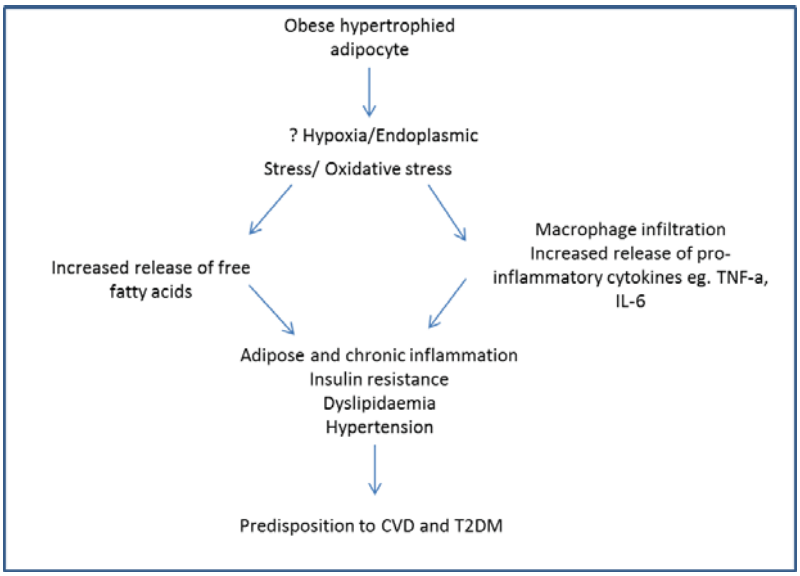


Figure 2.2 Flow chart depicting the potential links between obesity and metabolic disease. Adapted from: (Jung and Choi, 2014)

Chapter 3: Research Manuscript

Exploring the relationship between body composition and metabolic health amongst New Zealand European, Pacific Island and Māori women participating in the women's EXPLORE study.

Contributors:

Amanda Whitford: Data entry and analysis, statistical analysis, interpretation of results, author of the thesis

Rozanne Kruger: Main thesis supervisor, concept and research design, ethical application, execution of the study, recruitment, screening, interpretation of results, revision and approval of thesis, Principal investigator of the women's EXPLORE study.

Marilize Richter: Thesis co-supervisor, advisor for statistical analysis and interpretation of results, revision of thesis.

Bernhard Breier: Thesis co-supervisor, interpretation of results, revision of thesis.

This research took place at:

Massey University Human Nutrition Research Unit

84 Oteha Rohe, Albany

3.1 Abstract

Background: In New Zealand, 31.6% of adults are obese. Significant ethnic health inequalities exist; Pacific Islanders and Māori have the highest rates.

Objectives: To investigate the body composition and metabolic health profiles of healthy NZ European, Pacific and Māori women participating in the women's EXPLORE study.

Methods/Design: Cross sectional design investigating 233 European, 91 Pacific and 84 Māori women. Different body mass index (BMI) and body fat % (BF%) defined body composition profiles were analysed for anthropometric measurements, body fat location, and metabolic biomarkers.

Results: Obese (BF%) Māori women had higher android fat mass than obese (BF%) Europeans (2.53kg vs 2.23kg) with no difference in waist circumference. Non-obese (BMI) Māori had higher waist circumference than non-obese (BMI) NZ Europeans (78cm vs 73.5cm) with android fat differences. Regardless of body composition grouping, no ethnic differences were found for BF%. Obese Pacific women had higher HOMA-IR (5.12-5.45) and insulin (24.28- 23.28mU/L) than obese Europeans (2.10-2.61 and 10.07-11.24mU/L respectively), as did obese Māori (3.64-4.35 and 16.76-19.41mU/L respectively). Body composition measures with highest sensitivity across all biomarkers assessed were BF% ≥30 for Europeans, both BF% ≥30 and BMI ≥25 for Pacific, and BMI ≥25 for Māori.

Conclusion: Māori and Pacific women had significantly higher glucose metabolism markers than NZ Europeans despite no differences in BF%. When comparing Māori to NZ Europeans, a higher waist circumference was not always related to a higher android fat mass or vice versa, suggesting that WC may not be an accurate representation of abdominal fat for Māori. In spite of ethnic differences, BF% ≥30 and BMI ≥25 appear most sensitive to detect high biomarkers compared to abdominal measurements.

Key Words: obesity, insulin resistance, metabolic health, body mass index, body fat percentage

3.2 Introduction

Obesity and its related comorbidities are a major health problem in both developed and developing countries with worldwide prevalence estimated to be around 13 % in 2014. (Ng *et al.*, 2014; World Health Organization, 2014) Excess body fat is associated with increased risk of adverse metabolic health outcomes including insulin resistance (IR), type 2 diabetes (T2D), chronic inflammation, cardiovascular disease (CVD), (Ozenoglu *et al.*, 2010; Patel and Abate, 2013) and cancer. (Pischon *et al.*, 2008) These factors contribute to considerable reductions in quality of life, increased mortality, and a substantial economic burden. (Campfield and Smith, 1999; Lal *et al.*, 2012) In New Zealand, obesity rates have increased from 27% to 32% between 2006/2007 and 2015/2016, (Ministry of Health, 2016) mirroring the worldwide increasing trend. (Ng *et al.*, 2014) Māori and Pacific people make up a significant part of New Zealand's population and have adult obesity rates of 47.1% and 66.9% respectively compared to 29.5% in the NZ European (NZE)/other category, (Ministry of Health, 2016) highlighting the severity and the ethnic inequality of obesity in New Zealand.

Body mass index (BMI) is the widely used measure to define overweight and obesity. (Romero-Corral *et al.*, 2008; Gomez-Ambrosi *et al.*, 2012) This index is based on a formula using body weight and height to classify into categories with obesity defined as a BMI of >30kg/m^2. (World Health Organisation, 2000) While a high BMI often correlates with increased metabolic dysfunction, there are several limitations to this measure. (Huxley *et al.*, 2010; Ozenoglu *et al.*, 2010; Gomez-Ambrosi *et al.*, 2012) These include a lack of information regarding body fat percentage (BF%), lean body mass (LBM), and regional fat location, along with no consideration of cultural differences in body composition such as differences in frame size that may affect body weight. (Lear *et al.*, 2007; Ozenoglu *et al.*, 2010; Gomez-Ambrosi *et al.*, 2012) At a given BMI, Pacific Island and Māori ethnic groups

have been found to have a lower BF% compared to NZE, thus, a higher BMI threshold to define obesity was suggested for these groups. (Swinburn *et al.*, 1999; Rush *et al.*, 2009b) However, when metabolic components were considered, there is a lack of sufficient evidence to support the use of a higher BMI cut off value. (Taylor *et al.*, 2010) While BF% has been shown to provide a better indication of body fatness compared to BMI, it can be difficult and expensive to get an accurate measure of this. (Romero-Corral *et al.*, 2008) Although there is no clear consensus on how to define BF% obesity, values between 30-38% have been used for women. (De Lorenzo *et al.*, 2006; Di Renzo *et al.*, 2010; Romero-Corral *et al.*, 2010; Oliveros *et al.*, 2014) Central adiposity indicators such as waist circumference (WC), waist to hip ratio (WHR) and waist to height ratio (WtHR) require little time and equipment, however there is conflicting evidence to support the idea that any of these is superior to BMI when identifying metabolic risk profiles, particularly for insulin resistance and dyslipidaemia. (Balkau *et al.*, 2006; Lee *et al.*, 2008; Hsieh *et al.*, 2010; Sahakyan *et al.*, 2015) Although these measures focus solely on abdominal fat, this may be the most important measurement as fat in the android region, particularly visceral fat, is associated with worse metabolic outcomes than that located in the gynoid region. (Smith *et al.*, 2001; Fox *et al.*, 2007)

Obesity is associated with metabolic disturbances that may predispose to metabolic diseases such as T2D, CVD, and cancer. (Bray, 1999; Kahn *et al.*, 2006; Blakely *et al.*, 2009; Van Gaal, 2010) These include chronic inflammation, (Bullo *et al.*, 2003; McArdle *et al.*, 2013) IR, (Kahn *et al.*, 2006; McArdle *et al.*, 2013) dyslipidaemia, (Abbasi *et al.*, 2013), and high blood pressure. (Landsberg *et al.*, 2013) Chronic inflammation has a strong association with obesity and is a common factor in various states of metabolic disease. (Bullo *et al.*, 2003) Excessive adipose tissue results in an increased release of pro-inflammatory cytokines including tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6). (Bullo *et al.*, 2003; Roth *et al.*, 2004; Jung and Choi, 2014; Laforest *et al.*, 2015) TNF-α and IL-6 levels correlate

with levels of C-reactive protein (CRP), an acute phase protein that increases in relation to inflammation and that is used as an inflammation biomarker. (Pannacciulli *et al.*, 2001) Insulin resistance is another common feature of obesity, and is a well-established prerequisite to developing T2D, and risk factor for CVD. (Roth *et al.*, 2004; Jung and Choi, 2014) Inflammation and IR are inter-related components in the pathophysiology of obesity and may exacerbate each other creating a negative cycle of metabolic disruption. (Guilherme *et al.*, 2008; Gregor and Hotamisligil, 2011; Patel *et al.*, 2013) Increased free fatty acid (FFA) release and interrupted insulin signalling related to hypoxic conditions of the hypertrophied adipocytes are other potential mechanisms in the development of IR. (Guilherme *et al.*, 2008; Bluher, 2009) Obesity is also associated with hypertension and dyslipidaemia, often concurrently, both of which are risk factors for CVD. (Landsberg *et al.*, 2013; Jung and Choi, 2014) Dyslipidaemia is characterised by increased FFA and triglycerides (TG), small dense low density lipoprotein (LDL) particles, and reduced high density lipoprotein (HDL). (Jung and Choi, 2014) These various elements of metabolic dysregulation are interlinked and often people present with a combination of the above rather than isolated changes. (Lean, 2000)

Part of the critique of BMI as an indicator of metabolic disease risk is due to the discovery of a subgroup of people that have a normal BMI but a high percentage of body fat; being termed 'Normal Weight Obesity'. (De Lorenzo *et al.*, 2006; Romero-Corral *et al.*, 2010) This profile has been associated with metabolic risk factors usually seen with the obese profile (Di Renzo *et al.*, 2010; Kosmala *et al.*, 2012; Kim *et al.*, 2013). In this instance, using BMI to define overweight and obesity could result in missed opportunities for further screening of those that might be at risk of metabolic disease.

Significant health inequalities have been reported in New Zealand, where compared to NZE, Māori and Pacific people have lower life expectancy, poorer health, and are more

exposed to health risks. (Ministry of Health, 2002; Tobias *et al.*, 2009) There are multiple contributing factors for this inequality including being over-represented in lower socioeconomic groups, having poorer food security, and experiencing greater barriers to healthcare. (Ministry of Health, 2002; Ministry of Health, 2016) Obesity is related to major health inequalities, where Māori and Pacific people have higher prevalence of obesity related conditions including T2D, stroke, (Ministry of Health, 2016) and cancer, (Blakely *et al.*, 2009) compared to NZE. Despite these inequalities, there is limited research investigating differences in body composition between NZE, Pacific Island and Māori women and how this relates to metabolic health. The aim of this study is to investigate the body compositional and metabolic profiles of these ethnic groups, and to identify ethnic specific patterns between these profiles. This study takes a holistic approach, using multiple means of measurement including BMI, BF %, WC, WtHR, WTR, and android/gynoid (AG) regional composition to assess body fat profiles of New Zealand women. These profiles are analysed in relation to known biomarkers of metabolic health including blood lipids, markers of glucose metabolism, inflammatory markers, and metabolic hormones. The separation of the ethnic groups allows investigation and comparison of the groups to explore whether cultural patterns or differences exist. Given the elevated obesity rates in both Māori and Pacific Island adults, understanding how their body composition relates to metabolic health will be an important part of determining avenues for improving the associated health inequalities.

3.3 Subjects & methods

The current study is a sub study of the Women's EXPLORE ("Examining Predictors Linking Obesity Related Elements") study which aimed to investigate hidden and apparent body fat profiles of NZE, Pacific and Māori women in relation to predictive factors and metabolic risk profiles (Kruger *et al.*, 2015). The current study investigates the body composition and metabolic profiles of these women in search of patterns within and between ethnic groups.

NZE, Pacific Island and Māori women aged 16-45 years, who were post-menarcheal/pre-menopausal, with no known chronic disease, and not currently pregnant or lactating were screened by questionnaire for eligibility, then by BMI and BF% for grouping into one of the following EXPLORE body composition profile groups:

1) Normal BMI (<25kg/m²), normal body fat % (<30%) (NN)

2) Normal BMI (<25kg/m²), high body fat % (≥30%) (NH)

3) High BMI (≥25kg/m²), high body fat %(≥30%) (HH)

All Data collection occurred in the morning after an overnight fast, at the Massey University Human Nutrition Research Unit.

Body Composition

Measurements included height, and circumference of waist and hip using a stadiometer and Lufkin tape following the protocol set out by International Society for the Advancement of Kinanthropometry (ISAK). (Marfell-Jones *et al.*, 2012) Weight was measured using Air Displacement Plethysmography (BodPod). This data was used to calculate: BMI, WTR, WtHR. Body fat (%) was obtained using bioelectrical impedance analysis (BIA) for screening, then BodPod for analysis due to the greater accuracy. (Oliveros *et al.*, 2014; Kruger *et al.*, 2015) The DXA provided information for android and gynoid body fat and lean mass to allow analysis of fat location and associated disease risk. (Glickman *et al.*, 2004; Kruger *et al.*, 2015)

Metabolic biomarkers

A registered phlebotomist collected serum and plasma (ethylene diamine tetra acetic acid and heparin) blood samples between 7-10am, and pathology laboratory protocols for both collection and processing were followed. To ensure analysis for all participants occured at the same time, samples were frozen at -18C as separate aliquots in Eppendorf tubes, until sample

collection from all participants was completed. Analysis was performed by fully accredited laboratories or qualified laboratory technicians. Either routine enzymatic assays or commercially available kits were used to analyse the biomarkers, and depending on the required assay either Bioplex 200 plate reader or Biotek Synergy 2 Plate Reader was used to complete the analysis. (Kruger *et al.*, 2015)

Biomarker analysis included:

- Plasma glucose, insulin, glycated haemoglobin (HbA1c), total cholesterol (TC) , triglycerides (TG), high density lipoprotein (HDL), total cholesterol to HDL ratio (TC/HDL).
- Serum cs-CRP, IL-6, IL-10 and TNF-α, leptin, ghrelin

Insulin resistance was assessed indirectly using the Homeostatic model assessment (HOMA-IR) calculation of glucose (mmol/L) x insulin (mU/L)/22.5 (Bonora *et al.*, 2000). The Friedwald formula was used to calculate low density lipoprotein (LDL). (Friedewald *et al.*, 1972)

Blood pressure

Blood pressure (BP) was taken with a Riester Ri-Champion N digital blood pressure monitor following Standard Operating Procedure.

Data analysis and statistical analysis

During the data collection phase, it became apparent that most Pacific Island and Māori women did not have the same body composition profiles as NZE women and did not fit into the intended EXPLORE profile groups, particularly the NN and NH profile groups. Therefore, only the NZE women were able to be grouped and analysed by the EXPLORE profiles. In order to further explore body composition profiles, the data for all ethnicities were then grouped and analysed as obese or not obese as defined by BMI ≥30kg/m², and BF ≥35%.

The intended sample size was 75 women in each body composition group, for each ethnicity (total 225 women per ethnic group) in order to be able to detect a medium effect size *f* of 0.25 with 80% power when $p < 0.05$. (Kruger *et al.*, 2015) To detect an effect size of 0.8 with 80% power, 26 participants are needed in each group. Parametric data were summarised by mean ± standard deviation, while non-parametric data were log transformed and reported as geometric mean (95% confidence interval), or as untransformed median (25-75th percentile). Differences within ethnicities were analysed by independent T-test for parametric data or Mann Whitney test for non-parametric data. The differences between EXPLORE profile groups and ethnic groups were analysed with one way ANOVA and Tukey's post hoc tests for parametric data where significance was p value of <0.05, or Kruskal Wallis with Mann Whitney post hoc tests with Bonferroni correction and significance at $p < 0.0167$ for non-parametric data. Sensitivity was calculated as: true positives/(true positives+ false negatives), and specificity was calculated as: true negatives/(true negatives + false positives). (Lalkhen and McCluskey, 2008)

Cut off values for abnormal biomarker levels were: HDL <1mmol/L, LDL >3.4mmol/L, Chol/HDL >4.5, TG >2mmol/L, Glucose >5.4mmol/L, Insulin >13mU/L, HbA1c >40mmol/mol, CRP >5mg/L (Values provided by North Shore labs and consistent with widely used thresholds in the area) and HOMA-IR >2.27. (Taylor *et al.*, 2010) Statistics were completed using IBM SPSS Statistics version 22.0.

<u>Ethics:</u>

Ethical approval has been received from Massey University Human Ethics Committee: (Southern A), Reference No.13/13.

3.4 Results

Final participant numbers were 233 NZE, 91 Pacific Island, and 84 Māori women.

Table 3.1 shows the anthropometric and clinical characteristics of NZE woman categorised according to the three body composition profile (BCP) groups. The NN, NH and HH groups have a mean BMI of 21.2, 23.2, and 28.7 and a mean BF% of 26.0%, 33.4% and 39.1% respectively. There was an increasing trend in mean/median weight, BMI, BF%, WC, HC, WtHR, total fat mass (FM) and body location variables including android fat mass, and AG ratio from NN, to NH then HH, with all group differences being significant.

The mean/median metabolic biomarker levels were below the thresholds for disease risk for all groups. Compared with the NN group, both the NH and HH group had a significantly higher Chol/HDL ratio and higher leptin. Leptin was additionally significantly higher in the HH group than the NH group. The HH group had higher fasting insulin, HOMA-IR, CRP, and diastolic BP than both the other groups. Fasting glucose, LDL, TG, and systolic BP were higher and HDL was lower in the HH group compared with the NN group but not the NH group.

Table 3.2 shows the ethnic distribution of body composition for various BMI and BF% categories. When classified by obesity as BMI ≥30kg/m², this study included 299 non-obese and 107 obese subjects, compared with 227 non-obese and 179 obese subjects when classified by BF% ≥35%. Regardless of the method of classification, obesity was most prevalent in Pacific women, followed by Māori, then NZE. In all ethnicities, the prevalence of obesity was higher when BF % was used to classify rather than BMI (NZE 33% vs 13.3%, Pacific 66.7% vs 57.8%, Māori 50.6% vs 28.9% respectively).

Figures 1a and 1b show ethnic specific prevalence of high insulin, HOMA-IR, Chol/HDL and CRP in each of the BMI and BF% defined categories. Regardless of obesity definition, the proportion of obese NZE and Māori women with high Chol/HDL was over

50% greater than their Pacific counterparts, and they were more likely to have high CRP. Obese Pacific women were likely to have high insulin (85.4% and 76.8%) and high HOMA-IR (85.4% and 82.1%) for BMI and BF% groups respectively, while Māori were similar with high insulin (79.2% and 64.3%), and high HOMA-IR (87.5% and 69%). Obese NZE women had a lower prevalence of high insulin (37.9% and 24.7%) and HOMA-IR (48.3% and 39.7%).

Table 3.3 displays the differences between anthropometric and clinical characteristics of participants grouped by ethnicity and body composition defined by BMI.

For all ethnic groups, body composition measures were significantly higher in the BMI defined obese groups compared to the non-obese defined groups (See table 3). Abdominal measures WC, WHR and WtHR were all above the recommended ranges for metabolic risk in the obese groups for NZE (94.8cm, 0.81, and 0.59), Pacific (99.9cm, 0.82, and 0.61), and Māori women (100cm, 0.82, and 0.6), as were insulin and HOMA-IR for obese Pacific (24.28mU/L) and 5.450) and Māori (19.41mU/L and 4.35), and HOMA-IR for obese NZE (2.61). Insulin, HOMA-IR, Chol/HDL, TG, CRP, systolic and diastolic BP and leptin were higher in obese groups compared to non-obese for each ethnicity, while HDL and ghrelin were lower. Higher LDL in obese than non-obese was only seen for NZE and Māori women. For Pacific and Māori groups, this pattern was also seen for glucose. Obese Pacific women had lower IL-10 than non-obese, while obese NZEs had higher IL-10 than non-obese. Obese NZEs had higher TNF-α than those with lower BMI.

<u>Differences between Ethnic groups for non-obese BMI and obese BMI respectively</u>

<u>Non-obese BMI (<30 kg/m^2)</u>

Pacific and Māori women in this category (see table 3) had higher BMI, WC and WtHR and AG ratio than NZE women. Only Pacific women had higher weight, HC, FM, fat free mass (FFM), android fat mass, android fat % than NZE women. Only Māori women had

higher WHR, gynoid lean mass, and a lower gynoid fat % than NZE women. Higher HC in Pacific compared with Māori women was the only significant difference between these two ethnicities. Pacific and Māori women had higher insulin HOMA-IR, HbA1c, TNF-α and HDL than NZEs. Māori women had significantly higher IL-10 and lower TC and LDL than their NZE counterparts.

Obese BMI (≥30 kg/m^2)

Significant body composition differences were only found between NZE and Pacific women except for a higher FFM in Māori compared to NZE women. Pacific women had higher BMI, WC, FFM, android and gynoid lean mass, and gynoid fat %. All biomarkers of glucose metabolism were higher in Pacific women than in NZEs, while HDL and LDL were lower. Māori had higher glucose, insulin and HOMA-IR than NZEs. Pacific women had lower cholesterol and ghrelin than Māori.

Table 3.4 displays the differences between the anthropometric and clinical characteristics of participants grouped by ethnicity and body composition defined by BF%. For all ethnic groups, body composition measures were significantly higher in the obese groups compared to non-obese. WC and WtHR ratio were all above the recommended thresholds for metabolic risk in the obese groups for NZE (88.2 and 0.53), Pacific (99.0 and 0.59), and Māori (92.0 and 0.56). WHR was also above risk threshold for obese Pacific (0.82) and Māori (0.8), as were insulin and HOMA-IR for obese Pacific (23.3 and 4.57)) and Māori (16.8 and 3.59). Glucose, insulin and HOMA-IR, systolic and diastolic BP and leptin were significantly higher in obese groups compared to non-obese for each ethnicity, while HDL was lower. Obese Māori and NZE women had higher Chol/HDL, TG and CRP than non-obese women. Obese Pacific women had lower IL-10 and ghrelin than non-obese, while obese NZEs had higher TNF-α than non-obese NZEs.

Differences between ethnic groups for non-obese BF% and obese BF% respectively

Non-obese BF%

Pacific women were younger with higher weight, BMI, WC, HC, WtHR, FM, FFM, android fat mass and android % fat, gynoid fat mass, and AG ratio than NZE women. Māori women had higher BMI, WHR, gynoid lean mass, gynoid fat %, and AG ratio than NZEs, while Pacific women had higher BMI, HC, FM, android fat %, gynoid fat mass and fat % than Māori women.

Pacific women had higher insulin, HbA1c, HOMA-IR, along with lower HDL, and higher TNF-α than NZE women. Māori women had higher insulin and HbA1c, and higher TNF-α and IL-10 than European women. There were no metabolic differences seen between Māori and Pacific women.

Obese BF%

Pacific women were younger and had higher BMI, WC, HC, WHR, WtHR, FM, FFM, higher android fat and lean mass, gynoid fat and lean mass, and higher AG ratio than NZEs in this category.

Compared to NZEs, Māori had a higher FFM, android fat mass and lean mass along with higher AG ratio. Compared with Māori women, Pacific had higher BMI, WC, HC, WtHR, FM, FFM and gynoid lean mass.

Pacific women had higher insulin, HbA1c and HOMA-IR with no differences in inflammatory markers and lower cholesterol, LDL and HDL compared with NZE women. Māori women had higher insulin, HbA1c HOMA-IR, TG and TNF-α and lower TC and HDL than NZE women. Pacific women had higher insulin, HOMA-IR, ghrelin, and lower TC than Māori women.

Sensitivity and Specificity

Table 3.5 shows the sensitivity, specificity and correctly classified (%) for various

body composition measurements and cut off values in determining high insulin, HOMA-IR, Chol/HDL, TG, and CRP for each ethnicity. It is desirable to have both high sensitivity (Se), the ability to detect those with a condition/disease marker, and high specificity (Sp), the ability to rule out those who do not have the condition/disease marker but sensitivity is given higher priority to minimise failing to detect those at risk of disease. (Lalkhen and McCluskey, 2008) In an ideal world a sensitivity of 100 meaning that all those that had the disease/outcome would be detected is desirable, however this is extremely uncommon without a low specificity. Few body composition measures had both Se and Sp over 80. As prevalence of high results was fairly low for most biomarkers, the percentage correctly classified was more affected by specificity. For hyperinsulinaemia, BMI ≥30 and WC ≥88cm for Pacific, and WtHR ≥0.5 for Māori had Se and Sp around 80%, while BF% ≥25 had 89% Se for NZE but low Sp (49%). All measures were less sensitive for HOMA-IR than insulin regardless of ethnicity. For NZEs, body fat ≥30% had the highest Se for all measures; for Pacific women BMI ≥25kg/m² and body fat ≥30% were consistently highest in Se for the various measures, and for Māori women the measures highest in Se varied with biomarkers. There was a wide range in Sp for these measures, always lower than sensitivity. For NZEs the specificity range was 39-44, for Pacific Island it was 14-58, and for Māori it was 36-69. WtHR of ≥0.6 had the highest specificity for all biomarkers but with poor sensitivity.

3.5 Discussion

This cross sectional study investigated BMI and BF% defined body composition profiles in relation to anthropometric measures and biomarkers associated with metabolic disease risk of healthy NZE, Pacific Island and Māori women; the ethnic differences were also explored.

In all ethnic groups, prevalence of obesity was higher (~10-20%) when defined by BF% compared with BMI, which is consistent with previous research comparing the two measures. (Gomez-Ambrosi *et al.*, 2011; Gomez-Ambrosi *et al.*, 2012) For the NZ European group this is not surprising due to the focused sampling protocol for women with the 'hidden fat' profile in the normal BMI range. However, this profile was almost non-existent within the other two ethnicities, which was an interesting finding. The difference in prevalence between the two measures was smaller for Pacific women with only 8.9% difference between BMI and BF% obesity rates, compared to 23.2% and 21.7% in the NZ European and Māori groups. These results confirm that the use of BMI to diagnose obesity can miss some of those with a high BF%. (Romero-Corral *et al.*, 2008; Gomez-Ambrosi *et al.*, 2012)

The 'hidden fat' profile was found in NZE women using the original NWO definition of BMI ≥25 and BF% ≥30, however, very few Pacific Island and Māori women were identified with profile. These thresholds may be too low for the other ethnic groups, particularly for Pacific women as only 13.3% presented with a BMI <25, and 16.7% with a BF % <30. Additionally, previous research has shown that Pacific women and to a lesser extent Māori, have higher lean mass and lower BF% than NZE at a given BMI. (Rush *et al.*, 2007) Compared to those with a normal BMI and body fat%, having the NWO profile has been associated with higher lipid and glucose metabolism markers, (Marques-Vidal *et al.*, 2010) and higher inflammatory markers such as TNF-α and IL-6. (De Lorenzo *et al.*, 2007; Di Renzo *et al.*, 2010), but aside from Chol/HDL none of these markers were higher in the 'hidden fat' group compared to normal weight in this study. The high Chol/HDL may suggest

that lipids are the first biomarkers to be affected by increased body fat for NZEs. The NWO group had significantly higher BMI, abdominal measurements and android fat and gynoid fat than the lean group, with no differences found in fat free mass for either area. It has been suggested that the NWO profile must come with a reduced amount of muscle mass in order to still fit into the lower BMI category with a higher amount of fat, (Jean *et al.*, 2014) which may be the case for this group as they had the higher BMI without a change in android or gynoid lean mass between the groups. The lack of metabolic differences despite the higher body composition measures may be in part due to the young age of the participants in this study as several of the previous NWO studies have included much older participants up to 75-80 years old. (Marques-Vidal *et al.*, 2010; Gomez-Ambrosi *et al.*, 2011; Gomez-Ambrosi *et al.*, 2012) Body composition changes with age, (Kuk *et al.*, 2009; Prado *et al.*, 2012) particularly in women after menopause due to hormonal changes favouring a reduced lean mass and accumulation of abdominal fat which has been associated with disrupted glucose and lipid metabolism. (Francucci *et al.*, 2005) In this study women were specifically recruited to exclude hormonal influences, which may explain the findings. It would be interesting to see if the hidden fat group were more susceptible to these age related changes and the related metabolic dysfunction over time.

All ethnic groups were classified as either non-obese or obese by both BMI ($\geq$30kg/m^2) and BF% ($\geq$35) to further investigate their body composition and metabolic profiles. Pacific women had a higher BMI and FFM compared to NZEs in all BMI and BF% groups, and higher FM in all but the obese BMI group. They also had higher BMI than Māori women in the body fat % defined groups only. There were no BF% differences between the ethnic groups which is not surprising given previous findings that Pacific Islanders have a lower BF% for a given BMI compared to NZE and Māori. (Swinburn *et al.*, 1999; Rush *et al.*, 2009a) Māori had a higher BMI than NZEs in both the non-obese groups with no

differences in BF% supporting previous reports that Māori also have a lower BF% for a given BMI compared to NZEs, (Rush *et al.*, 2007; Rush *et al.*, 2009b) although the differences were only apparent in the normal BMI and BF% groups in this study.

The use of abdominal obesity measurements such as WC and WtHR have been proposed as alternative measures of body fatness, due to the increased metabolic risk associated with excess fat in the abdominal cavity. (Lee *et al.*, 2008; Sahakyan *et al.*, 2015) In this study unexpected ethnic differences between android composition and these measurements were seen. Pacific women had higher WtHR than Māori women in the BF% obese group with no differences in android composition. In contrast to this, research comparing WC and central fat mass of Māori and Pacific Island women (height adjusted) found that they had similar central fat for the same waist measurement. (Rush *et al.*, 2007) There were no differences in height between Māori and Pacific women in the high BF% group, however, the higher WtHR of Pacific women might be due to a shorter wider abdomen for the same amount of android mass as Māori women. Pacific Island women have been found to have a longer leg length than Māori women (height adjusted), thus, at the same height their upper body would have to be shorter. (Rush *et al.*, 2009a) Māori with obese BF% had higher android fat mass and android lean mass than their NZE counterparts, with no differences in the abdominal anthropometric measurements indicating that this compositional difference has not been detected by standard abdominal obesity measures. Additionally, Māori with non-obese BMI had higher WC and WtHR than NZEs in the same group, with no differences in android composition. Two previous studies have found Māori and NZE women to have similar amounts of abdominal fat when age, weight and height are considered, however, neither compared abdominal fat with WC or WtHR for these groups. (Rush *et al.*, 2007; Rush *et al.*, 2009b) These results suggest that there may be ethnic differences between abdominal measurements and android composition that may impact the ability of measures

such as WC and WtHR to accurately reflect android obesity if the same threshold is used. Investigation into the ethnic-specific cut off values of abdominal obesity measurements that best reflect android composition and related metabolic disease risk may be valuable for these groups.

Overall, the prevalence of biomarkers outside the reference ranges was low despite a high level of obesity. This will be influenced by the exclusion of those with diagnosed chronic disease, and possibly to the relatively young age of participants. The metabolically healthy obese profile has been labelled an unstable profile, (Hamer *et al.*, 2015) and the prevalence has been found to decrease with increasing age. (Velho *et al.*, 2010; Appleton *et al.*, 2013) The exception to this was obese Pacific and Māori women where a large percentage had high levels of insulin and HOMA-IR when obesity was defined by BMI (85.4% and 85.4% for Pacific, 79.2% and 87.5% for Māori, and 37.9% and 48.3% for NZEs respectively) and by BF % (82.1% and 76.8% for Pacific, 64.3% and 69% for Māori, and 24.7% and 39.7% for NZEs respectively). The ethnic differences in glucose metabolism markers became more apparent in Tables 4 and 5, where regardless whether grouped by BMI or BF %, Pacific women had higher insulin, HOMA-IR and HbA1c than NZEs in both non-obese and obese groups. Previous research looking at whether Pacific people are hyper-insulinaemic compared to Europeans concluded that there are no differences in insulin between the two ethnic groups when BMI is the same. (Simmons *et al.*, 2001) In this study, Pacific women had a higher BMI than NZEs in all groups so this may explain the higher insulin, however, with both definitions of obesity, the insulin and HOMA-IR of obese Pacific women were more than double that of their NZE counterparts. While high abdomen fat has been linked to increased risk of insulin resistance, (Stolic *et al.*, 2002; Fox *et al.*, 2007; Pou *et al.*, 2009) there were no android fat differences between Pacific and NZE women in the obese by BMI group, despite Pacific having higher markers of insulin resistance. Together, these

results indicate that Pacific women appear to be at higher risk of altered insulin resistance markers compared to NZEs which is in contrast to previous research that found that Polynesians were more likely to have defect in insulin secretion rather than insulin resistance (measured by fasting insulin and HOMA-IR). (Defay *et al.*, 2007) In this study both fasting glucose and HbA1c were generally within the recommend ranges for health, so it is unclear whether the high insulin and HOMA-IR observed actually means an increased risk of diabetes. However, when comparing Pacific and NZEs, HbA1c was higher in all Pacific groups alongside insulin and HOMA-IR. Additionally, a large case-control study found evidence for an association between increasing fasting insulin and HOMA-IR and risk of diabetes for Pacific women, although they were grouped with Asian women which may have influenced the results. (Song *et al.*, 2007)

Despite the absence of differences in BMI, BF% or abdominal measurements between Māori and NZEs in either of the obese groups, obese Māori women had higher insulin, HOMA-IR and/or HbA1c markers than obese NZEs in both groups, and higher glucose in the BMI defined obese group A higher android fat was only seen in the BF% defined group, so this cannot provide explanation for these differences. Māori have been found to be at higher risk of increased fasting insulin and decreased insulin sensitivity compared to NZEs at a given BMI, (McAuley *et al.*, 2002) and results suggest that the same may be true at similar BF %. Differences in proportions of visceral and subcutaneous fat may be influencing the biomarkers of glucose metabolism for these ethnic groups as higher visceral fat has been reported as an important risk factor for IR. (Smith *et al.*, 2001) The composition of these abdominal fat has been shown to differ between some ethnic groups, (Lear *et al.*, 2007) although whether this is the case for Māori and Pacific women is yet to be seen. Additionally, FFA were outside of the scope of this research but ethnic differences in these may explain glucose biomarker differences as raised levels have been implicated in the development of

insulin resistance. (Boden, 2001; Shah *et al.*, 2003) Further investigation into these factors may help to shed some light on the reasons for the ethnic disparities seen. Additionally, longitudinal research would help to identify whether the prevalence of high insulin and HOMA-IR, and the ethnic differences in glucose metabolism markers do correspond with high glucose, HbA1c and T2DM risk over time.

Inflammation and insulin resistance have been closely linked with the pathophysiology of obesity, (Pannacciulli *et al.*, 2001; Mathew *et al.*, 2013; McArdle *et al.*, 2013) so it is interesting to see that while insulin resistance markers were higher for Māori and Pacific women compared to NZEs regardless of grouping, the same pattern was not always seen with inflammatory markers. Compared to NZE women, Pacific had higher TNF-α in the non-obese groups (BMI and BF%), but not the obese groups, however, they also had higher gynoid fat mass and lean mass in the obese groups which may explain why TNF-α was not raised. Gluteo-femoral fat has been associated with metabolic protection against insulin resistance even in the presence of abdominal obesity, (Shay *et al.*, 2011) with potential reasons for this including higher insulin sensitivity of fat cells in this location and the secretion of more favourable cytokines, (OhJeeYoung, 2012) so perhaps this has a beneficial effect on circulating TNF-α. Although CRP has been independently associated with insulin resistance measures (fasting insulin and HOMA-IR) in a previous study, (Pannacciulli *et al.*, 2001) there were no ethnic differences in CRP for any groups despite differences in insulin and HOMA-IR. This may indicate ethnic differences in the relationship between insulin resistance and inflammation. The increased production of cytokines such as IL-6 and TNF-α by adipose tissue have been implicated in the metabolic disruption associated with obesity, (McArdle *et al.*, 2013; Eguchi and Manabe, 2014) however in this study, NZE were the only ethnicity where higher TNF-α was seen in the obese groups compared to non-obese, and no differences in IL-6 were observed. It is currently unclear

whether adipose tissue TNF-α and IL-6 levels are reflected by peripheral circulating measures, and it has been reported that circulating TNF-α has a fast clearance rate, resulting in typically low serum levels. (Zahorska-Markiewicz *et al.*, 2000) If adipose levels of these cytokines are raised with little effect on circulating levels, this could provide a mechanism for the higher CRP seen in obese compared to non-obese groups in this study, as both TNF-α and IL-6 have regulatory roles in liver CRP production. (Pannacciulli *et al.*, 2001)Additionally, obese Pacific women had lower IL-10 than non-obese, while obese NZEs in the BMI category had higher IL-10 than non-obese. Previous research is conflicting where on one hand IL-10 has been shown to increase with obesity, (Juge-Aubry *et al.*, 2005) while another study found that it decreased but only with android obesity. In this study all obese groups had higher android fat mass, fat % and AG ratio than the non-obese groups, (Manigrasso *et al.*, 2005) so this cannot explain the drop in IL-10 seen with obese Pacific women. IL-10 is an anti-inflammatory cytokine produced by adipose tissue that has been linked to insulin signalling in animal studies where IL-10 appears to reduce the negative effects of TNF-α and IL-6 on hepatic insulin signalling and the development of insulin resistance in the liver. (Kim *et al.*, 2004; Cintra *et al.*, 2008) The reduced levels in obese Pacific women may be a contributing factor to the higher fasting insulin and HOMA-IR levels seen in this group. More research is needed to identify what drives these ethnic differences in circulating IL-10 with obesity including whether there could be ethnic specific macrophage phenotype expression, as the M2 form secretes more IL-10 than the M1 form, (Perez de Heredia *et al.*, 2012) so this could provide a potential mechanism for the differences seen.

While the likelihood of raised insulin and HOMA-IR was lower for NZEs, they were more likely to have high Chol/HDL and CRP than Pacific women. This high Chol/HDL may be influenced by the 'hidden fat' profile of NZE women as this marker was raised in the 'hidden fat' group compared to the normal body fat group. Interestingly, when obesity was

defined by BF% there were no differences in Chol/HDL, LDL, TG or CRP between obese and non-obese Pacific women while differences did exist for the other ethnic groups. This indicates that it may not be the amount of body fat that drives lipid metabolism changes for Pacific women. Although android fat was higher in the obese Pacific group compared to non-obese, we could not differentiate between visceral fat and subcutaneous fat. If the non-obese group, had lower overall android fat but more visceral fat than the obese group, this may provide explanation for the lack of differences in these variables as VAT is highly metabolically active producing a high level of pro-inflammatory cytokines, and delivering its products into the hepatic portal system which can promote dyslipidaemia including high TG and low HDL. (Ebbert and Jensen, 2013) However, research looking at the cluster of metabolic abnormalities known as the metabolic syndrome found that android fat was a better predictor of metabolic dysfunction than visceral fat, although this study investigated elderly Korean women so the results may not be applicable to a younger Pacific Island population. (Kang *et al.*, 2011)

These ethnic differences in biomarkers may indicate ethnic specific metabolic responses to increased body fat. This type of pattern has been previously seen in a recent study concentrating on the metabolic syndrome components (blood pressure, low HDL, high TG, high glucose, elevated BP) where African groups with different ancestry presented with differences in which markers were elevated. (Balkau *et al.*, 2006) If ethnic differences do exist between body composition and the metabolic consequences, then different approaches will likely be needed to detect those who are at metabolic disease risk for each group.

While the data from this study alluded to patterns between body composition and metabolic biomarkers, these varied within and between ethnic groups and some metabolic differences seen between groups did not align with body compositional differences. The

sensitivity and specificity tests compared various body fat indicators with the most prominent metabolic risk factors. This revealed that there were no body composition measures that were superior at detecting risk across the range of biomarkers, or for a particular biomarker across all ethnicities indicating that different measures may be needed for NZEs, Pacific and Māori women. There were very few tests where both sensitivity and specificity were above 80, as high levels in one tend to result in low levels of the other. (Lalkhen and McCluskey, 2008) A solution has been suggested where a high sensitivity is first used to identify those that may have the metabolic outcome, then a second test with a high specificity is used to eliminate those that do not have the high metabolic outcome. (Lalkhen and McCluskey, 2008) For example, to identify those with pre-diabetes risk in terms of high insulin and high HOMA-IR in the current study, ethnic specific measures could be used. For NZE women BF% ≥30 has the highest sensitivity for both measures so this could be used first to identify those that are at risk, while WtHR ≥0.6 and BMI ≥32kg/m2 have the highest specificity so either could be used next to rule out those that are not at risk. For Pacific island women, BF% ≥30 and BMI ≥25 are most sensitive for insulin and HOMA-IR, and WtHR ≥0.6 is most specific. For Māori women, BMI ≥25 is most sensitive, which is supported by a previous study, (Taylor *et al.*, 2010) and WtHR ≥0.6 is most specific. Although this approach will not detect everyone with high markers, it may provide information on those at highest risk particularly as WtHR is the most specific measure for all ethnic groups and biomarkers, and has been independently associated with disease risk. (Ashwell and Gibson, 2016) This method may provide a starting point for determining who should be screened when there is limited time and resources. In a clinical environment a single biomarker like insulin would be of little use on its own, and this method of risk identification would be more useful if able to detect conditions like high HbA1c or the presence of metabolic syndrome. The current study was unable to investigate these conditions due to the selection for healthy participants, however, comparing these

sensitivity and specificity tests in those with and without metabolic disease is recommended to validate the usefulness of this approach.

3.6 Strengths and Limitations

Strengths of this research include the wide range of body compositional and metabolic variables analysed, which to our knowledge has not previously been done with these ethnic groups. The separation of the three ethnicities is another strength that allows the analysis of these groups individually and comparatively to try and understand the inequalities that exist. Limitations include the inability to recruit desired numbers of Māori and Pacific women. This may have reduced the power of the statistics to accurately detect differences between groups. As only NZE women were the only ethnic group that met the criteria of the EXPLORE profiles, the selection criteria may have influenced the results and reduced the accuracy of comparison with Pacific and Māori women. Additionally participants were selected on a volunteer basis so may not reflect the wider population. Due to the overall low prevalence of abnormal biomarkers even with women with high BMI and BF%, specificity had a bigger impact on correctly classified %, and numbers may have been too small to give an accurate idea of the sensitivity of the various body composition measures. Repeating these tests with similar numbers of those with and without raised biomarkers may help to validate our findings.

3.7 Conclusion

This study identified significant ethnic differences in glucose metabolism markers where Māori and Pacific women had much higher insulin, HOMA-IR, glucose and/or HbA1c than NZE across all groups. There were no body composition profiles that were consistently seen with these differences in metabolic markers, and no ethnic differences were seen for BF%. This study supports consideration of ethnicities (NZE, Pacific and Māori) separately when identifying the most prominent metabolic risk markers in relation to body composition

parameters in New Zealand women. The use of two body composition measures, one with high sensitivity and one with high specificity, is a promising method of detecting those at risk of metabolic diseases like T2D and CVD and can be tailored to each ethnic group to detect the most prominent metabolic risk factors. More research is needed to further understand the differences and driving factors in metabolic biomarkers seen between the ethnic groups in order to work towards a reduction in the health inequalities in these ethnic groups. Factors outside the scope of this study such as FFA, visceral vs subcutaneous fat quantity, or differences in the genetic response to excess body fat may provide further clarity on the patterns seen in this study.

3.8 References

Abbasi, F., Blasey, C. & Reaven, G. M. 2013. Cardiometabolic risk factors and obesity: does it matter whether BMI or waist circumference is the index of obesity? *American Journal of Clinical Nutrition,* 98(3)**,** 637-640. Available: DOI 10.3945/ajcn.112.047506.

Appleton, S. L., Seaborn, C. J., Visvanathan, R., Hill, C. L., Gill, T. K., Taylor, A. W., Adams, R. J. & North West Adelaide Health Study Team 2013. Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype. *Diabetes Care,* 36(8)**,** 2388-2394. Available: DOI 10.2337/dc12-1971.

Ashwell, M. & Gibson, S. 2016. Waist-to-height ratio as an indicator of "early health risk': simpler and more predictive than using a "matrix' based on BMI and waist circumference. *Bmj Open,* 6(3). Available: DOI 10.1136/bmjopen-2015-010159.

Balkau, B., Sapinho, D., Petrella, A., Mhamdi, L., Cailleau, M., Arondel, D., Charles, M. A. & D.E.S.I.R Study Group 2006. Prescreening tools for diabetes and obesity associated dyslipidaemia: comparing BMI, waist and waist hip ratio. The DESIR Study. *European Journal of Clinical Nutrition,* 60(3)**,** 295-304. Available: DOI 10.1038/sj.ejcn.1602308.

Blakely, T., Sarfati, D. & Shaw, C. 2009. What proportion of cancer is due to obesity? *The New Zealand Medical Journal,* 122(1290). Available: <Go to ISI>://MEDLINE:19319164.

Bluher, M. 2009. Adipose tissue dysfunction in obesity. *Experimental and Clinical Endocrinology & Diabetes,* 117(6)**,** 241-250. Available: DOI 10.1055/s-0029-1192044.

Boden, G. 2001. Free fatty acids-the link between obesity and insulin resistance. *Endocrine Practice : Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists,* 7(1)**,** 44-51.

Bonora, E., Saggiani, F., Targher, G., Zenere, M. B., Alberiche, M., Monauni, T., Bonadonna, R. C. & Muggeo, M. 2000. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity - studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care,* 23(1)**,** 57-63. Available: DOI 10.2337/diacare.23.1.57.

Bray, G. A. 1999. Etiology and pathogenesis of obesity. *Clinical Cornerstone,* 2(3)**,** 1-15. Available: DOI 10.1016/s1098-3597(99)90001-7.

Bullo, M., Garcia-Lorda, P., Megias, I. & Salas-Salvado, J. 2003. Systemic inflammation, adipose tissue tumor necrosis factor, and leptin expression. *Obesity Research,* 11(4)**,** 525-531. Available: DOI 10.1038/oby.2003.74.

Campfield, L. A. & Smith, F. J. 1999. The pathogenesis of obesity. *Best Practice & Research Clinical Endocrinology & Metabolism,* 13(1)**,** 13-30. Available: DOI 10.1053/beem.1999.0004.

Cintra, D. E., Pauli, J. R., Araujo, E. P., Moraes, J. C., de Souza, C. T., Milanski, M., Morari, J., Gambero, A., Saad, M. J. & Velloso, L. A. 2008. Interleukin-10 is a protective factor against diet-induced insulin resistance in liver. *Journal of Hepatology,* 48(4)**,** 628-637. Available: DOI 10.1016/j.jhep.2007.12.017.

De Lorenzo, A., Del Gobbo, V., Premrov, M. G., Bigioni, M., Galvano, F. & Di Renzo, L. 2007. Normal-weight obese syndrome: early inflammation? *American Journal of Clinical Nutrition,* 85(1)**,** 40-45.

De Lorenzo, A., Martinoli, R., Vaia, F. & Di Renzo, L. 2006. Normal weight obese (NWO) women: an evaluation of a candidate new syndrome. *Nutrition, Metabolism, and Cardiovascular Diseases* 16(8)**,** 513-23. Available: DOI 10.1016/j.numecd.2005.10.010.

Defay, R., Jaussent, I., Lacroux, A. & Fontbonne, A. 2007. Relationships between glycaemic abnormalities, obesity and insulin resistance in nondiabetic Polynesians of New Caledonia. *International Journal of Obesity,* 31(1)**,** 109-113.

Di Renzo, L., Galvano, F., Orlandi, C., Bianchi, A., Di Giacomo, C., La Fauci, L., Acquaviva, R. & De Lorenzo, A. 2010. Oxidative Stress in Normal-Weight Obese Syndrome. *Obesity,* 18(11)**,** 2125-2130. Available: DOI 10.1038/oby.2010.50.

Ebbert, J. O. & Jensen, M. D. 2013. Fat depots, free fatty acids, and dyslipidemia. *Nutrients,* 5(2)**,** 498-508. Available: DOI 10.3390/nu5020498.

Eguchi, K. & Manabe, I. 2014. Toll-like receptor, lipotoxicity and chronic inflammation: the pathological link between obesity and cardiometabolic disease. *Journal of Atherosclerosis and Thrombosis,* 21(7)**,** 629-639.

Fox, C. S., Massaro, J. M., Hoffmann, U., Pou, K. M., Maurovich-Horvat, P., Liu, C. Y., Vasan, R. S., Murabito, J. M., Meigs, J. B., Cupples, L. A., D'Agostino, R. B. & O'Donnell, C. J. 2007. Abdominal visceral and subcutaneous adipose tissue compartments -association with metabolic risk factors in the Framingham Heart Study. *Circulation,* 116(1)**,** 39-48. Available: DOI 10.1161/circulationaha.106.675355.

Francucci, C. M., Pantaleo, D., Iori, N., Camilletti, A., Massi, F. & Boscaro, M. 2005. Effects of raloxifene on body fat distribution and lipid profile in healthy post-menopausal women. *Journal of Endocrinological Investigation,* 28(7)**,** 623-631.

Friedewald, W. T., Fredrickson, D. S. & Levy, R. I. 1972. Estimation of concentration of low-density lipoprotein cholesterol in plasma, without use of preparative ultracentrifuge. *Clinical Chemistry,* 18(6)**,** 499-502.

Glickman, S. G., Marn, C. S., Supiano, M. A. & Dengel, D. R. 2004. Validity and reliability of dual-energy X-ray absorptiometry for the assessment of abdominal adiposity. *Journal of Applied Physiology,* 97(2)**,** 509-514. Available: DOI 10.1152/japplphysiol.01234.2003.

Gomez-Ambrosi, J., Silva, C., Galofre, J. C., Escalada, J., Santos, S., Gil, M. J., Valenti, V., Rotellar, F., Ramirez, B., Salvador, J. & Fruhbeck, G. 2011. Body adiposity and type 2 diabetes: increased risk with a high body fat percentage even having a normal BMI. *Obesity,* 19(7)**,** 1439-1444. Available: DOI 10.1038/oby.2011.36.

Gomez-Ambrosi, J., Silva, C., Galofre, J. C., Escalada, J., Santos, S., Millan, D., Vila, N., Ibanez, P., Gil, M. J., Valenti, V., Rotellar, F., Ramirez, B., Salvador, J. & Fruhbeck, G. 2012. Body mass index classification misses subjects with increased cardiometabolic risk factors related to elevated adiposity. *International Journal of Obesity,* 36(2)**,** 286-294. Available: DOI 10.1038/ijo.2011.100.

Gregor, M. F. & Hotamisligil, G. S. 2011. Inflammatory mechanisms in obesity. *In:* Paul, W. E., Littman, D. R. & Yokoyama, W. M. (eds.) *Annual Review of Immunology, Vol 29.* Available: DOI 10.1146/annurev-immunol-031210-101322.

Guilherme, A., Virbasius, J. V., Puri, V. & Czech, M. P. 2008. Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. *Nature Reviews Molecular Cell Biology,* 9(5)**,** 367-377. Available: DOI 10.1038/nrm2391.

Hamer, M., Bell, J. A., Sabia, S., Batty, G. D. & Kivimaeki, M. 2015. Stability of metabolically healthy obesity over 8 years: the English longitudinal study of ageing. *European Journal of Endocrinology,* 173(5)**,** 703-708. Available: DOI 10.1530/eje-15-0449.

Hsieh, S. D., Ashwell, M., Muto, T., Tsuji, H., Arase, Y. & Murase, T. 2010. Urgency of reassessment of role of obesity indices for metabolic risks. *Metabolism-Clinical and Experimental,* 59(6)**,** 834-840. Available: DOI 10.1016/j.metabol.2009.09.032.

Huxley, R., Mendis, S., Zheleznyakov, E., Reddy, S. & Chan, J. 2010. Body mass index, waist circumference and waist: hip ratio as predictors of cardiovascular risk-a review

of the literature. *European Journal of Clinical Nutrition,* 64(1)**,** 16-22. Available: DOI 10.1038/ejcn.2009.68.

Jean, N., Somers, V. K., Sochor, O., Medina-Inojosa, J., Llano, E. M. & Lopez-Jimenez, F. 2014. Normal-weight obesity: implications for cardiovascular health. *Current Atherosclerosis Reports,* 16(12). Available: DOI 10.1007/s11883-014-0464-7.

Juge-Aubry, C. E., Somm, E., Pernin, A., Alizadeh, N., Giusti, V., Dayer, J. M. & Meier, C. A. 2005. Adipose tissue is a regulated source of interleukin-10. *Cytokine,* 29(6)**,** 270-274. Available: DOI 10.1016/j.cyto.2004.10.017.

Jung, U. J. & Choi, M. S. 2014. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. *International Journal of Molecular Sciences,* 15(4)**,** 6184-6223. Available: DOI 10.3390/ijms15046184.

Kahn, S. E., Hull, R. L. & Utzschneider, K. M. 2006. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature,* 444(7121)**,** 840-846. Available: DOI 10.1038/nature05482.

Kang, S. M., Yoon, J. W., Ahn, H. Y., Kim, S. Y., Lee, K. H., Shin, H., Choi, S. H., Park, K. S., Jang, H. C. & Lim, S. 2011. Android fat depot is more closely associated with metabolic syndrome than abdominal visceral fat in elderly people. *Plos One,* 6(11). Available: DOI 10.1371/journal.pone.0027694.

Kim, H. J., Higashimori, T., Park, S. Y., Choi, H., Dong, J. Y., Kim, Y. J., Noh, H. L., Cho, Y. R., Cline, G., Kim, Y. B. & Kim, J. K. 2004. Differential effects of interleukin-6 and-10 on skeletal muscle and liver insulin action in vivo. *Diabetes,* 53(4)**,** 1060-1067. Available: DOI 10.2337/diabetes.53.4.1060.

Kim, J. Y., Han, S. H. & Yang, B. M. 2013. Implication of high-body-fat percentage on cardiometabolic risk in middle-aged, healthy, normal-weight adults. *Obesity,* 21(8)**,** 1571-1577. Available: DOI 10.1002/oby.20020.

Kosmala, W., Jedrzejuk, D., Derzhko, R., Przewlocka-Kosmala, M., Mysiak, A. & Bednarek-Tupikowska, G. 2012. Left ventricular function impairment in patients with normal-weight obesity contribution of abdominal fat deposition, profibrotic state, reduced insulin sensitivity, and proinflammatory activation. *Circulation-Cardiovascular Imaging,* 5(3)**,** 349-356. Available: DOI 10.1161/circimaging.111.969956.

Kruger, R., Shultz, S. P., McNaughton, S. A., Russell, A. P., Firestone, R. T., George, L., Beck, K. L., Conlon, C. A., von Hurst, P. R. & Breier, B. 2015. Predictors and risks of

body fat profiles in young New Zealand European, Māori and Pacific women: study protocol for the women's EXPLORE study. *SpringerPlus,* 4(1)**,** 128.

Kuk, J. L., Saunders, T. J., Davidson, L. E. & Ross, R. 2009. Age-related changes in total and regional fat distribution. *Ageing Research Reviews,* 8(4)**,** 339-348. Available: DOI 10.1016/j.arr.2009.06.001.

Laforest, S., Labrecque, J., Michaud, A., Cianflone, K. & Tchernof, A. 2015. Adipocyte size as a determinant of metabolic disease and adipose tissue dysfunction. *Critical Reviews in Clinical Laboratory Sciences,* 52(6). Available: DOI 10.3109/10408363.2015.1041582.

Lal, A., Moodie, M., Ashton, T., Siahpush, M. & Swinburn, B. 2012. Health care and lost productivity costs of overweight and obesity in New Zealand. *Australian and New Zealand Journal of Public Health,* 36(6)**,** 550-556. Available: DOI 10.1111/j.1753-6405.2012.00931.x.

Lalkhen, A. G. & McCluskey, A. 2008. Clinical tests: sensitivity and specificity. *Continuing Education in Anaesthesia, Critical Care & Pain,* 8(6)**,** 221-223.

Landsberg, L., Aronne, L. J., Beilin, L. J., Burke, V., Igel, L. I., Lloyd-Jones, D. & Sowers, J. 2013. Obesity-related hypertension: pathogenesis, cardiovascular risk, and treatment a position paper of the obesity society and the american society of hypertension. *Journal of Clinical Hypertension,* 15(1)**,** 14-33. Available: DOI 10.1111/jch.12049.

Lean, M. E. J. 2000. Pathophysiology of obesity. *Proceedings of the Nutrition Society,* 59(3)**,** 331-336. Available: DOI 10.1017/s0029665100000379.

Lear, S. A., Humphries, K. H., Kohli, S., Chockalingam, A., Frohlich, J. J. & Birmingham, C. L. 2007. Visceral adipose tissue accumulation differs according to ethnic background: results of the Multicultural Community Health Assessment Trial (M-CHAT). *American Journal of Clinical Nutrition,* 86(2)**,** 353-359.

Lee, C. M. Y., Huxley, R. R., Wildman, R. P. & Woodward, M. 2008. Indices of abdominal obesity are better discriminators of cardiovascular risk factors than BMI: a meta-analysis. *Journal of Clinical Epidemiology,* 61(7)**,** 646-653. Available: DOI 10.1016/j.jclinepi.2007.08.012.

Manigrasso, M. R., Ferroni, P., Santilli, F., Taraborelli, T., Guagnano, M. T., Michetti, N. & Davi, G. 2005. Association between circulating adiponectin and interleukin-10 levels in android obesity: effects of weight loss. *Journal of Clinical Endocrinology & Metabolism,* 90(10)**,** 5876-5879. Available: DOI 10.1210/jc.2005-0281.

Marfell-Jones, M. J., Stewart, A. & de Ridder, J. 2012. *International standards for anthropometric assessment.* Wellington: New Zealand, International Society for the Advancement of Kinanthropometry.

Marques-Vidal, P., Pecoud, A., Hayoz, D., Paccaud, F., Mooser, V., Waeber, G. & Vollenweider, P. 2010. Normal weight obesity: relationship with lipids, glycaemic status, liver enzymes and inflammation. *Nutrition Metabolism and Cardiovascular Diseases,* 20(9)**,** 669-675. Available: DOI 10.1016/j.numecd.2009.06.001.

Mathew, S., Kosmas, C. E., Siegel, R. R. & Vittorio, T. J. 2013. Toxicity of abdominal fat. *Health,* 5(8A3).

McArdle, M. A., Finucane, O. M., Connaughton, R. M., McMorrow, A. M. & Roche, H. M. 2013. Mechanisms of obesity-induced inflammation and insulin resistance: insights into the emerging role of nutritional strategies. *Frontiers in Endocrinology,* 4**,** 52-52. Available: DOI 10.3389/fendo.2013.00052.

McAuley, K. A., Williams, S. M., Mann, J. I., Goulding, A. & Murphy, E. 2002. Increased risk of type 2 diabetes despite same degree of adiposity in different racial groups. *Diabetes Care,* 25(12)**,** 2360-2361. Available: DOI 10.2337/diacare.25.12.2360.

Ministry of Health. 2002. *Reducing inequalities in health*. Wellington: New Zealand: Ministry of Health. Retrieved from http://www.health.govt.nz/system/files/documents/publications/reducineqal.pdf

Ministry of Health. 2016. *Annual Update of Key Results 2015/16: New Zealand health survey*. Wellington: Ministry of Health. Retrieved from http://www.health.govt.nz/publication/annual-update-key-results-2015-16-new-zealand-health-survey

Ng, M., Fleming, T. & Robinson, M. 2014. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013 (vol 384, pg 766, 2014). *Lancet,* 384(9945)**,** 746-746.

OhJeeYoung 2012. Regional adiposity, adipokines, and insulin resistance in type 2 diabetes. *Diabetes and Metabolism Journal,* 36(6)**,** 412-414. Available: DOI 10.4093/dmj.2012.36.6.412.

Oliveros, E., Somers, V. K., Sochor, O., Goel, K. & Lopez-Jimenez, F. 2014. The concept of normal weight obesity. *Progress in Cardiovascular Diseases,* 56(4)**,** 426-433. Available: DOI 10.1016/j.pcad.2013.10.003.

Ozenoglu, A., Ugurlu, S., Can, G., Sarkis, C. & Demirel, Y. 2010. Differences in the body composition and biochemistry in women grouped as normal-weight, overweight and obese according to body mass index and their relation with cardiometabolic risk. *Central European Journal of Medicine,* 5(6)**,** 724-732. Available: DOI 10.2478/s11536-009-0137-z.

Pannacciulli, N., Cantatore, F. P., Minenna, A., Bellacicco, M., Giorgino, R. & De Pergola, G. 2001. C-reactive protein is independently associated with total body fat, central fat, and insulin resistance in adult women. *International Journal of Obesity,* 25(10)**,** 1416-1420. Available: DOI 10.1038/sj.ijo.0801719.

Patel, P. & Abate, N. 2013. Body fat distribution and insulin resistance. *Nutrients,* 5(6)**,** 2019-2027. Available: DOI 10.3390/nu5062019.

Patel, P. S., Buras, E. D. & Balasubramanyam, A. 2013. The role of the immune system in obesity and insulin resistance. *Journal of obesity,* 2013. Available: DOI 10.1155/2013/616193.

Perez de Heredia, F., Gomez-Martinez, S. & Marcos, A. 2012. Obesity, inflammation and the immune system. *Proceedings of the Nutrition Society,* 71(2)**,** 332-338. Available: DOI 10.1017/s0029665112000092.

Pischon, T., Nothlings, U. & Boeing, H. 2008. Obesity and cancer. *Proceedings of the Nutrition Society,* 67(2)**,** 128-145. Available: DOI 10.1017/s0029665108006976.

Pou, K. M., Massaro, J. M., Hoffmann, U., Lieb, K., Vasan, R. S., O'Donnell, C. J. & Fox, C. S. 2009. Patterns of abdominal fat distribution: the framingham heart s. *Diabetes Care,* 32(3)**,** 481-485. Available: DOI 10.2337/dc08-1359.

Prado, C. M. M., Wells, J. C. K., Smith, S. R., Stephan, B. C. M. & Siervo, M. 2012. Sarcopenic obesity: a critical appraisal of the current evidence. *Clinical Nutrition,* 31(5)**,** 583-601. Available: DOI 10.1016/j.clnu.2012.06.010.

Romero-Corral, A., Somers, V. K., Sierra-Johnson, J., Korenfeld, Y., Boarin, S., Korinek, J., Jensen, M. D., Parati, G. & Lopez-Jimenez, F. 2010. Normal weight obesity: a risk factor for cardiometabolic dysregulation and cardiovascular mortality. *European Heart Journal,* 31(6)**,** 737-746. Available: DOI 10.1093/eurheartj/ehp487.

Romero-Corral, A., Somers, V. K., Sierra-Johnson, J., Thomas, R. J., Collazo-Clavell, M. L., Korinek, J., Allison, T. G., Batsis, J. A., Sert-Kuniyoshi, F. H. & Lopez-Jimenez, F. 2008. Accuracy of body mass index in diagnosing obesity in the adult general population. *International Journal of Obesity,* 32(6)**,** 959-966. Available: DOI 10.1038/ijo.2008.11.

Roth, J., Qiang, X. L., Marban, S. L., Redelt, H. & Lowell, B. C. 2004. The obesity pandemic: Where have we been and where are we going? *Obesity Research,* 12**,** 88S-101S. Available: DOI 10.1038/oby.2004.273.

Rush, E. C., Freitas, I. & Plank, L. D. 2009a. Body size, body composition and fat distribution: comparative analysis of European, Māori, Pacific Island and Asian Indian adults. *British Journal of Nutrition,* 102(4). Available: DOI 10.1017/s0007114508207221.

Rush, E. C., Freitas, I. & Plank, L. D. 2009b. Body size, body composition and fat distribution: comparative analysis of European, Māori, Pacific Island and Asian Indian adults. *British Journal of Nutrition,* 102(4)**,** 632-641. Available: DOI 10.1017/s0007114508207221.

Rush, E. C., Goedecke, J. H., Jennings, C., Micklesfield, L., Dugas, L., Lambert, E. V. & Plank, L. D. 2007. BMI, fat and muscle differences in urban women of five ethnicities from two countries. *International Journal of Obesity,* 31(8)**,** 1232-1239. Available: DOI 10.1038/sj.ijo.0803576.

Sahakyan, K. R., Somers, V. K., Rodriguez-Escudero, J. P., Hodge, D. O., Carter, R. E., Sochor, O., Coutinho, T., Jensen, M. D., Roger, V. L., Singh, P. & Lopez-Jimenez, F. 2015. Normal-weight central obesity: implications for total and cardiovascular mortality. *Annals of Internal Medicine,* 163(11). Available: DOI 10.7326/m14-2525.

Shah, P., Vella, A., Basu, A., Basu, R., Adkins, A., Schwenk, W. F., Johnson, C. M., Nair, K. S., Jensen, M. D. & Rizza, R. A. 2003. Elevated free fatty acids impair glucose metabolism in women - decreased stimulation of muscle glucose uptake and suppression of splanchnic glucose production during combined hyperinsulinemia and hyperglycemia. *Diabetes,* 52(1)**,** 38-42. Available: DOI 10.2337/diabetes.52.1.38.

Shay, C. M., Carnethon, M. R., Church, T. R., Hankinson, A. L., Chan, C. L., Jacobs, D. R., Lewis, C. E., Schreiner, P. J., Sternfeld, B. & Sidney, S. 2011. Lower extremity fat sass is associated with insulin resistance in overweight and obese individuals: the CARDIA study. *Obesity,* 19(11)**,** 2248-2253. Available: DOI 10.1038/oby.2011.113.

Simmons, D., Thompson, C. F. & Volklander, D. 2001. Polynesians: prone to obesity and Type 2 diabetes mellitus but not hyperinsulinaemia. *Diabetic Medicine,* 18(3)**,** 193-198. Available: DOI 10.1046/j.1464-5491.2001.00435.x.

Smith, S. R., Lovejoy, J. C., Greenway, F., Ryan, D., deJonge, L., de la Bretonne, J., Volafova, J. & Bray, G. A. 2001. Contributions of total body fat, abdominal subcutaneous adipose tissue compartments, and visceral adipose tissue to the

metabolic complications of obesity. *Metabolism-Clinical and Experimental,* 50(4)**,** 425-435. Available: DOI 10.1053/meta.2001.21693.

Song, Y. Q., Manson, J. E., Tinker, L., Howard, B. V., Kuller, L. H., Nathan, L., Rifai, N. & Liu, S. M. 2007. Insulin sensitivity and insulin secretion determined by homeostasis model assessment and risk of diabetes in a multiethnic cohort of women - The Women's Health Initiative Observational Study. *Diabetes Care,* 30(7)**,** 1747-1752. Available: DOI 10.2337/dc07-0358.

Stolic, M., Russell, A., Hutley, L., Fielding, G., Hay, J., MacDonald, G., Whitehead, J. & Prins, J. 2002. Glucose uptake and insulin action in human adipose tissue - influence of BMI, anatomical depot and body fat distribution. *International Journal of Obesity,* 26(1)**,** 17-23. Available: DOI 10.1038/sj.ijo.0801850.

Swinburn, B. A., Ley, S. J., Carmichael, H. E. & Planck, L. D. 1999. Body size and composition in Polynesians. *International Journal of Obesity,* 23(11)**,** 1178-1183. Available: DOI 10.1038/sj.ijo.0801053.

Taylor, R. W., Brooking, L., Williams, S. M., Manning, P. J., Sutherland, W. H., Coppell, K. J., Tipene-Leach, D., Dale, K. S., McAuley, K. A. & Mann, J. I. 2010. Body mass index and waist circumference cutoffs to define obesity in indigenous New Zealanders. *American Journal of Clinical Nutrition,* 92(2)**,** 390-397. Available: DOI 10.3945/ajcn.2010.29317.

Tobias, M., Blakely, T., Matheson, D., Rasanathan, K. & Atkinson, J. 2009. Changing trends in indigenous inequalities in mortality: lessons from New Zealand. *International Journal of Epidemiology,* 38(6)**,** 1711-1722. Available: DOI 10.1093/ije/dyp156.

Van Gaal, L. F. 2010. Mechanisms linking obesity with cardiovascular disease. *Diabetes Obesity & Metabolism,* 12**,** 21-21.

Velho, S., Paccaud, F., Waeber, G., Vollenweider, P. & Marques-Vidal, P. 2010. Metabolically healthy obesity: different prevalences using different criteria. *European Journal of Clinical Nutrition,* 64(10)**,** 1043-1051. Available: DOI 10.1038/ejcn.2010.114.

World Health Organisation. 2000. *Obesity: preventing and managing the global epidemic. WHO technical report series No. 894* (0512-3054). Geneva: World Health Organisation. Retrieved from http://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/

World Health Organization. 2014. *Obesity and overweight (fact sheet).* Geneva: World Health Organisation. Retrieved from http://www.who.int/mediacentre/factsheets/fs311/en/

Zahorska-Markiewicz, B., Janowska, J., Olszanecka-Glinianowicz, M. & Zurakowski, A. 2000. Serum concentrations of TNF-a and soluble TNF-a receptors in obesity. *International Journal of Obesity,* 24**,** 1392-1395.

Table 3.1 Characteristics of NZ European women classified in subgroups according to normal or high BMI % & body fat criteria

	Disease risk values	NN n= 64	NH n=59	HH n=89	*p*
Age (years)		28.3 (24.2, 36.7)	33.1 (25.8, 40.8)	33.8 (26.4, 40.4)*	0.029
Height (cm)		167 (165-173)	168 (164- 171)	167 (161- 171)	0.175
Weight (kg)		60.8 (55.6, 66.8)	64.8 (61.6, 68.1)*	80.1 (73.5, 85.7)*, **	<0.001
BMI (kg/m²)		21.2 (20.3, 22.9)	23.2 (22.2, 24.1)*	28.7 (26.3, 31.3)*, **	<0.001
Body Fat (%)		26.0± 2.46	33.4 (32.7- 34.2)†*	39.1 (37.8- 40.4)†*, **	<0.001
WC (cm)	≥80	69.0 (67.2, 72.8)[1]	73.5 (72.0, 76.5)*	86.8 (81.0, 94.3)*, **	<0.001
HC (cm)		97.0 (94.0, 101)[1]	102 (99.5, 104)*	110 (106, 115)*, **	<0.001
WHR ratio	>0.8	0.72± 0.04[1]	0.73± 0.04	0.79± 0.06*, **	<0.001
WtHR ratio	≥0.05	0.41 (0.40, 0.44)[1]	0.44 (0.43, 0.46)*	0.52 (0.49, 0.56)*, **	<0.001
Fat Mass (kg)		15.9 (13.7-18.0)	21.5 (19.7- 23.4)*	30.9 (25.2- 36.6)*, **	<0.001
Fat Free Mass (kg)		45.2± 5.33	43.1± 4.38	49.0± 5.6*, **	<0.001
Android Fat Mass (kg)		0.94 (0.79- 1.09)	1.29 (1.12- 1.55)*	2.12 (1.68- 2.62)*, **	<0.001
Android Lean mass (kg)		2.66 (2.40- 3.09)	2.88 (2.67- 3.09)	3.54 (3.07- 3.89)*, **	<0.001
Android fat %		26.2 (22.4- 29.8)	31.7 (28.4- 34.9)*	38.7 (33.2- 42.2)*, **	<0.001
Gynoid fat mass (kg)		3.53 (3.30- 3.82)	4.40 (3.81- 4.63)*	5.24 (4.67- 6.17)*, **	<0.001
Gynoid lean mass (kg)		6.68 (6.03- 7.48)	6.79 (6.09- 7.30)	7.95 (7.03- 8.91)*, **	<0.001
Gynoid fat %		34.3 (31.7- 36.4)	39 (36.5- 41.2)*	40.2 (36.7- 43.7)*	<0.001
Android: gynoid ratio		0.27 (0.26-0.28)†	0.32± 0.06*	0.41 (0.39- 0.43)†*, **	<0.001
Glucose (mmol/L)	>5.4	4.60 (4.20- 4.80)	4.60 (4.40- 4.85)[2]	4.70 (4.50- 4.90)[5]*	0.022
Insulin (mU/L)	>13	7.19 (4.83-9.73)	8.46 (5.18- 10.5)[2]	10.3 (7.08-14.10)[5]*, **	<0.001
HbA1c (mmol/mol)	≥40	27.5 (25.0, 29.0)	27.0 (25.0, 29.0)[2]	28.0 (26.0, 30.0)[4]	0.114
HOMA-IR	>2.27	1.38 (1.22- 1.57)†	1.73± 0.83[2]	2.13 (1.89- 2.39)[5]†*, **	<0.001
Cholesterol (mmol/L)	≥5	4.45 (4.10- 5.18)	4.70 (4.30- 5.20)[2]	4.60 (4.20- 5.28)[5]	0.291
HDL (mmol/L)	<1	1.78± .48	1.66± .37[2]	1.54± .35[5]*	0.002
Calc_LDL (mmol/L)	≥3.4	2.39 (1.87- 2.92)	2.68 (2.22- 3.21)[2]	2.70 (2.25- 3.26)[5]*	0.025
Chol/HDL	≥4.5	2.58 (2.23, 3.02)	2.89 (2.49, 3.58)[2]*	3.09 (2.66, 3.83)[5]*	<0.001
TG (mmol/L)	≥2	0.76 (0.58, 0.99)	0.80 (0.61, 1.05)[2]	0.85 (0.70, 1.13)[5]*	0.040
CRP (mg/L)	>5	3.00 (3.00, 3.00)	3.00 (3.00, 3.00)[2]	3.00 (3.00, 5.50)[6]*, **	<0.001
TNF-a (pg/mL)		5.85 (4.45- 7.26)	5.98 (4.78- 6.79)	6.47 (5.53- 7.76)	0.063
IL-6 (pg/mL)		2.04 (1.15, 2.77)	2.13 (1.35, 2.57)[1]	1.86 (1.44, 2.51)[3]	0.780
IL-10 (pg/mL)		11.1 (5.23- 16.5)	9.34 (6.46- 18.4)	13.7 (6.42- 19.3)[1]	0.226
Systolic BP (mmHg)	≥130	113 (106 -117)	113 (108- 121)	115 (111- 124)*	0.007
Diastolic BP (mmHg)	≥80	68.5 (64.3- 72.0)	69.0 (66.0- 77.0)	73.0 (70.0- 79.0)*, **	<.0.001
Leptin (pg/mL)		4053 (2542- 6136)	7212 (4700- 10716)[1]*	11992 (8101- 16982)[2]*, **	<0.001
Ghrelin (pg/mL)		45.9 (22.6- 65.5)	40.9 (25.5- 65.8)[1]	42.1 (20.9- 69.6)[2]	0.907

Abbreviations: NN normal BMI, normal body fat%; NH normal BMI, high body fat%; HH high BMI, high body fat%; BMI body mass index; WC waist circumference; HC hip circumference; WstHip waist to hip ratio; WstHeight waist to height ratio; HbA1c glycated haemoglobin, HOMA-IR homeostasis model assessment of insulin resistance; HDL high density lipoprotein; LDL low density lipoprotein; CRP C-reactive protein;TNF-a tumor necrosis factor alpha; IL interleukin; BP blood pressure.
Values are mean±SD or median (25th-75th quartiles) unless otherwise indicated
†Mean for the log transformed data values, back transformed to the original scale
Differences between groups were analysed by Kruskal Wallis and post hoc Mann Whitney with bonferroni correction significant at p <0.0167 or ANOVA with post hoc Tukeys significant at p <0.05, as appropriate
* significantly different than women in NN group, ** significantly different than women in NH group
[1–6] indicates number of participants with missing date for each variable

903

904

Table 3.2 Ethnic distribution in BMI and BF% groups

	Ethnicity		
	NZ Euro	Pacific	Māori
Body Composition Group	n (%)		
Non obese by BMI (<30kg/m²)	202 (86.7%)	38 (42.2%)	59 (71.1%)
Obese by BMI (≥30kg/m²)	31 (13.3%)	52 (57.8%)	24 (28.9%)
Non obese by BF% (<35%)	156 (67%)	30 (33.3%)	41 (49.4%)
Obese by BF% (≥35%)	77 (33%)	60 (66.7%)	42 (50.6%)

Abbreviations: BMI body mass index; BF% body fat %; NZ New Zealand

Table 3.3 Anthropometric and clinical characteristics of participants classified by BMI and ethnicity

		NZE			Pacific			Māori				
	At risk value	BMI <30	BMI ≥30	*p* ‡	BMI <30	BMI ≥30	*p* ‡	BMI <30	BMI ≥30	*p* ‡	*p* § BMI <30	*p* § BMI ≥30
		n=202	n=31		n=38	n=52		n=59	n=24			
Age (years)		30.79 (24.94- 39.21)	33.5 (30.08- 40.75)	0.087	24.46 (19.94- 33.81) *	28.28 (23.48- 37.90)	0.152	26.58 (20.33- 37.17)	34.63 (24.9- 39.98)	0.23	0.003	0.074
Height (cm)		167 (163.9- 171.1)	163.1 (158.2- 169.3)	0.024	166 (162.2- 169.4)	167.1 (164.4- 171.2)	0.23	165.5 (161.8- 169.7)	164.2 (159.5- 173.7)	0.96	0.12	0.098
Weight (kg)		65.81 (64.58- 67.06)†	93.39 (87.63- 99.54)†	<0.001	72.59± 7.52*	102.33 (98.74- 106.06)†*	<0.001	68.84± 8.51	98.56± 15.14	<0.001	<0.001	0.025
BMI (kg/m²)	≥30	23.25 (21.35- 25.45)	33.04 (30.84- 35.52)	<0.001	26.42 (24.23- 28.23)*	36.26 (32.41- 38.67)*	<0.001	24.98 (23.03- 27.78)*	34.04 (31.76- 38.49)	<0.001	<0.001	0.034
Body Fat (%)		30.7± 6.35	45.29± 6.29	<0.001	32.0± 4.94	42.9± 5.13	<0.001	30.6± 6.27	43.6± 5.06	<0.001	0.479	0.171
WC (cm)	≥80	73.5 (70- 79.5)[1]	94.8 (89.6- 100.1)	<0.001	78.7 (74.45- 82.85)*	99.9 (95.83- 106.08)*	<0.001	78 (73.1- 83.2)*	100 (92.05- 103)	<0.001	<0.001	0.014
HC (cm)		102 (97- 106)[1]	117.6 (112.5- 125)	<0.001	106.25 (102.45- 108.13)*	122.7 (116.55- 128)	<0.001	101 (97.6- 106.5) **	119.5 (114.35- 127.03)	<0.001	0.001	0.172
WHR		0.73 (0.70- 0.77)[1]	0.81 (0.78- 0.84)	<0.001	0.75 (0.72- 0.77)	0.82 (0.79- 0.88)	<0.001	0.76 (0.72- 0.80)*	0.82 (0.75- 0.86)	0.001	0.003	0.196
WtHR	≥0.05	0.45 (0.44- 0.45)[1]†	0.59 (0.56- 0.61)†	<0.001	0.48± 0.04*	0.61± 0.06	<0.001	0.47± 0.05*	0.60± 0.06	<0.001	<0.001	0.437
Fat mass (kg)		20.7± 6.28	41.9 (37.9- 46.3)†	<0.001	23.4± 5.13*	43.6 (41.0- 46.6)†	<0.001	21.4± 6.14	44.4± 10.8	<0.001	0.046	0.761
Fat free mass (kg)		45.7± 5.30	51.2± 6.57	<0.001	49.2± 4.81*	58.4± 5.52*	<0.001	47.4± 4.70	55.8± 6.72*	<0.001	<0.001	<0.001
Android Fat Mass (kg)		1.28 (0.95- 1.67)[4]	2.73 (2.34- 3.5)[2]	<0.001	1.54 (1.17-1.86)[2]*	3.19 (2.64- 3.73)[6]	<0.001	1.40 (1.00- 1.87)[1]	3.25 (2.60- 3.98)	<0.001	0.026	0.105
Android Lean Mass (kg)		3.00 (2.63- 3.25)[4]	3.96 (3.42- 4.70) [2]	<0.001	2.99 (2.60- 3.38)[2]	4.41 (3.94-.4.95)[6]*	<0.001	3.10 (2.79- 3.44)[1]	4.33 (3.75- 4.91)	<0.001	0.151	0.046
Android Fat %		30.3 (25.7- 34.9)[4]	42.2 (38.7- 44.4)[2]	<0.001	33.2 (29.73- 38.09)[2]*	42.09 (38.57- 43.58)[6]	<0.001	31.5 (25.11- 35.88)[1]	43.8 (39.41- 45.98)	<0.001	0.017	0.251
Gynoid Fat Mass (kg)		4.02 (3.5- 4.67)[4]	6.41 (5.37- 7.49)[2]	<0.001	4.43 (6.71- 8.48)[2]	6.44 (5.63- 7.57)[6]	<0.001	3.84 (3.39- 4.59)[1]	6.23 (5.36- 7.85)	<0.001	0.059	0.92
Gynoid Lean Mass (kg)		7.11 (6.33- 7.66)[4]	8.82 (7.97- 9.91)[2]	<0.001	7.32 (6.71- 8.48)[2]	9.94 (9.07- 10.77)[6]*	<0.001	7.52 (6.75- 8.04)[1]*	9.20 (8.35- 10.46)	<0.001	0.004	0.009
Gynoid Fat %		36.6 (33.68- 39.69)[4]	42.9 (39.50- 44.63)[2]	<0.001	37.2 (33.62- 39.46)[2]	39.16 (37.47- 42.0)[6]*	0.003	34.1 (31.62- 37.61)[1]*	41.5 (39.06- 43.18)	<0.001	0.002	0.016
Android/ Gynoid Ratio		0.31 (0.30-0.32)[4]†	0.46± 0.09[2]	<0.001	0.36± 0.07[2]*	0.49± 0.09[6]	<0.001	0.36± 0.09[1]*	0.50± 0.10	<0.001	0.001	0.181
Glucose	>5.4	4.62± 0.38[5]	4.66± 0.40[2]	0.556	4.66± 0.33[1]	4.89 (4.77-	0.005	4.6± 0.35[1]	4.95± 0.49*	0.003	0.717	0.024

(mmol/L)						5.01)[4]†*					
Insulin	>13		11.24 (8.95-			24.28 (15.87-			19.41 (14.12-		
(mU/L)		7.67 (5.17- 10.92)[5]	17.86)[2]	<0.001	11.35 (7.46- 12.97)[1]*	32.46)[4]*	<0.001	10.23 (6.49- 14.38)[1]*	25.84)*	<0.001	<0.001	<0.001
HbA1c	≥40											
(mmol/mol)		28 (26- 29)[5]	29 (25.75- 30.25)[1]	0.103	29 (28- 33)[1]*	30 (28- 33)[4]*	0.261	29.5 (27- 31.25)[1]*	30.5 (27.25- 34)	0.252	<0.001	0.027
HOMA-IR	>2.27	1.53 (1.42-1.65)[5]†	2.61 (2.14- 3.19)[2]†	<0.001	2.25 (1.88- 2.71)[1]†*	5.45± 2.86[4]*	<0.001	2.01 (1.73-2.34)[1]†*	4.35± 1.86*	<0.001	<0.001	<0.001
Cholesterol	≥5											
(mmol/L)		4.6 (4.1- 5.1)[5]	4.8 (4.35-5.55)[2]	0.103	4.3 (3.8- 5)[1]	4.1 (3.6- 4.6)[4]*	0.14	4.3 (3.8- 4.78)[1]*	4.5 (4.23- 5.08)**	0.06	0.005	<0.001
HDL	<1					1.23 (1.16-						
(mmol/L)		1.64 (1.59-1.70)[5]†	1.46± 0.38[2]	0.002	1.51± 0.31[1]*	1.31)[4]†*	<0.001	1.53± 0.40[1]*	1.24± 0.29	0.002	0.004	0.025
Calc_LDL	≥3.4											
(mmol/L)		2.54 (2.43- 2.65)[6]†	2.99± 0.80[2]	0.036	2.53± 0.84[1]	2.33± 0.67[4]*	0.233	2.36± 0.68[1]*	2.71± 0.62	0.033	0.034	<0.001
Chol/HDL	≥4.5	2.73 (2.38- 3.23)[5]	3.29 (2.95- 3.94)[2]	<0.001	2.93 (2.3- 3.62)[1]	3.29 (2.77- 3.97)[4]	0.039	3.01 (2.39- 3.44)[1]	3.9 (3.30- 4.41)	<0.001	0.499	0.08
	≥2					0.99 (0.87 -						
TG (mmol/L)		0.79 (0.75- 0.84)[5]†	1.03 (0.87-1.24)[2]†	0.002	0.80± 0.27[1]	1.13)[4]†	0.006	0.88 (0.79-0.99)[1]†	1.43± 0.66	0.001	0.132	0.084
CRP	>5	3 (3- 3)[6]	3 (3- 7.42)[2]	<0.001	3 (3- 3)[1]	3 (3- 4.37)[4]	0.003	3 (3- 3)[1]	3 (3- 5.4)	0.002	0.221	0.328
TNF-α												
(pg/mL)		5.97 (4.76- 7.33)[2]	6.88 (5.27- 8.51)[1]	0.031	7.41 (6.04- 9.22)[2]*	6.82 (5.6- 8.71)[4]	0.381	6.9 (5.77- 8.59)[1]*	7.62 (5.98- 8.5)	0.476	<0.001	0.48
IL-6 (pg/mL)		1.95 (1.27- 2.67)[3]	2.33 (1.49- 3.26)[1]	0.112	2.03 (1.59- 2.56)[2]	2.24 (1.87- 2.9)[4]	0.207	2.06 (1.56- 2.96)[1]	2.31 (1.57- 3.62)	0.531	0.3	0.95
IL-10												
(pg/mL)		10.3 (5.73- 18.34)[8]	16.08 (9.6- 20.15)[2]	0.039	14.77 (9.28- 22.95)[4]	9.55 (5.94- 18.19)[5]	0.029	14.24 (9.72- 23.19)[2]*	15.61 (6.95- 24.49)	0.942	0.003	0.059
Systolic BP	≥130								121 (114.25-			
(mmHg)		114 (109- 120)	117 (113- 129)	0.002	112 (107- 117.25)	121 (114- 130)	<0.001	112 (107- 119)	126.75)	0.002	0.498	0.613
Diastolic BP	≥80	70.77 (69.80-	75.2 (72.25,									
(mmHg)		71.74)†	78.27)†	0.002	70.5± 7.03	77.29± 9.73	<0.001	72.63± 8.7	77.96± 9.37	0.015	0.349	0.64
Leptin			17504 (14439-									
(pg/mL)		5802 (5275- 6390)[2]†	21218)[1]†	<0.001	8832± 4966[2]	18841± 9175[4]	<0.001	6196 (5184- 7405)[1]†	18263± 7899	<0.001	0.169	0.895
Ghrelin			28.59 (17.02-			14.36 (11.29-			24.37 (15.19-			
(pg/mL)		43.53 (24.91- 70.78)[2]	49.89)[1]	0.044	33.88 (16.03- 50.30)[2]	26.09)[4]*	<0.001	41.58 (21.09- 74.06)[1]	33.69)**	0.007	0.254	0.002

Abbreviations: BMI body mass index; WC waist circumference; HC hip circumference; WHR waist to hip ratio; WtHR waist to height ratio; HbA1c glycated haemoglobin, HOMA-IR homeostasis model assessment of insulin resistance; HDL high density lipoprotein; Calc LDL Calculated low density lipoprotein; TG triglycerides; CRP C-reactive protein; TNF-α tumor necrosis factor alpha; IL interleukin; BP blood pressure.

Values are mean±SD or median (25th-75th quartiles) unless otherwise indicated

†Mean for the log transformed data values, back transformed to the original scale; ‡ within ethnic groups; §between ethnic groups

Differences within ethnic groups were analysed by Mann Whitney or independent samples T-Test as appropriate

Differences between groups were analysed by Kruskal Wallis and post hoc Mann Whitney with bonferroni correction significant at $p < 0.0167$ or ANOVA with post hoc Tukeys significant at $p < 0.05$, as appropriate

* significantly different than NZE women, ** significantly different than Pacific women

[1−8] indicates number of participants with missing date for each variable.

Table 3.4 Anthropometric and clinical characteristics of participants classified by body fat % and ethnicity

	At risk value	NZE			Pacific			Māori			*P* § BF <35%	*p* § BF ≥35%
		<35% BF	≥35% BF	*p* ‡	<35% BF	≥35% BF	*p* ‡	<35% BF	≥35% BF	*p* ‡		
		n= 156	n= 77		n= 30	n= 60		n= 41	n= 42			
Age (years)		30.25 (24.69, 38.17)	34.33 (28.54, 41.08)	0.007	25.67 (19.48, 32.48)*	28.58 (20.94, 38.23)*	0.115	26 (19.38, 36.83)	32.38 (23.17, 40.33)	0.17	0.01	0.026
Height (cm)		167.49± 6.51	166.27± 6.83	0.184	167.4± 6.3	167.15± 5.52	0.843	166.35± 5.03	165.71± 7.03	0.636	0.576	0.523
Weight (kg)		64.18 (58.72, 68.55)	80.38 (70.19, 87.75)	<0.001	70.69 (67.97, 80.72)*	99.36 (86.79, 106.41)*	<0.001	66.31 (63.61, 70.87)**	85.21 (73.52, 100.17)**	<0.001	<0.001	<0.001
BMI (kg/m²)	≥30	22.96± 2.49	29.08 (27.87-30.35)†	<0.001	26.1± 2.71*	35.28± 5.34*	<0.001	24.22±2.85*, **	31.86± 5.99**	<0.001	<0.001	<0.001
Body Fat (%)		29 (24.7, 31.98)	39.9 (37.25, 44.55)	<0.001	29.9 (27.03, 32.93)	41.45 (39.35, 46.25)	<0.001	27.8 (25.45, 31.2)	40.45 (36.5, 43.83)	<0.001	0.146	0.165
WC (cm)	≥80	73.12 (72.12-74.09)¹†	88.24± 12.03	<0.001	78.59± 7.18*	98.95± 10.64*	<0.001	75.51± 6.33	91.97± 11.27**	<0.001	<0.001	<0.001
HC (cm)		100.5 (96, 104)¹	111 (105.25, 115.8)	<0.001	106 (101.88, 108.5)*	120.25 (112.1, 127)*	<0.001	100.2 (96.35, 103.3)**	113.3 (107.78, 123.08)**	<0.001	<0.001	<0.001
WHR		0.73 (0.72-0.74)¹†	0.79± 0.06	<0.001	.75± .05	.82± .06*	<0.001	.75± .04*	.80± .06	<0.001	0.017	0.004
WtHR	≥0.05	0.44 (0.43- 0.44)¹†	0.53± 0.08	<0.001	.47± .04*	.59± .06*	<0.001	.45± .04	.56± .07**	<0.001	<0.001	<0.001
Fat mass (kg)		18.6 (14.7- 21.8)	32 (27.6- 37.8)	<0.001	21.5 (18.2-24.5)*	40.7 (34.1-49.3)*	<0.001	18.6 (16.1- 21.7)**	33.3 (26.9-44.9)**	<0.001	0.002	<0.001
Fat free mass (kg)		46.1± 5.36	47.1± 6.54	0.263	51.3± 6.23*	56.2± 6.70*	0.001	48.3± 4.71	51.2± 7.65*, **	0.046	<0.001	<0.001
Android Fat Mass (kg)		1.10 (0.87- 1.42)	2.23 (1.79- 2.72)	<0.001	1.33 (1.11-1.84)*	2.83 (2.44-3.64)*	<0.001	1.16 (0.89- 1.46)	2.53 (2.08-3.46)*	<0.001	0.003	<0.001
Android Lean Mass (kg)		2.88 (2.57- 3.14)	3.38 (3.04- 3.97)	<0.001	2.95 (2.58- 3.37)	4.25 (3.62-4.85)*	<0.001	2.95 (2.69- 3.29)	3.82 (3.29-4.44)*	<0.001	0.207	<0.001
Android Fat %		28.4 (23.82- 31.86)	39.7 (35.13- 43.15)	<0.001	32.2 (27.75- 34-53)*	41.4 (38.52-43.44)	<0.001	28.4 (23.54-32.76)**	40.5 (37.59-44.41)	<0.001	0.003	0.079
Gynoid Fat Mass (kg)		3.78 (3.37- 4.46)	5.47 (4.66- 6.22)	<0.001	4.21 (3.70-4.91)*	6.37 (5.12-7.08)*	<0.001	3.61 (3.10- 3.96)**	5.50 (4.72-6.47)	<0.001	0.002	0.006
Gynoid Lean Mass (kg)		7.07 (6.29- 7.65)	7.68 (6.74- 8.82)	<0.001	7.37 (6.56- 8.74)	9.79 (8.46-10.55)*	<0.001	7.60 (6.85- 7.98)*	8.44 (7.24-9.71)**	<0.001	0.004	<0.001
Gynoid Fat %		35.76 (32.51-38.64)	41.83 (38.11- 44.04)	<0.001	36 (32.16- 38.84)	39.2 (37.52-41.68)	<0.001	32.6 (29.78-34.21)*, **	40.3 (38.44-42.22)	<0.001	<0.001	0.057
Android:gynoid ratio		0.28 (0.25- 0.35)	0.41 (0.36- 0.47)	<0.001	0.32 (0.29-0.38)*	0.46 (0.41-0.54)*	<0.001	0.31 (0.27- 0.41)*	0.46 (0.40-0.55)*	<0.001	0.001	0.001
Glucose (mmol/L)	>5.4	4.6 (4.3, 4.8)³	4.7 (4.5, 4.95)⁴	0.011	4.7 (4.4, 4.9)¹	4.9 (4.6, 5.1)⁴	0.011	4.5 (4.3, 4.9)¹	4.8 (4.5, 5.03)	0.019	0.516	0.105

Insulin (mU/L)	>13	7.19 (6.63- 7.80)[3] †	10.07 (9.01- 11.25)[4]†	<0.001	10.38 (8.53- 12.63)[1]†*	23.28± 12.02[4]*	<0.001	9.23 (7.68- 11.08)[1]†*	16.76± 8.16*, **	<0.001	<0.001	<0.001
HbA1c (mmol/mol)	≥40	28 (25.5, 29)[3]	28 (26, 30)[3]	0.305	29 (28, 31)[1]*	31 (28, 34)[4]*	0.118	30 (27, 32)[1]*	29 (27.75, 32.5)*	0.944	<0.001	<0.001
HOMA-IR	>2.27	1.46 (1.34-1.59)[3]†	2.10 (1.87- 2.36)[4]†	<0.001	2.14 (1.73- 2.64)†*	5.12± 2.84*	<0.001	1.87 (1.56- 2.25)†*	3.64± 1.87*, **	<0.001	<0.001	<0.001
Cholesterol (mmol/L)	≥5	4.61 (4.47- 4.75)[3]†	4.84 (4.65-5.04)[4]†	0.061	4.47± .81[1]	4.12± .82[4]*	0.054	4.37± .78[1]	4.46± .65*, **	0.575	0.088	<0.001
HDL (mmol/L)	<1	1.7± 0.42[3]	1.57± 0.38[4]	0.025	1.49± .30[1]*	1.28 (1.2- 1.36)[4]†*	0.007	1.59± .40[1]	1.32± .34*	<0.001	0.016	<0.001
Calc_LDL (mmol/L)	≥3.4	2.49 (2.37- 2.62)[4]†	2.78 (2.61- 2.97)[4]†	0.01	2.62± .75[1]	2.32± .74[4]*	0.079	2.35± .73[1]	2.57± .61	0.138	0.127	<0.001
Chol/HDL	≥4.5	2.7 (2.35, 3.18)[3]	3.09 (2.58, 3.91)[4]	<0.001	2.98 (2.58, 3.49)[1]	3.25 (2.63, 3.93)[4]	0.349	2.87 (2.31, 3.41)[1]	3.52 (2.89, 4.11)	0.001	0.183	0.145
TG (mmol/L)	≥2	0.77 (0.6, 1.03)[3]	0.85 (0.71, 1.13)[4]	0.008	0.78 (0.57, 0.97)[1]	0.87 (0.70, 1.2)[4]	0.063	0.85 (.62, 1.1)[1]	1.13 (.81, 1.5)*	0.004	0.609	0.019
CRP (mg/L)	>5	3 (3, 3)[3]	3 (3, 4.8)[5]	<0.001	3 (3,3)[1]	3 (3, 3.58)[4]	0.122	3 (3,3)[1]	3 (3, 4.52)	0.007	0.819	0.343
TNF-α (pg/mL)		5.91 (4.60- 7.24)[1]	6.46 (5.53- 7.73)[2]	0.015	6.84 (5.84- 8.95)[2]*	7.35 (5.91- 8.82)[4]	0.544	6.73 (5.74- 8.59)[1]*	7.55 (6.16- 8.75)*	0.316	0.001	0.02
IL-6 (pg/mL)		2.02 (1.21, 2.75)[2]	1.9 (1.48, 2.48)[2]	0.584	2.1 (1.64, 2.53)[2]	2.12 (1.76, 2.9)[4]	0.645	2.23 (1.59, 2.96)[1]	2.04 (1.57, 3.09)	0.781	0.462	0.3
IL-10 (pg/mL)		10.35 (5.62, 18.32)[5]	12.69 (6.75, 19.14)[5]	0.194	15.65 (9.1, 24.72)[4]	9.89 (5.95, 17.43)[5]	0.031	14.34 (8.42, 25.06)[1]*	15.01 (10.15, 23.52)[1]	0.992	0.01	0.058
Systolic BP (mmHg)	≥130	114 (108, 119)	115 (111, 124)	0.005	111.5 (107, 118.75)	119 (113, 127)	<0.001	112 (108, 116.5)	118 (110.5, 123.25)	0.03	0.854	0.236
Diastolic BP (mmHg)	≥80	70.24± 6.39	74.7± 8.41	<0.001	70.97± 7.77	76.15± 9.55	0.012	72.07± 8.27	76.21± 9.64	0.039	0.313	0.562
Leptin (pg/mL)		5074 (4564- 5642)[1]†	11925 (10359- 13729)[2]†	<0.001	7965± 5039[2]	15839 (13862- 18099)[4]†*	<0.001	4779 (3960- 5766)[1]†	13880 (11805- 16319)†	<0.001	0.146	0.016
Ghrelin (pg/mL)		44.89 (26.07, 73.56)[1]	35.03 (20.85, 62.62)[2]	0.065	29.05 (16.03, 87.13)[2]	16.18 (11.83, 32.34)[4]*	0.012	41.58 (20.17, 73.16)[1]	29.8 (17.17, 50.12)**	0.124	0.305	<0.001

Abbreviations: BMI body mass index; BF body fat; WC waist circumference; HC hip circumference; WHR waist to hip ratio; WtHR waist to height ratio; HbA1c glycated haemoglobin, HOMA-IR homeostasis model assessment of insulin resistance; HDL high density lipoprotein; Calc LDL Calculated low density lipoprotein; TG triglycerides; CRP C-reactive protein; TNF-α tumor necrosis factor a; IL interleukin; BP blood pressure

Values are mean±SD or median (25th-75th quartiles) unless otherwise indicated

†Mean for the log transformed data values, back transformed to the original scale;

Differences within ethnic groups were analysed by Mann Whitney or independent samples T-Test as appropriate

Differences between ethnic groups were analysed by Kruskal Wallis and post hoc Mann Whitney with bonferroni correction significant at p <0.0167 or ANOVA with post hoc Tukeys significant at p <0.05, as appropriate

* significantly different than NZE women, ** significantly different than Pacific women

[1–5] indicates number of participants with missing date for each variable.

Table 3.5 Sensitivity and specificity of anthropometric measures in relation to metabolic health indicators in NZE, Pacific and Māori women.

	NZE			Pacific			Māori		
	Sensitivity	Specificity	Correctly identified	Sensitivity	Specificity	Correctly identified	Sensitivity	Specificity	Correctly identified
Hyperinsulinaemia >13mU/L			%			%			%
BMI ≥25kg/m²	67	67	67	96	25	66	89	53	68
BMI ≥30kg/m²	31	91	81	84	81	82	54	89	74
BMI ≥32kg/m²	19	95	83	71	92	80	46	96	74
Body fat ≥30%	89	43	50	96	33	69	83	29	62
Body fat ≥35%	50	71	68	88	64	78	77	68	72
WC≥80cm	64	74	72	90	44	71	80	62	70
WC>88cm	36	87	79	88	78	84	54	89	74
WtHR ≥0.5	50	80	76	92	64	80	80	79	79
WtHR ≥0.6	22	99	87	43	94	65	23	98	66
WHR ≥0.8	36	83	76	61	72	66	51	77	66
HOMA-IR ≥2.27									
BMI ≥25kg/m²	60	70	67	90	20	69	81	54	68
BMI ≥30kg/m²	22	91	71	68	72	69	49	92	70
BMI ≥32kg/m²	14	96	72	58	88	67	40	97	67
Body fat ≥30%	78	44	54	90	32	73	74	44	60
Body fat ≥35%	45	73	65	77	60	72	67	67	67
WC≥80cm	55	77	71	80	36	67	72	62	67
WC>88cm	31	89	72	73	72	73	47	90	67
WtHR ≥0.5	42	83	71	80	60	74	67	77	72
WtHR ≥0.6	12	99	74	35	92	52	21	100	59
WHR ≥0.8	32	85	70	53	68	58	47	77	61
Chol-HDL >4.5									
BMI ≥25kg/m²	63	89	63	60	11	14	86	37	41
BMI ≥30kg/m²	31	89	85	60	44	45	57	73	72
BMI ≥32kg/m²	13	93	88	60	56	56	43	80	77
Body fat ≥30%	75	39	41	80	16	20	86	36	40
Body fat ≥35%	50	69	68	60	34	35	71	51	52
WC≥80cm	56	69	68	60	24	26	86	47	50
WC>88cm	38	85	82	60	40	41	57	73	72
WtHR ≥0.5	56	78	76	60	31	33	86	57	60
WtHR ≥0.6	13	96	90	60	75	74	29	91	85
WHR ≥0.8	44	82	79	60	54	54	86	69	71
TG >2mmol/L									
BMI ≥25kg/m²	71	63	63	100	14	18	86	37	41
BMI ≥30kg/m²	57	89	88	100	46	48	71	75	74
BMI ≥32kg/m²	43	94	92	100	58	60	57	81	79
Body fat ≥30%	100	39	41	100	17	21	86	36	40
Body fat ≥35%	43	68	67	100	36	39	71	51	52
WC≥80cm	71	69	69	100	26	29	86	47	50
WC>88cm	71	85	85	100	42	45	71	75	74
WtHR ≥0.5	71	77	77	100	33	36	86	57	60
WtHR ≥0.6	14	96	93	50	74	73	29	91	85
WHR ≥0.8	43	81	80	75	54	55	57	67	66
CRP >5									
BMI ≥25kg/m²	68	66	67	90	14	23	83	39	45
BMI ≥30kg/m²	32	90	82	90	49	54	58	76	73
BMI ≥32kg/m²	26	96	86	80	61	63	42	81	76
Body fat ≥30%	87	42	48	90	18	26	83	37	44
Body fat ≥35%	55	72	69	80	36	42	75	53	56
WC≥80cm	48	70	67	90	27	35	83	49	54
WC>88cm	39	87	80	90	45	50	50	74	71
WtHR ≥0.5	42	65	74	90	35	42	75	59	61
WtHR ≥0.6	16	97	86	60	78	76	33	93	84
WHR ≥0.8	29	81	74	50	54	54	50	67	65

Abbreviations: BMI body mass index; BF% body fat %; WC waist circumference; WtHR waist to height ratio; WHR waist to hip ratio; HOMA-IR homeostasis model assessment of insulin resistance; Chol/HDL cholesterol to high density lipoprotein ratio; TG triglycerides; CRP c-reactive protein; NZE New Zealand European.

Figure 3.1 Prevalence of high metabolic biomarkers in obese women by BMI (1a) and body fat % (1b)

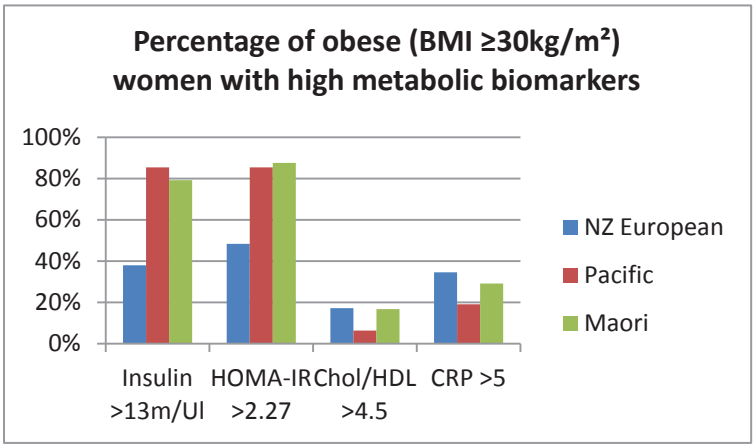


Figure 1a

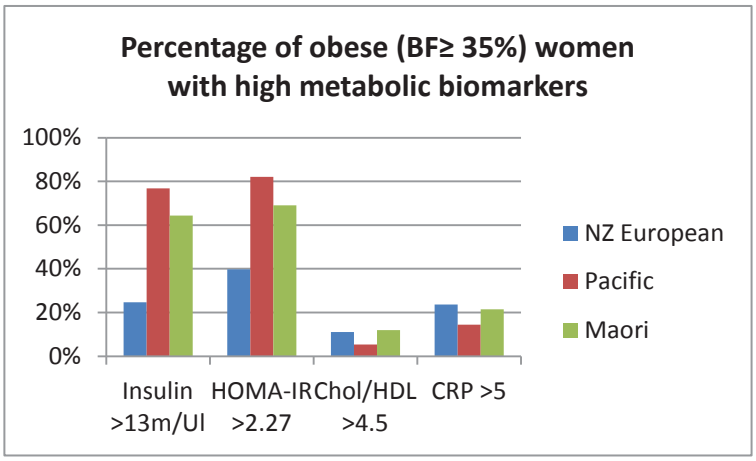


Figure 1b

Section 4: Conclusions and Recommendations

4.1 Overview and Conclusions

The aim of this research was to explore the body composition profiles and metabolic health profiles of healthy New Zealand women. The first objective was to use body mass index (BMI) and body fat percent (BF%) thresholds to investigate different body composition profiles of healthy NZ European (NZE), Māori and Pacific women in terms of anthropometry and body fat location. To do this, NZE women were analysed in the original 'EXPLORE' profile groups, to investigate whether the normal BMI (≤25), high BF% (≥30) (NH) profile was associated with increased biomarkers of metabolic disease risk, as previously described in literature. (Lorenzo *et al.*, 2006; De Lorenzo *et al.*, 2007; Kosmala *et al.*, 2012; Kim *et al.*, 2013) However, the prevalence of the normal BMI (≤25) and normal BF% (≤30%) (NN) and NH profiles were low for Pacific and Māori women. Due to this finding, participants were also grouped by presence or absence of obesity, with obesity defined as both BMI of ≥30kg/m² and BF ≥35%. The second objective was to examine the metabolic profiles of these women as indicated by biochemical markers of metabolic health. This was achieved by investigating a range of metabolic health biomarkers include glucose metabolism markers, lipid markers, inflammation markers and metabolic hormones. Separation of the ethnic groups allowed investigation of ethnic specific patterns between body composition profiles and markers of metabolic health. Similarities and differences were analysed both within and between ethnic groups.

This study supports previous findings that compared to NZE women, Pacific and Māori women have a lower BF% at a similar BMI, (Swinburn *et al.*, 1999; Taylor *et al.*, 2010) which is likely a contributing factor to the lack of NH profile seen in these ethnic groups. Our results also highlighted several other ethnic differences between these groups in terms of their body composition and metabolic biomarkers. A larger BMI in Pacific women may be contributing to the higher metabolic markers, particularly glucose metabolism markers, seen in Pacific compared to NZE women. However, Pacific women still had higher glucose metabolism markers in a group where total fat mass did not differ and the higher BMI appeared to be due to a higher fat free mass. Māori women had higher insulin and HOMA-IR than NZE women even when there were no apparent body composition differences which may suggest they have a higher risk of insulin resistance at a given body size. Despite the metabolic differences

between ethnic groups, there was no obvious indication that body fat content was responsible, as there were no significant differences in BF% between ethnic groups, and there were no clear patterns in total body fat (kg) as a potential explanation for these metabolic differences. Previous arguments against using BMI to define obesity and the associated metabolic disease risk have suggested that information like lean body mass, (Khaodhiar and Blackburn, 2001) BF%, (Gomez-Ambrosi *et al.*, 2012) and regional fat location (Pou *et al.*, 2009; Mooney *et al.*, 2013) are important factors to consider. However, in our study no clear patterns were seen with these factors and the metabolic differences between the ethnic groups.

Additionally, contrary to expectation, android composition differences did not always align with differences in waist measurements when comparing the ethnic groups, specifically between Maori women and the other ethnic groups. For example, the BF% obese Māori women had a higher android fat than the corresponding NZE group but there were no differences in WC, WHR, or WtHR. This suggests that different abdominal measurement thresholds may be needed to identify the same amount of android fat for NZ European, Pacific and Māori women.

Another surprising finding in this group of women was that higher inflammation markers were not always seen with higher insulin resistance markers despite reports that inflammation and IR are closely interrelated. (Kahn *et al.*, 2006; McArdle *et al.*, 2013) In the non-obese groups, Māori and Pacific women had higher glucose metabolism markers and TNF-α than their NZE counterparts, however in the BMI obese groups there were no ethnic differences in inflammatory markers despite higher glucose metabolism markers of Māori and Pacific compared to NZE women. This pattern was also seen for Pacific and NZE women in the BF% group. NZ Europeans had a lower prevalence of obesity, but a higher prevalence of CRP ≥5 compared to the other ethnic groups. Additionally, obese Pacific women had lower IL-10 than non-obese in both groups, while NZE women with a BMI ≥30 had higher IL-10 than their non-obese counterparts. It appears that the relationship between obesity, inflammation and insulin resistance is complicated, and may be influenced by ethnicity.

There were ethnic differences in the prevalence of biomarkers outside of the recommended ranges, and in which body composition measures were best able to detect this for each biomarker. Pacific and Māori women were more obese and were more likely to have raised insulin or HOMA-IR, while along with CRP, NZEs had a higher prevalence of raised Chol/HDL than Pacific women despite a lower prevalence of obesity. This suggests that the

relationship between obesity and metabolic outcomes might be different for each ethnic group, and therefore using one measure such as BMI to define obesity and identify those to screen for metabolic disease risk is unlikely to be optimal for all ethnicities. This notion is supported further by the differences seen between ethnicities in the sensitivity and specificity of the various body compositions measures to detect those with abnormal biomarkers. While BMI and BF% were generally the most sensitive measures overall for detecting high biomarkers, they generally had low specificity, meaning they had a poor ability to rule out those who did not have high biomarkers. There were also ethnic differences in the sensitivities of the body composition measures to detect high levels of the various biomarkers. For example for hyperinsulinaemia HOMA-IR BF% ≥30 was most sensitive for NZE women, while BF% ≥30 and BMI ≥25 were equally sensitive for Pacific women, and BMI ≥25 was most sensitive for Māori women. These ethnic specific measures were consistently the most sensitive across all biomarkers, however with Pacific and Māori groups, other measures such as WC ≥80cm and WtHR ≥0.5 were equally sensitive for TG, CRP, and Chol/HDL. Abdominal obesity measures were less sensitive than BMI and BF%, however WtHR ≥0.6 was the most specific measure for all ethnic groups across the range of biomarkers. Previous research has reported conflicting results for the ability of these abdominal measures to detect metabolic disease risk better than BMI. (Lee *et al.*, 2008; Hsieh *et al.*, 2010) As sensitivity is considered a greater priority than specificity our results lean in favour of using BMI and BF% thresholds due to having consistently high sensitivity across the range of biomarkers tested. These thresholds vary with ethnicity with the most sensitive being BF% ≥30 for NZEs, BF% ≥30 and BMI ≥25 for Pacific and BMI ≥25 for Māori women.

These results provide valuable insight into the differences that exist between these three ethnic groups in New Zealand in terms of body composition and metabolic health. These differences suggest a need to identify the most prominent metabolic risk markers for each ethnic group, and to identify which body composition measures best indicate this risk. The current study provides some initial insights into what these are with the higher prevalence of raised Chol/HDL in NZEs than the other ethnic groups, and the higher insulin and HOMA-IR found in Pacific and Māori women compared to NZEs. Further research is needed to confirm our findings. Due to the trade-off between sensitivity and specificity for each body composition measure, using a combination of measures may be a better approach to get a more accurate picture of overall metabolic health. The use of a highly sensitive measure first to rule out those with a metabolic condition, followed by a highly specific measure to rule out those who do not have the metabolic condition is a promising method of detecting those at highest risk when

time and resources for screening are limited. (Lalkhen and McCluskey, 2008) Although this method is not perfect, it provides a starting point to identify those who would most benefit from further screening and intervention. For example, NZEs with a BF% ≥30, Pacific women with a BMI ≥25 or a BF% ≥30, and Māori with BMI ≥25 could then have blood tests to assess biomarkers for glucose metabolism, lipids, and CRP. Due to the screening for a healthy population in the current study, our ability to test this approach was limited to a few biomarkers, as there were few metabolic abnormalities despite a high prevalence of obesity. The ability to identify which ethnic specific body composition profiles are most at risk of metabolic disease is just the first step in working towards reducing the ethnic inequalities seen with obesity and health in New Zealand. Understanding the driving factors behind the ethnic differences seen in this study, which may include biological, physiological and socio-economic factors, (Ministry of Health, 2002; Tobias *et al.*, 2009) is also going to be an essential part of working to reduce the development and inequality of chronic disease.

4.2 Strengths of the research

Strengths of this research include the separate analysis of the three ethnic groups, including two of those who are clearly disadvantaged when it comes to obesity rates and health disparities in New Zealand. Additionally, the extensive list of body compositional variables investigated is also a key strength as it covered all of the major anthropometric body composition measures commonly used, along with android and gynoid composition and compared these to a comprehensive list of metabolic biomarkers which, to our knowledge, has not previously been done with these ethnic groups. This study provides valuable information to guide future research on these ethnic groups, by identifying key differences within and between these groups, and where further investigation is required.

4.3 Limitations of the research

Limitations for this study include the smaller numbers of Māori and Pacific women compared to NZE women due to inability to recruit the desired numbers in the time frame allocated despite extending the recruitment phase. This may have affected the power of the statistics to accurately detect differences within and between ethnic groups. Initially women were recruited to fit into specific body composition profiles, which was ideal for the NZE cohort but Māori and Pacific did not fit into all of these. Therefore, the selection criteria was not random in terms of all body profiles accepted for the NZE group which may have influenced results and

reduced the accuracy of comparison to Pacific and Māori women. Additionally overall selection was not random and participants were selected on a volunteer basis so are possibly not reflective of the wider population. Volunteers for this type of research may be more health conscious than the general population and thus, less likely to be obese. Additionally, as this was cross sectional research investigating healthy women, we cannot conclude that any of the patterns seen will be associated with increased likelihood of disease. There were differences in age between Pacific and NZE women where the latter were significantly older. However, all participants were selected to be pre-menopausal as this is an important factor influencing age related body composition and metabolic risk for women. (Feng *et al.*, 2008; Kuk *et al.*, 2009) Although age differences may have influenced the results, the relatively young age of participants and their pre-menopausal status would likely have limited this. Due to the wealth of data involved in this study, further and more comprehensive analysis was outside of the scope of this thesis, but would likely provide useful insight into the patterns discussed here. Suggestions for further analysis include the investigation of the optimal cut off points for the various body composition measures, to allow identification of those at risk of abnormal metabolic markers. Additionally, performing logistic regression to explore the associations of the body composition measures with the metabolic biomarkers may yield valuable information.

4.4 Recommendations for future research

This study identifies several areas where research could be continued. As the body composition and fat location measures could not explain all of the metabolic differences seen between NZE, Māori and Pacific women, further exploration of potential influencing factors is required. Suggestions for this include free fatty acids, comparisons of subcutaneous and visceral fat profiles, and lifestyle factors that may affect metabolism such as dietary composition, exercise, living environment, and stress levels. In order to address the health inequalities that exist in New Zealand, understanding the driving factors behind the ethnic differences seen in this study is going to be an essential part of working to reduce the development of chronic disease.

The results of this study found ethnic differences in which metabolic disease risk biomarkers were more likely to be outside of reference ranges for health, suggesting ethnic specific metabolic consequences of excess body weight. Further research should confirm whether this is the case, and identify the best body composition measure/s to identify these ethnic specific metabolic disease risk factors. The method of using a measure with high sensitivity to identify

majority of those who do have the outcome being assessed, then subjecting these people to a second measure with a high specificity to rule out those who do not have the outcome identified, needs further investigation. It appears to be a promising way of determining those who should be screened first when time and resources are limited. As this study included only healthy participants, we could not test the sensitivity and specificity of the measures to detect health conditions such as pre-diabetes or metabolic syndrome, however, this would be more useful in a clinical environment than detecting high levels of individual biomarkers so it is recommended that this approach be explored on those with and without these disease states. Additionally, as this was a cross sectional design we cannot conclude that any of the metabolic profiles seen will relate to metabolic disease later on. Therefore it is recommended that longitudinal research be conducted to investigate whether the early metabolic changes detected in these healthy women, are indeed reflective of likelihood of future disease. This would be particularly useful to identify whether the high prevalence of elevated insulin and HOMA-IR in Pacific and Māori women, and the ethnic differences in glucose metabolism markers do correspond with risk of hyperglycaemia, raised HbA1c and Type II diabetes risk over time.

4.5 References

De Lorenzo, A., Del Gobbo, V., Premrov, M. G., Bigioni, M., Galvano, F. & Di Renzo, L. 2007. Normal-weight obese syndrome: early inflammation? *American Journal of Clinical Nutrition,* 85(1)**,** 40-45.

Feng, Y., Hong, X., Wilker, E., Li, Z., Zhang, W., Jin, D., Liu, X., Zang, T., Xu, X. & Xu, X. 2008. Effects of age at menarche, reproductive years, and menopause on metabolic risk factors for cardiovascular diseases. *Atherosclerosis,* 196(2)**,** 590-597.

Gomez-Ambrosi, J., Silva, C., Galofre, J. C., Escalada, J., Santos, S., Millan, D., Vila, N., Ibanez, P., Gil, M. J., Valenti, V., Rotellar, F., Ramirez, B., Salvador, J. & Fruhbeck, G. 2012. Body mass index classification misses subjects with increased cardiometabolic risk factors related to elevated adiposity. *International Journal of Obesity,* 36(2)**,** 286-294. Available: DOI 10.1038/ijo.2011.100.

Hsieh, S. D., Ashwell, M., Muto, T., Tsuji, H., Arase, Y. & Murase, T. 2010. Urgency of reassessment of role of obesity indices for metabolic risks. *Metabolism-Clinical and Experimental,* 59(6)**,** 834-840. Available: DOI 10.1016/j.metabol.2009.09.032.

Kahn, S. E., Hull, R. L. & Utzschneider, K. M. 2006. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature,* 444(7121)**,** 840-846. Available: DOI 10.1038/nature05482.

Khaodhiar, L. & Blackburn, G. L. 2001. Obesity assessment. *American Heart Journal,* 142**,** 1095-1101.

Kim, J. Y., Han, S. H. & Yang, B. M. 2013. Implication of high-body-fat percentage on cardiometabolic risk in middle-aged, healthy, normal-weight adults. *Obesity,* 21(8)**,** 1571-1577. Available: DOI 10.1002/oby.20020.

Kosmala, W., Jedrzejuk, D., Derzhko, R., Przewlocka-Kosmala, M., Mysiak, A. & Bednarek-Tupikowska, G. 2012. Left ventricular function impairment in patients with normal-weight obesity contribution of abdominal fat deposition, profibrotic state, reduced insulin sensitivity, and proinflammatory activation. *Circulation-Cardiovascular Imaging,* 5(3)**,** 349-356. Available: DOI 10.1161/circimaging.111.969956.

Kuk, J. L., Saunders, T. J., Davidson, L. E. & Ross, R. 2009. Age-related changes in total and regional fat distribution. *Ageing Research Reviews,* 8(4)**,** 339-348. Available: DOI 10.1016/j.arr.2009.06.001.

Lalkhen, A. G. & McCluskey, A. 2008. Clinical tests: sensitivity and specificity. *Continuing Education in Anaesthesia, Critical Care & Pain,* 8(6)**,** 221-223.

Lee, C. M. Y., Huxley, R. R., Wildman, R. P. & Woodward, M. 2008. Indices of abdominal obesity are better discriminators of cardiovascular risk factors than BMI: a meta-analysis. *Journal of Clinical Epidemiology,* 61(7)**,** 646-653. Available: DOI 10.1016/j.jclinepi.2007.08.012.

Lorenzo, A., Martinoli, R., Vaia, F. & Di Renzo, L. 2006. Normal weight obese (NWO) women: An evaluation of a candidate new syndrome. *Nutrition Metabolism and Cardiovascular Diseases,* 16(8)**,** 513-523. Available: DOI 10.1016/j.numecd.2005.10.010.

McArdle, M. A., Finucane, O. M., Connaughton, R. M., McMorrow, A. M. & Roche, H. M. 2013. Mechanisms of obesity-induced inflammation and insulin resistance: insights into the emerging role of nutritional strategies. *Frontiers in Endocrinology,* 4**,** 52-52. Available: DOI 10.3389/fendo.2013.00052.

Ministry of Health. 2002. *Reducing inequalities in health*. Wellington: New Zealand: Ministry of Health. Retrieved from http://www.health.govt.nz/system/files/documents/publications/reducineqal.pdf

Mooney, S. J., Baecker, A. & Rundle, A. G. 2013. Comparison of anthropometric and body composition measures as predictors of components of the metabolic syndrome in a clinical setting. *Obesity Research & Clinical Practice,* 7(1)**,** E55-E66. Available: DOI 10.1016/j.orcp.2012.10.004.

Pou, K. M., Massaro, J. M., Hoffmann, U., Lieb, K., Vasan, R. S., O'Donnell, C. J. & Fox, C. S. 2009. Patterns of abdominal fat distribution: the framingham heart s. *Diabetes Care,* 32(3)**,** 481-485. Available: DOI 10.2337/dc08-1359.

Swinburn, B. A., Ley, S. J., Carmichael, H. E. & Planck, L. D. 1999. Body size and composition in Polynesians. *International Journal of Obesity,* 23(11)**,** 1178-1183. Available: DOI 10.1038/sj.ijo.0801053.

Taylor, R. W., Brooking, L., Williams, S. M., Manning, P. J., Sutherland, W. H., Coppell, K. J., Tipene-Leach, D., Dale, K. S., McAuley, K. A. & Mann, J. I. 2010. Body mass index and waist circumference cutoffs to define obesity in indigenous New Zealanders. *American Journal of Clinical Nutrition,* 92(2)**,** 390-397. Available: DOI 10.3945/ajcn.2010.29317.

Tobias, M., Blakely, T., Matheson, D., Rasanathan, K. & Atkinson, J. 2009. Changing trends in indigenous inequalities in mortality: lessons from New Zealand. *International Journal of Epidemiology,* 38(6)**,** 1711-1722. Available: DOI 10.1093/ije/dyp15

Appendix A: Supplementary Methods

Study design

This study was part of a larger cross-sectional study named 'Examining Predictors Linking Obesity Related Elements' (EXPLORE) in pre-menopausal adult women. The EXPLORE study aimed to investigate how body composition (specifically body weight and body fat) profiles are related to the risk of chronic disease in pre-menopausal, post-menarcheal women. Further how diet, taste perception and physical activity patterns may impact on these profiles and how they may affect micro-RNA associated with body fat utilisation and storage. This sub-study of the women's EXPLORE study is aimed at investigating body composition and metabolic profiles of healthy New Zealand European (NZE), Pacific and Māori women between the ages of 16 to 45 years. To meet the aims of this study, which were to investigate these body composition profiles, their metabolic health outcomes, and whether ethnic differences exist, a cross-sectional design was implemented. A range of body compositional data was collected including well known measures of body fatness: body mass index (BMI), body fat % (BF%), waist circumference (WC), waist to hip ratio (WHR), waist to height ratio (WtHR), along with regional body composition data for the android and gynoid areas. Finally, biomarkers of lipid metabolism, glucose metabolism, inflammation, and metabolic hormones were collected along with blood pressure as these are key metabolic factors thought to be influenced by body composition. The initial study design is detailed in Figure A.1, however, as will be detailed next this had to be amended for Māori and Pacific ethnic groups.

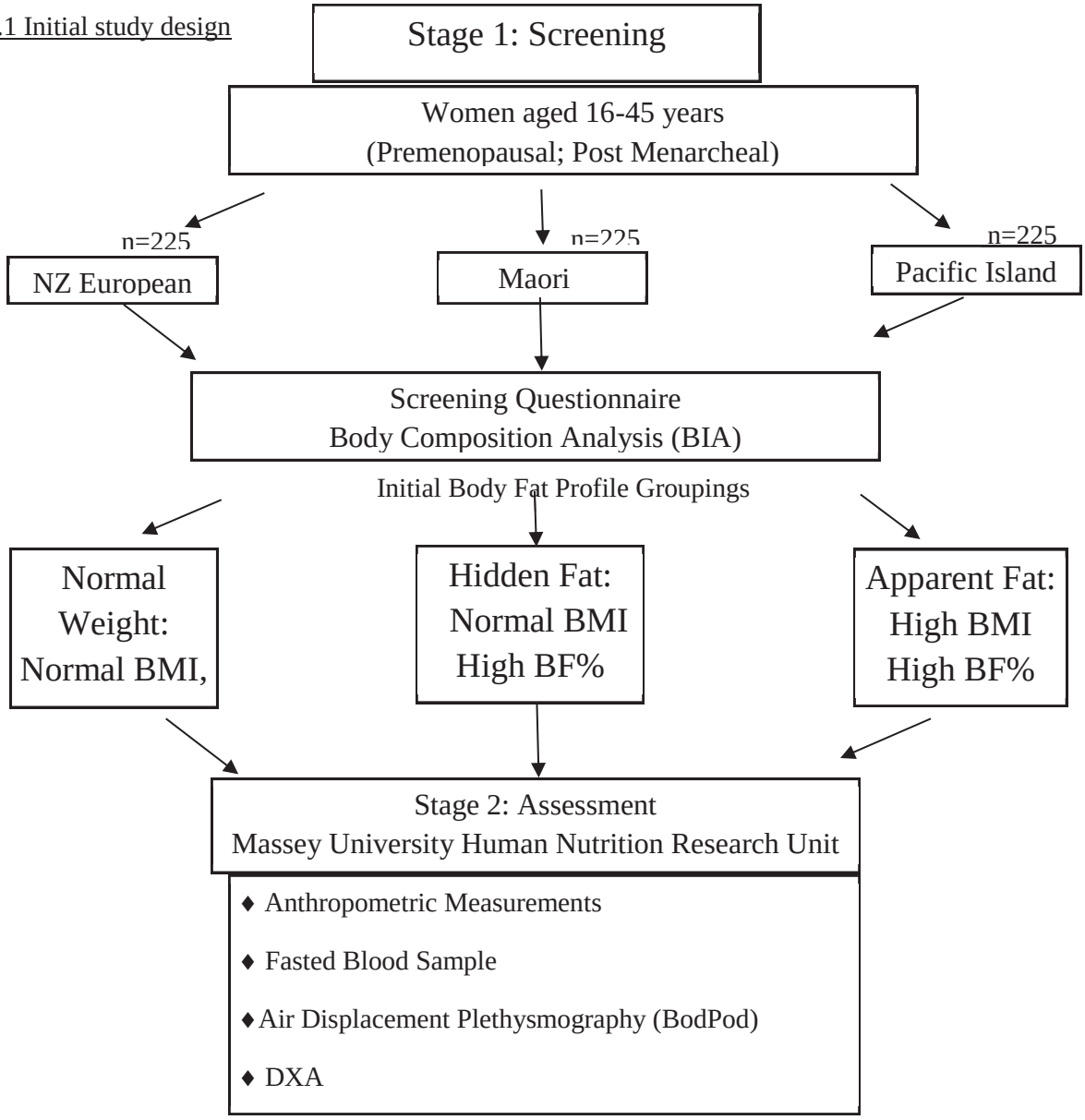
Study Sample

The women's EXPLORE study aimed to recruit 675 post-menarcheal, pre-menopausal NZ women on a volunteer basis between 2013 and 2015. Study participants were healthy New Zealand women of three ethnicities: NZE, Māori and Pacific Island. Ethnicity was self-reported, and at least one parent had to be of the same ethnicity. Participants were between 16-45 years old, post-menarcheal and pre-menopausal to eliminate changes in hormones and fat metabolism that may confound the results. Pregnant and lactating women were excluded due to changes in hormones and fat metabolism that maybe influence results, and those with diagnosed chronic disease were excluded as this study focusses on 'healthy' women. The final exclusion is those with dairy allergy relating to another aspect of the study outside of the scope of this sub-study.

Recruitment

Multiple avenues were employed to recruit study participants. Advertisements were placed in magazines, newspapers, websites, and broadcasted via radio. Posters and flyers were displayed and handed out in several locations including day care centres, schools, local businesses, and local events. Additionally, social media sites such as facebook were utilised, and information was sent out to mailing lists available through the university contacts and previous research. Due to the multicultural nature of this study, community liaisons assisted with the recruitment of Māori and Pacific participants, to ensure that a more culturally appropriate and personal face to face strategy was employed. Further information and registration of interest was available to interested individuals through a website for the study. Once registration of interest was received, potential participants were screened for suitability for the study

Figure A.1 Initial study design



Screening

At the beginning of the screening process, an information sheet was provided to potential participants, along with a consent form to be filled out prior to commencement of screening. Next a questionnaire was completed to assess whether inclusion and exclusion criteria were met. This was also available online. If all criteria were met, a bioelectrical impedance analysis (BIA) measurement was conducted to provide information on height, weight and body fat percentage. This information was used to group participants into one of three initial body fat profile groups as indicated by the pilot study: (Kruger et al., 2015)

1) "Normal Fat" group - normal BMI (<25kg/m²), normal body fat % (<30%) (NN)
2) "Hidden fat" group - normal BMI (<25kg/m²), high body fat % (≥30%) (NH)
3) "Apparent fat" group - high BMI (≥25kg/m²), high body fat %(≥30%) (HH)

The NZ European women's data were analysed according to the body composition profile categories as indicated above. Due to insufficient numbers of Pacific Island and Māori women able to be recruited both overall and in the NN and NH profile groups, Māori and Pacific Island women of any BMI and BF% were included in the study. Therefore, other body composition profiles were explored for all ethnic groups; specifically, obese and non-obese profiles via different BMI and BF% cut points. Obesity was defined as having a BMI ≥30kg/m², (World Health Organisation, 2000) or a body fat % >35 as this is in the middle of the range used for women and is a threshold frequently used in research in this area. (Romero-Corral *et al.*, 2010; Shea *et al.*, 2012; Gaba and Pridalova, 2016)
All the data collection and related assessments were conducted during the first 14 days of the participant's last menstrual period (follicular phase), and between 7 and 10 am in the morning after an overnight fast to ensure that food intake and menstrual cycle hormones did not confound any of the measurements. Data collection took place at the Massey University Human Nutrition Research Unit.

Body Composition Assessment

Measurements of height and circumferences of the waist and hip were taken using stadiometer and Lufkin tape and following the protocol set out by International Society for the Advancement of Kinanthropometry (ISAK). (Marfell-Jones *et al.*, 2012) Measures were taken in duplicate for accuracy. If two measures were taken the mean was used, and if three measures were taken the median was used. These figures were written on hard copy data

collection sheets and filed in participants folders. This data was used to calculate body compositions measurements: BMI, waist to hip ratio, waist to height ratio. These measurements provide information that will be used to assess the presence or risk of obesity. (NHLBI Obesity Education Initiative Expert Panel on the Identification, 1998) Weight was measured using Air Displacement Plethysmography (BodPod) (using thoracic gas volume method), as was total body fat % and lean mass as this is considered the gold standard methodology as it provides a higher accuracy than BIA. (Gomez-Ambrosi *et al.*, 2012) Participants were measured in swimwear or tight clothing, and had not participated in exercise in the two hours prior. The BodPod was calibrated in accordance with manufacturer's instructions prior to each participant's measurements. The siri model was used to estimate body composition. (Siri, 1961)

A Dual X-ray Absorptiometer (DXA; Hologic Discovery A, serial number 85296) with Hologic Discovery QDR software was used for whole body scan to provide information regarding the android and gynoid regional location of body fat following Massey University standards of practise (Glickman *et al.*, 2004; Kruger *et al.*, 2015). Two women were unable to be measured with the BodPod due to technical issues, so their body fat % measurement was taken from the 'WBTOT_PFAT' part of DXA output.

Biochemical Assessment of Metabolic Health

Participants had a blood test after an overnight fast (12 hours) with no food or liquids other than water during the previous 12 hours. A registered phlebotomist collected serum and plasma (ethylene diamine tetra acetic acid and heparin) blood samples between 7-10am, and pathology laboratory protocols for both collection and processing were followed. To ensure analysis for all participants occurs at the same time, samples were frozen at -18degrees Celsius as separate aliquots in Eppendorf tubes, until sample collection from all participants was completed. At this stage, analysis was performed by fully accredited laboratories or by qualified laboratory technicians.

The analysis included the following known biomarkers of metabolic health:

Table A.1 Biomarkers and laboratories used for analysis

Biomarkers	Laboratories where analysis took place
Cholesterol, TG, HDL- cholesterol, LDL-cholesterol (calculated), insulin, glucose, cs-CRP	North Shore Labs
HbA1c (glycated haemoglobin)	Canterbury Health Laboratories
Leptin, Ghrelin, TNF-α, IL-6, IL-10	Deakin University- Aaron Russell

The cholesterol, TG, HDL, insulin, glucose and CRP analyses were tested by Siemens dimension vista system, Flex reagent cartridge. HbA1c was tested using Biorad Variant HPLC system. Leptin, Ghrelin, TNF-α, IL-6, and IL-10 were measured using milliplex immunoassay kits following manufacturer's instructions with duplicate samples run. Bioplex 200 multiplex system (Bio-Rad Laboratories, Hercules, CA) was used to read plates, and Bioplex manager software (V.6.0, Bio-Rad Laboratories, Hercules, CA) was used to analyse the results.

Blood Pressure

Blood pressure was taken with a Riester Ri-Champion N digital blood pressure monitor following Standard Operating Procedure. Participants were seated and cuff was placed around the upper arm, level with the heart, with arm rested comfortably on a cushion or table top. After five minutes rest, three readings were taken at one minute intervals.

Data Analysis and Statistical Analysis

The intended sample size of 75 women in each body composition group, for each ethnicity (total 225 women per ethnic group) is able to detect a medium effect size f of 0.25 with 80% power when $p < 0.05$ (Kruger *et al.*, 2015). To detect an effect size of 0.8 with 80% power, 26 participants are needed in each group. Normality of the data was tested using Kolmogorov-Smirnov and Shapiro-Wilk tests, homogeneity of the data was tested using Levenes test. Parametric data were summarised by mean ± standard deviation, while non-parametric data were log transformed and reported as geometric mean (95% confidence interval) if normal after transformation, or as untransformed median ($25\text{-}75^{th}$ percentile) when still not normal after transformation or if failing to meet other assumptions for parametric testing including homogeneity of variance and absence of outliers in the data. Due to the need to compare

ethnic groups, parametric tests were only used if all ethnic groups were able to be analysed this way. Differences within ethnicities were analysed by independent T-Test for parametric data or Mann Whitney test for non-parametric data. The differences between EXPLORE profile groups and ethnic groups were analysed with one way ANOVA and post hoc Tukeys for parametric data where significance was p value of <0.05, or Kruskal Wallis with post hoc Mann Whitney with Bonferroni correction and significance at p <0.0167 for non-parametric data. Sensitivity, specificity and correctly classified % were estimated separately for each ethnicity. Statistics were completed using IBM SPSS Version 22.

Cut off values for abnormal levels were: HDL <1mmol/L, LDL >3.4mmol/L, Chol/HDL >4.5, TG >2mmol/L, Plasma Glucose >5.4mmol/L, Plasma Insulin >13mU/L, HbA1c >40mmol/mol, CRP >5mg/L (Values provided by North Shore labs and consistent with widely used thresholds in the area) and HOMA-IR >2.27 (Taylor *et al.*, 2010). HOMA-IR was calculated as glucose (mmol/L) x insulin (mU/L)/22.5 (Galvin *et al.*, 1992; Bonora *et al.*, 2000).

Two participants were excluded from the study after data collection due to having HbA1c readings in the diabetic range.

Ethics

Ethical application has been received and approved by Massey University Human Ethics Committee: (Southern A), Reference No.13/13.

Ethical considerations include informed consent, confidentiality of data collected, psychological implications of the data collection process and the potential distress in response to undesirable results.

Funding

The women's EXPLORE study was funded by the Netherlands-based Nutricia Research Foundation and New Zealand Lottery Health Research.

A.1 References

Bonora, E., Saggiani, F., Targher, G., Zenere, M. B., Albericheе, M., Monauni, T., Bonadonna, R. C. & Muggeo, M. 2000. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity - studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care,* 23(1)**,** 57-63. Available: DOI 10.2337/diacare.23.1.57.

Gaba, A. & Pridalova, M. 2016. Diagnostic performance of body mass index to identify adiposity in women. *European Journal of Clinical Nutrition,* 70(8)**,** 898-903. Available: DOI 10.1038/ejcn.2015.211.

Galvin, P., Ward, G., Walters, J., Pestell, R., Koschmann, M., Vaag, A., Martin, I., Best, J. D. & Alford, F. 1992. A simple method for quantification of insulin sensitivity and insulin release from an intravenous glucose-tolerance test. *Diabetic Medicine,* 9(10)**,** 921-928..

Glickman, S. G., Marn, C. S., Supiano, M. A. & Dengel, D. R. 2004. Validity and reliability of dual-energy X-ray absorptiometry for the assessment of abdominal adiposity. *Journal of Applied Physiology,* 97(2)**,** 509-514. Available: DOI 10.1152/japplphysiol.01234.2003.

Gomez-Ambrosi, J., Silva, C., Galofre, J. C., Escalada, J., Santos, S., Millan, D., Vila, N., Ibanez, P., Gil, M. J., Valenti, V., Rotellar, F., Ramirez, B., Salvador, J. & Fruhbeck, G. 2012. Body mass index classification misses subjects with increased cardiometabolic risk factors related to elevated adiposity. *International Journal of Obesity,* 36(2)**,** 286-294. Available: DOI 10.1038/ijo.2011.100.

Kruger, R., Shultz, S. P., McNaughton, S. A., Russell, A. P., Firestone, R. T., George, L., Beck, K. L., Conlon, C. A., von Hurst, P. R. & Breier, B. 2015. Predictors and risks of body fat profiles in young New Zealand European, Māori and Pacific women: study protocol for the women's EXPLORE study. *SpringerPlus,* 4(1)**,** 128.

Marfell-Jones, M. J., Stewart, A. & de Ridder, J. 2012. *International standards for anthropometric assessment.* Wellington: New Zealand, International Society for the Advancement of Kinanthropometry.

NHLBI Obesity Education Initiative Expert Panel on the Identification, E., and Treatment of Overweight and Obesity in Adults, 1998. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. *Obesity Research,* 6**,** S51-S210.

Romero-Corral, A., Somers, V. K., Sierra-Johnson, J., Korenfeld, Y., Boarin, S., Korinek, J., Jensen, M. D., Parati, G. & Lopez-Jimenez, F. 2010. Normal weight obesity: a risk factor for cardiometabolic dysregulation and cardiovascular mortality. *European Heart Journal,* 31(6)**,** 737-746. Available: DOI 10.1093/eurheartj/ehp487.

Shea, J. L., King, M. T. C., Yi, Y., Gulliver, W. & Sun, G. 2012. Body fat percentage is associated with cardiometabolic dysregulation in BMI-defined normal weight subjects. *Nutrition Metabolism and Cardiovascular Diseases,* 22(9)**,** 741-747. Available: DOI 10.1016/j.numecd.2010.11.009.

Siri, W. E. 1961. Body composition from fluid spaces and density: analysis of methods. *In:* Brozek, J., Henshal, A. (ed.) *Techniques for Measuring Body Composition.* . Washington: USA: National Academy of Sciences, National Research Council.

Taylor, R. W., Brooking, L., Williams, S. M., Manning, P. J., Sutherland, W. H., Coppell, K. J., Tipene-Leach, D., Dale, K. S., McAuley, K. A. & Mann, J. I. 2010. Body mass index and waist circumference cutoffs to define obesity in indigenous New Zealanders. *American Journal of Clinical Nutrition,* 92(2)**,** 390-397. Available: DOI 10.3945/ajcn.2010.29317.

World Health Organisation. 2000. *Obesity: preventing and managing the global epidemic. WHO technical report series No. 894* (0512-3054). Geneva: World Health Organisation. Retrieved from http://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/

Appendix B: Supplementary Results

Table B.1 Number and percentage of participants with abnormal biomarkers in each ethnic and body composition group (BMI and BF%)

	BMI-defined obesity (≥30kg/m²)						BF%-defined obesity (≥30%)					
	NZ European		Pacific		Māori		NZ European		Pacific		Māori	
	NO	O	NO	O	NO	O	NO	O	NO	O	NO	O
	n=202	n=31	n=38	n=52	n=59	n=24	n=156	n=77	n=30	n=60	n=41	n=42
Lipids:												
HDL (<1mmol/L)	6 (3%)	4 (13.8%)	0 (0%)	6 (12.5%)	6 (10.3%)	4 (16.7%)	5 (3.3%)	5 (6.8%)	0 (0%)	6 (10.7%)	3 (7.5%)	7 (16.7%)
LDL (>3.4mmol/L)	33 (16.8%)	8 (27.6%)	8 (21.6%)	2 (4.2%)	3 (5.2%)	4 (16.7%)	23 (15%)	18 (24.7%)	7 (24.1%)	3 (5.4%)	3 (7.5%)	4 (9.5%)
Chol/HDL (>4.5)	11 (5.6%)	5 (17.2%)	2 (5.4%)	3 (6.3%)	3 (5.2%)	4 (16.7%)	8 (5.2%)	8 (11%)	2 (6.9%)	3 (5.4%)	2 (5%)	5 (11.9%)
TG (>2mmol/L)	3 (1.5%)	4 (13.8%)	0 (0%)	4 (8.3%)	2 (3.4%)	5 (20.8%)	4 (2.6%)	3 (4.1%)	0 (0%)	4 (7.1%)	2 (5%)	5 (11.9%)
Glucose metabolism:												
Plasma glucose (>5.4mmol/L)	3 (1.5%)	0 (0%)	0 (0%)	3 (6.3%)	0 (0%)	6 (25%)	1 (0.7%)	2 (2.7%)	0 (0%)	3 (5.4%)	0 (0%)	6 (14.3%)
Plasma Insulin (>13mU/L)	25 (12.7%)	11 (37.9%)	8 (21.6%)	41 (85.4%)	16 (27.6%)	19 (79.2%)	18 (11.8%)	18 (24.7%)	6 (20.7%)	43 (76.8%)	8 (20%)	27 (64.3%)
HbA1C (>40)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.4%)
HOMA-IR (>2.27)	51 (25.9%)	14 (48.3%)	19 (51.4%)	41 (85.4%)	22 (37.9%)	21 (87.5%)	36 (23.5%)	29 (39.7%)	14 (48.3%)	46 (82.1%)	14 (35%)	29 (69%)
Inflammatory markers:												
CRP (>5)	21 (10.7%)	10 (34.5%)	1 (2.7%)	9 (19.1%)	5 (8.6%)	7 (29.2%)	14 (9.2%)	17 (23.6%)	2 (6.9%)	8 (14.5%)	3 (7.5%)	9 (21.4%)

Abbreviations: BMI body mass index; BF% body fat %; NO non-obese; O obese; HDL high density lipoprotein; LDL low density lipoprotein; Chol/HDL cholesterol to HDL ratio; TG triglycerides; HbA1c glycated haemoglobin; HOMA-IR homeostasis model of insulin resistance; CRP c-reactive protein

Table B.1 displays the prevalence of biomarkers above the reference ranges for disease risk, grouped by ethnicity and body composition group. The prevalence of high biomarkers was higher in obese groups than non-obese with the exception of Pacific women where prevalence of LDL >3.4mmol/L was lower in both obese groups compared to non-obese, and where Chol/HDL was lower in the BF% defined obese group

compared to non-obese. Additionally, NZE in the BMI defined groups had a higher prevalence of glucose >5.4mmol/L in the non-obese group compared to obese. High insulin and HOMA-IR was more common in Pacific and Māori women than NZE, while obese NZEs had higher CRP than obese Pacific women and to a lesser extent obese Māori, and higher Chol/HDL than obese Pacific women.

Table B.2 Spearman's correlation co-efficient (r_s) between body compositional measures, overall & by ethnicity

	Overall		NZ European		Pacific		Māori	
	BMI	BF%	BMI	BF%	BMI	BF%	BMI	BF%
BMI	-	0.814	-	0.756	-	0.877	-	0.849
		<.01		<.01		<.01		<.01
BF%	0.814	-	0.756	-	0.877	-	0.849	-
	<.01		<.01		<.01		<.01	
WC	0.934	0.817	0.889	0.754	0.938	0.874	0.960	0.848
	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01
WHR	0.640	0.551	0.564	0.500	0.608	0.554	0.571	0.445
	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01
WtHR	0.941	0.82	0.906	0.768	0.932	0.860	0.948	0.833
	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01

p value is below r_s value, p >0.05 is considered significant
Abbreviations: BMI body mass index; BF% body fat %; WC waist circumference; WHR waist to hip ratio; WtHR waist to height ratio

Table B.2 shows the Spearman's correlation co-efficient between the various body composition measures. For all ethnic groups WC, WHR, and WtHR correlated more strongly with BMI than BF%. The correlation between BMI and BF% was strongest for Pacific women, followed by Māori then NZE.

Table B.3 Spearman's correlation co-efficient (r_s) for body composition measurements and metabolic variables by ethnicity

	NZ European					Pacific					Māori				
	BMI	BF%	WC	WHR	WtHR	BMI	BF%	WC	WHR	WtHR	BMI	BF%	WC	WHR	WtHR
HDL	-0.238	-0.236	-0.306	-0.271	-0.267	-0.400	-0.261	-0.402	-0.355	-0.416	-0.448	-0.445	-0.501	-0.406	-0.494
	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01
TG	0.162	0.227	0.201	0.222	0.219	0.284	0.253	0.354	0.425	0.370	0.377	0.439	0.436	0.374	0.416
	0.015	<.01	<.01	<.01	<.01	<.01	0.010	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01
LDL	0.180	0.233	0.249	0.260	0.221	-0.077	-0.034	0.027	0.133	0.034	0.203	0.233	0.205	0.182	0.207
	<.01	<.01	<.01	<.01	<.01	0.240	0.379	0.405	0.112	0.379	0.034	0.017	0.032	0.051	0.031
Chol/HDL	0.313	0.336	0.407	0.391	0.365	0.241	0.172	0.314	0.382	0.344	0.511	0.515	0.545	0.417	0.535
	<.01	<.01	<.01	<.01	<.01	0.013	0.058	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01
Glucose	0.299	0.183	0.250	0.143	0.192	0.288	0.274	0.324	0.272	0.333	0.314	0.310	0.355	0.310	0.349
	<.01	<.01	<.01	0.016	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01
Insulin	0.321	0.378	0.389	0.307	0.370	0.564	0.489	0.559	0.385	0.575	0.487	0.456	0.491	0.329	0.490
	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01
HbA1c	0.126	0.020	0.130	0.119	0.109	0.208	0.132	0.184	0.148	0.222	0.170	0.121	0.192	0.224	0.206
	0.029	0.383	0.025	0.038	0.052	0.029	0.115	0.047	0.089	0.021	0.064	0.139	0.042	0.022	0.031
HOMA-IR	0.335	0.384	0.400	0.311	0.377	0.568	0.485	0.562	0.394	0.581	0.515	0.474	0.521	0.350	0.521
	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01	<.01
CRP	0.296	0.331	0.234	0.107	0.258	0.301	0.274	0.304	0.087	0.260	0.345	0.383	0.347	0.149	0.359
	<.01	<.01	<.01	0.214	<.01	<.01	<.01	<.01	0.214	<.01	<.01	<.01	<.01	0.091	<.01

p value is below r_s value, p >0.05 is considered significant

Abbreviations: BMI body mass index; BF% body fat %; WC waist circumference; WHR waist to hip ratio; WtHR waist to height ratio; HDL high density lipoprotein; LDL low density lipoprotein; Chol/HDL cholesterol to HDL ratio; TG triglycerides; HbA1c glycated haemoglobin; HOMA-IR homeostasis model of insulin resistance; CRP c-reactive protein

Table B3 shows the Spearman's correlation co-efficient (rs) or the various body composition measures and the metabolic variables grouped by ethnicity. Overall rs between body composition and metabolic variables were low with 0.581 being the highest which is for HOMA-IR and WtHR in Pacific women. For Pacific women WtHR most frequently had the highest correlation with the biomarkers, while for both NZ European and Māori women it was WC. For NZ European and Māori women, some similarities were seen where WC highest correlation out of the measures for HDL, Chol/HDL and insulin, and BF% had the highest correlation out of the measures for TG and CRP for both ethnic groups. For Pacific women, WtHR or WHR had the highest correlation for all measures except for CRP.

Table B.4 Areas under the receiver operating characteristic curve for body composition measurements in relation to biomarkers of metabolic health risk overall and by ethnicity

	High Blood Pressure (≥130/80)	Impaired fasting insulin (>13mU/L)	Low HDL (≤1mmol/L)	High Chol/HDL (≥4.5mmol/L)	High TG (≥2mmol/L)	High CRP >5	High HOMA-IR >2.27
All subjects	n= 405	n=392	n=392	n=392	n=392	n=390	n=392
BMI	0.689	0.824	0.719	0.609 *	0.783	0.695	0.720
BF%	0.669	0.788	0.698	0.628	0.741	0.708	0.850
WC	0.693	0.834	0.746	0.643	0.801	0.673	0.743
WHR	0.630	0.760	0.748	0.691	0.737	0.562 *	0.686
WtHR	0.690	0.827	0.757	0.648	0.782	0.673	0.729
NZ European	n= 232	n=225	n=225	n=225	n=225	n=224	n=225
BMI	0.640	0.719	0.692	0.631*	0.794	0.733	0.602
BF%	0.660	0.718	0.691	0.660	0.734	0.723	0.598
WC	0.647	0.747	0.754	0.670	0.839	0.683	0.656
WHR	0.594	0.721	0.797	0.719	0.788	0.588 *	0.635
WtHR	0.649	0.739	0.768	0.684	0.824	0.697	0.630
Pacific	n= 90	n=85	n=85	n=85	n=85	n=84	n=85
BMI	0.722	0.860	0.821	0.458 *	0.722 *	0.768	0.649
BF%	0.709	0.831	0.720 *	0.491 *	0.687 *	0.764	0.649
WC	0.749	0.876	0.801	0.520 *	0.745 *	0.770	0.678
WHR	0.682	0.778	0.741	0.550 *	0.735 *	0.555 *	0.605
WtHR	0.720	0.867	0.827	0.528 *	0.744 *	0.731	0.677
Māori	n= 83	n= 82	n= 82	n=82	n=82	n=82	n=82
BMI	0.633	0.815	0.683 *	0.739	0.781	0.712	0.676
BF%	0.571	0.787	0.671 *	0.707 *	0.760	0.698	0.631
WC	0.640	0.811	0.707	0.775	0.783	0.711	0.683
WHR	0.554	0.689	0.638 *	0.766	0.638 *	0.563 *	0.588
WtHR	0.624	0.822	0.710	0.766	0.741	0.701	0.694

Abbreviations: BMI body mass index; BF% body fat %; WC waist circumference; WHR Waist to hip ratio; WtHR waist to height ratio; HDL high density lipoprotein; Chol/HDL cholesterol to HDL ratio; CRP c-reactive protein; HOMA-IR homeostasis model of insulin resistance

* Result not statistically significant at $p<0.05$

Table B.4 displays the area under the curve for the various body composition measures and biomarkers associated with metabolic risk. These are given overall and split by ethnic group. Waist circumference had the highest AUC for three of the biomarkers for Māori and NZE women and for four of the biomarkers for Pacific women, however there were differences in which biomarkers these high WC AUC's related to. There was no biomarker for which one body composition measure had the highest AUC in all ethnic groups.

Appendix C: Consent Form

Institute of Food, Nutrition and Human Health

Massey University

Private Bag 102-904

North Shore Mail Centre

Albany, Auckland

New Zealand

T 09 414 0800

F 09 443 9640

Women's EXPLORE Study

PARTICIPANT CONSENT FORM

This consent form will be held for a period of five (5) years

I have read the Information Sheet and have had the details of the study explained to me.

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

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

Signature: ..... **Date:** .....

Full Name - printed .....

Appendix D: Screening Questionnaire

Women's EXPLORE Study

Personal Information, Health and Demographics Questionnaire

First name: _____

Family name: _____

Name you would like to be called by:_____

Medical Practitioner:_____

Address: _____

Phone: _____

What is your first language?

English ☐

Other ☐

If other, please state:_____

I would like to receive a brief report summarizing the main findings of the project:

Yes □ No □

I am willing to be contacted in future research projects within the Institute of Food, Nutrition and Human Health:

Yes □ No □

Do you have children? Yes □ No □

- How many children do you have? _____

- When was your youngest child born? __ / __ / ____ (DD/MM/YYYY)

When did your last period start? (Day/ month/year) _____

Are you pregnant? Yes □ No □

Do you have any surgical or cosmetic implants? Yes □ No □

Are you currently in paid employment? Yes □ No □

If yes,

Full time Yes □ No □

Part time Yes □ No □

If yes, specify hours per week:_____

Describe your job or paid employment or work:

TITLE / DESCRIBE HOURS PER WEEK

_____

_____

Do you follow a specific diet for health reasons? Yes □ No □

Please explain

_____

_____

Do you follow any diet for cultural or religious reasons? Yes □ No □

If yes, what type of diet do you follow? _____

_____

_____

Are you taking any form of medication, including traditional or homeopathic medicine and contraception?

Yes □ No □

Please specify the condition, the medication and the dosage in the table provided.

Condition	Medication	Dosage	Frequency

Are you taking any form of supplements, including tablets or drinks? Yes □ _____ No □

If yes, what are the name, brand and dosage of the supplements you are taking? _____

(Will send details by email Yes □ No □)

Supplement	Brand	Dosage	Frequency

Do you smoke cigarettes? Yes □ No □

If yes, approximately how many cigarettes per day:_____

Do you drink alcohol? Yes □ No □

If yes, approximately how many standard drinks per week:_____ _____

[1 standard drink = a glass of wine (120ml), 1 bottle/can of beer, 1 shot of spirits (45mL)]

Do you have any allergies? Yes □ No □

Please specify _____ _____

_____ _____

Appendix E: Anthropometry and blood pressure data sheet

Women's EXPLORE Study

Anthropometry & blood pressure

Data sheet - phase 2

Body Composition INDICATOR	MEASUREMENT	FINAL VALUE
Height	1.	
	2.	
	3.	
RECORDER:		
Weight	DXA (if not from Bodpod)	Bodpod
RECORDER:		
Waist circumference	1.	
	2.	
	3.	
Hip circumference	1.	
	2.	
	3.	

RECORDER:		
Blood Pressure	1.	
	2.	
	3.	
RECORDER:		

Appendix F: Instructions for authors for Nutrition Reviews

Narrative Reviews. Reviews of this type should contain the following sections and headings in addition to the abstract:

- Introduction (directly following the abstract)
- Conclusion (at the end of the text)
- Acknowledgements (after the Conclusion)
- Funding and sponsorship (as part of the Acknowledgments)
- Declaration of interest (as part of the Acknowledgments)
- References (after the Acknowledgments).

Between the Introduction and Conclusion, headings and subheadings are at the discretion of the author. They should be used to organize the text and guide the reader.

Length restrictions. Articles in any category must be formatted as indicated in the *Manuscript format* guidelines section and may not exceed 50 double-spaced pages in length, including references and illustrative material. Each article should be a focused, concise, and objective investigation of a clearly defined topic. The option to publish certain material as "Supporting Information" in an online-only format is provided, as outlined here. Authors are encouraged to make use of this option to accommodate material that may be of interest to the reader but is not integral to the work itself. Examples would include extensive summary tables and appendices.

Manuscript format. Manuscripts should be prepared electronically using word-processing software, preferably Microsoft Word. Article pages should be formatted as double-spaced and left-justified text with 1-inch margins and 12-point type. Pages and lines must be numbered.

Tables and illustrations. Tables and illustrations should be numbered in the sequence in which they appear in the text. They should appear in sequence after the reference list.
Tables. All tables should be included in the text file after the reference list. Each table should be constructed using the table functions of the word-processing program being used. A title should appear at the top of each table. A column heading should appear in the top cell of each column. Within the table, each data set should appear in a single cell; the return key should not be used within any cell. Text should be justified to the left. Numerical data should be justified to the decimal point. Capitalization should be restricted to the first letter of the

legend, the first letter in each cell, and applicable abbreviations or acronyms. Abbreviations used in the table should be spelled out in a footnote. When citing prior studies in tables please use the following format: Smith et al. (1998)[21].

Illustrations. All artwork should be submitted in digital format in separate files saved using the following convention: surname of first author_figure number (e.g., Smith_figure 1). Figure legends should be cited in the manuscript after the reference list. Charts and graphs downloaded from the Internet are not acceptable. Line artwork (vector graphics) should be saved in Encapsulated PostScript (EPS) format and bitmap files (halftones or photographic images) in Tagged Image Format (TIFF), with a resolution of at least 300 dpi at final size. Do not send native file formats. More detailed guidance for submitting electronic artwork can be found at http://www.blackwellpublishing.com/bauthor/illustration.asp. A free tool for converting files to other formats can be located at www.zamar.com.

References. The number of references cited should be tailored to the material being reviewed and be from reputable sources. As a general rule, articles in the Lead, Special, and Nutrition Science -> Policy categories do not typically include more than 200 references, while articles in the Emerging Science and Nutrition in Clinical Care categories do not typically have more than 120. References should be numbered sequentially upon first appearance in text, tables, and figures. They should be typed as superscripts and placed after commas and periods but before colons and semicolons. References cited only in figure or table legends should be numbered according to the first mention of the graphic in the text. Reference to unpublished work or personal communications should be avoided but, when essential, should be identified in the text as "unpublished data" or "personal communication from …", not in the reference list. When citing a series of consecutive numbers, provide the first and last with a dash between them (e.g., 5–7). When referring to a group of authors in the text, the format "Smith et al.[23]" should be used.

References cited only in figure or table legends should be numbered according to the first mention of the graphic in the text and should be cited in the text at that point. Reference to unpublished work or personal communications should be avoided but, when essential, should be identified in the text as "unpublished data" or "personal communication from …", not in the reference list. To ensure long-term accessibility, internet citations should only be used if that is the sole source of the information.

The reference list should be formatted according to AMA style. For each citation, sufficient information must be provided to allow a reader to know in what medium the material

appeared and to access the information. Please list all authors if there are six or fewer; for seven or more authors, list the first three followed by “et al.”

Appendix G: Instructions for authors for Asia Pacific Journal of Clinical Nutrition

Style Manuscripts should follow the style of the Vancouver agreement detailed in the 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals', as presented in JAMA 1997;277:927–34 (www.acponline.org/ journals/anals/01jan97/unifreqr.htm). APJCN uses US/ UK spelling and authors should therefore follow the latest edition of the Merriam–Webster's Collegiate Dictionary/Concise Oxford Dictionary. Please indicate your preference and use one or the other exclusively. If you do not specify, by default UK spelling will be used. A Guide for Medical and Scientific Editors and Authors (Royal Society of Medicine Press, London). Abbreviations should be used sparingly and only where they ease the reader's task by reducing repetition of long, technical terms. Initially use the word in full, followed by the abbreviation in parentheses. Thereafter use the abbreviation. At the first mention of a chemical substance, give the generic name only. Trade names should not be used. Drugs should be referred to by their generic names, rather than brand names. For vitamins, notation use is B-2, B-2, B-3, B-6 and B- 12 not B1, B2, B3, B6 and B12. "Fetal" is more etymologically correct than "Foetal". Note style for probability: *p*

Abstract and key words: The abstract should be structured with Background and Objectives, Methods and Study Design, Results, and Conclusions in 250 words or less. The abstract should not contain abbreviations or references. Five key words should be supplied below the abstract. Text Authors should use subheadings to divide the sections of their manuscript: INTRODUCTION, MATERIALS AND METHODS, RESULTS, DISCUSSION, ACKNOWLEDGMENTS, REFERENCES. Numerical results and p values should be presented in text, tables and figures with no more than 3 significant figures, unless there are exceptional circumstances. Examples would be: 52.37 kg which should be 52.4 kg p=0.15234 which should be p=0.152 Authors can make a case that their methodology requires further exception to these guidelines.

Tables: should be self-contained and complement, but not duplicate, information contained in the text. Each table must be formatted by using the table feature in WORD and presented as a separate file with a comprehensive but concise heading. Tables should be numbered consecutively in Arabic numerals in the sequence in which they are mentioned in the text. Use a single top rule, a single rule below the headings, and a single bottom rule. Do not use rules within the table body. Column headings should be clearly delineated, with straddle rules over pertinent columns to indicate subcategories. Column headings should Asia Pacific

Journal of Clinical Nutrition Managed by the First Affiliated Hospital of Zhengzhou University be brief, with units of measurement in parentheses; all abbreviations should be defined in footnotes. Footnote symbols: †, ‡, §, ¶, ††, should be used (in that order) and *, **, *** should be reserved for p values. The table and its legend/ footnotes should be understandable without reference to the text. All lettering/ numbers used in tables should be font style 'Times New Roman' and font size 8.5 or 9.

Figures: All illustrations (line drawings, bar charts and photographs) are classified as figures. Figures should be cited in consecutive order in the text. Figures should be sized to fit within the column (85 mm), intermediate (114 mm) or the full text width (177 mm). Line figures or bar chart figures should be drawn in a computer graphics package (e.g. EXCEL, Sigma Plot, SPSS etc.). All lettering used in figures should be font style 'Times New Roman' and font size 9.