The inter-relationships between body build, body composition, body fat distribution, metabolic syndrome and inflammation in adult Aboriginal and Torres Strait Islander people

by

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BMed FRACP

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

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April, 2013
Originality Statement

I hereby declare that the work herein, now submitted as a thesis for the degree of Doctor of Philosophy of the Charles Darwin University, is the result of my own investigations, and all references to ideas and work of other researchers have been specifically acknowledged. I hereby certify that the work embodied in this thesis has not already been accepted in substance for any degree, and is not being currently submitted in candidature for any other degree.

Jaquelyne Tataka Hughes
April 2013
Abstract

A centralised pattern of fat distribution is a major risk factor for diabetes and cardiovascular disease. In Australia, Aboriginal peoples and Torres Strait Islander peoples have a disproportionately higher burden of disease, including diabetes, cardiovascular disease and indicators of chronic kidney impairment than other Australians. Despite this burden of illness, few studies report a detailed examination of the body build and composition of Indigenous Australians. This is the first detailed study of body composition and health indicators in large numbers of Aboriginal people and Torres Strait Islander people.

The thesis reports on findings of two independent studies involving Indigenous Australians. A healthy young adult group who underwent detailed body composition and health assessment, and a larger population of Aboriginal adults and Torres Strait Islander adults who had a spectrum of chronic disease risk markers.

We have reported two key differences in the dimensions of the upper body (trunk) between Aboriginal adults and Torres Strait Islander adults. First, Aboriginal adults and Torres Strait Islander adults demonstrate a proportionately shorter trunk than Caucasians, and this was closely related to a central pattern of obesity in Aboriginal adults and Torres Strait Islander adults. Second, Torres Strait Islander adults have a broader skeleton than Caucasian adults who in turn have a broader skeleton than Aboriginal participants, and skeletal size was strongly associated with proportion of lean body mass.

Lean Aboriginal adults displayed numerous indicators of health. In contrast, even modest levels of overweight were strongly related to intra-abdominal fat deposition, and key cardiovascular risk markers: albuminuria, inflammation and low HDL-cholesterol. Adiposity was also related to the pattern of fat-related biomarkers (adipokines): high leptin and low adiponectin levels were associated with high body fat, and high intra-abdominal fat respectively. Finally, we propose a link that high leptin and low adiponectin levels are associated with albuminuria in Indigenous Australians, which is a known independent risk marker for both cardiovascular disease and kidney failure.
Acknowledgements

As a child, I thought skin tags, acanthosis nigricans, and being overweight were benign family traits among Torres Strait Islander family members. As a medical student and trainee-physician, I learned these traits indicated preventable chronic diseases that contribute to earlier mortality among many Aboriginal people and Torres Strait Islander people.

I am grateful for the dedicated guidance of my supervisors, Dr Louise Maple-Brown and Professor Kerin O’Dea. They provided a valuable opportunity for me to play a small part towards advancing the health status of adult Aboriginal peoples and Torres Strait Islander peoples with chronic diseases including chronic kidney disease through this study. Louise and Kerin have each been powerful mentors. They inspire and guide me to do better, again and again. I am extremely proud of this work, and it has not been without struggle. I have also acquired other valuable skills through this research project: including discussing health-risk in plain language, which has improved communication with my own nephrology patients; engaging individuals in health promotion and lifestyle change; confidently communicating with an academic audience; and developing my own advocacy skills.

I am grateful to the participants, more than 750, who live throughout Northern and Central Australia who willingly participated in this research project. Their willingness is an indication of the support by Aboriginal communities and Torres Strait Islander communities to move beyond describing chronic illness, but to find practical solutions to the burden of preventable chronic diseases.

The data presented in the thesis was collected and managed by a large team. I specifically acknowledge the Aboriginal staff and Torres Strait Islander staff with whom I worked closely: Maria Nickels and Sian Graham were research assistants who worked closely on my specific PhD project. Sian Graham and I worked exclusively together on the Healthy Top-Enders’ Study. Maria and Sian both worked on The eGFR Study; Loyla Leysley, a generous team-member who although based in Darwin, has an amazing network of contacts throughout Northern Australia. Mary Ward, my aunt, a long-serving nurse with the Thursday Island Hospital, a Torres
Strait Islander elder, and an invaluable and ongoing team member on Thursday Island who assisted in the baseline eGFR Study, and continues in the follow-up phase of the study. Special mention also goes to other former and current eGFR Study team members: Suresh Sharma, Kylie Tune and Alison Simmonds. Katrina Drabsch moved into the eGFR Study Project Manager role in 2010, and worked tirelessly arranging logistics of study recruitment, analysis of biochemical samples and data management and cleaning. This was an intense two years period. Katrina was always very generous towards assisting my PhD sub-study- thank you Katrina.

The PhD project was supported by numerous staff at Menzies School of Health Research. Susan Hutton, Joanne Bex and Julie Green in Operations; Data management and statistical support from Robyn Liddle, Linda Ward, Joseph McDonnell, Mark Chatfield and Matthew Stevens. I thank Kim Piera for her generous and careful attention to detail with processing ELISAs for adipokines on the many samples I had for this project.

Others, unrelated to Menzies deserve special mention: Dr Leonard Sunil Piers who has expertise in body composition techniques, but was also happy to advise on an appropriate analytical approach; Dr Jarrod Meerkin, who generously supplied his DXA unit, and his own time for the Thursday Island visit (described in Chapter 5); Dr Jerry Greenfield provided expert direction to devising the CT methodology, and introduced me to Ms Penelope Speight, who was a wonderful collaborator who assisted in the design of the computed tomography protocol, and flew to Darwin to set up the protocol with the dedicated staff of the Northern Territory Imaging group who performed the CT scans. Penny also provided very prompt and thorough analysis of data. Thank you to the NT Imaging Group: Business Managers, Mr Rama Genga and Mr Aaron Hatcher, radiology staff including Fiona Schenkel, and clerical staff who assisted with bookings. Thank you Yvonne Coleman, a brilliant graphic artist, who assisted in the design of feedback material to participants and communities, and more recently helped me format the thesis; Helen Fejo-Frith, Aboriginal elder, inspirational leader in her community in Darwin and a friend. Helen was often extremely busy, but always made me feel very welcome in her community, supported our study (The eGFR Study and Healthy Top-Enders’ Study), and facilitated community access and acceptance.
I gratefully acknowledge my funding sources. Thank you to the National Health and Medical Research Council (NHMRC) Training Scholarship for Indigenous Australian Health Research #490348, 2008-2011. Thank you to the Rio Tinto Aboriginal Fund who sponsored me as a Role Model for Health, 2007-2010. Thank you to the following for project support: Pfizer Cardio Vascular Lipid research grant (2009); Douglas and Lola Douglas Scholarship Australian Academy of Science Award (2008); NHMRC Centre of Clinical Research Excellence in Clinical Science in Diabetes, University of Melbourne (2010); Gurdiminda Indigenous Health Research Scholarship, Menzies School of Health Research (2008). The eGFR Study was funded by an NHMRC Project Grant #545202.

Finally I thank my family. Darwin is my family’s home, and the place where I grew up. I hadn’t lived in Darwin since high-school, and my husband Paul generously moved to Darwin in order for me to undertake this project, and again live among my family. I would not have been able to start or complete a PhD without his support. I acknowledge the many inspirational women in my life, who have all shaped me, and more recently supported me in this research journey: my mum, my grandma, my sisters and my aunts.
Publications

Refereed journals

Conference proceedings


Invited Oral Presentations with abstract publication


Publications from data indirectly related to the thesis
Maple-Brown, L., Lawton, P.D., Hughes, J.T., Sharma, S.K., Jones, G.R.D., Ellis, A.E., Hoy, W., Cass, A., MacIsaac, R.J., Sinha, A.K., Thomas, M.A.B., Piers, L.S.,


**Publications which are currently in progress from data directly related to this thesis**

Hughes J.T., L.J Maple-Brown et al. “The eGFR Study: Validation of lean body mass in Aboriginal and Torres Strait Islander adults by whole body DXA and indirect methods of body composition”

Personal Statement by the Researcher

One of the goals of the PhD study was to improve our understanding of the relationship of obesity with the development of kidney damage among Aboriginal peoples and Torres Strait Islander peoples. There were both professional and personal reasons behind the topic of this research. As a practicing nephrologist, this study was important to me in order to contribute to the evidence base to tackle obesity related chronic disease including chronic kidney disease.

As a Torres Strait Islander woman there was a layer of personal prompts stimulating this research: I know Torres Strait Islander peoples are different to Aboriginal peoples, but why are Torres Strait Islander people “bigger” than Aboriginal Australians or non-Indigenous Australians? It has also been an attempt to answer the very important question for Aboriginal and Torres Strait Islander peoples: “why does kidney disease affect my family?” The why question suggests someone may hear the question, understand what it is that you are asking, care enough to determine the reason, and be committed enough to return to share the answer. This question is best understood with the recognition of Australia’s recent history of paternalistic guardianship (“protectors”), assuming Aboriginal people and Torres Strait Islander people cannot care for themselves or their families. This was partnered with subtle undercurrents in my childhood, hearing things like “the doctor never explained that”, “they didn't take me seriously”, and the assumptions some make of others that perhaps, “they don’t need to know that” or “I’m too busy (or I don’t care enough) to understand why.” Therefore this research is an honest attempt to address the “why?” question, to make the effort to find answers, and also inform Aboriginal and Torres Strait Islander peoples. It has also allowed me to raise the profile of Aboriginal peoples and Torres Strait Islander peoples with diabetes and chronic kidney disease in the wider Australian health sphere.
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<th>Description</th>
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<tbody>
<tr>
<td>A:L</td>
<td>Adiponectin:Leptin ratio</td>
</tr>
<tr>
<td>ABS</td>
<td>Australian Bureau of Statistics</td>
</tr>
<tr>
<td>ACR</td>
<td>Albumin to creatinine ratio</td>
</tr>
<tr>
<td>AdipoR</td>
<td>Adiponectin receptor</td>
</tr>
<tr>
<td>AIHW</td>
<td>Australian Institute of Health and Welfare</td>
</tr>
<tr>
<td>AMP-kinase</td>
<td>AMP-activated protein kinase</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>ANZDATA</td>
<td>Australian and New Zealand Dialysis and Transplantation registry</td>
</tr>
<tr>
<td>ATP III</td>
<td>Adult Treatment Panel report, III</td>
</tr>
<tr>
<td>BIA</td>
<td>Bioelectrical impedance analysis</td>
</tr>
<tr>
<td>BIS</td>
<td>Bioelectrical impedance spectroscopy</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BSA</td>
<td>Body surface area</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>DSAT</td>
<td>Deep subcutaneous abdominal adipose tissue</td>
</tr>
<tr>
<td>DXA</td>
<td>Dual-energy x-ray absorptiometry</td>
</tr>
<tr>
<td>DXA-BMC</td>
<td>Bone mineral content measured by DXA</td>
</tr>
<tr>
<td>ECF</td>
<td>Extracellular fluid</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
</tr>
<tr>
<td>EGIR</td>
<td>European Group for the study of insulin resistance</td>
</tr>
<tr>
<td>ESKD</td>
<td>End stage kidney disease</td>
</tr>
<tr>
<td>FFM</td>
<td>Fat free mass</td>
</tr>
<tr>
<td>FFM%</td>
<td>Fat free mass as percent of body weight</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td>HDL</td>
<td>High density lipoprotein</td>
</tr>
<tr>
<td>HMW adiponectin</td>
<td>High molecular weight adiponectin</td>
</tr>
<tr>
<td>HOMA</td>
<td>Homeostasis model assessment</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>Homeostasis model assessment score of insulin resistance</td>
</tr>
<tr>
<td>HU</td>
<td>Hounsfield units</td>
</tr>
<tr>
<td>IAF</td>
<td>Intra-abdominal fat</td>
</tr>
<tr>
<td>ICF</td>
<td>Intracellular fluid</td>
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<tr>
<td>IDF</td>
<td>International Diabetes Federation</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
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<tr>
<td>IGT</td>
<td>Impaired glucose tolerance</td>
</tr>
<tr>
<td>IL-1ra</td>
<td>Interleukin-1 receptor antagonist</td>
</tr>
<tr>
<td>IL-6</td>
<td>Interleukin-6</td>
</tr>
<tr>
<td>IRS-1</td>
<td>Insulin-receptor substrate-1</td>
</tr>
<tr>
<td>kHz</td>
<td>Kilo hertz</td>
</tr>
<tr>
<td>L (1,2,3,4,5)</td>
<td>Lumbar vertebra</td>
</tr>
<tr>
<td>LDL</td>
<td>Low-density lipoprotein</td>
</tr>
<tr>
<td>M1 (M2)</td>
<td>M1 type macrophage (or M2 type macrophage)</td>
</tr>
<tr>
<td>MAP-kinase</td>
<td>Mitogen-activated protein kinase</td>
</tr>
<tr>
<td>MDRD4</td>
<td>Modification of diet in renal disease study, 4 variable formula</td>
</tr>
<tr>
<td>MF-BIA</td>
<td>Multi-frequency bioelectrical impedance analysis</td>
</tr>
<tr>
<td>mg/L</td>
<td>Milligram per litre</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>mRNA</td>
<td>Messenger ribonucleic acid</td>
</tr>
<tr>
<td>NAHS</td>
<td>National Aboriginal Health Strategy</td>
</tr>
<tr>
<td>NCEP</td>
<td>National Cholesterol Education Program</td>
</tr>
<tr>
<td>NT</td>
<td>Northern Territory</td>
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<tr>
<td>pg/ml</td>
<td>Picogram per millilitre</td>
</tr>
<tr>
<td>pH</td>
<td>Phase angle (in reference to bioelectrical impedance analysis)</td>
</tr>
<tr>
<td>PI3</td>
<td>Phosphatidylinositol 3-kinase</td>
</tr>
<tr>
<td>pmol/L</td>
<td>Picomol per litre</td>
</tr>
<tr>
<td>PPAR-g</td>
<td>Peroxisome proliferator-activated receptor</td>
</tr>
<tr>
<td>R</td>
<td>Resistance</td>
</tr>
<tr>
<td>RMSE</td>
<td>Root mean square error</td>
</tr>
<tr>
<td>SAD</td>
<td>Sagittal abdominal diameter</td>
</tr>
<tr>
<td>SAT</td>
<td>Subcutaneous adipose tissue</td>
</tr>
<tr>
<td>SFB</td>
<td>Selected frequency bioimpedance</td>
</tr>
<tr>
<td>SFT</td>
<td>Skin-fold thickness</td>
</tr>
<tr>
<td>SIRE</td>
<td>Self identified race or ethnicity</td>
</tr>
<tr>
<td>SSAT</td>
<td>Superficial subcutaneous abdominal adipose tissue</td>
</tr>
<tr>
<td>T9-S1</td>
<td>Vertebral levels: Thoracic, Sacral</td>
</tr>
<tr>
<td>TBK</td>
<td>Total body potassium</td>
</tr>
<tr>
<td>TBW</td>
<td>Total body water</td>
</tr>
<tr>
<td>TNFa</td>
<td>Tumour necrosis factor alpha</td>
</tr>
<tr>
<td>uA</td>
<td>Micro-Amps</td>
</tr>
<tr>
<td>ug/L</td>
<td>Micro-gram per litre</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>VAT</td>
<td>Visceral adipose tissue</td>
</tr>
<tr>
<td>VLDL</td>
<td>Very low density lipoprotein</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>WHR</td>
<td>Waist to hip ratio</td>
</tr>
<tr>
<td>Xc</td>
<td>Reactance</td>
</tr>
<tr>
<td>Z</td>
<td>Impedance</td>
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<tr>
<td>$\rho_c$</td>
<td>The Lin concordance correlation coefficient</td>
</tr>
</tbody>
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Chapter 1.

Introduction
1.1. General Comments about the Health of Australia’s Aboriginal Peoples and Torres Strait Islander Peoples

Up to half of the 17 years lower life expectancy among Indigenous Australians (relative to other Australians) occurs due to the burden of adult chronic diseases (Australian Institute of Health and Welfare (AIHW) 2008). This includes a disproportionate burden of cardiovascular disease risk experienced at younger ages, a higher than expected burden of disease among Indigenous Australian women (compared with Indigenous men and non-Indigenous women), and higher rates of chronic kidney disease (CKD) (McDonald 2010; Vos et al. 2009). Successful management of chronic disease risk involves a partnership between health practitioner and patient, where management plans are negotiated based on accurate information about pathophysiology, prognosis and treatment options, in the context of the patient’s expectations, and ultimately, their willingness to manage their disease. Since the metabolic syndrome may precede the development of cardiovascular disease by up to ten years, it’s early identification represents an ideal clinical opportunity to modify the chronic disease burden in this high risk population. Lifestyle modification is a key therapeutic goal in the treatment of metabolic syndrome ('Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report' 2002)- therefore the major responsibility is placed on the client. At this time, there is a paucity of detailed information describing the relationship of excess body fat with metabolic syndrome and the development of kidney damage in Aboriginal people and Torres Strait Islander people.

The Introduction of this thesis will be composed of five parts. First the terminology used in the thesis is discussed, as are the different origins (and the respective diversity) of Aboriginal peoples and Torres Strait Islander peoples are described. Second, the burden of chronic diseases including diabetes, chronic kidney disease and cardiovascular disease risk in Aboriginal people and Torres Strait Islander people will be reviewed. Third, since overweight and obesity are highly related to risk of both cardiovascular disease and diabetes, a review of body build and body composition techniques will be presented, including differences due to the impact of
aging, gender, chronic disease and ethnicity. Fourth, the relationship of adipose and lean mass in modifying metabolic and inflammatory processes, and chronic disease risk will be reviewed. Finally, the persisting knowledge gaps, and the specific aims of the thesis will be summarised.

1.2. Terminology

Differences between groups of people are often described on the basis of race, ancestry, ethnicity and indigenous status. Race and ethnic disparities in health remain rooted in persisting socioeconomic disparities within populations (Pearce et al. 2004). It was observed in a review of the medical literature, that while health may have been reported on the basis of ethnicity, race, or locality, many reports did not satisfactorily describe how race or ethnicity was defined (Shanawani et al. 2006). Hence, ‘race’ has been used as a proxy for other more accurate and informative variables, such as education and socioeconomic status (Paradies et al. 2007; Winker 2004). It is suggested that researchers should always indicate why race and/or ethnicity are believed to be important to their particular study (Winker 2004). The terms ‘race’, ‘ancestry’, ‘ethnicity’ and ‘indigenous’ status are briefly discussed below.

‘Race’ has been used to describe the biologic differences between groups that are assumed to be genetic (Pearce et al. 2004). The term ‘ancestry’ describes the comparisons of groups that are genetically divergent, but whom share cultural and environmental similarities (Rebbeck et al. 2005). This definition of ancestry contrasts with ‘race’ which characterises comparisons of groups that diverge in most respects (Rebbeck et al. 2005).

According to Callister et al. (Callister et al. 2007), ethnicity is not straightforward, and cannot be easily identified or measured. Ethnicity is a complex composite of biology, history, cultural orientation and practice, language, religion, lifestyle (Pearce et al. 2004), country of birth, and/or nationality (Callister et al. 2007). Ethnicity is also about affiliation (which can be different from descent or ancestry) (Callister et al. 2007). Self-identified race or ethnicity (SIRE) can also be viewed as a social construct (Rebbeck et al. 2005). As such, the membership or boundaries of
the SIRE evolves with time, reflecting and also influencing political and cultural events (Rebbeck et al. 2005).

People may identify with multiple ethnic groups, either through migration or ethnic-interracial marriage, or the ability to record more than a single ethnic group (Callister et al. 2007). It is suggested that assigning individuals to a single ethnic group is increasingly invalid (Callister et al. 2007). Several reasons exist as to why an individual assigns one ethnic designation, when they could record more than one based on ancestry (Callister et al. 2007); an individual may simplify their ethnicity down to one group (‘self-prioritization’); their responses may be based primarily on lived cultural experience, rather than ancestry; respondents may be influenced by the networks around them; an individual may be reflecting how others view them; respondents may record a single ethnicity as a political statement; economic incentives (and disincentives) may have influenced how individuals identify to a particular ethnic group (Callister et al. 2007).

The term ‘indigenous’ evolved through international law, and acknowledges the particular relationship of aboriginal people to a territory from which they originate (Australian Human Rights Commission (AHRC) 2005). Another definition of ‘indigenous’ peoples are those ‘(people) who originally, before intermarriage with newcomers from overseas, had no other race history except for the country in which they live’ (Flood 2006). The term ‘indigenous’ may also describe the experiences shared by a group of people that have lived in a country for a few thousand years in contrast with the experiences shared by a group of people who have lived in the same country for a few hundred years (Cunningham et al. 2003). Despite the uniqueness of indigenous nations throughout the world, indigenous peoples have shared a history of colonisation, associated with loss of culture, land, voice, population size, dignity, health and wellbeing (Durie 2004). It is those who are not ‘indigenous’ that have coined this term. As such, ‘indigenous’ in contrast to the dominant culture may describe ‘otherness’, or a ‘colonised people’ or those who have suffered from the emotional and social repercussions of cultural domination and denigration (Cunningham et al. 2003).
As opposed to a Christian philosophy, for example, which strongly identifies the world and the heavenly realm, it is suggested an indigenous view sees people as integral to the natural world, with a seamless relationship with the land, sea, mountains, rivers, animals and plants (Cunningham et al. 2003; Durie 2004). Many indigenous peoples throughout the world have a diverse profile. Cunningham et al. (Cunningham et al. 2003) suggest that Aboriginal peoples and Torres Strait Islander peoples have integrated into the wider Australian population to a greater extent than First Nation peoples in north America, who are largely concentrated in reservations (Cunningham et al. 2003).

Aboriginal with a lower case ‘a’ (aboriginal) describes an indigenous person from any part of the world, whereas Aboriginal (with a capital ‘A’) refers to the Aboriginal peoples of Australia (AHRC 2005). ‘Indigenous Australians’ refers to Australia’s first peoples, that is, either Aboriginal peoples or Torres Strait Islander peoples (AHRC 2012). While both groups are recognised as Indigenous Australians, Torres Strait Islander peoples have a separate identity, culture and flag to that of Aboriginal peoples (Flood 2006; Horton 1994; Shnukal 2001).

The Australian government definition of an Australian Aboriginal person or Torres Strait Islander person is three-fold; a person who is of Aboriginal or Torres Strait Islander descent and identifies as an Aboriginal person or Torres Strait Islander person, and is accepted as an Aboriginal person or Torres Strait Islander person by the community in which he or she lives or has lived (Gardiner-Garden 2000). The plural ‘peoples’ acknowledges the diversity among Australia’s Aboriginal population and Torres Strait Islander population. In the strictest sense, ‘Aborigine’ is the noun and ‘Aboriginal’ the adjective; however the preferred term is Aboriginal people(s) (CDIP Toolkit 2004).

In addressing inequalities in health, it is proposed that sustainable solutions to indigenous health problems need to acknowledge past practices, and allow people to heal and address social determinants of health (Cunningham et al. 2003). And yet defining ethnicity remains a sensitive issue for some Indigenous and other Australians, including when attributing illness to genetic origins in Indigenous populations without practically addressing social determinants of health (Paradies et
al. 2007). Perhaps the sensitivity around ethnicity for Indigenous Australians is also a reflection of a lack of awareness of the heterogeneity between different regions and communities, and diverse and complex aspects of health and wellbeing that may be unique in different areas (National Aboriginal Health Strategy (NAHS) 1989). The question of ethnicity for this thesis has relevance in understanding body composition and related health risk of Aboriginal Australians and Torres Strait Islander Australians. We have used self-identified ethnicity and asked participants how each of 4 grandparents identified their ethnicity in order to explore the complex relationships of body composition and chronic disease risk.

1.2.1. Use of terminology in the thesis

Several terms are used in the thesis, and require defining.

- Torres Strait Islander: peoples or persons (or participants) who are of Torres Strait Islander descent, are accepted as such by their community as a Torres Strait Islander person, and identify as a Torres Strait Islander person.
- Aboriginal: peoples or persons (or participants) who are of Aboriginal descent, are accepted by their community as an Aboriginal person and identify as an Aboriginal person.
- Both Aboriginal and Torres Strait Islander: peoples or persons (or participants) who are of both Aboriginal and Torres Strait Islander descent are accepted by their community as both Aboriginal and Torres Strait Islander, and identify as such.
- Indigenous: describes the collective population (or participants) who are Aboriginal or Torres Strait Islander or both Aboriginal and Torres Strait Islander.
- non-Indigenous: refers to Australians who are non-Aboriginal and non-Torres Strait Islander.
- Caucasian: refers to non-Indigenous Australians of a Caucasian background.
- other Australians: The wider Australian population with the exception of Aboriginal peoples and Torres Strait Islander peoples.

In Chapter 1, the terms to describe Aboriginal people(s) or Torres Strait Islander people(s) or Indigenous Australians are the terms used by authors that are cited in
this section, and the respective terminology of the authors has been retained. In the following chapters, the terms used to describe participants specifically refer to either Aboriginal adults, Torres Strait Islander adults, and adults who identify as both Aboriginal and Torres Strait Islander. Where comparisons are made between Caucasian participants and the rest of the study group, the term Indigenous Australians is used, though the intention is not meant in any way to disrespect the uniqueness and place of Aboriginal peoples in Australia, or the uniqueness and place of Torres Strait Islander peoples in Australia. These definitions are revisited in Chapter 5 and Chapter 6 with respect to stratification of participants in the PhD study.

1.3. Origins and Aspects of Culture of Aboriginal Peoples and Torres Strait Islander Peoples

More detail is provided for Torres Strait Islander people in this section since they are a smaller population and as a result less information regarding their culture and origins is published as compared with Aboriginal peoples. The information describing Aboriginal peoples is intentionally sparse for two reasons: first, there are many resources that describe Aboriginal culture and lifestyle. Secondly, since Aboriginal peoples of Australia are diverse peoples, a single summary of one group cannot adequately describe Aboriginal people in a different region of Australia. One must also consider that Aboriginal peoples and Torres Strait Islander peoples of today are more heterogeneous than these early descriptions.

Torres Strait Islander Peoples

The Oceania region was described in 1832, and included the peoples of Melanesia, Micronesia, and Polynesia, and the countries of Australia and New Zealand. Melanesia refers to the ethnic and geographical grouping of islands distinct from Polynesia and Micronesia. Today Melanesia includes New Guinea (Irian Jaya and Papua New Guinea), New Caledonia, Vanuatu, Fiji, and the Solomon Islands. Torres Strait Islander peoples are of Melanesian origin, distinct from Aboriginal peoples in both identity and culture (Florek 2005; Horton 1994; Lawrie 1972; Shnukal 2001). Torres Strait Islander peoples are described as more closely resembling the physical
appearance and (aspects of) culture of the people of Papua New Guinea (than Aboriginal peoples) (Flood 2006).

The Torres Strait region describes the hundred or so islands to the north of Cape York Peninsula in Queensland; to the south of Papua New Guinea; and between the Arafura Sea to the west and the Coral Sea to the east. The region was first settled by Torres Strait Islander peoples, who have been able to maintain sovereignty from the people of Papua New Guinea to the north, and Aboriginal people from mainland Australia to the south (Horton 1994). It is reported that the region has been in constant habitation by Torres Strait Islander peoples from ‘time immemorial’ (Horton 1994) or between 4000 (Morrissey 2001) up to 8000 years (Flood 2006). Flooding of the land bridge between the Australian mainland and Papua New Guinea created islands that were then settled by Torres Strait Islander people (Flood 2006).

There are four island regions within the Torres Strait (Horton 1994; Lawrence et al. 2004). The eastern group, composed of high volcanic islands and fertile soil, permitted cultivation and agriculture. As the eastern islands are also located within the region of the Great Barrier Reef, Islanders also enjoyed diets rich in marine life. The central group of low sandy islands and reefs permitted fishing. The top western (or northern) group near Papua New Guinea is characterised by its low islands of mud flats and mangroves, permitting fishing and crabbing. The western group of high islands are characterised by volcanic and granite rock, and sandy and acidic soils. The lifestyle of the western group included hunting and fishing, and cultivating gardens.

All Torres Strait Islander peoples are described as having exceptional seafaring skills, and closely observed and understood the natural environment, wind and stars for daily survival (Eseli et al. 1998). Within the region, Islanders were territorial with other Torres Strait Islander groups, and encountered each other for trade, warfare and marriage (Lawrence et al. 2004). Torres Strait Islander peoples were known for being fierce warriors and head-hunters, though the latter was not readily evident by the time of European contact (Florek 2005). The island of Moa, to the south of Mabuiag and Badu islands in the western Torres Strait was said to accommodate up to 500 people prior to 1875 (Florek 2005). The compiled legends
by Lawrie (Lawrie 1972) report a history of warfare between the peoples of Moa Island and their neighbours on Badu and Mabuiag islands, to the end that very few native Moa Island people exist now.

From the 1800’s, several events impacted on the lives of Torres Strait Islander peoples. First, an influx of people of diverse nationalities encroached on island life due to lucrative trepang harvesting (initially) and later pearling industries. The Queensland government saw this as an important economic opportunity, and consequently the Torres Strait was annexed to Queensland (and therefore Australia) in the late 1800’s (Lawrence et al. 2004). Around this time, Christianity was brought to the region by the London Missionary Society, and Torres Strait Islander peoples were principally ministered to by Pacific Island missionaries. With ethnic intermarriage, and an expanding Pacific Island community in the Torres Strait, the community of St Paul’s on Moa Island was established (Eseli et al. 1998). Where Torres Strait Islander peoples had initially been overlooked from the Aboriginal protection policy on the mainland, life changed significantly with the imposition of government appointed protectors. Protectors oversaw day to day life, quarantining earnings, limiting marital unions and movement throughout the region, and even relocating Aboriginal people from the mainland to settle in select communities (Hammond and Moa islands) in the Torres Strait (Lawrence et al. 2004; Morrissey 2001). Within a short timeframe, Torres Strait Islander peoples had encountered, worked with, and married Polynesians, Filipino, Japanese, Chinese and Aboriginal peoples. Later, with lifting of restrictions, many Islanders moved to the Australian mainland in search of work, settling throughout Queensland, the Northern Territory and Western Australia.

Maintenance of Torres Strait Islander culture occurred (among other practices) through the sharing of legends (Lawrie 1972), preservation and use of traditional languages (Ray 2003), dance, singing, use of drums, masks and the feathered headdress (Flood 2006; Lawrence et al. 2004). Torres Strait Island culture is strong today, maintaining the strength of the past, but reflecting the adaptability of the peoples to the often harsh encounters of recent history including the influences of missionaries, government protectors, and government policy (Florek 2005; Shnukal 2001). Part of the cultural adaptation included dance, style of housing, adopting
introduced languages (English and Creole), and spiritual and religious practices. The Torres Strait Regional Authority was established in the 1990’s in response to Islanders desires for self-governance (Lawrence et al. 2004; Morrissey 2001). This organisation allows the region to voice shared political and economic aspirations; even if historically Torres Strait Islander peoples existed in smaller clan and island groups.

**Aboriginal Peoples**

Australian Aboriginal peoples are described as having an ancient living culture and heritage (Flood 2006). Aboriginal peoples may have arrived in Australia via a land bridge from Asia, settling first in the north of Australia, and over time inhabiting the coastal then inland regions (Flood 2006). Australian Aboriginal peoples are believed to have arrived in Australia some 50,000 years ago (Flood 2006), and therefore are likely to have arrived at a time much earlier than the arrival of Torres Strait Islander peoples in Australia.

Aboriginal peoples survived and thrived on the Australian continent prior to European settlement, although having very limited means of preserving food, this meant frequently enduring feast and famine (Abbie 1969). Aboriginal peoples observed nature, could locate water, were expert trackers of animals and learnt to harvest food and medicines from the natural environment (Abbie 1969). Aboriginal men hunted for large animals, birds and fish, whereas Aboriginal women (and children) gathered plant-foods, smaller animals and in coastal areas, crustaceans (Abbie 1969; Flood 2006). They lived in hierarchical and often small communities, each member having specific roles, and understood the consequences of complex kinship relationships. Gathered foods were shared by the group. Cooking of a prized large animal was conducted by males, and a prized portion reserved for the capable hunter (Abbie 1969).
Similarities and Differences of the Culture and Lifestyle of Aboriginal Peoples and Torres Strait Islander Peoples prior to European Contact

Torres Strait Islander people were very close to nature, and closely observed changes in the stars, and winds to plan hunting, cultivation and sea travel (Eseli et al. 1998). Unlike Aboriginal peoples, Torres Strait Islander peoples cultivated crops (Abbie 1969; Flood 2006). In particular, Torres Strait Islander men hunted and were responsible for cultivating, harvesting and maintaining taro, yams and coconut in family (or clan) vegetable gardens (Flood 2006). Aboriginal people of the Cape York region would have been aware of the cultivating practices of Torres Strait Islander peoples. The lack of gardening and cultivation among Aboriginal peoples may have been because Aboriginal males observed this practice to be a woman’s role (Abbie 1969).

Although territorial, Torres Strait Islander people were keen traders (Flood 2006). Favourable trade winds occurred in the Dry Season (March-November) (Eseli et al. 1998). Traded items with the northern neighbours of Papua New Guinea included bow and arrow, drums (Flood 2006) and outrigging canoes (Horton 1994). Although many hunting tools are described, the bow and arrow were not a tool used by Aboriginal peoples (Abbie 1969). The spear was the predominant hunting tool of Aboriginal males, but a spear was also used by Torres Strait Islander hunters for fish, dugong and turtle. Aboriginal people of North-Eastern Arnhemland also traded with Macassan (Indonesian) seafarers who had been visiting Australian waters in the wet season from the late 1400’s to harvest trepang (McMillan 2007), until the government policy changed in the early 1900’s. Consequently, Aboriginal people in this region adopted some aspects of Macassan culture (McMillan 2007).

1.4. A Summary of the Diversity of Population, Culture, Lifestyle and Health Among Aboriginal Peoples and Torres Strait Islander Peoples in recent times

Indigenous Australians are a heterogeneous population (NAHS 1989). The most obvious distinctions within the Indigenous population as a whole are ethnicity (Aboriginal and Torres Strait Islander populations, and non-Indigenous ethnic
admixture), geography (remote, regional and urban), an Indigenous language as a first language, and lifestyle (urbanised, rural or culturally-rich within homelands).

In data from the 2006 Australian Bureau of Statistics national census, Aboriginal people or Torres Strait Islander people comprised 2.5% of Australia’s population, where 90% of people identified as an Aboriginal person, 6% as a Torres Strait Islander person (the majority of whom live in Queensland) and 4% as both Aboriginal and Torres Strait Islander (Australian Bureau of Statistics (ABS) 2006). As a group, Aboriginal people, Torres Strait Islander people and people who identify as both Aboriginal and Torres Strait Islander are classified as Indigenous Australians. The majority (76%) of Indigenous Australians live in urban or regional areas throughout Australia, although Indigenous Australians make up 24% and 45% respectively of people living in remote and very-remote areas of Australia (AIHW 2008). In the Northern Territory, 32% of residents identify as an Indigenous Australian. This compares to New South Wales, which has the largest population of Indigenous Australians in the country, and yet this equates to only 2% of the NSW population (ABS 2006).

The increasing prevalence of chronic diseases throughout the world has accompanied changes in lifestyle, especially in those who transition from rural/traditional lifestyles to industrial economies within short periods of time (Weil et al. 2010; Yajnik et al. 2008). There has been a variable transition in lifestyle for Aboriginal peoples and Torres Strait Islander peoples throughout Australia, with some groups having a longer transition period, particularly in south east Australia (Guest et al. 1992; O’Dea et al. 1993; Williams et al. 1987) and much more recent lifestyle transition in some areas of Northern Australia (O’Dea et al. 1988b).

The changes in lifestyle have also related to government policy to establish missions or government settlements (Brimblecombe et al. 2006) (groupings of Aboriginal peoples and or Torres Strait Islander peoples within settlements that did not reflect usual clan or language groups, adoption of Western-lifestyle practices and variable access to homelands), and inter-marriage or production of children with people of a non-Aboriginal or Torres Strait Islander background, referred to as ethnic-admixture. Northern Australia is a multicultural society. Within larger urbanised centres
Indigenous Australians have intermarried with Chinese, Malays, Europeans, and with other Aboriginal and Torres Strait Islander families (Shnukal 2001), which inevitably impacts on lifestyle, body size and composition.

The definition of Aboriginal health, paraphrased from the National Aboriginal Health Strategy (NAHS) incorporates one’s physical wellness within the context of the social, emotional and cultural well-being of their community, with aspirations that each individual obtain their full potential in life (NAHS 1989). Connectedness with traditional homelands, community and culture has also been linked with health, and was an expression of mastery and control over one’s life (Burgess et al. 2009; Rowley et al. 2008). Given the complexity of Indigenous Australian peoples and communities, different factors and pressures are likely to exist within different communities with regard to chronic disease risk. Much of the literature in this review describes Aboriginal peoples which reflect the larger population group, and which may have been more accessible than Torres Strait Islander peoples. Nonetheless, health statistics and policies describe Indigenous Australians, without any distinction of between within-group differences. One objective of this thesis is to explore the relationship of health and body composition of Aboriginal and Torres Strait Islander peoples separately in order to ascertain similarities and differences between them.

It is now extremely rare for Aboriginal people to live a wholly traditionally-oriented lifestyle. Increasing urbanisation even in remote parts of Australia has altered the daily lifestyle of many Aboriginal people. O’Dea et al. (O’Dea et al. 1988b) reported on the health and lifestyle of one small homelands community living a traditionally-oriented lifestyle in Arnhem Land in Northern Australia in the mid-1980’s: they lived in small clan groups and travelled frequently throughout their country; they relied on the local environment for plant and animal-based nutrition, and in this tropical community did not have refrigeration, so ate in proportion to food availability; they also observed special governances, including a hierarchy with access to community food. In addition, adults and children were demonstrably lean and healthy (although was accompanied by the suggestion of fasting insulin resistance). This contrasts to Aboriginal people living a more urbanised lifestyle. Despite the leanness of young adult males living either in the township of Derby or
rural community in Kalumburu in the West Australian Kimberley region, compared with healthy lean Caucasian males (mean BMI 21 kg/m$^2$), Aboriginal males were more likely to have an abnormal lipid profile (high triglycerides, low HDL-cholesterol) and higher 2-hour glucose and insulin responses and than lean Caucasian males (O’Dea et al. 1982).

Several studies link indicators of poverty with the development of diabetes, other cardiovascular risk factors and chronic kidney disease in Aboriginal communities (Cunningham et al. 2008; Hoy et al. 1997). Within remote Aboriginal communities of the Northern Territory, high rates of poverty, poor living conditions and unemployment were linked with high rates of preventable skin sores, lung disease (high rates of smoking), indicators of rheumatic heart disease, and renal disease (Hoy et al. 2003a). In an urban setting, relative to low educational attainment, lower socioeconomic status was more strongly associated with diabetes (Cunningham et al. 2008).

In Aboriginal communities with less-traditional lifestyles (even if situated in remote regions of Australia), older age was linked with higher degrees of overweight (measured by BMI), and diabetes (Brimblecombe et al. 2006). In comparison, this was not observed over a wide age-range in the small traditionally-oriented Aboriginal clan group referred to earlier (O’Dea et al. 1988b). Several investigators report more adverse chronic disease profiles among Aboriginal Australians living in remote regions, compared with urban areas. From 2001 data, Aboriginal people and Tores Strait Islander people living in the regions most remote from where dialysis services were situated were more likely to require treatment for severe kidney failure (Preston-Thomas et al. 2007). Similarly, for Aboriginal people with diabetes, those from remote communities exhibited a more adverse vascular risk profile than Aboriginal people in an urban community (Maple-Brown et al. 2007).

A divergence of health over time, between two closely situated Aboriginal communities in Central Australia highlight the impact of westernised living (with reliance on store-food and centralised services) and a community focussed on homelands-oriented lifestyle. Reliance on store-provided foods was associated with a higher prevalence of overweight and diabetes, especially in Aboriginal women
older than 35 years (McDermott et al. 1998; O'Dea et al. 1990). Yet in homeland-communities, BMI, rates of impaired glucose tolerance and smoking and cardiovascular deaths among Aboriginal residents were all lower than expected (Rowley et al. 2008). The positive health impacts of Aboriginal homeland communities was attributed by investigators to an individual’s positive sense of control over their lives and futures (Rowley et al. 2008), and positive engagement with culture and community (Burgess et al. 2009).

High quality diets, including regular fresh food and vegetables have not always been available to Aboriginal peoples and Torres Strait Islander peoples, through degradation of local traditional hunting grounds (Gault et al. 1996; O'Dea et al. 1988a), and reliance on community-stores supplying lower cost, energy-dense foods (Brimblecombe et al 2009; O'Dea et al. 1990). Remote Aboriginal communities impacted by urbanisation increasingly manifest overweight, insulin resistance, diabetes and cardiovascular disease (Gault et al. 1996). Accessing healthy nutrition (a basic necessity) in remote parts of Australia is a challenge, and poor nutrition has been linked with abnormal markers of endothelial dysfunction in one remote Aboriginal community (Rowley et al. 2003).

Poor quality diet, cigarette smoking and lack of regular physical activity explained almost 80% of the population-attributable risk of cardiovascular disease in a large international multi-ethnic study (Yusuf et al. 2004). It is significant therefore that adult Aboriginal people with established diabetes demonstrated an exceptionally positive capacity to improve glycaemic status and lose weight through the adoption of healthy diet and lifestyle habits (by returning to country, and relying on hunting and gathering foods) (O'Dea et al. 1980).

1.5. The Burden of Chronic Diseases and the Metabolic Syndrome in Aboriginal Peoples and Torres Strait Islander Peoples

Aboriginal and Torres Strait Islander Australians have a younger mean age than other Australians (21 v 37 years) (ABS 2006), due to a combination of high fertility rates in younger people, and lower life-expectancy among older people (AIHW 2008). Based on 2003 data, non-communicable diseases, such as cardiovascular
disease, diabetes, mental illness and chronic lung disease explained 70% of the life-years lost from death and disability (also called the health-gap) between Aboriginal and Torres Strait Islander Australians and other Australians (Vos et al. 2007). Aboriginal and Torres Strait Islander Australians younger than 54 years old were responsible for 60% of the health gap (35% in 35-54 year olds, and 25% in 15-34 year olds (Vos et al. 2009), compared with other Australians. Ischemic heart disease and diabetes were responsible for 37% of the health gap among Aboriginal and Torres Strait Islander Australian’s aged 35-54 years old (Vos et al. 2009).

This data on the extent of non-communicable diseases is supported by a high frequency of chronic disease risk markers which have been observed in Indigenous Australians at a younger age than for Australians generally (Dunstan et al. 2002; Glatthaar et al. 1985). The high frequency of cardiovascular disease risk markers in Indigenous Australians was demonstrated in a large cross-sectional adult screening study among Indigenous Australians in the Darwin urban region (of the Northern Territory) by examining the frequency of six cardiovascular disease risk factors (hypertension, dyslipidaemia, albuminuria, tobacco smoking, elevated waist to hip ratio and diabetes) (O'Dea et al. 2008). In this study, almost one third of adult Aboriginal people older than 35 years had diabetes and two additional cardiovascular risk factors, whilst among younger Aboriginal adults (less than 35 years old), 45% had at least 2 cardiovascular risk markers (O'Dea et al. 2008).

1.5.1. Chronic Kidney Disease

Individuals with end-stage kidney disease (ESKD) must rely on dialysis or another renal replacement therapy modality in order to sustain life due to insufficient excretory function of the kidney. ESKD is preceded by chronic kidney disease (CKD), of which two hallmarks are low glomerular filtration rate (GFR) and albuminuria (protein detected in the urine) (Levey et al. 2011; Mathew et al. 2007). The Australian and New Zealand Dialysis and Transplantation (ANZDATA) registry records longitudinal data of individuals with ESKD, collating information about the causes and consequences of severe renal disease. However, there are no comparable registries for Australians with chronic kidney disease.
The ANZDATA registry identifies Aboriginal peoples and Torres Strait Islander peoples collectively as Indigenous Australians (McDonald 2010). Several distinctions between Indigenous and other Australians are observed with respect to end stage kidney disease. First, type 2 diabetes and presumed glomerulonephritis are currently the most common causes of end-stage kidney disease (ESKD) in Indigenous Australians (McDonald 2010), however the attributed diagnosis may be clinically based, rather than biopsy proven. Type 2 diabetes was also identified as the most frequent co-morbidity of ESKD in Indigenous Australians (McDonald 2010). Second, in contrast to other Australians, ESKD affects Indigenous Australian females to a greater extent than Indigenous Australian males (Jose et al. 2009). Third, Indigenous Australians aged 35-64 years are reported to have at least 10 times higher an incidence rate of requiring dialysis treatment than similarly aged other Australians (McDonald 2010). The authors postulate the following reasons for this disparity: socioeconomic status (household income, overcrowding and unemployment) in addition to the early onset of Type 2 diabetes among younger Indigenous Australians that was described above. Finally, data from 2006 showed at a state level, the Northern Territory and Western Australia had the highest incidence rates of Indigenous Australians requiring treatment for ESKD (1192 and 774 per million population respectively) (Jose et al. 2009). From 2001 data, Indigenous Australians who lived in the most remote regions from where dialysis services were available had higher rates of ESKD than other Indigenous and non-Indigenous Australians (Preston-Thomas et al. 2007).

In many populations, it has been shown that two markers of chronic kidney disease, either low glomerular filtration rate (low GFR: a deficiency of water-soluble excretory function of the kidney) or albuminuria (the detection of albumin in the urine) (Levey et al. 1999; Levey et al. 2011) were independently associated with higher cardiovascular disease mortality (Keith et al. 2004). Among many Indigenous Australian communities, albuminuria has been identified more frequently than impaired GFR (Maple-Brown et al. 2011; Rowley et al. 2000). Albuminuria is reported to cluster with obesity and dysglycaemia which is also reported to explain high community levels of cardiovascular disease (Hoy et al. 2006b; Rowley et al. 2000).
Origins of Kidney Damage in Aboriginal people: Lessons from Renal Biopsy Studies

Remote living Aboriginal people (with no history of renal injury, and mean BMI 20 kg/m^2) were described as having glomerulomegaly in the setting of low nephron endowment compared with non-Indigenous Australians (Hoy et al. 2006a). The authors suggested glomerulomegaly (the compensatory hypertrophy of remaining glomeruli to maintain renal excretory function) was a significant susceptibility factor to additional renal insults and progressive kidney damage. This was suggested by their findings of even fewer glomeruli in the biopsies of Aboriginal people who had a history of hypertension compared with the biopsies of Aboriginal people with normal blood pressure (Hoy et al. 2006a). Many renal insults may occur over the life course in Aboriginal people, including low birth weight (due to poor maternal nutrition and smoking) (Hoy et al. 2010b), recurrent post-infectious nephritis episodes (in childhood and adult life), and adult-related disease morbidity (hypertension, overweight, smoking and diabetes) (Hoy et al. 2010a). Poverty, poor-community housing and infrastructure and a high-frequency of skin-sores have been linked with post-infectious glomerulonephritis (Hoy et al. 1997).

Moore et al. (Moore et al. 1996) described two key findings from a renal histopathology series of more than 200 Aboriginal people with hypertension, proteinuria or diabetes. First, a mixed pattern of renal injury was observed in Aboriginal people (where only 23% of biopsies had primary diabetic lesions, although 37% of the cohort had a clinical diagnosis of diabetes). Second, glomerulomegaly was conservatively observed in 11% of biopsies as a primary finding, though coincided with mesangiopathic renal lesions (a form of glomerulonephritis) in many other biopsies (Moore et al. 1996).

These biopsy reports suggest that remote-living Aboriginal people are more likely to have glomerulomegaly and therefore are more vulnerable to progressive kidney damage in the setting of additional insults. It is not known, since Torres Strait Islander people are not specifically identified in series of renal biopsy studies, if the same risk exists for Torres Strait Islander people as was demonstrated for Aboriginal people.
Finally, low nephron endowment has origins in neonatal development. Low-birth weight (less than 2500 grams) and intra-uterine growth restriction may impact nephron development, since nephrons develop in the final stages of pregnancy. Hoy et al. (Hoy et al. 2010b) suggested a link for neonatal under-development with cardiovascular disease risk in later life; proposing low-nephron endowment was more likely to occur in babies born of teenage mothers, and exposed to maternal smoking and under-nutrition. These babies were more likely to develop higher levels of insulin resistance, albuminuria and cardiovascular disease in adulthood (Hoy et al. 2010b). Obesity, type 2 diabetes and diabetes in pregnancy is a more recent phenomenon (Leonard et al. 2002; Valery et al. 2008), and the impact on kidney function and cardiovascular disease risk among Aboriginal people and Torres Strait Islander people in later-life requires further study.

1.5.2. Cardiovascular Disease Risk: Prediction Scores and the Metabolic Syndrome

Internationally cardiovascular disease is a major health concern, and several key risk markers have been identified. The Framingham risk tool identified a combination of older age, male-gender, current smoking, abnormal lipids (high total cholesterol and low HDL-cholesterol), high systolic blood pressure and having diabetes predicted a higher risk of cardiovascular disease over the next 10 years (Wilson et al. 1998). The Framingham community were largely middle-class Americans of Caucasian background (Wilson et al. 1998). The Framingham risk tool has not been validated as a risk assessment tool that is transportable to other ethnic groups, such as Aboriginal peoples or Torres Strait Islander peoples. As such, the Framingham risk tool did not fully explain the increased burden of cardiovascular risk in young Aboriginal women when evaluated in one remote Aboriginal community (Wang et al. 2003). Several investigators suggest other unmeasured non-traditional risk factors for cardiovascular disease risk require evaluation in Indigenous Australians including albuminuria, inflammation, clotting factors, family history and genetic factors, other atherogenic lipid parameters, psychological stress (Rowley et al. 2008) and low-birth weight (Hoy et al. 2010b).
More recently, the Interheart study identified nine risk factors which contributed to more than 90% of the population attributable-risk for myocardial infarction across all major populations, recruiting adults from 52 countries across Asia, North America, South America, Europe, Australia, the Middle-East and Africa. The Interheart study compared approximately 15,000 adults with a first myocardial infarction and 15,000 matched healthy adults from diverse ethnic and geographical regions internationally for the prediction of myocardial infarction (Yusuf et al. 2004). These risk factors were hypertension, abdominal obesity, diabetes, dyslipidaemia (specifically the ratio of apolipoprotein B to apolipoprotein A1), smoking, alcohol (nil v regular weekly alcohol consumption), physical activity (not active v weekly moderate-strenuous activity), poor quality diet (lack of daily fruit and vegetable v daily fruit and vegetable intake) and psychosocial stress (Yusuf et al. 2004). Of these nine factors, three factors were protective: exercise (weekly moderate-strenuous exercise), diet (daily fruit and vegetable intake) and alcohol (thrice weekly consumption of alcohol v abstainers). The Interheart study has therefore extended the known risk markers identified by the Framingham study to markers that are applicable across both Caucasian and non-Caucasian populations. The combination of non-smoking, regular moderate physical activity and daily consumption of fruit and vegetables was associated with a cumulative lower risk of acute myocardial infarction (odds ratio 0.21, 99% confidence interval 0.17-0.25) (Yusuf et al. 2004).

The Interheart study population did not include the assessment of Aboriginal peoples or Torres Strait Islander peoples. Although not directly assessing cardiovascular disease risk, Vos et al. (Vos et al. 2007) reported that 37% of the disease burden (the impact of death and disability), and 49% of the health gap (the life-years lost from death and disability) of Indigenous Australians were predicted (in order) by: tobacco use, obesity, physical inactivity, hyper-cholesterolaemia, alcohol, hypertension, low fruit and vegetable intake, illicit drugs, interpersonal violence, child sexual abuse and unsafe sex. Since cardiovascular disease is a major cause of disease burden and health gap in Indigenous Australians, the similarities of these factors with Interheart factors are noted. In contrast to a minor protective effect of alcohol intake on cardiovascular disease risk in the Interheart study, alcohol was more likely to exert harmful effects in Indigenous Australians, related to interpersonal violence and mental disease (Vos et al. 2009). Furthermore, alcohol has been linked to kidney
damage in some remote Aboriginal communities through weight gain, and diabetes-related kidney disease (Hoy et al. 1998).

The metabolic syndrome recognises a clustering of features linking abdominal obesity, insulin resistance, increased cardiovascular risk, and premature mortality (NCEP 2002; Alberti et al. 2006; Alberti et al. 1998). The metabolic syndrome received major attention following the 1988 Banting Lecture on insulin resistance in humans (Reaven 1988). Metabolic syndrome may exist for up to 10 years before the development of Type 2 diabetes. This pre-clinical period is an important opportunity to apply lifestyle interventions and medical management of risk factors to modify the emergence of coronary heart disease.

Several definitions for the metabolic syndrome are in use, summarised in Table 1.1 and include: the World Health Organisation definition (WHO) (Alberti et al. 1998), National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment panel III) definition (NCEP ATP III 2001), the European Group for the study of insulin resistance (EGIR) and the International Diabetes Federation (IDF) definition (Alberti et al. 2006).
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<tr>
<td>Glucose intolerance, IGT or diabetes and/or insulin resistance* together with 2 or more of the following</td>
<td>Insulin resistance (defined as hyperinsulinaemia- top 25% of fasting insulin values among the non-diabetic population. Plus 2 of the following:</td>
<td>Three or more of the following five risk factors:</td>
<td>Central obesity: waist circumference (ethnicity specific) plus any 2 of the following:</td>
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<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>≥6.1 but non-diabetic</td>
<td>≥5.6</td>
<td>≥5.6 or previously diagnosed diabetes.</td>
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<tr>
<td>Blood pressure (mmHg)</td>
<td>≥140/90</td>
<td>≥140/90 or treatment</td>
<td>≥130/85</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>≥1.7 and/or</td>
<td>≥2.0 or treatment and/or</td>
<td>≥1.7</td>
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<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>M: &lt;0.9; F: &lt;1.0</td>
<td>&lt;1.0 or treatment</td>
<td>M: &lt;1.03; F: &lt;1.29</td>
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<tr>
<td>Obesity</td>
<td>WHR: M: &gt;0.90; F: &gt;0.85 And/or BMI &gt;30 kg/m²</td>
<td>Waist (cm): M: ≥94; F: ≥80</td>
<td>Waist (cm): M: ≥102; F: ≥88</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>Urinary albumin excretion rate &gt;20ug/ml or ACR ≥30 mg/g (or ACR &gt;3.4 mg/mmol)</td>
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M=males; F=females. ACR refers to albumin to creatinine ratio. WHR refers to waist to hip circumference ratio. BMI refers to body mass index.

*Insulin resistance measured under hyper-insulinaemic euglycaemic conditions, glucose uptake below lowest quartile for background population under investigation.

The 2001 definition identified fasting plasma glucose of ≥6.1 mmol/L as elevated. This was modified in 2004 to be ≥5.6 mmol/L in accordance with the American Diabetes Association updated definition of impaired fasting glucose. Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased (e.g. 94-102 cm). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference. If BMI is >30 kg/m² then central obesity can be assumed, and waist circumference does not need to be measured. Table adapted from Alberti et al. (2006).
The key components of metabolic syndrome include central obesity, dysglycaemia, hypertension, and atherogenic dyslipidaemia (either or both of hypertriglyceridaemia and low HDL-cholesterol). The syndrome definitions indicate associations of features, rather than causality. Only the WHO definition considers albuminuria as a key component, linking albuminuria to vascular dys-regulation, whereas other definitions do not (Alberti et al. 2006). Some of these components can be performed routinely in the clinic while others require a research setting. Certain complex methodologies, such as hyper-insulinaemic-clamp testing are not appropriate for either the clinic or field setting. The NCEP criteria allow use of non-fasting HDL-cholesterol to indicate atherogenic dyslipidaemia, when fasting lipids are not available (NCEP ATP III 2001). In each definition, different thresholds of low concentration of HDL-cholesterol are defined for males and females. The IDF criteria identifies the importance of ethnicity-specific waist measures, thereby identifying risk may be different in different populations. Although several investigators recommend use of lower waist circumference thresholds in Aboriginal people (Wang et al. 2003), the exact threshold of a healthy waist circumference or central body fat measures have not been defined. Insulin resistance is defined as the top 25% of fasting insulin values among the non-diabetic population in the EGIR definition, and requires population specific data (Alberti et al. 2006). This may be problematic among Aboriginal peoples and Torres Strait Islander peoples, since assessment of insulin resistance is not routinely performed, and among some Aboriginal people, widely varying 2-hour insulin responses may accompany otherwise similar concentrations of fasting insulin (O'Dea et al. 1990).

Further research priorities were identified for the metabolic syndrome by Alberti et al. (Albertiet al. 2006) including

- The use of improved measurements of body fat and fat distribution using whole body dual energy x-ray absorptiometry (DXA), abdominal computed tomography (CT) or magnetic resonance imaging (MRI)
- Measurement of liver fat content
- Measurement of adipose-specific biomarkers (adiponectin and leptin),
- Measurement of fasting insulin and insulin resistance scores
- inclusion of albuminuria, and
• pro-inflammatory markers: c-reactive protein (CRP), tumour necrosis factor alpha (TNFα) and interleukin-6 (IL-6).

Numerous studies have described metabolic syndrome components in Aboriginal people and Torres Strait Islander people. In other populations, the relationship of inflammation and metabolic risk has been extended to more specific markers, including interleukins, and adiponectin (Carvalho et al. 2010; Krakoff et al. 2003; Yajnik et al. 2008). These markers, in combination with detailed assessment of body combination measures have not yet been assessed in Indigenous Australians. This is a goal of this thesis.

1.5.3. Overweight and Dysglycaemia

Aboriginal peoples have been reported to have a higher risk of developing diabetes at lower levels of body mass index than observed among European populations (Daniel et al. 1999; Rowley et al. 1997). Overweight in Aboriginal peoples is associated with numerous metabolic abnormalities, which frequently cluster together and worsen with weight gain from a relatively young adult age (by age 35 years) (O'Dea et al. 2008). Overweight in Aboriginal adults (both men and women) is strongly associated with an android or central fat distribution in the trunk and abdomen, rather than on the thighs, hips and distal limbs (Gault et al. 1996; Rowley et al. 1997). Heterogeneity in body size was evident between several remote Aboriginal communities of the Northern Territory, where Aboriginal females across the communities consistently had an elevated WHR across a range of body mass index (Kondalsamy-Chennakesavan et al. 2008). It has also been demonstrated among Aboriginal males and females of all adult age-groups (25-74 years old), compared with an age-matched Caucasian comparator group in the AusDiab study, that the adverse impacts of overweight and obesity are better indicated by a high WHR, than a high body weight or BMI (Kondalsamy-Chennakesavan et al. 2008).

Hoy et al. (Hoy et al. 2006b) noted in other work that high waist circumference (central obesity) in males and females, but not body mass index, was key to diabetes and cardiovascular disease risk in remote Aboriginal people. Even among lean and healthy Aboriginal people, a tendency to high fasting insulin concentrations has been
reported (O’Dea et al. 1990; O’Dea et al. 1988b). Improvements in insulin sensitivity in response to acute and sustained positive lifestyle changes have been reported in overweight Aboriginal adults. A recent study in overweight Aboriginal males showed aerobic exercise acutely invoked an anti-inflammatory and insulin-sensitising response (Mendham et al. 2012). Furthermore, weight-loss, in association with improvements in the metabolic abnormalities related to diabetes were shown following a 3 month lifestyle change among another group of adult Aboriginal people (O’Dea et al. 1980).

Type 2 diabetes was first identified in the Torres Strait in the 1960’s and its prevalence has since increased. Data from the late 1990’s showed Torres Strait Islander people had almost 3 times the rate of obesity, 6 times the rate of type 2 diabetes, and a higher frequency of dyslipidaemia (high triglycerides and low HDL-cholesterol concentrations) compared with age-matched Australians from the AusDiab Study (Leonard et al. 2002). In this study, Torres Strait Islander people exhibited very high rates of multiple cardiovascular risk factors. For example, 44.5% of women and 49.8% of men had three or more risk factors, and only 6.5% of women and 8.5% of men had no risk factors (Leonard et al. 2002).

In recent reports, young children in the Torres Strait were exhibiting clinical and biochemical signs of insulin resistance (Valery et al. 2008). Seventy nine percent of girls and 22% of boys had an enlarged waist circumference, and overall 46% of children were overweight or obese by BMI criteria. The metabolic syndrome was observed in 33% of children, some of whom were as young as 10 years old (Valery et al. 2008). The finding of high rates of insulin resistance in addition to obesity in girls and young women was highlighted as a serious concern for a self-perpetuating cycle of obesity, gestational diabetes, large for gestational-age babies and intergenerational metabolic illness in this community (Leonard et al. 2002; Valery et al. 2008).

1.5.4. Dyslipidaemia

Cholesterol is an important essential lipid used in all cell membranes and in the synthesis of steroid hormones and bile acids. It is carried in the blood in three major
lipoprotein classes, low-density lipoprotein (LDL-cholesterol, and Apo-B), high- 
density lipoprotein (HDL-cholesterol, and Apo-A), and very low density lipoprotein 
(VLDL), which is a triglyceride-rich particle and contains Apo-B100, Apo C and 
Apo E. In many populations, cardiovascular disease risk is highly associated with 
increased LDL-cholesterol, and inversely with HDL-cholesterol (Yusuf et al. 2004). 
A low HDL-cholesterol level may also be a marker of other atherogenic factors. 
LDL-cholesterol lowering remains a primary clinical focus in the prevention and 
management of atherogenic risk (NCEP ATP III 2001).

The dyslipidaemia observed in the metabolic syndrome is characterised by increased 
production of hepatic VLDL, small dense LDL-cholesterol, and a decrease in small 
dense HDL-cholesterol (Cornier et al. 2008). In the presence of high fasting 
triglycerides, small-dense LDL-cholesterol particles are found, even though the 
LDL-cholesterol level may not be elevated.

Unlike European populations, the dominant lipid abnormality in Indigenous 
Australians is elevated fasting triglycerides, and low HDL-cholesterol (Leonard et al. 
2002; Maple-Brown et al. 2009; O'Neal et al. 2008; Shemesh et al. 2007; Wang et al. 
2003). This pattern of dyslipidaemia is also observed in non-Indigenous Australians 
with central obesity or diabetes (O'Neal et al. 2008) or chronic kidney disease (Chan 
et al. 2009a).

Low concentration of HDL-cholesterol (≤1.0 mmol/L) is a consistent finding in 
Aboriginal Australians and in Torres Strait Islander peoples of both genders (relative 
to other Australians) (O'Neal et al. 2008). The atherogenic dyslipidaemia observed 
in Aboriginal women (similar to Aboriginal men) may contribute to their higher 
cardiovascular risk compared with non-Indigenous women (Hoy et al. 2006b; O'Dea 
et al. 2008; Wang et al. 2003). It may not be appropriate to use gender-specific 
thresholds in lipid abnormalities in Aboriginal Australians or in Torres Strait Islander 
peoples, and further longitudinal investigation of cardiovascular disease risk 
associated with low concentration of HDL-cholesterol among Indigenous women is 
required.
1.5.5. Albuminuria

Albuminuria is a core component of the WHO definition of metabolic syndrome, indicating vascular dys-regulation (Alberti et al. 1998). Several investigators advocate for the inclusion of albuminuria in metabolic syndrome definitions used within Indigenous Australian communities (Hoy et al. 1997; Hoy et al. 2003b; Rowley et al. 2000). Albuminuria has been reported to be an early marker of future severe renal disease, cardiovascular disease, all cause mortality and death from both renal and cardiac disease in one remote Northern Territory community (Hoy et al. 1997; Hoy et al. 2003b). The risk associated with albuminuria in one Aboriginal community occurred as both a dichotomous and continuous variable (Hoy et al. 2006b).

Albuminuria is observed among many Aboriginal communities throughout northern Australia, including in people who do not have diabetes. Fifteen percent of participants in a community health survey in Central Australia had isolated microalbuminuria (defined as ACR <34 mg/mmol) without any other metabolic syndrome features (Rowley et al. 2000). Higher degrees of albuminuria were associated with higher blood pressure, overweight and central weight gain, hyper-triglyceridaemia, insulin resistance, and higher age-adjusted prevalence of diabetes in that study. Albuminuria was strongly related to the metabolic syndrome after adjustment for concurrent microscopic haematuria among remote Central Australian Aboriginal people of that study (Rowley et al. 2000). The clustering of features of the metabolic syndrome (including albuminuria) across Australian Indigenous communities is consistent with the widespread burden of diabetes, renal disease (from diabetes and non-diabetes related conditions) and cardiovascular disease (AIHW 2008).

1.5.6. Inflammation

Inflammation is not a key feature of the metabolic syndrome, but has been identified among several key research priority areas for the syndrome (Alberti et al. 2006). C-reactive protein (CRP) is produced by the liver in response to inflammation, infection and injury. Chronically elevated levels of CRP are linked with increased risk of cardiovascular disease in many populations (Ridker et al. 1998). Among Aboriginal
people, CRP levels (either high or low) have been shown to be stable even after several years (Shemesh et al. 2009). C-reactive protein levels are associated with adiposity in Aboriginal people living in remote and urban communities (Hodge et al. 2010; Maple-Brown et al. 2010a; Shemesh et al. 2007). For example in one remote Aboriginal community, CRP levels were lower in very lean Aboriginal women than very lean Aboriginal men, but rose much more steeply in Aboriginal women than men as weight increased (Shemesh et al. 2007). The authors speculated that CRP and gender may be differentially linked to cardiovascular disease in Aboriginal people (Shemesh et al. 2007).

In another remote Aboriginal community (where high rates of kidney and cardiovascular disease and infection coexist), several independent predictors of CRP concentrations were reported: age, male gender, albuminuria, HDL-cholesterol, diastolic blood pressure, and inflammation (or immune system stimulation) (McDonald et al. 2004). Central adiposity was also associated with CRP concentration in this community. The authors hypothesised that the multi-determinant effects of CRP concentration were driven by high socioeconomic stress manifest as poor housing quality, overcrowding, poor nutrition and unemployment in this community (McDonald et al. 2004).

Inflammation was also related to endothelial dysfunction in a remote Aboriginal community of Western Australia. Very high concentrations of e-selectin and CRP were found in a community with high rates of chronic disease, insulin resistance and the metabolic syndrome (Rowley et al. 2003). E-selectin is a serum marker of endothelial dysfunction, and was positively correlated with CRP concentration in all participants, and with central obesity and high blood pressure in women. High concentrations of markers of inflammation and endothelial stress were associated with low concentrations of antioxidants (Rowley et al. 2003). The authors hypothesised that low concentrations of antioxidants may also reflect poor quality diet, tobacco use, diabetes, central obesity and psychological stress (Rowley et al. 2003).
1.6. Body Build and Body Composition

Whilst obesity is a powerful risk factor for diabetes and related conditions in many populations (Yusuf et al. 2004), there is a clear gap in knowledge with respect to 1) identifying appropriate thresholds regarding body size and 2) understanding the extent the extent of adverse health implications associated with overweight among Indigenous Australian’s (WHO 1999). Some studies have also indicated differences in body size between Aboriginal people and Torres Strait Islander people (Heitmann et al. 1997), yet guidelines addressing health risk in relation to body size for Indigenous Australians do not differentiate between these two groups. The accurate measurement of body composition including total and regional adipose depots is critical to better understanding the relationships of health and metabolic risk associated with weight gain, for both Aboriginal people and Torres Strait Islander people.

1.6.1. Body Composition Methods in Clinical Research

Body fat exists in numerous compartments in the human body. Because of the complexity of fat depots, a technique that accurately measures total human body fat does not exist (Ellis 2000; Wang et al. 1992). This section will describe several terms used in body composition studies ‘reference tests of body composition’, the ‘five-level model of body-composition’, and the ‘compartment model of body composition’. The complexity of the discussion of body composition tools highlights that accurate assessment is the goal, but remains practically challenging in large population studies.

Reference tests of body composition are the most accurate form of body composition assessment, and have been performed in whole human cadavers, including direct measurement of organs, and elemental studies. Since direct assessments on human cadavers are not realistic for population studies, methods utilising parallel assessment of a direct and indirect technique, which show both high correlation and agreement, are highly desirable in order to support the use of indirect methods in larger populations. Many have argued however, that body composition assumptions validated in reference populations may be inaccurate in populations who are
sufficiently different on the basis of health, body build or ethnicity (Deurenberg et al. 2003; Deurenberg et al. 2002a; Gallagher et al. 1997; Heitmann et al. 1997).

Wang et al. (Wang et al. 1992) proposed a five-level model of body composition, incorporating atomic (level 1), molecular (level 2), cellular (level 3), tissue-systems (level 4), and whole-body (level 5). Level 1 is the most complex of the five levels, and describes total body composition in its elemental form: oxygen alone accounts for more than 60% of total body mass. Six elements (oxygen, carbon, hydrogen, nitrogen, calcium and phosphorus) account for more than 98% of total body mass.

Total body weight is a function of fat mass and lean body mass (skeletal mass, muscle mass and water) (Valentin 2002). The skeletal muscle system accounts for 40% body mass in mature adults, and up to three quarters of skeletal muscle mass is found in the limbs (total appendicular skeletal muscle) (Valentin 2002). Age, gender and ethnicity were significant independent determinants of total appendicular skeletal muscle in a study of healthy adult African American people and Caucasian people (Gallagher et al. 1997). Bone can be described by any of the 5 levels proposed by Wang et al. (Wang et al. 1992): by tissue-systems (level 4), as extracellular solid (level 3- cellular), measured as mineral (level 2) and at the most complex level, as total body calcium and phosphorus (level 1). Likewise the determination of skeletal muscle can be approached from different levels: total body water (level 2) and electrolyte counting (level 1) can reliably predict lean body mass (Valentin 2002); total body nitrogen counting may determine protein (level 2) and therefore the muscular component (level 4) of lean-body mass. Hence the combinations of multi-compartment assessments that incorporate different levels of the five-level model present a picture of fat and lean-mass in the individual. Since there are different components and levels, there are many combinations of modalities that may be used to describe human body composition.

Clinicians require reliable and accurate body composition information for their high-risk patients. Tools that can be applied to larger populations are valuable for public health interventions. At the group and individual levels, these tools need to accurately detect changes in body composition in response to interventions. A
variety of techniques have been used in body composition studies in various populations in the literature.

1.6.1.1. Anthropometry

Anthropometry describes indirect measures of body composition derived using height, weight and body circumferences. Body mass index (BMI) refers to the ratio of weight/height\(^2\) (units are kg/m\(^2\)). It was first described as the Quetelet Index (in 1832), and had a change in terminology to BMI in 1972. In prospective longitudinal studies of both men and women of a Caucasian background, the body mass index was shown to have a J-shape relationship with mortality and cardiovascular disease, even after controlling for smoking status. The healthy range of BMI was identified from prospective longitudinal data for mortality risk, where the lowest risk in life-long non-smoking adult males and females occurred at BMI 24.3 kg/m\(^2\) and 23.9 kg/m\(^2\) respectively (Pischon et al. 2008).

BMI is simple to perform, and requires minimal intrusion to the individual. There are a number of assumptions when comparing BMI between individuals: it assumes increasing weight in overweight adults is due to gains in fat mass; it assumes similarities in relative body proportions (trunk-length and leg-length) between individuals and populations; it is a measure of total, and not regional body fat; it does not allow for changes in body weight due to changes in lean mass due to exercise, body building, sarcopenia or cachexia due to illness or aging.

Measurement of the waist and hip circumference, and their ratio are more recent tools of body size, and indicate abdominal obesity. Weight gain occurring by expansion of adipose tissue may deposit generally over the body, detected as both an expanded hip and waist circumference or centrally (at the waist). The pattern of weight gain in both individuals and populations may be variable, and are related to different health risk. Waist circumference is an indirect measure of both subcutaneous and intra-abdominal fat over the abdomen. There are several techniques of measurement of the waist circumference: at the level of the umbilicus; the position of minimum or maximum diameter over the abdomen; at the level of the iliac crest; or mid-way between the inferior costal margin and iliac crest (in the mid-
axillary line) (Callaway et al. 1988). The umbilicus may be more inferiorly displaced on an obese abdomen, in comparison to a lean abdomen. As long as bony landmarks can be palpated, mid-way between the costal margin and iliac crest is a satisfactory and reproducible measurement site for cross-sectional and longitudinal assessments (Alberti et al. 2006).

The hip circumference can also be measured by several techniques: at the widest circumference over the buttocks; at the level of the greater trochanter; or the site of maximal projection of the buttocks. Hip circumference incorporates both gluteal subcutaneous and gluteal lean mass (Seidell et al. 2001; Snijder et al. 2004a). Hip circumference is affected by the breadth of the pelvis (and therefore reflects body build) (Seidell et al. 2001), which may differ between populations (Katzmarzyk et al. 1999). The waist to hip ratio (WHR) is determined by waist circumference divided by hip circumference.

Many of the anthropometric variables (waist circumference, hip circumference, waist to hip ratio and body mass index) were shown to be highly correlated with more direct measures of total fat and lean mass (estimated with underwater weighing and computed tomography of the abdomen) among middle aged Canadians of European background (Seidell et al. 2001). Waist circumference was strongly associated with trunk fat mass measured by whole body DXA in both males and females (Snijder et al. 2004a). In addition, in both male and female Caucasian adults, those with higher trunk fat mass had higher fasting glucose, and homeostasis model assessment (HOMA) score (Snijder et al. 2004a). Larger waist and smaller hip circumferences were shown to be independently associated with low HDL-cholesterol, high triglycerides and insulin levels, however these relationships were confounded by assessment of the waist to hip ratio (Seidell et al. 1987). Higher hip girth has been related to a more favourable insulin sensitivity profile in men and women. However it was suggested this may be mediated by different mechanisms in men and women: a higher proportion of lean mass over the hips in Caucasian males, but a higher proportion of subcutaneous fat over the hips in females (Snijder et al. 2004a).

Compared to a body mass index alone, a combination of total and central obesity was shown to provide improved risk prediction in healthy adult males in prospective
longitudinal studies. Both BMI and central adiposity (measured as waist circumference divided by the width of the hips) were independently associated with the future development of diabetes in healthy men who were followed up for 18 years (Cassano et al. 1992). The lowest risk of diabetes was found in men with lowest BMI and lowest tertile of central adiposity (Cassano et al. 1992). These studies show that differences in body composition are inherently related to health risk, either in the form of differences in fat and lean mass over the gluteal region (shown by Snijder et al. (Snijder et al. 2004b) above) or preferential abdominal obesity, even in the presence of low BMI (shown by Cassano et al. (Cassano et al. 1992) above), and probably explains why WHR was a superior indicator of cardiovascular disease risk than body mass index or waist circumference in ethnically diverse (or heterogeneous) populations (Yusuf et al. 2004). Appropriate thresholds of body mass index, central obesity or the waist circumference may vary between populations, and remains a research priority in non-Caucasian populations (WHO 2000; Alberti et al. 2006).

1.6.1.2. Skin Fold Thickness

Skin-fold thickness (SFT) is the thickness of a double fold of skin and subcutaneous fat, designed for assessment of body fat in lean individuals, and part of an assessment of malnutrition. Sum of skin-fold thicknesses have been compared against underwater weighing methods to indirectly estimate body fat percent (Durnin et al. 1974). From that work, reference tables of body fat percent determined from sum of 4 skin-fold thicknesses were developed (Durnin et al. 1974). The assessment is simple to perform by a trained operator, is non-invasive, and when a minimum of 4 sites is measured (including central and peripheral sites), reflects subcutaneous fat mass in the body (Harrison et al. 1988). However, subcutaneous fat mass is affected by hydration, age (loss of subcutaneous fat with age), and may also vary in different ethnic populations (Harrison et al. 1988). Compression of the SFT site is affected by the size of the fold, and thicker skin-folds (obesity) are associated with more difficulty with reproducibility of the measure.
1.6.1.3. Hydrodensitometry

Underwater weighing, or hydodensitometry was one of the early body composition tools developed in the 1940’s and regarded for many years as a gold standard methodology in many laboratories (Ellis 2001). From a known body weight, body density and therefore fat percent may be derived. The specific methodology is complex to perform for both operator and participant, and the instruments need careful maintenance, so is regarded as a useful tool in the laboratory, but limited in field or clinical use (Ellis 2001). Abate et al. (Abate et al. 1995) described their methodology of hydrodensitometry: the client wears a light weight swimsuit and bathing cap; the client is then submerged up to the chin in a seated position and given 3000ml of gas (oxygen-helium-nitrogen) to rebreathe, and then is fully submerged in the water; the total volume of displacement is measured to the nearest 50 ml; the exhaled gas is analysed with mass spectrometry to measure the helium concentration; an equation is used to determine the total gas volume; total body volume minus total gas volume provides body density, and therefore body fat percent (Abate et al. 1995).

Hughes et al. (Hughes et al. 2004) required participants to have an overnight fast before the procedure, and performed 5-10 consecutive trials to determine body density. Individual variations in fat free mass occur in the presence of physical activity, gender, age, ethnicity, sexual maturity and human growth, yet these variations are not accounted for in formulae calculating fat free mass, which assume a constant density of skeletal muscle and bone mineral content (Ellis 2000). Underwater weighing has been used to evaluate body composition of the elderly (Hughes et al. 2004), and in field settings in indigenous populations (Swinburn et al. 1991). It has also been an adjunct tool of body composition along side skin-fold thicknesses and magnetic resonance imaging (Abate et al. 1995).

1.6.1.4. Body Fat Percent and Bioelectrical Impedance Analysis

Using whole body DXA and a 4-compartment model of body composition, differences in body fat percent were shown between healthy adults from different ethnic groups (Gallagher et al. 2000). As an indicator of healthy body fat percent range, among adult Caucasian men and women aged 20-39 years, those with a “healthy BMI range, 18.5 to <25 kg/m^2” had 9-20% and 21-32% body fat respectively (Gallagher et al. 2000). By comparison, Japanese participants had
higher percent body fat at any BMI than Caucasian and African American participants, and older participants had higher percent fat than younger participants (Gallagher et al. 2000).

Bioelectrical impedance analysis (BIA) is another indirect method of body composition, and an attractive tool for use in clinical and epidemiological studies (Lukaski et al. 1986). Using BIA, body composition is described by impedance (\(z\)), resistance (\(R\)) and reactance (\(Xc\)) of a conducting current of known frequency through tissue of a known length and uniform cross-sectional area. Resistance (\(R\)) is a good predictor of impedance, and impedance has a strong inverse relation with total body water (TBW) (Lukaski et al. 1986), from which fat-free mass (FFM) may be estimated. Fat free mass has a higher conductance of electrical current than fat mass. Conductance is affected by body fluids and electrolytes, and resistivity. Fat free mass was best predicted in both men and women aged 18-50 years by body height and bioelectrical resistance indicated by the equation \(\frac{Ht^2}{R}\) (Lukaski et al. 1986). The equation was validated in healthy adults using hydro-densitometry (underwater weighing) and sum of 4 skin fold thickness (Lukaski et al. 1986). \(\frac{Ht^2}{R}\) has been reported as an index of fat free mass in one study of Aboriginal adults (Piers et al. 2003).

Different measurement methods of BIA are described, which include upright and supine posture. In the supine posture, two electrodes placed on the dorsal surface of the hand, with minimum 5 cm separation, and two on the dorsum of the foot (a tetra-polar electrode arrangement). The two distal (or drive) electrodes of each limb impart a constant alternating current between 300-800 uA. The two proximal (measuring) electrodes of each limb measure the voltage-drop that occurs due to tissue resistance to current flow (Lukaski et al. 1986).

Single-frequency, multi-frequency bioelectrical impedance analysis (MF-BIA), and multi-frequency bioelectrical impedance spectroscopy (BIS) are available. At a single high frequency (50 kHz) only total body water (TBW) is measured. At a single low frequency (1 kHz) only extracellular fluid (ECF) is calculated. When MF-BIA is used (traditionally performed using 1 kHz and 50 kHz frequencies), then both ECF and ICF can be determined simultaneously. It is suggested that MF-BIA
may have greater clinical utility in circumstances of abnormal hydration such as liver and kidney disease (Thomas et al. 1992). Multi-frequency bioelectrical impedance spectroscopy uses more than one hundred frequencies in order to extrapolate outside the range to obtain resistance at extreme frequencies (approaching zero and infinity) (Thomas et al. 1992).

The use of bioelectrical impedance, its accuracy and reproducibility within an individual and comparing across populations requires care to the applied current and frequency used, proper and consistent electrode measurement sites and positioning, and consideration of the individual (or groups) body build and co-morbid illness. Prediction equations of body composition are generated from comparison against reference methods. Caution should be exercised when applying prediction equations based on BIA to another population with differing characteristics to the validated study population, since this may result in bias (Deurenberg et al. 2003). Characteristics which increase bias include gender and age, co-morbid illnesses and body build differences which may be a function of ethnicity. Comparing impedance measures between individuals will also rely on the adequacy of measurement techniques in the reference population, the rigor of the applied impedance equation, and the precision and accuracy of impedance instruments used. Despite these limitations, BIA has been used in large epidemiological studies because it is non-invasive, safe, and inexpensive and requires a protocol but not a highly skilled operator (Heitmann et al. 1997).

1.6.1.5. Whole Body Dual Energy X-ray Absorptiometry (DXA)

Dual-energy x-ray absorptiometry describes the differential attenuation of a photon or radiation source at two energy levels in tissue. DXA was first developed to measure bone mineral density where it partitioned bone (as calcium hydroxyapatite) from soft tissue, and later developed for assessment of total body composition. Phantoms with known fat and lean content are used to generate calibrating equations, used in the software to predict percentage of fat (or lean tissue). The use of whole body DXA in clinical studies of body composition has been a valuable advance on anthropometry, and more accurately identifies total fat mass, and lean mass, and body fat distribution. Body composition assessed by DXA has strong positive linear
correlations with reference tests of body composition (Scholler et al. 2005). Others have also supported the use of both computed tomography of the abdomen with DXA measured trunk soft tissue to better predict intra-abdominal fat burden, and metabolic risk (Carey et al. 1996; Jensen et al. 1995).

Whole body DXA is safe, with a scan dose equivalent to less than 2 hours (or <0.0001 dose) of annual background radiation exposure (Heymsfield et al 1990). Whole body DXA provides a non-invasive and rapid assessment of body composition. Several problems with the use of whole body DXA are described, and depend on reproducible and consistent positioning of the body (Brownbill et al. 2005; Hansen et al. 1999), accuracy with measurement of extreme obesity (Brownbill et al. 2005), DXA software (Hansen et al. 1999), accuracy of measurement between different commercial brands (Scholler et al. 2005), and availability of scanners since they are large, and often operated by radiology departments within hospitals or large research institutions. However, because of its ease of use to both the individual and researcher, whole body DXA has been described as a core reference test of body composition (Gallagher et al. 2000).

1.6.1.6. Computed Tomography

Abdominal imaging provides additional information (beyond a waist circumference) about abdominal fat partitioning (subcutaneous and visceral fat), and has enabled further study of cardio-metabolic risk associated with central obesity (Carey et al. 1996; Demerath et al. 2008; Greenfield et al. 2002; Seidell et al. 1987; Smith et al. 2001). Abdominal fat volume and cross-sectional area using computed tomography (CT) and magnetic resonance imaging (MRI) are also described (Abate et al. 1995).

Precise measurement and comparison of abdominal anatomy, including subcutaneous abdominal fat, and compartments of intra-abdominal fat are made possible with this imaging. Abdominal subcutaneous adipose tissue (SAT) is located anterior to the rectus abdominus muscle and identified as superficial subcutaneous abdominal fat (SSAT) and deep subcutaneous abdominal fat (DSAT), separated by a fascial plane (fascia superficialis) (Smith et al. 2001). The deep subcutaneous adipose tissue is continuous anteriorly and posteriorly, and identified near the inferior ribs and as
distally as the proximal thighs (Smith et al. 2001). The term intra-abdominal fat (IAF) is used interchangeably with visceral adipose tissues (VAT). IAF is anatomically identified as fat inferior to the margins of the rectus abdominis muscle, extending laterally around the peritoneum, quadratus lumborum and long back muscles (Demerath et al. 2008; Smith et al. 2001).

Abdominal fat is identified by its density, the Hounsfield unit (HU), between -50 to -150 HU (Jensen et al. 1995), using specialised software (Slice-O-Matic) or inbuilt software summatng designated Hounsfield units. Abdominal magnetic resonance imaging provides an opportunity to measure volume without a radiation dose. It may not always be practical, accessible or safe to perform sequential scans of the abdomen with computed tomography, particularly with high exposure to ionising radiation, especially with recurrent scans in intervention or longitudinal studies. However, the use of MRI for clinical research has been limited by expense and access to machines.

Intra-abdominal fat distribution was reported among healthy adult Caucasian participants using sequential MRI scans between the thoracic and sacral vertebrae (T9 to S1) (Demerath et al. 2008). From this technique, peak intra-abdominal fat area was shown to be more consistently observed higher in the abdomen (toward the head, relative to L4-L5 inter-vertebral space) in both men and women (Demerath et al. 2008). Caucasian males and females deposit intra-abdominal fat differently. At the level of L1-L3, males had more intra-abdominal fat than females (Grauer et al. 1984). Others have supported the level of L4 to predict intra-abdominal fat burden (Seidell et al. 1987; Smith et al. 2001). Abdominal fat partitioning (of intra-abdominal and subcutaneous fat) also differs between healthy males and females, of presumably Caucasian background: males had more intra-abdominal and less subcutaneous fat than women over a wide range of adiposity at L1, L3 and L5 vertebral levels (Grauer et al. 1984).

Despite others using one inter-vertebral level to indicate abdominal fat partitioning, in a study by Greenfield et al. (Greenfield et al. 2002) in premenopausal women (who had a mean BMI 24.9 kg/m²), significant intra-subject variability in visceral fat area was shown over 4 vertebral levels. In that study, the authors suggested that a
single CT slice (at any vertebral level) to predict intra-abdominal fat volume has clinical limitations, but was improved by using 2 levels. However, a further technique was proposed where a single CT slice assessing the ratio of visceral fat to total abdominal fat, in conjunction with a DXA central abdominal fat assessment, successfully predicted intra-abdominal fat burden, whilst also limiting the radiation exposure to the individual (Carey et al. 1996; Greenfield et al. 2002; Jensen et al. 1995). Hence combined modalities of cross-sectional CT with abdominal-region DXA could enhance the assessment of body composition whilst minimising radiation exposure to the participant.

1.6.2. Body Size, Alcohol and Cigarette Smoking

Many studies report high rates of smoking among Indigenous Australians, and alcohol abuse among some but not all Indigenous Australians (AIHW 2008; Vos et al. 2009). Alcohol and tobacco use (in addition to physical activity and diet choices) are an important consideration for body composition and obesity (Komiya et al. 2006). Smoking cessation has been linked with weight gain via a combination of lower resting metabolic rate, and higher food consumption (Moffatt et al. 1991). Among adult males, those who currently smoked cigarettes had higher abdominal fat burden than those who were non-smokers (Komiya et al. 2006). Adults with alcoholism are at higher risk of low bone mineral density and osteoporosis. Alcohol related muscle disorders are described, however these have generally been explained by concurrent morbidity (including chronic liver disease). Alcohol is not stored by the body, and has preferential metabolism. The chronic consumption of high quantities of alcohol is associated with suppressed lipid oxidation in the liver and skeletal muscle (Suter et al. 1997). Over time this presents an excess fat burden in the body. Over five years, chronic high alcohol consumption (at least 30 grams per day) in adult males was associated with a higher risk of obesity, compared with males who drank fewer units of alcohol (Wannamethee et al. 2003). When matched for age, body weight and body mass index, males with chronic alcohol abuse (but who did not have chronic liver disease) had a higher waist to hip ratio, lower percent body fat, and higher percent lean mass than age and BMI matched healthy males (Addolorato et al. 2000). The higher percent lean mass was explained by use of the DXA modality, measuring higher body water (extracellular fluid) rather than skeletal
muscle mass. However in this study, physical activity was a much stronger factor related to body fat, than alcohol (Addolorato et al. 2000).

1.6.3. Relationship of Body Shape and Composition with Gender, Aging, Health and Chronic Kidney Disease

Among people of European background, healthy men have more bone mass and skeletal muscle than women (Heymsfield et al. 1990), and more intra-abdominal fat, and less abdominal subcutaneous fat than women (Grauer et al. 1984). Women have more fat mass (Heymsfield et al. 1990; Valentin 2002), including more subcutaneous fat than men (Seidell et al. 1987). As stated earlier, healthy Caucasian men and women aged less than 35 years with a body mass index between 18.5 to <25 kg/m$^2$, were reported to have between 9-20% and 21-32% body fat respectively (Gallagher et al. 2000).

Controlling for BMI, older age was associated with higher body fat percent, though this rate of change was also affected by gender, ethnicity and individual differences (Gallagher et al. 2000). Older age was associated with lower skeletal muscle mass in a study of Caucasian women aged 51-84 years old (Hansen et al. 1999). Aging was associated with higher visceral fat mass and a higher ratio of visceral fat to subcutaneous fat mass in both genders, and particularly after the menopause in women (Cartier et al. 2009; Seidell et al. 1987).

The metabolic profile of an individual may better indicate the pattern of abdominal fat partitioning in adults that otherwise appear equally obese by indirect body measures. In overweight postmenopausal women (of European background), a combination of large waist circumference and high visceral fat area was associated with metabolic abnormalities (Messier et al. 2010). Also, metabolically healthy obese postmenopausal women had higher subcutaneous fat than females with a metabolically unhealthy profile even if both groups had similar visceral fat area (Messier et al. 2010). Among Caucasian males and females, compared with those with normal glucose tolerance, those with impaired glucose tolerance were older, and had a higher BMI, waist circumference and body fat percent (Snijder et al. 2004b). In a comparison of non-diabetic and otherwise healthy adult Caucasian males, Abate
et al. (Abate et al. 1995) showed obesity (defined by a mean BMI of 37 kg/m²) was associated with higher absolute mass in all abdominal compartments (subcutaneous abdominal fat, intra-peritoneal and retroperitoneal) compared with lean males (BMI 23 kg/m²). In another study involving young adult non-Caucasian males, obesity was associated with higher levels of inflammatory markers (CRP, interleukin-6, fibrinogen and plasminogen activator inhibitor 1) (Mauras et al. 2010). The studies do not implicitly allow comparison -however indicate that variable patterns of total and abdominal (subcutaneous and visceral) obesity impact on metabolic and inflammatory risk across levels of health and may vary between ethnic groups.

As noted above, skeletal muscle accounts for 40% body mass in mature adults, and up to three quarters of skeletal mass is found in the limbs (total appendicular skeletal muscle) (Valentin 2002). Skeletal muscle and bone mineral mass have been shown to diminish with age and chronic disease. By early adulthood, lean body mass (which includes skeletal muscle, connective tissue, organs and skeleton) comprises 80% and 70% of body mass in males and females respectively, which falls to 72% and 58% in elderly males and females (Valentin 2002). Age, gender and ethnicity were shown to be significant independent determinants of total appendicular skeletal muscle in a study of healthy adult African American and Caucasian people (Gallagher et al. 1997).

He et al. (He et al. 2003) demonstrated that total body potassium (TBK, an indicator of lean body mass) peaked at 30 years of age in healthy adults of varying ethnicity (Asian, African American, Hispanic and Caucasian). They also showed males had more TBK than women; and whilst a linear loss of TBK occurred in healthy aging, different slopes were observed in each ethnic group. Similar relationships of aging and skeletal muscle are observed by others (Gallagher et al. 1997; Hansen et al. 1999).

1.6.3.1. Kidney Disease

Whole body muscle mass has also been indicated by the study of serum creatinine, which is used as an indirect biomarker of kidney function (Levey et al. 1999; Taylor et al. 2006). Creatinine is a myocyte-derived end-product of metabolism, however,
Creatinine is difficult to use in predicting muscle mass because of the prolonged length of time required to collect urine samples (Taylor et al. 2006), and determining the origin of creatinine from either dietary or metabolic origins (Hsu et al. 2008).

Using serial whole body DXA scans, Fried et al. (Fried et al. 2007) investigated the relationship of change in lean muscle mass over time in an independently-mobile elderly populations who had a mean eGFR of 72.8 ml/min/1.73m² (by the modification of diet in renal disease study, 4 variable prediction equation of estimated glomerular filtration rate, MDRD4 formula) (Levey et al. 1999). They showed African American males had the highest skeletal mass (compared with African American females, and Caucasian males and females), but African American males also had the highest loss of skeletal muscle over the follow-up period. These results highlight that whilst serum creatinine is a major indirect determinant of estimated GFR, studies are lacking describing the relationship of serum creatinine with lean body mass (and therefore indirect kidney function measures) over time in aging individuals across different ethnic populations.

1.6.4. Body Composition Differences between Ethnic Populations

Differences in body composition (including the relationship of body fat percent with body mass index) have been reported between ethnic groups (Craig et al. 2003; Gallagher et al. 2000; He et al. 2003; Heitmann et al. 1997). This may reflect long term environmental and climatic adaptations among indigenous peoples (Roberts 1953). Variability of body composition within ethnic groups (such as Asians) has been reported (Gurrici et al. 1999). Gallagher et al. (Gallagher et al. 2000) reported different body fat percent levels between different ethnic groups (Caucasian, African American, and Japanese), when matched for body mass index. High body fat percent at lower body mass index was partly explained by body build (trunk to leg-length ratios, slenderness, and muscularity), and activity levels (Deurenberg et al 2002a).

Lean Australian Aboriginal people living in Northern Australia had very low body weight for size, a feature consistent with South East Asian and African peoples (Roberts 1953). The low weight relative to size of Aboriginal people and increased surface area over a compact trunk allowed a greater surface area for heat exchange
and efficient cooling (Roberts 1953). Health in Aboriginal adults was associated with low body mass index (Daniel et al. 1999; O’Dea et al. 1988b). Norgan (Norgan 1994) reported the lower BMI expected for a given height in Aboriginal males (relative to European population) was due to relatively longer leg-length for a given height.

1.6.4.1. Stature and Skeletal Proportions

As noted earlier, Lukaski et al. (Lukaski et al. 1986) reported body height and resistance (measured by bioelectrical impedance analysis) accurately predicted fat free mass in humans. Deurenberg et al. (Deurenberg et al. 2003) reported ethnic differences in relative leg-length and frame size between populations impacted on both expected body mass index and body fat percent. Without taking account of these observed stature differences, shorter limbs relative to overall height and a slender versus a stocky frame are reported to affect the accuracy of predicted fat percent and fat mass determined by bioelectrical impedance analysis (Gurrici et al. 1999). Using detailed body composition methods, muscle mass (determined by total body water and DXA), was shown to be highly correlated with the breadth of joints (assessed by sliding anthropometer), and also shown to be highly correlated with bone mineral content (using DXA) in Caucasians (Snijder et al. 1999). They also showed that participants with a slender frame had less lean mass, which may have occurred because of less bone mineral content, skeletal muscle, connective tissue or cartilage (Snijder et al. 1999).

Katzmarzyk et al. (Katzmarzyk et al. 1999) reported differences in skeletal dimensions and physique within Canadians of First Nation and European background. The First Nation women in this study were heavier, had a higher BMI than European women, and wider skeletal dimensions (bi-acromial, bi-epicondylar, bi-condylar and bi-cristale breadths) (Katzmarzyk et al. 1999). First Nation men however had only a trend to wider skeletal breadths (bi-epicondylar and bi-cristale breadths) than Caucasian men (Katzmarzyk et al. 1999). The reported physique of Australian Aboriginal people appears to be quite different compared with First Nation Canadians, although no direct comparisons have been made. Australian Aboriginal people are reported to have a linear body build, with narrow pelvis and
shoulder breadths and compact trunk (Roberts 1953), and retain slimness of physique in the lower extremities in overweight (O’Dea et al. 1993; O’Dea et al. 1988b; Roberts 1953). By comparison First Nation Canadian adults have a comparable or wider skeletal breadths than Europeans (Katzmarzyk et al 1999).

Stature (or body height) is modified at key growth periods in antenatal and early childhood, but are also impacted by socioeconomic stress. Precise measures of skeletal proportions, and growth of skeletal dimensions have been reported in a Caucasian paediatric population using whole body DXA (Abrahamyan et al. 2008). A constant ratio of long-bone length to stature was found in healthy children across the age range of 6-18 years old (Abrahamyan et al. 2008). Retrospective studies in Caucasians growing up during World War II suggests restricted growth results in shorter limb length thereby preserving growth of vital organs (trunk-length) (Davey Smith et al. 2001; Lawlor et al. 2002). In adult life, shorter relative limb length was associated with the development of adult onset diabetes and cardiovascular disease (Davey Smith et al. 2001; Lawlor et al. 2002). Aboriginal people are reported to have a longer distal limb segment (shin), which accounted for the longer relative leg-length for overall height (Abbie 1969). Aboriginal babies born small for gestational age are reported to remain small (by height and weight) in adulthood, though differences in body proportions were not reported (Hoy et al. 2010b).

1.6.4.2. Bioelectrical Impedance Analaysis and Ethnicity Differences in Populations

Most data about bioelectrical impedance analysis are reported among young, healthy Caucasian populations. Factors that contribute to population specificity of bioelectrical impedance prediction equations of body composition include: age, gender, the body build, and distribution of body water (extracellular versus total body water). Ethnicity may impact mostly in the area of body build with respect to height, limb length, and skeletal build (Deurenberg et al. 2002b; Gurrici et al. 1999). As noted above, electrical impedance is related to the length of the tissue under study. In a height adjusted analysis, Caucasian participants with shorter limbs had overall lower body impedance, which predicted higher fat free mass (and lower body fat percent), regardless of adiposity (Snijder et al. 1999). Differences in predicted
body composition using BIA are reported between ethnic groups: of Malay, Indian and Chinese people, Indians had the longest limbs, and Chinese the shortest limbs, whilst Malay participants had the most slender body build of the 3 groups (Deurenberg et al. 2002b). The difference in predicted body water (a surrogate of lean mass) from BIA, and measured using body water from deuterium dilution was explained by the differences in relative limb length (Deurenberg et al. 2002b). They also showed BIA in a slender framed person compared with a stocky frame (at the same height) predicts a higher body fat percent (Deurenberg et al. 2002b), consistent with findings in Caucasian people that were discussed above (Snijder et al. 1999). Deurenberg et al. (Deurenberg et al. 2002a) advocate that correction for differences in body build improves the differences in bias in predicted body composition amongst ethnic groups.

1.6.4.3. Ethnic Differences in Body Fat and Body Fat Distribution

At the same body mass index, Japanese adults have a higher body fat percentage than African American and European adults (Gallagher et al. 2000). At a similar age and height, adult Tongan people (in comparison to Caucasian people) have higher body mass index, but similar body fat percent and abdominal fat percent, which was explained by a more muscular physique (having also more total and abdominal lean mass) (Craig et al. 2003). There are several reports where the physique of females (skeletal proportions and measures of obesity) differs more across populations than the physique of males (Katzmarzyk et al. 1998, 1999; Piers et al. 2003; Wang et al. 2003). This is also observed in Tongan females, compared with Caucasian females (Craig et al. 2003). Despite similar age and height, Tongan females had a higher body mass index than Caucasian females (34.3 kg/m² v 26.2 kg/m²). With higher BMI Caucasian women had higher total and abdominal fat mass and higher body fat percent. In contrast, despite approximately 8 units higher BMI in Tongan females, this corresponded to only of 3.2% higher total body fat percent, and only 5.7% higher abdominal fat percent, which suggests a different pattern of body composition between the two groups of females.

Ethnic differences in abdominal fat partitioning among young adults with obesity have been reported (African American v Hispanics) (Lê et al. 2011; Liska et al.
Furthermore, in the assessment of diabetes-risk in young adults with obesity, the predominant pattern of visceral fat (compared with subcutaneous fat) was most strongly related to the expression of inflammatory markers (Lê et al. 2011).

As noted earlier, the Interheart study reported a high waist: hip ratio was associated with increased risk of myocardial infarction in a multiethnic cohort (Yusuf et al. 2004). This is consistent with Snijder et al. (Snijder et al. 2004b) who reported a higher hip circumference was associated with a more favourable metabolic profile in a multiethnic population, including Nauruan’s, Papuan New Guineans, Indians, and indigenous people from the Island of Rodrigues in the Indian Ocean. This relationship has several possible explanations. A higher hip circumference might represent improved insulin sensitivity offered by higher lean mass (Yki-Jarvinen, et al. 1985). Second, it may represent a higher gluteal subcutaneous fat mass in people with a higher hip girth (which is an effective storage of lipid), thereby associated with lower production of very low density lipoproteins which is associated with visceral fat in overweight. Finally, the authors suggest in the presence of higher hip girth, that waist circumference (a combination of both visceral and subcutaneous fat) might have proportionately higher subcutaneous fat than intra-abdominal fat (Snijder et al. 2004b).

1.6.5. Body Composition in Indigenous Australians

This thesis focuses on investigating the relationship of obesity with chronic disease risk markers in Aboriginal and Torres Strait Islander Australians. A wide variety of tools of body composition have been used to describe the Aboriginal people including early anthropological studies (Roberts 1953). The majority of studies of Indigenous Australians have described the level 5 model of body composition proposed by Wang et al. (Wang et al. 1992) using skin-folds, body circumferences and weight. Fewer studies describe body composition using bioelectrical impedance analysis, one study used whole body DXA to describe metabolic and inflammatory response to exercise within Aboriginal males (Mendham et al. 2012), and only one group has described a small, very detailed study using whole body DXA, and total body water and nitrogen counting comparing Aboriginal females and Caucasian females (Raja et al. 2003).
Many investigators of Indigenous health who have used indirect models of body composition such as skin-folds and bioelectrical impedance acknowledge the need for further validation with more sophisticated body composition tools (Piers et al. 2003; Rutishauser et al. 1986). Whilst many reports shed light on the relationships of overweight (using body mass index, skin-fold thicknesses and waist circumference), there has been a paucity of body composition studies utilising sophisticated methods of body composition techniques involving large numbers of Aboriginal people and Torres Strait Islander people. However, through the use of indirect methods of body composition, several distinctive body size and composition features are known with respect to Aboriginal people, including their uniqueness compared with Torres Strait Islander and Caucasian groups.

Roberts (Roberts 1953) reported that lean Australian Aboriginal people (both males and females) have some of the lowest weight, adjusted for stature and climate-region of ten indigenous international populations. Lean Australian Aboriginal adults were also reported to have a longer relative leg-length for overall height and narrowness of the skeleton (through the shoulders, and hips) which conferred a higher body surface area (Abbie 1976; Norgan et al. 1995; Roberts 1953). It was suggested the higher trunk surface area of Australian Aboriginal peoples allowed for more efficient heat exchange in tropical north Australia (Roberts 1953). Compared with Caucasian populations, lean Aboriginal people were observed to have healthy levels of body fat (measured by skin-fold thicknesses), but at much lower BMI than expected in European populations (Norgan 1994). This suggests an excellent capacity to store lipid within subcutaneous fat depots at low body mass index. This is consistent with a higher sum of skin-fold thickness measures at four sites in Aboriginal females at the same BMI than observed in European females in other studies (Piers et al. 2003; Rutishauser et al. 1986). Notably, a higher sum of four skin-fold thicknesses was due to higher trunk skin-folds in Aboriginal females than Caucasian females (Piers et al. 2003). Among healthy adult Aboriginal people (aged 25-35 years old), despite Aboriginal females having similar BMI, and Aboriginal males lower BMI than respective sex Caucasians, Aboriginal people consistently had a higher waist to hip ratio (Piers et al. 2003). This was also observed with older age among Aboriginal females, where older age was associated with higher body mass index and skin-fold
thickness, but with a truncal rather than general distribution of body fat (Kondalsamy-Chennakesavan et al. 2008; Rutishauser et al. 1986).

There is less published information about body size and composition measures among Torres Strait Islander people. Differences in body size and composition may be explained by differences in ethnic origins of Torres Strait Islander people (who are Melanesian). As described above, resistance is an indirect indicator of lean body mass (Lukaski et al. 1986). Aboriginal males and females have lower lean mass (estimated by bioelectrical impedance measures) than Caucasians after controlling for height (Piers et al. 2003). Whilst the relationship of weight and resistance (measured by bioelectrical impedance) was similar between Torres Strait Islander people, Caucasians and Samoans, Aboriginal people were shown to have a very different relationship of weight with resistance (Heitmann et al. 1997). It was suggested these differences occurred because of differences in skeletal proportions and linearity of body build (which were not measured in that study) and ultimately reflected that components of weight (fat and lean mass) were different between Aboriginal people and Torres Strait Islander people (Heitmann et al. 1997). In independent work, it was obvious to Piers et al. (Piers et al. 2003) using combined methods that the relationship of BMI, resistance and skin-fold thicknesses differed significantly between Aboriginal people and Caucasian people, and was likely due to different ratios of fat to fat free mass for a given BMI between groups.

Torres Strait Islander males and females had higher weight, height, waist and hip circumference (but not WHR) than Aboriginal males and females in a large epidemiological survey of cardiovascular disease risk (Li et al. 2010). Cardiovascular disease risk was equally indicated by a waist: hip ratio of >0.9 in all four gender-ethnicity groups, although a single indicator of waist or BMI was not identified across the four groups (Aboriginal and Torres Strait Islander males and females) (Li et al. 2010). The Framingham risk calculator (based on age, gender, smoking status, total cholesterol, diabetes and blood pressure), provides a 10 year cardiovascular risk score (Wilson et al. 1998). It was noted that while the Framingham risk calculator was able to show higher cardiovascular disease risk between Aboriginal people (males 1.4 and females 1.7 times higher risk) compared with levels observed in Caucasians from the AusDiab study, it did not match the
actual hospitalisations and premature mortality that was experienced by Aboriginal adults from one remote island community of the Northern Territory (Wang et al. 2003). Using the Framingham risk calculator, a similar 10-year cardiovascular risk score was observed between adult Aboriginal people (from Central Australia) and Torres Strait Islander people (assessed in the Torres Strait) (13 v 13.7%, p=ns) (Wang et al. 2006). Wang et al. (Wang et al. 2006) also evaluated the performance of anthropometric indices (waist, hip, WHR, BMI and waist to height ratio) with the 10-year risk score between Aboriginal and Torres Strait Islander people. It was shown that higher hip circumference had an inverse-linear relationship with 10 year cardiovascular disease risk in Torres Strait Islander people, compared with Aboriginal people; that body mass index was a poor predictor of cardiovascular disease risk across both groups, however WHR was the best predictor (across both groups) for risk of diabetes and dyslipidaemia. They recommend the waist to hip ratio as the best anthropometric measure across Aboriginal populations and Torres Strait Islander populations, to estimate cardiovascular disease risk (Wang et al. 2006).

As discussed above, Snijder et al. (Snijder et al. 2004a) suggested that in groups with high hip girth, similar to that reported in Torres Strait Islander people in the study by Li et al. (Li et al. 2010), the high waist circumference may reflect a higher proportion of subcutaneous fat than intra-abdominal fat. Abdominal fat partitioning in either Aboriginal people or Torres Strait Islander people has not been reported. Heitmann et al. (Heitmann et al. 1997) highlighted the steeper slope of the relationship between body weight (as an indicator of size) and bioelectrical resistance for Aboriginal people, compared with Torres Strait Islander people, Danes, and Samoans. They made the assumption that Aboriginal adults may have a different relationship of fat to lean mass for body weight, across a wide range of body weight that was not evident in Torres Strait Islander people (or the other ethnic groups) (Heitmann et al. 1997). They hypothesised that at low body weight, Aboriginal adults have higher fat mass, but at higher body weight, Aboriginal adults have less fat mass, which was distinct to this ethnic group (Heitmann et al. 1997). It is noteworthy that skeletal muscle (which as discussed above is a large determinant of lean body mass) is a key modulator of insulin sensitivity (Wolsk et al. 2010; Yki-Jarvinen et al. 1985), and anti-inflammatory processes (Mendham et al. 2012). Between individuals, healthy
males with higher relative lean mass have higher insulin-clearance rates than those with lower relative lean mass (Yki-Jarvinen et al. 1985). Body composition, particularly differences in lean mass, even in the setting of high body fat, may be an important link between differences in diabetes, and cardiovascular disease risk that Wang and Rowley et al. (Wang et al. 2006) reported above with respect to hip girth in Torres Strait Islander people, and the usefulness of WHR which has been shown across populations.

The availability of direct methods of body composition in a suitably representative Aboriginal population and Torres Strait Islander population has been challenging. Detailed body composition studies have not been undertaken in Torres Strait Islander people. There are two published studies that describe body composition and health risk using whole body DXA among Aboriginal people. Mendham et al. (Mendham et al. 2012) recently reported health related effects of obesity in ten Aboriginal males, who had no chronic medical conditions. The extent of body composition description in this group consisted of a mean body mass index of 32 kg/m², waist circumference of 103.6 cm, WHR of 0.95, and body fat percent (measured by whole body DXA) of 27.8%. The purpose of their report was to demonstrate abnormal resting levels of inflammatory and insulin markers, which improved significantly following aerobic exercise among middle aged males with this level of overweight (Mendham et al 2012). Despite the absence of overt illness, this group of males had total and central obesity which was accompanied by abnormal metabolic and inflammatory markers. They performed a pre and post-exercise assessment within the one group, and have not reported any comparison against other Aboriginal groups (including women, for metabolic syndrome or diabetes, or lean adults) nor have they compared with Caucasians. This is however a unique and important study showing the favourable short-term metabolic response to exercise in Aboriginal men.

Raja et al. (Raja et al. 2003) had access to a sophisticated laboratory with detailed body composition tools, yet their population sample was not representative of Aboriginal women across the country. They undertook the most comprehensive study of body composition among Aboriginal females, to measure fat free mass by total body water (using deuterium oxide and bioelectrical impedance analysis), total body mineral (using DXA) and total body protein (using in-vivo neutron capture
analysis of total body nitrogen). Their main conclusions include 1) that whole body DXA accurately (and with high correlation) reported fat and lean mass in “Aborigines” (authors term), even over a wide range of fat mass; 2) that both Aboriginal females and non-Indigenous females had similar total fat percent, and degree of central adiposity overall; 3) that older Aboriginal women had higher abdominal fat than older Caucasian women, and almost twice as much central fat than young Aboriginal women; and 4) that hip girth was highly correlated with total and abdominal adiposity in women (Raja et al. 2003).

The study facilities were available at a university teaching hospital in Sydney, and they compared the body composition of sixteen non-diabetic, age-matched Aboriginal females and Caucasian females. The study group comprised a wide age range, and its generalisability to other Aboriginal peoples or Torres Strait Islander peoples is therefore limited, especially with Aboriginal females in Northern or Central Australia, who are the people of interest in this thesis. Our main concerns with Raja et al.’s (Raja et al. 2003) findings were hip circumference was a surrogate of total and abdominal adiposity, which is inconsistent with the reporting of preferential central obesity particularly shown by WHR in Aboriginal females with age and overweight, that is not as apparent by body mass index or weight (Kondalsamy-Chennakesavan et al. 2008; Maple-Brown et al. 2007; O'Dea et al. 1993). As briefly discussed earlier in the chapter, the heterogeneity of Aboriginal people may derive from differences in lifestyle and adaptations to Western culture and ethnic admixture, which have played a role in Raja et al.’s (Raja et al. 2003) Aboriginal participants. Therefore whilst Raja et al.’s (Raja et al. 2003) study provided a comprehensive assessment of body composition in a small group of Aboriginal females, their findings require confirmation in further studies.

As reviewed above, studies examining the health risk associated with overweight and obesity indicate the particular importance of abdominal obesity, rather than a generalised pattern of excess body fat (Lê et al. 2011; Liska et al. 2007). Lean body mass is particularly important for insulin sensitivity (Yki-Jarvinen et al. 1985) and exercise is shown to both potently modify insulin resistance and demonstrate an anti-inflammatory response (Mendham et al. 2012). Two known features of body composition are described for Aboriginal and Torres Strait Islander people. First,
many studies indicate a stronger likelihood of abdominal obesity (rather than generalised pattern of overweight) in adult Aboriginal people (O'Dea et al. 1993; Piers et al. 2003). Second, differences in bioelectrical impedance (specifically resistance, an inverse indicator of lean body mass) suggest lower lean body mass for size among Aboriginal people than either Torres Strait Islander people or participants of a Caucasian background (Heitmann et al. 1997). Three hypotheses may be entertained: first, the pattern of abdominal fat partitioning is likely to differ between Aboriginal peoples and Torres Strait Islander peoples; second, the threshold of health risk may be potentiated by the proportion of lean mass in the individual; third, in relation to Indigenous Australians with ethnic admixture, the pattern of obesity is likely to more closely reflect the dominant racial group, though determining ‘dominant race’ may prove difficult. This may be difficult first, because people identify ethnicity for different reasons, and second because ‘characteristic’ body composition features for each race have not been defined, and given the diversity of peoples internationally, may never by defined. This third hypothesis is complex, and while important, is beyond the scope of this study.

1.6.6. The Link Between Inflammation and Adiposity Defined by Detailed Body Composition Assessments

Simplistically, the body is divided into 2 compartments, lean body mass, and fat mass. Body fat can be described as essential and non-essential fat. Essential fat includes the lipid component of cell membranes, brain and nervous tissue and small deposits of fat surrounding vital organs. An idealised body fat mass of healthy adults from Western Europe and North America was presented in the Annals of the International Commission on Radiological Protection (Valentin 2002). Based on data collected between the 1960’s until 1990, healthy 35 year old men and women were reported to have 14.6 kg and 18 kg of body fat respectively (Valentin 2002). Lean body mass however is not totally fat-free. Adipose tissue within stroma and lipid in cell membranes make up 2% of lean body mass (Valentin 2002).

Lipid is stored within mature fully differentiated adipocytes. Adipose tissue is composed of mature adipocytes (between 50-85%), stromal vascular cells (including resident macrophages), and endothelial cells (Maury et al. 2010). Adipose tissue is
biologically active and involved in the synthesis and secretion of proteins and cytokines (adipokines) linked with lipid metabolism, energy balance, insulin sensitivity and inflammatory pathways (Zou et al. 2008). Resident adipose tissue macrophages (M2 phenotype) are responsible for homeostasis and remodelling locally (Shah et al. 2008), are activated by the alternate pathway of complement activation and secrete anti-inflammatory cytokines (interleukin-10, and interleukin-1 receptor antagonist) (Shah et al. 2008). Adipose cell composition and the secretion of adipokines are influenced by total fat mass and regional adipose depots (Abate et al. 1995; Maury et al. 2010). These adipokines will be discussed in more detail later in the chapter.

Non-essential fat are the fat deposits associated with energy excess. Since non-essential body fat does not bind water or electrolytes, essentially all of the body's water and electrolytes are contained in the lean body mass compartment. It is on this basis that measures of total body water and total body potassium and nitrogen counting can reliably predict lean body mass. Non-essential fat (excess lipid) may be stored in numerous depots throughout the body: epicardial fat, skeletal muscle (either as inter-muscular adipose tissue or as intra-myocellular lipid), the liver and bone marrow (Gallagher et al. 2008) and the kidney (perirenal- between the capsule and kidney, and as intra-renal triglyceride content) (Li et al. 2011). Within the abdomen, visceral adipose tissue sub-compartments include omental adipose tissue (draining to the portal circulation), mesenteric adipose tissue, and retro-peritoneal adipose tissue (that drains to the systemic circulation).

Overweight is crudely indicated by weight gain, a high waist circumference and/or body mass index. Excess of both total and central adipose mass are reported to be associated with a higher risk of the metabolic syndrome, cardiovascular disease (Maury et al. 2010) and type 2 diabetes (Zou et al. 2008). Macrophage infiltration is common to chronic diseases associated with the metabolic syndrome (obesity, insulin resistance, hepatic fibrosis, arterial disease). In obesity, the inflammatory process in adipose tissue involves recruitment of activated macrophages (M1, pro-inflammatory phenotype) altering the balance of the predominantly anti-inflammatory state of resident macrophages (M2 phenotype) that is observed in the adipose tissue of lean individuals (Lumeng et al. 2007). Macrophage infiltration (M1 phenotype) into
adipose tissue occurs in response to adipocyte hypertrophy (from enlarged lipid droplets), is correlated with body mass index, and was observed preferentially in visceral adipose tissue (relative to subcutaneous adipose tissue) (Fontana et al. 2007; Shah et al. 2008). M1 phenotype macrophages are activated by the classical pathway of complement activation and overexpress pro-inflammatory genes (including for IL-6) (Lumeng et al. 2007). They also induce adipocyte neovascularisation, modify insulin signalling, and secrete inducible nitric oxide synthase, and pro-inflammatory cytokines (TNFα and IL-6). Furthermore in response to adipose inflammation, endothelial cells express selectins and cell adhesion molecules that facilitate the movement of white blood cells from the middle of the luminal blood flow to the periphery in preparation for entering the extra-vascular tissue, and consequent tissue inflammation.

The portal vein is the main blood supply to the liver, and drains visceral (omental and mesenteric) adipose tissue beds. Age, gender, ethnicity, physical activity and total fat mass are reported to influence the size of the visceral fat depot (Klein et al. 2007). Expanded visceral adipose tissue in particular, is associated with altered hepatic insulin sensitivity, lipid metabolism, and the production of acute phase proteins (like C-reactive protein) under the influence of IL-6. Less information exists about the effects of ectopic fat storage in non-visceral fat storage sites, or if cellular and receptor functions are equivalent in different adipose tissue sites, or in the presence of chronic disease, like diabetes.

1.7. The Relationship of Inflammatory Cytokines with Body Measures and Features of the Metabolic Syndrome and Chronic Disease

There are many published examples of the relationship between insulin resistance, inflammation and endothelial dysfunction. The use of these markers has been assessed in many Caucasian populations who are healthy, or have cardiovascular risk factors, and some chronic medical conditions. There are comparatively fewer studies in large populations of people of a non-Caucasian background. To our knowledge only one study has reported IL-6 levels in overweight Aboriginal males (Mendham et
al. 2012). There are no studies describing the relationship of adipose-derived cytokines among Aboriginal people or Torres Strait Islander people who have chronic disease risk markers or chronic kidney disease. A review of the literature is presented below, describing the relationship of insulin resistance and inflammation and adipose-derived biomarkers including C-reactive protein (CRP), interleukin-6 (IL-6), leptin, adiponectin, and resistin, including where they relate to measures of body composition, or their performance in non-Caucasian populations.

1.7.1. Interleukin-6

Interleukin-6 (IL-6) is reported to be released from visceral and subcutaneous adipose tissue beds (Fontana et al. 2007; Mohamed-Ali et al. 1997), though visceral adipose tissue was shown as the dominant site of IL-6 secretion among morbidly obese humans (Fontana et al. 2007; Maury et al. 2010). Up to 30% of systemically measured IL-6 was shown to be produced from adipose tissue macrophages (Zou et al. 2008). Healthy adult males had serum IL-6 concentrations less than 1.0 pg/ml (Wolsk et al. 2010), whereas chronically high IL-6 concentrations (such as >1, and up to 8 pg/ml) have been reported in people who are obese or have diabetes (Petersen et al. 2005).

IL-6 is involved in inflammation, tissue injury, host defence and insulin resistance (where it modifies hepatic glucose production and insulin secretion) (Cornier et al. 2008; Zou et al. 2008). IL-6 is produced under the influence of TNFa, and stimulates hepatocyte production of C-reactive protein. Several studies show IL-6 concentrations were positively associated with peripherally measured CRP concentrations (Fontana et al. 2007; Yudkin et al. 1999), fasting insulin concentrations (Maury et al. 2010; Shah et al. 2008), low HDL-cholesterol concentrations (Cornier et al. 2008), and with body mass index, obesity and the future development of diabetes.

High IL-6 concentrations are also observed acutely following exercise (Mendham et al. 2012), where it acts via skeletal muscle, although was associated with the co-secretion of anti-inflammatory cytokines (Wolsk et al. 2010). In overweight Aboriginal males, following acute exercise, IL-6 concentrations rose acutely and
declined over four hours, accompanied by the expression of IL-1ra (interleukin-1 receptor antagonist, an anti-inflammatory interleukin) and lowering of glucose and insulin concentrations compared with pre-exercise levels (Mendham et al. 2012). In healthy males, who were matched for body mass index, total fat-free mass and lower-limb fat-free mass, an IL-6 infusion (mimicking acute exercise) was associated with increased lipolysis (from the limb, but not abdominal adipose tissue), 20% lower insulin concentrations and higher glucagon concentrations (compared with those who received a placebo infusion) (Wolsk et al. 2010). The authors suggested that exercise-stimulated IL-6, therefore, prevents intra-myocellular lipid accumulation by mobilising energy from muscle fatty acid during exercise, whilst also improving insulin sensitivity (Wolsk et al. 2010).

Tumour necrosis factor alpha is reported to induce IL-6 production, and has been implicated in insulin resistance and lipolysis via reducing insulin-receptor substrate 1 (IRS-1) (Shah et al. 2008) and in the inhibition of lipoprotein lipase activity. TNFa concentrations were not significantly associated with aging (Cartier et al. 2009) or concentrations of other circulating adipokines (IL-6 or CRP) in a study of pre-menopausal women with obesity (Browning et al. 2008). Several studies show a lack of localisation of TNFa from abdominal adipose tissue, lack of association with BMI, body fat mass (Mohamed-Ali et al. 1997), or visceral adipose tissue in men or women (Browning et al. 2008; Cartier et al. 2009). In contrast, higher subcutaneous thigh fat was shown to be inversely related with IL-6 and TNFa concentrations in Caucasian males (Beasley et al. 2009), suggesting the importance of differing adipose depots to health risk. The inflammatory burden of obesity is much lower than systemic sepsis, hence serum levels of TNFa in obese populations may not always represent its true function (Cartier et al. 2009). Therefore TNFa will not be assessed in the proposed thesis study.

1.7.2. C-Reactive Protein

C-reactive protein (CRP) is an acute phase protein, synthesised in the liver in response to IL-6 stimulation. It is an ideal acute phase protein because there are no medical conditions associated with CRP-deficiency, and concentrations consistently rise following trauma, bacterial infection or inflammation. Like many biological
markers, CRP is not normally distributed (Macy et al. 1997; Ridker et al. 1998), and titres may change rapidly from as low as 1 mg/L in response to inflammation to a value of several hundred (mg/L) in the setting of acute infection. CRP concentrations are not influenced by age, gender or hormones in Caucasian populations (Macy et al. 1997; Tietz 1990). In population studies, high CRP concentrations were associated with metabolic syndrome, diabetes and cardiovascular disease risk (Onat et al. 2008; Ridker et al. 1998). CRP concentrations were also positively associated with waist circumference, body mass index, fasting blood glucose and insulin resistance (Cornier et al. 2008).

It has been suggested that CRP concentrations below 10 mg/L indicate the absence of acute inflammatory disease in an individual (Tietz 1990). CRP concentrations of less than 15 mg/L have been arbitrarily applied in studies of cardio-metabolic risk (Onat et al. 2008). However longitudinal studies of CRP concentrations in Aboriginal people in community health screening surveys show a wide spectrum of CRP concentrations (Shemesh et al. 2009). In healthy people, CRP concentrations were shown to be stable acutely (over three days) and chronically (over 6 months) (Macy et al. 1997). Shemesh et al. (Shemesh et al. 2009) showed high background concentrations of CRP when tested at baseline and after more than 2 years (4.5 v 5.1 mg/L, p=0.22), among Aboriginal people from a remote community, including more than two thirds of the 70 adults having levels higher than 3.0 mg/L at baseline and follow-up. They demonstrated CRP concentrations were stable at either high or low titre when retested up to 3 years later; that individuals did not have significant inter-person variability when tested between the baseline and follow-up assessment; and over time baseline CRP concentration provided a stronger association with cardiovascular disease risk in this community than traditional risk markers (Shemesh et al. 2009). In middle-aged women and other populations, models of cardiovascular disease risk were improved by the inclusion of CRP concentration as a predictor variable (Onat et al. 2008; Ridker et al. 1998).

Numerous Australian studies have linked elevated markers of inflammation with the metabolic syndrome, and adiposity. As discussed earlier at Chapter 1.5.6, a differential relationship of CRP with BMI was seen between Aboriginal males and females in a remote Aboriginal community, where Aboriginal females with obesity
had much higher CRP concentrations than Aboriginal males with similarly high body mass index (Shemesh et al. 2007). Others have also linked CRP concentrations with overweight in Aboriginal people in both urban and remote settings (Hodge et al. 2010; McDonald et al. 2004; Rowley et al. 2003; Shemesh et al. 2007). CRP levels remain stable, although IL-6 concentrations increased as part of an anti-inflammatory response following an acute episode of exercise (Mendham et al. 2012). Following a 6 month weight loss program in obese middle aged insulin-resistant Caucasian females, Browning et al. (Browning et al. 2008) reported the health improvement of participants following the intervention was more strongly related to changes in concentrations of CRP rather then IL-6.

Different populations report different mean and distribution of CRP titres, which may in part explain differences in cardiovascular disease and metabolic syndrome between groups (Anand et al. 2004). A high prevalence of insulin resistance and central obesity are reported in Indians from South-East Asia (Yajnik et al. 2008). IL-6 and CRP concentrations were also high among Indian males, and were influenced by place of residence (urban-slum, urban middle-class and rural-living), overcrowded living conditions, rapidity of lifestyle-transition, and measures of body fat (Yajnik et al. 2008).

1.7.3. Adiponectin
Adiponectin is produced from mature adipocytes (Maury et al. 2010) and may be measured in blood and urine (Shen et al. 2008). The adiponectin monomer readily associates non-covalently forming trimers, hexamers or multimers (the multimers are also referred to as high molecular weight adiponectin) within the adipocyte before secretion (Zou et al. 2008). Adiponectin (especially high molecular weight adiponectin) was shown to have anti-inflammatory, anti-atherogenic and insulin sensitising properties (Kadowaki et al. 2006). Peripheral insulin sensitivity was shown to be mediated by the receptor AdipoR1 in skeletal muscle, whereas hepatic insulin sensitivity was mediated via the receptor AdipoR2 (and insulin-receptor substrate -1 and AMP kinase) (Kadowaki et al. 2006). Adiponectin was negatively associated with obesity, type 2 diabetes, and cardiovascular disease in adults (Maury et al. 2010). Plasma adiponectin concentrations are higher in healthy females than
healthy males (Arita et al. 1999; Cnop et al. 2003; Hanley et al. 2003; Keun-Gyu et al. 2004; Peake et al. 2005) and in people with chronic kidney disease compared with those with preserved kidney function (Zoccali et al. 2002).

A low concentration of adiponectin at an initial assessment predicted the future development of diabetes among Pima Indians of Arizona (USA), even though participants had similar levels of obesity (BMI 36 kg/m², waist 112 cm) and insulin resistance (fasting insulin >250 pmol/L and 2-hr insulin both >795 pmol/L) (Krakoff et al. 2003). Multiple cytokines were assessed at baseline (adiponectin, IL-6, TNFa, high sensitivity CRP and markers of endothelial function) to predict the development of diabetes, of which low-adiponectin concentration was the strongest predictor (Krakoff et al. 2003). Among adult First Nation Canadians, after adjusting for more traditional cardiovascular disease risk markers (age, gender, triglycerides, HDL-cholesterol, hypertension and impaired glucose tolerance), incident diabetes was predicted by low adiponectin concentrations and by high leptin concentrations and low adiponectin: leptin (A:L) ratios (Ley et al. 2008). Among adults with chronic kidney disease, low baseline adiponectin concentrations predicted a future cardiovascular disease event (Zoccali et al. 2002).

1.7.4. Leptin

Leptin is secreted by adipocytes from subcutaneous adipose tissue (Maury et al. 2010), but also secreted in small amounts from gastric epithelium, muscle and placenta (Zou et al. 2008). Serum leptin concentrations was shown to be proportional to subcutaneous adipose tissue mass and nutritional status (Zou et al. 2008). In lean individuals, the fed state was associated with higher secretion of leptin, and the fasted state with leptin deficiency (Zou et al. 2008). The central effects of low leptin concentrations in a lean individual are to promote appetite, and reduce energy expenditure from the thyroid, reproductive systems and immune responses (Zou et al. 2008). Peripherally, leptin reduces the intracellular lipid content in muscle and the liver. Leptin exerts its insulin sensitising effects via mitogen-activated protein kinase (MAP kinase), phosphatidylinositol 3-kinase (PI3 kinase) and the insulin-receptor substrate (IRS-1) (Zou et al. 2008).
High concentrations of leptin may reflect leptin resistance (Maury et al. 2010), which refers to reduced sensitivity (and signalling) of the hypothalamic leptin receptors to the effects of leptin (Bluher et al. 2009), which are reported in obesity (Mantzoros et al. 2011). Leptin concentrations are shown to correlate with total adiposity (BMI) in Caucasian and non-Caucasian groups (Mente et al. 2010) and with fat mass, but not with trunk-fat mass in Caucasian females (Jenkins et al. 2001). Leptin concentrations are shown to be higher in people with renal disease, in part due to poor clearance by the kidney. Other kidney related effects of leptin include natriuresis, increased sympathetic nervous activity, and stimulation of reactive oxygen species, glomerulo-sclerosis (fibrotic damage in the nephron), and proteinuria (Wolf et al. 2002).

Among Peruvian women, those living in the urban city of Lima had higher fat mass, leptin and insulin concentrations than females living in the high-altitude region of Cuzco, which was partly explained by exercise, since both ate a similar diet, and had similar ethnic heritage (Lindgarde et al. 2004).

1.7.5. Resistin

The mechanisms and role of resistin in human health and disease are not fully understood. Resistin was found in high concentrations in adipocytes in mice, where it was first identified in studies involving peroxisome proliferator-activated receptor (PPAR-gamma receptor) response to insulin sensitising medication in the early 2000’s (Steppan et al. 2001). It is unclear how much the responses and relationships of resistin in mice models reflects the behaviour of human resistin (Park et al. 2011). Messenger ribonucleic acid levels (mRNA levels) for resistin were found in peripheral mononuclear cells in adipose tissue, but very low levels were found in adipocytes in humans (Cornier et al. 2008; Shah et al. 2008; Zou et al. 2008), hence it was suggested resistin was linked to insulin-resistance through inflammatory processes (Park et al. 2011). The descriptive studies in resistin discussed below outline associations, but do not reveal any mechanisms asserting the link of resistin with insulin resistance or inflammation, which again reinforces the current lack of clarity surrounding the role of resistin in human health and disease.
Females have higher resistin concentrations than males (Norata et al. 2007; Silha et al. 2003), and concentrations did not differ in females with respect to menopause status (Norata et al. 2007), or in adults when compared for obesity (by BMI) (Norata et al. 2007; Silha et al. 2003) or diabetes (Norata et al. 2007). Resistin concentrations were shown to be positively associated with waist circumference, blood pressure, adiposity, triglycerides, and negatively with HDL-cholesterol (Cornier et al. 2008; Zou et al. 2008).

There is inconsistent reporting of the relationship of resistin and HOMA in humans. Among adults (mean age 45 years), resistin concentrations were similar in lean (BMI <25 kg/m^2) and obese (BMI >30 kg/m^2) adults without diabetes (21.5 ug/L v 28.8 ug/L, p>0.05). Resistin concentrations also correlated with HOMA-IR, but not with body mass index (Silha et al. 2003). Norata et al. (Norata et al. 2007) examined the relationship of resistin in a large adult European cardiovascular disease risk screening study. They observed plasma resistin concentrations correlated with a higher frequency of metabolic syndrome factors in both males and females, and with a higher Framingham cardiovascular disease risk-prediction score. They also reported that resistin did not correlate with HOMA score, or insulin concentration (Norata et al. 2007). In this adult screening study, there was a stronger relationship of systolic blood pressure and HDL-cholesterol with resistin levels in females, but not in males, though they could not explain why this might have occurred (Norata et al. 2007). In a comparison of First Nation and Caucasian Canadian women without diabetes, Silha et al. (Silha et al. 2007) observed that First Nation females were younger, had higher truncal obesity, higher IL-6 and lower adiponectin concentrations, yet similar resistin and leptin concentrations. Resistin concentration was shown to be positively correlated with total fat mass, and trunk fat mass in First Nation, but not in Caucasian women. The lack of age-adjusted analysis may be an important omission in this study by Silha et al. (Silha et al. 2007), since age influenced resistin levels in work by others (Norata et al. 2007).
1.7.6. Inflammation, Insulin Sensitivity and Dyslipidaemia in Chronic Kidney Disease

The kidney is an essential organ in insulin metabolism (Rabkin et al. 1984). The relationship of kidney impairment with insulin resistance and cardiovascular disease risk has been the subject of multiple studies in people with kidney diseases (Charlesworth et al. 2005). Kidney disease can be categorised by function (creatinine clearance or other definition), by disease (primary renal disease or systemic renal disease, like type 2 diabetes), or by modality of therapy (chronic kidney disease, renal transplantation and dialysis).

Becker et al. (Becker et al. 2005) reported on the relationship of cardiovascular risk and insulin resistance in 227 Caucasian adults with non-diabetic chronic kidney disease, who were matched for body mass index with 78 healthy adults. The mean glomerular filtration rate of kidney disease patients was 63 ml/min/1.73m$^2$ (range 38-96 ml/min/1.73m$^2$). At baseline, serum adiponectin concentration was negatively related with body mass index, fasting triglycerides, insulin and glucose. Kidney disease patients had higher glucose and insulin concentrations and HOMA score than healthy people. Low adiponectin concentrations in kidney disease participants predicted a cardiovascular event in follow-up over a mean of 54 months (Becker et al. 2005).

Charlesworth et al. (Charlesworth et al. 2005) undertook a much more detailed study of insulin resistance in renal disease incorporating detailed body composition analysis and the postprandial behaviour of lipids. Individuals with stable non-diabetic chronic kidney disease were matched by age, gender and body-composition with healthy adults. Participants with chronic kidney disease were grouped above and below GFR 60 ml/min (measured by a 24 hour urine and plasma creatinine clearance study). Several findings were shown: individuals with kidney disease had a higher HOMA score for any measure of central fat mass than healthy people; the insulin resistant profile increases in kidney disease patients with a GFR less than 60 ml/min (compared those with higher GFR); at low GFR (<60 ml/min) insulin resistance occurred due to persistent pancreatic secretion of insulin; and finally in CKD, following a meal, a delayed normalisation of triglyceride concentrations was observed. The renal dyslipidaemia pattern of high triglycerides and low HDL-
cholesterol concentration was further evaluated by Chan et al. (Chan et al. 2009b) in 10 participants with CKD and twenty healthy adults who were carefully matched for anthropometry, insulin sensitivity and inflammatory profile. Despite similarities between CKD patients and healthy controls for waist circumference, weight, BMI, WHR and inflammatory markers, CKD patients had a higher HOMA score, and higher fasting triglyceride concentration. They reported through experimental studies, that high fasting triglyceride concentrations were due to the delayed catabolism of VLDL, which they proposed was due to abnormal catabolism of apo-C-111 or an unmeasured toxin associated with kidney damage (Chan et al. 2009b).

1.7.7. Obesity, Metabolic Syndrome, Adipokines and Kidney Damage

Adiponectin is produced by adipocytes (and not inflammatory cells). Visceral obesity refers to the storage of excess abdominal adipose tissue burden. In the setting of preferential visceral obesity, subcutaneous tissue adipocytes have abnormal structure and function: they have limited secretion of the ADIPO-Q gene, responsible for the lower adiponectin expression (Kursawe et al. 2010); have limited capacity for lipid storage (Kursawe et al. 2010); and develop additional supportive structures, including poorly formed and irregular blood vessels, deposit fibrotic connective tissue proteins, and express a pro-inflammatory response by tissue macrophages (Spencer et al. 2011). In a pig model of visceral obesity and early metabolic syndrome, abdominal visceral obesity was associated with fat deposition within the kidney (intra-renal fat), and higher renal expression of IL-6 (Li et al. 2011). The kidney responds to the additional excretory demands of excess adipose tissue, by increasing glomerular filtration rate -primarily by increasing the volume and quantity of new blood vessels in the cortex (Li et al. 2011). These newly formed cortical blood vessels were reported to be particularly small in size, were more tortuous and irregular than normal capillaries, and was postulated to be prone to excessive endothelial leakiness of inflammatory substances (Li et al. 2011).

Whilst adiponectin and leptin concentrations may be higher in individuals with kidney impairment (Adamczak et al. 2009; Wolf et al. 2002), several reports from human and animal models indicate these proteins are functional in the presence of
poor kidney function, and the presence of leptin may also propagate kidney damage (Tomaszewski et al. 2007; Wei et al. 2004; Wolf et al. 2002).

Leptin concentrations were positively related to creatinine clearance in healthy young adult males. A high frequency of metabolic syndrome factors (e.g. four compared with one factor) in young males without chronic disease, was associated with higher creatinine clearance, and glomerular hyperfiltration (Tomaszewski et al. 2007). In a mouse model, Wei et al. (Wei et al. 2004) showed high leptin concentrations preceded the development of glomerular hyper-filtration, which in turn preceded a decline in GFR in a model of early type 2 diabetes. Some other kidney-related effects of leptin include natriuresis, increased sympathetic nervous system activity, stimulation of reactive oxygen species, glomerulo-sclerosis (fibrotic damage in the nephron), and proteinuria (Wolf et al. 2002).

It has been suggested that since adiponectin concentrations are higher in situations of low eGFR and or albuminuria, the kidney could be a clearance site for adiponectin, however this has not been confirmed (Adamczak et al. 2009). Regardless, reports in humans and animals show adiponectin to be functional in the presence of kidney impairment. Adiponectin has been reported to act at the podocyte (Sharma et al. 2008) and proximal renal tubule (Shen et al. 2008), and the following reports suggest compelling evidence for its role in the repair of kidney injury (Komura et al. 2010; Peake et al. 2010).

Adiponectin receptors were shown to be equally functional and found in higher concentration in dialysis patients than healthy controls (Shen et al. 2007a). The authors suggested a negative biofeedback mechanism was operating in these patients in response to the complex inflammatory-vascular milieu of renal disease and dialysis (Shen et al. 2007a). In another study, despite similar serum adiponectin concentrations, adults with renal disease and proteinuria, had higher urinary adiponectin levels than was observed in healthy adults (Shen et al. 2008). In that study of proteinuria, adiponectin was detected in the renal tubules in intact physiologically active isoforms suggesting secretion in urine as opposed to local degradation products, where it bound to local adiponectin receptors and inhibited the
secretion of inflammatory proteins, such as monocyte-chemoattractant protein-1 (Shen et al. 2008).

In other work, adiponectin was reported to stabilise the activation of the classical pathway of complement, by binding to Factor H, an inhibitory complement protein (Peake et al. 2010). Finally, another report showed adiponectin concentrations and its respective mRNA levels were preserved in tissues in mice with subtotal nephrectomy (Komura et al. 2010). In these mice with low-GFR, adiponectin was associated with dampening the pro-inflammatory effects of TNF-a on the production of vascular adhesion molecules (Komura et al. 2010). However, when Cystatin C was applied to the model (mimicking severe clinical kidney impairment), the anti-inflammatory effects of high adiponectin concentrations were cancelled (Komura et al. 2010).

Sharma et al. (Sharma et al. 2008) makes a compelling argument for the relationship of low-adiponectin states with albuminuria in a mouse model. Adiponectin knock-out mice exhibit albuminuria, and higher levels of oxidative stress, than wild-type mice, and these manifestations worsen in the presence of diabetes (Sharma et al. 2008). Podocytes are specialised cells in the glomerular basement membrane of glomeruli, and act primarily to prevent leakage of large proteins, including albumin (Pavenstädt et al. 2003). Adiponectin was shown to have important functional effects in the kidney, and specifically the podocyte, irrespective of systemic effects of adiponectin. Adiponectin knock-out mice displayed podocyte-fusion (making nephrons highly permeable to large proteins including albumin) despite otherwise normal architecture of the filtering unit of the nephron (that is they have preserved glomerular basement membranes, mesangium and endothelium) (Sharma et al. 2008). Sharma et al. (Sharma et al. 2008) reported that exogenously supplied adiponectin directly improved the permeability of damaged podocytes and was associated with improved local AMP-kinase function. Overall, adiponectin knock-out mice who received supplemental exogenous adiponectin had higher serum adiponectin concentrations, restored podocyte function, and minimised albuminuria levels in as little as 10 days (Sharma et al. 2008). To date, there are no human studies of adiponectin supplementation.
1.8. Summary of the Introduction and Aims of the Study

The literature review has identified a number of factors relevant to the study of body size and composition, metabolic syndrome, cardiovascular disease risk, and kidney damage in Aboriginal peoples and Torres Strait Islander peoples. The disproportionate burden of adult chronic disease in Australian Aboriginal peoples and Torres Strait Islander peoples is strongly linked to a shorter life expectancy, and increased disease burden. The traditional cardiovascular risk factors of smoking, hypercholesterolaemia, hypertension and diabetes do not explain all of the increased risk in Indigenous Australian communities. Identifying early predictors of chronic illness, by the study of overweight, the metabolic syndrome, and chronic low-grade inflammation are widely reported in international populations. For Indigenous Australians, in the context of a high disease burden and health gap, compared with other Australians, preventing cardiovascular risk in healthy people and identifying higher than expected risk in people with established diseases like diabetes and chronic kidney disease are equally important. Some Aboriginal Australians have demonstrated a willingness to adopt lifestyle change and lose weight in short term studies (O’Dea 1984), and use preventative medicines in interventional studies in order to regress or stabilise chronic illness (Hoy et al. 2003b).

Among several Aboriginal communities, Aboriginal females experience a higher level of cardiovascular disease burden than age-matched Caucasian females (Wang et al. 2003), higher degree of inflammatory markers for the same degree of higher-adiposity as Aboriginal males (Shemesh. et al. 2007), and a higher proportion of Indigenous females than males receive dialysis treatment for end stage kidney disease (Jose et al. 2009). It has also been reported that Aboriginal and Torres Strait Islander people are requiring dialysis for end-stage kidney disease at a younger age than other Australians, largely attributed to type 2 diabetes (McDonald 2010), which is closely related to a large burden of diabetes and obesity in the communities (Leonard et al. 2002; O’Dea et al. 2008). Furthermore, a high frequency of albuminuria in many Indigenous community surveys was also reported (Hoy et al. 2003b; Maple-Brown et al. 2011; Rowley et al. 2000). In the context of the long-term risk of cardiovascular disease associated with indicators of kidney damage (impaired glomerular filtration rate and or albuminuria), recommendations suggest
addressing the burden of cardiovascular disease risk and diabetes would have the greatest mortality benefit (Keith et al. 2004).

Heterogeneity in body size is reported between Aboriginal groups, between Aboriginal people and Torres Strait Islander people, and between Caucasian and Indigenous Australians (Kondalsamy-Chennakesavan et al. 2008; Piers et al. 2003; Wang et al. 2006). Older Aboriginal females appear to have a very different body size than older females in other population groups: a disproportionate level of central obesity was reported in Aboriginal women, particularly with older age, despite lack of significant change in weight or body mass index (Kondalsamy-Chennakesavan et al. 2008). The waist to hip ratio, rather than the body mass index was identified as a better indicator of diabetes, dyslipidaemia and cardiovascular disease risk across differing Aboriginal communities (Kondalsamy-Chennakesavan et al. 2008), between Aboriginal and Torres Strait Islander people (Wang et al. 2006), and across multi-ethnic populations (Yusuf et al. 2004). Finally, differences between individuals and between populations in obesity, inflammation, insulin-resistance and chronic disease may be explained through specific differences in body build and composition (Deurenberg-Yap et al. 2002; Snijder et al. 2004a).

The relationship of metabolic syndrome factors with body size and cytokines produced from or associated with adipose tissue was also reviewed. There were no studies that described a stratified population including health, chronic disease and kidney damage in non-Caucasian populations which could provide a perspective to relate to Aboriginal people and Torres Strait Islander people. Published reports indicate several important findings: first, CRP and IL-6 resistance are reported to be closely related to intra-abdominal or central obesity (Fontana et al. 2007; Hodge et al. 2010); second, lean body mass has a role in anti-inflammatory pathways and peripheral insulin sensitivity (Wolsk et al. 2010; Yki-Jarvinen et al. 1985); third non-fasting serum markers, such as concentrations of adiponectin and leptin are related to insulin resistance, future cardiovascular disease events (Ley et al. 2008), and may be related to kidney damage (Sharma et al. 2008; Wei et al. 2004; Wolf et al. 2002).
**Aim**

The aim of this study was to understand how body build, composition, and markers of kidney damage relates to metabolic syndrome components in adult Aboriginal people and adult Torres Strait Islander people, within the context of two volunteering adult health screening studies.

**Objectives of the thesis**

There are five objectives of the thesis.

1. What are the earliest chronic disease risk markers evident in otherwise healthy young adult Aboriginal people?

2. To describe the characteristics of skeletal build in Aboriginal people and Torres Strait Islander people.

3. If differences are observed, how do observed differences in skeletal build relate to body composition in Aboriginal adults and Torres Strait Islander adults?

4. To determine the best indirect measures of body composition in the assessment of chronic disease risk in adult Aboriginal people and Torres Strait Islander people.

5. To examine the relationships of adipose-derived cytokines with body composition in healthy Aboriginal people, and in Aboriginal people and Torres Strait Islander people with markers of chronic disease.
Chapter 2.

Methods
2.1. Choice of Studies

The PhD study describes the clinical health assessment, body composition and inflammatory marker analysis in 4 groups of Northern Australians (Aboriginal participants, Torres Strait Islander participants, Aboriginal and Torres Strait Islander participants, and Caucasian participants). Two clinical studies form the basis of this PhD study into the relationship of body composition and health in adult Aboriginal people and Torres Strait Islander people.

The thesis study commenced in 2008 as a sub-study of the NHMRC funded “The eGFR Study.” The eGFR Study was an avenue to assess large numbers of adult Aboriginal peoples and Torres Strait Islander peoples across Northern, Central and Western Australia and the Torres Strait. It would not have been possible to undertake this PhD study without this larger study. After the first 12-18 months of data collection, preliminary data from The eGFR Study showed a stronger pattern of central obesity in Aboriginal women without diabetes who lived in remote compared to urban parts of the Northern Territory. This data was presented as part of the Young Investigator Award at the Australian and New Zealand Society of Nephrology Annual Scientific Meeting (2009).

The second study, the Healthy Top-Enders’ study was designed as a response to these findings of predominant central obesity: specifically do young healthy adults have a pattern of central body fat, and if present, is it related to a healthy or adverse metabolic profile? I was responsible for the design of the Healthy Top-Enders’ study, whereas I worked within the framework available in the eGFR Study. I was the lead investigator on the Healthy Top Enders’ study, whereas I was an Associate Investigator on The eGFR Study. The Healthy Top-Enders’ study enabled me to address the question of differences in body size between Aboriginal adults and non-Indigenous Australian adults, and examine the accuracy and clinical potential of portable tools of body composition.

These cross-sectional studies were developed to provide evidence for discrete and measurable factors that could be incorporated in longitudinal and intervention studies
and programs to modify cardiovascular disease risk in Aboriginal peoples and Torres Strait Islander peoples. Overcoming the social determinants that contribute to poor health, and designing and conducting a longitudinal or intervention study was beyond the scope of this thesis.

2.2. General Aspects Related to Both the Healthy Top-Enders’ and The eGFR Study

The study question “how does body build, composition, and markers of kidney damage relate to metabolic syndrome components” suggests a specific and ideal methodology. A balance of ideal versus realistic and achievable methodologies must be achieved. This realism considers facilities and modalities available for assessment across all study sites. It is also a negotiation between investigators and participants for the appropriate protocols required to answer key clinical-questions, and not necessarily what is beautifully ideal to answer a more detailed scientific hypothesis (that is beyond clinical relevance). Answers to these complex questions may require staged research timetables, demonstrating to the community where early findings support additional and more complex studies in order to improve the community’s health and well-being.

Across the identified study population, the facilities do not exist to provide supervised hyper-insulinaemic clamp tests. With this balance in mind, we have chosen to assess glycaemic status with an HbA1c and medical history. In a small sub-group, fasting bloods and insulin in addition to HbA1c were used. Estimates of insulin-resistance may be made using non-fasting surrogates such as lipoprotein and adiponectin levels. We have not analysed apo-lipoprotein levels, and have utilised non-fasting HDL-cholesterol, where fasting lipids were not available.

The availability of sophisticated tools of body composition in Northern Australia is quite limited to this geographically dispersed population. It will be necessary to validate portable tools of body composition against criterion methods, if they are available. The portable tools chosen in this thesis offered to all study participants include body mass index, waist to hip ratio and bioelectrical impedance analysis.
2.3. The eGFR Study: The Accurate Assessment of Kidney Function in Indigenous Australians

The eGFR Study was an NHMRC funded study (#545202) of the accurate assessment of kidney function in Indigenous Australians. Aboriginal people and Torres Strait Islander people with different degrees of health and illness were recruited for The eGFR Study between November 2007 to May 2011. Data collection for the PhD study commenced in 2008 with assessment of Aboriginal adults and Torres Strait Islander adults in The eGFR Study. The methodology of The eGFR Study has been reported in detail elsewhere (Maple-Brown et al. 2010b).

Data presented in this thesis relate to “The eGFR Study”, an adult health screening and kidney function test study, in major cities (Darwin, Cairns and Alice Springs) and regional and remote areas of Northern Australia. The larger eGFR Study assessed approximately 600 adults (Aboriginal people and Torres Strait Islander people). I was directly involved in the data collection and assessment of 250 eGFR Study participants across the Top-End of the Northern Territory (NT) and Far North Queensland. As an associate investigator to the study, I participated in the annual investigator meetings, monthly management group meetings, communications and steering of The eGFR Study, and was the study leader responsible for sample collection, laboratory processing and statistical analysis of adipose-derived cytokines.

The eGFR Study DXA sub-study involved 195 adults from The eGFR Study who underwent whole body dual-energy x-ray absorptiometry (DXA). This included 87 people in Darwin, and 108 people in Thursday Island. I was responsible for overseeing use of the whole body DXA facility in Darwin (Norland XR46), and sourcing a mobile unit (Hologic Delphi W) to travel to Thursday Island.

The Darwin DXA sub-study was conducted between July 2008 and March 2010. The Norland XR46 whole body scanner (Cooper Surgical Co., Trumbull, CT, USA) was installed in July 2008 as the first (and only) whole body DXA available in the Northern Territory. It was located in a private local radiology service, off site from the clinical assessments of The eGFR Study, which were usually performed at the
Menzies School of Health Research. In the Darwin eGFR DXA sub-study, I was responsible for all of the consents, recruitment, and coordination of the assessments. I performed most of the DXA scans, and also trained two research assistants who also performed the scans (SG, MN). All scan analysis was performed by a single operator (JH) using Illuminatus software (version 4.2.4a).

Only one transportable whole-body DXA device, a Hologic Delphi W (SN-70034) (Hologic Inc., Bedford, M.A.) was available in Australia during the recruitment period of the eGFR Study. This device was secured for a three week field trip on Thursday Island in February 2010. An experienced operator (Dr Jarrod Meerkin PhD, MSc (Hons), BApp.Sc., ESSAM EAP, Body Composition Australia), performed all of the scans, and used the same body positioning protocols as the Darwin DXA sub-study. Hologic data was analysed using the QDR system software for Windows (XP) Hologic software APEX 3.0 (Hologic). Data files were exported from the Hologic instrument, and stored securely at Menzies on an Access Database. I performed all further analyses of body composition, and comparison of body composition between groups.

The Thursday Island DXA sub-study field trip involved a team of people employed by the eGFR Study. I had several responsibilities in the preparation and conduct of the visit. As both a Torres Strait Islander, and a researcher, I actively engaged with the community and local health service to gain community support and participation. I also negotiated the involvement of the mobile DXA into The eGFR Study, and assisted in securing its use, and that of a trained operator. On site during the field trip, I advertised the DXA study, provided study information and recruitment of study participants and assisted with data collection (anthropometry, bioelectrical impedance analysis and skin-fold thickness).

The recruitment of participants in The eGFR study was focused on inclusion of Indigenous Australians from dispersed geographical locations throughout Northern Australia (including urban, regional, and remote sites). Whole body DXA was never foreseen as a body composition tool that would be available in all recruiting sites. Only Darwin and Thursday Island had accessible whole-body DXA scanning facilities available for study participants.
2.3.1. Participants

Aboriginal people and Torres Strait Islander people with a minimum age of 16 years were invited to participate in The eGFR Study. The eGFR Study was a national study across Western Australia, Central Australia, the Top-End Northern Territory and Far North Queensland. Within these large regions, research staff recruited participants from urban, regional and remote areas. A comparator group of Australians of Caucasian background was recruited across 5 pre-defined strata (described below) from Darwin, Northern Territory, Australia. This group was not intended to be a matched group for direct comparison with the Indigenous group, but rather a group in which the equation performance could be assessed in comparison to other published studies, thereby supporting the reference GFR methodology in the current study.

The geographical context of the study population in Northern, Central and Western Australia was guided by data from the Australian and New Zealand Dialysis and Transplantation (ANZDATA) Registry (Cass et al. 2001; Jose et al 2009). These regions identify Aboriginal people and Torres Strait Islander people with the highest incidence rates of requiring dialysis therapy for severe kidney disease (Cass et al. 2001; Jose et al. 2009). The study population was also sought from urban, regional and remote settings, since the disease burden in Indigenous Australians varies between these sites, and Indigenous Australians live in diverse geographic and residential settings.

The ethnicity of Indigenous Australians was self-identified as an Aboriginal person or as a Torres Strait Islander person or as both an Aboriginal and Torres Strait Islander person. Data pertaining to self-identified ethnic identity of Indigenous Australians (and their 4 grandparents) was collected, in order to improve our understanding of differences in body composition.

Participants were excluded if they were receiving dialysis, or had rapidly changing kidney function. Females who were pregnant or breastfeeding were also excluded. Participants were also excluded from analysis in this thesis study if their mobility
was severely impaired such that they could not stand independently (to measure their height).

The recruitment process involved partnership with health organisations, local community groups, employment of Indigenous facilitators in the local communities, and word of mouth. Where appropriate, local media advertising was also used to inform the community about the study, and opportunities for participation.

Participants were recruited across a spectrum of health and illness, and specifically recruited across five pre-defined health strata using the MDRD-4 formula (Levey et al. 1999) of estimated glomerular filtration rate (eGFR) as:

- **Strata 1.** “Healthy” group: this group was defined by the absence of type 2 diabetes, hypertension, chronic kidney disease (CKD) and albuminuria. The classification of “healthy” was on the basis of history, and confirmed in this assessment. The absence of CKD was by calculated eGFR (by MDRD-4) formula of greater than 90 ml/min/1.73 m$^2$ in the absence of diabetes or microalbuminuria.
- **Strata 2.** Participants with a history or biochemical assessment confirming type 2 diabetes (HbA1c >6.5%) or albuminuria (any level >2.5 mg/mmol in men and > 3.5mg/mmol in females) & eGFR >90 ml/min/1.73 m$^2$;
- **Strata 3.** Participants with an eGFR of 60-90 ml/min/1.73 m$^2$;
- **Strata 4.** Participants with an eGFR of 30-59 ml/min/1.73 m$^2$;
- **Strata 5.** Participants with an eGFR less than 15-29 ml/min/1.73 m$^2$.

### 2.3.2. Ethics

Letters of support from local community organisations and health services were provided for each of the major recruitment sites. Ethics approval was sought and provided from the major regions. This included approval by the joint Menzies School of Health Research –Northern Territory Department of Health Human Research Ethics Committee (ref: 07/54). The Top-End eGFR Study project was approved by the Aboriginal Ethics Subcommittee which has the power of veto over
research conducted in Indigenous Australians, and the main committee. The study was also approved by the following Research Ethics committees in other regions:

- Cairns and Hinterland Health Services District Human Research Ethics Committee (ref: #523).
- Central Australian Human Research Ethics Committee (ref: 2008.04.06)
- Western Australian Aboriginal Health Information and Ethics Committee (ref: 228 12/08)
- Royal Perth Hospital Ethics Committee (ref: 2009/026)

The eGFR Study DXA sub-study also received ethics approval from the Northern Territory Department of Health Human Research Ethics Committee (ref: 07/54) and the Cairns and Hinterland Health Services District Human Research Ethics Committee (ref: #523).

### 2.3.3. Clinical Assessment

Participants agreed to a number of clinical measures normally performed as part of routine clinical care for an adult health check, or chronic disease health assessment. Individuals were approached by the research officers to consider participation in the study. Informed consent was obtained, and participants were provided with information to avoid a large protein meal prior to the study. Due to the complexity of the assessment, participants were not asked to provide a fasting blood sample. A non-fasting blood sample was obtained.

A Welch Allyn Spot Vital Signs monitor (Welch Allyn Medical Products, Skaneateles Falls, USA) blood pressure machine was used with an appropriate sized cuff for the participants arm. Blood pressure and pulse rate were measured after a 5 minute rest with the participant sitting and arm resting on a pillow at the level of the heart. Three readings of systolic and diastolic blood pressure and pulse rate were recorded, separated by a 5 minute break. Medical history and medications were self-reported by participants, and where possible, confirmed by medical chart review.

The following blood tests were analysed at local laboratories: electrolytes, serum creatinine, liver function test, glycated haemoglobin (HbA1c), and non-fasting lipids
(HDL-cholesterol, triglycerides, LDL-cholesterol), C-reactive protein, full-blood count and urine albumin to creatinine ratio. The methods of serum creatinine varied by local laboratory, and have been previously described for The eGFR Study (Maple-Brown et al. 2010b). Assays for adipose-derived cytokines (adiponectin and leptin) are outlined in Chapter 2.4.4, in the description of the Healthy Top-Enders’ study.

Recruiting was limited to non-pregnant females. Female participants of childbearing potential were also asked to provide a urine sample for qualitative human chorionic gonadotrophin testing.

2.3.4. Questionnaire

The questionnaire included information about socio-economic status and related demographic information, and is found in Appendix 1. The questions related to place of residence, first language, language spoken at home, income source, employment status, education level, number of bedrooms and occupants in the house and housing tenure and landlord type if applicable, self-identified ethnicity of self and 4 grandparents and health behaviours (including cigarette smoking).

A Critique of the Definitions of Ethnicity in the thesis

The Australian government definition of an Aboriginal person or Torres Strait Islander person is a person who is of Aboriginal or Torres Strait Islander descent, self-identifies as such, and is accepted as such by their community. Additionally, ethnicity is a complex of racial background, lifestyle, cultural practices and beliefs (Callister et al. 2007).

I was both a designer and user of the ethnicity questions. The ethnicity question, of “how do you identify?” is a standard question used to assess inclusion in the eGFR Study. The questionnaire was initially framed as “Are you an Indigenous Australian?” When I commenced on the project, I found that while the question was sufficient for the purpose of the larger eGFR study, the question was deficient with respect to the PhD study regarding anticipated differences in body composition for those of Torres Strait Islander background compared to participants of Aboriginal background. The question was subsequently amended for Indigenous participants to
capture Aboriginal only, Torres Strait Islander only, and both Aboriginal and Torres Strait Islander. In this respect, we invited participants to self-identify (rather than assign) their ethnicity, which we believe was a strength of the thesis.

At our institution, the Aboriginal Ethics sub-committee of the Human Research Ethics Committee has the power of veto over studies involving Aboriginal peoples and Torres Strait Islander peoples. Some negotiation was required with the Chair of the Aboriginal ethics subcommittee to include the question about grandparents’ ethnicity. The Chair’s concern was first, that our ethnicity question conflicted with the Australian government definition of Indigenous Australian ethnicity, and second, to the purpose of the additional information (on grandparental ethnicity) that we proposed, since if an individual makes a personal identification as Aboriginal (or Torres Strait Islander) they are completely Aboriginal, regardless of other ethnic admixture. Our question was included to ascertain individuals of a predominantly Aboriginal rather than Torres Strait Islander background. In Chapter 5 and Chapter 6, the combination of personally identified ethnicity and the perceived ethnicity of all 4 grandparents was used to study differences in body composition between three groups, Aboriginal (only), Torres Strait Islander (only) and people of both Aboriginal and Torres Strait Islander background.

Assessing the background of four grandparents was an attempt to incorporate some of this, since lifestyle (diet and exercise), and environment (services and infrastructure) are also likely to impact on obesity risk (WHO 2000). These were not explicitly examined in this PhD study, though the intent was to better understand our participants. The participants did not mind answering the two ethnicity questions, since they appreciated the differences between Aboriginal and Torres Strait Islander peoples and that the questions were to be used to understand body composition, and obesity.

**A Critique of Smoking and Alcohol questions in the thesis**

A brief summary of alcohol and cigarette smoking effects are summarised above in Chapter 1.6.2. Briefly, the chronic consumption of high quantities of alcohol was related to suppressed lipid oxidation, weight gain and obesity (Suter et al. 1997); a higher basal metabolic rate and appetite suppression was reported among current
smokers (Moffatt et al. 1991); notably, the relationship of body size with these lifestyle factors is complex to measure, and difficult to capture in cross-sectional studies (Suter et al. 1997). The purpose of the thesis study was to describe in detail, and for the first time, the body composition of adult Indigenous Australian participants. Since there were no previously described detailed body composition studies available for large numbers of adult Aboriginal or Torres Strait Islander peoples, the investigator felt it was necessary for the feasibility of the study to focus the study design on body composition measures, rather than perform a comprehensive assessment of alcohol and tobacco use. Categorical questions (yes/no) for tobacco and alcohol use were asked of participants in both The eGFR Study and the Healthy Top-Enders’ study. A more detailed assessment of tobacco and alcohol use was not feasible within the study design, which as it stood involved a large amount of time given voluntarily by each participant. Differences in body composition were not assessed by alcohol use or volumes consumed, or by years of tobacco use. Longitudinal changes in body composition related to tobacco and alcohol use were not examined in the current analysis, but may be investigated in future research studies.

2.3.5. Anthropometry

2.3.5.1. Operators

Six trained research staff performed anthropometry assessments in The eGFR Study. Two research staff (including JH) attended an International Standards for Anthropometric Assessment course delivered by an exercise physiologist from the Australian Institute of Sport (May 2008). These two research officers were responsible for supervision, support and training of the additional staff. Periodic inter-operator variability studies were performed between all research staff conducting anthropometry. For The eGFR study, the maximum inter-operator differences, in circumference measurements, were as follows: waist 3.1%; hip 2.1%. The data collection form for The eGFR Study is included in Appendix 2.
2.3.5.2. Participants

Participants were asked to void early in the study appointment, and assessed in light weight clothing, and without shoes. Height was measured with a fixed stadiometer to the nearest 0.1cm, with the participant standing with heels together, and head in the Frankfurt plane. Weight was measured on a portable digital scale (Seca digital portable scale, Model 767 and 841, Seca Deutschland, Hamburg, Germany) to the nearest 0.1kg. A mean of two measures was used for analysis. A third measure was taken if the first two readings differed at all, and a mean of the three measures was then used. Body mass index (BMI) was calculated as weight (kg) divided by height squared (in metres).

The waist circumference was measured at the position midway between the most inferior ribs and most superior iliac crest in the mid-axillary line (Callaway et al. 1988; Harrison et al. 1988). A 2-metre non-stretch flexible steel measuring tape (Model W606PM Lufkin, Texas, USA) was placed in a horizontal plane to record circumferences at the end of normal expiration for waist to the nearest 0.1cm. Hip circumference was identified from the side as the widest projection over the buttocks below the iliac crest (Callaway et al. 1988). If an enlarged peritoneal fold was present, the hip circumference was taken underneath this. If the first two measurements of either waist circumference or hip circumference differed by more than 1.0cm, then a third measurement was taken for waist or hip as relevant. Waist: hip ratio was calculated as waist circumference divided by hip circumference.

2.3.6. Bioelectrical Impedance Analysis

Due to the vast distances between assessment sites in the eGFR Study, and timetable of assessment teams, two bioelectrical impedance analysis devices were used. These were either a multi-frequency bioelectrical impedance spectroscopy device (BIS, Model SFB7, ‘selected frequency bioimpedance’ 7 , Impedimed, Brisbane) or a single frequency (50 kHz) bio-impedance device (BIA) was used (Model DF50, Impedimed, Brisbane).

In The eGFR Study, only resistance, measured at 50 kHz was utilised in the current analysis. The same protocol for measuring bioelectrical impedance analysis was
used regardless of the type of BIA device. BIA or BIS was not performed if a participant had an indwelling cardiac device. Personal preparations were taken in all participants. Each person voided prior to the bioelectrical impedance assessment. All metal objects and shoes and socks were removed. Each person lay supine for a minimum of 5 mins (and maximum 10 minutes) before the test. The arms and legs were abducted to minimise skin touching. The skin at the electrode sites was cleansed with an alcohol wipe to remove dust and oils, and allow drying before applying the electrode dots. Eight electrodes (electrocardiograph-style gel electrodes) were placed in a tetra-polar arrangement, as previously described (Cornish et al. 1999). At the wrist, the proximal electrode was placed in the midline of the wrist at the level of the ulnar styloid process. The distal electrode was placed 5 cm distal to the proximal electrode. At the ankle, the proximal electrode was placed at the midpoint between the medial and lateral malleoli and the distal electrode was placed 5 cm distal to the proximal electrode.

Whole body impedance measurements were recorded. An 800 uA excitation current across 100 frequencies (from low to high frequency) were used in the bioelectrical impedance spectroscopy device. The BIS device stores resistance, reactance, impedance and phase angle over multiple frequencies. In the analysis of eGFR Study participants in this thesis, resistance measured at 50 kHz frequency was extracted using the Impedimed SFB7 Multi-Frequency Analysis software package (version 5.4.4.0). An 800 uA excitation current at a single high frequency (50 kHz) was used for the bioelectrical impedance analysis (BIA) assessment. Resistance, reactance, impedance and phase angle were transcribed onto the data collection form (see Appendix 2), and then transferred to a Microsoft access database for storage and analysis.

2.3.7. eGFR Study Body Composition Sub-Study: Whole Body DXA Assessments

2.3.7.1. Whole Body DXA, Darwin

The whole body DXA assessment was a sub-study designed to determine the accuracy of portable tools of body composition (bioimpedance). All DXA studies in
the Northern Territory were performed in Darwin on a single Norland XR46 whole body scanning device (Norland XR46, Cooper Surgical Co., Fort Atkinson, WI, USA). All scans were performed by a trained operator. Scan analysis was performed by the study investigator (JH) using the Illuminatus software (version 4.2.4a). Standard positioning of participants was observed at each scan. Scans were performed in light weight non-restrictive clothing, and after voiding. Females wore a lycra and Velcro ‘boob-tube’ over the gown to minimise spread (but not constriction) of breast tissue to overlap the upper limbs, so that trunk and upper limb soft tissue was clearly demarcated. In-vivo precision is affected by inherent system errors, operator technique, and the in-vivo nature of the measurement. We achieved best precision by performing a daily calibration of the instrument for bone mineral and soft tissue using phantoms, and using three trained operators at the Darwin site (JH supervised training of MN and SG), and one trained operator at the Thursday island site (JM). We used consistent positioning protocols, which were jointly designed by JH and JM prior to performing whole body DXA at both sites. The coefficient of variation for Norland whole body DXA over a three month period was 0.79% and 0.48% for fat and lean mass respectively.

Participants completed a single whole body scan. Participants lay supine on the examining table with vertex (head) in the middle of the scan width. As much as scan-width permitted arms were abducted from the torso. Legs were not abducted. To avoid movement artefact by eversion of the feet during the scan, and for client comfort, the feet were secured at the lower third of the foot in neutral position by a non-opaque strap.

Scan regions were defined as per Norland specifications: Norland Illuminatus DXA Operators Guide 2000-2007. 434D142 Rev. G. This allowed analysis of whole body bone mineral content, lean tissue mass and fat mass for the following 8 body regions shown by Figure 2.1: head, chest, mid-riff, pelvis, left and right upper limb and left and right lower limb. The trunk region encompasses the combined regions of the chest, midriff and pelvis.
Figure 2.1 Total and Regional Body Parameters with the Norland XR 46 Whole Body DXA Scanner used in Darwin.

- Chest window: upper cursor points were positioned above the junction of the left and right humerus and scapula. The bottom cursor points were positioned between the arms and torso, with the bottom edge barely enclosing the rib cage.
- Pelvic window: the trapezoid shaped window enclosed the pelvis, whilst minimally including tissue from midriff, leg and femoral neck tissues. Upper cursors were positioned just above the iliac crests, between the arms and torso. The lower (left and right) cursors were positioned so the line passed through the femoral neck close to the pelvis. The bottom edge of the pelvic cursor was positioned just below the pelvic symphysis.
- Leg window: the left and right leg cursors were positioned along the region of minimum body tissue between the thigh and hand on each side. The bottom edge of the leg window was positioned below the toes. The centre cursor was positioned to lie along the region of minimum body tissue between the left and right leg.
**Body Proportions**

Body proportions and limb measurements were made using the “ruler tool” function of the Norland software (reporting at 0.1mm accuracy), using easily identified bone landmarks (Abrahamyan et al. 2008). These measurements were chosen because of their good visibility on DXA scan images.

**Leg-length (mm):** a straight-line distance between two horizontal lines marking the most proximal and distal landmarks of the leg-length was used. The proximal landmark was the most superior aspect of the greater trochanter. The inferior landmark was the most inferior part of the malleolus.

**Trunk-Length (mm):** was defined as standing height minus leg-length (defined above).

**Tibia length (mm):** a straight-line distance from the joint space of the knee and the most inferior part of the malleolus.

**Femur length (mm):** a straight-line distance between the most superior aspect of the greater trochanter and the knee joint space.

**Pelvis width (mm):** the distance between the most superior aspect of the left and right greater trochanter.

**Shoulder width (mm):** shoulder width was described by the distance between the most lateral aspect of the left and right acromion.

**Upper Arm Length (mm):** the proximal aspect of the upper arm was the most lateral aspect of the acromion (used to describe shoulder width). The midpoint of the widest distance between the medial and lateral epicondyle of the humerus was used to demarcate the most inferior portion of the upper arm, and most superior aspect of the forearm.

**Forearm length (mm):** the proximal aspect of the forearm was described above in upper arm length. The distal aspect of the forearm is marked by the horizontal line between the ulnar styloid and carpal joints of the wrist.
Potential Limitation of Whole Body DXA, Darwin

Some participants in the Darwin-site of the eGFR Study who underwent whole body DXA received an intravenous injection of non-isotopic iohexol (300mg/ml, less than 3ml), to determine plasma clearance rate and therefore a direct real-time kidney function study (Maple-Brown et al. 2010b). None of the participants at the Thursday Island site received a DXA immediately after iohexol injection. Our preference was to wait three days minimum in all participants, and one week in participants with known GFR<30 ml/min/1.73m². This dose was very small, in comparison to larger doses used in oncology patients (Sala et al. 2006).

There is a theoretical risk in participants with poor kidney function that modalities such as CT and DXA may unintentionally interpret iohexol as lean mass. It would have been ideal in a subset or independent study to do sequential DXA scans before and after iohexol injection to determine if a predictable (or unpredictable) error in lean mass was found on DXA scans of these few clients. We were working within the timetabling confines of a private radiology unit supplying service to private and hospital patients, and within The eGFR Study protocol timetable, and this sub-analysis was not feasible.

2.3.7.2. Whole Body DXA, Thursday Island

A commercially available combined mobile bone mineral density and whole body DXA device was sourced for the Thursday Island study visit.

A Hologic Delphi W (SN-70034) model (Hologic Inc., Bedford, M.A. www.hologic.com) whole body DXA device that was permanently installed in a vehicle was transported to Thursday Island. The vehicle was stabilised so that the DXA device remained level for each scan. The device was calibrated each morning of scanning. A trained operator completed all scans, and analysed the results, using the QDR system software for Windows (XP) Hologic software APEX 3.0 (Hologic). Participants completed a single whole body scan.

The same whole body positioning used in the Darwin DXA study was used in the Thursday Island DXA study. Total mass (grams), lean mass (grams), fat mass...
(grams) and fat percent was calculated for the whole body and for individual regions of interest. These whole body regions were the head, upper limbs, lower limbs, and trunk, as shown in Figure 2.2.

![Figure 2.2 Total and Regional Body Parameters with Hologic Whole Body DXA (Thursday Island Study Site)](image)

Upon analysis the software places a matrix over the body for regional analysis. The operator defines the placement of these lines:

- Head: immediately below the mandible,
- Trunk: enclosing the chest, midriff and pelvis.
- Left and right upper limbs: the line was placed medial to the head of the humerus.
- Left and right legs: a line joins the outside of the thigh through to the middle of both legs by being placed through the femoral neck and lateral to the pubic ramus.

**Body Proportions**

A ruler tool function in the Hologic software was not available to the investigator at the later time of data analysis. PDF printouts of each participant’s whole body DXA scan were evaluated for body proportions. A single analyst (JH) measured the following body proportions with a ruler to the nearest 0.1cm. Data were converted to
proportion of height by comparing measured standing height with body length from the PDF printout.

The measurement methods for leg-length, trunk-length, pelvis-width, shoulder-width, upper arm length and forearm length, were the same as described for body proportions measured on the Norland DXA instrument. Variations to measurement in the Hologic study are as follows:

**Hologic body length:** vertex of head to the most inferior part of the malleolus or joint margin if the malleolus was not visible.

### 2.4. Healthy Top-Enders’ Study

The Healthy Top-Enders’ study was designed and conducted in Darwin, the capital city of the Northern Territory. The purpose was to determine ethnicity-dependent differences in a young general population; hence young adults participating in elite sporting programs, as well as pregnant women were excluded. Fifty-six adults (aged 17 to 25 years old), who were matched for age, gender and body mass index completed a detailed health, body composition and inflammatory cytokine assessment during October 2009 and May 2010. The Healthy Top-Enders’ study provides a healthy baseline of body composition, and assesses the relationships between inflammatory markers, total adiposity and abdominal fat partitioning.

Abdominal computed tomography (the criterion model of abdominal fat partitioning in the study), whole body DXA and bioelectrical impedance analysis were performed. Fasting blood samples (measuring a range of parameters including glucose and insulin, C-reactive protein (CRP), interleukin-6 (IL-6), resistin, and leptin, adiponectin, and high molecular weight (HMW) adiponectin) were collected. Insulin resistance was assessed by fasting glucose and insulin levels and HOMA score. In the thesis, the HOMA-IR score (Matthews et al. 1985), is here-after referred to as HOMA, and was defined as

\[ = \frac{(\text{fasting glucose, mmol/L} \times \text{fasting insulin, mU/L})}{22.5}. \]
The relationship of total and regional adiposity with inflammatory markers and cytokines was assessed.

I was the Principal Investigator in The Healthy Top-Enders’ study and was responsible for development of the protocol, obtaining human research ethics committee approval, community consultation and gaining support from the community. I trained an Indigenous research assistant (SG) to assist with completion of the detailed assessment protocol. I was also responsible for overseeing development of an Access database, procedures for data collection, data storage and data analysis.

Most of the body composition assessments in The eGFR Study and Healthy Top-Enders’ study have the same protocols to allow for comparisons between studies. Any variation to the methodology of the Healthy Top-Enders’ study has been described below.

2.4.1. Participants

Volunteering and consenting Indigenous Australians and non-Indigenous Australians aged at least 16 years and to maximum of 25 years were invited to participate. Each participant was required to be healthy, by self report, and not pregnant or breastfeeding. Health status was further evaluated in the protocol by blood pressure, urinalysis, and fasting blood tests (described below). Specific exclusion criteria beyond ethnic identity and age were chronic medical illnesses including pacemaker, anticoagulation for rheumatic heart disease, type 1 or type 2 diabetes, kidney impairment, peripheral vascular disease and cerebrovascular disease.

Indigenous Australians were accepted to the study if they self-identified as an Aboriginal person. As much as possible we recruited Aboriginal participants with 4 grandparents who identified as an Aboriginal person, and where possible, remote living Aboriginal participants who were in Darwin (for school or employment), or identified with a homeland region. Torres Strait Islander people who identified as only-Torres Strait Islander were excluded. Two participants identified as both
Aboriginal and Torres Strait Islander, and each had only 1 grandparent who identified as a Torres Strait Islander. Aboriginal participants were recruited and assessed first. Self-identifying non-Indigenous participants were recruited and matched to Aboriginal participants by gender and body mass index. Non-Indigenous participants were recruited if they had 4 grandparents who identified as Caucasian.

Fifty-six adults completed the assessments for the Healthy Top-Enders’ study. Data are presented in Chapter 3 and Chapter 4 for 52 participants. Three Aboriginal males with high BMI (including two with newly diagnosed diabetes as a result of the study assessment) were unable to be matched for BMI with non-Indigenous males, and were therefore not included in the analysis. One non-Indigenous female with a high BMI that was unable to be matched to an Aboriginal female was also excluded from the analysis presented in Chapter 3 and Chapter 4.

The identified demographic for this study (age 16-25 years) was in transition from child health services, and adult health services. Many of the clients did not have a dedicated primary health care practitioner. There was no single centre where young people congregate to learn information about the study. The target age group included young people either at high school or other further education, engaged in the workplace or training programs or unemployed people.

Recruitment relied upon several strategies. This included word of mouth, posters and launch of the study in the Indigenous academic unit of the Charles Darwin University. Community facilitators were employed to assist with making contact with potential Aboriginal participants, and assisted with translation if required. We actively liaised with Aboriginal communities in the Darwin region, Centrelink, Indigenous Employment and Housing organisations, meeting with young people in shopping centres, and recruited from a high school with a community-based boarding program for remote Indigenous students. We wanted to assess health and body composition in young adults who were non-elite athletes. We did not recruit from top-tier sporting organisations.
2.4.2. Ethics

Ethics approval for the Healthy Top-Enders’ study (application reference number 09/69) was provided by the Human Research Ethics committee (HREC) of the Northern Territory Department of Health and Families and Menzies School of Health Research, Darwin. Both the main ethics committee and the Aboriginal subcommittee of the Human Research Ethics Committee (which has the power of veto over applications concerning Aboriginal and Torres Strait Islander people) provided their approval.

2.4.3. Clinical Assessments

Individuals were approached by the research officers to consider participation in the study. Informed consent was obtained, and participants were provided with information to fast for a minimum 10 hours (and maximum 12 hours) overnight in preparation for a fasting blood test the following morning.

Medical history and medications were self-reported by participants, and where possible, confirmed by medical chart review. A questionnaire was administered by a trained research officer in English (attached at Appendix 3), and included demographic information, self-identified ethnicity of self and 4 grandparents and health behaviours. Female participants also consented to urine pregnancy testing (qualitative human chorionic gonadotrophin test) to confirm they were not pregnant.

Blood pressure was measured in the Healthy Top-Enders’ study using the same protocol described for blood pressure in The eGFR Study.

2.4.4. Biochemical Analyses

Venepuncture was performed after a minimum 10 hour overnight fast into seven vacutainers containing EDTA, fluoride, lithium heparin and plain (serum). Tubes were kept on ice and then centrifuged within 1 hour. An urgent courier service to a commercial laboratory (Westerns Diagnostic Pathology, Winnellie Darwin, NT) was routine to avoid deterioration in specific samples (insulin and PTH). Serum for
inflammatory cytokines was stored at Menzies in a minus 80 degree freezer. This protocol is described below.

The following biochemical analyses were performed by Westerns Diagnostic Pathology, a commercial laboratory in Darwin.

Glucose was analysed by enzymatic reference method with hexokinase on a Cobas Integra 800 machine using serum. Insulin was analysed with chemiluminescence immunometric assay on a Siemens Immunlite 2000 Xpi machine using serum. HbA1c was assayed using turbidimetric inhibition immunoassay (TINIA) for haemolysed whole blood on a Cobas Integra 800 machine using EDTA whole blood. Electrolytes (urea, creatinine, sodium and potassium), albumin, total protein, and lipids (total cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol) were measured on a Cobas Integra 800 machine using serum.

Urea was measured using kinetic test with urease and glutamate dehydrogenase. Creatinine was measured using buffered kinetic Jaffe reaction without deproteinization. Sodium and potassium were measured using ion-selective electrodes using undiluted specimens. Albumin was measured using colorimetric assay with endpoint method. Total protein was measured using colorimetric assay. Total cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol was measured using enzymatic colorimetric tests. High sensitivity C-reactive protein (CRP) was measured by latex enhanced nephelometric assay on a Beckman Immage device using serum.

Urine albumin was measured by immunoturbidimetric assay on a Cobas Integra 800 instrument. Urine creatinine was also analysed on a Cobas Integra 800 instrument by the buffered kinetic Jaffe reaction without deproteinization principle. Albumin to creatinine ratio in urine was calculated as urine albumin divided by urine creatinine (mg/mmol).

Plasma and serum samples that were retained at Menzies School of Health Research for analysis at a later date were centrifuged at 3000 RPM for 10 minutes by the
investigator (JH), then aliquotted in a class II biosafety cabinet into separate cryovials, then stored in a minus 80 degree freezer with corresponding urine samples.

The following analyses were conducted at Menzies School of Health Research by an experienced scientist (Ms Kim Piera). Human serum IL-6 (catalogue number: DY206), leptin (catalogue number: DY398), resistin (catalogue number: DY1359), and total adiponectin (catalogue number: DY1065) were assayed using an R&D Systems Duoset ELISA kit (R&D Systems, Inc. Minneapolis). High molecular weight adiponectin was assayed on an ALPCO multimeric ELISA kit (ALPCO Diagnostics, Salem US Catalogue Number: 47-ADPHU-E01 version ALPCO 6/1/2010). High sensitivity IL-6 (catalogue Number: HS600B) was also assayed on a Quantikine High Sensitivity ELISA (R & D systems, Minneapolis) as a number of Healthy Top-Enders’ study participants had IL-6 levels that were below detectable limits using the R&D Duoset ELISA kit. In our laboratory, the coefficient of variation for leptin, adiponectin and HMW adiponectin were: 0.09, 0.10, and 0.08 respectively.

Twice thawed serum was used for all of the above assays. The method for the initial thaw involved is as follows. Several serum tubes were thawed on ice at a time (over 5 minutes maximum). Tubes were inverted twice to mix, and then flicked to settle serum in the lid prior to aliquotting (which took approximately 30 seconds per sample). Tubes were then returned to the minus 80 degree freezer and thawed just prior to testing at a subsequent date.

2.4.5. Anthropometry

The protocol for anthropometry was the same in both studies. A single experienced operator performed all of the waist and hip circumferences in this study (JH). The data collection form for the Healthy Top-Enders’ study is attached in Appendix 4.

2.4.6. Bioelectrical Impedance Analysis

Bioelectrical impedance analysis was used on all Healthy Top-Enders’ study participants using the same protocol as those who completed BIA in The eGFR
Study. Whole body impedance measurements were recorded according to previously described methods (Cornish et al. 1999).

2.4.7. Complex Body Composition Assessments

2.4.7.1. Whole Body DXA, Darwin

The same protocol employed in the eGFR Study for whole body DXA was used in the Healthy Top-Enders’ study. Scanning was performed by a single trained operator (research assistant SG). Analysis of all scans was performed by a single investigator (JH). The same methodology for the measurement of body proportions in The eGFR Study was also used in the Healthy Top-Enders’ study (see Chapter 2.3.7.1).

2.4.7.2. Computed Tomography

The methodology for computed tomography in the Healthy Top-Enders’ study is reviewed in detail below. A further detailed description of the CT protocol is found in Chapter 3.2. All scans were performed by a trained radiographer at the Darwin Private Hospital, Darwin on the same day as the Healthy Top-Enders’ study protocol using an Aquilion 16 (Toshiba, Japan) computed tomography scanner. The protocol was written and provided by a collaborator (Penny Speight (PS), Radiographer and Radiation Scientist, Diabetes Clinical Research Unit, St Vincent’s Hospital, Sydney) who also provided local training and supervision of the protocol.

Participants wore light weight clothing, and were examined in the supine position. Three scans were taken at the end of light expiration. A scout view was taken to determine the reference points of each CT slice. Two cross sectional CT scans each 8 mm wide were performed, centred on the L2-L3, L4-L5 inter-vertebral disc spaces to assess abdominal adipose tissue distribution.

Each scan was obtained at 120kv (peak), with a scanning time of 3 seconds duration at arrested expiration (at the end of light expiration) and the majority were scanned at 100mA. Some overweight participants were scanned at higher values including two participants scanned at the maximum value of 350mA. Images were stored onto
CD and analysed by a single trained operator (PS) using a Gemini workstation (GXL Host System; Phillips, the Netherlands) (Samocha-Bonet et al. 2010). In each scan level of L2-L3 and L4-L5, the total adipose tissue area was measured by delineating manually the outer abdominal wall and then calculating the pixel distribution in this area with attenuation range –150 to –50 HU. The intra-abdominal region was defined by encircling the intra-abdominal cavity at the innermost aspect of the abdominal and oblique muscle walls surrounding the cavity and the posterior aspect of the vertebral body. The encircled area with attenuation range –150 to –50 HU was then calculated by the computed and taken as the intra-abdominal fat area (IAF) or visceral fat area (VFA). The subcutaneous fat area (SFA) was then calculated by subtracting the IAF area from the total adipose tissue area (TFA). Adipose area was calculated in mm$^2$ by the scanner-software, and divided by 100 to convert to cm$^2$. Total abdominal fat area, subcutaneous fat area and visceral fat area were reported at the level of L2-L3 and L4-L5. Sagittal abdominal diameter (SAD) of the abdomen (mm) was measured on the frozen CT image at inter-vertebral space of L2-L3 and L4-L5 in expiration.

The data was returned to the investigators in a secure spreadsheet after each scan, and stored securely in the Healthy Top-Enders’ study Microsoft Access database at Menzies School of Health Research.

2.5. Statistical Analyses

Statistical methods will be described in detail in each of the results Chapters (found in Chapters 3.2.3, 4.2.4, 5.2.4, and 6.2.4). Data recorded onto data collection forms were transcribed into an Access database. Data was analysed using STATA v10.0 (Stata Corporation, TX, USA). A summary of descriptive statistics are provided in Chapter 3.3, Chapter 4.3, Chapter 5.3, and Chapter 6.3), followed by tests of bivariate associations, and then multiple regression analyses.

Hypothesis testing in the thesis

In the PhD thesis a statistically significant difference between groups was considered for p values <0.05. In Chapter 3 and Chapter 4, due to smaller numbers of participants (compared with Chapter 5 and Chapter 6), statistically significant values
were considered when the p values were <0.05. In Chapter 5 and Chapter 6, whilst the overall numbers of participants were larger, several subgroups existed within the respective cohorts. Hence in Chapter 5 and Chapter 6, a stronger statistically significant relationship was considered if p values were <0.01.

**Model building, selection of variables and testing for interactions between pairs of variables.**

In the thesis, multiple regression analyses were performed using a backwards selection process. An initial model was built with all predictor variables (if clinically indicated to be associated or if a strong relationship with the outcome variable was demonstrated by bivariate analysis (by p value <0.05 and r value >0.8)). Predictor variables were retained in the regression model if they were not highly intercorrelated with other predictor variables using the variance of inflation test. Using a stepwise backwards process, the final significant model was obtained by removing one variable at a time if its main effect in the model had a p-value >0.05, and the likelihood ratio test for exclusion of the variable from the model was p>0.05. This process continued until the final model demonstrated all predictor variables with p value <0.05. The final assessment of the multiple regression models included an assessment of first-order interactions between all pairs of variables in the final model. All pairs of variables were tested for first order interactions (even if not biologically plausible). The interaction term was retained in the final model if it was biologically plausible (such as in Chapter 3 and Chapter 6).

**Issue of multiple comparisons and statistical power**

Two different cohorts are described in the thesis study. The Healthy Top-Enders’s study cohort were carefully recruited to be matched for age, gender, body mass index, and health, and a specified criteria for ethnicity. This contrasts with participants within The eGFR Study: who had a wider age range, may have been healthy or had complex medical issues, lived in different geographical settings, and again a specified criteria for ethnicity. Bivariate relationships were examined in all chapters of the thesis, however the strength of their associations are often confounded by unmeasured variables, and hence further tests were performed. An analysis of covariance (ANCOVA) was used in the Healthy Top-Enders’ study when examining differences in skeletal proportions (Chapter 3) and adiponectin
concentrations (Chapter 4). The intention of The eGFR Study was to examine if differences exist between Aboriginal participants and Torres Strait Islander participants, rather than demonstrate absolute differences between groups. Hence data was presented as unadjusted observed means, with an analysis of covariance to indicate when differences may be influenced by gender, ethnicity or the interaction term in Chapter 5. In the ANCOVA, at the level of statistical significance of $p=0.05$, there is an expectation that one in twenty comparisons between an exposure and the outcome would be statistically significant, even if no association between the exposure and outcome variable exists. Therefore, the main effect of the exposure variable was more strongly regarded when the $p$ value was $<0.01$ than comparisons with $p$ values closer to 0.05.

In Chapter 6; an analysis of covariance was initially performed to examine the main effect of ethnicity, gender, the ethnicity*gender interaction term and kidney function (as a continuous variable) on adiponectin concentrations in the whole cohort. As the main effect of ethnicity*gender or ethnicity was non-significant, subgroup analysis was not performed (by strata of kidney function- which is another way that kidney function can be described). Sub-group analyses are likely to be non-significant if the main effect is not significant in the overall population, and any significant results should be regarded with caution in this instance. In the Chapter 6 cohort, several potential subgroups existed (gender, ethnicity, strata of kidney function), and there were low and unequal numbers of participants in some of the subgroups to be examined- hence an analysis of covariance is not permitted in this setting. A Bonferroni correction for multiple comparisons was not used in this instance, as a multifactorial analysis method is preferred if unequal groups exist, there are multiple subgroups and as the Bonferroni method is overly conservative with respect to detecting differences between groups. Instead differences in adiponectin concentrations were examined with a multifactorial analysis (a multivariate regression model). The issue of multiple comparisons in the multiple regression analysis models was dealt with by addressing the number of variables used in the initial model (fewer than 10 variables were examined), and the $p$-value of the main effects in the final model. At the level of statistical significance of $p<0.05$, the expectation of a Type 1 error is $1/20$. In the analysis, the expectation of a Type 1 error is expected to be $<1$, due to selection of only 10 variables (i.e. fewer than 20
variables) in the initial multiple regression model. In the final multiple regression model, the final model was accepted if each of the main effects had p-values <0.01. Post test analysis for normality of residuals and assessment for interactions between pairs of predictor variables and leverage and undue influence in the final model.
Chapter 3.
Healthy Top-Enders’ Study:
Body Composition and
Skeletal Proportions in
Healthy Adult Aboriginal People
3.1. Introduction

Obesity and overweight are highly prevalent among Indigenous and non-Indigenous Australians (AIHW 2011). Obesity has also been linked to the development of several chronic diseases, including type 2 diabetes, vascular disease, kidney failure and some cancers (WHO 2000). Accurately assessing body composition among Aboriginal people has been limited due to the geographic dispersal of many Aboriginal people, and the limited portability of sophisticated body composition tools. Indirect and portable body composition methods such as height and weight, body circumferences, skin-fold thicknesses and bioelectrical impedance analysis have been used in community surveys (Kondalsamy-Chennakesavan et al. 2008; Piers et al. 2003; Rutishauser et al. 1986). However, these methods have not been validated against whole body dual energy x-ray absorptiometry (DXA).

Aim

The aim of this study was to (a) accurately describe skeletal proportions and body composition, and (b) accurately predict body composition in healthy young adult Aboriginal people using methods that can be easily used in field settings.

3.2. Methods

3.2.1. Participants and Measurements

The methods for this study have been previously described in detail in Chapter 2.4. Healthy young adults (16-25 years old) were approached to participate in the Healthy Top-Enders’ study. Ethnicity was self-identified, and Aboriginal participants were recruited first, with non-Indigenous participants recruited to be matched for age (within 1 year), gender, and body mass index (± 1.5 kg/m$^2$). Participants fasted for 10 hours, and assessments commenced at 8 am the following morning with a fasting blood test, mid stream urinalysis, and body composition assessments. All measurements were performed in standard light-weight clothing. These included height (0.1 cm), weight (0.1 kg), waist (0.1 cm) and hip (0.1 cm) circumferences. Resistance (R) was measured by bioelectrical impedance analysis using a tetra-polar
electrode arrangement recorded on a selected frequency bioimpedance device (SFB) (Impedimed, Brisbane) at 50 kHz while the participant lay supine, and observed standard preparations (see Chapter 2.3.6).

### 3.2.2. Dual Energy X-ray Absorptiometry

Participants also completed a whole body dual energy x-ray absorptiometry scan (DXA) (see Chapter 2.3.7.1). Fat mass, fat percent, lean tissue mass (referring to non-bone non-adipose tissue mass) and bone mineral content was reported by the Norland XR 46 whole body composition scanner. Midriff fat refers to fat measured in the space bordered by horizontal lines between the lowermost ribs, and iliac spines, extending laterally out to the margin of soft tissue in the abdomen (shown in Figure 2.1). Body regions were described as trunk (non-appendicular, and encompasses the DXA regions of interest in the chest, midriff and pelvis described in Chapter 2.3.7.1), and peripheral (appendicular, encompassing the regions of the upper and lower limbs). Fat free mass (FFM) was calculated as body weight minus fat mass recorded by the Norland software. Peripheral lean tissue mass refers to the sum of lean mass (non-bone non-adipose mass) of the four limbs. Trunk lean mass refers to the total lean mass minus the sum of head lean mass and peripheral lean mass.

Skeletal proportions were determined from Norland XR 46 ruler tool software using easily defined bony landmarks (Abrahanyan et al. 2008), and are depicted in the graphic below (Figure 3.1). Detailed measurements of skeletal proportions are described in Chapter 2.3.7.1. Leg length, tibia length, femur length, pelvis-width, shoulder-width, upper arm length and forearm length was measured using the DXA ruler tool software (in millimetres), and converted to centimetres for analysis. Trunk-length was reported in centimetres, as the difference between standing height and leg-length measured by DXA ruler tool. Skeletal proportions were also expressed as length’s adjusted for body height (e.g. leg length%= [(leg-length (cm)/height (cm))x 100]).
3.2.3. Statistical Analysis

Summary Statistics for Body Composition and Biochemical Data

Male and female participants in each ethnicity group were matched for body mass index, in order to compare lean with lean and overweight with overweight between groups. Most body composition data in this analysis of 52 healthy young adults was not normally distributed, and data are presented as median and inter-quartile range, and compared with the Kruskal-Wallis equality of populations rank test, a non-parametric test of comparison of medians between groups. An analysis of covariance was used to explore the difference in non-fat DXA measures between ethnic groups, after controlling for gender, height, and an ethnicity*gender interaction term.

Biochemistry was also non-normally distributed, and was expressed as median and inter-quartile range, and comparisons between groups was performed with log-transformed variables by the Kruskal-Wallis equality of populations rank test, as log transformation improved the distribution for some highly skewed biochemical
variables (such as CRP and ACR). In each sex an analysis of covariance (ANCOVA) was performed to examine for any differences in urinary albumin to creatinine ratio with fat free mass as a covariate.

Comparison of Skeletal Proportions between Groups

Data on skeletal proportions (as length, or length as percentage of standing height) were normally distributed, and presented as mean (standard deviation), and compared with an analysis of covariance (ANCOVA) in Table 3.3

Factor Analysis of Body Composition Measures

Factor analysis was used to examine the clustering of variables around ethnicity, fat and fat free mass in this cohort. The principal component method was used to reduce the information in many measured variables into a smaller set of “factors.” Kaiser’s criterion (eigen values >1) was used to determine the number of factors that best described the underlying relationship among variables. The extracted factors were rotated using the varimax rotation. Significant correlations were considered for variables loading at ≥0.40.

Assessment of the Accuracy of published Prediction Equations of Fat Free Mass using Bioelectrical Impedance Analysis

A number of published prediction equations for fat free mass based on bioelectrical impedance analysis exist. Raw data from participants in this study were applied to several previously published equations (and presented in Appendix Table 1). In addition a Tanita bioelectrical impedance device was used to record fat free mass when available. Participants stood on the electrode plates. An equation was not available with this device, and data was printed out after each reading. Tanita fat free mass (in kg) was assessed for agreement with measured fat free mass (by DXA) in a similar method to other prediction equations. The tests of agreement included analysis of distribution of differences between measured FFM (by DXA) and the prediction equation, the Lin concordance correlation coefficient (Steichen et al. 1998), and a paired t-test of the measured FFM and predicted FFM (Bland 2000). The ‘Lin concordance correlation coefficient’ (ρc) expresses an overall value for agreement of two methods by assessing accuracy, precision and bias. Excellent agreement is given by a ρc of close to 1.0, with narrow 95% confidence limits of the
statistic, and low p-value of the $\rho_c$ statistic. The Lin coefficient ($\rho_c$) assesses error of the prediction method by the correction of bias (C-b, where a value close to 1.0 indicates very low error), and produces a reduced major axis of the prediction method which is compared against the reference method (DXA) which has a slope of one, and intercept of zero (Steichen et al. 1998). Accuracy of the prediction method (against the reference method, DXA) is depicted graphically by assessing concordance of the reduced major axis to the 45 degree line of the reference method. Any departure of the reduced major axis from the reference line indicates low accuracy of the prediction method. Precision of the prediction method is assessed by how closely individual measures are to the reduced major axis (Steichen et al. 1998).

**Multivariate Analysis of Fat Free Mass in Participants**

The goal was to determine a prediction equation of fat free mass (FFM) in Aboriginal participants using portable tools which also included bioelectrical impedance analysis. In all participants, multiple regression analysis with a backwards selection of independent variables (which included gender, ethnicity, anthropometric measures and skeletal proportions) was used to predict FFM measured by whole body DXA (dependent variable). Selection of independent variables was based on a statistically significant bivariate relationship between the predictor variable and fat free mass (the outcome variable), where the r-value was $>0.8$, and p value for this relationship was $<0.05$. Selection was also based on clinical interpretation of the determinants of fat free mass, and variables that clustered with fat free mass in the factor analysis. Variables were retained in the model if they contributed low individual and mean variance inflation factor in the model, had a statistically significant p value ($p<0.05$) or the likelihood-ratio test was statistically significant ($p<0.05$) if the predictor variable was removed from the model (Dupont 2009; Kirkwood et al. 2003; Long et al. 2006). Post-test analysis of the regression model included analysis of residuals, assessing for all first-order interactions between pairs of independent variables, and assessing the model for undue leverage and Cook’s distance of individual participants with the independent variable (Dupont 2009).
3.3. Results

3.3.1. Participant Characteristics: Healthy Top-Enders’ study

31 Aboriginal adults and 21 non-Indigenous adults matched for gender, age and body mass index were assessed. All non-Indigenous participants reported four grandparents who identified as non-Indigenous (of European background). Seventy-four percent of Aboriginal participants (n=23) reported 4 grandparents who identified as an Aboriginal person. Six Aboriginal participants (2 males, 4 females) reported 3 Aboriginal grandparents and one non-Indigenous (European) grandparent. Two female participants reported 3 Aboriginal grandparents and one other grandparent a (Japanese, and a both Aboriginal and Torres Strait Islander grandparent respectively). One Aboriginal female reported 2 Aboriginal and 2 non-Indigenous (European) grandparents. Two thirds of Aboriginal participants (68%) identified with an Aboriginal community, which may have been within the Darwin area, or other regions.

Cigarette smoking was common in Aboriginal participants (Aboriginal v Caucasian: 61% v 24%, p<0.01). Aboriginal males were slightly younger than non-Indigenous males (19.3 v 22.0 years, p=0.04), though there was no difference in the age of female participants (Aboriginal v Caucasian: 20.3 v 20.3 years, p=0.62).

3.3.2. Body Composition: Healthy Top-Enders’ study

A small and non-statistically significant difference in median BMI between Aboriginal and non-Indigenous males is shown in Table 3.1 (2.2 kg/m², p=0.27). Despite no significant difference in total fat free mass, Aboriginal males had lower trunk lean mass than non-Indigenous males (p=0.03). While not statistically significant, despite similar WHR, Aboriginal males displayed a trend to lower total fat mass (p=0.20) and fat percent (p=0.34) than non-Indigenous males.

In the whole cohort, fat free mass was positively associated with standing height (r=0.85, p<0.0001), therefore comparison of body composition between groups were also adjusted for height. Aboriginal males had a similar height as non-Indigenous
males (p>0.05). Aboriginal males had lower absolute bone mineral content (DXA-BMC) and lower absolute trunk lean mass, however this failed to reach statistical significance using analysis of covariance (ANCOVA), after adjustment for height (BMC, p=0.26, trunk-lean mass, p=0.07).

Aboriginal females were 5.9 cm shorter than non-Indigenous females (p=0.003), and had higher waist to hip ratio, midriff fat mass and higher ratio of trunk:peripheral fat mass. DXA measures of fat mass were not related to height (p>0.05). Aboriginal females had lower absolute measures of bone mineral content, fat free mass, trunk lean mass, and lower ratio of trunk:peripheral lean mass than non-Indigenous females. After adjusting for height, Aboriginal females had lower bone mass (0.27 kg, p=0.015), trunk-lean mass (2.2 kg, p=0.014), and trunk:peripheral lean mass ratio (15%, p=0.002).
<table>
<thead>
<tr>
<th>Body Composition</th>
<th>Aboriginal Males (n=15)</th>
<th>Non-Indigenous Males (n=10)</th>
<th>p value</th>
<th>Aboriginal Females (n=16)</th>
<th>Non-Indigenous Females (n=11)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>173.3 (166.3, 181.2)</td>
<td>179.4 (172.5, 182.5)</td>
<td>0.17</td>
<td>161.7 (158.4, 164.8)</td>
<td>167.5 (163.5, 172.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62.9 (54.5, 77.6)</td>
<td>70.3 (65.7, 90.2)</td>
<td>0.12</td>
<td>62.9 (52.4, 78.5)</td>
<td>60.1 (52.9, 81.1)</td>
<td>0.77</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>78.5 (72.3, 91.2)</td>
<td>83.0 (78.6, 90.1)</td>
<td>0.54</td>
<td>82.0 (73.7, 97.9)</td>
<td>77.6 (65.1, 86.0)</td>
<td>0.10</td>
</tr>
<tr>
<td>Hips (cm)</td>
<td>96.0 (87.4, 106.6)</td>
<td>98.4 (93.4, 107.4)</td>
<td>0.22</td>
<td>102.2 (94.7, 107.1)</td>
<td>99.1 (90.5, 108.3)</td>
<td>0.67</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.7 (18.2, 25.8)</td>
<td>23.9 (21.3, 27.1)</td>
<td>0.27</td>
<td>24.1 (19.9, 28.4)</td>
<td>23.5 (19.3, 27.0)</td>
<td>0.52</td>
</tr>
<tr>
<td>WHR</td>
<td>0.84 (0.80, 0.86)</td>
<td>0.82 (0.79, 0.85)</td>
<td>0.41</td>
<td>0.81 (0.78, 0.88)</td>
<td>0.74 (0.72, 0.80)</td>
<td>0.01</td>
</tr>
<tr>
<td>Resistance (ohms)</td>
<td>567 (522, 633)</td>
<td>496 (457, 537)</td>
<td>0.17</td>
<td>717 (514, 774)</td>
<td>636 (579, 659)</td>
<td>0.11</td>
</tr>
<tr>
<td>Fat Mass (kg)</td>
<td>10.9 (5.2, 23.0)</td>
<td>17.6 (9.1, 25.9)</td>
<td>0.20</td>
<td>27.6 (21.0, 35.9)</td>
<td>23.2 (13.7, 38.9)</td>
<td>0.30</td>
</tr>
<tr>
<td>Fat Percent (%)</td>
<td>15.0 (10.0, 29.0)</td>
<td>24.5 (14.0, 29.0)</td>
<td>0.34</td>
<td>43.5 (39.0, 47.0)</td>
<td>34 (25, 47)</td>
<td>0.08</td>
</tr>
<tr>
<td>Midriff Fat (kg)</td>
<td>0.8 (0.4, 2.5)</td>
<td>1.7 (0.8, 2.6)</td>
<td>0.24</td>
<td>2.9 (1.7, 3.8)</td>
<td>1.3 (0.8, 2.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Trunk Fat Mass (kg)</td>
<td>4.1 (2.0, 10.9)</td>
<td>7.3 (3.0, 11.5)</td>
<td>0.20</td>
<td>13.9 (9.7, 18.6)</td>
<td>10.0 (4.9, 17.6)</td>
<td>0.14</td>
</tr>
<tr>
<td>Peripheral Fat Mass (kg)</td>
<td>6.6 (3.8, 12.0)</td>
<td>10.3 (6.1, 15.0)</td>
<td>0.18</td>
<td>14.3 (11.1, 16.3)</td>
<td>13.0 (8.8, 21.3)</td>
<td>0.55</td>
</tr>
<tr>
<td>Ratio Trunk:Peripheral Fat Mass</td>
<td>0.70 (0.46, 0.96)</td>
<td>0.70 (0.59, 0.84)</td>
<td>0.78</td>
<td>0.72 (0.82, 1.10)</td>
<td>0.72 (0.55, 0.83)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fat Free Mass (kg)</td>
<td>54.0 (48.5, 55.3)</td>
<td>57.6 (52.8, 62.7)</td>
<td>0.08</td>
<td>33.5 (32.4, 38.3)</td>
<td>39.2 (37.4, 42.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fat Free Mass (%)</td>
<td>84.2 (70.4, 90.2)</td>
<td>75.2 (70.7, 86.1)</td>
<td>0.35</td>
<td>55.3 (51.7, 60.2)</td>
<td>65.2 (52.0, 74.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>DXA-BMC (kg)</td>
<td>2.7 (2.5, 3.0)</td>
<td>3.0 (2.9, 3.5)</td>
<td>0.04</td>
<td>2.4 (2.2, 2.7)</td>
<td>2.9 (2.6, 3.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Trunk LTM (kg)</td>
<td>25.3 (24.0, 27.2)</td>
<td>29.2 (25.8, 30.5)</td>
<td>0.03</td>
<td>15.6 (14.8, 18.2)</td>
<td>19.3 (18.7, 19.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Peripheral LTM (kg)</td>
<td>26.0 (22.0, 28.1)</td>
<td>27.2 (25.0, 31.0)</td>
<td>0.24</td>
<td>16.9 (15.6, 19.8)</td>
<td>17.2 (16.6, 22.1)</td>
<td>0.73</td>
</tr>
<tr>
<td>Trunk: Peripheral LTM%</td>
<td>100.0 (90.0, 103.3)</td>
<td>103.0 (98.3, 107.6)</td>
<td>0.29</td>
<td>91.4 (86.7, 98.8)</td>
<td>103.8 (98.0, 115.2)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

BMI: body mass index; WHR: waist to hip ratio; LTM: lean tissue mass. BMC: bone mineral content. Data are expressed as median (inter-quartile range); p-value refers to comparison of differences in medians for body measures by the Kruskall–Wallis equality of populations rank test, by gender.
3.3.3. Biochemical Characteristics: Healthy Top-Enders’ study

Table 3.2 describes the biochemical results of participants. Aboriginal males had higher fasting triglycerides, and trended to higher fasting insulin compared with non-Indigenous males. Aboriginal females had a lower fasting HDL-cholesterol level and trended to higher CRP levels (p=0.06) compared with non-Indigenous females. All participants had a normal urine ACR, though a statistical difference was noted between Aboriginal and non-Indigenous females. In males, when urinary ACR was examined with fat free mass as a covariate, there was no statistically significant difference by ethnic group. In females, Aboriginal ethnicity was associated with lower urinary ACR. This relationship in females remained when fat free mass was included as a covariate.
<table>
<thead>
<tr>
<th>Biochemistry</th>
<th>Aboriginal Males (n=15)</th>
<th>Non-Indigenous Males (n=10)</th>
<th>P value</th>
<th>Aboriginal Females (n=16)</th>
<th>Non-Indigenous Females (n=11)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>120 (111, 129)</td>
<td>115 (111, 129)</td>
<td>0.82</td>
<td>123 (108, 132)</td>
<td>125 (120, 139)</td>
<td>0.87</td>
</tr>
<tr>
<td>Glucose (mmol/L) *</td>
<td>4.7 (4.4, 5.0)</td>
<td>4.8 (4.5, 5.2)</td>
<td>0.66</td>
<td>4.3 (4.1, 4.7)</td>
<td>4.4 (4.3, 4.9)</td>
<td>0.15</td>
</tr>
<tr>
<td>Insulin (mU/L) *</td>
<td>8.0 (4.0, 12.0)</td>
<td>3.0 (2.0, 9.0)</td>
<td>0.08</td>
<td>7.0 (4.0, 10.0)</td>
<td>5.0 (2.0, 10.0)</td>
<td>0.33</td>
</tr>
<tr>
<td>HbA1c (%) †</td>
<td>5.4 (5.3, 5.7)</td>
<td>5.4 (5.3, 5.4)</td>
<td>0.23</td>
<td>5.5 (5.3, 5.6)</td>
<td>5.5 (5.4, 5.6)</td>
<td>0.71</td>
</tr>
<tr>
<td>HOMA *</td>
<td>1.78 (0.82, 2.84)</td>
<td>0.65 (0.40, 1.84)</td>
<td>0.09</td>
<td>1.40 (0.76, 1.96)</td>
<td>0.96 (0.40, 1.96)</td>
<td>0.44</td>
</tr>
<tr>
<td>Urine ACR (mg/mmol)</td>
<td>0.3 (0.2, 1.3)</td>
<td>0.6 (0.3, 1.4)</td>
<td>0.42</td>
<td>0.6 (0.4, 1.4)</td>
<td>1.6 (0.7, 1.8)</td>
<td><strong>0.03</strong></td>
</tr>
<tr>
<td>Total cholesterol * † (mmol/L)</td>
<td>4.5 (3.7, 4.7)</td>
<td>4.0 (3.6, 4.2)</td>
<td>0.12</td>
<td>3.9 (3.5, 4.8)</td>
<td>4.6 (4.4, 4.9)</td>
<td>0.18</td>
</tr>
<tr>
<td>Triglycerides (mmol/L) * †</td>
<td>1.5 (1.0, 1.7)</td>
<td>1.1 (0.8, 1.2)</td>
<td><strong>0.05</strong></td>
<td>1.1 (0.6, 1.7)</td>
<td>1.0 (0.7, 1.6)</td>
<td>0.91</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L) * †</td>
<td>1.15 (1.10, 1.20)</td>
<td>1.25 (1.00, 1.60)</td>
<td>0.55</td>
<td>1.10 (1.00, 1.40)</td>
<td>1.60 (1.40, 1.80)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CRP (mg/L) ‡</td>
<td>1.7 (1.0, 6.9)</td>
<td>0.8 (0.5, 4.7)</td>
<td>0.13</td>
<td>3.1 (0.7, 9.6)</td>
<td>1.1 (0.5, 2.3)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

ACR: Albumin: Creatinine Ratio; Biochemistry expressed as median (inter-quartile range); eGFR refers to estimated glomerular filtration rate, expressed by MDRD formula. P-value: Comparison of differences in biochemical measures by log-transformed data by the Kruskall-Wallis equality of populations rank test, by gender. *n=14 Aboriginal males, and n=15 Aboriginal females who completed fasting blood tests. † n=9, and ‡n=10 (respectively) are numbers of non-Indigenous females completing biochemical assessments, due to difficult blood collection.
3.3.4. Skeletal Proportions: Healthy Top-Enders’ study

Aboriginal participants had a longer relative leg-length and a shorter trunk-length relative to overall height (leg-length%, trunk-length% respectively) (Figure 3.2), which was not due to gender.

![Figure 3.2](image)

Females, both 170 cm tall: Aboriginal female (left); non-Indigenous female (right).

**Figure 3.2** Longer leg-length Relative to overall Height was a consistent feature in Aboriginal participants demonstrated by two females each 170 cm tall.

The longer leg-length% was due to a longer distal limb segment (tibia). Aboriginal participants had a narrower pelvis-width and shoulder-width than non-Indigenous participants, but this failed to reach statistical significance when adjusted for standing height. Aboriginal females and males had similarly narrow pelvis-width percent (p=0.86) and shoulder-width% (p=0.21). However, non-Indigenous males had narrower pelvis-width% (0.73% narrower, p=0.05) and wider shoulder-width percent (1.46% wider, p<0.001) than non-Indigenous females.

Differences in total and components of height between Aboriginal and non-Indigenous participants are shown in Table 3.3.
<table>
<thead>
<tr>
<th>Metric</th>
<th>Aboriginal (n=31)</th>
<th>Non-Indigenous (n=21)</th>
<th>Main Effects</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>p values</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ethnic</td>
<td>Gender</td>
</tr>
<tr>
<td>Standing Height (cm)</td>
<td>167.3 (8.8)</td>
<td>172.6 (8.4)</td>
<td>0.004</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pelvis width (mm)</td>
<td>259.3 (22.8)</td>
<td>274.0 (16.8)</td>
<td>0.009</td>
<td>0.032</td>
</tr>
<tr>
<td>Shoulder width (mm)</td>
<td>339.4 (33.8)</td>
<td>358.8 (29.8)</td>
<td>0.006</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leg-length (mm)</td>
<td>855.7 (49.8)</td>
<td>835.8 (46.3)</td>
<td>0.066</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Femur length (mm)</td>
<td>452.1 (27.2)</td>
<td>449.0 (25.8)</td>
<td>0.598</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tibia length (mm)</td>
<td>403.6 (27.3)</td>
<td>386.8 (27.6)</td>
<td>0.018</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Upper Limb length (mm)</td>
<td>594.0 (38.9)</td>
<td>581.4 (41.7)</td>
<td>0.182</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Humerus length (mm)</td>
<td>340.6 (22.8)</td>
<td>342.0 (28.4)</td>
<td>0.798</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Radius length (mm)</td>
<td>253.5 (24.3)</td>
<td>239.5 (18.5)</td>
<td>0.011</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Trunk-length (cm)</td>
<td>81.8 (4.7)</td>
<td>89.0 (4.8)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Upper Limb length (%)</td>
<td>35.4 (1.3)</td>
<td>33.7 (1.2)</td>
<td>&lt;0.001</td>
<td>0.243</td>
</tr>
<tr>
<td>Humerus length (%)</td>
<td>20.4 (1.0)</td>
<td>19.8 (1.0)</td>
<td>0.051</td>
<td>0.713</td>
</tr>
<tr>
<td>Radius length (%)</td>
<td>15.1 (1.0)</td>
<td>13.9 (0.7)</td>
<td>&lt;0.001</td>
<td>0.225</td>
</tr>
<tr>
<td>Leg-length (%)</td>
<td>51.1 (1.2)</td>
<td>48.4 (1.2)</td>
<td>&lt;0.001</td>
<td>0.432</td>
</tr>
<tr>
<td>Femur length (%)</td>
<td>27.0 (0.9)</td>
<td>26.0 (0.8)</td>
<td>&lt;0.001</td>
<td>0.081</td>
</tr>
<tr>
<td>Tibia length (%)</td>
<td>24.1 (0.9)</td>
<td>22.4 (1.2)</td>
<td>&lt;0.001</td>
<td>0.627</td>
</tr>
<tr>
<td>Trunk-length (%)</td>
<td>48.9 (1.2)</td>
<td>51.6 (1.2)</td>
<td>&lt;0.001</td>
<td>0.432</td>
</tr>
<tr>
<td>Pelvis width (%)</td>
<td>15.5 (1.3)</td>
<td>15.9 (0.9)</td>
<td>0.233</td>
<td>0.275</td>
</tr>
<tr>
<td>Shoulder width (%)</td>
<td>20.3 (1.5)</td>
<td>20.8 (1.0)</td>
<td>0.132</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Data are mean (SD). P-value refers to differences between groups described by ANCOVA.
3.3.5. Factor Analysis of Body Composition Measures in Healthy Top-Enders’ study Participants

Factor analysis was used to identify the clustering of variables around fat mass, fat free mass and ethnicity in the Healthy Top-Enders’ Study (see Table 3.4). Variables included in the factor analysis model were gender and ethnicity, height, weight, waist, hips, WHR and BMI, trunk-length, trunk-length%, pelvis-width, resistance, fat mass, fat%, fat free mass, fat free mass%, and DXA indices of regional fat distribution. Three factors were identified by these 20 variables, and explained 85% of the total variance of the Principal Components Analysis. Fat mass clustered with other DXA measures of total and regional fat, with BMI and waist and hip circumferences, and WHR. Fat mass also clustered with low fat free mass percent. Fat free mass clustered with male gender, height, weight, trunk-length and pelvis-width, WHR, low-fat percent and low-resistance. The third factor highlighted the clustering of body measures around ethnicity. Non-Indigenous ethnicity was associated with longer trunk-length, longer trunk-length%, wider pelvis-width and low WHR, and explained 14% of the variance of the factor analysis. Therefore, Aboriginal ethnicity clustered with the inverse of these variables: high WHR, shorter trunk-length, shorter trunk-length% and narrower pelvis-width.
Table 3.4 Factor Analysis of Body Composition measures in Healthy Top-Enders’ study Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Factor 1 Fat Mass</th>
<th>Factor 2 Fat Free Mass</th>
<th>Factor 3 Non-Indigenous Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>-0.0706</td>
<td>0.8438</td>
<td>0.2810</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td><strong>0.7655</strong></td>
<td><strong>0.6071</strong></td>
<td>0.1257</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td><strong>0.8891</strong></td>
<td>0.3622</td>
<td>-0.2154</td>
</tr>
<tr>
<td>Hips (cm)</td>
<td><strong>0.9020</strong></td>
<td>0.2036</td>
<td>0.1610</td>
</tr>
<tr>
<td>WHR</td>
<td><strong>0.4526</strong></td>
<td><strong>0.4022</strong></td>
<td><strong>-0.5807</strong></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td><strong>0.9331</strong></td>
<td>0.2478</td>
<td>-0.0169</td>
</tr>
<tr>
<td>Resistance (ohms)</td>
<td>-0.2480</td>
<td><strong>-0.5614</strong></td>
<td>-0.1912</td>
</tr>
<tr>
<td>Trunk-Length (cm)</td>
<td>0.0058</td>
<td><strong>0.6898</strong></td>
<td><strong>0.6568</strong></td>
</tr>
<tr>
<td>Trunk-Length%</td>
<td>0.1106</td>
<td>0.0871</td>
<td><strong>0.8599</strong></td>
</tr>
<tr>
<td>Pelvis width</td>
<td>0.2044</td>
<td><strong>0.4784</strong></td>
<td><strong>0.4415</strong></td>
</tr>
<tr>
<td>Fat Free Mass (kg)</td>
<td>-0.0028</td>
<td><strong>0.9734</strong></td>
<td>0.0793</td>
</tr>
<tr>
<td>Fat Free Mass (%)</td>
<td><strong>-0.8434</strong></td>
<td><strong>0.5157</strong></td>
<td>-0.0630</td>
</tr>
<tr>
<td>Fat Mass (kg)</td>
<td><strong>0.9795</strong></td>
<td>-0.1422</td>
<td>0.0857</td>
</tr>
<tr>
<td>Fat Percent (%)</td>
<td><strong>0.8438</strong></td>
<td><strong>-0.5131</strong></td>
<td>0.0647</td>
</tr>
<tr>
<td>Midriff Fat (kg)</td>
<td><strong>0.8441</strong></td>
<td>0.0041</td>
<td>-0.1744</td>
</tr>
<tr>
<td>Trunk Fat Mass (kg)</td>
<td><strong>0.9840</strong></td>
<td>-0.1220</td>
<td>-0.0445</td>
</tr>
<tr>
<td>Peripheral Fat Mass (kg)</td>
<td><strong>0.9342</strong></td>
<td>-0.1605</td>
<td>0.2371</td>
</tr>
<tr>
<td>Trunk: Peripheral Fat Ratio</td>
<td><strong>0.8405</strong></td>
<td>-0.1405</td>
<td>-0.3393</td>
</tr>
<tr>
<td>Aboriginal Ethnicity</td>
<td>0.0401</td>
<td>-0.1242</td>
<td><strong>-0.8469</strong></td>
</tr>
<tr>
<td>Male Gender</td>
<td>-0.3242</td>
<td><strong>0.8580</strong></td>
<td>-0.1856</td>
</tr>
<tr>
<td>Variance Explained%</td>
<td>46.6%</td>
<td>24.1%</td>
<td>14.4%</td>
</tr>
</tbody>
</table>

n=52. Variables loading at ≥0.40 (considered to be a significant correlation) shown in bold. Ethnicity, 0= non-Indigenous, 1=Aboriginal. Gender, 0=female, 1=male.
3.3.6. Accuracy and Precision of Predicted Fat Free Mass Equations: Healthy Top-Enders’ study

The accuracy and precision of fat free mass of nine previously published prediction equations in males and eleven prediction equations in females, and the data output from the Tanita bipedal bioelectrical impedance device were assessed against measured fat free mass by whole body DXA. The detailed equations are presented in Appendix Table 1.

Among non-Indigenous males (Table 3.5), the differences in measured and predicted fat free mass were all normally distributed. Several prediction equations (A, B, C, F, H, I, J) demonstrated high concordance correlation coefficients (a measure of both precision and accuracy) in non-Indigenous males, in particular Equation I had the smallest absolute difference and narrow 95% limits of agreement.
Table 3.5  Agreement of Measured Fat Free Mass and Fat Free Mass Predicted from several Published Equations using Bioelectrical Impedance Analysis in non-Indigenous Males.

<table>
<thead>
<tr>
<th>Non-Indigenous Males (n=10)</th>
<th>Fat free Mass Mean (SD) (kg)</th>
<th>CV (%)</th>
<th>$\rho_c$ (p value)</th>
<th>Difference ** Mean (SD) (kg)</th>
<th>95% LOA (kg)</th>
<th>Pearson’s Correlation Coefficient r (p)</th>
<th>Paired T-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFM (DXA)</td>
<td>58.9 (8.0)</td>
<td>13.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ht$^2$/R</td>
<td>64.8 (13.7)</td>
<td>21.1</td>
<td>0.625 (0.000)</td>
<td>5.9 (8.3)</td>
<td>-10.5, 22.3</td>
<td>0.83 (0.003)</td>
<td>0.052</td>
</tr>
<tr>
<td>Tanita FFM *</td>
<td>59.8 (24.7)</td>
<td>41.3</td>
<td>0.465 (0.001)</td>
<td>-0.4 (19.0)</td>
<td>-37.6, 36.7</td>
<td>0.80 (0.029)</td>
<td>0.954</td>
</tr>
<tr>
<td>Equation A</td>
<td>59.2 (11.0)</td>
<td>18.6</td>
<td>0.816 (0.000)</td>
<td>0.3 (5.8)</td>
<td>-11.1, 11.7</td>
<td>0.86 (0.001)</td>
<td>0.871</td>
</tr>
<tr>
<td>Equation B</td>
<td>58.0 (8.7)</td>
<td>14.9</td>
<td>0.871 (0.000)</td>
<td>-1.0 (4.1)</td>
<td>-9.0, 7.1</td>
<td>0.88 (0.001)</td>
<td>0.477</td>
</tr>
<tr>
<td>Equation C</td>
<td>60.6 (10.2)</td>
<td>16.8</td>
<td>0.849 (0.000)</td>
<td>1.7 (4.8)</td>
<td>-7.6, 11.0</td>
<td>0.89 (0.001)</td>
<td>0.286</td>
</tr>
<tr>
<td>Equation F</td>
<td>61.7 (11.2)</td>
<td>18.1</td>
<td>0.825 (0.000)</td>
<td>2.7 (5.1)</td>
<td>-7.2, 12.7</td>
<td>0.91 (0.000)</td>
<td>0.122</td>
</tr>
<tr>
<td>Equation G</td>
<td>65.7 (12.6)</td>
<td>19.2</td>
<td>0.679 (0.000)</td>
<td>6.8 (6.0)</td>
<td>-5.0, 18.6</td>
<td>0.93 (0.000)</td>
<td>0.006</td>
</tr>
<tr>
<td>Equation H</td>
<td>59.1 (10.3)</td>
<td>17.4</td>
<td>0.903 (0.000)</td>
<td>0.2 (4.0)</td>
<td>-7.7, 8.1</td>
<td>0.93 (0.000)</td>
<td>0.893</td>
</tr>
<tr>
<td>Equation I</td>
<td>57.2 (9.0)</td>
<td>15.7</td>
<td>0.903 (0.000)</td>
<td>-1.7 (3.3)</td>
<td>-8.2, 4.8</td>
<td>0.93 (0.000)</td>
<td>0.132</td>
</tr>
<tr>
<td>Equation J</td>
<td>59.9 (9.5)</td>
<td>15.9</td>
<td>0.910 (0.000)</td>
<td>0.9 (3.6)</td>
<td>-6.1, 8.0</td>
<td>0.93 (0.000)</td>
<td>0.430</td>
</tr>
</tbody>
</table>

$\rho_c$ is Lin’s concordance correlation coefficient. LOA, limits of Agreement. **Differences refers to Measured minus predicted fat free mass (kg) expressed as mean (standard deviation). * Tanita FFM: in non-Indigenous males (n=7): FFM (measured) =*FFM 60.26 (7.8).
This contrasted with Aboriginal males (shown in Table 3.6), where a normal distribution of differences between measured and predicted fat free mass was observed in only four prediction equations. Only 2 prediction equations (H and I) demonstrated accuracy and agreement in predicted fat free mass in Aboriginal males, though the difference and limits of agreement were not as small as non-Indigenous males.
### Table 3.6 Agreement of Measured Fat Free Mass and Fat Free Mass Predicted from Several Published Equations using Bioelectrical Impedance Analysis in Aboriginal Males

<table>
<thead>
<tr>
<th>Aboriginal Males (n=15)</th>
<th>Fat free Mass Mean (SD) (kg)</th>
<th>CV (%)</th>
<th>$\rho_c$ (p value)</th>
<th>Difference ** Mean (SD) (kg)</th>
<th>95% LOA (kg)</th>
<th>Pearson’s Correlation Coefficient r (p)</th>
<th>Paired T-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFM (DXA)</td>
<td>53.58 (7.79)</td>
<td>14.5</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Ht^2/R$</td>
<td>63.30 (29.6)</td>
<td>46.7</td>
<td>0.260 (0.017)</td>
<td>9.7 (25.8)</td>
<td>-40.8, 60.3</td>
<td>0.58 (0.022)</td>
<td>0.167</td>
</tr>
<tr>
<td>Tanita FFM *¤</td>
<td>54.89 (9.87)</td>
<td>18.0</td>
<td>0.624 (0.004)</td>
<td>3.2 (7.2)</td>
<td>-10.9, 17.4</td>
<td>0.69 (0.040)</td>
<td>0.216</td>
</tr>
<tr>
<td>Equation A¤</td>
<td>56.94 (21.4)</td>
<td>37.6</td>
<td>0.399 (0.002)</td>
<td>3.3 (17.5)</td>
<td>-31.0, 37.6</td>
<td>0.63 (0.011)</td>
<td>0.479</td>
</tr>
<tr>
<td>Equation B¤</td>
<td>55.93 (15.8)</td>
<td>28.3</td>
<td>0.503 (0.001)</td>
<td>2.3 (12.3)</td>
<td>-21.8, 26.5</td>
<td>0.65 (0.009)</td>
<td>0.473</td>
</tr>
<tr>
<td>Equation C¤</td>
<td>57.37 (17.1)</td>
<td>29.7</td>
<td>0.503 (0.000)</td>
<td>3.8 (12.9)</td>
<td>-21.6, 29.1</td>
<td>0.69 (0.004)</td>
<td>0.277</td>
</tr>
<tr>
<td>Equation D¤</td>
<td>58.78 (19.0)</td>
<td>32.3</td>
<td>0.454 (0.001)</td>
<td>5.2 (14.7)</td>
<td>-23.6, 34.0</td>
<td>0.69 (0.004)</td>
<td>0.193</td>
</tr>
<tr>
<td>Equation G</td>
<td>58.39 (12.4)</td>
<td>21.2</td>
<td>0.674 (0.000)</td>
<td>4.8 (7.3)</td>
<td>-9.5, 19.1</td>
<td>0.83 (0.000)</td>
<td>0.023</td>
</tr>
<tr>
<td>Equation H</td>
<td>52.94 (10.6)</td>
<td>20.0</td>
<td>0.800 (0.000)</td>
<td>-0.6 (5.8)</td>
<td>-12.1, 10.8</td>
<td>0.84 (0.000)</td>
<td>0.678</td>
</tr>
<tr>
<td>Equation I</td>
<td>53.3 (12.4)</td>
<td>23.3</td>
<td>0.692 (0.000)</td>
<td>-0.3 (8.1)</td>
<td>-16.2, 15.7</td>
<td>0.77 (0.001)</td>
<td>0.898</td>
</tr>
<tr>
<td>Equation J</td>
<td>56.30 (13.5)</td>
<td>23.9</td>
<td>0.632 (0.000)</td>
<td>2.7 (9.2)</td>
<td>-15.2, 20.6</td>
<td>0.75 (0.001)</td>
<td>0.271</td>
</tr>
</tbody>
</table>

$\rho_c$ is Lin’s concordance correlation coefficient. LOA, limits of Agreement. **Differences refers to Measured minus predicted fat free mass (kg) expressed as mean (sd). Differences are not normally distributed (therefore prediction equation will not be accurate). * Tanita FFM: in Aboriginal males (n=9): FFM (measured) = *FFM 51.7 (7.8).
All equations tested showed poor agreement in females in both ethnic groups ($\rho_c<0.55$ in all equations for females) (shown in Table 3.7 and Table 3.8). In particular, all prediction equations over-predicted fat free mass in Aboriginal females (Table 3.7).
Table 3.7 Agreement of Measured Fat Free Mass and Fat Free Mass Predicted from Several Published Equations using Bioelectrical Impedance Analysis in Aboriginal females.

<table>
<thead>
<tr>
<th>Aboriginal Females (n=16)</th>
<th>Fat free Mass Mean (SD) (kg)</th>
<th>CV (%)</th>
<th>( \rho_c ) (p value)</th>
<th>Difference ** Mean (SD) (kg)</th>
<th>95% LOA (kg)</th>
<th>Pearson’s Correlation Coefficient ( r ) (p)</th>
<th>Paired T-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFM (DXA)</td>
<td>35.2 (5.5)</td>
<td>15.5</td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Ht(^2/R)</td>
<td>52.2 (37.8)</td>
<td>72.5</td>
<td>0.149 (0.015)</td>
<td>17.0 (34.6)</td>
<td>-50.8, 84.8</td>
<td>0.64 (0.008)</td>
<td>0.069</td>
</tr>
<tr>
<td>Tanita FFM *</td>
<td>42.2 (3.9)</td>
<td>9.2</td>
<td>0.442 (0.000)</td>
<td>5.8 (2.6)</td>
<td>0.8, 10.8</td>
<td>0.87 (0.000)</td>
<td>0.000</td>
</tr>
<tr>
<td>Equation A ( \hat{=} )</td>
<td>49.0 (30.5)</td>
<td>62.2</td>
<td>0.183 (0.013)</td>
<td>13.8 (27.3)</td>
<td>-39.7, 67.3</td>
<td>0.64 (0.007)</td>
<td>0.061</td>
</tr>
<tr>
<td>Equation B ( \hat{=} )</td>
<td>46.4 (20.1)</td>
<td>43.4</td>
<td>0.261 (0.009)</td>
<td>11.2 (16.9)</td>
<td>-22.0, 44.3</td>
<td>0.68 (0.004)</td>
<td>0.018</td>
</tr>
<tr>
<td>Equation C ( \hat{=} )</td>
<td>50.7 (25.3)</td>
<td>49.9</td>
<td>0.198 (0.015)</td>
<td>15.5 (22.0)</td>
<td>-27.7, 58.7</td>
<td>0.67 (0.005)</td>
<td>0.013</td>
</tr>
<tr>
<td>Equation D ( \hat{=} )</td>
<td>49.5 (20.9)</td>
<td>42.5</td>
<td>0.242 (0.008)</td>
<td>14.0 (17.4)</td>
<td>-20.2, 48.1</td>
<td>0.72 (0.002)</td>
<td>0.006</td>
</tr>
<tr>
<td>Equation E ( \hat{=} )</td>
<td>44.9 (11.8)</td>
<td>26.3</td>
<td>0.348 (0.003)</td>
<td>9.7 (8.7)</td>
<td>-7.3, 26.7</td>
<td>0.73 (0.001)</td>
<td>0.001</td>
</tr>
<tr>
<td>Equation F ( \hat{=} )</td>
<td>50.3 (23.4)</td>
<td>46.6</td>
<td>0.203 (0.017)</td>
<td>15.1 (20.3)</td>
<td>-24.7, 54.8</td>
<td>0.65 (0.006)</td>
<td>0.010</td>
</tr>
<tr>
<td>Equation G</td>
<td>45.2 (9.2)</td>
<td>20.4</td>
<td>0.384 (0.000)</td>
<td>10.0 (5.5)</td>
<td>-0.8, 20.7</td>
<td>0.84 (0.000)</td>
<td>0.000</td>
</tr>
<tr>
<td>Equation H</td>
<td>41.4 (7.8)</td>
<td>18.9</td>
<td>0.543 (0.000)</td>
<td>6.2 (4.4)</td>
<td>-2.3, 14.8</td>
<td>0.84 (0.000)</td>
<td>0.000</td>
</tr>
<tr>
<td>Equation I</td>
<td>46.6 (14.8)</td>
<td>33.0</td>
<td>0.354 (0.002)</td>
<td>9.7 (11.2)</td>
<td>-12.2, 31.6</td>
<td>0.766 (0.001)</td>
<td>0.003</td>
</tr>
<tr>
<td>Equation J</td>
<td>44.9 (15.8)</td>
<td>35.1</td>
<td>0.337 (0.003)</td>
<td>9.7 (12.3)</td>
<td>-14.4, 33.7</td>
<td>0.74 (0.001)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

\( \rho_c \) is Lin’s concordance correlation coefficient. LOA: limits of Agreement. **Differences refers to Measured minus predicted fat free mass (kg) expressed as mean (standard deviation). \( \hat{=} \) differences are not normally distributed (therefore prediction equation will not be accurate). * Tanita FFM: in Aboriginal females (n=12) FFM (measured)= *FFM 36.4 (5.1).
Table 3.8 Agreement of Measured Fat Free Mass and Fat Free Mass Predicted from Several Published Equations using Bioelectrical Impedance Analysis in non-Indigenous females.

<table>
<thead>
<tr>
<th>Non-Indigenous Females (n=11)</th>
<th>Fat free Mass Mean (SD) (kg)</th>
<th>CV (%)</th>
<th>( \rho_c ) (p value)</th>
<th>Difference ** Mean (SD) (kg)</th>
<th>95% LOA (kg)</th>
<th>Pearson’s Correlation Coefficient ( r ) (p)</th>
<th>Paired T-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFM (DXA)</td>
<td>39.8 (3.8)</td>
<td>9.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ht²/R ※</td>
<td>50.9 (17.7)</td>
<td>34.9</td>
<td>0.106 (0.285)</td>
<td>11.0 (16.7)</td>
<td>-21.8, 43.8</td>
<td>0.36 (0.272)</td>
<td></td>
</tr>
<tr>
<td>Tanita FFM *</td>
<td>45.8 (4.0)</td>
<td>8.7</td>
<td>0.357 (0.056)</td>
<td>5.0 (3.1)</td>
<td>-1.2, 11.1</td>
<td>0.68 (0.063)</td>
<td>0.003</td>
</tr>
<tr>
<td>Equation A ※</td>
<td>47.9 (13.4)</td>
<td>28.0</td>
<td>0.175 (0.177)</td>
<td>8.0 (12.2)</td>
<td>-15.8, 31.9</td>
<td>0.45 (0.161)</td>
<td>0.054</td>
</tr>
<tr>
<td>Equation B ※</td>
<td>45.8 (9.6)</td>
<td>21.0</td>
<td>0.236 (0.150)</td>
<td>6.0 (8.5)</td>
<td>-10.6, 22.7</td>
<td>0.47 (0.142)</td>
<td>0.041</td>
</tr>
<tr>
<td>Equation C</td>
<td>49.9 (11.3)</td>
<td>22.7</td>
<td>0.186 (0.114)</td>
<td>10.0 (9.8)</td>
<td>-9.2, 29.2</td>
<td>0.55 (0.083)</td>
<td>0.007</td>
</tr>
<tr>
<td>Equation D</td>
<td>48.8 (10.6)</td>
<td>21.6</td>
<td>0.213 (0.096)</td>
<td>9.0 (9.0)</td>
<td>-8.6, 26.5</td>
<td>0.57 (0.069)</td>
<td>0.008</td>
</tr>
<tr>
<td>Equation E</td>
<td>47.8 (7.2)</td>
<td>15.0</td>
<td>0.233 (0.081)</td>
<td>7.9 (5.9)</td>
<td>-3.6, 19.4</td>
<td>0.58 (0.064)</td>
<td>0.012</td>
</tr>
<tr>
<td>Equation F</td>
<td>48.5 (10.4)</td>
<td>21.5</td>
<td>0.193 (0.143)</td>
<td>8.7 (9.1)</td>
<td>-9.2, 26.6</td>
<td>0.50 (0.118)</td>
<td>0.010</td>
</tr>
<tr>
<td>Equation G</td>
<td>47.5 (7.6)</td>
<td>16.0</td>
<td>0.306 (0.020)</td>
<td>7.7 (5.5)</td>
<td>-3.2, 18.5</td>
<td>0.72 (0.012)</td>
<td>0.001</td>
</tr>
<tr>
<td>Equation H</td>
<td>44.3 (6.2)</td>
<td>13.9</td>
<td>0.477 (0.005)</td>
<td>4.4 (4.2)</td>
<td>-3.7, 12.6</td>
<td>0.75 (0.008)</td>
<td>0.006</td>
</tr>
<tr>
<td>Equation I</td>
<td>45.5 (8.6)</td>
<td>18.9</td>
<td>0.342 (0.039)</td>
<td>5.6 (6.8)</td>
<td>-7.7, 18.3</td>
<td>0.64 (0.033)</td>
<td>0.021</td>
</tr>
<tr>
<td>Equation J</td>
<td>45.7 (8.3)</td>
<td>18.3</td>
<td>0.337 (0.039)</td>
<td>5.8 (6.6)</td>
<td>-7.0, 18.7</td>
<td>0.65 (0.032)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

\( \rho_c \) is Lin’s concordance correlation coefficient. LOA, limits of Agreement. **Differences refers to Measured minus predicted fat free mass (kg) expressed as mean (standard deviation). ※ differences are not normally distributed (therefore prediction equation will not be accurate).

* Tanita FFM: in non-Indigenous females (n=8) FFM (measured)= *FFM 40.85 (3.89)
3.3.7. Determinants of Fat-Free Mass in Healthy Top-Enders’ study Participants

Fat free mass was positively associated with standing height ($r=0.85$, $p<0.0001$), and inversely related to resistance ($r=-0.52$, $p=0.0001$). A multivariate model of fat free mass is presented in Table 3.9. Variables entered into the model were height, weight, resistance (measured at 50 kHz), trunk-length, pelvis-width, male-gender and Aboriginal-ethnicity. The model explained more than 92% of the variance in fat free mass, and was dependent on an interaction between male gender and weight. This model had a normal distribution of residuals, and was not subject to undue leverage or Cook’s distance from any individual.

Table 3.9 Multiple Regression Analysis of Fat Free Mass (kg) in Healthy Top-Enders’ study Participants

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Beta-coefficient (95% Confidence Interval)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>0.426 (0.274, 0.578)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.123 (0.021, 0.226)</td>
<td>0.019</td>
</tr>
<tr>
<td>Resistance (ohms)</td>
<td>-0.008 (-0.015, -0.002)</td>
<td>0.011</td>
</tr>
<tr>
<td>Male Gender</td>
<td>1.520 (-0.711, 10.148)</td>
<td>0.725</td>
</tr>
<tr>
<td>Male X Weight (kg)</td>
<td>0.146 (0.021, 0.270)</td>
<td>0.023</td>
</tr>
<tr>
<td>Constant</td>
<td>-35.45 (-61.03, -9.85)</td>
<td>0.008</td>
</tr>
<tr>
<td>Model $R^2$</td>
<td>92.4%</td>
<td></td>
</tr>
<tr>
<td>RMSE</td>
<td>3.20</td>
<td></td>
</tr>
</tbody>
</table>

Data expressed as beta coefficient (95% confidence interval), p-value; n=52. Variables entered into the model included height, weight, resistance (measured at 50 kHz), trunk-length, pelvis-width, male gender and Aboriginal ethnicity.

The results of the multiple-regression analysis reflected the findings of the factor analysis presented in Table 3.4, but was not dependent on components of skeletal frame (trunk-length or pelvis-width) or ethnicity. Factor 3 in the Principal Components Analysis identified the clustering of ethnicity with skeletal proportions;
however this was not reflected in the multivariate regression model of fat free mass above. In Factor 2, pelvis-width, trunk-length and male gender clustered with fat free mass, but again were not reflected above in the multivariate regression model of fat free mass. Trunk-length was highly related to fat free mass ($r=0.71$, $p<0.0001$), but was also highly inter-correlated with height ($r=0.86$, $p<0.0001$), hence both variables could not contribute to a valid multivariate model of fat free mass. A valid multiple regression model focussing on skeletal proportions (without standing height), was prone to undue leverage and Cook’s distance from several participants. When these individuals were dropped from the model, trunk-length percent was no longer a significant independent variable predicting fat free mass, and a valid model was therefore unable to be generated.

3.4. Discussion: Healthy Top-Enders’ study, Body Composition and Skeletal Proportions

There are three main findings in this analysis. First, Aboriginal participants had a shorter trunk-length, and longer leg-length relative to height compared with non-Indigenous participants. Second, Aboriginal females had lower bone mass, lower trunk lean mass and higher fat measures than non-Indigenous females. Third, a central pattern of weight distribution (WHR), associated with more compact trunk dimensions was characteristic of Aboriginal participants in this study.

The first finding was a shorter trunk-length, and longer leg-length relative to height in Aboriginal compared with non-Indigenous participants. This analysis has confirmed, by precise and accurate methods, the previously described linear body build of Aboriginal people (Abbie 1969; Abbie 1976; Roberts 1953). It was suggested that the compact truncal dimensions of Aboriginal people was associated with higher relative body surface area, allowing more efficient thermoregulation (Roberts 1953).

The longer relative-limb length among Aboriginal adults was due to a longer distal portion of the limb, and has been observed from childhood (Abbie 1969). In the present analysis, the longer limb-length of Aboriginal participants was due to longer
tibial lengths, which confirms these reports (Abbie 1969). Healthy European children maintain a constant proportion of skeletal growth that is observed in adulthood (Abrahamyan et al. 2008). Growth retardation in European children during World War II was associated with sparing of trunk-length, and shortening of limbs, and later development of type 2 diabetes (Davey Smith et al. 2001), whereas Aboriginal people born small for gestational age are more likely to be proportionally small (Hoy et al. 2010b). We did not assess for birth weight and age of gestation in the Healthy Top-Enders’ study.

Skeletal-width and relative limb-length impacts on body build in many populations. In lean populations, longer relative leg-length, at a similar body fat percent was associated with a lower body mass index (Deurenberg et al. 2002a; Norgan et al. 1995). The heterogeneity in body build observed within and between racial groups has been explained by differences in relative limb-lengths, width of large joints, and skeletal breadth (Deurenberg et al. 2002b; Katzmarzyk et al. 1999; Norgan et al. 1995; Snijder et al. 1999).

Norgan et al. (Norgan 1994) described a similar estimated body fat percent (by skinfold thicknesses) in Aboriginal people occurred at much lower BMI than would be expected in Caucasian populations, and suggested this was due to lower sitting height ratios of Aboriginal people (i.e. a longer relative leg-length%). Others report excellent health status of Aboriginal adults with BMI’s lower than 18 kg/m² (O’Dea et al. 1988b).

In this study of adults with a broad spectrum of BMI, factor analysis showed truncal obesity (WHR) clustered with compact skeletal dimensions of the trunk. Truncal obesity with overweight in Aboriginal people with longer relative limb-length may explain Daniel et al.’s (Daniel et al. 1999) observation of a lower prospective risk of diabetes in a Central Australian Aboriginal community in those with lower rather than higher BMI (<22.5 v <25 kg/m²).

In this study, factor analysis also showed pelvis-width clustered with fat free mass. A broad pelvis and wider joint-widths were associated with a heavier body build in Europeans (Snijder et al.1999). This study has shown Aboriginal males and females
each had equally narrow skeletal widths. This contrasted with non-Indigenous participants, where as expected, males had wider shoulder breadths and narrower pelvis-width than females. Wider joints was shown to be highly correlated with bone mineral content (Snijder et al. 1999). Differences in bone mineral content between female ethnic groups in this study will be discussed further below.

An accurate and precise model of fat free mass was produced for study participants. The components of the fat free mass model were similar to the prediction equation H (Segal et al. 1988) shown in Appendix Table 1. Equation H incorporated height, bioelectrical resistance, weight and age, was validated in an obese population of Caucasians, and published in 1988. The use of published equations is limited if the new study population (such as Healthy Top-Ender study participants) is sufficiently different to the reference study population. “Equation H” showed the most promise for males in this study. The assessment group for “Equation H” were described as obese. Healthy Top-Enders’ study participants were recruited over a spectrum of normal and overweight BMI; however the means of each male ethnic group in the present analysis satisfied the published Equation H prediction model.

The published equations were not useful in females, and specifically over-predicted fat free mass in Aboriginal women. This was not surprising since Aboriginal women, shown in this analysis by precise and detailed analysis methods, have lower trunk-lean mass (even after adjustment for height) than non-Indigenous females. Overall, the clinical usefulness of prediction equations for an individual (rather than a group) may be limited, especially if used for longitudinal follow-up of that individual, as was demonstrated by the wide differences in measured and predicted values of fat free mass.

**Aboriginal Females: Body Composition Differences and its Potential Links with Metabolic Risk**

Aboriginal females have a more unique body composition relative to non-Indigenous females, than was observed between Aboriginal and non-Indigenous males when matched for age, height and BMI. Aboriginal males had a similar pattern of fat distribution, and total and regional lean mass as non-Indigenous males. This contrasted with Aboriginal females, who after adjusting for height, had lower bone
mineral content, lower trunk-lean mass and higher central body fat measures than non-Indigenous females.

The clinical significance of 300 grams lower bone mineral content in Aboriginal females compared with non-Indigenous females, when matched for age, height and BMI in this analysis is presently unknown. Lower bone mineral content may reflect narrower skeletal dimensions and a linear body build of Aboriginal participants, though differences in pelvis-breadths between female ethnic groups did not reach statistical significance after adjustment for height. There is very little information about bone health of Australian Aboriginal people, and only a few reports describe aspects of bone health in Aboriginal children and adults (Tan et al. 2010; Vanlint et al. 2011).

Aboriginal females as a group had similar fasting insulin levels, HbA1c and HOMA score, but lower trunk lean mass compared with non-Indigenous females. Lower lean mass percent has been linked with lower insulin clearance rates in healthy adults (Yki-Jarvinen et al. 1985). Understanding the relationship between percent lean body mass and diabetes risk in adult Aboriginal people is clinically necessary due to a high burden of chronic non-communicable diseases in older Aborigines (Vos et al. 2009) but was not possible with the present study design.

Aboriginal women demonstrate a strong tendency to central weight deposition (fat mass), observed by higher: WHR, midriff fat mass, and trunk:peripheral fat mass ratio. Central obesity in Aboriginal women is widely reported across Northern and Central Australian communities (Rowley et al. 1997; Wang & Hoy 2003). Rutishauser et al. (Rutishauser et al. 1986) compared the body shape and fat distribution of 114 Aboriginal women from the remote Kimberley region of Western Australia. Women aged 20 to 30 years old had higher: mid-arm circumference, waist and hip circumferences, WHR, and truncal skin-fold thickness than younger Aboriginal women (Rutishauser et al. 1986). Our findings of central weight distribution in adult Aboriginal women are consistent with Rutishauser et al. (Rutishauser et al. 1986) and also with Piers et al. (Piers et al. 2003). They reported a higher WHR, skin-fold measures and resistance in healthy Aboriginal women compared with Caucasian women (Piers et al. 2003).
Aboriginal women in the Healthy Top-Enders’ study had a high-risk metabolic profile characterised by central obesity, higher CRP, lower HDL-cholesterol and were also more likely to currently smoke cigarettes, compared with non-Indigenous females. Low HDL-cholesterol is frequently reported among Aboriginal women (O’Neal et al. 2008) with levels often as low as in Aboriginal men (Gault et al. 1996; Wang et al. 2003). Low HDL-cholesterol is also accompanied by abdominal obesity in Indigenous Australian men and women (O’Neal et al. 2008). Chronically elevated levels of CRP in healthy women are associated with higher future risk of cardiovascular disease (Ridker et al. 1998). The relationship of inflammation and adiposity in this study group is explored further in Chapter 4.

**Limitations**

Recruiting healthy young people, particularly men, to health and lifestyle studies is difficult (Dunstan et al. 2002; Glatthaar et al. 1985; O’Dea et al. 2008). Craig et al. (Craig et al. 2003) assessed the body composition of healthy Caucasian males in Sydney, and reported similar height and lean tissue mass to our data. Their male comparator group was older than the Tongan group in their study, and selected from employees in a major university teaching hospital (Craig et al. 2003). Liberato et al. (Liberato et al. 2008) described an Australian group of healthy males aged 18 to 25 years with a wide BMI and body fat percent range, recruited from universities and fitness centres. The Healthy Top-Enders’ study participants were not recruited from fitness centres, though a number of males (both Aboriginal and non-Indigenous) participated in premier division sports (Australian Rules football, rugby, and hockey). Our findings demonstrate shorter trunk-length% of Aboriginal participants, matched for age, BMI and height. Narrowness of the skeletal frame was anticipated in this study, and clustered with Aboriginal ethnicity in the Principal Components Analysis. However differences in skeletal widths between ethnic groups were not statistically significant after adjustment for height in the present analysis. This may reflect the restricted inclusion criteria of our study (healthy and BMI matched to Aboriginal adults who were recruited first), therefore we may have inadvertently recruited Caucasian participants with a more narrow skeletal body build. This should be explored in a larger cohort.
We report ethnicity-dependent differences in central obesity in Aboriginal adults associated with the linear skeletal build. However we have not measured other lifestyle, psycho-social, environmental or socio-economic status factors that are associated with adiposity and chronic disease risk (Cunningham et al. 2008; Yusuf et al. 2004). This study group was intended to demonstrate the body build and habitus of healthy young adult Aboriginal people of the current era, who were not engaged in an elite athletic program in order to provide a perspective on an older Indigenous chronic disease population (which is described later in the thesis).

**Conclusion**

In conclusion, among young healthy adults, the tendency to preferential central obesity in Aboriginal people is strongly associated with the linear body build, characterised by shorter trunk-length for overall height. This study size was relatively small, however, has shown clinically important differences in the body composition of Aboriginal females, compared with non-Indigenous females. The present study better informs the results of many studies of Indigenous Australians with chronic diseases (such as diabetes, cardiovascular disease and chronic kidney disease) where many cardiovascular disease risk markers are increasingly manifest after 35 years old. Further study focussing on limiting weight gain in young Aboriginal adults, and minimising additional risk factors (cigarette use) may confer long-term health benefits, especially for Aboriginal women.
Chapter 4.
Healthy Top-Enders’ Study:
The Relationship of Total and Abdominal Adiposity with Adipokines in Healthy Adult Aboriginal People
4.1. Introduction

Indigenous Australians represent a group of diverse peoples who collectively are reported to have higher rates of cigarette smoking, sedentary behaviour (AIHW 2011) and chronic diseases compared with other Australians. This includes a higher prevalence of overweight and type 2 diabetes, which affects Aboriginal people and Torres Strait Islander people at younger ages than other Australians (Hoy et al. 2007; O'Dea et al. 2008; O'Neal et al. 2008). Differences in the body build and body composition between healthy Aboriginal adults and non-Indigenous adults were demonstrated in Chapter 3, using anthropometry and whole body DXA. Norgan (Norgan 1994) described healthy Australian Aboriginal people had a lower body mass index (BMI) relative to expected levels in a Caucasian comparator group, and was associated with higher skin-fold thicknesses, especially in a truncal distribution in women. This was confirmed in a more recent assessment of body composition in healthy adult Aboriginal females who although having similar BMI (<22.5 kg/m$^2$) compared with non-Indigenous females, had a higher WHR, higher sum of skin-folds, and a higher truncal skin-fold thicknesses (Piers et al. 2003). Aboriginal males had a lower BMI (22.5 v 23.8 kg/m$^2$, p<0.05) and higher WHR than non-Indigenous males, but a similar distribution of skin-folds than non-Indigenous males (Piers et al. 2003). To date these body composition differences and particularly the abdominal obesity have not been further examined by a study of detailed abdominal fat partitioning in conjunction with objectives measures of health in Indigenous Australians.

Detailed body composition studies in combination with adipokines and other biomarkers have extended the relationship of health and chronic disease risk with overweight and central obesity (Abate et al. 1995; Cartier et al. 2009; Demerath et al. 2008; Smith et al. 2001). Across several healthy populations, females are reported to have higher subcutaneous abdominal fat, and lower visceral abdominal fat than males (Demerath et al. 2007). Older age has been reported to be associated with higher visceral fat areas (VFA) in both males and females (Cartier et al. 2009; Koh et al. 2008). In Caucasians, younger people are reported to tolerate a higher waist circumference at the same intra-abdominal fat area as older people (Lemieux et al 1996), which indicates the critical threshold of visceral adipose tissue that is
associated with metabolic abnormalities is likely to change with age, or is influenced by a difference in relative subcutaneous fat mass that occurs with aging.

Numerous studies have assessed the relationship of adipokines and markers of inflammation and insulin resistance in healthy people, people with the metabolic syndrome, and those with established chronic diseases. These measures include high-sensitivity C-reactive protein (CRP), interleukin-6 (IL-6), low HDL-cholesterol, adiponectin and leptin. CRP is a non-specific marker of inflammation, produced by the liver under the influence of IL-6. Chronic low-grade elevations in CRP are linked epidemiologically with cardiovascular disease in many populations (Ridker et al. 1998). As summarised above in Chapter 1.7.1, IL-6 is reported to be secreted from both intra-abdominal and subcutaneous adipose tissue (Mohamed-Ali et al. 1997), though in the setting of morbid obesity, the secretion of IL-6 localised more from intra-abdominal fat (omentum fat) than subcutaneous adipose tissue beds (Fontana et al. 2007).

Hyper-cholesterolaemia is a major cardiovascular disease risk marker (Wilson et al. 1998), although is not a major lipid abnormality in many surveys of Aboriginal people living in remote communities (Wang et al. 2003). Aboriginal people with chronic disease show a predominant pattern of high fasting triglycerides and low HDL-cholesterol which is also accompanied by high WHR (O’Neal et al. 2008; Wang et al. 2003). This pattern of dyslipidaemia is similar to the pattern of dyslipidaemia observed in people who have diabetes.

Adiponectin is an abundantly produced protein from mature adipocytes, and has anti-inflammatory, anti-atherogenic and insulin-sensitising properties (Wiecek et al. 2007). Healthy females have higher concentrations of adiponectin compared to healthy males (Peake et al. 2005). Compared with healthy people, lower adiponectin concentrations are reported in those who have diabetes (Bluher et al. 2005; Peake et al. 2005). Several reports have shown that low adiponectin concentrations in otherwise healthy adults predicted the future development of diabetes (Heidemann et al. 2008; Krakoff et al. 2003). Compared with adiponectin, the high-molecular weight (HMW) adiponectin isoform has been reported to more strongly relate to insulin sensitivity in adults (Hara et al. 2006).
Leptin is secreted from subcutaneous adipose tissue, and other non-adipose sites (Maury et al. 2010; Zou et al. 2008). Leptin concentrations are higher in obesity, and correlate with total adiposity, (Mantzoros et al. 2011) rather than central obesity (Jenkins et al. 2001). Leptin has been linked with inflammation. In Caucasian females (compared with males), higher CRP concentrations was strongly related to fat mass, but the investigators also observed this relationship was partly explained by leptin concentrations (Rossi et al. 2012). They did not perform detailed studies of body composition or assess other adipokines, but postulated that leptin may have a role in mediating the relationship of CRP with adiposity, particularly in women (Rossi et al. 2012). Others have reported an inverse relationship of BMI (or fat mass) with the ratio of adiponectin to leptin (A:L) in otherwise healthy adult Japanese men and women (Inoue et al. 2006). It has also been suggested that the combination of both low adiponectin and high leptin levels, or a low A:L ratio indicates insulin resistance in a number of populations (Inoue et al. 2006; Mente et al. 2010).

The combined assessments of detailed body composition with adipokines and other biomarkers have not been performed in Indigenous Australians to date. Identifying healthy body shape in Indigenous Australians that incorporates the absence of biomarkers known to be associated with development of chronic disease would be of significant clinical and public health value.

**Aim**

The aim of this study was to describe total and abdominal fat mass and its relationship with inflammatory and adipose related biomarkers in young healthy adult Aboriginal people.

**4.2. Methods**

The data in this chapter includes an analysis of abdominal fat partitioning and inflammatory and adipokine-related biomarkers in the Healthy Top-Enders’ study, which was described in Chapter 2.4 and Chapter 3.2.
4.2.1. Participants
As described in Chapter 2.4.1, 52 healthy adult Aboriginal participants and non-Indigenous participants who were matched for BMI, age and gender were recruited. They each provided written and verbal consent to undertake the study.

4.2.2. Setting
Since participants underwent computed tomography (CT) and whole body DXA, participants were recruited from the Darwin area, and the study protocol was completed in Darwin, the largest city in the Northern Territory.

4.2.3. Protocol
The clinical, biochemical and body composition protocols for the Healthy Top-Enders’ study are outlined in Chapter 2.4. In brief, participants fasted for 10-12 hours prior to the morning assessment. Fasting blood tests were collected and clinical measures and detailed body composition assessments were completed through the course of 4-5 hours under the supervision of two trained researchers (JH, SG). Two non-Indigenous females did not provide sufficient blood to complete an assessment of adipokines. One male and one female Aboriginal participant did not fast for the full 10 hours, and fasting lipids, insulin and HOMA were therefore not able to be assessed.

Current smoking status was described categorically (as yes or no), and a subjective assessment of the participants time spent in vigorous physical activity was also recorded, and used in the factor analysis (described below). The methods for the inflammatory marker assays have been described in detail in Chapter 2.4.4 and for whole body DXA in Chapter 2.4.7.1.

The methodology for computed tomography in the Healthy Top-Enders’ study was briefly addressed in Chapter 2.4.7.2, and the detailed protocol is outlined below. All scans were performed by a trained radiographer at the Darwin Private Hospital, Darwin on the same day as DXA and body measures using an Aquilion 16 (Toshiba, Japan) computed tomography scanner. The protocol was written and provided by a
collaborator (Penny Speight (PS), Radiographer and Radiation Scientist, Diabetes Clinical Research Unit, St Vincent’s Hospital, Sydney) who also provided local training and supervision of the protocol.

Participants wore light weight clothing, and were examined in the supine position. Three scans were taken at the end of light expiration. A scout view was taken to determine the reference points of each CT slice. Two cross-sectional CT scans each 8 mm wide were performed, centred on the L2-L3 (see Figure 4.1 below) and L4-L5 inter-vertebral disc spaces to assess abdominal adipose tissue distribution.

![Figure 4.1 Computed Tomography of the Abdomen at L2-3, Indicating Sagittal Abdominal Diameter, and Abdominal Fat Partitioning.](image)

Each scan was obtained at 120 kv (peak), with a scanning time of 3 seconds duration at arrested expiration (at the end of light expiration) and the majority were scanned at 100 mA. Some overweight participants were scanned at higher values including two participants scanned at the maximum value of 350 mA. Images were stored on CD and analysed by a single trained operator (PS) using a Gemini workstation (GXL Host System; Phillips, the Netherlands). This analysis protocol has been previously described (Samocha-Bonet et al. 2010).
In each scan level of L2-L3 and L4-L5, the total adipose tissue area was measured by delineating manually the outer abdominal wall and then calculating the pixel distribution in this area with attenuation range –150 to –50 HU. The intra-abdominal region was defined by encircling the intra-abdominal cavity at the innermost aspect of the abdominal and oblique muscle walls surrounding the cavity and the posterior aspect of the vertebral body. The encircled area with attenuation range –150 to –50 HU was then calculated by the computer and taken as the intra-abdominal fat (IAF) area or visceral fat area (VFA). The subcutaneous fat area (SFA) was then calculated by subtracting the IAF area from the total adipose tissue area (TFA). Adipose area was calculated in mm$^2$ by the scanner-software, and divided by 100 to convert to cm$^2$. Total abdominal fat area, subcutaneous fat area and visceral fat area were reported at the level of L2-L3 and L4-L5. Sagittal abdominal diameter (SAD) of the abdomen (mm) was measured on the frozen CT image at inter-vertebral space of L2-L3 and L4-L5 in expiration (see Figure 4.1 above).

The data was returned to the investigators in a secure spreadsheet after each scan, and stored securely in the Healthy Top-Enders’ study Microsoft Access database (Microsoft Office Access 2003, Microsoft Office Professional Edition, Microsoft Corporation, Redmond, Wash, USA) at Menzies School of Health Research.

4.2.4. Statistical Analysis

Summary data for body composition and biochemical variables are presented for 52 participants. Body composition and biochemical variables were not normally distributed and described as median and inter-quartile range. Comparison of median body measures between groups were performed using the Kruskall Wallis equality of populations rank test. Comparisons of median biochemical variables were performed based on log-transformed data, using the Kruskall Wallis equality of populations rank test. The relationship of log-adiponectin concentrations with the explanatory variables body fat percent and ethnicity was performed by an analysis of covariance (ANCOVA), to determine if concentrations differed within each gender on the basis of ethnicity after correcting for body fat percent.
Median body fat percent is presented in the summary table (Table 4.1) for individuals with a BMI <22.5 kg/m$^2$, and also for participants with BMI >25 kg/m$^2$, which reflects Daniel et al.’s (Daniel et al. 1999) suggestion of BMI <22.5 kg/m$^2$ was more indicative of health in Aboriginal peoples.

Healthy adult Caucasians (aged 20-39 years old) with a BMI <25kg/m$^2$ were reported to have less than 20% and 32% body fat in males and females respectively (Gallagher et al. 2000). This threshold of less than 20% and 32% in males and females respectively is used in the current analyses to denote lean and non-lean (overweight) groups. A comparison of body composition and biomarkers in this analysis was assessed around the gender-specific body fat percent threshold using chi squared test, described by Gallagher at al. (Gallagher et al. 2000). In males, differences in body composition and biochemical markers between ethnic groups was assessed within males who had a low body fat percent (BF<20%), and between males with a high body fat percent (BF>20%), in each category a comparison was made by the chi-squared test. Differences in body composition and biochemical measures was also assessed between BF<20% v BF>20%, again compared with the chi squared test. In females, differences between ethnic groups for body composition and biochemical measures was made within the high body fat percent group (BF>32%), and compared with the chi squared test, since very few Aboriginal women had body fat percent lower than 32%.

Univariate relationships of direct and indirect measures of body composition (anthropometry, whole body DXA and CT) were assessed against log-transformed biochemical measures to examine the strongest associations of these measures in participants. A full description of these relationships is found in Appendix Table 2 and Appendix Table 3.

A multivariate regression analysis of log-adiponectin concentration was performed in 50 participants with data for adiponectin. Predictor variables were included in the initial model if they had a strong bivariate relationship with log-adiponectin concentration (based on a Pearson’s correlation coefficient $r>0.8$, $p<0.05$), or if a clinical relationship with log-adiponectin existed. Variables were retained in the model if they contributed low individual and mean variance inflation factor in the
model, had a statistically significant p value (p<0.05) or if the likelihood-ratio test was statistically significant (p<0.05) if the independent variable was removed from the model (Dupont 2009; Kirkwood et al. 2003; Long et al. 2006). Post-test analysis of the regression model included analysis of normal distribution of residuals, assessing for multi-collinearity in the model, and an assessment for the impact of leverage and Cook’s distance of individual participants with the independent variable (Dupont 2009).

A factor analysis was used to examine the clustering around fat mass and abdominal obesity based on 50 participants with data for adiponectin (Table 4.4). The Principal Component method was used to reduce the information of the many measured variables into a smaller set of “factors.” Kaiser’s criterion (eigen values >1) was used to determine the number of factors that best described the underlying relationship among variables. The extracted factors were rotated using the varimax rotation. Significant correlations were considered for variables loading at ≥0.40. The variables included in the factor analysis included measures for which the cohort displayed a range of low to high results. Due to the selection criteria of health in the study, albuminuria and HbA1c were not included in the factor analysis modelling. Due to the inter-relatedness of HOMA and insulin, HOMA was assessed in the factor analysis in preference to fasting insulin.
4.3. Results

4.3.1. Body Composition Characteristics in Healthy Top-Enders’ study Participants

Table 4.1 describes the body composition characteristics of participants. Among participants with BMI<22.5 kg/m$^2$, there was a trend for Aboriginal males to have lower body fat percent than non-Indigenous males (10 v 14%, p=0.08). Among females with a BMI<22.5 kg/m$^2$, Aboriginal females had a higher body fat percent than non-Indigenous females (38 v 25%, p=0.05). There was no statistically significant difference in body fat percent between ethnic groups (of either sex) who had a BMI $\geq$ 25 kg/m$^2$.

Aboriginal and non-Indigenous females in this study had a similar body mass index (24.1 v 23.5 kg/m$^2$, p=0.52). The strong tendency of Aboriginal females toward abdominal obesity, which was demonstrated in Chapter 3, was shown by CT to be due to higher areas of subcutaneous and visceral fat compared with non-Indigenous females. Among males, the median visceral fat areas of Aboriginal and non-Indigenous males at L2-L3 and L4-L5 were not significantly different.

Non-Indigenous males had the highest absolute median sagittal abdominal diameter (SAD) (190mm) at L2-L3 and L4-L5, though SAD was not significantly different to Aboriginal males at either inter-vertebral level. SAD was higher at the level of L2-L3 in both Aboriginal male and female participants, compared with the SAD measured at L4-L5. In contrast, SAD was similar at L2-L3 and L4-L5 inter-vertebral levels in non-Indigenous males and females respectively.
Table 4.1  Body Composition Characteristics in Healthy Top-Enders’ study Participants

<table>
<thead>
<tr>
<th></th>
<th>Aboriginal Males (n=15)</th>
<th>Non-Indigenous Males (n=10)</th>
<th>P value</th>
<th>Aboriginal Females (n=16)</th>
<th>Non-Indigenous Females (n=11)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF % if BMI &lt;22.5 kg/m²</td>
<td>10.0 (8.5, 11.0)</td>
<td>14.0 (11.0, 20.0)</td>
<td>0.08</td>
<td>38.0 (31.0, 43.0)</td>
<td>25.0 (24.0, 28.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>BF % if BMI ≥ 25 kg/m²</td>
<td>31.0 (29.0, 37.0)</td>
<td>29.0 (25.0, 30.0)</td>
<td>0.21</td>
<td>46.5 (43.0, 51.0)</td>
<td>48.0 (47.0, 53.0)</td>
<td>0.41</td>
</tr>
<tr>
<td>L2-L3 SFA (cm²)</td>
<td>56.6 (12.8, 113.0)</td>
<td>51.8 (30.0, 117.5)</td>
<td>0.41</td>
<td>191.2 (93.6, 283.1)</td>
<td>81.0 (36.4, 172.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>L2-L3 VFA (cm²)</td>
<td>31.6 (21.0, 124.0)</td>
<td>57.0 (52.2, 81.0)</td>
<td>0.15</td>
<td>43.3 (29.3, 91.0)</td>
<td>22.0 (18.0, 49.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>L4-L5 SFA (cm²)</td>
<td>133.7 (38.5, 212.0)</td>
<td>152.0 (68.6, 231.7)</td>
<td>0.22</td>
<td>302.2 (170.1, 396.8)</td>
<td>158.0 (112.0, 321.1)</td>
<td>0.10</td>
</tr>
<tr>
<td>L4-L5 VFA (cm²)</td>
<td>26.1 (17.0, 80.0)</td>
<td>49.4 (36.5, 62.0)</td>
<td>0.24</td>
<td>43.3 (34.0, 83.0)</td>
<td>31.0 (24.0, 38.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>SAD L2-L3 (mm)</td>
<td>174.5 (164.7, 226.2)</td>
<td>192.5 (178, 210.8)</td>
<td>0.51</td>
<td>188.4 (170.6, 230.1)</td>
<td>168.0 (144, 18.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>SAD L4-L5 (mm)</td>
<td>165 (149.1, 223.9)</td>
<td>190.3 (160, 201)</td>
<td>0.54</td>
<td>177.7 (168, 233.1)</td>
<td>166.8 (133.9, 194.8)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Paired T-test L2-L3 v L4-L5 | <0.01 | 0.13 | - | 0.05 | 0.98 | -

Data presented as median (inter-quartile range).  BF % = Body fat percent.  *BMI <22.5 kg/m²: number in Aboriginal and non-Indigenous Males (8, 5); Females (5, 6).  ** BMI ≥25 kg/m²: number in Aboriginal and non-Indigenous Males (5, 5); Females: (8, 3).  | Paired T-test to compares abdominal heights at level L2-L3 and L4-L5 within each group.  Anthropometric and DXA data for this group are presented above in Chapter 3.
4.3.2. Biochemical and Adipokine Characteristics of Healthy Top-Enders’ study Participants

General biochemical data for participants were described above in Table 3.2. Table 4.2 describes the adipokine profile of participants. Aboriginal females had higher IL-6 concentrations (p=0.001) than non-Indigenous females. There was no other significant difference in adipokine concentrations between females by ethnic group.

Within ethnic groups, females had higher leptin concentrations (Aboriginal, p=0.001; non-Indigenous, p=0.01) and lower A:L ratio than males (Aboriginal, p=0.001, non-Indigenous, p=0.01). Non-Indigenous females also had higher adiponectin concentrations than non-Indigenous males (p=0.03). Aboriginal females had similar adiponectin concentrations (p=0.78), but higher resistin concentrations (p=0.03) than Aboriginal males.

Overall, ethnicity did not influence concentrations of adiponectin among young healthy adults (in males, ethnicity p=0.75; in females, ethnicity p=0.35). The notable finding was that in females, 10% higher body fat percent was associated with 0.2 units lower log-adiponectin concentrations.
Table 4.2 Biochemical Characteristics of Healthy Top-Enders’ study Participants

<table>
<thead>
<tr>
<th>Biochemistry</th>
<th>Aboriginal Males (n=15)</th>
<th>Non-Indigenous Males (n=10)</th>
<th>P value</th>
<th>Aboriginal Females (n=16)</th>
<th>Non-Indigenous Females (n=11)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin (ug/ml) †</td>
<td>3.56 (3.00, 4.08)</td>
<td>3.49 (2.51, 4.05)</td>
<td>0.82</td>
<td>3.62 (2.75, 5.38)</td>
<td>4.95 (4.65, 5.23)</td>
<td>0.19</td>
</tr>
<tr>
<td>Leptin (ng/ml) †</td>
<td>1.49 (0.96, 11.25)</td>
<td>4.18 (1.25, 7.14)</td>
<td>0.85</td>
<td>26.27 (17.59, 35.52)</td>
<td>21.24 (15.95, 31.33)</td>
<td>0.57</td>
</tr>
<tr>
<td>A:L Ratio (ug/ml) †</td>
<td>2.21 (0.20, 5.46)</td>
<td>1.16 (0.44, 3.05)</td>
<td>0.62</td>
<td>0.14 (0.09, 0.24)</td>
<td>0.23 (0.18, 0.31)</td>
<td>0.23</td>
</tr>
<tr>
<td>HMW adiponectin (ug/ml) †</td>
<td>1.18 (0.78, 1.83)</td>
<td>1.26 (0.56, 2.54)</td>
<td>0.78</td>
<td>1.65 (0.79, 2.55)</td>
<td>2.03 (1.72, 2.78)</td>
<td>0.34</td>
</tr>
<tr>
<td>HMWA fraction</td>
<td>2.8 (2.1, 3.3)</td>
<td>2.85 (1.81, 5.15)</td>
<td>0.91</td>
<td>2.42 (1.78, 3.22)</td>
<td>2.39 (2.00, 2.87)</td>
<td>0.95</td>
</tr>
<tr>
<td>Resistin (ug/ml) †</td>
<td>6.47 (5.46, 9.72)</td>
<td>6.67 (5.51, 8.43)</td>
<td>1.00</td>
<td>9.68 (8.15, 13.14)</td>
<td>7.43 (6.73, 9.83)</td>
<td>0.10</td>
</tr>
<tr>
<td>IL-6 (pg/ml) †</td>
<td>2.47 (0.93, 5.80)</td>
<td>1.12 (0.75, 25.87)</td>
<td>0.51</td>
<td>4.29 (1.58, 5.73)</td>
<td>0.92 (0.84, 1.08)</td>
<td><strong>0.001</strong></td>
</tr>
</tbody>
</table>

Data presented as median (inter-quartile range). HMW(A): high molecular weight (adiponectin); A:L ratio: adiponectin:leptin ratio; HOMA: homeostasis model assessment of insulin resistance. P value: comparison of differences in biochemical measures by log-transformed data by the Kruskall-Wallis equality of populations rank test, by gender. *n=14 Aboriginal males, and n=15 Aboriginal females completed fasting blood tests. † n=9, and ‡n=10 (respectively) are numbers of non-Indigenous females completing biochemical assessments, due to difficult blood collection.
4.3.3. Comparisons by Body Fat Percent Category

Gallagher et al. (Gallagher et al. 2000) reported that healthy adult Caucasians (aged 20-39 years old) with a BMI <25kg/m$^2$ were reported to have less than 20% and 32% body fat in males and females respectively. This threshold of less than 20% and 32% in males and females respectively is used in the current analyses to describe lean and non-lean (overweight) groups.

Males with less than 20 percent body fat

In this study, nine Aboriginal males and four non-Indigenous males had less than 20 percent body fat (BF<20%). Aboriginal and non-Indigenous males with BF<20% had similar indices of leanness, indicated by body fat percent (10 v 13% p=0.24), WHR (0.84 v 0.80, p=0.28) and BMI (19.1 v 20.4 kg/m$^2$, p=0.44). However, lean Aboriginal males (BF<20%) had lower VFA compared with non-Indigenous males at L2-L3 (22 v 52 cm$^2$, p= 0.01) and L4-L5 (18 v 36 cm$^2$, trend, p= 0.09) (Figure 4.2). Lean males (BF<20%) of both ethnic groups had similarly normal biochemical indicators of health, though Aboriginal males trended to higher fasting insulin levels (4.5 v 2.0 mU/L, p=0.06).

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**Figure 4.2** Median Visceral Fat Area in Males by Ethnicity and Body Fat Percent.

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Body Composition Differences in Males with more than 20 percent Body Fat

Males from both ethnic groups with higher body fat percent (BF>20%) had higher visceral fat area than leaner counterparts (BF<20%), though the magnitude of difference in VFA was higher in Aboriginal males (Figure 4.2). Aboriginal males with BF>20% had higher WHR (0.86 v 0.84, p<0.05) and VFA (L2-L3, 129 v 22 cm², p=0.002; L4-L5, 82 v 18 cm², p=0.002) compared to Aboriginal males with BF<20% (Figure 4.2). In contrast, among non-Indigenous males, an increase of only 30 cm² (81 v 52 cm², p=0.019) at L2-L3 and 25 cm² at L4-L5 (61 v 36 cm², p=0.033) was observed between those with BF>20% compared with those with BF<20% respectively.

Biochemical Differences in Males with more than 20 percent Body Fat

Regardless of ethnicity, males with BF>20% (compared to those with BF< 20%) had higher insulin and leptin levels, and lower A:L ratios (Insulin: non-Indigenous, 8.5 v 2.0, mU/L, p=0.05; Aboriginal, 13.0 v 4.5 mU/L, p<0.01; Leptin, non-Indigenous, 6.6 v 1.0, p=0.01; Aboriginal, 13.1 v 1.1, p=0.002; A:L ratio, non-Indigenous, 0.46 v 3.36 ug/ml, p=0.02; Aboriginal, 0.18 v 4.86 ug/ml, p=0.002). Aboriginal males with BF>20% also had higher CRP concentration (6.4 v 1.1 mg/L, p=0.01) and HOMA score (3.0 v 0.9, p<0.01) than Aboriginal males with BF<20%.

Despite both groups having BF>20%, Aboriginal males had a more deranged biochemical profile than non-Indigenous males (Figure 4.3), with higher HOMA score, and higher concentrations of insulin, CRP and leptin (Aboriginal v non-Indigenous: insulin, 13.0 v 8.5 mU/L, p=0.02; HOMA score, 3.02 v 1.82, p=0.02; CRP, 6.4 v 0.8 mg/L, p=0.05; Leptin, 13.1 v 6.6 ng/ml, p=0.05).
Body Composition and Biomarker Differences in Females by Body Fat Percent

Despite five Aboriginal females and 6 non-Indigenous females having a BMI ≤ 22.5 kg/m², only two Aboriginal females and four non-Indigenous females had less than 32% body fat (BF<32%). Fourteen Aboriginal females and seven non-Indigenous females had more than 32 percent body fat (BF>32%).

Females with BF>32% had similar BMI (Aboriginal v non-Indigenous: 25.6 v 24.4 kg/m², p=0.94), WHR (Aboriginal v non-Indigenous: 0.81 v 0.79, p=0.14) and body fat percent (Aboriginal v non-Indigenous: 45% v 39% p=0.33). Despite similarly high BF%, Aboriginal females had a pattern of preferential central obesity shown by higher trunk:peripheral fat ratio (0.95 v 0.79, p=0.02) due to higher levels of both subcutaneous and visceral fat area than non-Indigenous females.

Aboriginal females with BF>32% had lower HDL-cholesterol (1.10 v 1.50 mmol/L, p=0.01) and higher IL-6 (4.29 v 1.03 pg/ml, p<0.01) and trended to lower adiponectin levels (3.29 v 5.02 ug/ml, p=0.07) than non-Indigenous females with BF>32% (Figure 4.4).
Median Biomarker Concentrations in Females with more than 32% body fat - by ethnicity-

![Graph showing HDL-cholesterol, IL-6, and Adiponectin concentrations in Aboriginal females (black solid lines) and non-Indigenous females (grey dashed lines).](image)

Aboriginal females had lower HDL-cholesterol (p=0.01), higher IL-6 (p<0.01) and trended to lower adiponectin (p=0.07).

Figure 4.4 Median Fasting concentrations of HDL-cholesterol, Interleukin-6 and Adiponectin in Females with more than 32% Body Fat

4.3.4. Bivariate Relationships

Log-CRP was positively associated with log-HOMA and log-IL-6 and negatively associated with log-HDL-cholesterol and log-adiponectin in the study group (and shown in Appendix Table 2).

Waist circumference was strongly associated with intra-abdominal fat area (L2-L3 VFA and L4-L5 VFA) in the whole group (r=0.85), and in all four gender-ethnicity groups (see Appendix Table 3). L2-L3 VFA was most strongly correlated with sagittal abdominal diameter in the whole group (all, r=0.90, p<0.0001; males: Aboriginal, non-Indigenous males: r=0.93; r=0.94. Females: Aboriginal, non-Indigenous: r=0.92; r=0.80) (Appendix Table 3).

L2-L3 VFA was strongly related to log-CRP (r=0.51, p=0.0001), adiponectin (r=-0.56, p<0.0001), and HOMA (r=0.44, p=0.001), but this was all due to Aboriginal participants (Appendix Table 4).
4.3.5. Multivariate Modelling of Log-Adiponectin

Log-adiponectin was measured in 50 participants. Thirty-eight percent of the variance in log-adiponectin among 50 healthy Aboriginal and non-Indigenous adults was predicted by L2-L3 VFA and log-CRP (shown in Table 4.3). When VFA was not included in the model of log-adiponectin, WHR in combination with log-CRP explained 37% of variance of total adiponectin. SAD (at L2-L3) was not an independent predictor of log-adiponectin when it was included in the model with either VFA or WHR.

Table 4.3 Multiple Linear Regression Analysis of Log-Adiponectin *

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Beta Coefficient (95% Confidence Interval)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP *</td>
<td>-0.083 (-0.154, -0.011)</td>
<td>0.024</td>
</tr>
<tr>
<td>L2-L3 VFA (cm²)</td>
<td>-0.003 (-0.006, -0.001)</td>
<td>0.005</td>
</tr>
<tr>
<td>Constant</td>
<td>8.461 (8.313, 8.609)</td>
<td>0.000</td>
</tr>
<tr>
<td>Model R²</td>
<td></td>
<td>38.3%</td>
</tr>
</tbody>
</table>

Data are beta coefficient (95% confidence interval). *indicates log transformed adiponectin and CRP. Completed in n=50 who provided serum to assess adipokines. Variables entered into model were log-HOMA, log-CRP, waist, WHR, L2-L3 VFA, L4-L5 VFA, gender, aboriginal ethnicity and age.

4.3.6. Factor Analysis

Bivariate analysis may be confounded by associations of other variables; therefore a factor analysis was performed to explore the clustering of body composition and biochemical variables in fifty study participants who had adiponectin data. Three factors were extracted and explained 88% of the variance in the data, shown in Table 4.4 below. Factor 1 describes the combination of both “total and abdominal obesity” (45%), factor 2 describes “fat free mass” (22%), and factor 3 describes “metabolic markers” (20%). In factor 1, the combination of both high indicators of total adiposity (fat mass, body fat percent, BMI) and abdominal adiposity (SAD, trunk fat mass and WHR) was associated with the following biochemical measures: higher HOMA, CRP, leptin and lower adiponectin. In contrast, factor 3 was characterised by the clustering of metabolic syndrome factors (WHR, insulin, CRP, IL-6 and low
adiponectin) with Aboriginal ethnicity. Notably, current smoking and HOMA almost reached significance in factor 3.

Table 4.4 Factor Analysis of Body Composition and Biochemical and Lifestyle Measures in Healthy Top-Enders’ study Participants.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Factor1 “Total &amp; Abdominal Obesity”</th>
<th>Factor2 “Fat Free Mass”</th>
<th>Factor3 “Metabolic”</th>
</tr>
</thead>
<tbody>
<tr>
<td>L3-L3 SAD (mm)</td>
<td>0.8574</td>
<td>0.2874</td>
<td>0.3369</td>
</tr>
<tr>
<td>L2-L3 VFA (cm²)</td>
<td>0.7442</td>
<td>0.3825</td>
<td>0.3215</td>
</tr>
<tr>
<td>Fat Mass (kg)</td>
<td>0.9600</td>
<td>-0.2418</td>
<td>0.0151</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>0.0333</td>
<td>0.9184</td>
<td>-0.0507</td>
</tr>
<tr>
<td>Trunk FM (kg)</td>
<td>0.9550</td>
<td>-0.2176</td>
<td>0.1332</td>
</tr>
<tr>
<td>Fat Percent (%)</td>
<td>0.8030</td>
<td>-0.5803</td>
<td>-0.0030</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.9254</td>
<td>0.1754</td>
<td>0.0733</td>
</tr>
<tr>
<td>WHR</td>
<td>0.3987</td>
<td>0.3487</td>
<td>0.6527</td>
</tr>
<tr>
<td>HOMA *</td>
<td>0.4567</td>
<td>0.0252</td>
<td>0.3798</td>
</tr>
<tr>
<td>HDL-cholesterol <em>(mmol/L)</em></td>
<td>-0.1932</td>
<td>-0.1474</td>
<td>-0.6789</td>
</tr>
<tr>
<td>Adiponectin *(ng/ml)</td>
<td>-0.4323</td>
<td>-0.3273</td>
<td>-0.4448</td>
</tr>
<tr>
<td>CRP * (mg/L)</td>
<td>0.4333</td>
<td>-0.0004</td>
<td>0.6219</td>
</tr>
<tr>
<td>IL-6 * (pg/ml)</td>
<td>-0.0328</td>
<td>-0.0624</td>
<td>0.5002</td>
</tr>
<tr>
<td>Leptin * (pg/ml)</td>
<td>0.7976</td>
<td>-0.5130</td>
<td>-0.0730</td>
</tr>
<tr>
<td>Vigorous Activity %</td>
<td>-0.0430</td>
<td>0.2499</td>
<td>-0.2194</td>
</tr>
<tr>
<td>Aboriginal Ethnicity (v non-Indigenous)</td>
<td>-0.0883</td>
<td>-0.2264</td>
<td>0.6587</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>-0.0787</td>
<td>-0.2329</td>
<td>0.3944</td>
</tr>
<tr>
<td>Male Gender</td>
<td>-0.3111</td>
<td>0.8761</td>
<td>-0.1336</td>
</tr>
<tr>
<td>Variance Explained</td>
<td>45.2</td>
<td>22.0</td>
<td>20.3</td>
</tr>
</tbody>
</table>

n=50. *log transformed. Variables loading at ≥0.40 (considered to be a significant correlation) shown in bold. Ethnicity, 0= non-Indigenous, 1=Aboriginal. Gender, 0=female, 1=male; Smoker 0=non-smoker, 1=current smoker. Vigorous Activity % refers to percent of time spent in vigorous activity per week.
4.4. Discussion: Healthy Top-Enders’ study, Abdominal Fat Partitioning and Inflammatory and Fat-related Biomarkers

Three important findings are evident from this analysis. First, the pattern of overweight observed in young adult Aboriginal people is signified by the expansion of intra-abdominal fat, with females particularly displaying android obesity. Second, despite the young adult age and similar BMI, cardio-metabolic risk was more strongly related to the burden of intra-abdominal fat in Aboriginal compared with non-Indigenous participants. Third, insulin resistance (measured by fasting HOMA) was more pronounced in Aboriginal participants, and clustered with total and intra-abdominal adiposity, and high leptin and low-adiponectin levels.

Healthy Aboriginal females of a similar age to our study group have been previously described as having higher WHR and truncal subcutaneous skin-fold thicknesses than Caucasian females (Piers et al. 2003; Rutishauser et al. 1986). In this analysis, for the first time, we show that despite the young age of Aboriginal females, the high WHR is due to expanded abdominal subcutaneous and visceral fat areas. At lower than expected BMI, Aboriginal people have comparatively higher skin-fold thicknesses (subcutaneous fat) than Caucasians (Norga 1994; Roberts 1953). As was evident in Aboriginal males in the present analysis, the capacity of subcutaneous adipose tissue to store excess lipid in overweight may become more easily saturated with smaller increments of weight gain in Aboriginal people. At low BMI (<22.5 kg/m$^2$), Aboriginal males had similar body fat percent, associated with a relatively healthy metabolic profile, but had half the intra-abdominal fat area of Caucasian males. In contrast, with higher body weight (BMI>25 kg/m$^2$), Aboriginal and Caucasian males again had similar total fat percent, but Aboriginal males had a higher intra-abdominal fat burden, and more deranged metabolic abnormalities than Caucasians. Among Aboriginal females, although very few had low body fat percent, those with high BMI (>25kg/m$^2$) show a pattern of more serious biochemical abnormalities than overweight Caucasian females. We have therefore described, for the first time, differences in the critical visceral adipose tissue threshold between Aboriginal and Caucasian people, showing clearly that Aboriginal people have low metabolic tolerance for excess body weight.
Several reports support the use of CT at more than one inter-vertebral level to confirm visceral fat area (Demerath et al. 2008; Greenfield et al. 2002). High visceral fat area was demonstrated over L2-L3 and L4-L5 in Aboriginal males and females compared with Caucasians, in addition to higher SAD at L2-L3 relative to lower in the abdomen. In Asians, abdominal height (the sagittal abdominal diameter) was strongly related to VFA, whilst the breadth of the supine abdomen (transverse abdominal diameter) more strongly associated with subcutaneous adipose (Yim et al. 2010). VFA was strongly associated with SAD and with several metabolic syndrome factors in this analysis, which is consistent with other reports (Demerath et al. 2008; Koster et al. 2010; Ohrvall et al. 2000; Wennersberg et al. 2009). Since SAD has been shown to closely correlate with VFA by this study, and in other populations (Yim et al. 2010), SAD represents an important clinical risk marker across populations who have different body compositions.

The android pattern of obesity is characterised by upper body fat deposition, rapid lipolysis and liposynthesis, hypertension and the development of premature cardiovascular disease (Vague 1956). Android obesity is usually expected in males (Kvist et al. 1988), and was only confirmed in Aboriginal females by the detailed body composition methodology used. The metabolically healthy obese phenotype in Caucasian females is characterised by lower VFA, higher SFA (at the same waist circumference) and lower triglycerides, insulin levels and higher HDL-cholesterol (Messier et al. 2010). It was suggested that in obesity, low adiponectin levels permit unsuppressed lipase activity which promotes HDL clearance (Cnop et al. 2003). In the present analysis, 14/16 Aboriginal females had more than 32 percent body fat, and eleven had a low HDL-cholesterol (< 1.29 mmol/L). Low HDL-cholesterol is a recognised cardiovascular disease risk marker (Wilson et al. 1998), and in Indigenous males and females was associated with central obesity (O'Neal et al. 2008). The NCEP definition of low HDL-cholesterol has gender-specific thresholds (NCEP ATP III 2002) which recognises that Caucasian females do not readily deposit intra-abdominal fat (as shown in our analysis) unless very overweight, or post-menopausal (Messier et al. 2010). Use of different HDL-cholesterol levels to identify risk in male and female Indigenous Australians is therefore misleading, since Aboriginal women readily deposit intra-abdominal fat, and experience higher
Cardiovascular disease burden than similarly aged Caucasian females (Wang et al. 2003).

Chronic low-grade elevations in CRP concentrations are linked with increased risk of cardiovascular disease (Kaptoge et al. 2010; Ridker et al. 1998; Ridker et al. 2002). In the present analysis, Aboriginal participants demonstrated an adverse metabolic profile, though high CRP, IL-6 and low HDL-cholesterol and adiponectin levels were more characteristic of females; in contrast high HOMA score, and insulin and CRP concentrations was more characteristic of males. Aboriginal females have a large burden of cardiovascular disease that is not predicted by traditional cardiovascular risk factors (Wang et al. 2003). Aboriginal females from a remote community showed a strong linear relationship of CRP concentration with higher BMI that was not observed in males, and was also consistent with a high community-level prevalence of cardiovascular disease (Shemesh et al. 2007). In the present analysis, CRP concentrations had a strong inverse relationship with HDL-cholesterol and adiponectin concentrations and strong positive association with VFA. Therefore abdominal obesity is an important modifiable link to cardiovascular disease risk in Aboriginal women.

Adiponectin has anti-inflammatory, anti-atherogenic and insulin-sensitising properties (Wiecek et al. 2007). Two of the three factors identified in the Principal Components Analysis in this study linked body composition with metabolic syndrome factors and low-adiponectin levels. Factor-1 described the combination of high total and abdominal obesity which clustered with low adiponectin and high leptin, HOMA and CRP levels. Factor-2 clustered Aboriginal ethnicity with abdominal obesity, high CRP, low adiponectin and low HDL-cholesterol. First Nation Canadian populations with both of these characteristics (high leptin and low adiponectin concentrations) are reported to have a higher risk of incident diabetes (Ley et al. 2008). In the present analysis, low adiponectin levels were therefore shown to associate with inflammation, vascular risk and insulin resistance in young adults. Lower adiponectin levels were reported in people with predominant visceral obesity (Kursawe et al. 2010; Spencer et al. 2011). In addition, their subcutaneous abdominal adipocytes (compared with adults with subcutaneous predominant pattern of obesity) showed lower adiponectin gene expression, pro-inflammatory
macrophage activation, abnormal adipocyte size and lipid storage capacity (Kursawe et al. 2010; Spencer et al. 2011). Abnormal subcutaneous adipocyte size and storage capacity was postulated by the investigators to promote ectopic intra-abdominal adipose deposition (Kursawe et al. 2010).

Insulin sensitivity or resistance may be influenced by several factors including body composition (Yki-Jarvinen et al. 1985), renal clearance (Charlesworth et al. 2005; Rabkin et al. 1984), diet (Johnston et al. 2010) and physical activity (Mendham et al. 2012). High HOMA score clustered with high leptin and low adiponectin concentrations in the factor analysis in the present study. Adiponectin concentration was reported to be highly related to insulin sensitivity (Bluher et al. 2005) and low A:L ratio, or low adiponectin or low HMW adiponectin concentrations were shown to strongly indicate insulin resistance (Ley et al. 2008). Higher than expected triglyceride and insulin concentrations have been previously reported among lean healthy Aboriginal populations (O'Dea et al. 1980; O'Dea et al. 1988b). In addition, a higher risk of diabetes was reported among Aboriginal people with higher rather than lower BMI (Daniel et al. 1999). The present study has identified total and abdominal adiposity was linked with high HOMA, and since high relative abdominal adiposity occurs at a relatively low BMI in Aboriginal people, provides some evidence for the higher risk of diabetes at marginally elevated BMI reported above by Daniel et al. (Daniel et al. 1999).

Sedentary behaviour may also explain some of this insulin resistance; however it was not possible in the present study to undertake dynamic studies to explore this. Among overweight, but otherwise healthy middle aged Aboriginal males, Mendham et al. (Mendham et al. 2012) showed high fasting IL-6, CRP and insulin levels while at rest, but dramatic acute anti-inflammatory and insulin sensitising response following exercise. The persistence of insulin resistance in lean Aboriginal people may have been an important survival advantage in a demanding traditional nomadic lifestyle (O’Dea et al. 1988b). It is noted that the adverse metabolic profiles characterised by low physical activity and poor quality, energy-dense foods are improved in as little as seven weeks in Aboriginal people who undertake healthy lifestyle modification (O’Dea 1984).
Limitations
A number of limitations are identified in this study. Studies involving detailed health and body composition assessments in non-athlete adults are prone to recruitment difficulties. Ideally equal numbers of Aboriginal and non-Indigenous participants were sought in our study. Kvist et al. (Kvist et al. 1988) took 10 years to collate a “healthy” Caucasian cohort to demonstrate the equivalence of a single CT slice (either L2-L3 or L4-L5) with CT volume. Others have assessed healthy participants, but over a wider age range (Carey et al. 1996), or a specific community such as a church group (Craig et al. 2003) or employment group (Ohrvall et al. 2000). Our health and body composition assessments were strengthened by limiting recruitment to a narrow age-range, confirming health (rather than relying on self-reported health) (Gallagher et al. 2000), assessing direct with indirect body composition modalities, and extending the relationship of common biochemical studies with detailed adipokines. Detailed glucose homeostasis studies, and even 2 hour glucose and insulin (post oral glucose challenge) are more sensitive to demonstrate changes in insulin sensitivity. However, research facilities which enable supervised overnight fasting and euglycaemic clamp studies are not feasible in the Northern Territory. An oral glucose tolerance test would have been useful in this analysis however the complexity of the study protocol did not permit this additional assessment. Measurement of abdominal fat volume was also not possible, due to the high clinical demand on the single MRI scanning device (servicing Northern Australia), and the ethical limitation of large radiation doses in otherwise healthy people with fat volume measures by CT. Further study of Aboriginal females with less than 32% body fat would further assist in the understanding of magnitude of metabolic changes involved with excess body fat in females.

Conclusion
In conclusion, young adult Aboriginal people (and particularly women) display a higher risk of chronic disease with modest gains in body weight, compared with non-Indigenous adults. This has been demonstrated by higher truncal body fat, intra-abdominal fat area and lower peripheral subcutaneous fat with overweight. Furthermore abnormal concentrations of insulin, HOMA, inflammatory and adipokine markers was associated with this high-risk body composition, though were notably absent (except for a trend to insulin resistance) in Aboriginal participants
with low body fat, consistent with reports of excellent health in lean Aboriginal peoples. In Aboriginal peoples, diabetes risk may therefore be driven by a body composition typified by high total and abdominal adiposity. In combination with high community levels of cigarette smoking and sedentary behaviour, the high risk body composition of young adult Aboriginal people who are overweight requires urgent attention to modify the progression of risk towards the emergence of preventable chronic diseases.
Chapter 5.
eGFR Study DXA Sub-study:
The Relationship of Body Build and Composition with Components of the Metabolic Syndrome in Indigenous Australians who participated in the eGFR Study DXA sub-study
5.1. Introduction

Aboriginal peoples and Torres Strait Islander peoples are grouped under a unifying identity as Australia’s Indigenous peoples. A high prevalence of chronic disease and chronic disease risk markers are reported in both Aboriginal and Torres Strait Islander communities, and contribute to the wide disparity in health status of adults (Vos et al. 2009). Numerous studies in larger populations and over a number of regions of Australia have used portable anthropometric tools to associate body size with chronic disease indicators, including body circumferences (waist, hip), waist: hip ratio (WHR), body mass index (BMI), and in some studies bioelectrical impedance analysis. Studies involving detailed body composition in Australia’s Aboriginal peoples and Torres Strait Islander peoples are limited to one small study involving sixteen healthy Aboriginal and Caucasian females in a university research hospital facility in Sydney (Raja et al. 2003). Although differences in body fat were shown between the groups, the results may not be applicable to other settings, including participants with chronic disease, males, other Aboriginal groups and Torres Strait Islander people. Heitmann et al. (Heitmann et al. 1997) showed that the relationship of body size and bioelectrical impedance in Aboriginal people differed compared with Torres Strait Islander and Caucasian people. Waist circumference and body mass index are simple portable tools to assess obesity, yet have not been validated against sophisticated body composition methods in Aboriginal people and Torres Strait Islander people (beyond data presented in Chapter 4). Ascertaining the appropriate thresholds for total and abdominal obesity is a health priority in many non-Caucasian populations (WHO 2000).

Objectives

The primary objective was to explore ethnicity-dependent differences in body build and body composition among Indigenous Australian adults (Aboriginal, Torres Strait Islander, and Both-ATSI), who participated in the DXA sub-study of The eGFR Study (herewith referred to as “eGFR Study DXA sub-study”). The relationships of body build and body composition with components of the metabolic syndrome in Indigenous Australians was also assessed.
5.2. Methods

5.2.1. Participants

194 people from the Top-End region of the Northern Territory and Thursday Island in Far North Queensland were recruited in The eGFR Study and also completed whole body dual energy x-ray absorptiometry (DXA). One hundred and eighty nine people were assessed, including 51 Aboriginal participants, 81 Torres Strait Islander participants, 30 Both-ATSI participants (those of mixed Aboriginal and Torres Strait Islander heritage) and 27 Caucasian participants. The following people were excluded from the analysis: four participants were non-Indigenous, and non-Caucasian, and one morbidly obese Torres Strait Islander male (BMI >60 kg/m$^2$) had an inadequate whole body scan of soft tissue regions.

Participants were compared for differences in body composition based on self-identified ethnicity, and reported ethnicity of 4 grandparents. Ethnicity was defined as:

- **“Aboriginal”** participants: self-identified as an Aboriginal person and had no Torres Strait Islander grandparents;
- **“Torres Strait Islander”** participants: self-identified as Torres Strait Islander person (TSI) and had no Aboriginal grandparents;
- **“Both Aboriginal and Torres Strait Islander (Both-ATSI)”** participants: self-identified as both Aboriginal and Torres Strait Islander. They also had grandparents who identified as Both-ATSI, or had both an Aboriginal and a Torres Strait Islander grandparent. Additionally, if a person identified as either an Aboriginal person (alone) or Torres Strait Islander person (alone), but had an Indigenous grandparent who identified in another Indigenous group, the participant was classified in the Both-ATSI group. This occurred in five participants: 3 Aboriginal males and two Torres Strait Islander females were assigned to Both-ATSI based on grandparent ethnicity.
• “Caucasian” participants: self-identified as a non-Indigenous Australian and reported four grandparents who were of Caucasian background.

• “Indigenous”: refers to a combined cohort of Aboriginal participants, Torres Strait Islander participants and Both-ATSI participants.

All participants (n=189) reported their gender and age, completed an adequately positioned and analysed whole body DXA study, and permitted measurement of their height and weight. All participants were invited (but were not obliged) to complete other measures including anthropometry, blood pressure, bioelectrical impedance analysis, urinalysis for albumin to creatinine ratio, a non-fasting blood test and a medical and social questionnaire. All five metabolic syndrome factors were assessed in 165 participants.

5.2.2. Body Composition Analysis and Other Assessments

The assessment protocol for The eGFR Study is reported in Chapter 2.3. Each adult, at least 16 years old received information about the objectives of the study, and provided written informed consent to participate. Body composition was assessed by the following measures in all participants, regardless of assessment site: height, weight, waist and hip circumference. WHR and BMI were calculated. Bioelectrical impedance analysis (BIA) was recorded by tetra-polar electrode arrangement in the supine position after minimum 5 minutes rest. The participant was requested to void prior to the BIA test. Participants were not assessed with BIA if they had a metal indwelling device, or prosthesis. The protocols for height, weight, waist and hip circumferences and bioelectrical impedance are reported in detail in Chapter 2.

A questionnaire was administered by study staff to ascertain age, gender, medical history, smoking status, self-identified ethnicity and reported ethnicity of each 4 grandparents (see Appendix 1). A rested sitting blood pressure was also recorded. Non-fasting blood tests included serum creatinine, HbA1c, non-fasting lipids and C-reactive protein (CRP). A mid-stream urine was assessed for urinary albumin to creatinine ratio (ACR). Kidney function was reported in this analysis as estimated glomerular filtration rate (eGFR) by the 4-variable modification of diet in renal
disease study (Levey et al. 1999), based on serum creatinine measured in local laboratories, which was in accordance with Australian standard clinical care (Mathew et al. 2007).

Whole body DXA was offered at two sites (Darwin and Thursday Island) in the eGFR Study DXA sub-study. In Darwin, a whole body DXA scan (Norland XR-46) was offered to all eGFR Study participants between July 2008 and May 2010. This offer was extended to participants who resided in Darwin, or to participants who lived regionally or remotely when they were visiting Darwin. A Hologic whole body DXA scanner, mounted in a transportable vehicle was transferred from Sydney to Thursday Island coinciding with an eGFR Study recruitment visit over a two week period in February 2010. Participants at each scan location underwent the same preparation, wore light-weight clothing, and were scanned using the same positioning protocols.

The method of skeletal proportions was described in detail in Chapter 2.3.7.1. Data was reported as leg-length (most superior aspect of the greater trochanter to most inferior part of malleolus), and trunk-length (defined as standing height minus leg-length). Pelvis-width was defined by the inter-trochanteric distance, measured between the most superior aspect of the left and right greater trochanter. Leg-length and pelvis-width was calculated relative to standing height, reported as leg-length percent ([leg-length (cm)/ standing height (cm)] x 100%) and pelvis-width percent of height ([pelvis width (cm)/ standing height (cm)] x 100%).

Total fat mass, lean (non-bone) mass and bone mass were described for each participant. Trunk mass (fat or lean) concerns the regions enclosing the chest, midriff and pelvis. Peripheral mass (fat or lean) concerns the regions of upper and lower limbs (excluding the buttocks and head). Trunk:peripheral fat ratio was calculated as (trunk fat mass/peripheral fat mass).

There are no published soft tissue conversion equations for Hologic to Norland available to test in this group. We were unable to assess participants on each scan device on the same day.
5.2.3. Metabolic and Inflammatory Profile

Five metabolic syndrome factors were assessed categorically (as five individual factors and as a binary outcome measure of $\geq 3$ versus $<3$ factors) to assess the relationship of total fat mass and fat distribution between ethnic groups. The protocol was based on a non-fasting blood assessment.

- Diabetes was defined as a previous diagnosis of diabetes or an HbA1c $\geq 6.5\%$ where no former diagnosis was known (American Diabetes Association (ADA) 2011; Saudek et al. 2008; Selvin et al. 2011). Diabetes status was determined in 187 participants. Two older Aboriginal females who were not assessed at a health clinic did not provide a medical history or medications list in order to classify diabetes status, and were excluded in the analysis of the metabolic syndrome.

- Low non-fasting HDL-cholesterol (NCEP ATP III 2001) was defined as less than 1.0 mmol/L regardless of gender, since low levels of HDL-cholesterol are reported in both Indigenous men and women (O’Neal et al. 2008; Shemesh et al. 2008).

- Hypertension was defined as a positive medical history of hypertension, or either a systolic blood pressure $\geq 130$ mmHg or diastolic blood pressure $\geq 85$ mmHg on the day of assessment (NCEP ATP III 2001).

- Obesity was defined as a WHR $\geq 0.90$ in males, or $\geq 0.85$ in females, or a BMI $> 30$ kg/m$^2$ (WHO 1999).

- Albuminuria was defined as ACR $\geq 2.5$ mg/mmol in males, or ACR $\geq 3.5$ mg/mmol in females (Tapp et al. 2004). There were no females who were concurrently menstruating with borderline albuminuria (3.5-5 mg/mmol).
5.2.4. Statistical Analysis

The main purpose of the analysis was to describe body composition differences between adult Aboriginal participants and adult Torres Strait Islander participants, who comprised the two largest groups in this analysis. The unadjusted observed means within ethnic groups reflects data combined for both males and females. Since ethnicity and gender impact on body composition (Gallagher et al. 2000), analysis of covariance (ANCOVA), adjusting for these variables and the interaction term ethnicity*gender was presented in summary statistics. The relationship of body composition with biochemical abnormalities was also explored, however strong conclusions are limited in this analysis since the cohort was not a population-representative sample.

Data was expressed as means (standard deviation) for age, anthropometry, DXA body composition measures, and eGFR which were all normally distributed. Biochemical variables (except eGFR) were expressed as median (inter-quartile range). Differences between groups, and assessment of biochemical data in modelling was performed using log-transformed biochemical data.

A comparison of general characteristics and biochemistry was assessed (in Table 5.1). Differences in body size, skeletal proportions and composition was assessed between ethnic groups (in Table 5.2) using ANCOVA for continuous variables, and logistic regression for categorical variables. Data was presented as unadjusted observed means for each ethnic group. The main effects of ethnicity, gender and the interaction term (ethnicity*gender) was indicated by the p-value. As age, gender, and chronic disease affect body composition, differences in body measures and composition were further assessed for the impact of eGFR, diabetes, albuminuria and age between ethnic groups, and was presented in Appendix Table 5. The main effects were examined as follows: first, if the post-estimation test showed the ethnicity*gender interaction was not statistically significant (p>0.05), the interaction term was dropped from the model, and the main effect of ethnicity independent of gender was assessed. If the interaction term was statistically significant (p<0.05), assessment of body measures between ethnic groups was assessed separately in each gender.
The relationship of WHR and BMI was investigated in males and females separately with pair-wise correlations and demonstrated by scatter plots in Figure 5.1 and Figure 5.2 for males and females respectively. Differences in skeletal proportions between groups were also described in further detail (in Chapter 5.3.3). The relationship of lean body mass and resistance was examined by multivariate regression analysis, and shown in Table 5.3 and Table 5.4.

The frequency of five metabolic syndrome factors in participants (zero to five factors, and categorically as ≥3 v <3 factors) was presented by ethnic group in Table 5.5. Logistic regression with post-estimation testing indicated the significance of ethnicity, gender and the ethnicity*gender interaction term for each metabolic syndrome factor. Logistic regression was used to assess the odds of metabolic syndrome (≥ 3 factors v <3 factors) with DXA measures of adiposity, adjusted for age, gender, ethnicity, and eGFR (shown in Table 5.6). Inflammation is highly associated with cardiovascular disease risk and the metabolic syndrome, and the relationship of log-CRP with total and central adiposity and metabolic syndrome was explored in a multivariate regression model in Table 5.7.
5.3. Results: eGFR Study DXA sub-study

5.3.1. eGFR Study DXA sub-study: General and Biochemical Characteristics of Participants

Table 5.1 shows statistically significant ethnicity-dependent differences in kidney function (eGFR), albuminuria, and concentration of HDL-cholesterol. The Caucasian group were older, had a higher proportion of males, and a lower proportion of current smokers than the three Indigenous groups. Caucasian participants had a lower eGFR than Indigenous participants. Despite a lower proportion of impaired kidney function (eGFR<60 ml/min/1.73m$^2$), Aboriginal participants had a higher median ACR (and higher proportion of albuminuria) than other groups. Females had a higher log-CRP concentration than males. The relationship of log-CRP concentration with other variables is described in more detail below (in section 5.3.9).
### Table 5.1  eGFR Study DXA sub-study: General and Biochemical Characteristics of Participants.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aboriginal (n=51)</th>
<th>Torres Strait Islander (n=81)</th>
<th>Both-ATSI (n=30)</th>
<th>Caucasian (n=27)</th>
<th>P values</th>
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</thead>
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<td>Main Effects</td>
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<td></td>
<td></td>
<td></td>
<td>Ethnicity</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.0 (15.5)</td>
<td>46.6 (16.4)</td>
<td>46.5 (14.8)</td>
<td>56.1 (15.9)</td>
<td><strong>0.0413</strong></td>
</tr>
<tr>
<td>Male Gender n (%)</td>
<td>17 (33.3)</td>
<td>35 (43.2)</td>
<td>13 (43.3)</td>
<td>20 (74.1)</td>
<td><strong>0.0119</strong></td>
</tr>
<tr>
<td>eGFR &lt;60 ml/min/1.73m² (n %)</td>
<td>8/45 (17.8)</td>
<td>11/77 (14.3)</td>
<td>3/28 (10.7)</td>
<td>13/25 (52.0)</td>
<td><strong>0.0010</strong></td>
</tr>
<tr>
<td>Albuminuria (n %)</td>
<td>21/42 (50.0)</td>
<td>21/74 (28.4)</td>
<td>5/28 (17.9)</td>
<td>11/26 (42.3)</td>
<td><strong>0.0242</strong></td>
</tr>
<tr>
<td>eGFR &gt; 60 &amp; Albuminuria (n %)</td>
<td>15/37 (40.5)</td>
<td>13/66 (19.7)</td>
<td>2/25 (8.0)</td>
<td>2/12 (16.7)</td>
<td><strong>0.0255</strong></td>
</tr>
<tr>
<td>Diabetes (n %)</td>
<td>19/49 (38.8)</td>
<td>28/81 (34.6)</td>
<td>11/30 (36.7)</td>
<td>9/27 (33.3)</td>
<td>0.9591</td>
</tr>
<tr>
<td>Current Smokers (n %)</td>
<td>14/46 (30.4)</td>
<td>19/78 (24.4)</td>
<td>11/30 (36.7)</td>
<td>2/25 (8.0)</td>
<td>0.1027</td>
</tr>
<tr>
<td><strong>Biochemistry</strong></td>
<td></td>
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</tr>
<tr>
<td>eGFR (ml/min/1.73m²) *</td>
<td>84.7 (39.1)</td>
<td>84.1 (22.5)</td>
<td>90.3 (25.2)</td>
<td>61.9 (38.6)</td>
<td><strong>0.0033</strong></td>
</tr>
<tr>
<td>HbA1c (%) *</td>
<td>6.1 (5.6, 8.0)</td>
<td>5.9 (5.5, 6.5)</td>
<td>5.9 (5.5, 6.9)</td>
<td>5.7 (5.4, 6.1)</td>
<td>0.1769</td>
</tr>
<tr>
<td>Urine ACR (mg/mmol) *</td>
<td>3.5 (0.8, 50.0)</td>
<td>1.1 (0.5, 6.7)</td>
<td>1.1 (0.5, 1.9)</td>
<td>1.7 (0.5, 29.3)</td>
<td><strong>0.0142</strong></td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L) *</td>
<td>1.10 (0.90, 1.40)</td>
<td>1.00 (0.90, 1.20)</td>
<td>1.10 (0.80, 1.40)</td>
<td>1.10 (0.90, 1.60)</td>
<td><strong>0.0097</strong></td>
</tr>
<tr>
<td>CRP (mg/L) *</td>
<td>5.0 (2.0, 7.0)</td>
<td>2.5 (1.0, 5.8)</td>
<td>3.1 (1.0, 7.2)</td>
<td>2.0 (1.0, 5.0)</td>
<td>0.2556</td>
</tr>
</tbody>
</table>

Albuminuria: ≥2.5 or 3.5 mg/mmol for males and females respectively. Anthropometry and eGFR expressed as mean (SD); Biochemistry (except eGFR) expressed as median (inter-quartile range). Comparison of unadjusted observed means by generalised linear regression method for ethnicity and gender after ethnicity*gender interaction shown to be non-significant. Aboriginal: n=45 GFR, HDL, CRP; 44 HbA1c, 42-ACR. TSL: n=77 GFR, 75-HbA1c, 74-ACR, 73 HDL, 71 CRP. Both-ATSI: n=29 HDL, all other biochemistry n=28. Caucasian: n=25- GFR, HbA1c, CRP; n=26 HDL, ACR.
5.3.2. eGFR Study DXA sub-study: Body Composition Characteristics

Ethnicity-dependent differences in body size, skeletal proportions, fat measures, and lean mass are shown in Table 5.2. Aboriginal participants had the highest body fat percent and trunk:peripheral fat ratio than the other three groups, regardless of gender.

Participants with a Torres Strait Islander background (either Torres Strait Islander or Both-ATSI) had the lowest WHR despite the highest weight, highest body mass index, and highest total and regional lean mass.

The ethnicity*gender interaction term was significant for waist circumference (p=0.02). Therefore ethnicity-dependent differences in waist circumference were assessed separately in males and females. This revealed a trend to ethnicity-dependent differences in waist circumference in females (p=0.07), but not males (p=0.23). Caucasian females had a lower waist circumference than Torres Strait Islander females and Both-ATSI females.

The ethnicity*gender interaction term was significant for hip circumference (p=0.01). Torres Strait Islander and Both-ATSI females had a higher hip circumference than Aboriginal females and Caucasian females; whereas hip circumference was similar between Aboriginal females and Caucasian females. There was no ethnicity-dependent differences in hip circumference between males (p=0.94).
### Table 5.2 eGFR Study DXA sub-study: Body Size and Composition

<table>
<thead>
<tr>
<th>Characteristics of Participants</th>
<th>Aboriginal (n=51)</th>
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<th>Caucasian (n=27)</th>
<th>P values</th>
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<td>Main Effects</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ethnicity</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.8 (8.9)</td>
<td>167.5 (8.5)</td>
<td>166.3 (10.8)</td>
<td>172.7 (7.9)</td>
<td>0.2602</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.1 (16.4)</td>
<td>89.8 (19.8)</td>
<td>88.4 (21.0)</td>
<td>83.8 (17.7)</td>
<td><strong>&lt;0.0171</strong></td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>102.5 (14.4)</td>
<td>102.6 (15.7)</td>
<td>101.8 (15.3)</td>
<td>99.5 (17.1)</td>
<td>[ ]</td>
</tr>
<tr>
<td>Hips (cm) *</td>
<td>105.6 (11.0)</td>
<td>111.3 (13.6)</td>
<td>110.0 (11.5)</td>
<td>103.2 (9.2)</td>
<td>[ ]</td>
</tr>
<tr>
<td>WHR *</td>
<td>0.97 (0.12)</td>
<td>0.92 (0.09)</td>
<td>0.92 (0.08)</td>
<td>0.96 (0.11)</td>
<td><strong>0.0055</strong></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.4 (5.1)</td>
<td>31.9 (6.5)</td>
<td>31.8 (5.9)</td>
<td>28.0 (5.4)</td>
<td>0.008</td>
</tr>
<tr>
<td>Resistance (50 kHz) *</td>
<td>560.6 (112.3)</td>
<td>468.8 (92.4)</td>
<td>472.2 (89.4)</td>
<td>477.7 (82.6)</td>
<td><strong>&lt;0.0001</strong></td>
</tr>
<tr>
<td>Fat Mass (kg)</td>
<td>32.0 (10.5)</td>
<td>28.7 (11.1)</td>
<td>29.0 (12.4)</td>
<td>28.0 (11.9)</td>
<td>0.5572</td>
</tr>
<tr>
<td>Fat Percent (%)</td>
<td>39.0 (9.4)</td>
<td>32.1 (9.0)</td>
<td>32.8 (11.0)</td>
<td>32.3 (10.3)</td>
<td><strong>&lt;0.0001</strong></td>
</tr>
<tr>
<td>Lean Mass (non bone) (kg)</td>
<td>46.9 (12.3)</td>
<td>56.8 (13.1)</td>
<td>56.0 (15.1)</td>
<td>53.3 (10.6)</td>
<td><strong>&lt;0.0001</strong></td>
</tr>
<tr>
<td>Bone Mass (kg)</td>
<td>2.79 (0.48)</td>
<td>2.66 (0.52)</td>
<td>2.82 (0.63)</td>
<td>2.91 (0.63)</td>
<td><strong>0.0370</strong></td>
</tr>
<tr>
<td>Trunk Fat Mass (kg)</td>
<td>17.6 (6.1)</td>
<td>15.4 (6.3)</td>
<td>15.5 (7.1)</td>
<td>15.2 (7.6)</td>
<td>0.4272</td>
</tr>
<tr>
<td>Peripheral Fat Mass (kg)</td>
<td>12.8 (4.5)</td>
<td>12.3 (5.1)</td>
<td>12.3 (5.5)</td>
<td>11.5 (4.4)</td>
<td>0.9140</td>
</tr>
<tr>
<td>Trunk: Peripheral Fat Ratio</td>
<td>1.53 (0.31)</td>
<td>1.28 (0.30)</td>
<td>1.30 (0.33)</td>
<td>1.37 (0.46)</td>
<td><strong>&lt;0.0001</strong></td>
</tr>
<tr>
<td>Trunk Lean (non bone) (kg)</td>
<td>20.7 (5.5)</td>
<td>27.1 (6.2)</td>
<td>26.5 (7.1)</td>
<td>25.3 (5.0)</td>
<td><strong>&lt;0.0001</strong></td>
</tr>
<tr>
<td>Peripheral Lean (non bone) (kg)</td>
<td>23.3 (6.5)</td>
<td>26.1 (6.8)</td>
<td>25.9 (7.8)</td>
<td>24.6 (5.9)</td>
<td><strong>0.0001</strong></td>
</tr>
<tr>
<td>Leg-length as % of Height</td>
<td>50.5 (1.6)</td>
<td>51.4 (1.7)</td>
<td>49.9 (1.7)</td>
<td>49.3 (1.7)</td>
<td><strong>&lt;0.0001</strong></td>
</tr>
<tr>
<td>Pelvis-width as % of Height</td>
<td>16.4 (1.0)</td>
<td>19.9 (1.4)</td>
<td>19.0 (1.7)</td>
<td>18.6 (2.1)</td>
<td><strong>&lt;0.0001</strong></td>
</tr>
</tbody>
</table>


Data expressed as mean (SD); Comparison of unadjusted observed means by generalised linear regression method for ethnicity and gender after gender-ethnicity interaction shown to be non-significant. [ ]: ethnicity*gender was significant for waist and hip circumferences, and is discussed for each gender in the following text.
5.3.3. eGFR Study DXA sub-study: Body Composition Adjusted for Age, Gender, Diabetes and indicators of Kidney Damage.

As expected, age, gender, ethnicity and indicators of chronic disease influence body size and composition in this multi-ethnic stratified chronic disease cohort. A detailed presentation of these relationships is found in Appendix Table 5.

5.3.4. eGFR Study DXA sub-study: Relationship of BMI and WHR in Participants

As outlined in the methods (Chapter 5.2.3), obesity was defined as WHR $\geq 0.9$ in males or $\geq 0.85$ in females, or a BMI $> 30$ kg/m$^2$. Half of the cohort was obese by BMI criteria alone. There was a strong positive correlation between WHR and BMI in males and females, as indicated in Figure 5.1 and Figure 5.2 respectively. The relationship of WHR and BMI was not significant in each sex-stratified ethnic group. This may have been due to small numbers of participants. When the ethnicity term was included as a covariate, it also did not explain differences in the strength of the relationship between sex-stratified groups.
Scatter Plot WHR v BMI in Males, by ethnic group
-with linear trendline-

For 78 males with complete data for five metabolic syndrome factors

Figure 5.1 eGFR Study DXA sub-study: Scatter Plot of Waist to Hip Ratio v Body Mass Index in Males, by Ethnic Group.
Scatter Plot WHR v BMI in Females, by ethnic group
-with linear trendline-

For 85 females with complete data for five metabolic syndrome factors

Figure 5.2 eGFR Study DXA sub-study: Scatter Plot of Waist to Hip Ratio v Body Mass Index in Females, by Ethnic Group.
5.3.5. eGFR Study DXA sub-study: Skeletal Proportions

Leg-length as percent of height was examined after age-adjustment, since body height diminishes with age (Masharawi et al. 2008), however comparisons of pelvis-width as percent of height was not age-adjusted between groups.

Torres Strait Islander participants had the longest age-adjusted leg-length as percent of height of the cohort, which was longer than Aboriginal participants (51.4 v 50.5%, p<0.005), and Caucasians (51 v 49%, p<0.005). Aboriginal participants had a longer age-adjusted leg-length as percent of height than Caucasians (51 v 49%, p<0.005).

Figure 5.3 displays pelvis-width as percent of height. Aboriginal participants had the narrowest pelvis-width as percent of height than other groups, (Aboriginal v Both-ATSI: 16 v 19%, p<0.05; Aboriginal v Torres Strait Islander: 16 v 20%, p<0.005); Aboriginal v Caucasian, 16 v 19%, p<0.005). Torres Strait Islander participants had the widest pelvis-width relative to height of the cohort (p<0.005 compared with Caucasian and Aboriginal participants; p<0.05 compared with Both-ATSI).

Figure 5.3  eGFR Study DXA sub-study: Differences in Pelvis Width as percent of Height by Ethnic Groups

††p<0.005 compared to Aboriginal group; †p<0.05, ††p<0.005 compared to TSI group.

Figure 5.3  eGFR Study DXA sub-study: Differences in Pelvis Width as percent of Height by Ethnic Groups
Torres Strait Islander females compared with Torres Strait Islander males, had a shorter leg-length as percent of height (51 v 52%, p=0.023) and wider pelvis-width as percent of height (20 v 19%, p=0.010). Torres Strait Islander females also had a wider pelvis-width as percent of height than Caucasian females (20 v 19%, p<0.05).

Aboriginal females had a similarly narrow pelvis-width as percent of height as Aboriginal males (16 v 17%, p>0.05). The pelvis-width as percent of height was the narrowest in Aboriginal females (Aboriginal: 17%; Caucasian 19%; Both-ATSI 19%; Torres Strait Islander 20%, all p<0.005).

5.3.6. eGFR Study DXA sub-study: Lean Body Mass and Resistance

Lean mass was associated with weight (r=0.80, p<0.0001), body mass index (r=0.49, p<0.0001), and skeletal dimensions (leg-length percent, r=0.21, p=0.0041; pelvis-width as percent of height, r=0.19, p=0.0096). Resistance was strongly and inversely related to lean mass (r=-0.79, p<0.0001), weight (r=-0.69, p<0.0001), and pelvis-width as percent of height (r=-0.30, p=0.0001) in this cohort. Resistance was not related to fat mass (r=-0.12, p>0.05).

Ethnicity, gender and diabetes had significant main effects on both resistance and lean mass (shown above in Figure 5.4). As shown in Figure 5.4, females had higher resistance than males (p<0.0001). Within gender groups, Aboriginal male and female participants had higher resistance than Torres Strait Islander male and female participants respectively.
Figure 5.4 eGFR Study DXA sub-study: Bar Graph of Differences in Resistance, presented by Ethnicity and Gender

Skeletal parameters, weight and gender were significant independent variables in the multivariate regression model of resistance in this cohort (shown in Table 5.3).

Table 5.3 eGFR Study DXA sub-study: Multivariate Regression Model of Resistance (ohms)

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Beta Coefficient (95% Confidence Interval)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>-2.84 (-3.36, -2.32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>82.2 (62.4, 102.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Leg-length as percent of height</td>
<td>6.96 (1.42, 12.50)</td>
<td>0.014</td>
</tr>
<tr>
<td>Pelvis-width as percent of height</td>
<td>-11.86 (-16.68, -7.04)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Constant</td>
<td>563.1 (294.9, 831.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model $R^2$</td>
<td>63.7%</td>
<td></td>
</tr>
</tbody>
</table>

Data are beta coefficient (95% CI). Variables entered into the model were weight, gender, ethnicity, ethnicity-gender interaction, age, eGFR, diabetes, leg-length percent and pelvis width percent.
When the model of resistance did not include skeletal parameters, ethnicity was independently associated with resistance after controlling for weight and gender. Aboriginal participants had higher resistance than the other ethnic groups. That model accounted for 62% of the variance in resistance.

In the multivariate regression model of lean mass (Table 5.4), ethnicity, resistance weight, age and gender were significantly associated with lean body mass. However skeletal dimensions, eGFR and diabetes were not independently associated with lean body mass. After adjusting for weight, resistance, age and gender, Aboriginal participants had lower lean mass than Torres Strait Islander participants (by 2.4 kg), and Both-ATSI participants (by 2.3 kg). When ethnicity was oriented for Caucasian participants as the reference group, Torres Strait Islander and Both-ATSI participants had 2.9 and 2.8 kg higher lean mass than Caucasian participants respectively. This model explained more than 90% of the variance in lean body mass in participants.

Table 5.4 eGFR Study DXA sub-study: Multivariate Regression Model of Lean Mass (kg)

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Beta Coefficient (95% Confidence Interval)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>0.395 (0.350, 0.440)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Resistance (ohms)</td>
<td>-0.024 (-0.035, -0.014)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.115 (-0.157, -0.073)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>-11.43 (-13.0, -9.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Torres Strait Islander</td>
<td>2.389 (0.603, 4.174)</td>
<td>0.009</td>
</tr>
<tr>
<td>Both-ATSI</td>
<td>2.303 (0.167, 4.438)</td>
<td>0.035</td>
</tr>
<tr>
<td>Caucasian</td>
<td>-0.503 (-2.717, 1.714)</td>
<td>0.655</td>
</tr>
<tr>
<td>Constant</td>
<td>42.06 (33.46, 50.67)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model R²</td>
<td></td>
<td>90.8%</td>
</tr>
</tbody>
</table>

Reference ethnic group is Aboriginal. Data are beta coefficient (95% CI). Variables initially included in the model: weight, resistance, ethnicity, gender, gender by ethnicity interaction, age, leg-length percent, pelvis width as percent of height, eGFR and diabetes.
5.3.7. eGFR Study DXA sub-study: Metabolic Syndrome

In the eGFR Study DXA sub-study, 165 participants (87%) provided anthropometric and medical information to assess all five metabolic syndrome factors (albuminuria, low HDL-cholesterol, obesity, hypertension and diabetes) (Table 5.5).
<table>
<thead>
<tr>
<th>Metabolic Syndrome Factors n (%)</th>
<th>Aboriginal n=42</th>
<th>Torres Strait Islander n=68</th>
<th>Both-ATSI n=28</th>
<th>Caucasian n=26</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Main effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ethnicity</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17 (40.5%)</td>
<td>23 (33.8%)</td>
<td>10 (35.7%)</td>
<td>9 (34.6%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>21 (50.0%)</td>
<td>19 (27.9%)</td>
<td>5 (17.9%)</td>
<td>11 (42.3%)</td>
<td>0.0227</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (26.2%)</td>
<td>11 (16.2%)</td>
<td>4 (14.3%)</td>
<td>5 (19.2%)</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>37 (88.1%)</td>
<td>53 (77.9%)</td>
<td>22 (78.6%)</td>
<td>19 (73.1%)</td>
<td></td>
</tr>
<tr>
<td>Low HDL-cholesterol</td>
<td>10 (23.8%)</td>
<td>30 (44.1%)</td>
<td>11 (39.3%)</td>
<td>8 (30.8%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>With 3 or more factors</td>
<td>18 (42.9%)</td>
<td>23 (33.8%)</td>
<td>9 (32.1%)</td>
<td>8 (30.8%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>0 factors (n)</td>
<td>3</td>
<td>14</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1 factor (n)</td>
<td>9</td>
<td>10</td>
<td>9</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>2 factors (n)</td>
<td>12</td>
<td>21</td>
<td>6</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>3 factors (n)</td>
<td>10</td>
<td>12</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>4 factors (n)</td>
<td>7</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>5 factors (n)</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Definitions: Diabetes- previous diagnosis of diabetes or an HbA1c≥6.5%; Albuminuria- ≥2.5 or 3.5 mg/mmol for males and females respectively; Hypertension: positive medical history of hypertension, or blood pressure ≥130/85 mmHg. Low HDL- non fasting HDL-cholesterol <1.0 mmol/L. Obesity: WHR≥0.9 or ≥0.85 in males and females respectively, or BMI≥30 kg/m². [: The ethnicity*gender interaction was significantly associated with hypertension and obesity, which were discussed for males and females separately in the text.]
Caucasian participants were more likely to be older, and had a higher proportion of male participants compared with other groups. Aboriginal participants were also older than Torres Strait Islander participants (6.1 years, p<0.05). Seventy participants (42%) had at least 3 metabolic syndrome factors. There was no significant difference in the proportions of participants with ≥3 metabolic syndrome factors, or with diabetes between ethnic groups.

Aboriginal participants had higher odds of albuminuria than Torres Strait Islander participants (p=0.02) and Both-ATSI participants (p=0.01). Aboriginal participants had higher odds of hypertension than Torres Strait Islander participants (p=0.03). Caucasians also had a higher odds of hypertension than people of a Torres Strait Islander background (v Torres Strait Islander: p=0.001; v Both-ATSI: p=0.03). There was no difference in the proportions of females with obesity between ethnic groups. However, a higher proportion of Aboriginal males were obese compared with Torres Strait Islander males (p<0.001) and compared with Caucasian males (p<0.001). There was no ethnicity-dependent difference in the proportions of people with low HDL-cholesterol. However, females had lower odds of low HDL-cholesterol concentration than males (odds 0.42, 95% CI: 0.24, 0.89).

5.3.8. eGFR Study DXA sub-study: Relationship of Metabolic Syndrome with Body Size and Composition

The relationship of metabolic syndrome (the presence of ≥3 factors) with DXA indicators of adiposity, age and eGFR was examined with bivariate analysis and logistic regression.

In bivariate analysis, metabolic syndrome was significantly associated with (unadjusted odds ratio (95% confidence interval)): eGFR 0.98 (0.97, 0.99); age, 1.08 (1.05, 1.11); fat mass 1.06 (1.03, 1.09); trunk fat mass 1.13 (1.07, 1.20); and trunk:peripheral fat ratio 16.57 (5.44, 50.47). Metabolic syndrome was not related to peripheral fat mass (p>0.05).

As shown in Table 5.6, older age and lower eGFR were associated with a higher odds of metabolic syndrome when assessed in separate logistic regression models
with fat mass, trunk fat mass and trunk:peripheral fat ratio respectively. In adjusted analysis, the odds of metabolic syndrome increased by 1.10 (95% CI: 1.03, 1.18) for every 1 kg increase in trunk fat mass, and also increased by 8.67 (95% CI: 2.54, 25.60) for every unit increase trunk:peripheral fat mass ratio. Notably, trunk:peripheral fat ratio was strongly correlated with WHR in this cohort (r=0.78, p<0.0001).

Table 5.6 eGFR Study DXA sub-study: Multivariate Logistic Regression Models of Metabolic Syndrome. A model for each of Three Body Composition Measures is Presented.

<table>
<thead>
<tr>
<th>DXA body composition variable</th>
<th>Age</th>
<th>eGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat Mass</td>
<td>1.04 (1.00, 1.08)</td>
<td>1.07 (1.04, 1.10)</td>
</tr>
<tr>
<td>Trunk Fat Mass</td>
<td>1.10 (1.03, 1.18)</td>
<td>1.06 (1.03, 1.10)</td>
</tr>
<tr>
<td>Trunk: Peripheral Fat Ratio</td>
<td>8.67 (2.54, 25.60)</td>
<td>1.06 (1.03, 1.10)</td>
</tr>
</tbody>
</table>

Data are Odds ratio (95% Confidence Interval). n=162. Variables entered into the model included the DXA measure of adiposity (respectively) with age, gender, ethnicity and ethnicity*gender interaction term. Reference group for ethnicity is Aboriginal. All odds have p-value<0.05.

5.3.9. eGFR Study DXA sub-study: Relationship of log-CRP concentration with Body Composition and Metabolic Syndrome Factors

Albuminuria (log-ACR) was positively associated with age (r=0.36, p<0.0001, n=169), and as expected, was inversely related to eGFR (r=−0.42, p<0.0001).

In all participants combined, log-CRP was positively associated with log-ACR (r=0.22, p=0.01), and log-HDL-cholesterol (r=0.22, p=0.01), but was not related to age or eGFR. Females had 0.42 units higher log-CRP than males (p=0.01). Log-CRP remained positively associated with female gender, after adjusting for log-ACR. Log-CRP was strongly associated with BMI (r=0.39, p<0.0001), and waist (r=0.36, p<0.0001).
Log-CRP was also positively related to DXA measures of adiposity, in order of strength of association with trunk fat mass ($r=0.50$, $p<0.0001$); total fat mass ($r=0.49$, $p<0.0001$); peripheral fat ($r=0.43$, $p<0.0001$) and trunk:peripheral fat ratio ($r=0.20$, $p=0.01$). Females had a stronger positive relationship of log-CRP with DXA measures of adiposity than males: (trunk fat mass, $r=0.59$, $p<0.0001$; total fat mass, $r=0.55$, $p<0.0001$; peripheral fat mass, $r=0.43$, $p<0.0001$, trunk:peripheral fat ratio, $r=0.39$, $p=0.0001$).

The highest variance in log-CRP was explained (in order) by models based on trunk fat mass, total fat mass, waist circumference and trunk:peripheral fat ratio (shown in Table 5.7). Each of the four models initially included gender, and ethnicity and the ethnicity*gender interaction term, diabetes and log-ACR. The model of log-CRP was affected by multi-collinearity when log-HDL and log-ACR were both included. As albuminuria was a frequent abnormality in the cohort, log-ACR was retained in the model of log-CRP in preference to log-HDL.

Although females had a higher log-CRP than males (noted above), gender was not an independent determinant in the relationship of log-CRP with either total fat mass, and trunk fat mass. Gender was a significant determinant in models of log-CRP based on waist circumference or trunk:peripheral fat ratio.
Table 5.7 eGFR Study DXA sub-study: Multivariate regression model of log-CRP. Four models for each of four body composition measures are presented.

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>P value</th>
<th>Model 2</th>
<th>P value</th>
<th>Model 3</th>
<th>P value</th>
<th>Model 4</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat Mass</td>
<td>X</td>
<td></td>
<td>X</td>
<td>0.040</td>
<td>&lt;0.0001</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trunk Fat mass (0.054, 0.096)</td>
<td>&lt;0.001</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T:P Fat Ratio</td>
<td>X</td>
<td></td>
<td>X</td>
<td>&lt;0.001</td>
<td></td>
<td>X</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Waist (cm) (0.018, 0.038)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>X</td>
<td>0.028</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td>0.681</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>log-ACR (0.013, 0.146)</td>
<td>0.019</td>
<td>0.077</td>
<td>X</td>
<td>0.071</td>
<td>0.042</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes (-0.630, -0.033)</td>
<td>0.030</td>
<td>-0.340</td>
<td>0.018</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant (-0.361, 0.314)</td>
<td>-0.024</td>
<td>-1.983</td>
<td>&lt;0.001</td>
<td>-0.154</td>
<td>0.630</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model R²</td>
<td>27.7%</td>
<td>24.6%</td>
<td>24.0%</td>
<td>15.2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: T:P ratio refers to trunk:peripheral fat ratio. Data are beta coefficient (95% CI). Reference group is Aboriginal. Log-CRP was the dependent variable in multivariate regression modelling. Each model separately assessed the impact of fat mass, trunk fat mass, trunk to peripheral fat ratio and waist with each of the following variables: age, gender, ethnicity, ethnicity*gender interaction, diabetes, log-ACR and eGFR. Log-HDL with these variables produced significant model multi-collinearity, so was dropped, in preference to assess the impact of log-ACR.
5.4. Discussion: eGFR Study DXA sub-study

There are three important findings in this analysis. First, differences in skeletal proportions, lean mass and the distribution of body fat were demonstrated between ethnic groups, particularly between Aboriginal participants and Torres Strait Islander participants. Second, Aboriginal participants had a preferential pattern of central obesity compared with other ethnic groups of the same gender, even when adjusted for chronic disease markers. Third, total and central adiposity were strongly associated with markers of inflammation and the metabolic syndrome in this multi-ethnic adult study.

The heterogeneity of body build in Indigenous Australians was shown by distinct differences in lean mass and skeletal proportions in this analysis. In the present analysis, Torres Strait Islander participants had higher total lean mass, (and higher lean mass adjusted for body weight), yet Aboriginal participants and Torres Strait Islander participants had much longer relative leg-lengths than Caucasians. The two groups were also defined by differences in pelvis-widths (relative to height). The present analysis has confirmed Heitmann et al’s (Heitmann et al. 1997) hypothesis that differences in resistance were dependent on differences in skeletal proportions. We show that differences in skeletal proportions in this cohort were characteristic of ethnicity. Despite a more ethnically-admixed group of the present study (in comparison to the Healthy Top-Enders’ study group), the linear body build of Australian Aboriginal people (Abbie 1969; Roberts 1953) was again demonstrated by a narrow pelvis-width and longer leg-length relative to height compared with Caucasians in the present analysis. In adult females with similar height and relative limb-lengths, a broader skeletal frame was associated with higher BMI (and body weight), which as a group, distinguished First Nation Canadian from European females (Katzmarzyk et al. 1999). In European females with a similar BMI, those with a wider skeleton have lower measured-body fat percent (from underwater weighing), than would be otherwise predicted from the BMI (Snijder et al. 1999).

The Healthy Top-Enders’ study described Aboriginal participants and Caucasian participants who were matched for age, gender and body mass index (described in
Chapter 3. That study showed that shorter trunk-length percent of standing height was related to a central distribution of body weight (with weight gain), and is consistent with the findings of Aboriginal participants in the present analysis. The new finding in the present analysis was that higher skeletal breadth (than leg-length percent) more strongly indicated proportionately higher lean body mass.

Aboriginal females share more features of body build with Aboriginal males, than Torres Strait Islander females. Aboriginal participants, regardless of gender had narrow pelvis-breadth, and short trunk. In contrast, Torres Strait Islander females had slightly longer trunk-lengths and wider pelvis-breadths than Torres Strait Islander males. This difference between Aboriginal females and Torres Strait Islander females may explain why Aboriginal females have a strong tendency to central obesity, whilst Torres Strait Islander females show a more generalised pattern of obesity. Therefore Aboriginal people and Torres Strait Islander people each have a distinct body build, which in turn was distinct from Caucasian people. Defining differences in skeletal proportions was necessary to explain why body fat percent was lower in Torres Strait Islander people who otherwise had a higher BMI compared with Aboriginal participants in the present study.

Total and abdominal obesity was closely associated with cardiovascular disease risk markers in this cohort, and other populations (Yusuf et al. 2004). Fat mass is intrinsically difficult to measure independently (Ellis 2000; Wang et al. 1992), and is therefore inferred by measuring fat free mass. Valentin et al. (Valentin 2002) reported that lean mass comprised the majority of body weight in healthy non-overweight European adults. Resistance, measured with bioelectrical impedance was reported to correlate highly with skeletal mass (Janssen et al. 2000) and fat free mass (Lukaski et al. 1986). In the present analysis, more than 90% of the variance of lean mass in participants was explained by a model that included resistance, measured by bioelectrical impedance analysis, a relatively cheap, portable, safe and non-invasive body composition assessment tool. Other independent determinants of lean mass were ethnicity, gender, age and weight. Notably, eGFR and diabetes were not significant independent determinants of lean mass in the present cohort. The model prediction in the present analysis was as strong as other published models of skeletal mass in heterogeneous adult populations (Janssen et al. 2000). To reiterate from
above, in the present study group, lean mass was significantly and independently related to lower resistance. In turn, resistance was significantly and independently predicted by skeletal proportions (and pelvis-width was a stronger indicator of low resistance than leg-length%). When skeletal dimensions were included in the model of resistance, ethnicity was not significantly related; however, when skeletal dimensions were not included in the model, ethnicity was a significant independent determinant of resistance. The two models explained a similarly high variance of resistance.

Whilst all ethnic groups had a similar frequency of metabolic syndrome markers, Aboriginal participants in the present study were overweight and had a preferential central obesity compared with other groups. Others have reported that high WHR was associated with low HDL-cholesterol (O'Neal et al. 2008), or other metabolic syndrome factors (Rowley et al. 2003) in Indigenous Australians. Central obesity was also reported among Aboriginal adults who do not have chronic medical conditions (Piers et al. 2003; Rutishauser et al. 1986). Body mass index was not linearly related to WHR in Aboriginal participants in the present analysis, which is consistent with other reports: obesity-related risk between Aboriginal people and Torres Strait Islander people, and between Aboriginal groups have been more strongly identified by WHR, rather than BMI (Kondalsamy-Chennakesavan et al. 2008; Li et al. 2010). In the present study, high BMI in Torres Strait Islander participants was due to higher percent-lean mass, which distinguishes this group from Aboriginal participants. Even though the criteria for obesity in the metabolic syndrome in the present analysis was dependent on BMI or high WHR, Aboriginal males had a mean WHR>0.9 whilst their mean BMI was lower than 30 kg/m². This measure of obesity has been strongly linked with multiple metabolic syndrome factors (hypertension, diabetes and dyslipidaemia) in larger studies of Aboriginal people and Torres Strait Islander people (Li et al. 2010). In the present study, older age was associated per year with higher odds of metabolic syndrome. Whilst this study group was not population-representative, higher risks of cardiovascular and diabetes illness are reported at a younger age among Indigenous Australians than Caucasians, and this may stem from the early accumulation of intra-abdominal obesity of Aboriginal people in particular, that was demonstrated in the Healthy Top-Enders’ study (in Chapter 4).
Torres Strait Islander participants had the highest weight, body mass index, and hip girth but the lowest body fat percent in our analysis. Polynesian people (Tongans) have a body composition characterised by higher total and abdominal lean mass, associated with higher body mass index than Caucasians (Craig et al. 2003). The Tongan body build and composition bears some similarities with Torres Strait Islander participants in the eGFR Study DXA sub-study. The association of metabolic syndrome factors with body composition was not studied by Craig et al. (Craig et al. 2003), however, the relationship of hip-girth with metabolic syndrome abnormalities was reported in another multi-ethnic study by Snijder et al. (Snijder et al. 2004b). A larger hip-girth in adults without diabetes or hypertension was associated with a more favourable metabolic profile, than those with a narrower hip circumference (Snijder et al. 2004b).

The eGFR Study DXA sub-study cohort assessed adults across a spectrum of health and chronic disease within each ethnic group. Each group had a high frequency of metabolic syndrome factors. Cardiovascular disease risk has been independently associated with chronic low-grade inflammation (Ridker et al. 1998), albuminuria (Hoy et al. 2001b; Keith et al. 2004), dyslipidaemia (NCEP ATP III 2002) and central obesity (Yusuf et al. 2004). In the present analysis, log-CRP was highly inter-related with both albuminuria and low HDL-cholesterol. Log-CRP was related to DXA measures of adiposity, but was not related to DXA measures of lean mass. Rossi et al. (Rossi et al. 2012) recently reported that the different relationship of CRP levels with fat mass (determined by bioelectrical impedance) in Caucasian females (compared to males) nearly disappeared when adjusted for leptin levels. We do not report adipokines in this analysis, however the multivariate regression analysis of log-CRP using fat mass or trunk fat mass was not independently determined by gender, which may have been explained by use of precisely measured adiposity (with DXA) in the present study.

The findings of the present analysis are consistent with findings of a larger urban Indigenous Australian volunteer study of cardiovascular risk (Hodge et al. 2010). They showed CRP was inversely related to HDL-cholesterol, was higher in females,
and highly related to waist circumference, after adjusting for gender (Hodge et al. 2010).

Shen et al. (Shen et al. 2005) presented a literature review linking insulin resistance and the metabolic syndrome with kidney damage. Others report higher insulin resistance in patients with chronic kidney disease, even after adjusting for central body fat (Charlesworth et al. 2005). Aboriginal participants in this analysis were more likely to have albuminuria associated with relatively preserved GFR, which was consistent with reports in other Indigenous Australians (Maple-Brown et al. 2011). In addition, low eGFR was associated with higher odds of metabolic syndrome in the present analysis. Although participants in the present study were not population-representative, they demonstrate a high burden of cardiovascular disease risk.

The examination of metabolic syndrome in this analysis did not assess the impact of cigarette smoking, attitudes to exercise or success with diet and lifestyle modifications prior to this assessment. Finally, since indicators of chronic disease risk were shown to influence body composition (Appendix Table 5), the contribution of abdominal fat partitioning, and limb-fat, in addition to the proportion of total and central lean mass with metabolic syndrome factors warrants further investigation in larger numbers of Aboriginal people and Torres Strait Islander people.

**Strengths and Limitations of the study**

Skeletal proportions change through childhood (Abrahamyen et al. 2008), and the impact of early life nutrition may be observed in adult body size (Gunnell et al. 1998; Hoy et al. 2010b; Lawlor et al. 2002). We analysed a cohort of adults across a spectrum of health and chronic disease, and have not specifically targeted the recruitment of adults with early life nutritional deficits. Although age-related loss in trunk-length is reported in older adults without osteoporosis (Masharawi et al. 2008), the width of the skeleton should not change. The skeletal proportions and body composition observed in Aboriginal adults in the present analysis are consistent with findings of Aboriginal participants in the Healthy Top-Enders’ study (Chapter 3): they both have shorter relative trunk-height (and longer relative leg-length) for
overall height, show a narrow skeletal frame and high WHR in relation to BMI, and high trunk fat mass.

DXA has allowed precise measurement and description of the Torres Strait Islander body composition for the first time. This analysis has confirmed differences in skeletal proportions between Aboriginal people and Torres Strait Islander people, demonstrating proportionately higher lean body mass in people of Torres Strait Islander background than Aboriginal people, after adjusting for age, gender, resistance and body weight. Across populations with different body composition, this analysis has also confirmed the limitation of body mass index to indicate abdominal obesity, consistent with larger samples of Aboriginal people and Torres Strait Islander people (Li et al. 2008), and large international multi-ethnic populations (Yusuf et al. 2004).

This analysis has also demonstrated the relationship of metabolic syndrome and higher log-CRP with indicators of total and central obesity (using DXA measures or the waist circumference), which were not dependent on ethnicity. The data for Aboriginal participants in the present study is not inconsistent with a recent report by Mendham et al. (Mendham et al. 2012) of 10 overweight (but otherwise healthy) middle-aged Aboriginal males. They reported Aboriginal males with high body fat percent, WHR and BMI (respectively: 27%, 0.95, 32 kg/m²), had high biomarkers of inflammation and insulin resistance (Mendham et al. 2012).

Three limitations are identified in this analysis: first the study included a sample that was not population-representative; second, the definition of the metabolic syndrome used in the present analyses differs from the definition used in clinical practice, in that factors were measured at a single time point only in this study (rather than confirmed on repeat measurement); third, a different DXA device was used at the two study sites.

This study was conducted in a volunteer cohort, and was not intended to be a population-representative study, which was demonstrated by the similar proportion of metabolic syndrome between ethnic groups, although Caucasians had a quite different age and gender mix to the Indigenous groups. Severe kidney disease in
non-Indigenous Australians affects older people, who are more likely to be male, and who develop albuminuria in the setting of low eGFR compared with the pattern of kidney disease observed in Indigenous Australians. This reflects current differences in the median age and health burden between Indigenous and other Australians (ABS 2006; Vos et al. 2007). Chronic disease risk and anthropometry have been previously studied in Indigenous Australians, but more detailed investigations of body size have only been conducted in healthy groups (Piers et al. 2003; Raja et al. 2003). Therefore despite the limitations of this study, the findings are unique and provide a clinically valuable guide to identify high-risk adiposity in Aboriginal people and Torres Strait Islander people.

The definition of metabolic syndrome in this study differs from definitions used in clinical practice which require repeat measures over time for blood pressure and urine albumin to creatinine ratio. Several measures over time are required to clinically confirm the presence of albuminurina and hypertension. Whilst optimal, duplicate measures were not feasible in the PhD study, and this is an acknowledged limitation of research studies. Therefore this analysis is limited by the possible overestimation of rates of hypertension and albuminuria due to measurement at a single time point only.

Concern regarding the accuracy of body composition between different DXA brands has been reported (Hansen et al. 1999). Others have reported unadjusted DXA data, particularly when study sites are remote, and it was impossible to share the device between sites (Gallagher et al. 2000). There was only one whole body DXA machine available in the Northern Territory, a Norland XR 46 scanner, installed by a private company offsite from the research facility, in Darwin. There was also only one portable whole body composition scanner available in Australia in 2010 when the study visit was scheduled in Thursday Island, and no whole body scanning device in the nearest major centre to Thursday Island, Cairns, which was 2 hours flying distance away.

Total and regional fat mass using a Norland device was shown to be accurate over a wide range of adiposity against a 4-compartment body composition method in Aboriginal women (Raja et al. 2003). As mentioned above, a small study described
the biochemical abnormalities associated with overweight (using Norland DXA) in Aboriginal males (Mendham et al. 2012). Whole body DXA has never been described in a Torres Strait Islander population. Conversion equations for Hologic and Norland in a chronic disease population are not available at this time. Whilst the magnitude of fat and lean mass differences between ethnic groups may therefore be prone to bias (due to different DXA brands), the direction of difference in fat and lean mass are consistent with the direction of difference in anthropometry observed between groups.

Future studies should assess the accuracy and equivalence of different DXA devices in populations with chronic diseases. Where possible, future follow-up studies involving DXA should be performed with the same machine. Detailed body composition studies using other modalities such as computed tomography and magnetic resonance imaging are not available in Northern Australia for clinical research purposes, and if available, the high cost and/or radiation doses would have precluded assessments in such a large study population. As shown in the Healthy Top-Enders’ study (Chapter 4), differentiation of abdominal obesity to subcutaneous and visceral fat depots may have improved the prediction of metabolic syndrome factors, and better explained the higher burden of CRP in females relative to males in this cohort. Adipokines may be a useful surrogate of subcutaneous and visceral fat depots, where detailed body composition measures are not available.

**Conclusion**

In conclusion, despite a unifying identity of “Indigenous Australians”, we show different body compositions of Aboriginal compared with Torres Strait Islander participants in this study. Differences in skeletal width, despite similarities in trunk length, and an upper body fat distribution were demonstrated between Aboriginal participants and Torres Strait Islander participants, compared with Caucasian participants. Furthermore, Torres Strait Islander participants characteristically had higher relative lean mass for size than Aboriginal participants and Caucasians in the present analysis. This pattern of truncal adiposity was also more strongly associated with a higher frequency of metabolic syndrome factors in a volunteer survey across a spectrum of health and chronic disease. These results link total and central obesity
with metabolic syndrome and chronic inflammation in adult Aboriginal and Torres Strait Islander people.
Chapter 6.
The eGFR Study:
The Relationship Between Body Composition, Metabolic Syndrome and Inflammatory Markers in Adult Aboriginal and Torres Strait Islander People
6.1. Introduction: The eGFR Study

The increasing burden of insulin-resistance, metabolic syndrome and obesity throughout developed nations has been linked with an increasing burden of obesity-related kidney injury (Hunley et al. 2010; Shen et al. 2005; Wang et al. 2007). Albuminuria and low eGFR are indicators of chronic kidney disease (CKD) (Levey et al. 2011; Mathew et al. 2007). Both of these indicators are independently related to heightened cardiovascular disease risk in Aboriginal Australians and other populations (Hoy et al. 2001b; Keith et al. 2004). Keith et al. (Keith et al. 2004) advocated for interventions targeting cardiovascular disease mortality and diabetes, since they were more likely outcomes than progressive renal disease for adults with impaired kidney function.

**Albuminuria and Impaired eGFR in Indigenous Australians**

As observed in other populations (Chang et al. 2006; Thoenes et al. 2009), several investigators link albuminuria with overweight and central obesity in Indigenous Australians (Hoy et al. 2006b; Hoy et al. 2001b; Rowley et al. 2000). Albuminuria has been a more frequently reported marker of kidney damage in Indigenous Australians compared with impaired glomerular filtration rate (Hoy et al. 2001b; Maple-Brown et al. 2011). Although diabetes has been frequently observed in many Indigenous Australians (AIHW CKD 2011; Hoy et al. 2007; Leonard et al. 2002), albuminuria was often observed in individuals without diabetes (Hoy et al. 2001b). Albuminuria was also more likely to accompany multiple metabolic syndrome factors, rather than one or two factors in Aboriginal people from a remote Central Australian community (Rowley et al. 2000). However, when macroscopic albuminuria was observed, it was also more likely to be accompanied by low eGFR and subsequent kidney failure (Hoy et al. 2001b). The origins of kidney disease in Indigenous Australians were discussed in more detail in the Introduction (Chapter 1.5.1).

**Studies Linking Obesity, Metabolic Syndrome, Adipokines and Kidney Damage**

Low adiponectin and or high leptin concentrations are reported in overweight and obesity (Kursawe et al. 2010; Mantzoros et al. 2011). This combination of
adiponectin and leptin concentrations are also associated with cardio-metabolic disease (Hara et al. 2006) or incident diabetes (Ley et al. 2008) in the general population, and in groups with indicators of kidney damage (Becker et al. 2005; Looker et al. 2004).

Several studies link overweight with hyper-leptinaemia and glomerular hyperfiltration. A high burden of intra-abdominal fat was linked with glomerular hyperfiltration in a pig model of early metabolic syndrome (Li et al. 2011). Additionally, high leptin concentrations were shown to precede glomerular hyper-filtration, which in turn preceded the decline in GFR in a mouse model of early type 2 diabetes (Wei et al. 2004). Finally, Sharma et al. (Sharma et al. 2008) demonstrated the normal function of glomerular epithelial podocytes, and therefore the defence against albuminuria, was closely dependent on adequate serum adiponectin concentrations. While adiponectin and leptin concentrations are higher in the setting of impaired kidney function, activation of receptors for each adipokine has been shown to independently exert beneficial (adiponectin) and detrimental (leptin) effects in the kidney (Komura et al. 2010; Shen et al. 2007a; Shen et al. 2008; Wei et al. 2004). Obviously the beneficial effects of adiponectin at poor kidney function are not possible in the setting of hypo-adiponectinaemia.

Objective
This summary has outlined that a relationship exists between overweight and obesity, metabolic syndrome, abnormal adipokine concentrations and the risk of kidney damage. The first objective of this chapter was to describe adiponectin and leptin concentrations in adult Aboriginal people and Torres Strait Islander people with indicators of obesity and chronic disease. The second objective was to explore the relationship of adiponectin and leptin concentrations with indicators of kidney damage in adult Aboriginal people and Torres Strait Islander people.

6.2. Methods: The eGFR Study
The study was conducted in adults (minimum age 16 years), who presented for a health assessment and specialised kidney function test using plasma disappearance rate of intravenous iohexol (requiring minimum four hours), as part of The eGFR
Study. Participant information was provided in a plain language summary and with the use of local Indigenous facilitators where necessary. Written consent was provided.

Participants were recruited to the specialised kidney function test study (The eGFR Study) across pre-specified health strata as follows:

Healthy (Adults without diabetes, hypertension or albuminuria, and who have an eGFR $\geq 90$ ml/min/1.73m$^2$);

Diabetes with eGFR $\geq 90$ ml/min/1.73m$^2$;

eGFR 60-89 ml/min/1.73m$^2$

eGFR 30-59 ml/min/1.73m$^2$

eGFR <30 ml/min/1.73m$^2$

In this analysis, eGFR was calculated using the 4-variable MDRD equation (MDRD-eGFR) (Levey et al. 1999), and also by the CKD-EPI formula (CKD-EPI-eGFR) (Levey et al. 2009), based on serum creatinine measures from local laboratories.

6.2.1. Inclusion Criteria

755 participants were recorded in the eGFR Study dataset. Only Aboriginal participants and Torres Strait Islander participants are examined in this analysis (n=593). The definition of ethnicity used in Chapter 5.2.1 was also used in this analysis, as follows:

Aboriginal (n=465, 62%) refers to individuals who self-identify as an Aboriginal person, and have no Torres Strait Islander grandparents. Four participants from remote communities who self-identified as “Indigenous” and provided no details of grandparent ethnicity were assigned Aboriginal (2 in NT, 2 in WA).

Torres Strait Islander (n=128, 17%) refers to participants who self-identify as a Torres Strait Islander person, and have no Aboriginal grandparents.
6.2.2. Exclusion Criteria

We excluded other participants on the basis of ethnicity. ATSI (n=59, 7.7%) referred to participants who either identified as both Aboriginal and Torres Strait Islander, or had both an Aboriginal grandparent and a Torres Strait Islander grandparent, and were excluded from the current analysis.

Caucasian (n=103, 13%) referred to participants who self-identified as non-Indigenous and all four grandparents were of Caucasian background, and were excluded from the current analysis. An additional two participants did not provide any data to assign ethnicity and were also excluded from the analysis.

Pregnant and breastfeeding women and participants who were acutely unwell or had rapidly changing kidney function were excluded from The eGFR Study.

6.2.3. Protocol

Participants were invited to complete all components of the assessment. The assessment (attached at Appendix 2) comprised anthropometry (weight, height, and body circumferences), bioelectrical impedance analysis using supine tetra-polar arrangement of whole body right side, resting blood pressure, non-fasting blood tests and urine analysis (albumin to creatinine ratio, ACR). A medical and socio-demographic questionnaire was administered to participants regarding age, ethnic identity (of self and each of four grandparents), current medical conditions, and tobacco use (Appendix 1).

Non-fasting blood tests included concentrations of total and HDL-cholesterol, electrolytes, HbA1c, C-reactive protein (CRP), and were all performed by local pathology providers. Adiponectin and leptin concentrations were measured using enzyme linked immunosorbant assay (R&D, Minneapolis, USA) with coefficients of variation (which is the standard deviation/ average, (pg/ml)) in our laboratory of 0.10 and 0.09 respectively. Waist to hip ratio (WHR), body mass index (BMI) and adiponectin to leptin ratio (A:L ratio) were calculated.
6.2.4. Analysis

Characteristics of participants across groups are described in Table 6.1 and Table 6.2. Data are presented as mean (standard deviation) for normally distributed variables. Biochemical variables (except MDRD-eGFR) were not normally distributed, and described as median (inter-quartile range), and compared using log-transformed data. Biochemical data that was log-transformed was then exponentiated in order to present the average difference between groups. Results are described for differences between Aboriginal and Torres Strait Islander males and females separately. Comparisons between continuous and categorical variables were performed using Students t-test and chi-squared analysis respectively.

Five metabolic syndrome variables were assessed. Fasting blood tests or an oral glucose tolerance test were not available in this analysis. The definition of metabolic syndrome in this analysis was defined as three or more of the following:

- Diabetes- previous diagnosis of diabetes or an HbA1c ≥6.5% (ADA 2011; Saudek et al. 2008; Selvin et al. 2011).
- Albuminuria- ≥2.5 or 3.5 mg/mmol for males and females respectively (Tapp et al. 2004).
- Hypertension: positive medical history of hypertension, or a blood pressure ≥130/85 mmHg (NCEP ATP III 2002).
- Low non-fasting HDL-cholesterol: (NCEP ATP III 2001), <1.0mmol/L irrespective of gender (O'Neal et al. 2008).
- Obesity: WHR ≥0.9 or ≥ 0.85 in males and females respectively, or a BMI >30 kg/m² (WHO 1999).

The frequency of each metabolic syndrome categorical variable and metabolic syndrome (at least 3 factors) was assessed, and ethnic groups compared using chi-squared analysis (Table 6.1).

In the whole cohort, median concentrations of adipokines were compared using an analysis of covariance with the following covariates: ethnicity (categorical), gender (categorical), the interaction term (ethnicity*gender) and kidney function (continuous) as either log-ACR or MDRD-eGFR. The ethnicity*gender interaction
term was not significantly associated with differences in median adipokine concentrations (adiponectin, leptin or A:L ratio), and further subgroup analysis was therefore not permitted. However, higher concentrations of adipokines were significantly associated with lower kidney function in the aforementioned ANCOVA, and data for median adipokines was presented according to strata of kidney function in participants in Table 6.3 and Table 6.4, which is an acceptable convention for describing the severity of kidney damage in individuals or groups (Levey et al. 2011; Mathew et al. 2007).

Kidney function was categorised according to three albuminuria groups (Table 6.3): normo-albuminuria (<2.5 mg/mmol in males, <3.5 mg/mmol in females); microalbuminuria (≥2.5-25 mg/mmol in males, ≥3.5-25 mg/mmol in females), and macro-albuminuria (≥25 mg/mmol) (Tapp et al. 2004). Kidney function was also assessed categorically according to three strata according to eGFR expressed for eGFR by MDRD 4-variable formula of kidney function (MDRD-eGFR), and eGFR CKD-EPI formula (CKD-EPI-eGFR) of kidney function (in Table 6.4 and Appendix Table 11). The African-American correction for ethnicity was not applied for Aboriginal and Torres Strait Islander participants in the present analysis, since there is no a-priori reason to consider that the populations are similar. The three eGFR strata groups were defined as:

\[
\begin{align*}
eGFR & \geq 90 \text{ ml/min/1.73m}^2; \\
eGFR & 60-89 \text{ ml/min/1.73m}^2; \\
eGFR & <60 \text{ ml/min/1.73m}^2.
\end{align*}
\]

Bivariate associations of log-adiponectin and log-leptin concentrations were examined in adult Aboriginal people and Torres Strait Islander people with indicators of obesity (BMI, WHR and waist circumference) and chronic disease risk (concentrations of log-HDL log-CRP). As it was not permitted in an analysis of covariance to ascertain significant differences in median adipokines concentrations between numerous subgroups (gender, ethnicity, and strata of kidney damage), the association of adipokine concentrations with other variables was assessed with a multivariate regression model (for log-adiponectin concentration) and a Principal Components Analysis.
A multiple regression analysis was performed to identify predictors of log-adiponectin concentration in the cohort since bivariate associations may be prone to confounding, and secondly, as participants had complex medical co-morbidities, varying body size, and comprised of several sub-groups (gender and ethnicity). Thus log-adiponectin concentration was examined by the multivariate regression model (Table 6.5) with continuous measures of cardiovascular disease risk and kidney damage. At a p-value<0.05, one in twenty associations between a predictor and outcome variable may be statistically significant when an association does not actually exist. Hence only nine predictor variables were included in the initial multiple regression model in this analysis. Gender, ethnicity and adiposity (BMI, waist circumference, WHR) are clinically associated with log-adiponectin in other populations, and were five of the nine predictor variables. Two measures of kidney damage (log-ACR concentration, eGFR-MDRD), and two biomarkers of cardiovascular disease risk (concentration of log-HDL-cholesterol and log-CRP) that are often observed to be low among adult cohorts of Aboriginal and Torres Strait Islander peoples (and was also evident in Chapter 4) were also selected as predictor variables of log-adiponectin concentration among this cohort.

Predictor variables were retained in the regression model if they were not highly inter-correlated with other predictor variables using the variance of inflation test. Using a stepwise backwards process, the final significant model was obtained by removing one variable at a time if its main effect in the model had a p-value>0.05. This process continued until the final model demonstrated all predictor variables with p<0.05. Finally, all first-order interactions between pairs of variables in the final model were assessed. The interaction term was retained in the final model if it was biologically plausible. Model fit was also assessed by normality of distribution of residuals and assessment of leverage and influence (using Cook’s distance) in the final models.

A Principal Components Analysis was performed to examine the clustering of 15 body composition, biochemical and demographic measures (shown in Table 6.6). Hip circumference was not included in the Principal Components Analysis since it did not improve the clarity of an adipokine or metabolic profile when included with or without WHR. The Principal Component Analysis method was used to reduce the
information in many measured variables into a smaller set of “factors”. Kaiser’s criterion (eigen values >1) was used to determine the number of factors that best described the underlying relationship among variables. The extracted factors were rotated using the varimax rotation. Significant correlations were considered for variables loading at ≥0.40. Factor analysis was also performed to examine the clustering of variables in males and females without diabetes.

6.3. Results: The eGFR Study

Table 6.1 outlines participant characteristics (n=593) by gender and ethnic group. A higher proportion of Aboriginal males and females currently smoked cigarettes, compared to Torres Strait Islander males and females respectively. A higher frequency of albuminuria was observed in Aboriginal females compared to Torres Strait Islander females, and a similar trend in albuminuria was also observed between males.

Eighty-eight percent of participants (522/593) provided data to assess all five metabolic syndrome factors. Table 6.1 describes the frequencies of metabolic syndrome and individual components between ethnic groups, stratified for gender. There was no significant difference in the frequency of males and females of either ethnic group who had three or more metabolic syndrome factors. Of individual metabolic syndrome factors, Aboriginal females had a higher frequency of albuminuria, hypertension, and obesity than Torres Strait Islander females.

318/522 (61%) of participants who provided data to assess all five factors of the metabolic syndrome did not have diabetes. A high frequency of metabolic syndrome (≥3 factors) was still observed in men and women without diabetes (Males: Aboriginal v Torres Strait Islander= 22/94 v 10/28, p=0.19; Females: Aboriginal v Torres Strait Islander= 27/154 v 7/42, p=0.98). Aboriginal females without diabetes had a higher frequency of obesity compared to Torres Strait Islander females without diabetes (123/154 v 27/42, p=0.04).
<table>
<thead>
<tr>
<th>Metabolic Syndrome Factors n (%)</th>
<th>Aboriginal Males (n=167)</th>
<th>TSI Males (n=48)</th>
<th>p value</th>
<th>Aboriginal Females (n=298)</th>
<th>TSI Females (n=80)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>With 3 or more factors</td>
<td>76 (50.7)</td>
<td>23 (53.3)</td>
<td>0.74</td>
<td>131 (49.8)</td>
<td>27 (40.9)</td>
<td>0.20</td>
</tr>
<tr>
<td>Low HDL-cholesterol</td>
<td>66 (44.0)</td>
<td>24 (55.8)</td>
<td>0.17</td>
<td>99 (37.6)</td>
<td>29 (43.9)</td>
<td>0.35</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>71 (47.3)</td>
<td>15 (34.9)</td>
<td>0.15</td>
<td>121 (46.0)</td>
<td>20 (30.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes</td>
<td>56 (37.3)</td>
<td>15 (34.9)</td>
<td>0.77</td>
<td>109 (41.4)</td>
<td>24 (36.4)</td>
<td>0.45</td>
</tr>
<tr>
<td>Hypertension</td>
<td>75 (50.0)</td>
<td>19 (44.2)</td>
<td>0.50</td>
<td>133 (50.6)</td>
<td>20 (30.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>Obesity</td>
<td>122 (81.3)</td>
<td>35 (81.4)</td>
<td>0.99</td>
<td>229 (87.1)</td>
<td>51 (77.3)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

Data presented as n (%), except for age. *indicates missing data (see individual n in each group). Units for eGFR are ml/min/1.73m². †denominator represents only those with eGFR ≥60 ml/min/1.73m². Metabolic Syndrome Factors are defined as: Diabetes- previous diagnosis of diabetes or an HbA1c ≥6.5%; Albuminuria- ≥2.5 or ≥3.5 mg/mmol for males and females respectively; Hypertension: positive medical history of hypertension, or a blood pressure ≥130/85 mmHg; Low HDL-cholesterol: <1.0mmol/L (non-fasting) irrespective of gender; Obesity: WHR ≥0.9 or ≥0.85 in males and females respectively, or a BMI >30 kg/m². p value for categorical measures represents chi-squared difference between ethnic groups, within each gender.
6.3.1. The eGFR Study: Body Composition

The most distinct finding was the differing relationship of waist circumference and waist to hip ratio (WHR) between Aboriginal participants and Torres Strait Islander participants (shown in Table 6.2). Aboriginal males had a lower waist circumference but similar waist to hip ratio compared with Torres Strait Islander males. Aboriginal females had a similar waist circumference, but higher waist to hip ratio, reflecting a more central pattern of fat distribution compared with Torres Strait Islander females. Within males and females, Aboriginal participants had a lower BMI than Torres Strait Islander participants. In addition to lower body weight and body mass index, Aboriginal males and females had higher resistance (measured by bioelectrical impedance) consistent with a lower lean body mass, compared with Torres Strait Islander males and females respectively.

6.3.2. The eGFR Study: Biochemical Differences

Aboriginal males had a higher median CRP concentrations and trended to higher ACR concentration than Torres Strait Islander males. Similarly, Aboriginal females also had a higher median CRP concentration and ACR concentration than Torres Strait Islander females.

Females had higher adiponectin and leptin concentrations and lower adiponectin/leptin (A:L) ratios than males within ethnicity groups. Aboriginal females had higher leptin concentrations, and lower A:L ratio compared with Torres Strait Islander females.

Whilst there was no significant difference in median MDRD-eGFR between females, Aboriginal females had a higher CKD-EPI-eGFR than Torres Strait Islander females. There was no statistically significant difference in median MDRD-eGFR, CKD-EPI-eGFR, adiponectin concentration, leptin concentration or A:L ratio between Aboriginal males and Torres Strait Islander males (Table 6.2).
Table 6.2. The eGFR Study: Body Composition & Biochemical Characteristics of Participants (n=593)

<table>
<thead>
<tr>
<th></th>
<th>Aboriginal Males (n=167)</th>
<th>TSI Males (n=48)</th>
<th>p value</th>
<th>Aboriginal Females (n=298)</th>
<th>TSI Females (n=80)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height, cm *</td>
<td>173.4 (6.1), 165</td>
<td>174.2 (6.3), 48</td>
<td>0.42</td>
<td>162.5 (6.7), 296</td>
<td>162.4 (14.7), 80</td>
<td>0.88</td>
</tr>
<tr>
<td>Weight, kg *</td>
<td>84.2 (21.1), 167</td>
<td>97.5 (23.1), 48</td>
<td><strong>0.0002</strong></td>
<td>78.3 (19.5), 296</td>
<td>86.8 (20.7), 80</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Waist, cm *</td>
<td>99.3 (17.4), 161</td>
<td>105.3 (18.1), 46</td>
<td><strong>0.04</strong></td>
<td>99.9 (15.7), 275</td>
<td>101.6 (16.1), 74</td>
<td>0.41</td>
</tr>
<tr>
<td>Hips, cm *</td>
<td>101.1 (11.9), 163</td>
<td>109.0 (14.3), 46</td>
<td><strong>0.0002</strong></td>
<td>108.1 (14.8), 283</td>
<td>113.0 (14.4), 74</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>Waist: Hip ratio *</td>
<td>0.98 (0.10), 159</td>
<td>0.96 (0.09), 46</td>
<td>0.23</td>
<td>0.93 (0.09), 274</td>
<td>0.90 (0.08), 73</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>BMI, kg/m² *</td>
<td>27.8 (6.5), 165</td>
<td>32.2 (7.9), 46</td>
<td><strong>0.0001</strong></td>
<td>29.6 (7.0), 296</td>
<td>32.9 (7.5), 80</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Resistance, ohms *</td>
<td>513.4 (99.9), 139</td>
<td>428.6 (75.6), 46</td>
<td>&lt;<strong>0.0001</strong></td>
<td>618.2 (123.4), 269</td>
<td>509.8 (93.3), 68</td>
<td>&lt;<strong>0.0001</strong></td>
</tr>
<tr>
<td>MDRD-eGFR *</td>
<td>86.6 (31.8), 162</td>
<td>82.3 (25.9), 46</td>
<td>0.41</td>
<td>87.0 (35.5), 288</td>
<td>89.2 (24.0), 76</td>
<td>0.61</td>
</tr>
<tr>
<td>CKD-EPI-eGFR *</td>
<td>98.4 (81.0, 112.2), 162</td>
<td>90.7 (75.1, 105.5), 46</td>
<td>0.78</td>
<td>99.7 (75.6, 113.1), 287</td>
<td>84.5 (99.5, 113.1), 76</td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>HbA1c, % *</td>
<td>5.99 (5.58,7.32), 160</td>
<td>5.87 (5.70, 6.69), 47</td>
<td>0.58</td>
<td>6.05 (5.58, 7.32), 279</td>
<td>5.87 (5.47, 7.03), 73</td>
<td>0.52</td>
</tr>
<tr>
<td>Urine ACR, mg/mmol *</td>
<td>2.41 (0.70, 34.5), 160</td>
<td>1.11 (0.60, 14.01), 46</td>
<td><strong>0.05</strong></td>
<td>2.61 (0.80, 28.22), 278</td>
<td>1.51 (0.80, 6.69), 73</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/L *</td>
<td>1.00 (0.80, 1.20), 154</td>
<td>0.90 (0.60, 1.51), 45</td>
<td>0.31</td>
<td>1.11 (0.90, 1.30), 274</td>
<td>1.11 (0.70, 2.10), 62</td>
<td>0.19</td>
</tr>
<tr>
<td>CRP, mg/L *</td>
<td>5.0 (3.0, 10.0), 158</td>
<td>2.5 (1.0, 4.5), 42</td>
<td>&lt;<strong>0.0001</strong></td>
<td>7.0 (4.0, 15.0), 281</td>
<td>4.3 (1.7, 8.0), 71</td>
<td>&lt;<strong>0.0001</strong></td>
</tr>
<tr>
<td>Adiponectin, ug/ml *</td>
<td>3.01 (1.96, 4.32), 159</td>
<td>3.00 (2.02, 3.69), 45</td>
<td>0.34</td>
<td>3.56 (2.65, 4.77), 282</td>
<td>3.50 (2.81, 5.06), 68</td>
<td>0.76</td>
</tr>
<tr>
<td>Leptin, ng/ml *</td>
<td>7.18 (2.97, 19.00), 159</td>
<td>10.05 (3.96, 18.11), 45</td>
<td>0.46</td>
<td>35.32 (22.43, 56.58), 282</td>
<td>26.86 (17.99, 46.18), 68</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>A:L ratio, ug/ml *</td>
<td>0.36 (0.14, 1.30), 159</td>
<td>0.24 (0.14, 1.02), 45</td>
<td>0.32</td>
<td>0.08 (0.05, 0.19), 282</td>
<td>0.11 (0.07, 0.21), 68</td>
<td><strong>0.049</strong></td>
</tr>
</tbody>
</table>

Data presented as mean (SD), n (number) for anthropometry and MDRD-eGFR, and median (inter-quartile range), n for other biochemical data). A:L is Adiponectin: Leptin ratio. Units for eGFR (MDRD or CKD-EPI) are ml/min/1.73m². * refers to missing data, and is indicated by (n) in each gender-ethnicity group.
6.3.3. The eGFR Study: Adiponectin Concentrations according to Albuminuria Group

Overall, higher concentrations of adiponectin were associated with albuminuria (as a continuous measure, p<0.001), and female gender (p<0.001), but was not explained by the main effect of ethnicity*gender term (p=0.31), or ethnicity (p=0.83). Lack of differences in adiponectin concentrations between ethnic groups may be due to small participant numbers among the Torres Strait Islander group, especially those with impaired kidney function. Data for each ethnic group are presented for males and females in Table 6.3; however since the main effect of ethnicity*gender was not significant, a sub-group analysis of differences between groups was not permitted.

Table 6.3. The eGFR Study: Median Adiponectin Concentrations by Albuminuria Groups

<table>
<thead>
<tr>
<th>Albuminuria Group</th>
<th>Males</th>
<th></th>
<th></th>
<th>Females</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aboriginal</td>
<td>Torres Strait Islander</td>
<td>Aboriginal</td>
<td>Torres Strait Islander</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normo-albuminuria</td>
<td>2.77 (1.85,4.01)</td>
<td>3.07 (2.06, 3.69),</td>
<td>3.33 (2.63, 4.21)</td>
<td>3.50 (2.69, 5.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>28</td>
<td>148</td>
<td>46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micro-albuminuria</td>
<td>2.48 (1.77, 3.30)</td>
<td>2.46 (2.32, 3.09)</td>
<td>3.79 (2.65, 4.55)</td>
<td>3.20 (2.50, 3.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>6</td>
<td>49</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macro-albuminuria</td>
<td>3.96 (2.32, 5.76)</td>
<td>2.39 (1.78, 4.26)</td>
<td>3.95 (2.86, 5.79)</td>
<td>4.12 (2.95, 5.41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>11</td>
<td>85</td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are median adiponectin (IQR), (ug/ml), n. Albuminuria Group, ACR expressed as mg/mmol: Males: Normo-albuminuria: <2.5mg/mmol, micro-albuminuria ≥2.5- <25 mg/mmol, macro-albuminuria ≥25mg/mmol. Females: Normo-albuminuria: <3.5mg/mmol, micro-albuminuria ≥3.5- <25 mg/mmol, macro-albuminuria ≥25mg/mmol.
6.3.4. The eGFR Study: Adipokine Concentrations according to eGFR-Strata

Overall higher concentrations of adiponectin was associated with lower eGFR-MDRD (as a continuous measure, p<0.001) and female gender (p<0.001), but was not related to ethnicity*gender (p=0.37) or ethnicity (p=0.53). Similarly, high concentrations of leptin was associated with lower eGFR MDRD (p<0.001) and female gender (p<0.001), but again was not related to ethnicity*gender (p=0.07) or ethnicity (p=0.26).

The analysis of covariance for A:L ratio first assessed the main effects of eGFR-MDRD, ethnicity*gender, and gender and ethnicity as separate covariates. eGFR-MDRD was dropped from the analysis first, having the most non-significant main effect on A:L ratio (p=0.24). The ethnicity*gender interaction term approached significance for median A:L ratio concentrations (p=0.05), hence the concentration of A:L ratio was assessed separately by gender. In 350 females, Aboriginal ethnicity was associated with 0.28 units lower A:L ratio than Torres Strait Islander females (p=0.049). However the model of A:L ratio in females explained only 0.8% of the concentration of A:L ratio (and Model p=0.05). There was no statistically significant difference in A:L ratio in males on the basis of ethnicity (p=0.32). Lack of a strong ethnicity effect on adipokines (adiponectin, leptin or A:L ratio) concentrations (with respect to eGFR as a continuous measure) may have again resulted from small and unequal numbers of participants, particularly with poor kidney function.

Since kidney function may be expressed by eGFR strata, median concentrations of adiponectin and leptin are described in Table 6.4, although a sub-group analyses was not permitted since the main effect of ethnicity*gender or ethnicity was not significant in the cohort.
### Table 6.4. The eGFR Study: Median Adiponectin and Leptin Concentrations by eGFR-MDRD Strata

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aboriginal</td>
<td>Torres Strait Islander</td>
</tr>
<tr>
<td>Adiponectin (ug/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR≥90</td>
<td>2.77 (1.80, 3.79)</td>
<td>2.31 (1.85, 3.22)</td>
</tr>
<tr>
<td></td>
<td>82</td>
<td>14</td>
</tr>
<tr>
<td>eGFR 60-89</td>
<td>2.61 (1.97, 4.13)</td>
<td>2.77 (2.02, 3.70)</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>22</td>
</tr>
<tr>
<td>eGFR &lt;60</td>
<td>4.27 (3.11, 6.65)</td>
<td>3.89 (3.00, 4.26)</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>7</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR≥90</td>
<td>5.36 (2.09, 16.14)</td>
<td>6.38 (2.67, 11.23)</td>
</tr>
<tr>
<td></td>
<td>82</td>
<td>14</td>
</tr>
<tr>
<td>eGFR 60-89</td>
<td>8.54 (3.52, 15.48)</td>
<td>8.93 (4.02, 20.62)</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>22</td>
</tr>
<tr>
<td>eGFR &lt;60</td>
<td>16.51 (6.16, 26.60)</td>
<td>24.09 (13.02, 34.35)</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>7</td>
</tr>
</tbody>
</table>

Data are median (IQR), n. Units for Adiponectin (ug/ml), and Leptin (ng/ml). Kidney Function Strata expressed as eGFR MDRD in ml/min/1.73m².

### 6.3.5. The eGFR Study: Pair-wise Correlations of Adipokines with Body and Biochemical Measures

Log-adiponectin concentrations was most strongly and inversely related to waist circumference in Aboriginal males and females (males: \( r = -0.32, p = 0.0001 \); females: \( r = -0.20, p = 0.001 \)). In Torres Strait Islander females, adiponectin concentrations was more strongly and inversely related to WHR (\( r = -0.49, p < 0.0001 \)) than waist circumference (\( r = -0.29, p = 0.02 \)). Adiponectin concentrations were not related to waist circumference, WHR or BMI in Torres Strait Islander males. Leptin concentration was most strongly related to waist circumference in each gender-ethnicity group, than with WHR or BMI.
Overall log-CRP concentrations were most strongly and inversely related to A:L ratio in females (Aboriginal: \( r=-0.35, p<0.0001 \); Torres Strait Islander: \( r=-0.41, p=0.0007 \)). Log-CRP concentration was not significantly related to any adipokine measure in males. A complete description of bivariate relationships is presented in Appendix Table 7, Appendix Table 8 and Appendix Table 9.

6.3.6. The eGFR Study: Multivariate Regression Model of Adiponectin concentration

The independent determinants of the model of log-adiponectin concentrations (shown in Table 6.5) were male-gender, waist circumference, WHR, log-CRP concentration, log-ACR, MDRD-eGFR and the interaction term “MDRD-eGFR X Log-ACR”. Overall in this model, high WHR, waist circumference and log-CRP concentration were related to lower log-adiponectin concentrations. The model explained 25% of the variance of adiponectin concentrations in this cohort and had a normal distribution of residuals. All first order interactions were assessed. The only significant first order interaction in the final model included “eGFR-MDRD X albuminuria” (as expected). This model does not involve any individuals who exert high leverage or influence.

Table 6.5. The eGFR Study: Multivariate Regression Model of Log-Adiponectin Concentration

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Beta Coefficient (95% Confidence Interval)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDRD-eGFR (ml/min/1.73m²)</td>
<td>(-0.003 (-0.005, -0.001) ) *</td>
<td>0.003</td>
</tr>
<tr>
<td>Log-ACR</td>
<td>(0.087 (0.041, 0.133) ) *</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MDRD-eGFR X Log-ACR</td>
<td>(-0.001 (-0.001, -0.0003) )</td>
<td>0.001</td>
</tr>
<tr>
<td>Log-CRP</td>
<td>(-0.062 (-0.102, -0.021) )</td>
<td>0.003</td>
</tr>
<tr>
<td>WHR</td>
<td>(-1.136 (-1.696, -0.574) )</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist</td>
<td>(-0.004 (-0.007, -0.001) )</td>
<td>0.006</td>
</tr>
<tr>
<td>Male gender</td>
<td>(-0.129 (-0.214, -0.045) )</td>
<td>0.003</td>
</tr>
<tr>
<td>Constant</td>
<td>(9.931 (9.474, 10.388) )</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Model R², RMSE</strong></td>
<td><strong>24.6 %</strong>, 0.42</td>
<td></td>
</tr>
</tbody>
</table>

Data are beta coefficient (95% Confidence Interval), n=485. * refers to variables that are involved in an interaction. Variables entered in the model were: eGFR-MDRD, log-ACR, log-CRP, log-HDL cholesterol, WHR, waist, BMI, Aboriginal ethnicity, male gender.
The model of log-adiponectin involving WHR (presented in Table 6.5) was superior to a multivariate regression analysis involving hip circumference. Whilst the model of log-adiponectin concentration, dependent on hip circumference was significant (model variance, 28%, RMSE 0.409, n=485), inclusion of hip circumference resulted in WHR becoming a non-significant determinant. Hip circumference had a negative beta-coefficient for log-adiponectin (therefore high hip girth did not indicate a favourable adiponectin level), and the model was also more complex than indicated for WHR, since it was dependent on two additional interactions, “Waist X Hips” and “Male gender X Hips”.

A multivariate regression model of log-adiponectin concentration was performed with eGFR-expressed as CKD-EPI (log-CKD-EPI-eGFR). The final model was not dependent on any interaction terms between dependent variables. The independent determinants in the final model were: log-CRP concentration, WHR, waist, male-gender, and log-CKD-EPI-eGFR). This model explained 26% of the model variance in log-adiponectin. There were no first order-interactions, the residuals of the model were normally distributed, and there were no individuals who exerted undue influence or leverage.

6.3.7. The eGFR Study: Factor Analysis

A Principal Components (Factor) Analysis was performed. 15 variables were assessed in 454 Aboriginal and Torres Strait Islander participants, to determine the clustering into independent factors. Three factors were identified (Table 6.6), which describe a cumulative variance of 93%.
Table 6.6. The eGFR Study: Results of Factor Analysis (n=454)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Factor 1</th>
<th>Factor 2</th>
<th>Factor 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anthropometry &amp; Leptin</td>
<td>Diabetes &amp; Kidney Damage</td>
<td>Male Gender</td>
</tr>
<tr>
<td>Aboriginal (v Torres Strait Islander)</td>
<td>-0.0755</td>
<td>0.0926</td>
<td>-0.0148</td>
</tr>
<tr>
<td>Male (v Female)</td>
<td>-0.0632</td>
<td>0.0511</td>
<td><strong>0.7433</strong></td>
</tr>
<tr>
<td>Age, years</td>
<td>0.1964</td>
<td><strong>0.6333</strong></td>
<td>-0.1485</td>
</tr>
<tr>
<td>BMI, kg/m^2</td>
<td><strong>0.8945</strong></td>
<td>0.0031</td>
<td>-0.1675</td>
</tr>
<tr>
<td>WHR</td>
<td><strong>0.4614</strong></td>
<td><strong>0.5077</strong></td>
<td><strong>0.4003</strong></td>
</tr>
<tr>
<td>Waist (cm)</td>
<td><strong>0.9373</strong></td>
<td>0.2108</td>
<td>0.0095</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.3421</td>
<td><strong>0.6626</strong></td>
<td>0.0415</td>
</tr>
<tr>
<td>Smoker</td>
<td>-0.1855</td>
<td>-0.2827</td>
<td>0.1629</td>
</tr>
<tr>
<td>MDRD-eGFR, ml/min/1.73m^2</td>
<td>0.1102</td>
<td><strong>-0.5407</strong></td>
<td>0.1582</td>
</tr>
<tr>
<td>Log-HDL-cholesterol</td>
<td>0.0200</td>
<td>0.3398</td>
<td>-0.0650</td>
</tr>
<tr>
<td>Log-CRP</td>
<td>0.1815</td>
<td>0.0012</td>
<td>-0.1419</td>
</tr>
<tr>
<td>Log-ACR</td>
<td>0.0369</td>
<td><strong>0.6582</strong></td>
<td>-0.0765</td>
</tr>
<tr>
<td>Log-HbA1c</td>
<td>0.3380</td>
<td><strong>0.5928</strong></td>
<td>0.1035</td>
</tr>
<tr>
<td>Log-Adiponectin</td>
<td>-0.3476</td>
<td>0.1699</td>
<td>-0.2969</td>
</tr>
<tr>
<td>Log-Leptin</td>
<td><strong>0.5640</strong></td>
<td>0.1571</td>
<td><strong>-0.6524</strong></td>
</tr>
<tr>
<td>% Variance Explained</td>
<td>36.6</td>
<td>33.7</td>
<td>18.6</td>
</tr>
</tbody>
</table>

15 variables assessed in 454 participants. These three factors explain 93.1% of the total variance in factors. Variable loading ≥0.40 considered significant and highlighted in bold.

Factor 1 called “Anthropometry and Leptin” explained 37% of factor loading, and describes the clustering of high waist circumference, BMI and WHR with high leptin concentration. Notably loading due to adiponectin concentration was most strongly related to factor 1, but did not reach statistical significance (loading at -0.35). Factor 2 called “Diabetes and Kidney Damage” explained 34% of factor loading, and describes the clustering of diabetes, higher HbA1c, WHR, older age, and kidney damage (low eGFR, high log-ACR). Factor 3 called “Male gender” explained 19% of factor loading, and described clustering of male gender, high WHR and low leptin concentrations.
In participants without diabetes, two factors were each identified in males and females. Anthropometric variables of total and central obesity (BMI, waist circumference and WHR) clustered with high-leptin concentration and low-adiponectin concentration in both males and females. As expected age and kidney damage clustered in both males and females. However, in females without diabetes, the combination of total and central adiposity was associated with other metabolic factors (high log-HbA1c, high log-CRP concentration). The complete factor analysis for males and females without diabetes is presented in Appendix Table 10 and Appendix Table 11.

Factor analysis revealed similar clustering of variables for eGFR expressed as Log-eGFR–CKD-EPI in all participants, and in males without diabetes. In females without diabetes, factor 1 was the same as observed in eGFR expressed as MDRD. However, factor 2 identified the clustering of age, eGFR (inversely) and log-ACR, but did not cluster with log-HDL-cholesterol (in females).

### 6.4. Discussion: The eGFR Study

An assessment of adipokine concentrations, body measures and markers of chronic disease was performed in this analysis. Limitations of the study include that it was a volunteer cohort, and as such we are unable to comment if this was a population representative sample of Aboriginal and Torres Strait Islander peoples. Despite this, in this sample, high rates of chronic disease risk markers was observed in all adults, and was particularly marked among Aboriginal females. Firstly, Aboriginal females have a body composition associated with both high total and abdominal obesity (Table 6.2) which occurred at a lower body mass index than Torres Strait Islander females. Secondly, a higher frequency of metabolic syndrome markers, including albuminuria, and a higher CRP concentration and a combination of low-adiponectin and high-leptin was observed in Aboriginal females (compared to Torres Strait Islander females) (Table 6.2). Overall, indices of abdominal obesity along with indicators of kidney damage were associated with lower adiponectin concentrations in participants (Table 6.5). The findings of this analysis suggest a potential
A hypothesis: abnormal adipokine concentrations associated with the presence of both total and abdominal obesity are functionally linked to renal injury.

A High Burden of Chronic Disease Risk Markers in the Whole Cohort of Indigenous Australians

The frequency of cardiovascular disease risk markers observed in Aboriginal participants and Torres Strait Islander participants in this analysis are consistent with reports in other large community based studies of risk for Indigenous Australians (Leonard et al. 2002; O'Dea et al. 2008). Despite a high background risk in all groups, the particularly high-risk metabolic profile of females who had high measures of both total and central obesity was demonstrated by the present study. The description of metabolic syndrome and related risk has been reviewed in Chapter 1.5, and is therefore not revisited here. However, although the study was not likely to be population representative, it has demonstrated a large burden of cardiovascular disease risk markers, and the following discussion exploring the relationship of body composition, adipokines and kidney damage is likely to be highly relevant to many Aboriginal people and Torres Strait Islander people.

Adipokine Concentrations in Indigenous Australians

Overall, in the present analysis, median adiponectin concentrations were less than 4.0 ug/ml in male and female participants, including in participants without moderate kidney impairment (MDRD-eGFR >60 ml/min/1.73m²). In Asian populations without renal disease, adiponectin concentrations < 4.0 ug/ml were more likely to identify individuals with higher cardio-metabolic risk (Hara et al. 2006), although others suggest this threshold (<4.0 ug/ml) may not be universally appropriate for other ethnic groups (Im et al. 2006). Higher cardiovascular disease risk burden was also observed by a combination of high leptin and low adiponectin concentrations among Indian people (Kanjilal et al. 2008), which is also consistent with the pattern of chronic disease risk markers observed here.

Among healthy adult females (shown in Chapter 4), lower adiponectin concentrations in Aboriginal than non-Indigenous females was explained by a higher percent body fat, and not by ethnicity. In the present analysis, consistent with other studies of adults with kidney disease, adiponectin concentrations were higher in
participants with a lower eGFR than individuals with less impaired kidney function (Looker et al. 2004; Shen et al. 2007a). In the context of adults with kidney damage, the cardiovascular consequences of low adiponectin concentrations were demonstrated in other populations: in adults with moderate kidney impairment (GFR 60 ml/min/1.73m$^2$), those among the cohort with lower adiponectin concentrations were predicted to have a cardiovascular disease event in the ensuing 54 months of follow-up (Becker et al. 2005). Similar findings of low relative adiponectin concentrations and cardiovascular disease risk were observed in adults who required dialysis (Zoccali et al. 2002). Prospective follow-up of cardiovascular disease outcomes in The eGFR Study cohort will be required to identify if a threshold of A:L ratio, or adiponectin concentration may identify individuals with higher than background risk, for Indigenous Australian adults with and without significant kidney impairment. This is planned in the follow-up phase of The eGFR Study.

**Potential Link between Adiposity, Metabolic Syndrome, Adipokines and Renal Injury in Indigenous Australians**

**Body Composition**

As presented in Chapter 5, while Aboriginal people and Torres Strait Islander people both had relatively longer limbs and short torso for a given height, Torres Strait Islander participants had a significantly heavier body build: wider across the shoulders and pelvis and a more muscular build. A higher hip circumference relative to central body fat appeared to be protective for either factor 1 or factor 2 (in the Principal Components Analysis that included WHR rather than absolute hip circumference). Therefore, a higher BMI appears to be less of a risk in Torres Strait Islander participants, due to a higher lean body mass for size, than is observed for Aboriginal participants.

Waist circumference or BMI are indicative of central and total obesity, but are not sensitive enough to describe abdominal fat partitioning, particularly across different populations. CRP concentration was likely to be related to the burden of intra-abdominal fat in the setting of a large waist circumference in the multivariate model of log-adiponectin concentration in the present study. The model may have been further improved by the addition of sagittal abdominal diameter (which was not
measured in this study, but could be measured in future studies). Like the sagittal abdominal diameter, WHR was a superior indicator of intra-abdominal fat burden (than BMI) across populations with different body compositions (shown in the Healthy Top-Enders’ study, Chapter 4). WHR was also a superior indicator of cardiovascular disease risk than BMI across multi-ethnic international populations (Yusuf et al. 2004), and between Aboriginal populations and Torres Strait Islander populations with cardio-metabolic diseases (Kondalsamy-Chennakesavan et al. 2008; Li et al. 2010).

**High Resistance and CRP Concentration are Both Related to High Central Body Fat in Aboriginal People**

Aboriginal participants in this study had a body composition characterised by both high total and abdominal obesity. Despite similarities in body height in males and females between ethnic groups, higher resistance in Aboriginal participants in the present study indicates higher relative proportion of fat and therefore proportionately lower lean mass than Torres Strait Islander participants. As shown in Chapter 4, Aboriginal males and females with high WHR also had high percent body fat, high intra-abdominal fat burden and abnormalities in vascular disease risk biomarkers (particularly high CRP concentration, and low concentrations of HDL-cholesterol, and adiponectin).

In summary, heightened cardiovascular disease risk in Aboriginal participants and Torres Strait Islander participants was exemplified by the combined presence of high CRP concentration, abdominal obesity and kidney damage (shown in Appendix Table 11). These markers were all independent determinants of log-adiponectin concentration in the multivariate regression model in the present analysis (shown in Table 6.5).

**Body Composition and Adipokine Concentrations: Adipose Tissue**

The pathophysiological consequences of obesity, adipose tissue remodelling, and the expression of adipokines and other biomarkers was reviewed in the Introduction (Chapter 1.7.7). In Aboriginal participants in the present study, the pattern of predominant visceral obesity was shown to be related to low adiponectin
concentration, low A:L ratio and high CRP concentration (and IL-6 concentration, as seen in Chapter 4). The following studies explain how this pattern of body composition is related to this pattern of biomarkers.

Subcutaneous adipose tissue is the preferred storage site of lipid. Healthy lean Aboriginal adults have higher subcutaneous fat measures at very low body mass index than was expected compared with Caucasian populations (Norgan 1994). Subcutaneous adipocytes are responsible for the production of adiponectin, under the influence of ADIPO-Q gene (Kursawe et al. 2010). Visceral abdominal fat reflects excess lipid deposited within the abdomen that cannot be accommodated by subcutaneous depots. In individuals with predominantly visceral obesity, Kursawe et al. (Kursawe et al. 2010) reported subcutaneous adipocytes were unable to produce adiponectin. Visceral obesity was also associated with a local pro-inflammatory response of tissue macrophages (secreting inflammatory factors including IL-6), and associated with an abnormal extra-cellular matrix, fibrotic tissue and poorly developed local capillaries (Spencer et al. 2011). IL-6 was shown to be secreted from both subcutaneous and intra-abdominal adipose sites (Mohamed-Ali et al. 1997), but was preferentially secreted from intra-abdominal fat (measured by portal vein sampling) in individuals with large intra-abdominal fat burden or a predominant pattern of visceral obesity (Fontana et al. 2007).

Differences in abdominal fat partitioning were observed between Aboriginal adults and Caucasian adults in the Healthy Top-Enders’ study (Chapter 4). Differences in abdominal fat partitioning have been described between other ethnic populations (Beasley et al. 2009). As described above and in earlier chapters, overweight Aboriginal females readily deposit intra-abdominal fat with weight gain, but were also observed to maintain a high subcutaneous adipose mass, and have high percent body fat. The combination of high total and abdominal obesity in overweight Aboriginal females therefore explains the association of an abnormal metabolic and adipokine profile observed in the present analysis.

In contrast, overweight Torres Strait Islander females have a different body composition to that of overweight Aboriginal females, characterised by a more generalised obesity, and higher relative lean body mass than Aboriginal females.
This is consistent with overweight Torres Strait Islander females having higher leptin concentration, preserved A:L ratio, and lower CRP concentrations than Aboriginal females (Table 6.2). It was not feasible in the methodology of the study to examine abdominal fat partitioning of Torres Strait Islander peoples to determine if (and to what extent) a large waist circumference and hip circumference is associated with higher subcutaneous adipose depots than is observed in Aboriginal participants.

**Torres Strait Islanders: Protected by their Robust Body Build and Associated High Muscle Mass?**

Hip girth reflects gluteal lean mass and subcutaneous adipose tissue. Yki-Jarvinen et al. (Yki-Jarvinen et al. 1985) showed that individuals with higher relative lean mass had higher relative insulin clearance rates than individuals with lower relative lean mass. Across populations of different body builds, higher insulin sensitivity was reported to associate more strongly in those with higher hip circumferences (Snijder et al. 2004b). In females, higher hip circumference (and improved insulin sensitivity) was attributed to higher subcutaneous gluteal adipose tissue (Snijder et al. 2004a). In males, higher hip circumference (and improved insulin sensitivity) was attributed to higher gluteal lean mass (Snijder et al. 2004b). The most deranged adipokine profile observed in this cohort was in participants who had both a high WHR and high waist circumference (Table 6.6, Appendix Table 11). That Torres Strait Islander participants have high BMI, high waist circumference but lower WHR than Aboriginal participants is suggestive of a metabolic resilience which in the argument of Snijder et al. (Snijder et al. 2004a; Snijder 2004b) may be due to a combination of both higher gluteal subcutaneous adipose and lean mass in this ethnic group.

**Body Composition and Adipokine Concentrations: Lean Body Mass**

Dysglycaemia is a key risk marker of cardiovascular disease risk in Indigenous Australians (McDermott et al. 2004), and low lean mass for size may be an early predisposing factor for this in Aboriginal people. Aboriginal people may therefore have higher cardiovascular disease risk in the setting of low lean mass (and thus lower insulin clearance rates), and therefore a very low tolerance of higher body fat due to their unique body composition.
Whilst adipocytes have regenerative capacity, skeletal muscle cells do not. It is not known if Aboriginal participants in the present cohorts have a lower complement of myocytes (explaining the lower lean mass for size) which explains their difference in body composition, or if a challenging intrauterine environment was universally responsible for this. It was previously reported that remote-living Aboriginal people born with low birth weight were proportionately small in adult life, and had a higher risk of mortality from natural causes (Hoy et al. 2010b; Hoy et al. 1998). Two additional factors (not previously examined) relating to low relative lean mass for size may be differences in normal age-related change in sarcopenia between the two ethnic groups, which has been identified in other populations (He et al. 2003), or the additive burden of current smoking in Aboriginal people (more so than Torres Strait Islander people) with changes in body composition. These factors require a prospective study design.

The more preserved A:L ratio in overweight Torres Strait Islander females relative to overweight Aboriginal females may be indicative of a more preserved insulin-sensitivity profile due to larger gluteal lean mass, a more efficient subcutaneous adipocyte storage capacity with overweight (thereby preserved adiponectin secretion), and/or differences in ectopic adipose storage sites. Whole body MRI would have demonstrated any differences in abdominal fat partitioning, non-abdominal ectopic adipose depots, and relative gluteal fat and lean mass between Aboriginal and Torres Strait Islander people (however such facilities were not available at all recruitment sites). In this study, it was not feasible to perform assessments for insulin sensitivity in the field. Total adiponectin concentration was reported in this analysis, and has been inversely related to insulin sensitivity in other populations (Mente et al. 2010). The concentration of high-molecular weight adiponectin isoform has been described as a more superior indicator of insulin-sensitivity than total adiponectin or other adiponectin isoforms (Hara et al. 2006; Shen et al. 2007b), and may be an alternative marker of insulin-sensitivity profile between groups with different body composition.
Adipokines and Kidney Damage

Several reports indicate receptors for adiponectin and leptin remain functional in the presence of impaired kidney function (Shen et al. 2007a). Low adiponectin and high leptin concentrations are also likely to exacerbate kidney damage (Sharma et al. 2008; Wei et al. 2004). Low adiponectin concentrations were directly linked with podocyte damage and manifested as albuminuria (Sharma et al. 2008). In addition, obesity associated with high leptin concentrations resulted (in order) in early glomerular hyper-filtration, later nephron fibrosis, albuminuria and subsequent loss in GFR (Wei et al. 2004). Therefore in the setting of obesity, the combination of both high leptin and low adiponectin concentrations represents a high-risk situation for the development of kidney damage and cardiovascular disease risk.

Thus, several mechanisms indicate the relationship of hypo-adiponectinaemia and hyper-leptinaemia with renal injury. These mechanisms also provide some context to the pattern of albuminuria seen among Aboriginal and Torres Strait Islander populations. This pattern of renal injury due to obesity and hyper-leptinaemia is consistent with the reporting of albuminuria with multiple metabolic syndrome indicators, but preserved GFR in many studies involving Aboriginal people (Maple-Brown et al. 2011; Rowley et al. 2000). These studies may have therefore assessed participants at an earlier spectrum of renal injury, prior to the development of nephron fibrosis and GFR loss. McDermott et al. (McDermott et al. 2004) reported that Torres Strait Islander people with diabetes were more likely to have a higher HbA1c, but lower albuminuria and diastolic blood pressure compared to Aboriginal people with diabetes. The origins of albuminuria may therefore be different between the groups: where albuminuria manifests in the setting of diabetes in Torres Strait Islander people, however, reflects endothelial damage in Aboriginal people, since it is often observed in non-diabetic individuals, and often clusters with abdominal obesity (Rowley et al. 2000). The latter may be a reason for the high frequency of Indigenous Australians with the clinical diagnosis of “presumed glomerulonephritis without biopsy” recorded in the ANZDATA registry who require dialysis. As we propose above, this propensity to low A:L ratio (independent of indicators of kidney damage) may lie in the combination of low metabolic resilience with lower relative lean body mass (lack of insulin sensitivity), or a more pronounced visceral obesity (and low absolute adiponectin production and secretion).
Finally, Aboriginal people may have less resistance to kidney damage in the setting of low A:L ratio due to glomerulomegaly. As discussed above (Chapter 1.5.1), glomerulomegaly was frequently observed in remote living Aboriginal people (Bertram et al. 1998; Moore et al. 1996), represents a compensatory response to low nephron endowment (Hughson et al. 2003), and individuals with glomerulomegaly are prone to accelerated renal injury with additional insults (Hoy et al. 2010a). Therefore, Aboriginal people may be vulnerable to the effects of high leptin and low-adiponectin concentrations. It is not possible to comment how accurate this statement is for Torres Strait Islander peoples, since they were not represented in the kidney biopsy studies that examined nephron size and endowment (Bertram et al. 1998). Nonetheless, multiple renal insults are reported over the life-course in Aboriginal people (Hoy et al. 2010b), which may also contribute to nephron stress and later decline in kidney function in the setting of obesity and hyper-leptinaemia. In addition, our findings in Torres Strait Islander participants may be limited by small numbers in that group.

The opportunity to modify kidney damage in the setting of low adiponectin and high leptin requires investigation. Macro-albuminuria is associated with worse renal and cardiovascular outcome than micro-albuminuria (Hoy et al. 2001b). Albuminuria was reported to resolve in mice with low serum adiponectin levels in as little as 10 days following adiponectin supplementation, and was directly related to podocyte repair (Sharma et al. 2008). However, there are no human studies using supplemental adiponectin, though this may be clinically possible by lifestyle modification. Improvements in urinary protein excretion rate was observed following weight-loss in obese adults with albuminuria and early stage chronic kidney damage (Navaneethan et al. 2009). The study did not report if weight loss was primarily due to the loss of fat or lean mass, and did not report adipokines or the trajectory of kidney function (GFR) in response to weight loss. The relatedness of adiponectin, kidney function and central obesity identified in the multivariate model of adiponectin in the present analysis suggests that a lower WHR and/or lower degree of albuminuria may impact eGFR result, though it was not possible in this cross-sectional analysis to quantify the impact on eGFR trajectory from any such intervention to modify WHR or albuminuria. Hoy et al. (Hoy et al. 2001a) reported
macro-albuminuria was a major risk marker for renal and cardiovascular disease in one remote Aboriginal community, however the study should be repeated in a larger sample of Indigenous Australians across diverse geographic settings to identify other indicators of rapid GFR loss. Abdominal obesity or A:L ratio may be identified as a high risk indicator of progressive kidney damage, and this will be addressed in the follow-up phase of The eGFR Study.

Body Composition Differences and the Reporting of estimated GFR

This analysis presents estimated kidney function using eGFR formulae, in line with national standards of reporting kidney function (Mathew et al. 2007). The analysis does not include results of a reference test of kidney function, as that was beyond the scope of research questions addressed in the thesis. However, the potential bias of reporting kidney function in Aboriginal and Torres Strait Islander people is briefly considered.

Serum creatinine has been used for many years as an indirect biomarker of kidney function, reflecting dietary origins, and endogenous creatinine as a myocyte-derived protein (from lean mass). Formulae that indirectly report kidney function using creatinine interpret lean mass using age, gender and ethnicity (Levey et al. 1999; Levey et al. 2009), and express kidney function as estimated glomerular filtration rate, eGFR, in units of ml/min/1.73m². As described in the Introduction (Chapter 1), lean mass declines with age (Valentin 2002), males have more lean mass than females (Heymsfield et al. 1990) and African American people were shown to have higher lean body mass than Caucasian people (Gallagher et al. 2000; Levey et al. 1999). The normalised reporting of kidney function, by correcting for 1.73m² body surface area (as an index of nephron number), in order to compare between individuals was criticised by Ruggieri et al. (Ruggieri et al. 2010) in a recent review. Two specific reasons were the difficulty in accurately predicting body surface area, and second, a more overweight population today promotes a lower actual body surface area (for a given body weight) than was originally described in the reference group (from early 1900’s) (Ruggieri et al. 2010). The further potential bias of eGFR applies to any population with high levels of overweight and obesity (Jesudason et al. 2011).
The potential bias in eGFR for either Aboriginal people or Torres Strait Islander people may reflect one or all of:

1. Differences in skeletal proportions, that infer a different trunk geometry (shown in Chapter 3 and Chapter 5), and likely a different body surface area between Aboriginal, Torres Strait Islander and Caucasian groups
2. Differences in relative lean mass for size (shown in Chapter 3);
3. Lack of information regarding rates of sarcopenia with normal aging, since this was demonstrated in other ethnic groups when compared with Caucasian people, (He et al. 2003);
4. Aboriginal participants and Torres Strait Islander participants in the present analysis were overweight. A reference test of kidney function performed in combination with reference methods of body composition to control for lean and fat mass may provide useful clinical information regarding the accuracy of MDRD formula (and CKD-EPI formula) of kidney function in overweight and obese populations (Jesudason et al. 2011), and is planned in a future analysis as part of the larger eGFR Study.

**Limitations**

The study was not designed as a population-based study. Participants were recruited across five pre-defined strata of health, diabetes and kidney damage, and as such are unlikely to be representative of their own community or the wider population in either age or body composition. A difference in body size and composition between Aboriginal and Torres Strait Islander participants was presented in Chapter 5. In the present study, ethnicity was not a significant main effect explaining adiponectin or leptin concentrations in males and females. This may be interpreted in several ways.

The analytical approach in this Chapter described the cardio-metabolic risk markers in the cohort, and the associated concentrations of adipokines. Statistical power is dependent on the true difference between the ethnic groups (which is unknown with regards to adipokines), the sample size (including in subgroups, such as strata of kidney function), and the balance between the alpha level (the level of statistical significance set to detect a difference) and the number of comparisons to be made (the k value). If the number of comparisons is high, then the alpha level should be
It was challenging to achieve statistical power in this analysis. First, Torres Strait Islander peoples are a minority group compared with Aboriginal Australians; hence achieving an adequate sample size that was population representative was not likely. Second, whilst severe kidney disease is associated with morbidity for individuals, it is not a common finding in the general population, and is a less common finding in remote regions of Australia, particularly where the Torres Strait Islander participants were primarily recruited (Thursday Island). Large numbers of Torres Strait Islander adults were recruited in the present study, however fewer Torres Strait Islander participants had macro-albuminuria or low eGFR (<60 ml/min/1.73m$^2$) than Aboriginal participants. Low and unequal numbers of participants with poor kidney function has likely affected the statistical power in this analysis to detect differences between the groups. The findings from this analysis are likely to more strongly reflect the group of participants with the largest sample size (Aboriginal participants). The lack of difference in adiponectin concentrations in the Torres Strait Islander subgroup likely relates to the small number of participants in that group. Since a comparatively smaller sample of Torres Strait Islander participants was assessed, and there was no main effect of ethnicity between the groups for adipokines, further studies would be strengthened by the recruitment of similar numbers of Torres Strait Islander participants as Aboriginal participants in each strata, which would confirm the findings and our interpretation of the present analysis.

A multivariate regression model was the multifactorial method used to describe differences in adiponectin concentration in the study population. It was used in preference to an alternate method, such as the Bonferroni correction for several reasons: since the data was taken from a survey, the variables assessed in the model may have not been as independent as required (and this was addressed by the variance of inflation test for multicollinearity of variables in the multiple regression model); comparisons in adiponectin concentrations between participants involved multiple subgroups (for which Bonferroni method is overly conservative in describing differences); and unequal participants in each subgroup may have erroneously detected a difference when a true difference did not exist - where this can be addressed by the post test analysis of the multivariate regression model by assessing for interactions.
An alternative interpretation to the lack effect of ‘ethnicity’ on adipokine concentrations is also considered. Among the Aboriginal and Torres Strait Islander participants in the present analysis, a stronger biochemical indicator of cardiovascular risk was shown by body composition and particularly the propensity to total and abdominal obesity rather than an ethnicity term. In this analysis the study sample did not have a clearly defined control or healthy group. However, Chapter 4 provides this perspective, and showed there was no expectation that adiponectin concentrations differed between Aboriginal and Caucasian participants on the basis of ethnicity. In fact, adiponectin concentrations were lower in Aboriginal females (than non-Indigenous females) on the basis of higher percent body fat. Aboriginal Australians and Torres Strait Islander Australians are diverse peoples. The heterogeneity in the wider Indigenous population was reflected to some extent in the present analysis with respect to age, albuminuria, eGFR, smoking status, recruitment locality and comorbid illness. In spite of this heterogeneity, a higher cardiovascular risk profile was observed in individuals who have high total and abdominal obesity, and kidney damage. This finding is likely to be clinically useful, although should be confirmed in prospective studies. Thus, differences observed in the current study may relate to small participant numbers and hence a lack of statistical power in some groups, or alternatively may relate to differences in body composition (such as percent body fat) between groups.

Adipose related biomarkers and their association with other metabolic indicators of cardiovascular disease risk were the focus of the present analysis. In Chapter 5, the careful characterisation of body composition of Aboriginal compared with Torres Strait Islander participants was examined: a more robust body build with higher proportion of lean mass for size of Torres Strait Islander participants; and a linear skeletal build with lower lean mass, and capacity for higher WHR for the same BMI was evident in Aboriginal participants was presented from Chapter 5. We have thus demonstrated a greater knowledge of the body composition of Aboriginal and Torres Strait Islander participants with overweight and obesity through these studies. In the present analysis, ethnicity was not a significant main effect of low adiponectin concentrations; however the PhD study has shown that the two groups clearly diverge with respect to waist circumference and WHR when overweight. In better
understanding the two populations with respect to obesity risk, these two easily performed clinical measures may assist in identifying the clinical context of low adiponectin concentrations, and ideally stratify high risk individuals among a diverse population.

**Conclusion**
Torres Strait Islander people have a fundamentally different body build and composition compared with Aboriginal people. It was on the basis of differences in body build that the clearest indication of deranged adipokine concentrations was observed in this study population. Despite the assessment having been undertaken in a population with a high frequency of components of the metabolic syndrome, there was strong evidence for a relationship between abdominal obesity and an adverse adipokine profile, particularly in women. This requires further confirmation in a prospective study.

Opportunities to sustainably modify the high risk of cardiovascular disease and diabetes that is associated with albuminuria and impaired kidney function in Aboriginal people and Torres Strait Islander people should be a high priority in the short and long-term. This is likely to include prevention of excessive weight gain, particularly early in adult life, and early in the evolution of chronic disease to achieve critical gains in health. Lifestyle interventions incorporating detailed body composition and adipokine studies should occur in partnership with communities, and may require a tailored approach due to inherent differences in body build and composition between Aboriginal people and Torres Strait Islander people, and for different health strata.
Chapter 7.

Discussion and Conclusion
7.1. Addressing the Objectives of the thesis

The aim of this study was “to understand how body build, composition, and markers of kidney damage relate to metabolic syndrome components in adult Aboriginal people and adult Torres Strait Islander people, within the context of two volunteering adult health screening studies”.

**Objective 1. What are the earliest chronic disease risk markers evident in otherwise healthy young adult Aboriginal people?**

Abdominal obesity is the earliest chronic disease risk marker evident in otherwise healthy adult Aboriginal people. This was best demonstrated in Aboriginal males in the Healthy Top-Enders’ study (Chapter 4). Aboriginal males with a low body fat percent had lower intra-abdominal fat (IAF) area than lean Caucasian males. Both Aboriginal and Caucasian males with low body fat percent were objectively healthy, although a higher fasting insulin concentration (trend \( p=0.06 \)) was observed in Aboriginal males. Aboriginal males with higher body fat percent had higher intra-abdominal fat area, HOMA score, and concentrations of insulin and CRP than Caucasian males with high percent body fat.

Among females, despite a mean BMI <25 kg/m\(^2\) in the group, there was a trend for Aboriginal females to have higher body fat percent compared with BMI-matched non-Indigenous females. It was therefore not possible to determine the best biochemical profile associated with a lean physique in Aboriginal females. Aboriginal females had higher IAF area measured over two inter-vertebral levels of the abdomen than Caucasian females. This was a striking finding for two reasons: firstly, because it highlights an android pattern of obesity that has not been described for healthy young females of any ethnic group in the literature; secondly, high IAF areas are more characteristically seen in post-menopausal females. In the presence of high IAF areas, Aboriginal females in the Healthy Top-Enders’ study retained high abdominal subcutaneous fat areas, however had proportionately less limb fat, consistent with other reports of Aboriginal women (Piers et al. 2003; Rutishauser et al. 1986). This pattern of high total and abdominal adiposity in Aboriginal females was associated with high CRP concentration (trend) and IL-6 concentration.
Notably, despite the higher total and abdominal adiposity of young adult Aboriginal females, none had albuminuria. Lack of albuminuria in this group is consistent with reports, that (in the absence of a primary renal disease) albuminuria accompanies established metabolic risk markers, especially abdominal obesity, and does not precede it (Hoy et al. 2006b; Rowley et al. 2000). The relationship of albuminuria and central obesity has been demonstrated in other populations (Chang et al. 2006; Thoenes et al. 2009).

**Objective 2. To describe the characteristics of skeletal build in Aboriginal people and Torres Strait Islander people.**

Aboriginal males and females consistently had a longer leg-length as percent of height than Caucasian participants. This was observed in both the Healthy Top-Enders’ study, and the eGFR Study DXA sub-study. Aboriginal males and females in the Healthy Top-Enders’ study also had narrower absolute pelvis-width and shoulder-width. Aboriginal females in the eGFR Study DXA sub-study had the narrowest pelvis-width as percent of height than other female groups. The longer leg-length for overall height was primarily due to longer distal portion of the limb (tibia), which supports previous descriptions of Aboriginal people (Abbie 1969; Roberts 1953).

Two striking observations of the Torres Strait Islander skeletal build was first, the relatively longer leg-length than Caucasian and Aboriginal participants, and second, wider skeletal-breadths. Torres Strait Islander females consistently had a wider pelvis-width than Torres Strait Islander males, and wider than Aboriginal females. Aboriginal participants had the narrowest and lightest skeletal build of the three groups.

**Objective 3. How do observed differences in skeletal build relate to body composition in Aboriginal adults and Torres Strait Islander adults?**

In this study, lean body mass was positively related to standing height, skeletal width and inversely related to resistance (by BIA). Aboriginal participants in the Healthy Top-Enders’ study had similar body mass index to Caucasian participants,
proportionately longer leg-length and lower total fat free mass (though only a trend in males). However, despite matching for BMI, the differences in lean mass between Aboriginal males and Caucasian males failed to reach statistical significance when adjusted for height. Components of standing height were related to the pattern of fat distribution (where shorter trunk-length % identified a truncal-pattern of adiposity), but were not independently related to lean body mass between Aboriginal participants and Caucasian participants in the Healthy Top-Enders’ study.

Torres Strait Islander participants had the highest BMI, and lowest WHR of the eGFR Study DXA sub-study groups. Torres Strait Islander participants and Aboriginal participants both had proportionately longer leg-lengths than Caucasian participants in the eGFR DXA sub-study, and both groups also had high indices of truncal adiposity, though Aboriginal participants, regardless of gender had the highest body fat percent and trunk:peripheral fat ratio. Hence, longer leg-length in Aboriginal participants and Torres Strait Islander participants in the eGFR Study DXA sub-study was consistent with the preferential truncal pattern of adiposity shown in the Healthy Top–Enders’ study however Aboriginal participants had a stronger pattern of central obesity of the two groups. This may be influenced by differences in skeletal width and/or lean mass between the groups.

In multivariate analyses, of the two skeletal proportion measures, pelvis-width was most strongly (and inversely) related to resistance than trunk-length %, regardless of ethnicity. In turn, resistance was strongly and inversely related to lean body mass in the multivariate analysis in the eGFR Study DXA sub-study, and individuals of Torres Strait Islander background (either Torres Strait Islander or Both Aboriginal and Torres Strait Islander) had higher lean mass than Aboriginal participants. Hence, greater skeletal-width characterises people of a Torres Strait Islander background, and in turn independently determined higher lean body mass.

Torres Strait Islander females have a more muscular build but lower central obesity than Aboriginal females. Craig et al. (Craig et al. 2003) showed that Tongan women without chronic disease had a higher body mass index and lean mass, but lower tendency to central adiposity than overweight Caucasian females (without chronic disease). It is not clear if (or how) the presence of high lean mass influences the
pattern of ectopic fat distribution in overweight, though a higher proportion of lean mass has been associated with a more favourable metabolic profile relative to less muscularly built people (Yki-Jarvinen et al. 1985).

In other studies, the breadth of other large joints (using callipers), such as the knee or elbow also indicate the muscularity of body build (Snijder et al. 1999). These measures were not assessed in the current analysis, but could be determined from whole body DXA using the ruler tool function. This is another potential indicator of skeletal build that may be less intrusive to participants, and perhaps offer fewer technical difficulties with reproducibility since little overlying adipose or lean tissue is observed in the respective regions.

Finally skeletal dimensions indicate a tendency toward a particular body build, and have been widely described in different populations who are both lean and healthy (Deurenberg et al. 2002a; Gurrici et al. 1999; Katzmarzyk et al. 1999; Snijder et al. 1999). Accurately predicting body composition at an individual level remains difficult, since several factors influence actual body composition, including age, gender and physical activity. This analysis was unique, since it described an adult cohort with wide age distribution and chronic disease risk markers, including overweight. We have described differences in skeletal build and revealed clear differences in body fat distribution and the proportion of lean mass between Aboriginal participants and Torres Strait Islander participants.

**Objective 4. To determine the best indirect measures of body composition in the assessment of chronic disease risk in adult Aboriginal people and adult Torres Strait Islander people.**

Chronic disease risk was strongly indicated by central obesity in both the Healthy Top-Enders’ study and The eGFR Study. Aboriginal participants and non-Indigenous participants in the Healthy Top-Enders’ study each had a distinct body composition. Regardless of differences in body composition, intra-abdominal fat burden was most strongly indicated by the waist to hip ratio and sagittal abdominal diameter of the abdomen. WHR was a better surrogate of chronic disease risk than
BMI and indicated truncal distribution of body fat (observed by DXA), and CT measures of intra-abdominal fat burden.

In the eGFR Study DXA-sub-study, Aboriginal participants and Torres Strait Islander participants both had higher WHR than Caucasians, and higher than recommendations for health (Alberti et al. 2006). The presence of at least 3 markers of the metabolic syndrome, and higher CRP concentration has been independently related to higher risk of cardiovascular disease in other populations (Ridker et al. 1998). In the eGFR Study DXA sub-study, trunk:peripheral fat ratio (measured by DXA) was strongly correlated with WHR, and central obesity was most strongly linked with at least three metabolic syndrome markers in the multivariate logistic model of metabolic syndrome. In separate multivariate regression models, a high concentration of CRP was most strongly related (in order) to trunk fat mass, fat mass (both were not dependent on gender) and waist circumference. Gender and waist were independent determinants of log-CRP concentration in the multivariate regression analysis in the eGFR Study DXA sub-study, and all three (gender, waist circumference and log-CRP concentration) were independent determinants of log-adiponectin concentration in the multivariate regression analysis in The eGFR Study.

**Objective 5. To examine the relationships of adipose-derived cytokines with body composition in healthy Aboriginal people, and in Aboriginal and Torres Strait Islander people with markers of chronic disease.**

The thesis has identified that chronic disease risk starts with weight gain and manifests as intra-abdominal obesity in Aboriginal people. This weight gain precedes albuminuria. Albuminuria was shown to cluster with other chronic disease markers in other studies (Hoy et al. 2006b; Rowley et al. 2000), particularly abdominal obesity, hypertension, dysglycaemia and low HDL-cholesterol concentration.

Albuminuria was a significant independent determinant of adiponectin concentration in The eGFR Study. Even after controlling for gender and eGFR, higher ACR was associated with low adiponectin concentrations. The multivariate regression model of determinants of log-adiponectin also identified waist circumference, WHR, and
log-CRP concentration, suggesting a relationship between abdominal obesity and albuminuria, and is therefore consistent with reports in other populations (Chang et al. 2006; Thoenes et al. 2009).

As shown by factor analysis in participants without diabetes in The eGFR Study (Appendix Table 10, Appendix Table 11), ethnicity was not a key determinant of metabolic risk. In males and females, the combination of high leptin concentration and low adiponectin concentration clustered with a body composition typified by high total and abdominal obesity (rather than high total and general obesity). Both Aboriginal participants and Torres Strait Islander participants have high total and central obesity, however Aboriginal participants have a stronger pattern of central obesity of the two groups. This, together with the proportionately lower muscle mass of Aboriginal adults, is likely to explain the high burden of chronic disease in both groups, when compared with non-Indigenous Australians (Hoy et al. 2007; Li et al. 2010; Maple-Brown et al. 2009).

Females without diabetes had a more serious pattern of risk associated with high total and abdominal adiposity, indicated by the clustering of log-CRP concentration and HbA1c with high leptin concentration and low-adiponectin concentration. Log-CRP concentration was shown in the Healthy Top-Enders’ study to best indicate IAF burden. Therefore CRP concentration was likely to indicate the burden of IAF associated with a given waist circumference in these studies. The burden of IAF may have also been indicated by the sagittal abdominal diameter, and is worth pursuing the relationship of SAD, IAF and CRP concentrations in future studies.

HbA1c was the final factor clustering with high total and abdominal obesity measures in females without diabetes. Higher insulin sensitivity is related to higher insulin-clearance rates due to better preserved kidney function (Rabkin et al. 1984), higher relative lean mass (Yki-Jarvinen et al. 1985) and lower central abdominal fat (Charlesworth et al. 2005). Insulin sensitivity has also been strongly indicated by adiponectin concentrations (Hara et al. 2006), and lower adiponectin concentrations are associated with a higher burden of intra-abdominal fat (as shown in the Healthy Top-Enders’ study). Torres Strait Islander females had a better preserved A:L ratio (despite high total and abdominal obesity), and this may be due to higher lean body
mass for size (which we have conclusively shown in this study), but may also reflect a more favorable abdominal fat partitioning profile (higher subcutaneous fat to intra-abdominal fat burden), and perhaps a higher subcutaneous fat mass over the buttocks (contributing to higher hip circumference, and lower WHR). The relationship of lean body mass with health risk requires further investigation, which was beyond the scope of the present study.

Finally, in agreement with other human and animal models, the burden of progressive kidney damage was considered for females, and particularly Aboriginal females since several findings relevant to a model of kidney injury are plausible: the combination of high leptin and low adiponectin concentrations in overweight (in the eGFR Study), a higher burden of intra-abdominal fat for size (Healthy Top-Enders’ study), less metabolic resilience due to lower lean body mass for size (shown in Chapter 3, Chapter 4 and Chapter 5), and susceptibility to progressive kidney damage in the setting of glomerulomegaly (Bertram et al. 1998) which was described in Chapter 1. Studies of exercise and weight loss that measure both fat and lean mass and adipokine profile in conjunction with accurate measures of kidney function may provide evidence for this hypothesis.

7.2. Ethnicity, Ethnic Admixture, Body Composition and Metabolic Risk

The final aspect of body composition is the discussion of ethnic admixture in Indigenous participants. Genetics influence body composition, and ethnicity impacts lifestyle habits. Researchers have been encouraged to avoid describing differences between groups on the basis of ethnicity when other more sensitive and discriminating variables may be used (Winker 2004). As reviewed in Chapter 1, several factors are reflected in a respondent’s self-identified ethnicity: biology, ancestry, culture, the lived experience, and affiliation or membership (Callister et al. 2007).

The ‘lived experience of ethnicity’ was not examined in the current study, and may be pursued in future analysis of the data. The lived experience includes the impact of socioeconomic factors that impact on lifestyle choices, housing, drug and alcohol
use, family size and employment opportunity on chronic disease risk (Cunningham et al. 2008; Weil et al. 2010). Attitudes and opportunities to exercise presents an important aspect to obesity risk that should be examined in healthy young adult, and the more mature and at-risk population of Aboriginal and Torres Strait Islander peoples.

A strength of the PhD study was the stratification of participants based firstly on the self-assigned ethnicity of each participant, and secondly participants disclosing the ethnicity of each of their four grandparents. The resultant stratification of participants based on the definition of ethnic group used in the thesis (Chapter 2) permitted a careful examination of the differences in body size and composition between groups. The strong differences in body composition between groups may not have been as evident if the three Indigenous groups (Aboriginal, Torres Strait Islander and both Aboriginal and Torres Strait Islander) were not so carefully defined.

The relationship of admixture and obesity related health risk for Aboriginal peoples and Torres Strait Islander peoples was not examined in detail in this analysis. It remains a valid consideration however, given the large burden of preventable chronic diseases among adult Aboriginal and Torres Strait Islander peoples. Two aspects of ethnic admixture in relation to obesity-risk require consideration. First is to examine if ethnic admixture was considered in previously published studies. Secondly, one must consider in this era that defining groups based solely on a singly assigned ethnicity may of itself be a limitation in studies of body composition.

The Australian government definition of an Aboriginal or a Torres Strait Islander person (which has been appropriately used by many investigators) acknowledges group membership, self-identification, and descent (Gardiner-Garden 2000), and does not require an examination of minimum ancestry. The issue of admixture has been variably dealt with in previously published reports, which may indicate that assessing admixture in Australia in relation to chronic disease risk is difficult to measure, and may have also been a sensitive issue for both researchers and participants. Heitmann et al. (Heitmann et al. 1997) described the differences in body composition of Aboriginal people compared to Torres Strait Islander people,
but carefully excluded those with racial admixture. Others have described the relationship of diabetes between Aboriginal people of two different towns suggesting lifestyle impacts, but also the impacts of racial admixture, particularly in Southern Australia (Cameron et al. 1986; Guest et al. 1992; Williams et al. 1987).

Finally, the issue of body composition and ethnic admixture at the margin might be considered. Ethnicity may be viewed as a social construct (Rebbeck et al. 2005), and defined by affiliation and membership in the group (Callister et al. 2007). Outsiders to the ‘group’ may impose a notion that an individual at an ethnic margin is not fully included. However, this view may not be accepted by the ‘group’ and ethnic admixture at the margin may not even exist in terms of the relevant group according to this definition. For example, the Torres Strait was one of the first truly multicultural communities in Australia, and Islanders readily accepted and incorporated the new children and families that have resulted (Shnukal 2001). Yet body composition is likely to vary in admixed populations, but this change may of itself reflect any combination and dose of dietary patterns and habits, economic and social opportunities, differences in priorities, and racial heritage.

In the current analysis, the examination of differences in body composition was not based on the proportion of a participants’ non-Aboriginal ethnicity (or non-Torres Strait Islander ethnicity). Instead the intent was to differentiate Aboriginal ethnicity from Torres Strait Islander ethnicity and from non-Indigenous ethnicity, and identify a dominant pattern of body composition of each of these groups.

The Healthy Top-Enders’ study primarily recruited Aboriginal participants who had 4 grandparents who identified as Aboriginal, therefore the Healthy Top-Enders’ study more closely reflects the body composition and body-build of remote living Aboriginal people, and may not reflect that of Aboriginal peoples in urban areas, or Aboriginal peoples with greater non-Aboriginal ethnic admixture (Guest et al. 1992; Raja et al. 2003; Williams et al. 1987). The recruitment of participants in the Healthy Top-Enders’ study contrasts with The eGFR Study: Aboriginal, Torres Strait Islander and the both Aboriginal and Torres Strait Islander groups in The eGFR Study have some non-Indigenous admixture, and while their self-identified and grandparent ethnicity was known, analysis of differences in body composition and

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cardio-metabolic risk was not explored beyond their self-assigned ethnicity. This may be a limitation in understanding the full implications of the body composition differences in this study however it presents a real-life circumstance of this population group. Nonetheless, using our criteria of ethnicity, Aboriginal participants demonstrated a different body composition to Torres Strait Islander participants in our studies: other recommendations may be reflective of more admixed Indigenous Australians. A dominant body composition was best observed among the both Aboriginal and Torres Strait Islander group in Chapter 5, whose indicators of lean body mass were more strongly related to Torres Strait Islander participants rather than Aboriginal participants. This may be related to the recruitment of Torres Strait Islander participants in the Torres Strait, rather than from a population group elsewhere in mainland Australia, where the body composition might not as strongly reflect the Torres Strait Islander group.

Our response to this difficult issue of ethnic admixture is to assess objective measures of body composition in relation to health risk, as was performed in the thesis. That is, the waist to hip ratio, skeletal width, and trunk to height ratio may provide the best indicators of obesity-related risk even when ethnic admixture is not an issue. This could be most accurately ascertained with detailed methods of body composition validating against portable measures as we have done in the present studies, but in larger populations and accounting for other elements of ethnicity that have been discussed here.

7.3. Implications for Clinical Practice and Policy

Indigenous Ethnicity

Data relating to obesity-related diseases should capture self-identified ethnicity, and report for Aboriginal ethnicity, Torres Strait Islander ethnicity and both Aboriginal and Torres Strait Islander ethnicity separately rather than a convenient grouping as “Indigenous Australians”. This would best capture differences in Aboriginal peoples relative to Torres Strait Islander peoples, but would still be challenging to describe the both Aboriginal and Torres Strait Islander ethnicity group. Our recommendation is that WHR be used across populations with different body compositions, and
particularly in populations with variable ethnic admixture, since it provided the best assessment of obesity-related risk than a waist circumference or BMI.

**Central Obesity and Kidney Disease in Aboriginal & Torres Strait Islander Australians**

Inclusion of waist to hip ratio, in addition to the BMI may greatly improve the epidemiological study of central obesity with numerous outcomes in patients requiring renal replacement therapy. Central obesity is likely to be an important confounder in the relationship of outcomes of end-stage kidney disease with inflammation, cardiovascular morbidity and mortality, and diabetes outcomes. These additional measures could be incorporated by the Australian and New Zealand Dialysis and Transplantation registry, which already conducts a twice-yearly survey of renal replacement therapy patients through all Australian nephrology units.

**Relationship of obesity with renal hyperfiltration**

There is now justification for studying the relationship of adiposity with hyperfiltration injury in Indigenous Australians. From late 2011, eGFR Study participants were being followed up between 2 to 4 years after baseline assessment, presenting an ideal opportunity to compare baseline body size, adipokines, and clinical morbidity with current status (without a specific intervention beyond specialist advice to treating clinicians). Chronic kidney disease registries should be established in adults in Australia to monitor the trajectory of kidney function, albuminuria and identify high-risk clinical situations that may be amenable to lifestyle and therapeutic interventions.

**Maintenance of regular physical activity and high quality nutrition across the lifespan** and particularly during periods of rapid weight gain (adolescence and childbearing). Physical activity and nutrition were not assessed in this thesis, however are integral to controlling obesity-related chronic diseases in Indigenous Australians.
7.4. Limitations of the Methodology Used

Both the Healthy Top-Enders’ and eGFR Studies were conducted as intended from our chosen methods. Whole body DXA was completed in Thursday Island, a remote island in the Torres Strait, where whole body DXA could only be transported by barge. At the time, the Hologic brand DXA was the only transportable whole body DXA in use in Australia. We have not made adjustments for differences in DXA brand between the two sites since validating equations do not exist for overweight and obese adults with chronic disease risks. Other collaborative research studies conducting DXA across widely separated sites acknowledge this potential source of bias (and have not adjusted their results) (Gallagher et al., 2000). Unavoidably we had to use two different DXA machines for Aboriginal people in Darwin and Torres Strait Islander people on Thursday Island.

Multiple comparisons and statistical power

The descriptive body composition studies presented in Aboriginal participants and Torres Strait Islander participants in the thesis are novel. Chapter 5 and Chapter 6 provided an opportunity to describe the body composition and its metabolic associations among a large population of Aboriginal and Torres Strait Islander participants: hence the first study to describe a complex medical cohort of Aboriginal and Torres Strait Islander peoples. In the analysis of The eGFR Study, several subgroups of the cohort were identified. An analysis adjusting for the covariates of gender, ethnicity and the interaction term in Chapter 5 was performed, since several exposure variables (including demographic and clinical associations) were likely to influence the unadjusted mean (or median) values. This was particularly relevant for the non-Indigenous comparator in The eGFR Study (Chapter 5), who had similar indices of impaired kidney damage, but were also older than Indigenous participants.

Multivariate regression models were presented to describe the relationship of specific outcomes in the thesis (fat free mass, resistance, and log adiponectin concentration). The multivariate regression model was preferred to the Bonferroni correction analysis. The Bonferroni method was not used since the cohort comprised several potential subgroups, the predictor variables were not likely to be independent (such as high CRP concentration occurring with low HDL-concentration, which cannot be
accounted for by this method), and the presence of low and unequal numbers of participants in some subgroups is not handled well by the Bonferroni method— all these factors are accounted for in the approach by the multivariate regression model. In each multivariate regression model, a type 1 error was minimised by using ten or fewer predictor variables in the initial model, and ensuring after backwards selection process, that the final model was free of undue leverage or influence, did not contain interactions that were not biologically plausible, and finally, that each main effect in the final model had a p value <0.05. One objective of the thesis was to examine the relationship of body composition with adiponectin concentrations among Aboriginal and Torres Strait Islander peoples. This objective was thus framed in order to explore how indices of obesity (a potentially modifiable risk factor for cardiovascular diseases) related to adiponectin concentrations (an adipokine with several beneficial health qualities, including protective against albuminuria when found in sufficient quantity). The key finding of this analysis was ethnicity was not a key driver of low adiponectin concentrations, but was due to both kidney damage and obesity. As a result of the statistical methods employed, opportunities to modify cardiovascular disease risk are supported through minimising abdominal obesity. This presents an important opportunity to address the current health inequality of Indigenous Australians compared with other Australians.

The data presented in the thesis indicate a difference in body composition between Aboriginal participants and Torres Strait Islander participants. Differences in the biochemical profile between ethnic groups were not explained by ethnicity, but by indicators of adiposity (body fat percent in Chapter 4, and the waist circumference and WHR in Chapter 6). The recruitment of similar numbers of Torres Strait Islander and Aboriginal participants in Chapter 6 would have been ideal, and have minimised a concern about lack of statistical power in the analysis. However, recruiting similar numbers of participants was not an objective of the larger eGFR Study (for which the data in the thesis is a sub-study). However, as described in Chapter 1, Indigenous Australians are a minority group in Australia’s population. Furthermore, Torres Strait Islander peoples are a minority group relative to the Aboriginal population. Hence, the discrepancy in population size in wider Australia was also reflected in the discrepant size of Torres Strait Islander participants compared with Aboriginal participants in the thesis study. Thus our findings may be
limited by lack of statistical power due to small numbers of participants, particularly in sub-groups such as Torres Strait Islander participants.

7.5. Strengths of the study

Healthy Top-Enders’ Study

The Healthy Top-Enders’ study involved a detailed and methodologically rigorous assessment of metabolic and inflammatory parameters and adipocyte-derived proteins in combination with sensitive body composition measures. The purpose of the Healthy Top-Enders’ study was to compare the metabolic and inflammatory profile with total and regional adiposity in healthy adult Aboriginal people and Caucasian people.

Several studies have assessed body composition in healthy adults (including a comparison between Caucasian and other ethnic groups), but involved volunteering adults who had a higher mean age, and wider age range than assessed in the Healthy Top-Enders’ study (Carey et al. 1996; Craig et al. 2003). Body composition has been described in healthy adult populations, however relied on participants self-described health, rather than objective assessments of health (Gallagher et al. 2000). In the Healthy Top-Enders’ study, health was assessed by questionnaire, biochemical measures and blood pressure. The assessment of young adults in a narrow age-range, and confirmation of health by several objective measures in the Healthy Top-Enders’ study were important inclusion criteria, since a recent cardiovascular disease screening study identified the presence of two cardiovascular risk factors among many Indigenous adults younger than 35 years old (O’Dea et al. 2008). Limiting recruitment to non-elite athletes in the Healthy Top-Enders’ study was felt to provide the best perspective on older adults with chronic diseases. This recruiting decision was based on two known factors: adults participating in elite sporting programs may have variable body compositions (fat and lean mass) (Pineau et al. 2009); and exercise is associated with anti-inflammatory and insulin sensitising effects in young and older adults (Lambert et al. 2008; Mendham et al. 2012; Wolsk et al. 2010).

Differences in body composition have been previously reported between racial groups (Gallagher et al. 2000; Liska et al. 2007). Some studies assessing body
composition or diabetes have limited analysis to clearly defined Aboriginal people or Torres Strait Islander ethnic groups (Heitmann et al. 1997; O'Dea et al. 1993; Williams et al. 1987). Recruitment in the Healthy Top-Enders’ study was limited to adults with minimal non-Aboriginal or non-Caucasian ethnic admixture (respectively), defined by self-identified ethnicity, and the ethnicity of 4 grandparents. Recruitment of Aboriginal participants was sought first, before the recruitment of the age, gender and BMI-matched Caucasian comparator group. Several investigators acknowledge the difficulty of recruiting young healthy adults to detailed body composition and metabolic studies (Glatthaar et al. 1985), which may be overcome by extended recruitment periods (Kvist et al. 1988).

Inclusion of Indigenous research staff and facilitators are essential to engagement with the target population, and delivering the research program (Brimblecombe et al. 2006; Hoy et al. 1997; Hoy et al. 2003b; O'Dea et al. 1993; Williams et al. 1987). Cunningham et al. (Cunningham et al. 2006) identified numerous recruitment challenges for Indigenous health research studies, that were managed by involvement of Indigenous people in study design and delivery, involvement in steering committees, and principles of engagement with the local communities (Cunningham et al. 2006). The research team for the Healthy Top-Enders’ study comprised two Indigenous members (SG, and JH- also study leader). The Aboriginal research assistant (SG), was similarly aged to our target population (aged less than 30 years old), had grown up in the area, and had established local contacts within the community. The research team was extensively engaged with different sectors of the Indigenous community, sought support from local Indigenous facilitators in local urban Aboriginal communities, with employment program providers, Indigenous hostel providers, and secondary schools that supported and housed remote Indigenous students in private homes. The study investigators provided a thank-you gift as an acknowledgement of each participant’s time in the study, though this was not advertised at recruitment. These combined methods were designed to recruit a cross-section of healthy non-elite athlete adults.

Body build and body composition was assessed using a combination of instruments so that indirect and portable anthropometric tools could be compared against more sensitive and precise body composition instruments. This included a detailed
examination of differences in skeletal proportions using a ruler function with whole body DXA. Relative limb-length was previously described with sitting height ratios (Norgan et al. 1995). Since overweight is much more prevalent now than has been in the past, precise measures of skeletal proportions overcome any bias involved with sitting height ratios due to excess gluteal fat mass (Norgan et al. 1995). The bone landmarks used in our analysis approach could be easily identified by both clinical examination and DXA software, and were previously described in a paediatric population (Abrahamyan et al. 2008).

The relationship of total adiposity, and abdominal fat partitioning was examined by DXA and CT in the Healthy Top-Enders’ study. This combination of modalities has not been examined before, and addresses a specific knowledge gap surrounding body composition of Aboriginal adults. Furthermore, the relationship of precise measures of body composition was assessed with biochemical measures and adipokines in the Healthy Top-Enders’ study, which again addresses a specific knowledge gap surrounding the relationship of markers of inflammation and dyslipidaemia with central obesity in Aboriginal adults.

The use of a single abdominal CT slice as opposed to assessment of two inter-vertebral levels to describe visceral fat area has been described in different populations. In particular, Greenfield et al. (Greenfield et al. 2002) reported visceral fat area was more accurately described by measurement of two levels where feasible. The computed tomography protocol in the Healthy Top-Enders’ study involved measuring two inter-vertebral sites in the abdomen, as recommended by Greenfield et al. (Greenfield et al. 2002), who was also an investigator in this study, and whose laboratory provided expertise in the protocol and analysis of abdominal fat partitioning.

The eGFR Study
A large population of Aboriginal people and Torres Strait Islander people were recruited over diverse settings (urban, regional and remote areas) in order to assess the accuracy of the estimated measures of glomerular filtration rate. This included an assessment of body composition and markers of health and chronic disease. We do not report on the reference measure of kidney function in the thesis since that

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investigation was beyond the scope of the research aim of this study. However the eGFR Study cohort were an ideal group to assess the relationship of body composition with indicators of health, as described below.

First, recruitment across urban regional and remote settings reflects the diversity of lifestyles of Aboriginal peoples and Torres Strait Islander peoples. Second, since the study was designed to assess the accuracy of measures of eGFR, recruitment was targeted to regions in Northern, Central and Western Australia which have the highest incidence rates of Aboriginal people and Torres Strait Islander people who require treatment for end stage kidney disease (Cass et al. 2001). Third, whilst albuminuria has been frequently described in screening studies of Aboriginal people and Torres Strait Islander people, the assessment of both low eGFR and albuminuria has not been performed across such a large region, even though morbidity due to CKD and ESKD has become more frequent over the last 15-20 years (McDonald 2010).

The eGFR Study incorporated a detailed body composition sub-study, performed at study sites where whole body DXA was available. Whole body DXA was used to describe total and regional lean mass and adiposity in Darwin in the Northern Territory to best capture data in a predominantly Aboriginal population, and in Thursday Island to best capture data for a Torres Strait Islander population. There was no facility to measure body composition with DXA in Cairns, the nearest large regional centre to Thursday Island in far North Queensland. We therefore sought the availability of a transportable whole body DXA device to use in Thursday Island.

Through the use of whole body DXA, unique differences in body build and composition have been described for the first time among Torres Strait Islander people compared to Caucasian and Aboriginal adults. Specifically, whole body DXA among Torres Strait Islander people has allowed validation of sensitive measures of body composition against bioelectrical impedance; an examination of the relationships of body mass index and lean mass with skeletal proportions; and a comparison of total and regional fat distribution among Aboriginal people and Torres Strait Islander people.
The study hypothesis considered the role of ethnicity in the relationship of body build among Aboriginal adults and Torres Strait Islander adults. A combination of self-reported ethnicity and grandparent ethnicity was used to differentiate these groups. By recruiting and clearly identifying their separate identity, we have shown differences in body composition between Aboriginal and Torres Strait Islander people.

The detailed and precise measures of body composition examined in the Healthy Top-Enders’ study established a foundation to examine the relationship of body mass index and waist to hip ratio with adipocyte-related cytokines including adiponectin and leptin in adult Aboriginal people and adult Torres Strait Islander people in The eGFR Study. The thesis specifically recruited a healthy control group (Healthy Top-Enders’ study) to provide a perspective for adults with chronic disease, where health was specifically demonstrated by the absence of both visceral obesity and albuminuria. The eGFR Study has demonstrated through detailed and precise body composition measures, a population of Aboriginal people and Torres Strait Islander people who had both albuminuria and central obesity, and were also more likely to have other markers of chronic disease risk.

Differences in the expression of adipokines among Aboriginal people and Torres Strait Islander people, and across the stratified health categories has supported the findings of laboratory, human and animal-based studies that link visceral obesity with early and sustained kidney damage. There was no prior knowledge of the applicability of adiponectin and leptin concentrations in adult Aboriginal people and Torres Strait Islander people, therefore a complete adipokine profile in each participant was not performed. Samples which could be used to assess the adipokine profile (including high molecular weight adiponectin in serum, and a urinary adiponectin profile) are stored, and analysis is planned (subject to funding).
7.6. Future Studies

Numerous persisting knowledge gaps are identified through this detailed study of body composition, inflammation and chronic disease risk in Aboriginal people and Torres Strait Islander people. Potential research questions to some of these issues are outlined below.

The use of a 2-hour 75 gram oral glucose tolerance test and the measurement of fasting and 2-hour glucose and insulin in future studies of body composition and health risk in Aboriginal people and Torres Strait Islander people. This would provide a more robust evaluation of insulin sensitivity profile in individuals. It was not possible to incorporate this test into an already detailed thesis methodology. Glucose clamp methodology is not a realistic option for this population. Assessment of insulin sensitivity could also be achieved in a small study comparing a single serum adipokine measure (adiponectin, or high molecular weight isoform) with a frequently measured glucose tolerance test in Aboriginal adults and Torres Strait Islander adults, providing a useful clinical reference of insulin sensitivity in future studies.

Extending body composition and health risk studies to the potential renal transplant recipient. Transplantation offers numerous health advantages (over maintenance dialysis therapy), however access to transplantation and outcomes are poor for Indigenous Australians, compared to other Australians (McDonald 2010; Rogers et al. 2006). Currently a BMI more than 30 kg/m\(^2\) precludes transplant assessment in our area (Darwin, NT) due to anaesthetic and acute surgical risk. We suggest a BMI threshold of 30 kg/m\(^2\) is excessive in Aboriginal patients and does not present sufficient cardio-metabolic risk protection in the pre or post-transplant setting. A more appropriate cut-off may be the waist to hip ratio, with maximal threshold of 0.9 and 0.85 in Indigenous men and women respectively. Further study would be required to ascertain the long-term safety of these targets in Indigenous adults with severe renal disease.

Extending body composition and health risk studies to the dialysis patient. A paradox of low-BMI and higher cardiovascular risk is reported in Caucasian adults
requiring dialysis (Johansen 2010). We have shown a higher WHR for BMI in Aboriginal people was associated with an unfavourable cardio-metabolic profile, therefore, this reported paradox may not be accurate for Aboriginal people. Assessment of outcomes of diabetes complications and cardiovascular disease risk in relation to WHR may identify a healthy optimal level of adiposity in Indigenous Australians who require dialysis.

**Body surface area (BSA).** Body surface area is a function of measured weight and height in an individual. The normalisation of kidney function based on the $1.73\,m^2$ body surface area used in the reporting of estimated-GFR (Levey et al. 1999), was based on a theoretical mathematical model of surface area in 9 adults conducted in 1916 (Du Bois et al. 1916). The bias of normalised BSA for Indigenous Australians may result from different geometry of body build to the original sample compared with the present day, where higher prevalence of obesity is more likely to result in lower relative BSA. The use of whole body DXA (fat and lean mass and skeletal dimensions), in combination with body weight and body circumferences may provide the evidence for the relationship of weight to lean mass, and therefore lean mass to BSA. This may improve creatinine-based measures of body composition, rather than assuming the relationship of a given serum creatinine for lean body mass is similar for all populations.

### 7.7. Conclusion

The convenience of labelling Aboriginal people and Torres Strait Islander people as “Indigenous Australians” should now be considered inaccurate in reference to body size and obesity, since they each have very specific body composition characteristics.

This is the first study to apply precise and accurate measures of body composition to these high risk populations. Several important insights have emerged. First, despite both groups having a longer leg-length and shorter torso than Caucasians, Torres Strait Islander participants have a more robust skeleton and relatively more muscle mass for a given height and weight than Aboriginal participants. Second, the high relative lean mass is likely to protect Torres Strait Islander people to some extent from the adverse impacts of weight gain in comparison to Aboriginal people. Third,
Aboriginal participants (particularly women) appeared to have a more adverse metabolic response to even modest weight gain, with very little capacity to store excess lipid in peripheral subcutaneous fat depots (in contrast to Caucasian and Torres Strait Islander participants). Therefore, Aboriginal participants demonstrate a strong tendency to deposit fat intra-abdominally without substantial change in body mass index, in contrast to other ethnic groups. Finally, among Aboriginal participants and Torres Strait Islander participants the pattern of high leptin and low adiponectin concentrations was closely related to a combination of high total and abdominal obesity, and as discussed (in Chapter 6) has the potential to lay a foundation for the establishment of kidney damage, and associated cardiovascular disease risk.
Appendix
Appendix 1. eGFR Study Questionnaire

Only the relevant excerpts from eGFR Study that was analysed and presented in the thesis are included here.

**Date:**
**Participant ID Number:**
**Gender:** Male/ Female
**Date of Birth:**

**Q1. Background:**
a) Aboriginal
b) Torres Strait Islander
c) Both Aboriginal & Torres Strait Islander
d) Non-Indigenous (please specify)

**Q2.** Usual place of residence: ________________

**Q3.** What region do you identify as coming from?
- a) Top End- Northern Territory
- b) Central Australia- Northern Territory
- c) Northern Queensland
- d) Torres Strait- Queensland
- e) Kimberley- Western Australia
- f) Gold Fields- Western Australia
- g) Other: ________________

**Q4.** Which location do you identify as being your home? ________________

**Q5.** What is your First language? ____________________________

**Q6.** What language do you currently speak the most at home?
- a) English
- b) Aboriginal or Torres Strait Islander language
- c) Other: ____________________________
Q7. Are any of your grand-parents non-Indigenous (non-Aboriginal or Torres Strait Islander)? Please indicate.
   a) Mother’s mother: ____________________________
   b) Mother’s father: _____________________________
   c) Father’s mother: _____________________________
   d) Father’s father: ______________________________
Q8. How often do you drink alcohol?
   a) Daily
   b) Weekly
   c) Monthly
   d) Never
Q9. Cigarette Smoker
   a) Current
   b) Ex
   c) Never
   Age started: _________________________________
   Age stopped: _______________________________
   No. cig/day: _______________________________
Q10. Medical History. Do you have a prior history of?

<table>
<thead>
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<th>Condition</th>
<th>Yes</th>
<th>No</th>
<th>Year Diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney Disease</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cause:</td>
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<tr>
<td>Hypertension</td>
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<td>High cholesterol</td>
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<td>Chest Pain</td>
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<tr>
<td>Myocardial infarction</td>
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<tr>
<td>CVA/ TIA</td>
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<tr>
<td>Rheumatoid Arthritis</td>
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<tr>
<td>Osteoporosis</td>
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<tr>
<td>Rheumatic Heart Disease</td>
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</tbody>
</table>

Data Source:
   a) Medical record
   b) Participant
Q11. Recent Health.
   a) Have you had an infection in the last three months? Yes No
   b) Do you have an infection right now? Yes No
   c) Is this the same illness Yes No

Q12. Additional Medical History
   a) ____
   b) ____
   c) ____
   d) ____

Q13. Current Medications
   Name    Dose  Frequency  Route  Adherence (1/2/3/4/5)
   a) ____
   b) ____
   c) ____
   d) ____

Adherence code:
1. not very often (<25% of the time)
2. occasionally (25-75% of the time)
3. Most of the time (>75%)
4. Always (100%)
5. not asked
Appendix 2  eGFR Study Data Collection Form

Date:       Participant ID Number:
Gender: Male/ Female   Date of Birth:

**Urinalysis**

<table>
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<tr>
<th></th>
<th>Neg</th>
<th>trace</th>
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<tr>
<td>Nitrite</td>
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<td>Pos</td>
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<tr>
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<td>Trace</td>
<td>+</td>
<td>++</td>
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</tbody>
</table>

ACR sent   Yes No N/A

Females Menses: Yes No N/A
Pregnancy test: Pos Neg N/A

**Body Measures**

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<tr>
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<th>2(^{nd})</th>
<th>3(^{rd})</th>
<th>Operator sig</th>
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<tbody>
<tr>
<td>Height (cm)</td>
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<tr>
<td>Weight (cm)</td>
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<tr>
<td>Waist (cm)</td>
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<tr>
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**Blood Pressure**

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<td>3(^{rd})</td>
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**Blood collected for:**

EUC LFT CRP HbA1c FBC Non-fasting lipids Spare Serum
**Bioelectrical Impedance Analysis:** Right side whole body

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<td>Xc:</td>
<td></td>
</tr>
<tr>
<td>Ph:</td>
<td></td>
</tr>
<tr>
<td>Filename if BIS</td>
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</table>
Appendix 3 Healthy Top-Enders’ Study Questionnaire

Only the relevant excerpts from The Healthy Top-Enders’ study that was analysed and presented in the thesis are included here.

Date: Participant ID Number: Gender: Male/ Female Date of Birth:

Q1. How do you describe your background?
   a) Aboriginal but not Torres Strait Islander
   b) Torres Strait Islander but not Aboriginal
   c) Both Aboriginal & Torres Strait Islander
   d) Neither Aboriginal or Torres Strait Islander

Q2. We are assessing “Top-Enders”, but we know people move around a lot. What region of Australia do you most strongly identify with?
   h) Top End- Northern Territory
   i) Other: ____________________

Q3. Usual place of residence: ________________

Q4. Some people move for work (for example), but they call “home” somewhere else. What location do you call home? ________________

Q5. What was the first language you spoke when you were growing up? ________________

Q6. What language do you speak at home the most now?
   d) English
   e) Aboriginal or Torres Strait Islander language
   f) Other: ________________________________

Q7. The ethnic background of our family influences what body shape we develop. What is the background of each of your grandparents?
   e) Mother’s mother: ____________________________
   f) Mother’s father: ____________________________
   g) Father’s mother: ____________________________
   h) Father’s father: ____________________________
The questions now focus on your health and lifestyle.

Q8. We are interested in cigarette smoking. What category best describes you at this time?
   a) I have never smoked cigarettes
   b) I am currently smoking.
   c) I am an Ex-smoker

Q9. What age did you start? ____________

Q10. What age did you stop? ____________

Q11. How many cigarettes did you smoke each day?___

We are interested in your alcohol use.

Q12. Do you drink alcohol? Yes (go to next question) / No

Q13. If you drink alcohol, How would you describe your alcohol use?
   a) Light drinker
   b) Moderate drinker
   c) Heavy drinker

Q14. How often do you drink alcohol?
   a) Every day
   b) once a week
   c) once a month
   d) other: _______________________________

Q15. If you do drink alcohol, how much do you drink each time?
   a) 1-2 Alcoholic drinks
   b) 3-4 Alcoholic drinks
   c) 5-9 Alcoholic drinks
   d) more than 10 Alcoholic drinks

Medical History.

Q16. We know you have told us you are healthy. Please tell us if you have ever had a problem with any of the following conditions?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
<th>Year Diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cause:</td>
</tr>
</tbody>
</table>

246
Hypertension       Yes  No  Year Diagnosed
High cholesterol   Yes  No  Year Diagnosed
Chest Pain         Yes  No  Year Diagnosed
Myocardial infarction  Yes  No  Year Diagnosed
CVA/ TIA           Yes  No  Year Diagnosed
Rheumatoid Arthritis Yes  No  Year Diagnosed
Osteoporosis       Yes  No  Year Diagnosed
Rheumatic Heart Disease Yes  No  Year Diagnosed

Data Source:
   c) Medical record
   d) Participant

Q17. Recent Health.
       d) Have you had an infection in the last three months?  Yes  No
       e) Do you have an infection right now?   Yes  No
       f) Is this the same illness       Yes  No

Q18. Additional Medical History
       e) ____
       f) ____
       g) ____

Q19. Current Medications: Do you take any regular medications?  Yes     No
       Name   Dose  Frequency  Route  Adherence (1/2/3/4/5)
       e) ____
       f) ____
       g) ____

Adherence code:
1. not very often (<25% of the time)
2. occasionally (25-75% of the time)
3. Most of the time (>75% )
4. Always (100%)
5. not asked
Appendix 4  Healthy Top-Enders’ Study Data Collection Form

Date:                                                    Participant ID Number:
Gender: Male/ Female                                       Date of Birth:
Handedness: Right / Left

Fasting blood sample: Time taken _______ Fasted From (Date, Time):

________

Urinalysis
Glucose        Neg  trace  +  ++  +++  ++++
Blood          Neg  Trace  Small  Mod  Large
Protein        Neg  Trace  +  ++  +++  ++++
Nitrite        Neg  Pos
Leucocytes     Neg  Trace  +  ++  +++

ACR sent       Yes  No  N/A

Females
Menses:         Yes  No  N/A
Pregnancy test:  Pos  Neg  N/A

Body Measures

<table>
<thead>
<tr>
<th>Height (cm)</th>
<th>1&lt;sup&gt;st&lt;/sup&gt;</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt;</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt;</th>
<th>Operator sig</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>__________</td>
<td>__________</td>
<td>__________</td>
<td>__________</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight (cm)</th>
<th>1&lt;sup&gt;st&lt;/sup&gt;</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt;</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>__________</td>
<td>__________</td>
<td>__________</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Waist (cm)</th>
<th>1&lt;sup&gt;st&lt;/sup&gt;</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt;</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>__________</td>
<td>__________</td>
<td>__________</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hips (cm)</th>
<th>1&lt;sup&gt;st&lt;/sup&gt;</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt;</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>__________</td>
<td>__________</td>
<td>__________</td>
</tr>
</tbody>
</table>

Blood Pressure

<table>
<thead>
<tr>
<th>Systolic</th>
<th>Diastolic</th>
<th>Operator sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>__________</td>
<td>__________</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>__________</td>
<td>__________</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>__________</td>
<td>__________</td>
</tr>
</tbody>
</table>
**Blood collected for:**
EUC, CMP, LFT, CRP, BSL, HbA1c, FBC, Fasting lipids, Insulin, PTH  
Spare Serum

**Bioelectrical Impedance Analysis:** Right side whole body

<table>
<thead>
<tr>
<th>Z:</th>
<th>Xc:</th>
</tr>
</thead>
<tbody>
<tr>
<td>R:</td>
<td>Ph:</td>
</tr>
</tbody>
</table>

Filename if BIS:

<table>
<thead>
<tr>
<th>Whole Body Scan</th>
<th>Calibration date:</th>
<th>Date of scan:</th>
<th>Appointment time</th>
<th>Scan Operator:</th>
<th>SG/ JH: ___</th>
</tr>
</thead>
</table>

Notes:

<table>
<thead>
<tr>
<th>CT Attended</th>
<th>Yes</th>
<th>No</th>
<th>Data sent to St Vincent’s Hospital:</th>
</tr>
</thead>
</table>

Date:

Data Analysed and Returned from St Vincent’s Hospital:

<table>
<thead>
<tr>
<th>Data Analysed and Returned from St Vincent’s Hospital:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (Date)</td>
</tr>
<tr>
<td>Name</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>D</td>
</tr>
<tr>
<td>E</td>
</tr>
<tr>
<td>F</td>
</tr>
<tr>
<td>G</td>
</tr>
<tr>
<td>H</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>J</td>
</tr>
</tbody>
</table>

Bioelectrical impedance measures at 50 kHz. $\text{r}=$resistance; $\text{Xc}=$reactance; $\text{Z}=$impedance. Gender: male=1, female=0.

All equations are for use in populations older than 16 years.
## Appendix Table 2: Univariate Associations of Log-CRP with other Biomarkers: Healthy Top-Enders’ Study, Chapter 4

<table>
<thead>
<tr>
<th>CRP (mg/L)*</th>
<th>All (n=49)</th>
<th>Aboriginal Males (n=15)</th>
<th>Non-Indigenous Males (n=10)</th>
<th>Aboriginal Females (n=16)</th>
<th>Non-Indigenous Females (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOMA *</td>
<td>0.3963 (0.0048)</td>
<td>0.56 (0.09)</td>
<td>0.6431 (0.0097)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adiponecint (ng/ml)*</td>
<td>-0.5167 (0.0001)</td>
<td></td>
<td></td>
<td>-0.5973 (0.015)</td>
<td>-0.6589 (0.054)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)*</td>
<td>-0.5087 (0.0002)</td>
<td>-0.757 (0.01)</td>
<td>-0.4946 (0.0609)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6 (pg/ml)*</td>
<td>0.3446 (0.0143)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Biochemical variables are all log transformed. Values indicate correlation coefficient, r and p-value in brackets. Blank windows indicate non-statistically significant relationships (p>0.09). N=50 for adiponecint and IL6. N=49 for HOMA and HDL cholesterol.
### Appendix Table 3 Univariate Relationships of Body Composition Measures in Healthy Top-Enders’ Study, Chapter 4

<table>
<thead>
<tr>
<th></th>
<th>WHR</th>
<th>BMI (kg/m²)</th>
<th>L2-L3 SAD (mm)</th>
<th>Waist (cm)</th>
<th>Fat Percent (%)</th>
<th>Fat Mass (kg)</th>
<th>L2-L3 SFA (cm²)</th>
<th>L2-L3 VFA (cm²)</th>
<th>Trunk Fat Mass (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist (cm)</td>
<td>0.9267</td>
<td>0.7383</td>
<td>0.9496</td>
<td>0.9267</td>
<td>0.9496</td>
<td>0.9267</td>
<td>0.9496</td>
<td>0.9496</td>
<td>0.9267</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1.0</td>
<td>1.0</td>
<td>0.5902</td>
<td>1.0</td>
<td>0.5902</td>
<td>1.0</td>
<td>0.5902</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>L2-L3 SAD (mm)</td>
<td>0.7045</td>
<td>0.6398</td>
<td>0.8855</td>
<td>0.7045</td>
<td>0.8855</td>
<td>0.7045</td>
<td>0.8855</td>
<td>0.7045</td>
<td>0.8855</td>
</tr>
<tr>
<td>Fat Percent (%)</td>
<td>0.5246*</td>
<td>0.05430</td>
<td>0.3183***</td>
<td>1.0</td>
<td>0.3183***</td>
<td>1.0</td>
<td>0.3183***</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Fat Mass (kg)</td>
<td>0.5078</td>
<td>0.06375</td>
<td>0.8048</td>
<td>1.0</td>
<td>0.8048</td>
<td>1.0</td>
<td>0.8048</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>L2-L3 SFA (cm²)</td>
<td>0.0984</td>
<td>0.08741</td>
<td>0.7410</td>
<td>1.0</td>
<td>0.7410</td>
<td>1.0</td>
<td>0.7410</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>L2-L3 VFA (cm²)</td>
<td></td>
<td>0.8098</td>
<td>0.6946</td>
<td>1.0</td>
<td>0.6946</td>
<td>1.0</td>
<td>0.6946</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

n=52, P<0.0001, unless otherwise indicated: *P<0.005, **P<0.05, Trunk FM *P<0.001, L2-L3 VFA *P<0.004.
## Appendix Table 4

**Univariate Relationships of Visceral Fat Area (VFA) and Sagittal Abdominal Diameter (SAD) (L2-L3) and Biomarkers in the Healthy Top-Enders' Study**

<table>
<thead>
<tr>
<th>Variable 1</th>
<th>Variable 2</th>
<th>All (n=52)</th>
<th>Aboriginal Males (n=15)</th>
<th>Non-Indigenous Males (n=10)</th>
<th>Aboriginal Females (n=16)</th>
<th>Non-Indigenous Females (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L2-L3 VFA (cm²)</td>
<td>CRP</td>
<td>0.5090 (0.0001)</td>
<td>0.5528 (0.0326)</td>
<td>0.5719 (0.0206)</td>
<td>-0.6606 (0.0053)</td>
<td></td>
</tr>
<tr>
<td>Adiponectin</td>
<td>-0.5583 (&lt;0.0001)</td>
<td>-0.4717 (0.0759)</td>
<td>0.4954 (0.0604)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMA</td>
<td>0.4438 (0.0010)</td>
<td>0.5622 (0.0364)</td>
<td>0.7282 (0.0169)</td>
<td>0.4954 (0.0604)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| L2-L3 SAD (mm) | CRP | 0.5610 (<0.0001) | 0.5305 (0.0419) | 0.6477 (0.0067) |
| Adiponectin | -0.5419 (<0.0001) | -0.5526 (0.0327) | -0.6651 (0.0049) |
| HOMA | 0.5369 (<0.0001) | 0.4855 (0.0784) | 0.7858 (0.0070) | 0.6875 (0.0046) | 0.6043 (0.0489) |

SAD: sagittal abdominal diameter. * indicates biomarker data are log-transformed. Data are expressed as correlation coefficient (r) and p-value. Blank windows indicate non-significant relationships (p>0.08). In Aboriginal participants HOMA measured in n=14 males and 15 females. In non-Indigenous females, adiponectin measured in n=9, CRP measured in n=10.
Appendix Table 5  eGFR Study DXA sub-study: Main effects of Ethnicity, Gender, Age, eGFR, Albuminuria (continuously) and Diabetes on Measures of Body Size and Composition.

<table>
<thead>
<tr>
<th></th>
<th>Ethnicity</th>
<th>Gender</th>
<th>Age</th>
<th>eGFR</th>
<th>Diabetes</th>
<th>log-ACR</th>
<th>Ethnicity X Gender interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>0.0857</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.9574</td>
<td>0.7937</td>
<td>0.9551</td>
<td>0.9562</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.0122</td>
<td>&lt;0.0001</td>
<td>0.4176</td>
<td>0.2458</td>
<td>0.0004</td>
<td>0.2645</td>
<td>0.7822</td>
</tr>
<tr>
<td>Waist (cm) *</td>
<td>0.2468</td>
<td>0.1532</td>
<td>0.0185</td>
<td>0.4951</td>
<td>&lt;0.0001</td>
<td>0.2165</td>
<td>0.3226</td>
</tr>
<tr>
<td>Hips (cm) *</td>
<td>0.0063</td>
<td>0.0244</td>
<td>0.1819</td>
<td>0.2352</td>
<td>0.0049</td>
<td>0.9082</td>
<td>0.1529</td>
</tr>
<tr>
<td>Waist: Hip ratio *</td>
<td>0.0060</td>
<td>&lt;0.0001</td>
<td>0.0050</td>
<td>0.6184</td>
<td>&lt;0.0001</td>
<td>0.0765</td>
<td>0.5736</td>
</tr>
<tr>
<td>Body mass Index (kg/m²)</td>
<td>0.0033</td>
<td>0.8826</td>
<td>0.1216</td>
<td>0.1200</td>
<td>&lt;0.0001</td>
<td>0.2204</td>
<td>0.6884</td>
</tr>
<tr>
<td>Resistance (50 kHz) *</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.2870</td>
<td>0.1721</td>
<td>0.0018</td>
<td>0.8698</td>
<td>0.8912</td>
</tr>
<tr>
<td>Fat Mass (kg)</td>
<td>0.7448</td>
<td>&lt;0.0001</td>
<td>0.0154</td>
<td>0.1405</td>
<td>0.0136</td>
<td>0.5045</td>
<td>0.7768</td>
</tr>
<tr>
<td>Fat Percent (%)</td>
<td>0.0003</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.1227</td>
<td>0.2966</td>
<td>0.9185</td>
<td>0.5997</td>
</tr>
<tr>
<td>Lean Mass (non bone) (kg)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0112</td>
<td>0.3254</td>
<td>0.0018</td>
<td>0.1392</td>
<td>0.4204</td>
</tr>
<tr>
<td>Bone Mass (kg)</td>
<td>0.0144</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.9697</td>
<td>0.0167</td>
<td>0.8136</td>
<td>0.7959</td>
</tr>
<tr>
<td>Trunk Fat Mass (kg)</td>
<td>0.5920</td>
<td>&lt;0.0001</td>
<td>0.0097</td>
<td>0.1926</td>
<td>0.0015</td>
<td>0.4830</td>
<td>0.7691</td>
</tr>
<tr>
<td>Peripheral Fat Mass (kg)</td>
<td>0.9654</td>
<td>&lt;0.0001</td>
<td>0.0021</td>
<td>0.1740</td>
<td>0.1971</td>
<td>0.6421</td>
<td>0.8456</td>
</tr>
<tr>
<td>Trunk: Peripheral Fat Ratio</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0204</td>
<td>0.3931</td>
<td>&lt;0.0001</td>
<td>0.5351</td>
<td>0.6186</td>
</tr>
<tr>
<td>Trunk Lean (non bone) (kg)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.3493</td>
<td>0.2295</td>
<td>0.0003</td>
<td>0.0333</td>
<td>0.3417</td>
</tr>
<tr>
<td>Peripheral Lean (non bone) (kg)</td>
<td>0.0026</td>
<td>&lt;0.0001</td>
<td>0.0015</td>
<td>0.6460</td>
<td>0.0310</td>
<td>0.2333</td>
<td>0.5409</td>
</tr>
<tr>
<td>Leg-length% of Height</td>
<td>&lt;0.0001</td>
<td>0.0751</td>
<td>0.0031</td>
<td>0.2544</td>
<td>0.2296</td>
<td>0.6832</td>
<td>0.4306</td>
</tr>
<tr>
<td>Pelvis width as% of Height</td>
<td>&lt;0.0001</td>
<td>0.0149</td>
<td>&lt;0.0001</td>
<td>0.0120</td>
<td>0.3855</td>
<td>0.7544</td>
<td>0.6763</td>
</tr>
</tbody>
</table>

*: Aboriginal, n=47 for waist, hips, WHR. n=41 for Resistance. *TSI: n=75 for waist, hips, WHR. n=73 for resistance. * n=26 for Caucasians. log-ACR, age and eGFR are continuous variables.
Appendix Table 6  The eGFR Study: Median Adiponectin and Leptin Concentrations in Participants, across Strata of Kidney Function, expressed as eGFR CKD-EPI.

<table>
<thead>
<tr>
<th>Median Adiponectin and Leptin Levels in Participants, expressed in eGFR-CKD-EPI categories of Kidney Function</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aboriginal</td>
<td>Torres Strait Islander</td>
</tr>
<tr>
<td>Adiponectin (ug/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR≥90</td>
<td>2.72 (1.90, 3.96)</td>
<td>2.48 (1.99, 3.29)</td>
</tr>
<tr>
<td>eGFR 60-89</td>
<td>2.54 (1.76, 3.51)</td>
<td>3.01 (2.02, 4.13)</td>
</tr>
<tr>
<td>eGFR &lt;60</td>
<td>4.71 (3.19, 7.55)</td>
<td>3.89 (3.00, 4.26)</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR≥90</td>
<td>5.33 (2.07, 16.76)</td>
<td>6.27 (2.67, 11.92)</td>
</tr>
<tr>
<td>eGFR 60-89</td>
<td>9.96 (4.89, 15.48)</td>
<td>8.95 (4.02, 25.67)</td>
</tr>
<tr>
<td>eGFR &lt;60</td>
<td>16.51 (5.33, 26.10)</td>
<td>24.09 (13.02, 34.35)</td>
</tr>
</tbody>
</table>

Data are median (IQR), n. Units for Adiponectin (ug/ml), and Leptin (ng/ml). Kidney Function Strata expressed as eGFR-CKD-EPI in ml/min/1.73m².
Appendix Table 7  The eGFR Study: Pair-wise Correlations of Log-Adiponectin with Body & Biochemical Measures

<table>
<thead>
<tr>
<th>Log-Adiponectin Correlated with the following variables:</th>
<th>Aboriginal Males</th>
<th>Torres Strait Islander Males</th>
<th>Aboriginal Females</th>
<th>Torres Strait Islander Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist (cm)</td>
<td>-0.3153 0.0001 155</td>
<td>-0.2414 0.1145 44</td>
<td>-0.2018 0.0010 263</td>
<td>-0.2867 0.0196 66</td>
</tr>
<tr>
<td>Hips (cm)</td>
<td>-0.3486 &lt;0.0001 157</td>
<td>-0.1353 0.3813 44</td>
<td>-0.1097 0.0714 271</td>
<td>-0.0091 0.9425 66</td>
</tr>
<tr>
<td>WHR</td>
<td>-0.1611 0.0467 153</td>
<td>-0.2604 0.0878 44</td>
<td>-0.1534 0.0129 262</td>
<td>-0.4987 &lt;0.0001 65</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>-0.2984 0.0001 157</td>
<td>-0.2091 0.1681 45</td>
<td>-0.1654 0.0054 281</td>
<td>-0.2138 0.0800 68</td>
</tr>
<tr>
<td>eGFR</td>
<td>-0.2701 0.0006 157</td>
<td>-0.2614 0.0866 44</td>
<td>-0.3794 &lt;0.0001 280</td>
<td>-0.1956 0.1127 67</td>
</tr>
<tr>
<td>Log-CRP</td>
<td>-0.0022 0.6223 151</td>
<td>-0.2103 0.1869 41</td>
<td>-0.1772 0.0032 275</td>
<td>-0.2597 0.0367 65</td>
</tr>
<tr>
<td>Log-HDL</td>
<td>-0.0404 0.6223 151</td>
<td>-0.0690 0.6641 42</td>
<td>0.2093 0.0006 267</td>
<td>-0.0655 0.6128 62</td>
</tr>
<tr>
<td>Log-ACR</td>
<td>0.2277 0.0044 155</td>
<td>-0.0544 0.7291 43</td>
<td>0.1939 0.0014 269</td>
<td>-0.0264 0.8349 65</td>
</tr>
</tbody>
</table>

Pair-wise correlation relationships of log-adiponectin with measures, data are correlation coefficient, p value, and participant number.
Appendix Table 8  The eGFR Study: Pair-wise Correlations of Log-Leptin with Body & Biochemical Measures

<table>
<thead>
<tr>
<th>Log-Leptin Correlated with the following variables:</th>
<th>Aboriginal Males</th>
<th>Torres Strait Islander Males</th>
<th>Aboriginal Females</th>
<th>Torres Strait Islander Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist (cm)</td>
<td>0.8227</td>
<td>0.8405</td>
<td>0.6291</td>
<td>0.7310</td>
</tr>
<tr>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>155</td>
<td>44</td>
<td>271</td>
<td>66</td>
</tr>
<tr>
<td>Hips (cm)</td>
<td>0.7512</td>
<td>0.7510</td>
<td>0.6091</td>
<td>0.7195</td>
</tr>
<tr>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>157</td>
<td>44</td>
<td>263</td>
<td>66</td>
</tr>
<tr>
<td>WHR</td>
<td>0.6197</td>
<td>0.5828</td>
<td>0.2283</td>
<td>0.2864</td>
</tr>
<tr>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0002</td>
<td>0.0207</td>
</tr>
<tr>
<td></td>
<td>153</td>
<td>44</td>
<td>262</td>
<td>65</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.8050</td>
<td>0.7835</td>
<td>0.6273</td>
<td>0.7206</td>
</tr>
<tr>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>157</td>
<td>45</td>
<td>281</td>
<td>68</td>
</tr>
<tr>
<td>eGFR</td>
<td>-0.2190</td>
<td>-0.5173</td>
<td>-0.2121</td>
<td>0.0976</td>
</tr>
<tr>
<td></td>
<td>0.0059</td>
<td>0.0003</td>
<td>0.0004</td>
<td>0.4319</td>
</tr>
<tr>
<td></td>
<td>157</td>
<td>44</td>
<td>280</td>
<td>67</td>
</tr>
<tr>
<td>Log-CRP</td>
<td>-0.0178</td>
<td>0.1432</td>
<td>0.3107</td>
<td>0.3714</td>
</tr>
<tr>
<td></td>
<td>0.8263</td>
<td>0.3717</td>
<td>&lt;0.0001</td>
<td>0.0023</td>
</tr>
<tr>
<td></td>
<td>154</td>
<td>41</td>
<td>275</td>
<td>65</td>
</tr>
<tr>
<td>Log-HDL</td>
<td>0.0490</td>
<td>0.3186</td>
<td>0.0322</td>
<td>0.1547</td>
</tr>
<tr>
<td></td>
<td>0.5500</td>
<td>0.0397</td>
<td>0.6006</td>
<td>0.2300</td>
</tr>
<tr>
<td></td>
<td>151</td>
<td>42</td>
<td>267</td>
<td>62</td>
</tr>
<tr>
<td>Log-ACR</td>
<td>0.2694</td>
<td>0.4015</td>
<td>0.0821</td>
<td>0.1730</td>
</tr>
<tr>
<td></td>
<td>0.0007</td>
<td>0.0076</td>
<td>0.1794</td>
<td>0.1681</td>
</tr>
<tr>
<td></td>
<td>155</td>
<td>43</td>
<td>269</td>
<td>65</td>
</tr>
</tbody>
</table>

Pair-wise correlation relationships of log-adiponectin with measures, data are correlation coefficient, p value, and participant number.
## Appendix Table 9 The eGFR Study: Pair-wise Correlations of Log-A:L Ratio with Body & Biochemical Measures

<table>
<thead>
<tr>
<th>Log-A:L Ratio Correlated with the following variables:</th>
<th>Aboriginal Males</th>
<th>Torres Strait Islander Males</th>
<th>Aboriginal Females</th>
<th>Torres Strait Islander Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist (cm)</td>
<td>-0.8358 &lt;0.0001 153</td>
<td>-0.8320 &lt;0.0001 44</td>
<td>-0.6321 &lt;0.0001 263</td>
<td>-0.7256 &lt;0.0001 66</td>
</tr>
<tr>
<td>Hips (cm)</td>
<td>-0.7839 &lt;0.0001 157</td>
<td>-0.7182 &lt;0.0001 44</td>
<td>-0.5767 &lt;0.0001 271</td>
<td>-0.5981 &lt;0.0001 66</td>
</tr>
<tr>
<td>WHR</td>
<td>-0.8112 &lt;0.0001 157</td>
<td>-0.6060 &lt;0.0001 44</td>
<td>-0.2665 &lt;0.0001 262</td>
<td>-0.4474 0.0002 65</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>-0.8112 &lt;0.0001 157</td>
<td>-0.7702 &lt;0.0001 45</td>
<td>-0.6142 &lt;0.0001 281</td>
<td>-0.6791 &lt;0.0001 68</td>
</tr>
<tr>
<td>eGFR</td>
<td>0.0878 0.2744 157</td>
<td>0.3868 0.0095 44</td>
<td>0.0089 0.8820 280</td>
<td>-0.1623 0.1894 67</td>
</tr>
<tr>
<td>Log-CRP</td>
<td>0.0146 0.8571 154</td>
<td>-0.1972 0.2166 41</td>
<td>-0.3464 &lt;0.0001 275</td>
<td>-0.4081 0.0007 65</td>
</tr>
<tr>
<td>Log-HDL</td>
<td>-0.0573 0.4845 151</td>
<td>-0.2694 0.0845 42</td>
<td>0.0700 0.2542 267</td>
<td>-0.1528 0.2357 62</td>
</tr>
<tr>
<td>Log-ACR</td>
<td>-0.1465 0.0690 155</td>
<td>-0.3885 0.0100 43</td>
<td>0.0165 0.7880 269</td>
<td>-0.1534 0.2225 65</td>
</tr>
</tbody>
</table>

Pair-wise correlation relationships of log-adiponec tin with measures, data are correlation coefficient, p value, and participant number.
### Appendix Table 10 The eGFR Study: Results of Factor Analysis in Males Without Diabetes (n=113)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Factor 1</th>
<th>Factor 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total &amp; Central adiposity and Adipokines”</td>
<td>“Kidney Damage, HbA1c, WHR &amp; Age”</td>
</tr>
<tr>
<td>Aboriginal (v Torres Strait Islander)</td>
<td>-0.3028</td>
<td>0.2774</td>
</tr>
<tr>
<td>Age, years</td>
<td>0.2911</td>
<td>0.7153</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>0.9676</td>
<td>-0.0748</td>
</tr>
<tr>
<td>WHR</td>
<td>0.6629</td>
<td>0.6000</td>
</tr>
<tr>
<td>Waist</td>
<td>0.9719</td>
<td>0.1809</td>
</tr>
<tr>
<td>Smoker</td>
<td>-0.2951</td>
<td>0.0178</td>
</tr>
<tr>
<td>eGFR-MDRD, ml/min/1.73m$^2$</td>
<td>0.1109</td>
<td>-0.5889</td>
</tr>
<tr>
<td>Log-HDL cholesterol</td>
<td>-0.0357</td>
<td>0.2224</td>
</tr>
<tr>
<td>Log-CRP</td>
<td>-0.0617</td>
<td>0.2180</td>
</tr>
<tr>
<td>Log-ACR</td>
<td>-0.0017</td>
<td>0.6347</td>
</tr>
<tr>
<td>Log-HbA1c</td>
<td>0.1794</td>
<td>0.4012</td>
</tr>
<tr>
<td>Log-Adiponectin</td>
<td>-0.4594</td>
<td>0.1701</td>
</tr>
<tr>
<td>Log-Leptin</td>
<td>0.8093</td>
<td>0.2021</td>
</tr>
<tr>
<td>% Variance Explained</td>
<td>55.2</td>
<td>32.6</td>
</tr>
</tbody>
</table>

12 Factors assessed in 113 participants. These two factors explain 87.8% of cumulative variance in factors in non-diabetic males.
Appendix Table 11  The eGFR Study: Results of Factor Analysis in Females Without Diabetes (n=172)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Factor 1</th>
<th>Factor 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>“Total &amp; Central Adiposity &amp; Metabolic factors”</td>
<td>“Age, Kidney damage and HDL-cholesterol”</td>
</tr>
<tr>
<td>Aboriginal (v Torres Strait Islander)</td>
<td>0.1230</td>
<td>0.1897</td>
</tr>
<tr>
<td>Age, years</td>
<td>0.2285</td>
<td>0.5420</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.8076</td>
<td>-0.0539</td>
</tr>
<tr>
<td>WHR</td>
<td>0.5132</td>
<td>0.1275</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>0.9302</td>
<td>0.0009</td>
</tr>
<tr>
<td>Smoker</td>
<td>-0.0901</td>
<td>-0.2696</td>
</tr>
<tr>
<td>eGFR-MDRD, ml/min/1.73m²</td>
<td>0.0278</td>
<td>-0.4813</td>
</tr>
<tr>
<td>Log-HDL cholesterol</td>
<td>-0.1262</td>
<td>0.4079</td>
</tr>
<tr>
<td>Log-CRP</td>
<td>0.4586</td>
<td>0.1718</td>
</tr>
<tr>
<td>Log-ACR</td>
<td>-0.0291</td>
<td>0.5393</td>
</tr>
<tr>
<td>Log-HbA1c</td>
<td>0.4884</td>
<td>0.2444</td>
</tr>
<tr>
<td>Log-Adiponectin</td>
<td>-0.4351</td>
<td>0.1882</td>
</tr>
<tr>
<td>Log-Leptin</td>
<td>0.7055</td>
<td>0.1494</td>
</tr>
<tr>
<td>% Variance Explained</td>
<td>54.0</td>
<td>22.6</td>
</tr>
</tbody>
</table>

12 Factors assessed in 172 participants. These two factors explain 76.6% of cumulative variance in factors in non-diabetic females.
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