The Metabolic Syndrome.

Its validity, causes, consequences and uses.

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Summary

Obesity, hypertension, high blood glucose and triglycerides, and low HDL cholesterol are more likely to occur together. A clustering of these risk factors is defined clinically as the metabolic syndrome and indicates high risk of type 2 diabetes and cardiovascular disease. Using data from the nation-wide Australian Diabetes, Obesity and Lifestyle (AusDiab) study, and a comparable study in Mauritius, this thesis examined i) the prevalence of the metabolic syndrome in Australia, ii) whether obesity is the precursor to the development of the multiple abnormalities of the metabolic syndrome, iii) the health consequences of obesity, iv) whether waist cut-points for Europid and South Asian populations used in clinical definitions of the metabolic syndrome adequately reflect risk for type 2 diabetes and v) whether the metabolic syndrome is a valid and useful tool for the prediction of future type 2 diabetes. The AusDiab and Mauritius studies are both national, prospective cohort studies of adults. The AusDiab study involved 11,247 participants in 1999 with 6,537 of these followed-up five years later in 2004. The Mauritius study involved both five year (n=3,771) and eleven year (n=2,802) follow-up of a 1987 baseline cohort. The research reported here confirms i) a prevalence of the metabolic syndrome greater than 25% among Australian adults, regardless of the definition used, ii) that central obesity precedes the development of the other components of the metabolic syndrome, iii) that obesity confers a heightened five year risk for each of type 2 diabetes, the metabolic syndrome, hypertension, dyslipidaemia and cardiovascular disease, iv) that at waist circumference cut-points used in definitions of the metabolic syndrome, a considerably greater five-year risk of diabetes exists in South Asians compared to Europids and v) that the metabolic syndrome is a strong predictor of incident diabetes over five years, but is no better than measurement of fasting glucose alone or published diabetes risk prediction scores. These findings suggest that the metabolic syndrome is a highly prevalent condition that confers a considerably increased risk of type 2 diabetes. The metabolic syndrome is shown here to be no better than other available tools or fasting glucose for estimation of diabetes risk, although clinical definitions were not designed solely for this purpose. The status of obesity in the metabolic syndrome should be as a pre-cursor to the development of the other abnormalities, not simply as one of several type 2 diabetes and cardiovascular disease risk factors. Finally, the results here indicate that waist circumference cut-points in current metabolic syndrome definitions require revision, at least for those of South Asian ancestry.

Associated publications, presentations and awards

Publications by the candidate produced during candidature relevant to the thesis

Cameron AJ, Magliano DJ, Zimmet PZ, Welborn T, Shaw JE.
The Metabolic Syndrome in Australia: Prevalence using four definitions. *Diabetes Res Clin Pract*. 2007;77(3):471-478. (Impact factor 1.8)

Cameron AJ, Boyko EJ, Sicree RA, Zimmet PZ, Soderberg S, Alberti KGMM, Tuomilehto J, Chitson P, Shaw JE. Central obesity as a precursor to the Metabolic Syndrome in the AusDiab study and Mauritius. *Obesity*. 2008, 16; 12, 2707–2716. (Impact factor 3.1)

Cameron AJ, Dunstan DW, Owen N, Zimmet PZ, Barr ELM, Tonkin AM, Magliano DJ, Murray SG, Welborn TA, Shaw JE. Health and mortality consequences of obesity: evidence from the AusDiab study. In press, *Med J Aust*.

Cameron AJ, Sicree RA, Zimmet PZ, Alberti KGMM, Tonkin AM, Balkau B, Tuomilehto J, Chitson P, Shaw JE. Cut-points for waist circumference in Europids and South Asians. Submitted, *The Lancet*

Cameron AJ, Magliano DJ, Zimmet PZ, Welborn TE, Colagiuri S, Tonkin A, Shaw JE. The Metabolic Syndrome as a tool for predicting future diabetes. The AusDiab study. *J Int Med*. 2008; 264:177–186. (Impact factor 4.7)

Cameron AJ, Zimmet P, Soderberg S, Alberti K, Sicree R, Tuomilehto J, Chitson P, Shaw J. The metabolic syndrome as a predictor of incident diabetes mellitus in Mauritius. *Diabet Med*. 2007; 24(12):1460-9. (Impact factor 2.5)

Cameron AJ, Zimmet PZ, Shaw JE, Alberti KGMM. The Metabolic Syndrome: in need of a global mission statement. *Diabet Med* 2009;26(3):306-9. (Impact factor 2.5)

Additional publications by the candidate during candidature relevant to the thesis but not forming part of it.

Cameron AJ, Zimmet PZ. Expanding evidence for the Multiple Dangers of Epidemic Abdominal Obesity. *Circulation*. 2008;117;1624-1626. Appendix 1 (Impact factor 10.9)

Additional peer-reviewed publications by the candidate during candidature

Magliano DJ, Barr ELM, Zimmet PZ, **Cameron AJ**, Dunstan DW, Colagiuri S, Jolley D, Owen N, Phillips P, Tapp RJ, Welborn TA, Shaw JE. Glucose indices, health behaviours and incidence of diabetes in Australia: the AusDiab study. *Diab Care*. 2008 Feb;31(2):267-72. (Impact factor 7.9)

Sicree RA, Zimmet PZ, Dunstan DW, **Cameron AJ**, Shaw JE, Welborn TE. Differences in height and total body water explain gender differences in the response to the oral glucose tolerance test - the AusDiab study. *Diabet Med.* 2008; 25: 296-302. (Impact factor 2.5)

Barr ELM, Zimmet PZ, Welborn TA, Jolley D, Magliano DJ, Dunstan DW, **Cameron AJ**, Dwyer T, Taylor HR, Tonkin AM, Wong TY, McNeil J, Shaw JE. Risk of Cardiovascular and All-Cause Mortality in Individuals With Diabetes Mellitus, Impaired Fasting Glucose, and Impaired Glucose Tolerance. The Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). *Circulation*. 2007;116:151-157. (Impact factor 10.9)

Book chapters and non-peer-reviewed publications produced by the candidate during candidature

Cameron AJ, Shaw JE. Chapter 2, "Epidemiology of Metabolic Syndrome and Risk for Cardiovascular Disease and Diabetes" in the Atlas of Atherosclerosis and Metabolic Syndrome, Fifth edition, edited by Scott Grundy. 2009. Current Medicine Group, Philadelphia.

Cameron AJ, Shaw JE, Zimmet PZ. Chapter 7, "Diabetes and the Metabolic Syndrome", in Therapeutic Strategies in Lipid Disorders, edited by Tonkin, A., 2008. Clinical Publishing, Oxford.

Magliano DJ, **Cameron AJ**, Shaw JE and Zimmet PZ. "Epidemiology of Metabolic Syndrome" in The Epidemiology of Diabetes Mellitus, second edition, edited by Jean-Marie Eko´e, Marian Rewers, Rhys Williams and Paul Zimmet. 2008. John Wiley and Sons Ltd.

Cameron AJ, Zimmet PZ, Atkins RC, Shaw JE. The Australian Diabetes, Obesity and Lifestyle Study – Profiling Diabetes and Cardiovascular Disease Risk in the Nation. *European Endocrine Disease.* Vol 2. 2007.

Conference abstracts/presentations during candidature

Cameron AJ, Zimmet PZ, Alberti KGMM, Sicree RA, Tuomilehto J, Shaw JE. Questioning the appropriateness of recommended waist cut-points for Europids and Asian Indians based on relationships with incident diabetes. Oral poster presentation at the European Association for the Study of Diabetes (EASD) meeting, Rome, 2008.

Published abstract: Diabetologia, Vol 51, Suppl 1,S176; Meeting Abstract: 422

Sicree RA, Zimmet PZ, **Cameron AJ**, Dunstan DW, Magliano DJ, Welborn T, Shaw JE. Diabetes prevalence among migrant populations in Australia: prevalence and risk factor associations. Oral poster presentation at the European Association for the Study of Diabetes (EASD) meeting, Rome, 2008.

Published abstract: Diabetologia, Vol 51, Suppl 1,S178; Meeting Abstract: 427

Cameron AJ. Issues related to ethnicity in the use of waist circumference as a surrogate for visceral obesity in the Metabolic Syndrome. Presentation at the International Diabetes Federation Task Force on Epidemiology and Prevention of Diabetes meeting for a consensus definition of the Metabolic Syndrome, London, 2008.

Cameron AJ, Murray SG, Scholes B, Dunstan DW, Shaw JE. Do those with diagnosed diabetes have better diet and lifestyle patterns than those with newly diagnosed diabetes, IFG or IGT? Evidence from AusDiab. Oral presentation at the Australian Diabetes Society/Australian Diabetes Educators Association annual scientific meeting, Melbourne, 2008.

Cameron AJ, Shaw JE, Tonkin AM, Magliano D and Zimmet PZ, 2007, Is the Metabolic Syndrome a useful and necessary tool for prediction of diabetes? The AusDiab study. Oral presentation at the third Pre-diabetes and the Metabolic Syndrome conference, Barcelona, 2007.

Awards

2005 Heart Foundation of Australia (Victoria division): Top ranked postgraduate scholarship for Victoria

2007 Metabolic Syndrome Institute Award, Metabolic Syndrome Institute

2009 Commendation, Victorian Government Premier's Award for Health and Medical Research

Statement of contributions by candidate to the running of the AusDiab study.

The candidate has been involved in the AusDiab study as an epidemiologist since 2000. His contributions to the baseline survey include: responsibility for data cleaning and data management, liaison with academic partners and provision of data to approved researchers, authorship of reports to each Australian State Government as per the funding agreements and statistical analysis and authorship of peer-reviewed publications arising from the study. Between the baseline and five year follow-up surveys, the candidate was responsible for measures to maximise retention of participants, including maintaining annual contact with all participants, development of study newsletters and maintenance of the participant database. The candidate's contribution to the follow-up AusDiab survey include: assistance with the development of the successful NHMRC grant through which the survey was funded (including critical comment and revision, sample size estimates and sampling strategy development), development of survey tools (drafting of questionnaires, production of scannable forms, development of data entry and verification (real-time data checking) systems, assistance with the development of protocols and procedures manual and responsibility for all aspects of data management, database development, participant results letters and the storage and cleaning of final datasets. In addition, the candidate has authored and co-authored reports and peer-reviewed manuscripts resulting from this survey, and has regularly presented the results of the survey at health professional training courses and AusDiab collaborator meetings.

General declaration

In accordance with Monash University Doctorate Regulation 17/ Doctor of Philosophy and Master of Philosophy (MPhil) regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes 6 original papers published in peer reviewed journals and 1 unpublished publications. The core theme of the thesis is the validity, causes, consequences and uses of the Metabolic Syndrome. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Epidemiology Department, Baker IDI Heart and Diabetes Institute under the supervision of Associate Professor Jonathan Shaw and Professor Andrew Tonkin. The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of Chapters 1.2.6, 3.1, 3.2, 3.3, 3.4, 3.5.1, 3.5.2 and appendix 1, my contribution to the work involved the following:

Thesis chapter	Publication title	Publication status	Nature and extent of candidate's contribution
1.2.6	The Metabolic Syndrome: in need of a global mission statement.	Published	Design and drafting of manuscript (85%)
3.1	The Metabolic Syndrome in Australia: Prevalence using four definitions.	Published	Design, analysis, interpretation, drafting (55%)
3.2	Central obesity as a precursor to the Metabolic Syndrome in the AusDiab study and Mauritius.	Published	Design, analysis, interpretation, drafting (75%)
3.3	Health and mortality consequences of obesity: evidence from the AusDiab study.	In press	Design, analysis, interpretation, drafting (75%)
3.4	Questioning waist circumference cut-points for Europids and South Asians – an assessment of relationships with incident type 2 diabetes.	Submitted	Design, analysis, interpretation, drafting (85%)
3.5.1	The Metabolic Syndrome as a tool for predicting future diabetes. The AusDiab study.	Published	Design, analysis, interpretation, drafting (75%)
3.5.2	The metabolic syndrome as a predictor of incident diabetes mellitus in Mauritius.	Published	Design, analysis, interpretation, drafting (75%)
App. 1	Expanding evidence for the Multiple Dangers of Epidemic Abdominal Obesity.	Published	Drafting of manuscript (85%)

I have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Signed: ……………………………………………………………………………

Date: …………………………………

Copyright statement

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I certify that I have made all reasonable efforts to secure copyright permissions for third-party content included in this thesis and have not knowingly added copyright content to my work without the owner's permission.

Acknowledgements

List of abbreviations

NDI	–	National Death Index
CVD	–	Cardiovascular diseases
WHO	–	World Health Organization
NCD	–	Non-communicable diseases
OGTT	–	Oral glucose tolerance test
NCEP	–	(U.S.) National Cholesterol Education Program
ATPIII	–	Adult Treatment Panel III (of the National Cholesterol Education Program)
EGIR	–	European Group for the study of Insulin Resistance
IDF	–	International Diabetes Federation
HDL	–	High density lipoprotein (cholesterol)
BMI	–	Body mass index
WHR	–	Waist to hip ratio

Introduction

1.1 The metabolic syndrome and diabetes

Diabetes and the metabolic syndrome have been increasing in prevalence worldwide since at least the middle of the twentieth century. It appears that this trend is continuing apace into the new millennium.[1] The threat to health care systems, health financing and individual health and wellbeing that these two conditions represent in both developed and developing nations has been recently recognized in a United Nations resolution on diabetes, making diabetes only the second disease after AIDS to be recognized in this way.

Diabetes is now one of the most common non-communicable diseases globally, and the fourth or fifth leading cause of death in most developed countries.[2] The global prevalence was estimated to be 5.9% in 2007, representing almost a quarter of a billion people, about 90% of whom have type 2 diabetes. Projections suggest that this number will approach 400 million by 2025[2]. Strikingly, some 80% of those with diabetes in 2007 live in developing countries,[2] despite type 2 diabetes and the metabolic syndrome often being perceived as resulting from a "Western" lifestyle. The global epidemics of diabetes and the metabolic syndrome rest on the shoulders of an equally significant global rise in obesity.

The diabetes epidemic that many nations are now experiencing,[3] and which threatens to undermine the health budgets of most nations in the years to come,[4] has been shown to be part of a much broader underlying disorder. The core components of this condition include elevated plasma glucose as well as atherogenic dyslipidaemia, vascular dysfunction and inflammation, a pro-thrombotic state and a pro-inflammatory state.[5] Each of these components has several markers or constituents, as demonstrated in Figure 1. The metabolic syndrome is a clinical diagnosis designed to identify those with this characteristic clustering and is fast becoming the new focus for preventive efforts worldwide.

Figure 1. The core components of the metabolic syndrome (adapted from Grundy[5])
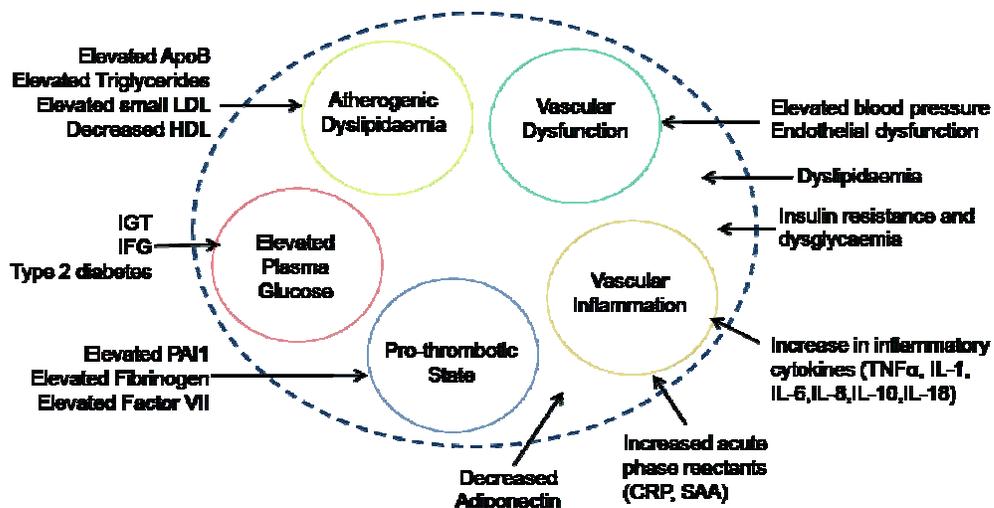
Considerable evidence now exists linking the metabolic syndrome and diabetes with an increased risk of cardiovascular diseases. Various estimates suggest that between one half and two thirds of deaths among people with diabetes are due to cardiovascular causes such as ischaemic heart disease and stroke.[6-8] Compared to those without diabetes, the risk of coronary artery disease, stroke and peripheral arterial disease is two to four times higher in the diabetic population, more particularly among women. Similarly, risk for cardiovascular diseases is elevated in those with the metabolic syndrome.[9] Many now see diabetes as having an equivalent risk for future cardiovascular disease events as that associated with previously diagnosed coronary heart disease.[10-12]

1.2   What is the metabolic syndrome?

1.2.1   Insulin resistance and the metabolic syndrome

The relationship of the metabolic syndrome to insulin resistance has been the cause of considerable controversy and a general misunderstanding of the significance of the metabolic syndrome. The terms metabolic syndrome and insulin resistance syndrome have often been used interchangeably, but the different names are a reflection of different underlying concepts and different goals.[13] Insulin resistance, which manifests as a reduction in insulin-mediated glucose disposal, has been recognized to be a precursor of hyperglycaemia and diabetes since the 1930s.[14] We now know that considerable variation exists in the insulin-mediated ability to dispose of glucose within the population.[15] Most insulin-resistant people are able to compensate with the production of extra insulin by the pancreatic beta cells. Individuals exhibiting otherwise normal glucose levels but hyperinsulinaemia are in fact not uncommon in the population. When the ability to compensate for insulin resistance can no longer be sustained, glucose intolerance and type 2 diabetes are the result.

Research has now shown that the hyperinsulinaemia required to maintain normal glucose levels in those with insulin resistance is actually a mixed blessing. In his 1988 Banting lecture,[16] Reaven spelled out the negative consequences of insulin resistance, which include an increased risk for glucose intolerance, high plasma triglyceride and low HDL cholesterol concentrations, and hypertension. Since these abnormalities increase the risk of cardiovascular disease (CVD), the most common cause of death in people with diabetes, it is assumed by association that insulin resistance must also have close links with CVD.

The "insulin resistance syndrome" was a label given to the numerous physiologic abnormalities and the related clinical outcomes that occur commonly in those with insulin

resistance.[13] The clinical syndromes associated with insulin resistance include not only type 2 diabetes and cardiovascular diseases, but also hypertension, polycystic ovary syndrome, non-alcoholic fatty liver disease, sleep apnoea and certain cancers.[13] It is true that those with insulin resistance do not necessarily develop any of these outcomes, and that all of these outcomes can occur in the absence of insulin resistance. Whether insulin resistance, the compensatory hyperinsulinaemia or another element such as obesity are responsible for the development of the abnormalities and clinical outcomes seen in the insulin resistance syndrome is gradually being clarified.[13]

The term "metabolic syndrome" has developed to describe those individuals at increased risk of type 2 diabetes and cardiovascular diseases due to the metabolic dysfunction apparent in the "insulin resistance syndrome", but without presuming an underlying cause. The obvious need for a clinical construct and research instrument has resulted in several recent clinical definitions of the metabolic syndrome being developed. As clinical constructs, these do not need to include all of the abnormalities associated with the metabolic dysfunction characteristic of the syndrome, and even include central obesity which is more often thought to be a cause rather than a consequence of metabolic dysfunction. An important goal of these definitions is to identify those individuals who do not yet have type 2 diabetes or cardiovascular diseases, but who are at high risk for both by virtue of a commonly observed clustering of metabolic risk factors. This thesis was designed to address several of the unanswered questions relating to commonly used clinical definitions of the metabolic syndrome.

1.2.2   Definitions of the metabolic syndrome

The four most widely recognized attempts to define the metabolic syndrome include proposals by: the World Health Organization (WHO) in 1998[17] (finalised in 1999[18]); the

European Group for the Study of Insulin Resistance (EGIR) also in 1999[19]; the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) in 2001[20] (updated in 2005[21]) and the International Diabetes Federation in 2006.[22]

The WHO recommendation that formed part of a consultation report on the definition, diagnosis and classification of diabetes mellitus and its complications was not designed to be an exact definition. Rather, it was formulated as a working guideline, to be improved upon in the future, that would enable comparability between studies, which to that time had been lacking. The WHO definition included a pre-requisite for either insulin resistance (measured using a euglycaemic clamp) or glucose intolerance (IFG, IGT or diabetes), in addition to at least two of obesity, hypertension, microalbuminuria and dyslipidaemia (hypertriglyceridaemia or reduced HDL cholesterol levels). In large scale epidemiology studies, the euglycaemic clamp method of measuring insulin resistance is impractical. Most studies therefore substitute this requirement with the calculation of insulin sensitivity using the HOMA model.[23]

Acknowledging that for risk prediction there was little point in the identification of those with the metabolic syndrome who already have diabetes, and that there was no simple way of measuring insulin resistance in individuals with diabetes, the European Group for the Study of Insulin Resistance (EGIR) proposed modifications to the WHO definition that should be used in non-diabetic subjects only. In addition, because of the difficulty in using a euglycaemic clamp method to measure insulin resistance, the EGIR version recommended that insulin resistance be defined as the top quartile of fasting insulin values in the non-diabetic population (a universal cut-off point for insulin measurement being impossible due to the different standards for assaying insulin). Obesity was defined by

waist circumference rather than BMI or waist to hip ratio (WHR), microalbuminuria was removed as a component and slightly modified cut-points for hypertension, triglycerides and HDL-cholesterol were proposed.[19] The focus of the proposal by the EGIR was the centrality of insulin resistance to the metabolic syndrome, arguing that no evidence to the contrary had as yet been presented. Exclusion of those with diabetes from this definition means that prevalence statistics cannot include the substantial proportion of the population with diabetes who also meet the criteria for the other components of the metabolic syndrome.

The U.S. NCEP Adult Treatment Panel (ATP) III definition of the metabolic syndrome proposed in 2001[20] (and updated in 2005 with ethnicity-specific cut-points for obesity)[21] was designed to be more amenable to measurement in clinical practice. The management of the metabolic syndrome according to ATPIII had two objectives: firstly to reduce the underlying causes (i.e. obesity and physical inactivity) of the components and their outcomes and secondly, to aid in identification of those requiring treatment for the component risk factors. A simplified structure included diagnosis with any three of five risk factors, and no requirement for an oral glucose tolerance test (OGTT), with the glucose component being based on measurement of fasting glucose only. Furthermore, no measurement of insulin resistance was included, reflecting the more clinically minded objectives of the ATPIII definition.

Finally, the International Diabetes Federation (IDF) definition[22] recognized that none of the previous recommendations had incorporated obesity criteria relevant to non-Caucasian populations. The IDF therefore proposed a definition that could be used as a diagnostic tool in clinical practice worldwide, with components identical to those used by the ATPIII, but

with overweight as a prerequisite component, and with ethnicity-specific cut-points for overweight.

The WHO, EGIR, ATPIII and IDF definitions are summarized in Table 1 of results chapter 3.1.

1.2.3 Metabolic Syndrome prevalence and choice of cut-points

Just as the prevalence of the component conditions (overweight, hypertension, hyperglycaemia and dyslipidaemia) is critically dependent on the definitions and cut-points used, so is the prevalence of the metabolic syndrome as a whole. The purpose of prevalence statistics for the metabolic syndrome is to provide an estimate of the current risk factor burden and the likely burden of cardiovascular diseases and type 2 diabetes that will result. In addition, prevalence statistics are useful for comparisons between populations or sub-populations, and for examination of trends over time. The existence of four competing definitions of the metabolic syndrome has been an impediment to these aims.

The prevalence of the metabolic syndrome, as well as its component conditions is entirely dependent on the choice of cut-points to dichotomize the population into those with and without the condition. The practice of dichotomizing continuous variables results in a loss of predictive power, but is necessary for clinical decision making and the creation of diagnostic categories. Calculation of a continuous metabolic risk score that takes advantage of the full spectrum of data available has been suggested, however such constructs have been recommended only for research purposes.[24]

Considerations in the choice of cut-points include:

- Whether cut-points should be related to relationships with a particular adverse outcome

- What that outcome is (or what those outcomes are)

- What percentage of the population is classified

- What statistical technique is most suitable for selecting cut-points

- Whether cut-points should vary by ethnicity, and

- Whether cut-points in the context of the metabolic syndrome should be the same as when the component is considered as a single risk factor

Given the number of competing priorities, it is not surprising that diagnostic criteria and cut-points are often chosen somewhat arbitrarily. Clinical definitions of the metabolic syndrome require cut-points for five or more risk factors as well as the choice of the structure of the syndrome itself, further complicating the choice of a definition.

The prevalence of the metabolic syndrome is dictated by multiple attributes of the population, many of which change over time. Genetic predisposition, levels of physical activity and inactivity, population age and sex structure, levels of over- and under-nutrition and body composition are all important. Regardless of the environmental and underlying genetic influences mediating the prevalence of the metabolic syndrome, a higher prevalence undoubtedly leads to a greater likelihood of undesirable outcomes such as type 2 diabetes and cardiovascular diseases. The prevalence of the metabolic syndrome in the AusDiab sample is reported in Chapter 3.1.

1.2.4 Underlying cause of the metabolic syndrome

As discussed earlier (Chapter 1.1.1), insulin resistance has been seen as the underlying cause of the numerous abnormalities and conditions associated with the metabolic syndrome. Epidemiologic research attempting to address the plausibility of this theory suffers from numerous problems,[25] and must be interpreted in the light of other basic

cellular or physiologic research. Insulin resistance is clearly associated with the clustering of abnormalities included in the metabolic syndrome, but whether it is the root cause is still the subject of debate. Obesity is an alternative candidate, but insulin resistance and obesity are closely linked and are not exactly mutually exclusive candidates for this role. Despite major advances in the understanding of the relationship between obesity and insulin resistance and their role in type 2 diabetes and cardiovascular disease, the physiologic mechanisms that link them are far from clear.[26] It is certainly true that both insulin resistance and obesity are closely linked with each of the component abnormalities of the metabolic syndrome (and each other). Recent evidence (chapter 3.2) supports the positioning of obesity at the start of the process that leads toward metabolic deterioration, and even before the development of insulin resistance. Figure 2 (adapted from Grundy)[27] illustrates the progression and outcomes of the process of metabolic deterioration and is supportive of the positioning of obesity prior to the development of the cardiovascular disease and type 2 diabetes risk factors that constitute the metabolic syndrome.

Figure 2. Progression and outcomes of the metabolic syndrome (adapted from Grundy)[28]
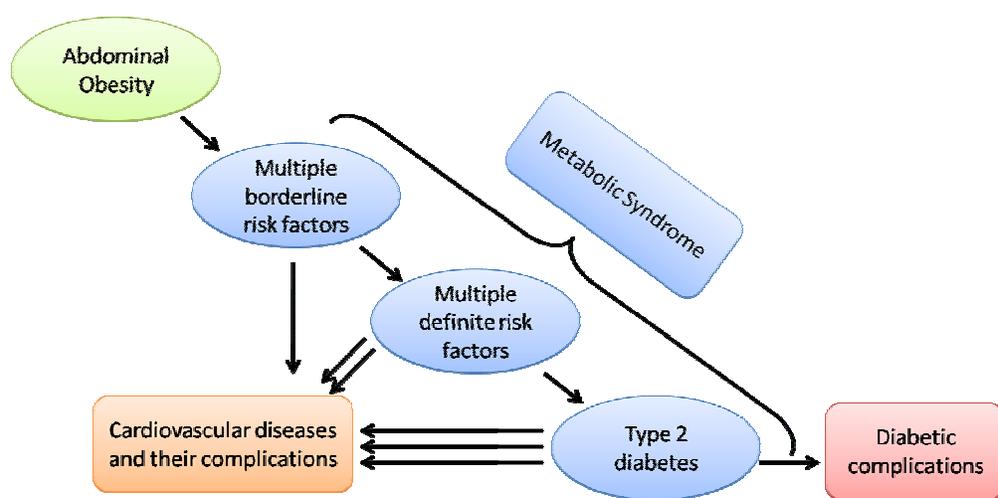
The recent discovery of novel factors such as inflammatory cytokines and endothelial dysfunction that are linked to components of the metabolic syndrome has led to the

development of a theory of an inflammation based causal pathway.[25] Since the

inflammatory process is thought to result from an excess of adipose tissue, obesity remains

as the preceding condition, but the metabolic syndrome components are linked through

their association with pro-inflammatory cytokines rather than insulin resistance (Figure

3).[25] Further critique of this model will no doubt come with new studies into the role of

inflammation and endothelial dysfunction on deterioration in metabolic syndrome

components. Whether a single mechanism can be identified as responsible for the metabolic

syndrome is doubtful considering the heterogeneity seen in the number and composition of

the constituent abnormalities.[22]

Figure 3. An inflammation centred paradigm of the metabolic syndrome (adapted from

Yudkin[25])
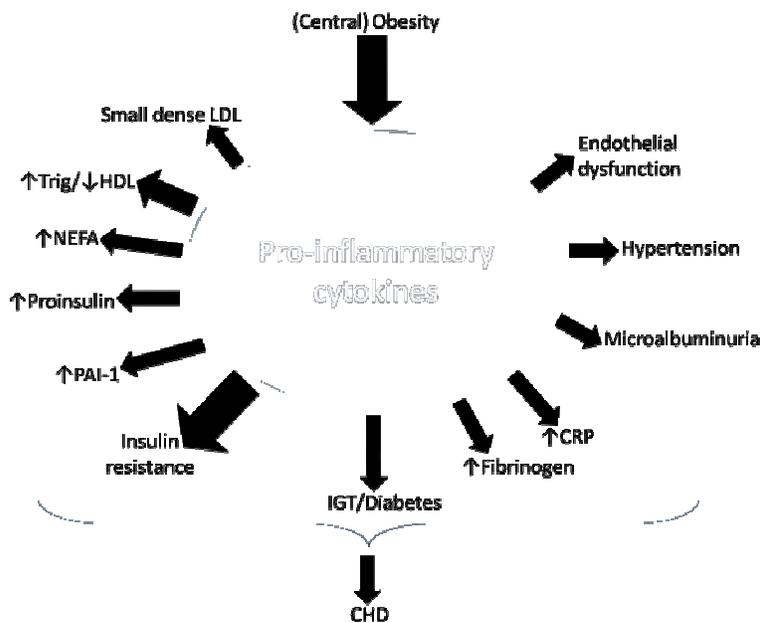
Factor analysis is one epidemiologic approach that lends itself to the exploration of the

underlying cause of the clustering seen in the metabolic syndrome. Factor analysis is a

statistical method that takes a large number of candidate variables and, based on the inter-

correlations between the variables, derives one or more factors consisting of smaller groups of related variables. A finding of one factor containing the variables of the metabolic syndrome may suggest a unifying physiologic mechanism (such as insulin resistance). Alternatively, if several factors are identified but a unifying factor is found in each factor, this could also be considered to be support for a common cause.[29]

Due to differences in methods of measurement, the variables included and also the populations included, earlier factor analyses varied in the number of factors identified and the nature in which they clustered together. A common finding was three or four factors. Insulin variables (as a proxy for insulin resistance) were found to commonly locate in a glucose and obesity factor, as well as a dyslipidaemia factor, with a separate blood pressure factor identified.[29] One of these studies was notable for the use of a euglycaemic clamp to measure insulin resistance. In this study, two factors were identified that were unified by the rate of insulin mediated glucose disposal. The fact that insulin resistance has commonly been found to locate on multiple factors can also be interpreted as evidence that it is a unifying feature of the metabolic syndrome. More recent work has specifically tested the hypothesis that a single factor united all of these sub-factors, showing good support for this model.[30, 31]

Those factor analyses which identified multiple factors may also be explained by the inclusion of multiple variables representing individual components of the metabolic syndrome. This can ensure that these variables cluster together, despite the fact that each of the components could also cluster together as a "second order" factor in a model including only single variables representing each component.[32]

If indeed a single unifying factor can explain the frequent clustering of abnormalities seen in the metabolic syndrome, it has not yet been conclusively identified. The difficulty in

elucidating the relationships between the components of the metabolic syndrome is a result of multiple challenges, including the complexity of a condition that involves multiple inter-connected disorders, the difficulty in accurately measuring insulin resistance in particular, but also the other components (including obesity), and the fact that environmental and genetic factors are usually not accounted for in most analyses.[25] It is likely that the issue of causation will only be resolved through a combination of approaches, including epidemiology, human and animal genetic studies and analysis of the physiologic and biochemical processes involved at the cellular, organ, organism and population levels. The identification of a causal pathway is important for understanding the pathophysiology of the metabolic syndrome and therapeutic approaches to addressing it. For clinical definitions, this knowledge may well be helpful for further refinement, but is not necessarily essential for their successful implementation.

1.2.5 Criticism of the metabolic syndrome

Clinical definitions of the metabolic syndrome and the concept as a whole have been heavily criticised.[25, 33-43] Indeed the research forming this thesis was intended to address some of the major evidence gaps regarding the syndrome. The major questions relating to the published clinical definitions of the metabolic syndrome include the following:[33, 35, 40]

- With four proposed definitions, is there any consensus about what constitutes the metabolic syndrome?

- Is there any evidence for the composition of clinical definitions, their biological basis and the cut-points for included components?

- Why have some identified risk factors for cardiovascular disease such as hs-CRP as an inflammatory marker been excluded?

- How do clinical definitions of the metabolic syndrome compare to other available alternatives for the prediction of type 2 diabetes and cardiovascular disease, and which is easier to use?

- Is the risk associated with the metabolic syndrome as a whole any greater than the sum of the risk related to its component parts?

- Does the treatment of the metabolic syndrome differ from the treatment of its individual components?

- Has the metabolic syndrome helped to provide a better understanding of the cause or pathogenesis of atherosclerotic cardiovascular disease?

- Should clinicians make the effort to measure and aggregate the individual components of the metabolic syndrome and does this improve patient outcomes?

- What is the evidence that the metabolic syndrome is a good predictor of long-term risk for cardiovascular diseases?

- Is the metabolic syndrome a useful construct for patients, particularly given the variation of severity among those who meet the clinical criteria, and does its use increase the uptake of lifestyle modification measures?

- Is it appropriate to introduce a new clinical diagnosis without a thorough evidence base or a complete understanding of the intentional and un-intentional consequences?

1.2.6 Uses for the metabolic syndrome

Cameron AJ, Zimmet PZ, Shaw JE, Alberti KGMM. The Metabolic Syndrome: in need of a global mission statement. Diabet Med 2009;26(3):306-9.

Declaration for Thesis Chapter

Declaration by candidate

In the case of Chapter , the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Paper conception and design, drafting of manuscript, critical revision, corresponding author	75

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Paul Z Zimmet	Critical revision, approval of final draft for publication	
Jonathan E Shaw	Critical revision, approval of final draft for publication	
KGMM Alberti	Critical revision, approval of final draft for publication	

Candidate's Signature	███████████████	Date ⅄/⌐/⁊⁹

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	International Diabetes Institute, Epidemiology Department, 250 Kooyong Rd Caulfield Vic 3162

Signature 1	█████████████████	Date ⅄·⌐·O⁹
Signature 2		I⁊·⌐·O⁊
Signature 3		⌐(⌐/⌐-/c⌐)

■ ■

The metabolic syndrome: in need of a global mission statement.

Cameron AJ, **Zimmet PZ**, **Shaw JE**, **Alberti KG**.

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AIMS: The value of clinical definitions of the metabolic syndrome has been questioned, with confusion surrounding their intended use and purpose. Our aim was to construct a mission statement that outlines the value of the metabolic syndrome in clinical and public health settings. METHODS: Case studies have been used to demonstrate three key points. RESULTS: We argue here for recognition of obesity as being a crucial element within the metabolic syndrome but perhaps even more important before its development. We also contend that the concept does indeed have a role as a risk prediction tool, and that it could provide a useful metric for the scale and progress of the looming global epidemic of diabetes and cardiovascular disease. CONCLUSIONS: Through appreciation of its purpose, and recognition of both its limitations and those attributes that make it unique and valuable, we believe we have demonstrated here that the metabolic syndrome deserves its place in the global toolbox of diabetes and CVD prevention.

1.3   Risks associated with the metabolic syndrome

A large number of studies have now been undertaken to quantify the major risks of the metabolic syndrome; for cardiovascular diseases[9, 44-66]; type 2 diabetes[9, 49, 54, 55, 58, 59, 61, 63, 67-82]; and all-cause and cardiovascular mortality.[9, 44-47, 64, 83-86] These studies concern the various published definitions of the syndrome. Meta-analysis of the predictive ability of the metabolic syndrome (using the 2001 ATPIII definition) indicate that it is only a modest predictor of both all-cause mortality (estimated relative risk ~1.2 to 1.4) and cardiovascular disease (estimated relative risk ~1.7 to 1.9).[9] Results for all available definitions, however, suggest it is a stronger predictor of type 2 diabetes (estimated relative risk 3.5 to 5.1).[82] The differential in risk associated with cardiovascular diseases and type 2 diabetes is likely due to the inclusion in clinical definitions of components such as fasting blood glucose and central obesity that are known to be more strongly associated with diabetes.[82] Strong risk factors for both conditions are missing from the metabolic syndrome, with other available tools that include these (in particular the Framingham risk algorithms for cardiovascular disease risk prediction) often shown to be superior for short-term risk prediction.[39] Most of those studies assessing risks associated with the metabolic syndrome have a follow-up period of less than twelve years. Therefore, predictive ability over the longer term is less well established. One analysis of total and cardiovascular disease mortality by Sundström over a follow-up of almost 33 years, however, suggests that the metabolic syndrome predicts mortality independently of other established risk factors such as smoking, diabetes, hypertension and cholesterol.[86] This result may indicate the long-term prognostic value of the metabolic syndrome over and above that achieved by short-term global risk calculators.

1.4 Research questions addressed in this thesis

This thesis has been developed as a thorough assessment of the value of clinical definitions of the metabolic syndrome. Numerous authors have criticised the development of such clinical definitions, citing a poor evidence base in relation to several of the suggested attributes of the syndrome.[25, 33-43] In addition to quantifying the number of Australians who meet the definition(s) of the metabolic syndrome, the research agenda formulated here was a response to some of the key questions relating to the aetiology, validity, uses and consequences of the available clinical definitions (see Chapter 1.2.5). Each of the primary research questions addressed is listed and expanded upon below, and forms the basis for the research comprising chapters 3.1 to 3.5.

1.4.1 Prevalence of the metabolic syndrome in Australia

The baseline AusDiab study is the only recent national Australian study to have accurately measured each of the components of the metabolic syndrome. Estimation of the number of Australians who meet the criteria for available definitions of the metabolic syndrome, and are therefore at elevated risk of future cardiovascular disease, is therefore possible using this dataset and was the primary aim of the first study. The IDF definition of the metabolic syndrome had only recently been proposed at the time this work was published. This work, therefore, provided an opportunity to examine the impact of the structure of this definition on the prevalence of the syndrome and the characteristics of those identified. A secondary aim of this research was to assess the risk differential between those who did and did not meet the criteria for the metabolic syndrome with regard to future cardiovascular disease outcomes (as assessed using equations from the Framingham study).

1.4.2 Obesity as a determinant of the metabolic syndrome

Epidemiologic evidence directly supporting the positioning of obesity before the development of the other components of the metabolic syndrome is not substantial. Despite this, in both inflammatory and insulin resistance-centred models, obesity is commonly assumed to be a causal factor in the aetiology of metabolic decline. Several longitudinal studies have examined the role of obesity in the development of the metabolic syndrome or its components but none has explicitly addressed the question of whether obesity precedes their development, the primary aim of this second study. Both the five year follow-up of the AusDiab cohort and the five and eleven year follow-up of a cohort from the Indian Ocean island of Mauritius have been used to address this question.

1.4.3 Metabolic and other health consequences of obesity

Given the centrality of obesity to the construct of the metabolic syndrome and its aetiology, this third study aimed to quantify the impact of overweight and obesity on multiple important clinical outcomes (including type 2 diabetes, the metabolic syndrome and each of its components and cardiovascular disease) as well as mortality. Obesity-related risks for these outcomes have not been previously reported for the Australian population, meaning that quantification of the burden of disease attributed to obesity in this country has relied on proxy data from other sources. This research project aimed to address this information gap, and provide further evidence with which to inform efforts aimed at addressing the epidemic levels of obesity seen in adult Australians.

1.4.4 Validity of ethnicity-specific cut-points for obesity used in the metabolic syndrome

The inclusion of ethnicity-specific waist circumference cut-points in the IDF definition of the metabolic syndrome was a recognition that the risk associated with a given waist circumference varies according to ethnicity. The WHO is yet to publish definitive waist

cut-points for use in different population groups (either within the construct of the metabolic syndrome, or independently), and few studies have been published relating obesity to prospective outcomes such as type 2 diabetes and cardiovascular disease in non-Caucasian populations. Furthermore, those studies that have sought to determine ethnicity-appropriate waist circumference cut-points have almost universally utilised receiver operating characteristic (ROC) curve analysis for this task. The aim of this fourth study was primarily to assess the appropriateness of the waist circumference cut-points recommended in the IDF metabolic syndrome definition. A secondary aim was to demonstrate the deficiencies in the use of ROC curve analysis for this task.

1.4.5 The metabolic syndrome as a tool for prediction of diabetes

While considerable evidence exists supporting the ability of published definitions of the metabolic syndrome to predict cardiovascular diseases, at the time of publication of this chapter, studies assessing their ability to predict incident type 2 diabetes were limited and were limited in their scope. The metabolic syndrome had been compared with a Diabetes Prediction Model (DPM) only for the (U.S.) National Cholesterol Education Program (ATPIII) definition of the metabolic syndrome, and little work had been done in comparing the metabolic syndrome with simpler risk indices such as the FINDRISC risk questionnaire and even a simple measurement of either fasting glucose or two-hour post load glucose. In addition, a thorough assessment of whether the metabolic syndrome predicts incident diabetes independently of its component parts had been lacking. This fifth study aimed to examine whether the metabolic syndrome is indeed a useful clinical tool for the prediction of diabetes, utilizing comparable data from both the AusDiab and Mauritius cohorts.

2 Methods and research design

2.1 Theoretical and conceptual framework

The research reported within this thesis is based on analysis of two epidemiologic research studies involving national, population-based cohorts in Australia and Mauritius. Analysis of data from epidemiologic studies allows the estimation of the prevalence and incidence of disease in defined populations (descriptive epidemiology), as well as the relationships between risk factors and disease (analytical epidemiology). The unique contribution of epidemiology is that it is conducted within human populations, meaning that results obtained are directly relevant to the population being studied.[87] Indeed, epidemiology offers the possibility of altering observed risk through interventions and the monitoring of their progress at the population level. The uncontrolled nature of epidemiologic research is also a potential limitation, with an inability to precisely control the environment in which the research is undertaken. Frequently, epidemiologic analysis relies on statistical adjustment for potential confounding factors and risk modifiers, which is not usually required in a well designed randomised clinical trial.

The results from population-based research, including those reported in this thesis, often include caveats resulting from an incomplete response, response bias, limited follow-up time and number of cases (and hence limited statistical power) and the changing nature of populations and risk factors over time. For this reason, the results of population-based epidemiology studies are not sufficient on their own to answer questions related to the pathogenesis or underlying cause of the metabolic syndrome,[25] and are usually interpreted in the context of more basic, but more controlled research in areas such as genetics, physiology and molecular biology.

Cross-sectional epidemiological studies (conducted at a single time point), as long as they are reasonably representative of the population from which the sample was drawn, enable the estimation of the prevalence of disease within a population, as well as the investigation of the association between risk factors and disease. Such studies, however, are limited in that one cannot be sure that the development of the disease was preceded by the presence of a putative risk factor. Hence, causality cannot be assumed from a cross-sectional association. For this reason, studies involving more than one time point (longitudinal studies) are very important. Such studies enable the investigation of temporal relationships between risk factors and disease that develop over the course of follow-up. However, because of the expense and logistic difficulties involved in following population-based samples up at multiple time points, longitudinal studies are not commonly undertaken. The AusDiab and Mauritius NCD studies are two of the largest national, population-based longitudinal cohort studies of diabetes and other non-communicable diseases undertaken. The datasets from these studies are therefore an important resource for answering many of the questions relating to the consequences of the metabolic syndrome in populations.

The incorporation of an oral glucose tolerance test (OGTT) in both studies allowed a "gold standard" diagnosis of diabetes at both baseline and follow-up. Self-report or the use of medical records cannot provide complete data on abnormal glucose metabolism because the early stages of these conditions are often asymptomatic. In the baseline AusDiab study, we found that only half of those with blood glucose levels in the diabetic range had previously been diagnosed.[88]

Full details of the sampling frame, methods and response for the longitudinal cohort studies utilised in the preparation of this thesis have been previously published.[89-92] A summary of

the methods of each is provided here, with details particular to each results chapter being

presented in the respective methods sections.

2.2 The Australian Diabetes, Obesity and Lifestyle (AusDiab) study

The AusDiab study is an ongoing longitudinal, population-based national study of diabetes, pre-diabetes, obesity, heart and kidney disease. The baseline phase of AusDiab, conducted between 1999 and 2000, was designed to provide the first national Australian prevalence figures for diabetes and pre-diabetic states using an oral glucose tolerance test.[88] In addition, the AusDiab study has been used to provide benchmark national data on the prevalence of obesity,[93] hypertension,[94] kidney disease[95] and physical activity and inactivity.[96, 97]

The second phase of AusDiab, completed in December 2005, was a five year follow-up of those who participated in the baseline survey. The results of the follow-up have provided data on the five-year incidence of those conditions measured at baseline.

2.2.1 Sample selection and weighting of the survey sample

The baseline AusDiab study involved a stratified cluster sample of all non-institutionalised adults aged 25 years or more in six census collection districts (randomly selected without replacement and selected proportional to population size) in each of the six Australian states and the Northern Territory (42 in total). Due to the logistic and economic constraints of the survey, and to avoid the bias of including an unrepresentative number of high prevalence groups, collection districts were excluded from the sample frame if they were classified as 100% rural, contained fewer than 100 eligible adults or if the percentage of Indigenous people was >10%. This accounted for a total of 5.8% of all eligible Australians. At the time of the survey, all participants had been usual residents in the household for a period of at least six months.[89]

A total of 20,355 individuals in 11,479 households were interviewed. Of these, 11,247 individuals participated in the baseline physical examination (response 55.3%). After consideration of non-response to the household interview, response to the physical examination was estimated to be to be 37% of the total eligible population.[89] Sample weights were applied to the baseline data to account for the clustered and stratified nature of the survey design. These weights were initially adjusted to ensure that the weighted sample matched the age and gender distribution within each collection district as obtained from the 1996 census. The weights were further adjusted so that the age and gender distribution within each state (and therefore the national sample) matched the estimated 1998 Australian residential population.[89, 98]

In 2004-2005, all eligible participants (n=10,788) who were surveyed at baseline were invited to attend a follow-up survey. Individuals ineligible for invitation to the follow-up survey included those who had specifically requested no further contact (n=128), those who were deceased (n=310) and those who were excluded due to having moved into a high care nursing facility or having a terminal or chronic illness that made their participation impossible (n=21). Of the eligible participants, 6,400 returned to take part in the 2004-2005 follow-up survey (response = 60.6%). A further 137 attended a local pathology collection centre for blood testing, but did not complete the full examination. Of those who did not take part in the physical examination, 2,200 agreed to complete a phone questionnaire on existing health conditions; including self reported diabetes, stroke, heart problems, kidney disease, fractures and gout.

Because of the level of non-response to the baseline and follow-up surveys and the response bias observed in both surveys, the follow-up sample is not considered to be suitable for estimation of national prevalence statistics. Furthermore, due to the percentage

of the total eligible population to participate in both the baseline and follow-up surveys being only 22%, it was not considered valid to weight the follow-up survey to adjust for this non-response. Rather, results from the follow-up survey should be considered to be from a national cohort that is not entirely representative of the total Australian population.

2.2.2 Protocols and procedures

The AusDiab physical examination commenced at around 7am each morning for approximately two weeks in each of the 42 clusters surveyed. Testing took around 2.5 hours, and closely followed the WHO recommended model for diabetes and non-communicable disease field surveys.[99] Testing relevant to this thesis included the following:

- Fasting blood sample (after a minimum 10 hour fast) for measurement of plasma glucose, insulin, HDL and LDL cholesterol, triglycerides and HbA1c.

- Oral glucose tolerance test, with a 75g glucose load following the fasting blood sample and a further blood sample taken exactly two hours after administration of the glucose load (pregnant women, and those taking insulin or oral glucose lowering medications were excluded).

- Height, weight, waist circumference and hip circumference.

- Blood pressure was measured using a standard mercury sphygmomanometer in Victoria (the first state studied in AusDiab) with two readings taken followed by a third if the first two readings differed by $\geq$10mmHg. Thereafter, blood pressure was measured in triplicate using a Dinamap semi-automatic recorder. Both methods were tested on every 20th participant in the

last six states (n=469). After a comparison of the two methods, in order to adjust for observed differences, diastolic blood pressure in Victoria was adjusted using the following regression equation: Victorian adjusted diastolic blood pressure = 4.636 + (0.905 * Victorian manual diastolic blood pressure.

- Questionnaires administered by trained interviewers included items assessing demographic characteristics (age, marital status, ethnicity), socio-economic status (income, education, occupation), physical activity, sedentary behavior (television viewing), smoking, alcohol consumption, dietary patterns, quality of life, health knowledge, attitudes and practices, diabetes knowledge (for those with diabetes), blood pressure and lipid lowering medication, health care utilization and previous cardiovascular diseases.

All participants were sent the results of biochemical tests and physical examinations shortly after the survey. Results were sent to general practitioners upon request, and significant abnormal results were flagged with advice to seek appropriate follow-up with their doctor.

Survey methods at the 2004-5 follow-up survey were similar to those used in the baseline survey, with all pathology and physical examinations repeated. Notable differences included the method of measurement for fasting insulin.

2.2.3 Cardiovascular disease event and mortality ascertainment

All participants who answered yes to the following question: "have you ever been told by a doctor or nurse that you have had a heart attack (including a 'coronary', coronary occlusion, coronary thrombosis or myocardial infarction), a stroke, a heart bypass operation

(including 'coronary bypass') or an angioplasty or stent for your heart (including 'coronary angioplasty', 'coronary stent' or 'balloon')?" were asked to provide consent to search their medical records of these events. Those who reported an event between the baseline and follow-up surveys were included in a medical record review for incident cardiovascular disease diagnosis.

De-identified information on discharge diagnoses, presenting symptoms, cardiac enzymes and troponin levels, electrocardiograms, operation reports and physician letters were abstracted from medical records. Two physicians (including one cardiologist) independently reviewed these records according to WHO/MONICA criteria[100] for myocardial infarction. Participants were excluded from adjudication if they did not provide consent to have their medical records reviewed (n=14), if medical records for the event could not be obtained (n=3) or if the event occurred in a hospital outside of Australia (n=3). Self-report followed by physician adjudication has been shown to be as accurate as data linkage to the Western Australian state-wide hospital morbidity database for the identification of cases (although the use of both techniques identified a slightly larger number of cases). A low false negative rate is also likely, with only 2% of cardiovascular disease events identified using data linkage of AusDiab participants from Western Australia not also self-reported by participants in the AusDiab follow-up survey.[101]

Death was ascertained by linking the AusDiab cohort to the Australian National Death Index (NDI), as previously reported.[6] Name, sex, date of birth, state, date of last contact, and date of death (if available) were used to match participants to the NDI. People not matched to the NDI were assumed to be alive. Only high level matches with the NDI database were accepted as confirmed deaths. Wherever possible, deaths were confirmed by direct communication with the decedent's family. The accuracy of the NDI for

ascertainment of vital status has been established.[102] The follow-up period for all-cause mortality was to the date of death or April 30, 2008, whichever occurred first.

2.2.4 Sample size and power

The sample size obtained in the baseline AusDiab survey was based on the expected precision of estimates to identify a national diabetes prevalence of 7.0%.[89] This figure was based on results of previous surveys, and the expectation that the diabetes rate had increased over time. The sample was stratified by state to achieve the secondary objective of the study, which was to deliver useful state-specific diabetes prevalence estimates. Little loss of efficiency was expected after accounting for this stratification. Following consideration of the clustered nature of the survey design (conducted at 42 sites throughout Australia), a sample size of 10,500 (1500 per state) was predicted to provide 95% confidence intervals of 6.2 – 7.8, around a diabetes estimate of 7.0%. This level of precision was considered to be acceptable, and the sample size within the funding and logistic constraints of the survey.[89] The final diabetes prevalence and 95% confidence interval from the baseline survey was 7.4% (5.9-8.8). Confidence intervals were wider than expected due to a greater than expected design effect for this variable of 8.34.[89].

The sample size of the baseline survey was calculated for estimation of total diabetes prevalence only and may not have been adequate for other outcomes and sub-analyses. Furthermore, the baseline survey was not designed with the purpose of forming a cohort to be followed up over time. It is therefore acknowledged that the results of the analyses presented in this thesis must be interpreted in light of the intended purpose of the study, and the sample size obtained at both the baseline and follow-up surveys. Specific details of the sample utilised are contained within the individual results chapters.

2.3 The Mauritius Non-communicable Disease (NCD) study

Mauritius is an island located in the South-Western Indian Ocean off the East coast of Madagascar. It has a population of approximately 1.3 million, consisting of 68% of South Asian origin, 3% of Chinese origin, 27% Creole (mixed African and Malagasy ancestry with some European and Indian admixture) and 2% Franco-Mauritian. A population-based baseline study was undertaken in Mauritius in 1987, with follow-up in 1992 and 1998. The Mauritius NCD study was used in this project as an important comparator for results obtained within the largely Europid AusDiab study. Many of the questions relating to the use and validity of the metabolic syndrome have not been addressed previously in populations of non-Europid ancestry. In particular, no other comparable longitudinal cohort study conducted in a South Asian population exists with which to assess the ability of the metabolic syndrome to predict diabetes, or the role of obesity in the pathogenesis of the metabolic syndrome.

2.3.1 Sample selection and response

In the Mauritius NCD study, all individuals aged 25-74 within ten locations (clusters) were surveyed in 1987, with three additional areas added in the 1992 and 1998 surveys. As well as follow-up of those who attended the previous survey(s), all other current residents in each of the areas tested were invited to attend the 1992 and 1998 surveys. Overall, 9688 individuals participated in the three surveys, with 27% participating in all three surveys.[92] Response to the 1987 survey was 80% of the eligible population (n = 5,083). Of these, 74.2% (n = 3,771) were followed up in 1992 and 55.1% (n = 2,802) were followed up in 1998.

2.3.2 Protocols and procedures

Survey methods in the 1987, 1992 and 1998 Mauritius NCD studies were broadly similar to those used in the AusDiab surveys, with a 75g oral glucose tolerance test utilised and fasting blood sample taken for measurement of lipids and insulin. Where differences existed in the measurement techniques between the AusDiab and Mauritius studies, these have been highlighted in the methods section of the relevant chapters.

Notable differences in methods between the AusDiab and Mauritius NCD surveys include different measurement location for waist circumference, and different assay techniques for several of the biochemical parameters. The impact of the different waist circumference measurement technique is addressed fully in Chapter 3.4. Microalbuminuria was not measured in the Mauritius NCD study, meaning that this component of the WHO definition of the metabolic syndrome could not be assessed in this cohort. Direct comparison of other biochemical measures between the AusDiab and Mauritius NCD surveys was not undertaken. Therefore any differences in assay method are not a limitation of this research.

2.4 Strengths and limitations of the AusDiab and Mauritius NCD studies

The great strength of the AusDiab and Mauritius NCD studies is that they both involve large, population-based cohorts followed up over time. The AusDiab study is the largest national and population-based study of diabetes to have used an oral glucose tolerance test, while the Mauritius NCD study is the only large population-based diabetes study to have followed up participants over three time points with an oral glucose tolerance test performed at each. Both studies involve large numbers of participants, providing statistical power for a variety of multivariable and stratified analyses. The high incidence of diabetes and obesity seen in both the AusDiab and Mauritius NCD cohorts provides large numbers of these outcomes, further enhancing statistical power.

The use of an oral glucose tolerance test in both studies at all time points allows a gold standard diagnosis of diabetes, including identification of both fasting and post-prandial glucose abnormalities and accurate assessment of those without diabetes or with pre-diabetes (impaired fasting glucose or impaired glucose tolerance). Accurate assessment of cardiovascular diseases is also a strength of the AusDiab study, with the validity of the process of medical record collection and adjudication confirmed through linkage of study participants from Western Australia to state morbidity databases. The use of similar cohort studies conducted in populations of different ethnicity ensures that findings observed in both studies are relevant to a large percentage of the world population.

The modest response rate to the baseline and follow-up surveys is the major limitation of the AusDiab study, with observed differences in the profile of the baseline cohort in comparison to the total Australian population aged over 25 years.[89] Because of this, the results from this study, despite it being population-based, are not necessarily representative of the entire Australian population. In addition, the short length of follow-up of the cohort

(five years for cardiovascular diseases, eight years for mortality) led to relatively low numbers of these events and limited statistical power for stratified or sub-analyses involving these outcomes. Because the AusDiab study was population-based with no over-sampling of minority groups, separate analysis of outcomes in indigenous Australians and other minority populations was not possible.

The baseline Mauritius NCD study was conducted almost 20 years ago. Therefore, the prevalence and characteristics of the metabolic syndrome in that population may have since changed. Furthermore, response to the five year follow-up in 1992 was 74.2%, which although higher than that achieved in the AusDiab study, still means that this sample was also population-based, but not necessarily representative of the entire Mauritian population.

The WHO definition of the metabolic syndrome suggests the use of a euglycaemic clamp, which is not practical in large scale epidemiology studies for practical reasons. The bottom quartile of HOMA%S was used as a surrogate to estimate insulin resistance.

2.5 Ethical approval and consent to participate

The Mauritius NCD survey protocols were reviewed and approved by the Alfred Healthcare Group Ethics Committee (Melbourne, Australia) as well as the Ministry of Health, Mauritius.

The AusDiab study protocols were approved by the ethics committee of the International Diabetes Institute (3/99, 3/2002). Additional ethical approval was received from the ethics committee of the Australian Institute of Health and Welfare (AIHW) for matching of the AusDiab cohort to the NDI.

Consent to access medical records from hospitals and general practitioners was obtained from those participants in the AusDiab study who reported a cardiovascular disease event during the previous five years at the follow-up study.

Approval for the research undertaken in the preparation of this thesis was obtained from the Monash University Standing Committee on Ethics in Research Involving Humans (SCERH) (2006/987MC).

Approvals for the work involved in the baseline and follow-up phases of the AusDiab study, and the work involved in the preparation of this thesis are included in Appendix 5.1.2.

All participants provided informed, written consent to participate at each of the baseline and follow-up AusDiab and Mauritius NCD studies.

3   Results of original research

3.1   The metabolic syndrome in Australia

Cameron AJ, Magliano DJ, Zimmet PZ, Welborn T, Shaw JE. The Metabolic Syndrome

in Australia: Prevalence using four definitions.

Diabetes Res Clin Pract. 2007;77(3):471-478.

Introduction

An unfortunate side-effect of the introduction of successive definitions of the metabolic

syndrome is the inability of researchers and clinicians to know which is preferred. The

creation of a definition by the IDF in 2005 was intended to result in a format that

highlighted the importance of obesity in the development of the other abnormalities of the

metabolic syndrome, and could be used globally. This definition, therefore, was designed to

replace, rather than compete with, the three definitions published previously. It is important

to understand how new definitions compare with the old, and whether they indeed are

superior and not just new. Prior to this publication, little was known of how the IDF

definition would perform in real populations with regard to the prevalence and the

characteristics of those identified. For this reason, this research study had the explicit aim

of comparing the IDF definition with those published previously, acknowledging that the

EGIR and WHO definitions in particular were no longer regularly used in research or

clinical work. For a new definition to receive widespread support, it is in fact important that

such thorough comparisons are made. This work provides the first estimates of the

proportion of adult Australians who meet the criteria for the metabolic syndrome, adding to

previous work resulting from the AusDiab study that showed epidemic levels of obesity

and increasing levels of diabetes and pre-diabetes.

Declaration for Thesis Chapter

Declaration by candidate

In the case of Chapter   , the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision	55

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Diana J Magliano	Analysis and interpretation of data, drafting of manuscript, critical revision, approval of final draft for publication, corresponding author	
Paul Z Zimmet	Study conception and design, critical revision, approval of final draft for publication	
Timothy A Welborn	Study conception and design, critical revision, approval of final draft for publication	
Jonathan E Shaw	Study conception and design, acquisition of data, interpretation of data, drafting of manuscript & critical revision, approval of final draft for publication	

Candidate's Signature	██████████████████	Date 2/11/07

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.

(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;

(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;

(4) there are no other authors of the publication according to these criteria;

(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and

(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	International Diabetes Institute, Epidemiology Department, 250 Kooyong Rd Caulfield Vic 3162	
Signature 1	████████████████	Date
Signature 2	████████████████ 29-11-07	24/11/07
Signature 3	████████████████	14/11/07
Signature 4	████████████████	29/11/07

The metabolic syndrome in Australia: prevalence using four definitions.

Cameron AJ, **Magliano DJ**, **Zimmet PZ**, **Welborn T**, **Shaw JE**.

International Diabetes Institute, 250 Kooyong Road, Caulfield, Melbourne, Victoria 3162, Australia.

OBJECTIVE: To compare the prevalence of the Metabolic Syndrome (MetS) defined by four definitions and to determine which definition best identifies those at high cardiovascular disease (CVD) risk and with insulin resistance. METHODS: AusDiab is a population-based survey of 11,247 Australians. Participants had anthropometry, blood pressure, and fasting biochemistry. Ten-year CVD risk was calculated. RESULTS: The prevalence of the MetS using the ATPIII, WHO, IDF, and EGIR definitions was 22.1% (95%Cl: 18.8, 25.4), 21.7% (19.0, 24.3), 30.7% (27.1, 34.3), and 13.4% (11.8, 14.9), respectively. Comparing those with to those without the MetS, the odds ratios (95%CI) for having a 10 year CVD risk > or =15% were 6.6 (5.4, 8.2), 5.5 (4.7, 6.5), 5.6 (4.8, 6.6), and 3.5 (3.0, 4.1), for the WHO, ATPIII, IDF, and EGIR definitions, respectively. The population attributable risk (PAR) of high CVD risk due to the MetS was highest for the IDF (23.4%). Insulin resistance was detected in 56.1, 69.7, 50.9, and 91.1% of those meeting the ATPIII, WHO, IDF, and EGIR definitions, respectively. CONCLUSION: The WHO definition was associated with the greatest CVD risk, but is not practical for clinical use. The higher PAR due to the IDF definition, with only slightly lower CVD risk than WHO, and clinical utility of the IDF definition, indicates that it may be a useful tool for CVD prevention.

3.2   Obesity as a determinant of the metabolic syndrome

Cameron AJ, Boyko EJ, Sicree RA, Zimmet PZ, Soderberg S, Alberti KGMM, Tuomilehto J, Chitson P, Shaw JE. Central obesity as a precursor to the Metabolic Syndrome in the AusDiab study and Mauritius. *Obesity*. 2008, 16; 12, 2707–2716.

Introduction

Central obesity is widely acknowledged to be a key part of the pathogenic process resulting in the abnormalities of the metabolic syndrome. The concern with which rates of childhood and adolescent obesity are viewed is an implicit acknowledgement that the obesity seen in children and young adults can have deleterious effects in later adulthood. Physiological evidence linking obesity with the outcomes of the insulin resistance syndrome is growing, even though the precise mechanisms involved are not entirely clear. Little evidence exists from epidemiology studies, however, that obesity is actually a precursor to the development of the component abnormalities of the metabolic syndrome, and does not simply develop concurrently. The scarcity of studies addressing this question is likely to be due, at least in part, to the lack of large-scale population studies that measure each of the components of the metabolic syndrome at multiple time points. Both the AusDiab follow-up study and studies conducted in Mauritius over three time points are an ideal setting to address this question, utilising data drawn from three different ethnic groups. If central obesity were to be shown to precede the development of the other components of the metabolic syndrome, this would have significant implications for the interpretation of existing clinical definitions. In particular, obesity would then be viewed not simply as one of multiple component abnormalities, but as a precursor that, even in the absence of any other obvious

metabolic deterioration, is a significant risk factor for future development of the metabolic syndrome and its serious clinical consequences. Furthermore, such a finding would emphasize the need for diabetes and cardiovascular disease prevention efforts to begin with attention to the epidemic levels of obesity seen in many developed, and increasingly developing nations. This research was explicitly designed to answer this important question.

Declaration for Thesis Chapter

Declaration by candidate

In the case of Chapter   , the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision, corresponding author	75

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Declaration by co-authors

The undersigned hereby certify that:

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(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;

(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;

(4) there are no other authors of the publication according to these criteria;

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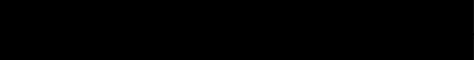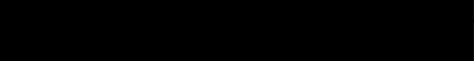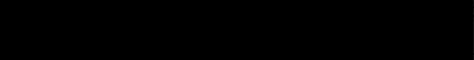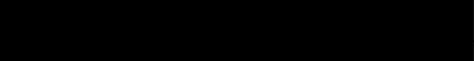
Central obesity as a precursor to the metabolic syndrome in the AusDiab study and Mauritius.

Cameron AJ, **Boyko EJ**, **Sicree RA**, **Zimmet PZ**, **Söderberg S**, **Alberti KG**, **Tuomilehto J**, **Chitson P**, **Shaw JE**.

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Evidence from epidemiologic studies that central obesity precedes future metabolic change and does not occur concurrently with the appearance of the blood pressure, glucose, and lipid abnormalities that characterize the metabolic syndrome (MetS) has been lacking. Longitudinal surveys were conducted in Mauritius in 1987, 1992, and 1998, and in Australia in 2000 and 2005 (AusDiab). This analysis included men and women (aged > or = 25 years) in three cohorts: AusDiab 2000-2005 (n = 5,039), Mauritius 1987-1992 (n = 2,849), and Mauritius 1987-1998 (n = 1,999). MetS components included waist circumference, systolic blood pressure, fasting and 2-h postload plasma glucose, high-density lipoprotein (HDL) cholesterol, triglycerides, and homeostasis model assessment of insulin sensitivity (HOMA-S) (representing insulin sensitivity). Linear regression was used to determine which baseline components predicted deterioration in other MetS components over 5 years in AusDiab and 5 and 11 years in Mauritius, adjusted for age, sex, and ethnic group. Baseline waist circumference predicted deterioration ($P < 0.01$) in four of the other six MetS variables tested in AusDiab, five of six in Mauritius 1987-1992, and four of six in Mauritius 1987-1998. In contrast, an increase in waist circumference between baseline and follow-up was only predicted by insulin sensitivity (HOMA-S) at baseline, and only in one of the three cohorts. These results suggest that central obesity plays a central role in the development of the MetS and appears to precede the appearance of the other MetS components.

3.3 Metabolic and other health consequences of obesity

Cameron AJ, Dunstan DW, Owen N, Zimmet PZ, Barr ELM, Tonkin AM, Magliano DJ, Murray SM, Shaw JE. Health and mortality consequences of obesity: evidence from the AusDiab study. In press, *Med J Aust.*

Introduction

The baseline AusDiab study demonstrated that the prevalence of overweight and obesity among adult Australians was around 60% in 1999-2000. The central place of obesity in the most recent IDF definition of the metabolic syndrome is recognition of its importance to the pathogenic process involved as well as the high risk for the metabolic syndrome and its outcomes that it conveys. In Chapter 3.2, obesity was demonstrated to be a precursor to the development of the other abnormalities of the metabolic syndrome. The completion of a physical follow-up of the AusDiab cohort in 2004-2005, as well as the ongoing linkage of the cohort to the National Death Index, allows for an assessment of the impact that the epidemic obesity observed at baseline has had on health and mortality outcomes in this cohort. The quantification of accurate risk estimates for the many outcomes associated with overweight and obesity is required for the calculation of the burden of disease for which they are responsible. Accurate risk estimates for many of the most important outcomes associated with obesity had not previously been published for the Australian population. Their calculation as part of this study will enable the more accurate assessment of the financial and health effects of obesity on Australians. Furthermore, the demonstration that overweight and obesity have multiple, serious negative health outcomes can be used as evidence for the regulatory and societal changes required to prevent or reverse the epidemic levels of obesity now apparent.

Declaration for Thesis Chapter

Declaration by candidate

In the case of Chapter ___, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
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The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.

(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;

(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;

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(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and

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Health and mortality consequences of abdominal obesity: evidence from the AusDiab study.

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Abstract

Objective: To provide an estimate of the morbidity and mortality due to abdominal overweight and obesity in the Australian population.

Design and Setting: Prospective, national, population-based AusDiab study.

Patients, Participants: Men and women aged ≥25 years at study entry in 1999/2000.

Main Outcome Measure(s): Five year follow-up (2000 to 2005) for incident health outcomes (type 2 diabetes, hypertension, dyslipidaemia, the metabolic syndrome and cardiovascular diseases) and eight year mortality follow-up. Logistic and Cox-proportional hazards regression was used to assess risk for incident health outcomes and mortality among those classified as abdominally overweight or obese compared to those with a normal waist circumference at baseline, and across quintiles of waist circumference and (for mortality only) waist to hip ratio.

Results: Abdominal obesity was associated with odds ratios of between 2 and 5 for incident type 2 diabetes, dyslipidaemia, hypertension and the metabolic syndrome. The risk of myocardial infarction among the obese was similarly increased in men (HR = 2.75 (95%CI 1.08-7.03)), but not women (HR=1.43 (0.37-5.5)). Abdominal obesity-related population attributable fractions for these outcomes ranged from 13% to 47% and were highest for type 2 diabetes. No significant associations were observed between all-cause mortality and increasing quintiles of abdominal obesity.

Conclusions: These findings confirm the considerably heightened risk conferred by abdominal obesity for type 2 diabetes, the metabolic syndrome (as well as its components) and cardiovascular disease, and provides important information with which to more precisely estimate the burden of disease attributable to obesity in Australia.

Introduction

Reports from the national Australian Diabetes, Obesity and Lifestyle (AusDiab) Study have previously been used to highlight the alarming levels of overweight and obesity now prevalent among adult Australians.[1] Overweight and obesity are increasingly common[2] and contribute significantly to multiple adverse health outcomes, including type 2 diabetes, cardiovascular diseases (CVD), the metabolic syndrome, hypertension and dyslipidaemia, as well as premature mortality.[3-6]

An absence of country-specific relative risk data has been identified by the World Health Organization (WHO) as a major limitation in the preparation of accurate estimates of burden of disease. Follow-up of the AusDiab cohort has now allowed an assessment of the strength of associations between abdominal obesity and each of type 2 diabetes, the metabolic syndrome and its components, myocardial infarction and all-cause mortality among a contemporary national sample of Australian adults.

Methods

Survey population

The study methods for the AusDiab study have been described in detail elsewhere.[7, 8] The AusDiab study was a nation-wide population-based stratified cluster survey of 11247 adults (44.9% men) aged ≥25 years in 1999-2000 (response was 55.3% of those completing a household interview and estimated to be 37% of the eligible population). In 2004-2005, 60.6% of the 10788 eligible participants returned for a follow-up physical examination. After excluding participants aged >75 years (n=285) due to the established lack of association between obesity and many health outcomes in the elderly,[9] as well as pregnant women (n=42), 6072 participants (54.7% women) were available for analysis of incident diabetes, metabolic syndrome and its components.[10]

Responders to the follow-up physical examination were more likely than non-responders to be non-smokers, tertiary educated, married and speak English at home.[8]

Survey methods

Waist circumference was measured twice, halfway between the lower border of the ribs and the iliac crest on a horizontal plane. If measurements varied by >2 cm, a third was taken. The mean of the two closest measurements was calculated. A 75g oral glucose tolerance test (OGTT) was conducted at baseline and follow-up surveys in all non-pregnant participants not using insulin or taking oral hypoglycaemic drugs. Biochemical parameters, height, weight and blood pressure were measured as previously described.[8] Diabetes was classified according to WHO criteria[11, 12] and the metabolic syndrome defined according to the International Diabetes Federation (IDF) definition.[13] Hypertension and cut-points for elevated triglycerides and low high-density lipoprotein cholesterol (HDL-C) were as described in the IDF definition of the metabolic syndrome. WHO waist circumference cut-points representing "increased" and "substantially increased" risk of obesity-associated metabolic complications in Europids were used to represent "overweight" (men 94cm; women 80cm) and "obesity" (men 102cm; women 88cm) respectively.[14] One week recall of leisure-time physical activity was assessed via the interviewer-administered Active Australia questionnaire, previously shown to have good test-retest reliability.[15, 16] Self-reported television viewing time over the previous week, smoking status and highest level of education achieved were assessed by interviewer-administered questionnaire.

Myocardial infarction and mortality follow-up

Of the 10242 eligible participants aged <75 years at baseline, 8396 completed an interviewer-administered CVD history questionnaire at the 2004-2005 physical examination, or by telephone. Those who did not consent to medical record adjudication or without complete myocardial infarction data (n=14) were excluded, leaving 8382

(81.8% of those eligible) available for analysis of incident myocardial infarction. Average follow-up time for myocardial infarction was 60.8 months, with 45 non-fatal events occurring during the follow-up period.

Incident myocardial infarction was ascertained by physician adjudication of medical records according to WHO/MONICA criteria for myocardial infarction[17], as previously described.[18] These methods have been validated against a hospital morbidity database. [18]

Death was ascertained by linking the AusDiab cohort to the Australian National Death Index (NDI), as described previously.[19] The accuracy of the NDI for ascertainment of vital status has been established.[20] The follow-up period for all-cause mortality was to the date of death or April 30, 2008, whichever occurred first. All those who died within two years of the baseline survey were excluded (n=107). Average mortality follow-up was 95.8 months, with 316 deaths occurring during the follow-up period.

AusDiab survey protocols were approved by the ethics committee of the International Diabetes Institute, Monash University's Standing Committee on Ethics in Research involving Humans and the Australian Institute of Health and Welfare. Informed consent was obtained from all participants.

Statistical methods

To test for linear trends in means and linear associations in proportions of baseline characteristics among normal, overweight and obese groups, one-way ANOVA (with a linear polynomial term) and chi-square tests for linear trend were used, respectively. Age-adjusted logistic regression was used to calculate odds ratios (OR) for incident diabetes, elevated triglycerides, hypertension, metabolic syndrome and reduced HDL-C, comparing those classified at baseline as overweight and obese with normal, and for

quintiles of waist circumference. The population attributable fraction (AF_p), was calculated for each gender using the following formula:[21]

$$AF_p = p(RR-1)/p(RR-1)+1$$

where p is the gender-specific proportion of obesity in the baseline AusDiab cohort[1]. Risk ratios (RR) were estimated from the calculated odds and hazard ratios (HR) for incident events using the method of Zhang and Yu[22]. Cox proportional hazard models were used to estimate all-cause mortality HR for quintiles of waist circumference and waist to hip ratio (included because it was shown in two other Australian cohorts to be more strongly associated with mortality than was waist circumference)[23, 24] and to estimate HR for myocardial infarction among those classified as overweight or obese compared to normal. For mortality analyses, the lowest adjusted risk for mortality was observed in the second quintile for waist to hip ratio. This group was therefore chosen as the reference group, with the higher mortality risk in the first quintile most likely due to weight-loss inducing conditions such as respiratory diseases and cancer. Proportionality of hazards was assessed with log-log plots of the relative hazards by time and Kaplan Meier plots of the observed versus predicted survival curves using Stata 10 (StataCorp, College Station, Texas, USA). All other analyses were conducted with SPSS 15.0 (SPSS Inc., Chicago IL, USA).

Results

Risk related to categories of abdominal obesity

Baseline physiological and demographic characteristics of the cohort stratified by baseline waist circumference categories are presented in Table 1. Strong linear associations ($p < 0.0001$) were seen between abdominal obesity and education, physical activity, television viewing, all lipid, glucose and blood pressure parameters, type 2 diabetes, the metabolic syndrome and history of CVD in both men and women.

Abdominal obesity-related adjusted ORs for the development of various clinical outcomes are shown in Figure 1. Among those classified as obese, compared to those with a normal waist circumference, the risk of type 2 diabetes, dyslipidaemia, hypertension and the metabolic syndrome was increased by between 2 to 5 times in women and men. The risk of myocardial infarction was similarly increased in men (HR = 2.75 (95%CI 1.08 – 7.03), p=0.035), but not women (HR=1.43 (95%CI 0.37 – 5.5), p>0.05). Those with waist circumference in the overweight range were at increased risk of the metabolic syndrome and its three components (hypertension, elevated triglycerides and low HDL-C). Risk for type 2 diabetes in men only, and myocardial infarction in women only was increased in the overweight, however this did not reach statistical significance. Since a larger cohort was available for analysis of myocardial infarction than other outcomes, we repeated this analysis after excluding those who only participated in the phone based follow-up of myocardial infarction (n=2069; 13/45 myocardial infarction events). HRs for overweight and obesity were 1.77 (0.3-10.6) and 2.06 (0.4-9.9) in women and 0.7(0.2-2.6) and 1.9 (0.7-5.1) in men (all p>0.05).

Risk over the range of waist circumference

To assess risk over the continuum of waist circumference, odds ratios for incident type 2 diabetes, the metabolic syndrome, hypertension and dyslipidaemia were plotted against quintiles of waist circumference. Myocardial infarction was not included because of the small number of cases in each gender-specific waist quintile. Increases in risk begin below the cut-point for overweight (Figure 2), with statistically significant increases in the odds of all outcomes in men, and elevated triglycerides, reduced HDL-C and the metabolic syndrome in women being observed by the second quintile of waist circumference (73.7-80.3cm in women; 88.2-94.2cm in men).

Mortality risk related to abdominal obesity

HRs for all-cause mortality over eight years of follow-up were plotted against quintiles of waist circumference and waist to hip ratio, adjusted for age, history of CVD, non-skin cancer and smoking status (Figure 3). Even though a weak J-shaped relationship between increasing levels of obesity and mortality was evident for waist to hip ratio in women, this did not reach statistical significance in any quintile. No trend of increasing risk of death with increasing obesity was evident for waist circumference in women, or either measure in men. Similar results were obtained after excluding smokers and those reporting a history of CVD or cancer; or when deaths in only the first year (rather than two years) of follow-up were excluded or when no deaths were excluded.

Obesity-related population attributable fraction

The obesity-related population attributable fraction was estimated for each non-fatal outcome. This was highest for type 2 diabetes (47.4% in men, 38% in women), similar for elevated triglycerides, reduced HDL-C and hypertension (all >30% in women and around 17% in men), and for myocardial infarction was higher in men compared with women (31.9% vs. 12.8%).

[Note: Results for Figure 1, as well as the risk per unit of BMI and per cm of waist circumference, are provided in tabular form as an online appendix]

Discussion

These findings provide further evidence of the serious negative health effects resulting from the high and increasing rates of overweight and obesity in Australia. Previous reports from the AusDiab study revealed that in 2000, 60% of adult Australians were overweight or obese[1], with the prevalence of obesity in Australia among the highest of any developed country.[25] Follow-up of the AusDiab cohort has now allowed us to report on the impact of what has been described as an obesity epidemic. The results presented here confirm that abdominal overweight, and more particularly obesity, are significant

risk factors for multiple negative health outcomes, and demonstrate the serious health consequences of the obesogenic environment in which we live.

We could not fully cover the spectrum of ill-health associated with obesity, with several conditions including osteoarthritis, cancers, chronic obstructive pulmonary disease (COPD), gall bladder disease, sleep apnoea and depression not assessed in the AusDiab study.[6, 26] We do however include four of the top five conditions for which obesity resulted in disability adjusted life years lost in the 1996 Australian Burden of Disease Study.[27] Indeed, CVD, hypertension and type 2 diabetes were responsible for 68% of the obesity-related burden of disease. A recent report estimated the annual direct and indirect financial costs of obesity in Australia to be AUD$3.8 billion, with over half of this borne by Government and society.[28]

A WHO report into the consequences of obesity highlighted a lack of relative risk data as a major evidence gap preventing more accurate burden of disease estimates.[26] Obesity-related risk is related to the demographic, behavioural and biomedical risk factor profile of the population, which differs between countries and over time. It is therefore difficult to extrapolate estimates from other populations to the Australian situation. The results presented here help to address this identified evidence gap, and are the first estimates of obesity-related relative risk for these conditions from a national Australian sample. Furthermore, they provide valuable evidence with which to more precisely calculate the total economic and health burden attributable to obesity , and to inform initiatives for addressing the already high levels of obesity present in Australia.

The population attributable fraction estimates presented require careful interpretation. These figures effectively compare the incidence observed in the AusDiab sample with a hypothetical population in which obesity is totally absent. Since no intervention currently exists to eliminate obesity, they must be thought of as purely theoretical.[29] Indeed, national obesity rates have not fallen through the use of targeted interventions in

any country.[30] A more detailed case study of the impact of obesity reduction interventions is obviously required. The risk estimates presented here will help to inform such endeavours in the Australian context.

Although body mass index (BMI) is the most frequently reported index of obesity, and a measure routinely used in WHO obesity surveillance initiatives, the recently announced Australian national obesity campaign ("Measure Up") is based on the promotion of waist circumference measurement to identify obesity.[31] Waist circumference is easily measured and has been shown to be both a better indicator of abdominal adiposity as well as a stronger predictor of many health outcomes than is BMI.[5, 26, 32] Evidence based cut-points for waist-circumference in different ethnic groups are lacking, and therefore those used in this report are appropriate only for Europid populations. For comparative purposes, analyses using BMI to categorize obesity are presented in an online appendix. Waist to hip ratio has been included in the analysis of mortality because it has been shown in two other population-based Australian cohorts to be more closely associated with mortality than was waist circumference.[23, 24] This trend was also present in the AusDiab cohort, even though the increased hazard ratios did not reach statistical significance, most likely due to a follow-up period of only eight years.

It is important to interpret this work in the context of the inherent limitations of the survey. Firstly, the risks associated with lesser degrees of overweight and obesity, particularly for myocardial infarction and mortality, may not become apparent without considerably longer follow-up than the five years (and eight years for mortality) used here. Other appropriately conducted and analysed studies with longer follow-up and more deaths have shown a strong and independent relationship between abdominal obesity and mortality.[24, 33, 34] Secondly, non-response to the baseline and follow-up surveys means that the results are from a population-based, but not necessarily

representative sample of Australians. Finally, due to small numbers of indigenous Australians in the sample, obesity-related risks for this population cannot be estimated.

Previous reports from AusDiab have demonstrated strong associations between abdominal obesity and time spent in both physical activity and television viewing[1], as well as the effects of these behaviours and sedentary time on markers of cardio-metabolic risk.[35-37] To address the obesity epidemic will require environmental and policy initiatives that provide realistic and achievable opportunities for Australians to be more active, to avoid too much time spent sitting and to avoid obesogenic food environments.[38] A recent report from the Obesity Working Group of the Australian National Preventative Health Taskforce has highlighted the multi-sectoral approach required to achieve the goal of preventing unhealthy weight gain in Australia.[30]

Conclusions

Follow up of the AusDiab cohort over five years has allowed us to simultaneously assess the impact of obesity on multiple health outcomes in adult Australians. We have confirmed here the considerably heightened risk for type 2 diabetes, the metabolic syndrome, hypertension, dyslipidaemia and CVD associated with abdominal obesity. This work now allows more precise estimation of the total financial and health burden attributable to obesity in Australia, and more accurate assessment of the impact of obesity prevention initiatives. Furthermore, it provides evidence with which to advocate for the environmental, policy and behavioural changes required to address obesity in this country.

Table 1: Cross-sectional associations of health and demographic characteristics with gender and waist circumference categories at baseline among non-pregnant adults aged <75 years who attended both baseline (1999-2000) and follow-up (2004-2005) AusDiab surveys and had waist circumference data.

				Waist category					
				Women			Men		
	All	Women	Men	Normal (<80cm)	Overweight (80-88cm)	Obese (>88cm)	Normal (<94cm)	Overweight (94-102cm)	Obese (>102cm)
n	6072	3321	2751	1336	783	1202	1100	794	857
Age (years)	50.5 (11.7)	50.3 (11.7)	50.9 (11.8)	46.9 (11.5)	51 (11.2)	53.6 (11.3)†	48 (11.8)	52.3 (11.4)	53.2 (11.2)†
BMI (kg/m^2)	26.9 (4.9)	26.7 (5.5)	27.2 (4)	22.5 (2.3)	26 (2.4)	31.9 (5.1)†	24.1 (2.2)	27 (2)	31.3 (3.5)†
Weight (kg)	76.9 (16)	70.7 (14.9)	84.4 (13.9)	59.4 (6.9)	68.8 (6.8)	84.5 (13.9)†	74 (8.1)	83.8 (7.4)	98.2 (12.5)†
Waist circumference (cm)	90.5 (13.8)	84.9 (13.3)	97.2 (11.1)	72.8 (4.6)	83.8 (2.3)	99.2 (9.5)†	87 (5.2)	97.6 (2.2)	110.1 (7.5)†
Hip circumference (cm)	104.8 (9.8)	105.3 (11.3)	104.3 (7.5)	96.8 (5.8)	104.1 (5.5)	115.4 (10.7)†	98.8 (4.7)	104.2 (4.1)	111.3 (6.8)†
Serum HDL-C (mmol/L)	1.4 (0.4)	1.6 (0.4)	1.3 (0.3)	1.7 (0.4)	1.6 (0.4)	1.4 (0.3)†	1.4 (0.3)	1.2 (0.3)	1.1 (0.3)†
Serum triglycerides (mmol/L)[1]	1.3 (1.8)	1.2 (1.7)	1.4 (1.8)	0.9 (1.6)	1.2 (1.6)	1.6 (1.7)†	1.2 (1.7)	1.5 (1.7)	1.8 (1.7)†
Fasting plasma glucose (mmol/L)[1]	5.5 (1.2)	5.3 (1.2)	5.7 (1.2)	5.1 (1.1)	5.3 (1.1)	5.7 (1.2)†	5.5 (1.1)	5.6 (1.1)	5.9 (1.2)†
2hr plasma glucose (mmol/L)[1]	5.9 (1.4)	5.9 (1.3)	5.8 (1.4)	5.3 (1.3)	5.9 (1.3)	6.7 (1.4)†	5.4 (1.4)	5.8 (1.4)	6.4 (1.4)†
Metabolic syndrome (IDF definition %)	33	27.9	39.2	0	28.1	59.3†	0.8	55	74.1†
Diabetes (%)[2]	6.5	5.4	7.7	1.4	2.7	12.1†	3.7	6.3	14.8†
Hypertension (%)[3]	29.6	26.7	33.1	12.9	25.3	43.1†	20.9	34.8	46.7†
Systolic blood pressure (mmHg)	128.1 (17.4)	125.2 (17.8)	131.7 (16.1)	118.5 (15.4)	125.7 (16.7)	132.3 (18.2)†	127.2 (15.2)	132.8 (15.9)	136.4 (16)†
Diastolic blood pressure (mmHg)	70.3 (11.6)	66.5 (10.9)	74.9 (10.7)	64.2 (10.4)	66.7 (10.1)	69 (11.4)†	72 (10.4)	75.5 (10.6)	78 (10.1)†
Previous CVD[4]	6.2	4.4	8.4	2.8	2.2	7.6†	5	9.3	11.7†
Current smoker (%)	11.9	10.4	13.8	10.8	8.9	11	14.3	13.5	13.2
Tertiary education (%)[5]	41.6	37.2	46.8	43.8	35.6	30.9†	53.3	44.8	40.6†
TV viewing (hours/wk)	12.5 (9.2)	11.8 (9)	13.3 (9.4)	10.2 (8)	11.6 (9)	13.7 (9.5)†	12 (8.9)	13.1 (8.6)	15 (10.5)†
Physical activity (hours/wk)	4.7 (5.5)	4 (4.9)	5.5 (6.1)	4.6 (5.2)	4.1 (5)	3.3 (4.4)†	6.4 (6.6)	5.2 (5.6)	4.8 (5.9)†

Data are:

[1] Geometric mean and standard deviation

[2] Diabetes based on WHO criteria, includes previously and newly diagnosed diabetes, excludes type 1 diabetes

[3] Hypertension defined as blood pressure greater than 130/85mmHg or on medication for hypertension

[4] Previous cardiovascular disease (CVD) includes self-reported stroke, heart attack or angina

[5] Higher education defined as education beyond high school (university or technical and further education)

† p<0.0001 (test for linear trend)

Table 2. Estimated fraction of incident outcomes that would not have occurred in the AusDiab population if no obesity was present (Population Attributable Fraction, AF$_p$).

	Estimated RR[†]		AF$_p$	
	Women	**Men**	**Women**	**Men**
Type 2 Diabetes	3.6	3.3	47.4	38.0
Elevated triglycerides	3.2	1.7	43.1	16.7
Reduced HDL	2.3	1.8	30.3	17.5
Hypertension	2.6	1.8	35.5	17.0
Myocardial infarction	1.4	2.7	12.8	31.9

[†] Risk ratio (RR) estimated from observed odds ratios and hazard ratios (Figure 1) using the method of Zhang and Yu.[22] These are presented because the calculation of AF$_p$ is based on RR, not odds or hazard ratios.[21]

Cut points: HDL-C <1.0 mmol/l (M), <1.3 mmol/l (F); Triglycerides ≥1.7 mmol/l; Hypertension defined as ≥140/90 mmHg or reporting antihypertensive use.

HDL-C – high density lipoprotein cholesterol.

Figure 1. Gender-specific, adjusted odds/hazard ratios[†] among Australian adults aged 25 to 75 years for the development of various clinical outcomes over five years in those classified as obese and overweight using waist circumference at baseline, compared to those with a normal waist circumference at baseline.
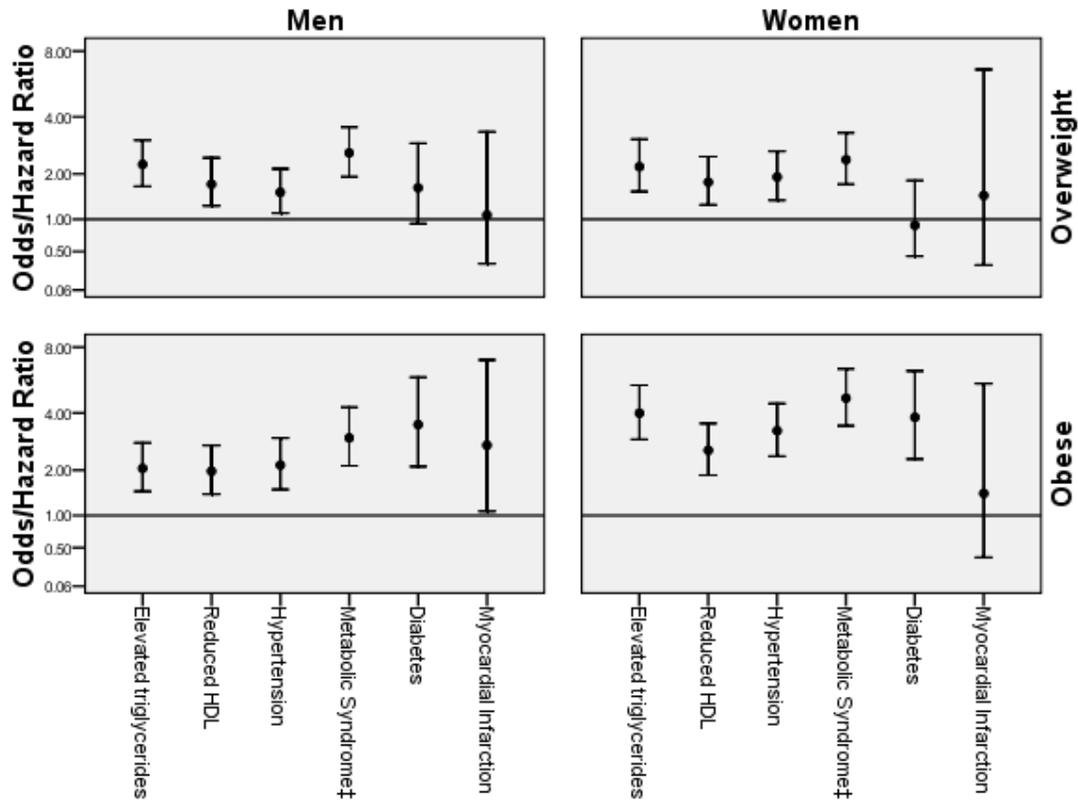
[†]Odds ratios for all outcomes, with the exception of myocardial infarction for which hazard ratios are reported. Analysis adjusted for age and smoking status (current or ex/never), and in the case of myocardial infarction, self-reported history of cardiovascular disease.

[‡]Metabolic Syndrome defined as ≥2 of the non-obesity components of the International Diabetes Federation definition.[13]

Cut points: HDL <1.0 mmol/l (M), <1.3 mmol/l (F); Triglycerides ≥1.7mmol/l; Hypertension defined as ≥140/90 mmHg or reporting antihypertensive use.

HDL – high density lipoprotein cholesterol.

Figure 2. Gender-specific, adjusted odds ratios[†] for the development of various clinical outcomes and biomedical markers of cardiometabolic risk over five years by quintiles of waist circumference[‡] at baseline among Australian adults aged 25 to 75 years.
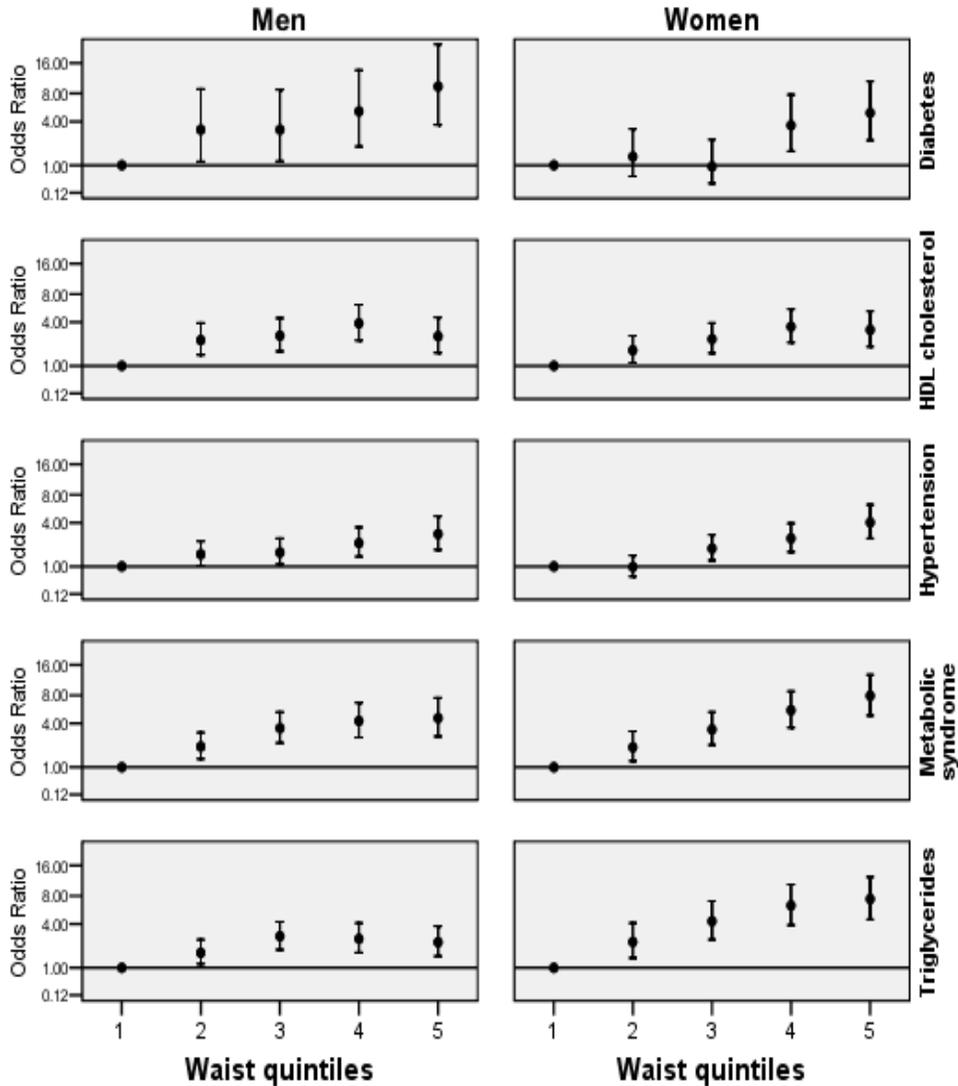
[†]Analysis adjusted for age and smoking status (current or ex/never).

[‡]Quintiles of waist circumference (cm.) – **Women**: 1 (<73.7); 2 (73.7-80.3); 3 (80.4-87.0); 4 (87.1-96.2); 5 (>96.2). **Men**: 1 (<88.2); 2 (88.2-94.2); 3 (94.3-99.3); 4 (99.4-106.2); 5 (>106.2).

Cut points: HDL <1.0 mmol/l (M), <1.3 mmol/l (F); Triglycerides ≥1.7mmol/l; Hypertension defined as ≥140/90 mmHg or reporting antihypertensive use. Metabolic Syndrome defined as ≥2 of the non-obesity components of the International Diabetes Federation definition.[13]

HDL – high density lipoprotein cholesterol.

Figure 3. Adjusted hazard ratios and 95% confidence intervals[†] for all-cause mortality over eight years according to quintiles of baseline waist to hip ratio and waist circumference in Australian adults aged 25 to 75 years.
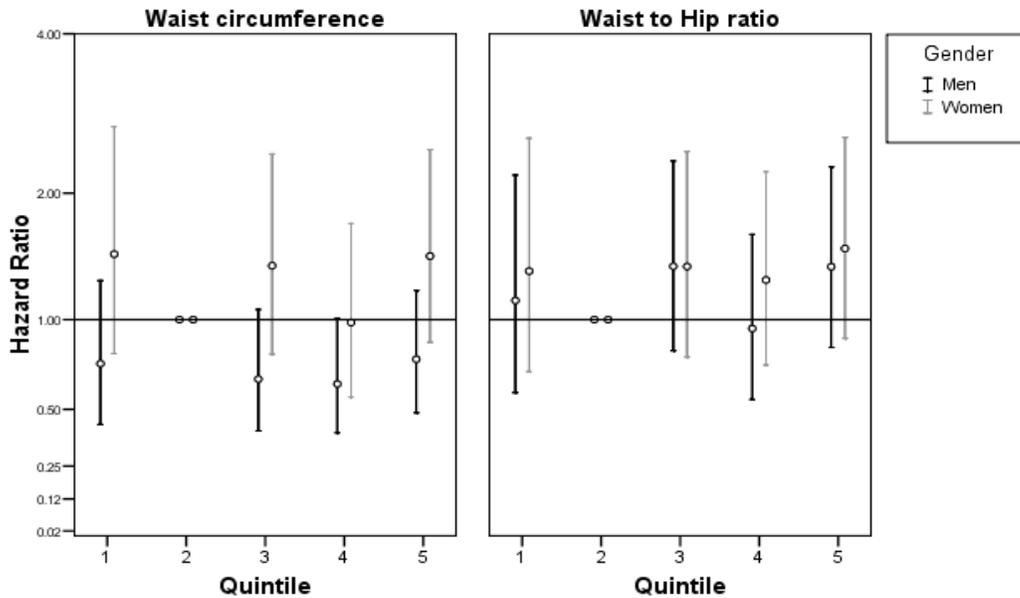
[†]Adjusted for age, self-reported history of cardiovascular disease (either angina, myocardial infarction or stroke), self-reported cancer (excluding skin cancer) and smoking status (current smoker vs. ex/never smoker). Those who died within two years of attending the baseline survey excluded from analysis.

[‡]Quintiles of waist circumference (cm.) – **Women**: 1 (<73.7); 2 (73.7-80.3); 3 (80.4-87.0); 4 (87.1-96.2); 5 (>96.2). **Men**: 1 (<88.2); 2 (88.2-94.2); 3 (94.3-99.3); 4 (99.4-106.2); 5 (>106.2). Quintiles of waist to hip ratio – **Women**: 1 (<0.75); 2 (0.75-0.79); 3 (0.80-0.82); 4 (0.83-0.87); 5 (>0.87). **Men**: 1 (<0.88); 2 (0.88-0.91); 3 (0.92-0.95); 4 (0.96-0.99); 5 (>0.99).

Appendix 1. **Gender-specific, adjusted odds/hazard ratios[†] among Australian adults aged 25 to 75 years for the development of various clinical outcomes over five years in those classified as obese and overweight at baseline compared to those who at baseline had a normal waist circumference and BMI respectively, and per unit of BMI or per cm. of waist circumference. [To be published online only]**

		OR/HR for overweight and obese compared to normal, and per cm. of waist circumference or per unit of BMI			
		Waist circumference		BMI	
		Men	Women	Men	Women
Diabetes	Overweight	1.7 (0.9,3.0)	0.9 (0.4,1.8)	2.1 (1.1,3.8)	1.6 (1.0,2.8)
	Obese	3.5 (2.1,5.9)	3.8 (2.3,6.3)	5.1 (2.8,9.5)	3.6 (2.2,6.0)
	Per cm/BMI unit	1.06 (1.04,1.08)	1.05 (1.03,1.06)	1.17 (1.12,1.23)	1.11 (1.07,1.14)
Elevated triglycerides	Overweight	2.3 (1.7,3.1)	2.2 (1.6,3.1)	2.3 (1.7,3.0)	2.9 (2.1,3.9)
	Obese	2.1 (1.5,2.8)	4.0 (3.0,5.4)	2.4 (1.7,3.5)	3.6 (2.6,5.0)
	Per cm/BMI unit	1.03 (1.02,1.04)	1.05 (1.04,1.05)	1.08 (1.05,1.11)	1.09 (1.07,1.11)
Hypertension	Overweight	1.6 (1.1,2.1)	1.9 (1.4,2.7)	1.5 (1.1,2.1)	2.1 (1.6,2.8)
	Obese	2.1 (1.5,3.0)	3.3 (2.4,4.4)	3.5 (2.3,5.2)	4.4 (3.1,6.2)
	Per cm/BMI unit	1.04 (1.02,1.05)	1.04 (1.03,1.05)	1.12 (1.07,1.16)	1.11 (1.09,1.14)
Metabolic Syndrome	Overweight	2.6 (1.9,3.6)	2.4 (1.7,3.3)	2.2 (1.6,2.9)	2.6 (1.9,3.5)
	Obese	3.0 (2.1,4.3)	4.7 (3.5,6.4)	4.0 (2.6,6.0)	4.4 (3.2,6.2)
	Per cm/BMI unit	1.05 (1.04,1.07)	1.06 (1.05,1.07)	1.14 (1.10,1.19)	1.13 (1.10,1.16)
Reduced HDL	Overweight	1.7 (1.3,2.5)	1.8 (1.3,2.5)	2.0 (1.4,2.7)	1.6 (1.2,2.2)
	Obese	2.0 (1.4,2.7)	2.6 (1.9,3.6)	1.9 (1.3,2.9)	2.0 (1.4,2.8)
	Per cm/BMI unit	1.02 (1.01,1.04)	1.03 (1.02,1.04)	1.06 (1.03,1.1)	1.07 (1.04,1.09)
Myocardial Infarction	Overweight	1.1 (0.4,3.4)	1.5 (0.3,6.6)	2.9 (0.8,9.9)	1.8 (0.5,7.3)
	Obese	2.8 (1.1,7.0)	1.4 (0.4,5.5)	4.7 (1.3,17.1)	2.5 (0.6,9.9)
	Per cm/BMI unit	1.03 (1.00,1.06)	1.04 (1.00,1.07)	1.10 (1.02,1.18)	1.07 (0.99,1.16)

[†]Odds ratios for all outcomes, with the exception of myocardial infarction for which hazard ratios are reported. Analysis adjusted for age and smoking status (current or ex/never), and in the case of myocardial infarction, self-reported history of cardiovascular disease.

[‡]Metabolic Syndrome defined as ≥2 of the non-obesity components of the International Diabetes Federation definition.[13]

Cut points: HDL <1.0 mmol/l (M), <1.3 mmol/l (F); Triglycerides ≥1.7mmol/l; Hypertension defined as ≥130/85 mmHg or reporting antihypertensive use.

HDL-C – high density lipoprotein cholesterol.

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3.4 Validity of ethnicity specific cut-points for obesity used in the metabolic syndrome

Cameron AJ, Zimmet PZ, Alberti KGMM, Sicree RA, Tonkin AM, Balkau B, Tuomilehto J, Chitson P, Shaw JE. Cut-points for waist circumference in Europids and South Asians. Submitted, *The Lancet*.

Introduction

The introduction of cut-points for waist circumference specific to particular population groups in the IDF definition (and later in revisions of the ATPIII definition) of the metabolic syndrome was an acknowledgement that the metabolic syndrome is a global tool that should be applicable to all populations. Unfortunately, the evidence base available for the selection of appropriate waist cut-points for different ethnic groups was not substantial, and the cut-points chosen did not necessarily reflect differences in the risk for common outcomes of the metabolic syndrome such as type 2 diabetes and cardiovascular diseases. In particular, little evidence existed from population-based longitudinal research studies of non-Caucasian populations. This study was designed to address this question through examination of the relationship between waist circumference levels and incident type 2 diabetes in the Caucasian AusDiab cohort, and South Asian participants from the Mauritius studies.

Almost universally, previous studies attempting to define optimal waist circumference cut-points (in both Caucasian and non-Caucasian populations) have been cross-sectional in design, and have relied on analytic techniques that identify the optimal combination of sensitivity and specificity on receiver operating characteristic (ROC) curves. This study was used as an opportunity to address the analytic flaws inherent in the use of ROC curves

for this purpose through demonstration of the link between optimal waist cut-points chosen

and the underlying prevalence of obesity in the population.

Declaration for Thesis Chapter

Declaration by candidate

In the case of Chapter   , the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision, corresponding author	85

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Richard A Sicree	Interpretation of data, critical revision, approval of final draft for publication	
Paul Z Zimmet	Study conception and design, critical revision, approval of final draft for publication	
KGMM Alberti	Study conception and design, critical revision, approval of final draft for publication	
Andrew M Tonkin	Interpretation of data, critical revision, approval of final draft for publication	
Beverly Balkau	Interpretation of data, critical revision, approval of final draft for publication	
Jaakko Tuomilehto	Study conception and design, critical revision, approval of final draft for publication	
Pierrot Chitson	Study conception and design, critical revision, approval of final draft for publication	
Jonathan E Shaw	Study conception and design, acquisition of data, interpretation of data, drafting of manuscript & critical revision, approval of final draft for publication	

Candidate's Signature		Date 08 . 01. 09

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.

(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;

(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;

(4) there are no other authors of the publication according to these criteria;

(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and

(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Baker IDI Heart and Diabetes Institute, Epidemiology Department, 250 Kooyong Rd Caulfield Vic 316

		Date
Signature 1		29/4/09
Signature 2		4/5/09
Signature 3		10/5/09
Signature 4		8.5.09
Signature 5		5.5.09
Signature 6		13.5.09
Signature 7		13.5.09
Signature 8		29/6/09

Manuscript title: Cut-points for waist circumference in Europids and South Asians.

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Keywords

Waist circumference, Obesity, Metabolic Syndrome, Type 2 diabetes, Ethnicity

Abstract

Background:

Differences in waist circumference cut-points for different ethnic groups reflect the higher risk of obesity-related outcomes at a given level of adiposity in certain ethnic groups. However, little evidence exists as to whether currently recommended Europid and South Asian cut-points for waist circumference are in fact associated with similar degrees of risk for type 2 diabetes. We sought to provide such evidence.

Methods:

Data were from 5515 Europid participants in the Australian AusDiab study (2000-2005) and 2214 ethnically South Asian participants in the Mauritius Non-Communicable Disease Study (1987-1992). Age-standardized diabetes incidence per cm of waist circumference was calculated and the Youden Index used to calculate waist circumference cut-points.

Findings:

At currently recommended cut-points (80 cm in South Asian and Europid women, 90 cm and 94 cm in South Asian and Europid men respectively), estimated annual diabetes incidence for a 50 year old Europid was < 0·6% for both sexes, and for a 50 year old South Asian, 5·3% for men and 2·2% for women. Annual diabetes incidence of 1% was observed for a 50 year old at a waist circumference approximately 40 cm greater in Europids compared to South Asians for both men (103 cm vs. 63 cm) and women (99 cm vs. 61 cm).

Waist circumference cut-points chosen by maximizing the Youden Index were shown to be dependent on the underlying level of obesity in the population.

Interpretation:

Based on considerably greater five-year risk of diabetes in South Asians compared to Europids at current waist circumference cut-points, the difference between cut-points in these ethnic groups should be greater. Approaches that select waist circumference cut-points using the Youden index are inappropriate and should not be used for this purpose.

Introduction

The continuing rise in the proportion of adults who are overweight and obese observed in most developed countries over the past three decades is now also being seen in developing countries.[1] The increasing global burden of chronic non-communicable diseases has been described as setting the agenda for global public health, with pandemics of obesity and type 2 diabetes threatening progress toward achievement of the Millennium Development Goals.[2] Obesity is associated with an increased risk of many diseases including type 2 diabetes, cardiovascular diseases and several cancers as well as premature mortality,[3–5] and is a precursor to the development of the components of the metabolic syndrome.[6] Because obesity is modifiable and often occurs many years before the development of the associated negative health outcomes, it is an ideal target for chronic disease prevention.

Increasingly, abdominal obesity has been shown to be a stronger indicator of associated risk than overall body fatness as measured by the body mass index (BMI).[1, 7–9] Waist circumference is easily determined and the most commonly used and valid surrogate measure of abdominal adiposity. Evidence-based cut-points for abdominal obesity are therefore important for both clinical and public health uses.

The cut-points of waist circumference for overweight and obesity recommended by the World Health Organization (WHO) (men 94/102 cm; women 80/88 cm)[1] were those statistically corresponding to a BMI of 25 and 30 kg/m^2, respectively in a small study involving a largely Europid population.[10] Specific cut-points for other ethnic groups have been published by some organizations,[11] but not the WHO. A large number of studies have attempted to define waist circumference cut-points related to ethnicity, mostly using approaches based on Receiver Operating Characteristic (ROC) curves. Little evidence exists from longitudinal studies with incident outcomes such as type 2

diabetes and cardiovascular disease. Despite an abundance of reports from cross-sectional studies, there remains a need for evidence to inform waist circumference cut-points in different ethnic groups.[12, 13]

Using data from two national, longitudinal cohort studies, our primary aim was to determine whether differences in currently recommended waist circumference cut-points between Europids and South Asians are an adequate reflection of the differences in risk for incident type 2 diabetes related to obesity between the two populations. We compared the following between the two populations:

1. The incidence of diabetes at currently recommended waist circumference cut-points.

2. The waist circumference at which the age-adjusted annual incidence of diabetes is 1%. This method compares the two populations at a fixed level of absolute risk.

3. The waist circumference at which diabetes incidence increases by 50%, 100% and 200% above that observed for the 10th percentile of waist circumference. This method compares the two populations at fixed levels of relative risk.

4. The age and waist circumference profile of those who developed diabetes in the two populations.

Finally, we assessed if determination of waist circumference cut-points by the Youden index (the waist circumference at which sensitivity + specificity for incident diabetes is maximized) was affected by the prevalence of obesity in the population.

Methods and Procedures

Population-based surveys

The study methods and response rates for both the AusDiab and Mauritius surveys have been described in detail elsewhere.[14, 15]

The AusDiab study was a nation-wide population-based stratified cluster survey of 11247 Australian adults (45% men) aged ≥25 years in 1999-2000. The response rate was 55% of those completing a household interview, estimated to be 37% of the eligible population. In 2004-2005, 59% (n=6400) of the 10788 eligible participants returned for a follow-up physical examination.

The Mauritius non-communicable disease survey began in 1987 and included all persons aged ≥25 years living in 10 randomly selected population clusters and a purposely selected area of Chinatown in Port Louis. Response rate was 80% (n=5083). Of those surviving and eligible, 74% (3771) were followed up in 1992.

Survey procedures

Those individuals with diabetes at baseline, pregnant women and those without data on waist circumference or diabetes status at baseline or follow-up were excluded from all analyses. Only those defined as having Europid ancestry in AusDiab, and South Asian ancestry in Mauritius were included. Ancestry was based on country of birth and language spoken at home in the AusDiab study, and self-reported ethnicity in Mauritius (Chinese, Creole or South Asian). After exclusions, the number available for longitudinal analyses in Mauritius 1987 to 1992 was 2214; and in AusDiab from 2000 to 2005, 5515.

In both studies, and at both time points, a 75g oral glucose tolerance test (OGTT) was performed on all non-pregnant participants, except those taking insulin or oral antidiabetic drugs. For the purpose of this report, diabetes was classified according to the WHO criteria.[16]

Biochemical measures and blood pressure for all surveys were obtained as previously described.[17, 18] In the AusDiab study, waist circumference was measured mid-way between the lower border of the ribs and the iliac crest on a horizontal plane. In Mauritius, waist circumference was measured as the minimum value of the horizontal plane between the xiphisternum and umbilicus.[18] In both surveys, two measurements to the nearest 0·5 cm were recorded. If the measurements varied by more than 2 cm, a third measurement was taken and the mean of the two closest measurements calculated. The AusDiab survey protocols were approved by the Ethics Committee of the International Diabetes Institute and the Monash University Standing Committee on Ethics in Research involving Humans (SCERH). The Mauritius survey protocols were reviewed and approved by the Alfred Healthcare Group Ethics Committee (Melbourne, Australia) as well as the Ministry of Health, Mauritius. Informed consent was obtained from all participants.

Statistical Analysis

Statistical analysis used SPSS 15·0 (SPSS Inc., Chicago IL, USA). Means (±SD) or proportions of various physical and demographic characteristics were calculated. Geometric means and geometric standard deviations were calculated for skewed variables (triglycerides, fasting and 2-hour post load plasma glucose). Gender- and population-specific logistic regression adjusted for age and age squared was used to estimate diabetes incidence for a 40, 50 and 60 year old, at 1 cm intervals of waist circumference. Improvement in the model after inclusion of a waist squared term was tested using a post-estimation likelihood ratio test. A similar logistic regression

including interaction terms of waist circumference and both sex and ethnicity was modelled in a dataset including participants from both surveys. The 10th percentile of waist circumference and the diabetes incidence for a 50 year old at this waist circumference were calculated for men and women in both populations. The waist circumference at which diabetes incidence was 50%, 100% and 200% greater than that seen at the 10th percentile of waist circumference was calculated in order to assess the strength of the relationship between waist circumference and diabetes in each population.

ROC curves for the prediction of diabetes were constructed and the waist circumference that maximised the sum of sensitivity and specificity (the Youden Index) calculated.[19] To assess the impact of the prevalence of obesity on the value of the Youden Index, ethnically and culturally similar populations with differing levels of obesity were required. Two approaches were used. Firstly, cut-points were calculated for prevalent diabetes (screen detected and diagnosed) in the 1987 and 1992 Mauritius surveys, regarded as separate cross-sectional surveys, and only including those who attended both surveys. The cohort attending the two Mauritius surveys was chosen because of the sharp increase in obesity levels between 1987 and 1992. Secondly, cut-points were calculated from two cohorts with "high" and "low" average waist circumference created from Europids in the AusDiab cohort. This was done by random selection of individuals within each decile of waist circumference, with the proportion included in the "high" cohort increasing from 30% of the lowest decile to 75% of the highest decile (and vice versa for the "low" cohort).

Role of the funding source

Results

The baseline physical and demographic characteristics of those who attended both surveys in the AusDiab and Mauritius studies are shown in Table 1. At baseline, Europid subjects from AusDiab were on average older, and had higher BMI, waist circumference, fasting plasma glucose and systolic blood pressure levels and a higher percentage reported tertiary education. Mean waist circumference was 19 cm greater in Europid than South Asian men (97 cm vs 78 cm) and 11 cm greater in Europid than South Asian women (84 cm vs 73 cm). Smoking was more common in men than women, and strikingly so among South Asians (56·8% in men vs. 1·4% in women).

[Insert Table 1 here]

Relationship between waist circumference and diabetes

Five year diabetes incidence was 3·8% (n=210) among Europid AusDiab participants, and 9·4% (208) in South Asian participants in the Mauritius study. Models predicting incident diabetes did not improve following the inclusion of a waist squared term (p>0·05) for either the South Asian or Europid populations (or in a combined dataset), suggesting a log-linear relationship between waist circumference and diabetes. In a combined dataset containing cases from both studies, interactions of waist circumference and sex and of waist circumference and ethnicity were not statistically significant (p>0·05). Relative to annual diabetes incidence at the 10th percentile of waist circumference (0·96% and 1·27% in South Asian women and men respectively, 0·25% and 0·35% in Europid women and men respectively), the increment in centimetres of waist circumference over which incidence increased by 50%, 100% and 200% was identical for Europid and South Asian women (9 cm, 15 cm and 24 cm respectively). In men, diabetes incidence increased by 50%, 100% and 200% over 7 cm, 12 cm and 20 cm in Europids and 6 cm, 10 cm and 17 cm in South Asians. The similar relationship between diabetes incidence and waist circumference in these populations is also

reflected in similar age- and sex-adjusted odds ratios of developing diabetes (1·05/ cm of waist circumference in Europids and 1·06/ cm in South Asians).

Difference in age-adjusted risk

Five-year incidence of diabetes (for a 50 year old) was higher among South Asian men and women at any level of waist circumference (Figures 1a and 1b), with a 1% annual incidence of diabetes occurring at a waist circumference approximately 40 cm greater in Europids compared to South Asians for both men (103 cm vs. 63 cm) and women (99 cm vs. 61 cm). Similar results were observed when the relationship was modelled for a 40 or 60 year old respectively.

Risk at currently recommended cut-points

At the currently recommended waist circumference cut-points (94 cm and 90 cm in Europid and South Asian men respectively; 80 cm in both Europid and South Asian women), estimated annual diabetes incidence for a 50 year old was 0·6% and 0·4% in Europid men and women, respectively, and 6·3% and 2·4% in South Asian men and women, respectively. The magnitude of difference was similar when the relationship was modelled for a 40 or 60 year old respectively.

Waist circumference and age profile of those developing diabetes

The 210 Europid participants who developed diabetes over five years were on average older (mean age 54 and 57 years for women and men respectively) and with a larger waist circumference (mean 93 cm and 104 cm for women and men respectively) than their 208 South Asian counterparts (mean age 44 years and 47 years; mean waist 83 cm and 79 cm for women and men respectively).

Effect of obesity prevalence on the Youden Index

To determine whether cut-points based on maximizing the Youden Index are affected by the prevalence of obesity in the population, we calculated such cut-points among ethnically and culturally similar populations with differing levels of abdominal obesity.

Figure 2a shows the mean waist circumference and cut-points calculated from the 1987 and 1992 Mauritius surveys, analysed cross-sectionally with the outcome of prevalent diabetes. Obesity levels and the corresponding cut-points identified were considerably greater in the 1992 cohort.

Figure 2b (using the 1999/2000 AusDiab survey for cross-sectional analysis) demonstrates that both the mean waist circumference and "optimal" cut-points calculated were greater in the sub-group selected to have higher average waist circumference than among those with lower average waist circumference.

Discussion

These results demonstrate that the difference between recommended waist circumference cut-points in Europid and South Asian populations (4 cm in men, no difference in women) does not lead to similar diabetes risk at the cut-points. High risk for diabetes in the South Asian population studied was observed at what have been traditionally regarded as normal waist circumference values (even for this ethnic group), suggesting that waist circumference cut-points in South Asians should be lower than currently recommended, for both men and women.

Our observations add to the accumulated evidence suggesting that people of South Asian ancestry develop risk factors for cardiovascular disease and type 2 diabetes at lower levels of waist circumference than Europids.[20]

Should the Youden Index/ROC curves be used to determine waist circumference cut-points?

Approaches based on ROC curve analyses have been used almost exclusively in studies aiming to choose waist circumference cut-points in different ethnic groups, although a few studies have used other methods.[21] Maximizing the Youden Index[19] has been recommended to determine an "optimal" point on a ROC curve, minimising the impact of the prevalence of the outcome while obtaining the cut-point with the optimal (equally weighted) combination of sensitivity and specificity.[22]

A serious, and largely ignored, limitation of the Youden Index for the selection of "optimal" waist cut-points is that such cut-points are linked to the prevalence of the risk factor (in this case, obesity) in the population. We have now demonstrated this in both the Mauritius and AusDiab studies. The Youden Index is simply the most efficient way of dividing a *specific* population, rather than reflecting the nature of a biological association between a risk factor and a disease. The cut-point identified will be particular to the tested population and its risk factors levels, and is unlikely to be the most efficient cut-point in another population, even one of the same ethnicity.

Our analysis of Europid and South Asian populations demonstrates that in them, the greater the level of abdominal adiposity, the greater the Youden Index-derived waist circumference cut-point. Similar results have been observed in immigrant populations in the United States and the United Kingdom, who demonstrate consistently higher Youden Index-derived waist circumference cut-points than ancestrally similar but slimmer populations living in either their native countries or countries with lower levels of adiposity.[23, 24] Furthermore, Youden Index-derived waist circumference cut-points in older populations have been shown to differ considerably from those obtained in younger, less obese populations.[25] Intuitively, cut-points should not change with the prevalence of obesity in a population. Therefore, the changeable nature of Youden

Index-derived cut-points means they are inappropriate for use beyond the specific population in which they were generated, and at that specific time.

Challenges in the choice of waist circumference cut-points

While there are obvious benefits in establishing waist circumference cut-points appropriate for different ethnic groups, the increasingly multi-cultural nature of many communities means that problems such as communicating the use of multiple cut-points within a single population and the calculation of cut-points for individuals of mixed ethnicity will become increasingly common. Furthermore, a method for recognising the age-dependency of the relationship between obesity and cardiovascular disease risk factors (often absent in the elderly)[26] has thus far not been developed.

The relation between waist circumference and diabetes risk is continuous. No natural cut-point exists, meaning that the choice of cut-point is essentially arbitrary and should account for both scientific and economic considerations. Demonstration of differences in risk at currently recommended cut-points as we have done here can help to inform this endeavour. Similar data utilising other outcomes and in other South Asian populations would also be helpful. The prevalence of obesity in different countries and the implications of a low cut-point for service provision and screening activities are financial considerations that should be taken into account. Different cut-points for a "healthy" waist circumference and the point at which country-specific decisions relating to service provision and screening are made may be required.

Limitations of this work and prospects for future data

The impact of different waist circumference measurement techniques in the AusDiab and Mauritius surveys is likely to be minimal. A study of mean waist circumference in a multi-ethnic population found the difference between measurements taken at the mid-point between the ribs and the iliac crest and the narrowest waist to be only 1·5 cm in men and 2·7 cm in women.[27] The particularly high incidence of diabetes in the South

Asian population in Mauritius may have affected the findings. The same study in a different South Asian population with a lower diabetes incidence and different exposure to diabetes risk factors may have resulted in less extreme differences than those observed here. Despite this, the extremely high incidence of diabetes at comparatively low levels of waist circumference in the South Asian population studied demonstrates that diabetes risk can increase at what have been traditionally thought to be very low levels of waist circumference. This message should in some way be reflected in the choice of cut-points for this population group. Finally, the South Asian participants in the Mauritian study who developed diabetes were considerably younger than those developing diabetes in the AusDiab study. Whether this is simply a reflection of the impact of obesity at a younger age in this population, or whether other factors are influencing this is unknown. The age standardisation of the South Asian and Europid population at age 50 may therefore have impacted the findings, although diabetes incidence for a 40 year old South Asian at currently recommended waist cut-points was still at least eight times higher than for a 50 year old Europid. Even if the South Asian population studied developed diabetes at a younger age, and this partly explained the high diabetes incidence at low levels of waist circumference, this does not change the conclusion that waist cut-points for the South Asian population should be lower than is currently the case.

Prospective studies such as those used here are the ideal setting in which to determine cut-points for waist circumference. Few similar studies in South Asians and other non-Europid populations exist. Therefore, similar cross-sectional studies in South Asians and other ethnic groups, and studies using outcomes other than incident diabetes may help inform the revision of ethnicity-specific waist cut-points. Two large, multinational studies that are as yet un-reported (the International Study of Prediction of Intra-Abdominal Adiposity and its Relationships With Cardiometabolic Risk [INSPIRE ME]

and INSPIRE ME IAA [Intra-Abdominal Adiposity study]) are likely to add to the evidence base in this area.

Conclusions

The purpose of cut-points for waist circumference is to identify those individuals at increased risk for obesity-related negative health outcomes in order to allow implementation of prevention strategies. Obesity is a precursor to the components of the metabolic syndrome,[6] and is important before the development of co-morbidities, not simply as a correlate for existing disease. As a preventive strategy, the choice of cut-points for obesity is therefore particularly important. The large increases in the prevalence of obesity and diabetes seen in South Asians in Mauritius and among South Asian immigrants to the UK[28] is now being seen throughout Asia due to swift economic development.[2, 29]

A consensus of opinion suggests that waist circumference cut-points should differ according to ethnicity. The results presented here suggest that currently recommended cut-points for South Asians have been set too high. Since most studies on this topic have used the Youden Index, which we demonstrate is inappropriate for this purpose, this work adds significantly to the evidence on which to base appropriate ethnicity-appropriate waist circumference cut-points.

Acknowledgements

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Tables and Figures

Table 1. Baseline characteristics[1] of Europid participants in the AusDiab study (2000 to 2005); and South Asian participants from Mauritius (1987 to 1992) longitudinal studies

	AusDiab (2000 to 2005)			Mauritius (1987 to 1992)		
	Total	**Men**	**Women**	**Total**	**Men**	**Women**
n	5515	2511	3004	2211	1014	1197
Age (years)	51•1 (12•6)	51•4 (12•8)	50•9 (12•5)	40•7 (12•0)	40•1 (11•5)	41•2 (12•3)
Weight (kg)	76•6 (15•6)	84•2 (13•5)	70•3 (14•3)	57•1 (11•9)	61•6 (11•1)	53•4 (11•2)
Waist Circumference (cm)	90•1 (13•4)	97 (10•7)	84•4 (12•7)	75•0 (10•2)	77•6 (8•8)	72•9 (10•8)
BMI (kg/m2)	26•8 (4•6)	27•1 (3•8)	26•5 (5•2)	23•3 (4•2)	22•8 (3•5)	23•7 (4•6)
Waist:Hip ratio	0•86 (0•09)	0•93 (0•06)	0•8 (0•07)	0•84 (0•08)	0•89 (0•06)	0•80 (0•06)
Systolic Blood Pressure (mmHg)	128•1 (17•3)	131•8 (16•1)	125 (17•6)	122•3 (17•4)	124•3 (16•9)	120•5 (17•7)
Fasting plasma glucose (mmol/L)[2]	5•4 (1•1)	5•5 (1•1)	5•2 (1•1)	5•1 (1•1)	5•2 (1•1)	5•1 (1•1)
2hr Plasma glucose (mmol/L)[2]	5•7 (1•3)	5•6 (1•3)	5•8 (1•3)	6•1 (1•3)	5•7 (1•3)	6•4 (1•3)
Serum Triglycerides (mmol/L)[2]	1•3 (1•7)	1•4 (1•7)	1•1 (1•7)	1•2 (1•8)	1•5 (1•9)	1•0 (1•7)
Serum HDL cholesterol (mmol/L)	1•4 (0•4)	1•3 (0•3)	1•6 (0•4)	1•3 (0•3)	1•3 (0•3)	1•3 (0•3)
Higher education[3]	40•8	45•6	36•7	2•1	3•9	0•6
Smokers	11•4	12•7	10•2	26•8	56•8	1•4
Incident diabetes[4]	3•8	4•3	3•4	9•4	11•1	7•9

Data are:

[1] Means (standard deviation) or percentages

[2] Geometric mean and standard deviation

[3] Higher education defined as education beyond high school (University or Technical and Further Education college)

[4] Diabetes diagnosed between baseline and follow-up, based on WHO criteria

Figure 1a. Estimated annual diabetes incidence for Europid and South Asian men at age 50 according to waist circumference, based on data from studies in Australia (2000-2005) and Mauritius (1987-1992) (Note – distribution curve of waist circumference also plotted).
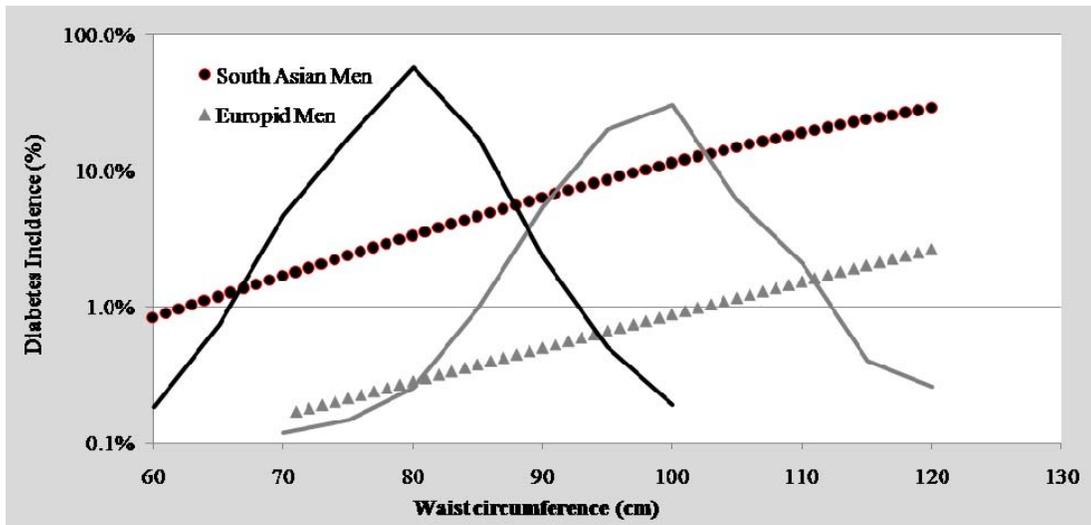
Figure 1b. Estimated annual diabetes incidence for Europid and South Asian women at age 50 according to waist circumference, based on data from studies in Australia (2000-2005) and Mauritius (1987-1992) (Note – distribution curve of waist circumference also plotted).
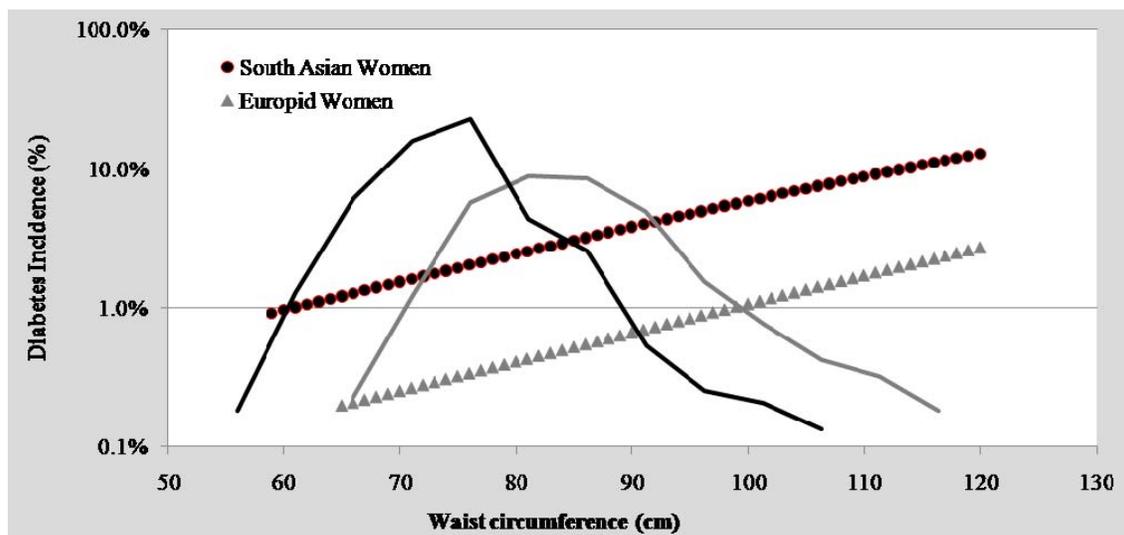
**Figure 2a. Mean waist circumference and "optimal" waist circumference cut-points chosen based on cross-sectional relationships with prevalent diabetes in Mauritius 1987 and 1992[1].**
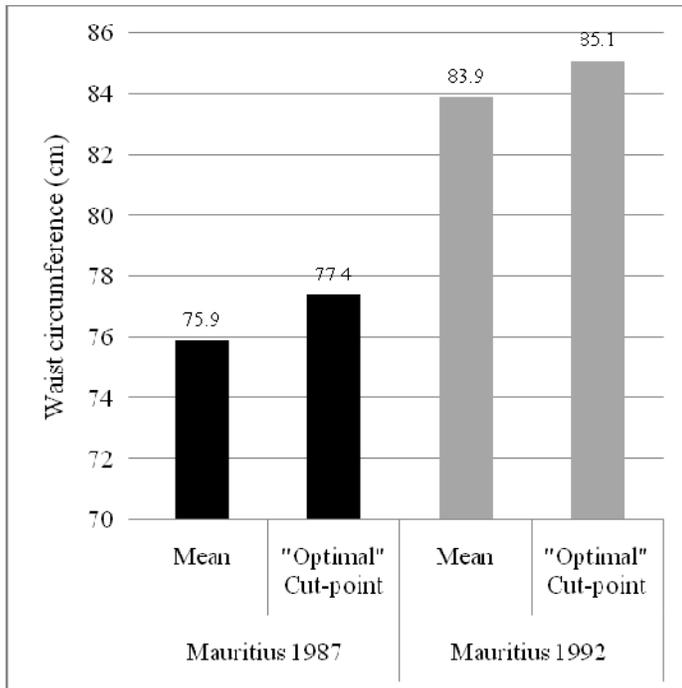
[1] Analysis only includes individuals who attended both the 1987 and 1992 Mauritius surveys.

Figure 2b. Optimal waist circumference cut-point based on relationships with incident diabetes among cohorts with high and low waist circumference[1] in the AusDiab study 1999-2000.
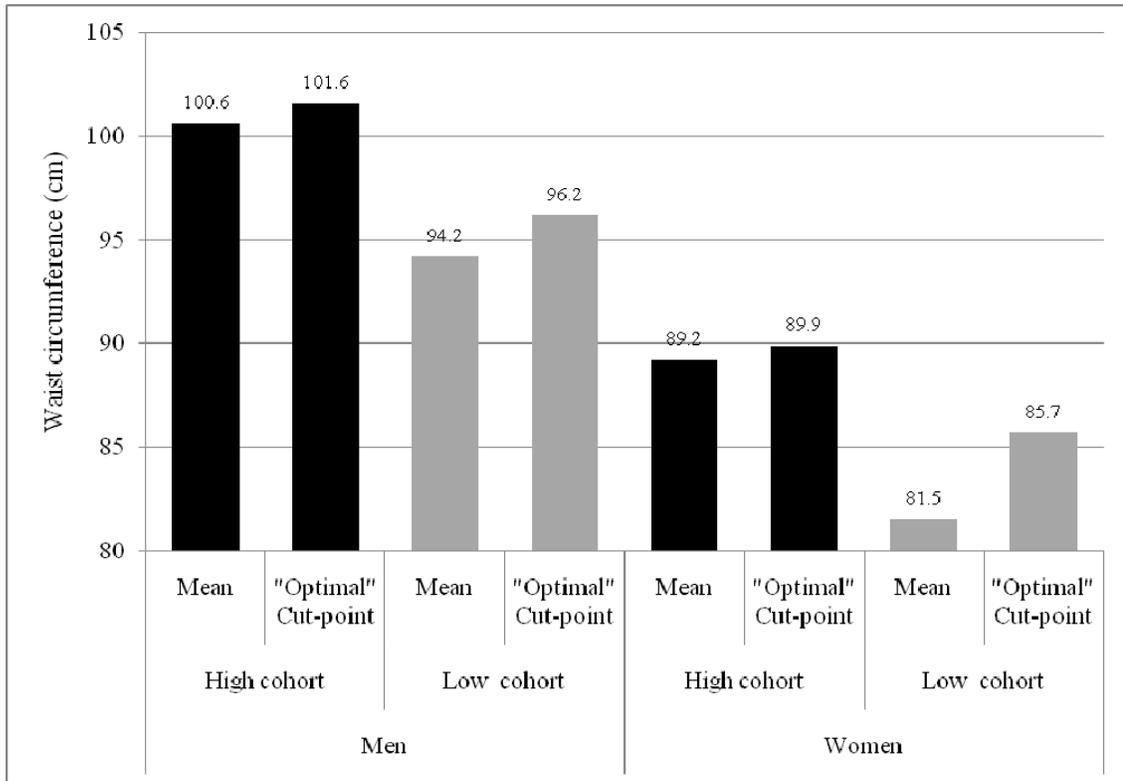
[1] Two equally sized cohorts with "high" and "low" average waist circumference respectively were created by random selection of individuals within each decile of waist circumference. The proportion chosen for the "high" cohort increased from 30% in the lowest waist decile to 75% in the highest waist decile. Conversely, the proportion of those chosen for the "low" cohort ranged from 30% in the highest waist decile to 75% in the lowest waist decile.

3.5 The metabolic syndrome as a tool for prediction of diabetes

Introduction

A key justification for the introduction of clinical definitions of the metabolic syndrome was to identify a population at high risk of Type 2 diabetes and cardiovascular disease. The various definitions were not intended solely to be risk prediction tools, however, given the absence of acknowledged risk factors for these conditions such as family history, smoking, ethnicity, age and sex. Several studies had previously shown the metabolic syndrome to be inferior to existing tools for cardiovascular disease risk prediction such as the Framingham algorithms. Less information existed regarding the ability of clinical definitions to identify those at high risk of future type 2 diabetes, particularly in non-Caucasian populations. No thorough comparisons had previously been made of the metabolic syndrome with other available tools such as the non-invasive FINDRISC diabetes risk questionnaire and diabetes risk prediction models such as that developed from the San Antonio Heart study. Whether the metabolic syndrome was any better than simple measurement of fasting glucose (or two-hours post glucose load) had also not been examined. The two studies reported here had similar aims, but were conducted in ethnically distinct populations (Caucasian and mixed South Asian/Creole/Chinese). Both provide a thorough assessment of the ability of available definitions of the metabolic syndrome, as well as other existing tools and glucose measurement, to predict incident type 2 diabetes. The Mauritius study further highlights the impact that definitions of obesity in this non-Caucasian population have both on the prevalence of the syndrome, and by extension, on its ability to identify those at high risk of future type 2 diabetes. A secondary aim of these studies was to address the question of whether the metabolic syndrome as a whole is any better than the combination of its

component parts for the prediction of diabetes. The insulin resistance syndrome, and following it, the metabolic syndrome, were both based on evidence suggesting that the component abnormalities clustered together, being more commonly observed together than would be expected by chance. This was thought to be suggestive of a common pathophysiology underlying their development, that if present, conferred an even greater risk for type 2 diabetes and cardiovascular disease than would be expected from the individual abnormalities themselves. No previous evidence that the clustering of abnormalities symptomatic of the metabolic syndrome conveyed an increased risk for diabetes had been published.

3.5.1 The metabolic syndrome as a tool for predicting future diabetes. The AusDiab study.

Cameron AJ, Magliano DJ, Zimmet PZ, Welborn TE, Colagiuri S, Tonkin AM, Shaw JE. *J Int Med*. 2008; 264:177–186.

Declaration for Thesis Chapter

Declaration by candidate

In the case of Chapter , the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision, corresponding author	75

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Diana J Magliano	Critical revision, approval of final draft for publication	
Paul Z Zimmet	Study conception and design, critical revision, approval of final draft for publication	
Timothy A Welborn	Study conception and design, critical revision, approval of final draft for publication	
Stephen Colagiuri	Critical revision, approval of final draft for publication	
Andrew M Tonkin	Critical revision, approval of final draft for publication	
Jonathan E Shaw	Study conception and design, acquisition of data, interpretation of data, drafting of manuscript & critical revision, approval of final draft for publication	

Candidate's Signature	■■■■■■■■■■	Date 2/11/07

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	International Diabetes Institute, Epidemiology Department, 250 Kooyong Rd Caulfield Vic 3162		
Signature 1	■■■■■■■		Date
Signature 2	■■■■■■■	27-11-07	19/11/07
Signature 3	■■■■■■■		14-05-09
Signature 4	■■■■■■■		19-5-09
Signature 5	■■■■■■■		20-11-07
Signature 6	■■■■■■■		29-11-07
Signature 7	■■■■■■■		

The metabolic syndrome as a tool for predicting future diabetes: the AusDiab study.

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OBJECTIVE: To compare the ability of the metabolic syndrome (MetS), a diabetes prediction model (DPM), a noninvasive risk questionnaire and individual glucose measurements to predict future diabetes. DESIGN: Five-year longitudinal cohort study. Tools tested included MetS definitions [World Health Organization, International Diabetes Federation, ATPIII and European Group for the study of Insulin Resistance (EGIR)], the FINnish Diabetes RIsk SCore risk questionnaire, the DPM, fasting and 2-h post load plasma glucose. SETTING: Adult Australian population. SUBJECTS: A total of 5842 men and women without diabetes > or =25 years. Response 58%. A total of 224 incident cases of diabetes. RESULTS: In receiver operating characteristic curve analysis, the MetS was not a better predictor of incident diabetes than the DPM or measurement of glucose. The risk for diabetes among those with prediabetes but not MetS was almost triple that of those with MetS but not prediabetes (9.0% vs. 3.4%). Adjusted for component parts, the MetS was not a significant predictor of incident diabetes, except for EGIR in men [OR 2.1 (95% CI 1.2-3.7)]. CONCLUSIONS: A single fasting glucose measurement may be more effective and efficient than published definitions of the MetS or other risk constructs in predicting incident diabetes. Diagnosis of the MetS did not confer increased risk for incident diabetes independent of its individual components, with an exception for EGIR in men. Given these results, debate surrounding the public health utility of a MetS diagnosis, at least for identification of incident diabetes, is required.

3.5.2 The metabolic syndrome as a predictor of incident diabetes mellitus in Mauritius.

Cameron AJ, Zimmet P, Soderberg S, Alberti K, Sicree R, Tuomilehto J, Chitson P, Shaw J. The metabolic syndrome as a predictor of incident diabetes mellitus in Mauritius. *Diabet Med.* 2007; 24(12):1460-9.

Declaration for Thesis Chapter

Declaration by candidate

In the case of Chapter , the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision, corresponding author	75

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Paul Z Zimmet	Study conception and design, approval of final draft for publication	
Stefan Soderberg	approval of final draft for publication	
KGMM Alberti	Study conception and design, critical revision, approval of final draft for publication	
Richard Sicree	Critical revision, approval of final draft for publication	
Jaakko Tuomilehto	Study conception and design, critical revision, approval of final draft for publication	
Pierrot Chitson	Study conception and design, critical revision, approval of final draft for publication	
Jonathan E Shaw	Study conception and design, acquisition of data, interpretation of data, drafting of manuscript & critical revision, approval of final draft for publication	

Candidate's Signature	██████████████	Date 2/11/07

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	International Diabetes Institute, Epidemiology Department, 250 Kooyong Rd Caulfield Vic 3162	
Signature 1	████████████████	Date 25-11-07
Signature 2	████████████████	3.3.08
Signature 3	████████████████	13-02-08
Signature 4	████████████████	2/11/07
Signature 5	████████████████	13/11/07
Signature 6	████████████████	17-5-07
Signature 7	████████████████	29/11/07
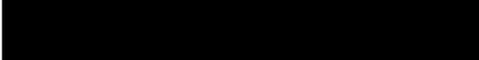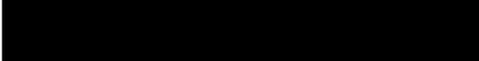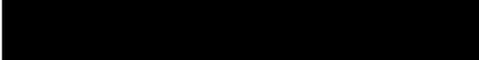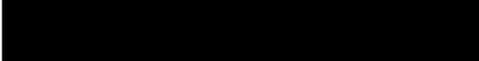
The metabolic syndrome as a predictor of incident diabetes mellitus in Mauritius.

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AIMS: To assess the utility of the metabolic syndrome (MetS) and a Diabetes Predicting Model as predictors of incident diabetes. METHODS: A longitudinal survey was conducted in Mauritius in 1987 (n = 4972; response 80%) and 1992 (n = 3685; follow-up 74.2%). Diabetes status was retrospectively determined using 1999 World Health Organization (WHO) criteria. MetS was determined according to four definitions and sensitivity, positive predictive value (PPV), specificity and the association with incident diabetes before and after adjustment for MetS components calculated. RESULTS: Of the 3198 at risk, 297 (9.2%) developed diabetes between 1987 and 1992. The WHO MetS definition had the highest prevalence (20.3%), sensitivity (42.1%) and PPV (26.8%) for prediction of incident diabetes, the strongest association with incident diabetes after adjustment for age and sex [odds ratio 4.6 (3.5-6.0)] and was the only definition to show a significant association after adjustment for its component parts (in men only). The low prevalence and sensitivity of the International Diabetes Federation (IDF) and ATPIII MetS definitions resulted from waist circumference cut-points that were high for this population, particularly in men, and both were not superior to a diabetes predicting model on receiver operating characteristic analysis. CONCLUSIONS: Of the MetS definitions tested, the WHO definition best identifies those who go on to develop diabetes, but is not often used in clinical practice. If cut-points or measures of obesity appropriate for this population were used, the IDF and ATPIII MetS definitions could be recommended as useful tools for prediction of diabetes, given their relative simplicity.

4 General discussion

4.1 Summary of main findings

Chapter 3.1. Results from the AusDiab study indicate that in 1999-2000, over one quarter of adult Australians met the criteria for either the IDF or ATPIII clinical definitions of the metabolic syndrome. The prevalence of each increases with age in both men and women to over 40% in middle age. Those who meet the IDF or ATPIII clinical criteria for the metabolic syndrome are at least five times more likely than those who do not to be classified as high risk (>15% over the coming ten years) for cardiovascular diseases according to algorithms from the Framingham study.

Chapter 3.2. Central obesity, measured using waist circumference, was shown to be a predictor of deterioration in each of six components of the metabolic syndrome tested. Increases in waist circumference were not similarly predicted by the baseline values of the metabolic syndrome components. This result is suggestive of a temporal relationship in which central obesity is the precursor to the development of the other components of the metabolic syndrome, and plays a key role in their development. This is the first such epidemiologic research to explicitly address the question of temporality in the development of the components of the metabolic syndrome. The results were confirmed in two population-based studies of ethnically diverse populations conducted in Australia (five year follow-up) and Mauritius (both five and eleven year follow-up). The reduction or prevention of central obesity should therefore be seen as the primary goal in the prevention of the metabolic syndrome.

Chapter 3.3. Obesity, and to a lesser degree overweight, have been shown to confer a heightened risk for each of type 2 diabetes, the metabolic syndrome, hypertension, dyslipidaemia and cardiovascular disease. The risk for each of the components of the metabolic syndrome, as well as type 2 diabetes, was shown to increase with increasing waist circumference, with elevated risk well below currently recommended waist circumference cut-points. No clear associations between obesity and mortality were observed, most likely due to the short length of mortality follow-up. These results provide important information with which to more precisely estimate the burden of disease attributable to obesity in Australia.

Chapter 3.4. The validity of ethnicity-specific waist circumference cut-points in clinical definitions of the metabolic syndrome was assessed through examination of the relationship between waist circumference and incident diabetes among a Europid population (the AusDiab study) and an ethnically South Asian population from Mauritius. The difference between recommended cut-points for these two groups (4cm higher for Europid men, identical for women) was shown to underestimate the difference in obesity related risk of diabetes and therefore should be greater. Additionally, this paper demonstrates, using examples from the AusDiab study and Mauritius, that approaches using ROC curve analysis to select waist circumference cut-points are dependent on the level of underlying obesity. Such methods are therefore inappropriate for this purpose.

Chapter 3.5. In similar studies conducted in Australia and Mauritius, the metabolic syndrome was shown to be a strong predictor for incident diabetes. In both studies, the IDF and ATPIII clinical definitions of the metabolic syndrome were shown to be no better than measurement of fasting glucose alone or published diabetes risk prediction scores for the prediction of incident diabetes over five years. In the Mauritius study, the waist

circumference cut-points used in the IDF and ATPIII metabolic syndrome definitions were shown to be set too high in this population of low mean waist circumference but high diabetes incidence. The metabolic syndrome was shown to be independent of its component parts as a predictor of diabetes only for the WHO definition in males in Mauritius and for the EGIR definition in males in AusDiab.

4.2 Limitations of the studies

4.2.1 Selection bias

The issue of selection bias needs to be considered separately for Chapter 3.1 and Chapters 3.2 to 3.5 due to the different research goals and study designs of these studies. Chapter 3.1 reports the prevalence of the metabolic syndrome among the baseline AusDiab sample, and is based on a cross-sectional research design. The goal of this study was to provide accurate national estimates of the prevalence of the metabolic syndrome. The presence of significant selection bias in the baseline AusDiab cohort would therefore invalidate this research, meaning that the results could only be reported as being representative of the cohort sampled, rather than the entire adult Australian population. Two methods of testing for the presence of selection bias in the AusDiab cohort are comparison of the cohort to the entire Australian population (from census data), and comparisons between responders and non-responders to the survey. The demographic profile of the cohort who attended the baseline survey was older and included a higher proportion of females compared to the 1998 demographic profile of all adult Australians obtained from the Australian Bureau of Statistics.[89] As reported in chapter 2.2.1, however, these age and sex differentials between the baseline AusDiab cohort and the adult Australian population were countered by weighting of the sample according to gender and age deciles of the estimated 1998 resident Australian population aged over 25 years. A second method of testing for response bias is to compare responders to the survey with non-responders. In this case, the term non-responders refers to those who completed a household interview but did not go on to undertake physical examination at the testing site. It is acknowledged that the profile of those non-responders who did not complete the household interview is unknown. Upon comparison of responders and non-responders, it was found that responders were more

likely to have suspected that they had diabetes, be born in the United Kingdom, speak English or have completed high school, technical education or University.[89] The differences in the percentage of responders and non-responders born in the United Kingdom (10.3 vs. 8.8%) and who speak English (96.1 vs. 93.6%) were small, despite being statistically significant, and would not be expected to affect prevalence estimates of the metabolic syndrome. Larger differences were noted for those who completed high school or further education (58.2 vs. 51.3%), and for those who suspected they had diabetes (1.5% vs. 0.5%). The education differential means that responders were likely to have been from a higher socio-economic strata, which could potentially bias metabolic syndrome prevalence estimates. Most cardiovascular disease risk factors, however, (i.e. glucose intolerance, dyslipidaemia, physical activity, alcohol consumption and smoking) are negatively associated with socio-economic status,[103] meaning that if a socio-economic response bias exists, it would likely result in an under-estimate of true prevalence rates. The difference between responders and non-responders in rates of suspicion of diabetes is suggestive of a respondent population with higher rates of diabetes. Analysis of the actual diabetes rate (based on the results of an oral glucose tolerance test), however, showed that of those who suspected they had diabetes, only one in twelve were subsequently found to meet the criteria for diagnosis. This compares with one in 25 of those who did not suspect they had diabetes. Given the low prevalence of undiagnosed diabetes in the sample, the effect of this bias on rates of diabetes and the metabolic syndrome is expected to have been negligible.[89] The decision to exclude all census collection districts classified as 100% rural, and those with an indigenous Australian population greater than 10% introduces an additional, unavoidable response bias. The decision to exclude rural collection districts was made because of the logistical difficulties involved in conducting household interviews and setting up a local testing site in such locations. The decision to exclude those districts with

a high proportion of indigenous Australians (as reported in Chapter 2.2.1), was made because of the known extremely high rates of diabetes in this population.[104] Because of the relatively small number of clusters (n=42) included in the survey, the chance inclusion in the sample of district(s) with a high proportion of indigenous Australians may have resulted in an inflated national diabetes prevalence rate. It is unlikely that this decision would have had any significant impact on rates of the metabolic syndrome, given that indigenous Australians comprise only 2% of the total population. The proportion of indigenous Australians in the AusDiab study was 0.8%. For the estimation of rates of diabetes or the metabolic syndrome in the Australian indigenous population, a dedicated survey or sub-survey including larger numbers from both urban and rural areas is required.

The studies reported in Chapters 3.2 to 3.5 do not aim to report national prevalence estimates, but rather use data from the longitudinal studies conducted in Australia and Mauritius to examine the impact of obesity and the metabolic syndrome on multiple health outcomes, including diabetes. As noted in Chapter 2.2.1, the percentage of the total eligible population included in the baseline AusDiab sampling frame to have been examined in both the baseline and follow-up surveys was 22%. Due to this low overall response, the cohort included in the follow-up AusDiab survey is not likely to be representative of adult Australians. This caveat is included as a limitation in the discussion of each of the relevant chapters. A low overall response to the AusDiab follow-up study does not invalidate the research reported. The major research questions considered were 1) Comparison of definitions of the metabolic syndrome and other tools as a predictor of diabetes, 2) Whether central obesity predicts deterioration in other components of the metabolic syndrome (and not vice versa), 3) The relationship of central obesity to incident diabetes in Europids vs. Asian Indians and 4) Health and mortality outcomes among the overweight and obese compared to normal weight individuals. While a greater response would increase the ability

to generalize the results to the entire populations from which the samples were drawn (at least at the time points at which the surveys were undertaken), for none of these questions does the representativeness of the sample invalidate the results.

4.2.2 Measurement bias/error

Full details of the protocols and procedures used in both the AusDiab and Mauritius studies have been provided in Chapter 2.2.2. A particular strength of the research on which this thesis is based is the gold standard measurement of diabetes status using a 75g oral glucose tolerance test at both baseline and follow-up. Furthermore, the ascertainment of cardiovascular disease events between baseline and follow-up in the AusDiab study using self-report followed by physician adjudication has been shown to be as accurate as data linkage to medical records databases,[101] and is likely to have resulted in a low false positive rate as discussed in Chapter 2.2.3.

Specific limitations relating to the physical and biological measurements undertaken in the AusDiab and Mauritius studies have been discussed in the relevant chapters. The most important of these include 1) the absence of microalbuminuria assessment (a required element of the WHO definition of the metabolic syndrome) in the Mauritius cohort, 2) the difference in waist circumference measurement technique in the AusDiab and Mauritius studies, 3) the estimation of insulin resistance using calculation of the HOMA model rather than direct measurement using a euglycaemic insulin clamp method, and 4) a change from manual to automated blood pressure measurement mid-way through the baseline AusDiab study (discussed in Chapter 2.2.2).

A potential bias related to measurement error is regression dilution. The measurement of a parameter at a single point in time (as is the case in the AusDiab and Mauritius studies) is unlikely to represent the true or usual value for an individual because of day-to-day

variation. The usual measurement can be thought of as the average of multiple measurements. The impact of regression dilution is to reduce the strength of positive associations observed. An analysis of blood cholesterol and blood pressure measurements in biennial measurements over 30 years in the Framingham study and single follow-up at 26 years in the Whitehall study suggested that regression dilution could cause the strength of associations to be under-estimated by one third in the first decade of follow-up, one half in the second decade and around two thirds in the third decade.[105]Therefore, the strength of associations observed in Chapters 3.3 to 3.5 may be underestimates of the true effects. Even though correction for the presence of regression dilution is possible,[106] it would require the regular measurement of a sub-sample of the population between baseline and follow-up, which did not occur in either the AusDiab or Mauritius studies.

4.2.3   Study/Research design

As for selection bias, any limitations of the research design need to be considered separately for each of the studies reported in Chapter 3. For estimation of the prevalence of the metabolic syndrome among Australian adults, a cross-sectional, population-based, stratified cluster survey is the most efficient and accurate research design. The limitations of this research design, however, include its cross-sectional nature, which means that the results are relevant to the Australian population at the time of the survey, seven years prior to the publication of Chapter 3.1. Furthermore, as discussed in Section 4.2.1, the exclusion from the sampling frame of districts with a high proportion of indigenous Australians or 100% rurality, as well as institutionalised individuals and those not physically able to attend a testing site means that the results of this survey, while applicable to the majority of Australians, are not applicable to all.

Chapter 3.2 involved the estimation of obesity and overweight-related risk for multiple health outcomes and mortality. The prospective nature of the study design was an appropriate method of assessing such risk, in that it avoids the doubt over temporal sequence or causality inherent in cross-sectional association studies. The major limitation inherent in the study design utilised was the limited period of follow-up (five years for all health outcomes and to April 30th, 2008 for mortality). While significant associations between overweight, obesity and many health outcomes were observed, several risk ratios tended toward an association, but did not reach statistical significance. Furthermore, no clear trends were observed for the association of obesity and mortality. Longer follow-up increases the number of cases of incident disease or death, thereby increasing the power of the study and allowing more precise estimation of effect sizes, and the ability to examine the effects of lesser levels of overweight and obesity on health and mortality outcomes. The strength of associations between obesity and mortality are known to increase with longer follow-up time due to confounding factors affecting the association in the years immediately following the study, and the fact that the effect of obesity often takes many years to manifest as actual health or mortality outcomes. Furthermore, the associations between obesity in early to middle age and mortality will not be apparent without much longer follow-up of the cohort.

The use of a prospective study design to assess the relationship between waist circumference cut-points (Chapter 3.4) and the metabolic syndrome (Chapter 3.5) with incident diabetes was the most appropriate research design for these studies. As discussed in Chapter 3.4, the majority of studies attempting to define ethnicity-appropriate waist cut-points have been cross-sectional in design, and therefore not prospectively related to clinical outcomes such as diabetes or cardiovascular diseases. Despite the prospective

nature of the study design and the gold standard measurement of the outcome (type 2 diabetes), the study design has several limitations. The first of these is the restriction to a single population comparison (South Asians living in Mauritius and Caucasians living in Australia). Confirmation of the results is required in different Asian populations, with different risk factor profiles and different rates of diabetes incidence. The differences in obesity related risk for incident diabetes at a particular waist circumference may not be as extreme in populations with lower diabetes incidence than that observed in Mauritius. Relating to both Chapters 3.4 and 3.5, the baseline Mauritius study was conducted over twenty years ago, and it is likely that the risk factor and obesity profile of the South Asian population on Mauritius will have changed considerably since that time. This should not necessarily affect the interpretation of the results observed in these chapters, however, since the results focus on the strength of the association between obesity/metabolic syndrome and diabetes, which should not be intimately related to the underlying risk factor profile of the population.

4.2.4 Chance and confounding

By their nature, chance findings are always possible in the results of epidemiological surveys. Unless the entire population or at least a very large proportion is surveyed, one cannot be sure that the results obtained are truly generalisable to the whole population under study. Chance effects are always possible, reflected in the use of confidence intervals and probability values to report results. Both techniques provide an estimation of the likelihood that the observed result is due to chance (or to be more precise, the likelihood of the observed finding being repeated). The choice of an appropriate sample size for the question under study is intended to minimise to a realistic level the possibility of a type 1 error (finding of an association when none actually exists) or type 2 error (not finding an

association when one does exist). Statistical significance (usually defined as being met when a p-value of less than 0.05 is achieved) is in reality an essentially arbitrary designation that does not give a thorough indication of the clinical importance of the result.[107] The inclusion of confidence intervals around an estimate, in addition to indicating how likely the results observed are to be real, also shows the range within which the "real" result is likely to sit.[107] The sample size of the two populations studied in this research were based on estimation of cross-sectional diabetes prevalence. As noted in Chapter 2, this therefore means that the results of other analyses need to be interpreted in the light of the sample size available. Prevalence estimates for each of the ATPIII, IDF and WHO definitions of the metabolic syndrome reported in Chapter 3.1 are each greater than 20%, with confidence intervals that go no lower than 18.8%. Therefore, the possibility that these high prevalence figures were a chance finding is remote.

For Chapters 3.3 to 3.5, which each include the assessment of outcomes over the course of the respective prospective studies, it is the number of outcomes observed, rather than the overall sample size that determines the precision of the observed estimates. The primary outcome in Chapters 3.4 and 3.5 was type 2 diabetes, while multiple outcomes including cardiovascular disease, the metabolic syndrome and mortality were assessed in Chapter 3.3. The absence of a statistically significant association between baseline overweight and each of type 2 diabetes and myocardial infarction in Chapter 3.3 are instances in which a greater number of events (via longer follow-up) may have resulted in statistically significant findings. The influence of follow-up time on the power of the studies has been discussed more fully in Chapter 4.2.3.

An additional factor influencing the possibility of type 1 or type 2 error is the number of statistical tests conducted. 95% confidence intervals and a p-value of <0.05 are appropriate

indications of the statistical significance of a single test or comparison. When multiple tests are undertaken, however, the likelihood of a chance finding increases accordingly. If 100 tests each had a p-value of 0.05, we should expect five percent to actually be cases of type 1 error (a significant finding when none truly exists). In Chapter 3.2, the number of individual regression analyses reported is considerable. For the AusDiab five year follow-up and both the five and eleven year follow-up of the Mauritius cohort, each of the seven metabolic syndrome components is included as a predictor of each of the other six components respectively. The total number of regression analyses reported is therefore 42x3 or 126. To account for the multiple comparisons undertaken, statistical significance was set at p<0.01.

Chapters 3.5.1 and 3.5.2 both include an assessment of the independence of the metabolic syndrome from its component parts in the prediction of incident diabetes. One of the persistent questions relating to the metabolic syndrome is whether it is any more useful to collect the components into a syndrome than it would be to consider the components individually. Previous studies have addressed this question both incidentally and explicitly. One study in the elderly appeared to suggest that the metabolic syndrome predicted a composite cardiovascular disease endpoint independently of its components.[108] Sundström addressed this question more fully in cohorts of males at age 50 and 70, with follow-up over 32 years and in cohorts both with and without pre-existing diabetes, stroke and cardiovascular disease. The ATPIII definition of the metabolic syndrome did not predict cardiovascular mortality independently of its individual components at any age and with or without the inclusion of those with pre-existing condition.[109] Our finding of an independent association with incident diabetes for the EGIR definition in men in AusDiab and the WHO definition in men in Mauritius suggests that there is a possibility that clinical definitions of

the metabolic syndrome may indeed reflect a construct that is more than just the sum of its parts, at least for the prediction of type 2 diabetes. The absence of a significant association for the IDF and ATPIII definitions in men and all definitions in women, however, reflects the fact that as defined, the metabolic syndrome may not identify a phenotype that is the best reflection of the acknowledged clustering of its components. As discussed in the respective results chapters, limitations of these analyses include the inability to discern true independence from the effect of non-linearity in the continuous variables included in the model (i.e. a threshold effect), sub-optimal measurement of the component variables or a reduction in measurement error from the pooling of multiple risk factors.[110]

4.3 Implications of the findings and recommendations

4.3.1 Implications for clinical definitions of the metabolic syndrome

The findings from this set of studies have direct implications for clinical definitions of the metabolic syndrome. In particular, Chapter 3.2 suggests that obesity should be thought of as a precursor to the metabolic syndrome, rather than simply as one of several type 2 diabetes and cardiovascular disease risk factors (as is suggested by the structure of the ATPIII definition). The IDF definition prioritises obesity by making it a required component. Critics of this definition are quick to point out that some individuals can have all the hallmarks of the metabolic syndrome without meeting the obesity criteria, and these individuals are excluded in this version of the syndrome. In reality, the majority of individuals meeting the criteria for either the ATPIII or IDF definitions of the metabolic syndrome will also meet the obesity criteria, whether it is a required component or not. In the AusDiab study, only 2.6% of those not meeting the IDF metabolic syndrome criteria would meet the criteria if obesity were not a required component (unpublished observation). Therefore, whether central obesity is a required component or not, the emphasis in clinical definitions needs to be on the fact that obesity is important in its own right (and in isolation) as a precursor to the development of the syndrome, not merely as one of several risk factors.

Chapter 3.4 is a direct assessment of the validity of the waist circumference cut-points for South Asians in the IDF definition of the metabolic syndrome. This study strongly suggests that based on the relationship between central obesity and the development of type 2 diabetes, the cut-points for South Asians as currently defined are set considerably too high. Further support for this suggestion comes from Chapter 3.5.2, where the ability of the metabolic syndrome to predict future diabetes in Mauritius was hampered by a very low

prevalence, resulting from the low prevalence of obesity in this population using the cut-points suggested. Furthermore, the influence of the underlying obesity prevalence on the choice of optimal cut-points using ROC curve based techniques is highlighted in studies assessing change in cut-points over time in Mauritius, and in subgroups with high and low obesity levels in AusDiab. Since the majority of studies attempting to define appropriate cut-points are based on ROC curve based analyses, this study suggests that the current evidence base with which to establish ethnicity-based waist circumference cut-points is minimal.

4.3.2 Implications for the metabolic syndrome as a concept

In both the largely Europid AusDiab study and the Mauritius NCD study, the metabolic syndrome, however defined, was found to be a strong predictor of future type 2 diabetes (Chapter 3.5). A stated key use for the metabolic syndrome is to help identify those at risk for type 2 diabetes and cardiovascular diseases, and this result further affirms this role. The comparison of the metabolic syndrome with other available diabetes risk prediction tools (both invasive and questionnaire based), however, confirms that the metabolic syndrome is not the best tool for this purpose. The fact that simple measurement of fasting glucose was shown to be as efficient as published definitions of the metabolic syndrome is evidence of the fact that, despite conferring increased risk for type 2 diabetes (and cardiovascular diseases), the metabolic syndrome was not designed as an optimal risk prediction tool. This finding, however, should not necessarily be interpreted as a suggestion that the metabolic syndrome is useless for the purpose of risk prediction. In fact, in Chapter 1.2.6, the metabolic syndrome was demonstrated to be a particularly useful tool for this purpose. As importantly, however, Chapter 1.2.6 highlights several other uses for the metabolic syndrome, suggesting that if the mission statement for the metabolic syndrome is correctly

interpreted, it should be a valuable tool in the campaign to prevent the devastating future burden of a global diabetes and cardiovascular disease epidemic.

4.3.3 Public health implications

The studies reported represent responses to several questions of public health interest. Firstly, Chapters 3.5.1 and 3.5.2 suggest that the metabolic syndrome should not be used in isolation as a device for prediction of future type 2 diabetes. The presence or absence of the metabolic syndrome is certainly a valuable piece of information, but must be considered only in relation to the presence and strength of other risk factors. Chapter 1.2.6 uses the results of Chapters 3.2 and 3.5 to place the metabolic syndrome firmly in context. Criticism of the metabolic syndrome (Chapter 1.2.5) has certainly been useful in stimulating research to answer many outstanding questions, and in many cases has raised valid concerns. The resultant confusion about the purpose of a clinical definition will hopefully subside with stronger evidence to support the concept and a unified definition based on data such as that presented in Chapters 3.2, 3.4 and 3.5.

The strong conclusion to be drawn from Chapters 3.2 and 3.3 is that obesity is a major risk factor for the development of the metabolic syndrome (in addition to other health outcomes) and should be the focus of public health interventions in isolation, as well as when accompanied by markers of metabolic deterioration. The important public health message is therefore to prevent the development of obesity, and to attempt this among those who have not yet developed additional components of the metabolic syndrome. Evidence now exists that lifestyle intervention is an effective means of preventing diabetes among those at high risk.[111] The results of several large randomised controlled and long-term trials examining the impact of lifestyle changes on the progression from pre-diabetic states to type 2 diabetes have been reported. Studies from China (Da Qing Study), the USA

(Diabetes Prevention Program or DPP), Finland (Diabetes Prevention Study or DPS), Japan (Japanese Diabetes Prevention Trial) and India (Indian Diabetes Prevention Program or IDDP-1) have all shown that effective lifestyle change can lead to a significant reduction in the incidence of type 2 diabetes among a high risk, pre-diabetic population.[112-116] Relative risk reductions of up to 58% (observed in both the Finnish and American studies) were observed. Since most individuals with the metabolic syndrome and type 2 diabetes have similar metabolic abnormalities and the modifiable risk factors for both are analogous, it is reasonable to assume that such interventions would also be effective in reducing diabetes incidence among those with the metabolic syndrome. Indeed, these studies also show that prevention of the metabolic syndrome is possible. Reductions in the incidence of the metabolic syndrome have now been observed in both the DPP and DPS intervention groups. Among those without metabolic syndrome at baseline, reduction in metabolic syndrome incidence of approximately 40% was observed compared to the control group.[117,118]

In addition to the observations of reduced diabetes incidence following lifestyle intervention, considerable evidence of the effects of lifestyle intervention and a reduction in time spent in sedentary pursuits on the individual metabolic syndrome components exists.[118-125].

Whether the highly intensive, supervised and fairly costly protocols employed in large randomised controlled trials can be translated from research into practice is thus far an unanswered question. Furthermore, no evidence currently exists to show that lifestyle intervention has any long-term effect on incidence of, or mortality from cardiovascular diseases, although this may change with longer-term follow-up.

An irony of the current epidemic of obesity and the metabolic syndrome is that under-nutrition has been, and in some cases continues to be, the focus of public health efforts in

the developing world. While hunger and malnutrition remain as enormous problems facing many under-developing nations, the rapid transition from traditional to western diets and lifestyles means that food insecurity and under-nutrition are present in the same countries where the metabolic syndrome and diabetes are on the rise.[126] Chapters 1.2.6 and 3.2 strongly suggest that obesity (even in isolation) is a key indicator of future metabolic deterioration, and that both obesity and the metabolic syndrome may be valuable as metrics for the future burden of type 2 diabetes and cardiovascular disease. These simple tools may be more applicable and successful for the prevention of future diabetes and cardiovascular disease than are sophisticated short-term risk algorithms, particularly in developing countries.

4.3.4   Recommendations for future research

The studies reported here have raised some questions relating to the use and make-up of clinical definitions of the metabolic syndrome suitable for further research. Suggestions of future research directions include:

- Evaluation of the predictive power of obesity and the metabolic syndrome for future diabetes and cardiovascular diseases with long-term follow-up, and the difference in predictive capacity over short, medium and long-term follow-up, and among those of different ages.

- Confirmation of the differences in obesity-related risk for future diabetes between Europids and South Asians in other cohorts, and the extension of this work to other ethnicities.

- Investigation of the possible uses of a continuous metabolic risk score, not as an alternative to dichotomous clinical definitions, but for use in a research context.

- Evaluation of whether the metabolic syndrome is indeed a useful construct to patients and clinicians. How do health care providers interpret a metabolic syndrome diagnosis given the variation of severity among those so defined?

- Does the diagnosis of metabolic syndrome increase uptake of lifestyle modification measures by patients?

- Confirmation of the findings in Chapter 3.2 of a temporal association between obesity and the other components of the metabolic syndrome in other cohorts (preferably with multiple follow-up tests), and using more advanced statistical methods such as discrete-time survival modelling.

- Re-evaluation of the prevalence of the metabolic syndrome in Australia and comparison with the estimates for 1999-2000 presented here.

- Assessment of the relationship between obesity and the metabolic syndrome with cardiovascular disease, kidney disease and particularly mortality in the AusDiab study but with longer-term follow-up than that used here.

4.4 Conclusions

This thesis was developed with the intention of adding to the evidence base for the use of clinical definitions of the metabolic syndrome. The primary findings are that the metabolic syndrome is a common condition in Australian adults; that it is related to a considerably increased risk for future diabetes; that in determining risk for future diabetes, other tools are more efficient than the metabolic syndrome; that obesity is a predictor of the development of the other components of the metabolic syndrome and therefore appears to precede their development; that obesity predicts not only the metabolic syndrome and its components but also other negative health outcomes; and that the waist circumference cut-points for South Asians used in the IDF and ATPIII definitions of the metabolic syndrome require revision based on comparisons of the associations with incident diabetes among South Asian and Europid populations. In summary, the metabolic syndrome is a useful concept and clinical tool, that with appropriate supporting research evidence and a clear framework for its use and implementation, should be helpful in efforts to reduce and prevent the burden of type 2 diabetes and cardiovascular disease with which it is associated.

5 Appendices

5.1.1 Appendix 1: Publications produced during candidature relevant to the thesis, but not forming part of the thesis.

Cameron AJ, Zimmet PZ. Expanding evidence for the Multiple Dangers of Epidemic Abdominal Obesity. *Circulation*. 2008;117;1624-1626.

Comment on:
Circulation. 2008 Apr 1;117(13):1658-67.

Expanding evidence for the multiple dangers of epidemic abdominal obesity.

Cameron AJ, **Zimmet PZ**.

5.1.2   Appendix 2: Ethical approval

MONASH University

Assoc Prof Jonathan Shaw
Department of Epidemiology and Preventive Medicine
Faculty of Medicine, Nursing and Health Sciences
Alfred Hospital

2 January 2007

2006/987MC - The epidemiology of the metabolic syndrome in Australia

Dear Researchers,

The above research project has been considered by the Standing Committee on Ethics in Research Involving Humans and approval has been given. This approval will be ratified at meeting A1/2007 on 5 February 2007. It is possible that issues may be raised by the Committee at that meeting. If you do not hear anything further you may assume that approval for the project is confirmed.

Terms of approval
1. This project is approved from 2 January 2007 to 30 June 2010 and this approval is only valid whilst you hold a position at Monash University.
2. It is the responsibility of the Chief Investigator to ensure that, if relevant, all information that is pending is forwarded to SCERH. You will then receive a letter from SCERH confirming that we have received the information.
3. It is the responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval and to ensure the project is conducted as approved by SCERH.
4. You should notify SCERH immediately of any serious or unexpected adverse effects on participants or unforeseen events affecting the ethical acceptability of the project.
5. **Amendments to the approved project:** Changes to any aspect of the project require the submission of a Request for Amendment form to SCERH and must not begin without written approval from SCERH. Substantial variations may require a new application.
6. **Future correspondence:** Please quote the project number and project title above in any further correspondence.
7. **Annual reports:** Continued approval of this project is dependent on the submission of an Annual Report. Please provide the Committee with an Annual Report <u>determined by the date of your letter of approval.</u>
8. **Final report:** A Final Report should be provided at the conclusion of the project. SCERH should be notified if the project is discontinued before the expected date of completion.
9. **Monitoring:** Projects may be subject to an audit or any other form of monitoring by SCERH at any time.
10. **Retention and storage of data:** The Chief Investigator is responsible for the storage and retention of original data pertaining to a project for a minimum period of five years.

All forms can be accessed at our website <u>www.monash.edu.au/resgrant/human-ethics</u>

We wish you well with your research.

per Mrs Lyn Johannessen
Acting Human Ethics Officer (on behalf of SCERH)

Cc: Adrian Cameron

International Diabetes Institute

ETHICS COMMITTEE

CERTIFICATE OF APPROVAL

This is to certify that Project No. 3/99

THE AUSTRALIAN DIABETES, OBESITY AND LIFESTYLE STUDY

Chief Researchers: Professor Paul Zimmet
Dr Daniel J. McCarty
Dr David Dunstan
Dr Maximilian deCourten

has been approved in accordance with your application and subsequent amendments on the understanding that you observe the National Health and Medical Research Council Statement on Human Experimentation.

It is now your responsibility to ensure that all people associated with this particular research project are made aware of what has actually been approved and any caveats specified in correspondence with the Ethics Committee. Any change to the application which is likely to have a significant impact on the ethical aspects of this project will require approval from the Ethics Committee.

A progress report is due in June 1999 and a summary of your findings is requested on completion of the project. An audit may be conducted by the Ethics Committee at any time. .

Extension of your project beyond this date will require approval from the Ethics Committee. Request for Amendment, Request for Extension, and Progress Report forms are available from The Secretary, Ethics Committee, International Diabetes Institute, 260 Kooyong Road, Caulfield 3162.

Approval date: 02/3/1999
Expiry date   02/3/2001

Chairperson, Ethics Committee

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International Diabetes Institute

ETHICS COMMITTEE

CERTIFICATE OF APPROVAL

This is to certify that Project No. 3/2002

THE AUSTRALIAN PROSPECTIVE DIABETES STUDY (APDS)

Chief Researchers: Professor Paul Zimmet
Dr Jonathan Shaw

has been approved in accordance with your application and subsequent amendments on the understanding that you observe the National Health and Medical Research Council Statement on Human Experimentation.

It is now your responsibility to ensure that all people associated with this particular research project are made aware of what has actually been approved and any caveats specified in correspondence with the Ethics Committee. Any change to the application which is likely to have a significant impact on the ethical aspects of this project will require approval from the Ethics Committee.

A progress report is due in June 2004 and a summary of your findings is requested on completion of the project. An audit may be conducted by the Ethics Committee at any time.

Extension of your project beyond this date will require approval from the Ethics Committee. Request for Amendment, Request for Extension, and Progress Report forms are available from The Secretary, Ethics Committee, International Diabetes Institute, 250 Kooyong Road, Caulfield 3162.

Approval date: 13/6/2003
Expiry date: 13/ 6/2005

Chairperson, Ethics Committee .

p\s\bumel\libby\crtupapds

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International Diabetes Institute

Ethics Committee

Certificate of Approval

This is to certify that Project 3/2002

THE AUSTRALIAN PROSPECTIVE DIABETES STUDY (APDS) EXTENSION

Chief Researchers: Professor Paul Zimmet
A/P Jonathan Shaw

has been approved as per your application and subsequent amendments on the understanding that you observe the National Health and Medical Research Council Statement on Human Experimentation.

It is now your responsibility to ensure that all people associated with this particular research project are made aware of what has actually been approved and any caveats specified in correspondence with the Ethics Committee. Any change to the application which is likely to have a significant impact on the ethical considerations of this project will require approval from the Ethics Committee.

Period of Approval: 14/6/2005 to 30/6/2010

Extension of your project beyond this date will require approval from the Ethics Committee. An annual progress report is required and is due on 30 June 2006. Request for Amendment, Request for Extension, and Progress Report forms are available from The Secretary, Ethics Committee, International Diabetes Institute, 250 Kooyong Road, Caulfield 3162.

Chairperson, Ethics Committee

Professor Paul Komesaroff...██████████.....

Date...........11 /......11........../...0 5....

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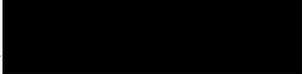
28 April 2004

Dr Jonathan Shaw
Director Research.IDI
250 Kooyong Rd
CAULFIELD3162

Dear Jonathan,

RE:Project 3/2002: THE AUSTRALIAN PROSPECTIVE
DIABETES STUDY (APDS)
Consent Form to Access Medical Records version 1: dated
19/4/04.
Patient Explanatory Brochure/Booklet versions dated March
2004.
Additional Questionnaires (birth weight and health care use)
Study Extension to 13/6/2006

Following recent consideration of your study amendment
application, I am pleased to advise that the Committee has
recommended that the above be approved.

Thank you for submitting your research proposal to the Ethics
Committee

Yours sincerely

Professor Paul Komesaroff
Chair IDI Ethics Committee

p/lp/apdsapproval
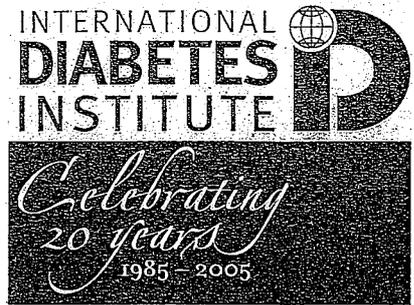
20th November 2006

Assoc Professor Jonathan Shaw
Co-Investigator ADPS
IDI, 250 Kooyong Rd
CAULFIELD 3162

Dear Jonathan,

**RE: A.P.D.S (Victorian Privacy Legislation)**

In reply to your request for an exemption under with the Victorian
Privacy Legislation, for matching the National Death Index to the
APDS cohort, I wish to inform you this has been approved.

It has been noted that researchers Adrian Cameron, Elizabeth Barr,
and Professor Andrew Tonkin are to be included on the APDS
(3/2002) submission.

Kind regards

Professor Paul Komesaroff
Chair. IDI Ethics Committee

INTERNATIONAL
DIABETES
INSTITUTE

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20 years
1985 – 2005

ABN 16 007 342 412
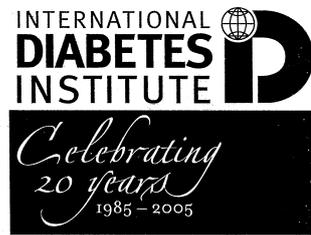
11/05/2007

A/Prof Jonathan Shaw
Director Research
IDI, 250 Kooyong Rd
CAULFIELD 3162

Dear Jonathan,

**RE; Project No 3/2002 The Australian Prospective Diabetes
Study. (APDS)**

PROTOCOL AMENDMENT Dated 8th May 2007

.

Following consideration of your request for approval of an
amendment to the above study by the Ethics Committee, I am
pleased to advise that the amendment has been approved.

Thank you for bringing these changes to the Committee's attention

Kind regards

Professor Paul Komesaroff
Chair
IDI Ethics Committee

P/lp/amendapprove

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