Does Metabolic Syndrome Increase Cardiovascular Risk?

A Systematic Review of the Literature

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A Dissertation submitted to Auckland University of Technology in partial fulfilment of the requirements for the degree of Master of Health Science

2011

School of Health Care Practice

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Attestation of Authorship

I, Kristine Penman, hereby declare that this submission is my own work and that to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

Acknowledgements

I would like to thank the following people for their support and assistance during this dissertation.

- My family for their unfailing support and encouragement without which this dissertation would never have become.
- My supervisor, Jane Koziol –McLain, for her ongoing guidance and encouragement, without whom this dissertation would certainly never have been completed.
- Dr Clem Le Lievre and Nick Garrett for assistance with the meta-analysis.

Abbreviations

The following abbreviations have been used in this dissertation

AGREE – Appraisal of Guidelines Research and Evaluation Tool;

BMI – body mass index;

BRHS – British Regional Heart Study;

CHD – coronary heart disease;

CI – confidence interval;

CVD – cardiovascular disease;

CVR – cardiovascular risk;

CVRA – cardiovascular risk assessment;

DPP – Diabetes Prevention Program;

EGIR – European Group for the study of Insulin Resistance;

ICD – International Classification of Disease;

IDF - International Diabetes Federation;

HLT – Healthy Lifestyle Team;

HR – hazard ratio;

KM– Kaplin Meier ;

MI – myocardial infarction;

NCEP-ATPIII – National Cholesterol Program Adult Treatment Panel III;

NZGG – New Zealand Guidelines Group;

PAR – population – attributable risk;

PECOT – population exposure comparison outcome time;

PHO – Primary Health Organisation;

SAHS – San Antonio Heart Study;

TIA – transient ischaemic attack;

WHO – World Health Organisation

Abstract

Cardiovascular disease is the leading cause of death in New Zealand. There is the potential to prevent up to 50% of these deaths through reducing cardiovascular risk. Metabolic syndrome has been considered to increase a person's risk of developing cardiovascular disease, however there is now much debate as to whether metabolic syndrome has anything to add to cardiovascular risk assessment. The latest New Zealand Guideline Group (2009) *New Zealand Cardiovascular Guidelines Handbook* does not include metabolic syndrome as increasing cardiovascular risk. The purpose of this dissertation is to determine whether metabolic syndrome increases cardiovascular risk by completing a systematic review.

A search of MEDLINE was completed to identify cohort studies published from 2003 to 2010 that explored the impact metabolic syndrome has on cardiovascular disease. The New Zealand Guidelines Group (2001)*Handbook for the Preparation of Explicit Evidence Based Clinical Practice Guidelines* was used to guide this systematic review. Eight articles met the chosen criteria and were subsequently critiqued. The results of these articles clearly demonstrate that metabolic syndrome significantly increases the risk of cardiovascular disease for people with metabolic syndrome compared with people who do not have metabolic syndrome, hazard ratio (HR) 1.57, 95% CI of 1.47-1.67.

The increased risk of having a cardiovascular event for people with metabolic syndrome illustrates the need to identify people with metabolic syndrome and provide education and support to assist with improving lifestyle factors. Nurses are in an ideal position to support and educate people with metabolic syndrome to achieve this and therefore reduce the risk and incidence of cardiovascular disease.

Chapter One – Introduction

Cardiovascular disease is the leading cause of death in New Zealand, accounting for 40% of all deaths (Hay, 2004). As many cardiovascular events are preventable, it is best practice to assess cardiovascular risk (CVR). CVR is the likelihood that the person will have a first cardiac event, such as a heart attack or stroke, in the next five years. The New Zealand Guidelines Group (NZGG) recommends CVR screening from the age of 45 years for men and 55 years for women (NZGG, 2009). The risk factors for cardiovascular disease (CVD) include hypertension, hyperlipidaemia, smoking, family history of premature CVD, diabetes, obesity, age and gender. Once assessed for CVR, a plan can then be implemented to reduce this risk if necessary.

Metabolic syndrome has been considered to increase the risk of both cardiovascular disease and type 2 diabetes (Eckel, Grundy & Zimmet 2005). Metabolic syndrome is a cluster of the following five risk factors: abdominal obesity, elevated fasting glucose, hypertension, low high-density lipoprotein and raised triglycerides. Three of these risk factors are required for a diagnosis of metabolic syndrome (Ash-Bernal & Peterson, 2006). However, both the validity and relevance of metabolic syndrome - which has also been termed metabolic syndrome X and insulin resistance or the insulin resistance syndrome – are contested by many health professionals. Thus there is much debate in the literature as to whether metabolic syndrome should be included in the calculation of CVR.

Metabolic syndrome was included in cardiovascular risk assessment (CVRA) in the New Zealand 2003 cardiovascular guideline (NZGG, 2003). This guideline was the first comprehensive evidence based guideline produced for New Zealand health care professionals to provide guidance on cardiovascular disease. Included in this 2003 guideline was the addition of an increase in cardiovascular risk of

5% if a patient met the criteria for metabolic syndrome. This has changed with the 2009 cardiovascular guideline; people with metabolic syndrome are calculated to have a lower risk than prior to 2009 i.e. five percent is not added to their CVR.

This change in assessment may serve to limit access to healthcare. For example, the Health Rotorua Primary Health Organisation's (PHO) Healthy Lifestyle Team (HLT) is limited to people with a CVR of at least 15%. Thus, some persons who were eligible for a referral to the HLT – offering education and support to improve modifiable risk factors – prior to 2009, are no longer eligible. In this dissertation I explore the impact metabolic syndrome has on CVR by way of a systematic review. I then review how this evidence impacts the patients, primary care delivery systems and policy. Application to practice is considered from my perspective having dual roles as both a practice nurse and the Clinical Nurse Leader for Cardiovascular Disease for Rotorua Area Primary Health Services. In this latter role, I assist practice nurses and general practitioners with the implementation and management of the CVRA program in Health Rotorua practices.

Background

Cardiovascular disease is defined in*The Assessment and Management of Cardiovascular Risk* (NZGG, 2003) guideline as including heart attacks, ischaemic strokes, angina, transient ischaemic attacks (TIA) and peripheral vascular disease. CVR is the likelihood that a person will have a first cardiac event in the next five years. A first cardiovascular event has been defined by the Framingham Heart Study as all those conditions listed previously, and also congestive heart failure (Anderson, Odell, Wilson & Kannel, 1991).

It has been estimated that up to 50% of cardiovascular events are preventable. It is therefore best practice to assess a person's CVR. There are many risk factors which contribute to person's CVR; these risk factors are generally identified as modifiable or non modifiable. Non modifiable risk factors are those which the person is unable to change, these include age, gender, ethnicity, diabetes and family history. Modifiable risk factors, which are amenable to change, include hypertension, smoking, obesity and hyperlipidaemia. Diabetes can be a modifiable risk factor in some individuals, however, only a small portion of people with type 2 diabetes are able to achieve this. The aim of CVRA is to assess risk and then reduce this risk by improving modifiable risk factors.

In order to calculate a person's CVR, certain measurements and lab values are required. These include height, weight, abdominal circumference, blood pressure, fasting lipids, fasting glucose, family history, ethnicity, age, sex and smoking status. CVR can be calculated either by charts, an example of which is the CVRA Charts developed by the NZGG (2009) (Appendices A(i) and A(ii)) or by electronic decision support tools (Appendices B(i) and B(ii). All the tools and charts developed in New Zealand are based on the Framingham Heart Study. The Framingham Heart Study commenced in 1948 with 5209 people living in Framingham, Massachusetts, USA.

This study comprised two thirds of the population of Framingham. The subjects were aged 30-62 in 1948 when the study commenced and were followed up every two years. The purpose of the study was to identify risk factors for CVD. The study continues today including the children and grandchildren of the original participants, now totalling 12,067 participants. The original participants are also still being assessed biennially (Framingham Heart Study, 2010). This is an extremely large, continuing cohort study which has produced, and is continuing to produce, extensive amounts of literature and evidence towards best practice.

Milne, Gamble, Whitlock and Jackson (2003) conducted a study to validate the Framingham Heart Study risk equation for the New Zealand population and concluded that the Framingham Heart Study is accurate at a population level. However, they also noted that the population of Maori, Pacific Island and Asian peoples in the New Zealand study was small; therefore they recommend further studies with these ethnic groups.

Once the CVRA is calculated, steps are taken to reduce this risk if it is elevated. Included in the 2009 NZGG CVD guideline is the appropriate management depending on the calculated CVR. The aim of CVRA is to reduce risk to below 15% if above this level and to generally reduce risk if lower than 15% (NZGG, 2003) as per the following table from the 2009 guideline.

Table 1 The recommended interventions, goals and follow-up based on cardiovascular risk assessment.

Cardiovascular risk	Lifestyle	Drug therapy	Treatment goals	Follow-up
CVD risk clinically determined * >20%	Intensive lifestyle advice on a cardioprotective dietary pattern with a dietitian, and physical activity Lifestyle advice should be given simultaneously with drug treatment	Aspirin, if not contra-indicated, a beta-blocker, statin and an ACE inhibitor (after MI) or aspirin, statin and a new or increased dose of a BP lowering agent (after stroke) Treatment for smoking cessation†	Efforts should be made to reach optimal risk factor levels	CVD risk assessments at least annually Risk factor monitoring every 3–6 months
CVD risk calculated >20%	Intensive lifestyle advice on a cardioprotective dietary pattern with a dietitian, and physical activity Lifestyle advice should be given simultaneously with drug treatment	Aspirin and drug treatment of all modifiable risk factors – BP lowering, lipid modification, glycaemic control (in people with diabetes) Treatment for smoking cessation†	Risk factors treated to a level that will lower 5-year cardiovascular risk to less than 15% (on recalculating risk)	CVD risk assessments at least annually Risk factor monitoring every 3–6 months
15–20%	Specific individualised lifestyle advice on a cardioprotective dietary pattern, and physical activity This lifestyle advice should be given by the primary health care team for 3–6 months prior to initiating drug treatment	Aspirin and drug treatment of all modifiable risk factors – BP lowering lipid modification glycaemic control (in people with diabetes) Treatment for smoking cessation† Drug therapy indicated simultaneously with lifestyle advice for people with isolated high risk factor levels‡	Risk factors treated to a level that will lower 5-year cardiovascular risk to less than 15% (by recalculating risk)	CVD risk assessments at least annually Risk factor monitoring every 3–6 months
10–15%	Specific individualised lifestyle advice on a cardioprotective dietary pattern, and physical activity This lifestyle advice should be given by the primary health care team	Treatment for smoking cessation† Non-pharmacological approach to treating multiple risk factors	Lifestyle advice aimed at reducing cardiovascular risk	Further CVD risk assessment in 2 years
<10%	General lifestyle advice on a cardioprotective dietary pattern, and physical activity	Treatment for smoking cessation† Non-pharmacological approach to treating multiple risk factors	Lifestyle advice aimed at reducing cardiovascular risk	Further CVD risk assessment in 5 or 10 years (see Table 4, page 9)

* People who have had a previous cardiovascular event (angina, MI, PCI, coronary artery bypass graft, TIA, ischaemic stroke or peripheral vascular disease) OR people with certain genetic lipid disorders (FH, FDB, FCH) OR people with diabetes and overt diabetic nephropathy OR people with diabetes and renal disease.

† Smoking cessation treatment should combine pharmacotherapy and behavioural support.

‡ People with isolated high risk-factor levels, either total cholesterol ≥8 mmol/L or TC:HDL ratio ≥8 or blood pressure ≥170/100 mm Hg, should have these risk factors treated and their risk recalculated.

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The NZGG (2009) guideline includes recommendations for the appropriate ages to commence CVRA (see Table 2). Maori, Pacific people and people from the Indian Subcontinent are screened 10 years earlier than people of other ethnicities. Maori have an increased prevalence of , and mortality from, CVD therefore it is important to screen both men and women 10 years earlier (Riddell, Jackson, Wells, Broad & Bannink, 2007). Furthermore men experience cardiovascular events earlier than women. Women do not commonly have cardiac events prior to menopause due to the cardioprotective effect of endogenous oestrogen therefore they are screened 10 years later than men (Collins et al., 2007).

The NZGG (2009) also recommend screening 10 years earlier people with other known cardiovascular risk factors and people at high risk of developing diabetes. These risk factors include people who smoke or have recently quit (within 12 months), a family history of premature CVD in a first degree relative (parents or siblings), impaired glucose tolerance, hypertension, hyperlipidaemia, obesity and a family history of diabetes (NZGG, 2009). Prior to the 2009 guideline people with metabolic syndrome were also screened 10 years earlier.

Table 2 NZGG (2009) Recommended Age to Commence Cardiovascular Risk Assessment

Recommendations on age to commence cardiovascular risk assessment		
	Men	Women
Māori, Pacific peoples and people from the Indian subcontinent	35 years	45 years
People with known cardiovascular risk factors or at a high risk of developing diabetes	35 years	45 years
Asymptomatic people, without known risk factors	45 years	55 years
People with diabetes – on diagnosis and then annually for both men and women		

Metabolic syndrome has been under the microscope for many years. It was first identified in the late 1980s (Metabolic Syndrome: Useful or not?, 2008). Since then there has been a great deal of research and literature published on the topic. This literature has included articles emphasising the need to identify people with metabolic syndrome in order to help prevent the development of both type 2 diabetes and cardiovascular disease. Kahn (2008) stated the individual risk factors included in metabolic syndrome, particularly the fasting glucose, predict the risk of diabetes and cardiovascular disease without needing a diagnosis of metabolic syndrome. Systematic reviews by Gami et al. (2007) and Galassi, Reynolds and He (2006) both concluded that people with metabolic syndrome had an increased risk of CVD.

Grundy (2006) advocates for metabolic syndrome assessment to provide multi risk factor management rather than just concentrating on one risk factor at the risk of neglecting other important risk factors. Huang (2009) also supports the concept of the metabolic syndrome, but identified that more research is required into metabolic syndrome, including studies of genetic links, pathophysiology and treatment. Balkau, Valensi, Eschwege and Slama (2007) summarises the situation with the following statement, "the metabolic syndrome provides an early, simple and cheap warning of patients at risk of cardiovascular disease and diabetes and emphasises the need to treat more aggressively those with multiple abnormalities" (p. 410). The debate regarding the value and validity of the diagnosis of metabolic syndrome is likely to continue into the next decade and beyond.

A common theme in the literature is the need for universal criteria for the metabolic syndrome. The World Health Organisation (WHO), the International Diabetes Federation (IDF) and the National Education Programme Adult Treatment Panel III (NCEP-ATPIII) definitions (Lorenzo, Hunt, Williams & Haffner, 2007) are the most commonly used definitions. A less commonly used definition is the European Group for

the study of Insulin Resistance (EGIR) definition. In New Zealand the definition for metabolic syndrome has been adapted from the NCEP-ATPIII definition (NZGG, 2005). Table 3 illustrates the risk factors included across the definitions for metabolic syndrome. All the metabolic syndrome risk factors listed in Table 3 are modifiable, except for an elevated fasting glucose, which may be modified if caused by obesity.

Table 3: Definitions of Metabolic Syndrome:

Risk Factor	NCEP-ATPIII	EGIR	IDF	WHO
Insulin Resistance/ Fasting Glucose	≥6.1mmol/L	Fasting insulin level >75th percentile in non diabetic population or ≥5.6mmol/L	≥5.6mmol/L or Type 2 diabetes	Fasting insulin level >75th percentile in non diabetic population or IGT or ≥6.1mmol/L or Type 2 diabetes
Waist Circumference	≥100cm (men) ≥90cm (women)	≥94cm (men) ≥80cm (women)	≥94cm (men) ≥80cm (women)	
Triglycerides	≥1.7mmol/L	≥2.0mmol/L	≥1.7mmol/L	≥1.7mmol/L
HDL Cholesterol	<1.0mmol/L (men) <1.3mmol/L (women)	<1.0mmol/L	<1.03mmol/L (men) <1.29mmol/L (women)	<0.9 mmol/L (men) <1.0 mmol/L (women)
Blood Pressure	SBP ≥130 or DBP ≥85	SBP ≥140 or DBP ≥90	SBP ≥130 or DBP ≥85	SBP ≥140 or DBP ≥90
BMI				≥ 30kg/m2

EGIR and WHO definitions require insulin resistance and two of the other factors to meet the criteria for metabolic syndrome. To meet the criteria of the IDF definition, abdominal obesity is required and two other factors. The NCEP-ATPIII definition requires any of the three risk factors.

Note - NCEP-ATPIII – National Cholesterol Program Adult Treatment Panel III; WHO – World Health Organisation; EGIR – European Group for the study of Insulin Resistance; IDF - International Diabetes Federation;

The 2003 and 2005 (NZGG) cardiovascular guideline defined metabolic syndrome as a factor which increased cardiovascular risk by 5%. All of the NZGG cardiovascular guidelines add 5% to the CVR for people with a family history of premature cardiovascular disease, and those of Maori, Pacific Island and Indian subcontinent descent. Therefore whether these people have metabolic syndrome or not does not add 5% to their CVR as it is only added once (NZGG, 2003, 2005, 2009). For example, a Maori man with metabolic syndrome whose father died of a heart attack aged 48yrs, only 5% is added to the CVR not 15%. Therefore this guideline change does not affect the above populations. In the 2009 guideline, however, metabolic syndrome no longer increases cardiovascular risk by 5% for any person (NZGG, 2009).

On the NZGG website, under FAQ's, the question of why metabolic syndrome no longer carries an extra 5% risk has been answered as follows -

> The definition of metabolic syndrome as an entity remains contentious and there is no clear evidence of its importance as a significant risk factor aside from the other recognised risk factors for CVD. The consensus of the Revision Team was to omit it as an additional risk factor in the interest of simplicity (NZGG 2010).

Other countries seem to have followed suit. The Australian CVD guideline does not include metabolic syndrome as increasing cardiovascular risk (National Vascular Disease Prevention Alliance, 2009). The American Heart Association's on-line self assessment for CVR includes metabolic syndrome as part of the assessment but having metabolic syndrome does not increase the CVR, despite giving detailed information on metabolic syndrome, stating that metabolic syndrome increases the risk of type 2 diabetes, stroke and heart attack (American Heart Association, 2010). The British Heart Foundation (2006) guideline only discusses metabolic syndrome in relation to those people with type 1 or 2 diabetes, advising people with diabetes should be considered for statin treatment if they have a number of risk factors, with metabolic syndrome included in these.

The decision to exclude metabolic syndrome in CVR appears to have been made using expert opinion, one of the components of best practice. According to Sackett, Rosenberg, Gray, Haynes and Richardson (1996), evidence based medicine combines the best available evidence with expert opinion and patient preference. This dissertation explores the literature pertaining to CVR and metabolic syndrome in order to complete the component of best practice, exploring the evidence.

The impact of reducing CVR for people with metabolic syndrome is demonstrated through the access to some services of which the entry criteria includes a CVR, as discussed prior. The Health Rotorua PHO implemented a Healthy Lifestyle Team (HLT) to support CVRA in Rotorua. Rotorua Area Primary Health Services contract with Health Rotorua PHO to implement the Cardiovascular Risk Assessment

Program. This program commenced in October 2007 to assess asymptomatic people in the appropriate age groups for CVR based on the NZGG Cardiovascular Guidelines (2003). The Healthy Lifestyle Team consists of a dietician, who is also the team leader of the program, four lifestyle coaches and a smoking quit coach. The single criterion for acceptance onto this program is a cardiovascular risk of more than or equal to 15%. Due to the 2009 change in CVD guideline, many people who were previously eligible for the HLT are no longer eligible. Table 4 outlines the case of a male who would be eligible to address his modifiable risk factors with the support of the HLT prior to March 2009 but not after. This man has a high BMI, elevated blood pressure and cholesterol, resulting in metabolic syndrome, and would potentially benefit from the support of the HLT.

Table 4: An Example of Cardiovascular Risk Assessment in February 2009 and April 2009

Gender	Male
Age	54
Ethnicity	NZ European
Smoking Status	Past
Average of two BP	150/88
Total Cholesterol	5.4
Triglycerides	1.9
LDL Cholesterol	3.6
HDL Cholesterol	0.9
Fasting glucose	5.4
Weight	112kg
Height	184cm
Waist Circum	116cm
BMI	33.1
CVR February 2009	15%
CVR February 2010	10%

Note: These assessments were completed via Best Practice, an electronic decision support tool (Appendices B(i) and B(ii).

This systematic review explores the literature related to CVR and metabolic syndrome to assist with coming to an understanding of the change in the NZGG (2009) guideline. This chapter has explored some of the literature pertaining to metabolic syndrome and CVR. The following chapter will demonstrate the method of collecting the evidence to evaluate this decision.

Chapter Two – Methods

The question, 'does metabolic syndrome increase cardiovascular risk' is asked in this dissertation using an evidence based practice framework. Evidence based practice in healthcare is essential to ensure patients are receiving the most up to date, effective and appropriate health care. Evidence based practice should include both preventative care as well as treatment decisions. CVRA is preventative care, aiming to prevent cardiovascular events, and should be based on the best available evidence. Systematic reviews are an important component of evidence based practice. Systematic reviews enable health professionals to quickly access best available evidence. Nurses do not have a lot of time to gather and appraise evidence; therefore systematic reviews assist nurses in this process. Also, many nurses do not have the skills required to appraise the evidence (Ciliska, Callum & Marks, 2008). It is much less time consuming, and a simpler process, to appraise a systematic review than to gather all the evidence required on a particular treatment or intervention. Nurses can then combine their own knowledge and experiences with the evidence in the systematic review to make evidence based decisions on care with their patients. The process of conducting a systematic review includes evidence synthesis which assists the reader in quickly evaluating the literature (Pearson, Field & Jordan, 2007).

This dissertation used the *Handbook for the Preparation of Explicit Evidence Based Clinical Practice Guidelines* developed by NZGG (2001) to guide this systematic review. While there are numerous systematic review guidelines (e.g., Joanna Briggs, Cochrane), the NZGG handbook was chosen for several reasons. Firstly it is a New Zealand publication, which is important as this will help validate the evidence for New Zealand health care. Also this handbook includes all the stages of evidence based practice. Finally this handbook is in a format that is clear to understand and follow and will meet the needs of this particular study. The following are the steps

of the NZGG (2001) handbook which have been used for this systematic review - topic identification and suitability screen, question formulation including PECOT, data acquisition, assessment of evidence, recommendations and dissemination and implementation. Bernadette Melnyk has written extensively on the steps of evidence based nursing and her literature has also been used to guide this dissertation.

In this chapter I will respond to the first three steps noted above. The assessment of evidence will be presented in Chapter four and five. The final recommendations and discussion will be presented in Chapter six.

I have used the Appraisal of Guidelines Research and Evaluation tool, AGREE (2001), to assess the 2009 Cardiovascular Guideline. The AGREE (2001) tool provides a framework to assess the quality of clinical practice guidelines; therefore it is the ideal means to assess the current 2009 CVR guideline. This appraisal will be discussed in Chapter three.

Topic Identification and Suitability Screen

Prior to devoting resources to a systematic review, the NZGG (2001) handbook advices identifying a topic which is clinically important and effects large numbers of people. I have identified the impact of metabolic syndrome on cardiovascular risk as the topic due to the change in the guideline as discussed in Chapter one. I see patients with metabolic syndrome who have a low CVR where previously it would have been 5% higher. I am concerned that there is no increase in CVR for people who are overweight. Two people can have the same CVR yet one can be a very overweight person whilst the other can have a normal waist circumference. Experience tells me that this does not seem correct; therefore I am keen to explore what evidence has been published on this issue. I feel a change in the guideline is unlikely to occur as a result of this study; however this investigation will give me evidence to discuss with other

nurses whom I educate. I would also undertake further discussion with medical staff if the literature does show an increase in CVR in those people with metabolic syndrome. As a Clinical Nurse Leader for Cardiovascular Disease, I do have some influence over the criteria for eligibility for the HLT. This research may demonstrate the need for a review of these criteria. It may be necessary to include people with a CVR risk of between 10 and 15% who have metabolic syndrome in the eligibility criteria. This will be considered further in the recommendations section of the dissertation.

A brief literature review highlighted many articles related to this topic. A review of the conclusions of some of these articles demonstrated the lack of consensus on metabolic syndrome and its effect on CVR. For example, Lorenzo et al., (2007) concluded that metabolic syndrome is associated with significant CVD risk as did a systematic review by Gami et al. (2007). Contrary to these finding, Kahn (2008) concluded that metabolic syndrome does not increase CVR any more than the risk factors considered individually. A recent article in *Best Practice Journal* (Metabolic Syndrome: useful or not? 2008) briefly discusses whether the synergistic effect of the individual risk factors is relevant or not. This article concludes that "the only value of the syndrome may be that it is useful simply as a basis for guiding risk assessment and promoting lifestyle interventions" (p. 57). Overall, the lack of consensus highlights the need for further systematic reviews on this topic.

Development of the question – PECOT

The second step of systematic reviews outlined in the NZGG handbook is the specification of the review question. The next step of evidence based practice, according to Melnyk, Fineout-Overholt, Stillwell & Williamson (2010), is asking the right question in order to lead the literature search to obtain the answers required. By formulating a five part question using PECOT this is more likely to occur. PECOT is

the acronym for population, exposure, comparison, outcome and time. By using the PECOT framework to formulate the research question, the important components of the question will be included and will assist with defining the literature search. “A well built PECOT question increases the likelihood that the best evidence to inform practice will be found quickly and efficiently” (Stillwell, Fineout-Overholt, Melnyk & Williamson, 2010, p. 59).

There are several types of PECOT questions, therapy, etiology, diagnosis, prevention, and prognosis questions. Prognosis questions estimate the clinical course over time (Melnyk & Fineout-Overholt, 2005; Stillwell et al. 2010). I wish to know the risk of a cardiovascular event over time; therefore a prognosis question is the best fit. Prognosis questions are best answered with cohort studies. Cohort studies usually follow a group of people for a certain length of time to determine whether exposure to a factor will influence their development of a disease or specific outcome (Petri & Sabin 2005). A well designed cohort study will help determine whether people with metabolic syndrome have an increased risk of CVD. The PECOT for this research is presented in Table 5.

Table 5 - PECOT

Population	men aged 45-70 women aged 55-70 without diabetes or prior cardiovascular disease
Exposure	metabolic syndrome
Comparison	No metabolic syndrome
Outcome	cardiovascular event
Time	five years

Data Acquisition

The third step of a systematic review is data acquisition. The selection criteria for appropriate articles to address the stated PECOT are outlined in Table 6. Terms used for searching databases are listed in Table 7. Filters that were used included date of publication and English language. I focussed my literature search on the years after the publication of the 2003 guideline, therefore 2003 to 2010 in order to obtain the most up to date research on this topic. This should also provide information on what is best practice related to metabolic syndrome and CVRA.

Table 6 - Article Inclusion Criteria

Cohort study
Participants mainly aged between 45 and 70 with no prior CVD or diabetes
Participants include those with and without metabolic syndrome
Participants that do not include ethnicities with increased risk as discussed (Maori, Pacific Island and from the Indian subcontinent).
Follow up for a minimum of five years

I first searched the Cochrane library for previous systematic reviews on this topic. While no Cochrane reviews were identified, reviews by Gami et al. (2007) and Galassi

et al., (2006) were identified when completing the above search. The results of these systematic reviews will be discussed in Chapter Five.

I searched Medline via OVID using the advanced search strategy and the MESH headings outlined in Table 7. I checked the references for the chosen articles to look for other similar articles but did not find any new articles not already found through the above searches.

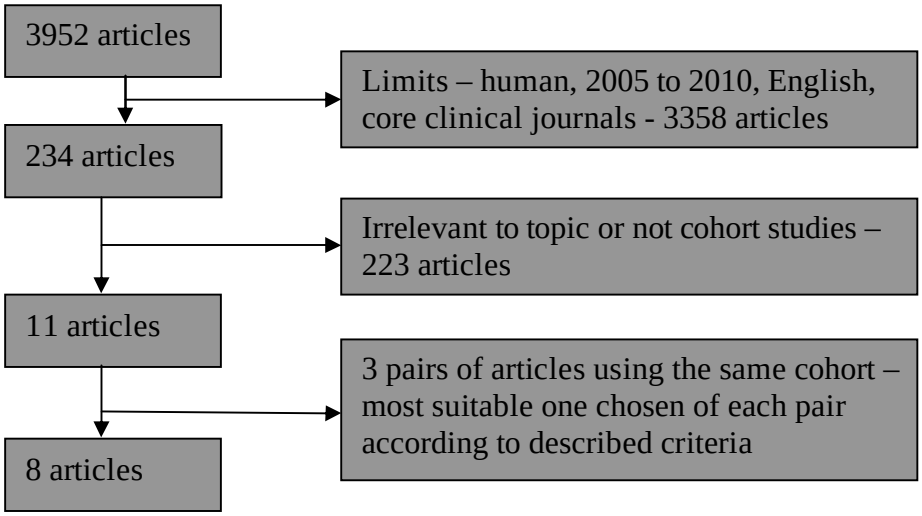
Table 7 – MESH Headings

Cardiovascular disease and
Risk and
Metabolic syndrome or
Metabolic syndrome X or
Insulin resistance

Data Acquisition Results

The first data type of interest was guidelines. The current NZGG (2009) guideline was selected to critique due to being the first guideline in New Zealand to exclude metabolic syndrome as increasing CVR by 5%. This assessment is reported in Chapter Three. The protocol for selection of cohort studies resulted in the identification of eight studies (see Figure 1). There were no studies which met the inclusion criteria published in 2003 and 2004 therefore 2005 is the earliest study used for this dissertation.

Figure 1: Flowchart of Article Inclusion



These articles are assessed and discussed in Chapter Four. I have used the Critical Appraisal Skills Program (CASP) (2004) *12 questions to help you make sense of a cohort study* to assist with the critique of the articles. The results are discussed and presented as a forest plot displaying the meta-analysis. A forest plot is a graphical display of the hazard ratios (HR) and confidence intervals (CI) and displays the meta-analysis. A meta-analysis combines the results from individual studies and produces an estimate of the overall effect being explored, in this dissertation metabolic syndrome (Petrie & Sabin, 2005). The data will also be assessed for homogeneity to determine whether the different studies have produced similar, homogenous data or less similar data, heterogenous data. Homogeneity will be determined by calculating the I^2. The I^2 is calculated as a percentage and the closer the I^2 is to 0% the more homogenous that data is. Data which is heterogenous needs to be viewed with caution (Petrie & Sabin, 2005).

Chapter Three – Guidelines Appraisal

The New Zealand Cardiovascular Guidelines Handbook: A summary resource for primary care practitioners (2nd ed. 2009) was assessed using the AGREE instrument (2001). The AGREE instrument (2001) provides a framework to assess the quality of a guideline and was developed by the New Zealand Guideline Group. This instrument comprises six domains: scope and purpose, stakeholder involvement, rigour of development, clarity and presentation, applicability and editorial independence. Each of these domains have between two and seven questions per domain and these are scored from one to four with one being strongly disagree and four strongly agree. These scores are then calculated per domain to provide a percentage per domain. The different domain scores are not added as they need to be assessed individually in order to assess both the areas of strength and the weakness in the guideline.

Figure 2 Guideline Appraisal

Domain 1 - Scope and Purpose

1. The overall objectives of the guideline are specifically described.

Strongly Agree			Strongly Disagree
4 **X**	3	2	1

Comments: There is a description of the purpose of the handbook in the opening pages of the handbook. This clearly defines the purpose as does the title.

2. The clinical questions covered by the guideline are specifically described.

Strongly Agree			Strongly Disagree
4	3 **X**	2	1

Comments: as above

3. The people to whom the guideline is meant to apply are specifically described.

Strongly Agree			Strongly Disagree
4 **X**	3	2	1

Comments: The age groups that require screening for CVR are clearly described.

Domain 2 - Stakeholder Involvement

4. The guideline development group includes individuals from all the relevant professional groups.

Strongly Agree			Strongly Disagree
4 **X**	3	2	1

Comments: The guideline lists all those on the guideline revision team, including their occupation and employer. These people include cardiologists, GP's, diabetes and cardiac nurses and a consumer.

5. The patients' views and preferences have been sought.

Strongly Agree			Strongly Disagree
4	3 **X**	2	1

Comments: There is only one patient included in the team of 24 who revised this guideline.

6. The target users of the guideline are clearly defined.

Strongly Agree			Strongly Disagree
4 **X**	3	2	1

Comments: The title of the handbook includes the target users, Primary Care Practitioners.

7. The guideline has been piloted among target users.

Strongly Agree			Strongly Disagree
4	3	2	1 **X**

Comments: There is no information re a pilot of this guideline.

Domain 3 - Rigour of Development:

8. Systematic methods were used to search for evidence.

Strongly Agree			Strongly Disagree
4	3	2 **X**	1

Comments: There is a small piece on the guideline review team conducting individual literature reviews but this is not described in any detail.

9. The criteria for selecting the evidence are clearly described.

Strongly Agree			Strongly Disagree
4	3	2	1 **X**

Comments: This information is not included.

10. The methods used for formulating the recommendations are clearly described.

Strongly Agree			Strongly Disagree
4	3	2	1 **X**

Comments: This information is not included.

11. The health benefits, side effects and risks have been considered in formulating the recommendations.

Strongly Agree			Strongly Disagree
4 **X**	3	2	1

Comments: The risks and benefits are clearly described for treatments discussed in the guideline with appropriate references.

12. There is an explicit link between the recommendations and the supporting evidence.

Strongly Agree			Strongly Disagree
4	3 **X**	2	1

Comments: The references in this guideline are related to the recommendations for management of certain cardiac conditions but there are no references in the cardiovascular risk assessment section.

13. The guideline has been externally reviewed by experts prior to its publication.

Strongly Agree			Strongly Disagree
4	3	2 **X**	1

Comments: There is no evidence that this guideline has been externally reviewed however there were 24 people on the guideline revision team, including many cardiology experts and a consumer.

14. A procedure for updating the guideline is provided.

Strongly Agree			Strongly Disagree
4	3 **X**	2	1

Comments: The comment has been made in the guideline of the need to update the guideline regularly and ensure up to date information is readily available.

<u>Domain 4 - Clarity and Presentation</u>:

15. The recommendations are specific and unambiguous.

Strongly Agree			Strongly Disagree
4 **X**	3	2	1

Comments: The recommendations are very clearly described and easy to follow.

16. The different options for management of the conditions are clearly presented.

Strongly Agree			Strongly Disagree
4 **X**	3	2	1

Comments: When appropriate, options for management are clearly presented, e.g. smoking cessation advice. Many recommendations for treatment or prevention of CVD events is quite prescriptive, therefore options are not always best practice.

17. Key recommendations are easily identifiable.

Strongly Agree			Strongly Disagree
4 **X**	3	2	1

Comments: This guideline is clearly laid out with appropriate heading and tables describing the recommendations.

18. The guideline is supported with tools for application.

Strongly Agree			Strongly Disagree
4 **X**	3	2	1

Comments: The risk tables are included in the guideline and the use of electronic decision support tools is mentioned as an alternative to risk tables.

<u>Domain 5 - Applicability</u>:

19. The potential organisational barriers in applying the recommendations have been discussed.

Strongly Agree			Strongly Disagree
4	3	2 **X**	1

Comments: There is no discussion on barriers to implementing the recommendations although there are not many barriers to these recommendations as most people in NZ have access to primary care where most interventions for prevention of CVD are centred.

20. The potential cost implications of applying the recommendations have been considered.

Strongly Agree			Strongly Disagree
4	3	2	1 **X**

Comments: There is no mention of the potential cost of applying the guidelines. If all recommended patients were started on smoking cessation treatment this would be a significant cost, however the benefits to the health system would be significant with a reduction in the need for hospital resources.

21. The guideline presents key review criteria for monitoring and/or auditing purposes.

Strongly Agree			Strongly Disagree
4 **X**	3	2	1

Comments: The guideline gives specific values for ideal blood pressure, lipids and other values.

Domain 6 - Editorial Independence:

22. The guideline is editorially independent from the funding body.

Strongly Agree			Strongly Disagree
4 **X**	3	2	1

Comments: The guideline states it was funded by the Ministry of Health and developed independently by the New Zealand Guideline Group.

23. Conflicts of interest of guideline development members have been recorded.

Strongly Agree			Strongly Disagree
4	3	2	1 **X**

Comments: There are no conflicts of interest or comments re this in the guideline.

Domain scores:

Domain 1: Scope and Purpose	89%
Domain 2: Stakeholder Involvement	67%
Domain 3: Rigour of Development	43%
Domain 4: Clarity and Presentation	100%
Domain 5: Applicability	44%
Domain 6: Editorial Independence	50%

The scores of the above domains are only the scores of one reviewer. This AGREE instrument (2001) recommends at least two reviewers but preferably four to increase the reliability of the assessment.

Overall Assessment:

Would you recommend these guidelines for use in practice?

Recommend - I would recommend these guidelines for use in clinical practice although consideration needs to be taken into account for the lack of evidence presented for changes to the guideline, in particular the exclusion of metabolic syndrome as increasing cardiovascular risk. The purpose of the guideline is clearly documented, a large number of experts and a consumer were involved in the guideline development, and the recommendations are clear and easy to follow.

The New Zealand Cardiovascular Guidelines Handbook: A summary resource for primary care practitioners (2nd ed. 2009) scored well in the scope and purpose and stakeholder involvement domains and reasonable well for clarity and presentation domain but not so well in the rigour of development, applicability and editorial independence domains. Particularly of concern is the score for rigour of development. The guideline scored low in some of these questions due to the lack of information regarding where the evidence was obtained (i.e. references, search strategies, and methods used when there was disagreement among the writers of the guideline). The final stage of the AGREE instrument (2001) is an overall assessment and recommendation for the guideline. These recommendations can range from strongly recommend to would not recommend and unsure. I would recommend these guidelines for use in clinical practice although consideration needs to be taken into account for the lack of evidence presented for changes to the guideline, in particular the exclusion of metabolic syndrome as increasing cardiovascular risk. This lack of evidence has given rise to this dissertation and the articles sourced to explore this topic will be discussed in the following chapter.

The purpose of the guideline is clearly documented, a large number of experts and a consumer were involved in the guideline development, and the recommendations are clear and easy to follow. In considering this assessment, it is important to realise the scores, as discussed above, are only the scores of one reviewer. The AGREE (2001) instrument recommends at least two appraisers assess a guideline with a preference of four appraisers to achieve a more reliable appraisal (AGREE, 2001). In addition, the guideline states in the beginning that it is a guideline and not intended to replace clinical judgement. This is an important fact that clinicians must remember when using a guideline. A guideline is intended to assist the health professional in decision making but not to replace health professionals' judgement of each patient's individual situation.

Chapter Four – Analysing the Literature

Eight studies were identified that best answer the question, "Does metabolic syndrome increase cardiovascular risk?" These eight studies are summarised in Table 8. I have used the Critical Appraisal Skills Program (CASP) (2004)*12 questions to help you make sense of a cohort study* to guide this critique. These 12 questions help to determine the reliability and validity of the research.

All of the selected studies focused on the impact metabolic syndrome had on CVD. All of the selected studies used the NCEP-ATPIII definition of metabolic syndrome. The study by Nilsson, Engstrom and Hedblad (2007) explored CVD related to three different definitions of metabolic syndrome - IDF, EGIR and the NCEP-ATPIII definition. Jeppesen et al., (2007) included two definitions, the NCEP - ATPIII and IDF definitions of metabolic syndrome. The studies which compared more than one definition of metabolic syndrome identified the percentage with and without metabolic syndrome for each definition. The studies also discussed CVD risk according to each definition. This assists with evaluating the results from each study, as it is then possible to compare outcomes accurately and objectively. Where several criteria for the metabolic syndrome have been used, these will be evaluated separately in the results in Chapter Five.

Many of the studies also explored other variables and their impact on metabolic syndrome and CVD. These included insulin resistance (Jeppesen et al., 2007), body mass index (Arnlov, Ingelsson, Sundstrom & Lind, 2010), and the risk of developing type 2 diabetes (Wilson, Agostino, Parise, Sullivan & Meigs, 2005; Wannamethee, 2008). For the purpose of this literature review I will focus on the results which answer the question regarding metabolic syndrome and the risk of CVD.

Table 8 Characteristics of Cohort Studies of Metabolic Syndrome and Risk of Cardiovascular Disease

Study author and publication year	Study Population and year of study	Cohort Recruitment year	Definition of metabolic syndrome	Met Syn %	Duration of follow up and % followed up	Outcomes measured	Controlled variables	Findings HR with 95% CI CVD unless stated Otherwise
Nilsson, Engstrom & Hedblad (2007)	5047 non diabetic men and women aged 46 to 68 years in Sweden	1991 to 1994	EGIR NCEP-A TPIII IDF	18.8 20.7 21.9	11years 100%	Cardiovascular events including both fatal/non fatal MI, stroke, or death from IHD. Used ICD 9 codes.	Age, sex. LDL-C, smoking, alcohol, education status and physical activity	EGIR – All - 1.35 (1.05-1.74) Men - 1.33 (0.97-1.82) Women – 1.42 (0.92-2.18) NCEP-A TPIII – All – 1.59 (1.25-2.03) Men – 1.71 (1.26-2.31) Women – 1.45 (0.97-2.17) IDF – All – 1.11 (0.86-1.44) Men – 1.17 (0.85-1.6) Women – 1.05 (0.68-1.62)

Lorenzo, Hunt, Williams, & Haffner (2006) San Antonio Heart Study	4105, Mexican American and non Hispanic men and women, aged 24 to 64 years in Texas Included those with diabetes – 9.9% cohort 1 8.5% cohort 2	Cohort 1 – 79 to 1982 Cohort 2 - 84 to 88	NCEP-ATPIII	Cohort 1 – Men 15.5 Women 10.8 Cohort 2 – Men 23.3 Women 18.7	8 years for both cohorts Cohort 1 71.4% Cohort 2 90%	Self reported MI, stroke, or coronary revascularisation Procedure at follow up and CVD on death certificates using ICD – 9 codes.	Age, sex, ethnic origin, socio economic status, total cholesterol, fam hx of CVD, and diabetes	Cohort 1 1.37 (1.02 -1.84) Cohort 2 1.75 (1.21-2.54) FRS at baseline Cohort 1 Men – 5.76% (5.57-5.96 Women – 1.46% (1.42-1.50) Cohort 2 Men – 6.68% (6.48-6.89) Women – 1.97% (1.91-2.03)
Noto, Barbagallo, Cefalu, Falletta, Sapienza et al (2008)	684 Mediterranean men and women aged 35 to 75 years in Italy Included 16% with diabetes	Not specified	NCEP-ATPIII	Women 31.5 Men 12.4	15 years Appears to be 100%	Cardio and cerebro vascular events. This included angina, MI, and stroke, fatal and non fatal.	Age and gender	All - 1.90 (1.46-2.46) Men – 1.58 (0.98-2.50) Women – 2.10 (1.52-2.91) KM survival % curves No mets and no IFG after 15yrs – 93% Mets and no IFG after 15yrs – 85%

Wannamethee (2008) British Regional Heart Study	5128 men aged 40 to 59 years in England, Wales and Scotland	1978 to 1980	NCEP-ATPIII	26	20years 99%	MI fatal and non fatal, stroke fatal and non fatal and angina.	Age, social class, smoking, physical activity and alcohol	Risk of CHD 1.57 (1.39-1.97) Risk of stroke 1.61 (1.26-2.06) Risk of all CVD events 1.53 (1.37-1.70) FRS compared with Met Syn for prediction of CHD – FRS significantly more predictive of CHD.
Jeppesen, Hansen, Rasmussen, Ibsen, Torp-Pedersen & Madsbad (2007)	2493 men and women aged 41 to 72 years in Denmark Included 2.6% with diabetes	1982 to 1984	NCEP-ATPIII IDF	16 21	Mean 9.4 years 100%	IHD, stroke and cardiovascular mortality Used ICD – 8 codes and ICD 10 codes	Age, gender, smoking and LDL-C	NCEP-ATPIII – 1.48 (1.05-2.12) IDF – 1.16 (0.83-1.63)

Arnlov, Ingelsson, Sundstrom, Lind (2010)	1758 men without diabetes aged 50 years in Sweden	1970 to 1973	NCEP-A TPIII	8.8	30 years 7 lost to follow up therefore almost 100%	Cardiovascular death, and non fatal stroke, MI and heart failure. Used ICD 9 and ICD 10 codes	Age, smoking status and LDL-C	Normal wt with Met Syn 1.63 (1.11-2.37 Overweight with Met Syn - 1.74 (1.32-2.30) Obese with Met Syn 2.55 (1.81-3.58) KM survival % curves Normal wt no Met Syn – at 15yrs – 93% normal wt and overwt with Met Syn at 15yrs – 87% obese and Met Syn at 15yrs – 70% normal wt no Met Syn – at 30yrs – 65% normal wt and overwt with Met Syn at 30yrs – 48% obese and Met Syn at 30yrs – 28%

Knuiman, Hung, Divitini, Davis & Beilby (2009)	3041 men and women aged 25 to 84 years in Australia	1994 to 1995	NCEP-ATPIII	5.2% aged 25-44 15.6% aged 45 to 64 years 18.7% aged 65-84yrs.	10 years Follow up no's not stated	Hospital admission or death from coronary heart disease or stroke using ICD 9 and ICD 10 codes.	Age, sex, smoking, LDL-C, SBP, HDL-C, trig and waist circumference	Risk of CHD 3.59 (1.43-8.99) Risk of stroke 0.66 (0.19-2.27) Risk of CVD 1.13 (0.70-1.81)
Wilson, Agostino, Parise, Sullivan & Meigs (2005) Framingham Heart Offspring Study	3323 white men and women, aged 22 to 81 years in USA	1989 to 1983	NCEP-ATPIII	Men 26.8 Women 16.6	8 years Follow up no's not stated	MI, angina, stroke, intermittent claudication and cardiac failure	Age	Men – 2.88 (1.99-4.16) Women – 2.25 (1.31-3.88 PAR Men – 33.7% Women – 15.8%

NCEP-ATPIII - National Cholesterol Education Program Adult Treatment Panel III, IDF - International Diabetes Federation, EGIR – European Group for the study of Insulin Resistance, MI – myocardial infarction, IHD – ischaemic heart disease, CVD – cardiovascular disease, CHD – coronary heart disease, LDL-C - low density lipoprotein cholesterol, HDL – C - high density lipoprotein cholesterol, SBP – systolic blood pressure, ICD – International Classification of Disease, HR – hazard ratio, CI – 95% confidence interval, KM survival % curves – Kaplan-Meier survival curves, wt – weight, Mets Syn – metabolic syndrome, IFG – impaired fasting glucose, FRS- Framingham Risk Score, PAR – population –attributable risk estimates

Knuiman et al. (2009) and the Wannamethee (2008) separated CVD into coronary heart disease (CHD), stroke and CVD. Wannamethee (2008) outlined CHD as including non fatal MI and angina as well as CHD death and excluded strokes with CVD including all of these events. Knuiman et al. (2009) has not defined CHD and CVD apart from explaining abbreviations.

The studies were published between 2005 and 2010. The studies are all cohort studies, an appropriate design to answer prognosis questions. The age of the populations studied in these cohort studies range from 24 to 85 with most of the studies age ranges falling between 45 to 70 years which is the appropriate ages to be screening for CVD according to the NZGG (2009). Lorenzo et al. (2006), included those aged 24-64yrs. Knuiman et al. (2009) and Wilson et al. (2005) included those aged 25-84 years and 22-81 years respectively. This could affect the results and will be discussed further in Chapter Five.

The majority of the studies had comprehensive recruitment systems enabling reasonable sample sizes, (see Table 8). The total number of participants from all the studies is 25,579 people. The percentage of participants per study ranged from 2.5% (Nilssen et al. 2007) to 19.3% (Wannamethee 2008) with the majority of the studies ranging from 9.7% to 20%. This demonstrates a reasonable spread of the participants throughout the eight studies, limiting the potential for one study to influence the results significantly. All the studies had more than 1000 participants except the study by Noto et al. (2008) which had a study group of 687. This was a smaller study based in a small town in Sicily.

Two studies included only male participants, Arnlov et al. (2010) and Wannamethee (2008), whilst the study by Nilsson et al. (2007) included 66% women. As previously discussed, men tend to experience CVD ten years earlier than women and are at a higher risk of CVD, therefore the studies including men only could produce

more significant results than those with both sexes. With reference to the study by Nilssen et al. (2007), this could produce less significant results due to women being two thirds of the participants. Four of the six studies including both sexes reported the results for men and women separately (see Table 8).

The study populations include people from Sweden (2), USA (2), Italy, Britain, Denmark, and Australia (see Table 8). This provides information on metabolic syndrome and CVD in different nationalities. Lorenzo et al. (2006) targeted a Mexican-American and a non Hispanic white population and the results of this study were adjusted for ethnicity. This is important due to the target population for this systematic review being people who are not from ethnicities at high risk for CVD. People of high risk ethnicities already have 5% added to their CVR, therefore whether they have metabolic syndrome or not, their CVR does not change, as discussed in Chapter One. High risk ethnicities include Maori, Pacific Island, Asian and other high risk ethnicities. Only two studies stipulate that the population are Caucasian people, therefore the rest of the studies included in this systematic review could include people of high risk ethnicities.

All studies chosen excluded people with prior CVD, five studies excluded those with diabetes, and while three studies included those with diabetes they reported the results separately, enabling these studies to be included for analysis (see Table 8).

The outcomes measured in all studies included mortality and morbidity due to CVD, myocardial infarctions and strokes. Other outcomes from the studies included angina, heart failure, claudication and other CVD. The differences in outcomes will need to be considered when evaluating the results, see Chapter Five.

Several studies used the World Health Organisations International Classification of Diseases (ICD) codes to determine outcomes (Centres for Disease Control and Prevention, 2010). These codes were used particularly to follow up patients who had

died during the course of the study. ICD codes are also used in New Zealand. By measuring outcomes using ICD codes, this enables more accurate comparison of outcomes. Many of the studies described a range of cardiovascular codes which include other cardiovascular events. The ICD codes from 8 through to 10 have been used in five of the eight studies. The studies that used ICD codes have specified which codes they have used to collect data on CVD. Jeppesen et al. (2007), and Nilsson et al. (2007) used the specific codes for MI, strokes and death from ischaemic heart disease. This provides reliable data with the outcomes required for this study. Arnlov et al. (2010), Knuiman et al. (2009), and the Lorenzo et al. (2006) used all the codes for diseases of the circulatory system. These codes include many diseases that are not specific to CVD as specified by this dissertation. This increases the likelihood that events will have been recorded which were not attributed to CVD, for example, aortic aneurysms and rheumatic fever. These are just two examples of a wide range of conditions covered by these codes. This brings into question the reliability of the data collected. This may explain why Knuiman et al (2009) calculated a HR for CHD of 3.59, significantly higher then the HR of other studies and may not be valid for the question asked re CVD.

Noto et al. (2008), Wannamethee (2008) and Wilson et al. (2005) did not use ICD codes. Noto et al. (2008) and Wilson et al. (2005) describe their methods of data collection and it appears to be comprehensive, increasing the likelihood that they have captured all CVD events accurately. Wannamethee (2008) do not specify how they collected the outcome data which makes it difficult to assess the reliability of this data.

The Lorenzo et al. (2006) measured outcomes by self reported events, and ICD 9 codes for participants whom had died. This could result in inaccurate recording of data. People do not always get their diagnosis correct and this could result in under or over reporting. The outcomes measured by self reporting were MI, stroke and coronary

revascularisation. People are unlikely to be unsure of a diagnosis of stroke and revascularisation however it is possible to be incorrect about the diagnosis of a heart attack due to some patients not taking in all that occurs whilst hospitalised.

All of the studies have adjusted calculations for several variables. These are included in Table 8 as controlled variables. All studies made adjustments for age while most studies also adjusted for sex, smoking and different cholesterol variables. Wilson et al. (2005) have only made adjustments for age, which will need to be considered when analysing results. Smoking is a high risk factor for CVD yet only five of the studies adjusted their data to reflect this. I am very surprised that not all the studies adjusted for smoking.

The follow up of subjects ranged from eight years to 30 years. An effective cohort study needs to follow participants for a long enough time to be able to accurately record the number of outcomes being researched. All of these studies followed up their participants for sufficient time to measure the number of cardiac events.

The percentages followed up ranged from 70 to 100% although two studies, Wilson et al. (2005) and Knuiman et al. (2009), did not state the percentage of follow up. The very low loss of patient to follow up assists with the reliability of the results. This has been achieved as many of the studies used death registers and hospital records to record data. Lorenzo et al. (2006) had lower levels of follow up, particularly in cohort 1, 71.4%. Lorenzo et al. (2006) used self reported events to record the data of the participants that were still alive at the follow up date. Almost 30% lost to follow up is a significant number which represents a significant amount of data not collected and could affect their results substantially. Cohort 2 of Lorenzo et al. (2006) had a follow up rate of 90% and all the other studies had a follow up rate of between 99 and 100% where the follow up rate is stated.

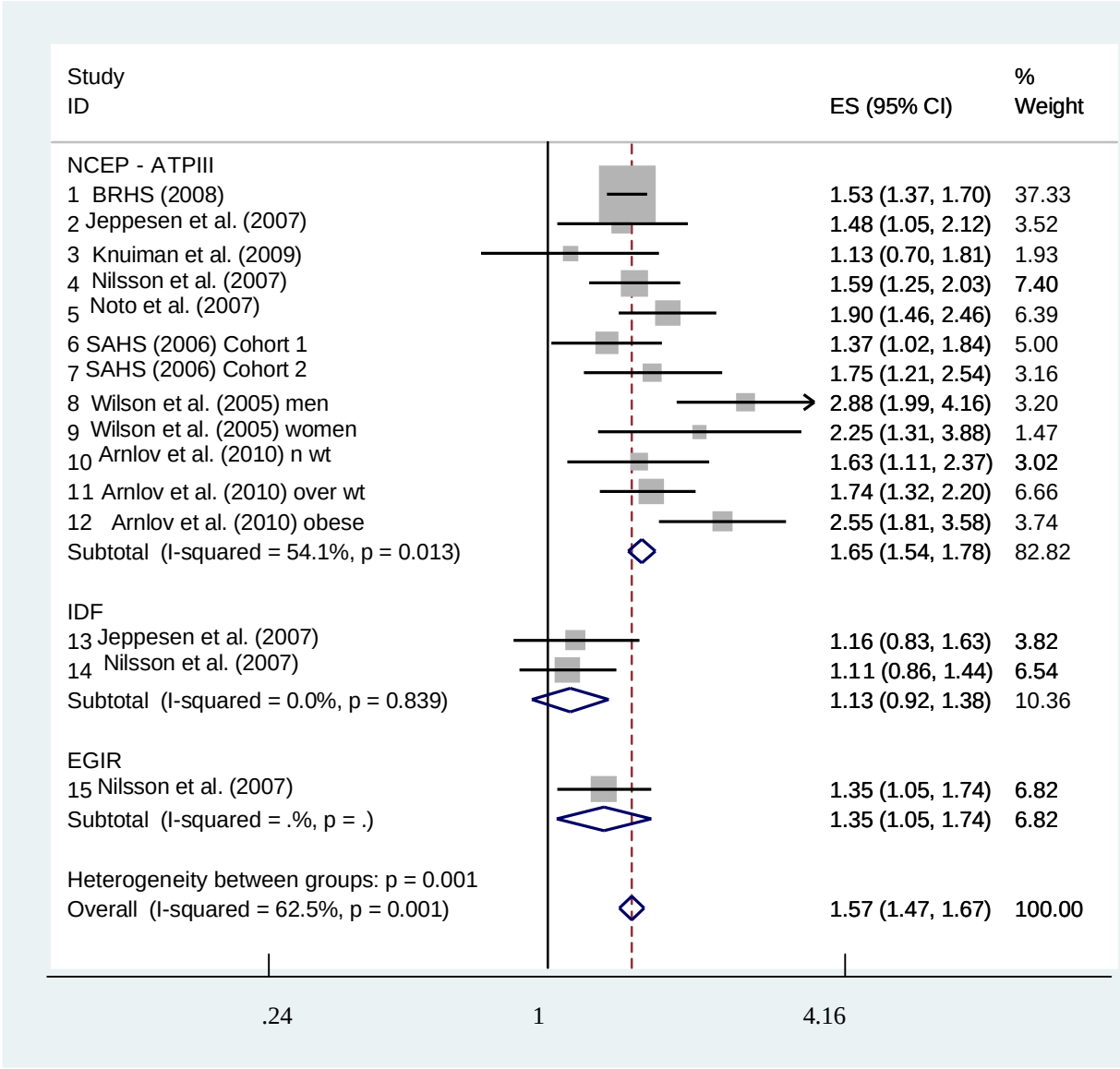
The following chapter will include the results from these eight studies and their significance in answering whether metabolic syndrome increases cardiovascular risk.

Chapter Five – Results

In this chapter I present and discuss the findings of the eight chosen studies. Seven of the eight studies produced statistically significant results using the NCEP-ATPIII definition of metabolic syndrome, except the study by Knuiman et al. (2009). The hazard ratios (HR) for all the other studies using the NCEP-ATPIII definition were more than 1.0 and the 95% confidence intervals (CI) were all statistically significant (the CI did not include 1), after controlling for the various variables discussed in Chapter Four.

The meta-analysis produced a HR of 1.57 with 95% CI 1.47 to 1.67 (see Table 9). The meta-analysis combines the results, HR and CI, of all eight studies to produce an estimate of the overall risk of CVD for people with metabolic syndrome compared with people without metabolic syndrome. The meta-analysis of the results is significantly heterogenous as the I^2 results is 62.5%. The meta-analysis for the IDF definition is homogenous as the I^2 is 0.0%. The meta-analysis of the studies using only the NCEP-ATPIII is slightly more homogenous with an I^2 of 54.1%, than the overall I^2 at 62.5%, see Table 9.

Table 9 - Forest Plot of Hazard Ratio (ES) and Confidence Interval



This effect size (ES) in this forest plot represents the HR. The study by Knuiman et al. (2009) produced the highest HR for CHD of all the studies, 3.59 and the lowest stroke, 0.66, (indicating a possible protective effect for metabolic syndrome) with the 95% CI being 0.19 – 2.27. The CI for stroke is not statistically significant as it crosses over the vertical line which indicates no treatment effect of 1.0 (see Table 9). There is a large variance in the CI's which also indicates that there were probably only a very small number of people who had a stroke in this study.

The study by Knuiman et al. (2009) indicates persons with metabolic syndrome have more than three times the risk of CHD. One of the reasons for this may be that Knuiman et al. (2009) is the only study which collected data with regard to the number of metabolic risk factors the participants had. The results of this study are comparing those participants with metabolic syndrome with those participants with no risk factors. The other studies in this systematic review have compared those with metabolic syndrome with those without metabolic syndrome. This could certainly produce a more statistically significant result as the participants on other studies could have one or two metabolic risk factors.

Knuiman et al. (2009) and Wilson et al. (2005) both included a wider age range 25-84 years and 22-81 respectively. The fact that the older age group is included in these studies (ages more than 70 years) will have impacted on these results, although they both adjusted for age so the impact should be reduced. Wilson et al. (2005) recorded the second highest HR of the studies (2.88 for men and 2.25 for women).

There was only one study which used the European Group for the study of Insulin Resistance (EGIR) definition of metabolic syndrome (Nilsson et al. 2007). This study compared these results with the NCEP-ATPIII and IDF criteria. The EGIR criteria are outlined in Table 2. The EGIR criteria require insulin resistance and any other two risk factors. Nilsson et al. (2007) produced a HR of 1.35 with a just statistically significant CI (1.05 – 1.74). Nilsson et al. (2007) and Jeppesen et al. (2007) used the IDF definition to define metabolic syndrome. The IDF criteria are outlined in Table 2. The IDF definition requires abdominal obesity and two other risk factors. These studies produced similar results with the HR being 1.16 (Jeppesen et al. 2007) and 1.11 (Nilsson et al. (2007). The 95% CI of both studies were not statistically significant, 0.83-1.63 (Jepessen et al. 2007) and 0.86-1.44, (Nilsson et al. 2007).

Noto et al. (2007) and Arnlov et al. (2010) calculated Kaplan Meier (KM) survival curves of the participants as well as HR. KM survival curves record the number of patients still alive without the disease, CVD for this data, at given time frames. This provides different outcome data to the HR. The HR records the CVD event as the outcome. The person who has had this CVD event may or may not be still alive.

Noto et al. (2007) found a 93% survival rate for people with no metabolic syndrome at 15 years compared with a survival rate of 85% for those with metabolic syndrome. Arnlov et al. (2010) separated the data as per body weight. Those who had normal weight and no metabolic syndrome also had a survival rate of 93% at 15 years in contrast with those of normal weight with metabolic syndrome who had a survival rate of 87% at 15 years. Those people who were obese with metabolic syndrome had a survival rate of only 70%. This indicates that metabolic syndrome decreases life expectancy, particularly for those who are obese. It is also necessary to consider that obesity is also a risk factor for many other diseases, not just CVD, which would impact on survival rates (see Table 8).

Wilson et al. (2005) also calculated population- attributable risk estimates (PAR) for the risk of CVD in those subjects with metabolic syndrome. The PAR gives the risk of CVD that can be attributed to metabolic syndrome. Wilson et al. (2005) determined that men with metabolic syndrome had a 33.7% PAR of developing CVD and women a 15.8% PAR. This gives a significant PAR for both men and women. For men, metabolic syndrome contributing 33% to CVD is very high.

Lorenzo et al. (2006), Wannamethee (2008) and Knuiman et al. (2009) calculated CVR using Framingham risk equations. Lorenzo et al. (2006) calculated CVR at baseline only, cohort 1 had a lower CVR than cohort 2. Noting the difference between the CVR of the two cohorts is the only discussion in this study on the CVR that was

calculated. Lorenzo et al. (2006) is the only study which included the results of the CVR calculation in the literature. The study by Knuiman et al. (2009) adjusted for the Framingham risk score, age and gender in one calculation. The HR and 95% CI for this calculation was very similar to that calculated when adjusting for all the variables listed in Table 8.

The above studies that calculated Framingham risk equations did not relate these to the results obtained. It would have been very useful if all studies had calculated CVR using Framingham risk equations and compared the Framingham Risk of those people with and without metabolic syndrome. This would then have answered the question posed in this dissertation very clearly, highlighting whether or not metabolic syndrome increased CVD risk or not.

Wannamethee (2008) concluded that CVR was a better predictor of non fatal MI or coronary heart disease (CHD) death than the metabolic syndrome. This same study also concluded that CVR and metabolic syndrome is a similar predictor of non fatal angina. The question posed for this dissertation is whether metabolic syndrome increases CVR rather than suggesting that metabolic syndrome should replace CVR as an assessment tool for calculating the risk of CVD.

Wannamethee (2008) and Arnlov et al. (2010) included only men in their population. Comparing the results of these two studies is a little difficult as the data analysis was quite different in both studies. Wannamethee (2008) gives a HR for all CVD events however Arnlov et al. (2010) gives the results as per BMI without calculating an overall HR for those participants with metabolic syndrome. Therefore it is not possible to accurately compare results.

The results of the Wannamethee (2008) can be compared with those of Noto et al. (2008), Wilson et al. (2005), and Nilsson et al. (2007) as all these studies included both men and women but separated their results as per gender. Wannamethee (2008)

and Noto et al. (2008) both calculated similar HR at 1.53 and 1.58 respectively. Nilsson et al. (2007) calculated a slightly higher HR of 1.71 but Wilson et al. (2005) calculated a much higher HR of 2.88. This is comparing only the NCEP-ATPIII definition of metabolic syndrome (See Table 8).

There were only three studies which reported the results for women separately, Noto et al. (2008), Wilson et al. (2005), and Nilsson et al. (2007). Wilson et al. (2005) and Noto et al. (2008) recorded a similar HR of 2.25 and 2.10 respectively. Nilsson et al. (2007) recorded a much lower HR of 1.45. As previously stated Noto et al. (2008) only adjusted for age and gender and Wilson et al (2005) only adjusted for age whereas Nilsson et al (2007) adjusted for many more variables. This could explain the variance in the results for women in these studies. I feel the results of Nilssen et al. (2007) are much more reliable given they controlled for a larger number of potential influencing factors (See Table 8).

Smoking is a risk factor which increases cardiovascular risk significantly. Jackson (2008) estimates that active smokers have up to an 80% increased risk of CVD. Therefore it is surprising that only five studies controlled for this when calculating HR. Lorenzo et al. (2006), Noto et al. (2008) and Wilson et al. (2005) did not control for smoking.

Wilson et al. (2005) only adjusted for age which could explain why they calculated the second highest HR, men 2.88 and women 2.25. These authors did not adjust for common risk factors for CVD, e.g. hypertension and hyperlipidaemia or smoking. The percentage of participants who had metabolic syndrome and smoked in the study by Wilson et al. (2005) was 25% for men and 29% for women. This could explain the higher HR calculated as this is a high percentage of people who smoke. This may have impacted on the results for women in particular, as this is a considerably

higher HR than has been calculated in the other studies and women usually have a lower risk of CVD than men.

Lorenzo et al. (2006) also had a high incidence of smokers, cohort 1 men 35.4%, women 24.6%, cohort 2 men 30.5% and women 20.7%. Lorenzo et al. (2006) also had a higher rate of CVD risk but did adjust for many other risk factors for CVD, see table 8. Noto et al. (2008) had a lower rate of smoking among participants, 17%, with 14% of those with metabolic syndrome recorded as smokers. Noto et al. (2008) recorded a similar HR to many of the other studies despite only adjusting for age and gender.

After taking into account all of the above factors, and the meta-analysis, the results of these studies demonstrate a statistically significant increased risk of CVD for people with metabolic syndrome compared with people without metabolic syndrome. This risk is one and a half times the risk of people with metabolic syndrome experiencing CVD than people without metabolic syndrome, according to this data. The next chapter will discuss the importance of identifying people with metabolic syndrome in order to assist with reducing their CVD risk and ways to support people to do this.

Chapter Six

Discussion and Recommendations

Metabolic syndrome increases a person's risk of having a cardiovascular event. The research presented in this dissertation has indicated that metabolic syndrome increases that risk significantly, one and a half times that of a person who does not have metabolic syndrome, HR 1.57 (CI 1.47-1.57). This is similar to the findings of Gami et al (2007), HR 1.78 (CI 1.58-2.00) and Galassi et al. (2006), HR 1.74 (CI 1.29-2.35). This evidence makes it difficult to understand why metabolic syndrome does not continue to be included as a significant risk factor in the NZGG (2009) cardiovascular guideline.

These findings suggest that it is very important to identify those people with metabolic syndrome and to assist them to reduce their risk, whether by lifestyle or pharmacological interventions, or both if necessary. The American Heart Association has a tool to identify people with metabolic syndrome. This website then suggests recommendations on reducing the risk of CVD for people with metabolic syndrome even though the American Heart Association does not add 5% to CVRA for those with metabolic syndrome (American Heart Association 2010).

Grundy (2007) supports identification of people with metabolic syndrome and discusses reducing the risk of diabetes and CVD in people with metabolic syndrome, stating that "because metabolic syndrome raises the risk of both diabetes and CVD, it is important to identify such patients as early as possible to institute lifestyle therapy" (p S4). For people with risk factors that are not severely elevated, lifestyle advice and support can often be sufficient to reverse metabolic syndrome and reduce the risk of having a cardiovascular event. Cassells and Haffner (2006) conclude that nurses are critical to assisting patients to make these lifelong changes to reduce their risk of cardiovascular disease and diabetes.

Nurses are in an ideal position to support people to improve their health through nurse led clinics. An example of this is the Primary Health Organisation's (PHO) funded Care Plus program. The Care Plus program gives people with chronic diseases access to free health care through their medical centre. The Care Plus program is usually managed by nurses who see the patients for education and support. This can include educating the patient about their chronic condition as well as assisting the patient to make goals to improve their health and live a healthier lifestyle. This empowers patients to manage their chronic conditions with increasing independence.

One component of the Diabetes Prevention Program (2005) compared the impact of lifestyle interventions, metformin and placebo on cardiovascular risk factors of patients with impaired fasting glucose. Impaired fasting glucose, or an elevated fasting glucose, is a component of metabolic syndrome. This study concluded that lifestyle interventions reduced CVD risk factors more than metformin or placebo.

As a practice nurse, I have enrolled many patients who have metabolic syndrome in the Care Plus program. Through this program they receive education and support to improve their diet and maintain regular exercise. The patients who are successful in this program reduce their CVR by reducing their risk factors with an improved lifestyle. Some of these people also improve their risk factors to the extent that they no longer have metabolic syndrome.

Unfortunately, since the commencement of this dissertation, the Health Rotorua PHO's Healthy Lifestyle Team (HLT) has been disestablished. This occurred at the end of June 2010 due to the funding for this program not being renewed by the DHB. I am unsure as to why the funding was not renewed although the coaches of the HLT did not reach their maximum caseloads, having received fewer referrals than expected, resulting in lower case loads for the coaches, which increased the cost per participant.

The medical centre where I am employed as a practice nurse referred more than half of the participants of the program. I was not aware that other practices in Rotorua were referring very few patients to the HLT and I do not know why other practices were not utilising this service to a greater extent. The underutilisation of the service was probably only one reason the HLT's funding was discontinued. Budget restraints for DHBs may also have had some impact on this decision. Nevertheless, Rotorua was one of the few DHBs in New Zealand offering this service and now we are no longer able to make it available to our patients.

Rotorua Area Primary Health Services (RAPHS) have employed a healthy motivational coach since the HLT were disestablished. This coach provides nutritional and physical activity support similar to what was offered by the HLT. Unfortunately this is only one person with a case load of 50 people. Rotorua has a population of approximately 65,000 people. One coach is insufficient to meet the needs of this large population. Rotorua has a high population of Maori, 36.4%, more than twice the national average of 14.6% (Statistics New Zealand, 2006). Maori people have an increased risk of CVD, as discussed in Chapter Two, therefore this service is needed in Rotorua.

The critique of the NZGG (2009) guideline using the AGREE tool recommended the use of the guideline whilst acknowledging the lack of evidence presented in the guideline with respect to metabolic syndrome not increasing CVR risk by 5%.

I would recommend a large cohort study be conducted in New Zealand, including New Zealand Europeans, Maori, and Pacific Islanders as well as other ethnicities, to determine whether metabolic syndrome increases CVR in the New Zealand population. This would be of immense value to New Zealanders, both health professionals and the general population. Unfortunately due to the fact that cohort

studies are very expensive due to the long duration of data collection and length of time before the outcomes are known, such a study is unlikely to occur.

Limitations

I have appraised the rigour of this systematic review using the University of Oxford (2005) appraisal criteria. This appraisal has highlighted some limitations in this study. This appraisal tool suggests articles should not be limited to English language only. I limited the search to English language for ease of reading articles. This means relevant articles could have been missed that were published in other languages. These articles could have had different results to those I have used for this systematic review. I also have not contacted experts to discuss unpublished studies; again this could provide further relevant studies.

Overall, however, this systematic review has met most of the criteria outlined in this appraisal tool. In particular, the PECOT is clearly stated, the article selection and inclusion criteria are clearly described, the results section includes a forest plot and a discussion of homogeneity and heterogeneity. These are all required for a quality systematic review.

Another limitation of this dissertation is that there is no literature included from New Zealand. I would have liked to have found information on metabolic syndrome and the New Zealand population but unfortunately there is no New Zealand data that met the inclusion criteria.

Finally, there is the potential for bias related to the appraisal of the NZGG (2009) guideline as this was only assessed by me when the recommendation is for four assessors, as discussed in Chapter Three.

Dissemination and Implementation

The outcomes in this dissertation need to be shared with the primary care health professionals. There are several ways to do this. I will send this dissertation to LOGIC, the journal of the College of Primary Health Care Nurses for consideration for publishing. This journal is read by many nurses in primary health care, including practice nurses. This is an important group of nurses who have the ability to identify and educate people with metabolic syndrome. Disseminating the findings presented in this dissertation to this group of nurses will have an impact on reducing the CVR of people in our community.

Another way of informing both nurses and general practitioners of the finding of this research is to present it at an evening education session. These occur monthly in the town where I work. This is an excellent way to inform a wider group of the findings. This will also allow for discussion and debate on the topic which would be interesting as some general practitioners do not believe metabolic syndrome is of any significance to the health of our patients. This dissertation has clearly demonstrated that this belief is not correct.

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Glossary

Confidence Interval (CI) – This is the range of values that which the population is expected to fall, this is usually 95% meaning we are 95% confident that the population will fall between these two values.

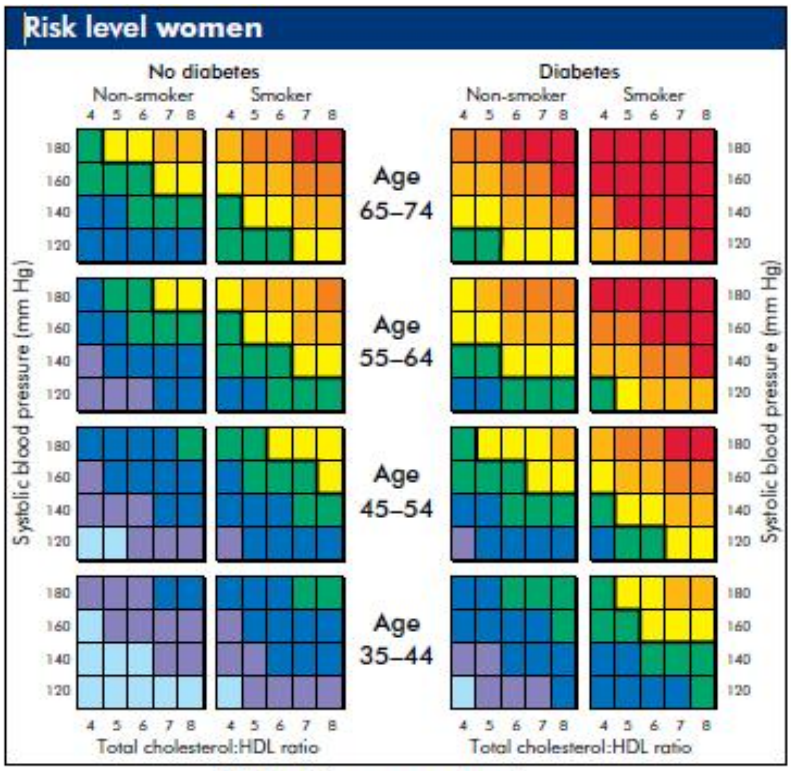
Hazard Ratio (HR) – The ratio of two risks, the risk of a disease in a group of individuals exposed to a factor divided by the risk of a disease in a group of individuals not exposed to the risk factor.

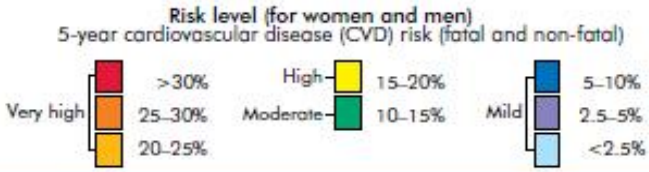
International Classification of Disease (ICD) – These codes are designed by the World Health Organisation and are the global standard to report medical conditions. They are regularly being updated with ICD – 10 being the current version.

Kaplan Meier Survival Curve (KM) – This displays the survival rate over a period of time. The survival rate is the percentage of people still alive without the factor of interest at given time frames. In this dissertation, the KM survival curves display the number of people still alive without CVD.

Population – Attributable Risk (PAR) – This is the proportion of a disease that can be attributed to a particular factor, in this dissertation, what percentage does metabolic syndrome contributes to the incidence of CVD.

Appendix A(i) – Cardiovascular Risk Charts - Women





How to use the Charts

- Identify the chart relating to the person's sex, diabetic status, smoking history and age.
- Within the chart choose the cell nearest to the person's age, systolic blood pressure (SBP) and total cholesterol (TC) TC:HDL ratio. For example, the lower left cell contains all non-smokers without diabetes who are 35–44 years and have a TC:HDL ratio of less than 4.5 and a SBP of less than 130 mm Hg. People who fall exactly on a threshold between cells are placed in the cell indicating higher risk.
- The risk charts now include values for SBP alone, as this is the most informative of conventionally measured blood pressure parameters for cardiovascular risk. Diastolic pressures may add some predictive power, especially at younger ages (eg, a diastolic pressure consistently >100 mm Hg in a patient with SBP values between 140 and 170 mm Hg).

Certain groups may have CVD risk underestimated using these charts, see Table 2 (page 5) for recommended adjustments.

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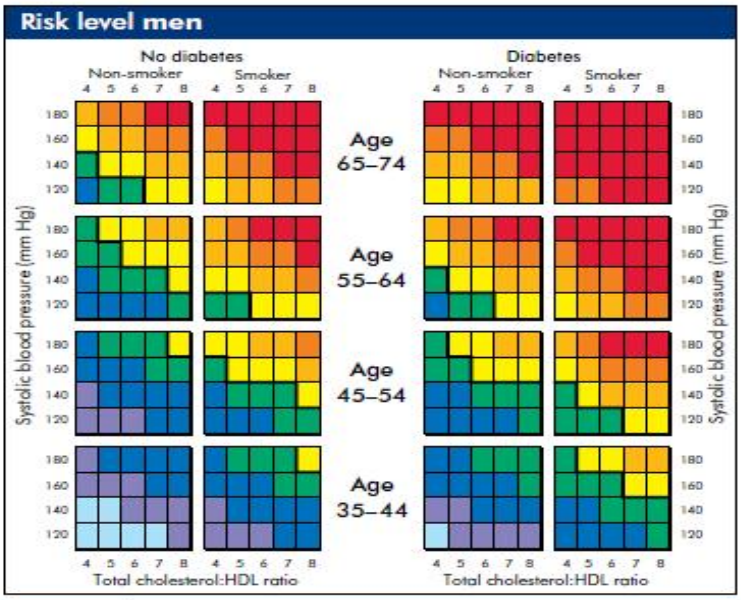
Appendix A(ii) – Cardiovascular Risk Charts - Men



Risk level: 5-year CVD risk (fatal and non-fatal)	Benefits: NNT for 5 years to prevent one event (CVD events prevented per 100 people treated for 5 years)		
	1 intervention (25% risk reduction)	2 interventions (45% risk reduction)	3 interventions (55% risk reduction)
30%	13 (7.5 per 100)	7 (14 per 100)	6 (16 per 100)
20%	20 (5 per 100)	11 (9 per 100)	9 (11 per 100)
15%	27 (4 per 100)	15 (7 per 100)	12 (8 per 100)
10%	40 (2.5 per 100)	22 (4.5 per 100)	18 (5.5 per 100)
5%	80 (1.25 per 100)	44 (2.25 per 100)	36 (3 per 100)

NNT = Number needed to treat

Based on the conservative estimate that each intervention: aspirin, BP treatment (lowering SBP by 10 mm Hg) or lipid modification (lowering LDL-C by 20%) reduces cardiovascular risk by about 25% over 5 years.

Note: Cardiovascular events are defined as myocardial infarction, new angina, ischaemic stroke, transient ischaemic attack (TIA), peripheral vascular disease, congestive heart failure and cardiovascular-related death.

Adapted with permission from: Rod Jackson, Head of the Section of Epidemiology and Biostatistics, School of Population Health, Faculty of Medical and Health Sciences, University of Auckland.

Appendix B (i) Cardiovascular Risk Assessment February 2009

Patient Summary - CVD Risk

Patient Details

Patient Name		NHI	
Date of Birth		Gender	**Male**

Clinical Details

Date of assessment	**15 February 2009**		
Height (cms)	**184**		
Weight (kgs)	**112**	BMI	**33.1**
Waist (cms)	**116**		
Cholesterol	**5.4**	Date of lipid tests	**15/05/2010**
HDL *(Fasting)*	**0.9**	Total Cholesterol:HDL ratio	**6**
LDL *(Fasting)*	**3.6**		
Triglycerides *(Fasting)*	**1.9**		
Most recent BP	**160/90**		
Previous BP	**140/86**		
Average BP	**150/88**		
Smoker	**No**		
Diabetes	**No**		
Plasma glucose *(Fasting)*	**5.4**	Date of test	**15/05/2010**
Metabolic Syndrome	**Yes**		

Clinical diagnosis of metabolic syndrome, due to the following factors:

- Truncal obesity ≥ 100cm
- Triglycerides ≥ 1.7mmol/L
- HDL < 1mmol/L
- Blood pressure: SBP ≥130 or DBP ≥85

Clinical Risk Factors

None

5 Year CVD Risk: 15%

Cardiovascular Risk	Lifestyle	Drug Therapy	Treatment Goals	Follow-up
15 to 20%	Specific individualised lifestyle advice on a cardioprotective dietary pattern, physical activity and smoking cessation. This lifestyle advice should be given by the primary health care team for 3 to 6 months prior to initiating drug treatment.	Aspirin and drug treatment of all modifiable risk factors (blood pressure lowering, lipid modification and glycaemic control). Drug therapy indicated for people with extreme risk factor levels	Risk factors treated to a level that will lower 5-year cardiovascular risk to less than 15% (by recalculating risk)	Cardiovascular risk assessments at least annually, risk factor monitoring every 3 to 6 months

Appendix B (ii) Cardiovascular Risk Assessment April 2009

Patient Summary - CVD Risk

Patient Details

Patient Name		NHI	
Date of Birth		Gender	**Male**

Clinical Details

Date of assessment	10 April 2009		
Height (cms)	**184**		
Weight (kgs)	**112**	BMI	**33.1**
Waist (cms)	**116**	Pulse	**n/a**
Cholesterol	**5.4**	Date of lipid tests	**n/a**
HDL *(Fasting)*	**0.9**	Total Cholesterol:HDL ratio	**6**
LDL *(Fasting)*	**3.6**		
Triglycerides *(Fasting)*	**1.9**		
Blood Pressure	**150/88**		
Smoker	**Past**		
Diabetes	**No**		
Plasma glucose *(Fasting)*	**5.4**	Date of test	**n/a**

Clinical Risk Factors

Cardiac History - Family

None

5 Year CVD Risk: 10%

Cardiovascular Risk	Lifestyle	Drug Therapy	Treatment Goals	Follow-up
10 to 15%	Specific individualised lifestyle advice on a cardioprotective dietary pattern, and physical activity. This lifestyle advice should be given by the primary health care team	Non-pharmacological approach to treating multiple risk factors	Lifestyle advice aimed at reducing cardiovascular risk	Further CVD risk assessment in 2 years

Comments