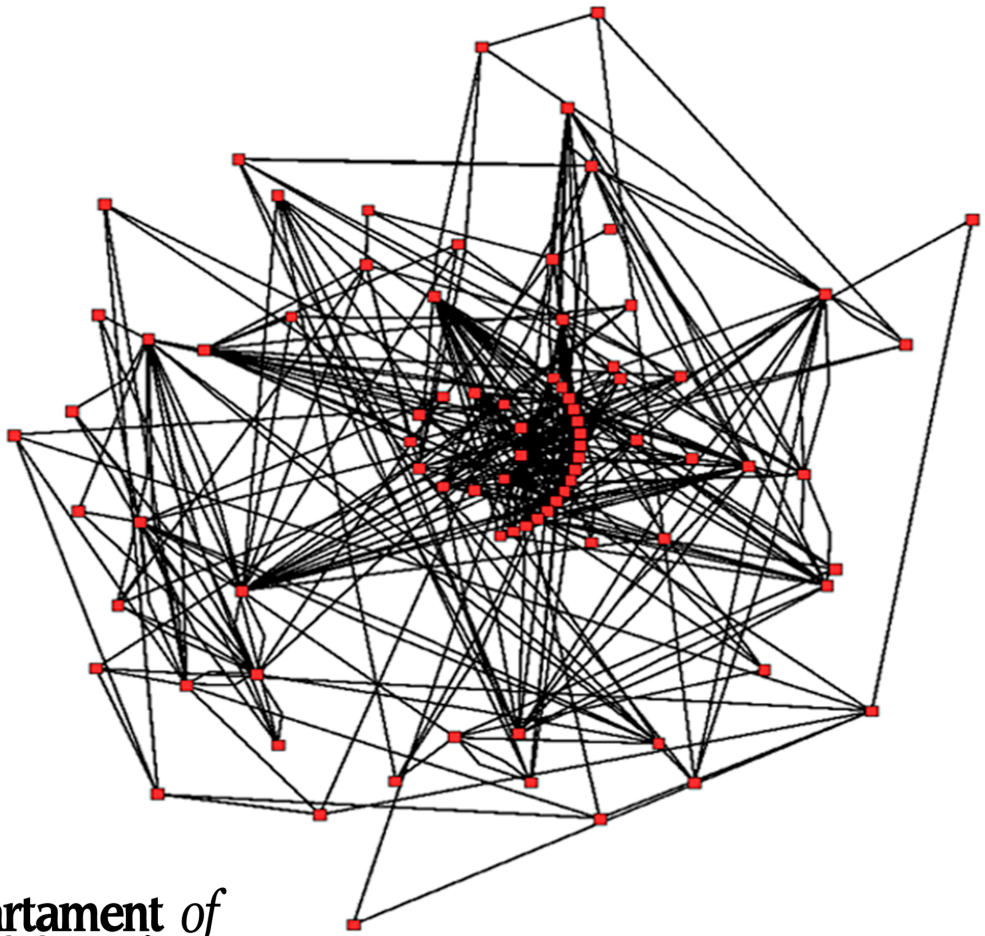
University of Leicester

Evidence Synthesis & Decision Modelling for Metabolic Syndrome

Milena Castro Mora

A thesis submitted for the degree of
Doctor of Philosophy in Biostatistics



Departament of Health Sciences

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I would really like to dedicate this thesis to life, but to understand life it is important to observe death... Perspectives can change when you feel the mortality, in front of your eyes... I would like to dedicate this thesis to the room 70 of the Hospital Mexico, San Jose... Pital de San Carlos, Moravia, Costa Rica, Latinoamerica, North Carolina, Chile... Leicester, Europe, Nirmal Pokhari, Nepal... Karl-Marx-Strasse

. ... .

Drake, Corcovado, Isla del Coco, My Mom's house.

Abstract

Evidence Synthesis & Decision Modelling for Metabolic Syndrome.

Milena Castro

Metabolic Syndrome (MetS) may be defined as a clustering of risk factors for diabetes mellitus (T2DM) and cardiovascular disease (CVD) which puts individuals at increased risk of developing these conditions and consequently leads to a reduction in life expectancy and increased morbidity. Although there are a number of definitions of MetS, essentially having any three of the following five risk factors confers a diagnosis of MetS; (i) impaired fasting glucose levels, (ii) raised blood pressure, (iii) raised triglycerides, (iv) low levels of high-density lipoprotein cholesterol (HDLC), and (v) increased waist circumference. A comprehensive decision model has been developed to combine different levels of evidence in a Markov model. This model is based in the behavior of MetS and its possible progression to T2DM and CVD, in order to evaluate the potential impact of a MetS based intervention at population level. Evidence synthesis methods are going to be incorporated in the model to integrate different levels of information. Firstly, a Mixed Treatment Analysis (MTC) of Randomized Controlled Trials (RCTs), which have evaluated a number of lifestyle and pharmacological interventions in individuals with MetS was undertaken. This information also assessed the possibility of reversing a diagnosis of MetS. Secondly, a systematic review of published literature was conducted to assess the evidence related with the association between the MetS and development of T2DM and/or CVD. A Bayesian approach to the problem has also been advocated which enables flexibility to develop a Markov model of this complexity. WinBugs offers a comfortable solution for the evaluation of a Markov model, given its Gibbs sampler. Main findings of this thesis are related with large amount of uncertainty, presuming a difficulty to provide a clear decision related to the application of MetS for prevention of T2DM and CVD.

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Chapter 1

Introduction

Metabolic Syndrome (MetS) has existed, as a concept, since the 1920s when Kylin determined a clustering of hypertension, hyperglycaemia, and gout (Cameron et al. [2004]; Eckel et al. [2005]; Kylin [1923]). It was until 1998, that the World Health Organization proposed a set of criteria to use as a tool for clinicians and researchers (Eckel et al. [2005]). MetS is a term describing the cluster of 3 or more cardiovascular risk factors, from a list of 5 established risk factors related to cholesterol, triglycerides, blood pressure, obesity and glucose intolerance (Alberti et al. [2006]; Cleeman et al. [2001]; Grundy et al. [2004]; Zimmet et al. [2005]). The lack of agreement between the different directions of the debate around the conformation of this criteria has led to a delay in its application to clinical practice (for example, there are no specific guidelines directed to the treatment of MetS in the British health care system). While there is still need for medical consensus on the use of the term, given its criticism, it is important to understand different stages of MetS to decide on the utility of this definition as a tool for prevention of cardiovascular disease. It is important to explore the possible impact that an intervention based on MetS criteria could have on a specific population.

Type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD), are non-communicable disease of major public health challenges world-wide. By year 1990, 83% of deaths between 15-59 years were in the developing world (Murray and Lopez [1997]; Zimmet et al. [2001]). Research about these diseases is overwhelming, mainly because of the complexity in their clinical definition (classification) resulting in an increased variability of the terms used across scientific publications. This panorama derives into a considerable list of different outcome definitions. Which is inherent to epidemiological behavior of CVD, because is determined as the sum of stroke and coronary heart disease outcomes. The type of events included as criteria for coronary heart disease

can present important variation over the literature, and therefore have a possible impact in use of this definition of CVD. This variation is more probable when studying the accumulation of evidence for chronic diseases across different populations, given the different uses of the terms over time and spaces of application. The exploration of the contradiction between the amount of information and the reality of these concepts could be the key to allow for an effective prevention of CVD.

This thesis aims to collate and synthesise evidence already published, assessing the MetS criteria to evaluate the possibility of applying a prevention strategy, such as an intervention based on MetS criteria. Understanding of MetS is important to develop the structure of a model for clinical and health policy decision making. The fundamental question that this thesis aims to answer is whether it is clinically useful and cost-effective to use MetS based interventions in order to have an impact on the incidence of CVD, T2DM and associated mortality? Therefore, the decision model will compile all the information extracted from the evidence synthesis, and will contribute to the discussion surrounding MetS. The outcomes of this analysis will expose important aspects to assess the impact of using MetS criteria in a population based prevention strategy.

In addition, since economic factors are also interacting within a public health framework, a comprehensive analysis for decision making is needed to evaluate different prevention strategies for T2DM and CVD. Therefore, the synthesis of evidence becomes crucial in order to accommodate different sources of information, and the use of Bayesian methods will not only enable the actual evidence synthesis analyses undertaken, but also provide a seamless transition between evidence synthesis and incorporation of these results within an economic decision model.

The following sections are going to specify the need of evaluating MetS using a comprehensive analysis. The definition of the problem and the research approach outlined in the introduction, are going to be supported with a background overview in Chapter 2 (Context and definition of MetS) and discussion of the statistical methodology in Chapter 3. Chapters 4 and 5 will describe the evidence synthesis and Chapter 6 is going to develop an economic decision model for a MetS population. Then, conclusions in Chapter 7 will integrate the main results into a discussion interpreting outcomes for decision making.

This section aims to introduce an overview of the structure of this thesis. Section 1.1 presents an argument of the importance of MetS, the definition of MetS is introduced in section 1.2. Section 1.3 presents a justification of the methodological approach of this thesis and section 1.4 presents an overview of the chapters composing the document.

1.1 Importance of Metabolic Syndrome: The global situation

The MetS criteria were developed to improve understanding of links between insulin resistance and vascular disease (Sattar et al. [2008]). Given the need for developing prevention strategies for T2DM and CVD, a broad evaluation of MetS could provide clear answers of finding a way of approaching solutions. The prevalence varies in urban populations from 8% (India) to 24% (USA) in men, and from 7% (France) to 43% (Iran) in women, and 30% in the UK (Khunti et al. [2010]). The prevalence of MetS is highly dependent on the prevalence of its individual components among populations.

Just as definitions used vary across countries, differences are also reflected in genetic background, diet, levels of physical activity, population age and sex structure, nutrition levels and lifestyle (Cameron et al. [2004]; Eckel et al. [2005]).

Alberti et al. [2006] have proposed the use of MetS as a diagnostic tool in clinical practice and the world-wide use of the criteria to be able to compare different populations from different regions. MetS criteria could be used to identify people at higher risk of developing T2DM and/or CVD.

MetS criteria was first introduced by Raeven (Eckel et al. [2005]) and as a result the definition has led research in different directions since then. The concept itself is constituted by many sources of variation, making a comprehensive overview challenging. The different aspects related with MetS prevalence across populations, that were mentioned previously in this section, represent sources of variation of MetS. The definition of MetS is a composition of risk factors and each contributes with variability. Each risk estimate involves a specific population with a specific condition, that associates with the other risk factors, these populations can encounter different interactions related with the habits that helped develop the condition. In order to develop a model that can reflect reality of MetS, these sources of variation should be considered within any model. In a complex model, like the one that this thesis is aiming to develop, there are a number of challenges for all sources of variation coming from MetS and that from all other sources are captured within the model. Since decision making is the ultimate aim of this thesis, for a population based intervention, there will be sources of variation that will be outside of the scope of this model; like individual patient level. Chapter 2 will present a detailed overview of the context of MetS. But firstly, a definition of MetS is necessary to start.

1.2 What is Metabolic Syndrome?

Given a list of the five determined risk factors for cardiovascular disease (impaired glucose intolerance, high cholesterol, high triglycerides, high blood pressure and high waist circumference), if a person presents any combination of 3 or more risk factors, would constitute a MetS diagnosis. The occurrence of this event (accumulation 3 or more risk factors) represents 16 possible combinations (3 of 5 risk factors) that can be present in a person that classifies with a positive result. Different organizations like World Health Organization (WHO), National Cholesterol Education Programs Adult Treatment Panel III (NCEP) and the International Diabetes Federation (IDF) have made an effort to specify MetS criteria for medical research and clinical practice (Alberti et al. [1998, 2006]; Cleeman et al. [2001]; Grundy et al. [2004]; Zimmet et al. [2005]). However, the simplicity in the numerical definition incorporates semantic heterogeneity; because, at the individual-patient level, the multiple combinations that the terms can evidence in the clustering of risk factors. The simple addition of components can introduce a particular variability from the combination of the components and its prevalences.

There is also a debate surrounding a constructive benefit for the design of a health intervention from clinical practice and detractors mention a possible benefit of increasing markets for therapies which they see as unwarranted (Gale [2008]). Chapter 2 presents a discussion about the validity of MetS. Advantages related with the term are pointed to a potential preventive property of T2DM and CVD, because of the simplicity to be applied in clinical practice and could have an impact in the reduction of population costs related with the diseases involved.

In Chapter 2, contextualizing issues of Metabolic Syndrome, a broad definition of the MetS is complemented with a literature review of the actual situation. Examination of this polemic context of MetS, provides clarity to the interpretation of outcomes resulting from the decision model developed. It shows an important role for the structuring of biological patterns presented when modelling a syndrome.

These two previous sections have presented the need of studying MetS to this level of detail, the following section introduces the approach that this thesis is undertaking to achieve sufficient understanding of MetS to be able to produce recommendations for its application and future research.

1.3 Why take a comprehensive decision modelling approach?

Synthesis of different sources of evidence is needed to analyze a broad overview of factors (medical, economic and statistical issues) related to the assessment of MetS criteria and its use as a prevention tool.

Chronic diseases like T2DM and CVD require a comprehensive approach given their complexity. There are many factors interacting in a population that can allow the progression of these diseases. A broad analysis incorporating different types of evidence becomes key to the understanding of the behavior of the syndrome. Since the cause of T2DM and CVD is linked to lifestyle factors marked by the long duration a person can have a chronic disease, it is necessary to take into account different possible sources of variation. Decision models allow the incorporation of information from different

sources (clinical and economic information) in a structured manner which supports decision making related to public policy.

1.4 Outline of the thesis

This thesis starts with an examination of the context of MetS Chapter 2: *contextualizing issues of Metabolic Syndrome: concept and antecedents* presents an overview of the history behind the concept of MetS. This review is required given more than 85 years of research using this term. However, this literature review corresponds to the need of exploring the linguistic understanding in order to produce precise interpretations of the data outcomes. What are the factors interacting around the concept of MetS? How is this important for the development of the analysis? How will this thesis contribute to the debate? What are the possible constraints of a MetS model?

Chapter 3: *Bayesian modelling and evidence synthesis: methodological introduction* will specify important details of the methods used to address the problem outlined in the background. What are Bayesian methods? What is evidence synthesis? How can these methods provide an answer to the problems posed? What is a comprehensive decision model? What are the limitations of this methodology?

There will be 3 main data outcomes. The first outcome of the thesis is presented in Chapter 4: *Appraisal of Interventions for Metabolic Syndrome Reversal: mixed treatment comparison analysis*, which explores possible treatments available to reverse progression of MetS. This analysis compares pharmacological and lifestyle interventions to discuss possible strategies for prevention. Which could be the best intervention? The Lifestyle changes are very complex, given that changing lifestyle trends in the

population require different levels of intervention, taking into account structural transformations; which are elements of the systems where the individuals are part of. In order to increase access to improve their quality of life, these interventions should be contextualized according to the characteristics of the environment where individuals live. Expanding the access to a healthy life could build a real possibility of developing a successful prevention program.

The second important outcome of the thesis is described in Chapter 5: *Assessing the risk of developing diabetes and cardiovascular disease: a cohort systematic review*. This chapter aims to estimate the potentially increased risk of the possible progression from MetS to diseases such as T2DM and CVD, and ultimately mortality death. It is important to estimate probabilities of the different biological stages of these chronic diseases. This information will support the structural transitions of the model. Positive relations between a pre-state of MetS and development of T2DM and CVD have been found previously.

The third and main outcome brings previous chapters together to converge in a comprehensive decision model. Results coming from this analysis are going to be developed in Chapter 6: *Modelling a population with Metabolic Syndrome*. An introduction to the methods can be found in Chapter 3: the methodology of the thesis.

All the different results of this comprehensive analysis are going to be discussed in the final Chapter 7: *Reviewing the evidence and discussion of possible solutions: conclusions*. This chapter summarizes the results of the different analyses undertaken for this research, discussing the impact of the findings of the thesis and proposing further work. New research questions that have arise after this synthesis of contributions to the knowledge of MetS. New information is needed to give the next step in prevention

of T2DM and CVD. The aim of the thesis is to contribute to the knowledge of MetS and consequently to illuminate the possibility of improving quality of life in people at increased risk of developing T2DM or CVD.

Chapter 2

Contextualizing issues of Metabolic Syndrome: *Concept & Antecedents*

Prevalence of cardiovascular disease (CVD) and diabetes mellitus (DM) are increasing worldwide (Murray and Lopez [1997]; Zimmet et al. [2001]).

In this chapter, clinical definitions lead the introduction to the Metabolic Syndrome (MetS) concept in the section 2.1, aiming to specify the language of this thesis. This glossary of core definitions will support the overview of the debate around the definition in section 2.2. An epidemiological review of the concepts related with the risk of developing T2DM and CVD will be discussed in section 2.3. Section 2.4 introduces the available therapies to treat a diagnosis of MetS, 2.5 describe the model proposed for the development of the analysis required to achieve the thesis aim and 2.6 will discuss evident constraints given the natural root of the problem being addressed. A summary will be presented in section 2.7. This chapter corresponds to a conceptual introduction to the problem, where each section compiles an introduction to each chapter-analysis presented in this thesis.

Moreover, scientific information about MetS itself and related consequences is abundant; showing the need of a synthesis of such amount of evidence for decision making. These following sections represent current general discussions and attempt to define this specific analysis. However, this thesis is aiming to compile substantial evidence to contribute to a comprehensive analysis of MetS.

The main ideas encapsulated in the concept of MetS and its antecedents are going to be summarized at the end of the chapter. Which is the main role of the MetS criteria in this analysis? How this criteria is going to be useful to start a research development for decision making related to prevention of T2DM and CVD?

2.1 Definition of Metabolic Syndrome

Since the MetS has been established as a starting point for this clinical economic evaluation, there is the need to discuss issues surrounding its definition. Lusis et al. [2008] defines MetS as *"a group of metabolic conditions that occur together and promote the development of CVD and T2DM"*. However, as the definition has included diagnosis of T2DM as part of the criteria, proposed by the World Health Organization Consultation (Alberti and Zimmet [1998]), this becomes an important issue when specifying a definition for this thesis. Revising the definition in Reaven [1988], it states that *"hyperinsulinemia, impaired glucose intolerance, increased plasma triglyceride concentration and decreased high-density lipoprotein cholesterol concentration, represent the risk factors initiating coronary artery disease in the population as a whole. It also raises the possibility that resistance to insulin stimulated glucose uptake and hyperinsulinemia are involved in the etiology and clinical course of three major related diseases (non-insulin dependent diabetes mellitus, hypertension and coronary artery disease)"*. Therefore, MetS may be defined as a clustering of risk factors for T2DM and CVD, that possibly increases the risk of developing these conditions and consequently leading individuals to a reduction in life expectancy and increased morbidity. Essentially having any three of the following five risk factors confers a diagnosis of MetS; (i) impaired fasting glucose levels, (ii) raised blood pressure, (iii) raised triglycerides, (iv) low levels of high-density lipoprotein cholesterol (HDL-C) and (v) increased waist circumference (Grundy et al. [2004]). Evidence using the World Health Organization definition is going to be excluded to avoid possible biases in the results.

Although there are a number of definitions of MetS, which will be more explicit in section 2.2; this section is going to describe each component used to constitute diag-

nostic criteria for MetS. The five risk factors mentioned correspond to a measurement method to assess different problems stated in the definition of MetS.

2.1.1 Components: *Biological definitions*

Each component represents a recognized risk factor for future cardiovascular events and for development of new onset diabetes. Individually, these components lead to a reduction of life expectancy. As each of them are a determined cardiovascular risk factor, there is a lot of research underlying these concepts. Here, biological terms are going to be introduced according to their clinical impact related to MetS. Figure 2.1 presents the 4 main components: hypertension, dyslipidaemia (cholesterol and triglycerides), obesity and glucose intolerance. The following paragraphs explain in detail, how these concepts underly the addition of the 5 risk factors; previously specified in section 2.1 to constitute a definition of MetS.

These definitions were based on the ”Health information for the public” section of the National Heart Lung and Blood Institute (Grundy; NHLBI).

Hypertension: Having high blood pressure means the force of blood pushing against the walls of the arteries as the heart pumps blood. A damage in the heart, can be produced if the pressure rises and stays high over time; it can also lead to plaque buildup (thickening and inelasticity of the arteries). The common cut point for systolic blood pressure is 130mmHg and for diastolic blood pressure is 85mmHg (the mmHg is millimeters of mercurythe units used to measure blood pressure), above those limits the subject will be diagnosed as hypertensive. In MetS criteria, hypertension is measured with evidence of high blood pressure such as intake of drug therapy for its

treatment.

This component is physiologically linked to a recognized risk factor for pathological conditions or events (as heart attack, heart failure, stroke, end-stage renal disease, or retinal hemorrhage).

Dyslipidaemia: is a condition marked by abnormal concentrations of lipids or lipoproteins. This composite disorder is related with levels of cholesterol and triglycerides.

Cholesterol: There are 2 types of cholesterol: low density lipoprotein (LDL) and high density lipoprotein (HDL). In terms of MetS, low levels of HDL (less than 1.3 mmol/L in women and less than 1.0 mmol/L in men) is considered a cholesterol disorder. The HDL helps remove cholesterol from the arteries. (Figure 2.1).

Triglycerides: A high triglyceride level means this type of fat is raised in the blood in the form of lipoproteins.

Hypertriglyceridemia: If a person show levels of triglycerides over 1.7mmol/L, then is diagnosed as having the risk factor present.

Obesity: refers to a condition that is characterized by excessive accumulation and storage of fat in the body. Excess fat in the stomach area is a greater risk factor for heart disease.

There are different ways of measuring obesity, which has determined the derivation in different classifications available, such as central or abdominal obesity (assessed by waist circumference) or overweight (assessed by body mass index (BMI)). According to Visscher et al. [2001] waist circumference may be more predictive of overweight than BMI.

The obesity sources will determine differences in treatment, but the way MetS criteria includes obesity ignores these differences by using a generalized rule of measuring waist circumference or BMI, which are used as quantified expressions of obesity.

Latest lifestyle modifications have been influenced by societal dynamics changing healthy diets and increasing reliance on mechanized objects reducing physical efforts; positioning obesity as an increasing problem in modern times. This situation could be an important key in the elevated incidence of related problems like CVD and T2DM.

Glucose: If a person presents a higher fasting blood glucose than 6.1 mmol/L, they will be diagnosed with impaired fasting glucose (Zimmet et al. [2001]). As higher levels of blood glucose can reach a T2DM condition, this component of MetS includes the diagnosis of T2DM in the definition presented by WHO and in the IDF definition an individual with T2DM could be included according to its stated definition; but the NCEP criteria considers a cut point in the glucose level to define a different classification algorithm excluding diagnosed diabetic patients (Figure 2.1).

2.2 The debate around the definition: *The Classification Problem*

The earliest publication describing a clustering of hypertension, gout and hyperglycaemia was in 1923, by Kylin. This paper provides a start for empirical observation of a definition that later will be revised to benefit comparable research(Eckel et al. [2005]). In 1988, Reaven presented a triad of diabetes, hyperlipidaemia and hypertension and

Definitions of Metabolic Syndrome			
Risk factor	*Organizational criteria*		
	WHO, 1999	**NCEP, 2001**	**IDF**
Hypertension	Taking antihypertensive therapy and/or BP > 140/90mmHg	Taking antihypertensive therapy or BP > 130/85mmHg	Systolic BP≥130 or diastolic BP≥85mmHg or treatment of previously diagnosed hypertension
Dyslipidaemia	Plasma TG > 1.7mmol/L (150mg/dL) and/or HDL < 0.9mmol/L (35mg/dL) in men and < 1.0mmol/L (40mg/dL) in women	Plasma TG > 1.7mmol/L (150mg/dL), HDL-cholesterol <1.0 mmol/L (40mg/dL) in men and 1.3 mmol/L (50mg/dL) in women	Plasma TG > 150mg/dL (1.7mmol/L) or taking specific therapy for this lipid abnormality or low HDL-cholesterol < 40mg/d (1.03mmol/L) in men and < 50mg/L (1.29 mmol/L) in women
Obesity	BMI > 30kg/m^2 and/or waist-to-hip ratio > 0.90cm in men and > 0.85cm in women	Central obesity (waist circumference>40 inches (102cm) in men and >35 inches (88cm) in women)	Central obesity (waist circumference ≥ 94cm for Europid men and ≥ 80cm for Europid women, with ethnicity specific values for other groups)
Glucose	Diagnosis of type 2 diabetes	Fastin blood glucose > 6.1mmol/L (110mg/dL)	Fasting blood glucose ≥ 100mg/dL (5.6mmol/L), or diagnosis of type 2 diabetes
Requirements for diagnosis	Diagnosis of type 2 diabetes plus any 2 other risk factors	Any 3 of the above disorders	Central obesity plus any 2 other risk factors

WHO=World Health Organization, NCEP=National Cholesterol Education Program Adult Treatment Panel-III, IDF=International Diabetes Federation, BP=bloodpresure, TG=triglycerides, BMI=body mass index, HDL=high density lipoprotein.

Figure 2.1: *Metabolic Syndrome definitions by organizational criteria*

stated insulin resistance as the common origin for all three disorders. Obesity was not part of the equation at the beginning (Gale [2005]), but scientific discussion has led criticism in opposite ways. It is in 1998, when a formal MetS definition was proposed by the World Health Organization, to be used in research and also aimed to facilitate clinical identification of individuals with increased cardiovascular risk factors (Alberti and Zimmet [1998], Balkau and Charles [1999], Eckel et al. [2005]). Eckel's first line of the paper specifies that *"the concept of the metabolic syndrome has existed for at least 80 years (Cameron et al. [2004])."* In 2001, a newer definition was proposed by the NCEP (EPD [2001]). This other definition excludes the confirmed diagnosis of T2DM of the definition of MetS. During the last 10 years, different authors have addressed the need of establishing a diagnosis for MetS (Reaven [2004], Grundy et al. [2004], Gale [2005], Kahn et al. [2005], Kahn [2006], Lusis et al. [2008]). Therefore,

the key point of the discussion gets reduced to a classification problem. Its clinical usefulness has been questioned, since there is no additional value besides the sum of its parts (Kahn [2006]; Reaven [2006]). This means that, by adding components to build a classification of MetS, the impact will be the same as there is no biological interaction identified and yet confirmed in terms of public value, for healthcare.

Research surrounding the criteria for MetS and its association with CVD and T2DM has became relevant to design prevention strategies (Sattar et al. [2008]). Which makes this debate of great importance, as the possibility of preventing these chronic disease is a goal in public health. Given the fact that each individual component constitutes a risk factor for CVD and/or T2DM, the MetS criteria is an evident tool for the prevention of possible outcomes like CVD and T2DM (Khunti and Davies [2005]).

The National Cholesterol Education Program (NCEP), the World Health Organization (WHO) and the International Diabetes Federation (IDF) (Alberti et al. [2006]; Cleeman et al. [2001]; Grundy et al. [2004]; Yasein et al. [2010]; Zimmet et al. [2005]) have made an effort proposing a definition of MetS with differences on the diagnostic cut points of the components and requirements to meet criteria.

Figure 2.1 shows specifications of MetS according to these 3 organizations. Main variations are evident in cut points, the use of BMI or central obesity concepts and the use of glucose cut point or diabetes diagnosis. A relevant contrast with requirements for diagnosis can be noticed between WHO and the others, this organization uses confirmed T2DM diagnosis. Whereas, NCEP is the only one setting a positive diagnosis with any combination of factors. By fixing one of the components a pattern is already defined, thus it is necessary to take this specifications into account, when analyzing the evidence.

This thesis considers evidence only from studies that used NCEP definition for their methodological design, to be congruent with the definition presented in section 2.1. Evidence from studies using WHO definition where collected but excluded from the synthesis of evidence methods used for the comprehensive analysis; given the requested diagnosis of T2DM (Eckel et al. [2005]).

The thresholds in the definitions of positivity for the criteria for MetS might present a source of variation for the synthesis and therefore the modelling; given the multiple possible combinations from the 5 risk factors. This could be controlled if individual patient data was available, but the efforts for this thesis did not collected any detailed data from the studies. The differences presented across definitions (WHO, NCEP and IDF) may have an impact in the amount of people that will be classified with having a diagnosis for MetS.

Differences are also presented according to the population under study. Across literature it is possible to find researchers using their own cut points to adapt criteria, producing more accurate diagnostics. Even though there are differences between definitions, the components are the same for all.

Kahn et al. [2005] has made a complete literature review where all the criticism is exposed. This publication states that the MetS has been imprecisely defined, questioning its certainty related with its pathogenesis and serious critiques to the predictive value for CVD. The British Medical Journal has published both sides of the discussion. One side suggest to drop the term given its redundancy in those who already have T2DM, and it affirms that there is no additional value for those who do not have this disease. The other side, supports the idea of using MetS criteria as a stepwise approach as a simple public health strategy to identify people at increased risk (Gale [2008]). When

some authors support the criteria for its potential for prevention of CVD and T2DM (Zimmet et al. [2003]), others highlight its lack of clinical use and the possibility of market creation as an outcome of the determination of a MetS diagnosis (Gale [2005]). Authors mentioned in this section, show that scientific community have behaved controversially about this matter.

This thesis is aiming to bring light to this discussion, by making the effort of getting evidence together for the different factors related with MetS and its potentiality to provide a health care solution. The work presented in this document, represents a pathway through the evidence available for MetS. Following section 2.3 is going to provide an overview of the antecedents of the relation between MetS and CVD/T2DM outcomes. Section 2.4 introduces the evidence available for the treatments identified for people with MetS. These two aspects of MetS are key to be integrated in a decision model, as a thesis result, introduced in section 2.5. Constraints of this model will be discussed in section 2.6.

2.3 Epidemiological issues: *Risk of Cardiovascular diseases & Type 2 Diabetes Mellitus*

The aim of this thesis requires to look at some important antecedents related with the assessment of the risk of developing CVD and/or T2DM and contrasting people with MetS. The main outcomes to be consider are mortality and morbidity (incidence measures), in order to obtain epidemiological results corresponding with the behavior and management of these diseases.

Association of MetS with T2DM has been reported (Sattar et al. [2008]) and there are previous estimations of the risk of MetS with CVD. A meta-analysis showed a relative risk (RR) of 1.78 for CVD in people with MetS (Ford [2005]; Gami et al. [2007]; Li et al. [2008]). The three publications had differences: Gami et al. [2007] observed incident and mortality events related with CVD, Ford [2005] looked at incident and mortality events related with CVD and incident T2DM and Li et al. [2008] only consider outcomes with stroke events. This situation shows a variation on the type of outcomes considered for each study. The criteria used for CVD also represents a diversity, as studies may have only looked at one particularity of the definition (like stroke). This thesis will consider all possible outcomes according to the events reported in the literature to be synthesized. The chronic nature of CVD and T2DM diseases requires a review incorporating fatal and non-fatal events combinations as a classification of the outcomes and obtain a more realistic quantification of the risk. Chapter 5 will develop a systematic review to update the studies included in the previous meta-analysis and to obtain data for the classifications of the outcomes to be contrasted.

MetS components as risk factors of CVD and T2DM have the potential to accelerate the process of developing these conditions and there is important evidence addressing an increased risk. It is essential to explain how this biological result behaves in populations.

Moreover, when investigation about these diseases is abundant there is still uncertainty of MetS criteria and its validity for prediction, leading to a saturation of research without an agreement after several years of debate and miss-guided application in clinical practice. After many years using the term without an agreement whether it is useful or not for the health care application, it behaves in a miss-guided manner where there can

be a health professional using the term, but is not a systematic procedure. Therefore, this could be a contradiction between the amount of information available and its lack of application. Given so much information not yet organized completely, this thesis is aiming to compile this evidence in a decision making scenario, and therefore offer a research guideline before it is applied to a population level.

2.4 Potential interventions for the Metabolic Syndrome

As a result of a establishment of a MetS definition, an intervention could be designed for prevention purposes. Therefore, Chapter 4 is dedicated to the analysis of possible interventions for the reversal or delay of the progression of MetS.

Pharmacological interventions are considered as part of the therapy that MetS components required. These treatments are already determined by medical guidelines for these conditions (for example, Metformin is used for the treatment of T2DM and the Statins for cholesterol). Lifestyle interventions are going to be considered as part of the need of producing a significant change in the life of a person, to really overcome the risk of developing CVD or T2DM. Obesity components in MetS definitions require exercise and diet solutions to allow a reversal of the diagnosis. Details of these treatments are presented in Chapter 4, where their effectiveness will be assessed.

Capewell and Graham [2010] have analyzed different scenarios of interventions for prevention of cardiovascular disease. Discussion about designing targeted interventions and/or overall population strategies is needed. The possibility of creating inequalities after the implementation of a prevention intervention can allow the population for the development of other type of problems that need to be evaluated before favoring

any decision on its application.

Considering the inherent lifetime in chronic disease, an intervention of this level can have unexpected consequences or might not work under a long term basis. Analysis of each factor interacting in these diseases is needed before deciding for a public policy.

2.5 Developing a model structure for Metabolic Syndrome population scenarios

Can MetS criteria be used as a screening strategy for prevention? Is an intervention cost-effective to prevent T2DM and CVD? MetS criteria can be useful to identify people at higher risk of developing CVD and T2DM, but its evaluation is needed before encouraging a health policy based on it. Synthesis of evidence is crucial to build a comprehensive analysis, Chapter 3 will introduce details of the methodology used for the development of the analysis.

Figure 2.2 shows the model designed for this thesis. The first part of the model refers to the identification of people with MetS. The second part shows people with MetS and the possibility of reversing this diagnose. A mixed treatment comparison was conducted for the interventions available, the details are shown in Chapter 4. The third part of the model assess the increased risk of developing T2DM, CVD and all cause mortality for people with MetS. The fourth section explains the aim of a systematic review that is being conducted to update the previous research (Chapter 5). Furthermore, a cost effective analysis will be performed for this part of the model in Chapter

6.

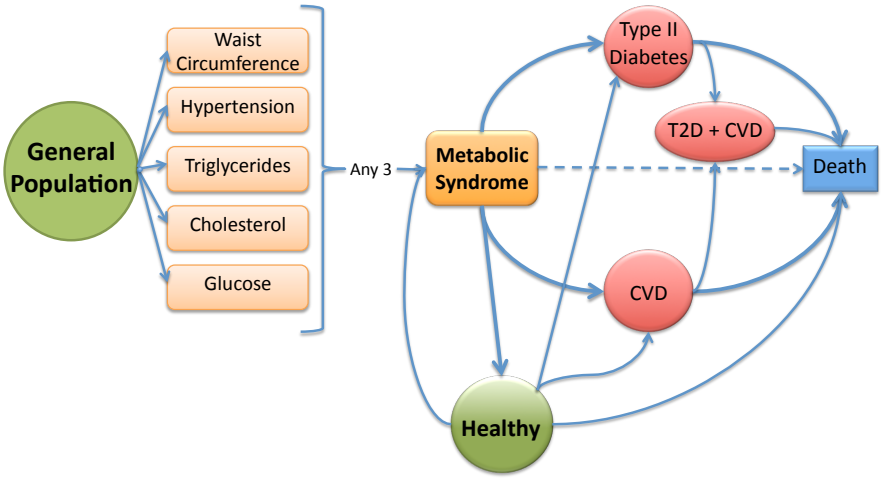


Figure 2.2: *Decision Model for the Metabolic Syndrome*

Since previous evidence has linked the MetS criteria with risk of developing T2DM and CVD (Ford [2005]; Gami et al. [2007]; Li et al. [2008]) structuring the model is as presented in Figure 2.2. There is a MetS state as a starting point of observation, then the possibility of reversing those diagnosed is represented as moving to a healthy state. Following a MetS state, are T2DM and CVD as a result of the progression of MetS. A combined state has been added, given the clinical possibility of a patient developing both diseases as a result of the progression of previous states. Death is a state that can be presented by any patient at any point of a lifetime and therefore is represented at the end of the model as a possible outcome of any of the previous states. The healthy state is also linked to T2DM and CVD, as a patient can develop this disease without being in a MetS state before.

2.6 Constraints of the model for the Metabolic Syndrome

As MetS criteria only incorporates 5 risk factors for CVD, this situation leaves out a list of risk factors that are interacting in the behavior of this disease. It is important to make this explicit as this thesis is only concentrating in the evaluation of MetS for prevention.

There are also sociological factors needed to take into account when developing a health policy and specifically in the design of a lifestyle intervention. An intervention is implemented to set up a pattern in the population that will hopefully decrease the prevalence of CVD, but this patterns could also lead the population into non-desirable consequences related with consumption. Obesity is a key risk factor of the MetS criteria, and is defined based on the increased calorie intake. The access to healthy food is restricted by the price (Capewell and Graham [2010]). The contents of the interventions should be contextualized according to the environment of the target population, in order to recommend interventions that are more likely to be effective and decrease the risk of changing the focus of the problem without providing a real solution. Society has the need to explore the real possibilities for a change to take place, and there are structural changes needed as well. Sedentarism is one of the patterns that is leading population to increase incidence of CVD and is important to look for the sources of this behavior to allow a real change in the trends.

Questions arise also, when there is the need for the health system to develop a strategy to prevent this situation increasing in frequency. As a lifestyle trend can be introduced with an intervention, ethical issues can present at the time of deciding on the lifestyle of

a person. The way a disease is communicated to the population can have psychological effects with the possibility of building a bigger problem along the side of the disease trying to be prevented. This situation takes place with the current debate of defining a metabolic syndrome.

All of these issues should be explored in more detailed, when a health policy is being considered.

2.7 Background summary

This chapter has presented a description of the definition of MetS, as clustering 3 or more cardiovascular risk factors from a list of 5. This definition has been the center of debate over 85 years, with authors defending it for prevention purposes and others stating a possible opening to the industry and its markets, introduced inside the debate around MetS (section 2.2). This thesis is going to assess MetS criteria for the development of a prevention strategy.

A comprehensive analysis (Chapter 6), from MetS treatments (Chapter 4) to the possibility of predicting the risk of CVD and T2DM (Chapter 5) is going to be developed as a result of this thesis. The next chapter describes the methodology implemented to evaluate the MetS criteria as an intervention to reduce the risk of developing T2DM or/and CVD in a population (Chapter 3).

Chapter 3

Bayesian Modelling & Evidence Synthesis: *Methodological*

Introduction

Statistical methods presented in this methodological chapter are aiming to improve the scientific understanding of MetS. I used a Bayesian approach to design an economic decision model based on synthesized evidence to support decision making in public health (Spiegelhalter et al. [2004]). This chapter has the intention to provide a basic conceptual overview of the statistical methods and is not going to describe all details of the theory supporting these models. This chapter represents a methodological introduction of core concepts implemented in a decision model framework using Bayesian methods and evidence synthesis. Therefore, the chapter is presented in three main sections (Decision models, Bayesian methods and Evidence synthesis) introducing technical concepts used to undertake the process of analysis needed. This thesis aims to evaluate MetS criteria as a possible intervention strategy, to have an impact in the possible progression of other diseases related (i.e. T2DM or CVD).

Definitions and specific assumptions related with any of the main concepts will be presented at the beginning of each section. In addition, it is important to outline discussion of their advantages and disadvantages for the decision process implemented in this thesis. This is introduced as the methodological concepts are presented in this chapter.

Description of specific analysis required for the process outlined in this methodological chapter and the purpose of this thesis, is going to be presented in the methodological section of the following chapters undertaking a decision process, Chapters 4 and 5 are evidence synthesis exercises about available treatments for MetS and the risk of progression to T2DM and CVD, respectively. Chapter 6 describes the decision model setting for a MetS criteria evaluation, integrating all the evidence produced in the firsts steps of the decision analysis. To open a methodological argument, decision issues are

exposed firstly in section 3.1, to address options surrounding a MetS model evaluation. Followed by an introduction to the basic concepts of a Bayesian approach in section 3.2 and evidence synthesis methods used to bring together all information needed for this specific decision process are described in section 3.3. A summary of this methodological chapter will be in section 3.4.

3.1 Decision Models

There will be many situations in life that will require a decision making process to intent to take the most appropriate action. Different levels of uncertainty are present in decision and evaluation processes. Therefore, a systematic analysis taking into account significant aspects to consider in a decision process; like the effectiveness to evaluate the clinical performance of an intervention for health care, and information on the costs of the implementation of the potential strategy (Briggs et al. [2006]). Collection of data for the cost and effectiveness of a specific strategy integrates a decision model, in this case, for health care evaluation.

Assumptions for decision models depend primarily, on the context of each specific problem and how the researcher perceives this context (Kansal [2004]). Implementation of probabilistic methods for decision making provides a framework to approximate reality, up to a certain extent, that would reduce uncertainty. Reduction of uncertainty has to be significant to be able to have a conclusive result from the decision process. Therefore, the methodology will have limitations introduced by the assumptions needed to be able to model the most natural version of the process implicit in the decision problem and it will be constraint by the specifications of the methods used.

Assumptions of the statistical methods are described in section 3.1.7, where decision trees, Markov models and combinations are introduced. Measures like the quality-adjusted-life-year (QALY), the incremental cost-effectiveness ratio (ICER) and the cost-effectiveness acceptability curve (CEAC), that are used for economic evaluation will be described in section 3.1.8.

There are different decision analysis approaches (Bouyssou [2000]), this thesis will undertake an economic evaluation using stochastic models for an analytical process of decision making based on the integration of a cost-effectiveness analysis using evidence synthesis methods to extract the information needed for the decision problem (described in section 3.1.1).

The model in this thesis, incorporates different levels of information (cost and utilities), and consequently performs an evaluation to process a decision for the use of MetS criteria as an strategic intervention for the prevention of T2DM and/or CVD. Output of the model allows a more integral understanding of diseases involved. Incorporating clinical estimations with economical data available to develop a wider observation of the patterns of the phenomena under study and possible consequent diseases; could allow the development of more understanding by the integration of previous knowledge. This provides the possibility to execute more accurate decision making; in order to elaborate a consequence addressing a real improvement in quality of life.

Application of a model without previous evaluation can lead to creation of more complications, resulting in higher cost for following efforts to reverse mortal disease. The presence of a condition on an individual, that can be used as a risk factor (as a clinical indicator), could lead clinical practice to implement assessment of this specific condition as a prevention program. When the study of a population confirms the need

of delivering efforts to reduce the risk of progression of conditions that can decrease the quality of life, the program becomes a social importance for their survival. However, limitations in data and the need to undertake more research to be able to integrate evidence from other sources of variation require to be acknowledged. The potential influence of the interactions implicit in reality, but constraint in the model. The population aimed to be modeled is immerse in specific social, economic and political environments that will constitute the context of a model. Also, given particularities of the behavior of chronic disease, the model has a dependent variable over time. Chronic diseases are developed in people over a long period of time. Therefore, time becomes an important issue to consider carefully in the interpretation of the effect under study. Simulation methods developed for the decision process should implement different rates to incorporate aging processes using different mortality rates for specific age groups.

Briggs et al. [2006] recognizes different stages of developing a decision model for economic evaluation. This section uses Briggs structure to describe the methodological process of the model presented for this thesis. This introduction to decision models shows the analytical discussion underlying the model, by stating a decision problem coming from a complex debate of the usefulness of MetS criteria to identify people at higher risk of developing CVD, T2DM or death (section 3.1.1). Constraints of this thesis are going to be reflected in section 3.1.2, with possible extensions for future research. The parts of the model will be explained to justify introduction of specific methods in this thesis in section 6.1. Issues related to the process of populating the model are also exposed in section 3.1.4 and necessary concepts to take into account in the design of a model, especially uncertainty and heterogeneity inherent to situa-

tions under observation are described in section 3.1.5. A justification for the use of decision models is presented in section 3.1.6. Description of specific decision methods considered for this thesis are described in section 3.1.7. Specific measures used for cost-effectiveness analysis are presented in section 3.1.8.

3.1.1 Decision Problem

Is an intervention based on MetS criteria for clinical practice useful to prevent the progression to T2DM, CVD and all-cause mortality, in UK? MetS criteria is going to be evaluated, if appropriate to use an intervention based on the identification of people with MetS in clinical practice, given the greater risk related with the development of T2DM and/or CVD in people with this condition.

Does the metabolic syndrome criteria present a possibility to reduce mortality for these causes in the UK? Is it useful to improve quality of life by introducing a prevention program? Is it cost-effective? The fact that MetS could be a state where people with this diagnosis could develop CVD, T2DM or death at an earlier age compared to individuals in a healthy state, identifies a question over the quantification of this risk.

There is evidence suggesting a significant risk for people with MetS, meaning a higher probability of developing T2DM or CVD than people without this previous diagnosis of MetS (Ford [2005]; Gami et al. [2007]; Li et al. [2008]). This thesis dedicates Chapter 5 to undertake an update of this previous reviews, implementing an analysis of the concept of MetS and its variability.

There are different treatments assessed with randomized control trials to measure the effect on the reversal of MetS (Anderssen et al. [2007]; Athyros et al. [2005]; Azad-

bakht et al. [2005]; Clearfield et al. [2005]; Esposito et al. [2004, 2006]; Geluk et al. [2005]; Orchard et al. [2005]; Phelan et al. [2007]; Ramachandran et al. [2007]; Sattar et al. [2003]; Stewart et al. [2005]; Van Gaal et al. [2005]; Villareal et al. [2006]). Chapter 4 presents an analysis of these different therapies (lifestyle interventions, pharmacological therapies or combination of both) to evaluate which intervention has the maximun effect on the reversal of MetS and how this interventions interact.

This information produced in Chapters 4 and 5 will be integrated in Chapter 6; costs and health utilities associated to each state of progression of the diseases involved in this analysis will be incorporated to constitute the model evaluating the impact of MetS as a strategy for the prevention of T2DM and/or CVD. Section 6.1 explains details of costs, health utilities and how the model was structured. Cost-effectiveness evaluation is decisive for the viability of application of a prevention strategy. The aim is to compare clinical and economical cost-data of hard states of CVD and T2DM with a state placed in clinical practice to identify people at increased risk (MetS). This identification of people make possible targeted interventions from a clinical practice perspective. If MetS has a strong predictive association, the interventions could be justified. Thereafter, the need of analyzing the social cost of a guideline based on this criteria, where other variables can have an important role defining a public health strategy.

The population effectiveness could be reflected in the impact on life expectancy, if the intervention under observation could have a significant impact over time. If the probability of progression gets reduced in each health state, mortality could be delayed as a consequence. This situation is expected to be the most beneficial for the population targeted. The influence in the cost would be expected to be reflected in a reduction of

costs when a cohort develop hard states like T2DM or CVD; if the intervention has a positive impact in the population, less people would be living with T2DM or CVD, therefore it would reduce the cost of health care as these specific hard states (T2DM and CVD) represent expensive diseases in public health. This affirmation is supported by the long time that people live with these specific conditions and the recurrent probability of suffering an event that compromises their quality of life.

Assessment of the potential of MetS as possible useful criteria for prediction of outcomes of interest, provides an analytical discussion to decide whether to elaborate a realistic strategy and permit the proportion of the population at high risk to be prevented from mortality outcomes or a poor quality of life given their health conditions.

Population based studies confront limitation concerning the management and collection of evidence. Moreover, it is important to consider that possible influential factors determine certain behavior of the model given the presence of different options the model could have.

3.1.2 Boundaries of the Model

There are several issues concerning the behavior of patterns in reality. The influence of these possible patterns is important to be recognized, but is better to not complicate the model by keeping control over the important transitions and their limitations that possible options could raise. A model can always be extended to measure issues of interest, but is critical to assess the advantages, disadvantages and possible implications a change or addition to the original model could develop; especially if resulting decisions mislead improvement of quality of life.

The model presented consider diseases (CVD and T2DM) under study like aggregated concepts and does not take into account possible complications (especially in T2DM) or other states that can be developed between the diagnosis and death events. Complications like blindness, amputations or any other different than cardiovascular events were not included in this analysis, because data reported was not consistent in the results presented using this specifications. Modelling this requires an adequate data identification to be able to introduce the possibility of this complications to any level of information (cost, utilities, clinical research) and evaluation of how it can be implemented in the structure proposed by this analysis, but this is not part of the scope of this thesis.

Moreover, there is no research data for some of the transitions, like a probability of developing T2DM after a CVD stage and others discussed in Chapter 6 and the process of populating the model. Lack of individual patient data limits the analysis to aggregated published information. Debate surrounding predictive value of MetS could be expanded to political implications.

These constraints of the model are crucial for the interpretation of its outcomes. It becomes important to be clear on the limitations that a model presents and evaluate if there are important possible risks for the population involve in the eventual application of the strategies under study. Other issues are related with the debate surrounding the predictive value of MetS (introduced in Chapter 2), placing a question over the definition and the variability introduced by the different proposed definitions (WHO, IDF, NCEP). Each source of information introduces variability to the model, increasing heterogeneity in the behavior of the simulation.

The process of analyzing a structure for a decision model reflects the boundaries, as it is

possible to visualize options taken into account for this thesis. Since reality becomes an abstract matter in this decision problems, definition of a logic for the model to follow is crucial to establish relations between transitions. Therefore, it is important to elaborate clear ideas for the collection of data.

3.1.3 Structuring a Decision Model

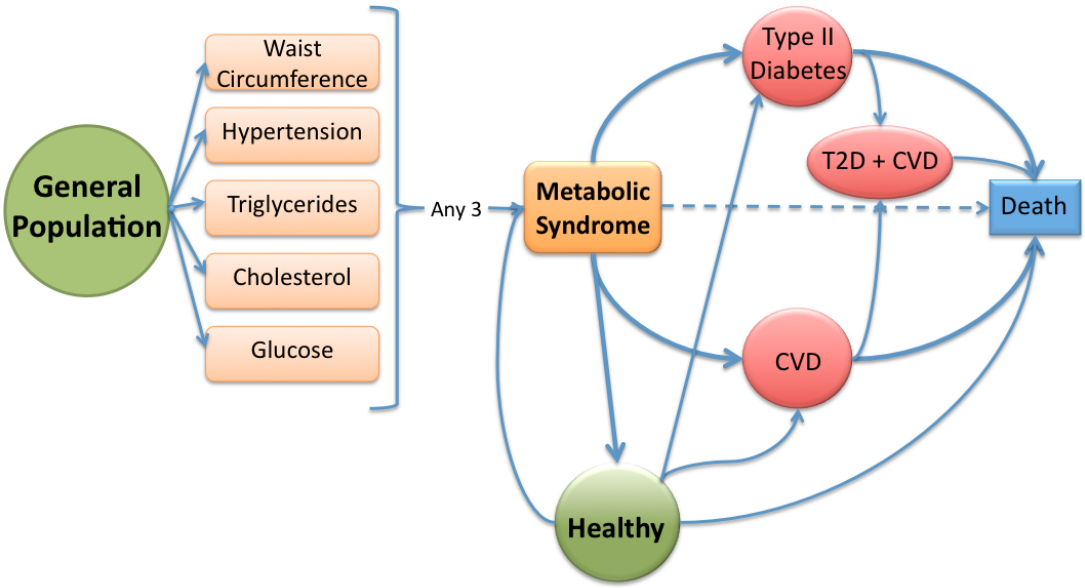


Figure 3.1: *Decision model structure used for this analysis*

To be able to direct answers for the questions raised by the decision problem it is important to establish how the relations are going to be incorporated in the model. Options previously defined help building the picture of the model and the purpose of the transitions are determined by the aim introduced in the problem.

Figure 3.1 shows how the model follows biological and clinical logics of events. People with MetS are identified from the general population if they have any combination

of three risk factors shown in the 5 first boxes in the figure (Waist circumference, Hypertension, Triglycerides, Cholesterol and Glucose); when people are identified with MetS in the yellow box, there are different possibilities, one will be related with the progression to T2DM, CVD (red circles) and all-cause mortality (blue rectangle), and second will be the option of reversing a MetS diagnosis and go back to a healthy state highlighted with green in the diagram of the model. The diagram shows also the option of developing a complication after T2DM and CVD states leading patients to a red oval state combining both diagnosis together, before the link with death at the end of the model. There is a central warning for people with MetS, given a higher risk for CVD and T2DM with an additional level of risk combining the presence of both conditions. Other components of the model measure probabilities of the reversal of MetS, and consequently the risk of developing CVD and T2DM from a healthy state. All states converge in a common end point for all outcomes integrating death causes.

The model is constituted by different inputs: probabilities, costs and utilities. This measures are going to provide information on transition rates between health states defined in the model. The utility parameters represent a measure of health condition, when lower values represent the worse possible health state and 1 represents perfect health condition (Briggs et al. [2006]). The cost data is collected from the total amount of capital needed to treat a patient in a particular health state, healthier states will cost less than states indicating progression to hard states like T2DM and/or CVD. This part of the process will be described in section 3.1.8.

MetS represents a chronic state and the consequence outcomes are also chronic. Thus, time is an important variable for risk changes. Identification of evidence requires determination of the model relations drawn.

3.1.4 Identifying and Synthesizing Evidence

Once a structure is proposed, the process of populating the model begins. This step of decision modeling represent challenges to bring together all relevant information to be synthesized and feed the relations stated in the structure. Clinical evaluation involves rigorous analysis demanding a systematic approach for the identification of relevant evidence, hence making evidence synthesis a critical aspect to perform a better assessment of the decision problem.

Evidence synthesis methods utilized for the collection of data required are going to be introduced in the last section 3.3 of this methodological Chapter, after Bayesian methods in section 3.2. There is the need to integrate all possible and relevant information to develop wider observation ensuring a decision making process to be engaged with the reality of the object under study. Comprehensive decision modeling gives the advantage of facilitating understanding of uncertainty in the evidence (Briggs et al. [2006]; Cooper et al. [2004]).

There are also other aspects to consider in the process of building a model, which relate to inherent dynamics of populations under study and possible behavior of patterns producing an influence. These aspects have to be included in the analytical process to be able to interpret results coming from the evaluation of the model.

3.1.5 Uncertainty & Heterogeneity

Variability. There are implicit differences between individuals under study. Individual cases hold particularities given their own experience and associated health-related quality of life. Probabilistic models take into account this variability inherent to any

clinical situation, however additional data collection cannot reduce it. As populations hold different sources of variability and even when individual details of the behavior of disease under observation, there is a need of understanding population variability to design more inclusive outputs of the model. Application of strategies excluding important issues could initiate undesirable performance and creation of more complications, nevertheless is important to recognize the difficulty in integrating all possible particular issues concerning chronic disease in a model designed for population decision making.

Parameter uncertainty. Refers to the precision of parameter estimation inputed in the model. Given limited evidence, precision of the parameter can be compromised, therefore incorporation of additional information should reduce uncertainty. This concept challenges compilation of evidence for chronic disease, as additional information can take long time to collect. Hence the need to use available information effectively to point new research to increase understanding of patterns and evaluation of possible population decisions becomes crucial to address safe solutions to improve quality of life in real time.

Decision uncertainty. Parameter uncertainty determines whether a decision is strongly supported by evidence or otherwise can lead to mistaken decisions. It is important to take into account the real impact of a possible implementation to avoid generation of more complications in the population and consequently incur in expenses with costly implications in economic and clinical levels. Distribution of cost-effectiveness relating to the options under comparison can be used to indicate the probability that the correct decision has been taken.

Heterogeneity. The effort of including variables related to subject characteristics that

can explain a proportion of the variability in a determined population. Even though, when uncertainty will remain in those parameters, exploring heterogeneity by subgroup estimates conditioning cost-effectiveness and decision uncertainty to individual characteristics can address more accurate decisions.

In the following description of the model determination of this thesis, there are different methodologies that were incorporated to address issues stated in previous paragraphs. After the definition of a comprehensive decision model, Bayesian methods becomes crucial given its technical flexibility and other advantages that are going to be discussed in section 3.2, together with an introduction of essential concepts for the compilation of Bayesian models, like Markov Chain Monte Carlo for parameter estimation. Thereafter, basic concepts of evidence synthesis are also going to be described in the third section 3.3 of this chapter with a presentation of the process undertaken for the collection of valuable information and populate the model. Specific analyses for evidence synthesis are going to be explained in the corresponding chapters referring to particular parts of the model previously described.

3.1.6 Why a Comprehensive Decision Model?

Developing a comprehensive decision model allows the incorporation of all parameter uncertainty taken into account for the decision problem. It also facilitates the assessment of structural uncertainty and heterogeneity, and correlation induced by the same study informing separate components of the decision model.

This thesis uses a probabilistic Markov model integrating clinical and economical variables to develop a decision process. In order to propose solutions for health care prob-

lems it is necessary to explore the alternative options available. Economic evaluation becomes a key to design realistic strategies, and obviously it is crucial to contrast the economic scenarios with their clinical applicability.

The development of a decision model allows an evaluation of the consequences of interest, in this case, prevention reflected in the improvement of quality of life of a population. But it is important to recognize a big limitation in sociological terms, as this models do not assess the social impact that a prevention program could have in the population. Therefore, incorporation of qualitative studies is necessary before implementing an intervention of any kind.

Moreover, the main advantage of decision modelling is the ability to analyse evidence from randomized trials and cohort studies together with external information related with the cost and utilities inherent to the evidence previously generated. This evaluation is needed in the process of decision making for the elaboration of useful health policies.

3.1.7 Methodological Definition of Decision Models

A decision model is a systematic approach to decision making under uncertainty. A decision analytic model uses mathematical relationships to define a series of possible consequences that would flow in a set of alternative options being evaluated. The likelihood of each consequence is expressed in terms of probabilities and each consequence has a cost and an outcome. The key concept behind decision modelling is the ability to incorporate variability and uncertainty associated with the decision of interest (Briggs et al. [2006]).

A modelling approach found in literature is system-based approach applied to MetS and its genetic understanding. These models integrate genomic, molecular and physiological data, also incorporating genetic and biochemical approaches targeting a better appraisal of the complexity of MetS (Lusis et al. [2008]). Different approaches have been applied to the study of T2DM. Kansal [2004] summarizes key issues of different models developed for the understanding of T2DM. From minimal models to progression models, Kansal [2004] writes about the difference between models for acute events than for chronic disease, making time scale an important issue to include in the simulation. According to Briggs et al. [2006] the type of model applied in this thesis is a cohort model. The most common forms of this type of models used in similar context (economic evaluation) are the decision tree and the Markov model.

Decision trees: Represent a way of displaying the decision algorithm. They are usually based on a tree graph constituted by nodes indicating decision alternative options. Pathways are mutually exclusive sequences of events and are the routes through the tree. Probabilities show the likelihood of a particular event occurring at a chance node. The first probabilities in the tree show the probability of an event and subsequent probabilities are conditional (Briggs et al. [2006]).

Markov models: Are commonly used in decision analysis to manage the added complexity of modelling options with multiplicity of possible consequences. These models are used for the evaluation of screening programs, diagnostic technologies and therapeutic interventions. The flexibility of the Markov model relates to the fact that it is structured around mutually exclusive disease states, representing the possible consequences of the options under evaluation. Discrete time periods can easily be incorporated in Markov models, as a set of possible transitions between the disease states

over cycles (time periods). Cost and effects are integrated as a mean value per state per cycle, and expected values are calculated by adding the costs and outcomes across the states and weighting according to the time the patient is expected to be in each state. The restriction that this model has is related to a memoryless assumption. This assumption means that once a patient has moved from one state to another, the model will have no memory regarding where that person has come from or the timing of that transition (Briggs et al. [2006]). For the composition of the Markov model aimed for this thesis, a circularity was identified in the range of definitions available for the concept of MetS. The definition criteria proposed by the World Health Organization includes T2DM diagnosis. Therefore, the evidence identified using this particular definition were excluded from the analysis. It is important to acknowledge that it is assumed the bias is controlled and that all determined states of the model structure are mutually exclusive.

This assumption is reflected in how individuals transit from state to state according to biological relations. There is the possibility to relax the memoryless issue, by adding nodes simulating another state. This state represents a pathway to a different node, that can be a single state or even a network; where individuals transiting in this part of the model, have specific population estimated rates, during the simulation process of the cohort.

Combination of decision trees and Markov models: Markov models are a form of recursive decision tree, and for some evaluations they can be used jointly. If a transition between Markov states are characterized in terms of a tree, then combination of both types of model is required (Briggs et al. [2006]).

Interesting examples of Markov models applied to the study of T2DM are Zhou et al.

[2005] with a comprehensive model to assess the impact of screening, prevention, and treatment strategies on T2DM and its complications, comorbidities, quality of life and cost. Gillies [2008] presents a model taking into account options like undiagnosed/diagnosed impaired glucose tolerance as a predictor of T2DM. The state of T2DM was also divided into undiagnosed, screen diagnosed and clinically diagnosed. Markov models were integrated with a decision tree to address decision issues in relation to the medical practice of concepts in a T2DM context.

When the setting of the structure of the model compiles all the options to be evaluated in the simulation and the evidence needed to support the hypothesis has been collected and imputed in the model, then there is the need to assess outcomes of the model.

Cohort simulation and model outcomes: The method used for the evaluation of decision models is known as cohort simulation. The proportion of the cohort ending in one state is multiplied by the correspondent transition probability of the consequence, and derives the proportion starting in another state. The simulation provides enough information for the calculation of expected values like life expectancy and expected costs, which constitute the main outcomes for a cost-effectiveness analysis.

3.1.8 Cost-Effectiveness Analysis

The final step in the decision analysis process is the interpretation of the outcomes of the model. Cost-effectiveness measures represent a helpful summary to be able to assess the usefulness of the intervention reflected on the possible impact that it could have on the populating being simulated.

The comprehensive perspective requires the analysis of different levels of information.

Given a medical context where an important component of health is reflected in a perspective of quality of life and together with a measure of the impact in economical terms can provide important information about the possible behavior of MetS criteria in a population dynamic. The following paragraphs will define measures used for the analytical treatment of the outcomes and its strategy for the evaluation of an economic decision model.

Quality adjusted life years (QALY): this measure is used to assess the clinical effectiveness of the intervention or screening program under observation. QALY is an indicator combining the length of life and the health-related quality of life, this allows mortality and morbidity to be analyzed (Briggs et al. [2006]). ***Utilities:*** this is a measure used to express a health score. Values between 0 and 1 are used to provide a utility weight, where 1 represents perfect health. Values less than 0 can be used, but would not be appointed when mortality is being represented. Utility weights are applied to each life year to obtain an estimate of the QALYs.

The cost-effectiveness plane: Figure 3.2 represents all possibilities in the cost-effectiveness analysis. The vertical axis represents the cost difference (ΔC) per patient between the intervention and the control (comparator). The horizontal axis represents the effectiveness difference (ΔE). Each of its resulting quadrants of the plane complete a range of options where the decision evaluation can be located. The slope of the line joining any point on the cost-effectiveness plane and the origin is equal to the ***incremental cost-effectiveness ratio (ICER)*** (Briggs et al. [2006]). The ICER represent an important statistic in cost-effectiveness analysis. Equation 3.1 shows the specific calculation of

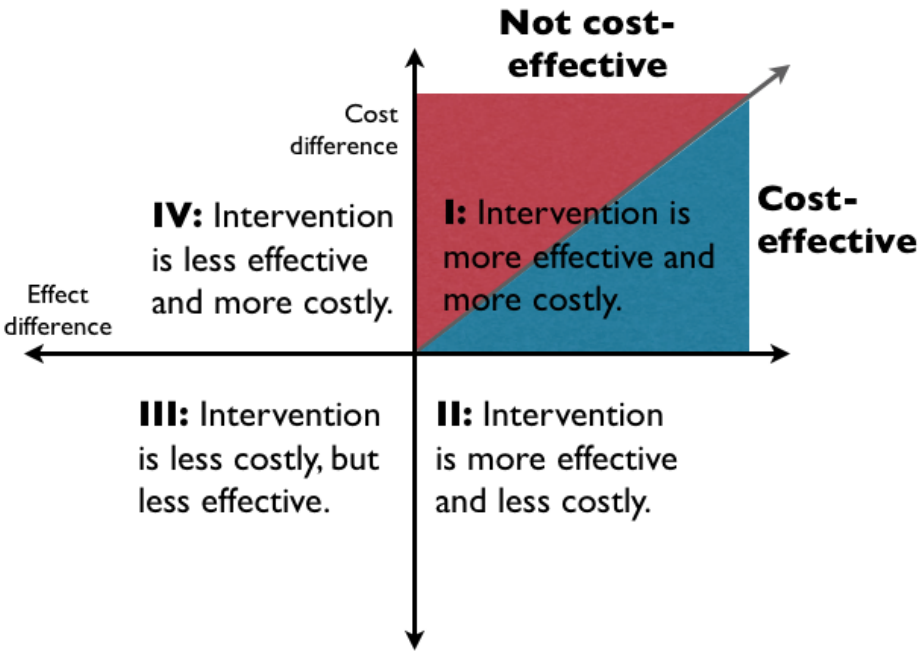


Figure 3.2: *Cost-effectiveness plane*

the ICER, dividing the cost difference by the effectiveness difference:

$$\Delta C/\Delta E \tag{3.1}$$

Markov models will simulate different positions resulting from the model settings, providing a visual perspective of the variability and position of the average model results. If an intervention based on MetS criteria, after obtaining results from the cohort simulation model, provides a cost difference under the willingness-to-pay threshold (λ) (cost per QALY that a health care provider would be preparing to pay to achieve a unit of effectiveness), then the intervention is consider cost-effective and could have a potential to be implemented for clinical practice. Equation 3.2 represents the cost-effectiveness evaluation.

$$\Delta C/\Delta E < \lambda \tag{3.2}$$

When an intervention is more effective than the comparator and requires less resources (situation of the II Quadrant in figure 3.2) or when an intervention is less effective and is more costly (IV Quadrant), these represent a straight forward decision; if the intervention results in II Quadrant facilitates a positive decision to implement the intervention that is forecasting a good benefit with less resources. These situations give dominated results for the new treatment or intervention under evaluation. If results point to the III Quadrant, decision could be influenced by the contextual needs of the health care evaluation.

The willingness-to-pay threshold (λ) can be explored by summarizing the uncertainty that fall under λ. Therefore, if different values of λ are plotted against a probabil-

ity of being cost-effective, the resulting curve shows the behavior of the evidence in support of the intervention being cost-effectiveness (acceptable). This use of the outcomes of the model for its analysis represent a ***Cost-effectiveness acceptability curve (CEAC)***.

Development of an economic evaluation model for MetS is a novelty of this research. After many years of constant research using MetS concept, it becomes an important task to bring all evidence together and evaluate population-based questions. Health care issues are recurrent when chronic disease represent a challenge in the administration of public health resources; creating the need of integrating daunting information of different research questions that will fit and create options simulated in the model to be able to undertake an evaluation of important aspects to make the most appropriate decision for public health.

The next section is going to introduce Bayesian methods. Issues related with these methods in relation to the development of a Markov decision model are going to be described. Bayesian models are frequently used for the implementation of complex situations requiring a comprehensive approach (Cooper et al. [2004], Kansal [2004], Zhou et al. [2005], Briggs et al. [2006]).

3.2 Bayesian Methods

Figure 3.3: *Thomas Bayes*

Bayesian inference was initiated after a posthumous publication by Thomas Bayes in 1763. He developed a solution of probability theory known as *Bayes theorem*. This result relates the conditional and marginal probabilities of two random variables. The implicit subjectivity and complexity of these statistical models has produced controversial debates over decades, however these methods have been used more frequently in recent years. The development of statistical tools like WinBUGs (statistical software for the Bayesian analysis using Markov chain Monte Carlo methods) has made the computation of complex statistical models straightforward (Spiegelhalter et al. [2004]).

The idea of a Bayesian approach requires the specification of beliefs related to the plausibility of the results excluding the data available. This is defined as a prior belief and is introduced as a prior distribution in the analysis. The likelihood is constructed

from the data and then, using the Bayes theorem the likelihood is combined with the prior distribution to produce a third density known as the posterior distribution. This section explains in general terms these ideas.

The Bayesian approach was defined as: The explicit quantitative use of external evidence in the design, monitoring, analysis, interpretation of a health-care evaluation (Spiegelhalter et al. [2004]). Therefore, in the case of a health care economic evaluation, there is the need of gathering exhaustive evidence relevant to the intervention (based on MetS criteria) that could be applied to prevent people to progress to T2DM or CVD diseases. Bayesian methods combine external evidence to feed each part of this economic evaluation. Advantages given by this approach are related with the flexibility of developing a unique model for each particular situation, the efficiency in utilizing all the evidence available, the usefulness in providing predictions with a clear interpretation for decision making, planning research and public policy. Ethical issues also conform an advantage in terms of randomisation and fully exploiting experience of past patients. Decision making could be based on available randomised control trials (RCTs), but under a systematic approach integrating different types of evidence (RCTs, Cohort studies and other relevant evidence), information brings efficiency to the decision making process. RCTs need a controlled selection of the subjects to be observed and randomisation implies bioethical issues when the study is on human beings, specifically if there are known differences on the effect of the treatments under observation and can have an impact on the health of the volunteered patients participating in the study. RCTs also are designed for short term observations. The incorporation of longitudinal data into the evaluation model, enables the use of wider observations (while including the information from the experience of past patients). The ability of

combining all available evidence to approximate the decision problem up to what has been studied about the event of interest (in this case is about MetS criteria), provides a decision panorama and highlights new important paths to direct research needed. The data and the model in Bayesian methods, are assumed to be random quantities (Spiegelhalter et al. [1999],Gilks et al. [1996]).

This thesis adopted a Bayesian approach to make complete use of the benefits given by these models. In Chapter 4 there will be a comparison between classical and Bayesian methods to give a clear idea of the advantages of performing the analysis with a Bayesian perspective. An analysis of the evidence available on the treatments for MetS is going to be performed with Classical statistical methods besides the Bayesian approach. This is to compare and assess the outcomes provided between the two methodologies. This argument can be found at the end of Chapter 4 in the discussion and limitations section.

Given the Bayes' theorem as the core concept of this methods, following sections are going to describe basic Bayes theory used to develop the model approaching the decision problem of this thesis.

3.2.1 Bayes' Theorem

The Bayes theorem shows a relation between two conditional probabilities. It expresses a posterior probability using prior information of the events under observation combined with relevant data collected. The calculation of the likelihood is obtained with the conditional density of the data given the parameters (Spiegelhalter et al. [2004]). The Bayes theorem for binary events a and b, representing two mutually ex-

clusive events (i.e. a as the proportion of people with a disease and b as the proportion of people without the disease), can be expressed as follows:

$$p(b|a) = \frac{p(a|b)}{p(a)} \times p(b) \tag{3.3}$$

A prior probability $p(b)$ is transformed to a conditional probability $p(b|a)$ when the occurrence of the event a is taken into account. This statement assumes a formal mechanism for learning from experience (Spiegelhalter et al. [2004]).

The Bayes' Theorem for general quantities, where θ is the parameter of interest, y is the data, $p(\theta|y)$ is the posterior distribution of the parameter after including the data, $p(y|\theta)$ is the conditional likelihood of the data given the parameter, and $p(\theta)$ is the prior distribution of the parameter of interest. Equation 3.4 is deduced from probability theory and clearing $p(y)$ to be the denominator of the conditional statements providing the likelihood $p(y|\theta) \times p(\theta)$, to obtain Equation 3.5.

$$p(y, \theta) = p(y|\theta) \times p(\theta) = p(\theta|y) \times p(y) \tag{3.4}$$

$$p(\theta|y) = \frac{p(y|\theta) \times p(\theta)}{p(y)} \tag{3.5}$$

In order to obtain the marginal distribution $p(y)$ from the joint distribution $p(y, \theta)$ of continuos variables, equation 3.6 shows the integration required to produce a distribu-

tion on y, when the conditional distribution is averaged by the prior distribution:

$$p(y) = \int p(y|\theta)p(\theta)d\theta \tag{3.6}$$

When there are multiple parameters the marginal posterior would be express as follows:

$$p(\theta|y) = \int \int_{\phi} p(\theta, \phi|y)d\phi \tag{3.7}$$

The complexity of these models may not be analytically tractable and require the use of alternative approaches for the integration of $E[f(\theta)|y]$, which can be impossible to apply (Gilks et al. [1996], Spiegelhalter et al. [2004]). Asymptotic approximations are used as alternative for integration using the Laplace approximation (Kass et al. [1988]), numerical integration techniques (Quadrature) can also be used, but numerical evaluation is difficult and inaccurate and Monte Carlo integration (Markov Chain Monte Carlo), in which software like WinBUGS is available and practical for this simulation. (Gilks et al. [1996]). Section 3.2.2 will describe details of MCMC and WinBUGS related concepts.

3.2.2 Estimation of Model Parameters

Markov Chain Monte Carlo (MCMC) is a method used to integrate over the posterior distribution of the model parameters given the data. Monte Carlo integration draws samples from the distribution, then create sample averages to approximate expectations. These samples are calculated by running a Markov chain for long time

(Gilks et al. [1996]).

Gibbs Sampling is a specific technique of MCMC and consists in sampling from full conditional distributions (Gilks et al. [1996]). In the 'long run' samples drawn from conditionals will converge to marginal distributions. The joint posterior distribution can be express by $P(\Theta) = P(\theta_1, \theta_2, \cdots \theta_p|y)$, where Θ is the parameter of interest and y represent the data. Hence a full conditional posterior distribution is used to generate consecutive samples of the parameter (j):

$$P(\Theta_j|\Theta_{(-j)}, y), j = 1 \cdots p \tag{3.8}$$

given the value of the rest of the parameters ($-j$) and the data (y). If Θ^0 represents the initial value for the parameter, the Gibbs sampler provides a series of observations from the full conditional distribution represented in Equation 3.8. Equation 3.9 shows the algorithm description for each of the p parameters sampled.

$$\begin{aligned} \theta_1|\theta_2^0, \theta_3^0 \cdots \theta_p^0, y \sim [-,-] \Rightarrow \theta_1^1 \\ \theta_2|\theta_1^1, \theta_3^0 \cdots \theta_p^0, y \sim [-,-] \Rightarrow \theta_2^1 \\ \vdots \\ \theta_p|\theta_1^1, \theta_3^1 \cdots \theta_{p-1}^1, y \sim [-,-] \Rightarrow \theta_p^1 \end{aligned} \tag{3.9}$$

A Markov chain applies the algorithm m times to produce the series of observations

needed to estimate the parameter of interest.

$$\begin{aligned} \theta_1 &= (\theta_1^1 \cdots \theta_1^m) \\ &\vdots \\ \theta_p &= (\theta_p^1 \cdots \theta_p^m) \end{aligned} \tag{3.10}$$

In order to **assess convergence** there are diagnostic tools used for it. Length of burn and sample the MCMC chains; checking autocorrelation and to run the model with different starting values with multiple chains.

If the values being sampled present a chain with erratic behavior, then is showing lack of convergence. This situation could be because the chain has not been ran long enough. In order to make sure the impact of the initial values is minimized on the posterior inference, a burn-in period can be defined to discard the first set of values of the Markov chain. The beginning of the chain can be erratic due to the initial values specified, also it is important to run multiple chains with different initial values to avoid areas where it might be stuck and does not shows a steady trajectory (Spiegelhalter et al. [2004]).

Autocorrelation can also be an issue between simulations. When sequential draws of a parameter are correlated producing a pattern of serial correlation in the chain. This means the Gibbs sampler will take longer time to explore the entire posterior distribution. These diagnostic tools are useful to determine the length of the chain. Complexity of these techniques require the support of specific software like WinBUGS

3.2.3 WinBUGS

WinBUGS is the software used to perform MCMC models. It is straightforward to assess Bayesian analysis, because of its flexibility of language for model specification (BUGS: Bayesian inference Using Gibbs Sampling). This tool provides a way of evaluating Bayesian models, obtaining summary statistics of the posterior distribution, checking of convergence, run multiple chains and can generate its own list of initial values. Building-up a model in WinBUGS can become a slow process as errors in the code are not necessarily obvious. If WinBUGS is trying to compile a model that is not yet featured, it can crash or provide very wrong results. The use of this software requires understanding of MCMC methods.

3.2.4 Prior Distributions

Prior distributions represent frequency distributions of previous beliefs of the phenomena being observed. This prior information constitutes the subjective part of Bayesian models as often there is no data available to inform the priors. Objective priors can be obtained from previous data of the parameter of interest. Specific distributions were used to obtain possible values of the parameters of interest. A sensitivity analysis of prior distributions is presented in Chapter 4 to choose the distribution for the Mixed Treatment Comparison model.

3.2.5 Direct Probability Statements

The Bayesian approach gives the possibility to calculate specific probability statements. Unobserved variables can be assigned *a posteriori* conditional distribution given the data collected on the observed variables (Dempster [1963]). The Bayesian framework provides a direct probability of the problem under study.

$$P(\theta > c) \tag{3.11}$$

Where θ is the parameter and c is a specific possible outcome of the parameter. If uncertainty is actually being explained to a satisfactory level by the Bayesian model, the resulting probability will be the real probability of the event under study of happening.

3.2.6 Summarizing the Posterior Density

It is necessary to give a complete interpretation of the posterior distribution. In order to take a decision it is required to compute different estimates that allow a clear understanding of the results. This section describes point estimates (mean, median and mode) and interval estimates (credible intervals and highest posterior density intervals). This measures conform the results of the analysis and should be complemented with estimations of uncertainty like, standard error.

Point Estimates

The common statistical measures of central tendency are the mean, median and mode. This type of estimation is very informative if the posterior distribution is symmetric and unimodal, given that the three measures are going to be estimating the same point. This situation may not be similar for all cases, therefore if the distribution is skewed is important to report all of them (Spiegelhalter et al. [2004]).

The conditional mean of θ given y is defined as (Lee [1997]):

$$E(\theta|y) = \int \theta p(\theta|y) d\theta \tag{3.12}$$

The conditional variance is defined as:

$$V(\theta|y) = E(\theta^2|y) - E(\theta|y)^2 \tag{3.13}$$

The median is defined as any value y_0 such that:

$$P(\overline{y} \leq y_0) \geq 1/2 \tag{3.14}$$

and

$$P(\overline{y} \geq y_0) \geq 1/2 \tag{3.15}$$

The mode is defined as the value at which the probability density function is a maximum (Lee [1997]).

Interval Estimates

The interpretation of the posterior density should be completed with interval estimates as a measure of uncertainty. For this section, two types of intervals are going to be considered: 95% credible Intervals and highest posterior density intervals.

Credible Intervals: The 95% credible Interval [CrI] gives 95% probability that the true θ lies in the interval. Each tail area has equal probability (θ_L, θ_U), where $p(\theta < \theta_L|y) = 0.025$, and $p(\theta < \theta_U|y) = 0.975$. If the distribution is skewed there will be some parameter values with lower posterior probability than value outside the interval, therefore this intervals are not appropriate.

The posterior probability density function of the parameter of interest can be used to estimate and answer probability questions. Probability is equal to the area under the probability density function. If the posterior density is continuous, a direct probability statement can be $P(0.1 < y < 0.9)$, where the probability is equivalent to the area under the curve between the two values of the range (Curran [2005]). The calculation can start with a determined value for the probability, like $p = 0.95$, for the 95% credible interval. Providing the interpretation as the 95% of credibility that the true value of the parameter of interest is between l and u.

Highest Posterior Density (HPD) Intervals: The HPD intervals are useful when the posterior distribution is skewed. It is adjusted in a way that each tail give a similar probability, so the interval is calculated from the narrowest possible area including the required probability; therefore the shortest credible interval is from the region with highest posterior density. If the distribution has multiple modes, then the HPD will be composed with a group of intervals (Spiegelhalter et al. [2004]).

3.3 Evidence Synthesis

Evidence-based health care is becoming an important tool to certify public policies and decision making. To compile all the scientific evidence produced is not a trivial task, therefore the synthesis is crucial to identify the best health strategy based on relevant and reliable research. The following sections introduce details related with the process of synthesis of evidence.

Next section 3.3.1 describes systematic reviews methods used for the analysis presented in Chapter 4 and Chapter 5. Details of meta-analysis methods are introduced in sections 3.3.2 and 3.3.3. Section 3.3.4 describes techniques utilized for the exploration of heterogeneity in meta-analysis models.

3.3.1 Systematic Reviews

Systematic reviews are used to identify all the scientific evidence and to compile together all the research done in a particular area of study in a structural way. To organize all the evidence related with a specific research question becomes complex when the scientific knowledge is abundant. Therefore, the task of combining the evidence systematically, is crucial in order to obtain reliable results and be able to replicate the review.

Authors consulted for this section started with Higgins et al. [2008] (Cochrane handbook on systematic reviews) and include Goodwin and Geddes [2004] stating the relevance of these methods for their support in decision making and clinical practice. Stroup et al. [2000] and Moher et al. [2009] presented a reporting format for the re-

sults of a systematic review; Meta-analysis of observational studies in epidemiology (MOOSE) and the Preferred reporting items of systematic reviews and meta-analysis (PRISMA), respectively. Sutton et al. [2000] was also consulted for the meta-analysis methods. See Moreno et al. [2009a,b] for publication bias criticism.

Systematic reviews differ from qualitative narrative reviews in the way the information is organized for its analysis. A systematic approach ensures a structural way of collecting relevant data for a specific research question. Given a known structure it is possible to use meta-analysis methods to assess the evidence collected in a way that can be replicated (Goodwin and Geddes [2004]). This techniques allows more informed decisions to be taken.

Given the scientific progress and increasing knowledge relevant to health care, research developing a more collective observation is needed to solve issues related with divergent results. This sparsity of the knowledge becomes a serious problem when there is the need of making decisions for health policy and clinical practice. Systematic reviews are one of the first steps in the chain by which research evidence can inform policy and practice (Sutton et al. [2000]).

The identification of all the evidence is fundamental for the quality of the results of a review. It is necessary to design complete search strategies to be sure all the evidence is included. These search strategies are used in databases like EMBASE and MEDLINE. A weak data extraction can lead to bias results or ignore important related information. Definition of the inclusion and exclusion criteria identifies the specific evidence for the search strategies. The quality of a study is also relevant to the results of a systematic review. All type of studies are subject of bias and therefore their quality can have influence on the estimates (Egger et al. [2001]). Each type of study requires different

quality assessment as they differ on its methodological features.

Juni et al. [1999] has discussed the problematic around the use of scores for quality assessment of trials and recommends methodological aspect to be assessed individually as the results can differ depending on the scale used. Results from Juni et al. [1999] analysis shows non-conclusive results about the use of a particular score for quality assessment. Comparison of 25 different scales presented a pattern influencing the interpretation of a meta-analysis. This issue should be explored, as it is very critical to address a particular conclusion from the interpretation of results. In observational studies synthesis the subjectivity around a quality assessment can be significantly different than trials and represent a challenge.

Since systematic reviews are based on published research, **publication bias** is a present issue for these methods. Research with statistically significant results is potentially more likely to be submitted or published, leading to a preponderance of false-positive results in the literature. This situation represents an important problem in evidence synthesis, as the combination of identified published studies may lead to incorrect estimates of the parameters. Therefore it is necessary to implement evaluation of possible publication bias. The use of funnel plots facilitates the visual assessment. Large studies appear toward the top of the graph and tend to cluster around the mean effect size drawing a funnel with small studies at the bottom. The effect size is plotted in X axis and the standard error on the Y axis. If there is no evidence of publication bias studies will be distributed symmetrically about the mean effect size (due to sampling error); if the studies present a pattern with a significant area of missing studies towards the bottom of the graph, it is showing presence of bias (Borenstein et al. [2009]).

If the funnel reflects evidence of bias, then corrections can be made; and the situation

can show the need of undertaking more research to be able to conclude about the problems under study (Moreno et al. [2009a,b]). Egger's test can be used to fit a regression analysis to provide an estimate adjusted with the publication bias effect.

The next sections introduces the meta-analysis methods used for the statistical synthesis of the data extracted from the studies included in the systematic reviews on Chapters 4 and 5.

3.3.2 Meta-Analysis

Meta-Anlysis methods combine the study estimates related to a research hypotheses in particular (Sutton et al. [2000]). There are two types of assumptions, that determine two methods: Fixed effects (FE) and Random effects (RE). These methods are going to be described as follows:

Fixed Effects Methods

The principal assumption for a fixed effect model is that there is no heterogeneity between the study results. The method exposed in this section is the inverse variance-weighted method, where a weight is given to each study estimate. This weight is calculated proportional to the precision of the trial. A pooled estimate of the treatment effect is shown by the equation 3.16. Where $i = 1, , k$ is the number of studies to be combined, T_i is the observed effect size, θ_i is the underlying population effect size, but for a fixed effects model all population effect size are assumed equal ($\theta_1 = \theta_2 \cdots \theta_k$, the studies are assumed to be estimating a single true underlying effect size), and w_i is the weight given by the inverse of the variance v_i $(w_i = 1/v_i)$ (Sutton et al. [2000]).

The formulae 3.17 shows the variance of the pooled estimate $\overline{T}$, shown in equation 3.16.

$$\overline{T} = \frac{\sum_{i=1}^{k} w_i T_i}{\sum_{i=1}^{k} w_i} \tag{3.16}$$

$$var(\overline{T}) = 1/\sum_{i=0}^{k} w_i \tag{3.17}$$

Random Effects Methods

When the assumption of equal population effect size θ_i is not realistic for some cases, a random effects model should be considered. This method assumes the estimates of the studies have different effect sizes and takes into account the heterogeneity between trials. A random distribution is assumed from the collection of study specific effect sizes (Sutton et al. [2000]). The equation 3.18 shows the case, where $\overline{T}_i$ is the estimate of the pooled effect size and θ_i is the true effect size in the *i*th study, and e_i is the error of the estimation ($e_i \sim N(0, v_i)$). The variance is represented in the formulae 3.19, where τ_θ^2 is the random effects variance and v_i is the variance related to sampling error in the *i*th study. When $\tau = 0$ it becomes a fixed effects model.

$$\overline{T}_i = \theta_i + e_i \tag{3.18}$$

$$var(\overline{T}_i) = \tau_\theta^2 + v_i \tag{3.19}$$

For a fixed effect model T is estimated by weighting each study effect size with the precision ($w_i = 1/v_i$), producing a single fixed effect estimate (Equation 3.16). In the case of random effects each study will be providing an estimate for T_i (Equation 3.18), adding a random effect to the estimation (e_i). If Equation 3.20 is used in Equation 3.16 the random effect pooled estimate is obtained.

$$w_i^* = \frac{1}{[(1/w_i) + \overline{\tau}^2]} \tag{3.20}$$

Since the fixed effect estimate assumes $\theta_i = \theta_k$, τ becomes 0 in the absence of variation, thus Equation 3.19 is reduced to Equation 3.17.

3.3.3 Bayesian Meta-Analysis

Bayesian methods were introduced in Section 3.2 and their advantages were exposed. In the context of meta-analysis, all evidence regarding the problem under observation can be taken into account, allowing a summary of the current state of knowledge (Sutton et al. [2000]). This thesis is aiming to collate all evidence available in MetS for the analysis of its behavior and measure its usefulness for a potential intervention to prevent progression to chronic disease. The Bayesian approach makes more efficient use of the evidence obtained for this specific comprehensive evaluation.

The log odds ratio (LOR) represents a measure of the effect size extracted from each study selected for the meta-analysis. The generic meta-analysis model for fixed effect is represented by $T_i = LOR_i$. Equation 3.21 shows the Bayesian fixed effect model,

where a prior distribution needs to be defined for $\mu \sim N(0, 100^2)$.

$$T_i \sim N(\mu, v_i) \tag{3.21}$$

Where v_i is the observed variance. A normal distribution can be used for this prior. If there is no information on previews believes of the effect size to specify a prior distribution, then vague priors are used to let data dominate the posterior density (Lambert et al. [2005]). The Bayesian model for random effects is given by:

$$T_i \sim N(\theta_i, v_i) \tag{3.22}$$

where θ_i represent the estimated effect size in the study i^{th} and v_i is the variance of the estimation. θ_i is defined as a normal distribution with δ and τ_θ^2 as the random effect variation.

$$\theta_i \sim N(\delta, \tau_\theta^2) \tag{3.23}$$

In random effects models a prior is needed for μ and for τ (μ is the pooled effect size and τ is the between study heterogeneity), $\mu \sim N(0, 100^2)$ as a vague prior and τ^2 can take different priors like Uniform ($U(0, k)$), Half Normal ($HN(0, h)$) or Gamma ($1/\tau^2 \sim G(0.001, 0.001)$).

Given the fact that data is often collected in groups, there is the need to specify the model for binary data. If a two-arm study is considered, in which r_A and r_B are the observed number of outcomes of n_A and n_B, respectively. Equation 3.24 presents the

first part of the model:

$$\begin{aligned} r_{Ai} &\sim Bin(\pi_{Ai}, n_{Ai}) \\ r_{Bi} &\sim Bin(\pi_{Bi}, n_{Bi}) \end{aligned} \tag{3.24}$$

where π_A and π_B are the two unknown parameters for the two arms of the study. Applying the $logit$ transformation of each of the two parameters, then

$$\begin{aligned} logit(\pi_{Ai}) &= \mu_i \\ logit(\pi_{Bi}) &= \mu_i + \theta_i \end{aligned} \tag{3.25}$$

where μ_i is the log odds of an event in the control group of the i^{th} study and θ_i becomes the parameter of interest (log odds ratio), which is assumed to follow a normal distribution and prior distributions need to be define for μ and τ_θ^2.

$$\theta_i \sim N[\mu, \tau_\theta^2] \tag{3.26}$$

with μ representing the pooled effect estimate, on a log odds ratio scale, and τ_θ^2 is the between study heterogeneity (Sutton et al. [2000]).

3.3.4 Exploring Heterogeneity

This section present methods used to explore heterogeneity and explain its sources (Higgins and Thompson [2002]). Random effects models do not provide a justification for heterogeneity. Exploration for heterogeneity is important in order to find associations between study or patient characteristics and the outcome measure. There are two methods to explore heterogeneity:

Subgroup Analysis can be used to explore heterogeneity at a level of study or patient characteristics. One type considers subsets defined by study or patient characteristics (i.e. quality, length of follow-up). The other type of subgroup analysis explores subsets of patients within the studies.

Meta - Regression: The model presented in 3.23 can be extended to include a covariate, x_i. Equation 3.27 representing general quantities and Equation 3.28 for binary data representation

$$\theta_i \sim N(\mu + \beta x_i, \tau_\theta^2) \tag{3.27}$$

$$logit(\pi_{Bi}) = \mu_i + \theta_i + \beta x_i \tag{3.28}$$

The parameter in model 3.29 can be estimated using Restricted Maximun Likelihood (REML) in a number of classical statistics packages; i.e. metareg in Stata, or a Bayesian approach can be adapted by placing prior distributions on μ, β and τ. As β is a regression parameter it can take values as the real line and therefore a vague prior could be $N(0, 100^2)$.

Adjusting for Baseline Risk: The model 3.29 can be extended to include an adjustment for baseline risk. The baseline risk reflects risk of outcome event for a patient under the control condition and indicates average risk of patient in that trial if they were not treated. Differences in patient characteristics among studies may result in different treatment effects.

$$logit(\pi_{Bi}) \sim N(\mu_i + \delta_i + \beta(\mu_i - \bar{\mu}), \tau_\theta^2) \tag{3.29}$$

with β representing the impact of the underlying effect at baseline and δ_i is the underlying log odds in the i^{th} study.

3.4 Summary of the Methodology

The methodology described in this chapter have introduced the basic concepts to support a decision model framework. Bayesian methods are going to be used to develop a Markov decision model in WinBUGS. Evidence synthesis is going to be performed to collect all evidence needed to populate the decision model. The result of this thesis is a comprehensive decision model for a clinical and economic evaluation of a possible intervention dedicated to the prevention of T2DM and CVD. The intervention is going to be based on MetS criteria.

Chapter 4 presents the results of a synthesis of evidence of treatments for the reversal of MetS and Chapter 5 describes a systematic review undertaken for the assessment of the risk to develop T2DM and CVD in patients with MetS. Chapter 6, then presents all this information integrated in a comprehensive decision model and incorporates

economic data to complete the evaluation of MetS.

Chapter 4

Appraisal of Interventions for Metabolic Syndrome Reversal: *Mixed Treatment Comparison Analysis*

This Chapter aims to identify the best intervention for the reversal of MetS. The intervention identified could be a potential tool for the prevention of T2DM and CVD. There were 13 Randomised Controlled Trials (RCTs) identified and 12 different interventions (Control, Diet, Exercise, Lifestyle with supervised exercise/exercise advice, Antiobesity, Antidiabetics, Antiobesity plus Lifestyle, Antidiabetics plus Lifestyle, Statins, Fenofibrate and Statins plus Fenofibrate), these interventions are presented in section 4.1.2, as part of the description of this systematic review, in section 4.1. Indirect and direct evidence was combined and classical methods were compared with Bayesian models, which are based in a Mixed Treatment Comparison framework, explained in section 4.2. Additive and hierarchical models were also developed for the analysis of the networks drawn from the studies included in this analysis.

Two networks were defined: the first has 4 treatments in which cluster: $a)$ the Lifestyle interventions (Diet and Exercise), $b)$ the Pharmacological treatments (Antidiabetics, Antiobesity and Statins), $c)$ the combination of both and $d)$ control group. The second network, including 12 treatments, was built by splitting the previous network into more specific interventions. The selected trials were included, if the treatments remained connected, to at least one node of the network. The reduced network concentrates more studies in each node, providing more evidence to each treatment comparison. The network is extended, by splitting the nodes into others equivalent and more specific arm-groups; that are observed in the trials. The node representing Lifestyle interventions (in the reduced network), in which Diet and Exercise (represented in the extended network), are clustered. If there are not enough information collected, some trials could disconnect from the network. More evidence could be needed to connect, any particular study, with the single matching treatment that is already represented in

the network. Details about the networking process is presented in section 4.2.1 and Figures 4.4 and 4.5 show the diagram of the two networks developed in this chapter.

The risk of healthy individuals of developing MetS or developing T2DM, CVD or have any mortality event are integrated in Chapter 6; where the decision model is developed and interventions are going to be evaluated with comprehensive evidence of the MetS context. The increased risk of individuals with MetS of developing T2DM, CVD or overall mortality sets a high importance on its resolution; these risks are calculated and discussed in Chapter 5, where results of a systematic cohort review are presented. The results produced for this analysis will feed the evidence of resolution of the syndrome and determine the basis for further links with T2DM and CVD. Figure 4.1 illustrates the part of the model where this chapter fits in. The red arrow indicates the transition of the model, where this analysis is going to provide evidence synthesis. All the blue arrows represent other transitions of the model requiring to be filled with correspondent evidence. The reason to start the analysis in the transition from MetS to Healthy is because: a, the comprehensive model will start the simulation in that state for the evaluation stated for this thesis; and b, if there is a significant possibility to reverse MetS added to a demonstrated risk of developing T2DM and/or CVD, then there could be greater probabilities to have an impact in the risk of developing T2DM and CVD. A prevention strategy could be based on the identified intervention, and it could be customized according to the evidence obtained in this analysis.

This chapter will describe the assessment of available treatments for MetS to calculate probabilities of reversing MetS diagnostics under different types of interventions (lifestyle, pharmacological or both). Section 4.1 presents details of the systematic re-

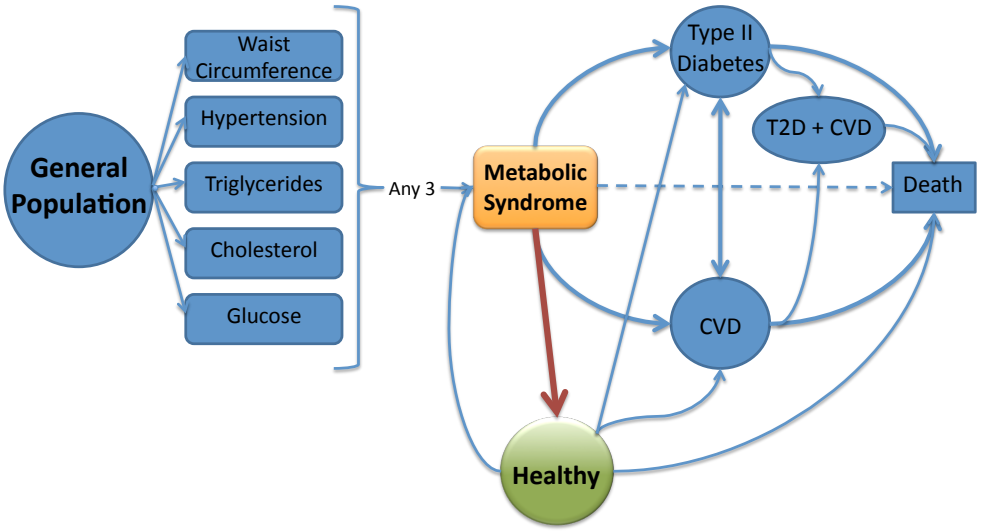


Figure 4.1: *Mixed Treatment Comparison analysis in the Model diagram.*

view that provided the data needed for the Mixed Treatment Comparison. Section 4.2 describes the statistical methods to perform this specific analysis. The analysis will be divided in two parts: section 4.3 and section 4.4, corresponding to a proposal of a Reduced network and an Extended network of analysis. Results from the analysis will be discussed in section 4.5. A summary of the chapter is presented in 4.6.

4.1 Systematic Review Details

This systematic review is the start of the comprehensive analysis stated for this thesis. Chapter 2 described the main problem, as a decision analysis evaluating MetS criteria (Section 2.5) and discussion about potential interventions based in MetS and its possible impact as a prevention strategy to prevent T2DM and/or CVD was started in Section 2.4. The evidence collected for the main model will be assemble in Chapter 6. The epidemiological situation related with MetS was introduced in Section 2.3; this analysis starts with a known risk associated with MetS and higher probabilities of developing T2DM and CVD (Ford [2005]; Gami et al. [2007]; Li et al. [2008]). An update of these estimations calculated by these authors is going to be presented in Chapter 5.

Therefore, there is the need of assessing potential interventions introduced in Section 2.4. This chapter develops a systematic review to obtain evidence about the possible reversal of a MetS diagnosis (representing the transition from MetS to Healthy states in the main model), appraising different interventions with effectiveness evidence available (from RCTs). This analysis will provide options for the model to be evaluated, depending on the variety of interventions.

4.1.1 Background

The aim of the review is to identify, which of the stated interventions is more effective in reversing a diagnosis of MetS. Given the diversity of the interventions, the analysis represents a methodological challenge, showing the need of combining the evidence available and taking into account this variability. Combination of this evidence will provide support in identifying the best strategy for the prevention of T2DM and CVD.

The importance given to MetS criteria have the particular interest of understanding its prognostic significance, as there is a rising pattern on the prevalence of MetS. The prevention of T2DM and CVD highlights the need of developing strategies, and MetS criteria is aimed to be easy to use in clinical setting. Lifestyle (diet and exercise) are currently recommended as the initial management approach for people with MetS, with the addition of pharmacotherapy if lifestyle alone is ineffective and/or individuals are at high CVD risk (Alhyas et al. [2011]; Grundy et al. [2005]).

However, the optimal way to achieve lifestyle changes is unclear. Similarly, whilst several pharmacological agents including lipid lowering, anti-diabetic, and anti-obesity drugs have the potential to provide incremental benefit, their clinical and cost effectiveness in MetS is undecided.

Several RCTs of interventions (lifestyle and/or pharmacological) aimed at the primary prevention of CVD and/or T2DM have been conducted but no systematic review of the evidence has until now been published. The outcome evaluated is determined by the reversal of MetS; therefore data can be extracted from trials under the context of T2DM and CVD prevention, as there are no RCTs addressing this specific use of the

concept of MetS, yet published. Therefore data has to be derived from epidemiological studies.

4.1.2 Interventions

There were 12 different interventions (Control, Diet, Exercise, Lifestyle with supervised exercise/exercise advice, Antiobesity, Antidiabetics, Antiobesity plus Lifestyle, Antidiabetics plus Lifestyle, Statins, Fenofibrate and Statins plus Fenofibrate) identified. Evidence available for all of the evaluated interventions comes from 13 different RCTs (1. Anderssen et al. [2007], 2. Azadbakht et al. [2005], 3. Esposito et al. [2004], 4. Stewart et al. [2005], 5. Clearfield et al. [2005], 6. Villareal et al. [2006], 7. Orchard et al. [2005], 8. Ramachandran et al. [2007], 9. Esposito et al. [2006], 10. Phelan et al. [2007], 11. Van Gaal et al. [2005], 12. Geluk et al. [2005] and 13. Athyros et al. [2005]).

There are four categories of interventions defined for the analysis. It is important to discuss about each type of intervention to explore the variability within each group of treatments and take it into account with respect to the complexity of the models, which will be developed in Chapter 6. **Table 4.1** presents the list of studies included, the categorization for each treatment in each study, the number of reversed and not reversed cases, the sample size for each treatment and period of follow-up. The sample size considered for the calculation of the correspondent proportions (at baseline and resolved MetS) defining the outcome, were based only on individuals with MetS. **Table 4.1** present the number of individuals with MetS after the intervention and the number of individuals that could resolve their MetS diagnosis, by each study-treatment. The table summarizes study characteristics of included trials (proportions add horizontally).

Table 4.1. **Study details of all the trials included in the analysis and description of each intervention group.**

#	Trial	Year	Def'n	Intervention Group		Sample size	Metabolic Syndrome				Follow-up Period
							Present		Resolved		
							#	%	#	%	
1	Anderssen	2007	IDF	Diet	Individulised diet	34	22	64.7%	12	35.3%	1 year
				Exercise	Supervised Exercise	34	26	76.5%	8	23.5%	1 year
				Lifestyle	Diet + Exercise	43	14	32.6%	29	67.4%	1 year
				Control	No intervention	26	23	88.5%	3	11.5%	1 year
2	Azadbakht	2005	NCEP	Dash Diet	Individualised diet	38	24.7	65.0%	5	35.0%	6 mths
				Diet	Individualised diet	38	30.8	81.0%	3	19.0%	6 mths
3	Esposito	2004	NCEP	Diet	Individualised Diet + guidance physical activity	90	30	33.3%	60	66.7%	2 years
				Control	Lifestyle advice	90	72	80.0%	18	20.0%	2 years
4	Stewart	2005	NCEP	Exercise	Supervised Exercise + guidance on diet	22	13	59.1%	9	40.9%	26 weeks
				Control	Lifestyle advice	22	14	63.6%	8	36.4%	26 weeks
5	Bo	2007	NCEP	Lifestyle	Individualised diet + Exercise Advice	119	50	42.0%	69	58.0%	1 year
				Control	Unstructured advice	120	92	76.7%	28	23.3%	1 year
6	Villareal	2006	NCEP	Lifestyle	Individualised diet + Supervised Exercise	15	5	33.3%	10	66.7%	26 weeks
				Control	No intervention	9	9	100.0%	0	0.0%	26 weeks
7	Orchard	2005	NCEP	Antidiabetic	Metformin + standard lifestyle	570	439	77.0%	131	23.0%	3 years
				Lifestyle	Individualised diet + Exercise Advice	549	340	61.9%	209	38.1%	3 years
				Control + Lifestyle	Placebo + Lifestyle advice	592	485	81.9%	107	18.1%	3 years
8	Ramachandran	2006	WHO	Lifestyle	Individualised diet + Exercise Advice	58	36	62.1%	22	37.9%	3 yrs/median 30 mths
				Antidiabetic	Metformin	57	32	56.1%	25	43.9%	3 yrs/median 30 mths
				Antidiabetic + Lifestyle	Metformin + Lifestyle	56	43	76.8%	13	23.2%	3 yrs/median 30 mths
				Control	Standard advice	62	49	79.0%	13	21.0%	3 yrs/median 30 mths
9	Esposito	2006	NCEP	Antidiabetic	Rosiglitazone	50	30	60.0%	20	40.0%	1 year
				Control	Placebo + Diet advice	50	45	90.0%	5	10.0%	1 year
10	Phelan	2007	NCEP	Antiobesity	Sibutramine	19	12	63.2%	7	36.8%	1 year
				Lifestyle	Individualised diet + Exercise Advice	18	5	27.8%	13	72.2%	1 year
				Antiobesity + Lifestyle	Sibutramine + Lifestyle	21	8	38.1%	13	61.9%	1 year
				Antiobesity + Brief Lifestyle	Sibutramine + Brief lifestyle	20	17	85.0%	3	15.0%	1 year
11	Van Gaal	2005	NCEP	Antiobesity	Rimonabant 20mg	228	84	36.8%	144	63.2%	2 years
				Antiobesity (diferent dose)	Rimonabant 5mg	228	123	53.9%	105	46.1%	2 years
				Control	Placebo	108	60	55.6%	48	44.4%	2 years
12	Geluk	2005	NCEP	Statin	Pravastatin	114	68	59.6%	46	40.4%	4 years
				Control	Placebo	114	67	58.8%	47	41.2%	4 years
13	Athyros	2005	NCEP	Statin	Atorvastatin	100	25	25.0%	75	75.0%	12 mths
				Fenofibrate	Fenofibrate	100	24	24.0%	76	76.0%	12 mths
				Statin + Fenofibrate	Atorvastatin + Fenofibrate	100	23	23.0%	77	77.0%	12 mths

The incidence of MetS was the measure used to define the outcome of reversal of MetS. Studies using definition other than NCEP were included in the analysis, but is important to take into account as a source of variability in the meta-analysis. Studies identified are from 2004, before that year the concept of MetS was not used in a RCT. The concept has existed over 90 years by now, but its application in research is very recent.

The control group: was defined differently across the studies. There were only two trials where the control had no treatment and the individuals in the group were adviced not to change lifestyle. (Anderssen et al. [2007]; Villareal et al. [2006]). The rest of the studies gave at least some type of advice on lifestyle changes. Furthermore, there is the need of analysing the impact of the control interventions and the related heterogeneity added to this research. **Table 4.1** displays the intervention for the control group in each trial. The cases of MetS presented in these groups are going to be used for the adjustment for baseline risk, given heterogeneity of the placebo interventions applied across studies (section 4.3.2).

Lifestyle Interventions: were even more heterogeneous in nature than the control groups. The exercise interventions differ within trials and also the lifestyle combined intervention (diet plus exercise). Two trials used a supervised exercise intervention (where individuals were coached and directed for specific needs on exercise) and did not give any specific intervention for the control group (Anderssen et al. [2007]; Villareal et al. [2006]). The remaining studies just gave an advice on physical activity. A sensitivity analysis on the network of evidence was conducted to evaluate the impact of splitting the lifestyle category in two (Individualized diet plus supervised exercise compared with Individualized diet plus exercise advice). The selected extended net-

work considers both types of exercise interventions, as indirect evidence can be produced to compare them and provides explanations for heterogeneity between studies. The intervention using a supervised exercise is compared with lifestyle components and the therapy that only provides an exercise advice is used in studies assessing drug treatments.

Pharmacological Treatments: were also heterogeneous and contained a number of classes of pharmaceuticals. It was decided to consider three categories of drugs, Antidiabetics (Metformin and Rosiglitazone), Antiobesity (Sibutramine and Rimonabant in two different doses 20mg and 5 mg) and Statins (Pravastatin, Atorvastatin and Fenofibrate) (Athyros et al. [2005]; Esposito et al. [2006]; Geluk et al. [2005]; Orchard et al. [2005]; Phelan et al. [2007]; Ramachandran et al. [2007]; Van Gaal et al. [2005]).

Combined Interventions: Two trials used a combination of both lifestyle interventions and pharmacological treatments (Phelan et al. [2007]; Ramachandran et al. [2007]). Ramachandran used Metformin and Phelan used Sibutramine. Both studies used individualized diet and exercise advice as lifestyle intervention.

This analysis is targeting MetS populations: adults with ages from 18 years old identified as having MetS according to a recognized definition. Therefore, all definitions of MetS are included in the systematic review and given the lack of evidence the analysis will be supported with the information being contributed by the trials using definitions different than NCEP. **Table 4.1** shows all trials considered for the analysis.

4.1.3 Search Strategy and Data Extraction

The trials included had a follow-up period of at least 24 weeks, outcomes of incidence of T2DM and/or CVD or reversal of MetS and compared lifestyle, pharmacological, or surgical interventions, with placebo, usual care or active control (drug intervention or lifestyle). Because the focus of the review was primary prevention, studies where more than 10% of the population had established CVD and/or T2DM were excluded. No language restrictions were applied but only studies published as full-length articles were included.

Data used was extracted mainly from 13 studies selected, after undertaking a specific search strategy to identify RCTs observing the effectiveness of interventions for the primary prevention of T2DM and/or CVD in people with MetS. A search strategy was defined for MEDLINE (1950 to Dec 2007), EMBASE (1980 to Dec 2007), CINAHL (1982 to Dec 2007), BNI (1985 to Dec 2007), The Cochrane Library (Issue 4, 2007), Science Citation Index (Web of Knowledge) (1980 to Dec 2007), and PubMed (2004 to Dec 2007). MeSH terms and keywords were combined with the CRD/Cochrane Highly Sensitive Search Strategy RCT filter (Higgins et al. [2008]) and tailored to individual bibliographic databases. Search results were obtained from a strategy ran in December 2007. Updates to this review should be undertaken, as new important research has been published; but in terms of the aim of this thesis, updates to the data collected could be implemented in the model and evaluate expand the understanding of the behavior of MetS criteria.

Abstracts and titles were independently assessed by 2 reviewers and potentially relevant articles retrieved and compared independently against the inclusion criteria with

differences resolved through discussion and referral with a third reviewer where necessary. Foreign language papers were translated sufficiently to ascertain compliance with the inclusion criteria with full translation if necessary. Where studies met all the inclusion criteria but data were incomplete, authors were contacted for additional data and/or clarification. Papers were subsequently excluded if no reply was received. Experts in the field of MetS and first authors of included papers were contacted in an attempt to identify further papers not identified through electronic searching, and the reference lists of included papers and relevant reviews were also scanned.

The quality of selected studies was assessed by using a scoring system based on the Delphi list (Verhagen et al. [1998]) (recommended by the Centre for Reviews and Dissemination (CRD) (Khan et al. [2001]) and was chosen in preference to Jadad score (Jadad et al. [1996]) due to its inclusion of allocation concealment as well as several other key indicators known to influence the internal validity of trials. One mark was awarded for each criterion met giving a total possible nine marks. Half a mark was awarded where baseline characteristics of intervention and control groups were analysed and included some but not all of the following: age, sex, weight/BMI and all components of the metabolic syndrome (NCEP/IDF definitions). Half a mark was also awarded to studies with both lifestyle and pharmacological intervention groups which were only able to blind subjects randomised to pharmacological treatment or placebo. Claims by authors to have analysed results on an intention-to-treat (ITT) basis were verified with reference to primary data. Where a trial was reported to be randomised but the method used was not described, no mark was given.

Data were extracted independently by 2 reviewers using a form designed specifically for this review (with reference to the Cochrane handbook (Higgins et al. [2008]) and

CONSORT guidelines (Moher et al. [2001]) and were checked for consistency prior to analysis of results. All papers relating to a particular study were retrieved including those on design and methodology (if reported separately) and original trial results in the case of sub-group analyses. Data reported in the narrative of each paper were checked with that presented in tables where applicable. Where minor inconsistencies were evident (affecting one paper only (Anderssen et al. [2007]; Esposito et al. [2004])), data were extracted from tables as this was considered to be more likely to be accurate.

The challenge presented for the methodological issues, given the sources of the data, is going to be addressed with a strategic analysis based on networks of evidence (Salanti et al. [2008]). While, Chapter 3 introduced core concepts related to the systematic reviews in section 3.3.1 and Bayesian methods in Section 3.2, this analysis requires the specification of a Mixed Treatment Comparison model introduced in Section 4.2. Results are presented by network in Sections 4.3 and 4.4. Additive models are also going to be compared using the two networks proposed (Reduced section 4.3.3 and Extended in section 4.4.1). Hierarchical models are included in the analysis of the extended network in section 4.4.2. Heterogeneity will be explored with covariates in a meta-regression model using follow up length and quality of studies, as variables. Baseline risk is also included in the analysis for heterogeneity in section 4.3.2. Section 4.5 presents the discussion outlined.

The 13 studies identified did not evaluate all the treatments of interest. This situation represents a methodological challenge, given the need of assessing all available treatments for the reversal of MetS. Therefore, Mixed Treatment Comparison methods becomes crucial for this analysis.

4.2 Mixed Treatment Comparison Methods

Healthcare decision making process becomes more complex when different treatment options are available. Therefore, there is a need to use methodologies combining all evidence to provide an improved strategy for these type of decisions. Problems arise with the lack of RCTs analyzing direct pairwise comparisons with all available interventions, specially with increased number of treatments. Other issues take place, if direct evidence is inconclusive, but indirect or combined evidence can reach a clearer conclusion (Caldwell et al. [2005]). Bayesian Mixed Treatment Comparison (MTC) methods give a clear solution combining direct evidence and indirect evidence, providing a more efficient way of analyzing the evidence.

In addition, classical methods can be useful, but they present different problems discussed in this section, as a comparison between both methodologies was performed to address the limitations of the data available on the different interventions for the reversal of MetS and the different issues identifying the best treatment.

Firstly, it becomes important to present the concept of network of evidence, clarifying direct evidence between pairwise comparisons. Then, both methodologies (Classical and Bayesian) are introduced in the following subsections. Results are presented by network designed in sections 4.3 and 4.4, after description of MTC methods.

4.2.1 Network of Evidence

The number of interventions available for the reversal of MetS presents a challenge for the analysis of the data. RCTs have been performed for different intervention options,

but the number of trials is almost similar to the number of treatments to evaluate. This indicates high sparsity of the studies and therefore, the need for designing a network of interventions to set an analysis including all of them. Analyzing the data using this methodology gives an efficient utilization of all the available evidence and overcomes to the limitations presented by the sparsity.

Therefore, two networks were drawn. One that integrates similar interventions, like different diets and exercise interventions were combined in a Lifestyle intervention group, the different pharmaceutics were synthesized in a pharmacological intervention group and a third group with combined interventions together. This network aims to analyze the data more efficiently, by reducing sparsity and providing more evidence for each comparison of therapies. The second network is an expansion using all the different interventions constituting each node in the first network. Sparsity, in this case, is showing how heterogenous these interventions can be and represents the need for analysis of decision making related with MetS, as different therapies can be used. More research should be directed for the intervention that shows better performance, concentrating efforts for the prevention of complex diseases like T2DM or CVD.

The networks can be represented graphically as diagrams of all pairwise comparisons based on the studies available for the different treatment options. Figure 4.2 shows a network of evidence example, with three nodes representing available treatment options. Lines connecting nodes, represent evidence available for that particular comparison; which will constitute the direct evidence provided by the network. In this case, there is no direct estimate for the comparison between B and C nodes. Figure 4.3 shows the network of evidence with an indirect estimate for B and C comparison, drawn from the information of the direct evidence. Treatments must have at least one

link making them part of the network, otherwise the estimation of indirect evidence is not possible.

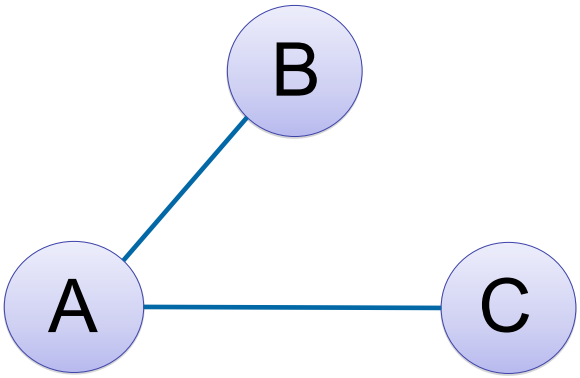


Figure 4.2: *Network of evidence example, with nodes A, B and C*

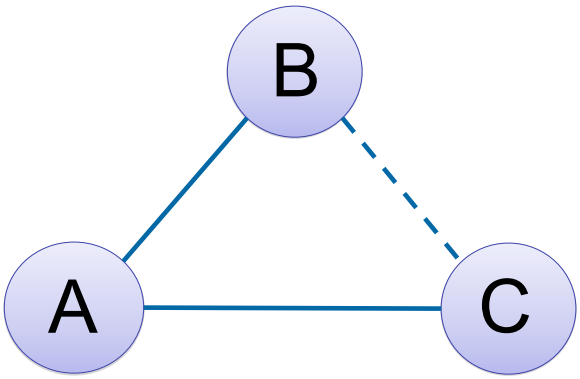


Figure 4.3: *Network of evidence showing an indirect estimate for unconnected nodes.*

Network analysis allows the combination of direct and indirect evidence, as all pair-wise comparisons may not be explored by any of the trials. Therefore, consistency becomes an important assumption for both types of estimates (Salanti et al. [2008]). According to Salanti, consistency and inconsistency models can be set. This thesis

adopted a consistency model, given the type of data and its needs of combination for the calculation of indirect evidence needed.

The principle of consistency allows the estimation using direct and indirect data. Combination of both types of evidence give a more efficient use of the data in a decision making framework. Assuming there are three treatments, A, B and C from Figures 4.2 and 4.3, the three possible pair-wise comparisons are AB, AC, and BC. Therefore, three unrelated estimates of the treatment effects $\hat{\mu}_{AB}$, $\hat{\mu}_{AC}$ and $\hat{\mu}_{BC}$, can be obtained out of three separate meta-analyses. If the three estimates are assumed to be consistent, a consistency model can be stated by the inter-relation of the three parameters in the following form:

$$\mu_{BC} = \mu_{AC} - \mu_{AB} \tag{4.1}$$

Then, the parameter μ_{BC}, which is the effect of B relative to C, can be estimated using both direct BC data and indirect data on AC and AB, defining the principle of consistency (Salanti et al. [2008]).

Geometry & Asymmetry

Characteristics related with geometry and asymmetry can reveal interesting network dynamics. Geometry refers to the overall pattern of comparisons among different treatments whereas the asymmetry describes the extent to which specific comparison or treatment is more represented in the network than others (Salanti et al. [2008]). Exploring these properties can help to understand the context of the treatments and support the analysis.

Two different networks were designed. First, a reduced network clustering classes of interventions. This network consisted of 4 nodes (Control, Lifestyle, Pharmacological and Pharmacological plus Lifestyle) and was developed from 12 trials. One trial of fenofibrate was not connected to the rest of the network and so was not included (Athyros et al. [2005]). The network diagram is shown in Figure 4.4.

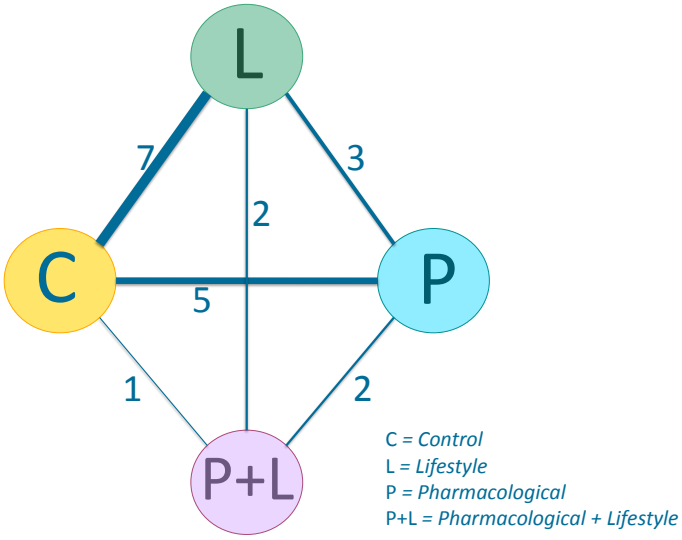


Figure 4.4: *Reduced Network.*

In addition, an extended network incorporate 11 treatments (Control, Diet, Exercise, Lifestyle with supervised exercise/exercise advice, Antiobesity, Antidiabetics, Antiobesity plus Lifestyle, Antidiabetics plus Lifestyle, Statins, Fenofibrate and Statins plus Fenofibrate) was built from 13 trials. Figure 4.5 shows the diagram of the network.

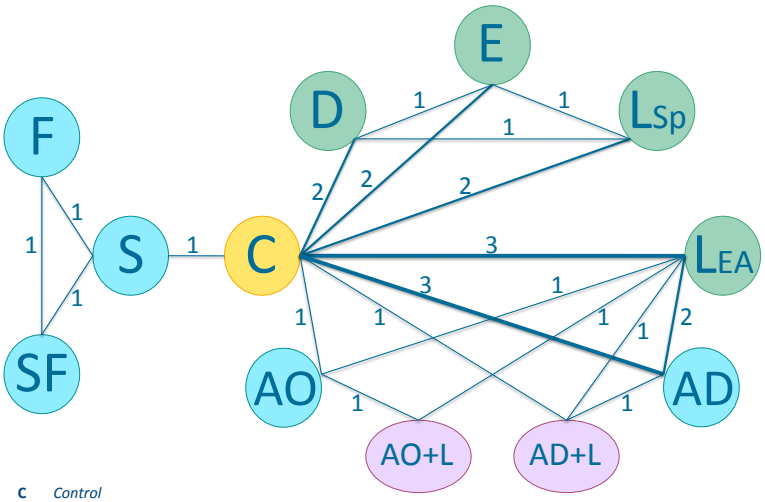


Figure 4.5: *Extended Network*

4.2.2 Classical Approach

Classical methods can be used to combine evidence. Since classical methods are not part of the main methodological aim of this thesis, they were not explained in Chapter 3, therefore an introduction is presented in this section. Nevertheless, there are some limitations, which are discussed later. Indirect and direct evidence is going to be assessed in order to perform a combination of both types of evidence. When there is a network that has direct evidence as shown in Figure 4.2 for segments AB and AC, but there is a segment BC without direct evidence, producing a network not completely connected. Then, the segment BC can be estimated indirectly as shown in the diagram in Figure 4.3.

Indirect/Direct evidence

Direct pairwise comparisons using classical models were calculated when data was available, given the lack of direct evidence for some of the comparisons. Indirect estimates are possible to obtain, but it is necessary to ensure all sources of uncertainty and correlation as considered (Bucher et al. [1997]). Each of the estimates is surrounded in a specific context of variation. All sources of variation should be accounted for its interpretation. Stata was used to determine all the direct estimates, by performing each of the meta-analysis to combine direct evidence. Indirect estimates, then can be obtain by:

$$ln(OR_{Ind}) = ln(OR_{AB}) - ln(OR_{AC}) \tag{4.2}$$

$$V(lnOR_{Ind}) = V(lnOR_{AB}) + V(lnOR_{AC}) \tag{4.3}$$

where Ind =*Indirect estimate (BC)* & $V = Variance$. Assumption of consistency applies to this setting. Given the possibility to obtain an estimate, from the direct evidence, to provide information on the missing direct comparisons, the resulting value is a measure of the effect size for that particular comparison. The log odds ratio is frequently used in this framework. Equation 4.2 shows the estimate and its variance in Equation 4.3.

Combination of evidence

The combination of indirect and direct evidence is possible with classical methods (Bucher et al. [1997]). There is the need for both types of estimates to be consistent. In classical methods, as the number of indirect estimates increases the combination becomes complex in order to decide which estimate to use. An example of this situation will be presented for the extended network and multiplicity of options for the treatment combinations.

4.2.3 Bayesian Approach

Bayesian Mixed Treatment Comparison (MTC) methods (Caldwell et al. [2005]; Lu and Ades [2004]) were used to assess the effectiveness of interventions for the reversal of MetS. The MTC approach provides estimates for all the possible pairwise comparisons if the treatments are connected by a network, combining the direct evidence available and the indirect evidence from all the comparisons.

The key assumption is that indirect comparisons are the same as those which would be obtained if a head to head comparison had been performed. For fixed effects analysis, assumes that the relative effect of one treatment compared with another is the same across all the trials. For random effects models it is assumed that the common distribution is the same across all trials.

Bayesian meta-analysis was introduced in section 3.3.3, and MTC is a particular case of meta-analysis. It is possible to define r as the reversal in the i study in the j intervention and has a Binomial distribution ($r_{ij} \sim Bin[\pi_{ij}, n_{ij}]$). Then, using a network of evidence specified in section 4.2.1 (Equation 4.1), the MTC model can be written as

follows:

$$\theta_{ij} = log\left(\frac{\pi_{ij}}{1-\pi_{ij}}\right) \tag{4.4}$$

$$\theta_{ij} \sim N[\mu_i + d_j - d_{b_i}, \tau^2] \tag{4.5}$$

Where θ_{ij} is a reparameterization of the likelihood specified above ($r_{ij} \sim Bin[\pi_{ij}, n_{ij}]$), therefore the logit of Equation 4.4 (logarithm of the odds) is defined with a normal distribution, as shown in Equation 4.5. τ is the common between study standard deviation, for a random effects model taking into account variability given by the differences of the studies. d_{b_i} is the baseline comparator for study *i* (corresponding to the specific treatment, to be use as the reference for a particular comparison), contrasting the treatment effect represented by the pooled effect size as d_j, which is the pooled logarithm of the Odds (LOD) for treatment *j*, $d_j = 0$ when $j = b_i$ and μ_i is the baseline effect for study *i*, representing the study-type effect. For fixed effects model it is assumed that $\tau = 0$.

The prior distributions used for the model were $\mu_i \sim N[0, 1000]$, $d_j \sim N[0, 1000]$, given no previous information on these estimates and let data to dominate the posterior distribution. For random effects models a prior for $\tau \sim Unif[0, 2]$ was specified, after a sensitivity analysis performed, the analysis is described in section 4.3.

The WinBUGS free software was used to implement all the Bayesian models. A burn-in of 10,000 simulations followed by a sample of 50,000 on which the posterior distribution was estimated. This run length and burn-in were defined to ensure convergence

of compiling models. Convergence was assessed by checking trace plots, the level of autocorrelation and running multiple chains with radically different starting values. Section 3.2.2 explained these concepts of MCMC.

The Deviance Information Criteria (DIC) is a tool used as a method for comparing fixed and random effects models. The DIC is a measure of the expected posterior loss when adopting a particular model. When comparing two Bayesian models, smallest DIC suggest a better fit of the model to the data observed. (Spiegelhalter et al. [2002]).

The absolute treatment effects were estimated and ranked the best treatment in each simulation. The percentage of the ranking across all simulations was used to obtain the probability of being the best treatment.

4.3 Reduced Network

The reversal of Metabolic Syndrome was expressed as an odds ratio (OR) in each particular pairwise comparison. **Table 4.2** presents the OR for each class of intervention (Control, Lifestyle, Pharmacological and Pharmacological plus Lifestyle). Posterior means of the odds ratios for the reduced network are presented in the up-right part of the table. The lower-left part shows the classical direct estimates. Fixed effects and random effects estimates are shown respectively in each box; the first box providing odds ratios is Lifestyle treatments compared with Control interventions, the Bayesian fixed effect estimate for the OR is 3.45 with a standard error of 0.35 and the Bayesian random effect estimate for this comparison is 4.90 with a standard error of 2.19. The diagonal box providing the classical estimates for the comparison (L vs C), shows a

fixed effect OR of 3.31 with a standard error of 0.05 and a random effect OR of 3.77 with a standard error of 0.10. There are 7 studies (n) contributing with evidence for this specific comparison. The letter shown in the box is the treatment showing an effect over the other type of intervention; in this case, Lifestyle is showing around three times more odds of reversing MetS than the Control intervention.

Table 4.2 Odds Ratios (OR) for Reduced Network
n=number of studies

Bayesian MTC [FE / RE]

	Control		**L**ifestyle		**P**harmacological		**P+L**	
C	**OR**	n	**3.45**		**1.56**		**1.75**	
	SE		0.35		0.16		0.52	
		OR		**4.90**		**1.99**		**2.86**
		SE		2.19		0.95		3.42
L	**3.31**	7	**OR**	n	**0.45**		**0.51**	
	0.05		SE		0.05		0.15	
		3.77		**OR**		**0.44**		**0.62**
	L	0.10		SE		0.23		0.62
P	**1.46**	5	**0.51**	3	**OR**	n	**1.13**	
	0.04		0.05		SE		0.33	
		1.68		**0.49**		**OR**		**1.54**
	P	0.09	*L*	0.20		SE		1.71
P+L	**1.13**	1	**0.52**	2	**1.11**	2	**OR**	n
	0.19		0.15		0.15		SE	
		1.14		**0.52**		**1.31**		**OR**
	P+L	0.44	*L*	0.15	*P*	0.55		SE

Classical Direct [FE / RE]

In both classical and Bayesian results, lifestyle interventions appear to be more effective in terms of the reversal of the MetS than the rest of the treatments; both Bayesian and Classical fixed effects (FE) models gave similar estimates of the OR which were both over 3 (3.45 95% CrI [2.81, 4.20] and 3.31 95% CI [2.67, 4.09], respectively). The

OR of these interventions compared to pharmacological treatments was 2.22 (Bayesian random effects). Shown in **Table 4.2** with the inverse scale: $1/0.45 = 2.22$. The estimates for the combined intervention were not significant, as there is only one study with direct evidence there is no possibility to conclude for this type of treatments. The uncertainty was clearly higher for the Bayesian models as indirect evidence is included in the estimates.

These issues are shown in the Figure 4.6 where the intervals for direct evidence are smaller and it illustrates the evidence of heterogeneity between the trials. These ORs are in the inverse scale, because of the visual standardization needed, given the level of heterogeneity estimates this form is easier to compare across all studies and different interventions. Estimates close to values of 1 are showing no treatment effect. Forest plots are comparing interventions with control groups. Studies analyzed in lifestyle interventions had one arm-group with one of these type of interventions; and if the study presented another intervention for pharmacological or for the combined therapy, it was included for the correspondent meta-analysis.

Evidence for Lifestyle interventions shows high variability and is reflected on the I^2 with a value of 70%. Pharmacological interventions were more consistent showing a I^2 of 66%, but also concentrating important variability. Bayesian estimates provide a wider credible interval than classical methods, as it is taking into account that variability.

In the Bayesian fixed effects model, the ranking of the treatments gave a probability of 0.99 of lifestyle interventions of being the best treatment; for the Bayesian random effects (RE) model, the probability was 0.85. All the other treatments had very low probabilities in both models, only the probability for the combine intervention (P+L)

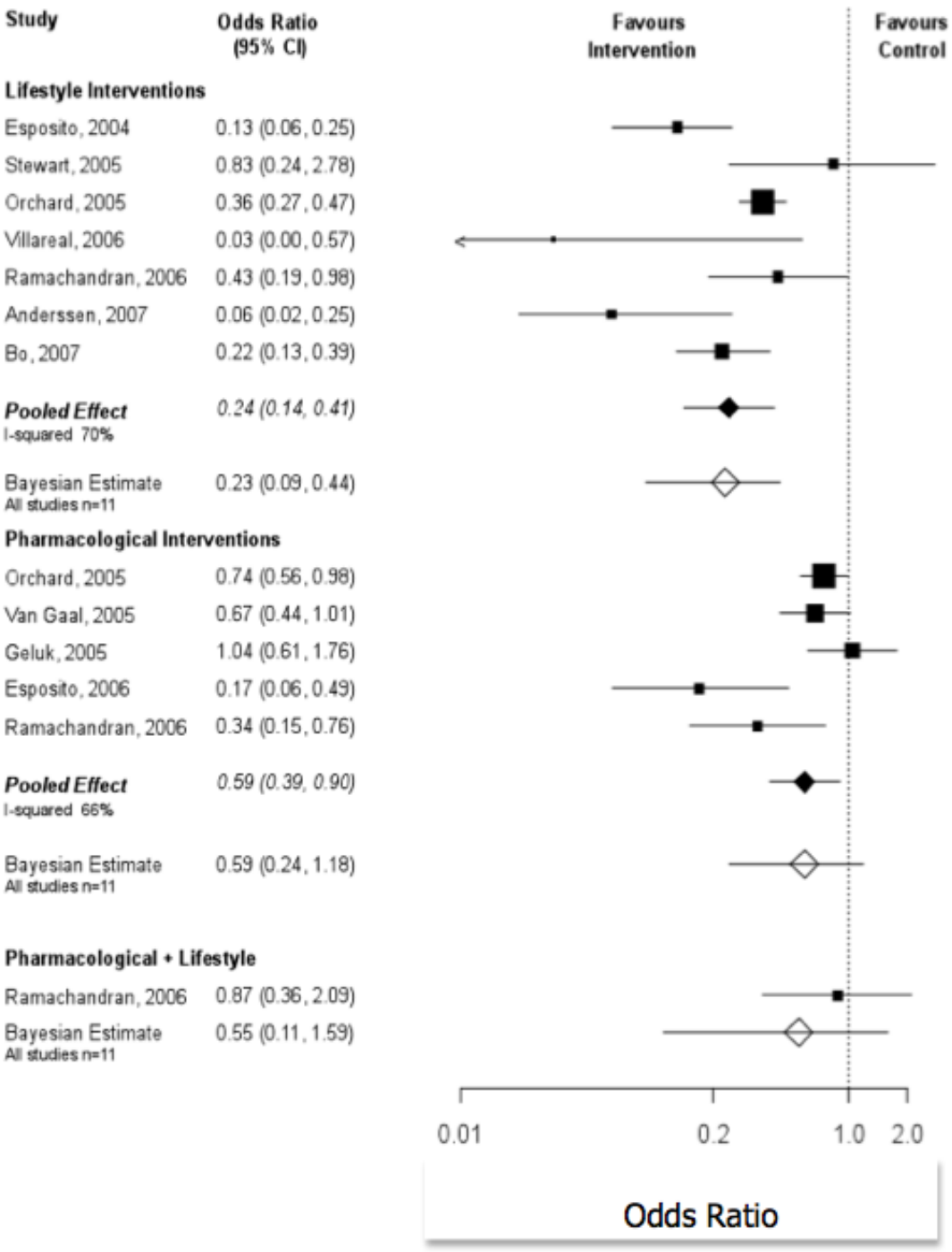


Figure 4.6: *Forest Plot: Interventions vs Control*

was 0.12 in the Bayesian random effects model; reflecting the lack of evidence stated. This situation with the combined intervention could be an interaction implicit by the psychological effect of this addition of therapies; where people performed an unknown disorganized pattern reducing the possible added effect of the combination. This issue should be address with the production of more evidence related with these type of interventions.

Table 4.3: Indirect Estimates

Estimate	Comparison	LOR	OR	VAR	SE
CL	CP-LP	0.456	1.578	0.050	0.225
	CPL-LPL	0.336	1.399	0.221	0.470
CP	CL-LP	1.619	5.049	0.053	0.230
	CPL-PPL	0.103	1.108	0.054	0.710
CPL	CL-LPL	1.607	4.989	0.035	0.187
	CP-PPL	0.211	1.235	0.315	0.561
LP	CL-CP	1.163	3.200	0.019	0.139
	LPL- PPL	-0.233	0.792	0.331	0.575
LPL	CL-CPL	1.271	3.566	0.208	0.456
	LP-PPL	-0.245	0.783	0.349	0.590
PPL	CP-CPL	0.108	1.114	0.206	0.453
	LP-LPL	-0.012	0.988	0.066	0.257

Note: C = Control, L = Lifestyle, P= Pharmacological,
LOR = Log Odds Ratio, OR = Odds Ratio,
VAR = Variance, SE = Standard Error

Tables 4.3 and **4.4** present the estimates calculated with the classical method. **Table 4.3** shows the indirect estimates obtained by the contrast of comparisons available for the calculation of indirect estimates for each possible comparison. The indirect estimates that were pooled from the comparisons available for each treatment comparison; and combined estimates of this evidence with the direct effect estimations are presented in **Table 4.4**. Results from classical and Bayesian models gave similar results, giving

Table 4.4
Odds Ratios for Classical Models

Combined Evidence

	Control	**L**ifestyle	**P**harmacological	**P+L**
C	**OR**	**2.24**	**2.23**	**4.16**
	SE	0.07	0.06	0.08
L	**1.54**	**OR**	**2.66**	**1.23**
	0.08	SE	0.05	0.11
P	**4.37**	**2.96**	**OR**	**1.01**
	0.09	0.05	SE	0.09
P+L	**4.34**	**2.02**	**1.02**	**OR**
	0.07	0.15	0.09	SE

Indirect Evidence

validity to the results. However, Bayesian models make more efficient use of the evidence and calculate more realistic variability, by taking into account all the indirect evidence combined. Multiple comparisons can become a complex task when number of treatments increase and there is lack of direct evidence for some comparisons. This situation will be explored with the extended network in section 4.4.

The goodness of fit of the Bayesian model was evaluated by calculating the total residual deviance, which should be equal to the number of data points. The total residual deviance for the fixed effects model was 50.57 and for the random effects model was 28.98, against 26 data points. The DIC for the fixed effects model was 189.77 and for the random effects model was 167.19. Both results suggest that random effects models are fitting better.

The median for τ in the random effects model was 0.80 with a 95% credible interval of [0.39, 1.58]; this shows evidence of high heterogeneity. A sensitivity analysis (Spiegelhalter et al. [2004]) was undertaken to assess the impact of the prior distribution for the

between-study standard deviation, including use of half-normal and inverse gamma for the precision. Figure 4.7 shows the log odds ratio for each prior. All the priors produced similar results on the log odds ratio; therefore, a uniform [0,2] prior distribution was used for the between-study standard deviation in the random effects model. With these results there is the need of exploring consistency of the studies, which are explored in section 4.3.1 and adjustment for baseline risk and other covariates, in order to explain heterogeneity observed, will be describe in section 4.3.2. Then, an added value of intervention analysis is developed in section 4.3.3. Discussion of these results will be develop in Section 4.5, together with results from the extended network to be introduced in Section 4.4.

4.3.1 Consistency & Sensitivity analysis

It is important to consider the consistency of all the trials used to fit the MTC model. If some inconsistency is found, sensitivity analysis should be performed in order to measure the impact of inconsistent studies. Sensitivity analysis is performed to ensure quality of the assessment and consistency in the evaluation of the results with and without the studies or data points that appears to be inconsistent. The next section explains the measures used to assess consistency and their interpretation.

P-Values (Cross-validation & Mixed)

Firstly, it is necessary to introduce some definitions of the core terms used in this section. The deviance uses the likelihood function to provide a measure of the fit of

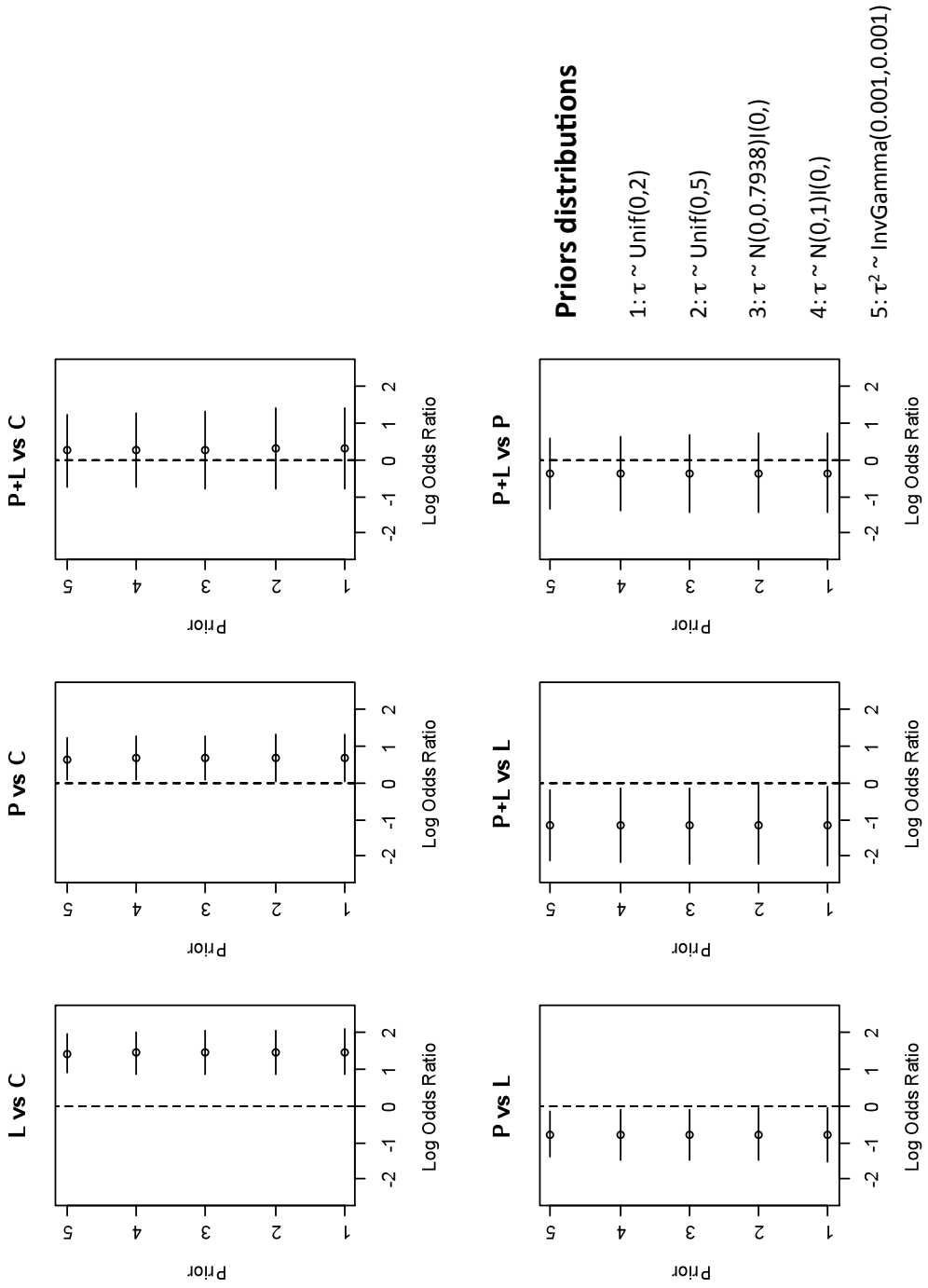


Figure 4.7: *Sensitivity Analysis for the Prior of τ*

the model to the data points and it can be calculated as follows:

$$Deviance = -2log(likelihood) \tag{4.6}$$

Therefore, if the likelihood is large the model fit closer and the deviance becomes smaller. The saturated model is a model with a parameter for every observation to fit the data accurately. Then, if the deviance for the saturated model is subtracted, the residual deviance can be obtained as presented in equation 4.7. The residual deviance is expected to be equal to the number of unconstrained data points.

$$D_{res} = -2(loglikelihood_{model} - loglikelihood_{sat}) \tag{4.7}$$

When inconsistencies are found with one or more studies, then sensitivity analysis is needed to evaluate the impact of these studies on the results (Lu and Ades [2006]). The principle of consistency mentioned in section 4.2.1 is evaluated with these methods. An inconsistency means the study arm is not providing coherent information to the rest of the studies, therefore it might not be adding consistent evidence due to particularities of the intervention in that specific study, like small sample size or intervention characteristics. It becomes important to explore the sources of the inconsistency as it can introduce bias. Methods such as cross-validation and mixed p-values can be calculated to examine more in depth the consistency.

Crossvalidation estimates a predictive distribution for omitted data points using remaining data. Mixed P-values are a predictive measure of the data points, but uses the full data set to approximate a cross-validation p-value. A mixed predictive model

checking based on the complete data. Running a single MCMC simulation and then resampling the output assumes to remove the influence of a single study effect, then the cross-validation is checked with a posterior predictive model based on the full data set, replicating the observation generated at each iteration from its conditional distribution $p(y_i^{rep}|\Theta_i, y)$ (Marshall and Spiegelhalter [2003]). Both predictions pretend to explore the probability of difference between the observed and predicted effects, where lower p-values indicate statistically significant inconsistency. These p-values are expected to correspond with the measures of deviance.

Results: Consistency diagnostics

Analysing the consistency of the data in the reduced network, one study was identified as an outlier (Villareal et al. [2006]). The consistency was assessed by calculating the deviances for each treatment reported in the RCTs and the residual deviance of the model with Equation 4.7. The deviance of the Villareal et al. [2006] study should be around 2 points, because it has two arms, but this trial obtained a value grater than 4 points. This result shows a deviance for a 4-arm trial, making the inconsistency evident. The number of unconstrained data points is equal to the number of arms of a study, as previously defined.

Figure 4.8 shows the deviances for each study, where the blue diamonds represent the studies with two arms and should be around the first line (accumulating a value of approximate 2 in their deviance); the red squares represent the studies with three arms and should be around the level of the second line (accumulating a value of approximate 3 in their deviance); the green triangle represent the study with four arms and should be around the fourth line accumulating a value of approximate 4 in its deviance.

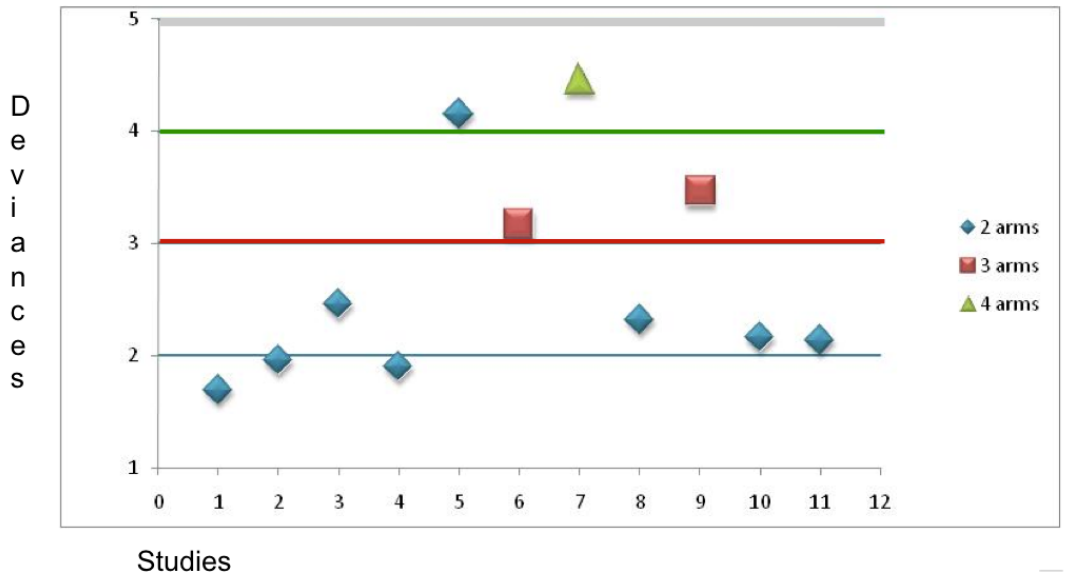


Figure 4.8: *Deviances by study*

Therefore, one of the blue diamonds reaches the fourth line, classifying it as an outlier. The sensitivity analysis conducted to evaluate the impact of taking this study out of the analysis showed no significant difference for the estimates. **Table 4.5** shows the odds ratios of the model without the Villareal et al. [2006] study and are very similar to the results presented previously in Table 4.2.

To explore more in depth the observed inconsistency with this study, mixed-p values and cross validation was calculated to support the analysis. The lowest mixed p-values were approximately 0.17 in three trials (Esposito et al. [2004]; Ramachandran et al. [2007]; Villareal et al. [2006]). There was no evidence of significant difference between the observed and the predicted estimates. This result means there is very low probability that there are differences between the observed and the predicted effects, therefore the inconsistency found with is not statistically significant. However, cross-validation values were obtained for the Villareal et al. [2006] study (p = 0.08) and for

Table 4.5
Odds Ratios for Reduced Network without
Villareal et al. [2006]

Bayesian MTC [FE / RE]

	C		L		P		P+L	
C	**OR**	n	**3.36**		**1.54**		**1.72**	
	SE		0.34		0.15		0.51	
		OR		**4.14**		**1.86**		**2.51**
		SE		1.56		0.73		2.13
L	**3.34**	7	**OR**	n	**0.46**		**0.51**	
	0.05		SE		0.05		0.15	
		3.89		**OR**		**0.48**		**0.64**
	L	0.11		SE		0.22		0.50
P	**1.46**	5	**0.51**	3	**OR**	n	**1.11**	
	0.04		0.05		SE		0.32	
		1.68		**0.49**		**OR**		**1.42**
	P	0.09	*L*	0.20		SE		1.20
P+L	**1.13**	1	**0.52**	2	**1.11**	2	**OR**	n
	0.19		0.15		0.15		SE	
		1.13		**0.52**		**1.31**		**OR**
	P+L	0.19	*L*	0.15	*P*	0.54		SE

Classical Direct [FE / RE]

the Esposito et al. [2006] study (p = 0.09), which were the trials with just 2 arms, making its computation less complex than the others. These values are over 0.05, providing non significant results for inconsistencies observed. Esposito et al. [2006] was calculated an even higher crossvalidation value, but this study did not show inconsistent deviance in Figure 4.8. The Villareal et al. [2006] study could be giving this particular outcome, because of random error related with the small sample size used for the trial. An additional factor that can be influencing this result is the intervention design, as it was the study that did not provide a particular session for the control group similar to other studies.

After this complete analysis of the consistency across data available for this combination of evidence, there were no statistical significant values associated with inconsistencies observed. However, heterogeneity represents an issue inside this context of health care evaluation, next section is going to explain results obtained while exploring the observed heterogeneity.

4.3.2 Explaining Heterogeneity

Given the inherent variability between studies it is necessary to investigate in detail different possible explanations of heterogeneity of the developed models (Higgins and Thompson [2002]; Thompson [1994]). This section gives a closer view inside variables that can be generating this variability. Models used for this analysis were Bayesian random effects models, as heterogeneity is intended to be explained. Variables related with quality of the studies and follow up were collected to evaluate the heterogeneity in a meta-regression, fitting those variables as covariates. In order to explain heterogeneity related with the underlying risk of reversing a diagnosis of MetS, the evidence is based on the control interventions defined in each randomized control trial included.

Baseline risk and other covariates

As presented in Chapter 3 (Methods) in section 3.3.4, meta-analysis methods can be extended to include study level covariates as part of the analysis in order to explain between-study heterogeneity of treatment effects. General covariates such as length of follow-up and quality of studies can be included in the MTC model, which can be

denoted by:

$$\theta_{ij} \sim N[\mu_i + d_j - d_{b_i} + \beta X_{ij}, \tau^2] \tag{4.8}$$

Where μ_i is the baseline effect of study i, $d_j - d_{b_i}$ represents the MTC estimates previously defined in equation 4.5, β is the covariate coefficient and represents the adjustment effect of X_{ij}, which is the data collected for the observed covariate. Length of follow up, quality of studies and baseline risk are possible covariates to evaluate in this model. The analysis can be complemented with three different covariate models. One, assuming all interactions between types of interventions are identical; this model uses common βs for the classes of interventions defined (Lifestyle, Pharmacological and combination of both), assuming that the influence of the covariate will be the same for each treatment effect. Second, assuming interactions are different and unrelated, therefore the effects of the three types of interventions are assumed independent and a β is estimated for each treatment effect, as shown in Equation 4.9. A third model, assumes interactions are different but exchangeable.

$$\theta_{ij} \sim N[\mu_i + d_j - d_{b_i} + (\beta_{ij} - \beta_i)X_{ij}, \tau^2] \tag{4.9}$$

One important variable to explore in terms of heterogeneity is baseline risk among trials; it can reflect differences in patient characteristics (e.g. age, medical history, co-morbidities, etc) that may produce different treatment effects across studies. Baseline risk is defined as, the risk of outcome event for a patient under the control condition and indicates average risk of patient in a particular study, if they were not treated. It is usually considered in terms of the log odds of an event in the control arm of each study.

Underlying risk of study population can modify the treatment/intervention effect in a determined trial. The MTC model presented in Equation 4.5 can be also extended to include baseline risk. When $X_{ij} = \mu_i$, the model becomes a MTC analysis adjusting for baseline risk, denoting the following:

$$\theta_{ij} \sim N[\mu_i + d_j - d_{b_i} + \beta(\mu_i - \bar{\mu_i}), \tau^2] \tag{4.10}$$

$$\theta_{ij} \sim N[\mu_i + d_j - d_{b_i} + (\beta_{ij} - \beta_i)\mu_i, \tau^2] \tag{4.11}$$

where μ_i is the baseline effect of study i and substitutes the X_i values to adjust evidence by the effect at baseline. Equation 4.11 denotes a model with separate effects (β) on the baseline risk, providing a coefficient for each of the interventions. Exchangeable models can also be developed to evaluate the correlations involve in the interventions.

Results: Heterogeneity diagnostics

Adding length of follow-up as a covariate to the model, gave a β of -0.004 (95% CrI [-0.0135, 0.0048]). Comparing the DIC of this model (167.228) with the DIC of the original model (167.195), showing negligible difference. The total residual deviance was 28.75, also presenting very low variation (the original model had 28.94 and the number of data points was 26). The results for the analysis of the quality as a covariate calculated a β = 0.04 95% CrI [-0.266, 0.386]) were similar, with a DIC of 167.022 and a total residual deviance of 28.43. This situation means that the length of follow-

up and the quality of the studies are unlikely to have any answer for the heterogeneity observed, since the DIC and the residual deviance, showed that the models including both covariates considered for this analysis, have no better goodness of fit compared with the original model.

To explore the baseline risk, specific models were constructed. Modifications to the data were required in order to be able to undertake the analysis. As there was a study without a defined control group Phelan et al. [2007], making the comparison with the rest of the trials more complex, it was excluded from this analysis. Phelan et al. [2007] and Ramachandran et al. [2007] studies were the trials with a combined intervention; so when Phelan et al. [2007] was excluded, this made Ramachandran et al. [2007] the study characterized by the inclusion of a fourth arm with this type of treatment, therefore the fourth arm of this trial was excluded. This changes reduced the analysis data set, producing a need of developing a comparator model without baseline risk using this specific data set.

The inherent heterogeneity on the control group, makes the analysis of baseline risk more complex, as it is difficult to define a common baseline risk across all the studies. In order to explain the heterogeneity related with the underlying risk of each study, a MTC model fitted with a covariable is developed. The underlying risk is based on data from the control interventions defined in the randomized control trials included. As there was a study without a defined control group (Phelan et al. [2007]) and the fourth arm of Ramachandran et al. [2007] were removed from the analysis, given that the last one was the only study with four arms in the experimental design after taking out the previous study. Adjusting the MTC analysis for baseline risk (restricted to the 10 studies which used a common control group), but assuming a common effect for

all interventions, appeared to produce a more parsimonious model. A change in the DIC of 3.797 and residual deviance of 21.53 points from the common effect model, compared to 25.31 points from the comparator model (against a total of 22 data points). The model estimated a negative effect of baseline risk on the logarithm of the odds ratio scale (-1.04, 95% CrI -1.29, -0.71), indicating that as the baseline risk of reversal increases, the effectiveness of the interventions reduces. In terms of effect on the OR, a 1% increase in the baseline probability of reversal reduces the OR for the interventions (lifestyle, pharmacological and both) by 12%. To interpret this result a transformation of the β coefficient is required.

$$e^{\mu} = \left(\frac{p}{1-p}\right) \tag{4.12}$$

$$\mu = log\left(\frac{p}{1-p}\right) \tag{4.13}$$

$$p = \left(\frac{e^{\mu}}{1+e^{\mu}}\right) \tag{4.14}$$

Providing a baseline probability of 8% (p=0.08580) of reversing MetS. This probability will be estimating all interventions as the model estimates a common coefficient. If a 1% is increased in the baseline probability the effect in the odds ratio for the interventions will be approximately

$$e^{\beta \times c} \tag{4.15}$$

$$c = \mu^* - \mu \tag{4.16}$$

$$\mu^* = log\left(\frac{p + 0.01}{1 - p + 0.01}\right) \tag{4.17}$$

The value of μ is obtained when the logit is applied to the probability:

$$log\left(\frac{0.08580}{1 - 0.08580}\right) = -2.366905 \tag{4.18}$$

Then adding 0.01 to the baseline probability, a value of μ^* for an increase of 1% can be obtained:

$$log\left(\frac{0.09580}{1 - 0.09580}\right) = -2.244788 \tag{4.19}$$

Therefore the effect in the odds ratio can be calculated:

$$e^{-1.04(-2.244788+2.36595)} = 0.8816074 \tag{4.20}$$

The reduction of the odds ratio is observed by obtaining the inverse of the previous result.

$$\begin{aligned} 1 - 0.8816074 &= 0.1183926 \\ &\sim 12\% \end{aligned} \tag{4.21}$$

Whilst the level of baseline risk for which lifestyle and pharmacological interventions (compared to control) are no longer clinically effective are 48% and 43% respectively; this means that the interventions will not be effective if the baseline risk increases up to that levels (if a population under study have a high underlying risk of developing MetS, the odds of reversing it decreases). The baseline probability of reversing MetS for each study varies from 3% in the Villareal et al. [2006] study to 44% in the Van Gaal et al. [2005] study, reducing the effect of the pharmacological therapy for this last study. These results show a high level of heterogeneity in the baseline risk across studies.

The between-study standard deviation was significantly reduced illustrating the degree of heterogeneity in effect explained by baseline risk (0.54, 95% HPDI 0.24, 0.93), the comparator model obtained a standard deviation of 0.74. However, allowing for separate effects of baseline risk on the effectiveness of the various interventions did not further improve model fitness (change in DIC 0.53 and a residual deviance of 21.55).

Given the fact that the trial of Villareal et al. [2006] showed to be an outlier (Figure 4.8), the model for the common β was analyzed without it to measure the impact of influence of this study on the heterogeneity. This model calculated a β of -0.72 (95%CrI [-1.39; -0.05]) and had a standard deviation of 0.57, in which comparing with the previous results, taking out this study does not decreases significantly the heterogeneity.

4.3.3 Added-value of Intervention

Interventions available for the reversal of MetS are particularly complex. As they consist in groups of components, this raises the research question of whether an intervention with an specific component or a combination of components will be more effective. Welton et al. [2008] describes two models with a MTC framework for complex interventions with several different components. This analysis is useful to address research questions related with the effectiveness of interventions with a particular component or combination of components. Thus, the intervention with Lifestyle and Pharmacological treatment as components, can be explored more in depth to understand the possible interaction within. These results are going to be compared with the previous results obtained. The additive models allows inclusion of other interventions that the trials have not taken into account, as the model have a parameter for each component. This situation will be easier to observe in the extended network with more possibilities for combination of the intervention components.

Main Effect Model

In this model there is a separate effect for each of the different components of an intervention. The total intervention effect d_k is a sum of the relevant component effects, $d_{Lifestyle}$, $d_{Pharmacological}$ for a particular intervention, k. So for the combined intervention $d_k = d_{Lifestyle} + d_{Pharmacological}$. In this case, since there is only one combination the model is fairly straight forward.

$$d_k = d_{Lifestyle} * I_{k \supset Lifestyle} + d_{Pharmacological} * I_{k \supset Pharmacological} \tag{4.22}$$

Where the notation $I_{k \supset Lifestyle}$ means that intervention k contains a Lifestyle component.

Two-way Interaction Model

This is an extention of the main effects model with additional terms for the combination of each pair of components. This model allows interventions with particular pairs of components to have either a bigger or smaller effect than would be expected from the sum of their effects alone. A model can be written:

$$d_k = d_{Lifestyle} + d_{Pharmacological} + d_{Lifestyle*Pharmacological} \tag{4.23}$$

$$\begin{aligned} d_k &= d_{Lifestyle} * I_{k \supset Lifestyle} + d_{Pharmacological} * I_{k \supset Pharmacological} \\ &\quad + d_{Lifestyle*Pharmacological} * I_{k \supset \{Lifestyle, Pharmacological\}} \end{aligned} \tag{4.24}$$

Where the notation $I_{k \supset \{Lifestyle, Pharmacological\}}$ indicates whether an intervention has both Lifestyle and Pharmacological components.

This models are estimating an intervention effect denoted by d_k, which is calculated from the addition of each individual effect of each component of the intervention being estimated.

Results: Added value of intervention analysis

Table 4.6 presents the odds ratios for both models designed. Residual deviance for Main effects model was 28.8 compared with 29.3 for the two-way interaction model and the number of data points (26), showing the first model fitting better. DIC for both models was $\sim$167.74. Main effects mean for heterogeneity was 0.96 and 0.83 showing similar results with previous Bayesian models.

Table 4.6
Odds Ratios for Additive Models

Main effects

	C	L	P	P+L
C	**OR**	**3.41**	**1.57**	**5.46**
	SE	1.33	0.70	3.76
L	**4.61**	**OR**	**0.51**	**1.57**
	1.98	SE	0.29	0.70
P	**1.99**	**0.47**	**OR**	**3.41**
	0.89	0.24	SE	1.33
P+L	**0.35**	**0.10**	**0.23**	**OR**
	0.35	0.18	0.42	SE

Two way interaction

These results are showing a significant effect from the Lifestyle interventions with an OR of 3.41 (95% CrI [1.62; 6.63]) for the Main effect model and an OR of 4.61 (95% CrI [2.14; 9.35]) for the Two way interaction model, compared with a control intervention. Pharmacological interventions appear to be better than placebo interventions, but not better than Lifestyle therapies. The combined intervention (P+L) presented dramatically different results between these two models; this situation can be explained by the lack of evidence in this intervention and a possible interaction. Main effects model calculated an intervention effect of 1.53 (95% [0.42; 2.68]), showing a sig-

nificant effect of the interaction. However, Two way interaction model generated a negative interaction effect of -1.312 (95% CrI [-2.81; 0.15]) and giving non significant results. Variability of the odds ratios was reduced from 3.76 (Main effects model) to 0.35 (Two way interaction model) evidencing that the consideration of the interaction effects could be explaining the differences found, nevertheless more research is needed to be able to conclude on this issue.

These results from the reduced network are going to be supported with the analysis of an extended network considering different components of the interventions used in the trials. Even when sparsity is an issue with this network, the results of this exploratory analysis will highlight where more research is needed, by exposing the network details accounted in each of the reduced network nodes.

4.4 Extended Network

A complete analysis of the network is helpful in order to explain the lack of direct evidence, sparsity and heterogeneity of the interventions and therefore the studies. This analysis will compare 12 treatment options drawn from the data that could be integrated in the extended network (Figure 4.5). This network includes Lifestyle interventions in two options (with supervised exercise and exercise advice); Lifestyle interventions used in the combined therapy provided exercise advice only. This network is going to be analysed with classical, Bayesian, Additive and Hierarchical models. Only Additive models provide a longer list of treatment options, given its structure.

Classical methods can be used to estimate indirect evidence in this network. The nodes that can be used to calculate the indirect estimates for each comparison are presented

in **Tables 4.7.a** to **4.7.d**. The table shows each possible comparison with the therapies specified for the extended network, the number of direct and indirect estimates available for each comparison and the nodes that make possible the estimation of indirect evidence. For example, the first comparison in the table is comparing the control intervention with diet and there are 2 direct estimates, as shown in Figure 4.5. The indirect estimates for this comparison can be obtained from nodes Exercise (E), given the estimate between Diet and Exercise and the 2 estimates for Exercise and Control comparisons; also, the calculation for another indirect estimate is possible given the estimates between Lifestyle supervised, Diet and Control. In cases like the 18^{th} comparison (Diet and Antiobesity+Lifestyle), estimates can be obtained using indirect estimates to complete evidence needed to be able to calculate the desired comparison; the 8^{th} estimation is used to calculate an indirect estimate for Control to Antiobesity+Lifestyle, then the direct estimates available for Control and Diet are integrated together to generate an indirect estimate.

Since inclusion of Statin treatments (the 9^{th} comparison in Table 4.7.a) are possible because of the one comparison with Control, it gets disconnected when trying to obtain indirect evidence. The lack of direct evidence with other treatments of the network restricts calculation of indirect estimates.

Limitations with classical models are related with the amount of trials available for each comparison narrowing the possibilities of obtaining results for all of the potential comparisons, that can be drawn from the available interventions. Combination of evidence is calculated when comparisons provide direct and indirect evidence; it was possible to use 19 direct estimates from a total of 66 pairwise comparisons. ORs from fixed and random effects models are in **Table 4.8**.

With Bayesian models it was possible to obtain a full set of estimates for each pairwise comparison (**Table 4.8**). Nevertheless, some of the odds ratios became unstable, therefore the need to explore other types of models to study the nature of the very high ORs (e.g. Control and Lifestyle with exercise supervised). Additive and Hierarchical models were developed to explore a better fit with the data. These models have the potential of making more efficient use of the data available, as the complexity of interventions is determined by the addition of different therapies into one. This situation requires an analysis of each of those differences implicit in the interventions assessed by the RCTs. Exploration of the effect of separate components can improve understanding of the combined interventions.

Table 4.7.a

Comparisons for Extended Network

	Comparisons		Estimates		
			Direct	Indirect	Nodes
1	Control	Diet	2	2	E & Lsup
2		Exercise	2	2	D & Lsup
3		Lifestyle (SupE)	2	2	E & D
4		Lifestyle (AdvE)	3	3	AO, AD+L & AD
5		Antidiabetics	3	2	LEA & AD+L
6		Antidiabetics +L	1	2	LEA & AD
7		Antiobesity	1	1	LEA
8		Antiobesity+L	0	2	AO & LEA
9		Statin (S)	1	0	Network disconnection
10		Fenofibrate (F)	0	1	S
11		S + F	0	1	S
12	Diet	Exercise	1	2	Lsup & C
13		Lifestyle (SupE)	1	2	E & C
14		Lifestyle (AdvE)	0	1	C
15		Antidiabetics	0	1	C
16		Antidiabetics +L	0	1	C
17		Antiobesity	0	1	C
18		Antiobesity+L	0	1	Use No 8 to C
19		Statin (S)	0	1	C
20		Fenofibrate (F)	0	1	Use No 10 to C
21		S + F	0	1	Use No 11 to C

Table 4.7.b

Comparisons for Extended Network *–continued from previous page*

Comparisons			Estimates		
			Direct	Indirect	Nodes
22	Exercise	Lifestyle (SupE)	1	2	C & D
23		Lifestyle (AdvE)	0	1	C
24		Antidiabetics	0	1	C
25		Antidiabetics +L	0	1	C
26		Antiobesity	0	1	C
27		Antiobesity+L	0	1	Use No 8 to C
28		Statin (S)	0	1	C
29		Fenofibrate (F)	0	1	Use No 10 to C
30		S + F	0	1	Use No 11 to C
31	Lifestyle (SupE)	Lifestyle (AdvE)	0	1	C
32		Antidiabetics	0	1	C
33		Antidiabetics +L	0	1	C
34		Antiobesity	0	1	C
35		Antiobesity+L	0	1	Use No 8 to C
36		Statin (S)	0	1	C
37		Fenofibrate (F)	0	1	Use No 10 to C
38		S + F	0	1	Use No 11 to C

Table 4.7.c

Comparisons for Extended Network *–continued from previous page*

	Comparisons		Estimates		
			Direct	Indirect	Nodes
39	Lifestyle (AdvE)	Antidiabetics	2	2	C & AD+L
40		Antidiabetics +L	1	2	C & AD
41		Antiobesity	1	2	C & AO+L
42		Antiobesity+L	1	1	AO
43		Statin (S)	0	1	C
44		Fenofibrate (F)	0	1	Use No 10 to C
45		S + F	0	1	Use No 11 to C
46	Antidiabetics	Antidiabetics +L	1	2	C & LEA
47		Antiobesity	0	1	C
48		Antiobesity+L	0	1	LEA
49		Statin (S)	0	1	C
50		Fenofibrate (F)	0	1	Use No 10 to C
51		S + F	0	1	Use No 11 to C
52	Antidiabetics +L	Antiobesity	0	1	LEA
53		Antiobesity+L	0	1	Lea
54		Statin (S)	0	1	C
55		Fenofibrate (F)	0	1	Use No 10 to C
56		S + F	0	1	Use No 11 to C

Table 4.7.d

Comparisons for Extended Network *–continued from previous page*

	Comparisons		Estimates		
			Direct	Indirect	Nodes
57	Antiobesity	Antiobesity+L	1	1	LEA
58		Statin (S)	0	1	C
59		Fenofibrate (F)	0	1	Use No 10 to C
60		S + F	0	1	Use No 11 to C
61	Antiobesity+L	Statin (S)	0	1	Use No 8 to C
62		Fenofibrate (F)	0	2	Use 8 & 10 to C
63		S + F	0	2	Use 8 & 11 to C
64	Statin (S)	Fenofibrate (F)	1	1	SF
65		S + F	1	1	F
66	Fenofibrate (F)	S + F	1	1	S

Tables 4.7.a to **4.7.d** also present the 66 possible comparisons from the 12 interventions used for this extended analysis of the network. **Table 4.8** presents results for classical, Bayesian and Hierarchical models, showing the missing estimates from classical models and the complete list for the others. Additive model results are presented in Appendix A (7.4), because the additional treatment options produce a very long table.

Table 4.8 **Estimates obtained for the extended network by type of model.**

Comparison		Classical				Bayesian				Hierarchical			
										Common Prec		Different Prec	
		FE	95% CI	RE	95% CI	FE	95% CrI	RE	95% CrI	RE	95% CrI	RE	95% CrI
Control	**Diet**	7.07	3.84 13.00	7.07	3.84 13.00	7.16	3.90 12.40	7.72	2.03 21.04	6.11	2.36 13.41	6.58	2.42 14.42
	Excersice	1.60	0.63 4.05	1.60	0.63 4.05	2.55	0.99 5.44	2.85	0.62 8.53	3.27	1.06 7.73	2.99	0.92 7.43
	Lifestyle (Sup)	18.25	5.27 63.18	18.25	5.27 63.18	26.64	9.78 60.43	36.31	6.57 128.4	15.06	3.56 43.50	20.14	4.56 57.14
	Lifestyle (Adv)	2.99	2.37 3.77	3.08	2.22 4.27	3.32	2.62 4.15	4.25	1.72 9.13	4.23	2.22 7.81	3.98	2.12 7.43
	Antidiabetics	1.60	1.23 2.08	2.56	1.07 6.12	1.77	1.37 2.26	3.15	1.22 7.48	2.54	1.21 4.92	2.26	1.14 4.41
	AD + Lifestyle	1.14	0.48 2.72	1.14	0.48 2.72	1.13	0.50 2.15	1.78	0.31 5.78	1.91	0.54 5.17	1.72	0.47 4.66
	Antiobesity	1.50	0.99 2.29	1.50	0.99 2.29	1.33	0.88 1.95	1.25	0.28 3.32	1.30	0.49 2.77	1.40	0.56 2.78
	AO + Lifestyle					5.14	1.49 13.24	5.97	0.55 24.02	3.54	0.75 10.64	4.15	0.81 13.33
	Statin	0.96	0.57 1.64	0.96	0.57 1.64	1.00	0.57 1.65	1.35	0.21 4.60	1.40	0.47 3.32	1.45	0.53 3.06
	Fenofibrate					1.13	0.45 2.36	2.47	0.11 9.30	1.67	0.40 4.66	1.65	0.46 3.91
	S+F					1.20	0.47 2.52	2.70	0.12 9.88	1.72	0.42 4.82	1.69	0.48 4.01
Diet	**Excersice**	0.56	0.20 1.63	0.56	0.20 1.63	0.37	0.14 0.80	0.47	0.08 1.53	0.60	0.17 1.41	0.52	0.14 1.34
	Lifestyle (Sup)	3.80	1.47 9.82	3.80	1.47 9.82	3.84	1.51 8.42	5.80	0.98 20.85	2.65	0.78 7.40	3.34	0.88 9.32
	Lifestyle (Adv)					0.51	0.26 0.89	0.80	0.14 2.60	0.82	0.27 1.89	0.73	0.23 1.86
	Antidiabetics					0.27	0.14 0.48	0.60	0.10 2.02	0.50	0.15 1.27	0.42	0.12 1.14
	AD + Lifestyle					0.17	0.06 0.39	0.34	0.03 1.36	0.38	0.07 1.20	0.32	0.06 1.07
	Antiobesity					0.20	0.09 0.38	0.23	0.03 0.83	0.26	0.06 0.70	0.26	0.07 0.70
	AO + Lifestyle					0.78	0.19 2.21	1.13	0.06 5.16	0.69	0.11 2.32	0.77	0.11 2.84
	Statin					0.15	0.06 0.31	0.25	0.02 1.05	0.28	0.06 0.81	0.27	0.07 0.77
	Fenofibrate					0.17	0.05 0.41	0.49	0.01 1.97	0.33	0.05 1.08	0.31	0.06 0.94
	S+F					0.18	0.06 0.44	0.51	0.01 2.02	0.34	0.06 1.11	0.32	0.06 0.98
Excersice	**Lifestyle (Sup)**	6.73	2.43 18.62	6.73	2.43 18.62	11.70	3.96 28.14	16.70	2.56 61.16	5.63	1.00 18.03	8.19	1.27 24.55
	Lifestyle (Adv)					1.58	0.58 3.47	2.35	0.37 8.13	1.61	0.52 4.14	1.72	0.48 4.67
	Antidiabetics					0.84	0.31 1.86	1.77	0.26 6.30	1.01	0.25 2.88	0.99	0.25 2.80
	AD + Lifestyle					0.54	0.15 1.40	0.99	0.08 4.15	0.73	0.14 2.32	0.75	0.13 2.54
	Antiobesity					0.63	0.22 1.44	0.69	0.07 2.53	0.50	0.12 1.40	0.62	0.13 1.77
	AO + Lifestyle					2.44	0.48 7.62	3.34	0.17 15.70	1.41	0.19 5.17	1.81	0.22 6.98
	Statin					0.48	0.15 1.15	0.76	0.06 3.17	0.54	0.12 1.60	0.64	0.13 1.90
	Fenofibrate					0.53	0.14 1.47	1.97	0.03 5.70	0.65	0.11 2.20	0.73	0.12 2.29
	S+F					0.57	0.14 1.55	2.15	0.04 6.10	0.67	0.11 2.33	0.74	0.13 2.35
Lifestyle (Sup)	**Lifestyle (Adv)**					0.15	0.05 0.35	0.21	0.03 0.74	0.41	0.08 1.11	0.29	0.06 0.97
	Antidiabetics					0.08	0.03 0.19	0.16	0.02 0.57	0.24	0.05 0.69	0.17	0.03 0.57
	AD + Lifestyle					0.05	0.01 0.14	0.09	0.01 0.37	0.20	0.02 0.75	0.13	0.02 0.52
	Antiobesity					0.06	0.02 0.15	0.06	0.00 0.24	0.14	0.02 0.48	0.10	0.02 0.36
	AO + Lifestyle					0.24	0.04 0.76	0.30	0.01 1.35	0.33	0.04 1.17	0.31	0.03 1.28
	Statin					0.05	0.01 0.11	0.07	0.00 0.28	0.15	0.02 0.52	0.11	0.02 0.39
	Fenofibrate					0.05	0.01 0.15	0.11	0.00 0.48	0.17	0.02 0.62	0.12	0.02 0.46
	S+F					0.06	0.01 0.16	0.12	0.00 0.53	0.18	0.02 0.63	0.13	0.02 0.47
Lifestyle (Adv)	**Antidiabetics**	0.54	0.42 0.69	0.74	0.29 1.89	0.54	0.42 0.68	0.82	0.28 2.02	0.64	0.26 1.29	0.60	0.27 1.19
	AD + Lifestyle	0.50	0.22 1.12	0.50	0.22 1.12	0.34	0.15 0.65	0.45	0.08 1.46	0.47	0.13 1.24	0.45	0.12 1.18
	Antiobesity	0.13	0.04 0.47	0.13	0.04 0.47	0.41	0.25 0.62	0.33	0.07 0.88	0.33	0.11 0.72	0.38	0.13 0.78
	AO + Lifestyle	0.63	0.16 2.43	0.63	0.16 2.43	1.56	0.45 4.03	1.48	0.15 5.64	0.88	0.19 2.60	1.09	0.22 3.41
	Statin					0.31	0.16 0.53	0.39	0.04 1.45	0.36	0.10 0.89	0.40	0.12 0.88
	Fenofibrate					0.34	0.13 0.74	1.52	0.02 2.73	0.43	0.09 1.24	0.45	0.11 1.09
	S+F					0.36	0.14 0.79	1.65	0.03 2.87	0.44	0.10 1.30	0.46	0.11 1.12
Antidiabetic	**AD + Lifestyle**					0.64	0.29 1.22	0.63	0.10 2.01	0.82	0.21 2.33	0.81	0.21 2.19
	Antiobesity					0.76	0.47 1.18	0.48	0.08 1.39	0.57	0.17 1.23	0.68	0.20 1.24
	AO + Lifestyle					2.94	0.83 7.64	2.26	0.16 9.10	1.51	0.29 4.71	2.00	0.35 6.49
	Statin					0.58	0.30 1.00	0.53	0.05 1.92	0.60	0.17 1.44	0.70	0.19 1.32
	Fenofibrate					0.65	0.24 1.40	1.06	0.03 3.66	0.71	0.15 1.94	0.78	0.18 1.64
	S+F					0.69	0.26 1.50	1.19	0.03 3.88	0.73	0.16 2.00	0.80	0.19 1.68
AD + Lifestyle	**Antiobesity**					1.35	0.55 2.86	1.24	0.11 4.55	0.91	0.20 2.54	1.12	0.23 3.23
	AO + Lifestyle					5.18	1.15 15.44	5.97	0.27 26.04	2.29	0.48 7.67	3.16	0.57 12.02
	Statin					1.02	0.38 2.29	1.50	0.09 5.99	0.99	0.19 3.08	1.17	0.22 3.48
	Fenofibrate					1.14	0.32 2.98	5.84	0.05 10.65	1.19	0.18 4.13	1.31	0.21 4.12
	S+F					1.21	0.34 3.17	6.37	0.06 11.18	1.23	0.19 4.24	1.34	0.22 4.23
Antiobesity	**AO + Lifestyle**	4.71	1.51 14.69	4.71	1.51 14.69	3.92	1.17 9.97	5.53	0.64 20.97	3.04	0.60 9.43	3.15	0.62 9.94
	Statin					0.79	0.38 1.45	1.96	0.14 7.22	1.22	0.37 3.21	1.14	0.41 2.71
	Fenofibrate					0.88	0.31 1.98	14.77	0.08 13.33	1.44	0.33 4.38	1.29	0.38 3.47
	S+F					0.94	0.33 2.13	15.25	0.09 14.10	1.49	0.34 4.57	1.32	0.40 3.60
AO + Lifestyle	**Statin**					0.27	0.06 0.74	0.97	0.02 3.05	0.62	0.09 2.16	0.57	0.09 1.93
	Fenofibrate					0.30	0.06 0.92	66.01	0.02 5.05	0.73	0.08 2.72	0.64	0.09 2.26
	S+F					0.32	0.06 0.97	70.24	0.02 5.37	0.76	0.09 2.81	0.66	0.09 2.33
Statin	**Fenofibrate**	1.06	0.55 2.01	1.06	0.55 2.01	1.12	0.56 2.04	1.48	0.22 4.98	1.25	0.42 2.99	1.18	0.47 2.58
	S+F	1.12	0.58 2.14	1.12	0.58 2.14	1.19	0.59 2.18	1.59	0.23 5.50	1.30	0.44 3.11	1.22	0.49 2.68
Fenofibrate	**S+F**	1.06	0.55 2.03	1.06	0.55 2.03	1.12	0.55 2.05	1.50	0.22 5.28	1.18	0.37 2.86	1.12	0.43 2.48

The aim of this analysis is related with the identification of the best intervention, therefore the extended network becomes crucial for decision making; given the variability within the therapies, it is important to determined whether a particular combination of components is more effective than others. This is possible to explore with the extended network, however the lack of evidence is a significant issue, making the analysis an exploratory overview needing more research to be conclusive. The reduced network analysis was undertaken by concentrating the evidence and to be able to draw conclusions on the best strategy for reversal of MetS; the extended network will expose with more detail which could be the next step in research for prevention of T2DM and CVD.

Goodness of fit measures are presented in **Table 4.9**, for all the models developed for the extended network. Additive model results are described in section 4.4.1 and Hierarchical models are described in section 4.4.2.

Table 4.9

Model Goodness of Fit Measures

Model		SE	DIC	Residual Deviance	Data Points
Bayesian	FE	-	204.477	37.39	31
	RE	0.65	195.457	31.56	
Additive	Main Effects	0.76	195.317	32.00	31
	Two-way Interaction	0.53	195.685	32.58	
Hierarchical	Common	0.55	194.839	32.28	31
	Different	0.49	195.611	33.11	

4.4.1 Additive Models

The Welton et al. [2008] method is also applied to the extended network. This methodological exercise can contrast the impact of the two different networks in the additive model performance and its results. Figure 4.9 shows the list of all the possible interventions from the extended network, to be assessed with additive models. The components are combined exhaustively to obtain all possible combinations for the actual context. With the Main effects model was possible to obtain estimates for all pair-wise comparisons drawn from 30 interventions; giving 18 more treatment options not researched in any of the trials. Figure 4.9 indicates all of the treatment options compared to a control group. The rest of the comparisons are presented in the Appendix A (7.4), as pair-wise combinations provide 435 estimates. The appendix presents all estimates from additive models, the mean, the standard error, the 95% credible interval and the median are also shown for each of the comparisons.

The sparsity of the network represents a big issue for the estimates and the results are incongruent, as the odds ratio for the comparisons, with lack of direct evidence, are large with very wide credible intervals. This situation produced inconclusive results about any of the interventions or interactions under observation.

For the Two-way interaction model the results are more extreme and the possibility to estimate treatments with more than 3 components is not allowed, even-thought there are 22 treatment options, 10 more than Bayesian models. Result tables for these models are attached in Appendix A (7.4).

Main Effects			Two way Interaction	
Control vs	Diet	1	Diet (D)	**vs Control**
	Eadv	2	Eadv	Exercise advice
	Esup	3	Esup	Exercise supervised
	AD	4	AD	Antidiabetic
	AO	5	AO	Antiobesity
	S	6	S	Statin
	F	7	F	Fenofibrate
	D+Eadv	8	D+Eadv	
	D+Esup	9	D+Esup	
	D+AD	10	D+AD	
	D+AO	11	D+AO	
	D+S	12	D+S	
	D+F	13	D+F	
	Eadv+AD	14	Eadv+AD	
	Eadv+AO	15	Eadv+AO	
	Eadv+S	16	Eadv+S	
	Eadv+F	17	Eadv+F	
	Esup+AD	18	Esup+AD	
	Esup+AO	19	Esup+AO	
	Esup+S	20	Esup+S	
	Esup+F	21	Esup+F	
	D+Eadv+AD	22		
	D+Eadv+AO	23		
	D+Eadv+S	24		
	D+Eadv+F	25		
	D+Esup+AD	26		
	D+Esup+AO	27		
	D+Esup+S	28		
	D+Esup+F	29		

Figure 4.9: *Interventions assessed with the Additive models*

Given the lack of evidence and the huge proportion of possible estimates obtained from these models, results are not sensible. Hierarchical models could present a better fit of the data, with the same amount of estimates obtained for the Bayesian models.

4.4.2 Hierarchical Models

The extended network implies further challenges, given the issue related with similar number of trials and treatment options; that was mentioned in section 4.2.1, where the

concept of network of evidence is introduced. Hierarchical models are going to be applied to the data available to obtain benefit of their structure and observe if there is a better fit of the model to the data extracted. Hierarchical models organize the analysis with a joint probability model to estimate parameters that are correlated in some way. Using a population distribution to structure some dependance into the parameters avoids problems of overfitting, making better use of the data when estimating a higher number of parameters than data points. (Gelman et al. [2004]).

In this case, Lifestyle and Pharmacological interventions have shown a particular correlation in the context of the reversal of MetS, from previous analysis presented in this chapter. Therefore, both interventions can represent a cluster of similar therapies targeting the same effect (like diet and exercise for lifestyle and different types of pharmaceutics). The evidence collected allows the analysis of the correlation between the interventions. The second level of analysis in hierarchical models will estimate effect sizes for all possible pair-wise comparisons from the list of 12 available treatment options (also used with classical and Bayesian models). This type of model analyse the data in levels of aggregation. Therefore, lifestyle interventions were defined in the same cluster and pharmacological interventions in another cluster, where each cluster represent different treatments addressing lifestyle modifications and pharmacological interventions. Also combination of both types of intervention is possible. This model can compare the same number of combinations of interventions as in Bayesian models. Equation 4.25 presents the Hierarchical model, where $\overline{y}_{ij}$ represents the vector of data of each treatment option in each study. The data is estimating a parameter ψ_{ij} with variance s_{ij}^2 and this parameter is determined by the average over the uncertainty in ψ_{ij}:

$$
\begin{aligned}
\overline{y}_{ij} &\sim N(\psi_{ij}, s_{ij}^2) \\
\psi_{ij} &= \Theta_i + \sigma_i z_{ij} \\
\Theta_i &= \mu + \tau \varepsilon_i \\
z_{ij} &\sim N(0,1) \\
\varepsilon_i &\sim N(0,1) \\
(i = 1, \ldots, I; &\qquad j = 1, \ldots, n_i)
\end{aligned}
\tag{4.25}
$$

The distribution of the priors must assume symmetry, which is represented probabilistically by exchangeability. Parameters are exchangeable in their joint distribution if $p(\psi_1, ..., \psi_j)$ is invariant to permutations of the indexes $(1, ..., j)$ (Gelman [2007]). This feature of Hierarchical models makes possible the borrowing of strength between clusters of interventions, providing estimates from a more stable model.

Two models were designed, one with a common precision and other with a different precision for each class of interventions. The precision is defined as the inverse of the variance $1/\sigma^2$ (Spiegelhalter et al. [2004]). Using a common precision assumes vari-

ability is the same for all the parameter estimates and the different precision assumes each parameter variance follows a distribution.

Results: Hierarchical model analysis

Hierarchical models allows levels of interventions, where each level cluster groups of treatments that are similar. Results for Hierarchical models are presented in **Table 4.8** showing odds ratios are more stable than Bayesian models. **Table 4.9** shows the comparison of all goodness of fit measures for all the models used with the extended network. Looking at the residual deviance Bayesian random effects are better than the rest, but looking at the DIC, hierarchical models with a common precision fit better.

The inclusion of additive and hierarchical models into this analysis of the extended network, gave a wider observation of the interactions drawn from the networks of evidence. Hierarchical models provided a better fit of the data compared with the other models. While additive models performed less efficient, because data available is not enough for the amount of parameters, hierarchical models efficiently structured the data, to obtain better estimates. Lifestyle interventions presented higher odds ratios, compared to placebo interventions. Lifestyle interventions with a supervised exercise component needs to be more investigated, as its estimation calculates a very high odds ratio; but far from meaning a very strong effectiveness, it is showing lack of evidence (there are only 2 trials with evidence for this specific treatment option Anderssen et al. [2007]; Villareal et al. [2006]). In the network (Figure 4.5), this node shows a disconnection, therefore indirect evidence introduced nuisance in the estimation.

Additionally, control interventions used for these studies, were defined by the absence of intervention and did not provide any advice for lifestyle; for example Villareal et al. [2006] control group participants were told not to make any changes in their lifestyle habits and Anderssen et al. [2007] participants were instructed that after the 1-year trial period, they would be offered dietary advice and supervised physical training. This situation could be influencing more extreme differences contrasting the other interventions. Even though, more research is needed in order to obtain real results about this statement.

Lifestyle interventions with an exercise advice component instead of supervision, calculated a moderate odds ratio of 4.23 (95% CrI [2.22; 7.81]) providing the best estimate compared to control, after dietary treatments with an odds ratio of 6.11 (95% CrI [2.36; 13.41]).

It is important to contrast these results from the extended network as a complementary analysis of the reduced network results. This discussion is developed in the next section, together with conclusions drawn from the results of this extensive analysis.

4.5 Discussion & Limitations

This chapter proposed two networks of evidence and four different model structures. Starting with classical methods, Bayesian, additive and hierarchical perspectives were also applied accordingly to the needs of each network. This section outlines main results from the analysis and its limitations. A discussion of the models used for the analysis of each network is going to be contrasted with conclusions about the treatment options presented in this chapter.

According to all the evidence synthesized with the different models, lifestyle interventions were more effective than other interventions at reversing MetS. These results were consistent between the two networks presented in the analysis. The reduced network analysis had 4 possible therapies to contrast, and all of the interventions were defined as clusters of specific therapies related with any of the 4 main intervention groups. The extended network had 12 treatment options that were drawn from splitting the previous nodes, defined in the reduced network, to the specific therapies in each cluster. The reduced network results provided good estimates of the effect sizes in each clustered intervention, producing valuable evidence. The extended network is basically widening the research question to all specific therapies available; therefore, making it potentially possible to speculate which therapies are better in each of the intervention clusters defined in the reduced network. Nonetheless, more evidence is needed to be able to conclude on specifications of lifestyle interventions, individualized dietary programs combined with either supervision or advice on physical activity requirements.

It is important to highlight that the reduced network showed the best set of interventions (lifestyle therapies), whereas extended network showed were more research is needed. This is because of the specification of therapies in the nodes, making one node from the reduced network to be separated into therapy nodes, that represent different treatment interventions applied in the included trials; therefore if the estimates produced by the models are not reasonably sensible, it shows that the estimation has became unstable due to lack of evidence. The extended network analysis can answer the question of which of the components of the clustered interventions are making the intervention groups more effective; however heterogeneity has been a considerable is-

sue across the analysis, representing a source of uncertainty for the general results. Trials have concentrated in particular features of lifestyle interventions (for example it is cheaper to provide simple advice on increasing physical activity than provide a personal trainer to manage the physical activities of the participants) and pharmacological interventions gather a range of different pharmacotherapies. Number of trials was similar for the lifestyle and pharmaceutical interventions. If more research is produced on the different parts of the network that are particularly needed, to obtain better specific estimates of the interventions assessed in this meta-analysis; then this analysis would reach the ability to provide a clear cut intervention that effectively reverses a MetS diagnosis.

Lack of studies presented a real challenge for the analysis and consequently complicating conclusions related with these results. Complexity of the MetS definition still requires a more profound analysis and the lack of individual patient data do not allow identification of which is the specific risk factor of the MetS criteria that is being reversed. These statements represent the main limitations of this analysis.

Performance between classical and Bayesian methods was evidently better from Bayesian models. Classical methods were confusing in the process of estimation of the specific indirect possible estimates, specially when the treatment options increased. Lack of RCTs assessing all the interventions limited the amount of possible pair-wise comparisons to be estimated with classical models. Bayesian models made more efficient use of the data and had better model fit for both networks.

In the reduced network analysis, Bayesian and additive models presented similar results. All of the interventions performed better than the control groups, pharmacological interventions were better than the combined intervention. There were no signifiant

inconsistencies found across the evidence. Covariate models showed no significant effect size influence from measurements of the quality of the trials and the length of follow up. When adjustment based on the underlying risk of the population of each trial was taken into account, models presented an important reduction of the between study variation. There was an inverse effect found between the baseline risk and the odds ratio for the interventions, if the baseline risk of the population increases the effect of the intervention gets reduced. These results showed a large heterogeneity in the probability of reversal across studies, having an impact on the effect of interventions and therefore, minimizing these effects. The control interventions were a range of general lifestyle advices related with dietary and exercise habits, introducing different effects and making the analysis more complex for comparability and interpretation. Villareal et al. [2006] was the study with a real control group in the sense that the participants were told to continue with their regular habits, the rest of the studies provided leaflets or related advice on lifestyle changes.

In order to be able to have clear cut conclusions, the extended network was proposed aiming to show specific relations with better effectiveness; however, network diagram shows lack of direct evidence (adding weight to indirect evidence). Given the presence of high sparsity in the extended network, hierarchical models were included in the analysis. This model fitted better for the extended network, but there is also high uncertainty justified by the low direct evidence in this network. Additive models produced a very long list of treatment options and estimates were not sensible for drawing conclusions from them.

The combined intervention (lifestyle and pharmacological) results are not providing evidence to support the addition of both types of therapies. Several issues might be

involved in this result including lack of RCTs observing this intervention. Combination of these therapies could be having an important psychological effect influencing the results. Combined treatments showed an important need to undertake more research, as this was the type of therapy with less evidence. This situation makes a conclusion unclear in deciding for a specific intervention to be applied in a population.

The estimates calculated with this level of evidence showed lifestyle interventions to have better effectiveness in all the models presented. Hence, more research is needed in order to have clearer conclusions about the specifications of therapies.

After all this analysis, the Bayesian MTC model (Equation 4.5) from the reduced network was identified as the most appropriate, for its incorporation in the decision Markov model (section 6.2.1). The model producing results on **Table 4.2** adjusted ORs by the follow up, in order to provide estimates by year. This model was the most parsimonious for its integration in the Markov model and also showed better goodness of fit to the data available. *Lifestyle Interventions (OR 4.48, SE 1.605), Pharmacological therapies (OR 2.05, SE 0.771) and both treatments together (OR 1.55, SE 1.313)).* Showing Lifestyle as the most effective intervention for the reversal of MetS.

This chapter represents an exhaustive analysis of the available evidence and will be an important part of the main model. This analysis provided valuable information about the possible strategies that can be more effective for the prevention of T2DM and CVD. If a MetS condition has an elevated risk of developing T2DM and/or CVD and a specific therapy is found more effective for the reversal, then probabilities of having an impact in the prevention of these diseases could increase. Issues related with the risk between MetS and other diseases is debated in Chapter 5 and assessment of the impact in prevention is going to be addressed in Chapter 6.

4.6 Summary of the Mixed Treatment Comparison Analysis

This chapter has synthezised the evidence available from the different therapies researched by the RCTs. Two networks were proposed for the analysis of the data extracted from published studies. This analysis identified four different concepts to cluster the treatments (control, lifestyle, pharmacological and both together). Complexity of the data required a Mixed Treatment Comparison analysis. The reduced network results from the different models applied (classical, Bayesian and additive) concluded that lifestyle interventions had better effect size compared to the baseline group and to pharmaceutics. Models developed for the extended network included hierarchical methods to fit complex structures of the data available. These last models had a better fit for the extended network and highlighted the evidence towards lifestyle interventions to be more effective than others. Neverthless, more research is needed.

This analysis constitutes a source of evidence for the comprehensive decision model to be populated in Chapter 6, where the code of the model selected will be part of the main model code. Chapter 5 describes the systematic review undertaken for the assessment of the risk associated with MetS and development of T2DM and CVD. Chapter 7 summarizes the main results of this thesis.

Chapter 5

Assessing the Risk of Developing Cardiovascular Disease & Diabetes:

Cohort Systematic Review

The systematic review presented in this chapter aims to update the assessment of the risk between MetS and T2DM and/or CVD. This chapter is after the previous analysis, of available treatments for the reversal of MetS, because at the start of the analysis there were some systematic reviews providing important evidence of the risk. At the last version of this thesis document, the review undertaken was already out of date. This chapter was an up to date of the estimated risk in 2008. However, it is the best available evidence for the estimate of the relative risk of MetS associated with T2DM and CVD. Different meta-analyses were performed according to several characteristics of the data extracted (e.g. type of cardiovascular events, type of statistical scale [hazard ratio, odds ratio, relative ratio]).

People with Metabolic Syndrome (MetS) are at increased risk of developing T2DM and CVD events (Ford [2005]; Gami et al. [2007]; Li et al. [2008]), but not all of the cardiovascular end points have been assessed; these antecedents are going to be described in Section 5.1. A comprehensive systematic review and meta-analysis were undertaken to quantify the risk of CVD, Coronary Heart disease (CHD), Stroke, T2DM and all-cause mortality in individuals with MetS.

There were identified, from EMBASE and Medline, 62 prospective cohort studies in which MetS diagnosis was assessed at inception and individuals were followed up between 1972 to 2004. Studies included had a mean sample size of 4,945 individuals (Range: 154 to 60,754). Random effects meta-analysis models were used to calculate a pooled Relative Risk (RR) for each outcome. Only adjusted estimates (minimal adjustment by age and sex) using the National Cholesterol Education Program (NCEP) definition for MetS were included, all references and study characteristics are shown in **Table 4.1 (a, b and c)**. Sensitivity analyses were performed to explore heterogeneity

related to differences in scale of effect size (hazard ratios, odds ratios or relative risk) and type of events (fatal, non-fatal or both together). Assessment of publication bias was performed with previously evaluated methods (Moreno et al. [2009a]).

MetS diagnosis could be used as a tool to identify people at higher risk of developing T2DM, CVD outcomes and/or Mortality. The design and evaluation of appropriate screening strategies for individuals with MetS is of major public health importance for prevention of chronic diseases like T2DM or CVD.

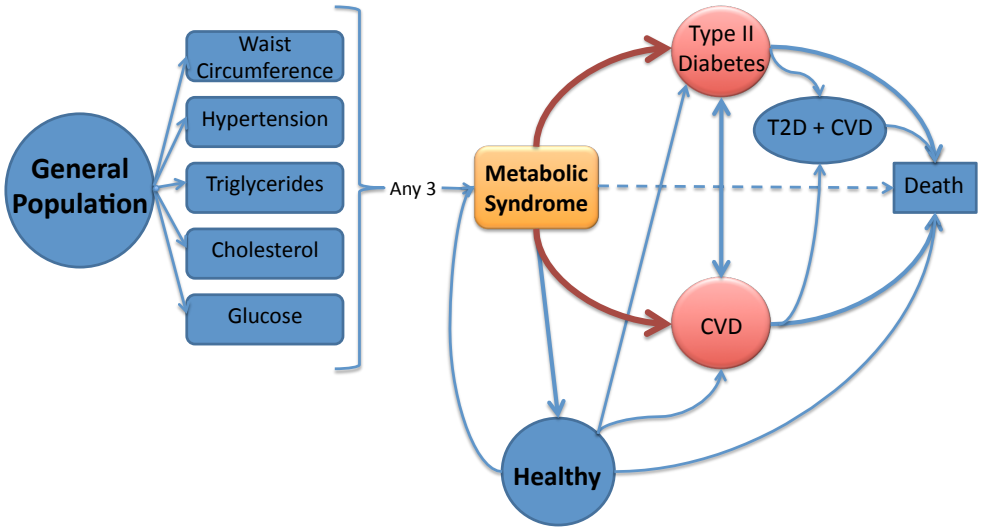


Figure 5.1: *Cohort Systematic Review in the Model diagram*

Figure 5.1 highlights were this analysis fits in the overall model of the thesis. Evidence identified after this analysis is going to feed the probabilities of transiting from the MetS state to T2DM or CVD states. Red arrows in Figure 5.1 demonstrate the tran-

sitions between states. Evidence for the transition from MetS to healthy was presented in Chapter 4. Chapter 6 presents a model for the evaluation of the previously defined interventions with additional economic and population data for a comprehensive assessment (cost effectiveness analysis).

Reporting of this systematic review follows guidelines from Stroup et al. [2000]. This chapter starts introducing the previous research preceding the production of this systematic review in Section 5.1. Data sources and search strategies of articles are described in Section 5.2. Systematic review techniques and meta-analyses methods used are going to be presented in Section 5.3. Then, Section 5.4 describes the results obtained from this analysis. Discussion and limitations are developed in Section 5.5 and the chapter closes with a summary in the last Section 5.6

5.1 Antecedents for a systematic review

Prevalence of CVD and T2DM are increasing worldwide (Murray and Lopez [1997]; Zimmet et al. [2001]). Epidemiological issues related with the assessment of the risk associated with MetS and CVD and/or T2DM were introduced in Section 2.3. Research surrounding the debate over the criteria for a MetS definition and its association with CVD and T2DM has became relevant to design prevention strategies (Sattar et al. [2008]). The National Cholesterol Education Program (NCEP), the World Health Organization (WHO) and the International Diabetes Federation (IDF) (Yasein et al. [2010]) had made an effort proposing a definition of MetS with differences on the diagnostic cut points of the components and requirements to meet criteria, as shown in Section 2.1 in Figure 2.1. Moreover, when investigation about these diseases is

overwhelming there is still uncertainty of MetS criteria and its validity for prediction, leading to a saturation of research without an agreement after several years of debate and miss-guided application in clinical practice. These means that after a considerable time researching about MetS concept and its latest and slow start of its application in clinical trials, there is a need to analytically process all the evidence available. The MetS criteria incorporates many components requiring different levels of research to be able to conclude on its usefulness.

Association of MetS with T2DM has previously been reported extensively (Sattar et al. [2008]) and there are previous estimations of the risk of MetS with CVD (Ford [2005]; Gami et al. [2007]; Li et al. [2008]). Two of them have considered WHO and NCEP definitions and relative risk as a scale for the effect size (Ford [2005]; Gami et al. [2007]). Li et al. [2008] only used stroke as outcome. And Sattar et al. [2008] used an NCEP definition, hazard ratios for the effect sizes estimations, did not include death as a possible outcome and only used 2 prospective cohorts for the analysis.

Ford [2005] estimated a relative risk of 1.27 (95% CI [0.90; 1.78]) for all-cause mortality, 1.65 (95% CI [1.38; 1.99]) for CVD, and 2.99 (95% CI [1.96; 4.57]) for T2DM. These estimates are pooled from the studies that used the NCEP definition for MetS. Three studies were identified by Ford [2005] reporting all-cause mortality outcomes, seven studies were identified reporting CVD outcomes and four studies were identified using T2DM as outcome.

Gami et al. [2007] found 37 eligible studies from 43 cohorts. This meta-analysis did not provide estimation of the risk for the outcome of T2DM. The reported relative risk of cardiovascular events and death was 1.78 (95% CI [1.58; 2.00]). The association was found to be stronger in women and relative risk was significantly higher for studies

using factor analysis or the WHO definition (RR 2.68 and 2.06 compared to 1.67 for NCEP).

However, the chronic complex nature of CVD and T2DM requires a review incorporating fatal and non-fatal as possible endpoints of the outcomes under observation. Consideration of CVD as a composed definition from the possibility of the occurrence of fatal and non-fatal events is handled by the available literature in diverse combinations of the concepts. To obtain a more realistic quantification of the risk, this issue of the CVD definition can be taken into account as part of the heterogeneity implicit in the term. These issues related with the language used by the publications identified for this analysis, are going to be described in more detail in the inclusion criteria section 5.2.2; where data sources will be introduced.

This cohort systematic review summarizes epidemiological evidence of the association between MetS and the development of CVD, T2DM and consequently related mortality. The use of MetS as a prevention tool could enable targeted interventions in identified people with the syndrome. An extension of the analyses published with previews calculations of the risk, will provide an up to date review and the possibility to quantify the association with inherent features of the outcomes under observation. Synthesis of evidence becomes crucial for decision making related to health care evaluation.

5.2 Data sources

A systematic review of prospective cohort studies in individuals with MetS was undertaken. Relevant published articles were identified from databases including EMBASE from 1980 and Medline from 1950 to February week 1, 2008.

Guidelines for the identification of the studies were specified and used for the data extraction; however, a protocol was not formally written. Extensive detail of the strategy was discussed previous to the start of the review. Two independent reviewers performed an evaluation of the study selection and data extraction. The search strategy details and inclusion criteria used for the identification of the articles, is going to be presented in the next sections (5.2.1 and 5.2.2).

5.2.1 Search strategy

The amount of cohort studies to be identified for this analysis has possibly substantially increased since publication of previous meta-analysis. This makes the development of a search strategy a crucial step for this review. The need to be comprehensive in the selection expands the number of terms to be incorporated in the strategy.

Identification of articles was designed based on 3 common characteristics, that all the cohort studies should have defined in the publication: (1) *a baseline* characteristic was considered to identify cohorts that used people with MetS at cohort inception (number of participants with a MetS diagnosis had to be greater than 0%); (2) the different terms used for the *outcomes* of interest were also incorporated in the search strategy parameters and (3) the *study design* terms were used to identify articles by the methodology. Figure 5.2 represents a diagram of the search strategy terms. Independent searches were ran for each of these research concepts to obtain the universe of all the possible articles that can apply for those terms. These independent searches were combined and the intersection of all three sets determines the list of articles to check and select studies for the meta-analyses.

Figure 5.2 shows the different terms used for the baseline of the articles. Metabolic syndrome is the most common term used lately, initial research for MetS also used terms like Insulin Resistance Syndrome, Egir and Reaven. These two last terms were proposed by the person who introduced the term as expressed in Chapter 2. In the Figure 5.2 a word 'or' is highlighted in red under each of the independent concepts of interest, means all the terms specified below were link with a relation of addition of all the results. This creates a universe of possibilities for articles using those specific terms. The same procedure is performed with the other terms used for the 3 common characteristics of the articles to be identified from the search strategy results. In order to obtain a list of the articles with the three terms together, the intersection of these three universes needs to be selected. The word 'and' (also highlighted with red) shows the implementation in the search strategy manager. Results were obtained for both databases (EMBASE and Medline) using the online library resources available at the University of Leicester. 5,345 articles were identified from the initial search of relevant abstracts and titles, by merging the two databases results and cleaning the duplicates.

Support for the implementation of the search strategy and the handling of references using software like EndNotes, was obtained from the librarian of the Health Sciences department of the University of Leicester.

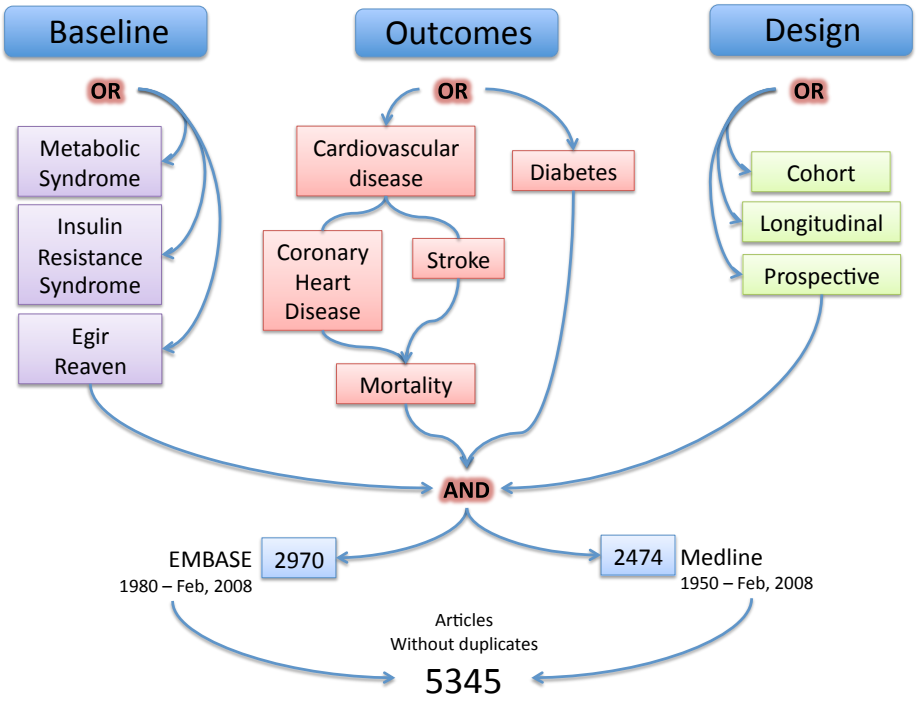


Figure 5.2: *Literature search strategy*

All possible medical names and statistical terminology were integrated to refine the search strategy in titles, abstracts and keywords. No restrictions on language were applied. Validation of search strategy was designed through a filter to find references used on previous published systematic reviews in MetS (Ford [2005]; Gami et al. [2007]; Li et al. [2008]). The articles used by the authors were located in the search strategy resulting list, to ensure evidence already identified was covered and also aiming to identified additional new research using those particular terms. If any article was not found, then specific terms were added to expand the universe and be able to include similar articles. When the search strategy terms were fully validated, a clean search was obtained for the selection of the new articles. Description of the procedures fol-

lowed for the selection of the cohort studies and identification of evidence for all of the outcomes of interest is presented in the next section.

5.2.2 Inclusion criteria

Articles were selected according to verification of a prospective design, if the study assessed the risk in relation to at least one of the possible outcomes (Coronary Heart Desease (CHD), Stroke, CVD and T2DM) and the cohort had a proportion (greater than 0%) of people with MetS. Studies with outcomes defined as *mortality* (fatal events) or *events* (non-fatal, fatal/non-fatal combined or major cardiovascular events) in general were investigated to assess the risk. The articles presented a particular heterogeneity determined by the different terms used for CVD. For this review, the concepts of CHD and stroke together define CVD outcomes ($CHD + Stroke = CVD$). The reporting of evidence uses all these terms across the literature, nonetheless some articles reported only one part of the outcome or presented the detailed part ($CHD + Stroke$), or directly presented a composed CVD. Articles did not consistently reported whether the outcomes under study were defined as specific fatal events or otherwise, therefore the 'events' word is referring to all possible types of events described above. Figure 5.3 shows the results of the procedures for the selection of articles and presents the number of studies included by outcome and type of event specified in the article.

A research fellow from the department of Health Sciences performed an independent study selection and estimate extraction. Then, results were compared and verified for any difference found; articles were consulted again for the differences accounted.

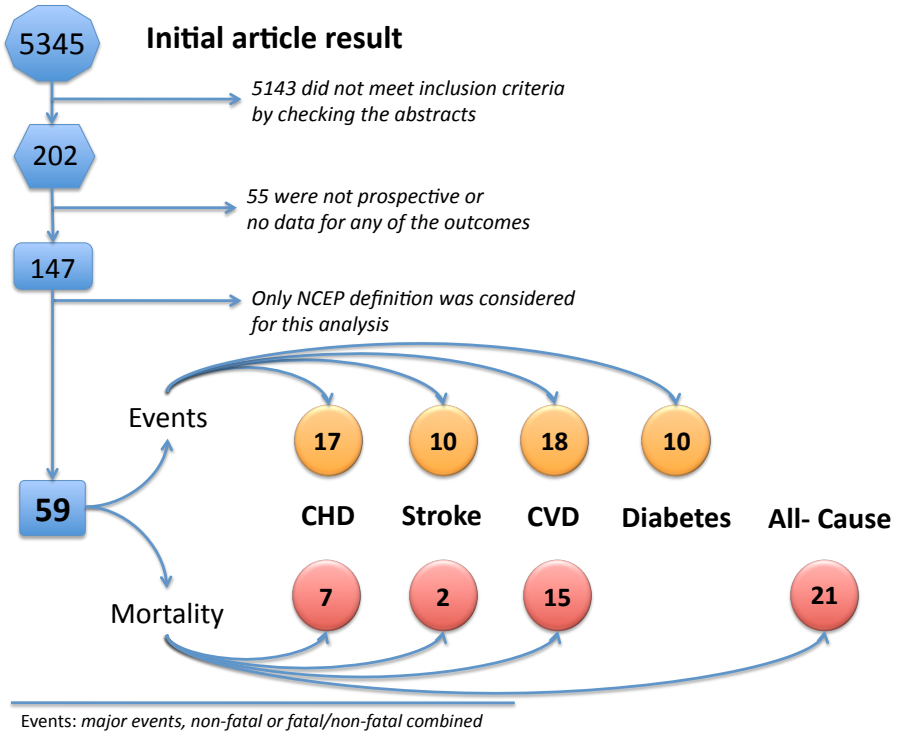


Figure 5.3: *Article selection by outcome*

5.3 Data extraction

A group of variables were extracted related with study-patient characteristics: age, sex, present disease at inception, country, sample size and inception year of the cohort. These characteristics are presented in **Table 5.1 (a, b and c)**. Hazard ratios, relative risks and odds ratios were extracted together with confidence intervals, standard errors or any measure of uncertainty. Adjustment criteria applied to the estimates was also collected. No attempt was made to identify unpublished studies or contact authors.

Table 5.1.a Characteristics of Cohort Studies of Metabolic Syndrome and Incident Cardiovascular disease, Type 2 Diabetes Mellitus and All-cause mortality.

	Author	Publication year	Country	Study	Cohort Inception year	Sample size	Follow (mean, median or length)	Age (mean)	Men (%)	MetS (%)	Baseline (%)				Outcomes				
											DM	CVD	HT	CHD	CVD	CHD	Stroke	DM	All-cause
1	Andreadis E.	2007	*Greece*		1992	1,007	2.1	59	45	42			100			✔	✔		
2	Boden-Albala B.	2008	*USA*	Northern Manhattan Study	1993	3,298	6.4	69	37	44	17		0	22	✔		✔		
3	Brevetti G.	2006	*Italy*		2004	154	1.3	67	74	51						✔			
4	Butler J.	2006	*USA*		1997	3,035	6.0	74	49	38	15		51			✔			
5	Cameron A.	2007	*Mauritius*		1987	3,685	5.0	43	46	14	13							✔	
6	Chen H.	2006	*Taiwan*	Cardio Vascular Disease risk FACtors Two-township Study (CVD-FACTS)	1991	3,453	10.4		43	26							✔		
7	Cheung B.	2007	*Hong Kong*	Hong kong Cardiovascular Risk Factor Prevalence Study Cohort (CRISPS)	1995	1,679	6.4	45	47	8	0							✔	
8	Chien Kuo-Liong	2007	*Taiwan*	Chin-Shan Community Cardiovascular Cohort Study	1990	3,602	11.0	55	46	23		0				✔	✔		
9	Dekker J.	2005	*Dutch*	Hoorn Study	1989	1,364	10.0	61	45	19	0	0			✔				✔
10	Diehm C.	2007	*Germany*	German epidemiological trial on Ankle Brandial Index (getABI)	2001	6,880	3.0	72	53	44	28				✔				
11	Echahidi N.	2007	*Canada*		2000	5,304	4.0	64	77	45	31								✔
12	Guize L.	2007	*France*		1999	60,754	3.6	52	65	10		0							✔
13	Hanley A.	2005	*USA*	Insulin Resistance Atherosclerosis Study	1992	822	5.2	55	44	26	0							✔	
14	Hillier T.	2005	*USA*	Osteoporotic Fractures (SOF)	1986	9,677	12.2	65	0		7				✔	✔			✔
15	Holvoet P.	2004	*USA*	Health ABC study	1997	3,033	5.0	74	48	38	19	13				✔			
16	Hong Y.	2007	*USA*	Atherosclerosis Risk in Communities Study (ARIC)	1987	14,699	9.0	54	43	30	11		34	0		✔			✔
17	Hunt K.	2004	*USA*	San Antonio Heart Study	1984	2,815	12.7	43	43	25	11	7			✔				✔
18	Hunt K.	2007	*USA-Mexico*	San Antonio Heart Study	1979	4,996	15.5	48	43	23	10	3				✔			
19	Jeppesen J.	2006	*Denmark*	MONItoring of trends and determinants in CArdiovascular disease	1982	2,493	9.5	58	64	15	2	0	8		✔				
20	Kasai T.	2006	*Japan*		1984	748	8.0	59	87	42	39			22		✔			✔
21	Katzmarzyk P.	2005	*Canada*	Aerobics Center Longitudinal Study (ACLS)	1979	19,173	10.2	44	100	20		8			✔				✔
22	Ko G.	2006	*China*		1994	5,202	2.1	56	44	61	100				✔				✔
23	Kurl S.	2006	*Finland*	Kuopio Ischemic Heart Desease Risk Factor study	1984	1,131	14.3	52	100	10	0	0	0				✔		
24	Lakka H.	2002	*USA*	Kuopio Ischemic Heart Desease Risk Factor study	1984	1,209	11.6	52	100	9	0	0			✔	✔			✔
25	Langenberg C.	2006	*USA*	Rancho Bernardo Study	1972	2,118	20.0	71	46	12	14	13			✔	✔	✔		✔
27	Larsson I.	2005	*Sweden*		1994	1,135	8.0	49	46	26									✔
	Lawlor D.	2006	*UK*	British Women's Heart and Health Study	1999	3,589	4.0	70	0	30				0		✔			

Table 5.1.b Characteristics of Cohort Studies of Metabolic Syndrome and Incident Cardiovascular disease, Type 2 Diabetes Mellitus and All-cause mortality.

***continued from previous Table 5.1.a*

	Author	Publication year	Country	Study	Cohort Inception year	Sample size	Follow up (mean, median or length)	Age (mean)	Men (%)	MetS (%)	Baseline (%)				Outcomes				
											DM	CVD	HT	CHD	CVD	CHD	Stroke	DM	All-cause
28	Li Yan	2007	*China*	Chinese Multi-provincial Cohort Study (CMCS)	1992	2,659	10.0	42	44	17	0							✔	
	Liu J.	2007	*China*	Chinese Multi-provincial Cohort Study (CMCS)	1992	30,378	10.0	48	53	18	7	0			✔	✔	✔		
3	Maggi S.	2006	*Italy*	Italian Longitudinal Study on Aging	1992	5,632	4.0	72			7					✔	✔	✔	
	Marroquin O.	2004	*USA*	Women's Ischemia Syndrome Evaluation (WISE study)	1996	755	3.5	58	0	57	32	38			✔				
5	McNeill	2005	*USA*	Atherosclerosis Risk in Communities Study (ARIC)	1987	12,089	11.0	54	43	23	0	0					✔		
	McNeill AM.	2006	*USA*	Cardiovascular Health Study	1989	3,585	4.0	72	38	36						✔	✔		
9	Meigs J.	2007	*USA*	Framingham Offspring Study	1991	2,803	11.0	54	45	27	0	0			✔			✔	
	Monami M.	2006	*Italy*		2000	882	3.0	65	47	68	100								✔
3	Nilsson P.	2007	*Sweden*	Malmo Diet and Cancer Study	1991	5,047	10.7	58	40	20	0	0			✔				
	Onat A.	2002	*Turkey*	Turkish Adult Risk Factor Study	1997	2,398	3.0	49	50	33	6	8				✔			
4	Onat A.	2006	*Turkey*	Turkish Adult Risk Factor Study	1990	1,534	2.0	52	45	34	0	10			✔				
	Onat A.	2007	*Turkey*	Turkish Adult Risk Factor Study	1997	3,401	5.9	27	49		0			0		✔		✔	
4	Persson M.	2007	*Sweden*	Malmo Diet and Cancer Study	1991	4,480	10.0	58	38	16	0	0			✔				
	Protopsaltis I.	2007	*Greece*		1989	600	10.1	60	54	61	100								✔
4	Rana J.	2005	*Netherlands*	GENetic Determinants of Restenosis (GENDER)	1999	901	0.8	62	71	50						✔			✔
	Ravaglia G.	2006	*Italy*	Conselice Study of Brain Ageing (CSBA)	1999	981	4.0	74	44	27									✔
4	Resnick H.	2003	*USA*	Strong Heart Study	1989	2,283	7.6	55	43	35	0	0			✔				
	Saely C.	2006	*Austria*			750	4.0	62	68	37	21	100			✔				
4	Sattar N. (a)	2008	*Scotland*	British Regional Heart Study (BRHS)	1978	2,737	7.0	69	100		0				✔			✔	
	Sattar N. (b)	2008	*Scotland*	Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)	1997	4,812	3.2	76			0				✔			✔	
5	Scuteri A.	2005	*Italy*	Cardiovascular Health Study	1992	2,175	4.1	73	58	35		0			✔				
	Stern M.	2005	*USA*	SAHS & MCDS	1979	3,682	10.0								✔				✔
5	Takeuchi H.	2005	*Japan*	Tanno and Sobetsu Study	1993	808	6.0	60	100	24	0			6		✔			

Table 5.1.c Characteristics of Cohort Studies of Metabolic Syndrome and Incident Cardiovascular disease, Type 2 Diabetes Mellitus and All-cause mortality.

***continued from previous Table 5.1.a and Table 5.1.b*

Author	Publication year	Country	Study	Cohort Inception year	Sample size	Follow up (mean, median or length)	Age (mean)	Men (%)	MetS (%)	Baseline (%)				Outcomes				
										DM	CVD	HT	CHD	CVD	CHD	Stroke	DM	All-cause
Tanamsup S.	2007	*Thailand*	Electricity Generation Authority of Thailand (EGAT)	1985	3,216	17.0	44	79	19		0			✔				✔
Thomas G.	2006	*China*	Hong Kong Cardiovascular Risk Factor Study	1994	2,863	8.5	49	48	17					✔				✔
Tong P.	2007	*China*		1995	4,350	7.1	54	43	55	100	0				✔			
Vaccarino V.	2008	*USA*	Women's Ischemia Syndrome Evaluation (WISE study)	1996	652	5.9	57	0						✔				
Wang J.	2007	*Finland*		1986	1,025	13.5		36	43	0				✔	✔			✔
Wang J.	2007	*China*	Beijing Project	1999	541	5.0	48	50		0			0		✔		✔	
Wang J.	2008	*Finland*		1986	991	13.8	69	36	42	0	0					✔		
Wassink A.	2008	*Netherlands*	Secundary Manifestations of ARTerial disease (SMART)	1996	3,196	3.2	60	75	43	21	29	78		✔	✔	✔		✔
Wilson P.	2005	*USA*	Framingham Heart Study Offspring Study	1989	3,323	8.0	51	58	18	0	0	13		✔	✔			

DM=*Diabetes Mellitus*, CVD=*Cardiovascular disease*, HT=*Hipertension*, CHD=*Coronary Heart Disease*

No specific scale was used for quality characteristics extraction, however discussion about a quality assessment of the review and a detailed publication bias analysis is going to be performed. An exhaustive analysis of the publication bias that could be accounted in the review, can provide evidence of the statistical quality of the studies included.

Treatment of estimate duplicates and statistical methods are specified in sections below (5.3.1 and 5.3.2).

5.3.1 Multiple Studies

The prospective feature and the multiple outcomes analysis presented some situations where exclusion criteria was needed to eliminate estimate duplicates. In such situations the latest estimate was considered, if studies presented estimates of cohorts with repeated measures across time and publications corresponded to the same outcome. Different outcomes at different times were treated as the same study with multiple outcomes adding more information to the analysis. For published articles showing results from different cohort studies, estimates were considered as separate studies, if information was available.

5.3.2 Statistical analyses

Synthesis of the evidence was undertaken with the use of meta-analysis models introduced in Section 3.3. Subgroup analysis techniques were specified for three different meta-analysis by outcome using three independent variables extracted (gender of the cohort, scale of the risk measures and the reported type of events). Each outcome was

assessed with adjustment by gender, where studies were arranged by the gender of the cohort (if the article reported a male or female cohorts, or reported a mixed cohort or estimates for both genders combined). A similar analysis was performed to observe the different scale size effects and reported type of events. STATA (version 10.0) was used to calculate pooled Relative Risks (RR) from hazard ratios, relative risks and odds ratios with their correspondent 95% confidence intervals (CI). Estimates extracted were adjusted by age and sex, but other risk factors such as smoking habits, levels of cholesterol, treatments or lifestyle variables could be part of a minimal adjustment applied. Only minimal levels of adjustment were used for the meta-analysis as variables used presented considerable heterogeneity. Unadjusted estimates were excluded.

Meta-Analyses

Random-effect models were used to calculate pooled effect estimates for each outcome. I-squared heterogeneity test (x^2 test) was also calculated. This test assesses whether observed differences in estimates obtained from the meta-analysis, are statistically significant or are produced by random factors (Higgins and Thompson [2002]). Separate meta-analysis for each event and fatal outcome were developed. Since one study could present more than one outcome there is the need of developing different analysis in order to avoid duplicates in the estimates for each possible end point.

Publication Bias

Small study effects was assessed with contour-enhanced funnel plots. Eggers regression was used to assess asymmetry of the funnel plots (Peters et al. [2006]). Larger

studies with greater investment of time and money are more likely to be of high methodological quality and published, even if their results are negative (Sterne et al. [2001]). Funnel plots were explained in section 3.3.1. Trim & fill and variance weighted regression-based methods (which are extensions of the Egger's test) were also considered for the evaluation of the potential impact of publication bias (Hedges and Vevea [1996]; Moreno et al. [2009a,b]; Peters et al. [2006]). The trim and fill method pools an estimate from a reduced data set obtained after the trim of the asymmetric studies. Then, an adjusted pooled effect estimate is obtained after filling or imputing the counterparts of the asymmetric studies (Hemingway et al. [2010]).

Sensitivity analysis

Given the nature of CVD, T2DM and the additional role of mortality, it is important to explore sources of variability implicit in cohort studies and this systematic review. Observational studies accumulate a number of particularities related with the design making necessary the extraction of variables to measure possible sources of uncertainty. Sensitivity analysis was conducted to study heterogeneity shown in data extraction. Odds ratios, hazard ratios and relative risk were included as different ways of assessing the risk of developing any of the outcomes. There were different types of event defined by the authors. Articles referring to the counting of 'events' were not specified as fatal or non-fatal, risk estimations were extracted as general "events". Also, if the article specified "non-fatal" events and both types of events combined ("fatal/non fatal") were pooled together as 'events'. Meaning that the use of this counts of events, cannot be interpreted as events independent of mortality. Influence plots were used to assess the influence of individual studies on the pooled RR for each study.

5.4 Data synthesis

Data synthesis includes only studies using NCEP definition for the baseline of the cohort. This definition was chosen over WHO and IDF definitions, because it does not include diagnosis of T2DM as part of the components or requirements to meet the MetS criteria. Exposure of MetS was defined from the incidence of MetS in individuals after follow up periods in the cohort studies. Studies that did not report a proportion of the cohort with MetS, as baseline prevalence, were excluded. Cohorts did not consistently reported the use of drug treatments, however this is an important issue for MetS, as some of their components imply a drug treatment already defined for that specific component (like hypertension).

The main results of this chapter are going to be described in following sections, starting with the identification of articles in section 5.4.1. A qualitative summary of the studies included in the meta-analyses is presented in section 5.4.2. Then, a summary of the estimates obtained from the set of meta-analyses are described by outcome in section 5.4.3 and adjustment for publication bias results are shown in section 5.4.4.

5.4.1 Search results and study inclusion

5,345 articles (Figure 5.2) were identified after merging the results from both databases used, 96% were not related with the assessment of the risk of metabolic syndrome (Figure 5.3). 202 full articles were obtained after reviewing and classification of titles and abstracts from the original set; 55 were excluded because their design was not of a prospective cohort with at least some months of follow up or the article had no data related to the risk of developing any of the outcomes. In total 147 articles were

reviewed, but only 62 are included in this meta-analysis. One japanese study was excluded, as it was the only one with no english abstract. There were other non-english studies, one spanish, one german, two chinese and one extra japanese; all of these had at least an english abstract were data could be obtained. A meeting with a medical expert with knowledge of the german language was arranged to verify the data extraction on the german article. Experts for other languages like chinese or japanese were not identified for consultation.

When analysing frequencies by definition of MetS, there were 120 estimates from 62 selected articles using NCEP definition and having at least a minimal level of adjustment. Articles that presented estimates adjusted by specific baseline prevalences (particular conditions present in different proportions within the cohort) were filtered to use estimations with healthier people at baseline. For some cases, enough data was extracted in order to obtain a combined estimate including all different populations of the observed cohort. These procedures were undertaken to be able to use the estimates of these articles and reduce the introduction of bias, given by the particular adjustments of the data in only a few articles. Details about particular issues related with the design or the estimate calculation were considered for the cleaning of the database. Articles with more than one cohort were considered as separate estimates. The article reporting the latest publication and the highest follow up length was chosen when multiple publications of the same cohort were accumulated. The data extraction was cleaned to avoid estimates overlapping and to obtain good quality data.

5.4.2 Qualitative summary

Cohort studies included were incepted from 1972 to 2004 (**Table 5.1(a-b)**). Mean sample size of cohorts was around 4,945 individuals, with a minimum of 154 subjects and 60,754 the largest. Participants were approximate 58 years old. Studies had a minimum of 0.8 to 20 years of follow up (mean=7.8 years), 52% of men in average (some cohorts chose 100% women or men) and prevalence of MetS was around 30% in average (7.5% minimum and 68.4% maximum) at baseline. A 15% of the studies did not report prevalence of outcomes under observation at baseline (Brevetti et al. [2006]; Chen et al. [2006]; Larsson et al. [2005]; McNeill et al. [2006]; Rana et al. [2005]; Ravaglia et al. [2006]; Stern et al. [2005]; Thomas et al. [2006]; Vaccarino et al. [2008]). Exclusion of these studies was considered a loss of important evidence.

Authors used the age and the gender as common variables for adjustment, but majority of estimates were adjusted by smoking habits, alcohol consumption and physical activity. Cardiovascular risk factors were also used as variables to adjust the estimates by cholesterol levels, ethnicity, social status, therapy intake. Others variables considered were related with the purpose of the study itself and the populational distribution. Different combinations of these variables were used across all cohorts.

5.4.3 Summary estimates

Selected estimates were meta-analysed by outcome, type of event and gender Pooled estimates showed a statistically significant higher risk for all outcomes, for those individuals with MetS compared to those without. Estimates by gender also showed an increased risk in people with MetS. Figure 5.4 present pooled estimates (RR) for each

outcome. Cohort estimates represent the number of studies included for that specific pooled estimate.

For the articles that only reported events of the outcome and did not provide any further information on the composition of these observed event, were classified for the meta-analysis of events in general. But it is not possible to define this concept as an addition of incidence and mortality, because this might not necessarily be the case for all the studies. There could be some studies only observing incidence or only mortality, however it was not clear in the related articles. Estimates for general events tend to be lower than mortality ones, which could hint a predominance of the incidence, as evidence collected for these estimates. Nevertheless, this cannot be confirmed unless the details of the composition of this category are disclosed.

All-cause mortality. There were 21 cohorts combined with a pooled RR of 1.50 (95% CI: 1.29-1.76). In **Figure 5.4**, pooled RRs by gender of the cohort, are shown. There is 1 cohort with women only, showing a RR of 2.50 (95% CI: 2.18-2.87) and 2 male studies with a non-significant RR.

CVD. Studies included in this analysis were defined as general CVD or as addition of CHD and stroke events by the authors. Summary estimates for CVD were pooled from 15 estimates for mortality and 19 for events. In both cases magnitude of the RR was significant 1.81 (1.45-2.35) for fatal events and 1.67 (1.47-1.89) for general CVD events. There were 2 studies in women for mortality (RR 3.32, 95% CI: 2.70-4.09) and 2 studies for general events (RR 2.61, 95% CI: 1.66-4.11). And there were other 2 studies presenting estimates for mortality in men (RR 2.07 95% CI: 1.17-3.66).

Coronary heart disease. Specific estimates for CHD only were 7 for mortality and 17 for events. The effect size was markedly higher for mortality with RR 2.26 (1.46-

Figure 5.4: *Relative risk for cardiovascular and diabetes outcomes and association with metabolic syndrome, by gender of the cohort and type of events reported in the article*

3.51) compared to a RR of 1.71 (1.51-1.93) for general events. There were only 2 specific gender cohorts looking at fatal events with a RR of 4.50 (95% CI: 3.36-6.03) for women and a RR of 3.40 (95% CI: 1.37-8.43) for men.

Stroke. These outcomes accumulated only 2 estimates for fatal events (RR 1.67, 95% 1.05-2.63) in contrast with 10 estimates for general events (RR 1.77, 95% 1.37-2.29). And there was only 1 male specific cohort (RR 2.00, 95% 1.01-3.96).

T2DM. There were 10 estimates for diabetes with a RR of 4.40 (95% 3.35-5.78). Sensitivity analysis observing the impact of different scales used presented no major difference within each scale. Differences in events definitions were also explored, showing no marked contrast between the 3 groups (events, non-fatal and fatal/non-fatal together).

Corresponding forest plots for each of the meta-analysis performed in this chapter are presented in **Appendix B**: from B1 to B8 are meta-analyses by gender of the cohorts, from B9 to B16 are the meta-analyses by scale of the effect size and from B17 to B19 forests plots presented are by type of events. Figures from B20 to B26 are specific funnel plots for each of the outcomes. In general, the forest plots show a higher relative risk, in adults with MetS, associated with T2DM. CVD outcomes are more prevalent across the studies selected for the review. Fatal strokes are the outcomes with less published studies, therefore higher uncertainty in the risk estimation. The different risk scales (Hazard, Odds and Risk ratios) are providing similar estimates of the risk. Looking for differences across type of events (non-fatal, events and both, as the available linguistic classification of CVD events), estimates were relatively similar.

Heterogeneity tests obtained small p-values ($p = 0.00$) for CVD, all-cause mortality and all event estimates in mixed gender cohorts. Relative risks derived from small

number of cohort estimates available (under 5 cohort estimates), tested non significant for heterogeneity, as shown in Figure 5.4. This situation is expected from a collection of evidence observing outcomes with components implicit in their definition; for example the issues related with CVD and its overlapping definition with CHD and stroke, producing variability across publications. All-cause mortality presented variability in its definition. Scale differences did not showed significant differences within the pooled estimation.

5.4.4 Publication Bias

The funnel plots presented visual asymmetry showing less small studies reporting higher relative risk than larger cohorts for all-cause mortality, CVD outcomes, T2DM and stroke events (fatal stroke was excluded from this analysis for having only 2 studies involved). This means there could be small studies missing. If the funnel plot is symmetric, the small studies would reflect their counterparts, the large studies. Appendix B20 presents an asymmetric funnel plot for articles reporting all-cause mortality outcomes. This funnel shows majority of studies concentrating at the top right of the figure and only one study very close to the base of the axis. The absence of more studies towards the base of the funnel is evidence of publication bias. Small studies tend to have less statistical power and negative results are more likely to be rejected for publication (Sterne et al. [2001]). This situation is more extreme for T2DM; and for the case of CHD events and mortality; funnel plots did not show important patterns of small study asymmetry. Whereas for CVD events, funnel plot showed more asymmetry than the funnel for CVD mortality outcomes. Stroke events also showed visual evidence of publication bias. Funnel plots for each of the outcomes of this analysis are

presented at the end of **Appendix B** (Figures from B20 to B26).

Egger′s test calculated significant asymmetry for all-cause mortality (p=0.006) and fatal CVD (p=0.010); however test results for CVD events (p=0.745), fatal CHD (p=0.886), CHD events (p=0.687), stroke events (p=0.748) and T2DM (p=0.393) were uncertain of the effect of small studies. Egger tests the hypothesis of a significant effect of the small studies creating the asymmetry in the funnel plot. In other words, whether the asymmetry is important or not. Previous estimates were adjusted using Egger′s regression coefficients. This adjustment reduced the estimate for all-cause mortality to 1.15 (95% CI: 1.12-1.18) with a 23% reduction and CVD mortality to 1.24 (95% CI: 1.18-1.31) with 33% reduction. Publication bias adjustment results are presented in **Table 5.2**. Given the visual asymmetry, adjustment was estimated for all outcomes to measure the possible impact, only CHD mortality did not required adjustment (estimate marked in Table 5.2 with an asterisk). Relative risks remained statistically significant after publication bias adjustment. Discussion can be developed after such results. This adjustment has been previously evaluated by Moreno et al. [2009a], where evidence of the better performance of regression based adjustments was presented. Then number of studies included in this analysis allows quality of the adjustment. The validity of this adjustment could be investigated by undertaking methods for the tracking of small studies not yet published.

This evidence synthesis presents updated results of the estimates and shows important results related with publication bias, as described in this section. Discussion of the arguments produced by this research are going to be developed in Section 5.5.

Table 5.2. Relative risk for outcomes associated with metabolic syndrome, and small study bias adjustment

Outcome	RR	95% Confidence Interval	RR Publication Bias Adjusted	95% CI	% Reduction	P-Value
Mortality						
All-cause	1.50	(1.29 - 1.76)	1.15	(1.12 - 1.18)	23	<0.001
CVD	1.85	(1.45 - 2.35)	1.24	(1.18 - 1.30)	33	<0.001
CHD*	2.26	(1.46 - 3.51)	2.12	(1.75 - 2.56)	6	<0.001
Stroke	1.67	(1.05 - 2.63)	.	. .		.
Events						
CVD	1.67	(1.47 - 1.89)	1.61	(1.49 - 1.73)	4	<0.001
CHD	1.71	(1.51 - 1.93)	1.64	(1.51 - 1.78)	4	<0.001
Stroke	1.77	(1.37 - 2.29)	1.58	(1.34 - 1.85)	11	<0.001
Diabetes	4.40	(3.35 - 5.78)	3.60	(2.87 - 4.52)	18	<0.001

Events: *major events, non-fatal or fatal/non-fatal combined*

5.5 Discussion & Limitations

This results confirm a strong association between MetS and incident CVD and incident T2DM, based on the findings of 59 prospective studies. This meta-analysis allowed a wider observation of the association across different population world wide and establish a clearer epidemiology of these diseases.

Strongest association was found in coronary heart disease and specially in T2DM, supporting previous findings (Sattar et al. [2008]). Statistical analysis was performed assuming independence of the outcomes and its variants, but discussion relating them all given their chronic feature is crucial for the understanding of the patterns presented. Combination of the components of the MetS produce different scenarios that makes necessary an analysis of the whole concept together, given the lack of individual patient

data it is important to assume a correlated effect by the presence of any 3 or more risk factors. Moreover, all of the pooled estimates showed a clear higher risk of developing any of the outcomes under study.

Sensitivity analysis showed sources of heterogeneity were not strongly influential on the results. Definition of the outcomes determined a complicated scenario when studies looked at a large number of endpoints for CVD, increasing events heterogeneity. Most of the studies showing risk for general events did not give a specification of the severity of these events. Therefore, the need of analyzing the effect of these differences across studies to help interpretation. Moreover, CVD constitutes a wide concept also, incorporating coronary heart disease and stroke showing cohort studies provide evidence related with interactions in populations (counfounding).

The number of studies included in the meta-analysis is sufficient to measure uncertainty of any of the variables extracted from the cohorts. Hence this analysis could be defined as a extended observational study. Heterogeneity issues were analyzed to assure only qualified estimates of inclusion. Minimal levels of adjustment were considered as a quality indicator; however there is a lot of variability across all different factors chosen for adjustment. Observational studies have different levels of unmeasured bias implicit, but these biases are linked to reality of interactions related with MetS, thus a meta-analysis including a large number of this type of studies gives a more realistic estimate of the risk (in consequence more accurate of the global situation), equivalent to a synthesis of 3 decades of observation of different populations. This means quantity of estimates available can provide an overview of the review quality. The analysis of publication bias provides evidence of the implicit quality of each study.

Even though, publication bias is a real issue in these results, specially for all- cause and CVD mortality. There is a markedly difference in the behavior of patterns between CVD and CHD, observing the funnel plots in **Appendix B**. The increased proportion of studies looking at CVD more than CHD, raises the question of why is CHD less reported? Given the fact that CHD is a component of CVD, this situation could be explained by the variability illustrated by the definition each author uses for the endpoints. Moreover, the majority of studies showed results for more than one outcome (in different combinations); separating CHD and Stroke makes studies more specialized, but at the end aiming to give an estimate of the risk for a composite CVD, leading more observation over this outcome and concentrating higher risk in larger studies. Reduction after small study bias adjustment on the relative risks for events was a lot smaller than for mortality outcomes, this could be explained by a wider inclusion of endpoints in this classification.

Strengths of this analysis incorporate a comprehensive evaluation of all possible outcomes related with the nature of these chronic diseases, allowing comparison of patterns. Inclusion of a large number of cohorts to extract available evidence to produce updated quantifications of the risk in various populations. A wide search strategy was developed and validated aiming to identify the all cohort studies related with the proposed research question. Previous meta-analysis did not explore risk for different components of the outcomes (Ford [2005]; Gami et al. [2007]; Li et al. [2008]). Publication bias was also not considered in the previous meta-analysis. This review reported important evidence of publication bias that was taken into account for the calculation of the relative risks.

Studies without a clear definition of MetS were not included. Sensitivity analysis could

be used to explore the impact of the studies without reported baseline prevalences of the outcomes. However, in general studies observed outcomes according to its baseline composition. The predictability of MetS compared to individual factors could not be assessed with the data available, as individual patient data would be needed for that analysis.

Large systematic reviews require the extraction of a range of variables to allow the possibility of evaluating the heterogeneity given by each detail of prospective studies. Measured variation across studies of different levels allow a better evaluation of the quality of the review, by performing sensitivity analysis to explore ways of reducing heterogeneity. Limitations of this analysis go over the bias underlying observation in large cohort studies. Lack of data reported for baseline diseases in some cases made uncertain the discrimination of studies.

Further work in analyzing more trends to cover the need of observational biases to reduce uncertainty. Methods should expand to be able to evaluate integrated lifestyle characteristics that determine the development of the MetS, making more efficient to meta-analyse complex aggregated information and therefore obtaining more accurate estimates compatible with reality. There is the need to understand about all implications of MetS with a more integral approach and design proper lifestyle strategies to build a real possibility to reduce incident CVD, T2DM and therefore mortality for related causes. New research should be directed to answer a question of cost-effectiveness of clinical applied strategies in practice and quantification on reducing prevalence.

There is more research needed for the evidence of publication bias. If there is a real trend, then questions related with the causes of this bias should be addressed. Conflict

of interest could be influencing the research of MetS. The use of drug treatment also represents a big question for the cohorts; the lack of individual patient data limits the possibility to measure the possible interactions in the application of MetS criteria (depending on the combination of prevalent components).

Identification of people with MetS in the general population represent a starting point for prevention of CVD and T2DM. It would be a great achievement to encourage people to get more involved in their general health, by translating the information of these issues and allowing for real transforming actions to reduce the disease progression. If people are informed and they develop knowledge about how to decrease their risk, can establish an effective probability of reducing these diseases incidence. Moreover, as prevalence of CVD and T2DM has been increasing in recent years more research is necessary in how to eradicate the roots of lifestyle conditions leading to a chain of mortal events.

5.6 Summary of the Cohort Systematic Review

This chapter produced important evidence related with the risk of developing T2DM and/or CVD in people with MetS. Estimates presented from the analysis are going to be used for the calculation of transition probabilities of the relevant links of the model.

After synthesis of evidence of the risk of progression in individuals with MetS and assessment of potential therapies for its reversal (Chapter 4), a complete model can be built in Chapter 6, integrating information about the costs and the utilities related with the MetS context. The evidence of the risk and the identification of treatments, provide

important tools for the evaluation of an intervention based on MetS criteria to have an impact in the incidence of T2DM and CVD. A discussion of all the evidence presented in the thesis will be in Chapter 7.

Chapter 6

Modelling a population with Metabolic Syndrome: *Health economic evaluation*

Once enough evidence have been synthesized, it can be integrated in a Markov model. With the use of Bayesian methods, a Markov model is going to be developed for decision making, regarding the use of MetS criteria in interventions targeting prevention of T2DM and/or CVD. These interventions are assessed for their applicability to health care services and their possible impact in society related to the introduction of changes for the benefit of the population. This benefit should develop a knowledge transfer for the population in terms of improvement of quality of life and therefore a related increase in life expectancy. Two different meta-analyses have been performed, a complete systematic review updating the quantification of the risk of MetS in the progression to T2DM or CVD outcomes (Chapter 5); and a second review performed a Mixed Treatment Comparisons analysis to assess available treatments for MetS reversal (Chapter 4). These results are going to be incorporated in the Markov model, along with the incidence rates from the UK population (incidence rates for all the state transitions progressing from MetS, see **Table 6.1**). The model incorporates a time horizon of 55 years (1 year = 1 cycle), given the chronic nature of the problem under study. UK costs will also be identified from literature and utilities estimated for broad populations are going to be integrated with all the previous evidence identified for this thesis. Year 2009 is the base year for the costs included in the model. These inputs will describe the disease patterns that the model follows.

Only evidence using NCEP definition for MetS was used in this chapter, as the aim of the thesis includes prevention of T2DM; other definitions like WHO or IDF add presence of the outcome at baseline. Inclusion of studies using these other terms would provide an endogenous result, given the need of the research design to evaluate an intervention that does not contain the outcome of interest. The assessment is aiming to

demonstrate if the intervention can effectively prevent from progression to T2DM and CVD. Undertaking a health economic evaluation for the MetS criteria, compiles the evidence collected in this thesis and allows the analysis of a broad observation. There is a need to incorporate economical factors to evaluate the development of a prevention policy (strategy) using this criteria. Even when this research is not at the stage of the application of a public policy, it is important to project the possible consequences of the use of these model results; and provide a discussion from early research stages to be able to improve the assessment of the different therapy options.

This chapter provides a detailed description of the data sources and its extraction to support decisions related with MetS criteria. Challenges in structuring and developing a Markov model in WinBUGS, the main outcomes of this evaluation and sensitivity analysis are reported in the following sections.

Section 6.1 describes how the structure of the model was defined for this analysis. This section shows how the model is going to be populated according to survival probabilities in each state-transition. Then the calculation of transition probabilities using the incidence rates (λ's) is explained in section 6.2. Data sources for each state transition is also specified. Section 6.4 presents the economic data collected and section 6.5 describes the utilities used for each state and its sources of information. Then, section 6.6 provides specifications for the model related with the starting proportions of individuals according to each state. Section 6.8 describes the results obtained from the model. Section 6.9 provides the sensitivity analysis, comparing a base case with different variations of the model. A discussion and a summary of the chapter are developed in sections 6.10 and 6.11.

6.1 Populating the Model: Specification of the model structure

The main model developed in this thesis evaluates the impact of introducing MetS-based interventions for prevention of T2DM and CVD, which are posterior states of progression from MetS state (according to the evidence presented in Chapter 5). The model has been built with different sources of evidence, that are described in section 6.2.

The MetS state is the starting node of the model developed, followed by a healthy state for people who reverse the condition of MetS and states for T2DM and CVD. Figure 6.1 shows all the relational links for each transition studied. Each λ represents a transition rate in the model and its calculation is explained in section 6.2. Incidence rates are required for each transition, adjusted for intervention and treatment effects to complete the Markov model (evidence from Chapter 4).

In Figure 6.1, the first λ_1 is represented with an orange arrow transiting from the MetS state to the healthy state, in the model structure diagram. The MetS state is represented with a purple pentagon to express the five risk factors involved in the MetS definition (obesity, high cholesterol, high tryglicerides, impaired glucose and hypertension). The healthy state is a green circle with different options for the following transitions. This transition will be using empirical evidence obtained in Chapter 4 to calculate a transition probability for a UK population (**Table 6.1** shows calculated values for all transitions of the model). Details of the incorporation of this evidence is provided in section 6.2.1. This is where the Markov simulation starts.

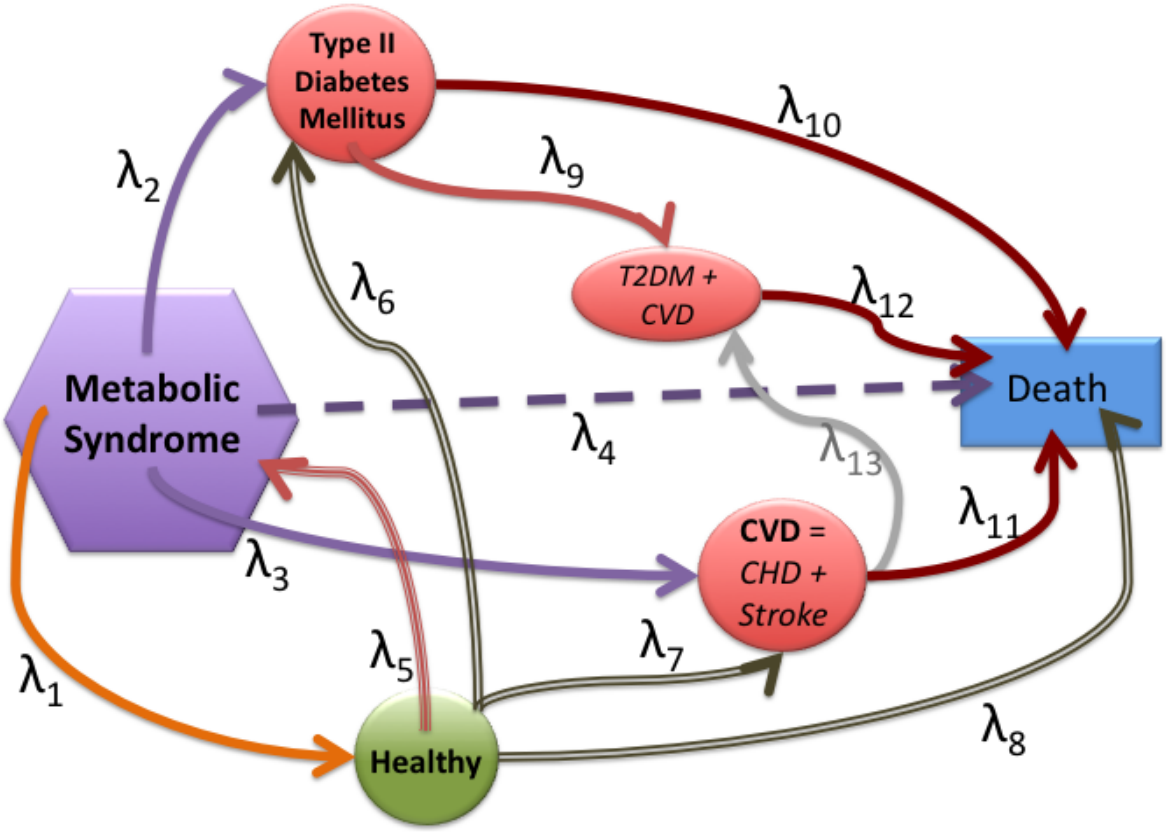


Figure 6.1: *Schematic diagram of the model rates and specific transitions*

λ_{2-4} are represented with purple arrows from MetS to T2DM and CVD states, these two last states are drawn as red circles. Transition from MetS to death is showed with a dotted purple arrow. Death is pictured as a blue rectangle, to direct transitions to all-cause mortality and introduce aging to the model. Evidence for this transition was produced in Chapter 5 and its incorporation into the model will be described in section 6.2.2.

λ_5 shows the transition from the healthy state back to the MetS state and it is represented with a red triple line arrow in Figure 6.1. Details of the evidence for this specific transition will be provided in section 6.2.3. Healthy transitions to T2DM, CVD and all-cause mortality (λ_{6-8}) are presented with dark green double arrows. Data identified for this part of the model is described in section 6.2.4.

λ_9 transition is drawn with a solid red arrow to the combined state of T2DM and CVD state. The combined state is shown with a red oval in the diagram. Evidence feeding this part of the model assumes CVD is produced as a complication from T2DM. λ_{10-12} are shown in the model diagram with dark red arrows transiting from T2DM and CVD states to a death state. Evidence imputed in the model for these transitions is presented in section 6.2.5.

Transition (λ_{13}) is drawn in gray because it shows a possible option of the model to be considered, but not included. Transiting from CVD to a combined state of T2DM and CVD together is biologically possible, but evidence available was limited; therefore, it was decided to exclude this transition from the model structure to avoid bias from the available information, that was reporting CVD as a complication of T2DM. Issues related with this transition assumption over the model and evidence for the transition from CVD to the combined state (λ_{13} represented with a gray arrow) will be discussed

in section 6.2.6.

Table **6.1** show all data used for the model, incidences, odds ratios, risk ratios and the references of the source data. The estimated specific state incidences were identified for MetS, T2DM and CVD for the UK population. These incidences are represented with λ_i, and were used to obtain the transition probabilities. and parameters were calculated for the sthocastic nodes. Evidence from the MTC (Chapter 4) and the risk review (Chapter 5), is presented in the Table as the estimates for the broad population. This estimates are inputing the odds ratios of MetS reversal and the increased relative risk of developing T2DM and/or CVD from a MetS state.

The proposed model considers logical disease pathways related with MetS. If the model provides cost-effective results for the use of MetS interventions and also show a reduction of the incidence for T2DM and/or CVD (with a possible impact in life expectancy), then MetS criteria could be considered useful for the prevention of T2DM and CVD. Screening strategies for the identification of people with MetS can be incorporated in the model using decision trees, but first it is necessary to evaluate whether MetS could represent an effective tool to reduce the incidence of T2DM and CVD in the UK population.

The Markov model uses transition rates to move a cohort of adults with a diagnosis of MetS and age of 45 years old between states over a number of cycles. Each cycle represents one year of simulation, therefore the model was defined with a time horizon of 55 years. These transition rates were calculated using evidence available for each specific state-transition presented in the model (Figure 6.1). The data was extracted from studies that provided evidence for each state in different levels: incidences and risks, treatment effects, costs (section 6.4) and utilities (section 6.5). Inputs related

with the incidences were considered for the UK population and the odds and risks ratios were synthesized using worldwide available evidence. This definition of the data incorporated in the model is aiming to assess a decision making process for a British population behavior of the incidences, using optimal estimates of the risk ratios.

Table 6.1. Source data for model by population level; relative risk, incidence, utilities, costs and mortality rates for each state-transition.

			UK population estimates								Broad population estimates					
			per 1000 person years			Beta Dist.					LogNormal Dist					
State	Transition	$\lambda_{i=}$	Incidence	SE	$p=1-e^{-\lambda}$ Transition Prob	Alpha	Beta	Source	Author	Year	Odds /Risk Ratio	SE	95% CrI	Mean	SE	Source
Mets	**Healthy**	λ_1		0.022	0.136	160.10	1015.39	MTC								
Therapy:	*Lifestyle*										4.48	1.605	2.40 - 8.31	Empirical		MTC
	Pharmacological										2.05	0.771	1.05 - 3.85	Empirical		MTC
	Both										1.55	1.313	0.45 - 4.06	Empirical		MTC
Mets	**Diabetes**	λ_2			0.017	2.77	161.87	CSR			3.60	1.051	2.87 - 4.52	1.28	0.116	CSR
Mets	**CVD**	λ_3			0.028	7.74	266.08	CSR			1.61	1.016	1.49 - 1.73	0.48	0.038	CSR
Mets	**Death**	λ_4									1.15	1.006	1.12 - 1.18	0.14	0.013	CSR
Age	**45-54**				0.004											
groups	**55-64**				0.010											
	65-74				0.027											
	75-84				0.068											
	85+				0.165											
Healthy	**Mets**	λ_5	20.00	0.061	0.020	268.73	13302.79	SAHS	Han, TS.	2002						
Healthy	**Diabetes**	λ_6	4.72	0.003	0.005	153787.29	32505219.00	QDScore	Hippisley-Cox, J.	2009						
Healthy	**CVD**	λ_7	17.82	0.101	0.018	98.01	5451.39	CARDS	Colhoun, HM.	2004						
Healthy	**Death**	λ_8						DHSE		2000						
Age	**45-54**		3.20		0.003											
groups	**55-64**		8.40		0.008											
	65-74		23.60		0.023											
	75-84		60.90		0.059											
	85+		156.80		0.145											
Diabetes	**T2+CVD**	λ_9	13.11	0.001	0.013	78.00	5910.50	UKPDS	Clarke, P.M.	2004	1.62	1.080	1.13 - 2.33			CSR
Diabetes	**Death**	λ_{10}	11.45	0.020	0.011	0.31	26.83	DECODE	Group	1999	1.38	1.054	1.09 - 1.75			CSR
CVD	**Death**	λ_{11}	37.00	0.075	0.036	0.19	5.03	SHS	Hamer, M.	2009	2.61	1.056	2.04 - 3.34			CSR
T2DM+CVD	**Death**	λ_{12}	284.40	0.140	0.248	2.10	6.38	UKPDS	Clarke, P.M.	2004	.					

CI: *Confidence Interval*, SE: *Standard Error*, SAHS: , QDScore: *Risk Score*, HTA: *Health Tecnology Assessment*, DHSE: *Department of Health Statistics for England and Wales*, UKPDS: *UK Prevention Diabetes Study*, DECODE: *Diabetes Epidemiology: Collaborative Analysis Of Diagnostic Criteria in Europe*, SHS: *Scottish Health Survey*, PCD: *Preventing Chronic Disease ($=1.65)*, CVD: *Cardiovascular disease*, CHD: *Coronary Heart Disease*, MTC: *Mixed Treatment Comparison (Chapter 4)*, CSR: *Cohort Systematic Review (Chapter 5)*, OTHR QOLE: *One Thousand Health-Related Quality Of Life Estimates.*

6.2 Converting Incidence rates to transition probabilities

Incidence rates are needed to feed the transitions of the structure of the Markov model proposed. This section describes the sources of the incidence rates obtained for each transition integrated into the model.

In order to convert incidence rates (λ's) to transition probabilities an exponential distribution was assumed due to the time homogeneous Markov nature of the model. The stochastic processes implicit in the Markov chains implies that each state transition probability, depend only on relevant information about the current time (Briggs et al. [2006]; Gilks et al. [1996]). This memoryless assumption was introduced in section 3.1.7. Exponential distributions have a memoryless property. Survival analysis can be used to obtain transition probabilities, the Survivor function represents the time people remain in a particular state, S(t), is given by:

$$S(t) = e^{-\lambda t} \tag{6.1}$$

and the event of interest is moving from one state to another state, assuming an exponential distribution parametrized by λ_i, therefore the one year transition probability, P(1), is given by:

$$P(1) = 1 - e^{-\lambda} \tag{6.2}$$

As P(1) is a probability and therefore bounded between 0 and 1, a Beta distribution is

the best probability distribution to use in order to incorporate uncertainty. If a random variable, x, has a Beta distribution, $Be(\alpha, \beta)$, with hyper-parameters α and β, then the mean $E(x)$ and variance $V(x)$ are defined by:

$$E(x) = \alpha/(\alpha + \beta) \tag{6.3}$$

$$V(x) = \alpha\beta/((\alpha + \beta)^2(\alpha + \beta + 1)) \tag{6.4}$$

Consequently if estimates of $E(x)$ and $V(x)$ can be obtained, then Equations 6.3 and 6.4 can be used in a "Method of Moments", which is a method of estimation of population parameters like mean and variance (Collett [2003]), to obtain appropriate values of α and β. Equation 6.2 produces an estimate of E(P), then using the delta method (Cox [1974]) and Equation 6.2 an estimate of V(P) can be derived.

The variance of λ, V(λ), can itself be obtained from the variance of log(λ) using a delta method. If λ is estimated as d/y, where d is the number of events and y is the total person years at risk, then $V(log(\lambda))$ is $1/d$. Thus, if $\lambda = e^z$, with $z = log(\lambda)$, then:

$$
\begin{aligned}
V(\lambda) &= \left(\frac{d\lambda}{dz}\right)^2 \times var(z) \\
&= (e^z)^2 \times var(z) \\
&= \lambda^2 \times var(z) \\
&= \frac{\lambda^2}{d}
\end{aligned}
\tag{6.5}
$$

Applying the delta method to 6.2 yields:

$$
\begin{aligned}
V(P) &= \left(\frac{dP}{d\lambda}\right)^2 \times var(\lambda) \\
&= \frac{e^{-\lambda 2} \times \lambda^2}{d} \\
&= \frac{\lambda^2 e^{-2\lambda}}{d}
\end{aligned}
\tag{6.6}
$$

Once the hyperparameters (α and β) have been obtained for each state transition, then the stochastic features of the model can be implemented to calculate probabilities on how the simulation will transit between the states. Following sections will describe details of calculation of the incidence rates (λs) for each state transition. **Table 6.1** shows all the probabilities and its calculated parameters for all the state transitions of the Markov model. **CODE 1, 2 and 3** show the WinBUGS code for the definition of each state transition in the model, with their respective calculated parameters for Beta distributions.

CODE 1: **Definition of a transition matrix**

```
# Stochastic decision model: Base case.

model {

# States, Transitions<-p
   #1=Healthy,
   #2=MetS,
   #3=T2 Diabetes,
   #4=CVD,
   #5=T2+CVD,
   #6=Death

# Age groups for HD and MD transitions, K
  #1=45-54,
  #2=55-64,
  #3=65-74,
  #4=75-84,
  #5=85+

# Treatment groups for MH, j
  #1=Control,
  #2=Lifestyle Intervention,
  #3=Pharmacological
  #4=Lifestyle+Pharmacological

#Transitions from healthy state

for (j in 1:4) {
for (k in 1:5) {

p[j,k,1,2] ~ dbeta(268.73412,13302.787)  # H to M
p[j,k,1,3] ~ dbeta(153787.29,32505219) # H to T2 0.005
p[j,k,1,4] ~ dbeta(98.014537,5451.3929) # H to CVD 0.018
p[j,k,1,5] <- 0
p[j,k,1,6] <- HD[k]  # H to D
p[j,k,1,1] <- 1 - (p[j,k,1,2]+p[j,k,1,3]+p[j,k,1,4]+p[j,k,1,6])

lambda13[j,k]  <- -log(1-p[j,k,1,3])
lambda14[j,k] <- -log(1-p[j,k,1,4])
lambda16[j,k] <- -log(1-HD[k])
}}
```

CODE 2: **Definition of a transition matrix**

```
#Transition from MetS state to healthy

# Integrate MTC into decision model - 4 treatments

for (k in 1:5) {
#p[1,k,2,1] ~ dbeta(160.1025,1015.3931)  # M to H - Control
p[1,k,2,1] <-  prob.mh  # M to H - Control
p[2,k,2,1] <- ((p[1,k,2,1]/(1-p[1,k,2,1]))*OR[1,2])/(1+(p[1,k,2,1]/(1-p[1,k,2,1]))*OR[1,2])
p[3,k,2,1] <- ((p[1,k,2,1]/(1-p[1,k,2,1]))*OR[1,3])/(1+(p[1,k,2,1]/(1-p[1,k,2,1]))*OR[1,3])
p[4,k,2,1] <- ((p[1,k,2,1]/(1-p[1,k,2,1]))*OR[1,4])/(1+(p[1,k,2,1]/(1-p[1,k,2,1]))*OR[1,4])  }


# Use RRs from Cohort Systematic Review for effect of MetS

logrr23.m <- log(3.60)
logrr23.s <- (log(4.52)-log(2.87))/(2*1.96)
logrr23.p <- 1/(logrr23.s*logrr23.s)
logrr23 ~ dnorm(logrr23.m,logrr23.p)
rr23 <- exp(logrr23)

logrr24.m <- log(1.61)
logrr24.s <- (log(1.73)-log(1.49))/(2*1.96)
logrr24.p <- 1/(logrr24.s*logrr24.s)
logrr24 ~ dnorm(logrr24.m,logrr24.p)
rr24 <- exp(logrr24)

logrr26.m <- log(1.15)
logrr26.s <- (log(1.18)-log(1.12))/(2*1.96)
logrr26.p <- 1/(logrr26.s*logrr26.s)
logrr26 ~ dnorm(logrr26.m,logrr26.p)
rr26 <- exp(logrr26)
```

CODE 3: **Definition of a transition matrix**

```
# Transitions from MetS, T2DM, CVD and T2DM+CVD

for (j in 1:4) {
for (k in 1:5) {
#p[j,k,2,3] ~ dbeta(2.7740265,161.87177)  # M to T2 0.017
p[j,k,2,3] <- 1-exp(-lambda13[j,k]*rr23)
#p[j,k,2,4] ~ dbeta(7.7445077,266.08191) # M to CVD 0.028
p[j,k,2,4] <- 1-exp(-lambda14[j,k]*rr24)
p[j,k,2,5] <- 0
#p[j,k,2,6] <- MD[k]   # M to D
p[j,k,2,6] <- 1-exp(-lambda16[j,k]*rr26)
p[j,k,2,2] <- 1 - (p[j,k,2,1] + p[j,k,2,3] + p[j,k,2,4] + p[j,k,2,6])

p[j,k,3,1] <- 0
p[j,k,3,2] <- 0
p[j,k,3,3] <- 1 - (p[j,k,3,5]+p[j,k,3,6])
p[j,k,3,4] <- 0
p[j,k,3,5] ~ dbeta(77.996773,5910.4975)   # T2 to CVD+T2
p[j,k,3,6] ~ dbeta(0.3089547,26.828762)   # T2 to D

p[j,k,4,1] <- 0
p[j,k,4,2] <- 0
p[j,k,4,3] <- 0
p[j,k,4,4] <- 1 - p[j,k,4,6]
p[j,k,4,5] <- 0
p[j,k,4,6] ~ dbeta(0.18972,5.0332918)   # CVD to D
#p[j,k,4,6] ~ dbeta(2.19,121.676)   # CVD to D sensitivty analysis

p[j,k,5,1] <- 0
p[j,k,5,2] <- 0
p[j,k,5,3] <- 0
p[j,k,5,4] <- 0
p[j,k,5,5] <- 1 - p[j,k,5,6]
p[j,k,5,6] ~ dbeta(2.0981077,6.377917)  # T2+CVD to D
#p[j,k,5,6] ~ dbeta(0.07,1.345)  # T2+CVD to D sensivity analysis
} }

for (j in 1:4) {
for (k in 1:5) {
p.test[j,k] <- p[j,k,1,1]*p[j,k,2,2]*p[j,k,3,3]*p[j,k,4,4]*p[j,k,5,5]
p.neg[j,k] <- 1-step(p.test[j,k]) }}
```

6.2.1 λ_1: MetS transition to Healthy

The Mixed Treatment Comparison (MTC) performed in Chapter 4 was used to inform the decision model for the transition from MetS to the healthy state. Figure 6.2 shows the network chosen specifically for this analysis, each number represents the number of studies for that specific comparison. The transition probability from MetS to healthy

for the control group was estimated using a random effect meta-analysis on the log hazard scale in order to produce an overall pooled log hazard estimate, which was then transformed on to a probability scale to produce a one year transition probability of 0.136 *(SE 0.022)*. Also odds ratios for each of the treatments studied (*Lifestyle (OR 4.48, SE 1.605), Pharmacological (OR 2.05, SE 0.771) and both together (OR 1.55, SE 1.313)).* These ORs were estimated with a Bayesian Mixed Treatment Comparison analysis in Chapter 4. The MTC model (Equation 4.5), incorporated in the Markov model, was a random effects model adjusting by follow up, to obtain a year estimate. Table **6.1** shows the transition probability using the incidence rate of λ_1 and the Beta parameters estimated for this relation between MetS to healthy state. The MetS state is the start of the simulation. **CODE 4** shows the WinBUGS code for the incorporation of the MTC analysis into the model.

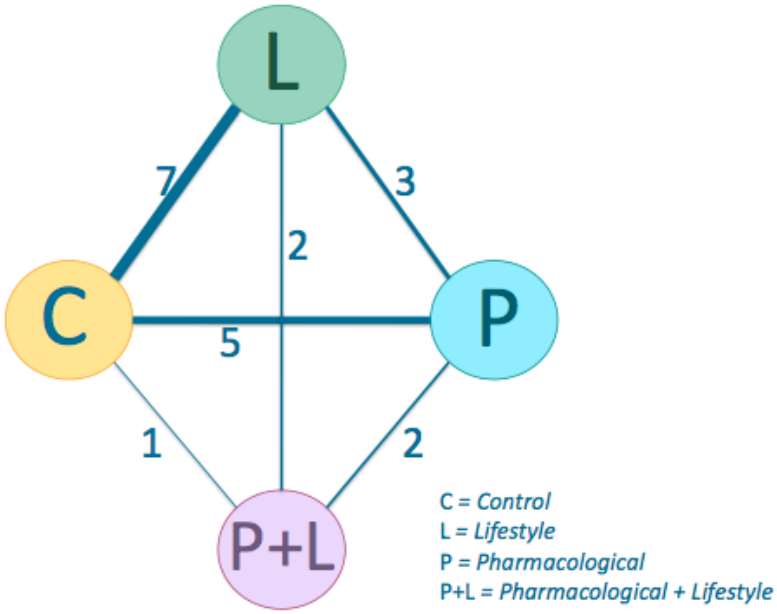


Figure 6.2: *Network of treatments for MetS*

CODE 4: **Integration of the Mixed Treatment Comparison Analysis**

```
# MTC Model - 4 treatments

for(i in 1:nstud) {
        w[i,1]<-0
        delta[i,tx[i,1]]<-0
        mu[i] ~ dnorm(0,.0001)

        for (k in 1:na[i]) {
        r[i,k] ~ dbin(pr[i,k],n[i,k])
        logit(pr[i,k]) <- mu[i] + delta[i,tx[i,k]]
        }

        for (k in 2:na[i]) {
        # Model
        delta[i,tx[i,k]] ~dnorm(md[i,tx[i,k]],taud[i,tx[i,k]])
        md[i,tx[i,k]] <- d[tx[i,k]] - d[tx[i,1]] + sw[i,k]
        taud[i,tx[i,k]] <- tau *2*(k-1)/k
        w[i,k] <- (delta[i,tx[i,k]] - d[tx[i,k]] + d[tx[i,1]])
        sw[i,k] <- sum(w[i,1:k-1])/(k-1) }
        }

d[1]<-0
for (k in 2:ntreat) {d[k]~dnorm(0,0.0001) }
sd~dunif(0,5)
tau<-1/(sd*sd)

#Adjusting the probability to one year

for (k in 1:9) {
loghaz[k] <- log(r[k,1]/(n[k,1]*fup[k]))
loghaz.prec[k] <- r[k,1]
loghaz[k] ~ dnorm(theta[k],loghaz.prec[k])
theta[k] ~ dnorm(mu.loghaz,tau.loghaz) }
mu.loghaz ~ dnorm(0.0,0.001)
tau.loghaz <- 1/pow(sd.loghaz,2)
sd.loghaz ~ dunif(0,2)
prob.mh <- 1 - exp(-exp(mu.loghaz))

# All pairwise log odds ratios and odds ratios
for (c in 1:(ntreat-1)) {
        for (k in (c+1):ntreat) {
                                        LOR[c,k]<- d[k] - d[c]
                                        log(OR[c,k])<- LOR[c,k]  } }
```

6.2.2 $\lambda_{2,3,4}$: MetS transition to T2DM, CVD and All-cause mortality

The systematic review undertaken in Chapter 5 provided evidence to the model for the estimation of the transition probabilities related with the risk of developing T2DM, CVD and All-cause mortality. Table **6.1** shows the UK population incidence rates estimated for MetS to T2DM. The transition probability for λ_2 ($P(\lambda_2) = 0.017$) was calculated from the multiplication of the transition probability of λ_6 (corresponding to the transition from a healthy state to T2DM), by the risk ratio estimated from the cohort systematic review presented in Chapter 5. This is the risk of developing T2DM given a MetS diagnosis ($RR = 3.60$).

For the transition from the state of MetS to the state of CVD, a transition probability for $P(\lambda_3)$ is obtained by the multiplication of the transition probability of $P(\lambda_7)$ estimated for the transition between healthy and CVD ($P(\lambda_7) = 0.018$) and the risk of developing CVD when a MetS diagnosis has been assessed positive ($RR = 1.61$); therefore the transition probability is $0.018 \times 1.61 = 0.028$.

The transition rates between MetS to All-cause mortality represented by λ_4 were specified according to 5 age groups (45-54, 55-64, 65-74, 75-84, 85+). Incidence rates increase with age, therefore it is necessary to adjust the transition rates by age according to the number of cycles integrated in the model. λ_4 integrates aging into the model. The mortality rates for the healthy states to death (represented by λ_8) for all age groups were extracted from the Office of National Statistics of UK. These rates were multiplied by the pooled risk ratio of having a fatal event given a previous MetS diagnosis ($RR = 1.15$), to obtained the range of transition probabilities needed for the different

age groups in the transition from MetS to All-cause mortality.

Estimates from the systematic review introduced in Chapter 5 are presented for a broad population in Table **6.1**. Risk ratios were estimated for each MetS transition, to T2DM (*3.60 SE 1.051*), to CVD (*1.61 SE 1.016*) and to a death state (*1.15 SE 1.006*). The effect estimates of the risk ratio are assumed to follow a LogNormal distribution. Credible intervals and LogNormal parameter estimates to be used in this specific transition are also presented in Table **6.1**. Box **1** shows the WinBUGS code for the incorporation of these probabilities into de model.

6.2.3 λ_5: Healthy transition to MetS

The San Antonio Heart Study (Han et al. [2002]) was used to extract the incidence of MetS. This study was designed as a cohort study with a follow up of 8 years. They observed Mexican Americans and non-Hispanic whites with ages between 25 and 64 years. The incidence of MetS was computed by dividing the number of people who developed MetS *(267)* with the total number of people in the study *(n = 1637)* multiplied by the number of years of follow-up *(8 years)*. The longitudinal characteristic of this identified study provides a reliable estimation of the incidence of MetS in a specific population. The estimated incidence rate can be represented as follows:

$$\begin{aligned} \lambda_5 &= 267/(1637 \times 8) \\ &= 0.02038790 \\ &= 0.02 \end{aligned} \tag{6.7}$$

Therefore, the estimation of the standard error is given by:

$$\begin{aligned} SE &= 1/\sqrt[2]{267} \\ &= 0.06119901 \\ &= 0.06 \end{aligned} \tag{6.8}$$

Using the result from 6.7 a transition probability can be obtained as follows:

$$\begin{aligned} P(\lambda_5) &= 1 - e^{-0.02} \\ &= 0.01980133 \\ &= 0.020 \end{aligned} \tag{6.9}$$

This study performed an observational description of a mixed population in the area around the borders between USA and Mexico. It is important to remark the lack of evidence from other regions of the world, this can be introducing high uncertainty for the estimation of λ_5. The **CODE 1** introduces the implementation of this data in the Stochastic decision model using WinBUGS. **Table 6.1** shows the Beta parameters calculated for this model.

6.2.4 $\lambda_{6,7,8}$: Healthy transition to T2DM, CVD & Death

Three different sources were used for the transitions related with the healthy state. A cohort study to estimate a 10 year risk of acquiring T2DM was identified (Hippisley-

Cox et al. [2009]). This prospective cohort used data from 355 general practices in England and Wales and also validated the score (QDScore). This score was a result of the analysis of the factors observed in the cohort for their predictability related with T2DM, ($\lambda_6 = Incidence = 4.7, SE = 0.004$). This was a weighted average between women age standardized rate 4.19 (4.09 to 4.29) and men 5.54 (5.43 to 5.66) per 1000 person years.

Estimates used for the CVD transition (λ_7) were extracted from Shepherd et al. [1995] ($Incidence = 10.02, SE = 0.58$). This estimate was calculated using the information from the placebo groups of the study. This randomized control trial was designed to assess the effectiveness of pravastatin in the reduction of the incidence risk of non fatal myocardial infarction and death of coronary heart disease. The average follow up of was 4.9 years. It is important to appoint that there are limitations with this data, as it comes from a trial observing a group of 6595 men, with ages from 45 to 64 years old. This observation may introduce some selection bias as trials can only observe from voluntary patients that consciously participate in the study, however this is the best available evidence and the control group provide evidence of a cohort observation for an estimation of the incidence related with development of CVD from a healthy state. Men participating in this trial did not have MetS at baseline, but presented hypercholesterolemia, as it is the target of the treatment with pravastatin.

For mortality estimates (λ_8), statistics from the Department of Health Statistics for England and Wales were used. Extracted from Gillies [2008], page 126. Incorporation of these mortality rates apply the effect of aging in the model, as mortality rates were extracted according to age groups defined. Details of data used for this transition can be found in Table **6.1** and WinBUGS code is presented in Box **1**.

6.2.5 $\lambda_{9,10,11,12}$: T2DM & CVD transitions to Death

The combined state of CVD and T2DM was considered as a complication of T2DM (λ_9), as the evidence to feed this transition from T2DM to CVD is extracted from the United Kingdom Prospective Diabetes Study (UKPDS) (Clarke et al. [2004]). This study was designed to estimate lifetime health outcomes of patients with T2DM like progression of the disease to CVD. There were 3642 patients involved in this study.

The Decode study (group on behalf of the European Diabetes Epidemiology Group [1999]) was used for the transition between T2DM and mortality (λ_{10}). This analysis assessed baseline data from 13 prospective European cohort studies, for a total of 18,048 men and 7,316 women with a minimum of 30 years old. Mortality was evaluated according to different diagnostic glucose categories.

Estimates calculated by Hamer and Stamatakis [2009] were used for the transition from CVD to death (λ_{11}). This study examined the mortality associated to different types of physical activities (domestic, walking, sports) in patients with established CVD. Scottish Health Surveys were used to extract the data for the analysis. 175 people died during the follow up period (average of 5.6 years) from a total of 837 men and women with a CVD diagnosis confirming their clinical condition.

The UKPDS (Clarke et al. [2004]) also was used for the estimates of the combined state of T2DM and CVD to death (λ_{12}). This is possible as the combined state does not compile evidence related with a progression in the other direction (from a baseline of CVD to T2DM), therefore CVD is still considered as a complication resulting from the degenerative effect of T2DM. Table **6.1** presents the different values found for the

data needed for the model and specifyied transitions. Box **1** shows the incorporation of parameters calculated for this part of the model.

6.2.6 λ_{13}: Transition from CVD to T2DM+CVD

Evidence for the transition from CVD state to the combined state T2DM and CVD together was very difficult to identify. Figure 6.1 shows this relation in the model with a gray arrow; because, even when there can be people developing CVD and then T2DM, there is no enough research about this transition. Investigation have tended to focus on the examination of the T2DM and its complications considering CVD, but CVD research looking at the risk of developing T2DM as a posterior outcome of CVD was not identified. Therefore, the potential bias on the available research concentrating in one direction of the relation led the elimination of λ_{13} to be more realistic with the interpretation of the results.

Efforts to find evidence for this transition were related with undertaking search strategies for published literature, about studies observing a specific group individuals with CVD; and not used as a complication from a cohort with T2DM as a baseline characteristic. However, there is lack of published evidence observing individuals with previous CVD diagnosed and using the development of T2DM as outcome.

After defining each transition of the model structure different information is required to obtain a simulation close to the reality of this context. Following sections describe the incorporation of data related with the intervention, costs and utilities to characterize each health state of the model.

The model being fitted is a discrete-time discrete-state Markov model, for predicting

costs and benefits over time. These models assume that in each cycle an individual is in one of a number of states; besides the Markov property, however it depends on the cycle and other progressive risk factors (Spiegelhalter and Best [2003]).

A discrete-time model is assumed:

$$t = 1, ..., T \tag{6.10}$$

It is assumed that, within each cycle t a subject remains in one of K states, and that all transitions occur at the start of each cycle. The probability distribution at the start of the first cycle $t = 1$ is represented by a row vector π_1. A transition matrix Δ_t where i, j^{th} element is the probability of moving from state i to state j between cycle $t - 1$ and t. A marginal probability distribution π_t during cycle $t < 1$, follows this relation (Spiegelhalter and Best [2003]) for different transition matrices,

$$\pi_t = \pi_{t-1}\Delta_{st} \tag{6.11}$$

If the cost of spending a cycle in state k is c_k, $k = 1, ..., K$, using appropriate year prices, and there is a fixed cost input c_0. Then the total cost assumed by each patient in the population is, with discount costs (Spiegelhalter and Best [2003]),

$$E[C] = c_0 + \sum_{t=1}^{T} \frac{\pi_t c'}{(1 + \delta_c)^{t-1}} \tag{6.12}$$

If utilities of being in each state are given by a row vector b, also discounted per cent per cycle, the total expected QALYs for each patient is (Spiegelhalter and Best

[2003]),

$$E[B] = \sum_{t=1}^{T} \frac{\pi_t b'}{(1+\delta_b)^{t-1}} \tag{6.13}$$

6.3 Incorporating the intervention

As the principal aim of the model is to evaluate the effect of an intervention based on MetS, the model needs specification of it. A three year intervention was defined based on the study period of the Diabetes Prevention Program (Herman et al. [2003]). This study evaluated intensive lifestyle and pharmacological therapies like metformin as it is focused on T2DM. These results demonstrated lifestyle interventions to reduce the incidence of T2DM by 58% when compared with the placebo intervention and the metformin therapy reduced the incidence of T2DM by 31% over 2.8 years. The intervention under observation with the model presented in this Chapter will also assess prevention of CVD and all-cause mortality. Therefore, MetS was determined as the optimal criteria to achieve this aim, given the cluster of risk factors related with both T2DM and CVD. Chapter 4 was performed to evaluate the effectiveness of different therapies to reverse a diagnosis of MetS, presenting the main assumption related with the effective reversal of MetS to have an important impact in preventing individuals to progress to T2DM, CVD and all-cause mortality. If this argument is realistic the simulation performed by the model should show individuals spending more time in a healthy state and significantly less time in states like T2DM or CVD. The Mixed Treatment Comparison model developed in Chapter 4 without covariates was integrated into the model as described in section 6.2.1. The costs integrated for the 3-year intervention

are going to be describe in section 6.4.2.

6.4 Calculating the Costs

In order to specify a model that can also provide information contrasted economically, the costs related with the health states previously defined are also incorporated into the Markov simulation. **Table 6.2** presents the costs per person year. A health economic evaluation requires the identification of evidence related to the clinical factors involved in the model. The costs of the interventions under study are also incorporated in the model, to obtain an estimate of the total cost that would be involved in the implementation of a MetS-based intervention for the UK population. This additions to the model allows the analysis of economic behaviors that are closely link to the clinical pattern that is being represented by the model structure. These results will also provide information to assess each possible intervention economically. This analysis is undertaken from the perspective of health system and to have an impact in society.

This section specifies the sources of information related with the costs associated with each health state represented in the model and the costs estimated for the lifestyle and pharmacological interventions to be evaluated in the cost-effectiveness analysis.

6.4.1 Costs associated with the health states

Different sources were identified to extract the data needed to incorporate cost information related with each state of the model. Since this analysis is aiming to provide a solution strategy for UK, the identification of the costs is constrained to this population.

Table **6.2** presents the data related with the costs in each state transition.

The cost of being in **MetS** state was estimated with data extracted from Smith et al. [2010], which uses evidence from the Diabetes Prevention Program (Herman et al. [2005]). Data related with costs of MetS using UK prices was difficult to identify, Smith et al. [2010] undertook a cost-effectiveness analysis of a modified diabetes prevention program intervention (for 3-year period) to reduce risk of T2DM and CVD in Southwestern, Pennsylvania (2005-2007); making this study the best available evidence for this type of cost estimates. The healthcare costs in USA are significantly higher than in UK, therefore this estimate was adjusted to the UK prices in healthcare by obtaining drug and clinical attention costs specific to the UK. The information needed for the MetS state cost has to be restricted to the individual cost of having this diagnosis and it depends on the specific combination of risk factors that the individual is showing; however given the lack of individual patient data, the costs are representing an average of the related factors. The average cost of treating a subject with diagnosed MetS was calculated at £52,33 per person year, with a standard error of £6,38. A Gamma distribution was used to incorporate the stochastic nodes related with the cost in each state. Cost data are constrained to be non-negative and are based of counts of resource use weighted by unit costs; count data is usually represented by the Poisson distribution, however the gamma distribution is conjugate to the Poisson, meaning that posterior parameter distributions for Poisson data are often characterized by gamma distributions and it is constrained to the interval 0 to the positive infinity, making gamma distribution appropriate to represent the uncertainty in cost parameters, given is highly skewed characteristic (Briggs et al. [2006]). Calculated Gamma parameters (α, β) specified to each health state are presented in Table **6.2**.

The costs of having a diagnosis of **T2DM** were extracted from the United Kingdom Prospective Diabetes Study (Clarke et al. [2005]). This study assessed the impact of complications deriving from T2DM on healthcare costs. The evidence identified for the cost of T2DM was based in individuals who have not developed any complication, providing the best reference for the Markov simulation.

For the costs associated with **CVD**, synthesis of evidence was crucial, given the variability presented by the definition of CVD. Different sources were identified in Picot et al. [2009] and Ward et al. [2007], where evidence specific for CHD and Stroke was obtained; however the best available information was identified from the UKPDS, where costs are provided by specification of fatal and non-fatal myocardial infarction, fatal and non-fatal stroke and heart failure. This data was combined and adjusted to obtain specific costs of CVD and excluding the cost of T2DM, as CVD events are consider diabetes-related complications. Gamma parameters were calculated after combination of specific CHD and Stroke event costs. In the case of the combined state **T2DM and CVD**, the UKPDS information provided the best evidence; given the previous determination of this state considering CVD as a T2DM complication. The health state and death state were consider costless for healthcare.

Table **6.2** also presents evidence used for the utilities incorporated in the model, which are going to be explain in the Section 6.5. **CODE 5** presents the WinBUGS code for the economic evaluation and its incorporation into the decision model. Inflation factors for the appropriate number of years were used to adjust costs to 2009 prices.

Table 6.2. Costs for each state in the economic decision model.

State	Mean	SE	Gamma Dist * Alpha	Gamma Dist * Beta	Source	Author	Year
			UK population estimates				
Cost for chronic disease in £							
Mets	52.33	6.38	67.34	1.29	PCD, Herman et al.*	Smith, K.	2010
Diabetes	157.00	6.38	606.03	3.86	UKPDS, HTA	Clarke, P.M.	2004
CHD**	45.00	3.00			HTA	Picot, J.	2009
Stroke**	34.00	3.00			HTA, Ward et al.*	Picot, J.	2009
CVD	330.09	32.65	102.22	0.31	*UKPDS	Clarke, P.M.	2003
T2+CVD	527.04	32.39	264.81	0.50	UKPDS	Clarke, P.M.	2003

SE: *Standard Error,* HTA: *Health Tecnology Assessment,* UKPDS: *UK Prevention Diabetes Study,* PCD: *Preventing Chronic Disease ($=1.65)*, CVD: *Cardiovascular disease*, CHD: *Coronary Heart Disease.*

CODE 5: **Incorporation of costs of healthy states**

```
# Costs - adjusted to 2009 prices

diab.cost0 ~ dgamma(606.02623,3.8600397)
diab.cost <- diab.cost0*1.03*1.028*1.032*1.043*1.04
mets.cost ~ dgamma(67.336248,1.2866799)
cvd.cost ~ dgamma(102.22309,0.3096852)
cvdt2.cost0 ~ dgamma(264.80522,0.5024371)
cvdt2.cost <- cvdt2.cost0*1.03*1.028*1.032*1.043*1.04

cost[1] <- 0
cost[2] <- mets.cost
cost[3] <- diab.cost
cost[4] <- cvd.cost
cost[5] <- cvdt2.cost
cost[6] <- 0
```

6.4.2 Costs of Lifestyle & Pharmacological Interventions

Costs of **lifestyle interventions** were based on the Diabetes Prevention Program (Herman et al. [2003, 2005]). This costs were converted to UK currency and adjusted to 2009 prices using economic inflation data. A log-normal distribution was used for the stochastic integration of these evidence, given its skewness. The log-normal distribution enjoys similar characteristics of the gamma distribution for costs. Table **6.3** presents the costs values for the interventions in british sterling pounds. The cost for the **pharmacological therapies** evaluated in this analysis, were extracted from the British National Formulary of Great Britain and Association [2009] (BNF). The ADDITION study (Sandbaek et al. [2008]) was used to obtain estimates of proportions of individuals with conditions needing drug treatments. This study is a randomized control trial of the effectiveness of intensified multifactorial treatment on 5-year cardiovascular morbidity and mortality rates in people with screen-detected T2DM in the Netherlands, UK and Denmark. Therefore a binomial distribution was determined for the stochastic incorporation into de Markov simulation of the costs related with pharmacological therapies. The model uses this proportions to calculate costs for individuals with MetS needing this specific treatment. This was defined as not every single subject with MetS needs a pharmacological therapy related with specific combinations of the risk factors involved in MetS. Given MetS is defined as a cluster of risk factors, different combinations of these factors can be identified in a group of individuals, with a MetS diagnosis.

The costs extracted from the BNF are then multiplied by the proportions estimated to obtain the cost of the pharmacological intervention during the 3-year period of the intervention. Proportions were obtained for blood preassure, cholesterol and tryglicerides,

and glucose interventions. Beta hyperparameters were specified for these proportions ($p_i \sim Beta[1,1]$, where i is representing the three different proportions incorporated in the model).

Table 6.3. Costs of Intervention in £

	Lifestyle Interventions				Pharmacologial therapy				
	Mean	SE	LogNormal Dist		Therapy		£	Binomial Dist	
			μ	σ				Proportion	Sample
Year 1	1,162.00	31.429	7.06	0.027	ACE Inhibitor	Lisinopril	15.48	0.920	1981
Year 2	564.07	21.894	6.33	0.039	Statin	Pravastatin	20.52	0.933	1981
Year 3	583.18	22.270	6.36	0.038	Anti-diabetic/ Glucose control	Metformin	33.48	0.241	1981

SE: *Standard Error. Source: DPP, Herman W.H. and British National Formulary.*

CODE 6 shows the WinBUGS code used to integrate the costs of the lifestyle interventions and **CODE 7** shows the code for the costs related with the pharmacological interventions.

CODE 6: **Integration of costs of lifestyle interventions**

```
# Use  DPP costs for lifestyle intervention (exchange & 2009 prices)
# and fitting a log-Normal distribution to aggregated costs

life.sup.mean1 <-
(1399/1.52)*1.018*1.017*1.029*1.03*1.028*1.032*1.043*1.04
life.sup.var1 <-
((1189/1.52)*1.018*1.017*1.029*1.03*1.028*1.032*1.043*1.04)
life.sup.sigma12 <- log(1+life.sup.var1/pow(life.sup.mean1,2))
life.sup.prec1 <- 1/life.sup.sigma12
life.sup.mu1 <- log(life.sup.mean1) - 0.5*life.sup.sigma12

life.sup.mean2 <-
(679/1.52)*1.018*1.017*1.029*1.03*1.028*1.032*1.043*1.04
life.sup.var2 <-
((577/1.52)*1.018*1.017*1.029*1.03*1.028*1.032*1.043*1.04)
life.sup.sigma22 <- log(1+life.sup.var2/pow(life.sup.mean2,2))
life.sup.prec2 <- 1/life.sup.sigma22
life.sup.mu2 <- log(life.sup.mean2) - 0.5*life.sup.sigma22

life.sup.mean3 <-
(702/1.52)*1.018*1.017*1.029*1.03*1.028*1.032*1.043*1.04
life.sup.var3 <-
((597/1.52)*1.018*1.017*1.029*1.03*1.028*1.032*1.043*1.04)
life.sup.sigma32 <- log(1+life.sup.var3/pow(life.sup.mean3,2))
life.sup.prec3 <- 1/life.sup.sigma32
life.sup.mu3 <- log(life.sup.mean3) - 0.5*life.sup.sigma32


life.sup1 ~ dlnorm(life.sup.mu1,life.sup.prec1)
life.sup2 ~ dlnorm(life.sup.mu2,life.sup.prec2)
life.sup3 ~ dlnorm(life.sup.mu3,life.sup.prec3)

life.sup <- (life.sup1+life.sup2+life.sup3)*add.p[2]

cost.intv[1] <- 0
cost.intv[2] <- life.sup
cost.intv[3] <- cost.pharm3
cost.intv[4] <- life.sup + cost.pharm4
```

CODE 7: **Integration of costs of pharmacological interventions**

```
# Cost proportions from ADDITION

# BP intervention - ACE inhibitor, Lisinopril, BNF page 105
# Cholesterol/tryglicerides intervention - Statin, Pravastatin, BNF  page
# Glucose intervention - Metformin, BNF page 383


cost.pharm3 <- time[3,2]*cost.pharm
cost.pharm4 <- time[4,2]*cost.pharm

cost.pharm <- p.bp*15.48 + p.trychol*20.52 + p.fp*33.48

add.bp ~ dbin(p.bp,1981)
add.trychol ~ dbin(p.trychol,1981)
add.fp ~ dbin(p.fp,1981)

p.bp ~ dbeta(1,1)
p.trychol ~ dbeta(1,1)
p.fp ~ dbeta(1,1)
```

6.5 Integrating the Utilities of the health states

A cost-effectiveness analysis involves incorporation of quality of life weights for each of the health states under consideration in the Markov model. Integration of this evidence will provide estimates related with improvement of quality of life obtained after introducing the interventions of interest. In order to obtain quality adjusted life years as principal outcomes from the model, as explained in section 3.1.8, a measure of utility is needed. These outcomes will be supporting the understanding of British population patterns for health decision making. Different sources were identified for the utility estimates. Table **6.4** presents estimates used for the utilities in the Markov simulation.

For the MetS state, the utility estimate was identified in the Diabetes Prevention Program (Herman et al. [2005]), however this estimate (0.73) is based on a different population of interest. The ADDITION study (Sandbaek et al. [2008]) was used to obtain an estimate for the UK population (0.825), based on the EQ-5D score (Dolan [1997]). The T2DM state utility was extracted from the UK Prospective Diabetes Study (Clarke et al. [2002]). Also the utilities for the combined state T2DM and CVD were extracted from this study, as this state is considering CVD like a complication progressing from T2DM. The utilities for CVD were extracted from the report of *One Thousand Health-Related Quality of Life Estimates* (Tengs and Wallace [2000]). Studies for the estimation of health utilities are few and this report provides utilities for CVD that were not identified in other studies. This report combines evidence from 154 documents yielding 1000 original quality of life weights, however is important to mention the difficulty in the identification of quality evidence related with the utility estimates, making this source the bet available evidence to be use for cost-effectiveness analysis. The lack of

this evidence could be introducing bias to the model. Parameters from a Beta distribution were calculated for the stochastic integration of the utilities.

CODE 8 presents the WinBugs code incorporating utilities into the decision model and calculation of model outcomes like the total cost and total utilities for each intervention. This section of the code also presents an undiscounted calculation of QALYs; meaning that this calculation does not take into account the population norms of aging as it is a summary of the time spent in each state multiplied by its state utility. The calculation of QALYs taking into account aging are presented in **CODE 11** in Section 6.7.

Model outcomes are defined as a totalization of cost and utilities are calculated for each of the interventions including control as a reference for comparison of the interventions. The ICER is calculated as the ratio of the difference in cost and the difference of the utilities, this difference is contrasting the therapies of interest with the control intervention. The model also calculates probabilities of each intervention to be cost-effective at different thresholds of willingness to pay from the healthcare providers. The range of the inversion needed to achieve significant effects were set from £100 to £150,000. The threshold of interest for this analysis is £20,000, therefore the interventions have to show important effectiveness when an investment of that level is implemented or be effective for less in order to be consider by the UK authorities.

Table 6.4. Utilities for each state in the economic decision model.

State	Mean	SE	Beta Dist Alpha	Beta	Source	Author	Year
Broad population estimates							
Utilities of intervention							
Mets	0.825	0.140	5.26	1.12	ADDITION	Sandbaek, A.	2008
Diabetes	0.725	0.035	117.27	44.48	UKPDS	Clarke, P.M.	2002
CHD**	0.670	0.140			OTHR QOLE	Tengs, T.	2000
Stroke**	0.540	0.210			OTHR QOLE	Tengs, T.	2000
CVD	0.605	0.252	1.67	1.09	**Average (CHD, Stroke)	Tengs, T.	2000
T2+CVD	0.403	0.057	29.44	43.61	UKPDS	Clarke, P.M.	2002

SE: *Standard Error,* UKPDS: *UK Prevention Diabetes Study,* CVD: *Cardiovascular disease*, CHD: *Coronary Heart Disease,* OTHR QOLE: *One Thousand Health-Related Quality Of Life Estimates.*

CODE 8: **Integration of utilities**

```
# Utilities

mets.util ~ dbeta(5.2624878,1.1191474) # 0.825
diab.util ~ dbeta(117.27245,44.482653) # 0.725
cvd.util ~ dbeta(1.671705,1.0914438) # 0.605
cvdt2.util ~ dbeta(29.439466,43.611319) # 0.403

util[1] <- 1
util[2] <- mets.util
util[3] <- diab.util
util[4] <- cvd.util
util[5] <- cvdt2.util
util[6] <- 0

# Alternative calculation of qalys – undiscounted

for (j in 1:4) {
tot.util2[j] <- time[j,1]*util[1] + time[j,2]*util[2] + time[j,3]*util[3] + time[j,4]*util[4] +
time[j,5]*util[5] + time[j,6]*util[6] }

for (j in 1:4) {
tot.costa[j] <- sum(cost.distot[j,])
tot.cost[j] <- tot.costa[j] + cost.intv[j]
tot.util[j] <- sum(qaly.distot[j,]) }

for (l in 2:4) {
diff.cost[l] <- tot.cost[l] - tot.cost[1]
diff.util[l] <- tot.util[l] - tot.util[1]

ICER[l] <- diff.cost[l]/diff.util[l]

# CEAC

for (k in 1:18)  {
INB[l,k] <- K[k]*diff.util[l] - diff.cost[l]
Q[l,k] <- step(INB[l,k]) }  }
```

6.6 Defining starting states

The model specification requires a starting proportion for each state of the model structure (starting states). A Dirichilet distribution can be used for the transition matrix. Proportions for the states of MetS, T2DM and CVD were extracted from the ADDITION study (Sandbaek et al. [2008]). The rest of the states (T2DM+CVD and Death) were fixed at 0 for the start. These values were incorporated into the model as a multinomial distribution with a vague Dirichilet distribution, to let the data dominate this prior. However for the base case model developed, the entire cohort starts in MetS state; the starting proportions using ADDITION data will be discussed as part of the sensitivity analysis in Section 6.9. **CODE 9** shows the WinBUGS code for the definition of starting states for the simulation of the model.

$$r_{ij} \sim multinomial(\pi_{ij}, N_i) \tag{6.14}$$

$$\pi_{ij} \sim dirichilet(1, 1, 1) \tag{6.15}$$

$$\pi_{i1} + \pi_{i2} + \pi_{i3} = 1 \tag{6.16}$$

The dirichilet distribution is an extension of the beta distribution and can be used to model more than two outcomes. In these case three proportions are going to be integrated in the model for Healthy state, MetS state and T2DM state, in order to simulate the different possibilities there are for people to enter in a process like the one aiming

by this thesis. π_{ij} represent each of the proportions integrated in the Markov model using the ADDITION data to be compared with the base case model, where there is no distribution of these proportions. In CODE 9 is reflected as 1 for the second state defined in the model (MetS), meaning the full cohort will start in MetS.

CODE 9: **Definition of starting states**

```
# Using ADDITION for starting states
add.start[1:3] ~ dmulti(add.p[1:3],add.N)
add.p[1:3] ~ ddirch(alpha[1:3])

# Starting vector/states
for (j in 1:4) {
start[j,1] <- 0   #Healthy
start[j,2] <- 1   #Metabolic Syndrome
start[j,3] <- 0   #Diabetes
start[j,4] <- 0   #CVD
start[j,5] <- 0   #T2+CVD
start[j,6] <- 0 } #Death

# s = proportion of people in each state at time t, (treatment, state, time=1)
#for (j in 1:2) {   #treatments from MTC
#for (i in 1:6) {    #States
#s[j,i,1] <- start[j,i] } }

for (j in 1:4) {
s[j,1,1]<-start[j,1]
s[j,2,1]<-start[j,2]
s[j,3,1]<-start[j,3]
s[j,4,1]<-start[j,4]
s[j,5,1]<-start[j,5]
s[j,6,1]<-start[j,6] }
```

6.7 Characterizing the population for simulation

For these Markov model, the proportion of people in each state at each yearly cycle of the model (time), was calculated using the inprod command in WinBUGS. This command uses the transition rate between states and the estimated proportion of people to be in each state at the previous time (previous cycle simulation). Each cycle represent a year in time. **CODE 10** shows the definition of the cycle proportions calculated. Transition rates were varied depending on the year cycle of the model, to be able to simulate population aging, from 45 year of age at the start of the model to 100 years of age when the model reaches the 55^{th} cycle. The sensibility analysis takes into account other lengths (20 years) of the horizon defined for the base case in section 6.9 and also different ages at entry (40 and 60 years).

The base case scenario assumes the aging effect is given by the state condition determined, therefore utilities by age were set at 1 and uses the utilities previously incorporated in each health state described in section 6.5. However, in order to incorporate aging, population norms for the healthy state utilities were based on the EQ-5D scale from the UKPDS (Clarke et al. [2004]). The ADDITION study collected quality of life data using EQ-5D questionnaries, on screen detected population. This algorithm was developed using a representative sample of the UK population and elicited direct valuations for EuroQol health states using the time trade-off method (Dolan [1997]; Srinivasan [2011]). Model with defined health utilities are presented in the sensitivity analysis in section 6.9.

As a result of modelling aging in the Markov model, it provides the ability of obtaining estimation of QALYs and cost depending on age. Therefore, the code presents a

calculation of these model outcomes taking into account the different QALY and cost for each state according to the age. Incorporation of aging into the model is shown in **CODE 11**. The complete code is presented in Appendix C.

CODE 10: **Definition of cycles for time estimation**

```
# Updates proportion and definition of cycles

for (j in 1:4) {    #Treatments
for (i in 1:5) {    #States

for (t in 2:10) {                                  #Time to run the model/cycles
s[j,i,t]<- inprod(s[j,1:5,t-1], p[j,1,1:5,i]) }    #Run the model for t cycles

for (t in 11:20) {                                 #Time to run the model/cycles
s[j,i,t] <- inprod(s[j,1:5,t-1], p[j,2,1:5,i]) }   #Run the model for t cycles

for (t in 21:30) {                                 #Time to run the model/cycles
s[j,i,t] <- inprod(s[j,1:5,t-1], p[j,3,1:5,i]) }   #Run the model for t cycles

for (t in 31:40) {                                 #Time to run the model/cycles
s[j,i,t] <- inprod(s[j,1:5,t-1], p[j,4,1:5,i])  }  #Run the model for t cycles

for (t in 41:55) {                                 #Time to run the model/cycles
s[j,i,t] <- inprod(s[j,1:5,t-1], p[j,5,1:5,i]) }  } }  #Run the model for t cycles

for (j in 1:4) {
for (k in 1:5) {
time[j,k]<- sum(s[j,k,])  }
time[j,6]<- 55-(time[j,1]+time[j,2]+time[j,3]+time[j,4]+time[j,5]) }

for (t  in 1:55){
for (j in 1:4) {
for (k in 2:5) {
qaly.state[j,k,t]<- s[j,k,t]*util[k]
cost.state[j,k,t] <- s[j,k,t]*cost[k]  }  }}
```

CODE 11: **Incorporation of aging**

```
# Use UK EQ5D age-adjusted population norms for HEALTHY state

for (j in 1:4) {
# 45-54
for (t in 1:10) {
qaly.state[j,1,t]<- s[j,1,t]*util.healthy[1]
cost.state[j,1,t] <- s[j,1,t]*cost[1]   }
# 55-64
for (t in 11:20) {
qaly.state[j,1,t]<- s[j,1,t]*util.healthy[2]
cost.state[j,1,t] <- s[j,1,t]*cost[1]   }
# 65-74
for (t in 21:30) {
qaly.state[j,1,t]<- s[j,1,t]*util.healthy[3]
cost.state[j,1,t] <- s[j,1,t]*cost[1]   }
# 75+
for (t in 31:55) {
qaly.state[j,1,t]<- s[j,1,t]*util.healthy[4]
cost.state[j,1,t] <- s[j,1,t]*cost[1]   }
}


# Defining calculation of QALYs and Cost of each state

for (t  in 1:55){
for (j in 1:4) {
qaly.tot[j,t] <- qaly.state[j,1,t] +   qaly.state[j,2,t] +  qaly.state[j,3,t]  + qaly.state[j,4,t] +
qaly.state[j,5,t]
qaly.distot[j,t] <- qaly.tot[j,t] * pow(0.965,t-1)
cost.tot[j,t] <- cost.state[j,1,t] +   cost.state[j,2,t] +  cost.state[j,3,t]  + cost.state[j,4,t] +
cost.state[j,5,t]
cost.distot[j,t] <- cost.tot[j,t] * pow(0.965,t-1)
 }}
```

6.8 Results of a Base Case

A base case model was developed for a cohort simulation of 55 years. Individuals have an initial age of 45 years old and 100% of them start at MetS state. The intervention assessed was 3 years long. Results are based on a sample of 50,000 simulations, after a 'burn-in' of 10,000 simulations. Table **6.5** shows the resulting values for total cost, total

QALYs and estimation of the incremental cost-effectiveness ratio (ICER). Table **6.6** presents estimation of time (years) spent in each state by type of intervention. Figures 6.4 and 6.5 show the cost-effectiveness plane and the cost-effectiveness acceptability curve respectively.

Lifestyle interventions average cost, per person, is £2,338 and it is higher than average pharmacological cost per person (£2,179). These therapies implemented separately are individually lower than the cost of both together £2,851. QALYs across interventions were more favorable for lifestyle interventions (16.81); giving pharmacological interventions a total QALY of 16.43 and for both therapies combined the total QALY was 16.19, showing small advantage over control. Differences between the three types of interventions under evaluation are minimal or might not be significant to this level of information.

Table 6.5. Results from the model

	Total Cost			Total QALYs			ICER		
	Mean	95% CrI		Mean	95% CrI		Mean	95% CrI	
Control	2,148	1,328	2,948	16.02	12.94	19.07			
Lifestyle	2,338	1,582	3,078	16.81	14.41	19.46	132.3	-2,422	3,070
Pharmacological	2,179	1,360	3,018	16.43	13.68	19.26	534.2	-3,820	4,638
Both	2,851	1,950	3,802	16.19	13.10	19.19	672.4	-9,762	11,000

Table **6.6** presents the time spent in each health state (Healthy, MetS, T2DM, CVD, T2DM plus CVD and Death) according to the different types of intervention (Lifestyle, Pharmacological and Both). The table suggest that the highest effect can be identified for MetS in the Lifestyle intervention if it is compared with a control group. After being in a lifestyle intervention, people spent more time in Healthy state (18.45 years)

Table 6.6. Time spent in each state by type of intervention (years)

	Control			Lifestyle			Pharmacological			Both		
	Mean	95% CrI		Mean	95% CrI		Mean	95% CrI		Mean	95% CrI	
Healthy	13.18	9.64	16.44	18.45	15.77	20.30	16.02	11.88	19.09	14.27	8.03	18.98
MetS	6.89	4.65	9.37	3.23	2.08	5.02	4.90	2.86	7.76	6.13	2.91	10.57
Diabetes	4.78	3.10	6.36	3.71	2.48	4.78	4.21	2.73	5.68	4.56	2.87	6.48
CVD	11.03	4.25	17.39	10.59	4.16	16.58	10.78	4.17	16.97	10.96	4.24	17.30
Diabetes+CVD	0.28	0.14	0.50	0.22	0.11	0.38	0.25	0.13	0.44	0.27	0.13	0.49
Death	18.84	12.55	25.83	18.80	12.89	25.40	18.83	12.71	25.59	18.80	12.57	25.76

Figure 6.3: *Literature search strategy*

and less time in MetS (3.23 years) compared with control, 13.18 years in Healthy state and 6.89 years in MetS state. Credible intervals are wider for pharmacological and both interventions (there is less information for these interventions than for lifestyle interventions). The important result is the increment on the duration in healthy state after the intervention in MetS state, showing an important effect from Lifestyle interventions; this difference is of 5 years of effect between the control group and lifestyle interventions. The pharmacological and combined interventions are less effective from lifestyle interventions, therefore it is expected that people in MetS will take longer time in this state, as it will take more time for them to be able to reverse a MetS condition if they are intervene with a less effective therapy.

The incremental costs were £132.3 per QALY gained for the lifestyle interventions, £534.2 per QALY gained for pharmacological therapies and £672.4 per QALY gained for the combined therapy compared to a control intervention. Showing the combined therapy as the less cost-effective. Credible intervals for the incremental cost-effectiveness ratios (ICER) show important uncertainty, see Table **6.5** for these results. Figure 6.4 presents the cost-effectiveness plane for the simulation of the base case,

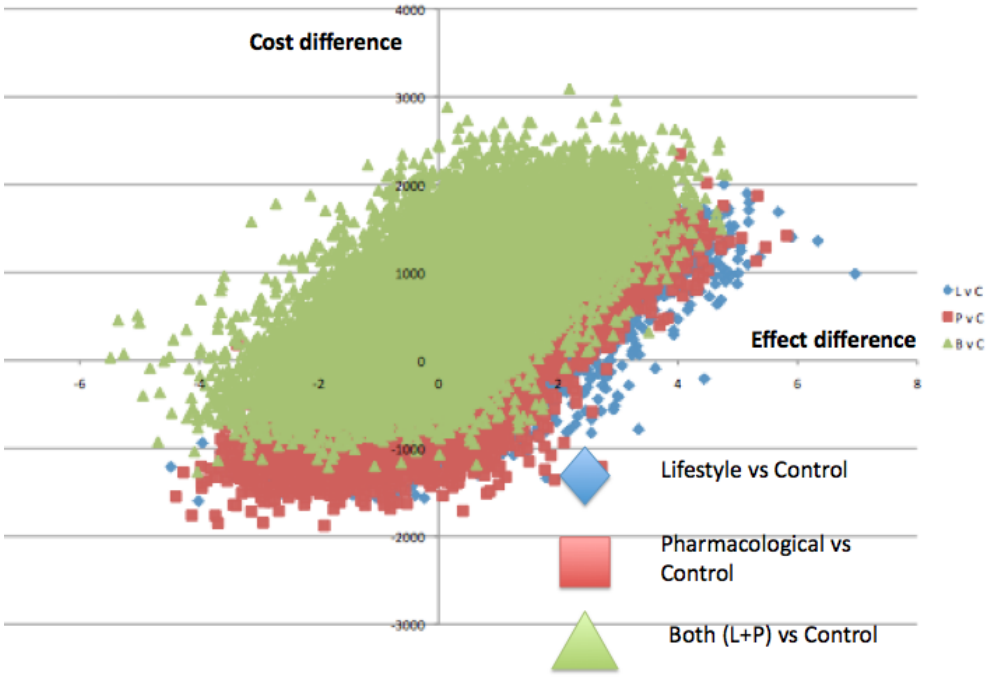


Figure 6.4: *Cost-effectiveness plane*

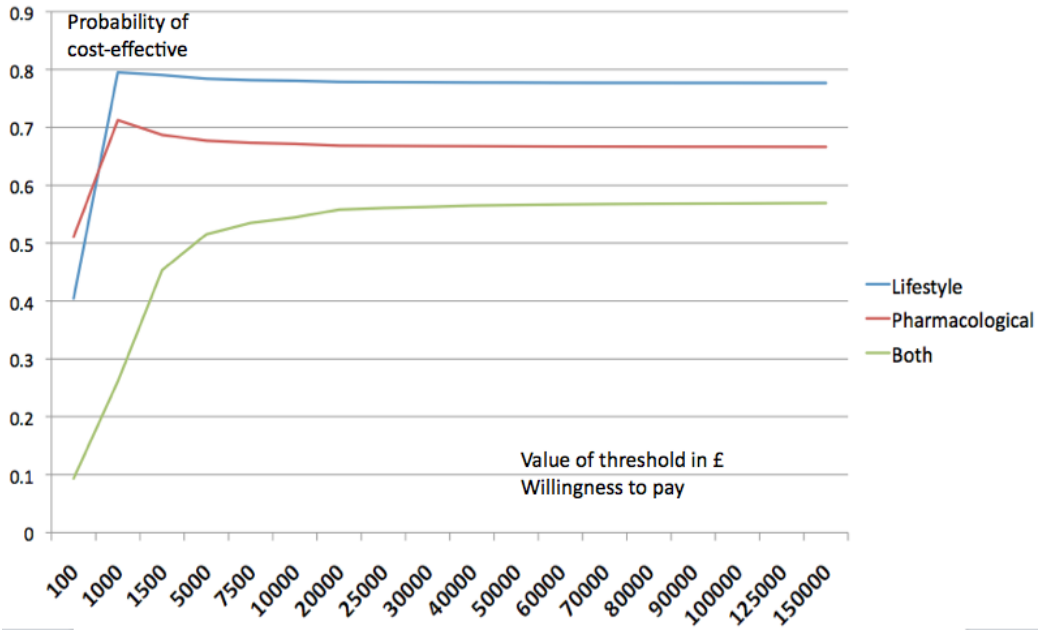


Figure 6.5: *Cost effectiveness aceptability curve*

showing a wide range of possibilities and important uncertainty in the model, meaning there is more evidence needed. The cost-effectiveness plane plot the cost difference in the vertical axis and the effect difference in the horizontal axis, therefore the slope of a straight line from the origin provides the ICER. It is noticeable, that the range of values for the simulation take an important area over the cost-effective range of the plane, however the three therapies show values were the new therapies are dominated by the control, showing considerable uncertainty for a decision making. A new therapy is dominated if the cost is higher and less effective, also it is said a new treatment is dominated if it is more costly and more effective, then a decision is required on the threshold that the healthcare provider is willing to pay for additional units of benefit Briggs et al. [2006]. A control group is necessary for reference of comparison. According to the ICERs, lifestyle and pharmacological are economically favorable in contrast to the willingness to pay. Probabilities of cost-effectiveness at £20,000 are 0.7786 for lifestyle interventions and 0.6683 for pharmacological interventions, see Figure 6.5, where the probabilities of cost-effectiveness are plotted against the willingness to pay threshold for each of the interventions. An interesting result of the base case model is the achievement of a high cost-effective probability for a threshold of £1000, giving lifestyle interventions a probability of 0.7951 and pharmacological therapies a probability of 0.7124, reaching the highest point of the cost-effectiveness acceptability curve. These results show favorable potential for these interventions.

The aim of the Markov model was to assess a MetS criteria based interventions and observe whether the intervention had an effect on life expectancy or that people will spend significant time in a healthy state, decreasing the proportion of people progressing to T2DM or CVD. The risk of progression was evaluated in the Cohort Systematic

review presented in Chapter 5 and this evidence is based on observational studies contrasting people with and without MetS to calculate the risk of developing T2DM or CVD. Therefore, the research question of the Markov model relies on the assessment of the cost-effectiveness of an intervention to prevent people of progression. Nonetheless, the death state is not significantly reduced for any of the interventions, meaning they do not reach an effect in life expectancy; under this specific circumstances modelled.

These results show a need of undertaking a sensitivity analysis to explore where the differences, presented by the results of this base case analysis, are coming from. Next section 6.9 presents a description summarizing sensitivity analysis results.

Many sociological variables are implicit in observational studies; this situation explodes the possibilities of interpretations of these results. As well, the inclusion of costs into the model, sets an economical panorama for the population under study. These issues should be contrasted in order to have a better interpretation and explore the needs of the modelling. The model holds a wide range of information, therefore is crucial to undertake a review of sociological factors that can be affecting the model and its usefulness for decision making.

6.9 Sensitivity Analysis

This process of analysis was performed to explore heterogeneity produced by the differences on the assumptions of the model. Tables **6.7** present the results of the sensitivity analysis. There were 12 different models defined for the comparison with the base case scenario; these models were related with the healthy utilities, MetS utilities, MetS

proportions, time horizon, lifestyle intervention, age at entry, healthy costs).

In terms of costs, all models presented little differences and showed the same numerical pattern (Lifestyle interventions as the second most expensive after both types of interventions combined). The utilities also present minimal differences between models. Calculation of the ICER was controversial as uncertainty of the model provides so many options for its calculation resulting completely unstable even after high levels of iterations of the model in WinBUGS. All of the models presented one of the treatments with a dominated result reflected in the ICER estimation (marked in the table as (*)), meaning that the new treatment under evaluation is not better than the control.

Table **6.7** presents the specifications of each of the models and the base case characteristics. Table **6.7 a, b** and **c** present the results for each of the variations of the Markov model implemented for this analysis. Results of the average total cost and total utilities are shown for each model. As the ICER presented important uncertainty, an ICER calculated by the implementation in the Markov model is presented as "MCMC ICER" and a calculation of the ICER based on the results presented in the table was computed for comparison.

Table 6.7. Sensitivity analysis of the model

	Base case	Sensitivity Analysis
Healthy utilities	1	Utilities(0.85,0.80,0.78,0.73)
MetS utilities	0.825	0.73
MetS proportions	100% MetS	ADDITION starting states
Time horizon	55 years	20 years
Lifestyle intervention	3 years	1 year (year 1 costs + 25% reduction in effect)
Age at entry	45	50, 60
Healthy costs	No costs	Undiagnosed Diabetes costs: £77.284
MTC prior	U(0,5)	U(0,2); U(0,10)

The tables also present the probability of the treatment of being cost-effective at a threshold of £20,000 and a threshold of £1,000, as the cost-effectiveness acceptability curve showed the maximum effectiveness at this second threshold.

When aging is incorporated in the model, as discounted health utility according to the age group, lifestyle interventions show a dominated result. This could be explained as the impact that the lifestyle intervention should have in order to overcome the effect of age in the population. It is important to take into account that lifestyle changes could be harder according to the age and the model is simulating people starting at 45 years old that have already developed their lifestyle patterns, presenting a challenge for these type of interventions. However, results are showing these interventions to be more effective for a long term effect. If the MetS utility is changed to 0.73, the model shows a reduction of the utility for the control group compared with the base case, and the rest of the utilities are slightly reduced. This model presented the combined intervention to be dominated. The model taking into account proportions of individuals starting in healthy, MetS and T2DM states using the ADDITION data, presented similar estimates for the total cost and total utilities compared with the base case scenario, however the ICER estimation becomes more uncertain as credible intervals are wider and probability of being cost-effective for a threshold of £20,000 decreases to 0.62 for lifestyle interventions and the probability for a threshold of £1,000 is even lower (0.41). If time horizon is reduced to 20 years, utilities and costs are reduced; but maintaining the same pattern of the base case, showing lifestyle interventions the more appropriate decision. ICER uncertainty also gets reduced in this version of the model, but also presenting a both interventions to be dominated. Probabilities of lifestyle interventions of being cost-effective for this horizon goes up to 0.92 for a threshold of £20,000.

Table 6.7.a Results: Sensitivity analysis of the Markov model

	Total Cost			Total QALYs			MCMC ICER				ICER	CE-Prob at £20k	CE-Prob at £1k
Base case	**Mean**	**95% CrI**		**Mean**	**95% CrI**		**Mean**	**2.5% CrI**	**Median**	**CrI**			
Control	2,148	1,328	2,948	16.02	12.94	19.07							
Lifestyle	2,338	1,582	3,078	16.81	14.41	19.46	132	-2,422	342	3,070	241	0.78	0.80
Pharmacological	2,179	1,360	3,018	16.43	13.68	19.26	534	-3,820	366	4,638	76	0.67	0.71
Both	2,851	1,950	3,802	16.19	13.10	19.19	672	-9,762	545	11,000	4,135	0.56	0.26
Healthy Utilities: Aging													
Control	2,148	1,328	2,948	14.60	11.61	17.64							
Lifestyle(*)	2,338	1,582	3,078	14.78	12.43	17.43	1,468	-3,770	428	4,733	1,056	0.57	0.48
Pharmacological	2,179	1,360	3,018	14.69	12.03	17.50	612	-3,556	440	4,600	344	0.54	0.53
Both	2,851	1,950	3,802	14.65	11.76	17.59	373	-11,810	558	12,940	14,060	0.50	0.17
MetS Utility													
Control	2,145	1,324	2,944	15.51	12.46	18.58							
Lifestyle	2,336	1,585	3,078	16.56	14.15	19.21	372	-2,307	280	2,706	182	0.83	0.87
Pharmacological	2,181	1,356	3,014	16.06	13.28	18.91	5,123	-3,816	322	4,475	65	0.71	0.77
Both(*)	2,848	1,940	3,811	15.73	12.56	18.78	-1257	1,015	504	9,748	3,195	0.57	0.30
MetS Proportions at starting states													
Control	1,918	1,228	2,577	16.65	14.51	19.04							
Lifestyle	2,314	1,645	2,961	16.92	14.92	19.21	-2,956	-4,930	573	5,995	1,467	0.62	0.41
Pharmacological	1,943	1,259	2,605	16.79	14.73	19.12	223	-3,071	418	3,942	179	0.57	0.59
Both(*)	2,518	1,817	3,206	16.71	14.56	19.10	-2715	-10,870	603	11,070	10,000	0.52	0.18
Time Horizon													
Control	1,137	783	1,445	11.67	9.51	13.22							
Lifestyle	1,403	1,087	1,680	12.32	10.92	13.46	794	-1,375	394	2,939	409	0.92	0.80
Pharmacological	1,191	811	1,579	12.01	10.19	13.34	177	-4,053	203	4,351	159	0.80	0.77
Both(*)	1,825	1,369	2,313	11.81	9.63	13.29	-3301	-27,930	941	27,190	4,914	0.59	0.14

Related to the lifestyle intervention costs, a model considering an intervention of only one year of duration was developed. Also a model with the same length for the lifestyle intervention and a 25% reduction in the effect of the treatment was defined. For both models the lifestyle intervention presented lower cost than control and better clinical effects. The incremental cost was -£84 and -£106 per QALY gained with the lifestyle interventions, respectively to each model. Lifestyle interventions showed a probability of being cost-effective at £20,000 of 0.78 for the model considering only the one year intervention and 0.80 for the model considering the 25% reduction in effect. These probabilities are increased at a threshold of £1,000, to 0.88 and 0.89 respectively for lifestyle interventions.

If different types of cohorts are introduced in the model by changing the age at the start of the simulation for 50 and 60 years, results demonstrate the same cost and utility pattern. However with the 60 year old cohort, costs get slightly reduced. Clinical benefits are still showing lifestyle interventions to be more effective.

When health costs are incorporated in the model, an increment is reflected in the average total cost. Sensitivity analysis for the prior distribution of the Mixed Treatment Comparison to a uniform bounded from 0 to 2 and a second model with a uniform from 0 to 10, was also undertaken, but showing very similar results to the base case scenario.

Table 6.7.b Results: Sensitivity analysis of the Markov model

Lifestyle Intervention: 1 year cost	Total Cost			Total QALYs			MCMC ICER				ICER	CE-Prob at £20k	CE-Prob at £1k
	Mean	95% CrI		Mean	95% CrI		Mean	2.5% CrI	Median	97.5% CrI			
Control	2,148	1,328	2,948	16.02	12.94	19.07							
Lifestyle	2,082	1,327	2,823	16.81	14.41	19.46	412	-4,397	189	4,612	-84	0.78	0.88
Pharmacological	2,179	1,360	3,018	16.43	13.68	19.26	534	-3,820	366	4,638	76	0.67	0.71
Both(*)	2,596	1,694	3,546	16.19	13.10	19.19	271	-6,973	434	7,823	2,635	0.56	0.37
Lifestyle Intervention: 1 year cost + 25% reducction in effect													
Control	2,148	1,328	2,948	16.02	12.94	19.07							
Lifestyle	2,058	1,306	2,797	16.87	14.50	19.50	-85	-4,456	154	4,461	-106	0.80	0.89
Pharmacological	2,179	1,360	3,018	16.43	13.68	19.26	534	-3,820	366	4,638	76	0.67	0.71
Both(*)	2,596	1,694	3,546	16.19	13.10	19.19	271	-6,973	434	7,823	2,635	0.56	0.37
Age at entry: 50 years													
Control	2,084	1,295	2,835	15.87	12.86	18.79							
Lifestyle	2,276	1,552	2,970	16.67	14.34	19.18	835	-2,383	334	2,998	334	0.79	0.80
Pharmacological	2,116	1,329	2,907	16.29	13.60	18.99	224	-3,952	354	4,421	354	0.68	0.72
Both(*)	2,787	1,918	3,694	16.05	13.02	18.92	1202	-10,370	552	11,550	552	0.56	0.26
Age at entrey: 60 years													
Control	1,896	1,200	2,530	15.36	12.53	17.96							
Lifestyle	2,097	1,462	2,678	16.17	14.04	18.35	751	-2,136	315	2,659	248	0.82	0.82
Pharmacological	1,932	1,229	2,615	15.78	13.27	18.16	-770	-3,878	320	4,397	86	0.70	0.74
Both(*)	2,598	1,816	3,406	15.54	12.67	18.07	1712	-12,310	575	13,030	3,900	0.57	0.24

Table 6.7.c Results: Sensitivity analysis of the model

Health Costs	Total Cost			Total QALYs			MCMC ICER				ICER	CE-Prob at £20k	CE-Prob at £1k
	Mean	95% CrI		Mean	95% CrI		Mean	2.5% CrI	Median	CrI			
Control	2,721	1,917	3,481	16.02	12.94	19.07							
Lifestyle	3,184	2,440	3,898	16.81	14.41	19.46	-55	-2,083	484	3,255	586	0.77	0.67
Pharmacological	2,896	2,121	3,654	16.43	13.68	19.26	643	-2,729	418	3,800	427	0.67	0.64
Both(*)	3,481	2,677	4,283	16.19	13.10	19.19	873	-10,050	646	11,520	4,471	0.56	0.22
MTC Prior U(0,2)													
Control	2,146	1,324	2,956	16.02	12.98	19.07							
Lifestyle	2,340	1,587	3,072	16.81	14.43	19.46	1,258	-2,520	342	2,945	246	0.78	0.79
Pharmacological	2,177	1,352	3,016	16.43	13.73	19.25	306	-3,856	366	4,590	76	0.67	0.71
Both(*)	2,847	1,949	3,805	16.18	13.10	19.16	865	-9,855	552	11,120	4,381	0.56	0.26
MTC Prior U(0,10)													
Control	2,148	1,328	2,948	16.02	12.94	19.07							
Lifestyle	2,338	1,582	3,078	16.81	14.41	19.46	132	-2,422	342	3,070	241	0.78	0.80
Pharmacological	2,179	1,360	3,018	16.43	13.68	19.26	534	-3,820	366	4,638	76	0.67	0.71
Both(*)	2,851	1,950	3,802	16.19	13.01	19.19	672	-9,762	545	11,000	4,135	0.56	0.26

6.10 Discussion & Limitations

For the assessment of interventions based on MetS criteria, a Markov model has been described in this chapter. A health economic evaluation was undertaken to identify a cost-effective treatment of MetS. Therefore, the assessment underlies the effectiveness of treating a MetS population associated to the prevention of CVD and T2DM. If individuals can be prevented at an early stage of developing hard outcomes like cardiovascular events or T2DM, could have an impact in the quality of life by incrementing the probabilities of being healthy for longer time in their lives.

This model integrates different levels of information, cost-utility data was identified to complete a comprehensive decision model. It can be extended to evaluate more complex interventions or different modelling approaches. Sources of the model should be updated and obtain the support of undertaking more systematic reviews of different sources. There is the need of prioritizing where more evidence is needed to improve the quality of the information and therefore to have an impact in the reduction of the uncertainty of the model. Also, the model does not take into account the side effects of the drugs involved in the interventions.

Sensitivity analysis was performed, in order to observe the behavior of the model contrasting variations in the modelling. Given changes with regards to the model inputs/distributions and a number of methodological assumptions, the results showed very little sensitivity. Modeling a full cohort in MetS state was contrasted with a model were there are proportions defined for the start of the model in the states of MetS, Healthy and T2DM. The impact of this change incremented the overall utilities.

A replication of the model could be developed to assess a cohort without MetS, in order to evaluate the contrast of using MetS criteria or other diagnostic strategies for the identification of cost-effective population prevention strategies. However, this chapter concentrated in developing a model for a MetS population. Given the debate surrounding the certainty of MetS as a recognized condition, this thesis stands in a conservative position, describing an evaluation of the criteria of MetS itself. The interventions to be identified as cost-effective are based on the evidence supporting the effectiveness of interventions reversing MetS conditions and the incremented probability associated with the development of CVD and T2DM for the proportion of the population with signs of MetS.

The healthcare providers could identify people with MetS in order to allocate them in a prevention program. The use of lifestyle and pharmacological combined intervention was dominated in the incremental cost-effectiveness analysis, with the use of both of them independently producing greater health gain at lower cost. Given the fact that the lifestyle intervention and the pharmacological therapies are more effective independently, the use of both presents correlation. The specification of the therapy is more effective than the additional information given by the combined intervention. Besides, there could be an psychological interaction effect in the individuals under both interventions, making them more erratic in the compliance of their treatment. However, more evidence is needed for these assumptions. The evidence synthesis undertaken in Chapter 4, presented lack of clinical trials concerning this specific combination of treatment.

Pharmacological intervention was cost-effective compared to standard care (ICER £534 with a probability of 0.67 at a threshold value of £20K/QALY), and lifestyle inter-

vention was cost-effective compared to pharmacological. When lifestyle is compared to standard care, the model shows this intervention as the most cost-effective (ICER £132 with a probability of 0.78 at a threshold value of £20K/QALY). However, the base case scenario showed higher probabilities of being cost-effective for lifestyle and pharmacological interventions at a lower threshold value (0.80 and 0.71 respectively at a threshold value of £1K/QALY). The Markov model suggests a lifestyle change could produce the best effect, resulting more cost-effective. It is important to further explore individual patient data to understand the behavior of MetS in itself, as recommendation of lifestyle interventions only could impact in a trivial mistake, as a proportion of the population under observation requires pharmacological treatment, given the specific combination of the risk factor present.

This analysis has made evident the needs of information at any level. Specifically, the model is aiming a lifetime impact, therefore sources of information have to be abundant in order to be able to inform all possible relations drawn in the diagram of Figure 6.1.

This chapter described the process of evaluating a comprehensive decision model for MetS. If a 3 year intervention is applied to health care system in the UK, according with a Markov model implemented in WinBUGS. There is an improvement in quality of life, however an effect in life expectancy was not observed to this level of information.

6.11 Summary of the Decision model for MetS interventions

This chapter summarizes the aim of this thesis. The evaluation of a possible intervention based on the criteria of the MetS. Firstly, evidence related with the associated risk of developing CVD and T2DM was inputed into the model (Chapter 5), then integrating evidence on the probabilities of the reversal of a MetS diagnosis with different treatments available (Chapter 4), plus data collected about the different costs related with the health states and the intervention under evaluation. All this information was compiled with a Markov model in order to measure if the proposal of an intervention based on MetS criteria could be useful to prevent at least an increase on the incidences of CVD or T2DM.

Lifestyle and pharmacological interventions independently are showing to be cost-effective in reversing a MetS condition and therefore preventing people to progress to T2DM and CVD. However, more evidence is needed to improve the model parameter estimation.

Chapter 7

Reviewing the Evidence & Discussion of Possible Solutions: *Conclusions*

This final chapter aims to present a summary of all the evidence collected for this comprehensive analysis. Thereafter, the need to build a critical discussion around the results of the cost-effectiveness analysis is exposed to drive main conclusions. Limitations are going to be contrasted with the benefits of the analysis, in order to provide a conclusion based on a wider discussion.

Section 7.1, describes the main ideas developed in each chapter. Brings all the specific points of the analysis of this thesis. Section 7.2, develops a discussion using the findings of this process of investigation. Section 7.3 aims to complement the limitations discussion with the suggestion for possible further work deriving from the experience and results of this thesis. Section 7.4, summarizes main findings of the thesis.

7.1 Summary of the thesis

The background described in Chapter 2, gave a position for the decision problem presented in this thesis, the possibility of using the MetS criteria as a diagnostic tool to support a prevention strategy. Therefore, the need of exploring more about the behavior of a possible application of the MetS criteria as an intervention, to support prevention of chronic disease (Zimmet et al. [2003]). Previous evidence have found a relationship between MetS criteria and T2DM plus CVD (Ford [2005]; Gami et al. [2007]; Li et al. [2008]; Sattar et al. [2008]). There is also a discussion on the applicability of MetS criteria. Gale affirms that this criteria has been developed with a market expansion interest instead of producing a real clinical benefit. MetS criteria was mainly developed to make research comparable (Gale [2005]; Kahn et al. [2005]).

This overview draws a question in whether the MetS criteria is an effective tool or not.

Chapter 3, makes explicit the methodological strategy that was addressed in Chapter 2. There is the need to contribute to this discussion, because the environment is requiring a solution (Murray and Lopez [1997]; Zimmet et al. [2001]). Therefore, it is important to evaluate strategies based on MetS criteria and explore for more practical and effective solutions, for preventions at a population level. Given the accumulated publications related with MetS, T2DM and CVD, the model combines this evidence to offer a good quality information for decision making. However, when solutions are needed, uncertainty has to be reduced in more pragmatic ways. It is important to acknowledge, the MetS concept is linked to different sociological aspects of life that are not incorporated in the model. This could provide a closer overview of the concepts under study, more immediate results, and consequently faster application of a learning process. This thesis proposed the use of a comprehensive decision model to compile evidence about the MetS and its relationship with T2DM and CVD. This thesis used a Bayesian approach, because of the technical advantages for the implementation of evidence synthesis models and integration of different types of models into a main Markov model (using MCMC from WinBUGS).

Chapter 4, presented an intervention assessment. The use of MTC methods provided a methodological solution for the type of evidence available. Given the need of evaluating treatments related with the reversal of MetS (as main outcome), the identified studies compared only a few of the possible interventions to treat MetS. Therefore, the need of implementing a method able to integrate direct and indirect evidence. The type of treatments included, were related with lifestyle changes (diet and exercise), pharmacological therapy (Metformin, Rimonabandt, Sibutramine, Statins and Fenofibrate) or combination of both. The heterogeneity of the interventions was considerable; spe-

cially in the control groups, were all studies did different interventions related with lifestyle advice or complete placebo (no intervention). The main result of Chapter 4, was the better performance from lifestyle interventions.

There is also, another important question taking place in Chapter 5. Is MetS related to a higher risk of developing T2DM or CVD? Individuals with MetS were at higher risk (compared to those without a positive diagnosis of MetS and after adjusting for age and sex) of All-cause mortality with a age-sex-adjusted RR of 1.50 and 95% CI 1.29-1.76, CVD mortality (RR 1.85, 95% CI 1.45-2.35), CHD mortality (RR 2.26, 95% CI 1.46-3.51) and Stroke mortality (RR 1.67, 95% CI 1.05-2.63). Articles reporting CVD events had similar results (RR 1.67, 95% CI 1.47-1.89), CHD events (RR 1.71, 95% CI 1.51-1.93), Stroke events (RR 1.77, 95% CI 1.37- 2.29) and DM with the highest RR of 4.40 (95% CI 3.35-5.78). Metabolic Syndrome diagnosis can be used as a tool to identify people at higher risk of developing T2DM, CVD outcomes and/or Mortality.

Chapter 6, describes the process of evaluating a comprehensive decision model for MetS in WinBUGS. If a 3 year intervention is applied to health care system in the UK, according with a Markov model implemented in WinBUGS, there is an improvement in quality of life. An effect on life expectancy was not observed. Lifestyle interventions showed a better performance to the population level for MetS state. Lifestyle interventions are more expensive than pharmacological, but both interventions together are more expensive compared to each intervention. There is the need to inform with more evidence each relation of the model, as uncertainty is evident in these results, complicating a clear conclusion.

This last Chapter 7, is aiming to remind the concept of the main problem stated in

the introduction (Chapter 1) and to expose a discussion about the main results of this thesis.

7.2 Discussion & Limitations

The main outcome of this thesis is the approximation to a debate of, whether an intervention based on MetS criteria would be able to prevent chronic disease like T2DM and CVD, in a cost-effective way. The evidence available is not showing the benefit of using MetS criteria to prevent chronic disease under study (T2DM and CVD). The comprehensive approach of this thesis is requiring more evidence feeding this model, to allow conclusive outcome. An over-parametrized model could lead to conclusions that are not enough, in the sense of interpreting clear cut decisions. The model needs to incorporate constant updates of the evidence to achieve quality on the estimations produced. If a linear regression and a multilevel model are contrasted, in both cases the coefficients are equally estimated but the variance-covariance matrix of the observations has more structure in the multilevel model than the regression. This phenomenon could affect the robustness of the inference of the Markov model developed, therefore more research is needed to provide an appropriate use of the model.

The increasing mortality of causes like T2DM and CVD represent a public health problem (Murray and Lopez [1997]; Zimmet et al. [2001]). A public health problem requires a public solution, but how this solution is proposed and developed, represent a big issue for society. According to the results of the MTC, lifestyle interventions had better performance, in contrast to the pharmacological therapies or even combination of both types of intervention. These results show a need of making changes to a

lifestyle level. In other words, they have the possibility to be at the base of public policy discussions. Thereafter, when exploring the underlying risk of the studies included in the meta-analysis, important heterogeneity is found between the characteristics of the control interventions or the absence of one. The higher the probability of reversal in the control group, lower the chances of the intervention to be effective. Showing that the pharmacological interventions could be minimized by this effect. This situation only increments the complexity of the discussion for public application, representing just a component of a comprehensive perspective.

Lifestyle problems have lifestyle roots, therefore it is important to raise the question of, how possible is to produce a lifestyle change? Which is the real access to a healthy life? Why changing to a lifestyle level? In order that an intervention to be worth, it should be able to produce changes to a long term basis. This is evident from the results of the model, as a 3 year intervention did not have an impact in the long term of the simulation. Then, it becomes a temporary solution that could have the potential of incrementing economical related problems. The intervention proposed could be creating undesired inequalities in the population, if not considered before in a accurate perspective. Targeted interventions require support from structural changes that allow the change in the population (Capewell and Graham [2010]).

If the intervention works only on the basis that people maintain these habits as long as they are in the intervention, there is the possibility of making a contrast between the previous habits and the habits produced by the intervention. Then, those habits will be making people change and will be related to sources where people can access what is needed, in order to be able to achieve a healthy state, that has been recommended. A change then could be produced only on the type of consumption, if these changes are

not carefully understood. That eventually will go back to the original habits. Which it could be expected if there are economical differences on the type of consumption needed for a healthy lifestyle. This situation will be producing inequalities related with economical factors related with the effects of the intervention under study, that should be explored in more detail in future research of MetS. In this sense, publication bias seems to be relevant to consider, as evidence of reporting bias is present in the results of the cohort systematic review undertaken to assess the risk of developing T2DM and CVD in Chapter 5.

More statistical modeling needs to be performed not only in order to implement the contribution of Sharp and Thompson [2000], but also in order to account the partial observability represented by the papers which are published in contrast to studies which do not arrive to be accepted in the main stream journals. This last issue could be modeled following the partial observability models as introduced by Manski [1995], as and endogenous effect should be explore more in depth in the models developed, producing interpretation challenges. The relation between the MetS criteria and the risk of developing T2DM and CVD have been confirmed by the data collected for this thesis. But publication bias is a major issue in these results and there are still problems with the definition (described in Chapter 2). Is it really necessary to apply a criteria, with serious doubts on its definition, to provide an epidemiological solution? The presence of publication bias in these particular part of the evidence represents a risk to the conclusions and recommendations to be made out of this work. However, this synthesis represents a start in research related with MetS that integrates different types of evidence in a Markov model.

The distribution of a population in the model according to their transitions from one

state to the other, determined the approach of this thesis. There is a health problem that needs to be explored for solutions to allow an improvement of quality of life in people who are suffering these type of conditions, that deteriorates life in general terms. Therefore, this thesis is taking a position to evaluate methods of identifying high risk people at a population level, in such a way that their results allow, in future research, to critically evaluate the pertinence of these models to the phenomenon under study.

The evidence synthesized in this thesis showed a need of investigating more in the different possibilities that there could be to actually produce an observable change in the health structure of the population under simulation. The creation of health policies requires a type of research considering different factors related with the implementation of the specific context of the policy. Questions like, who develops the policy? Which institutions are related? Who undertakes the research?

It seems relevant to consider many aspects that could be excluded in the modelling. An important issue is the fact that while an intervention is implementing, some people with MetS could die during that time. Therefore, the type of meta-analysis models developed in this thesis requires to be complemented with censored data models, as those introduced by Cox. It is also important to consider the proportion of subjects in the whole population who will never experience the event of interest. If this is correctly taken into account, the censored data models need to be carefully chosen, if not bias estimations could be pointed Oulhaj and San Martin [2012].

Such a wide observation aimed with this thesis, required different levels of analysis. For example, the systematic review in Chapter 5, conforms just a step in the process of synthesis. Observational studies provide many levels of information that increase

heterogeneity (Egger et al. [2001]).

Improving the information level (in quality and quantity terms) of the model will introduce more evidence to the structure proposed by the Markov model. This could result in a more accurate explanation of the reality aimed by the model. An important limitation is related with the lack of qualitative information related with having a MetS diagnosis. Qualitative evidence could be contrasted to obtain estimated ranges of reaction in the population under study. An effect can be observed after applying specific interventions, therefore to answer the question of how convenient are these effects for the population? is a crucial argument to be assessed and elaborated according to the needs and real access of the population of interest.

Crucial evidence generated during this process of analysis is showing that a lifestyle factor is an important determinant of the trend progressing to T2DM and CVD from a previous MetS condition. The cohort simulated in the thesis is aged 45 years at start. If a lifestyle pattern is involved, then the impact of the intervention has to be very effective to produce a significant change. An intervention could be introduced at an earlier age to assess the incremental on the probabilities of prevention, given the lifestyle factors to be important determinants of health. Alternative clinical and educational programs could be developed for these purposes.

7.3 Further Work

After the extensive process of the revision of this thesis many issues are raised for future research. to be developed and provide results contrasting other alternatives to the problem stated in this document. This methodological exercise represents aimed a

description of the observable patterns of the available evidence. The first main meta-analysis presented in Chapter 4, reaches interpretability for underlying risk variance of the studies. However, the evidence from the control groups of the randomized control trials, showed important heterogeneity in the definition of each intervention for the control group.

More complex sensitivity analysis can be developed for validity assessment of the model. From its fundaments to its possible extensions. Tornado diagrams can represent a useful tool to support this analysis. Other analyses to be implemented are explained in the following sections.

7.3.1 Reporting bias and outcome correlation

It is important to consider the correlation between the outcomes related with CVD definitions. Reporting bias is a relevant issue, as outcome report does not follow a standardized terminology. This situation shows an important variability from CVD terms to specific CHD or Stroke events. The articles often did not clarified whether type of reported event included fatal events or specific non-fatal events. This discussion leads to a need of exploring the assumptions based on the evidence reported in published studies. Results from Chapter 5 showed evidence of considerable publication bias.

To provide a closer examination of the correlation of the outcomes a multivariate meta-analysis can be fitted to assess the impact of outcome reporting bias. A study using simulations for a bivariate fixed effects meta-analysis (Kirkham et al. [2012]). However, for this analysis it is relevant to understand the behavior of the terminology of CVD as,

CHD and Stroke are contained in the first term; therefore modelling of these outcomes requires specification of physiological characteristics of the terminology defining the outcomes. In order to understand more on which are the reasons of not reporting particular terms or either the research design should take these characteristics of the outcome into account from the beginning.

A problem related to reporting bias is the problem of publication bias in the sense that the meta-analyses reported in this thesis are based on published papers only, and not consider the studies which were submitted but rejected. In other words, not all the studies produced around the world are published. In order to show, at a conceptual level, which would be the impact of this partial observability phenomenon, let us denote by Y a dependent variable, representing the outcomes of studies. Let X be a vector of predictors which influence the outcome Y. Finally, let D be a binary random variable such that $D = 1$ means that a study was published, and $D = 0$ otherwise. Using this notation, we have the following decomposition:

$$\begin{aligned} P(Y|X) =& P(Y|X, D = 1)P(D = 1|X) \\ &+ P(Y|X, D = 0)P(D = 0|X) \end{aligned} \tag{7.1}$$

where

- $P(Y \mid X)$ denotes the distribution of Y given X. This model is differently specified, but for this conceptual discussion it is not necessary to make precise a specific model; the only issue to be considered is that the process generating Y given X must be decomposed into two sub-processes described below.

- $P(Y \mid X, D = 1)$ represents the distribution of the outcome given the predictors of a published study.
- $P(Y \mid X, D = 0)$ represents the distribution of the outcome given the predictors of a non published study.
- $P(D = 1 \mid X)$ represents the distribution of a published study given the predictors.
- $P(D = 0 \mid X)$ represents the distribution of an unpublished study given the predictors.

A first conclusion that can be derived from the above decomposition is the following: suppose a meta-analysis claims that the potential publication bias has not an impact on the results. Then it is implicitly assumed that

$$P(Y \mid X, D = 1) = P(Y \mid X, D = 0). \tag{7.2}$$

It follows that $P(Y \mid X, D = 1) = P(Y \mid X, D = 0) = P(Y \mid X)$; that is, it is assumed that the publication is an exogenous variable with respect to the distribution generating Y given X, which can be doubted. An exogenous variable means, for this piece, that there is an external function of the risk estimates, that is shown by the publication bias. Chapter 5, illustrated a pooled risk estimate with publication bias evidence. Ideally, scientific information is not influenced by the editorials.

If the publication bias is taken into account, it is important to analyze which probabilities of decomposition (7.1) can be identified (and therefore estimated) from the data. In a first approach, it seems reasonable to assume that there not exists information (or the information is not available) about the unpublished studies. In this case,

$P(Y \mid X, D = 1)$ is not identified and therefore it is an unknown. Denoting it as γ. If moreover there is information about the numbers of unpublished studies, then $P(D = 0 \mid X)$ is identified and, therefore, estimable from the data. Consequently, (7.1) is rewritten as

$$P(Y \mid X) = P(Y \mid X, D = 1)P(D = 1 \mid X) + \gamma P(D = 0 \mid X). \tag{7.3}$$

Since γ is not identifiable and, consequently, not estimable, the meta-analysis reporting should consider the following inequalities:

$$\begin{aligned} P(Y \mid X, D = 1)P(D = 1 \mid X) \\ \leq P(Y \mid X) \leq \\ P(Y \mid X, D = 1)P(D = 1 \mid X) + P(D =\mid X). \end{aligned} \tag{7.4}$$

The larger this interval is, the lager the impact of publication biased. In a future work, this phenomenon will be carefully analyzed. It can be mention that Manski [1995] has used this approach to evaluate the impact of public policies in education.

7.3.2 Epistemological issues

A systematic review of the literature related to MetS for a more ethnographic perspective, should be undertaken. Meaning to explore also the cultural behaviors associated with an increased prevalence of risk factors. This contrast can provide qualitative information that will support the process of understanding results from observational

studies. A comprehensive perspective should aim to access evidence from all the relevant areas of knowledge that are involved in a population level problem.

It also becomes crucial to investigate the model according to observation of the economical environment. Costs of implementation are not exclusively economical, also sociological. Leading to a new research question of Which is the behavior of MetS considering the socio-political and economical environment of the population under simulation? and How should these costs and measures be implemented into a statistical model, for better understanding of the economical dynamics in the model?

7.3.3 Further development of the estimation process

Extensions of the model can be proposed, in order to explore more possibilities with the information available and produced day by day. One option of the model would be the incorporation of a state for people that are completely healthy and other branch for people who have been previously diagnosed with MetS. Are people with at least one previous diagnosis of MetS at higher risk than healthy individuals? The Markov assumption can be relaxed by having different transitions to major states (CVD or T2DM) depending on whether subjects had entered in a MetS state or come from a completely healthy state. Another key extension of the model would be to incorporate a screening model before subjects transit to appropriate states in the current model. An example of how this model would be is presented in Gillies [2008].

To incorporate more analysis of the meta-analysis undertaken to feed the Markov model. Comparison of different MetS criteria for the estimation of the risk of developing T2DM or CVD. Comparison of other types of criteria to identify people at

high risk that could be contrasted with MetS for its evaluation. These comparisons lead to a better understanding of the behavior of conditions derived from MetS. Disclosure of individual patient data used in the different analyses, could provide evidence for the investigation of the dynamics related with the composition of prevalences of the different components of MetS in the participants of the study. The possible estimation of probabilities related with the combinations of risk factors; this information would help to know which of the combinations of the risk factors is more likely to progress to T2DM or CVD. Expected value of information can be explored to investigate added value of collecting more information (Briggs et al. [2006]).

Efforts could also be addressed for the incorporation of qualitative research of all the emotional processes involved in these diseases. Contrasting qualitative information with quantitative support can lead to a better understanding of the phenomenon under observation. This thesis represents an important effort of compiling a wide range of evidence, however it is only a start for the development of these models as they can be cumulative. In other words, more evidence is produce, more updated the models will be, leading to more accuracy of the estimations calculated.

Technology can provide an important tool to accomplish extraction of data needed. Specialized software used in social sciences for literature reviews, could be applied for the acceleration of the extracting process. However, this could lead to problems related with validity and understanding a wide range of articles will require a full reading, for discussion and interpretation of results. Therefore, information could be systematically organized to update models and increase their precision. This also would allow the closer observations to important issues of the modelling and the understanding of reality for a better decision making in health.

7.4 Conclusions

Available evidence from different interventions highlighted the performance of Lifestyle interventions for their impact in the effectiveness. However, less information was available for comparisons relating combination of lifestyle and pharmacological interventions together, in relation with the amount of evidence for lifestyle interventions (more direct comparisons available) (Chapter 4).

There is large amount of information relating the risk of MetS and CVD and T2DM. There is the need to update it again and compile more evidence relating different specifications of the semantics of the definitions present in this thesis. Publication bias has to be evaluated in more detail (Chapter 5).

Lifestyle interventions are more cost-effective than the rest of interventions. More information is needed as there is a lot of uncertainty in the results of the MCMC simulation (Chapter 6). The main impact of the lifestyle interventions was detected while being in MetS state. Since the intervention is based on MetS criteria the effect is reflected specifically for the people assessed with this criteria.

The debate introduced in Chapter 2 can not be ignore in the interpretation of results. Decision making process should be able to consider and evaluate all possible options and their impact. Population interventions are delicate matter when the health of a broad population can be compromised. Discussion is crucial for the encourage of better understanding of the main issues relating health problems.

There is the need of a psychological, sociological and political evaluation of these results. Lifestyle changes are showing to be the answer of the prevention of chronic disease. But complexity of its application can be controversial. Therefore, method-

ological challenges are present, to be able to incorporate different type of sources of information required to have more understanding of the problems under observation. Also development of technological tools to implement the data extraction from large amounts of publications available. Chronic diseases have a specific challenge, when they are related to a long period of time and can be present in a lifetime, incorporating a source of increasing variability and uncertainty needing an examination. Implementing the possibility of processing the data extraction with more efficiency in terms of minimizing the time, can provide more updated information and providing a better support for decision making process. Economical intervention factors should be consider more carefully, as not all economical classes have the same access to healthy lifestyles (Capewell and Graham [2010]).

The complexity of the events modeled in this thesis, shows a need of the incorporation of more research and consideration of other levels of information. In order to control related structures of the context of this model. The additional direct value to the published literature is the synthesis of that evidence into a Markov model; that can be updated and actively used for decision making related with future research. From the methodological and biological characteristics of the model to its potential for clinical practice applications. There is a need to build more agreement on the debate. What is going to be more important: the effectiveness or the cost? What is exactly the effect expected from this application?

Chapters 4, 5 and 6 can be published, however an update should be undertaken for the systematic reviews. Chapter 4 presents an unpublished analysis with Mixed Treatment Comparison methods and different models like, additive and hierarchical models were compared methodologically. Chapter 5 was assumed as update of the previous sys-

tematic reviews (Ford [2005]; Gami et al. [2007]; Li et al. [2008]). This review also incorporates in the analysis a diverse classification of outcomes, in order to integrate all evidence related with MetS. Chapter 6 is the model developed from the integration of all the previous evidence synthesis with additional information about the utilities, the cost and the incidences of MetS, T2DM and CVD.

Appendix A

Additive models results from the extended network presented in Chapter 4.

Main Effects

		mean	sd	2.50%	median	97.50%
Control	Diet	12.25	10.05	2.96	9.74	36.30
	Eadv	0.38	0.39	0.06	0.29	1.22
	Esup	3.86	3.98	0.75	2.96	12.21
	AD	2.06	1.58	0.56	1.70	5.65
	AO	1.22	1.24	0.23	0.96	3.76
	Statin	1.38	1.76	0.23	1.01	4.71
	Fenofibrate	2.84	13.23	0.10	1.12	13.87
	D+Eadv	3.07	1.51	1.10	2.82	6.58
	D+Esup	42.24	55.75	6.36	28.61	156.40
	D+AD	25.87	49.15	3.34	16.72	101.50
	D+AO	15.30	34.40	1.44	9.41	62.78
	D+S	17.75	50.29	1.49	9.81	76.10
	D+F	41.00	458.10	0.75	10.91	189.70
	Eadv+AD	0.74	1.14	0.08	0.49	2.89
	Eadv+AO	0.50	1.24	0.03	0.28	2.23
	Eadv+S	0.53	1.32	0.03	0.29	2.36
	Eadv+F	1.19	9.76	0.02	0.32	5.56
	Esup+AD	8.28	19.95	0.88	5.03	33.77
	Esup+AO	4.87	12.87	0.39	2.82	20.30
	Esup+S	5.55	16.99	0.39	2.99	24.47
	Esup+F	12.59	99.53	0.20	3.33	60.20
	D+Eadv+AD	6.02	5.59	1.29	4.76	18.18
	D+Eadv+AO	4.01	6.28	0.41	2.70	14.94
	D+Eadv+S	4.28	7.52	0.47	2.84	16.25
	D+Eadv+F	9.18	56.25	0.22	3.14	43.78
	D+Esup+AD	92.95	621.30	7.62	49.08	403.50
	D+Esup+AO	53.97	190.90	3.42	27.54	250.30
	D+Esup+S	65.42	583.20	3.48	29.23	291.40
	D+Esup+F	151.80	1877.00	1.85	32.53	685.80
Diet	Eadv	0.07	0.24	0.00	0.03	0.36
	Esup	0.55	1.65	0.04	0.30	2.42
	AD	0.26	0.34	0.03	0.17	0.96
	AO	0.15	0.24	0.01	0.10	0.59
	Statin	0.17	0.33	0.01	0.10	0.71
	Fenofibrate	0.36	2.38	0.01	0.11	1.82
	D+Eadv	0.38	0.39	0.06	0.29	1.22
	D+Esup	3.86	3.98	0.75	2.96	12.21
	D+AD	2.06	1.58	0.56	1.70	5.65
	D+AO	1.22	1.24	0.23	0.96	3.76
	D+S	1.38	1.76	0.23	1.01	4.71
	D+F	2.84	13.23	0.10	1.12	13.87
	Eadv+AD	0.14	0.80	0.00	0.05	0.75
	Eadv+AO	0.10	0.64	0.00	0.03	0.52
	Eadv+S	0.10	0.63	0.00	0.03	0.55
	Eadv+F	0.27	4.39	0.00	0.03	1.10
	Esup+AD	1.25	8.59	0.05	0.51	5.92
	Esup+AO	0.72	4.44	0.02	0.29	3.44
	Esup+S	0.80	3.73	0.02	0.31	4.13
	Esup+F	2.01	23.52	0.01	0.34	8.74
	D+Eadv+AD	0.74	1.14	0.08	0.49	2.89
	D+Eadv+AO	0.50	1.24	0.03	0.28	2.23

	D+Eadv+S	0.53	1.32	0.03	0.29	2.36
	D+Eadv+F	1.19	9.76	0.02	0.32	5.56
	D+Esup+AD	8.28	19.95	0.88	5.03	33.77
	D+Esup+AO	4.87	12.87	0.39	2.82	20.30
	D+Esup+S	5.55	16.99	0.39	2.99	24.47
	D+Esup+F	12.59	99.53	0.20	3.33	60.20
Eadv	Esup	17.25	36.56	1.86	10.25	72.10
	AD	11.29	30.19	0.89	5.97	51.37
	AO	5.79	14.16	0.50	3.33	25.51
	Statin	7.26	23.42	0.45	3.49	33.82
	Fenofibrate	18.23	280.90	0.24	3.90	79.22
	D+Eadv	12.25	10.05	2.96	9.74	36.30
	D+Esup	320.10	1698.00	8.52	99.25	1765.00
	D+AD	257.20	2371.00	3.56	58.42	1363.00
	D+AO	128.10	1097.00	2.01	32.36	690.30
	D+S	178.10	2113.00	1.90	34.35	856.10
	D+F	642.10	22700.00	1.17	38.16	1707.00
	Eadv+AD	2.06	1.58	0.56	1.70	5.65
	Eadv+AO	1.22	1.24	0.23	0.96	3.76
	Eadv+S	1.38	1.76	0.23	1.01	4.71
	Eadv+F	2.84	13.23	0.10	1.12	13.87
	Esup+AD	41.25	238.10	2.11	17.55	196.20
	Esup+AO	20.73	77.92	1.16	9.86	97.23
	Esup+S	27.74	354.40	1.06	10.39	128.40
	Esup+F	72.16	1703.00	0.59	11.57	295.70
	D+Eadv+AD	25.87	49.15	3.34	16.72	101.50
	D+Eadv+AO	15.30	34.40	1.44	9.41	62.78
	D+Eadv+S	17.75	50.29	1.49	9.81	76.10
	D+Eadv+F	41.00	458.10	0.75	10.91	189.70
	D+Esup+AD	826.80	10940.00	10.61	170.60	4288.00
	D+Esup+AO	413.30	4994.00	5.97	95.23	2134.00
	D+Esup+S	649.30	19040.00	5.65	101.10	2659.00
	D+Esup+F	2283.00	113500.00	3.62	112.40	5185.00
Esup	AD	0.90	1.42	0.10	0.58	3.60
	AO	0.53	1.30	0.04	0.33	2.20
	Statin	0.61	1.91	0.04	0.34	2.68
	Fenofibrate	1.30	10.14	0.02	0.38	6.54
	D+Eadv	1.34	1.76	0.17	0.95	4.72
	D+Esup	12.25	10.05	2.96	9.74	36.30
	D+AD	13.58	67.53	0.55	5.67	66.91
	D+AO	8.01	47.01	0.25	3.17	40.25
	D+S	9.80	91.09	0.27	3.35	47.14
	D+F	27.25	790.60	0.15	3.68	98.40
	Eadv+AD	0.28	0.52	0.02	0.17	1.23
	Eadv+AO	0.19	0.59	0.01	0.09	0.88
	Eadv+S	0.20	0.50	0.01	0.10	0.98
	Eadv+F	0.43	3.36	0.00	0.11	2.16
	Esup+AD	2.06	1.58	0.56	1.70	5.65
	Esup+AO	1.22	1.24	0.23	0.96	3.76
	Esup+S	1.38	1.76	0.23	1.01	4.71
	Esup+F	2.84	13.23	0.10	1.12	13.87
	D+Eadv+AD	2.65	4.80	0.24	1.61	10.98
	D+Eadv+AO	1.77	5.71	0.09	0.91	8.01

	D+Eadv+S	1.90	7.84	0.10	0.95	8.64
	D+Eadv+F	4.22	38.91	0.05	1.06	20.20
	D+Esup+AD	25.87	49.15	3.34	16.72	101.50
	D+Esup+AO	15.30	34.40	1.44	9.41	62.78
	D+Esup+S	17.75	50.29	1.49	9.81	76.10
	D+Esup+F	41.00	458.10	0.75	10.91	189.70
AD	AO	0.83	1.16	0.08	0.57	3.15
	Statin	0.96	2.19	0.08	0.59	3.83
	Fenofibrate	2.08	15.01	0.04	0.66	9.91
	D+Eadv	2.22	2.70	0.31	1.65	7.39
	D+Esup	29.05	55.46	2.44	16.84	126.70
	D+AD	12.25	10.05	2.96	9.74	36.30
	D+AO	10.46	28.07	0.59	5.51	47.36
	D+S	12.62	62.60	0.61	5.78	57.45
	D+F	32.19	575.70	0.33	6.40	133.70
	Eadv+AD	0.38	0.39	0.06	0.29	1.22
	Eadv+AO	0.36	1.31	0.01	0.16	1.76
	Eadv+S	0.39	1.39	0.01	0.17	1.87
	Eadv+F	0.91	9.51	0.01	0.19	4.10
	Esup+AD	3.86	3.98	0.75	2.96	12.21
	Esup+AO	3.30	12.13	0.16	1.67	15.15
	Esup+S	3.85	14.60	0.16	1.75	18.11
	Esup+F	9.25	97.54	0.09	1.95	41.97
	D+Eadv+AD	3.07	1.51	1.10	2.82	6.58
	D+Eadv+AO	2.89	6.87	0.15	1.59	12.91
	D+Eadv+S	3.19	14.08	0.17	1.68	13.86
	D+Eadv+F	7.42	92.67	0.09	1.85	32.94
	D+Esup+AD	42.24	55.75	6.36	28.61	156.40
	D+Esup+AO	36.62	139.30	1.45	16.17	181.10
	D+Esup+S	45.78	423.20	1.46	17.24	218.70
	D+Esup+F	113.40	1724.00	0.83	19.04	473.80
AO	Statin	1.97	7.38	0.14	1.05	8.93
	Fenofibrate	4.54	85.45	0.07	1.16	21.36
	D+Eadv	3.94	4.29	0.65	2.91	13.54
	D+Esup	59.62	165.90	3.99	30.04	286.10
	D+AD	36.97	116.40	2.17	17.27	183.80
	D+AO	12.25	10.05	2.96	9.74	36.30
	D+S	26.68	189.00	1.03	10.22	127.50
	D+F	75.20	2712.00	0.56	11.41	287.60
	Eadv+AD	0.98	3.04	0.06	0.51	4.52
	Eadv+AO	0.38	0.39	0.06	0.29	1.22
	Eadv+S	0.71	4.28	0.02	0.30	3.43
	Eadv+F	1.71	50.49	0.01	0.33	7.90
	Esup+AD	12.03	65.21	0.60	5.24	57.23
	Esup+AO	3.86	3.98	0.75	2.96	12.21
	Esup+S	7.97	48.11	0.28	3.13	40.80
	Esup+F	20.60	579.40	0.16	3.45	89.27
	D+Eadv+AD	7.85	17.51	0.89	4.95	31.93
	D+Eadv+AO	3.07	1.51	1.10	2.82	6.58
	D+Eadv+S	5.75	26.23	0.36	2.94	25.47
	D+Eadv+F	12.94	200.30	0.18	3.25	62.25
	D+Esup+AD	131.30	595.60	5.37	51.22	669.40
	D+Esup+AO	42.24	55.75	6.36	28.61	156.40

	D+Esup+S	97.06	1015.00	2.51	30.39	475.10
	D+Esup+F	287.50	11680.00	1.41	33.65	980.80
Statin	Fenofibrate	2.29	9.87	0.12	1.11	10.26
	D+Eadv	4.08	5.61	0.45	2.79	15.53
	D+Esup	56.67	134.00	3.33	28.51	278.60
	D+AD	36.69	202.80	1.87	16.49	176.70
	D+AO	21.58	96.87	0.84	9.27	102.70
	D+S	12.25	10.05	2.96	9.74	36.30
	D+F	30.70	192.70	0.90	10.89	145.00
	Eadv+AD	1.04	5.97	0.04	0.48	4.77
	Eadv+AO	0.69	3.22	0.02	0.27	3.41
	Eadv+S	0.38	0.39	0.06	0.29	1.22
	Eadv+F	0.98	11.02	0.02	0.32	4.35
	Esup+AD	12.02	135.30	0.50	5.00	56.09
	Esup+AO	6.64	27.91	0.23	2.81	32.36
	Esup+S	3.86	3.98	0.75	2.96	12.21
	Esup+F	10.19	97.55	0.24	3.28	46.76
	D+Eadv+AD	8.22	21.08	0.64	4.73	35.31
	D+Eadv+AO	5.59	24.58	0.23	2.68	25.86
	D+Eadv+S	3.07	1.51	1.10	2.82	6.58
	D+Eadv+F	7.51	63.85	0.27	3.12	33.03
	D+Esup+AD	138.00	3203.00	4.55	48.79	663.90
	D+Esup+AO	76.05	759.70	2.02	27.22	390.30
	D+Esup+S	42.24	55.75	6.36	28.61	156.40
	D+Esup+F	113.30	1241.00	2.15	32.13	545.40
Fenofibrate	D+Eadv	6.65	71.18	0.17	2.54	32.71
	D+Esup	105.40	3043.00	1.44	25.98	511.50
	D+AD	64.33	813.80	0.80	14.92	325.10
	D+AO	40.09	750.90	0.37	8.42	187.30
	D+S	24.83	312.80	0.72	8.84	120.20
	D+F	12.25	10.05	2.96	9.74	36.30
	Eadv+AD	1.69	14.21	0.02	0.44	8.82
	Eadv+AO	1.24	24.47	0.01	0.25	5.89
	Eadv+S	0.71	6.44	0.02	0.26	3.59
	Eadv+F	0.38	0.39	0.06	0.29	1.22
	Esup+AD	19.60	205.30	0.22	4.51	96.43
	Esup+AO	11.33	137.40	0.10	2.56	56.52
	Esup+S	7.40	42.41	0.20	2.66	36.83
	Esup+F	3.86	3.98	0.75	2.96	12.21
	D+Eadv+AD	13.46	75.48	0.26	4.30	69.55
	D+Eadv+AO	9.68	121.10	0.10	2.44	47.00
	D+Eadv+S	5.74	40.31	0.22	2.54	26.71
	D+Eadv+F	3.07	1.51	1.10	2.82	6.58
	D+Esup+AD	225.10	3693.00	2.07	44.32	1121.00
	D+Esup+AO	139.20	3273.00	0.95	24.93	664.40
	D+Esup+S	89.08	1417.00	1.83	25.97	436.50
	D+Esup+F	42.24	55.75	6.36	28.61	156.40
D+Eadv	D+Esup	17.25	36.56	1.86	10.25	72.10
	D+AD	11.29	30.19	0.89	5.97	51.37
	D+AO	5.79	14.16	0.50	3.33	25.51
	D+S	7.26	23.42	0.45	3.49	33.82
	D+F	18.23	280.90	0.24	3.90	79.22
	Eadv+AD	0.26	0.34	0.03	0.17	0.96

	Eadv+AO	0.15	0.24	0.01	0.10	0.59
	Eadv+S	0.17	0.33	0.01	0.10	0.71
	Eadv+F	0.36	2.38	0.01	0.11	1.82
	Esup+AD	3.71	17.46	0.24	1.79	16.94
	Esup+AO	1.87	5.84	0.13	1.01	8.15
	Esup+S	2.30	9.73	0.12	1.06	10.79
	Esup+F	5.31	51.83	0.06	1.18	25.63
	D+Eadv+AD	2.06	1.58	0.56	1.70	5.65
	D+Eadv+AO	1.22	1.24	0.23	0.96	3.76
	D+Eadv+S	1.38	1.76	0.23	1.01	4.71
	D+Eadv+F	2.84	13.23	0.10	1.12	13.87
	D+Esup+AD	41.25	238.10	2.11	17.55	196.20
	D+Esup+AO	20.73	77.92	1.16	9.86	97.23
	D+Esup+S	27.74	354.40	1.06	10.39	128.40
	D+Esup+F	72.16	1703.00	0.59	11.57	295.70
D+Esup	D+AD	0.90	1.42	0.10	0.58	3.60
	D+AO	0.53	1.30	0.04	0.33	2.20
	D+S	0.61	1.91	0.04	0.34	2.68
	D+F	1.30	10.14	0.02	0.38	6.54
	Eadv+AD	0.05	0.22	0.00	0.02	0.25
	Eadv+AO	0.03	0.20	0.00	0.01	0.17
	Eadv+S	0.03	0.13	0.00	0.01	0.19
	Eadv+F	0.07	0.82	0.00	0.01	0.37
	Esup+AD	0.26	0.34	0.03	0.17	0.96
	Esup+AO	0.15	0.24	0.01	0.10	0.59
	Esup+S	0.17	0.33	0.01	0.10	0.71
	Esup+F	0.36	2.38	0.01	0.11	1.82
	D+Eadv+AD	0.28	0.52	0.02	0.17	1.23
	D+Eadv+AO	0.19	0.59	0.01	0.09	0.88
	D+Eadv+S	0.20	0.50	0.01	0.10	0.98
	D+Eadv+F	0.43	3.36	0.00	0.11	2.16
	D+Esup+AD	2.06	1.58	0.56	1.70	5.65
	D+Esup+AO	1.22	1.24	0.23	0.96	3.76
	D+Esup+S	1.38	1.76	0.23	1.01	4.71
	D+Esup+F	2.84	13.23	0.10	1.12	13.87
D+AD	D+AO	0.83	1.16	0.08	0.57	3.15
	D+S	0.96	2.19	0.08	0.59	3.83
	D+F	2.08	15.01	0.04	0.66	9.91
	Eadv+AD	0.07	0.24	0.00	0.03	0.36
	Eadv+AO	0.07	0.59	0.00	0.02	0.39
	Eadv+S	0.08	0.64	0.00	0.02	0.41
	Eadv+F	0.20	3.56	0.00	0.02	0.78
	Esup+AD	0.55	1.65	0.04	0.30	2.42
	Esup+AO	0.48	3.31	0.01	0.17	2.47
	Esup+S	0.55	2.93	0.01	0.18	2.90
	Esup+F	1.48	24.38	0.01	0.20	5.87
	D+Eadv+AD	0.38	0.39	0.06	0.29	1.22
	D+Eadv+AO	0.36	1.31	0.01	0.16	1.76
	D+Eadv+S	0.39	1.39	0.01	0.17	1.87
	D+Eadv+F	0.91	9.51	0.01	0.19	4.10
	D+Esup+AD	3.86	3.98	0.75	2.96	12.21
	D+Esup+AO	3.30	12.13	0.16	1.67	15.15
	D+Esup+S	3.85	14.60	0.16	1.75	18.11

	D+Esup+F	9.25	97.54	0.09	1.95	41.97
D+AO	D+S	1.97	7.38	0.14	1.05	8.93
	D+F	4.54	85.45	0.07	1.16	21.36
	Eadv+AD	0.19	1.52	0.00	0.05	1.05
	Eadv+AO	0.07	0.24	0.00	0.03	0.36
	Eadv+S	0.15	3.23	0.00	0.03	0.72
	Eadv+F	0.52	41.80	0.00	0.03	1.45
	Esup+AD	1.95	29.14	0.04	0.54	9.09
	Esup+AO	0.55	1.65	0.04	0.30	2.42
	Esup+S	1.29	33.05	0.02	0.32	6.28
	Esup+F	4.71	446.80	0.01	0.35	12.71
	D+Eadv+AD	0.98	3.04	0.06	0.51	4.52
	D+Eadv+AO	0.38	0.39	0.06	0.29	1.22
	D+Eadv+S	0.71	4.28	0.02	0.30	3.43
	D+Eadv+F	1.71	50.49	0.01	0.33	7.90
	D+Esup+AD	12.03	65.21	0.60	5.24	57.23
	D+Esup+AO	3.86	3.98	0.75	2.96	12.21
	D+Esup+S	7.97	48.11	0.28	3.13	40.80
	D+Esup+F	20.60	579.40	0.16	3.45	89.27
D+S	D+F	2.29	9.87	0.12	1.11	10.26
	Eadv+AD	0.24	8.05	0.00	0.05	1.08
	Eadv+AO	0.14	1.46	0.00	0.03	0.71
	Eadv+S	0.07	0.24	0.00	0.03	0.36
	Eadv+F	0.23	5.96	0.00	0.03	0.92
	Esup+AD	2.58	192.60	0.03	0.51	8.68
	Esup+AO	1.03	12.86	0.01	0.29	5.04
	Esup+S	0.55	1.65	0.04	0.30	2.42
	Esup+F	1.82	52.74	0.02	0.34	7.00
	D+Eadv+AD	1.04	5.97	0.04	0.48	4.77
	D+Eadv+AO	0.69	3.22	0.02	0.27	3.41
	D+Eadv+S	0.38	0.39	0.06	0.29	1.22
	D+Eadv+F	0.98	11.02	0.02	0.32	4.35
	D+Esup+AD	12.02	135.30	0.50	5.00	56.09
	D+Esup+AO	6.64	27.91	0.23	2.81	32.36
	D+Esup+S	3.86	3.98	0.75	2.96	12.21
	D+Esup+F	10.19	97.55	0.24	3.28	46.76
D+F	Eadv+AD	0.37	6.66	0.00	0.04	1.71
	Eadv+AO	0.27	7.49	0.00	0.03	1.10
	Eadv+S	0.14	1.99	0.00	0.03	0.73
	Eadv+F	0.07	0.24	0.00	0.03	0.36
	Esup+AD	3.51	103.40	0.01	0.46	14.14
	Esup+AO	1.85	50.01	0.01	0.26	8.05
	Esup+S	1.11	10.19	0.01	0.27	5.51
	Esup+F	0.55	1.65	0.04	0.30	2.42
	D+Eadv+AD	1.69	14.21	0.02	0.44	8.82
	D+Eadv+AO	1.24	24.47	0.01	0.25	5.89
	D+Eadv+S	0.71	6.44	0.02	0.26	3.59
	D+Eadv+F	0.38	0.39	0.06	0.29	1.22
	D+Esup+AD	19.60	205.30	0.22	4.51	96.43
	D+Esup+AO	11.33	137.40	0.10	2.56	56.52
	D+Esup+S	7.40	42.41	0.20	2.66	36.83
	D+Esup+F	3.86	3.98	0.75	2.96	12.21
Eadv+AD	Eadv+AO	0.83	1.16	0.08	0.57	3.15

	Eadv+S	0.96	2.19	0.08	0.59	3.83
	Eadv+F	2.08	15.01	0.04	0.66	9.91
	Esup+AD	17.25	36.56	1.86	10.25	72.10
	Esup+AO	13.25	52.10	0.54	5.79	65.94
	Esup+S	18.24	244.60	0.50	6.17	85.46
	Esup+F	47.58	945.80	0.29	6.83	186.10
	D+Eadv+AD	12.25	10.05	2.96	9.74	36.30
	D+Eadv+AO	10.46	28.07	0.59	5.51	47.36
	D+Eadv+S	12.62	62.60	0.61	5.78	57.45
	D+Eadv+F	32.19	575.70	0.33	6.40	133.70
	D+Esup+AD	320.10	1698.00	8.52	99.25	1765.00
	D+Esup+AO	262.70	2885.00	2.93	55.76	1362.00
	D+Esup+S	435.20	13380.00	2.71	59.75	1690.00
	D+Esup+F	1490.00	62190.00	1.78	65.91	3161.00
Eadv+AO	Eadv+S	1.97	7.38	0.14	1.05	8.93
	Eadv+F	4.54	85.45	0.07	1.16	21.36
	Esup+AD	69.38	998.70	1.40	18.31	348.70
	Esup+AO	17.25	36.56	1.86	10.25	72.10
	Esup+S	48.11	938.50	0.73	10.81	217.60
	Esup+F	167.00	8977.00	0.43	11.97	449.20
	D+Eadv+AD	36.97	116.40	2.17	17.27	183.80
	D+Eadv+AO	12.25	10.05	2.96	9.74	36.30
	D+Eadv+S	26.68	189.00	1.03	10.22	127.50
	D+Eadv+F	75.20	2712.00	0.56	11.41	287.60
	D+Esup+AD	1444.00	35410.00	7.81	179.90	6630.00
	D+Esup+AO	320.10	1698.00	8.52	99.25	1765.00
	D+Esup+S	1254.00	44650.00	4.07	105.30	4135.00
	D+Esup+F	6656.00	557900.00	2.74	117.70	7488.00
Eadv+S	Eadv+F	2.29	9.87	0.12	1.11	10.26
	Esup+AD	58.74	656.60	1.32	17.37	300.20
	Esup+AO	29.01	231.80	0.70	9.75	150.00
	Esup+S	17.25	36.56	1.86	10.25	72.10
	Esup+F	50.55	997.10	0.71	11.35	230.50
	D+Eadv+AD	36.69	202.80	1.87	16.49	176.70
	D+Eadv+AO	21.58	96.87	0.84	9.27	102.70
	D+Eadv+S	12.25	10.05	2.96	9.74	36.30
	D+Eadv+F	30.70	192.70	0.90	10.89	145.00
	D+Esup+AD	1283.00	46570.00	7.19	170.10	5771.00
	D+Esup+AO	621.80	15600.00	4.00	93.94	2907.00
	D+Esup+S	320.10	1698.00	8.52	99.25	1765.00
	D+Esup+F	1322.00	69540.00	4.09	110.80	4332.00
Eadv+F	Esup+AD	105.80	1695.00	0.63	15.71	501.10
	Esup+AO	53.21	759.50	0.33	8.89	253.80
	Esup+S	35.87	314.80	0.59	9.29	188.50
	Esup+F	17.25	36.56	1.86	10.25	72.10
	D+Eadv+AD	64.33	813.80	0.80	14.92	325.10
	D+Eadv+AO	40.09	750.90	0.37	8.42	187.30
	D+Eadv+S	24.83	312.80	0.72	8.84	120.20
	D+Eadv+F	12.25	10.05	2.96	9.74	36.30
	D+Esup+AD	2858.00	185200.00	3.86	152.80	8502.00
	D+Esup+AO	1392.00	51540.00	2.06	85.95	4393.00
	D+Esup+S	857.50	28910.00	3.34	90.38	3490.00
	D+Esup+F	320.10	1698.00	8.52	99.25	1765.00

Esup+AD	Esup+AO	0.83	1.16	0.08	0.57	3.15
	Esup+S	0.96	2.19	0.08	0.59	3.83
	Esup+F	2.08	15.01	0.04	0.66	9.91
	D+Eadv+AD	1.34	1.76	0.17	0.95	4.72
	D+Eadv+AO	1.29	5.25	0.03	0.54	6.37
	D+Eadv+S	1.43	9.64	0.04	0.56	6.88
	D+Eadv+F	3.55	73.88	0.02	0.62	14.95
	D+Esup+AD	12.25	10.05	2.96	9.74	36.30
	D+Esup+AO	10.46	28.07	0.59	5.51	47.36
	D+Esup+S	12.62	62.60	0.61	5.78	57.45
	D+Esup+F	32.19	575.70	0.33	6.40	133.70
Esup+AO	Esup+S	1.97	7.38	0.14	1.05	8.93
	Esup+F	4.54	85.45	0.07	1.16	21.36
	D+Eadv+AD	3.53	12.43	0.18	1.68	16.74
	D+Eadv+AO	1.34	1.76	0.17	0.95	4.72
	D+Eadv+S	2.89	80.00	0.08	1.00	12.91
	D+Eadv+F	6.37	160.10	0.05	1.09	27.69
	D+Esup+AD	36.97	116.40	2.17	17.27	183.80
	D+Esup+AO	12.25	10.05	2.96	9.74	36.30
	D+Esup+S	26.68	189.00	1.03	10.22	127.50
	D+Esup+F	75.20	2712.00	0.56	11.41	287.60
Esup+S	Esup+F	2.29	9.87	0.12	1.11	10.26
	D+Eadv+AD	3.84	21.16	0.14	1.59	18.30
	D+Eadv+AO	2.67	25.64	0.05	0.90	12.64
	D+Eadv+S	1.34	1.76	0.17	0.95	4.72
	D+Eadv+F	3.31	26.11	0.06	1.05	15.50
	D+Esup+AD	36.69	202.80	1.87	16.49	176.70
	D+Esup+AO	21.58	96.87	0.84	9.27	102.70
	D+Esup+S	12.25	10.05	2.96	9.74	36.30
	D+Esup+F	30.70	192.70	0.90	10.89	145.00
Esup+F	D+Eadv+AD	6.66	77.07	0.06	1.44	32.63
	D+Eadv+AO	4.86	86.66	0.02	0.82	21.54
	D+Eadv+S	2.53	15.00	0.05	0.86	13.09
	D+Eadv+F	1.34	1.76	0.17	0.95	4.72
	D+Esup+AD	64.33	813.80	0.80	14.92	325.10
	D+Esup+AO	40.09	750.90	0.37	8.42	187.30
	D+Esup+S	24.83	312.80	0.72	8.84	120.20
	D+Esup+F	12.25	10.05	2.96	9.74	36.30
D+Eadv+AD	D+Eadv+AO	0.83	1.16	0.08	0.57	3.15
	D+Eadv+S	0.96	2.19	0.08	0.59	3.83
	D+Eadv+F	2.08	15.01	0.04	0.66	9.91
	D+Esup+AD	17.25	36.56	1.86	10.25	72.10
	D+Esup+AO	13.25	52.10	0.54	5.79	65.94
	D+Esup+S	18.24	244.60	0.50	6.17	85.46
	D+Esup+F	47.58	945.80	0.29	6.83	186.10
D+Eadv+AO	D+Eadv+S	1.97	7.38	0.14	1.05	8.93
	D+Eadv+F	4.54	85.45	0.07	1.16	21.36
	D+Esup+AD	69.38	998.70	1.40	18.31	348.70
	D+Esup+AO	17.25	36.56	1.86	10.25	72.10
	D+Esup+S	48.11	938.50	0.73	10.81	217.60
	D+Esup+F	167.00	8977.00	0.43	11.97	449.20
D+Eadv+S	D+Eadv+F	2.29	9.87	0.12	1.11	10.26
	D+Esup+AD	58.74	656.60	1.32	17.37	300.20

	D+Esup+AO	29.01	231.80	0.70	9.75	150.00
	D+Esup+S	17.25	36.56	1.86	10.25	72.10
	D+Esup+F	50.55	997.10	0.71	11.35	230.50
D+Eadv+F	D+Esup+AD	105.80	1695.00	0.63	15.71	501.10
	D+Esup+AO	53.21	759.50	0.33	8.89	253.80
	D+Esup+S	35.87	314.80	0.59	9.29	188.50
	D+Esup+F	17.25	36.56	1.86	10.25	72.10
D+Esup+AD	D+Esup+AO	0.83	1.16	0.08	0.57	3.15
	D+Esup+S	0.96	2.19	0.08	0.59	3.83
	D+Esup+F	2.08	15.01	0.04	0.66	9.91
D+Esup+AO	D+Esup+S	1.97	7.38	0.14	1.05	8.93
	D+Esup+F	4.54	85.45	0.07	1.16	21.36
D+Esup+S	D+Esup+F	2.29	9.87	0.12	1.11	10.26

Two way Interaction

		mean	sd	2.50%	median	97.50%
Control	Diet	8.51	6.237	2.509	7.269	21.9
	Eadv	0.2477	3.239	0.006721	0.07757	1.092
	Esup	1.858	1.922	0.3305	1.396	6.223
	AD	8.784	10.92	1.3	6.122	31.46
	AO	1.164	0.93	0.2885	1.035	2.823
	Statin	1.21	1.014	0.3069	1.008	3.331
	Fenofibrate	1.848	5.346	0.1639	1.096	7.703
	D+Eadv	11.24	52.05	0.5668	5.657	48.44
	D+Esup	5.847	13.64	0.7258	3.857	21.49
	D+AD	5.04E+06	3.20E+08	9.17E-07	0.318	234400
	D+AO	2.31E+14	4.50E+16	3.17E-09	0.939	3.02E+08
	D+S	1.08E+15	2.36E+17	2.94E-09	0.9741	3.55E+08
	D+F	2.44E+15	5.08E+17	3.04E-09	1.004	3.84E+08
	Eadv+AD	54760	1.13E+06	4.87E-07	0.403	150100
	Eadv+AO	1.01E+13	1.84E+15	3.57E-09	1.06	3.40E+08
	Eadv+S	2.97E+15	6.61E+17	2.93E-09	0.9589	3.73E+08
	Eadv+F	2.10E+15	4.62E+17	2.97E-09	1.012	2.97E+08
	Esup+AD	1.77E+16	3.97E+18	2.91E-09	1.03	4.24E+08
	Esup+AO	4.66E+17	1.04E+20	3.10E-09	0.9472	3.48E+08
	Esup+S	1.00E+14	1.85E+16	3.78E-09	1.039	3.59E+08
	Esup+F	1.03E+13	1.57E+15	2.48E-09	0.9818	3.23E+08
Diet	Eadv	0.09447	3.812	5.08E-04	0.01058	0.2688
	Esup	0.2975	0.6161	0.03204	0.1904	1.164
	AD	1.421	2.957	0.1268	0.8492	5.991
	AO	0.1875	0.3076	0.02584	0.1406	0.6038
	Statin	0.1964	0.31	0.02683	0.1382	0.7
	Fenofibrate	0.3127	1.383	0.01676	0.1494	1.397
	D+Eadv	2.072	23.79	0.06069	0.773	8.613
	D+Esup	1.262	11.73	0.05546	0.5292	5.354
	D+AD	1.15E+06	7.21E+07	1.24E-07	0.0428	37460
	D+AO	1.27E+14	2.76E+16	4.35E-10	0.1302	4.27E+07
	D+S	2.20E+14	4.83E+16	4.14E-10	0.1326	4.99E+07
	D+F	6.08E+14	1.25E+17	4.09E-10	0.1377	5.14E+07
	Eadv+AD	8927	190500	6.61E-08	0.05528	21020
	Eadv+AO	6.90E+11	1.13E+14	4.65E-10	0.1406	4.53E+07
	Eadv+S	1.44E+14	3.18E+16	4.23E-10	0.1354	5.48E+07
	Eadv+F	4.70E+14	1.04E+17	3.98E-10	0.1362	4.22E+07
	Esup+AD	1.73E+15	3.86E+17	3.88E-10	0.1402	5.98E+07
	Esup+AO	2.53E+16	5.65E+18	4.03E-10	0.1309	4.78E+07
	Esup+S	1.08E+13	1.82E+15	4.85E-10	0.1438	5.29E+07
	Esup+F	1.25E+12	1.53E+14	3.16E-10	0.1349	4.38E+07
Eadv	Esup	78.74	1438	0.8959	17.62	318.4
	AD	777.7	15270	1.838	78.65	3189
	AO	38.61	445.5	0.7093	13.24	172.9
	Statin	45.57	490.6	0.7461	13.05	186.4
	Fenofibrate	100.9	2342	0.5609	14.02	292
	D+Eadv	3989	143800	0.6194	73.08	5970
	D+Esup	162.1	883.6	2.59	50.07	854
	D+AD	6.95E+07	5.10E+09	9.64E-06	3.837	3.41E+06
	D+AO	2.77E+15	5.32E+17	3.43E-08	11.88	4.28E+09
	D+S	5.05E+15	1.05E+18	3.23E-08	12.18	5.03E+09

	D+F	1.09E+16	2.27E+18	3.17E-08	12.55	5.56E+09
	Eadv+AD	1.08E+06	2.64E+07	5.00E-06	4.832	1.77E+06
	Eadv+AO	2.84E+14	4.06E+16	3.68E-08	13.72	5.09E+09
	Eadv+S	3.49E+17	7.80E+19	3.28E-08	12.49	5.35E+09
	Eadv+F	1.75E+16	3.62E+18	3.16E-08	12.36	4.34E+09
	Esup+AD	8.95E+17	2.00E+20	2.96E-08	12.71	6.47E+09
	Esup+AO	1.78E+19	3.99E+21	3.37E-08	12.09	4.96E+09
	Esup+S	1.59E+15	2.63E+17	3.95E-08	12.63	5.27E+09
	Esup+F	7.73E+13	7.44E+15	2.62E-08	12.49	4.73E+09
Esup	AD	8.286	19.36	0.5085	4.463	37.29
	AO	1.095	1.935	0.1001	0.7377	4.096
	Statin	1.164	2.711	0.1064	0.7273	4.662
	Fenofibrate	1.806	7.42	0.0695	0.7908	8.705
	D+Eadv	10.84	84.6	0.2576	4.073	51.92
	D+Esup	10.34	170.6	0.1595	2.79	45.54
	D+AD	1.77E+06	9.37E+07	5.38E-07	0.2274	211200
	D+AO	1.85E+14	3.54E+16	2.31E-09	0.7062	2.22E+08
	D+S	3.55E+14	7.33E+16	2.01E-09	0.6938	2.54E+08
	D+F	4.72E+15	1.03E+18	2.18E-09	0.6987	2.87E+08
	Eadv+AD	61550	1.63E+06	3.15E-07	0.2841	107300
	Eadv+AO	1.23E+13	2.36E+15	2.56E-09	0.7472	2.73E+08
	Eadv+S	9.52E+15	2.13E+18	1.96E-09	0.6918	2.74E+08
	Eadv+F	1.75E+15	3.87E+17	2.02E-09	0.7132	2.29E+08
	Esup+AD	1.06E+16	2.38E+18	1.99E-09	0.7189	2.87E+08
	Esup+AO	3.25E+17	7.27E+19	2.09E-09	0.6785	2.39E+08
	Esup+S	9.68E+13	1.94E+16	2.48E-09	0.737	2.61E+08
	Esup+F	1.04E+13	1.70E+15	1.63E-09	0.7178	2.45E+08
AD	AO	0.2685	0.895	0.02095	0.1631	1.021
	Statin	0.2838	0.9298	0.02173	0.1631	1.211
	Fenofibrate	0.4786	3.892	0.01448	0.1785	2.194
	D+Eadv	1.247	2.106	0.162	0.9362	4.204
	D+Esup	1.442	10.59	0.06237	0.6291	6.532
	D+AD	3.08E+06	2.51E+08	1.29E-07	0.05296	51710
	D+AO	3.65E+13	6.04E+15	4.86E-10	0.1575	5.11E+07
	D+S	2.34E+14	5.08E+16	4.59E-10	0.1548	6.49E+07
	D+F	3.13E+14	6.49E+16	5.09E-10	0.1625	6.75E+07
	Eadv+AD	16310	6.51E+05	6.17E-08	0.06028	29930
	Eadv+AO	2.51E+12	4.86E+14	5.16E-10	0.1684	6.38E+07
	Eadv+S	1.92E+14	4.26E+16	4.64E-10	0.151	6.49E+07
	Eadv+F	3.12E+14	6.88E+16	4.45E-10	0.1594	5.21E+07
	Esup+AD	4.38E+14	9.77E+16	4.69E-10	0.161	6.99E+07
	Esup+AO	4.98E+16	1.11E+19	4.69E-10	0.1584	5.95E+07
	Esup+S	2.29E+13	4.70E+15	5.76E-10	0.1667	6.02E+07
	Esup+F	4.67E+12	8.08E+14	3.49E-10	0.1592	5.51E+07
AO	Statin	1.562	4.951	0.2114	0.9788	6.101
	Fenofibrate	2.59	19.54	0.1284	1.058	11.6
	D+Eadv	14.73	120.6	0.4618	5.598	68.42
	D+Esup	8.089	75.81	0.5487	3.776	33.47
	D+AD	7.17E+06	5.12E+08	8.77E-07	0.3105	253400
	D+AO	2.17E+14	4.49E+16	3.07E-09	0.9691	3.33E+08
	D+S	1.09E+15	2.34E+17	2.91E-09	0.9736	3.68E+08
	D+F	3.47E+15	7.14E+17	3.11E-09	1.036	3.99E+08
	Eadv+AD	65370	1.97E+06	4.64E-07	0.3979	151100

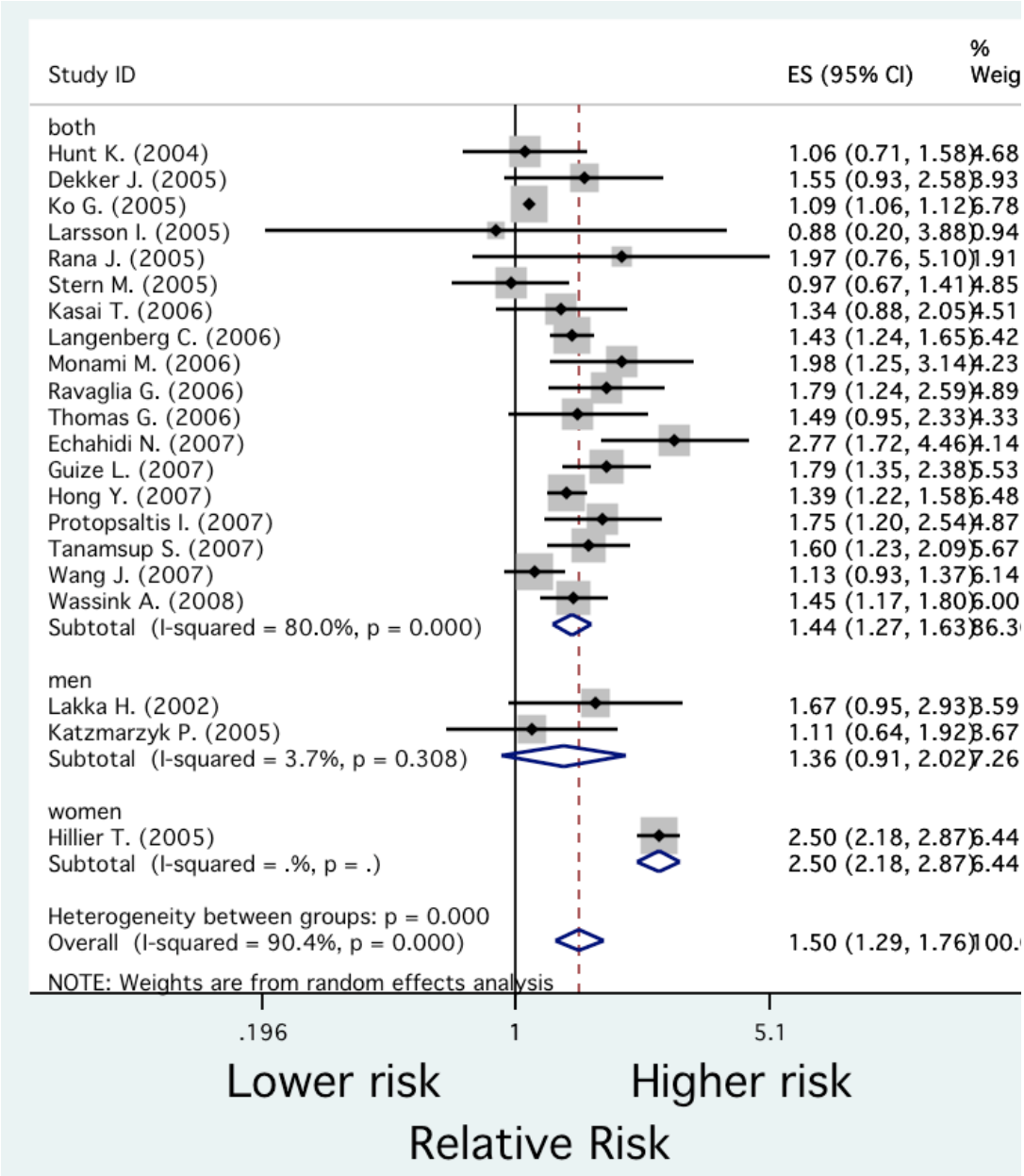
	Eadv+AO	6.13E+12	8.41E+14	3.34E-09	1.071	3.83E+08
	Eadv+S	3.34E+15	7.43E+17	2.93E-09	0.9821	4.03E+08
	Eadv+F	1.86E+15	4.12E+17	2.90E-09	1.019	3.05E+08
	Esup+AD	1.30E+16	2.91E+18	2.92E-09	0.9976	4.38E+08
	Esup+AO	2.85E+17	6.38E+19	2.81E-09	0.9519	3.32E+08
	Esup+S	8.57E+13	1.51E+16	3.61E-09	1.06	3.75E+08
	Esup+F	1.56E+13	2.60E+15	2.38E-09	1.014	3.40E+08
Statin	Fenofibrate	1.76	14.14	0.1909	1.084	6.404
	D+Eadv	13.54	52.92	0.3902	5.676	65.65
	D+Esup	7.502	57.87	0.5007	3.819	30.55
	D+AD	1.72E+07	1.46E+09	8.59E-07	0.3201	274800
	D+AO	2.22E+14	3.40E+16	3.09E-09	0.9443	2.98E+08
	D+S	8.19E+14	1.77E+17	2.97E-09	0.9631	3.62E+08
	D+F	1.51E+15	3.18E+17	3.02E-09	0.9907	3.86E+08
	Eadv+AD	54530	1.19E+06	4.57E-07	0.4025	1.50E+05
	Eadv+AO	5.03E+12	6.95E+14	3.57E-09	1.046	3.54E+08
	Eadv+S	5.32E+15	1.18E+18	2.56E-09	0.9457	3.93E+08
	Eadv+F	6.23E+14	1.29E+17	2.84E-09	1.013	2.92E+08
	Esup+AD	2.83E+16	6.32E+18	2.79E-09	1.004	4.33E+08
	Esup+AO	3.83E+17	8.57E+19	2.91E-09	0.9556	3.46E+08
	Esup+S	1.29E+14	2.50E+16	3.59E-09	1.056	3.66E+08
	Esup+F	9.66E+12	1.36E+15	2.40E-09	1.004	3.38E+08
Fenofibrate	D+Eadv	19.55	418.6	0.2283	5.204	90.87
	D+Esup	15.62	1181	0.2753	3.501	43.58
	D+AD	4.02E+07	3.46E+09	7.24E-07	0.281	299800
	D+AO	7.63E+14	1.39E+17	2.75E-09	0.8658	2.83E+08
	D+S	9.43E+14	2.06E+17	2.59E-09	0.8793	3.73E+08
	D+F	2.56E+15	5.51E+17	2.63E-09	0.8957	3.98E+08
	Eadv+AD	45200	921300	3.78E-07	0.3796	155300
	Eadv+AO	6.96E+12	8.47E+14	3.08E-09	0.9598	3.32E+08
	Eadv+S	2.34E+16	5.24E+18	2.28E-09	0.8836	3.48E+08
	Eadv+F	5.90E+14	1.20E+17	2.48E-09	0.9019	2.61E+08
	Esup+AD	8.91E+16	1.99E+19	2.38E-09	0.906	3.93E+08
	Esup+AO	1.55E+17	3.47E+19	2.58E-09	0.8793	3.23E+08
	Esup+S	1.39E+14	2.63E+16	3.14E-09	0.949	3.32E+08
	Esup+F	8.09E+12	1.11E+15	1.97E-09	0.8851	3.24E+08
D+Eadv	D+Esup	2.762	39.49	0.04936	0.6735	11.9
	D+AD	5.83E+06	3.43E+08	1.30E-07	0.05873	66960
	D+AO	2.69E+13	3.45E+15	5.28E-10	0.1772	5.79E+07
	D+S	3.43E+14	7.22E+16	5.06E-10	0.1722	7.82E+07
	D+F	7.26E+14	1.52E+17	5.14E-10	0.1799	7.97E+07
	Eadv+AD	21700	682100	6.18E-08	0.0654	35880
	Eadv+AO	1.75E+12	3.19E+14	5.31E-10	0.1839	7.37E+07
	Eadv+S	1.27E+14	2.79E+16	4.74E-10	0.1728	8.31E+07
	Eadv+F	3.50E+14	7.72E+16	4.99E-10	0.1793	6.27E+07
	Esup+AD	1.17E+15	2.60E+17	4.73E-10	0.181	8.66E+07
	Esup+AO	7.79E+16	1.74E+19	4.86E-10	0.1776	7.05E+07
	Esup+S	3.66E+13	5.78E+15	5.92E-10	0.1883	7.04E+07
	Esup+F	7.96E+12	1.36E+15	3.93E-10	0.178	6.91E+07
D+Esup	D+AD	4.05E+06	3.29E+08	2.04E-07	0.07937	82410
	D+AO	2.33E+13	2.45E+15	7.23E-10	0.2427	8.01E+07
	D+S	7.65E+14	1.69E+17	7.61E-10	0.2454	9.95E+07
	D+F	7.34E+14	1.61E+17	7.01E-10	0.2665	1.08E+08

	Eadv+AD	20140	686700	1.05E-07	0.09995	41410
	Eadv+AO	3.68E+12	6.59E+14	8.08E-10	0.2779	9.16E+07
	Eadv+S	3.18E+14	6.99E+16	6.86E-10	0.2494	1.11E+08
	Eadv+F	3.72E+14	8.10E+16	6.99E-10	0.2518	8.14E+07
	Esup+AD	2.25E+15	5.02E+17	7.11E-10	0.2581	1.22E+08
	Esup+AO	3.78E+17	8.46E+19	7.70E-10	0.2422	1.01E+08
	Esup+S	3.43E+13	5.64E+15	8.72E-10	0.2684	9.83E+07
	Esup+F	2.23E+12	3.33E+14	6.14E-10	0.2502	9.56E+07
D+AD	D+AO	5.85E+16	6.77E+18	9.79E-11	2.165	5.21E+10
	D+S	4.56E+16	6.84E+18	7.80E-11	2.311	5.00E+10
	D+F	1.36E+17	1.92E+19	8.02E-11	2.33	5.05E+10
	Eadv+AD	7.39E+12	3.18E+14	2.18E-12	1.304	1.53E+11
	Eadv+AO	2.78E+16	3.71E+18	6.42E-11	2.749	3.66E+10
	Eadv+S	3.60E+16	6.29E+18	8.11E-11	2.313	6.25E+10
	Eadv+F	2.09E+18	4.22E+20	1.04E-10	2.091	4.71E+10
	Esup+AD	1.19E+19	2.43E+21	7.69E-11	2.309	5.27E+10
	Esup+AO	9.75E+17	1.31E+20	7.73E-11	2.225	5.68E+10
	Esup+S	1.14E+17	1.66E+19	1.06E-10	2.13	4.40E+10
	Esup+F	4.99E+16	5.53E+18	6.33E-11	2.335	4.24E+10
D+AO	D+S	9.18E+18	1.09E+21	1.05E-12	0.9243	1.24E+12
	D+F	3.84E+21	6.54E+23	8.48E-13	1.07	1.32E+12
	Eadv+AD	5.81E+15	1.17E+18	8.81E-12	0.2864	5.71E+09
	Eadv+AO	9.47E+23	2.11E+26	1.04E-12	1.087	1.16E+12
	Eadv+S	1.44E+21	2.31E+23	1.04E-12	1.103	1.10E+12
	Eadv+F	5.45E+20	1.18E+23	9.28E-13	1.103	9.29E+11
	Esup+AD	3.58E+20	7.90E+22	7.19E-13	1.072	1.29E+12
	Esup+AO	7.69E+20	1.60E+23	9.85E-13	1.088	9.25E+11
	Esup+S	4.21E+20	5.89E+22	1.24E-12	1.072	1.20E+12
	Esup+F	1.04E+22	1.86E+24	8.90E-13	1.062	8.83E+11
D+S	D+F	2.27E+20	3.97E+22	9.73E-13	0.9964	1.20E+12
	Eadv+AD	3.52E+18	7.83E+20	8.80E-12	0.2908	6.32E+09
	Eadv+AO	4.95E+20	7.31E+22	1.19E-12	1.145	1.12E+12
	Eadv+S	2.07E+23	4.62E+25	1.01E-12	1.023	1.27E+12
	Eadv+F	1.02E+22	2.24E+24	8.59E-13	1.039	1.11E+12
	Esup+AD	3.66E+21	5.25E+23	6.82E-13	0.9673	1.02E+12
	Esup+AO	3.47E+22	6.68E+24	9.43E-13	1.043	1.09E+12
	Esup+S	5.71E+20	1.21E+23	9.91E-13	1.047	1.02E+12
	Esup+F	4.25E+21	6.23E+23	7.73E-13	1.029	1.05E+12
D+F	Eadv+AD	2.86E+17	6.39E+19	9.22E-12	0.2979	5.25E+09
	Eadv+AO	3.69E+20	6.68E+22	9.23E-13	1.054	1.12E+12
	Eadv+S	3.04E+23	6.77E+25	7.80E-13	0.9254	1.31E+12
	Eadv+F	9.74E+23	2.14E+26	8.90E-13	0.9854	1.23E+12
	Esup+AD	1.90E+24	4.00E+26	8.61E-13	0.9889	1.36E+12
	Esup+AO	6.72E+23	1.50E+26	9.62E-13	0.9706	1.18E+12
	Esup+S	3.12E+25	6.97E+27	1.11E-12	0.9904	1.05E+12
	Esup+F	1.07E+22	2.38E+24	6.59E-13	1.003	1.36E+12
Eadv+AD	Eadv+AO	1.09E+18	2.22E+20	2.70E-10	3.509	1.07E+11
	Eadv+S	1.20E+22	2.69E+24	1.69E-10	3.639	1.08E+11
	Eadv+F	6.39E+17	1.14E+20	1.71E-10	3.568	9.30E+10
	Esup+AD	1.69E+18	2.60E+20	1.56E-10	3.442	1.12E+11
	Esup+AO	9.48E+21	2.12E+24	1.83E-10	3.734	8.89E+10
	Esup+S	1.50E+20	2.44E+22	1.83E-10	3.678	9.10E+10
	Esup+F	1.06E+17	2.26E+19	1.47E-10	3.663	1.18E+11

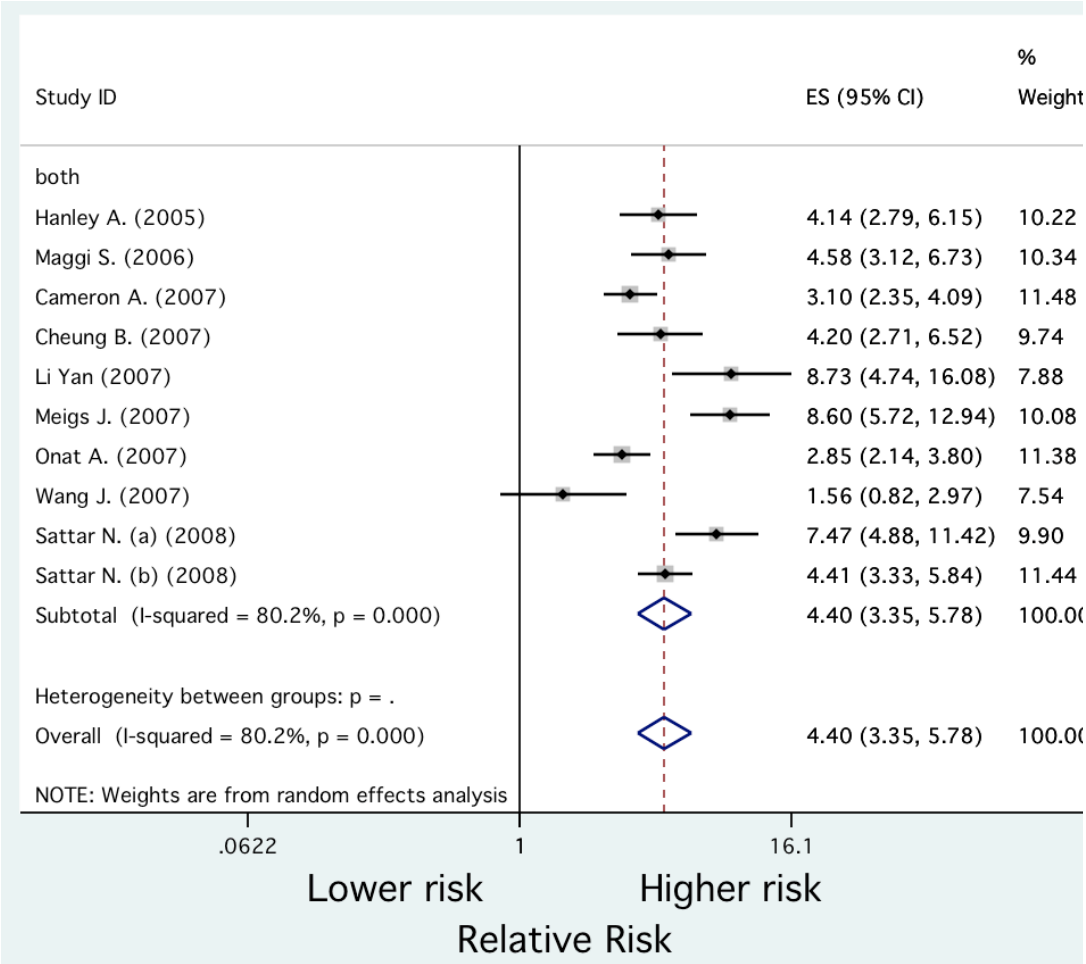
Eadv+AO	Eadv+S	7.32E+21	1.60E+24	1.14E-12	0.9029	1.06E+12
	Eadv+F	7.43E+27	1.66E+30	9.24E-13	0.8433	8.85E+11
	Esup+AD	2.39E+20	4.81E+22	8.29E-13	0.9046	9.77E+11
	Esup+AO	3.69E+20	7.89E+22	9.18E-13	0.9277	1.07E+12
	Esup+S	2.60E+21	5.63E+23	7.03E-13	0.985	1.22E+12
	Esup+F	2.72E+21	6.01E+23	8.11E-13	0.8962	9.80E+11
Eadv+S	Eadv+F	1.98E+21	3.61E+23	8.29E-13	0.9623	1.30E+12
	Esup+AD	1.30E+22	2.84E+24	9.20E-13	0.968	1.28E+12
	Esup+AO	5.60E+29	1.25E+32	1.04E-12	0.9887	1.20E+12
	Esup+S	4.71E+20	7.77E+22	1.08E-12	1.029	1.43E+12
	Esup+F	6.28E+21	1.23E+24	8.37E-13	0.9901	8.75E+11
Eadv+F	Esup+AD	9.45E+20	2.09E+23	9.37E-13	0.9882	1.45E+12
	Esup+AO	1.80E+24	4.00E+26	9.78E-13	0.9825	1.54E+12
	Esup+S	8.56E+20	1.68E+23	9.09E-13	1.096	1.10E+12
	Esup+F	5.35E+20	6.92E+22	7.84E-13	0.915	1.11E+12
Esup+AD	Esup+AO	3.30E+22	5.60E+24	8.20E-13	1.01	1.41E+12
	Esup+S	1.77E+23	3.13E+25	9.89E-13	1.083	9.65E+11
	Esup+F	1.80E+21	2.45E+23	8.35E-13	1.055	9.69E+11
Esup+AO	Esup+S	2.68E+22	6.00E+24	9.20E-13	1.083	1.03E+12
	Esup+F	1.33E+22	2.25E+24	9.95E-13	0.9697	8.44E+11
Esup+S	Esup+F	1.31E+20	1.64E+22	8.09E-13	1.011	8.81E+11

Appendix B

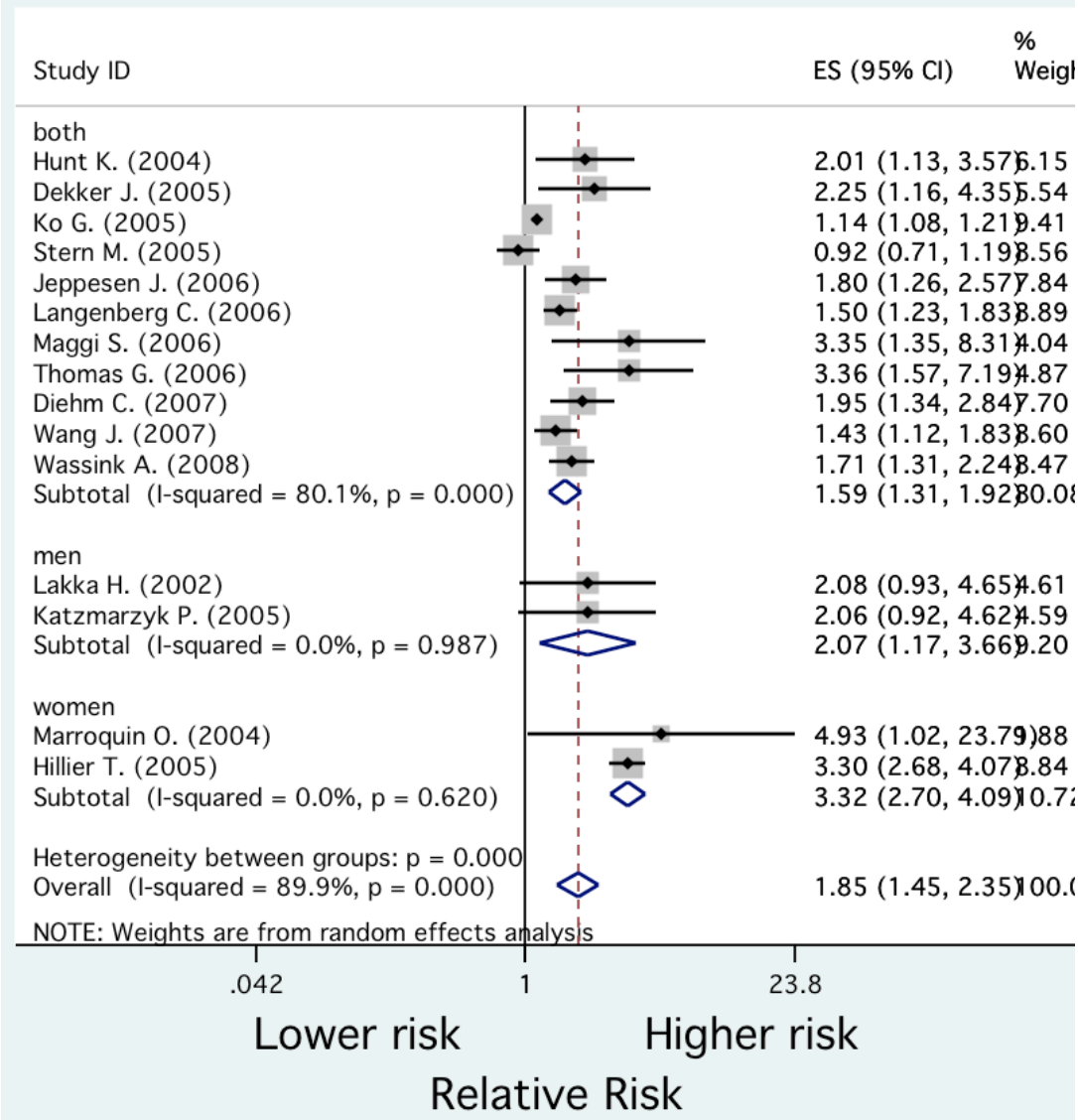
Forest plots and Funnel plots from Chapter 5.



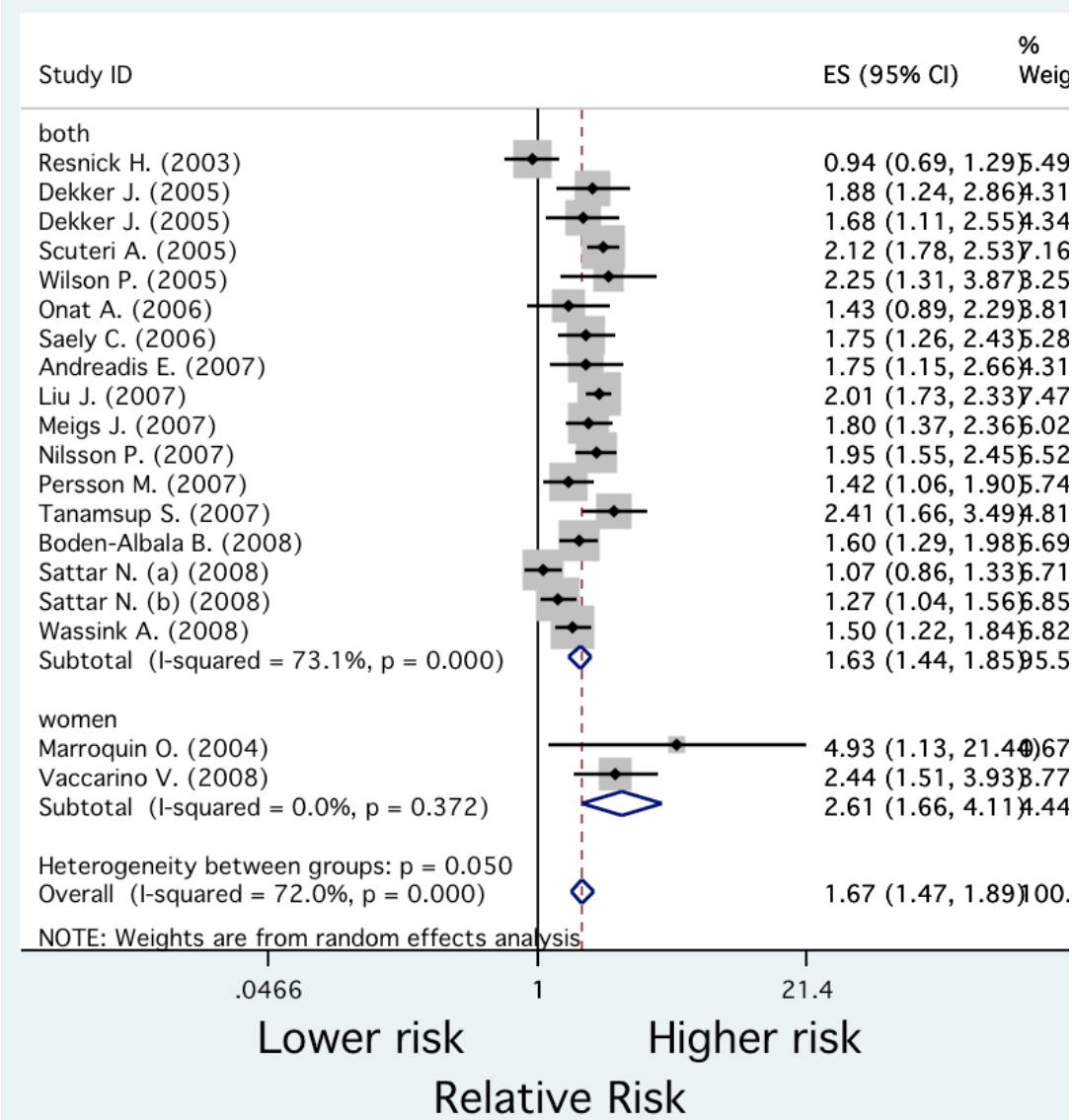
B1. Forest plot for All-cause mortality by Gender



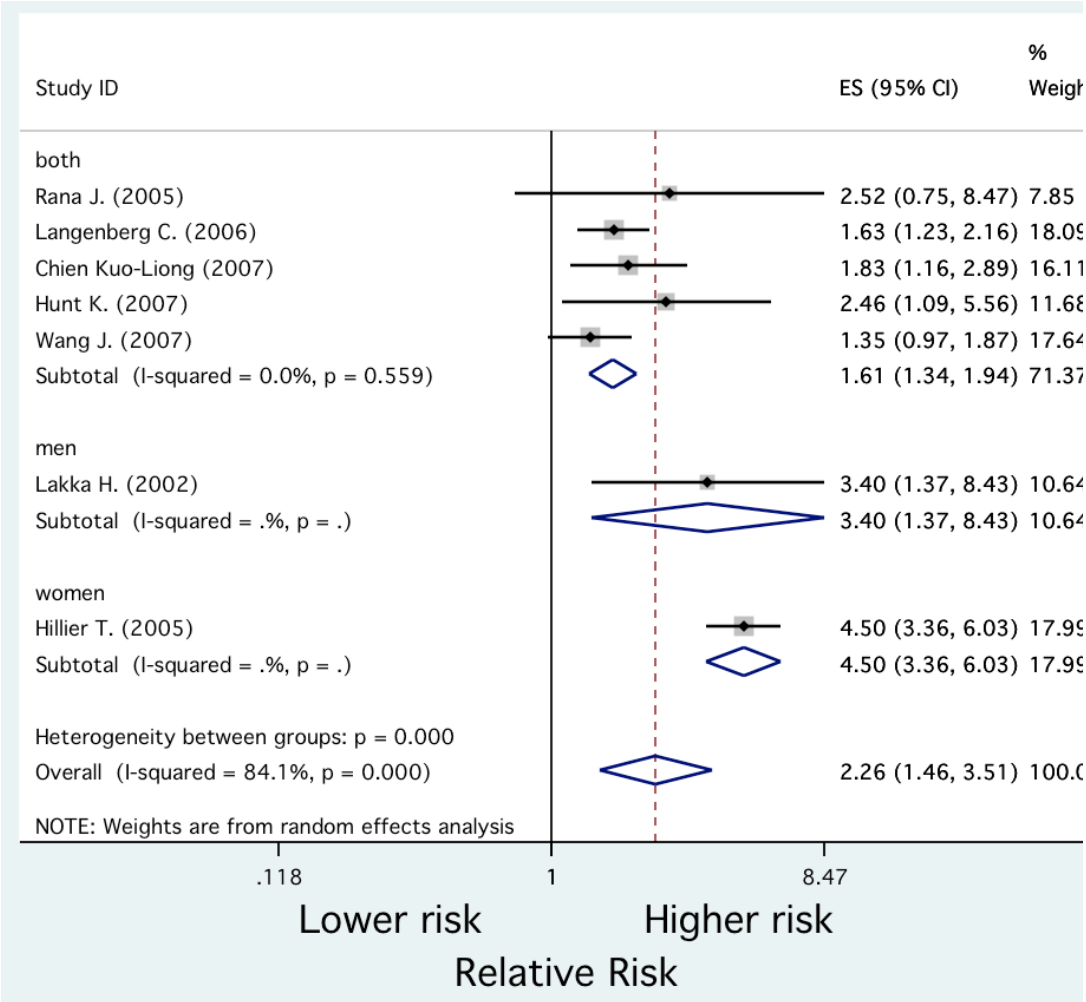
B2. Forest plot for T2DM by Gender



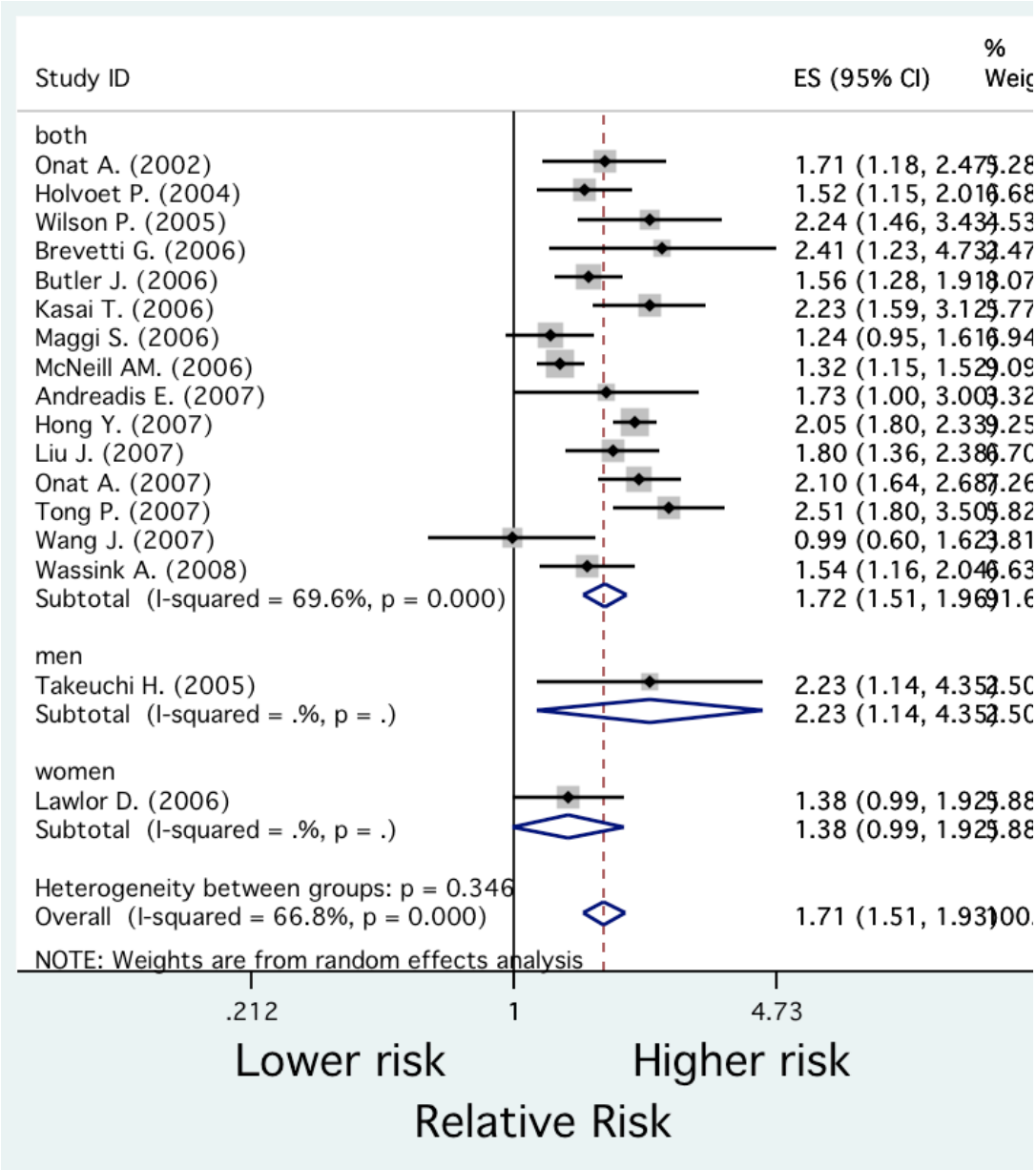
B3. Forest plot for fatal CVD by Gender



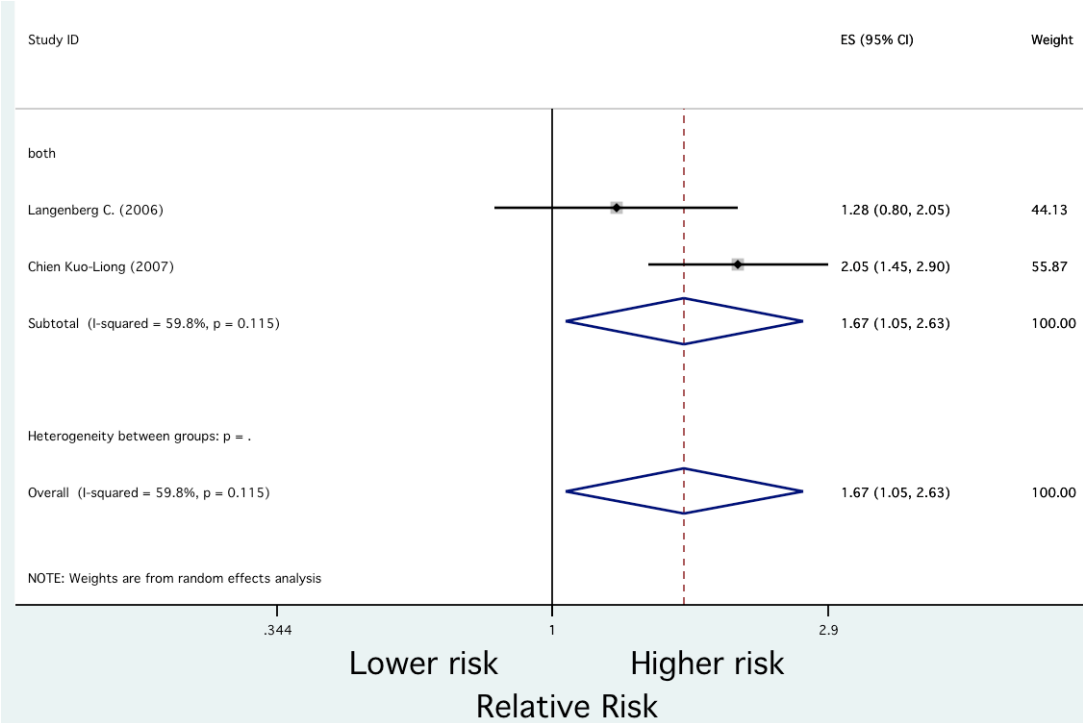
B4. Forest plot for CVD events by Gender



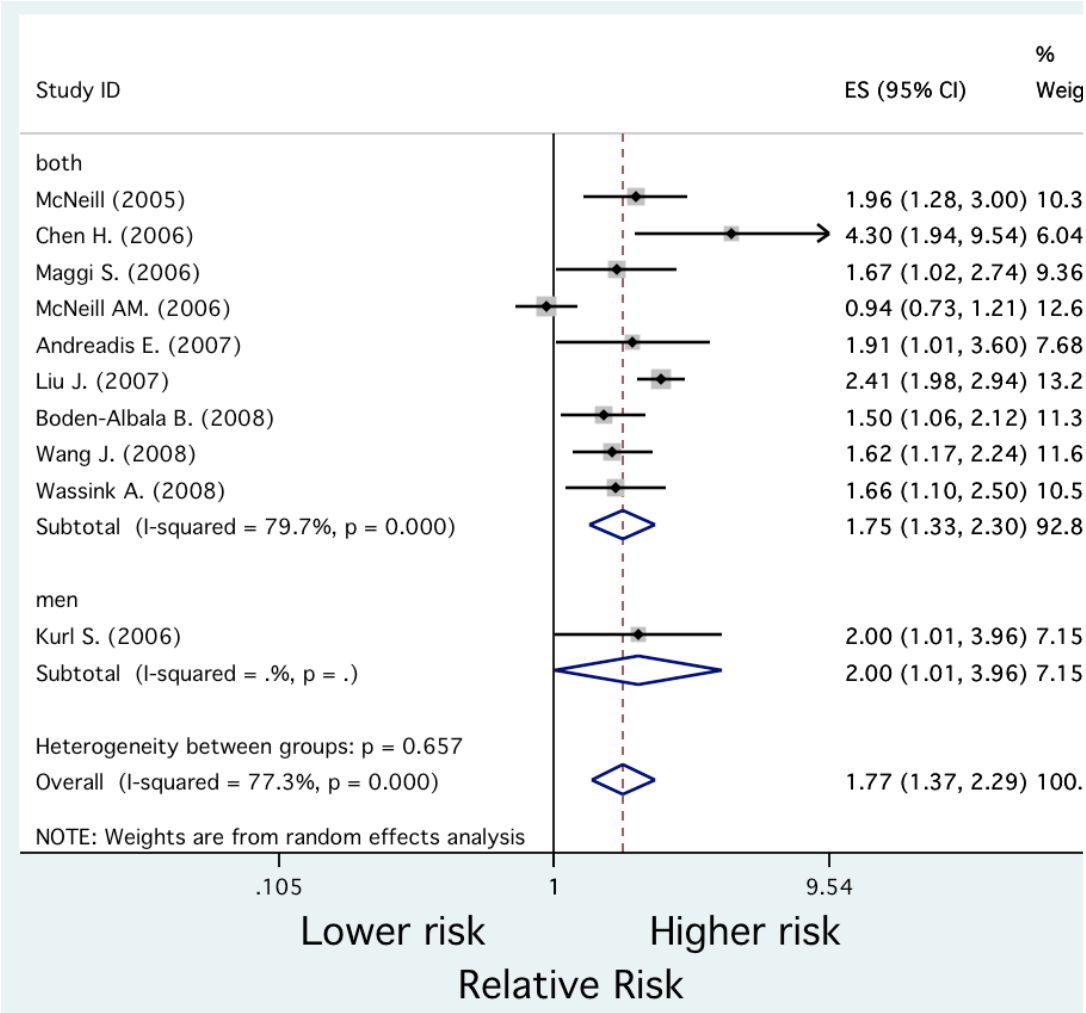
B5. Forest plot for fatal CHD by Gender



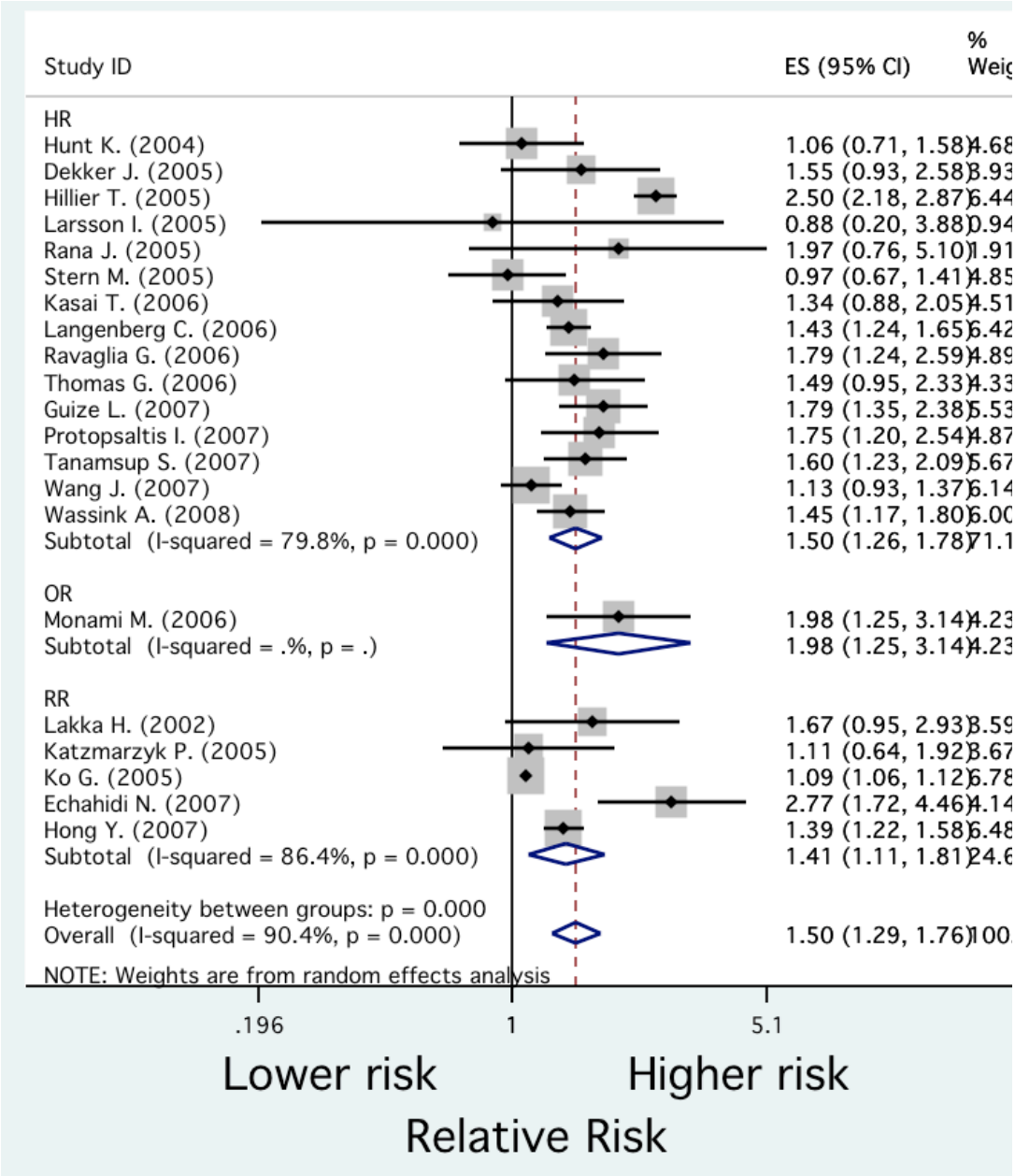
B6. Forest plot for CHD events by Gender



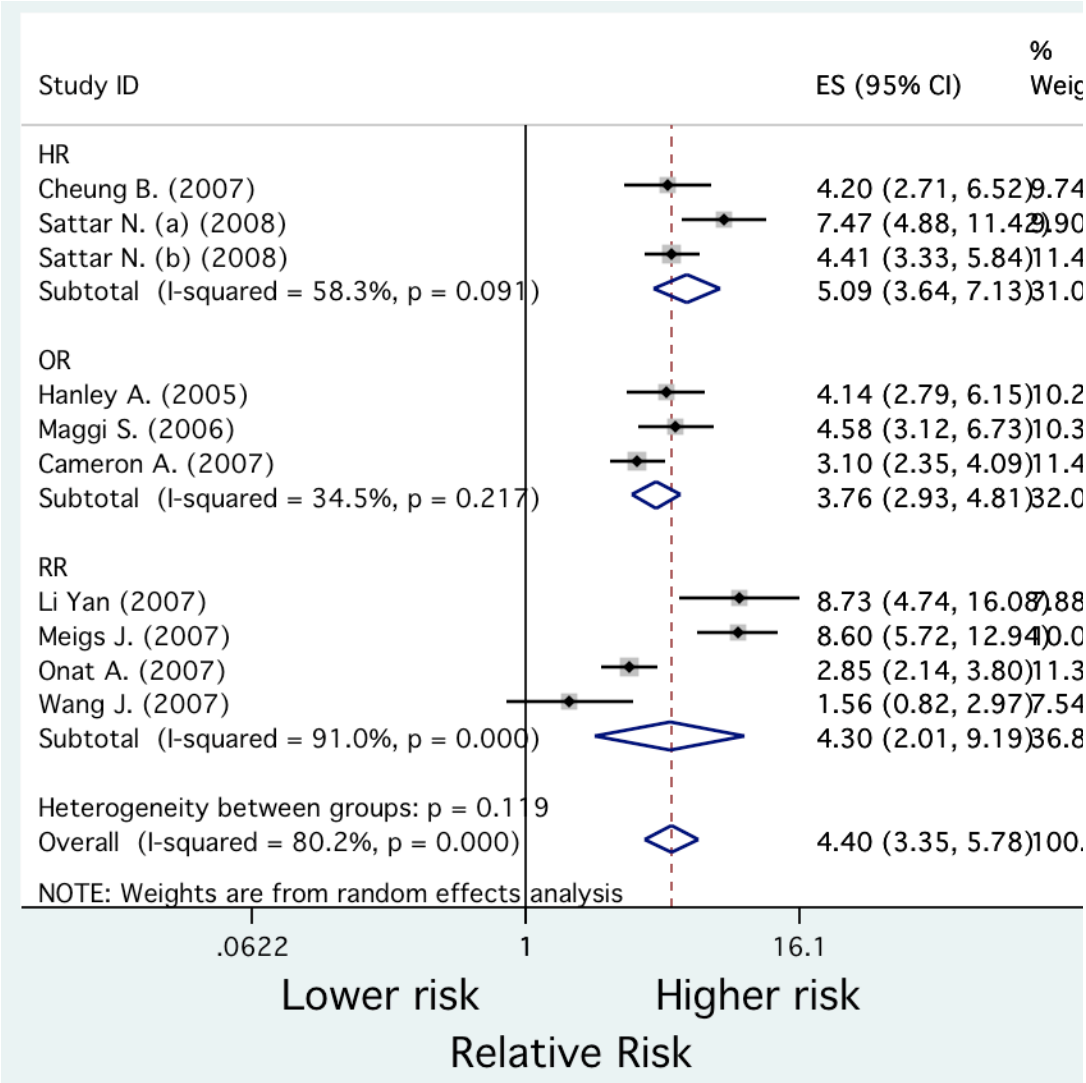
B7. Forest plot for fatal stroke by Gender



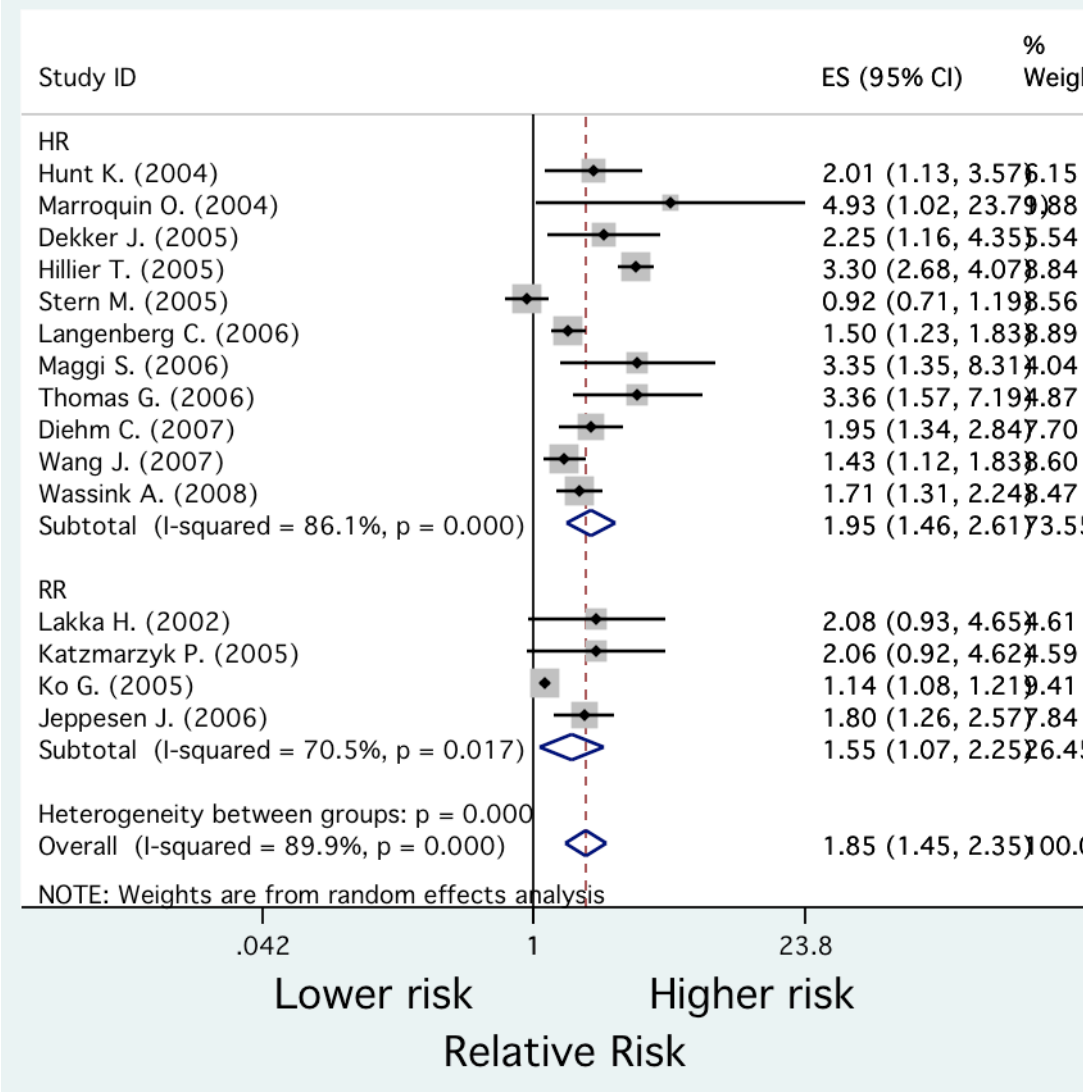
B8. Forest plot for stroke events by Gender



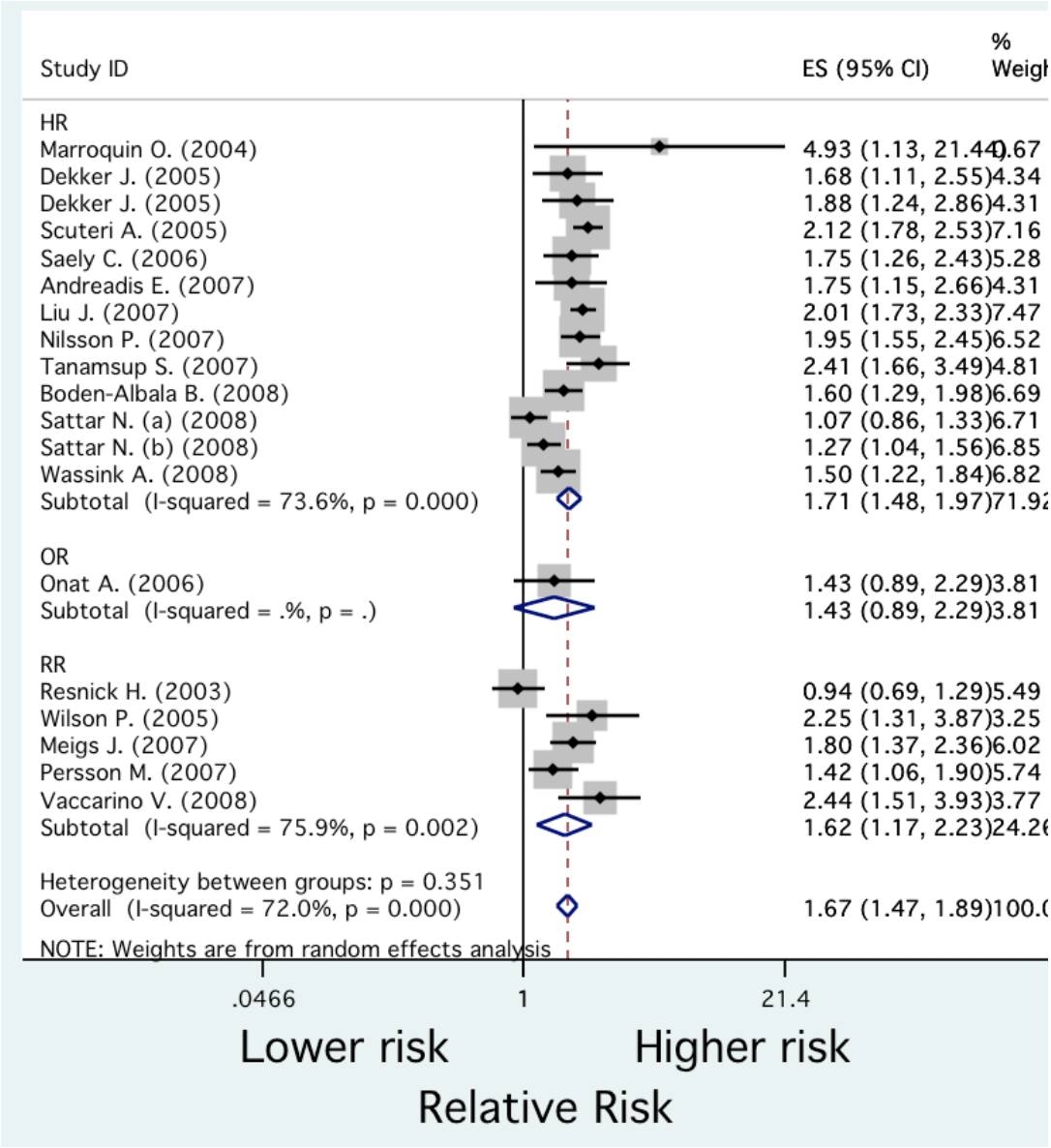
B9. Forest plot for All-cause mortality by Scale



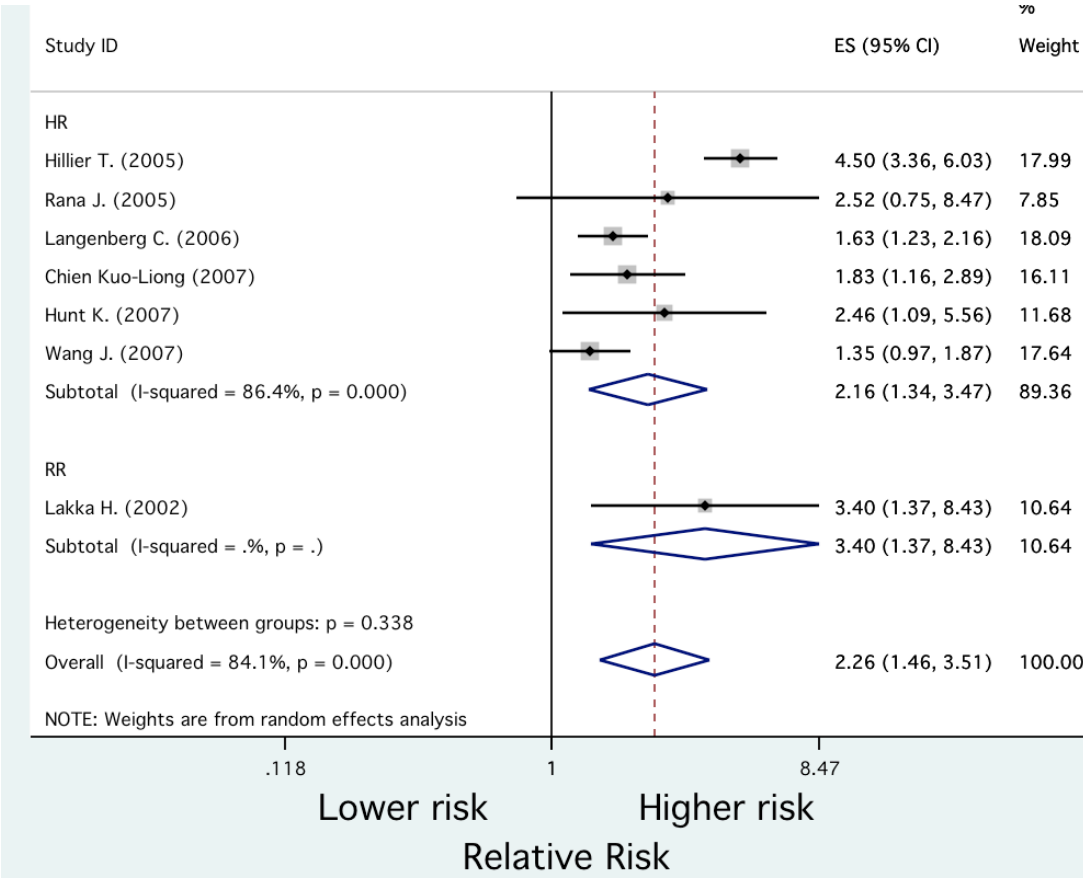
B10. Forest plot for T2DM by Scale



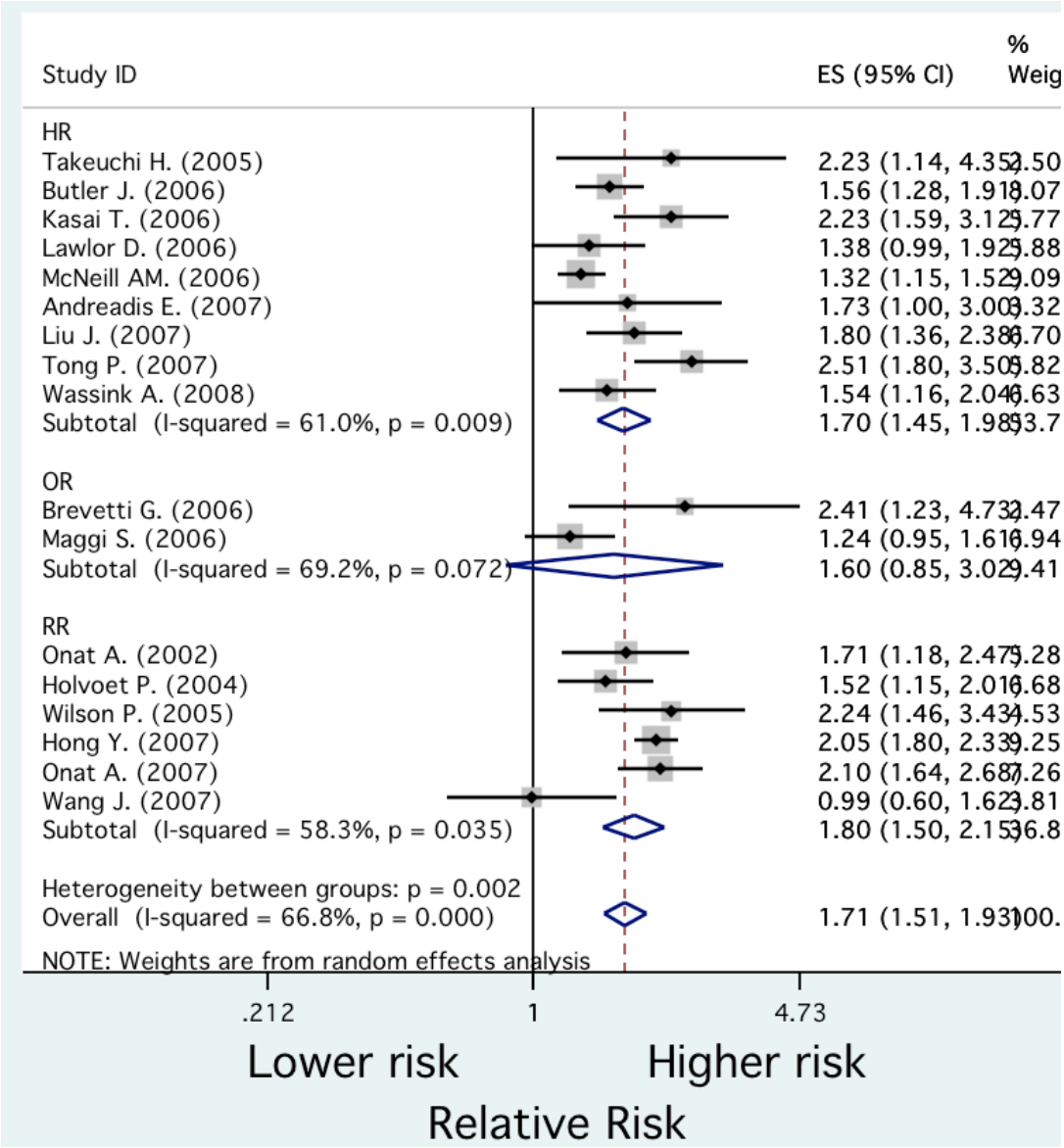
B11. Forest plot for fatal CVD by Scale



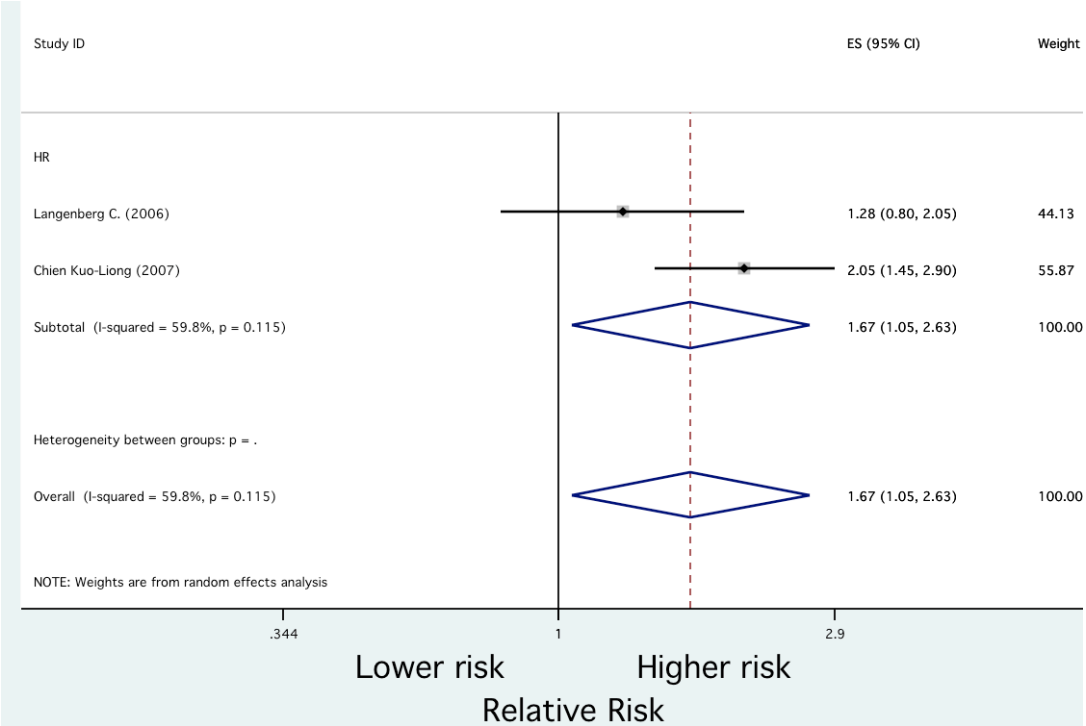
B12. Forest plot for CVD events by Scale



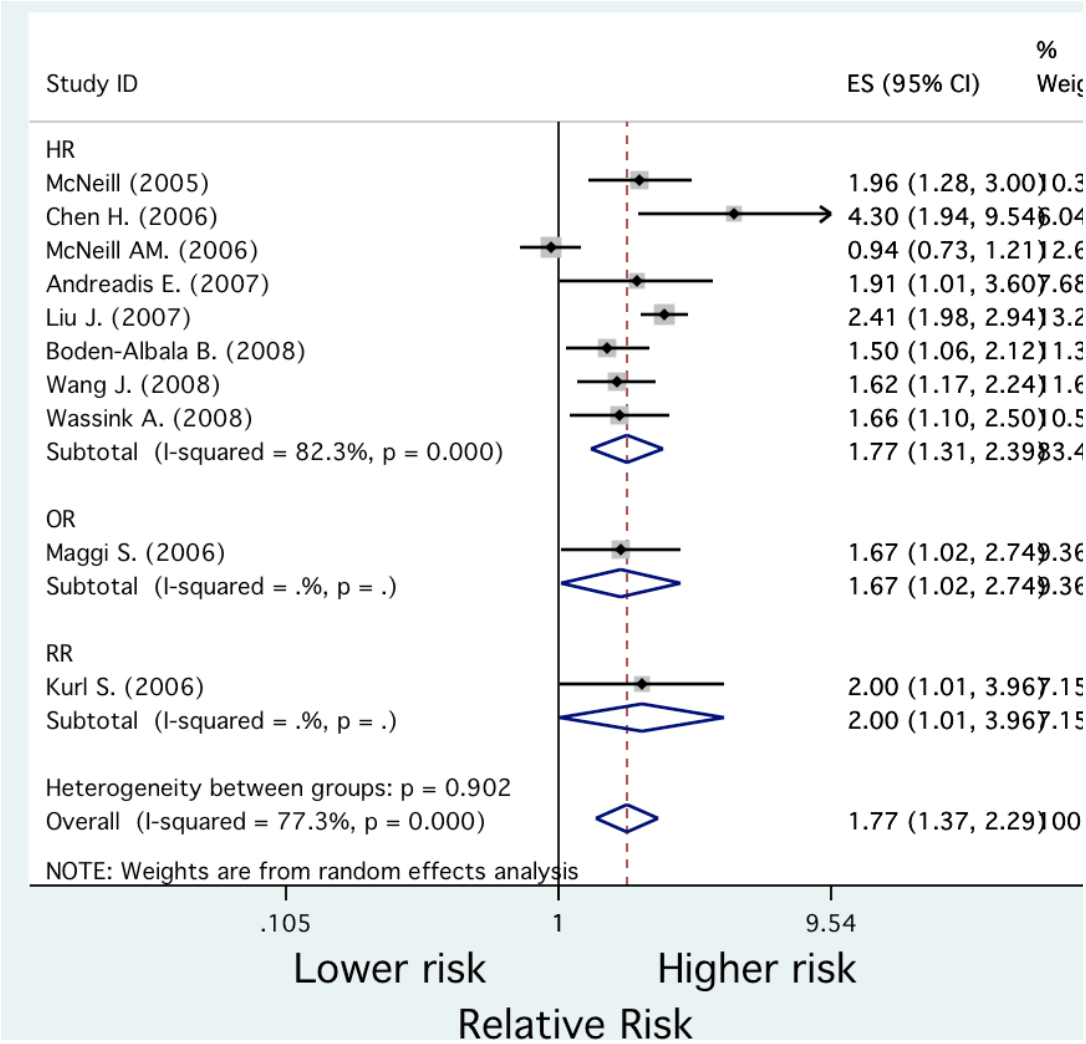
B13. Forest plot for fatal CHD by Scale



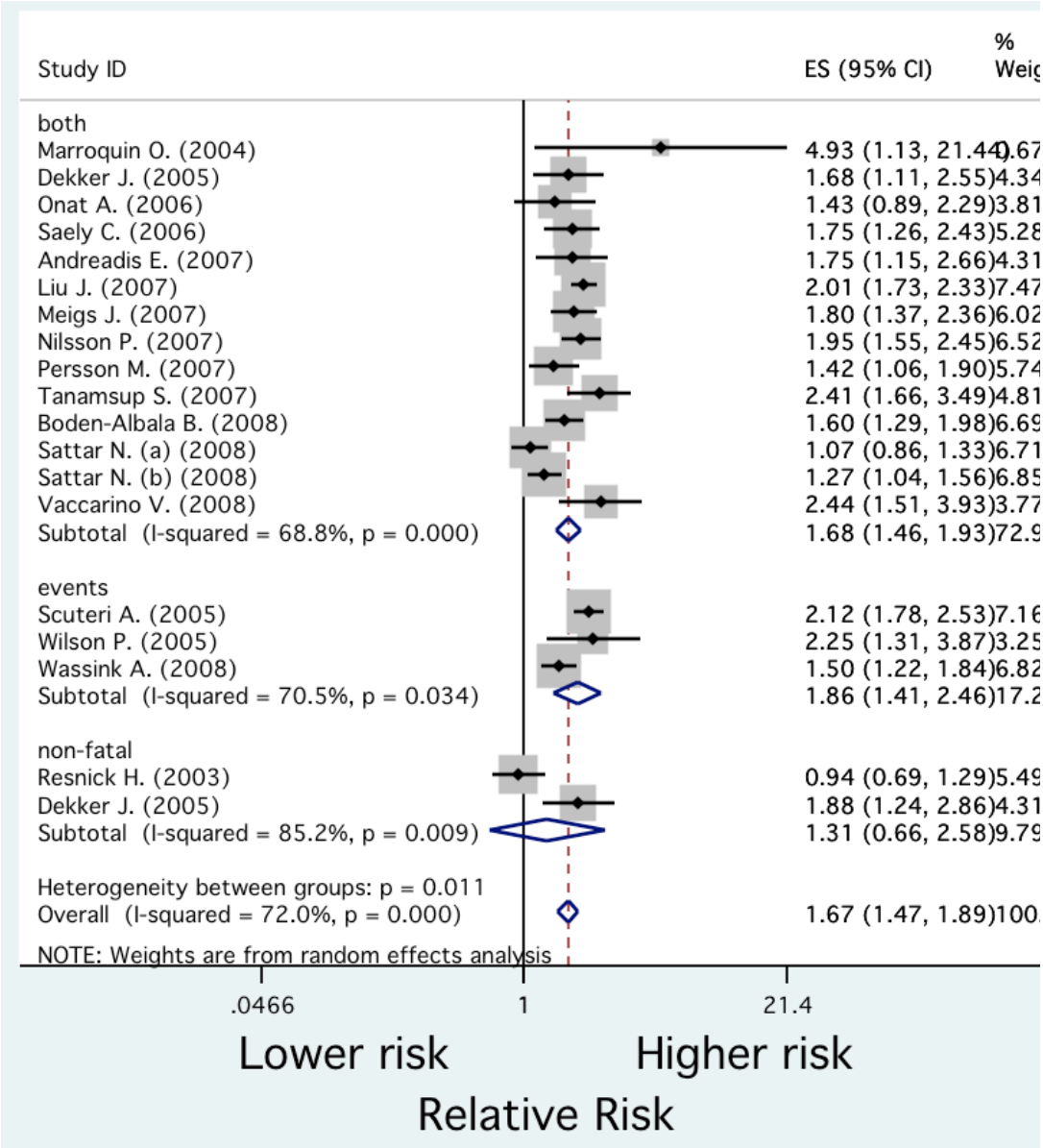
B14. Forest plot for CHD events by Scale



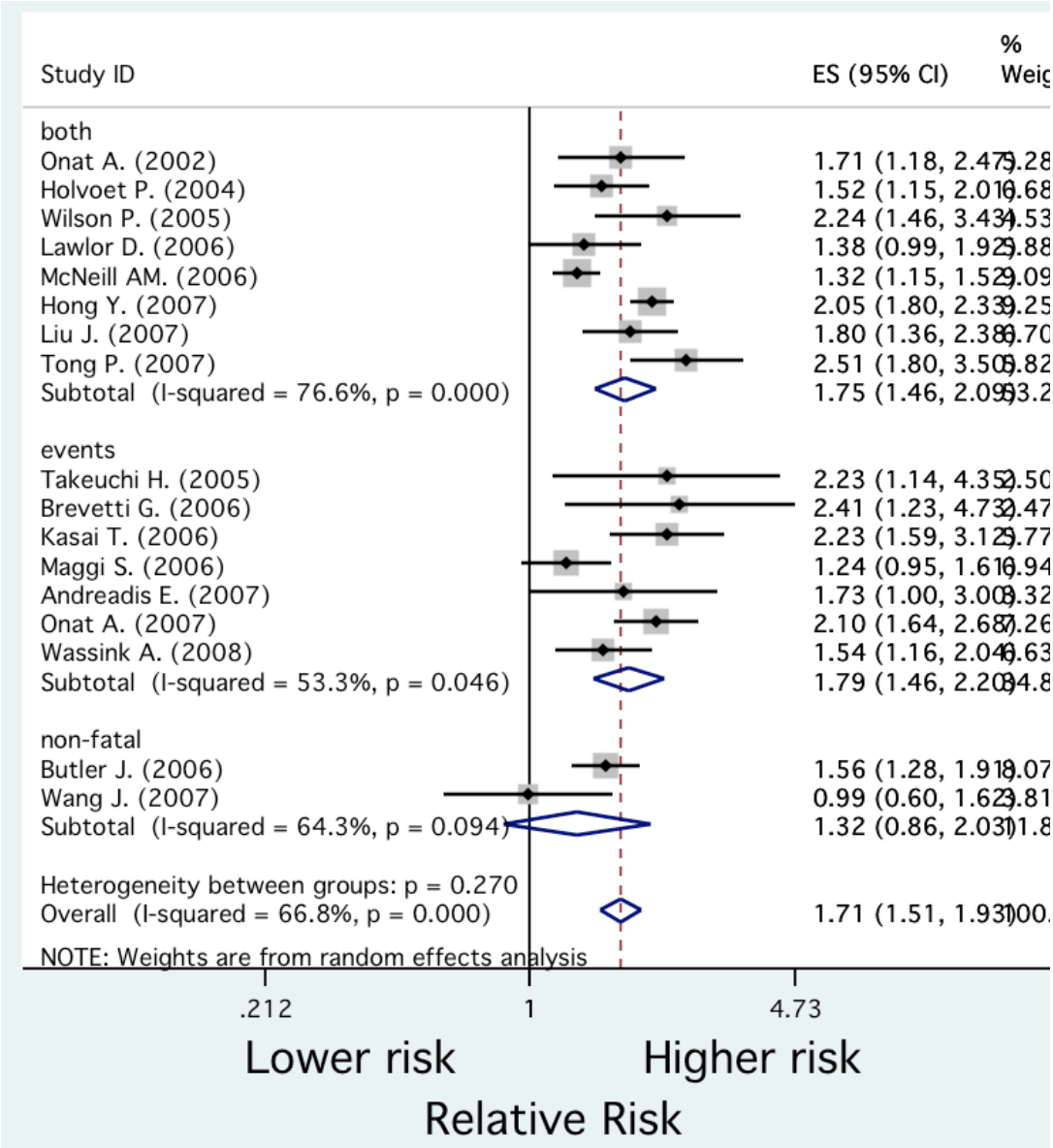
B15. Forest plot for fatal stroke by Scale



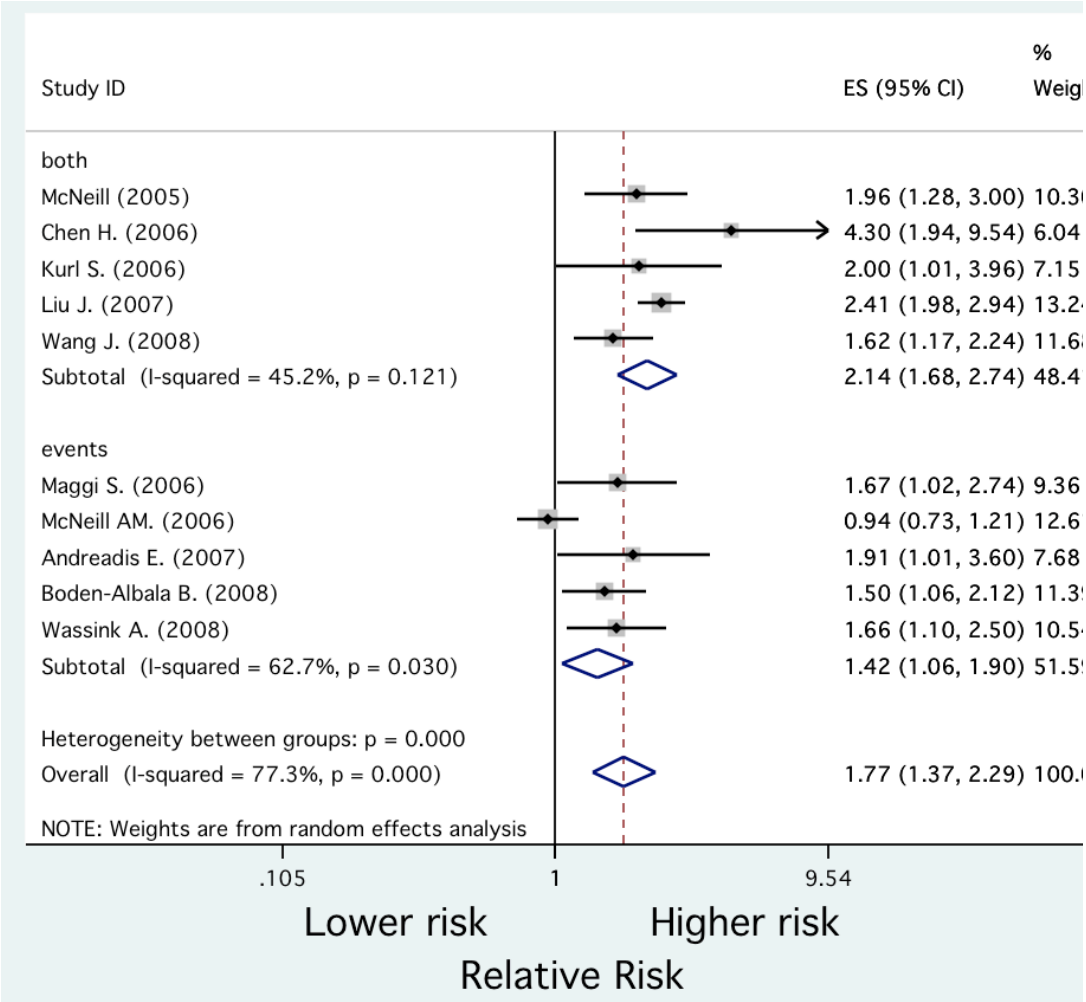
B16. Forest plot for stroke events by Scale



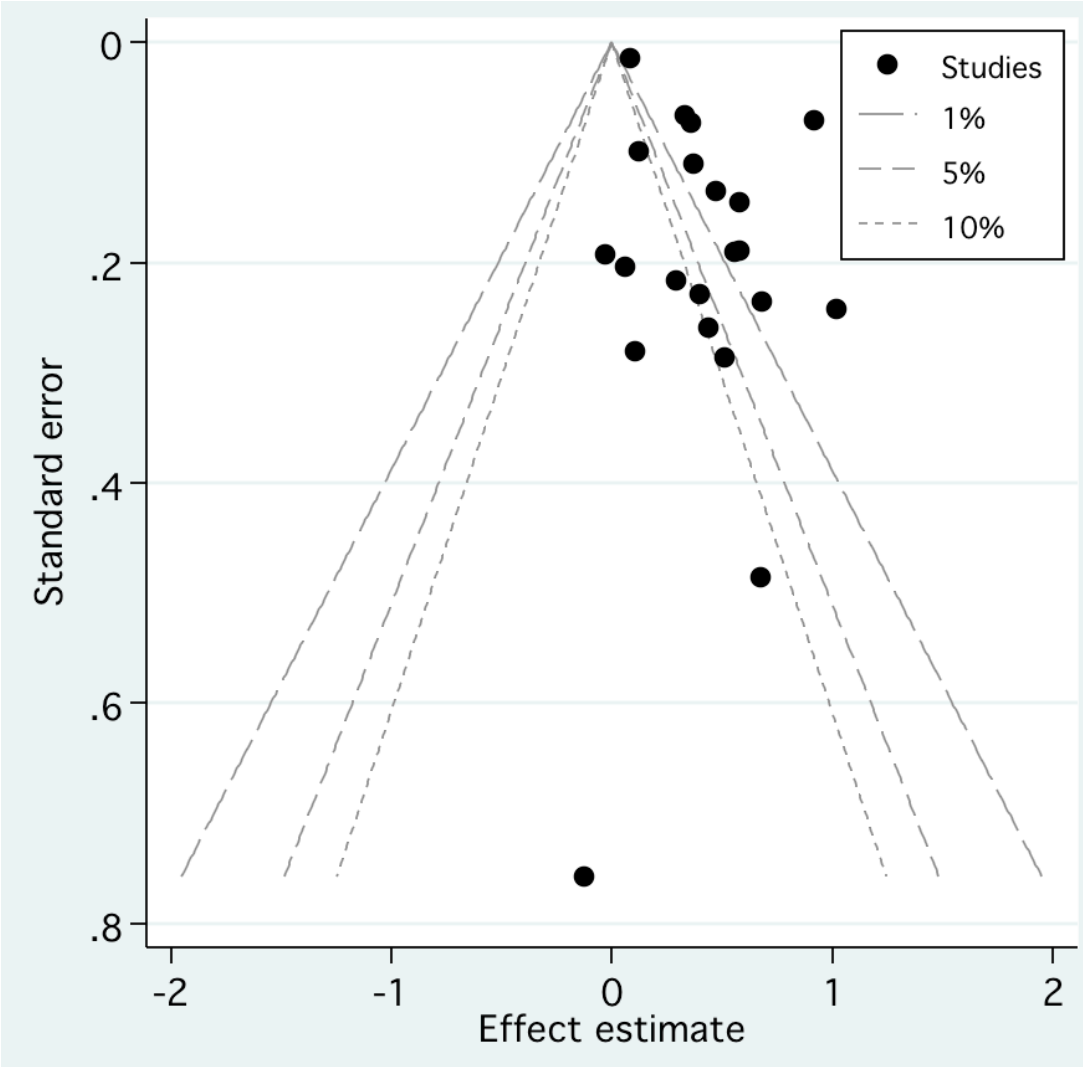
B17. Forest plot for CVD events by Type of Event



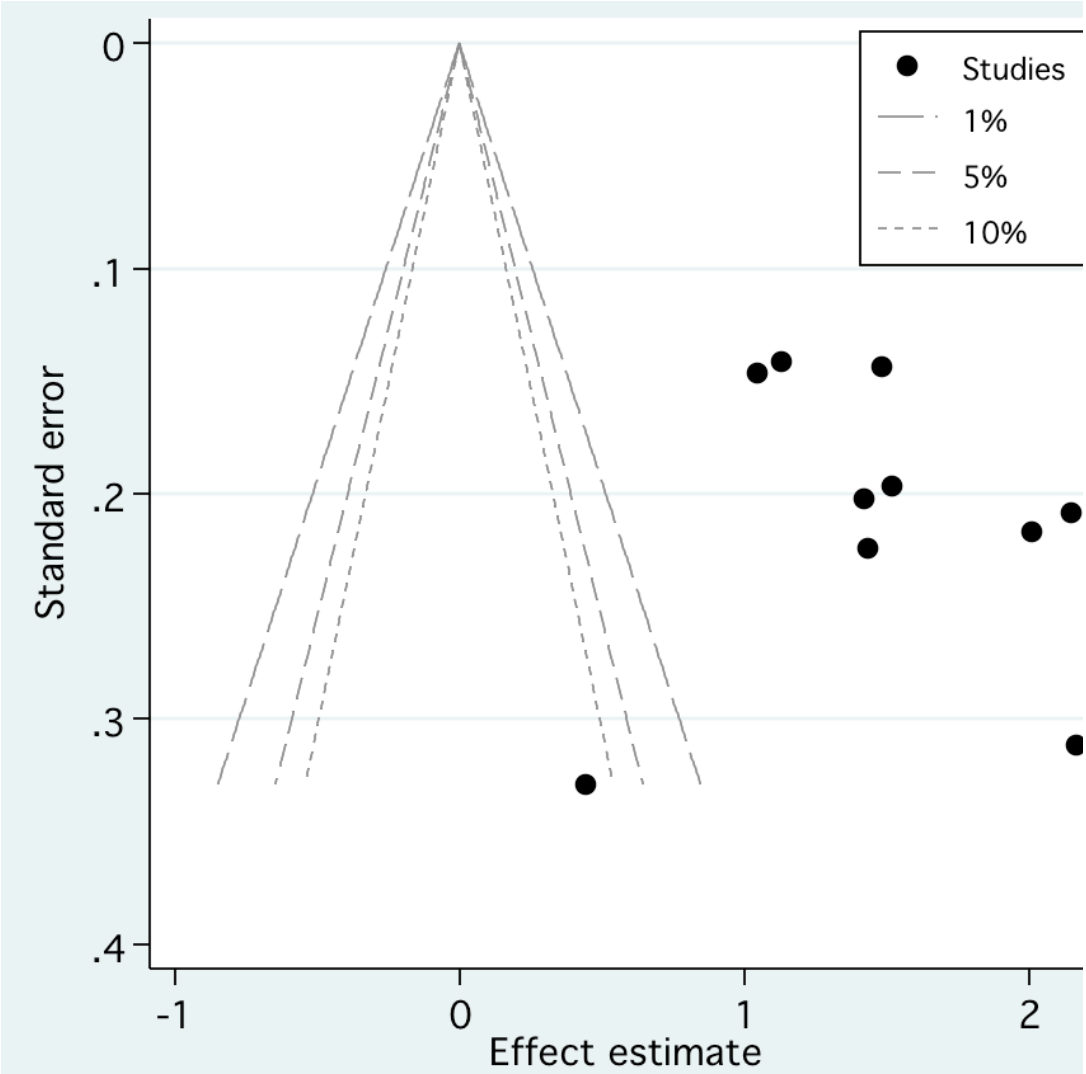
B18. Forest plot for CHD events by Type of Event



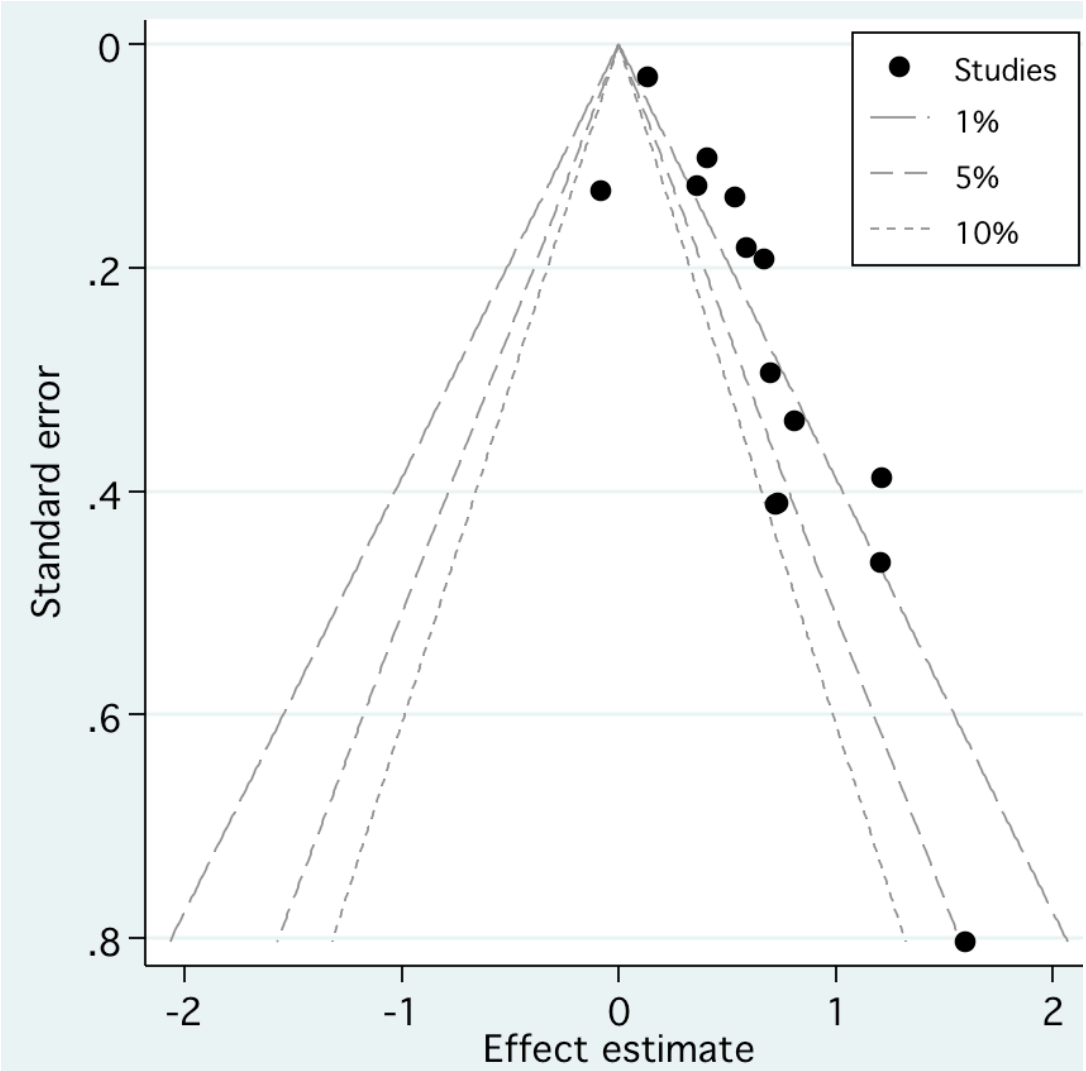
B19. Forest plot for Stroke events by Type of Event



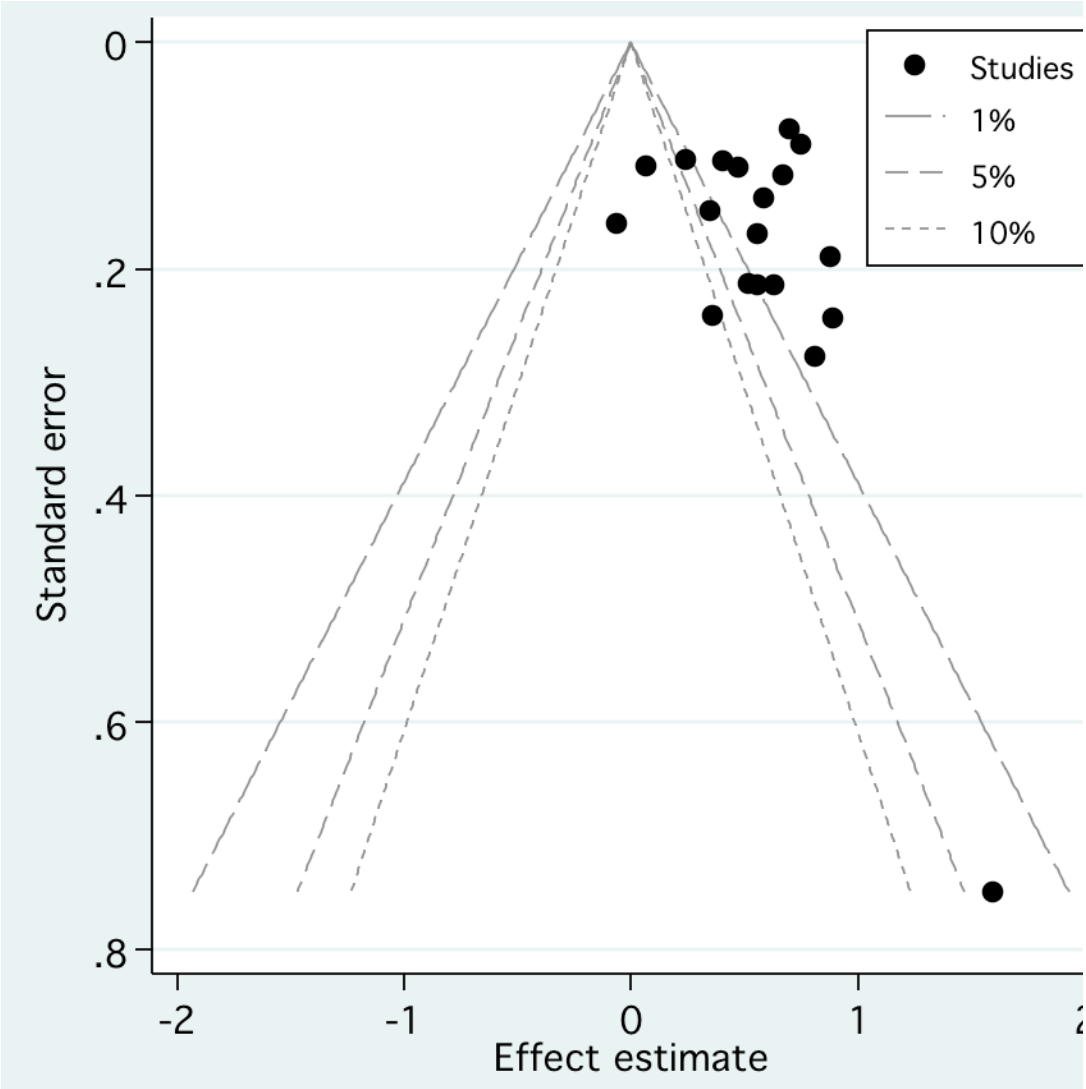
B20. Funnel plots for All-cause mortality



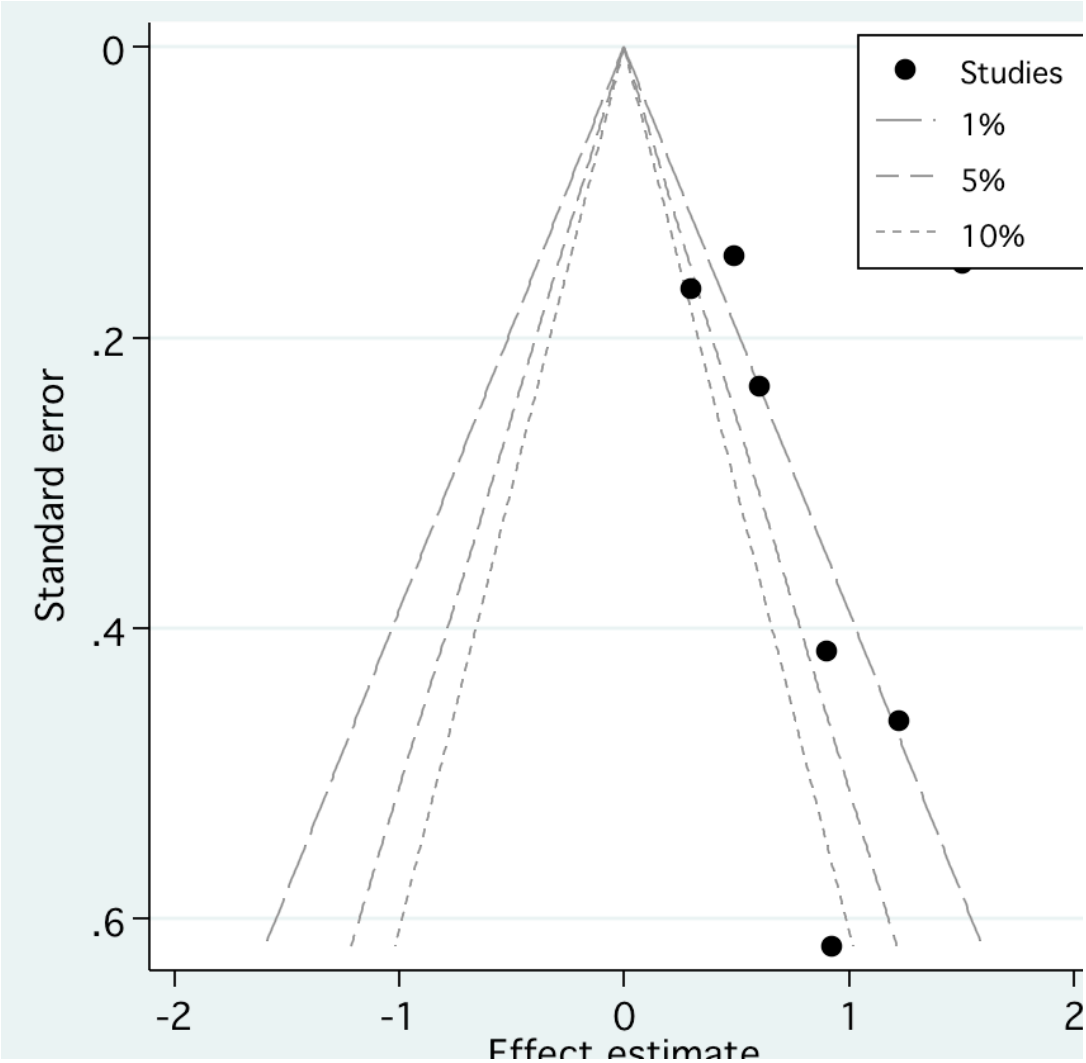
B21. Funnel plots for T2DM



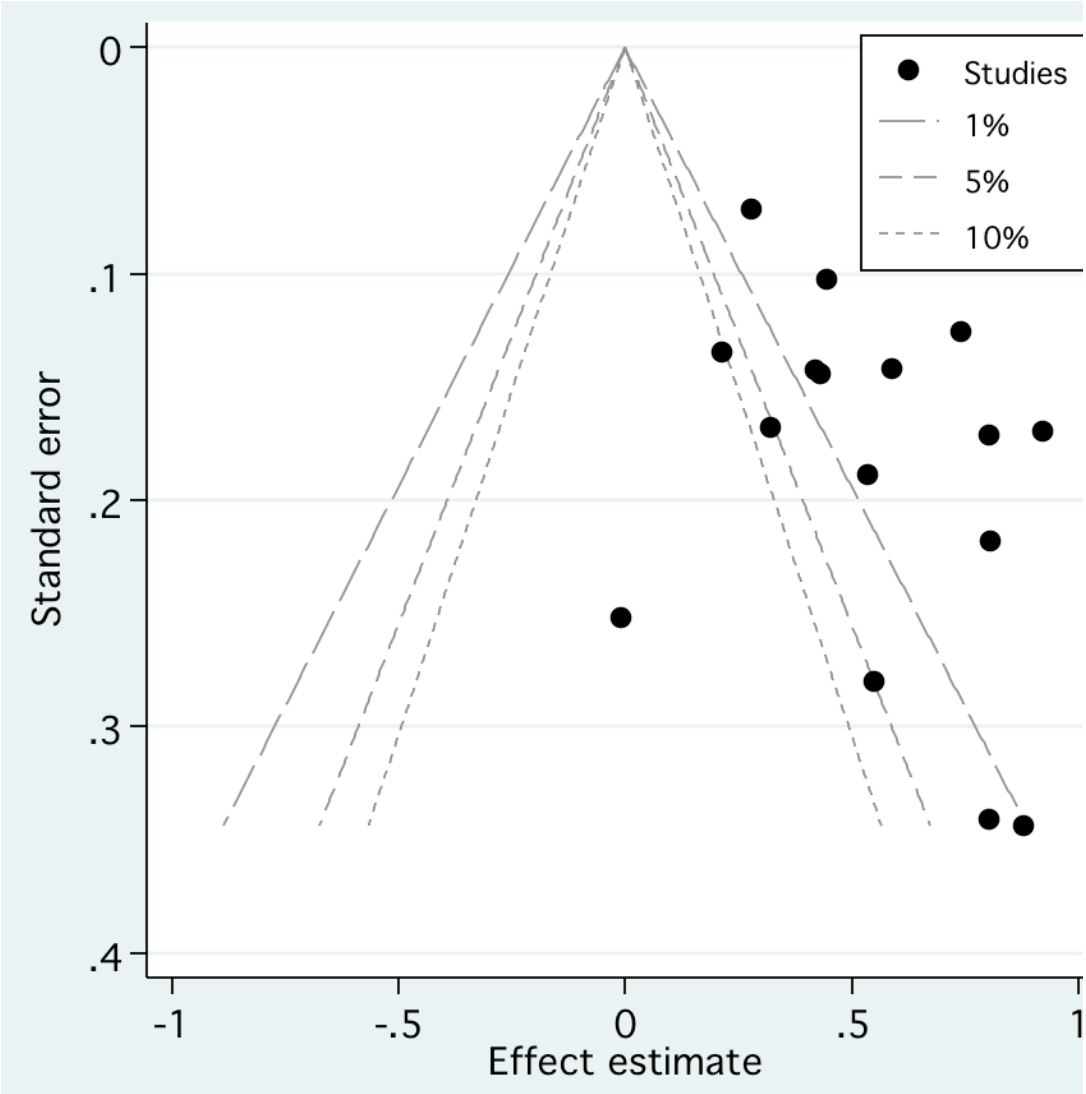
B22. Funnel plots for fatal CVD



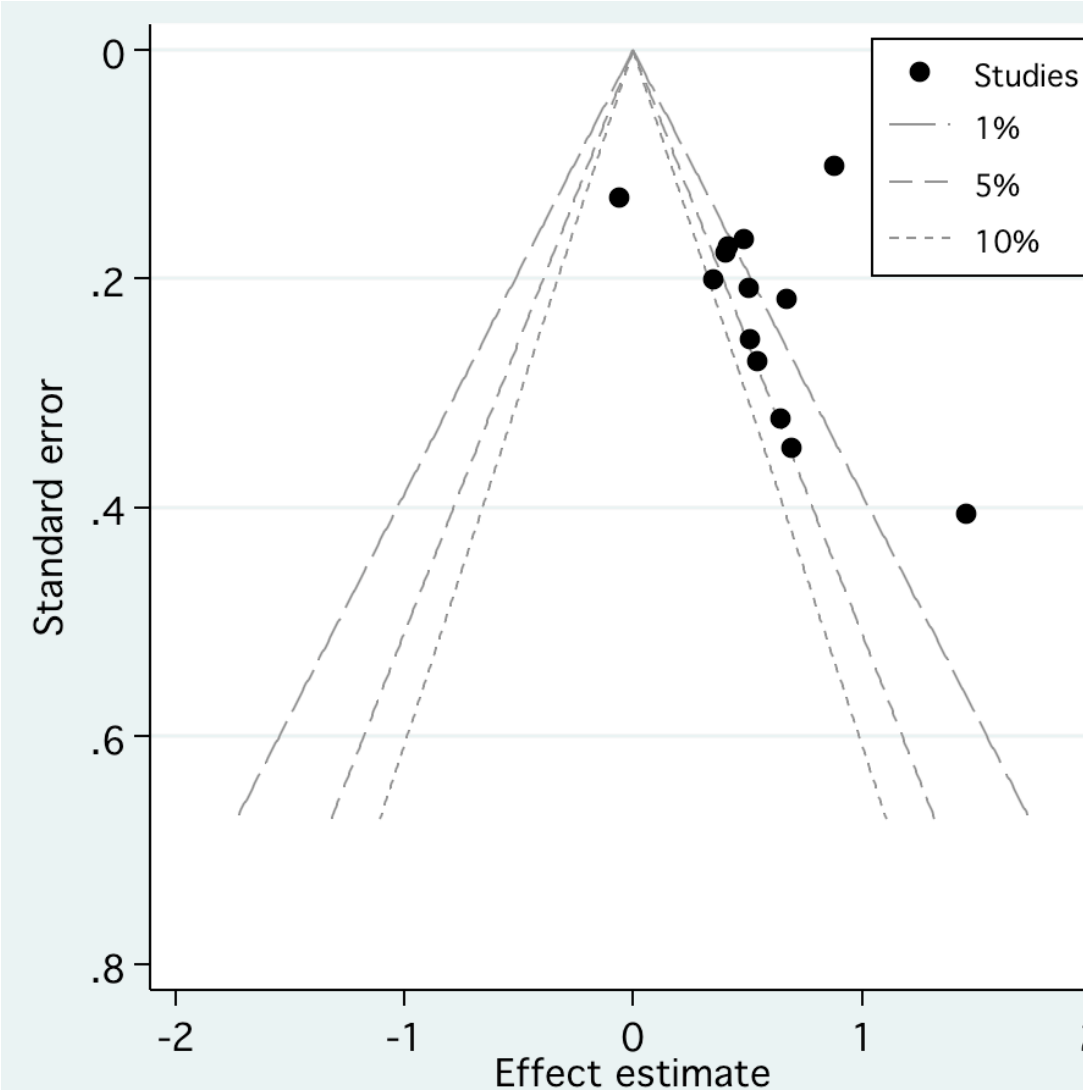
B23. Funnel plots for CVD events



B24. Funnel plots for fatal CHD



B25. Funnel plots for CHD events



B26. Funnel plots for stroke events

Appendix C

Comprehensive Decision Model in WinBUGS code from Chapter 6.

CODE 1: **Definition of a transition matrix**

```
# Stochastic decision model: Base case.

model {

# States, Transitions<-p
    #1=Healthy,
    #2=MetS,
    #3=T2 Diabetes,
    #4=CVD,
    #5=T2+CVD,
    #6=Death

# Age groups for HD and MD transitions, K
   #1=45-54,
   #2=55-64,
   #3=65-74,
   #4=75-84,
   #5=85+

# Treatment groups for MH, j
   #1=Control,
   #2=Lifestyle Intervention,
   #3=Pharnacological
   #4=Lifestyle+Pharmacological

#Transitions from healthy state

for (j in 1:4) {
for (k in 1:5) {

p[j,k,1,2] ~ dbeta(268.73412,13302.787)  # H to M
p[j,k,1,3] ~ dbeta(153787.29,32505219) # H to T2 0.005
p[j,k,1,4] ~ dbeta(98.014537,5451.3929)  # H to CVD 0.018
p[j,k,1,5] <- 0
p[j,k,1,6] <- HD[k]  # H to D
p[j,k,1,1] <- 1 - (p[j,k,1,2]+p[j,k,1,3]+p[j,k,1,4]+p[j,k,1,6])

lambda13[j,k]  <- -log(1-p[j,k,1,3])
lambda14[j,k] <- -log(1-p[j,k,1,4])
lambda16[j,k] <- -log(1-HD[k])
}}
```

CODE 2: **Definition of a transition matrix**

```
#Transition from MetS state to healthy

# Integrate MTC into decision model - 4 treatments

for (k in 1:5) {
#p[1,k,2,1] ~ dbeta(160.1025,1015.3931)  # M to H - Control
p[1,k,2,1] <-  prob.mh  # M to H - Control
p[2,k,2,1] <- ((p[1,k,2,1]/(1-p[1,k,2,1]))*OR[1,2])/(1+(p[1,k,2,1]/(1-p[1,k,2,1]))*OR[1,2])
p[3,k,2,1] <- ((p[1,k,2,1]/(1-p[1,k,2,1]))*OR[1,3])/(1+(p[1,k,2,1]/(1-p[1,k,2,1]))*OR[1,3])
p[4,k,2,1] <- ((p[1,k,2,1]/(1-p[1,k,2,1]))*OR[1,4])/(1+(p[1,k,2,1]/(1-p[1,k,2,1]))*OR[1,4])  }



# Use RRs from Cohort Systematic Review for effect of MetS

logrr23.m <- log(3.60)
logrr23.s <- (log(4.52)-log(2.87))/(2*1.96)
logrr23.p <- 1/(logrr23.s*logrr23.s)
logrr23 ~ dnorm(logrr23.m,logrr23.p)
rr23 <- exp(logrr23)

logrr24.m <- log(1.61)
logrr24.s <- (log(1.73)-log(1.49))/(2*1.96)
logrr24.p <- 1/(logrr24.s*logrr24.s)
logrr24 ~ dnorm(logrr24.m,logrr24.p)
rr24 <- exp(logrr24)

logrr26.m <- log(1.15)
logrr26.s <- (log(1.18)-log(1.12))/(2*1.96)
logrr26.p <- 1/(logrr26.s*logrr26.s)
logrr26 ~ dnorm(logrr26.m,logrr26.p)
rr26 <- exp(logrr26)
```

CODE 3: **Definition of a transition matrix**

```
# Transitions from MetS, T2DM, CVD and T2DM+CVD

for (j in 1:4) {
for (k in 1:5) {
#p[j,k,2,3] ~ dbeta(2.7740265,161.87177)  # M to T2 0.017
p[j,k,2,3] <- 1-exp(-lambda13[j,k]*rr23)
#p[j,k,2,4] ~ dbeta(7.7445077,266.08191) # M to CVD 0.028
p[j,k,2,4] <- 1-exp(-lambda14[j,k]*rr24)
p[j,k,2,5] <- 0
#p[j,k,2,6] <- MD[k]   # M to D
p[j,k,2,6] <- 1-exp(-lambda16[j,k]*rr26)
p[j,k,2,2] <- 1 - (p[j,k,2,1] + p[j,k,2,3] + p[j,k,2,4] + p[j,k,2,6])

p[j,k,3,1] <- 0
p[j,k,3,2] <- 0
p[j,k,3,3] <- 1 - (p[j,k,3,5]+p[j,k,3,6])
p[j,k,3,4] <- 0
p[j,k,3,5] ~ dbeta(77.996773,5910.4975)   # T2 to CVD+T2
p[j,k,3,6] ~ dbeta(0.3089547,26.828762)   # T2 to D

p[j,k,4,1] <- 0
p[j,k,4,2] <- 0
p[j,k,4,3] <- 0
p[j,k,4,4] <- 1 - p[j,k,4,6]
p[j,k,4,5] <- 0
p[j,k,4,6] ~ dbeta(0.18972,5.0332918)   # CVD to D
#p[j,k,4,6] ~ dbeta(2.19,121.676)   # CVD to D sensitivty analysis

p[j,k,5,1] <- 0
p[j,k,5,2] <- 0
p[j,k,5,3] <- 0
p[j,k,5,4] <- 0
p[j,k,5,5] <- 1 - p[j,k,5,6]
p[j,k,5,6] ~ dbeta(2.0981077,6.377917)  # T2+CVD to D
#p[j,k,5,6] ~ dbeta(0.07,1.345)  # T2+CVD to D sensivity analysis
} }

for (j in 1:4) {
for (k in 1:5) {
p.test[j,k] <- p[j,k,1,1]*p[j,k,2,2]*p[j,k,3,3]*p[j,k,4,4]*p[j,k,5,5]
p.neg[j,k] <- 1-step(p.test[j,k]) }}
```

CODE 4: **Integration of the Mixed Treatment Comparison Analysis**

```
# MTC Model - 4 treatments

for(i in 1:nstud) {
        w[i,1]<-0
        delta[i,tx[i,1]]<-0
        mu[i] ~ dnorm(0,.0001)

        for (k in 1:na[i]) {
        r[i,k] ~ dbin(pr[i,k],n[i,k])
        logit(pr[i,k]) <- mu[i] + delta[i,tx[i,k]]
        }

        for (k in 2:na[i]) {
        # Model
        delta[i,tx[i,k]] ~dnorm(md[i,tx[i,k]],taud[i,tx[i,k]])
        md[i,tx[i,k]] <- d[tx[i,k]] - d[tx[i,1]] + sw[i,k]
        taud[i,tx[i,k]] <- tau *2*(k-1)/k
        w[i,k] <- (delta[i,tx[i,k]] - d[tx[i,k]] + d[tx[i,1]])
        sw[i,k] <- sum(w[i,1:k-1])/(k-1) }
        }

d[1]<-0
for (k in 2:ntreat) {d[k]~dnorm(0,0.0001) }
sd~dunif(0,5)
tau<-1/(sd*sd)

#Adjusting the probability to one year

for (k in 1:9) {
loghaz[k] <- log(r[k,1]/(n[k,1]*fup[k]))
loghaz.prec[k] <- r[k,1]
loghaz[k] ~ dnorm(theta[k],loghaz.prec[k])
theta[k] ~ dnorm(mu.loghaz,tau.loghaz) }
mu.loghaz ~ dnorm(0.0,0.001)
tau.loghaz <- 1/pow(sd.loghaz,2)
sd.loghaz ~ dunif(0,2)
prob.mh <- 1 - exp(-exp(mu.loghaz))

# All pairwise log odds ratios and odds ratios
for (c in 1:(ntreat-1)) {
        for (k in (c+1):ntreat) {
                                        LOR[c,k]<- d[k] - d[c]
                                        log(OR[c,k])<- LOR[c,k]  } }
```

CODE 5: **Definition of starting states**

```
# Using ADDITION for starting states
add.start[1:3] ~ dmulti(add.p[1:3],add.N)
add.p[1:3] ~ ddirch(alpha[1:3])

# Starting vector/states
for (j in 1:4) {
start[j,1] <- 0    #Healthy
start[j,2] <- 1    #Metabolic Syndrome
start[j,3] <- 0    #Diabetes
start[j,4] <- 0    #CVD
start[j,5] <- 0    #T2+CVD
start[j,6] <- 0 }  #Death

# s = proportion of people in each state at time t, (treatment, state, time=1)
#for (j in 1:2) {    #treatments from MTC
#for (i in 1:6) {     #States
#s[j,i,1] <- start[j,i] } }

for (j in 1:4) {
s[j,1,1]<-start[j,1]
s[j,2,1]<-start[j,2]
s[j,3,1]<-start[j,3]
s[j,4,1]<-start[j,4]
s[j,5,1]<-start[j,5]
s[j,6,1]<-start[j,6] }
```

CODE 6: **Definition of cycles for time estimation**

```
# Updates proportion and definition of cycles

for (j in 1:4) {     #Treatments
for (i in 1:5) {     #States

for (t in 2:10) {                                    #Time to run the model/cycles
s[j,i,t]<- inprod(s[j,1:5,t-1], p[j,1,1:5,i]) }      #Run the model for t cycles

for (t in 11:20) {                                   #Time to run the model/cycles
s[j,i,t] <- inprod(s[j,1:5,t-1], p[j,2,1:5,i]) }     #Run the model for t cycles

for (t in 21:30) {                                   #Time to run the model/cycles
s[j,i,t] <- inprod(s[j,1:5,t-1], p[j,3,1:5,i]) }     #Run the model for t cycles

for (t in 31:40) {                                   #Time to run the model/cycles
s[j,i,t] <- inprod(s[j,1:5,t-1], p[j,4,1:5,i])  }    #Run the model for t cycles

for (t in 41:55) {                                   #Time to run the model/cycles
s[j,i,t] <- inprod(s[j,1:5,t-1], p[j,5,1:5,i]) }   } }   #Run the model for t cycles

for (j in 1:4) {
for (k in 1:5) {
time[j,k]<- sum(s[j,k,])  }
time[j,6]<- 55-(time[j,1]+time[j,2]+time[j,3]+time[j,4]+time[j,5]) }

for (t  in 1:55){
for (j in 1:4) {
for (k in 2:5) {
qaly.state[j,k,t]<- s[j,k,t]*util[k]
cost.state[j,k,t] <- s[j,k,t]*cost[k]  }   }}
```

CODE 7: **Incorporation of aging**

```
# Use UK EQ5D age-adjusted population norms for HEALTHY state

for (j in 1:4) {
# 45-54
for (t in 1:10) {
qaly.state[j,1,t]<- s[j,1,t]*util.healthy[1]
cost.state[j,1,t] <- s[j,1,t]*cost[1]   }
# 55-64
for (t in 11:20) {
qaly.state[j,1,t]<- s[j,1,t]*util.healthy[2]
cost.state[j,1,t] <- s[j,1,t]*cost[1]   }
# 65-74
for (t in 21:30) {
qaly.state[j,1,t]<- s[j,1,t]*util.healthy[3]
cost.state[j,1,t] <- s[j,1,t]*cost[1]   }
# 75+
for (t in 31:55) {
qaly.state[j,1,t]<- s[j,1,t]*util.healthy[4]
cost.state[j,1,t] <- s[j,1,t]*cost[1]   }
}


# Defining calculation of QALYs and Cost of each state

for (t  in 1:55){
for (j in 1:4) {
qaly.tot[j,t] <- qaly.state[j,1,t] +   qaly.state[j,2,t] +  qaly.state[j,3,t]  + qaly.state[j,4,t] +
qaly.state[j,5,t]
qaly.distot[j,t] <- qaly.tot[j,t] * pow(0.965,t-1)
cost.tot[j,t] <- cost.state[j,1,t] +   cost.state[j,2,t] +  cost.state[j,3,t]  + cost.state[j,4,t] +
cost.state[j,5,t]
cost.distot[j,t] <- cost.tot[j,t] * pow(0.965,t-1)
  }}
```

CODE 8: **Incorporation of costs of healthy states**

```
# Costs - adjusted to 2009 prices

diab.cost0 ~ dgamma(606.02623,3.8600397)
diab.cost <- diab.cost0*1.03*1.028*1.032*1.043*1.04
mets.cost ~ dgamma(67.336248,1.2866799)
cvd.cost ~ dgamma(102.22309,0.3096852)
cvdt2.cost0 ~ dgamma(264.80522,0.5024371)
cvdt2.cost <- cvdt2.cost0*1.03*1.028*1.032*1.043*1.04

cost[1] <- 0
cost[2] <- mets.cost
cost[3] <- diab.cost
cost[4] <- cvd.cost
cost[5] <- cvdt2.cost
cost[6] <- 0
```

CODE 9: **Integration of costs of lifestyle interventions**

```
# Use  DPP costs for lifestyle intervention (exchange & 2009 prices)
# and fitting a log-Normal distribution to aggregated costs

life.sup.mean1 <-
(1399/1.52)*1.018*1.017*1.029*1.03*1.028*1.032*1.043*1.04
life.sup.var1 <-
((1189/1.52)*1.018*1.017*1.029*1.03*1.028*1.032*1.043*1.04)
life.sup.sigma12 <- log(1+life.sup.var1/pow(life.sup.mean1,2))
life.sup.prec1 <- 1/life.sup.sigma12
life.sup.mu1 <- log(life.sup.mean1) - 0.5*life.sup.sigma12

life.sup.mean2 <-
(679/1.52)*1.018*1.017*1.029*1.03*1.028*1.032*1.043*1.04
life.sup.var2 <-
((577/1.52)*1.018*1.017*1.029*1.03*1.028*1.032*1.043*1.04)
life.sup.sigma22 <- log(1+life.sup.var2/pow(life.sup.mean2,2))
life.sup.prec2 <- 1/life.sup.sigma22
life.sup.mu2 <- log(life.sup.mean2) - 0.5*life.sup.sigma22

life.sup.mean3 <-
(702/1.52)*1.018*1.017*1.029*1.03*1.028*1.032*1.043*1.04
life.sup.var3 <-
((597/1.52)*1.018*1.017*1.029*1.03*1.028*1.032*1.043*1.04)
life.sup.sigma32 <- log(1+life.sup.var3/pow(life.sup.mean3,2))
life.sup.prec3 <- 1/life.sup.sigma32
life.sup.mu3 <- log(life.sup.mean3) - 0.5*life.sup.sigma32


life.sup1 ~ dlnorm(life.sup.mu1,life.sup.prec1)
life.sup2 ~ dlnorm(life.sup.mu2,life.sup.prec2)
life.sup3 ~ dlnorm(life.sup.mu3,life.sup.prec3)

life.sup <- (life.sup1+life.sup2+life.sup3)*add.p[2]

cost.intv[1] <- 0
cost.intv[2] <- life.sup
cost.intv[3] <- cost.pharm3
cost.intv[4] <- life.sup + cost.pharm4
```

CODE 10: **Integration of costs of pharmacological interventions**

```
# Cost proportions from ADDITION

# BP intervention - ACE inhibitor, Lisinopril, BNF page 105
# Cholesterol/tryglicerides intervention - Statin, Pravastatin, BNF  page
# Glucose intervention - Metformin, BNF page 383


cost.pharm3 <- time[3,2]*cost.pharm
cost.pharm4 <- time[4,2]*cost.pharm

cost.pharm <- p.bp*15.48 + p.trychol*20.52 + p.fp*33.48

add.bp ~ dbin(p.bp,1981)
add.trychol ~ dbin(p.trychol,1981)
add.fp ~ dbin(p.fp,1981)

p.bp ~ dbeta(1,1)
p.trychol ~ dbeta(1,1)
p.fp ~ dbeta(1,1)
```

CODE 11: **Integration of utilities**

```
# Utilities

mets.util ~ dbeta(5.2624878,1.1191474) # 0.825
diab.util ~ dbeta(117.27245,44.482653) # 0.725
cvd.util ~ dbeta(1.671705,1.0914438) # 0.605
cvdt2.util ~ dbeta(29.439466,43.611319) # 0.403

util[1] <- 1
util[2] <- mets.util
util[3] <- diab.util
util[4] <- cvd.util
util[5] <- cvdt2.util
util[6] <- 0

# Alternative calculation of qalys – undiscounted

for (j in 1:4) {
tot.util2[j] <- time[j,1]*util[1] + time[j,2]*util[2] + time[j,3]*util[3] + time[j,4]*util[4] +
time[j,5]*util[5] + time[j,6]*util[6] }

for (j in 1:4) {
tot.costa[j] <- sum(cost.distot[j,])
tot.cost[j] <- tot.costa[j] + cost.intv[j]
tot.util[j] <- sum(qaly.distot[j,]) }

for (l in 2:4) {
diff.cost[l] <- tot.cost[l] - tot.cost[1]
diff.util[l] <- tot.util[l] - tot.util[1]

ICER[l] <- diff.cost[l]/diff.util[l]

# CEAC

for (k in 1:18)  {
INB[l,k] <- K[k]*diff.util[l] - diff.cost[l]
Q[l,k] <- step(INB[l,k]) }  }

}  #End model
```

Appendix D

Report of interventions used in different studies in the Mixed Treatment Comparisons analysis for the identification of the best treatment strategy for adults with Metabolic Syndrome. Chapter 4.

Report of interventions used in different studies in the Mixed Treatment Comparisons analysis for the identification of the best treatment strategy for adults with Metabolic Syndrome.

#	Trial, Publication Author	Year	MetS Def'n	Intervention Group		Details
1	Anderssen	2007	IDF	Diet	Individulised diet	Dietary counseling was given together with the spouse at the start, and then to the participants alone after 3 and 9 months. The advice was individualized and adapted according to each person's dietary history and risk profile (estimated from total cholesterol, HDL, triglycerides, blood preassure, and body weight. The intervention focused primarily on energy restriction in those who were overweight. Fish and fish products, and reduced intake of saturated fat and cholesterol, were recomended to all participants, but especially to those whose elevated total cholesterol was the more important component of the risk profile. In order to assess dietary compliance, each participant responded to a 180-item food frequency questionaire Smoking habits were recorded by a questionaire as well as estimated through serum thiocyanate concentration.
				Exercise	Supervised Exercise	The exercise program entailed supervised endurance-based exercise, such as aerobics, circuit training, and fast walking jogging, three times per week. The duration of each workout was 60 min. The intensity of the training was 60-80% of the participant's individual peak heart rate as measured by a treadmill test at baseline. The exercise group and combined diet and exercise group intermingled during supervised training sessions. The attendance of each workout was recorded, as was additional physical activity performed by some participants. A Polar Sportstester heart rate recorder (Polar Electro OY, Kempele, Finland) was used to measure training intensity.
				Lifestyle	Diet + Exercise	Combined the exercise program with dietary counseling.
				Control	No intervention	Participants in the control group were told not to change their lifestyle during the trial, but as all the other participants, they were advised againt smoking. At randomization, the control group participats were told that after the 1-year trial period, they would be offered dietary advice and supervised physical training.

#	Trial, Publication Author	Year	MetS Def'n	Intervention Group		Details
2	Esposito	2004	NCEP	Diet	Individualised Diet + guidance physical activity (Lifestyle)	Patients consuming the intervention diet were given detailed advice about the usefulness of the experimental diet. Through a series of monthly small-group sessions, intervention parients received education in reducing dietary calories (if needed), personal goal-setting, and self-monitoring using food diaries. Behavioral and psychological counseling was also offerded. The dietary advice was tailored to each patient on the basis of 3-day food records. The recommended composition of the dietary regimen was as follows: carbohydrates, 50% to 60%; proteins, 15% to 20%; total fat, less than 30%; saturated fat, less than 10%; and cholesterol sonsumption, less than 300 mg per day. Moreover, patients were advised to consume at least 250 to 300 g of fruits, 125 to 150 g of walnuts per day; in addition, they were also encouraged to consume 400 g of whole grains (legumes, rice, maize, and wheat) daily and to increase their consumption of olive oil. Patients were in the program for 24 months and had monthly sessions for the second year. Compliance with the program was assessed by attendance at the meetings and completion of the diet diaries. All patients in both groups also received guidance on increasing their level of physical activity, mainly by walking for a minimum of 30 minutes per day but also by swimming or playing aerobic ball games (eg. soccer)
				Control	Control + Lifestyle advice (Control)	Patients consuming the control diet were given general oral and written information about healthy food choices at baseline and at subsequent visits but were offered no specific individualized program However, the general recommendation for macronutrient composition of the diet was similar to that for the intervention group (carbohydrates, 50%-60%; proteins, 15%-20%; and total fat, <30%). Moreover, patients in the control group also had bimonthly sessions with study personnel during the 2-year study. All patients in both groups also received guidance on increasing their level of physical activity, mainly by walking for a minimum of 30 minutes per day but also by swimming or playing aerobic ball games (eg. soccer)
3	Stewart	2005	NCEP	Exercise	Supervised Exercise + guidance on diet (Lifestyle)	Supervised exercise was performed three times per week, and followed American College of Sports Medicine guidelines.34 The prescribed number of sessions was 78 (3 days 26 weeks). If a participant fell short of 62 sessions at 6 months (80% compliance), an extra month was allowed. A stretching warm-up was followed by resistance training consisting of two sets of 10 to 15 repetitions per exercise, at 50% of one-repetition maximum. The same seven exercises that were used for strength testing were used for resistance training. When the participant could complete 15 repetitions of an exercise with little difficulty, the weight was increased. Following resistance training, aerobic exercise was per-formed for 45 minutes. The participant could use a treadmill, stationary cycle, or stair stepper. A heart rate (HR) monitor (Polar, Inc., Lake Success NY) was worn and an alarm beeped when HR was outside the target heart range, set at 60% to 90% of maximum HR from the baseline exercise test. Em- phasis was placed on maintaining HR toward the higher end of the range as tolerated. As fitness improved, the exercise workload was increased to maintain target levels.
				Control	Control + Lifestyle advice (Control)	All participants were given the National Institute of Aging Guidelines for Exercise (http://www.nia.nih.gov/exercisebook) and the American Heart Association Step I Diet (http://www.americanheart.org) at the time of screening, and were asked to maintain their normal caloric intake during the study. Participants in both groups reported twice monthly for BP safety checks. If the SBP was 159 or DBP 99 mm Hg, the participant was assessed weekly; the participant was withdrawn if BP was above range for 4 consecutive weeks.

#	Trial, Publication Author	Year	MetS Def'n	Intervention Group		Details
4	Bo	2007	NCEP	Lifestyle	Individualised diet + Exercise Advice (Lifestyle)	
				Control	Unstructured advice (Control)	
5	Villareal	2006	NCEP	Lifestyle	Individualised diet + Supervised Exercise (Lifestyle)	Each participant was pre- scribed a balanced diet to provide an energy deficit of approxi- mately 750 kcal/d.34 Daily calorie requirement was deter- mined by estimating resting energy expenditure and multiplying the obtained value by 1.3.35 The diet contained approximately 30% of energy as fat, 50% as carbohydrate, and 20% as protein. Total calorie intake was adjusted to prevent more than a 1.5% loss of body weight per week, with the goal of 10% weight loss at the completion of the study. Participants were in- structed to take a multivitamin supplement daily.The curricu- lum from the the Diabetes Prevention Program's Lifestyle Change Program36 was used and modified for this study. Subjects met weekly as a group with a study dietitian experienced in group behavioral therapy. Standard behavioral strategies, including goal setting, self-monitoring, stimulus control techniques, prob- lem-solving skills, identification of high-risk situations, and re- lapse prevention training, were used to modify eating habits. Each participant was given the 2003 edition of The Doctors Pocket Guide of Calorie, Fat and Carbohydrate Counter,37 a book with information on the calorie content of foods, food diary sheets, and a binder in which to file educational materials distributed during group sessions. Subjects participated in group exercise training sessions on 3 nonconsecutive days each week. Each session was supervised by a physical therapist. The exercise pro- gram focused on improving flexibility, endurance, strength, and balance. Each session lasted 90 minutes and began with 15 min- utes of warm-up flexibility exercises followed by 30 minutes of endurance exercise, 30 minutes of strength training, and 15 minutes of balance exercises.
				Control	No intervention (Control)	Subjects assigned to the control group were instructed to maintain their usual diet and activi- ties during the study period. They were prohibited from par- ticipating in any weight loss or exercise program.
6	Orchard	2005	NCEP	Antidiabetic	Metformin + standard lifestyle	Standard lifestyle recommendations plus metformin, 850 mg twice per day
				Lifestyle	Individualised diet + Exercise Advice	An intesive program of lifestyle intervention. The goals of the lifestyle program were to achieve and maintain a weight reduction of at least 7% of clinical body weight through a healthy low-calorie, low-fat diet and to engage in physical activity of moderate intensity, such as brisk walking, for at least 150 minutes per week. Participants were seen quarterly, when blood pressure was assessed. Fasting glucose levels were determined at the 6-months visits, and fasting lipid levels and waist circumference were measured annually.
				Control + Lifestyle	Placebo + Lifestyle advice	Standard lifestyle recommendations plus placebo

#	Trial, Publication Author	Year	MetS Def'n	Intervention Group		Details
7	Ramachandran	2006	WHO	Lifestyle	Individualised diet + Exercise Advice	Subjects followed lifestyle modification (LSM)
				Antidiabetic	Metformin	Subjects were treated with metformin (MET)
				Antidiabetic + Lifestyle	Metformin + Lifestyle	Subjects were given LSM plus MET
				Control	Standard advice	Subjects were given standard health care advice (control)
8	Esposito	2006	NCEP	Antidiabetic	Rosiglitazone	Patients were instructed to follow a weight-maintaining diet consisting of 50% carbohydrates, 30% lipid (<10% saturated fat), and 20% protein throughout the study and underwent a 6-week run-in period, after which they were randonmly assigned to receive either rosiglotazone (4mg/day, n=50) or matching placebo (n=50) for the 12-month double-blind phase. Patients were seen at screening visit (before run-in), 1 week before randomization for baseline determinations, at randomization, and at 1 month interval for physical examination.
				Control	Placebo + Diet advice	

#	Trial, Publication Author	Year	MetS Def'n	Intervention Group		Details
9	Phelan	2007	NCEP	Antiobesity	Sibutramine	Fifty-five subjects were assigned to receive sibu- tramine alone. They had eight brief visits (10 to 15 minutes each) with a primary care provider at weeks 1, 3, 6, 10, 18, 26, 40, and 52. During week 1, subjects were given a daily dose of 5 mg of sibutramine (provided by Abbott Laboratories, which otherwise had no involvement in the study), and the dose was increased to 10 mg at week 3 and to 15 mg at week 6. Subjects received a copy of "On Your Way to Fitness,"19 a pamphlet that provides tips for healthy eating and activity. They were not instructed to keep records of food intake or activity, and the primary care providers gave only general encouragement. Weight and vital signs were mea- sured at all visits. The primary care providers in- cluded three internists and one nurse practitioner, none of whom specialized in obesity management.
				Lifestyle	Individualised diet + Exercise Advice	A total of 55 subjects were assigned to receive life- style modification alone. They attended weekly group meetings from weeks 1 through 18, sessions conducted every other week from weeks 20 through 40, and a follow-up visit at week 52. Meetings in- cluded 7 to 10 subjects, lasted 90 minutes, and were led by trained psychologists. For the first 18 weeks, sessions followed the LEARN (Lifestyle, Exercise, Attitudes, Relationships, and Nutrition) Program for Weight Control,20 which instructed subjects to complete weekly homework assignments that in- cluded keeping daily records of food and calorie in- take and physical activity. Records were reviewed at weekly meetings. From weeks 20 through 40, ses- sions were conducted with the use of the Weight Maintenance Survival Guide.
				Antiobesity + Lifestyle	Sibutramine + Lifestyle	Sixty subjects were assigned to combined therapy. They were given the same two treatments as those in the first two groups, but with a slight modifica- tion. They received sibutramine, attended medical visits, and attended group sessions of lifestyle counseling that followed a version of the LEARN Pro- gram for Weight Control22 that was adapted to in- clude sibutramine.
				Antiobesity + Brief Lifestyle	Sibutramine + Brief lifestyle	A total of 54 subjects received sibutramine and met with a primary care provider (10 to 15 minutes per session) on the same schedule as subjects in the group given sibutramine alone. They also were given the two treatment manuals21,22 and were in- structed to complete homework assignments, in- cluding daily food-intake and activity records, which they reviewed during visits with the primary care providers. (Additional details about treatment implementation are provided in the Supplementary Appendix, available with the full text of this article at www.nejm.org.)

#	Trial, Publication Author	Year	MetS Def'n	Intervention Group		Details
10	Van Gaal	2005	NCEP	Antiobesity	Rimonabant 20mg	Treatments were allocated to patients using the interactive voice responding system according to the predefined randomisation list (1: 2: 2 ratio for placebo, 5 mg rimonabant, and 20 mg rimonabant, respectively). A central laboratory (ICON Laboratories, Farmingdale, USA, and Dublin, Ireland) ensured that the randomisation of treatment was balanced within each centre and was stratified based on the loss of bodyweight (<=2 kg or >2 kg) recorded during the run-in period, per protocol. During the double-blind period, patients were seen every 14 days during the first month and thereafter every 28 days until the end of the study. Basal metabolic rate was estimated with the Harris Benedict formula, and 600 kcal were subtracted by a dietician to calculate a recommended daily energy intake for each patient. At each visit, patients received dietary counselling and were encouraged to increase physical activity. Bodyweight, waist circumference, and blood pressure were measured at screening, at randomisation, and at every treatment visit, whereas lipid profile, fasting glucose, and insulin were measured every 3 months by use of standard procedures in the central laboratory (ICON Laboratories).
				Antiobesity (diferent dose)	Rimonabant 5mg	
				Control	Placebo	
11	Geluk	2005	NCEP	Statin	Pravastatin	
				Control	Placebo	The group without pravastatin treatment is labelled as control group.
12	Athyros	2005	NCEP	Statin	Atorvastatin	All subjects received lifestyle advice. This included exercise (walking for at least 30 minutes 5 days a week or equivalent exercise) and low-fat (NCEP ATP III) hypocaloric diet. After estimating the appropiate energy intake for a specific subject (according to his/her job and leisure time activity), we provided him/her (according to the suggestions of a dietician) with a computer-generated diet (taking into consideration his/hers dietary preferences) with a daily energy intake of 2092 J less than that estimated as appropriate. The compliance to the diet was established at every visit with a 3-day food intake questionnaire.
				Fenofibrate	Fenofibrate	
				Statin + Fenofibrate	Atorvastatin + Fenofibrate	

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