Modelling health and healthcare for an ageing population

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Abstract

Population ageing has received much attention as a contributing cause of spiralling healthcare expenditure. This study primarily aims to estimate the impact of population ageing on key diseases, and to develop a flexible modelling framework that can inform policy decisions.

This research provides a proof-of-concept model where individual Discrete Event Simulation models for three diseases (heart disease, Alzheimer's disease, and osteoporosis) were extended from existing published models to simulate the general UK population aged 45 years and older, and combined within a single model. Using external population projection data incorporating potential demographic changes, the methods for projecting future healthcare expenditures for the three diseases were demonstrated and the relative benefits of improving treatment of each of the diseases evaluated.

Secondary outcomes include the development of a pragmatic literature search method which can be used for literature within diffuse topic areas, and a literature repository for future researchers to explore the existing literature on ageing and healthcare expenditure.

Expenditure for the three diseases is projected to increase from £16 billion in 2012 to £28 billion in 2037. A key finding from this work is that the estimates of costs, quality-adjusted life years (QALYs), and the projected expenditure for healthcare services can differ when multiple diseases are modelled in a single model compared with the summed results from single disease models. This implies that policy decisions on the allocation and planning of healthcare resources based on the results from individual disease models can be different from those based on linked models. The novel approach of linking multiple disease models with correlations incorporated provides a new methodological option primarily for modellers who undertake research on comorbidities. It also has potential for wider applications in informing decisions on commissioning of healthcare services and long-term priority setting across diseases and healthcare programmes, hence ultimately contributing to the improvement of population health.

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List of abbreviations

AchEIs	Acetylcholinesterase inhibitors
AD	Alzheimer's Disease
ADCS	Alzheimer's Disease Cooperative Study
ADL	Activities of Daily Living
AHEAD model	Assessment of health economics in Alzheimer's disease model
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
ASCOT-LLA	ASCOT-Lipid Lowering Arm
ASSIA	Applied Social Sciences Index and Abstracts
BMD	Bone Mineral Density
BMI	Body Mass Index
BNF	British National Formulary
CABG	Coronary artery bypass graft
CBO	Congressional Budget Office
CDR	Clinical Dementia Rating
CERAD	Consortium to Establish a Registry in Alzheimer's Disease
CFAS	Cognitive Function and Ageing Studies
CHD	Coronary heart disease
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CLI	Critical limb ischaemia
CMS	Centers for Medicare and Medicaid Services (US)
COMPARE	Comprehensive Assessment of Reform Efforts
COPD	Chronic Obstructive Pulmonary Disease
CPQ	Cost per QALY
CVD	Cardiovascular disease
DES	Discrete Event Simulation
DG-ECFIN	European Commission – Directorate General for Economic and Financial Affairs
EED	Economic Evaluation Database
EMBASE	Excerpta Medica dataBASE
ENEPRI	European Network of Economic Policy Research Institutes
ENEPRI/AHEAD	ENEPRI/Aging, Health Status and Determinants of Health Expenditure

EQ-5D	EuroQol five-dimensional questionnaire
ESRI	Economic and Social Research Institute
FEM	Future Elderly Model
FTC	Full time care
GDP	Gross Domestic Product
HCE	Healthcare expenditure
HCHS	Hospital and Community Health Services
HD	Heart disease
Health ABC study	Health, Aging, and Body composition study
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health Related Quality of Life
HSE	Health Survey for England
HTA	Health Technology Assessment
IC	Intermittent claudication
ICER	Incremental cost-effectiveness ratio
LASER-AD	London and South-East Region Alzheimer's Disease
LTC	Long Term Care
MEDLINE	Medical Literature Analysis and Retrieval System Online, or MEDLARS Online
MeSH	Medical Subject Headings
MI	Myocardial infarction
MMSE	Mini Mental State Examination
MONICA	Multinational Monitoring of Trends and Determinants for Cardiovascular Diseases
MORE	Multiple Outcomes of Raloxifene Evaluation
MRC	Medical Research Council
NBER	National Bureau of Economic Research (US)
NHAR	Nottingham Heart Attack Register
NHS	National Health Service (UK)
NICE	National Institute for Health and Care Excellence (UK)
NIHR	National Institute for Health Research
NMB	Net monetary benefit

NNR	Number Needed to Read
OA	Osteoarthritis
OECD	Organisation for Economic Co-operation and Development
ONS	Office for National Statistics (UK)
PAD	Peripheral artery disease
PCI	Percutaneous Coronary Interventions
PenTAG	Peninsula Technology Assessment Group
POHEM	Population Health Model
PPACA	Patient Protection and Affordable Care Act
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PTCA	Percutaneous transluminal coronary angioplasty
QALY	Quality-adjusted life year
RA	Rheumatoid arthritis
RCT	Randomised Controlled Trial
RITA	Randomized Intervention Treatment of Angina
RR	Relative risk
SAPAT	Swedish Angina Pectoris Aspirin Trial
SD	System Dynamics
SDs	Standard deviations
SHEMO	Sheffield Health Economic Model for Osteoporosis
SHTAC	Southampton Health Technology Assessment Centre
SLSR	South London Stroke Register
SOA	Societies of Actuaries
TA	Technology Appraisal
TIA	Transient ischaemic attack
TNT	Treating to New Targets study
TTD	Time to death
TTNE	Time to next event
UN	United Nations
WHO	World Health Organization
WOSCOPS	West Of Scotland Coronary Prevention Study

CHAPTER 1 INTRODUCTION

1.1. Background

Population ageing is a dynamic process in which the proportion of older people in the population increases, resulting in a shift in the age structure of a population from younger to older groups. An older population typically includes people aged 60 – 65 years and over. In many developed regions, the age of 65 years is used to define an older person due to the statutory pension and retirement age, however, the United Nations (UN) often adopts 60+ years to refer to the older population. The World Health Organization (WHO) expects the number of people aged 60 years and older to increase from 900 million in 2015 up to 2 billion by 2050 (World Health Organization, 2015). The old-age dependency ratio, which is calculated as the number of persons aged 15 to 64 years divided by the number of persons aged 65 years or over, has been decreasing worldwide over the last five decades (from 12 in 1950 to 8 in 2013). This is expected to continue to decline in the next 40 years and estimated to be 4 in 2050 resulting in fewer people of working age. This can impose fiscal pressures on support systems for the older population including both public transfers from the government (such as healthcare and cash benefits) and private transfers (such as intergenerational support for care) of economic resources (United Nations, 2013).

This demographic transition is occurring in both developing and developed parts of the world, and the population changes are mainly driven by a decline in mortality and fertility. The fertility rate has nearly halved between 1950-1955 and 2000-2005 from 5.0 children per woman to 2.7 globally (United Nations, 2001). According to the UN, fertility has been declining faster in less developed countries from 6.2 children per woman to 2.9 between 1950-1955 and 2000-2005 (United Nations, 2001). Furthermore, people are now expected to live longer due to a reduction in mortality rates at older ages. In all regions of the world, life expectancy at birth has increased by almost 20 years between 1950-1955 and 2000-2005.

In the UK, life expectancy at birth was 78.1 years for men and 82.1 years for women in 2010. The Office for National Statistics (ONS) projects this to increase to 84.0 years for men and 87.3 years for women in 2037 (Office for National Statistics, 2013c). Fertility rates have been falling as well from 2.45 children for women born in the mid-1930s to 1.84 children for women born

after 1990 (Rutherford, 2012). Long-term mortality and fertility assumptions by ONS project the population of the UK to gradually become older with the number of people aged 65 and over to increase by 23% from 10.3 million in 2010 to 12.7 million in 2018 (Rutherford, 2012). The number of people aged 80 years and above is projected to more than double from about 2.5 million to 6 million by mid-2037 (Office for National Statistics, 2013c).

The ageing population has received much attention as a contributing cause of spiralling healthcare expenditure. Healthcare expenditure is related to, but distinguished from, healthcare needs, demand, and service utilisation. Healthcare is 'needed' for anticipated improvements in health, and the need for healthcare is often measured at various levels by the perception of individuals or healthcare professionals, health status indicators such as blood pressure, and observed geographical variations such as comparison of infant mortality by regions. Need is an important determinant of demand (Gravelle et al., 2003). Demand is associated with the behaviour of the consumer, and thus, demand for healthcare is the healthcare that both patients and the national health system are willing and able to consume. Interplay between demand for, and supply of, healthcare will determine the utilisation of healthcare services. Demand will be partially reflected by the actual utilisation of the healthcare services. Through such utilisation, demands for healthcare are met, and healthcare expenditures are incurred. As older individuals tend to need more healthcare and related social care services than younger individuals due to a higher prevalence of both acute and chronic diseases, the anticipated changes in the age composition of the population are expected to significantly increase future expenditure on these services (European Commission Directorate-General for Economic and Financial Affairs, 2009).

Hence, the impact of the projected demographic changes on future health and social care expenditure is a growing concern for many governments and health authorities across the world (European Commission Directorate-General for Economic and Financial Affairs, 2009). Overall health spending grew by nearly 5% annually in real terms in Organisation for Economic Co-operation and Development (OECD) countries over the period 2000-2009, and the total healthcare expenditure as percentage of gross domestic product (GDP) in the UK increased from 5.9% in 1981 to 9.6% in 2010 (OECD, 2012). In addition, total expenditure on long-term social care services in the UK is projected to increase from 1.49% of GDP in 2002 to 3.14% in 2051; with the public expenditure element comprising 0.96% to 1.94% growth (Hancock et al., 2007a).

However, demographic changes such as population ageing form only one of many factors that can influence healthcare expenditure. Rising healthcare expenditure may reflect changes in the level of need and/or demand, or changes in the pattern of healthcare utilisation. As economies get richer, consumption patterns tend to move towards services including healthcare services, instead of tangible goods such as cars and clothes. In addition, more healthcare needs may be met due to improvements made to access to, or provision of, healthcare services.

A number of studies have suggested that ageing *per se* may not be the major driver of rising healthcare expenditure, but has at best a modest effect on both the per-capita and aggregate healthcare costs when adjusted for non-demographic variables associated with demand- and supply-side of a healthcare system (Gerdtham et al., 1993, Reinhardt, 2003, Seshamani and Gray, 2004c, Breyer and Felder, 2006, Christiansen et al., 2006, Werblow et al., 2007, Zweifel et al., 1999). Although the probability of death is positively correlated with the age of an individual (Payne et al., 2007) and per-capita healthcare expenditure increases with age (Meerding et al., 1998, Alemayehu and Warner, 2004), these studies found that healthcare costs are concentrated on the time period immediately preceding death, and the age effect on costs becomes much smaller when time to death of individuals is controlled for. This has been termed the *'red herring'* argument (Zweifel et al., 1999). For example, Zweifel et al. (1999) showed that age itself was largely irrelevant as a determinant of healthcare expenditure in the last two years of life using data from two sickness funds in Switzerland. Due to the changing mortality patterns, estimates of future healthcare costs based solely on the age composition of the future population may differ from those based on the proximity of the population to death.

A wide range of demand-side, supply-side, as well as regulatory (or institutional) factors influence healthcare expenditure. Demand-side factors include demographic changes such as population ageing, the health status of a population, income, and the population's health-seeking behaviour (e.g. healthy lifestyles and the use of preventative health services) and their perceived needs (Christiansen et al., 2006, Astolfi et al., 2012, Schulz et al., 2004). Supply-side factors such as technological advances, changes in treatment practices, productivity, and price of healthcare services may explain changes in healthcare expenditure (Astolfi et al., 2012). Some studies suggest that the effect on healthcare expenditure of some factors that change at a relatively fast pace such as technological progress may outweigh that of population changes (Meara et al., 2004, Christiansen et al., 2006). These factors would in turn be associated with the capacity, facilities, resources and governance of the healthcare sector (Layte et al., 2009).

Regulatory factors including the economic context of the country, institutional characteristics of healthcare system and political framework conditions, such as political influence on decisions on healthcare policy, also play a role (Astolfi et al., 2012, Schulz et al., 2004). For example, Erixon and van der Marel (2011) argue that the way in which healthcare provision is organised is a strong determinant of expenditure increases as inflation in the healthcare sector is higher than that in the other sectors due to low productivity growth and the labour-intensive nature of healthcare.

A number of studies have investigated the impact of age composition of the population, economic, and institutional factors, such as GDP of the country; patterns of care delivery; and ratio of public and private financing on health and social care expenditure (Seshamani and Gray, 2004b, Breyer and Felder, 2006, Christiansen et al., 2006, Werblow et al., 2007). Efforts have also been made across countries to estimate the likely impact of the challenges of an ageing population arising from both the demand for, and supply of, health and social care services (European Commission Directorate-General For Economic Financial Affairs, 2006, Department of Economic and Social Affairs Population Division, 2009, Congressional Budget Office, 2007).

Studies have found that the health status of a population is an important determinant of the utilisation of healthcare services, and thus expenditure (Layte et al., 2009, Christiansen et al., 2006, Astolfi et al., 2012, OECD, 2006, Westerhout and Pellikaan, 2005). There is some evidence that disability rates among the elderly have been falling, indicating improvements in health status (Manton et al., 1997, Parker and Thorslund, 2007, Cutler, 2001). Jacobzone et al. (2000) documented that the reduction in prevalence of disability rates was mainly found among the age groups 65 to 80 years in a sub-group of OECD countries.

There are contrasting views on the relationship between mortality (increase in life expectancy) and morbidity (health status at the end of life). Fries (1980) argues that gains in life expectancy would mean an increased period of healthy life, thus a shrunken period of morbidity termed "compression of morbidity". A counterargument proposed by Olshansky et al. (1991) is the theory of "expansion of morbidity" suggesting that increased longevity extends the time with diseases and disabilities. An alternative theory known as "dynamic equilibrium" assumes that gains in life expectancy lead to approximately the same increase in time of healthy life, and thus the period of end-of-life morbidity remains unchanged (Manton, 1982). Empirical evidence generally favours the compression of morbidity hypothesis. In many industrialised countries, the decline in age-specific disability outweighs the age-specific mortality decrease in

recent years, leading to the expansion of disability-free years of life (Jagger et al., 2005, Mathers et al., 2004, Payne et al., 2007, Crimmins, 2004). Although the prevalence of some chronic diseases such as diabetes, cancer, and arthritis has risen, recent evidence indicates that the severity of these diseases among older people is falling (Mathers et al., 2006, Crimmins, 2004, Payne et al., 2007).

The recently observed downward trend in age-specific severity of chronic diseases and prevalence of disabilities may signal a reduction in healthcare demand, but linking the disability trend to a reduction in health expenditures is not straightforward because other factors and interactions between them will also have an impact. In a study by Jacobzone et al. (2000), the disability trends showed disparate results across countries, and it was noted that the economic impact of these trends is unclear and depends on the arrangements of institutional care services in the relevant countries, such as the level of subsidisation.

The theories on trends in life expectancy, health status and healthcare expenditure and the relationships between them have significant implications for the modelling of health and healthcare. Failure to incorporate inter-relationships between the factors influencing healthcare expenditure may jeopardise the validity of the model results. It is important to have a model that incorporates as many relevant factors as practicable, and can answer policy questions regarding possible consequences/implications of changing demographic and non-demographic factors in the coming decades. Based on the background provided in this section, the following sections will outline the research questions posed by the thesis and how they are addressed.

1.2. Research questions and objectives

This PhD aims to provide a model that can help answer research questions arising in relation to healthcare expenditure for an ageing population. The questions this PhD study tries to address will define the purpose of the model and inform the choice of modelling methodology, and are summarised below.

(1) What will happen to healthcare expenditure on key diseases if current trends continue?

The main question that the model in this thesis will address is 'what would happen if no action on healthcare services and health policy that may influence future healthcare costs is taken and the current trends in demographic changes and health status of the population continue?' Some models forecasting overall health and healthcare expenditure have attempted to describe the current status of the system (European Commission European Foresight Monitoring Network, 2009, Astolfi et al., 2012). For instance, the US Congressional Budget Office (CBO) produces 75-year projections of total expenditures on various federal programmes such as Medicare and Medicaid (Congressional Budget Office, 2005, Congressional Budget Office, 2008, Congressional Budget Office, 2007). The models aid long term fiscal planning and the main part of their projections assume that no significant changes would be made in policy over the projection period.

More detailed outcomes can be derived from the models describing the current healthcare system. In relation to identifying the viable policy options, the next question asked is 'what would be the effect of the current trends on specific diseases?' and 'costs of which diseases will increase the most?' The results could support exploring policy opportunities to constrain future spending on specific diseases. The models asking these questions could also be used to identify the major drivers of disease-level health expenditure growth (OECD, 2006). Projections based on the current trends in factors influencing demand for disease-specific healthcare services can be altered to reflect potential changes in those factors.

(2) Will the estimation of future expenditure change if diseases are modelled simultaneously, rather than individually?

The estimation of disease-level outcomes is typically performed using a model involving a single disease. However, due to some overlapping costs associated with co-morbidities, such as hospitalisation and care home use for multiple disease conditions, and possible correlations between diseases, such as the higher incidence of Alzheimer's disease among people with cardiovascular conditions, the estimates from a single-disease model may differ from those from a model incorporating multiple diseases and relevant correlations between them. The next question to explore in relation to this is 'will the estimation of future healthcare expenditure change if multiple diseases are modelled simultaneously, rather than individually?'

(3) In which diseases, will investment, to reduce consequences of the disease, be most profitable?

One may think of potential policies or interventions that can impact on some of the factors influencing expenditure such as the adoption of improved treatments and prevention programmes. An estimation of the current trends and status of the healthcare system naturally leads to questions such as 'what would happen if some actions are taken' and 'in which diseases, will investment be most beneficial to reduce the health and economic consequences of the disease?' This includes the assessment of possible consequences of potential interventions and policies on the healthcare sector. Policy decisions can make intended changes in the delivery of care and public healthcare costs. Also, models can help to assess the possible consequences of hypothetical unanticipated changes by conducting various 'what-if' scenario analyses. For example, the US RAND's Comprehensive Assessment of Reform Efforts (COMPARE) micro-simulation model was developed to project how individuals, households, and firms would respond to healthcare policy changes, and applied to evaluate the likely effects of a new law designed to expand health insurance coverage, the Patient Protection and Affordable Care Act (PPACA)(Eibner et al., 2010a). Such ex ante analyses tested various scenarios associated with policy designs and model assumptions on behavioural responses.

In the process of undertaking this research, two other research questions were explored:

(4) Can a framework be established to guide literature searching in diffuse topic areas? and;

(5) Could a freely available repository containing relevant literature be set up for future researchers in order to save time?

This study aims to estimate the impact of population ageing on disease-level healthcare expenditure and to develop a flexible modelling framework that can inform questions (1) – (3) incorporating a wider range of potential influences on healthcare expenditure. The outcomes of the model can assist the efficient planning of healthcare resources and the evaluation of potential interventions and policy changes. The methodology will enable simulation of future healthcare demand in a way which is flexible enough to explore the impact on demand of variations in the influencing factors incorporated in the model.

Health economics aims to achieve the optical allocation of limited healthcare resources for the efficient production of population health (Higgins and Green, 2011). In other words, efficiency is attained when society makes choices which maximise the health outcomes gained from the resources allocated to healthcare (Palmer and Torgerson, 1999). The efficient use of healthcare resources is defined as producing the maximum possible improvement in outcome obtained from a given set of resource inputs such as healthcare workforce, capital, and medical technology and equipment ('technical efficiency') and achieving the right mixture of healthcare programmes to maximise the health of society ('allocative efficiency') (Palmer and Torgerson, 1999). The method proposed in this PhD focusses on achieving allocative efficiency rather than technical efficiency, as it concerns the efficient allocation of healthcare resources between the diseases and health care conditions, rather than a technically efficient use of resource inputs.

Economic evaluation techniques can be used to inform both technical and allocative efficiency in healthcare. Economic evaluation is defined as "the comparative analysis of alternative courses of action in terms of both their costs and consequences", and aims to inform decisions on clinical practices, adoption of a technology and resource allocation (Drummond et al., 2005). Cost-utility analysis (CUA) is a type of economic evaluation in which interventions, which produce different consequences in terms of quantity and quality of life, are expressed in utilities and are compared in terms of incremental costs and quality-adjusted life years (QALYs), a measure which comprises both length and quality of life (Drummond et al., 2005). When QALYs are used, resource allocation decisions can be made by comparing competing interventions in terms of the incremental cost per QALY gained. Economic evaluation often requires decision analytic modelling as data and evidence needed for decision-making come from various sources. Decision analytic models provide a structured approach to synthesising the evidence of clinical and economic outcomes to produce detailed estimates of the consequences of different healthcare interventions that can inform decisions (Briggs et al., 2006, Weinstein et al., 2003).

This PhD provides a proof-of-concept model that can be used, modified, and expanded to incorporate other relevant factors and diseases. The model is an individual-level Discrete Event Simulation (DES) model linking multiple diseases. It records annual accrual of costs of preventing, treating, and managing selected diseases, which were used to estimate population-level costs. Existing disease-specific models that have been used for health technology assessment (HTA) were reviewed and replicated wherever possible in this model.

The model expands the existing HTA modelling frameworks to serve the aim of projecting healthcare expenditure for an ageing population using the methodology presented in this thesis. Given the benefit of the individual- and disease-level modelling, it is anticipated that this thesis can help answer key policy questions, producing more detailed outcomes compared with the models that estimate aggregate healthcare expenditures. Hence, the outcomes of the model developed in this thesis are expected to allow healthcare expenditures to be attributed to disease conditions and demographic characteristics of age and gender, providing important information for health policy makers on the selected diseases. Such results can be used to assess current resource allocations in the healthcare system, and aid discussions concerning ageing populations and changing disease patterns. The model can also help analyse time trends, identify the drivers of healthcare spending, and provide an input into the future modelling of health care expenditures.

1.3. Thesis structure

The subsequent chapters of this thesis are structured to follow the process undertaken towards the development of a linked-disease model of selected diseases of the elderly. Figure 1.1 shows how the chapters in this thesis are related.

Figure 1.1. Structure of the thesis
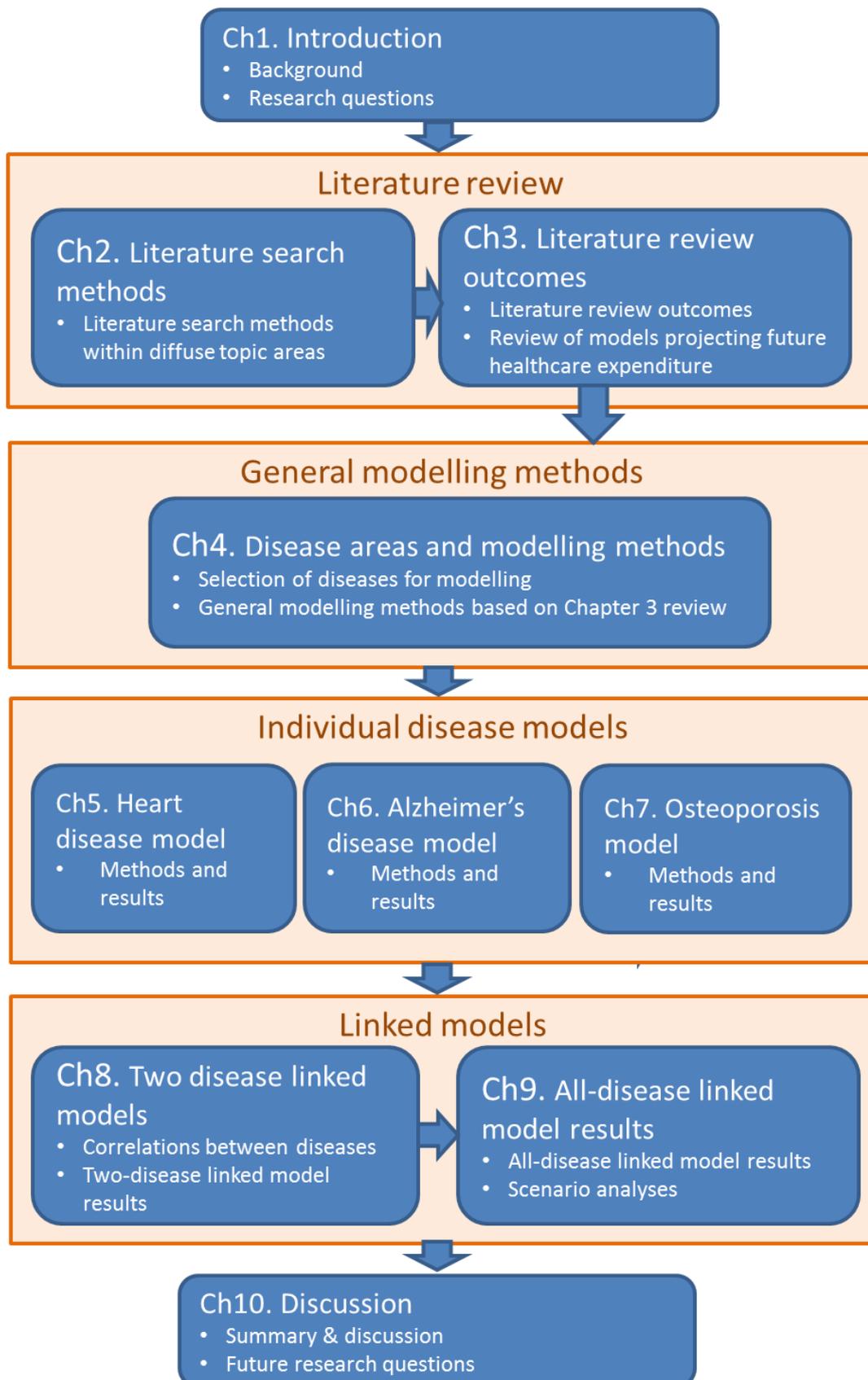
In order to develop an understanding of existing methodologies and of the data requirements needed for the construction of a new model, a review of the previous research attempting to model the health and healthcare of the future population was undertaken. Chapter 2 presents the method of developing search strategies to identify pertinent research. Given the diffuse nature of the topic area and the substantial variation in the literature discussing issues relevant to population ageing and healthcare demands, designing pragmatic search strategies and subsequent categorisation of the information retrieved was essential. The searches made use of a core set of papers that were deemed representative of the diffuse literature set in order to reduce the number of overall papers identified. Chapter 3 describes the outcomes of the literature searches and review, including the results of categorising the information available from the extant literature; the development of a freely-accessible literature repository established to assist future researchers; and an overview of the models projecting future healthcare demand classified according to their methodology, which could inform the choice of the modelling methods for this thesis.

Based on the review of the existing projection models, Chapter 4 designs the model constructed for this thesis. It describes the disease areas selected and the modelling methodology adopted. It also reports the general methods used to develop the individual disease models presented in subsequent chapters and outlines how the individual disease models were linked.

Chapters 5, 6, and 7 describe the disease-level modelling for three selected diseases: heart disease, Alzheimer's disease, and osteoporosis, and report the outcomes of the individual disease models, respectively. The general UK population with and without history of any of the included health events was modelled for the purpose of estimating population-level healthcare expenditure. The model structure was developed to incorporate both prevalent and non-prevalent individuals to capture all future patient-related benefits and costs (Hoyle and Anderson, 2010). The results of projected annual costs of treating and managing the three diseases were also reported. Chapter 8 describes the correlations between the diseases that were incorporated in the model and the results from models where pairs of diseases were linked. Chapter 9 reports the results from the model where all included diseases were linked and correlated and examines the implications of these results for health technology assessment and the projection of future healthcare expenditure. Finally, Chapter 10 summarises the findings of this PhD study and discusses the limitations and directions for future research.

CHAPTER 2   A METHODOLOGY FOR DEVELOPING PRAGMATIC SEARCH STRATEGIES: A CASE STUDY IN HEALTHCARE EXPENDITURE FOR OLDER POPULATIONS

This chapter describes the search methods used to identify abstracts from the literature to screen when conducting a review of health and healthcare expenditure for an ageing population. Section 2.1 introduces some of the challenges in identifying relevant literature within a diffuse subject area. Section 2.2 describes the method proposed in this thesis to develop a pragmatic search strategy, and Section 2.3 shows how the method was implemented in five databases. Section 2.4 reports grey literature search methods. Section 2.5 discusses limitations of the proposed approach.

2.1. Background – Literature search

Literature on the impact of ageing on healthcare expenditure is anticipated to be broad and diffuse given that it can involve a wide range of demographic, economic, and institutional factors (Gerdtham et al., 1993, Reinhardt, 2003, Seshamani and Gray, 2004c, Breyer and Felder, 2006, Christiansen et al., 2006, Werblow et al., 2007). It is therefore difficult to conduct a systematic review – as defined by Higgins and Green (Higgins and Green, 2011) – relevant to a broad research question.

It is recognised that there are challenges in identifying relevant literature for reviews of diffuse topics in health and social sciences (Grayson and Gomersall, 2003, Matthews et al., 1999, Papaioannou et al., 2010). The issues associated with ageing and healthcare expenditure are widespread and multifaceted, both in terms of the sources chosen for the search and the methods of searching.

Cross-disciplinary topics require the searching of multiple databases across multiple subject areas to maximise recall and maintain acceptable precision (defined as the proportion of relevant reports among those identified by a search) (Matthews et al., 1999, Taylor, 2009,

McFadden et al., 2012, Taylor et al., 2007). For example, in a review on student experiences of e-learning, Papaioannou et al. (2010) found that the 30 included studies identified from the database searching were derived from ten different sources. In a review of the health effects of social interventions on walking and cycling, only four of the 69 relevant studies found were from a *"first-line"* health database such as MEDLINE (McNally and Alborz, 2004). Searching multiple sources of literature has time and cost implications. Golder et al. (2008) also noted that the optimal number and combination of databases to search is unknown.

Choosing search terms for reviews of diffuse topics can present difficulties both in the use of indexes and free text searching (Papaioannou et al., 2010). Indexing may be inconsistent, and may not be available in some databases. In addition, some free-text terms may be used in multiple contexts which increases the number of irrelevant references retrieved (Matthews et al., 1999). Moreover, social science terminology is often *"non-technical"* and therefore overlaps *"ordinary everyday language"* (Grayson and Gomersall, 2003) as language in the social sciences *"varies according to the preferences of authors, schools of thought, cultures, and journals as well as with time and place"* (Taylor, 2009). Furthermore, abstracts can lack detail or may be non-existent (McNally and Alborz, 2004, Taylor, 2009, Papaioannou et al., 2010).In diffuse topic areas, database searches often cannot be restricted by study type such as randomised controlled trials (RCTs).This can greatly increase the number of references identified, demonstrating the need for efficient search strategies (Papaioannou et al., 2010).

An iterative approach to constructing search strategies for diffuse topics is often recommended, whereby a scoping search is conducted and additional index and/or free-text terms are identified from the relevant references (Ogilvie et al., 2005). This may also include contact with experts and/or checking of reference lists (Relevo and Balshem, 2011). Long et al. (2002) describe the stages of this process as *"scoping, refinement and confirmation"*. However, additional search methods are important. McNally and Alborz (2004) found unique potentially relevant references by supplementary methods such as snowballing and consultation with experts within a review on access to health care for people with learning disabilities. Snowballing is a literature searching technique that involves reference list checking or citation searching of a relevant source document (Booth et al., 2012, Webster and Watson, 2002, Hinde and Spackman, 2015). Golder et al. (2008) used these supplementary methods of reference checking in six databases (AgeLine, EMBASE, Health Management Information Consortium (HMIC), MEDLINE, PsycINFO, Social Sciences Citation Index) along with contacting authors to identify all included references in a review on the effectiveness of respite care.

Due to the diffuse topic area and the wide breadth of the literature discussing issues regarding population ageing, a comprehensive search was not considered feasible due to the potentially large number of hits identified, or the number needed to read (NNR). Therefore, a 'pragmatic' search strategy, with the objective of being efficient, was developed at the planning stage of the review.

This chapter describes the methods used to identify a pragmatic search strategy for conducting a literature review within a diffuse subject area of health and healthcare for an ageing population. The primary topics of papers intended to be retrieved were : i) studies estimating the future health and healthcare demand for an ageing population and ii) studies examining the effect of policies or interventions designed to tackle issues arising from population ageing on healthcare demand. Secondary topics included: trend analyses of healthcare spending; the determinants of healthcare spending; and the relationships between health and social care utilisation. The searches were limited to the literature written in English and those published before October/November 2011.

The proposed approach is predicated on the belief that it is more efficient and pragmatic to refine search strategies so that the NNR which need to be sifted is greatly reduced compared with broad searches. This approach differs from standard search methods for systematic reviews that are used when specific target literature exists. A set of 'seed' papers from which subsequent searches would be expanded to retrieve the target literature were identified *a priori* by scoping searches and discussions with experts. It was deemed that an acceptable search strategy would need to be capable of identifying all of the seed papers. Search strategies that were acceptable and retrieved relatively few hits were considered pragmatic. The results of the pragmatic search strategy were sifted as normal with all relevant literature synthesised in the final review. The estimated efficiency improvement associated with the final search strategy was reported with respect to the precision of searches and total sifting time. The later part of this chapter also reported a different approach used to search grey literature.

2.2. Methods for developing pragmatic search strategies

2.2.1. Steps in developing search strategies

Figure 2.1 summarises the iterative approach used in this thesis to heuristically develop pragmatic search strategies. An initial set of papers that could be used as a seed to retrieve wider literature of interest were identified. The search strategy was broadened to identify all the seed papers and then refined to reduce the number of hits whilst maintaining identification of all seed papers. The process of broadening and then refining the literature search was undertaken for all of the databases interrogated. The identified literature was sifted as normal.

Each of the steps in Figure 2.1 is described in more detail in the following sections.

Figure 2.1. Step-by-step approach to developing pragmatic search strategies
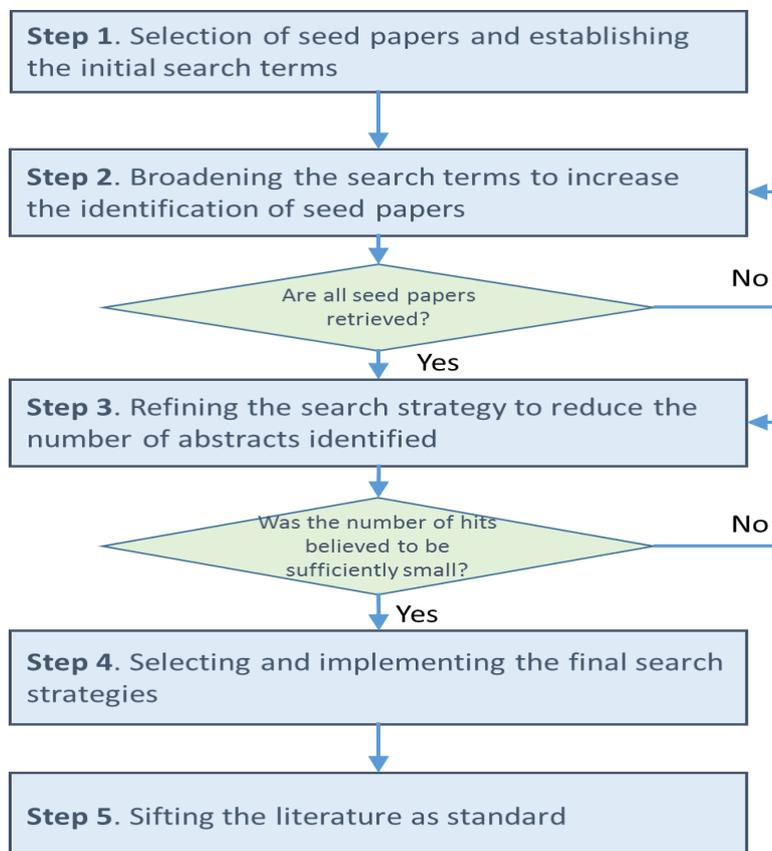
2.2.2. Step 1: Selection of seed papers and establishing the initial search terms

In Step 1, an initial set of papers deemed as key studies in the target literature were identified. These papers were intended to be used as the seeds for subsequent searches aimed at identifying the wider literature of interest and do not represent the totality of the evidence available.

The search terms for the initial searches involved the main elements of the search question: ageing and healthcare demand (including healthcare needs and utilisation). The synonyms of the two elements were developed separately and all the terms in each category were combined with the Boolean operator 'OR'. Then, the two sets of terms were combined using the Boolean operator AND within selected databases. Table 2.1 shows both free-text terms and MeSH headings that were likely to be relevant. The MeSH headings were selected as part of initial key terms as the Medline database was used for scoping searches. Adaptations were made to the included MeSH headings for searches in other sources such as EMBASE and Google Scholar.

Table 2.1. Search terms

Ageing terms	Healthcare demand terms
MeSH headings	
Aging	Health Expenditures
Aged	Health Care Costs
"Aged, 80 and over"	"Delivery of Health Care"
Frail Elderly	"Health Services Needs and Demand"
Health Services for the Aged	Health policy
Population Dynamics	Long term care
Adult, older	Hospitals
Life Expectancy	"Cost of Illness"
Longevity	Hospitalizations
	Nursing homes
	Health Services Research
Free text terms	
("Population ag?ing")	(health?care.ab,ti.)
(ag?ng.ab,ti.)	
(older.ab,ti.)	
(elder$.ab,ti)	
("Proximity to death")	

The method of identifying a set of seed papers was as follows. The initial ad-hoc searches using the terms in Table 2.1 and recommendations from researchers experienced in policy analysis and systematic reviews identified relevant literature. Related papers were then obtained via citation searching. The searches were supplemented by alternative methods of "snowballing" via reference list checking and using personal knowledge and/or contacts. Papers were considered for inclusion in the set of seed papers based on whether their inclusion: increased the range of relevant subject matters discussed; broadened the range of sources of papers; and raised the level of cross-reference within the seed papers set indicating their impact on the other research. In order to enhance the coverage of the seed papers, when a new strand of the literature was found within the seed papers, further literature was searched and examined for inclusion. The search was stopped when data saturation was deemed to be at an acceptable level, i.e. additional literature identified did not add to the existing set in terms of the subject, methodology or source of data (Booth, 2010). Subject headings assigned to these seed papers were also used to complement the initial search terms to establish a more comprehensive collection of terms. The above methods resulted in an

initial set of twelve seed peer-reviewed journal papers (Zweifel et al., 1999, Lloyd-Sherlock, 2000, Spillman and Lubitz, 2000, Reinhardt, 2003, Schulz et al., 2004, Seshamani and Gray, 2004a, Borger et al., 2006, Payne et al., 2007, Werblow et al., 2007, Hakkinen et al., 2008, Palangkaraya and Yong, 2009, Caley and Sidhu, 2011).

The details of these papers including the rationale for inclusion are shown in Table 2.2 and are listed in chronological order. Hereafter, these twelve papers are referred to as the seed papers.

Table 2.2. The initial set of seed peer-reviewed journal papers

Studies	Source	Summary	Rationale for inclusion
Zweifel et al. (1999)	Medline keyword search using the term 'proximity to death'	Claims that health care expenditure (HCE) may depend on remaining time to death rather than calendar age. Statistical analysis was conducted using HCE data of deceased Swiss individuals.	An early study claiming 'proximity to death' rather than age itself is a determinant of HCE.
Lloyd-Sherlock (2000)	Pubmed search for review papers using the term 'population ageing and policy'.	Highlights key issues arising from population ageing. Outlines patterns of ageing and their implications for policy in different settings.	Policy related paper.
Spillman and Lubitz (2000)	Cited in ENEPRI 2006 and Werblow et al. (2007).	Estimates total national healthcare expenditures according to the age at death. Simulates expenditures using demographic projections of two cohorts: people turning 65 in 2000 and those turning 65 in 2015.	An early study on long-term care spending using Medicare data.
Reinhardt (2003)	Citated in ENEPRI (2006).	Argues that the impact of ageing on US healthcare demand will be small, as the ageing is too gradual to be ranked as a major cost driver.	Summary of expenditure studies. US survey based simulation results.
Schulz et al. (2004)	Cited in ENEPRI (2006).	Estimates the isolated ageing effect on utilisation (not expenditure) in hospital and LTC sectors using German data. 'Static ageing approach' is used. Also estimates the share of potential informal carers to be required in the future.	Supply-side projections of HCE are made. European datasets used.
Seshamani and Gray (2004a)	Cited in Werblow et al. (2007).	Raises methodological concerns on the method used in the paper by Zweifel et al.(1999); Discusses appropriate methods for model-based cost projections.	Discusses methodological issues. UK data.
Borger et al. (2006)	Google scholar using the term 'projection of healthcare demand'	Reports US Centres for Medicare and Medicaid Services (CMS) projection results. Makes projections of future private and public healthcare spending by sector (e.g. LTC). The main topic is not ageing. However, the effect of population ageing on LTC spending is mentioned.	No age-related MeSH terms assigned. Searches to identify this may help expand the search to other relevant papers.
Payne et al. (2007)	Cited in a recent paper by Caley and Sidhu (2011)	Reviews the 'cost-of-dying' studies comparing HCE for the deceased with HCE for survivors and the 'time-to-death' studies modelling changes in expenditure as death approaches; Examines the relationships between age, mortality, and morbidity among the elderly and time trends of those relationships.	A review of studies examining the relationship among HCE, age and death. A summary of methods used in existing models.

Werblow et al. (2007)	Google search using the terms 'ageing and health care expenditure'	Estimates the effect of age on HCE using Swiss sickness fund data. Investigates whether 'proximity to death' rather than age *per se* is a significant determinant of all components of HCE.	An estimate of the effect of age on HCE.
Hakkinen et al. (2008)	Pubmed search for articles 'related to' Werblow et al. 2007.	Tests the 'proximity to death' claim on different components of HCE using Finnish data. Also investigates the effect of income.	A summary of relevant methodological issues.
Palangkaraya and Yong (2009)	Web of Science^{SM} title search using the term 'health care demand'.	Suggests that population ageing may not be the main driver of health expenditure at the aggregate level. Evaluates the impact of 'known' factors using country-level OECD data.	Different methodological approach deriving a demand function based on economic theory.
Caley and Sidhu (2011)	Medline search using the keywords 'aging' and 'healthcare demand'	Compares three models for estimating future healthcare costs using i) current age-specific expenditure, ii) morbidity postponed to a later point in life, and iii) morbidity compression or expansion.	Use of routinely available UK data. Recent paper.

2.2.3. Step 2: Broadening search terms to increase the identification of seed papers

The initial phase of the exploratory searches was aimed at identifying as many of the seed papers as possible. A search strategy would be deemed acceptable only if all the seed papers were identified.

 The performance of a small number of key search terms in identifying the seed papers was tested with terms incrementally added in an attempt to identify all of the seed papers in the database. Using the terms previously specified in Step 1 (Section 2.2.2), various limits, subheadings, and focus/explode options were explored to identify pragmatic search strategies. The process of adding and/or broadening search terms was continued until all the seed papers within the database were found, or it became apparent that a supplementary search would be required to identify the missing papers as they were not identified despite broad searches and a large number of identified records.

2.2.4. Step 3: Refining search terms to reduce the number needed to read (NNR)

Once all seed papers were identified, subsequent steps involved refining the search strategies to reduce NNR. The refinement of the search strategies (with specific search terms added and/or removed) was made iteratively until it was deemed no substantial reduction could be made in NNR unless it was at the expense of identifying a seed paper.

It was possible that iteratively amending the search terms when attempting to increase precision resulted in a local (the best among the strategies tried), rather than global (the best possible) optimum. To counter this possible limitation, once an initial 'optimal' strategy was identified, a secondary search strand with different initial search terms was conducted (only within Medline and EMBASE) to determine if a fewer NNR whilst maintaining high coverage could be found.

2.2.5. Step 4: Selecting and implementing the final search strategies

The process of developing pragmatic search strategies was illustrated using five databases: Medline (1948 – November 2011); EMBASE (1980– November 2011); EconLit (1961 – October 2011); Applied Social Sciences Index and Abstracts (ASSIA) (1987 – November 2011); and CINAHL (1982- November 2011). These were searched independently. EconLit, ASSIA, and CINAHL were also included as this group contained one of the seed papers (Palangkaraya and Yong, 2009) which was not available in either Medline or EMBASE.

The final search strategy for each database was typically determined as the search that identified all the seed papers with the fewest hits. Where wider search strategies had potential to identify a different section of the literature and did not increase NNR excessively, these were retained at the discretion of the reviewer for comprehensiveness.

The search results from individual databases were combined and then de-duplicated, and the combined results were sifted as standard. This was done only for the final search strategies as the time required to do this for all interim search strategies would have been considerable.

2.2.6. Step 5: Sifting the literature as standard

The literature identified from the final searches was sifted as in standard systematic literature reviews. The output of the sifting process is reported in Chapter 3 in detail. Summary statistics are provided in this chapter.

2.3. Implementation of the search method

A detailed account of how the method described earlier was implemented is given for each of the databases considered in this section. The final search results obtained using this method are summarised at the end of this section. All exploratory searches were conducted between the 21st November 2011 and the 13th December 2011.

2.3.1. Implementing Steps 1-3: Selecting seed papers, and broadening and refining the search strategy

MEDLINE searches

A summary of all exploratory search results and the corresponding full search statements are given in Table 2.3 and Appendix 2.1, respectively. Table 2.3 shows which of the seed papers in Table 2.2 were identified from each search. One of the 12 seed papers (Palangkaraya and Yong, 2009) was unavailable in Medline, but was included in the table for comparability with tables for other databases.

The initial phase of the exploratory searches involved increasing coverage. A small number of search terms were first used to see whether they identify the seed papers (Searches 1-2). These narrow 'focussed' searches involved limiting part of search terms specified in Table 2.1 to records where the term was the major concept of the study while including free-text terms related to ageing. As these 'focussed' searches failed to provide high coverage, searches were widened by using broader terms and adding more ageing- and healthcare-related terms to identify more of the seed papers (Searches 3-5). Additionally, some subject headings assigned to the seed papers regarding the utilisation of long-term and hospital care services were added to Search 5. As these improved the number of the seed papers identified, all search strategies following Search 5 used these terms.

All of the initial searches failed to identify one of the seed papers by Borger et al. (2006). This was due to the main topic of the paper not being population ageing but the projection of future healthcare expenditure. A supplementary search (detailed later) was conducted to

further identify papers discussing future healthcare demand but not necessarily focussing on ageing issues. This supplementary search to identify the Borger et al. study (Borger et al., 2006) combined two MeSH terms – Health Expenditures/ AND Forecasting/ - and produced 613 records (accessed on 01 December 2011). The final search strategy involved combining these results from the supplementary search with the main search output with the Boolean operator OR.

The subsequent steps involved refining the search strategy to improve precision and thus, fewer NNR than the 22,771 identified by Search 5. Although this resulted in a lower coverage in some cases (Searches 6-7), there was generally a marked reduction in the NNR depending on the terms included and limiters/sub-headings applied (see Appendix 2.1). The exclusion of the 'health policy' term reduced the number retrieved while maintaining the high coverage of the seed papers. As the use of focussed terms in Search 10 may have caused relevant studies indexed differently from the seed papers to be missed, Search 11 used similar, but non-focussed terms. However, Search 11 increased the NNR by more than 2000 with no increase in coverage. Search 10 identified all 10 papers contained in Medline with fewest number of records (n=4,188).

In order to reduce the possibility of identifying a local optimum, an alternative attempt at improving precision was undertaken. Search 12 involved broadening ageing- and/or healthcare-related terms used in Search 4 – a strategy that achieved relatively high coverage with a moderate number of hits – by adding keywords identified in the literature from previous searches. Search 13 was based on Search 12 with added terms associated with increased life expectancy. Terms effective in identifying more papers in Searches 5-11 were added to Search 4 to yield Search 13. Finally, additional attempts were made to combine sets of good search strategies – Searches 10-11 and 12-13 – with varying levels of breadth of search terms (Searches 14-17). Whilst Searches 10-17 each detected all 11 available seed papers, Search 16 in combination with the 613 hits from the supplementary search was chosen as the final search strategy due to the fewest hits (n=4,407).

Table 2.3. MEDLINE search results (Access date: 01 Dec. 2011; Database: Ovid MEDLINE(R) 1948 to November Week 3 2011)

No.	Search details	Seed papers												Number of hits	Number of seed papers identified (coverage)
		Zweifel et al. 1999	Lloyd-Sherlock 2000	Spillman and Lubitz 2000	Reinhardt 2003	Schulz et al. 2004	Seshamani and Gray 2004	Borger et al. 2006	Payne et al. 2007	Werblow et al. 2007	Hakkinen et al. 2008	Palangkaraya and Yong 2009	Caley and Sidhu 2011		
	Availability:	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	**Max.= 11**	
1	Narrow search using focussed ageing terms	√	x	x	x	x	x	x	x	√	√	NA	√	729	4 (36%)
2	Narrow search with focussed HC[†] terms	√	x	√	x	x	√	x	√	√	√	NA	√	7578	7 (64%)
3	Broad ageing and HC terms	√	√	√	√	x	√	x	√	√	√	NA	√	29673	9 (82%)
4	Broad title & abstract search for age terms & focussed HC terms	√	√	√	√	x	√	x	√	√	√	NA	√	4442	9 (82%)
5	Broad age & HC terms with long-term and hospital care terms added	√	√	√	√	√	√	x	√	√	√	NA	√	22771	10 (91%)
6	As Search 5, but no Aged/ term	√	√	x	√	√	√	x	√	√	√	NA	√	6408	9 (82%)
7	As Search 5, but more specific HC terms, hence similar to Search 4	√	√	x	√	√	√	x	√	√	√	NA	√	4361	9 (82%)
8	As Search 7, but with '*Longevity' added	√	√	√	√	√	√	x	√	√	√	NA	√	4391	10 (91%)
9	As Search 8, but with *Aged/ or *Health Services for the Aged/ added	√	√	√	√	√	√	x	√	√	√	NA	√	5585	10 (91%)
10	As Search 9, but no health policy term & with Life expectancy term added	√	√	√	√	√	√	x	√	√	√	NA	√	4188	10 (91%)
11	As Search 9, but no health policy term with broader other HC terms added	√	√	√	√	√	√	x	√	√	√	NA	√	6445	10 (91%)
12	As Search 4, but broader age & HC terms	√	√	√	√	√	√	x	√	√	√	NA	√	4804	10 (91%)
13	As Search 12 but with 'longevity & life expectancy' added	√	√	√	√	√	√	x	√	√	√	NA	√	5330	10 (91%)

No.	Search details	Seed papers												Number of hits	Number of seed papers identified (coverage)
		Zweifel et al. 1999	Lloyd-Sherlock 2000	Spillman and Lubitz 2000	Reinhardt 2003	Schulz et al. 2004	Seshamani and Gray 2004	Borger et al. 2006	Payne et al. 2007	Werblow et al. 2007	Hakkinen et al. 2008	Palangkaraya and Yong 2009	Caley and Sidhu 2011		
	Availability:	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	**Max.= 11**	
14	Broad combination of Searches 11 and 13 (HC terms from 11 & ageing terms from 13)	√	√	√	√	√	√	x	√	√	√	NA	√	8873	10 (91%)
15	As Search 13, but with broader terms	√	√	√	√	√	√	x	√	√	√	NA	√	5770	10 (91%)
16	Narrow combination of Searches 11 and 13 (HC terms from 13 & ageing terms from 11)	√	√	√	√	√	√	x	√	√	√	NA	√	3860	10 (91%)
17	As Search 16, but with broader age terms	√	√	√	√	√	√	x	√	√	√	NA	√	5442	10 (91%)

√**:** Included; X: Not included; NA: Not available in the database; HC: healthcare.

EMBASE searches

The full strand of search results and the search statements for EMBASE are available in Appendix 2.1. Two of the seed papers (Palangkaraya and Yong, 2009, Caley and Sidhu, 2011) were not available in EMBASE. The initial broad search retrieved all but one of the included seed papers (Borger et al. (2006)) but produced greater than 20,000 hits (Search 1). It was judged that wider searches which could retrieve this paper would produce too many hits to be practical.

Initial attempts to reduce NNR using a limited number of ageing- and healthcare-related terms found only slightly more than half of the seed papers. Searches where the 'health care cost' term was focussed (Search 5) failed to detect the paper by Reinhardt (Reinhardt, 2003). Hence, subsequent search strategies were designed to incorporate the broader health care cost term. The most effective of those efforts was to remove the term 'older' from title and abstract searches (Search 11). This reduced NNR without a loss of coverage.

As in the Medline searches, all of these searches missed the same paper - Borger et al. (Borger et al., 2006). A separate search combining the EMTREE terms *"health care cost"/ and forecasting/ using the 'AND' operator produced 566 records (accessed on 01 December 2011) identified the Borger et al. study. When the results from Search 11 were combined with this complementary search, the stand-alone results of 3,584 records increased to 4,112 records.

The EMBASE search strategy that identified all available seed papers with the smallest number of results (Search 11 in conjunction with the supplementary search) was proposed for the final search.

EconLit, ASSIA, and CINAHL databases

As the projection of healthcare demand has significant economic and policy implications, the EconLit, ASSIA and CINAHL databases were also searched. Although these databases contained few of the seed papers, this search result was combined with results from other databases for greater inclusivity and identified one of the seed papers that the others did not (Palangkaraya and Yong, 2009).

The search results from, and relevant search strategies for, these databases can be found in Appendix 2.1, respectively.

In EconLit, free text searching in the title, abstract and keyword fields was performed due to lack of subject indices equivalent to the MeSH terms. Although only five of the seed papers were available in the database, both broad and narrow free-text searches successfully identified all of those available. As this database excludes purely clinical papers, most of the retrieved documents appeared to be more relevant to the research topic compared with those from other databases. A simple search using 'ageing or aging' AND 'healthcare or health care' identified all five studies and the number of records was 159 (accessed on 21 November 2011). However, from the experience of further identifying papers by Schulz et al. (2004) and Spillman and Lubitz (2000) in Medline by adding the terms 'long-term care' and 'longevity', a search statement more comparable with the Medline searches was established (Search 4). This would allow a more comprehensive search including relevant papers that might have been missed in the simple search due to the small number of seed papers available in the database. The resulting Search 4 produced 542 records (accessed on 13 December 2011).

In the ASSIA database, relevant subject headings similar to those used for Medline searches were identified using the 'thesaurus' function. The mapped ageing terms were then combined with the healthcare-related terms identified in the same manner. Varying the number of subject headings included in the two categories of terms did not materially alter the search results: both broad and narrow searches identified all five articles available in the database and produced very similar numbers of hits. As with the EconLit search, a more comprehensive search strategy was chosen as the additional workload implication was not significant.

The CINAHL database was searched using free-text and MeSH terms where possible. The comprehensive use of ageing and healthcare terms produced 1334 records, of which 752 records were studies on humans written in English and 357 were non-Medline records. No more attempts were made to reduce NNR as the 752 records were not considered excessive.

2.3.2. Implementing Step 4: Selecting and implementing the final search strategies

The iterative process of broadening and subsequently refining search strategies for each of the databases included resulted in 7745 hits after de-duplication within and across all databases. A summary of the final search results from the selected search strategies is provided in Table 2.4. All of the selected final search strategies had coverage of 100% at identifying the seed papers available within the database. The final search strategy used for MEDLINE is reported in Table 2.5. Details of the final searches for other databases can be found in Appendix 2.2.

Discrepancies in the numbers reported in Tables 2.3, Appendix 2.1 and Table 2.4 are due to the final searches being undertaken at a later date than the exploratory searches. Additionally, the application of the language and subject heading limits considerably reduced NNR.

Duplicates were first removed within each of the databases and subsequently across all five databases (both using the automated function within reference managing software (Endnote X3, Thomson Reuters) and manually), resulting in the final number of retrieved records totalling 7745. It is noteworthy that only 12% (= 1063/8808) of hits were removed as these papers had already been identified in a separate database, implying that there was not a considerable overlap between databases due to the diffuse nature of the literature on this topic.

Table 2.4. Final search results from peer-reviewed journal databases (Search date: 19 Jan 2012)

Database	Results	Results after de-duplication
MEDLINE	3731	3713
EMBASE	3052	3031
EconLit	549	548
ASSIA	757	757
CINAHL	760	759
Total for all databases	**8849**	**8808**
Total (after de-duplication across all databases)		**7745** (1063 further removed from de-duplication across all databases)

Table 2.5. Final search strategy for MEDLINE

MEDLINE <1946 to January Week 2 2012> (accessed on: 19 January 2012)
1   "proximity to death".mp. (64)
2   older.ab,ti. (200935)
3   *Aging/ (101582)
4   *Population Dynamics/ (7148)
5   Life Expectancy/ (12347)
6   *Longevity/ (6274)
7   ag?ing.ab,ti. (105283)
8   1 or 2 or 3 or 4 or 5 or 6 or 7 (354785)
9   Health Care Costs/ (22138)
10   Hospitals/ut [Utilization] (2816)
11   Long-Term Care/ut [Utilization] (323)
12   *"Health Services Needs and Demand"/ (13692)
13   "Delivery of Health Care"/ec, lj, ma, mt, og, st, sn, sd, td, ut [Economics, Legislation & Jurisprudence, Manpower, Methods, Organization & Administration, Standards, Statistics & Numerical Data, Supply & Distribution, Trends, Utilization] (30683)
14   Health Expenditures/ec, lj, sn, sd, td [Economics, Legislation & Jurisprudence, Statistics & Numerical Data, Supply & Distribution, Trends] (5469)
15   9 or 10 or 11 or 12 or 13 or 14 (71870)
16   8 and 15 (**3814**)
17   Health Expenditures/ (11889)
18   Forecasting/ (64816)
19   17 and 18 (603)
20   16 or 19 (**4353**)
21   limit 20 to (english language and humans) (**3731**)

2.3.3. Implementing Step 5: Sifting the literature as standard

Although more details will be available in Chapter 3, the sifting of the 7745 hits resulted in 891 relevant papers at the title and abstract level. A significant improvement in precision was achieved compared with the broad search. If it is assumed that all 891 papers were identified within the broad Medline search (Search 5), the precision was improved from approximately 4% (891/22771) to 11.5% in the final search (891/7745). Moreover, this broad search did not identify Borger et al. (2006).

The improvement was also made in terms of time: including the extra time taken for a single reviewer to identify the seed papers (2 weeks), and conduct the exploratory searches using Steps 1-4 (2 weeks) and supplementary searches (3 days), but excluding the time taken to develop the inclusion and categorisation criteria (2 weeks – see Chapter 3), the total sifting

time for the final search results of 7745 papers was approximately 3 months, assuming 22 working days of 8 hours each month. This compares with 5.2 months, the estimated time that would have been taken to sift 22,771 papers identified from the Medline Search 5. This was calculated on the assumption that one reviewer sifts all papers and the sifting rate is 200 papers per day for 22 working days per any calendar month. These values were established based on the reviewer's experience acquired whilst sifting the results from the pragmatic search. The estimated time saved was 2.2 months in the review for this thesis. However, this could vary by topic of the review, sifting methods, the number of papers identified from searches constructed with and without the pragmatic approach, and reviewers' experience.

It is noted that additional themes in the literature outside of those that were the focus of the seed papers were identified such as: models projecting future health and social care expenditure (146 papers); policies and interventions intended to tackle the issues of ageing population (251 papers); trends in healthcare expenditure (67 papers); and major disease areas for an ageing population (155 papers).

2.4. Grey literature search

Relevant literature is likely to be located in policy documents and within the grey literature arena as population ageing has significant implications for health and social policy, which is of interest to bodies such as national governments, international organisations and industry. Hence, web pages of such organisations and grey literature databases deemed to be relevant were hand-searched via free-text scanning of title and abstract or executive summary. Information on grey literature sources with the description of search fields targeted within each information source is available in Table 2.6. The focus of the search was on the identification of key up-to-date literature that might not be captured by the conventional literature searches.

Table 2.6. Grey literature sources

Organisation/ Database	Web link	Website information	Search fields	Search methods
Age UK - Knowledge Hub	http://www.age uk.org.uk/profes sional-resources-home/knowledg e-hub-evidence-statistics/publica tions/	The knowledge hub within the Age UK website provides access to the findings of UK and international research on older people.	All publications with more focus on Evidence reviews (more in-depth reports providing evidence for decision making)	Free text searching for 'healthcare' and 'expenditure/co st'.
Centers for Medicare and Medicaid (CMS), US	http://www.cms. hhs.gov/home/rs ds.asp	The website provides access to selected reports from CMS research programmes conducted in-house or via research contracts.	The Research, Statistics, Data & Systems section.	Free text scan of titles of all research programmes.
Comprehensiv e Research Group in Operational Research, Management Science and Information Systems (CORMSIS) University of Southampton	http://www.soto n.ac.uk/maths/re search/projects/ healthcare_mod elling.page	The CORMSIS Health Care webpage provides brief information on PhD projects being conducted on modelling healthcare.	Health Care section within the CORMSIS website.	Free text scan of all projects.
Congressional Budget Office (CBO, US)	http://www.cbo. gov/publications /bysubject.cfm?c at=9	The US CBO publishes budget reviews, economic outlook reports, and reports on various issues including education, environment, housing, government management, etc.	All 'health' publications from 2005 were searched.	Free text scan.
Department of Health	http://www.dh.g ov.uk/en/Publica tionsandstatistics /index.htm	The website is intended to enable NHS and social care professionals to find information about policy and to receive guidance and advice on best practice.	All publications.	Search using the terms 'ageing healthcare demand expenditure' while limiting records to ones

				containing 'ageing' within summary.
Economic and Social Research Institute (ESRI, Ireland)	http://www.esri.ie/publications/search_for_a_publication/ http://www.esri.ie/UserFiles/publications/20091023164031/RS013.pdf	The ESRI produces research that contributes to understanding economic and social change in the new international context and that informs public policymaking and civil society in Ireland.	All publications with focus on Working papers.	Keyword search using the term 'ag(e)ing'.
European Commission - Directorate General for Economic and Financial Affairs (DG ECFIN)	http://ec.europa.eu/economy_finance/publications/index_en.htm http://ec.europa.eu/economy_finance/structural_reforms/ageing/index_en.htm	DG ECFIN aims to improve the economic wellbeing of the EU citizens. It produces reports on EU policies and relevant issues.	i) Economic Publications section. (Types of reports searched: European Economy-Economic Papers, Occasional Papers, ECFIN Economic Briefs) ii) Ageing and Welfare state policies section.	Free text scan of titles of all papers within the search fields.
European Network of Economic Policy Research Institutes (ENEPRI)	http://www.enepri.org/	The ENEPRI brings together 23 national economic policy research institutes from most of the EU countries. It provides information on various projects regarding demography, ageing, and health and social care.	i) Research Reports section. ii) Webpage of the AHEAD project (Ageing, Health Status and Determinants of Health Expenditure).	Free text scan of all Research reports titles.
FUTURAGE PROJECT	http://futurage.group.shef.ac.uk/	FUTURAGE is a two-year project funded by the European Commission, under the Seventh Framework Programme, to create the definitive road map for ageing research in Europe for the	Consultation reports (aimed to identify research priorities) Workshop	Free text scan of all report titles & summary within the search fields.

		next 10-15 years.	reports Documents related to Healthy ageing theme.	
Health, Econometrics and Data Group (HEDG), University of York	http://www.york.ac.uk/res/herc/research/hedg/wp.htm	The aim of HEDG is to provide expertise in the development and application of quantitative research methods capable of informing health policy. It publishes journal articles and a number of working papers.	Working papers.	Free text scan of all titles and abstracts.
Health Management Information Consortium (HMIC) database	gateway.ovid.com/	The HMIC database brings together the bibliographic database of two UK health and social care management organizations: the Department of Health's Library and Information Services (DH-Data) and King's Fund Information and Library Service.	HMIC (1979 to Jan. 2012)	Search terms used in Medline search 16 were mapped to HMIC headings. (Search terms used include 'Ageing', 'Population Dynamics', 'health expenditure', etc.)
HM Treasury, UK	http://archive.treasury.gov.uk/	Web page of the UK's economics and finance ministry.	All sections of the HM Treasury main website and the archive.	Title search in all sections. Advanced search for 'Documents' using the terms 'ageing' and 'healthcare'
House of Commons Health Committee	http://www.parliament.uk/business/committees/committees-a-z/commons-select/health-committee/	A web page within the UK Parliament website for Health Committee, one of the 19 Select Committees related to UK government departments.	Reports, Special Reports, and Written Evidence sections (2005-current).	Free text scan of all reports in the search fields.
National Bureau of Economic	http://www.nber.org/papers/	The NBER is a private, non-profit, economic research organization. The website	Working papers and other publications	1. Working paper search using the terms

		provides access to a large number of working papers, many of which are on fiscal policy, pension reform, and effect of insurance on healthcare utilisation.	listed on the website.	'ageing health?care demand'. 2. Full-text search using 'population aging health care demand utilization'. 3. Title search using 'aging'.
Research (NBER), US				
NatCen Social Research, UK	http://www.natcen.ac.uk/our-research/health-and-lifestyle/ageing	British research centre for independent social research.	All documents in the Health and Lifestyle - Ageing research section.	Free text scan of all available reports.
National End-of-life care intelligence network (NEoLCIN)	http://www.endoflifecare-intelligence.org.uk/resources/publications/default.aspx	The NEoLCIN, supported by the Department of Health's National End of Life Care Programme, aims to improve the collection and analysis of information related to the quality, volume and costs of end of life care provided by the NHS, social services and the third sector.	All End-of-life models.	Free text scan.
NHS Evidence & NICE	http://www.evidence.nhs.uk	NHS Evidence provides access to selected, quality health and social care evidence. It brings together hundreds of information sources including the Cochrane Library, NICE, Scottish NHS, Royal Colleges and HTA databases.	Types of information searched: i) Systematic reviews, ii) Evidence Summaries, iii) Grey Literature, iv) Primary Research, v) Policy and Service Development, and vi) Health Technology Assessments.	Search terms: "projection healthcare demand ageing population" and search filters for selected types of information were applied. More specified terms used due to the wide coverage of the database.
Nuffield Trust	http://www.nuffieldtrust.org.uk/p	An independent source of evidence-based research	All publications (2000-current).	Search terms: 'ageing' term.

	ublications/predicting-social-care-costs-feasibility-study	and policy analysis for improving health care in the UK. The publications list covers research reports, conference proceedings, etc.		Free text scan of lists of all publications since 2000 was scanned.
Organisation for Economic Co-operation and Development (OECD)	http://www.oecd.org/publications/0,3353,en_2649_201185_1_1_1_1_1,00.html	The website contains OECD publications including Outlooks, Country Surveys and statistics. It provides links to reports on a wide variety of topics including healthcare.	OECD iLibrary.	Search terms: 'ageing/aging' AND 'healthcare'.
Oxford Institute of Population Ageing	http://www.ageing.ox.ac.uk/publications	The Institute undertakes research into the implications of population change.	All Working papers and articles published in a review journal, Ageing Horizons (2004-2010).	Free text scan of all documents in the search fields.
Personal Social Services Research Unit (PSSRU)	http://www.pssru.ac.uk/search.htm	The PSSRU has branches in three UK universities, carrying out independent research on social and health care services.	Discussion papers.	Search terms used: 'projection', 'demand', and/or 'ageing'.
RAND Corporation	http://www.rand.org/health/projects/compare.html http://www.rand.org/labor/roybalhp/projects/health_status/fem.html	A non-profit research institution that aims to improve policy and decision-making on health, education, national security, international affairs, law, business, etc. The website contains information on various specialised research centres and projects within RAND.	1. General search of all publications. 2. By research area: i) Health and Health Care, ii) Population & Aging 3. By research group: i) RAND Roybal Center for Health Policy Simulation, ii) Comprehensive Assessment of Reform Efforts (COMPARE) project	1. Search terms: "ag(e)ing". 2. Free text scan of 'Reports' titles under the two research areas i) and ii). Also, RAND Health Publications on Health Care Costs. 3. Free text scan of all publications from the two research groups.

Society of Actuaries (SOA)	http://www.soa.org/files/pdf/aging_curves.pdf	The SOA website contains information of actuaries' professional interest such as educational opportunities, and research outputs.	Research Projects on Aging & Long Term Care.	Free text scan of all reports available on the website.
UK Network for Modelling & Simulation in Healthcare (MASHnet)	http://mashnet.info/case-studies/	MASHnet brings together all parties engaged in healthcare modelling and simulation. The website introduces some case studies and provides web links to the relevant models.	'Case Studies' section.	Free text scan of all Case Studies.
World Health Organisation (WHO)	http://www.who.int/publications/en/ http://www.who.int/topics/ageing/en/	The website of WHO, the directing and co-ordinating authority on international health within the United Nations' system contains various publications including health guidelines and standards, and periodical reports such as World Health Report, World Health Statistics, etc.	All publications. Publications categorised under the Health topic - Ageing	i) Free-text search using 'impact/effect of ageing on healthcare demand' ii) Title search using the terms 'ageing or aging'.

The results from the grey literature search are reported in Table 2.7. Reported are the number of records retrieved by applying the search methods described in Table 2.6, and the number of documents identified as potentially relevant among those retrieved in cases where the search retrieved a large number of records or was not easily reproducible due to lack of a search function on the website.

Table 2.7. Search results for grey literature

Organisation	Search date	Search Results – Number of papers identified	Number of papers considered potentially relevant
Age UK - Knowledge Hub	14/02/2012	158 results: Evidence Reviews search using 'healthcare'. 157 results: All publications search using 'expenditure'.	3
Centers for Medicare and Medicaid (CMS), US	13/02/2012	None identified.	0
CORMSIS, University of Southampton	08/02/2012	None identified.	0
Congressional Budget Office (CBO, US)	14/02/2012	17 results: potentially relevant presentations/reports/letters were identified from Health Publication lists.	17
Department of Health	07/02/2012	12 results retrieved.	4
Economic and Social Research Institute (ESRI, Ireland)	08/02/2012	15 results: Keyword search for 'ageing'. 19 results: Working paper search using 'ag(e)ing'.	6
European Commission - Directorate General for Economic and Financial Affairs (DG ECFIN)	08/02/2012	4 results: Projection of healthcare expenditure report (2010) and Ageing reports 2006/2009/2012 were identified.	4
European Network of Economic Policy Research Institutes (ENEPRI)	31/01/2012	103 results: relevant Research Reports.	22
FUTURAGE PROJECT	08/02/2012	None identified.	0
Health, Econometrics and Data Group (HEDG), University of York	08/02/2012	176 results: Working papers accessible on the web page.	6

Health Management Information Consortium (HMIC) database	16/02/2012	649 results: Search results (limited to records published since 2005).	0
HM Treasury, UK	13/02/2012	3 results: 2 Derek Wanless' reports (interim and final) and responses to them, and Public Expenditure Statistical Analyses.	3
House of Commons Health Committee	14/02/2012	6 results: relevant reports identified. Integration of social and health care, workforce planning, etc.	6
National Bureau of Economic Research (NBER), US	08/02/2012	Search 1. 45 results: Working paper search. Search 2. 185 results: 'population aging health care demand utilization'. Search 3. 48 results: Title search using 'aging'.	14
NatCen Social Research	14/02/2012	23 results: Among 23 studies available under the 'Ageing' topic, reports on The English Longitudinal Study of Ageing (Waves 0-4) and the Health Survey for England (2004-2009) were found potentially relevant.	2
National End-of-life care intelligence network (NEoLCIN)	06/02/2012	3 results: End of life care modelling tools identified as potentially relevant.	3
NHS Evidence & NICE	06/02/2012	402 results (overlapped with database searches): Systematic reviews (15), Evidence Summaries (13), Grey Literature (16), Primary Research (171), Policy and Service Development (129), Health Technology Assessments (58)	0
Nuffield Trust	08/02/2012	162 results: Total number of publications since 2000. A search with 'ageing' term found no paper.	5

Organisation for Economic Co-operation and Development (OECD)	09/11/2011	23 papers found relevant.	23
Oxford Institute of Population Ageing	14/02/2012	4 working papers and 6 journal articles were identified as potentially relevant.	10
Personal Social Services Research Unit (PSSRU)	14/02/2012	347 discussion papers available.	9
RAND Corporation	08/02/2012	1. 34 and 2071 results from search using "ageing" and "aging", respectively - RAND Health (193), RAND Europe (22), and RAND Center for the Study of Aging (82). 2. i) Health and Health Care: 896 reports. ii) Population & Aging area: 395 reports. iii) RAND Health Publications on Health Care Costs: 43 records. 3. i) 5 Projects found ii) 2 full-length reports identified.	22 (22 records were identified as potentially relevant from Searches 1-3).
Society of Actuaries (SOA)	08/02/2012	None identified.	0
UK Network for Modelling & Simulation in Healthcare (MASHnet)	14/02/2012	16 results: Total 16 case studies.	4
World Health Organisation (WHO)	14/02/2012	284 results: Title search using "ageing or aging".	8
Total number of papers		**6,313**	**171** **(158 after de-duplication and sifting)**

A total of 158 papers after deleting duplications and sifting were identified as relevant from the grey literature. The inclusion was focussed on 'recent' studies discussing the modelling of health and social care demand or relevant policies – typically those published in or after the year 2000, unless considered to have direct relevance to the topic – on the assumption that the peer-reviewed literature searches of five databases would have already identified other categories of important studies.

2.5. Discussion

The proposed method for developing a pragmatic search strategy to cover a broad topic with a range of themes and methodological approaches was implemented in five databases, and significantly reduced the NNR compared with the broad searches performed at the scoping search stage. The final search strategies selected achieved coverage of 100% and identified 7745 records. This compared with over 29,000 hits in Medline (Search 3) using broad ageing and healthcare terms and over 21,000 hits in EMBASE (Search 1); searches that collectively identified only ten of the eleven seed papers included in these databases and which could not find the paper excluded from these databases.

However, the suggested approach is not without limitations. Intrinsically, the 'heuristic' approach does not guarantee a 'global' optimum, but could identify a 'local' optimum. As subsequent searches are likely to be based on previous search terms, the final search strategy is potentially sensitive to the initial search terms. This could result in identifying a selected set of the literature as papers unlike the seed papers may not be retrieved by this approach. This was partly mitigated in this review by the use of alternative sets of search terms.

Furthermore, the approach may be difficult to use for searching grey literature. The iterative approach may be applicable only to databases that support advanced search functions such as combinations or exclusions of search terms, and be easier to implement in databases using subject indexes. Unlike the established databases for peer-reviewed studies, sources of grey literature often employ diverse and non-standardised indexing mechanisms. As population ageing has significant implications for health and social policy, it is possible that relevant literature is located in policy documents and the grey literature arenas. However, no systematic method of searching grey literature was adopted in this chapter.

Additionally, the method relies on the degree to which the seed papers cover all the key issues required in order to address the research question. If the papers omit some key areas altogether, then it is possible that entire sections of relevant literature would not be identified, and including further seed papers in the search retrospectively can lengthen the review process. Furthermore, it is not possible to know the comparative sensitivity of each exploratory search as the number of relevant papers within the search in addition to the initial seed papers is not known, which makes it difficult to compare the coverage of searches. However, the risks of this can be minimised if the researchers engaging in searches for such a

diffuse topic area: determine in advance the nature of the key issues within the broad area; undertake background work, such as scoping searches, consulting experts, and discussing the research question widely. This allows greater confidence in the selection of a limited number of seed papers. In this case study, efforts were made to ensure the papers covered a variety of relevant disciplines, perspectives and types of publications, to reduce the chances that the initial selection would rule out entire areas of literature. Additional themes were identified in the sifted papers. It is therefore possible that searches that identify all seed papers with a greater number of hits may identify one or more relevant papers not identified in the selected strategy.

A conventional non-iterative subject search without using seed papers may identify papers not identified from the pragmatic search. Supplementary searches as used for MEDLINE and EMBASE databases were needed to identify one of the seed papers not identified in the pragmatic search (Borger et al., 2006). However, given the estimated time saved of 2.2 months, researchers should consider the trade-off between additional papers that may be identified from the conventional approach and the increased time to sift associated with the use of the conventional method. Although the saved time estimate is specific to this case study, it illustrates that the proposed approach provides a potential option for use in diffuse topic areas. When the pragmatic approach is chosen, it is recommended that reference lists from all included papers are checked and citation searching is undertaken for each seed paper identified in order to increase coverage.

Although the generalisability of this approach to other diffuse topic areas is currently unproven, there appears no obvious reason why the proposed approach would not have the potential to deliver similar benefits in terms of identifying relevant literature, reducing the NNR and thus, reducing the time required to sift in other topic areas. Although the actual number of papers required in other topic areas may differ, this would be a matter of judgement in the early stages of exploratory searches and discussion with experts.

Within the healthcare sector, there has been an increasing emphasis on evidence-informed policy. As policy decisions often relate to diffuse and complex questions, the corresponding literature review is likely to require a pragmatic search method to support robust decision-making. Recent literature addressing good practice in search methodologies recommends the adoption of methods that balance precision and coverage i.e. identifying the best available on a given topic without producing an unmanageable volume of results (NICE, 2012); and also

suggests the use of iterative searching when pre-defined search strategies are not directly applicable (Marsh, 2010).

This chapter showed that thoughtfully-designed search strategies can significantly reduce the NNR, whilst identifying a set of seed papers that were deemed to capture the important topics of the target literature. In the review for this thesis, all the seed papers were retrieved and the NNR was substantially reduced using iterative search strategies compared with broad searches. Furthermore, the broad searches did not identify all seed papers despite the considerable number of hits.

CHAPTER 3   OUTCOMES OF LITERATURE REVIEW

3.1. Introduction – Literature Review

In this chapter, the documents retrieved from the literature searches described in Chapter 2 are reviewed to synthesise information available from previous research.

Due to the diffuse subject area and the wide range of the literature potentially relevant to the modelling of health and social care demand, a systematic method and labelling system for categorising the identified literature was established. This chapter reports: **i)** the criteria for selecting studies to be included in the main review; **ii)** separate criteria for selecting supplementary studies to be kept for future reference; **iii)** the system of tagging/labelling used for studies selected in steps i) and ii); and **iv)** the results of applying i) – iii). In addition to the review of the general studies, a review of models for projection of health and social care expenditure which are the primary topic of the literature search is presented.

This chapter also introduces a freely-accessible literature repository containing both the peer-reviewed and grey literature identified in a review of population ageing and health and social care demand, in order to aid others undertaking reviews on related topics. It describes the literature that the repository contains, how it was developed, and how it can be used freely by others to help extract, summarise and categorise such broad-themed literature on population ageing and health and social care demand.

It is expected to be useful for those wishing to undertake horizon scanning at the initial stage of their research. The papers in the repository have been classified under a set of tags showing the main theme of the papers. For instance, if one wishes to explore existing research on a range of factors that may influence health and social care demand in the UK, a retrieval of relevant literature can be achieved by selecting a combination of the most relevant tags set within the repository – e.g. 'factors influencing demand' and 'UK' in this case.

Sections 3.2 and 3.3 cover the review methods including study selection criteria and categorisation; Section 3.4 describes the creation of the literature repository; and Section 3.5 presents the results of the literature review of all studies included and categorised. The results of a review of models projecting future health and social care expenditure, which inform the methods of the models developed for this thesis, are covered in Section 3.6.

3.2. Study selection: Methods to include studies

3.2.1. Studies included in the main review

Inclusion and exclusion criteria were developed separately for studies to be included in the main review and studies that are potentially relevant but not included in the review. All studies identified by the literature search were included to form a larger repository for future researchers, but only a proportion of these studies that were deemed directly relevant to modelling were included in the main review of the thesis. In this review, the primary topics of the target papers included studies estimating the future health and healthcare demand for an ageing population and studies examining the effect of policies or interventions designed to tackle issues arising from population ageing on healthcare demand. Secondary topics included: trend analyses of healthcare spending; the determinants of healthcare spending; and the relationships between health and social care utilisation.

The documents retrieved from the literature searches (n=7745) were sifted based on titles and abstracts in order to select studies relevant to the topic. Due to the broad range of topics contained in the identified literature, the decision process used to determine whether to include or exclude papers was turned into a formal algorithm (Figure 3.1). These study selection criteria were developed simultaneously with the categorisation of studies, as both involved a similar procedure. Hence, Figure 3.1 also shows broad categories of papers. Categorisation was necessary in order to facilitate the development of organised selection algorithms, and quick retrieval and subsequent synthesis of the identified literature. An initial categorisation of study type was conducted by examining randomly selected citations with a view to establishing broad selection criteria based on study types. The initial criteria were expanded to reflect types of information provided by papers or further types of studies that

arose while sifting. The updated criteria were applied retrospectively to the citations sifted earlier for consistency when there were major changes to the selection criteria.

From the initial selection of studies (approximately 300) used to identify broad categories of studies within the literature, studies were classified into two groups: studies informing methodology; and studies informing the parameters that may be required to model health and healthcare demand. Following this, the group of studies informing parameters was further divided into sub-categories according to the relevant component of the model. Amendments to the categorisation of papers were continued until it became apparent that it was unlikely that major changes were needed.

Figure 3.1 was designed to include papers expected to help structure the model to be developed or studies discussing important evidence for modelling health and health services at the population level, and to exclude studies addressing 'specific' or 'non-generalisable' issues associated with ageing and healthcare demand (e.g. studies conducted on a population from a small locality) or providing information of limited applicability. Commentaries and editorials published before 2007 were included only when they discussed issues closely relevant to projection of demand, methodology, and factors influencing demand. General commentaries published after 2007 were more widely included (e.g. those describing any of the issues relevant to ageing and health and social care demand).

It is noted that the criteria were not aimed to identify every study relevant to each category of information, but to identify all available 'modelling' studies directly relevant to the estimation of health and social care demand and to categorise the literature associated with these modelling studies to establish a set of key themes. Developing a set of tags used for more detailed categorisation is described in Section 3.3.

Figure 3.1. Flow diagram of study selection criteria: Characteristics of included and excluded studies in the main review
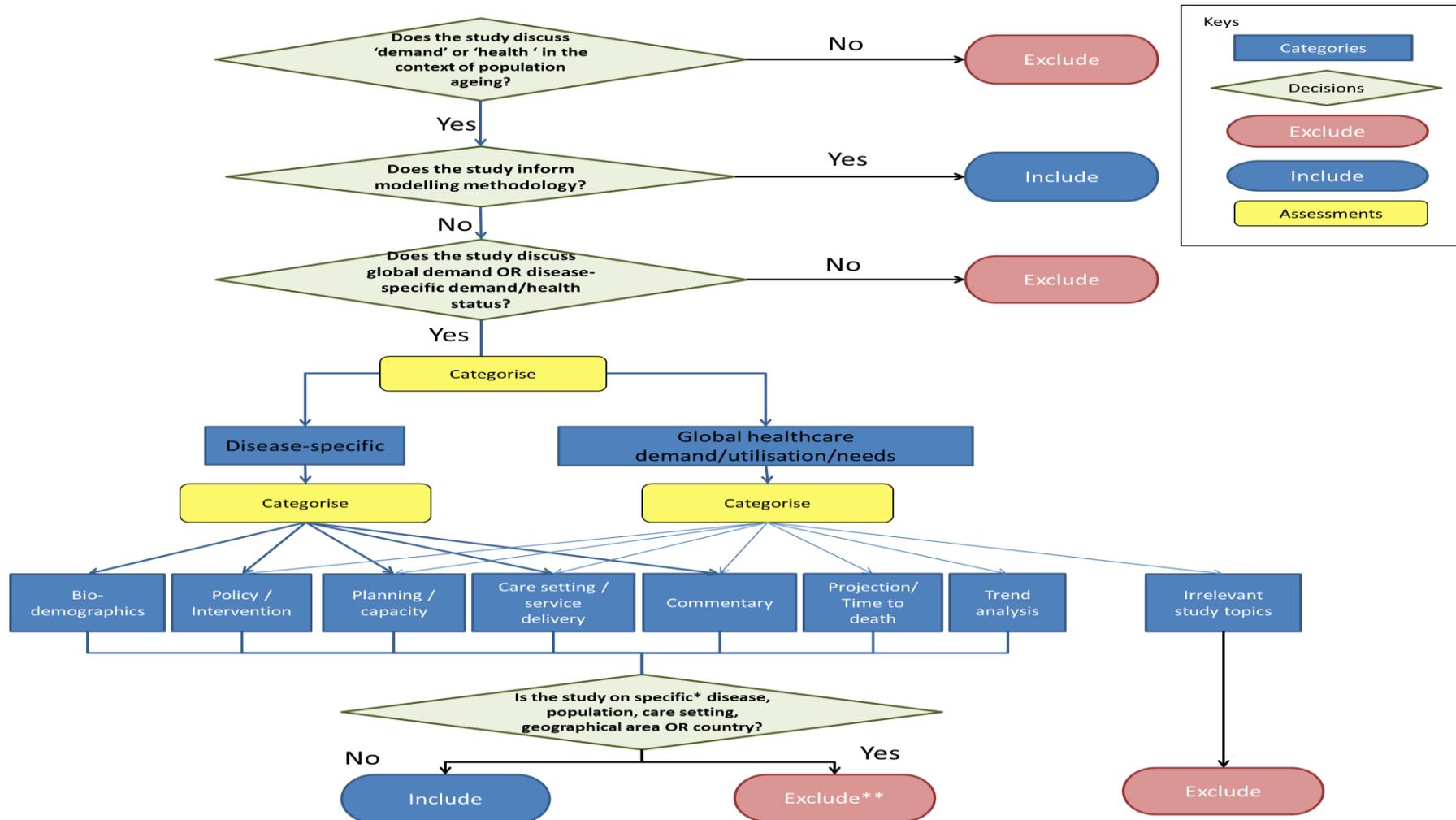
*Specific: of limited applicability due to very narrowly defined disease, population, care setting, geographical area or country, and thus unlikely to have significant impact on health or healthcare demand at a broader population level; **Considered for inclusion in the set of supplementary studies (see Section 3.2.2)

3.2.2. Supplementary studies included in the repository

The focus of the PhD thesis was not fully defined during the initial stage where there existed many potential research questions. As a variety of potentially relevant studies have been identified, it was deemed sensible to keep a subset of papers for future reference. Hence, in addition to the literature for the main review (i.e. papers directly relevant to the modelling of health and social care demand for an ageing population), the remaining identified literature was saved as supplementary set of literature for future reference. As these were thought to be relevant to future researchers, they were also included in the literature repository.

These 'supplementary' studies were set aside, and could be retrieved if it were believed that the paper could contain relevant information for future modelling. Thus, a separate set of inclusion criteria for the supplementary studies was developed – also using an iterative approach – simultaneously with the criteria for selecting studies to be included in the main review. The types of supplementary studies are summarised in Table 3.1.

In general, supplementary studies not included in the main review were those 'broadly relevant' to methodology and/or parameters required to model health and health/social care demand, but on a specific disease, population, care setting, geographical area or country, rather than directly related to modelling health/social care demand. The supplementary studies also involve general background/commentary articles on demand/utilisation, relevant policy and service delivery that may be used for general discussion rather than being incorporated into a model, papers discussing relevant issues specified in the main inclusion criteria but whose impact is anticipated to be limited.

It is acknowledged that the categorisation between studies for the main review and supplementary studies could be subjective. For example, a certain policy adopted in a state of the US may be included in the main review if it can be generalisable to other localities, while a nation-wide US policy may not be included as it is specific to the US system.

Table 3.1. Criteria for supplementary studies that were not included in the main review

Studies informing	Types of supplementary studies
Both Methodology & Parameters	• Cost of illness that is prevalent among the elderly and studies on economic impact of a certain disease • Needs assessment for broad areas of care
Methodology	• Studies discussing relevant projection studies with no analyses of the authors' own (e.g. review). • Methodologies that may be used for some parts of a model but not for the estimation of health or social care demand/expenditure. • Studies describing potentially relevant data sources, but not necessarily within an older population.
Parameters	***Diseases*** • Disease-specific service utilisation; Papers discussing aspects of ageing relevant to health and social care • Transitions between states of major diseases • Cause of death/ place of death studies • Relevant clinical studies showing the relationship between major diseases of the elderly. • Primary research (RCTs) ***Policy & Intervention*** • Disease specific interventions/policy (e.g. treatment pathways for cancer); National policy and managerial issues arising from population ageing • Studies discussing implications of broadly relevant policies and interventions on health and social care (e.g. housing and de-institutionalisation) • Technological progress in elderly care • Financing health and social care • Impact of health insurance coverage on utilisation/ Cost sharing studies/ Risk adjustment/assessment, capitation studies that describe factors influencing global healthcare expenditures. • Studies on certain US interventions e.g. issues related to managed care ***Planning & Capacity*** • Workforce flexibility/capacity in certain types of services for older people • Healthcare system efficiency ***Service delivery & Care settings*** • Links between health and social care for a certain type of service (e.g. integrated care design) • Issues specific to a care setting (e.g. residential care, home help, etc.) • Current status of the elderly care & service delivery system for a specific care type or disease • Determinants of (demand for) informal care provision

3.3. Categorisation of studies – Tagging system

A system of tagging was established in which each item of identified literature was assigned one or more tags representing the information that the paper provided. The tags were: disease area; type of policy/intervention examined; factors that influence healthcare demand; and methodology used. Under the broad tags, sub-tags were created to describe detailed information. By using the same set of tags for both the studies to be included in the main review and those in the supplementary set, all information on a theme could be retrieved simultaneously.

The tagging structure was expanded and updated using an iterative approach. An initial list of tagging terms was established based on the types of studies identified to create the initial selection criteria. Tags were then expanded to describe types of data provided by the study of interest and further types of studies identified while sifting. Also, new or more detailed tags were added if the existing tags did not provide appropriate descriptions of the information expected from the study although the tagging terms were kept as general as possible to keep the number of tags manageable.

The list of tags developed is shown in Table 3.2. Due to the wide range of the studies retrieved, multiple tags were applied to individual records. For example, the combination of the tags 'Service utilisation', 'Disease – mental', and 'UK' would indicate a study analysing the utilisation of mental health services by the UK population.

A hierarchy in the tagging structure was expressed by the use of a hyphen, e.g. 'Disease – cancer' was used to indicate the 'cancer' category within the 'Disease' hierarchy.

'Disease' tags and 'Factors influencing demand' tags were included to identify major disease areas related to population ageing and the determinants of healthcare demand or expenditure, respectively. Disease-related tags were assigned both for broad disease areas (e.g. mental diseases) and for specific disease (e.g. dementia). Also, tags covering a wide range of issues such as 'Factors influencing demand' were further sub-categorised to identify groups of determinants of healthcare demand or expenditure. The combination of the assigned tags may be used to retrieve papers relevant to a specific topic for the synthesis of the review findings and the narrower categories of studies. For example, a combination of 'Trend analysis', 'Global healthcare demand' and 'US' would locate studies on global healthcare demand trends in the US.

The same set of tags was applied to all citations whether they are included, excluded or included in the supplementary set. Some of the excluded items were given a tag describing reasons for exclusion. However, studies were classified differently depending on the anticipated significance of the evidence provided by the study. For example, a study on a national dementia prevention programme with a large participating population may be included in the main review while a similar intervention led by a local authority for a short period of time may be excluded.

Table 3.2. Final tagging structure

I. METHODOLOGY	
Methodology	*Types of analysis*
Methodology[1]	
Projection	Background
Projection - healthcare demand	General[2]
Projection - Long Term Care	Clinical
Projection - retrospective	Commentary
Modelling - other	Conference proceedings
	Primary Research (RCTs)
	Database[3]
	Review
	Time to death[4]
	Local study
	Letter
	Needs assessment
	International comparison
	Trend analysis
	Actuarial analysis
	Economic analysis
	Statistical analysis

II. PARAMETERS	
Diseases and conditions	*Cost analysis*
	Cost analysis
Disease – mental	Cost of illness[12]
Disease – behavioural	
Disease – dementia	*Policy*
Disease – depression	Policy
Disease – delirium	Financing
Disease – neurodegenerative	Workforce and capacity[13]
Disease – neurologic	Insurance[14]
	Political
Disease – cancer	
Disease – colorectal	
Disease – liver	*Intervention*
Disease – pancreatic	Intervention
Disease – renal	Intervention - admin
	Intervention - care pathways
Disease – cardiovascular	Intervention - cost containment
Disease – cerebrovascular	Intervention - effectiveness
Disease – hypertension	Intervention - integrated care
Disease – stroke	Intervention - prevention
	Intervention – technology
Disease – respiratory	
Disease – COPD	
	Relationships between
Disease – diabetes	

Disease – obesity

Disease – disability
Disease – falls[5]
Disease – frailty
Disease – incontinence
Disease – urologic
Disease – learning disabilities
Disease – malnutrition

Disease – musculoskeletal
Disease – osteoarthritis
Disease – osteoporosis
Disease – arthritis
Disease – pain
Disease – sarcopenia

Disease – pneumonia
Disease – sensory (hearing, vision, etc.)
Disease – oral
Disease – multiple[6]

Bio-demographics/Epidemiology of major diseases
Population health status[7]
Bio-demographics[8]

Utilisation/Resource use/Needs/Demand

Global healthcare demand[9]
Service utilisation[10]
Drug expenditure
Factors influencing demand[11]

parameters/Other Topics
Demand and supply
Delivery system
Efficiency
Relationship - health status and care setting
Relationship - health status and demand
Relationship - health status and disease
Relationship - health status and risk factors
Relationship - hospital and social care

Care setting
Community Care
Institutionalisation
Independent living
Home care
Hospital care
Informal care
Long Term Care
Palliative care
Primary care
Social Care
Self care
Residential care
End of life care

Country/Location
Asia
Europe
US
UK
AUS
Canada

1. General methodology; 2. Not only healthcare demand issues, but discusses more general issues including healthcare; 3. Includes self-reported data. Papers discussing data source and data usage; 4. Describes/tests time to death as one of the 'Factors influencing demand'; 5. Includes accidents and injuries; 6. Indicates co-morbidity; 7. Specific or general health states of population of interest; 8. Includes mortality, life expectancy, fertility issues; Epidemiological studies; Population dynamics. Also, includes transition/disease progression issues; 9. To distinguish from demand for a certain type of healthcare, represent demand relevant to a whole sector of healthcare; 10. Utilisation of specific type of healthcare; 11. Broad tag for studies discussing factors determining demand (global healthcare demand, or long term care). Demand also includes demand, cost, expenditure, and utilisation. Anything that may affect the health and social care 'expenditure' or 'demand' (not health status itself);
12. Burden of illness studies; 13. Includes planning issues; 14. Includes cost-sharing issues

3.4. Forming a literature repository

As part of the review output, a literature repository was established. Both studies included in the main review and those tagged as supplementary were included in the repository. The purpose of the repository is two-fold: first to ensure retrieval of papers on issues that may emerge as important to the models developed for this thesis; and second, given the considerable effort required to identify and classify the diffuse literature, the repository provides a useful resource for those researching the topic of ageing and healthcare. The repository is thought to be particularly useful for those who are at an early stage of research regarding ageing and healthcare demand and wish to quickly retrieve relevant literature. Section 3.5.4 will describe the method of accessing and using the repository.

3.5. Results of the literature review

3.5.1. Study selection

The series of decisions shown in Figure 3.1 were followed to categorise the studies according to the type of information they provide. Studies informing 'Methodology' included i) studies estimating the future health and healthcare demand of an ageing population; ii) studies that are not directly on healthcare demand projection but whose methodology and underlying concepts may be applicable to other models; and iii) studies examining the effect of policies or interventions designed to tackle issues arising from population ageing on healthcare demand. Excluded were: studies addressing 'specific' or 'non-generalisable' issues associated with ageing and healthcare demand (e.g. studies conducted on a population from a small locality); and studies providing information of limited applicability.

The group of studies informing parameters were divided into those informing parameters on certain diseases and those on global healthcare demand (Figure 3.1). Both of these groups were further categorised into: studies on bio-demographics; policies and interventions; planning & capacity; service delivery & care setting based on the main theme of the paper; and commentaries or narratives providing background information. 'Global healthcare demand' included: studies informing factors determining global healthcare or long term care demand ('Factors influencing demand' category); studies projecting future healthcare or long term care demand, utilisation or expenditure ('Projection' category); studies on time trends of total health and/or long term care demand ('Trend analysis' category); and studies discussing proximity to death as one of the determinants of healthcare expenditure ('Time to death' category). The 'time to death' category was added as a separate topic as a number of studies discussing 'Factors influencing demand' focussed on this issue.

Studies discussing issues identified as irrelevant, for example, those on private healthcare systems such as the US healthcare market and their associated policies; performance of a certain care setting; inequality and geographical variation; and political debate on healthcare policies were excluded. The sub-categories used in Figure 3.1 are also defined in more detail. The 'bio-demographics' category under the 'disease' heading includes papers on demand for

services for major disease areas of the elderly and bio-demographic aspects of population ageing, and epidemiological studies of selected diseases. The 'policies & interventions' studies included those discussing policies or interventions that may impact on global health and social care demand from a whole population perspective, or may have a significant impact on the health and social care status of the elderly. 'Planning & capacity' included those discussing national workforce and capacity issues, or papers that help identify constraints (e.g. workforce availability) and factors permitting services for older people. A broader category was the 'Service delivery/Care settings' which included studies informing relationships between health and social care utilisation, or discussing service delivery issues that may inform the structure of a model. Commentaries directly related to modelling healthcare demand or narratives providing background information formed another category.

Applying the criteria also involved defining major disease areas relevant to population ageing. Only the diseases considered likely by the author to have significant impact on the health and healthcare demand of the elderly population were included. Therefore, acute diseases with a low possibility of hospitalisation and/or severe morbidity were not included. The iterative approach did not generate a complete set of relevant diseases. Instead, the importance of the newly identified disease was assessed by comparing it with those already included. The distribution of studies on different disease areas is reported in Section 3.5.2.

3.5.2. Categorisation of the literature

Categories of studies to be included in the main review

891 studies were included in the main review. A broad categorisation was performed by the type of analysis and the information provided by the study.

The full sifting and tagging of the literature identified a few 'major' types of studies that are related to modelling or methodology with a relatively high number of studies included. The distribution of papers across these types is summarised in Table 3.3. The major areas of the review among the identified types were the first five in Table 3.3: 'Factors influencing demand'; 'Projection'; 'Methodology'; 'Trend analysis'; and 'Time to death' categories.

There were 146 'projection' studies that could inform the models to be developed for this thesis, 65 of which were exclusively on health care sector including 'hospital care' and 'primary care' (see tags in Table 3.2 Final tagging structure), and 33 were on long term care and community care. The type of care described in the rest of the studies was either unclear based on titles and abstracts or both health and social care. 'Projection' studies could also include statistical analysis models for prediction and reviews of projection models.

The distribution of studies across some of the most important categories of tags is presented in Figure 3.2. Some tags were more likely to be assigned together due to their relevance. For example, 55 out of the 112 'Methodology' papers were also 'Projection' studies as 'Methodology' could indicate projection methods, and of the 59 'Time to death' studies, 41 were also included in the 'Factors influencing demand' category.

Table 3.3. Sub-categorisation results of the studies screened to be included by type/topic of studies*

	Description	Number of papers
Categories relating to modelling/methodology		

Factors influencing demand	A broad category for studies discussing factors that may influence health or social care demand.
	
	Studies on factors influencing demand for the following selected types of care (with the highest numbers of studies included)**:
	
	    o Global healthcare demand (78)
	    o Long term care/Social care (50)
	    o Hospital care (30)
	    o End of life care (14)
	    o Community/Home care (6)
	    o Drug expenditure (5)
		330

Projection	Studies estimating/projecting future healthcare or long term care demand; Studies on specific types of health and long term care, or on a specific population whose methods are considered potentially useful.	146
Methodology	Studies that may inform methodology for future modelling; Also includes studies on countries whose healthcare systems significant differ from that of the UK	112
Trend analysis	Studies discussing/estimating time trends of total health and/or long term care demand; Studies on demographic trends discussed in relation to future health or social care demand.	67
Time to death	Studies discussing proximity to death (in terms of methodology or as one of the determinants of healthcare demand)	60
Other categories		
Policy/Intervention	All studies discussing policies or interventions considered having potentially significant impact on health and social care demand; Includes commentaries discussing healthcare system reform; Majority were on	251

	'global' health or social care demand, but some were related to certain diseases or care settings. For selected types of care**,
	     ○ Long term care (57)
	     ○ Commentary (28)
	     ○ Integrated care (26)	

Commentary	Commentaries discussing issues related to health or social care demand and population dynamics; Also includes commentaries providing general background on relevant issues.	70
Workforce and capacity	Studies discussing whether the current system/workforce can meet the growing demand from a national/wide population perspective; Also includes planning issues.	35

* Numbers in brackets ( ) denote the number of studies within the category; **Numbers for sub-categories do not add up to total as multiple, but not an exhaustive list of, relevant tags were assigned to each citation.

Figure 3.2. Distribution of studies included in the main review across some of the most important tags*
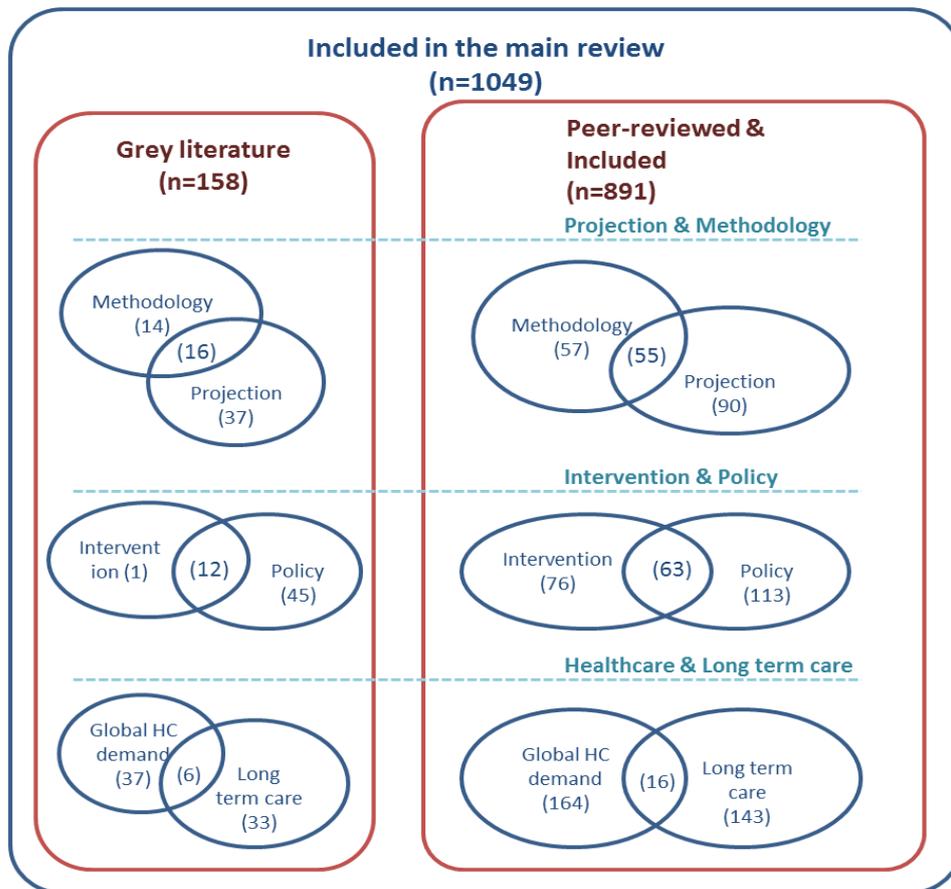
*The relative size of the boxes and circles does not represent the proportion of studies included in that category.

Categories of supplementary studies

In general, the supplementary studies (n=1214) that were not included in the main review were those 'broadly relevant' to methodology and/or parameters required to model health and health/social care demand, for specific diseases, populations, care settings, geographical areas or countries. These studies were not considered directly related to modelling health/social care demand. The categories of the supplementary studies are available in Table 3.4, and the distribution of supplementary studies across a few tags is shown in Figure 3.3.

A large number of studies belonged to the 'Intervention', 'Policy' and/or 'Service utilisation' categories. The total number of studies assigned any combinations involving at least one of the three tags was 432. This is fewer than the summation of the individual categories (n=699) due to papers being assigned more than one of these categories. Studies on interventions were sub-divided by intervention type and by disease category. Not all citations were assigned a tag representing a specific disease or intervention type: those not assigned a disease tag may be cost analysis or service utilisation studies covering more general conditions; the tags for the type of intervention were assigned only when it was clear from the title and abstract.

Table 3.4. Sub-categorisation of the supplementary studies at title and abstract level*

Category	Description	Number of papers
Intervention	Interventions for certain diseases/care settings/populations. By selected intervention type**: - Prevention (67) - Care pathways (30) - Cost containment (25) - Effectiveness study (12) - Integrated care design (20) - Use of new technology (31)	300
Policy	Any studies evaluating, discussing, or suggesting policies; Also includes studies discussing health and social care reforms, resource allocation, or financing issues.	224
Service utilisation	Studies on utilisation of health or social care for the treatment of a disease or within a specific care setting; Relevant to 'Cost analysis' category.	175
Commentary	Commentaries potentially useful for theme-setting.	114
Cost analysis	Majority associated with the cost of treating a certain disease; Cost of treatment or interventions, etc.	100
Delivery system	Studies describing delivery system for a certain kind of care (e.g. long term care, cancer treatment, etc.).	100
Cost of illness	Burden of disease studies based on prevalence and incidence estimates for a whole population	75
Needs assessment	Studies on assessment of needs of older people for a type of care (e.g. mental health care, residential care, etc.);	67
Methodology - other	Methodologies that are not directly relevant to estimating health or long term care demand, but may be used for future modelling.	61
Informal care	Studies discussing factors influencing provision	56

	of informal care, or general issues related to informal care.	
Workforce and capacity	Studies discussing whether the current system/workforce can meet the growing demand; Also includes planning issues; Only studies of narrower scope (e.g. on a certain care setting or a population) or broad commentaries were included in this category.	54

* Numbers in brackets ( ) denote the number of studies within the category; **Numbers for sub-categories do not add up to total as multiple, but not an exhaustive list of, relevant tags were assigned to each citation.

Figure 3.3. Distribution of supplementary studies across some of the most important tags*
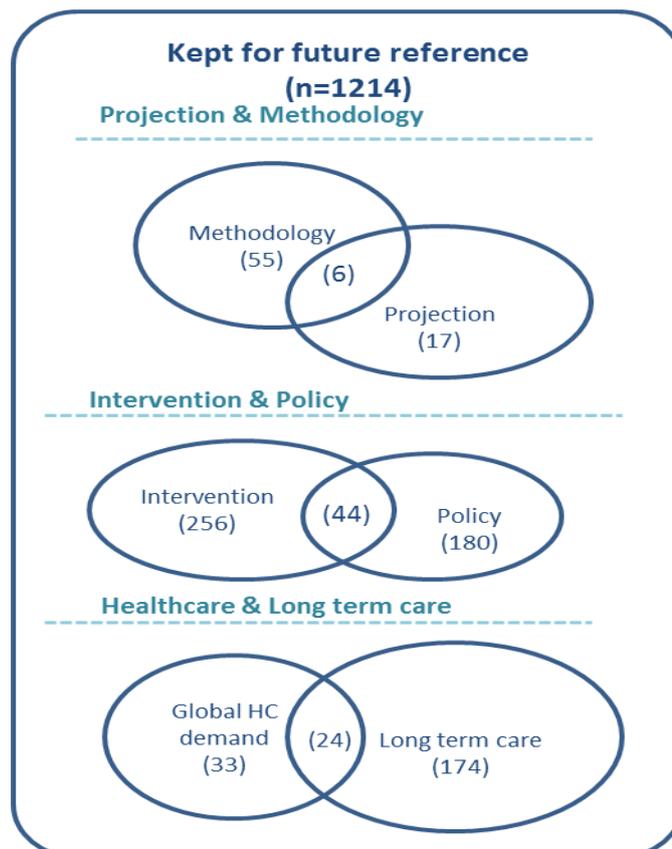
*The relative size of the boxes and circles does not represent the proportion of studies included in that category.

Disease areas

Of the 891 included papers, only a small proportion (n=155) were assigned a disease tag, which was expected as the aim was not to identify studies on a specific disease in the main review. Among the 1214 studies included in the supplementary group, 469 were given a disease tag. Table 3.5 shows the distribution of studies across selected disease areas. Broad terms were employed to include a wide range of diseases, but narrowly defined disease names could also be used where a large number of papers addressed such diseases. Although the number of studies on a particular disease does not represent the importance of the disease, it is likely to be indicative of the disease areas most discussed in the literature in the context of population ageing.

Mental health diseases including dementia, functional disability, musculoskeletal diseases including osteoporosis and arthritis and cardiovascular diseases were the diseases most frequently identified.

Table 3.5. Breakdown of studies by disease tag assigned*

Studies included in the main review	Supplementary studies
Disability - functional (31) Dementia (18)/ Mental & Depression (25) Musculoskeletal (16) Cardiovascular (14) Diabetes (9) Obesity (9) Multiple (Co-morbidity) (12) Hypertension (4) Cancer (3)	Dementia (67)/Mental & Depression (87) Musculoskeletal (56) Cardiovascular (49) Cancer (37) Falls & Injuries (35) Disability - functional (25) Multiple (co-morbidity) (25) Diabetes (18) COPD/Respiratory (11) Obesity (10) Stroke (9) Hypertension (5)

*Numbers in brackets do not add up to total as not all papers were assigned a disease tag.

3.5.3. Grey literature

A total of 158 relevant articles were identified from the grey literature. The same study selection criteria and tagging scheme described previously were applied to the grey literature, although a smaller number of tags were used for the grey literature, and the selection was more focussed on the UK or European healthcare system.

The categories and number of studies identified from the grey literature search are reported in Table 3.6. Among the 49 papers identified as projecting future demand for health and social care, 27 were related to global healthcare or hospital care, 26 to long term, social or residential care, and eight were projecting both. The remaining four articles were related to informal care (2), or the projection of bio-demographic trends (2). Fifteen out of the 30 papers considered to inform methodology were also assigned the 'projection' tag. A large proportion of the papers discussed policy implications of population ageing, or evaluated existing or hypothetical policies (n=58). The issue of financing future health and social care appeared in seven of these 58 articles.

Table 3.6. Categories of the included grey literature*

Type of study	Number of articles
Studies discussing policies and interventions	58
Projection studies**	49
Studies discussing factors influencing health and social care demand	32
Studies considered to inform modelling methodology	30
Bio-demographics and population health status	25
Trend analyses of health and social care expenditure	13

*Numbers of articles do not add up to total as multiple tags could be assigned to each citation and the types of studies are not mutually exclusive; **Numbers reported here are the number of individual papers, rather than that of models used for their results.

3.5.4. Using the literature repository

A total of 2263 papers (891 peer-reviewed and 158 grey-literature studies included in the main review, and 1214 supplementary studies) on the topic of population ageing and healthcare demand/utilisation were stored within a literature repository. All studies in the repository were classified under the tagging system described in Section 3.3.

The repository is freely accessible for any future researchers. The complete file containing all citations can be downloaded in the form of an Endnote® library file (Thomson Reuters) at https://www.myendnoteweb.com/ (username and password available upon request to the author) and can be exported to other reference management software that supports the Endnote file format. Searching the repository can provide an overview of relevant literature for those interested in any of the topics covered, especially if they do not wish to undertake a systematic search; it can provide an initial trawl for those wishing to develop their own systematic search on one of the topics covered; and it can complement a standard systematic search that may not be 100% sensitive.

As the tags are not mutually exclusive, one may use a combination of tags to retrieve information of interest. Each citation has a 'research notes' field where the tags corresponding to the study were recorded (the 'keywords' field contains the keywords that the author(s) of the study specified when publishing their paper). Users can search references by typing the names of the tags representing the topic of interest in the search. The use of double quotes ("…") would return references containing the exact tagging phrase in the quotation marks. Due to the limited search functionality within the web-based Endnote, users may export the records to other reference managing software and use an advanced search function to retrieve documents containing tags of interest in the 'research notes' field.

The distribution of studies across some of the most important categories of tags is presented in Figure 3.4. Due to the large number of tags, this figure shows only a section of tags that made up a high proportion of the identified literature. Figure 3.5 provides an example of how combinations of tags could help retrieve relevant papers if one wishes to explore the population-level demographics and disease status associated with dementia and cognitive impairment.

Figure 3.4. Distribution of studies included in the data repository across some of the most important tags
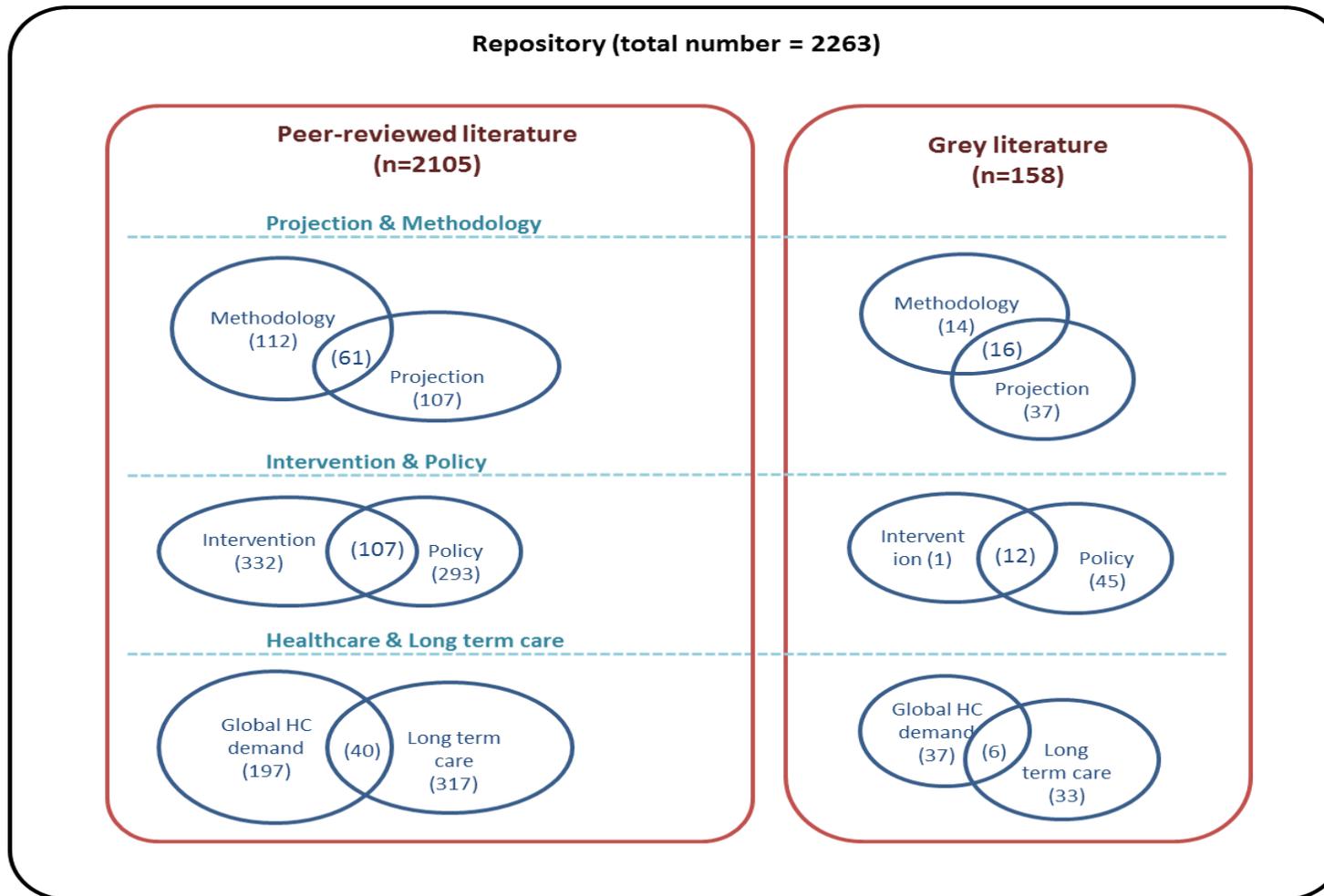
Numbers in brackets ( ): the number of papers included.

Figure 3.5. Illustration of how to retrieve literature from the repository

- Topic of interest: Population-level demographics and disease status associated with dementia and cognitive impairment

'Population health status' tag (n=96)

'Bio-demographics' tag (n=250)

[A] 'Population health status' *OR* 'Bio-demographics' (n= 301)

[A] *AND* [B] (n= 32)

'Disease - mental' tag (n=111)

'Disease - dementia' tag (n=88)

[B] 'Disease - mental' *OR* 'Disease – dementia' (n=194)
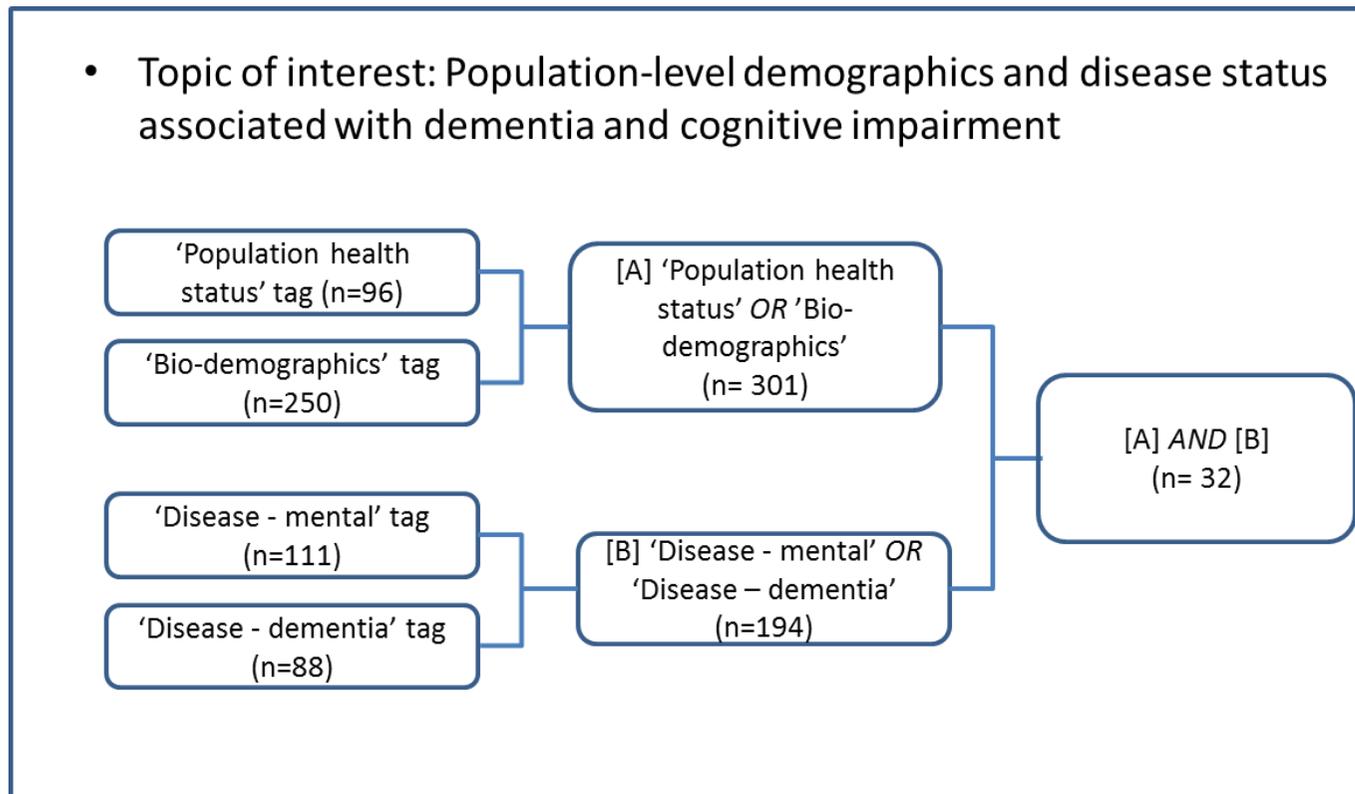
3.6. Review of methods for projection of health and long-term care demand

3.6.1. Summary of models for projection of health and long-term care demand

For the purpose of this review, 'projection' is considered to encompass forecasting. Projected results were assumed to be dependent upon scenarios and assumptions representing the analysts' beliefs which may or may not be realised, while 'forecasting' would involve obtaining the most likely estimate of the actual value or its trajectory. Studies projecting future health and/or long term care demand were identified from the literature search.

Figure 3.6 summarises how these 'projection' studies have been identified from both the peer-reviewed journals and the grey literature. Of 7745 papers identified, 146 papers were related to the projection of health and long term care demand at the title and abstract level. The full-text of these papers were retrieved and examined to identify those that are directly projecting health and/or social care demand or expenditure using a model-based approach. Based on the full-text, 77 modelling studies were identified, and a set of 49 projection papers identified from the grey literature were also included, increasing the total number of projection modelling studies to 126. A further 16 papers were added from the references of the articles already included, resulting in a final set of 142 projection papers as shown in Figure 3.6.

Figure 3.7 shows the linkages between the 142 papers identified from both the published and grey literature, and the breakdown of the methods used in these studies. Three broad categories of models were identified: statistical/econometric models (30 papers), macro-simulation (88 papers), and micro-simulation models (24 papers). Multiple papers were associated with individual models with the 142 papers relating to a total of 77 models: 11, 52, and 14 models for the three broad categories, respectively.

Figure 3.6. PRISMA diagram for studies on the projection of health and social care demand

Figure 3.7. Graphical representation of broad methodologies used for all projection models identified

Statistical / Econometric models

ENEPRI/AHEAD
- Christiansen et al. (2006)
- Khoman and Weale (2007)
- van Elk et al. (2010)

OECD econometric analyses
- Hagemann and Nicoletti (1989)
- Gerdtham et al. (1993)
- Oxley and MacFarlan (1994)
- Antioch et al. (1997, 1999)

US CMS short term projection
- Burner et al. (1992)
- Poisal et al. (2007)
- Smith et al. (1998, 1999a, 1999b)
- Keehan et al. (2008)
- Heffler et al. (2002, 2003)
- CMS (2009, 2011)
- Borger et al. (2006, 2008)
- Truffer et al. (2010)

- Wrobel et al. (2003)

Stand-alone models

Statistical models: Econometric technique
- Wang (2009)

Statistical models: Regression-based methods (e.g. Two-part model)
- Zhao et al. (2001, 2005)
- Breyer and Felder (2006)
- Bhattacharya et al. (2004)
- Hashimoto et al. (2010)
- Powers et al. (2005)
- Lowthian et al. (2011)

Macro-simulation - cell-based otherwise stated

SIMPOP model - multi-state
- Jagger et al. (2007, 2011)

PSSRU LTC macro-simulation
- Wittenberg et al. (1998, 2001, 2002, 2008a)
- Comas-Herrera et al. (2001, 2003a, 2003b, 2006, 2007, 2011)
- Wittenberg et al. (2006)
- King et al. (2010)

PSSRU informal care
- Pickard et al. (2007)
- Pickard (2007, 2008)

Hong Kong LTC model
- Leung et al. (2007)
- Chung et al. (2009)

PSSRU macro-simulation for younger adults
- Wittenberg et al. (2008b)
- Snell et al. (2011)

CBO Long term budget projection
- CBO (1999, 2005, 2007, 2008)
- Manchester and Schwabish (2010)

CBOLT model
- CBO (2009, 2012)

Danish model
Cohort components method (Cell-based)
- Madsen et al. (2002)
- Serup-Hansen et al. (2002)
- Polder et al. (2006)

Dutch burden of illness model - Multi-state life table method
- Feenstra et al. (2001)
- Struijs et al. (2005)

OECD & EU-EPC
- EC EPC (2000, 2001)
- Dang et al. (2001)
- Bains and Oxley (2004) - OECD book

EC-EPC Ageing Reports
- DG-ECFIN (2006a, 2006b)
- DG-ECFIN (2008, 2009)
- DG-ECFIN (2011, 2012)
- Przywara (2010)

ENEPRI/AGIR project
- Pellikaan and Westerhout (2004)
- Westerhout and Pellikaan (2005)
- Schulz (2005)

- OECD (2006)

Stand-alone models

Cell-based method
- Russell (1981)
- WHO (2002) - LTC tool-kit
- Schofiled and Earnest (2006)
- Schneider and Guralnik (1990)
- Lee and Miller (2002)
- Garrett and Martini (2007); Martini et al. (2007)
- Gerdtham (1993)
- Joyce et al. (2003)
- Golinowska et al. (2007) - ENEPRI/AHEAD Social budget model
- Reuben et al. (1993)
- Schulz et al. (2004)
- Kinosian et al. (2007)
- Mendelson and Schwartz (1993)
- Batljan and Lagergren (2004)
- Begg et al. (2008)
- Warshawsky (1994)
- Ministry of Health (2004); Frizelle (2005)
- Iwamoto and Fukui (2009)
- Roos et al. (1998)
- Lagergren (2005)
- Layte et al. (2009) - ESRI
- Fox et al. (2001)
- Karlsson et al. (2006)
- Colombier and Weber (2011)
- Polder et al. (2002)
- Strunk et al. (2006)
- Caley and Sidhu (2011)

Cohort components method
- Rice et al. (1983)

Monte Carlo simulation
- Weinberg (1995) - MC simul.

Multi-state & Markov type models
- Hare et al. (2009)
- Boyle et al. (2010)

Semi-Markov model
- Klidemoes et al. (2010)

Life table method
- Lau et al. (2011)

Economic-Demographic model (macro-economic model)
- Warshawsky (1994)
- Mackellar et al. (2004) - IIASA Economic Demographics growth model
- Ferraresi and Monticone (2009) - Semi-aggregate model

System Dynamics model
- Desai et al. (2008)
- Tuulonen et al. (2009)
- Whole Systems Partnership (2011)

Micro-simulation

PSSRU-CARESIM
- Hancock et al. (2007)
- Wittenberg et al. (2011)

Wanless social care review
- Malley et al. (2006)
- Wanless review (2006)

PSSRU dynamic micro-simulation
- Forder and Fernandez (2009, 2011, 2012)
- Fernandez and Forder (2010, 2011)

RAND Micro-simulation

RAND COMPARE
- Eibner (2009)
- Eibner et al. (2010, 2011)

RAND Future Elderly
- Goldman et al. (2004)
- Goldmand et al. (2009)

- van Meijgaard et al. (2009)

DYNASIM - population health model
- Zedlewski et al. (1990)
- Zedlewski and McBride (1992)

Stand-alone models
- Houle et al. (1997) - POHEM Statistics Canada model
- Cahow (2004) - PhD thesis
- Dormont et al. (2006)
- Basu and Gupta (2008) - Nova Scotia model
- Klewmarken and Lindgren (2008) - SESIM Swedish micro-simulation
- Davis et al. (2010) - NZ policy model

Multistate life-table & Micro-simulation
- Lubitz et al. (2003)

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Figure 3.7 was structured as follows: the smallest boxes represented individual papers, individual papers were grouped in a dotted box if they were either published by the same organisation (or authors) using the same method, or conducted as part of the same project, arrows were used when a paper made an explicit reference to another paper as a predecessor of their model, with the remainder of the papers were considered as stand-alone models. Stand-alone studies by definition cannot be linked to other studies, papers within the stand-alone model boxes but were grouped if they used a similar method. The majority of the models (n=53) were stand-alone models that do not have links with other models. These results indicate the large number of models relating to the projection of health and long-term care demand.

3.6.2. Methods used for projection of health and long-term care demand

Models were classified into three groups – statistical/econometric models; macro-simulation models; and micro-simulation models – based on the type of the approach taken and the level of aggregation of the model. The statistical/econometric model is distinguished as it defines a statistical relationship between parameters and the projected demand/expenditure. The distinction between macro- and micro-simulation models is based on the level of aggregation of the model. Individual entities such as persons, families, and firms are followed in micro-simulation models, whereas macro-simulation uses aggregate values for groups of those individual entities. The macro-simulation models are further divided into four categories: cell-based; multi-state including Markov models; macro-economic models; and system dynamics. The following sections explain the main characteristics of the three groups of models with a description of a few selected studies that were considered to show representative characteristics of the method. Section 3.6.2.4 compares and contrasts the methods that were described in this section.

3.6.2.1. Statistical/econometric models

Statistical or econometric projection models refer to models which establish a statistical relationship between the total or per-capita cost and population characteristics, such as age, or

economic variables, such as GDP, in the form of mathematical equations: these equations can be either deterministic (where the entire set of variable states are uniquely determined by parameter values and initial conditions, so is the output of the model) or stochastic (where there is inherent randomness, thus the same set of parameters and initial conditions will yield different outputs). Typically, these models attempt to use standard statistical techniques to predict the future demand for health and social care and incorporate various socio-economic and health variables. Although macro- and micro-simulation models may also involve performing statistical estimations to obtain estimates to populate parameters within the model, models in this category are included only if they use a statistical approach for the main expenditure/demand projection.

A total of 30 papers associated with 11 models were included in this category (Figure 3.7). A summary of all these models is given in Table 1 in Appendix 3.1. Out of the 11 models, there were three groups of linked papers: the ENEPRI/AHEAD project (Khoman and Weale, 2007); OECD econometric analyses (Gerdtham et al., 1993, Antioch et al., 1999); and the US CMS projections (Centers for Medicare and Medicaid Services, 2009), which was linked to be Wrobel et al. (2003).The remaining models were stand-alone.

The majority of the studies (24 of 30 papers) used regression-based linear models. For example, the OECD econometric analyses (Gerdtham et al., 1993, Antioch et al., 1999) used regression approaches to develop coefficients that can be used to forecast public hospital expenditure for a cross-country comparison of total expenditure and its components. A more complex use of different models could be found in the National Health Expenditures (NHE) projection studies published by the US Centers for Medicare and Medicaid Services (CMS) (Centers for Medicare and Medicaid Services, 2009, Heffler et al., 2003, Borger et al., 2006, Keehan et al., 2008). The CMS model combined projections for Medicare and Medicaid spending based on the Medical Insurance Trustees' report (The US Department of the Treasury, 2008) with projections for private health spending based on a multi-equation econometric model. The structure was a 'top-down' approach in which the growth in healthcare spending is primarily determined at the aggregate level based on historical trends and relationships in health spending. It also combined a number of exogenous projections made by various public and private organisations for different components of the model, e.g. the Medicare and Medicaid spending projections are given as exogenous variables for the projection of private spending. Recent updates made to the baseline projection model include the expansion of model to add new sub-models for spending by sponsor, or those who hold the ultimate

responsibility for financing such as employers and households, and changes made in response to the recent policy change such as the passage of the Patient Protection and Affordable Care Act of 2010 (Centers for Medicare and Medicaid Services, 2011).

Most (6/7) of the 'stand-alone' models also adopted regression-based methods such as two-part model. A two-part model first estimates the probability of service use, and the level of expenditure conditional on the service use in order to derive the expected healthcare expenditure. One study by Wang (2009) used a rather different approach. In its short-term econometric projections, it used an auto-regression model with one- or two-period lagged independent variables such as health expenditure and GDP growth rates. The use of stock returns was proposed as proxies for some factors likely to influence healthcare expenditure on the assumption that healthcare industry returns would contain some information on future expenditure growth.

3.6.2.2. Macro-simulation models

The macro-simulation method is defined as a projection method in which the unit of analysis is groups of people with similar characteristics and the projection outcomes for the total population are obtained by aggregating the group-level estimates (Comas-Herrera et al., 2003). Typically, the population is sub-divided according to socio-demographic characteristics such as age and gender. The actual disaggregation methods vary depending on the purpose and type of the model.

In total, 88 papers used the macro-simulation method. These were associated with 52 models – 39 individual and 13 linked models. Table 2 in Appendix 3.1 summarises all of these models. As in the previous section, this section also describes studies considered to be representative of the sub-groups of papers shown in Figure 3.7 as an example.

The remainder of this section will describe four categories of the macro-simulation method: i) cell-based model; ii) multi-state & Markov type of models; iii) macro-economic model; and iv) System dynamics. The paper by Warshawsky (1994) was counted only once, although it was included in two of these categories. These broad categories were determined by the method used to project the future expenditure on or 'demand' for health and long term care services, irrespective of the methods used to project other components of the model.

The largest proportion of the macro-modelling studies belonged to the cell-based model

category (75 papers (85%); 40 models (77%)). This method involves dividing the total population into demographic 'cells' by selected population characteristics that may influence the level of demand for health and social care services such as age, gender, health status, functional disability, and household composition. It assumes that the population can be broken down into homogeneous groups of people, often termed 'cells'. Total expenditures are calculated by multiplying the projected number of people in each cell by the respective expected expenditure profiles and aggregating these group-level expenditures across all cells for each projection year. The numbers of people in the cells each year are usually obtained from external sources such as census and national population estimates. This allows inflows of people over time, as projected in the source data.

Examples of country-specific models that adopted a cell-based macro-simulation approach are the UK long term care projection models developed by the Personal Social Services Research Unit (PSSRU) (see Figure 3.7)(Wittenberg et al., 2006, Wittenberg et al., 2008, Comas-Herrera et al., 2003, Comas-Herrera et al., 2001). This series of models have been modified and updated over time and aim to project long term care expenditure and associated social care staff required. Key projection outcomes were future numbers of disabled older people, future levels of long term care services and disability benefits, future public and private expenditure on long term care and future social care workforce requirement.

The Wanless Social Care review published by the King's Fund builds on this PSSRU model. The macro-simulation model was linked with a micro-simulation model also developed by PSSRU, or the CARESIM model (Malley et al., 2006, Wanless et al., 2006, Hancock et al., 2007b). Estimates of the proportion of care recipients eligible for local authority support under different charging regimes and the proportion of costs met by users are incorporated into the cell-based model.

There were studies that used the cohort component method (Figure 3.7). It is in principle a type of population projection model in which different components of demographic changes – births, migration, and deaths – are estimated (Rice et al., 1983, Madsen et al., 2002, Serup-Hansen et al., 2002, Polder et al., 2006). However, its expenditure projection was based on the same method as the cell-based method: each age group, or cohort, is followed through successive calendar years, and the number in each cohort is multiplied by the average expenditure to calculate the total costs.

Markov and multi-state approaches model a cohort of individuals which are grouped according to pre-defined states (Sonnenberg and Beck, 1993). However, they differ from the cell-based macro-simulation model as they used transition matrices to determine the number of people in each state, rather than these values being exogenously determined as in cell-based models.

A Markov model simulates the movements of a cohort over a pre-specified number of time cycles. The numbers of people at each state are used to calculate the cost for each time cycle, and the per-cycle costs are aggregated across all modelled cycles to calculate a total cost.

Multi-state models can be considered as a type of Markov model (Schoen, 1988). The term 'multi-state model' was used separately from Markov models in this thesis in the sense that new inflows of people are allowed in the model to reflect the actual population changes (open model) as opposed to a closed model such as Markov models with the fixed number of initial entry. If the transition matrices differ according to the age band to which a cohort belongs, the new cohorts will make transitions at different rates to that for the existing population depending on the year that they entered the model.

The implementation of the method may vary. Kildemoes et al. (2010) used a Markov model which started with a fixed cohort to project future drug utilisation per user and then applied population projection results to estimate population-wide treatment prevalence and expenditures. Unlike the Markov model, in the dynamic multi-state models used by Hare et al. (2009) and Boyle et al. (2010), model entry rate was determined by the population projections. In this sense, the multi-state life table method was considered as a type of multi-state approach (Lau et al., 2011, Feenstra et al., 2001, Struijs et al., 2005). The multi-state life-table method was also a population projection model as for models in the cell-based simulation category as it is a way of obtaining estimates of population characteristics such as mortality and expected life years spent without disabilities. However, the multi-state life-table method differs from the cohort component method where population sizes in different states are calculated by the sum of those in relevant components of the population as it follows transitions between states – associated to population projection – of successive birth cohorts and added new incident cases each modelled year. The multi-state life-table method generally aims to estimate the prevalence of a certain condition or treatment, but can also be used to estimate total costs related to that condition or treatment.

Macroeconomic models share the same general idea of the cell-based method, however, the macroeconomic approach differs in that it is based on a set of mathematical relationships

theoretically consistent in terms of the equilibrium of demand and supply of goods and services. The method may be considered as a variant of the multi-state model in which transition probabilities are 'implicitly' governed by some macroeconomic parameters such as unemployment in order to maintain global accounting consistency. A simple example of such macroeconomic consistency is the total number of residents in institutional settings not exceeding the total number of beds available in such care settings at any point in time. This type of consistency can be used to study linkages between demography, macro-economy, labour market, healthcare system, etc. Parameters for different modules are generally estimated by solving a series of mathematical equations via the partial equilibrium approach (Soede et al., 2004).

Demographic projections or trends are inputs in the macro-economic model which attempts to describe the operation of the components of an economy or an economic system. The projections of aggregate economic activity and labour market outcomes for different population groups can be fed into models of relevant systems to obtain specific outcomes of interest. By solving the inter-related equations using econometric techniques, the total cost as percentage of GDP can be obtained.

Although the macroeconomic model could potentially be included in the statistical model group as it is expressed in a set of mathematical relationships, it was considered as a type of macro-simulation method for this review as it is essentially based on the macro-level disaggregation of the population and the estimation method was not one of conventional statistical techniques but rather one based on economic theory. The 'semi-aggregate' approach termed by Ferraresi and Monticone (2009) and the social security model by MacKellar et al. (2004) used the economic-demographic macro model built within a macro-economic framework. The economic-demographic model was based on the 'demographic cells' and the projection is made by aggregating across the cells.

System dynamics (SD) aims to enhance an understanding of the dynamic behaviour of complex systems. The model tracks changes in system states over time and updates the variables which represent the population of different states. The rate of change in each state may vary over time or as a function of the system state itself. SD does not incorporate individual-level modelling although individuals with a particular set of characteristics may still be considered dependent on the model specification. In this sense, the SD simulation model can be considered as a complex dynamic multi-state model and thus a macro-simulation model.

The numbers of people in each state are governed by rates of event and entry of new cohorts. The 'flows' of people caused by the events of falling ill or dying change the composition of 'stock' variables such as the well, ill, or dead populations. The events are influenced by risk factors, with various types of relationships can be modelled using SD. Causal relationships between the health states may be included and the model can be run in continuous time. SD can also accommodate the non-linearity in the relationships between system states and parameters.

Desai and colleagues (Desai et al., 2008) developed an SD model to model demand for older people's services in the county of Hampshire in England and to test the effectiveness of different interventions for three age groups of service clients (65-74, 75-84, and 85+). The model used in Tuulonen et al. (2009) separately simulated the number of patients with four different eye diseases and the cost of treating them for the whole Finnish population divided into five age-groups.

3.6.2.3. Micro-simulation models

In micro-simulation models, the unit of analysis is individual entities such as individuals, families, or households. The micro-level modelling involved simulating and tracking the social and economic characteristics and behaviour of these individual units rather than measuring changes in aggregate values (Klevmarken and Lindgren, 2008), and often covers a wider economy rather than a healthcare system only. Micro-simulation is a broad term embracing diverse modelling techniques and various forms of model structures. It may also vary in terms of the method for micro-data generation. For instance, the rules and assumptions applied to a simulation model may be determined by applying separate statistical techniques to obtain estimates of model parameters, and multiple modules designed to address a specific section of a model may be linked to one another.

The micro-simulation model category included 24 papers. A summary of all micro-simulation models reviewed in this thesis are given in Table 3 in Appendix 3.1. Characteristics of the micro-simulation models studies will be exemplified below by describing some of the studies included in this category (see Figure 3.7).

The Future Elderly Model (FEM) built by the RAND Corporation is a dynamic simulation model that aimed to project healthcare spending and estimate the effect of changes in health status

and disease treatments on the future expenditures. It consists of three separate models: a health status transition model, trend model for population 'rejuvenation', and healthcare expenditure model. The health status model predicts the health conditions and functional status of sample individuals over time (Goldman et al., 2004). The results of this model are used to model expenditures. Although the FEM does not model supply-side factors that may influence healthcare costs, it incorporates various factors related to disease prevalence and interactions between all health states, and attempts to investigate the implications of a number of potential healthcare scenarios.

The Population Health Model (POHEM) is a micro-simulation model tracking diseases and risk factors (Houle et al., 1997). The simulation creates and ages a large representative sample of Canadian population. Each simulated person experiences various events, such as smoking initiation and cessation, weight loss and gain, and incidence and progression of certain diseases. Like the FEM, POHEM can be flexibly altered to investigate a range of 'what if' scenarios. Different versions of this model have been used to estimate healthcare costs for more targeted populations such as patients with cancer and diabetes.

Projections based on micro-simulation methods may be made on more targeted outcomes depending on the objective of the model. In the micro-simulation model developed by Davis et al. (2010), the main outcomes were utilisation of general practice services and changes in practice patterns. In addition, micro-simulation models could be linked with other types of models. The CARESIM micro-simulation model developed by PSSRU simulated how much each individual aged 65 years and over would have to pay towards the cost of social care in case they need such care. The outputs of CARESIM model were used in the PSSRU macro-simulation model to estimate the long term care expenditure by source of finance (Malley et al., 2006, Hancock et al., 2007b). PSSRU has also published a newer dynamic micro-simulation model (Forder and Fernández, 2012, Fernández and Forder, 2011) that was developed from the static micro-simulation model used for the Wanless review (Wanless et al., 2006). This was commissioned by the UK Department of Health and the Dilnot Commission secretariat as part of analytical support for the development of options for long term care funding system reform.

3.6.2.4. Comparison of the methods

The methods discussed in previous sections are summarised in Table 3.7.

Table 3.7. Summary of examples of all method categories

Method name	Simplified model for cost estimation	Differences
1. Statistical/Econometric model		
Statistical/ Econometric model	E[per capita cost] = a + b*(Age band)	a and b are estimated and used for total cost calculation.
2. Macro-simulation model		
Cell-based model	$$\sum_i [(average\ per\ capita\ cost\ for\ i\ th\ cell) \times (number\ of\ people\ in\ i\ th\ cell)]$$	The population is divided into demographic 'cells', or groups, based on characteristics such as age and gender
Markov model	$$\sum_i [(average\ per\ capita\ cost\ for\ state\ i\ in\ year\ t) \times (number\ of\ people\ in\ state\ i\ in\ year\ t)]$$	Fixed cohorts; Movements between states governed by transition probabilities
Multi-state model	For year t, $$\sum_i [(average\ per\ capita\ cost\ for\ state\ i) \times (number\ of\ people\ in\ state\ i)]$$	Similar to Markov models, but based on population in- & out-flows, not on fixed cohort.
Macro-economic model	A series of equations: GDP = the number of working population * wage Total healthcare expenditure as percentage of GDP= (the number of the elderly people*per-capita cost) / GDP Change in total population= (change in the working population) + (change in the elderly population).	The relationships between demographics and economic variables are built based on the macro-economic theory.
System dynamics	One possibility is: $$\sum_i [(average\ per\ capita\ cost\ for\ state\ i) \times (simulated\ number\ of\ people\ in\ state\ i)]$$	Similar to multi-state, but the rates of events and relationships between states can be built more flexibly.
3. Micro-simulation model		
Micro-simulation model	Cannot be summarised easily in an algebraic expression due to complexity and diversity of the method.	The unit of analysis is individual entities such as individuals, families, or households.

Statistical or econometric projection models were models based on a statistical relationship between the total or per-capita cost and population characteristics. The use of statistical/econometric modelling method may be a convenient option; however, it may not be considered as a reliable option for the projection of healthcare demand, given the large number of interrelated factors affecting health care spending and the very complex network of reciprocal relationships between the factors and health spending (Przywara and European Commission, 2010). It may be more suitable for models that entail a small number of parameters and limited interaction between them. Therefore, the econometric analysis may be used to estimate part of inputs required in a larger model such as technological development and non-demographic determinants of expenditure, rather than as the main control of a projection model.

Macro-simulation method assumes groups of people with similar characteristics as the unit of analysis and the projection outcomes for the total population are obtained by aggregating the group-level estimates.

The models were divided into four groups: cell-based; multi-state including Markov models; macro-economic models; and system dynamics. The cell-based approach can produce different results depending on how these cells are defined. This cohort-based method requires less computation efforts, and relatively less data, compared to individual-level models. Large multinational studies could be possible because of this relative convenience. However, it cannot reflect interactions between population changes with other economic factors as population projections are exogenously determined. It would also be difficult to investigate total uncertainty in the estimates due to the use of average utilisation rates, and the aggregate outcomes may be biased if the variables used to split the 'cells' do not successfully explain demand for care.

Multi-state and Markov models track transitions between a set of health states or risk behaviours, and therefore changes in the size and composition of the population in each state are endogenously determined. As with other cohort-based methods, the multi-state and Markov models may be run at less computational cost. Depending on the model structure and assumptions adopted they can also take account of duration of stay in each state and co-morbidity. In particular, multi-state models can account for population growth as they allow new entrants to the model. However, only a limited number of states may be modelled before the model becomes overly complex and it is difficult to incorporate individual behaviours regarding demographic changes and healthcare options. This type of method may be more

appropriate for the modelling of a specific disease in which a set of closely related states can be defined according to disease progression or pathways.

Macro-economic models can provide a coherent framework for the demographic and economic interactions. Such a model specification may work well when modelling a system in which demand for health or long term care is met by consumer expenditures and largely driven by market forces of demand and supply. However, parameterisation based on macro-economic theory may be difficult in the healthcare area as the majority of European healthcare systems rely on state funding, and the relationships between economy, healthcare utilisation, and demographic changes may not always hold.

In contrast, system dynamic models can account for interactions between modelled individuals and a large number of factors relevant to the target outcome including behavioural influences. As all three studies that used this method concentrated on regional or disease-specific services, this may suggest that the SD is appropriate for detailed modelling of a narrowly defined system but may not be practical for the modelling of a large-scale system.

In summary, macro-simulation models comprised the highest proportion of the identified projection studies. They were based on relatively simple relationships between model components, and could be adopted for comparative analysis of projection results in different jurisdictions due to the relative ease of obtaining similar datasets. However, group-level modelling makes it difficult to take account of the heterogeneity of individuals and thus to assess the distributive impact of policy changes.

Micro-simulation models can mimic the heterogeneity of the population and the complex relationships between model elements. Hence, they have been used to evaluate both the aggregate and distributional effects of individual factors influencing health expenditure. Also, given the richness of the outcomes that can be obtained through micro-simulation exercises and the ability to assess the potential impact of interventions before implementing them, this approach has been popular in forecasting the effect of alternative policy scenarios. For example, the effect of changes in tax systems can be examined by applying different tax rules to information about individuals, families or firms. However, micro-simulation often requires a wide range of datasets and greater modelling efforts, which make the model nearly infeasible in some cases.

The projection models in all of the three categories incorporated all or some common components: on the demand-side, demographic projections, population health status modelling, and quantity or intensity of health or long-term care utilisation; and on the supply side, unit costs of the health or social care services and care workforce required to meet the demand. By defining relationships between these components across different time periods and combining them, the projections of future demand were made. Differences between the categories of methods previously described come from the methods used to define and estimate such relationships between the components.

3.7. DISCUSSION

This chapter reported the results of the literature review. The review identified 7745 relevant studies and a further set of 158 articles from the grey literature were also identified. 142 papers identified from the retrieved literature described the models projecting future health and long-term care demand. The aim of the chapter was to identify areas suitable for further research and to provide a resource for future researchers.

This chapter also described a literature repository containing literature identified on the estimation of health and long term care demand for an ageing population. The repository included studies that are broadly relevant to the topic of population ageing and health and long term care in order to assist future research with a different focus within the diffuse topic of 'ageing'. 2,263 papers were included in the repository.

There were limitations of the review conducted in this chapter. Sifting and categorisation was undertaken by one reviewer due to this study having been conducted as a PhD project. Hence, no cross-checking was involved. Categorisation structure was developed iteratively with subjective decisions made by the reviewer on the main theme of the paper. The tags used in the literature repository differ from the indexing terms adopted in databases such as Medline and EMBASE. Furthermore, no systematic method of searching grey literature was adopted in this study.

However, it is believed that the literature repository created covers the core themes within the literature around population ageing and demand for health and social care, which is a topic of

increasing interest to many researchers worldwide. It makes available a free and easily searchable resource which reflects the screening of 7,745 papers and the categorisation and inclusion of 2,263 papers. Given the very broad and diffuse nature of the literature on this topic, the repository can be a valuable resource for researchers wishing to quickly identify papers relevant to specific topics in this area, and can therefore save considerable time and duplication of research effort.

Also, three broad categories of the projection models – statistical/econometric, macro-simulation, and micro-simulation models – were defined based on the methods used to estimate relationships between the components. The review of projection models provides valuable information on the choice of a modelling method for this thesis, which is described in Chapter 4.

CHAPTER 4   DECIDING ON DECISION PROBLEMS ADDRESSED IN THIS THESIS – DISEASE AREAS AND MODELLING METHODS

4.1. Overview of the modelling methods

4.1.1. Rationale for the research

A recently published UK Parliament report on ageing focussed on the implications of an ageing population with regards to individual life and public policy for the coming decade, and warned that 'the NHS is facing a major increase in demand and cost consequent on ageing and will have to transform to deal with this' (House of Lords, 2013). The increase in life expectancy will result in a larger number of the oldest-old people and the increasing prevalence of the long term conditions experienced by older people (House of Lords, 2013). Hence, the demand for health services to treat such conditions will change dramatically with the ageing of baby boomers, and those diseases are likely to be long term conditions that are costly to treat.

Important questions to address include: 'What are the key disease areas that will be most affected by population ageing?'; 'How much will the demand for services to treat those diseases increase?'; and 'which diseases would benefit most from prevention measures?' Hence, the main aims of the modelling undertaken within this research include: estimating the implications of key disease areas for the future healthcare demand; identifying/comparing potential interventions to reduce the demand; and projecting the future healthcare expenditure/demand for the ageing population.

This thesis addresses the question of how much budgetary impact a selection of key diseases would make on healthcare resources. This differs from conventional health technology assessment (HTA) which relates to how to use resources more efficiently within a budget constraint. Whilst the HTA compares decision options such as treatments or interventions from a micro-economic perspective for a person or a group of individuals in a specific population, this study estimates the budget impact of the diseases from a macro-economic

perspective at the total population level assuming the use of current (or assumed) treatments or interventions. In addition, estimates are provided of: relative gains of eradicating a disease; and relative gains of improved measures to reduce burden of disease.

As discussed in Chapter 3, the majority of the existing published models estimating future health and social care expenditure were based on a macro approach of grouping the total population by characteristics that influence the utilisation of health services and attaching average cost to each of the groups. It was considered that this type of model would not produce outcomes that are detailed enough to answer the proposed questions. It was considered that a better approach would be to target a selection of key disease areas that older people are more likely to develop and provide indicative values of their cost implications. The modelling approach proposed in this study is not intended to make precise *forecasts* of the exact level of future health expenditure across all diseases, as not all diseases were covered, and potential changes in healthcare were not considered in the base case. However, indicative results are presented and the modelling provides a proof-of-concept examination of the method of the linked disease-expenditure model.

4.1.2. Chosen modelling approach

In this research, a disease-based approach is used to focus on selected key diseases that are anticipated to significantly influence healthcare expenditure as the population ages. Models for the key diseases are initially constructed individually and then linked to incorporate interactions between the diseases and competing risks of events, which may be fatal. Within individual disease models, expenditure on services to treat or manage the disease is estimated. This allows an assessment and comparison of the fiscal importance of the selected diseases and the possible impact of hypothetical prevention and treatment interventions targeted at these diseases. By comparing the potential benefits of improving the treatments or reducing risk factors for the diseases, it is also possible to inform investment and resource allocation decisions. For example, it can provide information to answer questions such as 'for which disease could the highest economic gains be made if the response rate of treatments related to the selected diseases increased by 10%?'

Diseases were modelled at an individual patient level. Individual-level modelling captures variability and uncertainty around model outcomes, and produces more detailed simulation

results that make possible further analyses using the simulated outcomes. It also reduces the need for a very large number of health states that would be required if a cohort-based model was used, particularly when time since events and individual characteristics are important.

The key outcomes of this study are summarised in Box 4.1.

Box 4.1. Key population-level outcomes expected from the model

1) Within the individual disease models, what is the total anticipated cost of each disease?

2) In the combined model, what are the total cost of all the included diseases and total costs per disease? What proportion of the total all-disease cost can be attributed to each disease?

3) In the combined model, how much savings can eradicating Disease A make, and how many QALYs or life years can it provide? How does that saving compare to the individual disease model results? By comparing the cost outcomes and savings estimated in the combined model and in the individual model, the value of linking the individual disease models can be estimated.

4) Which disease would benefit most from an improved intervention? For example, how much money (QALYs or life years) can an additional 10% efficacy in drugs for treating Disease A save (give)?

5) At a fixed cost-utility threshold, how much can we spend on an intervention? For example, how much could be charged for Drug T or a government programme with hypothetical efficacies to have a cost per QALY of £20,000? How can we best invest healthcare resources?

4.1.3. Novelty of the chosen approach

To the author's knowledge, none of the models reviewed in this thesis (Chapters 2 and 3) have used such an approach. The vast majority of the demand projection models focussed on the 'care' side of the demand rather than diseases. Often future health status was incorporated as one of the individual or population characteristics with estimates used for the probabilities of

contracting the disease, rather than explicitly modelling the diseases to simulate the future health status. For example, within the RAND Corporation's COMPARE micro-simulation model (Eibner et al., 2010b), which was used to project the effect of health reforms on health insurance coverage and costs, and estimate impacts on businesses of different sizes, workers and their dependents, the courses of disease-related events were not modelled. In another model by RAND, the Future Elderly Model (FEM), disease onsets were modelled in a binary manner (i.e. with or without diseases), and their progression was not explicitly simulated (Goldman et al., 2004).

There are other examples of models that adopted a disease-based approach, but differed from the approach used in this thesis in terms of the purpose of the model and the manner in which the model was constructed. The POHEM model from Statistics Canada was used to evaluate the health and healthcare system impacts of new prevention or treatment policies targeted to specific risk factors or to particular diseases (Houle et al., 1997). It has been modified to model certain chronic diseases individually (breast, lung and colorectal cancers, diabetes, acute myocardial infarction, and osteo-arthritis) (Kopec et al., 2010). However, the disease-specific versions of the model have not been linked to project the combined health expenditure. Another example is the model developed by the Australian Institute of Health and Welfare (AIHW) which provided projections of future health spending on a specific set of diseases (cardiovascular disease, road traffic injuries, dementia, musculoskeletal disorders, lung cancer and diabetes), incorporating different drivers of health expenditure for each disease. However, it used an aggregate cell-based approach for each disease modelled, and projections were made at only a few time points although it adopted a 30-year time horizon.

The SIMPOP model (Jagger et al., 2011) has some similarities to the modelling approach in this thesis. It did not estimate healthcare expenditures, but simulated the impact of multiple diseases such as coronary heart disease (CHD), stroke, and dementia on disability states. The estimated disability states were then used in the PSSRU macro-simulation model in order to derive social care needs and expenditure. However, the objective of the model was to estimate the demand for social care services rather than healthcare, and the main outcome of the model was the disability status rather than states of specific diseases.

There also have been models that focussed on a single disease incorporating demographic changes (Hoogendoorn et al., 2011). However, the main purpose of these models was not to estimate the effect of population ageing on healthcare demand and they did not attempt to

link multiple disease models. There were some cases where a set of diseases were modelled simultaneously as a risk factor for multiple diseases. They did not take the form of linking individually modelled disease models, but included a fairly crude level of disease modelling. For example, the Foresight micro-simulation model developed by the UK National Heart Forum estimated public health expenditures associated with diseases where obesity is a significant risk factor. Common disease pathways (recovery, continuance, and death) were applied to all the included diseases (diabetes, coronary heart disease, stroke, and colorectal and breast cancers). Then, the average NHS expenditure per patient for these diseases was applied to calculate the future burden of obesity-related diseases.

The following sections provide an overview of the modelling process used within the thesis and sets out the common methods used for all individual disease models in detail.

4.2. Justification for disease selection

As seen in the literature review in Chapter 3, no models projecting future healthcare expenditure based on multiple disease models were identified, leaving this an area for research. Diseases with significant cost implications for an ageing population were considered for inclusion in the model. Where it was difficult to make head-to-head comparisons between the costs, other criteria considered important for the future healthcare expenditure were also used. The criteria used for selecting the diseases are summarised in Box 4.2.

Box 4.2. Criteria for selecting diseases to model

- Diseases with major cost implications: High costs to the UK NHS and PSS* of treating/managing the diseases
- Diseases of the elderly: Diseases with significant mortality and morbidity burden for older population and diseases whose incidence is expected to increase as population ages.
- Whether there are sufficiently recent HTA reports undertaken for the disease in order that a peer-reviewed model could be replicated.
- Establishing a balance between different disease areas in order to cover a spectrum of conditions.
- Diseases of hard endpoints, rather than those being risk factors for other diseases themselves, such as diabetes and hypertension

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*Personal Social Services

The major criterion for selecting the diseases to model was the current costs of the diseases to the UK NHS and Personal Social Services (PSS). Diseases expected to bear increasing importance for an ageing population, in that they become more prevalent as a population ages, were given a priority.

The presence of recently published (or in press) NIHR HTA reports was considered as it was deemed as evidence of the importance of the disease to major stakeholders such as decision-makers in local government, policy-makers (including the National Institute for Health and Care Excellence (NICE)), health professionals, and the general public. Given the limited time scale of the PhD study, the use of the peer-reviewed existing models was considered a reasonable approach.

A balance between different disease areas was also considered as one of the criteria. Including diseases from one or two areas of diseases whose mechanisms are similar may be misleading in estimating the broad impact of population ageing on healthcare expenditure and the interactions between diseases. Among diseases of significant economic, mortality and morbidity burdens, a spectrum of diseases that affect different parts of the body were included.

Diseases with hard endpoints were preferred to those which were risk factors for other diseases such as diabetes and hypertension. It was believed that such diseases could be embedded in the chosen disease areas as a risk factor, and the consequences of the diseases could be represented in the models of other diseases.

In order to identify a set of candidate diseases that could potentially be included in the model, non-systematic web searches were conducted for studies listing the most expensive diseases of the elderly using search terms such as 'the most costly (expensive) diseases', 'diseases of the elderly', 'economic burden of diseases', 'NHS budget' and combinations of these terms. Further searches were performed for reports from governmental agencies and international organisations such as the UK Department of Health, NHS evidence, Organisation for Economic Co-operation and Development (OECD), and World Health Organization (WHO). No single source of data was identified comparing the economic costs of major diseases of the elderly in the UK. US Data from MEPS-HC (Medical Expenditure Panel Survey- Health Care) reported the top five most costly conditions for the US non-institutionalised population aged 65 and older. The highest expenditures among the elderly were for care and treatment of heart conditions ($48.4 billion). Treatment of cancer ranked second ($32.2 billion), followed by osteoarthritis and other non-traumatic joint disorders ($24.8 billion), hypertension ($23.8 billion), and trauma-related disorders ($20.5 billion) (Soni and Roemer, 2011).

Given the lack of UK data, it was considered that the breakdown of the total NHS budget might indicate the relative importance of broad disease categories. The largest spending category in

the 2010/11 programme budgeting data was mental health problems, accounting for 11% of the overall programme budget. Expenditure on circulatory problems was the second largest spend (7.2%), followed by cancers and tumours (5.4%). These three areas have represented the top three spending categories since 2004/05. These values primarily represent the cost breakdown for the total population, rather than the older population.

Although the adopted approaches and the purpose of the models differed, it was considered that the existing models could provide an indication of important diseases in the elderly. For example, the FEM model by RAND focussed on a few of the most prevalent diseases among the elderly: hypertension; diabetes; cancer (lung, breast, prostate, colon, uterine, throat, bladder, kidney, and brain); chronic obstructive pulmonary disease (COPD); acute myocardial infarction; coronary heart disease; and stroke – to assess the impact of chronic illnesses.

Considering these disease lists, heart conditions, cancer, musculoskeletal diseases, mental health diseases, and respiratory diseases were chosen as candidate disease areas. To compare the costs of each of the candidate diseases, recent burden of disease studies published between 2003 and 2013 for these diseases were identified via Web (Google) and Medline searches using combinations of terms relating to the disease name and cost or burden of illness. Further literature citing or cited by the studies from the simple searches was identified via snowballing of the literature. Background sections of NICE guidance were also inspected in search of relevant literature on the cost of diseases. The burden of disease studies were searched at a single disease level that can be modelled individually, rather than the broad categories of candidate disease areas.

The identified studies estimating the costs of diseases of the elderly were based on different methods of calculation with different coverage of the cost items. Also, the searches were not conducted in a systematic manner. However, estimates from these studies might indicate the economic implications of the diseases that older people are more likely to develop.

Table 4.1 summarises the estimates of healthcare costs including social care costs in the case of dementia for the candidate diseases whose costs were ranked high in recent UK studies. The most recent estimates representing costs to the UK NHS and PSS, excluding informal care costs and indirect costs from productivity loss and premature deaths, were chosen for comparison.

Table 4.1. Summary of UK cost estimates related to diseases of the elderly (direct costs only).

Disease	Estimated Cost	Cost Year	Cost inflated to 2012[1]	Source
Cardiovascular disease	£14.4 billion	2006	£17.1 billion	Allender et al. (2008)
Dementia	£10.5 billion	2010	£11.2 billion	Fineberg et al. (2013)
Osteoporosis	£3.36 billion	2010	£3.57 billion	Hernlund et al. (2013)
Osteoarthritis	£1 billion[2]	2010	£1 billion	Estimated from Chen et al. (2012)
COPD	£1 billion	2011	£1 billion	Department of Health (2011)
Rheumatoid arthritis	£560 million[3]	2008	£623 million	National Audit Office (2009)
Colorectal cancer	£494 million[3] (€595 million)	2009	£529 million	Luengo-Fernandez et al. (2013)
Breast Cancer	£482 million[4] (€581 million)	2009	£515.76 million	Luengo-Fernandez et al. (2013)

1. Costs were inflated using the Hospital and community health service (HCHS) pay and price inflation index; 2. UK direct costs only; sum of costs of non-steroidal anti-inflammatory drugs (NSAIDs), NSAIDs iatrogenic, proton pump inhibitors (PPIs), arthroscopy, and joint replacement surgeries; 3. NHS cost only; 4. Using conversion rate of 0.83 £/€ (accessed on 11/11/2013).

Cardiovascular diseases (CVD) were shown to be the most costly disease in the UK. A study by Allender et al. (2008) estimated that the cost of CVD to the UK healthcare system was £14.4 billion in 2006. In addition, productivity losses accounted for £8 billion annually and the annual cost of informal care of people with CVD was also £8 billion. Another study showed a significant burden of cardiovascular diseases: the combined cost of CVD to the NHS and the UK economy is estimated to be £29.1 billion in 2004 (Luengo-Fernández et al., 2006).

According to Fineberg et al. (2013), the annual cost of dementia on the health and social care system was estimated at £10.5 billion (£19 billion including indirect costs), more than the cost of cancer, coronary heart disease and stroke put together. Dementia imposes a significant economic burden not only on the health care system, but also on patients, on family and friends who provide unpaid care, and on the wider economy and society. Also, it affects a large

number of people, especially the older population. There are estimated to be about 820,000 people living with dementia in the UK (Luengo-Fernandez et al., 2010). The incidence will rise as population ages (Matthews and Brayne, 2005), and the number of people with dementia is predicted to increase to 2 million by 2050 with the annual cost of care estimated to be nearly £60 billion (Lewis et al., 2014).

Musculoskeletal conditions also represented a significant economic burden on the UK health and social care system with the annual cost estimated to be £5.7 billion in 1995/96 and 1.0 million people affected each year, resulting in 11.6 million lost working days in 2004/05 (Nicholson et al., 2006). However, studies comparing economic costs of different musculoskeletal diseases in the UK had not been identified. The WHO's Global Burden of Disease 2000 project selected osteoarthritis, rheumatoid arthritis, osteoporosis, and low back pain as the four major musculoskeletal conditions in terms of its disability burden (years of life with disability).

A recent report by Hernlund et al. (2013) showed that the cost of osteoporosis-related incident fractures, excluding the costs of prevention and long term disability, amounted to nearly €4 billion in 2010 (€3.98bn= £3.36bn when using conversion rate of 0.8413£/€). It also estimated that the cost of osteoporotic fractures represented 3% of the total healthcare spending in EU. A model based analysis by Burge et al. (2001) estimated the costs of osteoporosis-related fractures for the UK population aged 50-99 to be £1.8 billion in 2000 using a Markov model of the natural history of osteoporosis to predict fracture numbers.

The total costs of rheumatoid arthritis (RA) in the UK, including indirect costs and work related disability, have been estimated at between £3.8 billion and £4.75 billion per year (Pugner et al., 2000). Direct NHS cost for RA was estimated to be £560 million annually (National Audit Office, 2009).

There was a paucity of data on the economic cost of osteoarthritis (OA) in the UK (Parsons et al., 2011). The NHS Executive had calculated annual costs for OA at £320 million (Scott et al., 1998). A recent study by Chen et al. (2012) estimated osteoarthritis-related costs in the UK by category of treatment. The annual cost of OA summed up to £1 billion across all treatment categories. However, it included the cost of joint replacement surgeries which can be caused by other conditions than OA.

Respiratory disease is one of the most costly disease categories; the UK NHS care cost was about £3.0 billion in 2004 (British Thoracic Society, 2006). Among the respiratory conditions,

chronic obstructive pulmonary disease (COPD) involves significant costs from long-term medical management and disability-related care, costing the UK £1 billion a year (Department of Health, 2011). Over 27,000 people were estimated to have died from COPD in 2004 and more than 1 million bed days were related to COPD in England (British Thoracic Society, 2006). It is estimated that it is nearly ten times more costly to treat severe COPD than mild COPD, and some 2.7 million people are estimated to be living with the disease without knowing it (Department of Health, 2011). Hence, the prevention and early identification of the disease could deliver significant savings.

Cancer was also a significant cost burden. A recent report by Bupa (Bupa, 2011) estimated that the current cost of cancer diagnosis and treatment is £9.4billion in 2010, but will rise to £15.3 billion by 2021 – an increase of £5.9billion. It was stated that the increase in the overall cost of cancer diagnosis and treatment was, in part, the result of the UK's ageing population, which is predicted to lead to a 20% growth in cancer rates by 2021.

A study by Leal and Luengo-Fernandez (2012) suggested that the total cost of cancer is greater than £15 billion a year in the UK, including the healthcare costs, unpaid care costs by family and friends, and lost earnings due to absence from work and premature death: this total included £7.6 billion in economic costs, £5.6bn for health and £2.6bn for unpaid care.

However, the diversity in the natural progression, diagnosis, treatment, and prognosis of cancers at different parts of the body makes it difficult to generalise all cancers in one model. Therefore, the costs of individual cancers were compared.

Leal and Luengo-Fernandez (2012) reported that lung cancer was the most expensive, costing £2.4 billion a year, bowel cancer cost £1.6bn, breast cancer £1.5bn and prostate cancer £800 million, including productivity loss. In a large European study by Luengo-Fernandez et al. (2013), breast cancer accounted for the highest healthcare costs in EU (€6.73 billion; 13% of all cancer-related health-care costs), followed by colorectal cancer (€5.57 billion; 11%), prostate cancer (€5.43 billion; 11%), and lung cancer (€4.23 billion; 8%). The healthcare cost in the UK was estimated to be €595 million for colorectal cancer, €581 million for breast cancer, €461 million for lung cancer, and €413 million for prostate cancer in 2009.

The set of selected diseases and the rationale for the selection are described in Section 4.2.1.

4.2.1. Selected diseases

Based on the 2012 costs reported in Table 4.1, the burdens of the candidate diseases are compared in Figure 4.1. The diseases selected for modelling are shown in diagonal-lined area, with a rationale for their selection in the text below.

Figure 4.1. Cost of illness (price inflated to 2012)
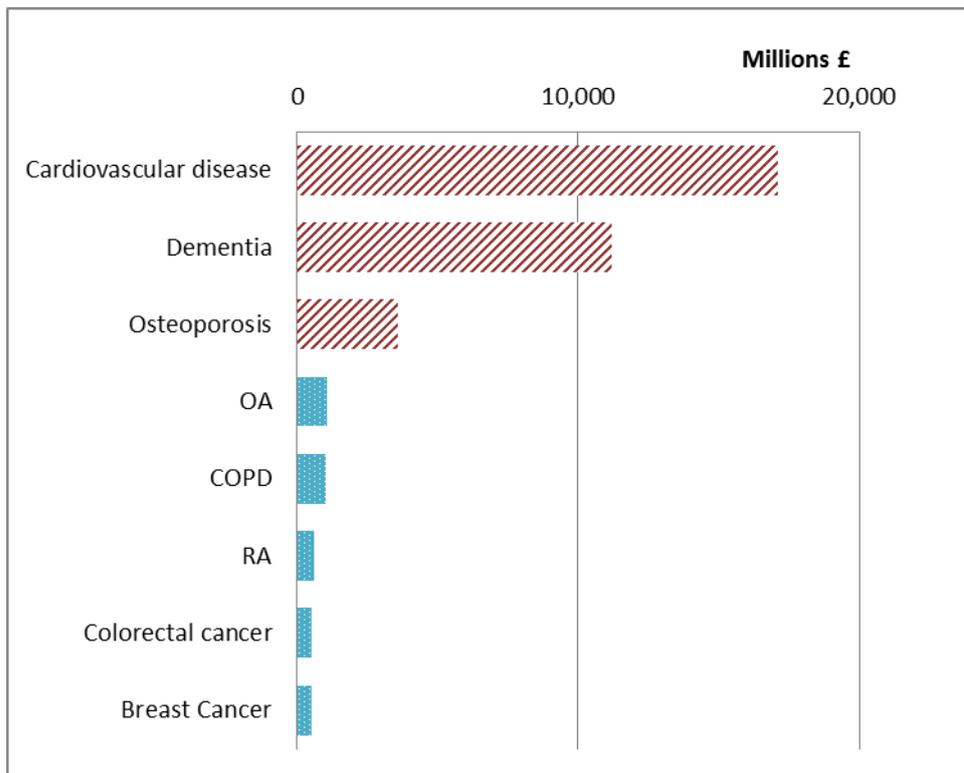
The most expensive disease category was cardiovascular disease. Heart conditions, such as coronary heart disease (CHD) and myocardial infarction (MI), and stroke were selected for modelling as they account for the largest proportion of mortality and prevalent cases in cardiovascular disease among older individuals (British Heart Foundation, 2014), and impose significant economic burden on the overall healthcare system (House of Lords, 2005).

Dementia was selected for modelling considering its cost, the balance between the chosen diseases, and likely impact of population ageing. Amongst brain disorders, dementia was the

most expensive category of spending (Fineberg et al., 2013), and affects older people in particular, and is expected to be significantly affected by population ageing as the incidence is positively correlated with age. Only the most common form of dementia, Alzheimer's disease (AD), was modelled in this thesis as the current NICE guidance and relevant model-based studies (including HTA reports) focussed on AD (see Chapter 6 for details).

It was considered appropriate to include one or more musculoskeletal disorders due to the increase in prevalence and incidence with age. Amongst the musculoskeletal conditions, osteoporosis was deemed appropriate to include in the model due to its high cost. OA was not selected as previous models have been built for OAs at different anatomical sites such as knees, hips, and joints of hands, which make it difficult to include given the aim of the thesis. Furthermore, the incidence of OA is difficult to estimate as the onset is not well-defined due to the discrepancy between the symptomatic OA and OA based on the radiological changes. RA was considered for inclusion as it was anticipated to be increasingly costly and prevalent due to it mainly affecting people aged 65 years and older (Fejer and Ruhe, 2012). However, RA was not chosen for the modelling given that the cost of RA did not exceed that of OA and COPD.

Cancer in collective terms is one of the major cost categories on the UK healthcare system. However, it was not selected for the modelling as individual cancers require a separate model and the top two costly cancers (breast cancer and colorectal cancer) were not shown to be as expensive as other diseases compared, incurring costs around £500 million, respectively.

Examining the economic burden of illness on the NHS spending and the society and other aspects of the candidate diseases, the three most expensive diseases with significant mortality and disability burdens for the elderly – heart disease (including stroke and MI), Alzheimer's disease, and osteoporosis – were selected for modelling (diagonal-lined areas in Figure 4.1).

4.3. Modelling methods

This section reports modelling methods commonly adopted for models described in subsequent chapters. Section 4.4 describes general methods for linking individual disease models.

4.3.1. Choice of modelling approach – Discrete event simulation

Given the complexity of the model in conjunction with the set of diseases included in the model, individual-level modelling was considered appropriate. Cohort-based models, where a cohort of patients move between modelled states typically based on the mean transition probabilities, can be a simple and convenient option if patients can be adequately modelled through an aggregate model and the number of health states is manageable. However, an individual-level model provides a better option to incorporate heterogeneity among patients. While cohort models can account for different characteristics of individuals such as age, risk factors, and history of other diseases, the number of dimensions of the modelled states become exponentially large, which can cause problems in a model with a large number of defined health states.

Although a Markov model can be constructed at the level of individual patients, Discrete Event Simulation (DES) models allow for greater flexibility in the times when events can occur. In DES models, simulation time is advanced from time of one event to the next, whereas a state transition model with discrete time intervals, e.g. Markov model, updates the model states at fixed time points. Individual patient Markov models can also have difficulty in finding the appropriate length of time cycles. If time cycles are too short, computation time is increased due to the need to recalculate events for each cycle. If time cycles are too long, it may be inappropriate to assume only one event can occur in one cycle. DES models can save computation time by making these per-cycle calculations unnecessary, and there is not a possibility of multiple events occurring within a defined period.

In DES, a 'time to event' approach is used, and thus transition probabilities for pre-specified equal-length cycles as in Markov models are not required. Hence, events can occur at any

point in time and repeatedly over time. Multiple events can occur within a short period of time, compared with Markov models allowing only one event to occur within one cycle.

At entry and each event state in a DES model, the values of time to event are sampled for the next transition. The age of the individuals at entry and times to events are accumulated to calculate the total life years lived by the simulated patients. Using this approach, it is possible to apply varying event rates conditional on the time since the event and the patient's time-variant characteristics. For example, in the heart disease model, time to next event values were sampled from a distribution with a rate that differs between the first year and subsequent years after myocardial infarction (MI), and depending on the patient's age band (age groups: group 1. < 55 years; group 2. 55-65 years; group 3. 65-75 years; group 4. 75-85 years; group 5. >85 years). Rates of transitions were updated by repeatedly checking whether a sampled time-to-event value exceeds any of the future time points sectioning the first and subsequent years of an event, or the age bands. If a sampled value passed through the earliest sectioning point, a new time-to-event value was sampled using an updated rate associated with the time period after the cut-off point and added to the time to the cut-off point. To illustrate, if a time to next event value sampled based on the first year rate is greater than 1 year, a new value is sampled from a distribution with the subsequent years event rate and the final time to event value is calculated as (1+the re-sampled value) years. If this individual was scheduled to move to the next age band in 3 years, and the re-sampled time to next event value was greater than 2 years, the event rate would change before the transition as scheduled by the sampled value. The 2-year cut-off is calculated as 3 years to a next age band *minus* 1 year at which the time to event value was re-sampled. In this instance, a new time to event is sampled again from a distribution associated with the new age band and the final time to next event becomes (3+the sampled value) years.

As a result, an individual-level DES model was used as the main type of the disease models. Individual patients are simulated to move through different disease events according to the individual-specific event schedules sampled from appropriate time-to-event distributions. The use of DES allowed multiple health states and a number of patient characteristics to be incorporated with less computation time. For example, patients with a history of CVD events are associated with higher risks of having further CVD events and the times of such events could be recorded within the individual-level model to accurately model such relationships.

The analysis was undertaken from the perspective of the UK NHS and PSS in line with the reference case preferred by the NICE (National Institute for Health and Care Excellence, 2013).

Estimates representing all direct health effects and the use of UK NHS and PSS resources were used. A lifetime horizon was used to fully assess the long term effect of potential preventative interventions. The model is built using the simulation software SIMUL8 (©SIMUL8 Corporation).

4.3.2. Modelling process

For each disease included, a review of the existing models is undertaken. The aim of this mini-review is to identify the most appropriate model structure, data sources, and the current recommended treatments, and to modify and expand this model, rather than attempting to develop a new conceptual model and populate it, given the time constraints of this study. Searches for the existing models were based on recently published HTA reports if available. If the HTA report included a recent systematic review of the existing models for economic evaluation of relevant health technologies from published literature and industry submissions, the models included in that review were also examined. Supplementary searches using keywords identified from the reviewed studies were undertaken to ensure that models published after the HTA report are also included. The NHS Economic Evaluation Database (EED) database was also searched.

Based on the review of the existing models for each disease, the model that is considered most appropriate is replicated or adapted, when believed necessary. The results from the model are compared with those of the existing models to externally validate the model. The set of individual disease models that are developed in this manner are linked to each other in order to estimate the total impact of these diseases on healthcare expenditure.

4.3.3. Model assumptions

The key methodological assumptions that apply to the larger linked model and its components are summarised in Table 4.2.

Table 4.2. General model assumptions

Category	Assumption
Time to event	Where possible, parameters of time-to-event distributions are functions of patient history and other patient characteristics.
Competing risks	Only the event simulated to occur at the earliest time affects transitions between modelled events.
Post-event states	Once patients experience one of the modelled events, their disease history is recorded and the relevant costs and utility decrements are applied until death.
Cost	Where costs in the initial year differ from those in subsequent years, this is included in the model.
	Costs were additive following a series of multiple health events, i.e. the individual-specific cost is a combination of the current event cost and the (subsequent-year) costs associated with all events that the individual patient had previously experienced.
	When the patient experiences the same event multiple times, the same first-year and subsequent-year costs was applied only once (i.e. the cost is not multiplied by the number of times that the event occurred).
Utility	Multiplicative utilities are assumed. That is, if a patient experiences a series of health events over time, the utility multipliers relevant to all the current and previous events are applied.
	When the patient experiences the same event multiple times, the corresponding utility multiplier was applied only once.

4.3.4. Model Population

As a base-case, the general UK population with or without history of any of the modelled health events (that is, both the prevalent and non-prevalent cohorts) were considered. In order to estimate the ageing impact on healthcare demand, the UK population aged 45 and over, rather than only the elderly, were modelled. Hypothetical individuals were randomly

generated using the mid-2012 UK population estimates by age and gender published by the UK Office for National Statistics (ONS) (Office for National Statistics, 2013d).

A modelled individual is assigned an age sampled from the age distribution for the UK population aged 45 and over. When constructing the age distribution, as data on the proportion of people aged 90 years and over were unavailable for each year of age, a constant mortality rate obtained from data on Deaths registered in England and Wales (Office for National Statistics, 2013a) was assumed for all people aged 90-99 years. Using this annual mortality rate, the proportion of people in the 90-99 age group at each year of age was estimated by assuming that the proportion of people aged (x+1) years decreases from that of people aged x years at the rate of the annual mortality, and scaling the proportions of people at each year of age 90-99 years to match their sum with the total proportion of people aged 90-99 years. Hence, the proportions of people aged 90-99 years tailed off at a constant rate.

Following the sampling of age, the gender of the individual was sampled from separate sets of probability distributions for male and female populations estimated from the UK ONS Population estimates, which were conditional on the five-year age band to which the person belongs (Office for National Statistics, 2013d). The population aged 45 years and over entering in the base year of 2012 had an average age of 61.9 years. Among them, 52% were female.

These individuals generated within the model were used as the common initial population for all disease models, and followed through the linked model. Individuals were simulated to leave the model when they reach 100 years of age with a non-disease death scheduled to occur at the mid-point of the following year, if they had not been simulated to die before this time point.

Demographic and/or socio-economic trends may be incorporated by varying model parameter values depending on the year in which the population enter the model. Demographic information such as the number of people in each age and gender group and prevalence of the included diseases on the future populations is obtained from the 2012-based population projections made by ONS (Office for National Statistics, 2013c).

The following section describes the methods for estimating projected expenditures.

4.3.5. Population dynamics and annual cost projection

One of the key outcomes in which it is assumed policy makers are interested in is the total cost on the healthcare system of a disease. In this thesis, total costs incurred for a calendar time period, such as annual projected costs for the next decade, were estimated. The estimated annual costs could be compared with the current budget for the disease, and validated against the actual expenditures in previous years.

The model in this thesis followed the starting cohort representing the UK population aged 45 years and older in the base year (2012), until death. As this population ages over time, the modelled population was rejuvenated every year with a new cohort of people aged 45 years entering the model. As the simulation model in this thesis recorded time from model entry rather than actual calendar time, no such mechanisms as yearly population rejuvenation were integrated in the model. Instead of the timed entry of new cohorts into the model, the model was run for the future cohorts of 45 year olds separately and the results for the base year population and future cohorts were combined. Year 0 denoted the base-year hereafter, and years 1, 2, and 3 referred to the first, second, and third year after the base-year (i.e. 2013, 2014, and 2015) for convenience of describing the entry year of each cohort.

The model estimated lifetime costs and (quality-adjusted) life years of the base year population and the new cohorts of 45 year olds entering the model each year. Hence, a crude summation of lifetime costs and QALYs across all cohorts would represent costs and QALYs accrued until deaths of all people who *entered* the model during the projection horizon, rather than those incurred for a specific time period. This would provide results from a closed model, where individuals that entered the model in the beginning of modelled time are followed until the end of model time and no further entry of individuals is made over time. In this case, the time interval of interest is the entire time horizon of the model, not a specific calendar time period such as the year 2015 which is the focus of this thesis.

In order to estimate the total annual cost of a disease, per-capita annual costs from the starting cohort representing the UK population in the base year and the following new cohorts of 45 year-olds with differing entry times are multiplied by the number of individuals in the relevant age and gender group. The stream of results are combined and discounted to the base year (2012) to calculate the total discounted costs.

For this calculation, the model time horizon was split into yearly periods since model initiation. Whenever the total lifetime cost was calculated, the costs of relevant years were also updated. For example, the costs accrued between years 2 and 5 were split according to the year in which the cost was incurred and saved in separate cost slots for years 2, 3, 4, and 5. These annual costs incurred by the base-year population and the yearly inflows of individuals were then scaled to the population level by multiplying them by the number of people in a relevant population in the UK, and combined to estimate the total population-level cost of a disease.

Figure 4.2 is a simple representation of the methods for calculating the total annual costs for all populations related to different calendar years. Each rectangle represents the cost incurred in a year by a cohort that entered the model in one of the modelled years. The vertical summation of the rectangles gives the total cost for any relevant year. For example, the total cost for the year 2015 is the sum of the following costs: 1) the cost incurred in 2015 by the base-year population; 2) the cost incurred in 2015 by a cohort that were 45 year old in the entry year 2013; 3) the cost incurred in 2015 by a cohort that were 45 year old in the entry year 2014; and 4) the cost incurred in 2015 by a cohort that were 45 year old in 2015. For ease of calculation, it was assumed that all populations entered the model in the beginning of a year.

Figure 4.2. Calculation of total annual costs
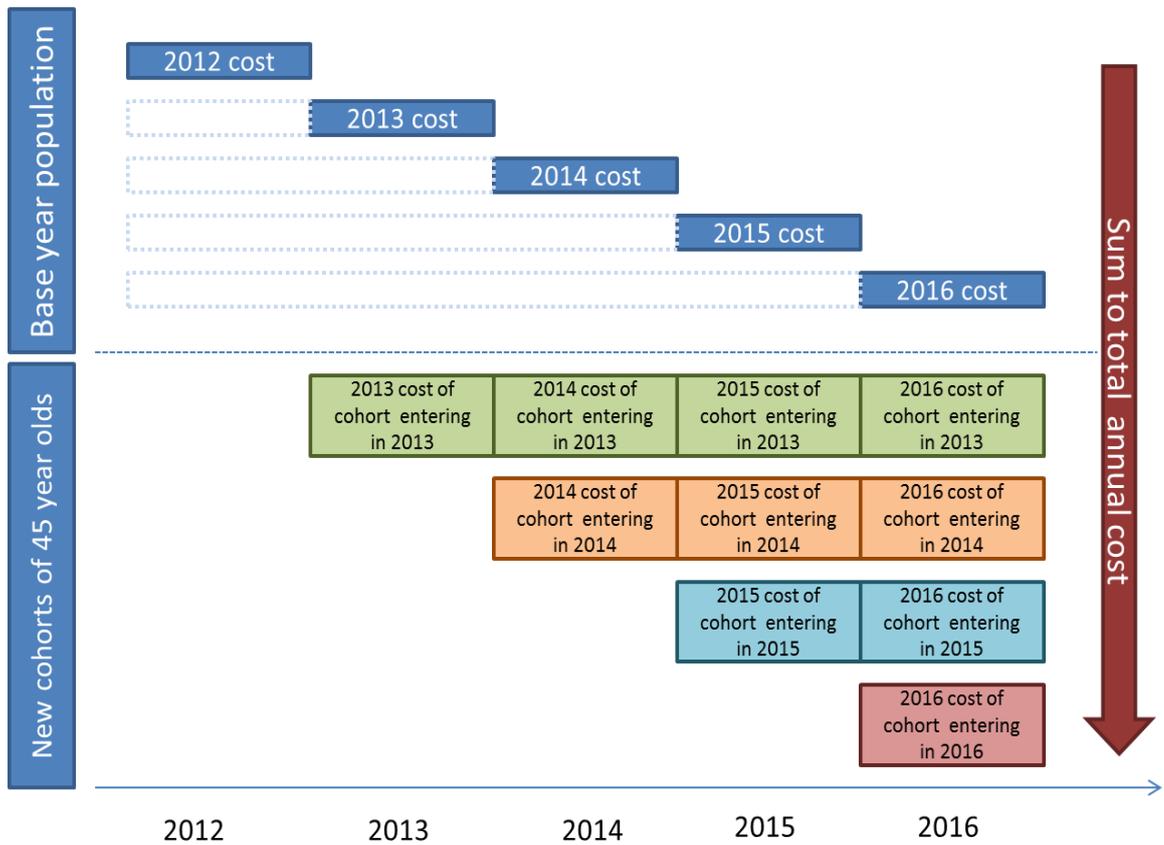
Each rectangle in Figure 4.2 represents the total annual cost of a cohort that entered the model in a certain year. Algebraically, it is calculated as:

$$Total\ annual\ cost\ of\ cohort\ i\ in\ year\ j = \left[Per\ capita\ cost_{ij} \right] \times \left[Number\ of\ people_{ij} \right]$$

, where $Per\ capita\ cost_{ij}$ denotes a per-capita cost for cohort i in year j and $Number\ of\ people_{ij}$ represents a multiplier used to scale the per-capita cost to the population level.

The total projected cost for a calendar year j is the sum of these values across all cohorts relevant to the year j as below.

$$Total\ annual\ cost\ for\ year\ j = \sum_{i \in I} \left[Per\ capita\ cost_{ij} \times Number\ of\ people_{ij} \right]$$

, where I denotes a set of all cohorts that have already entered the model by year j.

These calculations were similar to those used in the cell-based macro-simulation models described in Chapter 3. In the cell-based models, an average cost per person in a 'cell' specified by a combination of pre-determined characteristics of the population such as age and gender was multiplied by the projected number of people in that cell with the cell-level costs summed across all cells that consist of the total population.

Using the model outcomes, this calculation could be performed in two methods. Method 1 is where the per-capita cost is a cost per person *alive* within the model each year. Hence, the per-capita cost is calculated as annual costs for the model population divided by the number of people who are *alive* within the model in year j, and $Number\ of\ people_{ij}$ is the number of people who are projected to be alive at year j by ONS. Costs per person alive would typically increase over time due to the ageing of the remaining population within the model. Time trends in mortality are reflected in both the ONS population projections and the per-capita costs as they account for the population size each year. Also, the use of annual ONS population projections allows their assumptions on birth rates, mortality rates, and migration to be incorporated in the cost projections.

Method 2 is to use the cost per person who *entered* the model and the constant number of people from the ONS population projections over the projection period. The per-capita cost decreases over time as the costs incurred by the remaining individuals within the model are divided by a constant denominator – the total number of people simulated – for all projection years, whilst the number of people in the UK population from the ONS projections remains constant at the level of the population size in the year of the model initiation (e.g. 27 million people for the base-year population). Mortality trend is reflected in the per-capita costs obtained from the simulation model in this method. If the modelled mortality perfectly replicates the mortality, migration, and fertility assumed in the ONS Population Projection (Office for National Statistics, 2013c), the results from Methods 1 and 2 should be the same.

Method 2 was adopted for this thesis as it was simpler where the calculation was not based on 'cells', but just two groups, i.e. 'population aged 45 years and older at base year' and 'future 45-year-olds'. Hence, the calculation would not replicate the method used in the cell-based projection models reviewed in Chapter 3.

In summary, the population-level annual costs are calculated in three steps: 1) per-capita cost for each year estimated from the simulation model; 2) the size of the relevant population from the ONS population projections to scale up the per-capita costs from step 1; and 3) the

summation of the results across all populations related to the specific calendar year, to estimate the total population-level cost in the corresponding year.

Per-capita results for the new incoming cohorts of 45-year-olds were obtained separately for males and females in order to reflect projected changes in the gender composition of future cohorts. The gender proportions reported in ONS mid-2012 Population Estimates (Office for National Statistics, 2013d) were applied to the sex specific results from the model to derive a weighted average of the population-level per-capita costs without increasing the number of simulation runs required. Projected numbers of people aged 45 years at each year and the gender proportions are obtained from the 2012-based population projections (Office for National Statistics, 2013c) and reported in Table 4.3.

The data provided the mid-year population projection, not at the beginning of the year. However, for simplicity, it was assumed that all populations enter the model in the beginning of a calendar year. The impact of the base year population on total annual costs would diminish due to the decrease in the proportion of the base-year population amongst all populations as more people aged 45 years enter the model over time, and those new cohorts generally stay longer in the model due to their younger age.

Table 4.3. Projected numbers of people aged 45 years and gender proportions

Year	Total No. of people	Male%	Female%	Year	Total No. of people	Male%	Female%
2013	924,106	49.27%	50.73%	2029	856,751	49.58%	50.42%
2014	921,371	49.19%	50.81%	2030	880,455	49.92%	50.08%
2015	896,609	49.18%	50.82%	2031	881,070	50.07%	49.93%
2016	915,488	49.07%	50.93%	2032	877,732	49.68%	50.32%
2017	884,136	49.36%	50.64%	2033	905,041	50.19%	49.81%
2018	845,689	49.38%	50.62%	2034	907,723	50.63%	49.37%
2019	808,204	49.31%	50.69%	2035	925,318	51.18%	48.82%
2020	793,088	49.40%	50.60%	2036	948,039	51.16%	48.84%
2021	777,446	49.42%	50.58%	2037	934,265	50.70%	49.30%
2022	761,594	49.66%	50.34%	*Selected years*			
2023	773,552	49.55%	50.45%	2041	891,329	51.62%	48.38%
2024	829,705	49.54%	50.46%	2046	828,270	51.30%	48.70%
2025	866,036	49.36%	50.64%	2051	889,025	51.35%	48.65%
2026	866,160	49.31%	50.69%	2056	950,432	51.41%	48.59%
2027	859,835	49.16%	50.84%	2061	956,886	51.43%	48.57%
2028	861,633	49.33%	50.67%	2062	959,164	51.43%	48.57%

Source: UK ONS (2013) Mid-2012 Population Estimates: United Kingdom

4.3.6. Non-disease deaths

Data on mortality rates not associated with the diseases included in the model were obtained from the UK ONS interim life tables based on the data for the years 2009-2011 (Office for National Statistics, 2013b). Time to non-disease death was drawn from the time to death (TTD) distributions by age and gender estimated for each age up to 100 years and gender by calculating the proportion of people who survived each year, and were applied for all individuals aged 45-100 years.

As the interim life tables include all-cause mortality, the deaths caused by the health events included in the model were subtracted from the number of survivors when estimating the TTD distributions. The mortality rates associated with diseases were obtained from the Mortality Statistics: Deaths registered in 2012 (Office for National Statistics, 2013a). For heart disease, death rates reported for heart disease (ICD-10 code I00-I52) and stroke (I64) were combined, and subtracted from the all-cause mortality rates as detailed in Chapter 5.

Probability profiles, or discrete probability distributions, where the values of time to non-disease death are attached to probabilities of the values being sampled were created for each age and gender. The distributions for age at death unadjusted for disease-related deaths are given in Figure 4.3. To illustrate, only the distributions for males and females at a few selected ages are shown. It is noted that the probability of death at the age of 100 years was higher as mortality rates for those aged over 100 years were combined due to the age limit of the model population.

Figure 4.3. Distributions of age at death for the UK population aged 45 years (unadjusted for disease-related deaths)

a) 45 years male

a') 45 years female

b) 65 years male

b') 65 years female

c) 85 years male

c') 85 years female
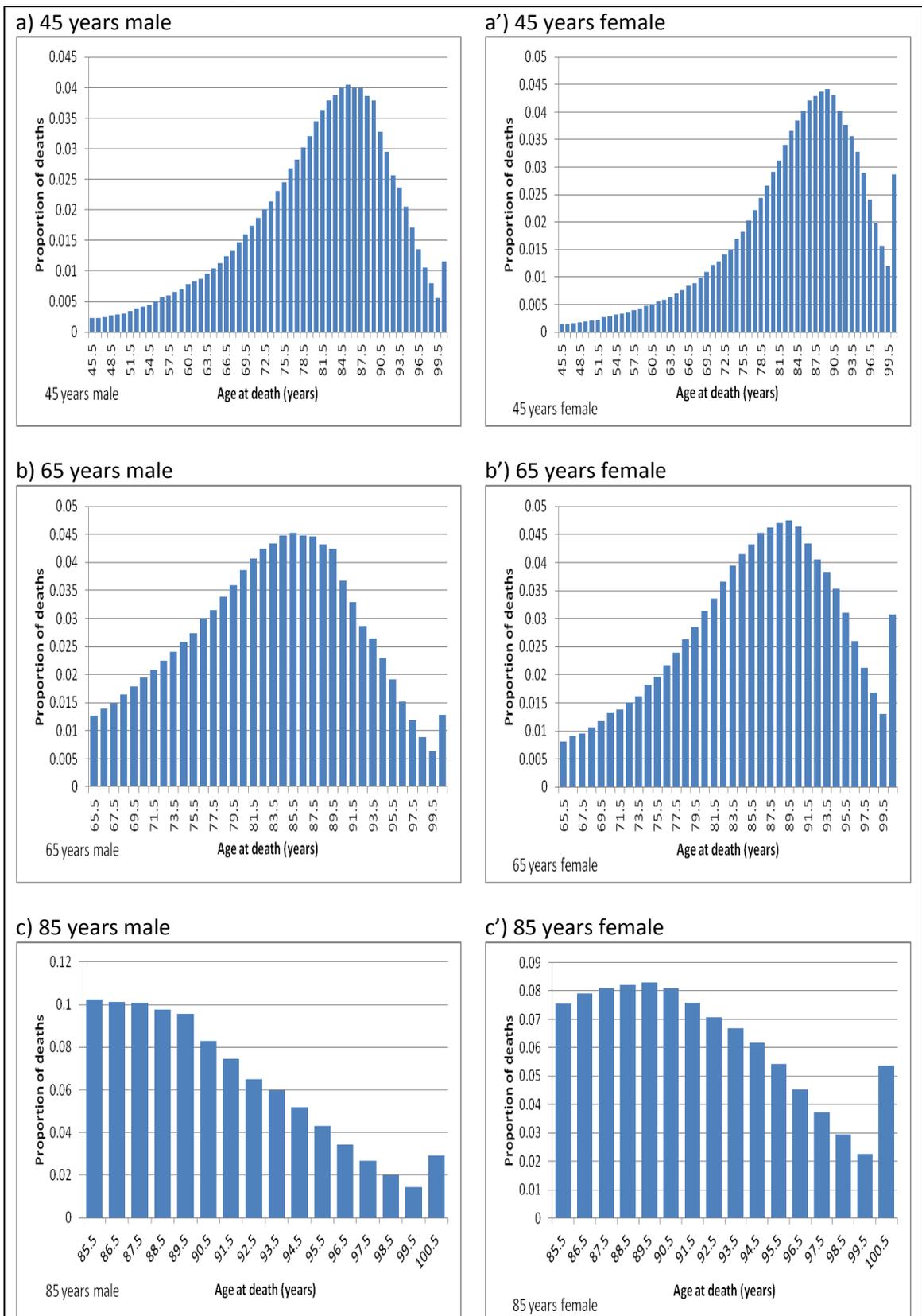
4.3.7. Utilities

Baseline utility values by age and gender in the UK general population were estimated from a statistical model in the study by Ara and Brazier (2010). Deterministic values were used in the base-case model (Table 4.4).

Table 4.4. Baseline utility by age and gender

Utility values								
Age	Male	Female	Age	Male	Female	Age	Male	Female
45	0.893	0.872	65	0.815	0.794	85	0.710	0.689
46	0.890	0.869	66	0.810	0.789	86	0.704	0.683
47	0.887	0.865	67	0.806	0.784	87	0.698	0.677
48	0.883	0.862	68	0.801	0.780	88	0.692	0.671
49	0.880	0.858	69	0.796	0.775	89	0.686	0.665
50	0.876	0.855	70	0.791	0.770	90	0.680	0.659
51	0.873	0.851	71	0.786	0.765	91	0.674	0.652
52	0.869	0.848	72	0.781	0.760	92	0.667	0.646
53	0.865	0.844	73	0.776	0.755	93	0.661	0.640
54	0.861	0.840	74	0.771	0.750	94	0.654	0.633
55	0.857	0.836	75	0.766	0.745	95	0.648	0.627
56	0.853	0.832	76	0.761	0.739	96	0.641	0.620
57	0.849	0.828	77	0.755	0.734	97	0.635	0.613
58	0.845	0.824	78	0.750	0.729	98	0.628	0.607
59	0.841	0.820	79	0.744	0.723	99	0.621	0.600
60	0.837	0.816	80	0.739	0.718	100	0.614	0.593
61	0.833	0.812	81	0.733	0.712	101	0.607	0.586
62	0.828	0.807	82	0.728	0.706			
63	0.824	0.803	83	0.722	0.701			
64	0.820	0.798	84	0.716	0.695			

Source: Ara and Brazier (2010)

Events may occur at intervals longer than a year, with the age of the individuals change between events. For simplicity, the utility value corresponding to the age at the half point of such intervals was applied. For example, if the first event occurred at age 52 and the second at age 60, then the utility value related to the halfway in the interval, that is, age 56, was used for the calculation of QALYs accrued between the events.

4.3.8. Costs

The cost estimates used in the existing models reviewed prior to modelling each disease were assumed to be correct. Typical data sources of medication and hospital costs included the British National Formulary (BNF) (Joint Formulary Committee, 2014) and Healthcare Resource Group (HRG) data (National Casemix Office, 2007). These costs were inflated to the 2012 price using the Hospital and Community Health Services (HCHS) pay and price inflation index (Curtis, 2013). Although the indices were available up to the year 2012/2013, costs were inflated to 2011/2012 as the data from which the model population was generated were based on mid-2012 estimates. For drug costs, the 2014 price was obtained from the BNF (Joint Formulary Committee, 2014). Given that the drug price typically decreases or remains at the same level over time, the mismatch between the drug price year and other cost year was deemed acceptable.

The costs of interventions and prevention policies to be evaluated within this study were obtained from other published studies examining such interventions or policies, and from sources such as the BNF. Future medical costs for 'unrelated' diseases other than the diseases incorporated in the model were not included. However, there has been controversy over what constitutes 'related' and 'unrelated' costs (Meltzer, 1997).

4.3.9. Discounting

As recommended by NICE (National Institute for Health and Care Excellence, 2013), an annual discounting rate of 3.5% was assumed for both costs and benefits as a base case. It was used for one-off costs incurred at a specific point in time (discrete rate).

In DES models, time cycles are not fixed and thus no assumption on the time point within cycles when a health state cost is incurred is made. Hence, a continuous discounting rate corresponding to the discrete rate was applied to any on-going costs (e.g. costs that are continuously incurred after an event) and QALYs that accrue over time. When the annual discount rate is 3.5%, the continuous discounting rate, r, is 0.0344 as $e^r = 1.035$. Assuming the discount rate remains constant over time, the discounted outcome is calculated using the survival function of an Exponential distribution, $S(t) = e^{-rt}$, where time $t \geq 0$ and $r > 0$. The total discounted cost or benefit accrued up to the time t_1 is subtracted from the total

discounted value accrued up to t_2, where t_1 and t_2 are event times and $t_1 < t_2$, to calculate the cost or benefit accumulated between t_1 and t_2. Each of these total accrued values is equivalent to the integral of an exponential survival function with the failure rate being the discount rate. Algebraically, the discounted cost or benefit accrued between t_1 and t_2 is $A \cdot \frac{(e^{-r \cdot t_2} - e^{-r \cdot t_1})}{-r}$, where $t_1 < t_2$, A is an undiscounted ongoing cost or benefit, and r is the continuous discount rate.

4.4. General methods for linking individual disease models

4.4.1. Modelling methods for linked model

Individual disease models are linked in a single model with a common entry point for all simulated individuals. In the linked model, the competing risks across all individual disease models are compared and individuals are directed to move to the event corresponding to the earliest scheduled time to event.

Individuals enter the combined model with the values of all patient characteristics relevant to the modelled diseases sampled at the entry point. These characteristics may be used for the sampling of times to next event and/or the calculation of costs and QALY accruals. They enter the model through the central routing point where the transition to the next event is executed. Once the patients move to the event and all relevant parameters are updated, they return to the central router to be routed out to a next event. This process is repeated until a patient is simulated to die. By recording the history of previous events the model can account for co-morbidities, in terms of utility and influence on risks of future events.

Figure 4.4 shows the linkages between individual disease models. Individuals may enter the model with one or more of the diseases (or without diseases) and move immediately to the central routing point and directed to the same or different diseases with the history of the previous disease event. Conceptually, individuals initiate at the central routing point before moving to any disease or death event.

Figure 4.4. Model linkage
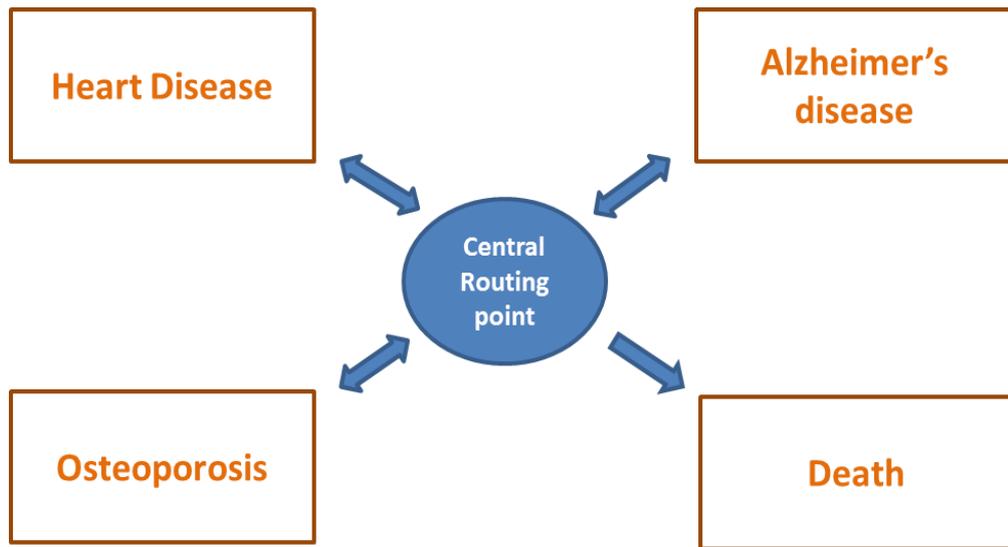
Individuals in the linked model move between events via a central router. In the individual disease model, the transitions were made to the next event from the last event state, but in the linked model, individuals can move to the next event only through the central router (see Figure 4.5). The central router directs simulated individuals to the event with the earliest event time across all diseases included. Before moving to the next event, the individual visits the central router where the disease-level times to next event are compared, and the patient routed accordingly. The times to all further predicted events are then reduced by the time to the next event to account for the passing of time.

Figure 4.5. Role of Central Router

Table 4.5 illustrates this time update and routing, following an individual from the model entry. Times to next event are updated at each event and the simulation time is shown alongside. For simplicity, the actual events (e.g. stroke and myocardial infarction) have not been documented. In this process, both the time and type of previous events are recorded. The most recent time-to-event values within each disease model are kept for comparison of time to next event (TTNE) across diseases at the central router. These TTNE values are updated based on the previous event; if the previous event was from one disease, TTNEs for the other diseases are subtracted by the time spent for that previous event. For example, if the previous event was one of the heart disease events, the most recent TTNE value for Alzheimer's disease events are updated by subtracting time passed since sampling of that value. By recording the history of previous events, the model accounts for co-morbidities.

Then, any other time-related variables are recalculated in the central router after TTNE across all included diseases is determined. These variables include, for example, time left before the effect of treatments stopping, time left before the first year of any cardiac events or osteoporotic fractures, or any time periods that require time recording due different event rates, costs, or utility weights being applied.

In this thesis, the heart disease and Alzheimer's disease models were linked first, and osteoporosis was added to the two-disease model. The following chapters will report results from the two- and three-disease linked models.

Table 4.5. An illustration of time changes at the central router – How individuals move between events in the linked model

Simulation time	Location (Event where updates occur)	Time to next disease event
Time 0	Entry	Time to next heart disease event: Sampled to be 2.5 years Time to next Alzheimer's disease event: Sampled to be 12 years Time to next osteoporosis event: Sampled to be 4.5 years
Time 0	Central router	• Time to next event: 2.5 years (heart disease event)
Time 2.5	Heart disease event	Next heart disease event: Sampled to be 6.8 years
Time 2.5	Central router	Next heart disease event: 6.8 years Next Alzheimer's disease event: Updated to 9.5 (12-2.5) years Next osteoporosis event: Updated to **2** (4.5-2.5) years • Time to next event: 2 years (osteoporosis event)
Time 4.5	Osteo event	Next osteoporosis event: Sampled to be 7.3 years
Time 4.5	Central router	Next heart disease event: Updated to **4.8** (6.8-2) years Next Alzheimer's disease event: Updated to 7.5 (9.5-2) years Next osteoporosis event: 7.3 years • Time to next event: 4.8 years (heart disease)
Time 9.3	Heart disease event	Next heart disease event: Sampled to be 8.2 years
Time 9.3	Central router	Next heart disease event: 8.2 years Next Alzheimer's disease event: Updated to 2.7 (7.5-4.8) years Next osteoporosis event: Updated to **2.5** (7.3-4.8) years • Time to next event: 2.5 years (osteoporosis)
		⋮ The process continues until death

4.4.2. General methods for incorporating correlations between diseases

At the common entry point, individuals are assigned the values of patient characteristics relevant to all modelled diseases such as age, gender, baseline cognitive function scores and presence of heart disease history. At the model initiation, times to first event for all diseases included are sampled to be compared at the central router. Once individuals move to an event state as directed at the central router, all relevant parameters are updated at the event state and return to the central router to be routed out to a next event, and this process is repeated.

In the linked model, possible correlations between diseases in terms of incidence and/or prevalence rates are incorporated. Wherever possible, data on the incidence and prevalence of one disease with and without the other diseases will be obtained. For example, in the model linking AD and heart disease, the incidence of AD for the total population would be split into that for population with heart disease and for population without heart disease. If the risks of developing the diseases are independent, the incidence (or prevalence) of the disease will be the same regardless of the presence of the others. However, if there are correlations, the presence of one disease may increase or decrease the probability of another.

When a disease is assumed to progress based on time, the rate of this disease progression was applied for all events – not only those associated with the corresponding disease, but all other diseases. For example, cognitive function and functional capacity scores for AD patients decline over time. This time-based decline was applied in all heart disease, AD and osteoporosis related events. In the same way, if the effect of a treatment differs according to the time lapsed after treatment initiation, the model adjusted for the treatment effect at all other disease events in order to reflect the treatment effect at all event times.

Individuals with multiple diseases may have a higher risk of death. Co-morbidities were taken into account for disease-related death as competing risks; even when the individual is in an event associated with one disease, time to death related to the other prevalent diseases is compared in order to reflect the possible correlation. This means that the disease-related mortality rate for individuals with multiple diseases is the maximum of mortality rates associated with the co-existing diseases. The combined disease-related death rates could be lower than the crude sum of death rates related to each of the diseases included. However,

this was not incorporated in the linked model due to lack of data encompassing the three diseases included.

Death may not be related to any of the diseases explicitly modelled. Non-disease mortality rates in the linked model were defined as all-cause mortality minus death rates associated with the diseases included in the model.

Costs incurred by those with co-existing conditions may be higher or lower than the crude sum of costs of all diseases that the individual has. The possible correlations between diseases with respect to the cost of treatment and management were explored, and included in the model wherever possible. Where no data could be found, costs were assumed to be additive; if an individual has two or more diseases, the cost for each of the co-existing diseases was added to the total.

Wherever possible, utility weights accounting for comorbidities were used. However, it was expected to be difficult to find appropriate data given that utility weights are typically reported for a single disease. In such cases, utility weights for QALY calculation were assumed to be multiplicative; a utility for one disease was multiplied by that for another disease that is present in the same individual. Hence, the effect of disease is reduced where there is already a prevalent disease.

4.4.3. Modelling framework

The modelling methods described in Sections 4.3 and 4.4 and the main steps involved in applying the modelling framework are summarised in Figure 4.6.

Subsequent chapters are structured to reflect the steps described in this modelling framework. Chapters 5-7 describe individual disease models for HD, AD and osteoporosis, respectively. Chapter 8 details the literature identified on the correlations between the diseases and how the identified data were used. Chapter 9 reports results from the linked models and scenario analyses.

Figure 4.6. Modelling framework used in this thesis

1. Individual disease modelling

For each disease to be included in the model,
1) Determine the scope of the model (disease events, population, time horizon, etc.)
2) Conduct a review of existing models associated with the disease of interest
3) Create a conceptual model: Determine the structure of the model and disease events to include, based on the review
4) Implement the conceptual model into DES model code
5) Verify and debug the model while doing Steps 1)-4)
6) Repeat 1)-5) for all diseases
7) Validate the individual model results against the results from the existing models identified in Step 2)

2. Model linkage

1) Link the individual disease models by creating a central routing point, so as to determine time to next event across all included diseases
2) Move the model code that updates time-related individual attributes after a time to next event is determined to the central router

3. Correlations between diseases incorporated

1) Conduct a review of evidence on correlations between disease events included in the model
2) Adjust the prevalence, incidence, and other parameters for the correlations identified
3) Validate the results from the correlation-adjusted model against those before incorporating correlations
4) If required, calibration of model parameters is conducted

4. Analyses

1) Determine the appropriate number of simulated individuals to obtain robust results.
2) Produce base-case estimates of cost-effectiveness and future healthcare expenditure using the linked model results.
3) Conduct scenario analyses by incorporating relevant changes in the model.
4) Analyse the model results.

CHAPTER 5 INDIVIDUAL DISEASE MODEL 1 – MODELLING HEART DISEASE

5.1. Background

Cardiovascular disease (CVD) is defined as a disease of the heart and blood vessels. The most common manifestation of CVD is coronary heart disease (CHD), also known as coronary artery disease and ischaemic heart disease. The prevalence of CVD increases with age and is higher among men (World Health Organization, 2012).

Potentially important risk factors for CVD events include risk factors that cannot be modified such as age and sex, and modifiable risk factors such as high blood pressure, high blood cholesterol levels, obesity (or high body mass index or physical inactivity), and cigarette smoking (Frayn and Stanner, 2005). People with diabetes are also at an increased risk of CVD (American Heart Association, 2013).

Although the definitions of prevention of CVD vary across studies, primary prevention generally refers to interventions that aim to prevent cardiovascular events in people who have no clinical evidence of CVD, whilst secondary prevention aims to prevent further CVD events in those for whom there is already manifested clinical evidence of CVD (NICE Technology Appraisal (TA) 94). For simplicity, CVD is referred to as heart disease hereafter.

5.2. Review of existing heart disease models

A rapid (non-systematic) review of recent heart disease models was undertaken. Searches for the existing models were based on recently published HTA reports if available. If the HTA report included a recent systematic review of models for economic evaluation of relevant health technologies, the models included in that review were also examined. Searches using keywords identified from the reviewed studies were undertaken to identify models published

after the HTA report. The NHS Economic Evaluation Database (NEED) database was also searched. The modelling methods, structure, and data sources of heart disease models published between 2009 and 2013 were identified and used to inform decisions on the model for this study.

A total of 15 papers relating to 12 models were identified from this review. Table 5.1 summarises the modelling methods used in the identified models.

Among the twelve heart disease models, six models used UK sourced data, and were conducted from the perspective of the UK NHS and PSS. The majority of the identified models for heart disease employed an aggregate-level state-transition model (10 models). Seven of the reviewed models assessed the cost-effectiveness of statin treatments; all concluded that statins were considered cost-effective when applying a threshold value generally accepted in the relevant country. The models were divided into those including interventions for primary prevention of cardiovascular events, which aim to prevent CVD events in people who did not previously experience the events, and those for secondary prevention, whose aim is to prevent further CVD events in people who already experienced one or more CVD events (NICE, 2006). Four models assessed interventions for primary prevention, five for secondary prevention, and three models included both primary and secondary prevention interventions.

Among the UK models, two models (Lindgren et al., 2009, Ward et al., 2006) included both primary and secondary prevention populations. The model by Ward et al. (2006) was considered appropriate to choose as the basis of the model in this thesis, as the current guidance recommended by the UK NICE was based on their model (as of December 2013), and it used data collated from a variety of sources unlike Lindgren et al. (2009) which was mainly based on a single clinical trial. Where applicable, sources of data and key assumptions reported in Ward et al. (2006) were considered as the main reference for the model in this thesis.

Table 5.1. Summary of the existing models included in the review

Study	Aim	Model type	Individual / Cohort-level	Countries	Target population	Primary vs. Secondary prevention	Structure	Health states	Cycle length / Time horizon	Notable assumptions	Conclusion
De Smedt et al. (2012)	To quantify the clinical and cost-effectiveness of optimizing secondary prevention	individual-based state-transition model	individual	Belgium, Bulgaria, Croatia, Finland, France, Italy, Poland, and the UK	EUROASPIRE III survey participants (i.e. patients aged 18-80 years and admitted to a hospital for an acute coronary event or a cardiac procedure)	Secondary prevention	All patients start in the CABG/ PTCA/ MI/ angina disease state. Every cycle, patients can suffer one of a coronary event, a stroke, or heart failure and move to the CHD state, CVD state, or CHF state, respectively. Once in one of these subsequent event states, patients enter a post-event state after one cycle	Three disease states (CHD, CVD, CHF), two post-event states (post-CHD, post-CVD), and a death state	6-month cycles; 10 year horizon.	Patients suffering a MI will move to the CHD state. Patients suffering a stroke will move to the CVD state, patients suffering a heart failure will progress to the CHF state.	Overall, optimizing secondary prevention based on the 2003 joint European guidelines is cost-effective compared with the current degree of cardiovascular prevention with an ICER of €12,484/QALY, when using a willingness to pay threshold of €30,000/QALY.
Ohsfeldt et al. (2012)	To examine the cost-effectiveness of rosuvastatin for primary prevention of major CVD for various risk levels over a long-term horizon	Monte Carlo simulation model	Individual	Sweden	Patients with a 10-year Framingham CVD risk >20 % were simulated in the model using the characteristics of the JUPITER clinical trial patients.	Primary prevention	Three health stages were included: 1) event free for the duration of the JUPITER trial, 2) event free beyond the 4 years of the trial for those without a CVD event, and 3) post–CVD event stage for those who experience a non-fatal CVD event.	1) Initial CVD prevention during RCT 2) Initial CVD prevention – Post RCT and 3) post–CVD event stage.	1 year cycles; Lifetime horizon	Initial and subsequent CVD events and death were estimated over the long term (20 years and lifetime of patients [to age 100 years] CVD events tracked in the model include: non-fatal MI; non-fatal stroke; unstable	Considering the generally accepted threshold value in Sweden, treatment with rosuvastatin 10 mg or 20 mg daily is cost-effective compared to relevant doses of simvastatin in the primary prevention of CVD for Swedish patients with high baseline CV risk (10-year Framingham

											angina; CABG; PTCA; CVD death; non-CVD death; venous thromboembolism (VTE) death; and non-fatal VTE.	CVD risk >20 %).
Galper et al. (2012); Lazar et al.(2011)	To assess the cost effectiveness of non-invasive stress testing to guide the use of aspirin and statins for primary prevention of coronary heart disease (using the US CHD Policy model).	Markov model	Cohort	US	US men aged 45 years in 2011 and women aged 55 years in 2011 who had an intermediate risk (10%–20%) of developing a CHD event in the next 10 years on the basis of the Adult Treatment Panel III (ATP III) guideline point system.	Primary prevention	Markov cohort model of CHD incidence, prevalence, mortality, and costs among people aged 35 to 84 years in the US. The demographic-epidemiological sub-model predicts CHD incidence and non-CHD mortality among people without CHD, stratified by age, sex, blood pressure, smoking status, high-density lipoprotein cholesterol level, LDL cholesterol level, diabetes mellitus, and use of aspirin or statin therapy.	CHD events, CHD death, and non-CHD mortality.	1 year cycle; Lifetime horizon	As reliable evidence for effective primary prevention of acute myocardial infarction with aspirin exists only for men (relative risk of 0.77), only eligible male patients were prescribed aspirin; For the primary analysis, effectiveness and treatment adherence rates were assumed to be equivalent to those observed in clinical trials.	Using a national-scale computer simulation model of CHD in US adults, we project that universal treatment of intermediate-risk women with statins and intermediate-risk men with statins plus aspirin, regardless of their LDL levels, would be a cost-effective CHD primary prevention policy.
Gillespie et al. (2012; 2010)	To examine the cost-effectiveness of the Secondary Prevention of Heart disEase in geneRal practicE (SPHERE)	Markov model	Cohort	Ireland	Patients with CHD (documented MI, CABG, PTCA, or angina).	Secondary prevention	Patients start the Markov simulation in the 'CHD' state. In each cycle, individuals can experience a fatal event or a recurrent nonfatal CHD event (MI or angina) or survive the year without	Disease progression was modelled with three discrete health states: 'CHD',	1 year	A series of published risk equations formed the basis for the transition probabilities in the model. In the case of stable angina SA and	The SPHERE intervention dominated control.

intervention (tailored care plans where *practices* received training in prescribing and behaviour change, administrative support, etc.; and *patients* received motivational interviewing, target setting for lifestyle change, review visits).						experiencing a recurrent CHD event. Individuals who experience a MI progress to the 'Post-MI' state, a 1-year tunnel state, in which they are at an elevated risk relative to the general population for 1 year. If they survive this year, they return to the 'CHD' state for the beginning of the next cycle. An individual who is predicted to experience a fatal event transitions to the 'Dead' state.	'Post-MI' and 'Dead'.		unstable angina UA, while the model includes differing rewards in terms of costs and utilities, it is assumed that there is no additional risk in the subsequent year, and the individual remains in the 'CHD' state.	
Earnshaw et al. (2011)	To examine the cost-effectiveness of aspirin with or without a proton-pump inhibitor (PPI) to prevent gastrointestinal bleeding, while preventing CHD, in men with various risks of CHD and GI bleeding.	Markov model	Cohort	US	Men in the base-case analysis were assumed to be healthy, middle aged men with starting age of 45 years, no history of CHD events, and 10%, 10-year CHD risk.	Primary prevention	Men began treatment in the healthy state. During each cycle, men could remain in the healthy state; progress to initial, non-fatal cardiovascular events such as angina, MI, or stroke; have upper GI bleeding; or die.	Angina, stroke, MI and GI bleeding	1 year; Lifetime horizon	Men who had CVD events were assumed to stay in the sub-acute state for the remainder of that cycle and then entered a post-event health state during which they received optimal secondary preventive care. Men can progress from any health state to death	Treatment with aspirin for CHD prevention is less costly and more effective than no treatment in men older than 45 years with greater than 10-year, 10% CHD risks. Adding a PPI may only be cost-effective for selected men at increased risk for GI bleeding.
Grosso	To assess the cost-utility of	Markov model	Cohort	UK	Patients with hypertension	Primary preventi	The entire cohort starts in the 'Well' state, and	'Well', 'Coronary	1 year;	10 year time horizon was used.	Candesartan, the most widely

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Author	Objective	Model		Country	Population	Prevention	Model description	Events	Horizon	Risk equations	Results
et al. (2011)	adopting losartan or candesartan in the management of hypertension and heart failure				and high risk of heart failure.	on	can transition annually to the coronary heart disease and cerebrovascular disease states, or they can survive or die from either MI, stroke events, or other causes. A risk sub-model was then used to calculate the age- and sex-related probabilities of stroke and CHD risk for each year in the model, based on Framingham risk equations.	Heart Disease (CHD)', 'Stroke' and 'Death'	10 year horizon		prescribed angiotensin II receptor blocker (ARB), shows small difference in reducing blood pressure when compared with losartan, and does not appear to be cost-effective based on current and near future acquisition costs of losartan. No robust evidence supporting the superiority of candesartan over losartan was found in the treatment of heart failure.
Soini et al. (2010)	To evaluate the cost-effectiveness of generic atorvastatin 20 mg (A20), branded rosuvastatin 10 mg (R10), generic simvastatin 40 mg (S40) and the combination of generic S40 + branded ezetimibe 10	Markov model	Cohort	Finland	Patients not meeting the target goal of low-density lipoprotein cholesterol (LDL-C) with S40. Different populations were considered including patients with or without diabetes, with various serum cholesterol	Secondary prevention	A probabilistic Markov model based on the recurrent CHD component of a broader model. Patients have an annual probability of experiencing a recurrent non-fatal event (MI or angina), a fatal event (CHD death and non-CHD death), or no CHD event.	Recurrent non-fatal events (MI or angina), and fatal events (non-CHD death or CHD death) or no CHD event.	1 year cycle; Lifetime horizon	The risk of a fatal CHD event was predicted using Anderson's individual event risk equations. The target population inputs for age, systolic BP and SC were assumed to be similar to values of high risk subjects who have CHD and/or DM (n=450) in the representative	In the Finnish secondary prevention population that is not at goal on S40, switching generic S40 to S40 þ EZ10 is more cost-effective than switching S40 to generic A20 or R10.

	mg (S40 + EZ10) for the secondary prevention of coronary heart disease (CHD).				profiles, and of either gender.					population-level FINRISK 2002 study.	
Ara et al. (2009)	To evaluate the cost-effectiveness of high-dose statins (atorvastatin 80 mg/day, rosuvastatin 40 mg/day and simvastatin 80 mg/day) versus simvastatin 40 mg/day in individuals with acute coronary syndrome (ACS), whose symptoms include acute MI and angina.	Markov model	Cohort	UK	Individuals with acute coronary syndrome (ACS) who have experienced a recent ACS event.	Secondary prevention	All individuals start in one of the three health states, unstable angina, non-fatal MI or revascularisation. Age-related transition probabilities were used to model the probabilities associated with the first year or subsequent year events. Individuals who did not experience an event in the current year moved to the corresponding 'post' health state, and subsequent year event rates were applied.	Unstable angina, MI, revascularisation, stroke, CVD mortality, and non-CVD mortality.	1 year cycle; Lifetime horizon	Combined health states were included in which transitions rates to future events were assumed to be the maximum value associated with the events previously experienced. Individuals do not move to a health state with smaller costs and a greater quality of life.	When using a threshold of £20,000 per QALY, the probabilistic base-case analysis showed that all the statin regimens compared (simvastatin 80 mg/day, atorvastatin 80 mg/day and rosuvastatin 40 mg/day) would be considered cost-effective compared with simvastatin 40 mg/day in individuals with ACS.
Taylor et al. (2009); Rosen et al. (2010)	To examine the cost effectiveness of high-dose versus low-dose statin therapy in CHF patients. To assess the cost effectiveness of Atorvastatin 80mg versus A10 in	Markov model	Cohort	US, UK, Spain, and Germany	Patients with stable coronary heart disease	Secondary prevention	Major CVD event status (stable CHF/CHD, one major event, various combinations of two major events), minor events and survival. Separate major event states include MI, stroke, CHF, revascularization, and resuscitated cardiac arrest, as well as all	Major cardiovascular events [MI, stroke, CHF, revascularisation, resuscitated cardiac arrest	1 year; Lifetime horizon	Health states involving two major events allow for all possible combinations of events (excluding RCA). A second event is considered in the model only if it occurs within 1 year of the first event. Patients in	Intensive lipid-lowering treatment with 80 mg atorvastatin appears to be a cost-effective use of health-care resources vs moderate statin treatment with atorvastatin 10 mg in secondary cardiovascular

	secondary cardiovascular prevention						possible combinations of two major events (excluding resuscitated cardiac arrest). Minor events include PAD, TIA, and angina.	(RCA)], Minor cardiovascular events [PAD, TIA, angina], and Death.		major event states are subjected to the long-term utility and survival consequences of their specific cardiovascular event(s). Minor events result in only short-term cost and utility consequences.	prevention.
Bennett et al. 2009	To examine the cost-effectiveness of various coronary heart disease (CHD) treatments (including medical and surgical treatments)	Cell-based policy model	Cohort	Ireland	Men and women aged 25 to 84 years in Ireland	Primary and secondary prevention	The model utilises a very large Microsoft Excel spreadsheet to integrate data on: CHD patient numbers, uptake of specific medical and surgical treatments, effectiveness of specific treatments, and median survival in patients with and without CHD	MI, revascularisation, angina, and heart failure.	NA	Other information on the model is available on the IMPACT website (http://www.liv.ac.uk/PublicHealth/sc/bua/impact.html), as well as on http://www.ispor.org/publications/value/ViHsupplementary.asp.	ICERs favoured simple medical treatments using aspirin, beta-blockers, ACE inhibitors, spironolactone, and warfarin for MI, secondary prevention, angina, and heart failure (<€3000/LYG) and statins for secondary prevention (<€7000/LYG)
Lindgren et al. (2009)	To assess the cost effectiveness of four alternative treatment strategies in patients with hypertension and three or more cardiovascular risk factors in	Markov model	Cohort	Sweden, and the UK.	Men and women aged between 40 and 79 years, with either untreated hypertension, or treated hypertension while not being treated with a statin or	Primary and secondary prevention.	Patients in the event-free state stand a risk of experiencing any of the three events (MI, revascularisation, and stroke) which in the case of strokes and MIs may or may not be fatal. Patients in the event states either die or remain within their current state for the	Event free, MI, revascularisation, stroke and death	1 year cycles; Lifetime horizon	The three event states (MI, revascularisation and stroke) were implemented as tunnel states to allow for differentiation of costs and lost utility over time.	Applying the threshold values generally used in the UK and Sweden, a combination of amlodipine-based therapy and atorvastatin appears to be cost effective in patients with hypertension and three or more

	the UK or Sweden.				fibrate, and have a total cholesterol concentration of 6.5 mmol/L or lower.		rest of the simulation. This means that only first events are explicitly incorporated in the model.				additional risk factors
Ward et al. (2006)	To appraise the cost effectiveness of the use of statins for the management of patients at increased risk of death or other cardiovascular events from CHD and to advise on any patient groups for whom statins might be particularly appropriate.	Markov model	Cohort	UK	Patients at increased risk of death or other cardiovascular events from coronary heart disease	Primary and secondary prevention	For the primary prevention analyses, all patients commence the evaluation in the event free health state. During each annual cycle of the model, a proportion of patients enter one of the qualifying event health states while the remainder remain in the event free state. For the secondary prevention analyses all patients commence in either post MI, post stable angina, post unstable angina, post TIA or post stroke health states.	MI, stable angina, unstable angina, CHD death, TIA, stroke, CVD death or death through other causes	1 year cycles; Lifetime horizon;	The proportion of patients in each of the health states is governed by age dependent time-variant transition matrices which describe the annual probability of moving to an alternative health state.	Using a threshold of £20,000 per QALY, the results of the probabilistic sensitivity analysis show that statin therapy is cost effective for all patients with a history of coronary heart disease

EUROASPIRE: European Action on Secondary and Primary Prevention by Intervention to Reduce Events; ICER: incremental cost-effectiveness ratio; CABG: coronary artery bypass graft; PTCA: percutaneous transluminal coronary angioplasty; CHD: coronary heart disease; CVD: cardiovascular disease; CHF: congestive heart failure; PAD: peripheral artery disease; TIA: transient ischemic attack; GI: gastrointestinal;

5.3. Model Overview and Structure

5.3.1. The model structure and health events included

An individual-level DES model was used to track the clinical pathways of patients at risk of cardiovascular disease: individual patients are simulated to move through different disease events according to the individual-specific event schedules sampled from appropriate time-to-event distributions.

Figure 5.1 depicts the structure of the DES model that was used for this analysis. The rest of this section describes how the health events have been selected and provides an overview of the model structure.

Figure 5.1. The structure of the model
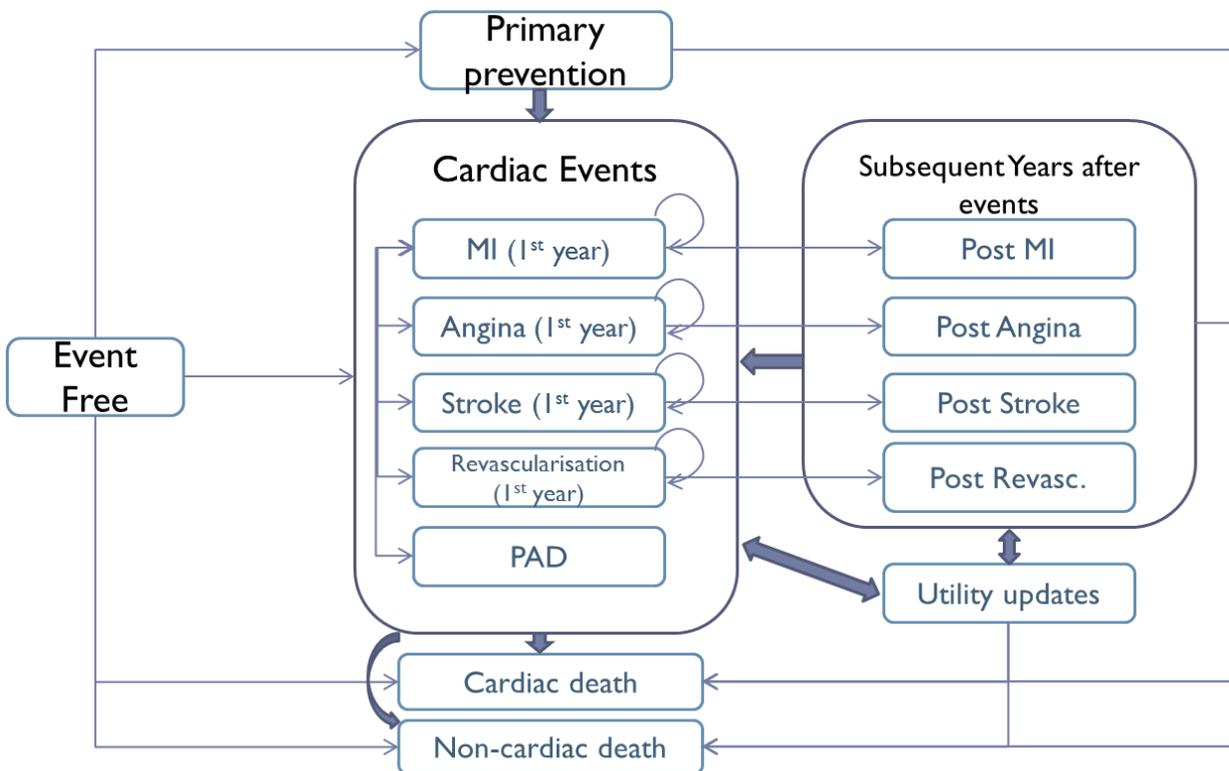
MI: myocardial infarction; PAD: peripheral artery disease; Revasc: revascularisation

The model includes health events that were commonly used in other published heart disease models. The health states included in the existing models reviewed in Section 5.2 are summarised in Table 5.2. The major events included were MI, angina, and stroke; all models in the review included MI, whereas angina and stroke were also frequently included. More than half of the models (n=7) included revascularisation, such as coronary artery bypass graft (CABG) and percutaneous transluminal coronary angioplasty (PTCA), as one of the health states (Ara et al., 2009, Bennett et al., 2009, Ohsfeldt et al., 2012, Rosen et al., 2010, Taylor et al., 2009, Lazar et al., 2011, Galper et al., 2012, De Smedt et al., 2012, Lindgren et al., 2009). Although this is an intervention rather than a cardiac event, it was chosen to be an included event due to its significant cost and health implication.

Although peripheral arterial disease (PAD) was included in only one model in the review, it was included in the model developed for this thesis. PAD, a deficit caused by ischaemia due to impaired blood flow to a limb, is a chronic disease, and was considered potentially related to high healthcare costs for the older population. Hirsch et al. (2008) estimated the mean Medicare expenditure for the treatment of PAD to be over $13,000 per person although this is based on the US data which may be considerably different from the UK cost. However, there is a paucity of UK-sourced evidence on the economic burden of PAD. One UK study by Hart and Guest (1995) estimated that critical limb ischaemia (CLI) —the most severe manifestation of PAD that can lead to major amputation or death if not treated promptly – costs the NHS more than £200 million annually.

Although the HTA report by Ara et al. (2009) excluded PAD due to the paucity of trial data, it reported that PAD is also associated with high risks of MI, stroke, amputation, and death, as well as significant quality of life impairments. Also, the high prevalence implies significant NHS costs associated with PAD. The prevalence of PAD is estimated to be high among the elderly, and increase with age. The worldwide prevalence was estimated to be nearly 10%, rising to 15-20% in people aged 70 and over (Criqui et al., 1992). The Edinburgh Artery Study estimated that approximately 20% of people aged from 55 to 75 years have evidence of PAD in the legs (Fowkes et al., 1991), and around 4.5% of people in this age group within the UK were estimated to be affected by intermittent claudication (IC), the most common symptom of PAD (Squires et al., 2011, Norgren et al., 2007).

Considering that PAD has not generally been included for the purpose of estimating the healthcare cost of the disease, the inclusion of this event into the heart disease model extends the coverage of major cardiovascular events beyond most current models.

Table 5.2. Health states included in the models identified in the review

Study	MI	Angina	Stroke	Revasc*	TIA	CHF	Cardiac arrest	PAD	Death
De Smedt et al. (2012)	√	√	√	√	√	√	x	x	√
Ohsfeldt et al. (2012)	√	√	√	√	x	x	x	x	√
Galper et al. (2012); Lazar et al.(2011)	√	√	√	√	x	x	√	x	√
Gillespie et al. (2012; 2010)	√	√	x	x	x	x	x	x	√
Earnshaw et al. (2011)	√	√	√	x	x	x	x	x	√
Grosso et al. (2011)	√	x	√	x	x	x	x	x	√
Soini et al. (2010)	√	√	x	x	x	x	x	x	√
Ara et al. (2009)	√	√	√	√	x	x	x	x	√
Taylor et al. (2009); Rosen et al. (2010)	√	√	√	√	√	√	√	√	√
Bennett et al. (2009)	√	√	x	√	x	√	x	x	√
Lindgren et al. (2009)	√	x	√	√	x	x	x	x	√
Ward et al. (2006)	√	√	√	x	√	x	x	x	√
Number of times included	12	10	9	7	3	3	2	1	12

MI: myocardial infarction; CHF: congestive heart failure; *Revasc=Revascularisation procedures include coronary artery bypass graft (CABG) and percutaneous transluminal coronary angioplasty (PTCA); VTE: venous thrombo-embolism;

Although a transient ischaemic attack (TIA) was included in some of the existing models (Taylor et al., 2009, NICE, 2006, De Smedt et al., 2012), it was excluded in this model as TIA was considered associated with relatively minor implications for costs and mortality, and relatively low event rates compared with the other events included in the model.

Fatal events – cardiac death and non-cardiac death – are also included as absorbing events. Transitions to these events can be made from any other non-fatal health events. Although both events result in death, the separation was made due to different event rates applied from the other states.

The final set of health events included were deaths from MI, stroke, angina, revascularisation, and PAD, and non-cardiac deaths. The modelled population progresses through the health events discussed above. The health events are divided into two temporal categories: first-year and subsequent years after the event. Individuals without a previous CVD event could remain in the event-free state, progress to initial, non-fatal cardiovascular events, or die (either from a cardiac or non-cardiac cause). People who had previously had one of the CVD events but do not experience a further event in the following year are assumed to enter the corresponding 'subsequent year' event state during which the cost of treatments and health related quality of life (HRQoL) could differ from those in the first year after the event. No difference was made between the first year and subsequent years after PAD as there was no clinical evidence identified distinguishing the two periods (see Figure 5.1).

Individuals' history of heart disease events is recorded. People enter the model with a set of characteristics sampled from appropriate probability distributions. Upon the occurrence of each event, the values of times to next events are drawn from distributions whose parameters are conditional on individual disease history and risk factors. For example, individuals who survived both MI and stroke have a higher rate of stroke recurrence. It was assumed that patients could have a revascularisation surgery only in the first-year following a cardiac event, or after the model entry due to available data reporting only the first year probabilities (Ara et al., 2009). Other general methodological assumptions applied to the heart disease model are described in Section 4.1.

Due to the difference in utility values for first and subsequent years after a cardiac event, an event called 'utility cut-off point' was added to the model. Due to the model using continuous time, it is possible for an individual to have multiple events within a 12-month period, and thus

to be affected by two or more first-year utility modifiers. The use of a utility cut-off point ensures that changes in HRQoL are handled appropriately.

5.3.2. Modelled population

The population in the base-case model consists of three groups of people: those not receiving any CVD interventions, those receiving an intervention for the primary prevention of CVD, and those receiving secondary prevention. The base-case population was used for the assessment of cost-effectiveness outcomes unless otherwise stated.

Individuals without history of any of the included health events commence at the event-free state (Figure 5.1). Among them, a proportion of people receive a preventative intervention before their first event (denoted a primary prevention population). Primary prevention is provided for people at an increased risk of cardiac events but without a prior CVD event. Some individuals are assigned a history of one or more previous heart disease events on entry. These are subject to secondary prevention, where interventions are targeted at people who have experienced one or more prior CVD events.

Primary prevention

For primary prevention, statin therapy is currently recommended for adults in the UK whose 10-year risk of developing CVD estimated using a risk calculator or by clinical assessment, is greater than 20% (NICE, 2006). Due to the lack of data on the UK prevalence of current statin use by age, the percentages of people whose the 10-year risk of developing CVD was higher than 20% in the general population were estimated from the Health Survey for England (HSE) 1998 (Department of Health, 2005), and applied by age group and sex as in Ward et al. (2006). As the HSE study included the general population in both primary and secondary prevention, it is noted that the reported percentages of people with 10-year CVD risks greater than 20% may overestimate the proportions of people on primary prevention. As the data were reported in the form of annual coronary heart disease (CHD) risks including MI and angina, but not PAD and stroke, the proportions of people at the annual CHD risk of greater than 2% reported in Ward et al. (2006) were taken as a proxy and shown in Table 5.3. Although it is noted that the

10-year risk converted from a 2% annual risk is less than 20% (18.3%), this was not thought to add significant inaccuracy and individuals at each age group were randomly assigned to the primary prevention group according to these proportions.

Table 5.3. Percentage of the UK population who will be given statins for primary prevention

	45-54	55-64	65-74	75-84	85+
Male	6%	27%	57%	76%	86%
Female	1%	4%	11%	8%	2%

As the people receiving statins for primary prevention are a high-risk population by definition (those whose 10-year CHD risk is greater than 20%), the base-case model assigned different baseline event rates to those who are on primary prevention and those who are not.

However, there are some difficulties in assigning higher risks to the primary prevention population due to the lack of data on the baseline risk levels for those in the primary prevention. Furthermore, the risk assessment used to determine the use of statin is based on a risk for multiple events, which means the 10-year risk of >20% should be split between the multiple events whilst maintaining the overall event rates across the primary prevention and no-statin populations.

The base case model assigned different base rates for high-risk (primary prevention) and lower-risk (no-prevention) groups. The base-case assumes that the primary prevention group had the 10-year CHD risk of 20% which was used as a threshold in the risk assessment. The 20% risk was split between angina, sudden cardiac death, and MI according to the distribution of the age/sex specific incidence rates of these events on the *pro rata* basis. The incidence rates assumed were obtained from the Bromley Coronary Heart Disease Register (Sutcliffe et al., 2003). For example, the ratio between the incident cases of angina, MI, and sudden cardiac death for females aged 35-44 years was 2:1:1. The 20% risk of angina, MI and sudden cardiac death were then split into 10%, 5%, and 5%, respectively. The baseline event rates calculated in this way were used for all transitions to MI, angina, and cardiac death (including sudden cardiac death) for the primary prevention population. The relative risks associated with the use of statins were applied to these baseline rates assumed. The estimated 10-year risk levels are

reported in Table 5.4. To the author's knowledge (personal communication with two senior research fellows at the University of Sheffield – Robert Ara and Sue Ward), this calculation has not been undertaken previously. It is noted that the risk levels for those in the primary prevention group are maintained at 20% across all age groups, although the proportions of people receiving statins for primary prevention differed between age groups.

Sudden cardiac death rate was added onto the baseline cardiac death rate for all age groups and time periods (first and subsequent years) as this was a part of the cardiac death category with the event rates for people aged 75 and over assumed to be the same as that for those aged 65-74 due to absence of data. Using the updated risks of cardiac death, the sampling procedure described in Section 4.1, where event rates are repeatedly updated conditional on the sampled time to event value, was applied.

Table 5.4. 10-year risk estimated assuming 20% of CHD risk for primary prevention group.

Age group	Men				Women			
	Angina	MI	Sudden cardiac death	Total	Angina	MI	Sudden cardiac death	Total
45-54	0.106	0.076	0.018	0.20	0.158	0.029	0.013	0.20
55-64	0.122	0.052	0.026	0.20	0.152	0.034	0.014	0.20
65+	0.105	0.061	0.034	0.20	0.111	0.053	0.035	0.20

The individual's level of CHD risk changes over time and so does the probability of receiving statins for primary prevention. Individuals who did not receive the primary prevention intervention on model entry may have different event risks as they age, and be given the intervention before their first cardiac event. Hence, changes to the primary prevention status were made dynamically; if the age band an individual belongs to changes before the earliest time to next cardiac event, the use of primary prevention was re-assessed using the changed proportion of people with the 10-year CHD risk greater than 20%. Times to next event were re-sampled using the changed event rates based on the new age band and the primary prevention status. Following the initiation of primary prevention, the time to cardiac events were re-sampled in order to take protective effects of statins in consideration.

As an illustration, take a 52-year-old individual not assigned for primary prevention at time 0. Time to the earliest cardiac event was sampled to be 4 years. As time before reaching the next 55-64 age band (3 years) is shorter than this, the primary prevention status is reassessed at time 3, based on rates for those aged 55-64 years. If the individual is sampled to receive primary prevention at time 3, times to all cardiac events are sampled for a population on primary prevention aged 55-64 years. Say the sampled time to next cardiac event is 12 years. As time to next age band is now 10 years (from 55 to 65 years of age), the change in the age band occurs before the next cardiac event, and thus, time to next event is resampled at time 13 (3+10 years) using rates for a population on primary prevention aged 65-74 years. Final time to cardiac event is the accumulated time passed due to resampling *plus* time to next cardiac event sampled in the last loop without resampling.

The change to the status of primary prevention could occur only at discrete times when the individuals' age band changes. This was due to the source data reporting the proportions of people receiving statins rather than the rate of change to primary prevention. In order to split the time before the initiation of the primary prevention therapy and the time after, a separate event state was added to the model. Individuals whose primary prevention status was changed after model entry were sent to this event, and relevant costs were accrued from the time when the primary prevention therapy was initiated.

However, as more individuals start receiving the primary prevention intervention when moving to a next age band and time to event is resampled, the proportions of individuals receiving the intervention at model entry reported in Table 5.3 could not be used for people who start receiving statins when the age band changes after the initial assignment of the primary prevention status on model entry. In order to maintain the percentage of people who receive the primary prevention intervention in each age band at the same level as the estimates reported in Table 5.3 over time, the proportions of people who are additionally assigned to receive primary prevention intervention after model entry were estimated to be the difference in the proportions reported in Table 5.3 between consecutive age bands (Table 5.5). For females aged 75 years and over, the proportions of people whose status changes were estimated to be negative. However, it was assumed that individuals already receiving statins remain on the therapy without further individuals starting the therapy.

Table 5.5. Proportions of individuals who start receiving primary prevention when age band changes

Age (years)	45-54	55-64	65-74	75-84	85+
Male	-	22%	41%	44%	42%
Female	-	3%	7%	0%*	0%*

Secondary prevention

On model entry, individuals who are assigned a history of one or more heart disease events receive statins for the secondary prevention of the cardiac events. Prevalence rates reported in the published literature were used to estimate the proportions of individuals with previous heart disease events (Table 5.6). For the prevalence of angina, MI and stroke by age and gender, the British Heart Foundation Statistics Database was used (Townsend et al., 2012). The published prevalence figures for angina were assumed to include both stable and unstable angina with the incidence ratio of unstable to stable angina was used to split the two, as reported in Ward et al. (2006). For PAD IC, the prevalence rate reported in Squires et al. (2011) was used; it reported two prevalence rates for populations aged 55 years and 74 years only, which were assumed for groups aged <70 and >=70 years, respectively. It was assumed that all individuals entering the model did not have a previous revascularisation or did not experience it within one year. Hence, all patients entered the model without a history of previous revascularisation. Independence was assumed between the prevalence of these events.

Table 5.6. Prevalence of diseases: Initial distribution of event histories for secondary prevention

	MI	Stroke	Stable angina	Unstable angina	PAD IC
Men					
45-54 years	0.021	0.012	0.018	0.006	0.02
55-64 years	0.063	0.03	0.066	0.014	0.02
65-74 years[†]	0.144	0.071	0.103	0.039	0.02
75+ years[‡]	0.166	0.131	0.159	0.068	0.07
Women					
45-54 years	0.007	0.009	0.009	0.003	0.02
55-64 years	0.016	0.023	0.026	0.006	0.02
65-74 years[†]	0.033	0.042	0.060	0.023	0.02
75+ years[‡]	0.091	0.107	0.112	0.047	0.07

No patients commence with a history of revascularisation; † 65-70 years for PAD; ‡ 70+ years for PAD.

History of multiple diseases is accounted for by applying the event rates from the disease that is associated with the shortest average time to the event in question. Therefore, the individuals are subject to the same event rate regardless of the order of the previous events.

The algorithms used to find the underlying event rates conditional on previous events or primary prevention status are given in Figures 5.2- 5.6. The *rates from* each event shown as the final step in the algorithms will be discussed in Section 5.4.1.

It was assumed that previous revascularisation does not affect future event rates, apart from when the individual did not have any other events previously or the individual is currently at the revascularisation state (Figure 5.6). As a constant rate of transition to PAD was assumed regardless of the state from which the individuals make transitions, no algorithms were needed to find the maximum risk of having PAD. At model initiation, it was assumed that all events had occurred more than 1 year previously and the rates associated with subsequent years were used.

The algorithms were structured so that the highest risk of having the event was selected. The risks of having the event in question from all possible events that individuals could previously have had were compared. The maximum risk of the event were determined conditional on the type and timing (i.e. first or subsequent years) of previous events and the primary prevention status of an individual. For example, when an individual is at MI event, the first-year rates of the transition to stroke from MI and subsequent year rates from the other events were compared (Figure 5.4). For ease of computation, figures in the third decimal point or lower in the event rate values were ignored when finding the maximum event rate.

A different event rate was applied when the individual was at the MI event due to the high probability of having revascularisation within 1 year after MI (Figure 5.6). For the other event rates, the event rates derived from the National Audit of Percutaneous Coronary Intervention (PCI) covering 2012 data (National Institute for Cardiovascular Outcomes Research, 2013) and the total number of people aged 45 years and over in the UK (Office for National Statistics, 2013c) were used to estimate the national average rates.

The primary prevention population without history of previous events was given the initially assigned risks of MI, angina, and sudden cardiac death (Table 5.4) as they were the minimum event rates that could be selected. For comparison with the 10 year CHD risk of 20% and over for the primary prevention population, the 10-year risk of having MI or angina for men aged 70 years in the secondary prevention group was around 70%, 34%, and 20% if they previously had MI, PAD, and stable angina, respectively. The corresponding level of risk for no-statin group was around 18%. It is noted that as the data sources often included people at increased risk of

cardiac events, the baseline event rates used for people not receiving statin treatments may

be overestimated.

Figure 5.2. Algorithms determining the transition rate to MI
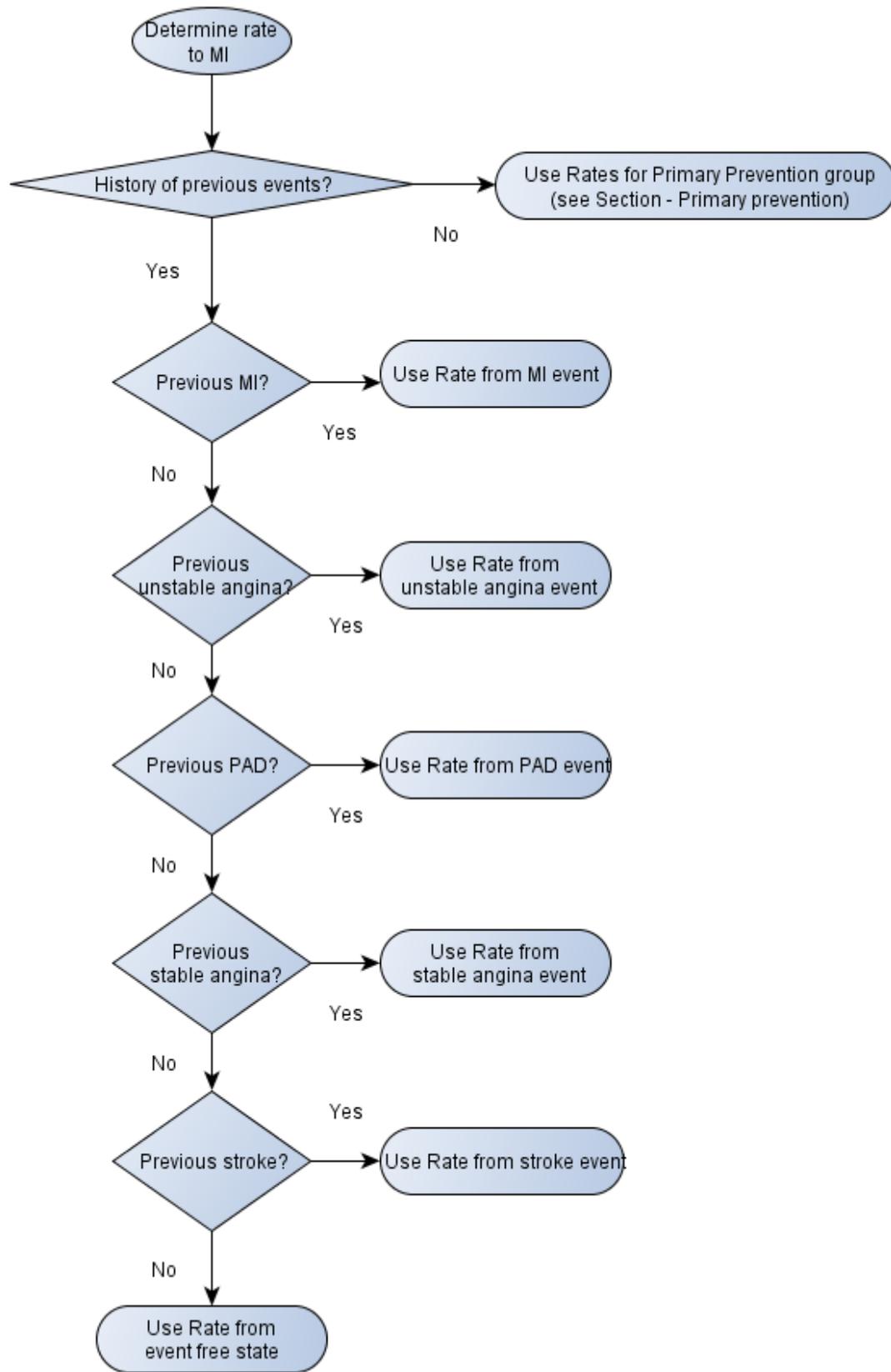
Figure 5.3. Algorithms determining the transition rate to MI at model initiation
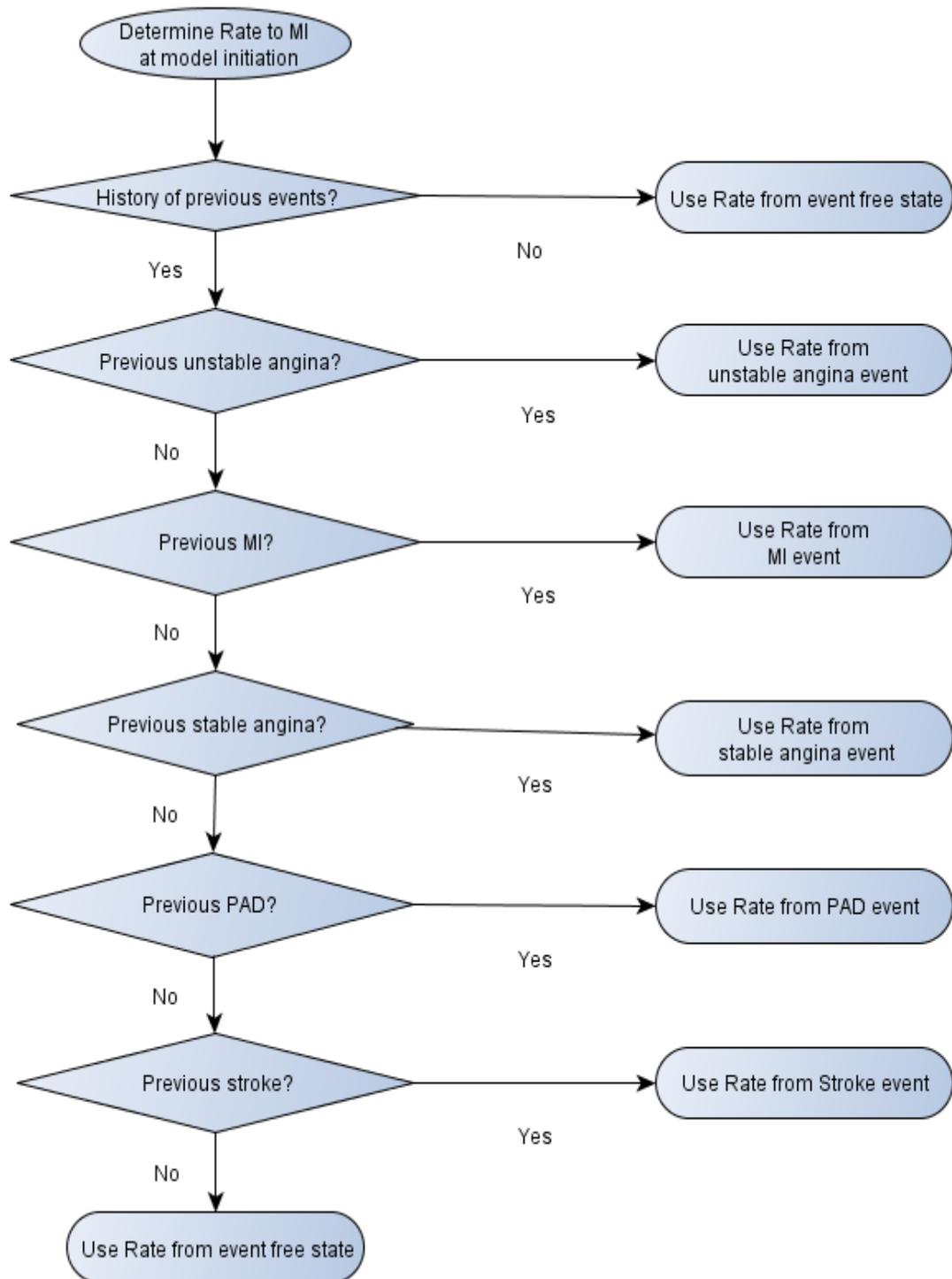
Figure 5.4. Algorithms to find the transition rate to stroke
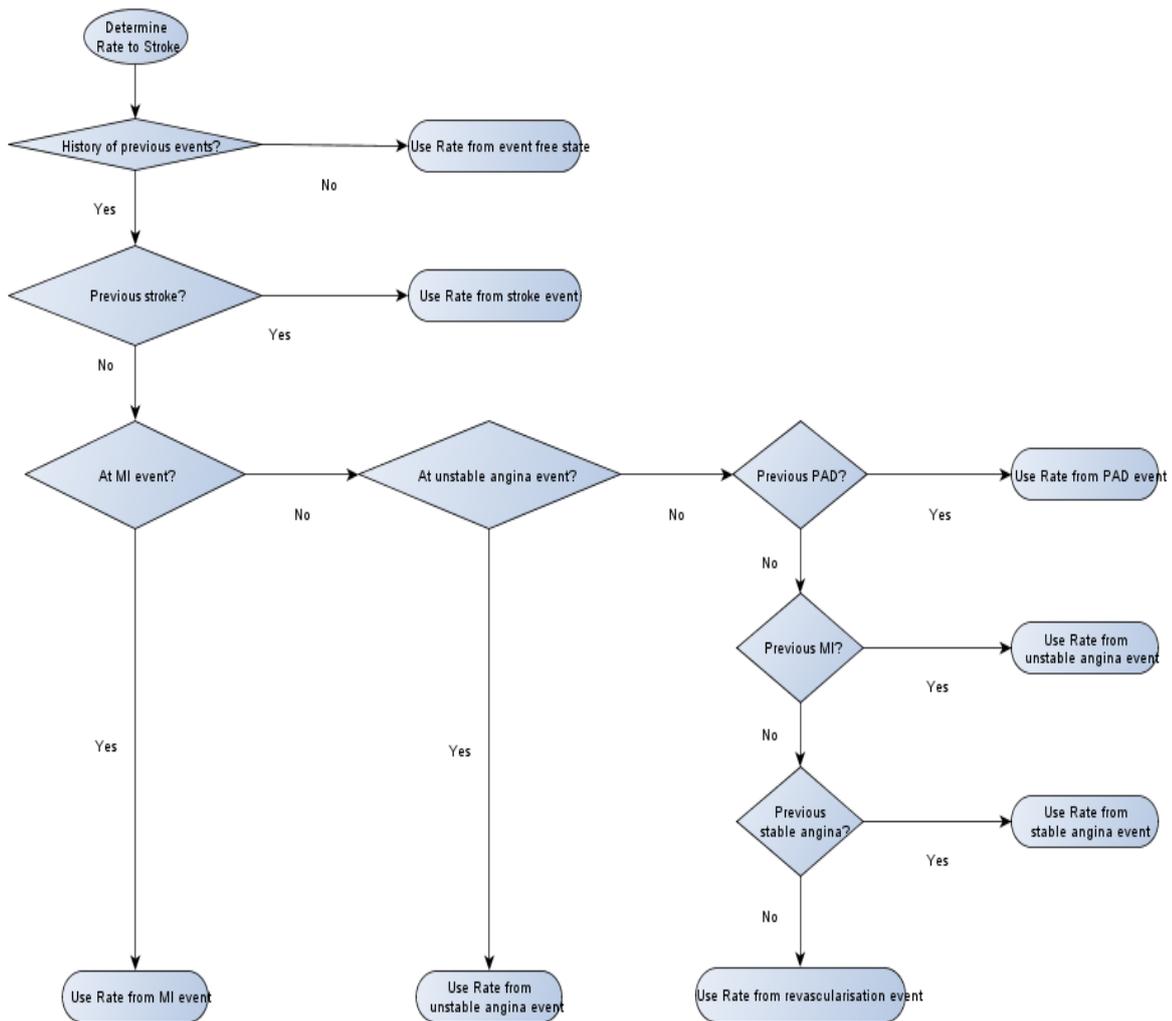
Figure 5.5. Algorithms to find the transition rate to angina
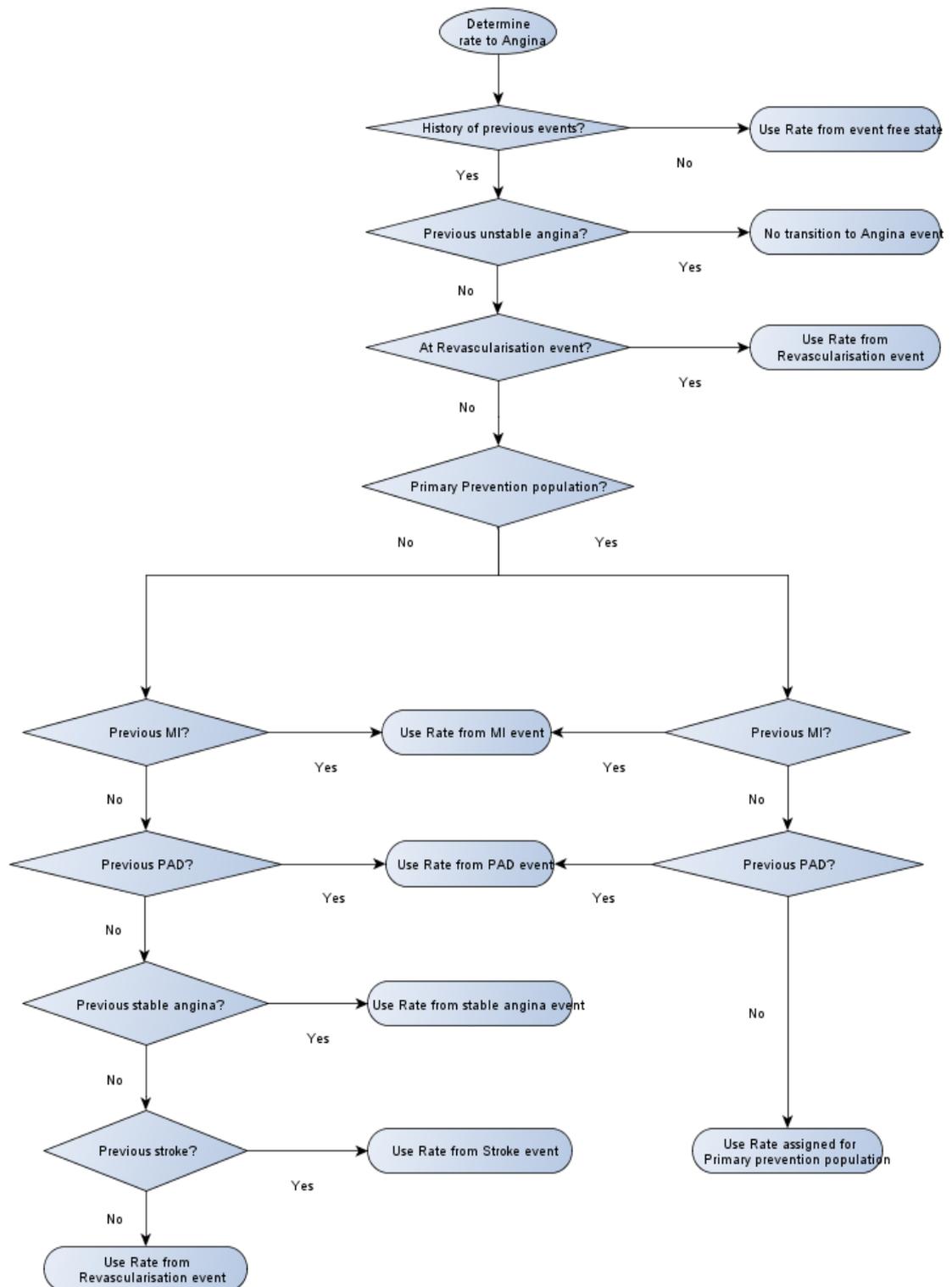
Figure 5.6. Algorithms to find the transition rate to revascularisation
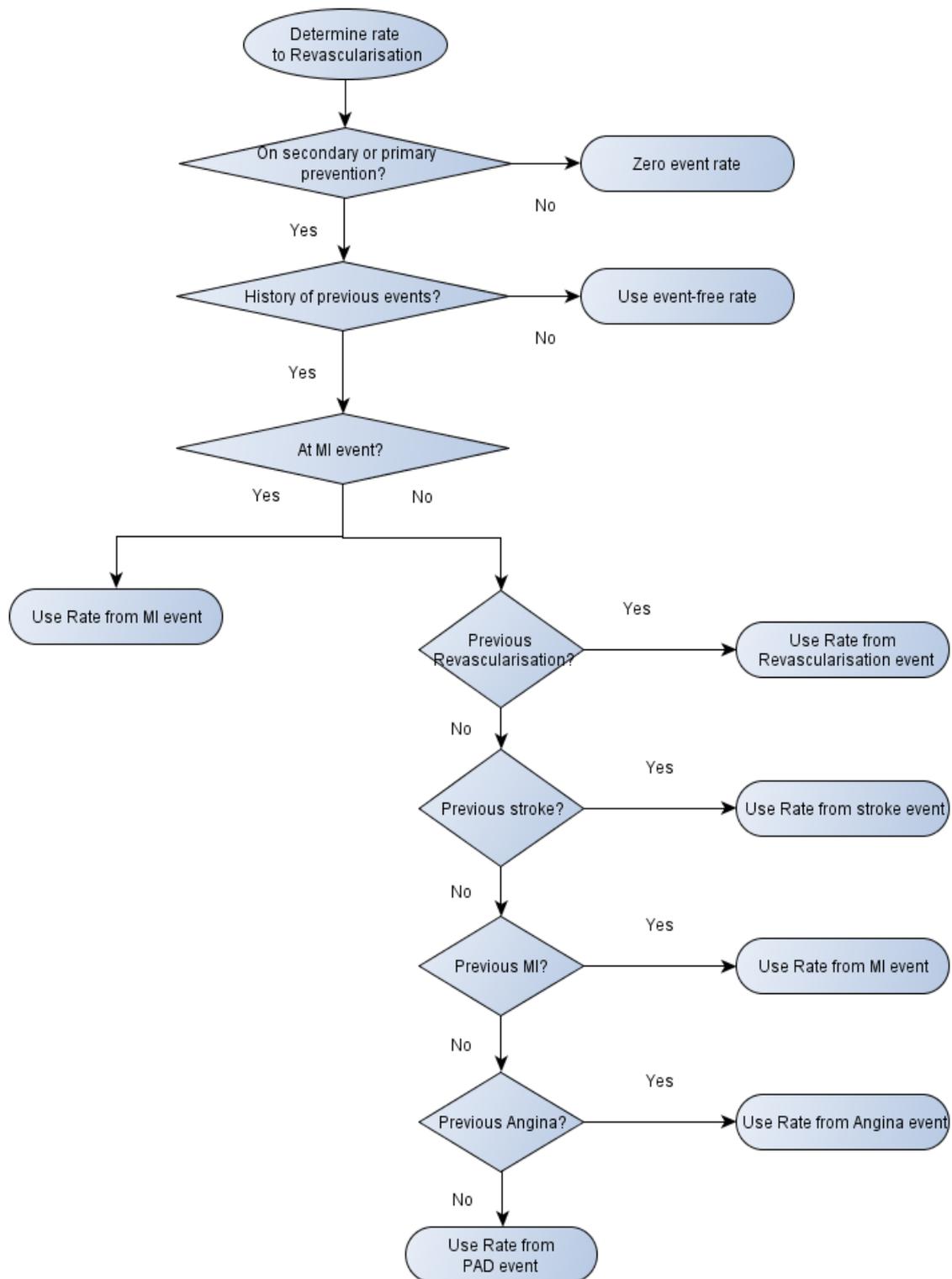
Future healthcare costs are projected including both the starting cohort representing the UK population in the base year and the new cohorts of 45 year-olds. All costs incurred by all relevant cohorts that are simulated to be alive in the model are combined and discounted to the base year (2012) to produce the total population-level cost projections. The 2012-based principal projections of the number of 45 year olds in the UK by single year of age and sex were previously reported in Table 4.3 in Section 4.3.5.

5.3.3. Default treatments assumed

Statins were assumed to be used both for the secondary prevention of CVD events in patients with CHD (including angina or MI), PAD, or a history of stroke, and for primary prevention in patients who are at increased risk of coronary events.

Different CVD treatments were assumed for the conditions included in the model (See Section 5.4.2). Statin therapy is recommended for primary and secondary prevention: primary care and statin costs were assumed for both populations. For those having a revascularisation, it was assumed that 45% of the procedures were coronary bypass grafting surgery (CABG) and 55% percutaneous transluminal coronary angioplasty (PTCA) (Taylor et al., 2009).

All patients with angina were assumed to be receiving sotalol treatments with a half of them receiving aspirins as well (Juul-Moller et al., 1992). Only the standard care assumed in Kearns et al. (2013) was used as the base-case treatment for people with PAD. No use of endovascular therapies such as PTCA was assumed for these patients.

5.4. Parameters & Data sources

5.4.1. Event Rates

This section describes the event rates used for the base-case model. The data sources were identified from the six UK-based studies included in the review in Section 5.2 (Ward et al., 2006, Grosso et al., 2011, Taylor et al., 2009, De Smedt et al., 2012, Lindgren et al., 2009, Ara et al., 2009). The most appropriate parameter estimates reported for similar populations and contexts in the six studies and their sources of data were used for the model in this research. The baseline risks for individuals not receiving statin treatments were obtained. However, if data were identified from sources that did not specify the use of statins such as disease register, the baseline rates could include people receiving statins and those not on statins. UK-sourced data were used wherever possible, and age-dependent time-variant rates of transitions between health events were preferred. Where the parameters reported in the modelling studies and the original sources differed due to the transformation of the reported values into the format that can be used in their model or the estimation of multiple age-variant values from a single estimate reported for the whole study population, those used in the modelling studies were used for the ease of use.

Baseline event rates used for the base-case model are summarised in Tables 5.7-5.12. The relative risks associated with statin use were applied to the baseline event rates to estimate time to events for patient groups receiving the treatment.

As described in the previous section, all included disease states except PAD (MI, stroke, angina, and revascularisation) were split into two temporal categories – first year and subsequent years after the event – due to the difference in the rates for transitions to other events, costs, and/or utility weights between the first year of the event and thereafter.

Various sources for cardiac death rates were used dependent on the 'from' state of the transition (See Table 5.2). The rate of transition to cardiac death varied with the age group and the temporal period (first year or subsequent years after the event), and time to cardiac death was sampled from an exponential distribution using the appropriate rate.

The event rates used in the model are summarised in the next sections by the origin of transitions, with each section followed by a summary table of the estimates (Tables 5.7-5.12). In addition, rates of transitions to fatal stroke and PAD were described in separate sections as they applied regardless of the origin of transitions.

Transitions from Event-free state (at model initiation)

Event rates differed depending on whether an individual is on primary or secondary prevention interventions, or is untreated. Rates of transitions from the event-free state are summarised in Table 5.7.

For secondary prevention population with a history of one or more previous cardiac events, the underlying event rate was identified using the algorithms in Section 5.3 and time to next event was sampled from this exponential distribution. At model initiation, only the subsequent-year transition rates, not the higher first-year rates, were used, assuming that their latest previous event occurred earlier than one year before the model initiation (individuals were not experiencing any of the included cardiac events when they entered the model).

Primary prevention population were assigned the 10-year CHD risks of 20% as reported in Table 5.4. For other events that were not included in the CHD risks (MI, angina, and sudden cardiac death), events rates for population receiving no preventative interventions were used.

Initial events rates for those on neither primary nor secondary prevention interventions were obtained from published literature that reported rates of first-ever CVD events. Rates for transitions to initial non-fatal MI for male population were taken from the West Of Scotland Coronary Prevention Study (WOSCOPS) by converting the five year probability of MI reported for placebo group (7.8%) to an event rate (Shepherd et al., 1995). Although WOSCOPS typically included middle-aged males (mean age 55.1 and 55.3 years for the placebo and pravastatin arms, respectively, with the standard deviation of 5.5 years for both arms), it was preferred to the Framingham Heart Study as a number of studies suggested that the Framingham study may overestimate the MI rate (Hense et al., 2003, Marrugat et al., 2003). However, in order to estimate the rates of non-fatal MI in women, the combination of WOSCOPS and the Framingham heart study results was used by applying the ratio of MI rate for women to that for men from the Framingham heart study to the rate for men obtained from WOSCOPS study

(D'Agostino et al., 2008). MI was assumed to not be immediately fatal, but having an MI increased the risk of cardiac death as the data did not specify the cause of death.

Initial rates for fatal and non-fatal stroke, angina, and cardiac death were derived from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) trial results (Lindgren et al., 2009) as their statistical analyses incorporated only the first ever events. The exponential regression equations were estimated using the trial results based on a simple set of covariates – age at event and sex. These equations were inserted in the model for the rates of transitions to stroke, revascularisation, and cardiac death. The equation for revascularisation rate was not used for people not receiving preventative interventions, as the trial involved high-risk people with hypertension and reported a disproportionately high number of revascularisation procedures in comparison with the number of revascularisation currently being performed in the UK. For those not receiving primary or secondary prevention, the national average rate of revascularisation was used. It was assumed that only primary prevention population – but not secondary, as they follow the underlying event rates algorithms – can receive the procedure. The proportion of stroke being fatal was estimated from the logistic regression results reported in the ASCOT study results. Angina event rates were obtained from the ASCOT-LLA (Lipid Lowering Arm) data (Sever et al., 2003). This rate was assumed to be independent of the age and gender of the individuals as the data did not specify the number of events by age and gender.

Due to paucity of data, transitions to PAD were estimated from the Edinburgh Artery Study data (Leng et al., 1996) on the incidence of ischaemic claudication (IC) among the general population.

Table 5.7. Baseline annual rates of transition from event-free state

Baseline rates for individuals not receiving statin treatment			
From	**To**	**Estimates**	**Sources**
Event free	MI	Rate for men = 0.01624; Rate for women = 0.01123	WOSCOPS (Shepherd et al. 1995) and Framingham studies (D'Agostino et al. 2008)
	Stroke	Exponential mean of Exp(9.218 + (-0.064)*age at event + (-0.176)*gender) for time to event distribution $T \sim Exp(\hat{\lambda})$. Then, the prob of stroke being fatal applied. P(fatal stroke)=e^xb/[1+e^xb] where xb= -4.874 + 0.043*age – 0.074*gender.	ASCOT trial (Table 2. Lindgren et al. 2009)
	Angina	Rate = 0.0027 per patient-year.	ASCOT-LLA data (Sever et al., 2003)
	Revascularisation	For only primary and secondary prevention populations, Exponential mean of Exp(5.250 + (-0.013)*age at event + (0.479)*gender) for time to event distribution $T \sim Exp(\hat{\lambda})$. Otherwise, the national average rate of revascularisation was used.	ASCOT trial (Lindgren et al., 2009) National Audit of PCI (National Institute for Cardiovascular Outcomes Research, 2013)
	PAD	Rate= 0.021149= the incidence of PAD with intermittent claudication.	Edinburgh Artery Study (Leng et al., 1996)
	CVD death	For individuals not receiving any interventions, Males (females): 45-54 years 0.000639 (0.000178); 55-64 years 0.001711 (0.000573); 65-74 years 0.004275 (0.001994); 75-84 years 0.013182 (0.008621); 85 years and over 0.040947 (0.035576). For only primary and secondary prevention populations, Exponential mean of Exp(6.576 + (-0.035)*age at event + (0.437)*gender) for time to event distribution $T \sim Exp(\hat{\lambda})$.	Mortality Statistics: Deaths registered in 2012 (Office for National Statistics, 2013a) ASCOT trial (Lindgren et al., 2009)

Transitions from MI

Transition rates for patients in the MI state for progression to a second MI, stroke, and cardiac death were taken from the data used for the NICE technology assessment report (Ward et al., 2006) (Table 5.8). The original data were derived from the Nottingham Heart Attack Register (NHAR). Annual probabilities reported in Ward et al. (2006) by age were converted to rates using an equation $r = -\frac{1}{t}\ln(1 - probability)$ assuming a constant rate r per time unit t (Fleurence and Hollenbeak, 2007). Data reported in Ara et al. (2009) were also based on the NHAR study, but were slightly different. However, the estimates reported in Ward et al. (2006) were used in the model as they covered wider age groups based on regression analyses.

Time to next event values were sampled from a distribution with an appropriate rate by repeatedly checking whether a sampled time-to-event value passed any of the future time points sectioning the first and subsequent years after MI or the age bands (age groups: Group 1 < 55 years; Group 2 55-65 years; Group 3. 65-75 years; Group 4. 75-85 years; Group 5. >85 years) and updating the rate accordingly (for further explanation, see Section 4.1).

Rates to angina and revascularisation from the MI event were estimated by converting the probabilities reported in individual trial results (Fox et al., 2005, Taylor et al., 2009) as Ward et al. (2006)'s model did not include these transitions. Both of the rates were assumed constant across all age groups as the data did not report age-dependent rates. It was assumed that the patient could receive revascularisation only within one year after MI as the data reported only the first year rate, i.e. if the sampled time to revascularisation was greater than 1 year, then it was assumed not to occur.

Table 5.8. Baseline annual rates of transitions from myocardial infarction

Baseline rates for individuals not receiving statin treatment			
From	**To**	**Estimate**	**Sources**
MI	MI	For age groups 1-5: First (subsequent) year(s) rates: 0.13697 (0.01633), 0.12239 (0.01806), 0.10747 (0.01867), 0.09146 (0.0180), 0.07375 (0.01613).	NICE TA94 Table 52 (NICE, 2006); Nottingham Heart Attack Register (NHAR).
	Stroke	For age groups 1-5: First (subsequent) year(s) rates: Group 1 (< 55): 0.00150 (0.0004), Group 2 (55-65): 0.00321 (0.00100), Group 3 (65-75): 0.00682 (0.00220), Group 4 (75-85): 0.01420 (0.00471), Group 5 (> 85): 0.02819 (0.00914).	NICE TA94 (Table 52); Nottingham Heart Attack Register (NHAR);
	Angina	Exponential rate = 0.05975	Ara et al. 2009. Table 8. (Fox et al. 2005)
	Revascularisation	First year rate = 0.504347	TNT trial (Taylor et al., 2009)
	PAD	Rate= 0.021149= the incidence of PAD with intermittent claudication.	Edinburgh Artery Study (Leng et al. 1996)
	CVD death	For age groups 1-5: First (subsequent) year(s) rates: Group 1 (< 55): 0.01755 (0.00541), Group 2 (55-65): 0.03387 (0.00955), Group 3 (65-75): 0.06465 (0.01603), Group 4 (75-85): 0.12059 (0.02482), Group 5 (> 85): 0.21791 (0.03615).	NICE TA94 (Table 52); Nottingham Heart Attack Register (NHAR).

Transitions from Stroke

The baseline rates of transitions from stroke are summarised in Table 5.9.

The same rates of having an MI after stroke were assumed for the first and subsequent year(s), as in Ward et al. (2006). Transition rates by age group were applied using the same technique of sampling and re-sampling the time to next event values whilst comparing the sample value with the time to next age band, as used for transitions from MI.

Data for stroke recurrence rates (transitions from stroke to another stroke) were obtained from the South London Stroke Register (SLSR) (Mohan et al., 2009). Although data reported in Ward et al. (2006) and Ara et al. (2009) were also based on the same SLSR study, the source paper was used to differentiate the event rates by further patient characteristics. Baseline probabilities reported in the study were converted to 0-1, 1-5 and 5+ year rates of transitions, and hazard ratios reported for people with a history of previous MI and in different age groups (<65 years, 65-74 years, >75 years) were applied to the baseline rates.

The rate of transition from stroke to angina was assumed to be the same as the rate of transition from the event-free state to angina. This was different from the rate used in Ward et al. (2006) where no transition to angina was assumed from the stroke state as it was considered unrealistic. A constant revascularisation rate taken from the UK average rate of revascularisation was used due to lack of age-specific data as for the transition from MI, assuming all revascularisation procedures were performed for people aged 45 and over.

Table 5.9. Baseline annual rates of transitions from Stroke

Baseline rates for individuals not receiving statin treatment			
From	**To**	**Estimate**	**Sources**
Stroke	MI	Rates by age group: Group 1 (< 55): 0.00160, Group 2 (55-65): 0.00310, Group 3 (65-75): 0.00552, Group 4 (75-85): 0.00803, Group 5 (> 85): 0.01045.	NICE TA94 (Table 52); Nottingham Heart Attack Register (NHAR).
	Stroke (Stroke recurrence)	Baseline rates for 0-1, 1-5, 5-10 years for individuals aged <65: 0-1 year rate= 0.06401 (mean = 15.6237); 1-5 year rate= 0.02694; 5-10 year rate= 0.01887. Then, probability of stroke being fatal= $e^{xb}/[1+e^{xb}]$, where xb= -4.874 + 0.043*age – 0.074*gender, was applied.	Mohan et al. 2009 – Stroke recurrence; ASCOT trial (Lindgren et al. 2009)
	Angina	Rate = 0.0027	Assumed the same as the rate of transition from event free to angina state (NICE TA 94 Table 52)
	Revascularisation	Rate= 0.01056	TNT trial (Taylor et al. 2009)
	PAD	Rate= 0.021149= the incidence of PAD with intermittent claudication.	Edinburgh Artery Study (Leng et al. 1996)
	CVD death	For age groups 1-5: First (subsequent) year(s) rates: Group 1 (< 55): 0.00924 (0.00421), Group 2 (55-65): 0.02245 (0.00985), Group 3 (65-75): 0.05340 (0.02102), Group 4 (75-85): 0.12466 (0.04207), Group 5 (> 85): 0.27839 (0.07796).	NICE TA94 (Table 52); Nottingham Heart Attack Register (NHAR).

Transitions to Fatal Stroke

If the reported data did not explicitly state that the event probabilities were for non-fatal stroke only, then a proportion of the patients who experience a stroke was assumed to die due to the stroke. Thus, the transitions to stroke from event free, stroke, angina and revascularisation states included a subset of patients having a fatal event and subsequently moving to cardiac death state. The proportion of fatal stroke among all stroke events was estimated using the logistic regression equation reported in the ASCOT trial results (Lindgren et al., 2009) with an exception of transitions from revascularisation state where a 50% probability of stroke being fatal was assumed as in Ara et al. (2009).

Transitions from Angina

Rates of transitions from angina are given in Table 5.10. Individuals were assumed to have stable angina first and then progress to unstable angina, which requires more intense medical treatments. Once unstable angina was developed, it was assumed that patients cannot improve to stable angina.

Different event rates from angina state were applied depending on whether the patient has stable angina or unstable angina. Data for the transitions from stable angina to other events were obtained from the Swedish Angina Pectoris Aspirin Trial (SAPAT) (Juul-Moller et al., 1992), as this was the only study that included a population without history of MI or unstable angina in a Medline search conducted by Ward et al. (2006). Constant event rates for transitions from stable angina to MI and stroke were assumed as the trial data did not report the event rates by patient characteristics. The proportion of angina patients who experienced a relevant event over the median follow-up of 50 months was converted to a constant rate in the model for this thesis. As the SAPAT study aggregated both non-fatal and fatal stroke, the logistic regression equation from the ASCOT trial was used to calculate the probability of a stroke being fatal based on the patient's age and gender. The rates of progressing to unstable angina from stable angina were obtained from the study by Ward et al. (2006). The rate of transition to revascularisation was assumed the same as that from the event-free state.

Estimates for the rates of transitions from unstable angina were obtained from the NICE TA report (Ward et al. 2006) where the major sources of data were the NHAR (Gray and Hampton, 1993) and the SLSR study (Addo et al., 2011, Mohan et al., 2009, Wolfe et al., 2002).

Table 5.10. Baseline annual rates of transitions from angina

Baseline rates for individuals not receiving statin treatment			
From	**To**	**Estimates**	**Sources**
Angina	MI	1) From Stable angina: Rate = 0.01520; 2) Unstable angina 5%, 4.9%, 4.7%, 4.3% from 1st year event. 3.5%, 6.3%, 11.2%, 18.5% from subsequent yrs event for those aged <55, 55-65, 65-75, 75-85 yrs, respectively.	Juul-Moller et al. (1992); Ara et al. (2009), Table 8; Gray and Hampton (1993)
	Stroke	1) From Stable angina: Rate = 0.00791; Then, the prob of stroke being fatal applied, probability = $e^{xb}/[1+e^{xb}]$, where $xb = -4.874 + 0.043*age - 0.074*gender$. 2) From Unstable angina: For age groups of <65, <75, <85, >85 years, [1st year rate] To non-fatal stroke: 0.2%, 0.5%, 1%, 2%; To fatal stroke: 2.6%, 4.3%, 7%, 10.3%; [subsequent yrs rate] To non-fatal stroke: 0.1%, 0.1%, 0.3%, 0.7%; → Fatal stroke: 0.4%, 0.5%, 0.6%, 0.7%.	1) Juul-Moller et al. (1992); NICE (2006); Lindgren et al. (2009) 2) Ara et al. 2009 (HTA) Table 8.; Gray and Hampton (1993)
	Angina (unstable)	Annual probability from stable angina to unstable angina: Group 1 (< 55): 0.0013, Group 2 (55-65): 0.0029, Group 3 (65-75): 0.0060, Group 4 (75-85): 0.0091, Group 5 (> 85): 0.0122.	NICE TA 94: Table 52.
	Revascularisation	Rate=0.00269	Assumed the same as the minimum revascularisation rate from PAD state. (Leng et al. 1996)
	PAD	Rate= 0.021149= the incidence of PAD with intermittent claudication.	Edinburgh Artery Study (Leng et al. 1996)
	CVD death	1) If no history of angina= Group 1 (< 55): 0.009, Group 2 (55-65): 0.0035, Group 3 (65-75): 0.007, Group 4 (75-85): 0.007, Group 5 (> 85): 0.007. 2) From unstable angina = (CHD and CVD death rates combined for 1st and subsequent years.	NICE TA94 (Table 52); Nottingham Heart Attack Register (NHAR).

Transitions from Revascularisation

Sources of data on rates for all transitions from the revascularisation state to all non-fatal events and cardiac death were identified from Ara et al. (2009) (Table 5.11). Constant event rates were assumed, and the estimates were obtained from the RITA-2 and RITA-3 trial data (Henderson et al., 2003, Fox et al., 2005). The probability of stroke being fatal was taken to be 50% as assumed in Ara et al. (2009). As the trial data reported only the first year probability of having another revascularisation operation after the first, it was assumed that a revascularisation procedure could be repeated only within one year (Taylor et al., 2009).

Table 5.11. Baseline annual rates of transitions from revascularisation

Individuals not receiving statin treatment			
From State	**To State**	**Estimate**	**Sources**
Revascularisation	MI	Rate= 0.03874	Fox et al. (2005); Ara et al. (2009)
	Stroke	Rate=0.002 with 50% of stroke being assumed to be fatal.	Henderson et al. (2003); Ara et al. (2009)
	Angina	Rate = 0.032523	Henderson et al. (2003); Ara et al. (2009)
	Revascularisation	First-year rate of having a 2nd revascularisation= 0.14491	TNT trial (Taylor et al. 2009)
	PAD	Rate= 0.021149= the incidence of PAD with intermittent claudication.	Edinburgh Artery Study (Leng et al. 1996)
	CVD death	Rate = 0.005785	RITA-2 trial (Henderson et al., 2003)

Transitions from PAD

Table 5.12 summarises the baseline rates of transitions from PAD used in the model for this thesis. A population of patients with IC, which is the most common symptom of PAD, and CLI, a more severe symptom, was considered for modelling. No distinction between the first and subsequent years after PAD was made as the main data source did not distinguish the two time periods with regards to the transitions to other cardiovascular events.

PAD was modelled in a simplified manner. The model included only IC and CLI, and their drug treatment costs. Only one transition to PAD was allowed, and once patients experienced PAD, they were assumed to have it for the rest of their lives and could not have a second PAD event. Only symptomatic PAD which requires medical treatments was considered in the model.

Transition rates from PAD to other non-fatal CVD events were obtained from the Edinburgh Artery Study (Leng et al., 1995, Leng et al., 1996). Event rates were converted from the proportion of people who experienced the event over the five year follow up, and constant rates over time were assumed as the data reported only the total numbers of events. The same age-specific cardiac mortality rate as that for people without history of CVD events was used due to lack of data, thus assuming no influence of PAD on mortality.

Table 5.12. Baseline rates of transitions from peripheral arterial disease

Baseline rates for individuals not receiving statin treatment			
From	**To**	**Estimate**	**Sources**
PAD	MI	Rate = 0.01711	Edinburgh Artery Study (Leng et al. 1996)
	Stroke	Rate= 0.01408	Edinburgh Artery Study (Leng et al. 1996)
	Angina	Rate= 0.02019	Edinburgh Artery Study (Leng et al. 1996)
	Revascularisation	Rate=0.00269	Edinburgh Artery Study (Leng et al. 1996)
	PAD	Rate=0	Assumed
	CVD death	Exponential mean of Exp(6.576 + (-0.035)*age at event + (0.437)*gender) for time to event distribution $T \sim Exp(\hat{\lambda})$.	The same rate as the transition from event free to CVD death: ASCOT trial (Lindgren et al. 2009)

Transitions to PAD

New cases of PAD with IC in the Edinburgh Artery Study were used for the estimation of transition rates to PAD. The annual incidence of IC is difficult to measure as the methods for identifying IC do not always detect the presence or absence of PAD and a large proportion of people with IC are left undetected (Norgren et al., 2007). The incidence of symptomatic PAD in general population aged 55 and over was used for all transitions to PAD event from other disease states due to the lack of published evidence (Leng et al., 1996). Age dependent incidence was not included as it was not statistically significant in the Edinburgh Artery Study (Leng et al., 1996). However, there was some evidence of an increase with age in earlier longitudinal studies (Kannel and McGee, 1985, Widmer et al., 1985).

Among patients with IC, approximately 20% progress to develop severe symptoms with CLI over a 5-year period and 1-2% undergo amputation over a lifetime (National Clinical Guideline Centre, 2012). In the model for this thesis, 20% of people with IC were randomly sampled to develop CLI at the time of developing PAD for simplicity.

Effectiveness of statin treatments

Statin treatments was assumed to reduce the risks of coronary events (MI, angina, and fatal CHD events) and stroke. As described in earlier sections, the model assumes that a proportion of individuals entering the model are receiving a statin treatment for primary and secondary prevention of CVD events.

The relative risks (RRs) of events associated with statin use were applied to the baseline risks converted from the event rates reported in Tables 5.7-5.12 (transition rates), and are shown in Table 5.13.

The estimates of RRs reported in the assessment report for NICE TA94 were used for MI, angina and cardiac death events (Ward et al., 2006). Ward et al. (2006) used the same RRs for primary and secondary prevention populations for the events included in this study as there was no significant difference in their meta-analyses between the effectiveness of statins in primary and secondary prevention. Although the base-case model in Ward et al. (2006)

assumed no impact of statin treatment on the probabilities of stroke, the RR estimates for simvastatin 40mg per day reported in the study by Ara et al. (2009) were used for all transitions to stroke in this study. Both Ward et al. (2006) and Ara et al. (2009) conducted meta-analyses of placebo-controlled studies to derive the RRs. These values incorporate the relationship between the reductions in LDL (low-density lipoproteins) cholesterol level and the risks of events to estimate the RRs associated with statin therapies at different doses.

Table 5.13. Relative risks associated with statin use compared with placebo

Transitions to	Relative Risk	Source
MI	0.656	Ward et al. (2006) (NICE TA94)
Non fatal stroke	0.754	Ara et al. (2009): Simvastatin 40mg/day
Fatal stroke (from Angina state)	0.876	Ara et al. (2009): Simvastatin 40mg/day
Stable Angina (from event free state)	0.59	Ward et al. (2006) (NICE TA94)
To Fatal CHD event (CVD death)	0.74	Ward et al. (2006) (NICE TA94)
Non CVD death (from event free state)	0.656	Ward et al. (2006) (NICE TA94)

Non-disease mortality

Non-cardiac mortality rates used to construct distribution profiles for time to non-disease death were calculated by subtracting cardiac mortality rates from the all-cause death probability profiles presented in Section 4.3.6. Cardiac mortality rates were estimated by combining the rates reported for heart disease (ICD-10 code I00-I52) and stroke (I64) using data obtained from the Mortality Statistics: Deaths registered in 2012 (Office for National Statistics, 2013a). Cardiac mortality rates used to calculate the non-disease mortality are shown in Table 5.14. These were the same rates used for transitions to cardiac death from event-free state.

Figure 5.7 shows distributions for time to non-cardiac death for a few selected age groups. As the cardiac death rates were constant across the 10-year age bands whilst the all-cause mortality rates were specified at every age x between 45 and 100 years, the probability profiles created were not smooth, but had a few stepped decreases at the age cut off values.

Table 5.14. Cardiac death rates used to estimate non-cardiac mortality rates*

	Age group				
Sex	45-54	55-64	65-74	75-84	85 and over
Male	0.000639	0.001711	0.004275	0.013182	0.040947
Female	0.000178	0.000573	0.001994	0.008621	0.035576

*Adapted from Table 8 in Deaths registered in England and Wales, 2012 (Office for National Statistics, 2013a)

Figure 5.7. Illustration of distributions for time to non-cardiac death

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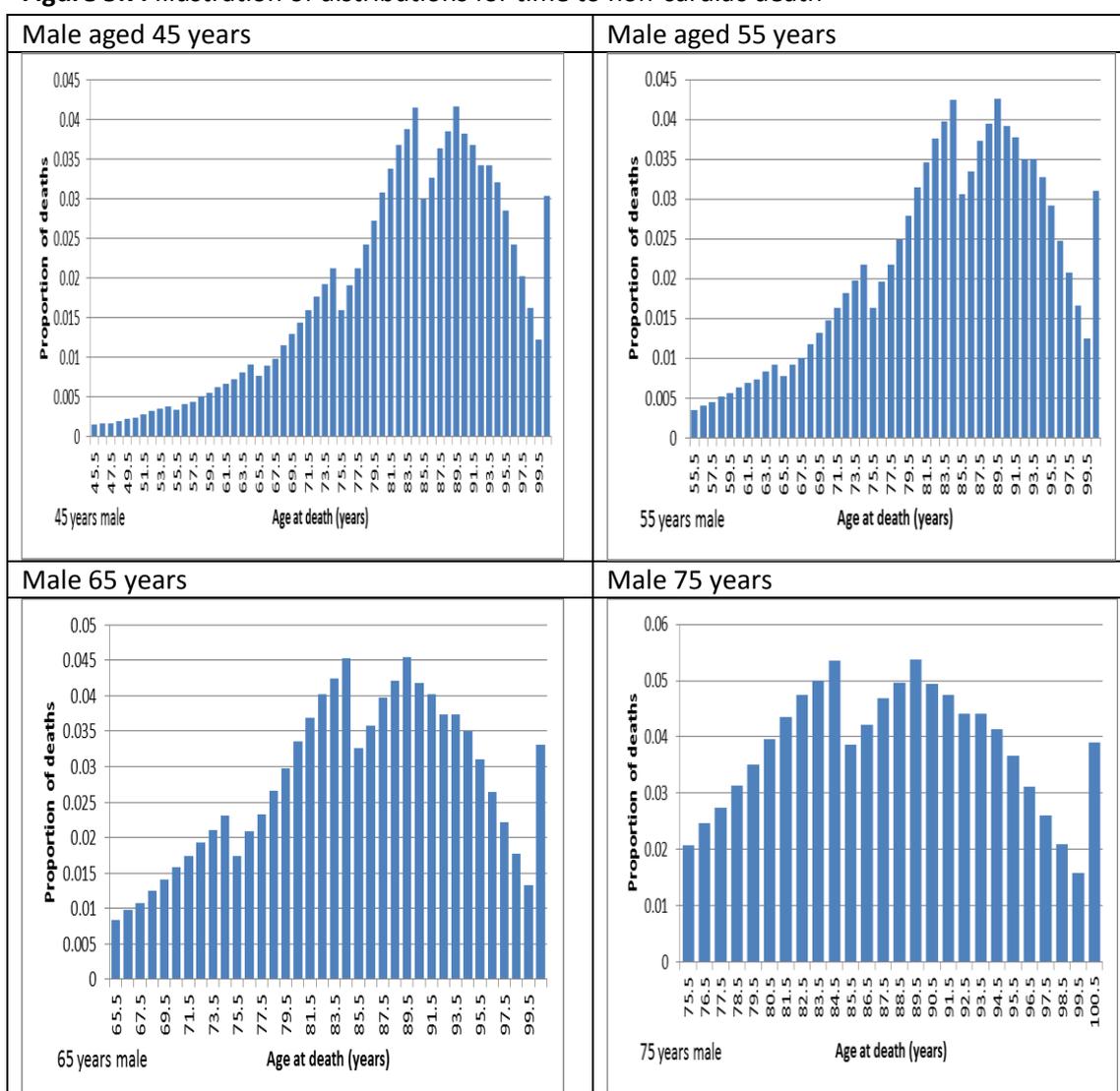
5.4.2. Costs

The same cost estimates as used in the HTA report by Ara et al. (2009) and the NICE TA report (NICE TA94, 2006) were used (Table 5.15). Where the cost data were not available in these studies, individual clinical studies cited as the source of data in the existing models reviewed in Section 5.2 were searched. All cost estimates were inflated to the year 2011/2012 using the HCHS index (Curtis, 2013).

Different costs for first year and subsequent years after the event occurrence were applied except for angina and PAD where the first year and subsequent year costs were assumed to be the same. The first year costs for MI, stroke, unstable angina, and revascularisation included hospitalisation costs. The cost of a revascularisation procedure was assumed to occur in the first year, and no on-going treatment costs were assigned.

As described in Section 4.4.2, costs were additive – if the patient had already experienced MI prior to having a stroke, then both the subsequent-year cost of MI and stroke were incurred. If a current stroke patient had a previous stroke, then only the first year cost of the current stroke was added in order to avoid double counting.

The cost of statin treatments was estimated using the method described in the Technology Assessment Report for NICE TA guidance by Ward et al. (2006). All statins in current use were evaluated collectively: the weighted annual cost of statins based on the current prescribing patterns in the UK for a variety of statins was estimated using the number of prescriptions of each statin at each dose level reported in Ward et al. (2006) and the list price of different statins from BNF 2014 (Joint Formulary Committee, 2014). There was a mismatch between the drug price year (2014) and the base year for the model (2012) due to the unavailability of BNF data. Generic products of pravastatin and fluvastatin have become available since Ward et al. (2006) was published. Hence, the same ratio of branded to generic use of simvastatin was applied to pravastatin and fluvastatin when calculating the weighted annual cost of these statins. The annual cost of statin was estimated at £144.12, which was lower than £273 reported in Ward et al. (2006) due to the availability of new generic drugs and the prices of other statins remaining approximately the same.

For PAD, conservative estimates of costs were used. The monthly drug treatment costs for patients with IC and CLI reported in Kearns et al. (2013) were used to calculate the annual cost.

The costs of CLI and amputation were averaged assuming a proportion (2%) of patients with CLI will undergo an amputation surgery (National Clinical Guideline Centre, 2012).

Table 5.15. Cost estimates used in the base-case model

Event	Data within source	Price year	Estimates (2011/2012 price)	Original Source
MI - 1st year	£3,996	2007	£ 4,519.10	Ara et al. (2009) estimated using British National Formulary (2008)
MI - subsequent year	£171	2004	£ 214.89	NICE TA 94 (GP contacts + medication costs)
Stroke - 1st year	£8,066	2007	£ 9,121.88	Ward et al. (2006)
Stroke - subsequent yr	£2,266	2007	£ 2,562.63	Ward et al. (2006)
Stable angina	£171	2004	£ 214.89	NICE TA 94 (GP contacts + medication costs)
Documented angina	£ 587.07	2005	£ 713.94	Taylor et al. (2009)
Revascularisation - 1st yr	£ 5,857	2007	£ 6,623.71	Taylor et al. (2009); HRG
PAD (IC)	£180	2009-2010	£189.31	Kearns et al. (2013)
PAD (CLI)	£624	2009-2010	£656.29	Kearns et al. (2013)
Statin treatment	£144.12	2014	£144.12	British National Formulary (2014); Estimated using the method by Ward et al. (2006)

5.4.3. Utilities

Baseline utility values by age and gender were given in Chapter 4.

The utility values associated with the health states included in the model were obtained from the NICE TA94 and the HTA report by Ara et al. (2009). Table 5.16 describes the original sources of these values. All the utilities were estimated using the EQ-5D, and were assumed to be multiplicative. Utility multiplier values were assumed to increase by 10% after the first year of the event as assumed in Ara et al. (2009). It was assumed that the history of

revascularisation procedure did not affect the utility level, and the utility decrement for stable angina was used for individuals with history of angina. As a base-case, deterministic values for utility multipliers were used.

Alongside the current event, the history of the other health events was incorporated in the utility multiplier. For example, if a man aged 65 years who has just had a stroke has a history of MI, then the utility decrements for both stroke (first year multiplier for stroke: 0.629) and that for MI (subsequent-year multiplier: 0.836) were applied to the baseline utility (0.815: see Table 4.3); the utility weight for this person is thus 0.429 (i.e. 0.815*0.629*0.836).

When more than one cardiac event occurs within one year, the first-year periods of those events overlap. For the time periods overlapping, utility multipliers associated with the events were applied multiplicatively. For instance, if an individual experiences an MI at time=2.3 years and subsequently a stroke at time=2.7 years, then for time between 2.3 and 2.7 years, only the utility multiplier for the first year of MI would be applied (0.760) whilst for time between 2.7 and 3.3 years, utility multipliers associated with both first-year MI and first-year stroke would be applied (0.760*0.629=0.478). In the same way, for time between 3.3 and 3.7 years, utilities associated with subsequent years of MI and first year of stroke are used (0.836*0.629=0.526) In the model for this thesis, whenever individuals reach these time points, they are directed to the 'utility cut off point' event in order to update variables related to utility multiplier.

Table 5.16. Utility multipliers by health state

State	First year - Mean (S.E.)	Subsequent years -	Original Sources
MI	0.760 (0.018)	0.836 (10% increase)	Goodacre et al. (2004)
Stroke	0.629 (0.04)	0.692 (10% increase)	Tengs and Lin (2003)
(Stable) angina	0.808	0.889 (10% increase)	Melsop et al. (2003)
Unstable angina	0.77	0.847 (10% increase)	Goodacre et al. (2004)
Revascularisation	0.78	0.858 (10% increase)	Serruys et al. (2001)
PAD IC	0.70	0.70	Kearns et al. (2013)
PAD CLI	0.35	0.35	Kearns et al. (2013)

5.5. Results

5.5.1. Base-case results

In order to identify the appropriate number of simulated individuals to ensure stable results, first-order uncertainty was examined. This uncertainty is associated with the random variability of stochastic outcomes between simulated observations, and can be decreased by increasing the number of simulated observations as it is not due to intrinsic uncertainty around parameters or the model structure.

First-order uncertainty around the main outcomes – cost and QALY outcomes with a default treatment – are reported in Figure 5.8 (a)-(b) with incremental cost and QALYs shown in Figure 5.8 (c)-(e), comparing results from the base-case model where individuals in the primary or secondary prevention received statins and the model where statin was not used. Each figure includes error bars to show the standard error in the mean estimates of (incremental) cost and QALYs, and showed the mean and jackknife confidence interval for the cost per QALY gained (Figure 5.8 (e)). The jackknife approach was used to estimate a confidence interval for the mean cost per QALY with a reduced level of bias associated with the classical estimation of non-linear statistics (Iglehart, 1975, NICE Decision Support Unit, 2014). The results in Figure 5.8 were reported only for the age 45 years and over population who entered the model in the base year of 2012.

The cost and QALYs with statin treatments stabilised when the number of simulated individuals was greater than 20,000. Uncertainty around the incremental costs and QALYs, and the cost per QALY comparing the statin and no-statin scenarios significantly decreased after 50,000 individual runs. The mean (discounted) cost per QALY gained with 200,000 simulated individuals was £1,927 and the 95% jackknife confidence interval was £1,582-£2,261. Based on the results in Figure 5.8 and given the short time spent on extra individual runs, the chosen number of individuals to be simulated was 200,000.

Figure 5.8. First order uncertainty in relation to the number of patients simulated

a) Cost with statin treatment

Undiscounted | Discounted

b) QALYs with statin treatment

Undiscounted | Discounted

c) Incremental cost of statin therapy compared with no therapy (discounted)

Undiscounted | Discounted

d) Incremental QALYs of statin therapy compared with no therapy (discounted)	
Undiscounted	Discounted
Incremental QALYs of statin therapy for heart disease	Incremental QALYs of statin therapy (disc)
e) Cost per QALY gained – statin therapy vs. no statin therapy (jack-knife C.I.)	
Undiscounted	Discounted
Cost per QALY of statin therapy	Cost per QALY of statin therapy (disc.)

*The mean results and uncertainty with 100, 500, 1000, 5000, 10000, 20,000, 50,000, 70,000, 90,000, 100,000, 150,000, and 200,000 simulated individuals were examined.

Table 5.17 shows the lifetime costs and QALYs per person in the base-case model using 200,000 simulated individuals. The base-case model population (UK population aged 45 years and older) consists of individuals receiving statins for the secondary prevention of CVD, those receiving statins for primary prevention, and those who are not given statins. The primary prevention population was assumed to have a 10-year CHD risk of 20% for all age groups as previously described, and secondary was dependent on patient characteristics.

The lifetime cost accrued by an individual in the base-case population was £8,091 (£14,224 when undiscounted) with 9.249 (13.843 when undiscounted) QALYs gained. Results for the future incoming cohorts of males and females aged 45 years showed higher costs and QALYs than the base-case population due to the increased life years lived.

Table 5.17. Base-case population results (with the default statin therapy)

With statin therapy	Cost	Discounted Cost	QALYs	Discounted QALYs	Life years
Base-case population	**£ 14,224**	**£ 8,091**	**13.843**	**9.249**	**21.319**
Men aged 45 years	£ 21,138	£ 9,979	21.908	13.342	32.469
Women aged 45 years	£ 22,823	£ 9,972	23.155	13.667	35.453

Based on n=200,000 simulated patients; 2012 prices

Cost per QALY gained for the statin treatment compared to no statin treatment was £1,927 (£1,754 per QALY using undiscounted values) (Table 5.18). This mean ICER was generally lower than those reported in other studies: In NICE TA94, the ICERs for the use of statin treatment in secondary prevention using discounted costs and QALY values ranged from £10,000 to £16,700 per QALY gained. For primary prevention, the report estimated discounted cost per QALYs to range from £9,000 to £21,000 for males at aged 45 years and £14,000 to £30,000 for females. The ICERs increased to over £100,000 per QALY gained at aged 85. The study by Ara et al. (2009) compared different doses of statin treatment instead of statin treatments vs. no statin, and reported costs per QALY from £5,300 to £60,000 for various statin regimes and scenarios. However, it is noted that the cost per QALY estimates from the model for this thesis are not directly comparable with the results from the published studies mentioned above which focussed on specific patient populations as opposed to the general population (including those on primary and secondary prevention therapies modelled in this thesis). More detailed results for primary and secondary prevention populations are reported in next sections.

Table 5.18. Base-case result per person based on n= 200,000 simulated individuals

	Undiscounted		Discounted	
	Statin therapy	**No statin**	**Statin therapy**	**No statin**
Cost	£ 14,224	£ 13,197	£ 8,091	£ 7,569
QALYs	13.843	13.257	9.249	8.978
Incremental Cost	£ 1,027		£ 522	
Incremental QALYs	0.586		0.271	
ICER (£/QALY)	£ 1,754		£ 1,927	

A likely cause of the lower ICERs in the model for this thesis is that the cost of statins was updated including generic drugs that recently became available. When using the cost estimated by inflating the 2004 drug cost reported in Ward et al. (2006) to 2012 price, the mean ICER was increased to £7,330 (£6,045 when using undiscounted values). Added event of PAD could also lower the ICERs.

5.5.2. Results for secondary prevention population

In order to compare the model with the existing models from published literature, the model was run separately for populations on the statin therapy for the secondary and primary prevention. In the base-case model, individuals could have multiple previous heart disease events at model entry through random allocation. However, when running the model only for secondary prevention population, individuals were assigned only one previous heart disease event on a pro rata basis according to the prevalence of the included disease events scaled to sum to 100% in order for all individuals to receive the secondary prevention therapy.

Table 5.19 presents lifetime per-capita costs, QALYs, and life years lived for the secondary prevention population. The use of statins for the secondary prevention of heart disease events for all population aged 45 years and over produced a cost per QALY gained of £2,351. This is in line with the conclusion of the majority of existing studies that supported statins as a cost effective use of resources for secondary prevention of CVD (see Section 5.2).

Table 5.19. Costs and QALYs associated with the use of statin for *secondary prevention* of cardiac events

Secondary prevention population	Undiscounted		Discounted	
	Statin therapy	**No statin**	**Statin therapy**	**No statin**
Cost	£ 27,364	£ 25,394	£ 16,758	£ 15,735
QALYs	12.055	11.150	8.051	7.615
Incremental Cost	£ 1,970		£ 1,023	
Incremental QALYs	0.905		0.435	
ICER (£/QALY)	£ 2,177		£ 2,351	

The results by age and gender based on 200,000 simulated secondary prevention patients are shown in Table 5.20. For comparison purposes, it also reports the cost-effectiveness results reported in Ward et al. (2006) (Table 5.20 (b)). This was taken from one of their scenario analyses which took into account the reduction in stroke risks and CVD death for comparison with the model results in this section, as their base-case considered the effect of statins within the scope of coronary heart disease only (Scenario 2 Table 81 in Ward et al. (2006)).

The results in Table 5.20 a) showed that there was little difference between the cost-effectiveness results in men and women, and it was more cost effective to commence treating patients at younger ages than older ages.

Table 5.20. Secondary prevention population results by age and gender: Comparative results (statin vs. no statin) n= 200,000

a) Cost-effectiveness results for secondary prevention population by age and gender from the model for this thesis

Gender	Age	Undiscounted			Discounted		
		Incre. Cost (£)	Incre. QALYs	ICER (£/QALY)	Incre. Cost (£)	Incre. QALYs	ICER (£/QALY)
Male	45	£2,167	1.426	£1,520	£903	0.578	£1,562
	55	£2,018	1.069	£1,887	£1,040	0.522	£1,993
	65	£1,583	0.703	£2,252	£968	0.411	£2,354
	75	£1,126	0.411	£2,741	£798	0.284	£2,815
	85	£598	0.163	£3,672	£485	0.130	£3,735
Female	45	£2,525	1.586	£1,592	£892	0.606	£1,471
	55	£2,805	1.141	£2,458	£1,341	0.525	£2,557
	65	£2,143	0.783	£2,738	£1,237	0.439	£2,820
	75	£1,295	0.435	£2,974	£891	0.291	£3,063
	85	£641	0.164	£3,923	£510	0.129	£3,960

b) Comparative cost-effectiveness results by age and gender reported in Ward et al. (2006)*

Gender	Age	Undiscounted			Discounted		
		Incre. Cost (£)	Incre. QALYs	ICER (£/QALY)	Incre. Cost (£)	Incre. QALYs	ICER (£/QALY)
Male	45	£10,452	0.700	£13,600	£4,651	0.462	£9,200
	55	£7,722	0.565	£12,500	£4,041	0.411	£9,000
	65	£5,238	0.397	£11,800	£3,218	0.314	£9,100
	75	£3,332	0.227	£13,000	£2,382	0.193	£10,900
	85	£1,911	0.115	£14,500	£1,563	0.103	£13,100
Female	45	£11,650	0.776	£13,800	£4,871	0.493	£9,100
	55	£8,768	0.644	£12,400	£4,312	0.452	£8,600
	65	£6,163	0.499	£11,200	£3,562	0.387	£8,400
	75	£3,979	0.297	£11,900	£2,701	0.248	£9,600
	85	£2,257	0.148	£13,200	£1,784	0.132	£11,700

*Reported in thousands. Rounding errors could be included

5.5.3. Results for primary prevention population

A proportion of individuals were assumed to receive the statin treatment at model entry for primary prevention of heart disease (Section 5.3.2). The results reported in this section were obtained from the model where all individuals were assumed to receive statins for the primary prevention.

The statin therapy for the primary prevention of heart disease for the base-case population of people in the UK aged 45 years and over was cost-effective with the cost per QALY gained of £2,446 (Table 5.21). Compared with the cost-effectiveness results for the secondary prevention population, the use of statins for primary prevention was associated with higher incremental costs and QALYs leading to slightly higher ICER of £2,446 per QALY gained.

Table 5.21. Costs and QALYs associated with the use of statin for *primary prevention* of cardiac events

Primary prevention; All population	Undiscounted		Discounted	
	Statin therapy	**No statin**	**Statin therapy**	**No statin**
Cost	£ 11,755	£ 9,968	£ 6,659	£ 5,518
QALYs	14.341	13.384	9.516	9.050
Incremental Cost	£ 1,788		£ 1,141	
Incremental QALYs	0.957		0.467	
ICER (£/QALY)	£ 1,868		£ 2,446	

A summary of cost and effectiveness of statin therapy for primary prevention by age and gender compared with no statin use is given in Table 5.22. The results by age and gender also showed that using statins for primary prevention of heart disease events would be a cost-effective use of resources with ICERs for all age and gender groups being lower than £3,000 per QALY gained.

Table 5.22. Results for primary prevention population using statins by age and gender

Gender	Age	Undiscounted			Discounted		
		Incre. Cost (£)	Incre. QALYs	ICER (£/QALY)	Incre. Cost (£)	Incre. QALYs	ICER (£/QALY)
Male	45	£2,750	1.658	£1,659	£1,516	0.680	£2,228
	55	£2,149	1.189	£1,808	£1,358	0.582	£2,331
	65	£1,598	0.778	£2,052	£1,126	0.459	£2,453
	75	£1,005	0.418	£2,404	£783	0.289	£2,707
	85	£488	0.189	£2,577	£416	0.151	£2,755
Female	45	£2,617	1.714	£1,527	£1,445	0.648	£2,229
	55	£2,276	1.235	£1,843	£1,394	0.563	£2,475
	65	£1,727	0.816	£2,116	£1,175	0.457	£2,570
	75	£1,095	0.469	£2,332	£830	0.313	£2,654
	85	£544	0.226	£2,410	£455	0.177	£2,570

Incre.=Incremental

5.5.4. Population-level cost projections

In order to project future annual costs for the population aged 45 years and older, costs accrued by the base year population of all individuals aged 45 and over in the base year were combined with costs incurred by incoming cohorts of people becoming 45 years old every year (see Section 4.3.5). Per-capita cohort costs from the base year population and the yearly incoming cohorts of 45 year-olds were multiplied by the projected number of individuals in the relevant age and gender group. The stream of cohort-level costs for each calendar year was combined to estimate total population-level costs. The per-capita costs and QALYs for these incoming cohorts of males and females aged 45 years at model entry are reported in Table 5.23.

The population-level costs of heart disease incurred by this combined population for the period of 2012 – 2037 are summarised in Figure 5.9 and Table 5.24. This projection horizon was determined by the availability of the ONS population data, and it is acknowledged that the results will become more uncertain as the extrapolation period increases as it is anticipated that treatments will change. Figure 5.9 presents the per-capita cohort-level costs obtained from the model simulation results and the total population annual costs projected by combining the per-capita costs with the ONS estimates of the projected number of future populations (Principal Population Projections data)(Office for National Statistics, 2013c). The per-capita annual costs for the base-year population and the incoming cohorts of 45-year-olds (Figure 5.9 a) and b)) increase in the beginning of the projection horizon due to the population ageing to have overall higher incidence than the base year, and then decrease as individuals die over time. The undiscounted annual cost of heart disease for the base year 2012 was estimated to reach approximately £9.4 billion and increase to over £18.3 billion in 2037.

Table 5.23. Per-capita results for male and female populations aged 45 years

(with statin therapy available)	Males aged 45 years	Females aged 45 years only
Cost	£ 21,138	£ 22,823
Cost (discounted)	£ 9,979	£ 9,972
QALYs	21.908	23.155
QALYs (discounted)	13.342	13.667
Life years lived	32.469	35.453

Figure 5.9. Projection of total population-level annual costs for the treatment of heart disease

Per capita cohort annual costs

a) Base year population

b) An incoming cohort of 45 year olds

Total population-level annual costs
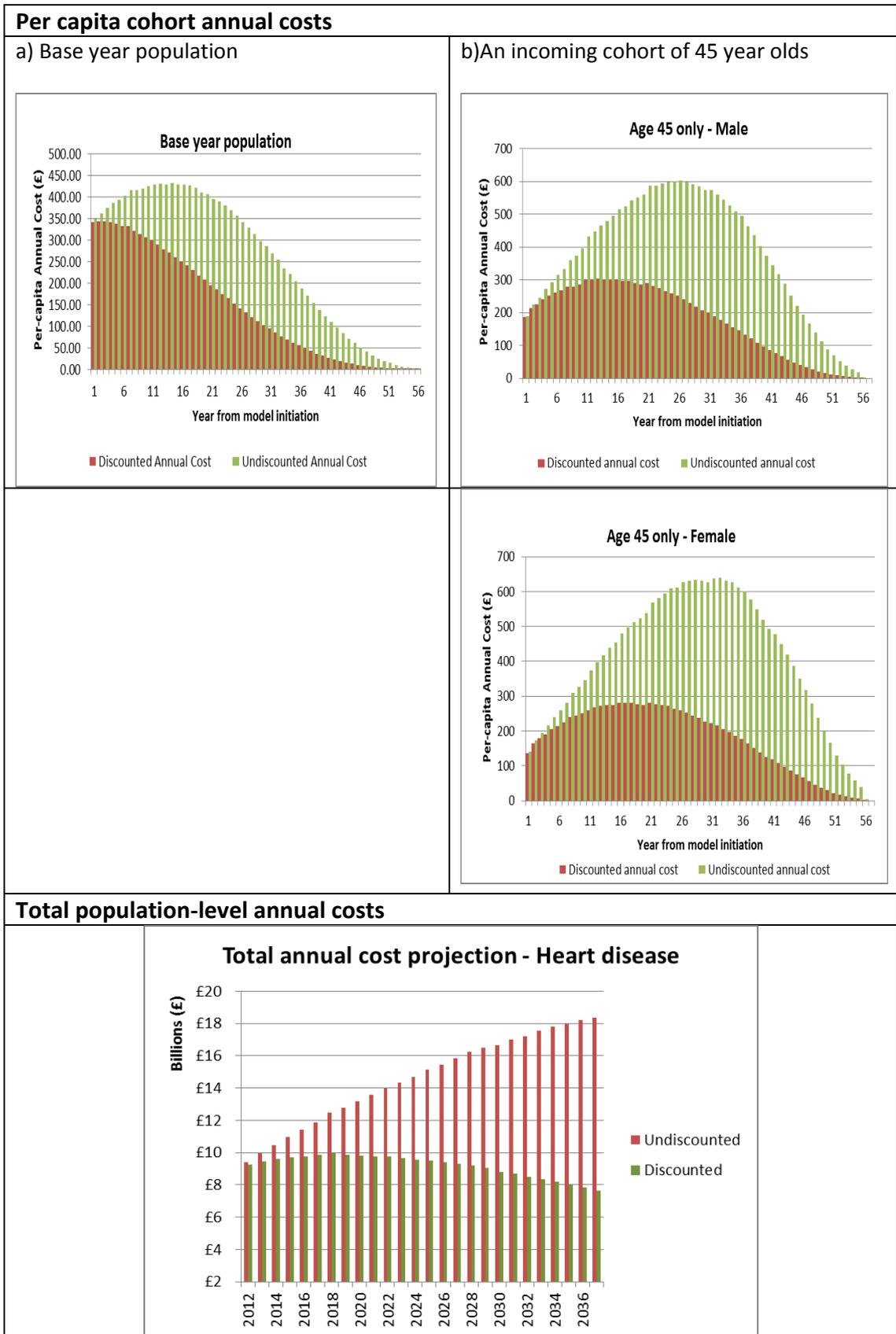
Table 5.24. Projected annual costs: 2012 – 2037

Year	Total cost (£, millions)		Total cost discounted to 2012 (£, millions)		Year	Total cost (£, millions)		Total cost discounted to 2012 (£, millions)	
Base year (2012)	£	9,424	£	9,261					
2013	£	9,952	£	9,451	2026	£	15,451	£	9,383
2014	£	10,472	£	9,609	2027	£	15,850	£	9,300
2015	£	10,979	£	9,733	2028	£	16,239	£	9,206
2016	£	11,421	£	9,783	2029	£	16,502	£	9,039
2017	£	11,885	£	9,836	2030	£	16,649	£	8,811
2018	£	12,500	£	9,995	2031	£	17,014	£	8,699
2019	£	12,766	£	9,863	2032	£	17,196	£	8,495
2020	£	13,160	£	9,824	2033	£	17,534	£	8,370
2021	£	13,567	£	9,785	2034	£	17,794	£	8,206
2022	£	13,985	£	9,745	2035	£	18,022	£	8,030
2023	£	14,352	£	9,663	2036	£	18,202	£	7,836
2024	£	14,677	£	9,547	2037	£	18,344	£	7,630
2025	£	15,163	£	9,530	**Total (2012-2037)**	£	379,100	£	238,631

5.6. Discussion and Limitations

The model in this chapter was based on the model by Ward et al. (2006) with an added event of PAD and updated parameter estimates after a review of existing heart disease models. Although the ICER values varied, the use of statins for both primary and secondary prevention of cardiac events was cost-effective in line with the results reported in the study by Ward et al. (2006) and the other existing studies.

In common with the existing models, the model developed for this thesis was not free from limitations. As the model was based on the existing models identified from the review of recent UK models, many of the limitations that exist in those models also apply to the model in this thesis. For simplicity, many individual characteristics that can affect the event probabilities such as cholesterol level, blood pressure, body mass index (BMI), diabetes status and smoking status are not reflected in the model. Instead, age and gender specific event rates reported in the studies reviewed in Section 5.2 were used. Although conducting systematic reviews or meta-analyses of recent studies for each parameter might have identified more accurate estimates, the data reported in the existing models were used given the time scale of this PhD. For the same reason, time-constant hazards were assumed for some event rates. Also, MI was assumed to not be immediately fatal as the data available did not specify the cause of death. Although it was modelled that having an MI subsequently increased the risk of cardiac death, this assumption could have cost and QALY implications.

In addition, the sources of event rates data were based on different populations. For example, the WOSCOPS study recruited only males with hypercholesterolemia (Shepherd et al., 1995), while the ASCOT-LLA study was for hypertensive patients with low cholesterol level (Sever et al., 2003). Also, due to the possible discrepancy between people receiving primary and secondary prevention therapies within the general population and the population in studies from which event rates were obtained as trials often included individuals with specified CVD risk factors such as hypertension and diabetes, the event rates used in this thesis might be overestimates.

Also, potential correlations between events included in the heart model were not explicitly modelled as instead, independent, random sampling was used in this model. This might lead to overestimation of the cost if a group of patients with one of the heart disease conditions has a higher probability of having another disease event which has common cost items such as monitoring visits to a clinic.

The total annual costs were subject to a high level of uncertainty as the per-capita annual costs were multiplied by large numbers representing the total UK population aged 45 and over and the projected UK population aged 45 years. A small change in base-year population per-capita costs could then result in a considerable difference in total annual costs.

CHAPTER 6 INDIVIDUAL DISEASE MODEL 2 – ALZHEIMER'S DISEASE

6.1. Background

Dementia is typically a disease of later life, which is defined by the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) as:

A syndrome consisting of progressive impairment in memory and at least one other cognitive deficit (aphasia, apraxia, agnosia, or disturbance in executive function) in the absence of another explanatory central nervous system disorder, depression, or delirium (American Psychiatric Association, 2000).

The overall prevalence of dementia standardised to the England and Wales population aged 65 years and older was estimated to be 6.6% for 1991 (MRC CFAS, 1998). The incidence rates for dementia increase with age for both sexes rising from 6.9 (6.3) per 1000 person years for male (female) aged 65-69 years to 58.4 (71.7) for male (female) aged 85 years and over in England and Wales (Matthews and Brayne, 2005).

A Dementia UK report (Alzheimer's Society, 2007) estimated that the annual costs of dementia in 2007 amounted to £17 billion. Since 2007 the total cost of dementia has continued to rise: the Dementia 2012 report (Alzheimer's Society, 2012) produced updated figures for 2012, and estimated the annual cost at £23 billion to the NHS, local authorities and families. It was further estimated that there are 800,000 people living with the condition, with an average cost of £29,746 per person with dementia. The greatest proportion of direct costs of dementia care was associated with institutional support in care homes: Accommodation accounted for 41% of the total cost. This was often provided at a crisis point, is always costly and often precipitated by a lack of effective support (Alzheimer's Society, 2012).

Over a third of the total cost (36%) was due to informal care inputs by family members and other unpaid carers. Not included in this amount is the estimated £690 million in lost income for those carers who have to give up employment or cut back their work hours. This lost

employment was estimated to be a loss of £123 million in taxes paid to the Exchequer (Alzheimer's Society, 2012, Alzheimer's Society, 2009).

The most common form of dementia is Alzheimer's disease (AD), accounting for approximately 62% of all dementia cases (72% when considering mixed dementia including AD) (Alzheimer's Society, 2007) which is additionally characterised by the presence of neurofibrillary tangles and amyloid plaques in the cerebral cortex, observed at post-mortem.

The severity of AD is often defined by, among others, Mini Mental State Examination (MMSE) score. Three acetylcholinesterase inhibitors (AChEIs) – donepezil, rivastigmine and galantamine – have marketing authorisations in the UK and are recommended as options for managing mild to moderate AD (measured by the MMSE score 10–26) by NICE (NICE, 2011). Memantine hydrochloride has a UK marketing authorisation for the treatment of people with moderate-to-severe AD (MMSE score of ≤20), and is recommended by NICE as an option for managing moderate AD for people who cannot take AChEIs due to intolerance or contraindication, and as an option for managing severe AD (MMSE<10) (NICE, 2011). As described in Chapter 4, the model developed for this thesis considers AD only rather than other forms of dementia. This is due to the existing model-based studies focussing on AD and the highest prevalence of AD among all types of dementia.

6.2. Literature review of published model-based economic evaluations of Alzheimer's disease

A recently published Health Technology Assessment (HTA) report (Bond et al., 2012) included a systematic review of economic models for assessing the cost effectiveness of pharmacological interventions for Alzheimer's disease, and was used as a basis of a review of recently published model-based cost-effectiveness analyses (after 2009). Economic evaluations not based on a modelling approach such as those using trial data directly without a model were excluded from consideration.

The PenTAG (Peninsula Technology Assessment Group) model used in the most recent HTA report by Bond et al. (2012) was based on a previous HTA report by Loveman et al. (2006) which used a Markov-type disease progression model based on the Assessment of Health Economics in Alzheimer's Disease (AHEAD) model (Caro et al., 2001). The Southampton Health

Technology Assessment Centre-AHEAD (SHTAC-AHEAD) model by Loveman et al. (2006) evaluated mild to moderately severe AD and employed a predictive risk equation from the AHEAD model to determine a monthly hazard for the progression of AD up to a point where full-time care (FTC) is required.

The AHEAD model was originally built to assess the cost-effectiveness of galantamine and uses three possible health states: pre-FTC, FTC and death. Risk equations to predict the likelihood of patients requiring FTC and dying were estimated using regression-based statistical models which were functions of patient characteristics including age, presence of psychotic symptoms, cognitive function, age at disease onset and duration of AD. Numerous applications have been made using the same AHEAD structure such as Suh (2009), Migliaccio-Walle et al. (2003), Green et al. (2005).

Although the PenTAG model used a model structure similar to that of the AHEAD model, the AHEAD-based equations used in the SHTAC model were replaced with a statistical model estimating time to FTC developed from UK-sourced data. Taking into account the criticism that the SHTAC model had received and given the concerns in the literature over the use of cognitive function alone to model AD progression, a number of amendments including the incorporation of population baseline characteristics in the estimation of the disease progression, have been made to the SHTAC-AHEAD model in the PenTAG model.

Earlier models included those based on data derived from the Consortium to Establish a Registry in Alzheimer's Disease (CERAD) database, which holds data on 1145 dementia patients examined annually between 1986 and 1995. The CERAD-Clinical Dementia Rating (CERAD-CDR) model by Neumann et al. (1999) follows AD progression through stages of cognitive function and residential settings based on annual transition probabilities estimated from the CERAD data. Although the model used the CDR scale which incorporates functional ability, AD progression was effectively determined by cognitive function, as stated in Loveman et al. (2006) and Green et al. (2011). Furthermore, the use of annual cycles and dated US data sources may hinder the application of the CERAD-based models to the model for this thesis.

More recent models by Getsios et al. (Getsios et al., 2010, Getsios et al., 2012) used a DES approach. However, Bond et al. (2012) stated that effectively a 3-month cycle was used as in a Markov model because patient characteristics were updated at fixed intervals. Thus although it was claimed that this was a DES approach, the model calculated two of the most important parameters in determining costs and effects (patient-care costs and utilities) using weighted

averages in the same manner as a cohort-based model. Hence, it included elements of both individual sampling and cohort modelling approaches.

A model using a system dynamics approach called the National Dementia Strategy implementation simulator (The Whole Systems Partnership, 2011) was identified. However, it was mainly aimed at supporting local partners such as local health authorities and regional NHS Trusts in examining the impact of implementing a government intervention called the National Dementia Strategy. It was considered that the model would not fit the purpose of this thesis.

Notably, Getsios et al. (2009) included a screening stage in the model. However, none of the studies mentioned above modelled the onset of Alzheimer's disease as these studies modelled people already with Alzheimer's disease, not the general population. In the model developed for this thesis, the AD onset and diagnosis were included to accommodate both prevalent and non-prevalent populations (see Section 6.3.1).

6. 3. Methods of Alzheimer's disease modelling

6.3.1. Scope and structure of the model

The model developed for this thesis aimed to simulate individuals with and without dementia and to estimate costs associated with prevalent and future occurrences of dementia. AD was taken as the scope of the model in this study as the current NICE guidance and relevant HTA reports focussed on AD. The disease occurs mainly in older people, referred to as late-onset dementia, but it may also occur in people under 65 years, referred to as young-onset dementia. This model includes only the late-onset Alzheimer's disease.

A DES model was constructed based on the Markov model used in the HTA report by Bond et al. (2012): this model will be called the PenTAG model hereafter. Many of the existing AD models identified in the systematic review in Bond et al. (2012) were based on the AHEAD model by Caro et al. (2001). The PenTAG model (Bond et al., 2012) and the previous HTA model by the SHTAC (Loveman et al., 2006) which the current and previous NICE guidance was based on, respectively, also adopted a structure similar to the AHEAD model. As the PenTAG model addressed some of the limitations identified within the SHTAC model, this was chosen

as the basis of the model in this thesis. Individual-level modelling used in the model for this thesis enabled heterogeneity in disease progression and other outcomes to be captured, and changes in multiple attributes on continuous scales to be tracked. Thus, it was not based on average effectiveness and costs, which was one of the criticisms of the AHEAD model (Loveman et al., 2006).

A simulated population representative of the UK population aged 45 and over enters the model. Some already have AD when entering the model. Those who do not have AD may or may not develop AD before death. It is assumed that it takes some time for AD to be diagnosed as the development of symptoms is insidious. After a diagnosis of AD, the model structure replicates the simple three-state model as in the PenTAG model (Bond et al., 2012). The model structure is shown in Figure 6.1. As the existing HTA models (Loveman et al., 2006, Bond et al., 2012) included only people with AD, the onset and diagnosis of AD were added to the structure of the PenTAG model in order to model a general population. Given the purpose of the model in this thesis, it was considered that the benefit of a simpler model (excluding the care pathways) would outweigh the potential inaccuracy in the estimation of disease progression and intermediate health states, provided that the model is capable of estimating the total costs and QALYs of treating patients with AD.

Figure 6.1. Structure of the Alzheimer's disease model
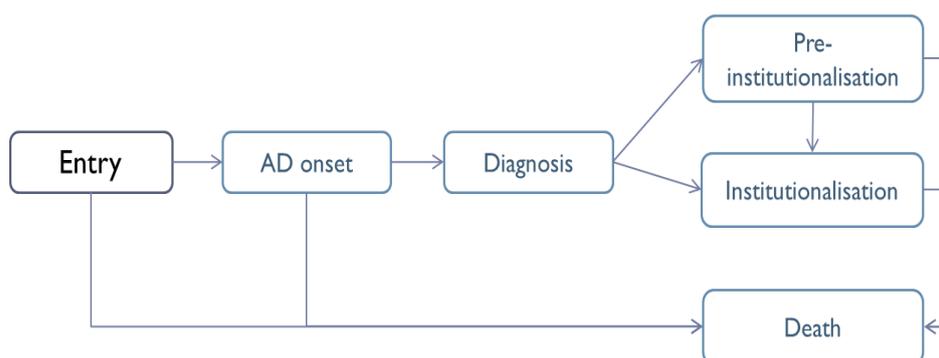
The model in this thesis assumed the progression of disease to a point where the patients require institutionalisation. The institutionalisation state was defined in Bond et al. (2012) as 'living in a residential home or a nursing home (not as short respite care) or in hospital on a long-term or permanent basis'. For people with diagnosed AD, the state before

institutionalisation was termed 'pre-institutionalisation'. The 'institutionalisation' state was chosen as a health state as in the PenTAG model. Many of the models identified in the review conducted by Bond et al. (2012) used health states described solely by the level of cognitive function such as MMSE. However, the use of the endpoint 'institutionalisation' was deemed more appropriate as institutionalisation can be determined by multiple factors (e.g. cognitive and functional ability, socio-economic status), rather than just MMSE given the concerns in the literature over the use of cognition alone to model disease progression. The previous HTA report by Loveman et al. (2006) adopted this approach and the endpoint of FTC was used instead of health states determined solely by cognitive function. The PenTAG model removed the FTC state and replaced it with institutionalisation as it was deemed that pre-FTC and FTC states are too heterogeneous to apply single cost and utility values. Also, the equations used for time to FTC were based on a US study whilst the PenTAG model used a UK dataset which reflected time to institutionalisation, rather than FTC.

Hence, the transitions between events were based on both cognitive and functional factors, not only on cognition factors. Time to institutionalisation and death for people with AD were sampled based on the age, MMSE score which measures cognitive function, and Barthel Activities of Daily Living (ADL) score which measures functional capacity of the individual (see Section 6.3.4.4). The proportion of people with AD in institutional care was dependent on the severity of AD. It was assumed that if an individual becomes institutionalised, then they could not return to the pre-institutionalised state. It was assumed that no time passes when individuals move from diagnosis to the pre-institutionalisation event. A treatment discontinuation event was also incorporated to reflect the assumptions used in the PenTAG model (Figure 6.1). Transitions to death could occur at any point in time and from any disease event.

Amongst the three AChEIs – donepezil, galantamine and rivastigmine – and memantine that NICE currently recommends as options for the treatment of AD, donepezil and memantine were taken as default treatments: memantine was used for people with MMSE < 10 at diagnosis, and individuals with 10≤ MMSE ≤26 at diagnosis received donepezil. It was assumed that donepezil was discontinued as soon as an individual becomes institutionalised whilst memantine could still be used when institutionalised as it was licensed for moderate-to-severe AD.

6.3.2. Modelled population

Both prevalent and non-prevalent cohorts are included in the model (see Chapter 4). The general UK population aged 45 years and over with or without AD entered the model with age and gender values randomly sampled from the UK mid-2012 population estimates published by the ONS (Office for National Statistics, 2013b). However, the PenTAG model included only patients who already have a diagnosed dementia as their population. Due to the discrepancy between the population modelled in the PenTAG model and the current study population, the data obtained from the PenTAG model were applied only to people who have experienced the diagnosis event.

6.3.3. Model assumptions

The key model assumptions are summarised in Box 6.1. Many of these were also used in the PenTAG model.

Box 6.1. Key model assumptions

Assumptions

- Patients cannot return to pre-institutionalisation from the institutionalisation state.

- An infinite capacity of institutionalised care is assumed.

- Both MMSE and ADL (cognitive and functional) are used to predict the time to institutionalisation.

- Drug treatments delay time to institutionalisation, but do not directly affect life expectancy.

- Costs associated with the pre-institutionalisation state were all assumed to fall on the NHS or PSS budget, while 28% of the post institutionalisation costs (accommodation costs) were assumed to be met by the patients or their families.

- No costs of carers were incorporated in this model. The review on the costs associated with Alzheimer's disease conducted by Bond et al. (2012) did not identify data on such costs.

- When an AD diagnosis is made, all people with AD start a drug treatment.

- A constant rate of treatment discontinuation was assumed.

- Six months after treatment initiation, the effect of treatment stops. This was due to the longest follow-up to compare across different drugs and outcomes evaluated in the PenTAG model being 6 months. Individuals receiving the treatment after the 6 months will still incur the cost. However, the drug treatment stops affecting the rate of change in MMSE and ADL score after 6 months (see Section 6.3.6).

6.3.4. Modelled events & data sources

6.3.4.1. Individual characteristics at model entry

Individual characteristics associated with AD, such as the presence of the disease, MMSE score, ADL score, and Barthel ADL score, are assigned conditional on the age, gender, and previously sampled dementia-related variables in order to incorporate correlations between the variables.

At model initiation, of those individuals who already have AD, there are three groups: 1) those who are undiagnosed; 2) those who are already diagnosed; and 3) those who are institutionalised.

The prevalence of AD at the start of the simulation was set as in Table 6.1 (MRC CFAS, 1998). The MRC CFAS data were chosen as this was a large UK study and stratified by age. Those who were simulated to have AD at model entry moved to the Onset event at time zero, but not necessarily the diagnosis state (data in Table 6.1 were assumed to provide estimates of true prevalent cases, not diagnosed cases). As the prevalence was reported for all dementia, it was assumed that in each age group, 72% (62% AD only; 10% mixed dementia including AD) of people with dementia has AD (Alzheimer's Society, 2012). As this model includes only the late-onset AD, the prevalence of AD for people aged 65 years and under was set to zero.

Table 6.1. Prevalence of dementia at model initiation

Age-group (years)	Alzheimer's disease		All types of dementia	
	Men	Women	Men	Women
<65	0*	0*	0*	0*
65-69	0.01008	0.0108	0.014	0.015
70-74	0.02232	0.01584	0.031	0.022
75-79	0.04032	0.05112	0.056	0.071
80-84	0.07344	0.10152	0.102	0.141
85+	0.14112	0.198	0.196	0.275

*It was assumed that individuals aged <65 years did not have dementia in this model as the model focusses on late-onset AD.
Source: (MRC CFAS, 1998)

The incidence of AD was required for sampling of time to the onset of AD. Table 6.2 shows the incidence estimates for all dementia in the UK. It was assumed that 72% of dementia onset was AD (Alzheimer's Society, 2012).

Table 6.2. Incidence of dementia and Alzheimer's disease

	Total Dementia		Alzheimer's disease	
Age-group	Men	Women	Men	Women
<65	0	0	0	0
65-69	0.0069	0.0063	0.0050	0.0045
70-74	0.0145	0.0061	0.0104	0.0044
75-79	0.0142	0.0148	0.0102	0.0107
80-84	0.0170	0.0312	0.0122	0.0225
85+	0.0584	0.0717	0.0420	0.0516

(Matthews and Brayne, 2005, Alzheimer's Society, 2012))

Table 6.2 shows that the incidence rate of AD typically increases as a person ages. In order to account for this, the incidence rate was updated and time to AD onset was re-sampled every time the individual's age was simulated to move to the next age group. This procedure was detailed in Section 4.3 Modelling Methods.

Initial MMSE values were assigned to individuals entering the model conditional on the presence of AD. As MMSE is used for diagnosis of all types of dementia, distributions of MMSE reported for dementia patients were also used for people with AD. Different discrete distributions of MMSE were estimated for groups of people with and without dementia using the results of MRC CFAS study (Huppert et al., 2005). The distribution reported for people with dementia reported in Huppert et al. (2005) was normalised so that the sum of the probabilities would become 1. Parametric distributions for discrete random variables could not be uniquely determined using all the summary statistics reported, and one parameter distributions, such as the Poisson distribution, did not give a good fit. Non-parametric probability profiles of MMSE for population without dementia were fitted by trial and error by age group and sex using summary statistics (mean, median, and 5th, 10th, 25th, 75th, 90th, and 95th percentiles) of normative MMSE values for people without dementia reported in Huppert et al. (2005). Median and other percentile values were first matched with the reported values using these

equal probability estimates, and then the mean of the distribution was matched by adjusting and smoothing the probabilities for adjacent MMSE values. Probability values were adjusted by 0.025 intervals for the ease of computation. When an interval between two consecutive percentile values reported are two or more MMSE scores apart, equal probabilities were assigned to the MMSE values in-between. The distributions used in the model are shown in Figure 6.2. Higher probabilities were assigned to higher MMSE values because of the skewed nature of the distribution. Those aged 64 years and under were assigned the full MMSE value of 30; those without dementia could also have MMSE less than 26 (Huppert et al., 2005).

Figure 6.2. Initial MMSE distributions by age group and sex for the initial population without AD
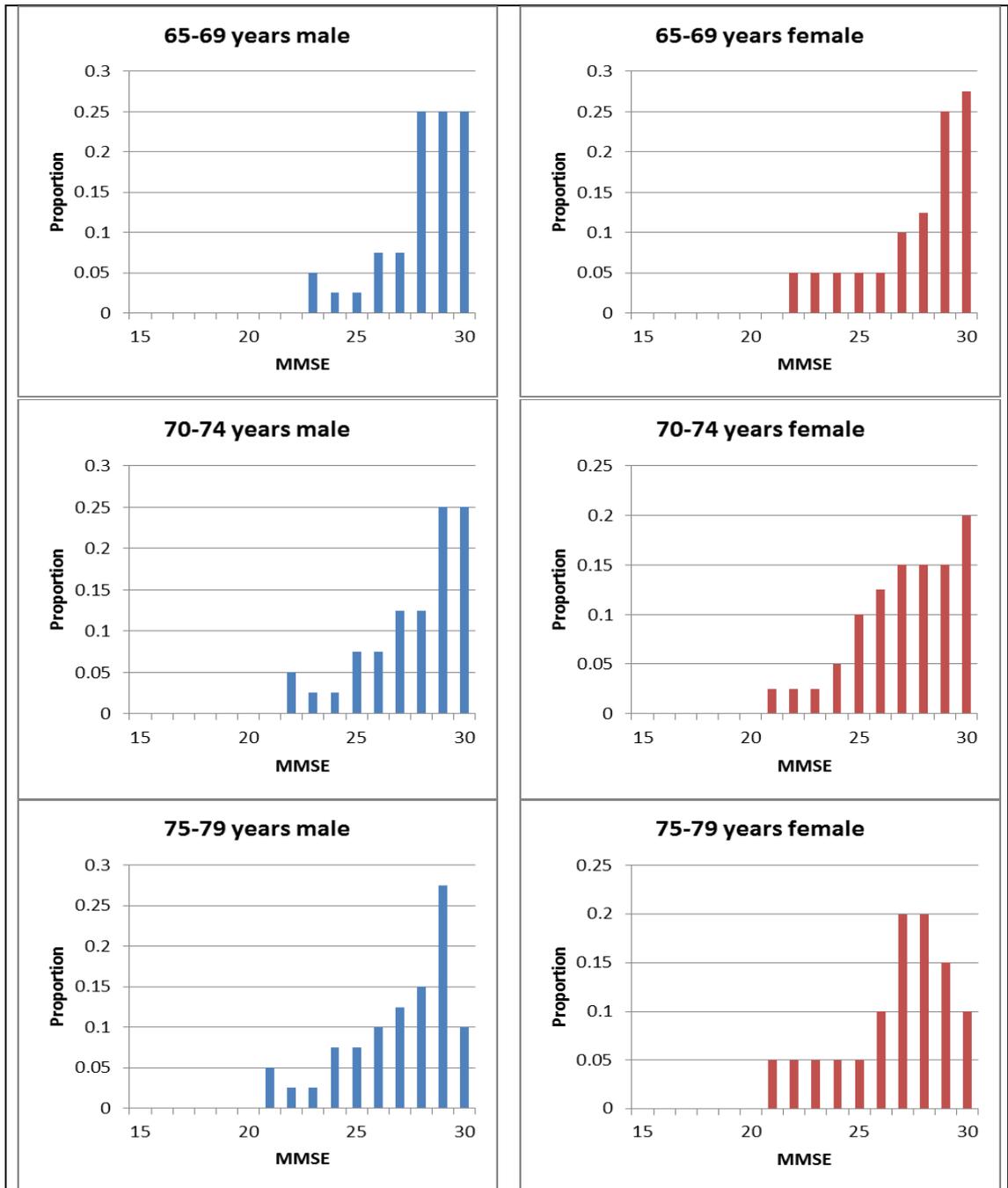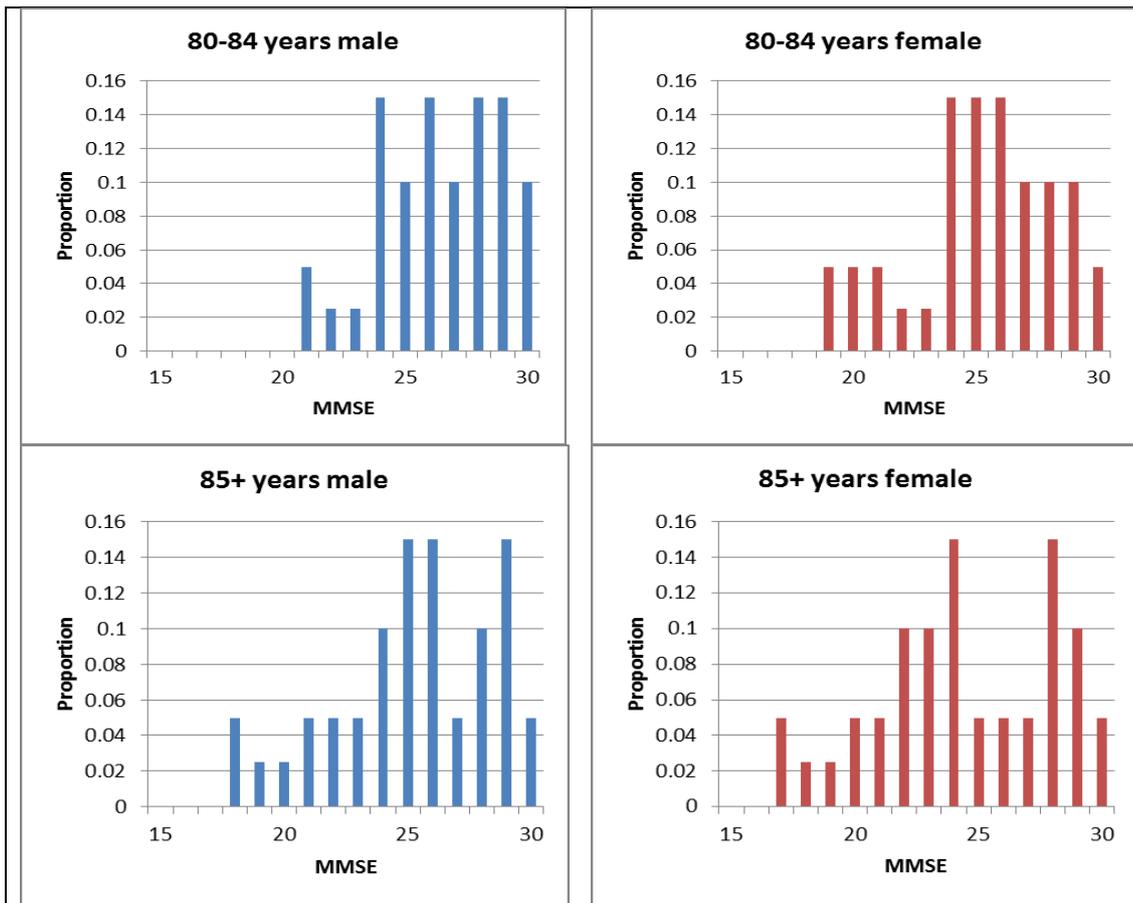
Physical functions (measured by ADLs and Instrumental ADLs (IADLs) that measure functional ability required for independent living) are correlated with the cognitive functions measured by MMSE (Warren et al., 1989). The Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) is one of the most widely used ADL scales for Alzheimer's disease. The ADCS-ADL Inventory is a 23-item assessment of ADLs that is scored from 0 (greatest impairment) to 78. It evaluates activities of daily living. Conditional on the MMSE score of the modelled individual, an ADCS-ADL score was sampled from a generalised beta distribution with lower and upper bounds of 0 and 78 using the mean of the patients in the London and South-East Region Alzheimer's Disease (LASER-AD) study (Livingston et al., 2006). Baseline ADCS-ADL scores for the LASER-AD participants (*n*=198) were used as shown in Table 6.3. Individuals with AD would generally have lower ADCS-ADL scores. However, as people without AD could have an MMSE score lower than 26, it is possible that some with AD have higher ADCS-ADL scores than some without AD.

Table 6.3. Baseline ADCS-ADL (Alzheimer's Disease Cooperative Study – Activities of Daily Living) scores

Disease status		Mean	99% C.I. width
Mild	(MMSE >=20)	54.6	15.0
Moderate	(15<= MMSE < 19)	40.0	15.2
Moderately severe	(10<=MMSE<15)	37.0	21.7
Severe	(MMSE < 10)	18.9	15.0

The parameters of the Beta distributions were estimated using the method of matching moments. Standard deviation was estimated assuming that the reported 99% confidence interval covers +/-2.58 standard deviations as would be the case for a Normal distribution. However, as the standard deviation was based on the symmetric Normal distribution, when the actual beta distribution is skewed, the variance of the sampled ADL values using the parameters estimated from this method could be inaccurate.

The deterministic mapping reported in Bond et al. (2012) was used to calculate the Barthel score. The Barthel score is an index that measures functional capacity. A study by Wolstenholme et al. (2002) used a UK dataset and reported that the MMSE and the Barthel ADL Index are significant predictors of both time to institutionalisation and cost of care. However, as none of the studies included in the review by Bond et al. (2012) used, or reported, this measure, the reported ADCS-ADL scores were mapped onto the Barthel scale. The assumed statistical relationship in Bond et al. (2012) between the ADCS-ADL index and Barthel ADL index is shown in Eq.6.1.

$$Barthel\ score = 0.534 \times (ADCS - ADL\ score) - 0.0036 \times (ADCS - ADL\ score)^2 \quad \textbf{[Eq.6.1]}$$

The model in this thesis used the data on the proportion of patients who, at the start of the model, were in the institutionalised state from the LASER-AD study also used by the PenTAG model (Bond et al., 2012). This estimated that 10% of the mild to moderate AD cohort and 40% for the moderate to severe cohort would be institutionalised. It was assumed that 5.6% of people with MMSE >19, 27.1% of people with MMSE 15-19, and 59% people with MMSE < 15 were in the institutionalisation state at time zero (Livingston et al., 2006).

6.3.4.2. Mortality

Distributions for time to non-disease death were obtained using all-cause mortality data from the UK death statistics (Office for National Statistics, 2013a). The presence of AD could affect the mortality rates by having a competing risk of death from the pre-institutionalisation and institutionalisation events. An equation used in the PenTAG model (Bond et al. 2012) was adopted to sample time to death for people with AD (see Section 6.3.4.4). The assumed time to death was the earliest between the time to death sampled from the UK all-cause death distributions and time to death estimated from the survival equation used in the PenTAG model.

6.3.4.3. Onset & diagnosis of Alzheimer's disease

The onset and diagnosis of AD were modelled as separate events. Onset of AD did not mean the patient receives a drug treatment as the condition might not be diagnosed. The PenTAG model estimated time to institutionalisation and death based on a patient's age, MMSE, and Barthel score (equations provided in Section 6.3.4.4). The same equations were used in the model in this thesis using the values when a patient was diagnosed with AD.

Not all people with dementia are diagnosed. The dementia diagnosis rate in England is estimated to be 48% (Alzheimer's Society, 2012). This was used as the proportion of people with AD who were diagnosed and were receiving a drug treatment at the start of the model time, and these people start the simulation at the Diagnosis event.

All individuals who developed AD including those who entered the model with AD at the start of the model without a diagnosis were assigned a sampled value of time to diagnosis. Those who did not have AD at model initiation may develop dementia and get assigned a time to diagnosis at the 'onset' event. The break-down of individuals with or without AD and with or without diagnosis at model initiation is shown in Table 6.4.

Table 6.4. Distribution of individuals at model initiation

	No Alzheimer's disease (AD)		With diagnosed AD		With AD but not diagnosed		Total	
Age group	Men	Women	Men	Women	Men	Women	Men	Women
<65 years	100.00%	100.00%	0.00%	0.00%	0.00%	0.00%	100%	100%
65-69 years	98.99%	98.92%	0.48%	0.52%	0.52%	0.56%	100%	100%
70-74 years	97.77%	98.42%	1.07%	0.76%	1.16%	0.82%	100%	100%
75-79 years	95.97%	94.89%	1.94%	2.45%	2.10%	2.66%	100%	100%
80-84 years	92.66%	89.85%	3.53%	4.87%	3.82%	5.28%	100%	100%
85+ years	85.89%	80.20%	6.77%	9.50%	7.34%	10.30%	100%	100%

Time taken to receive a diagnosis of AD since AD onset was provided in Table 6.5. Time to dementia diagnosis was assumed to equate to the time to diagnosis of AD. Data reported in Alzheimer's Society (2012) were rescaled excluding the 'don't know' category.

Table 6.5. Time to diagnosis of Alzheimer's disease

	Raw data before scaling	Assumed proportion in each category	Cumulative proportion
< 12 months*	22%	24.44%	24.44%
1-2 years	37%	41.11%	65.56%
3-4 years	23%	25.56%	91.11%
5-6 years	5%	5.56%	96.67%
Over six years**	3%	3.33%	100%
Don't know	5%	N/A	N/A

*A minimum time of 3 months was assumed.
**A maximum of 10 years was assumed.
Source: Alzheimer's Society (2012)

Time to diagnosis since AD onset was estimated using a sample from a Uniform [0,1] distribution. The random number not only informed which time interval the value falls on, but also it determined the time value itself. For example, if the random number was 0.4, the time to diagnosis is between 1 and 2 years as 0.4 is between 0.2444 and 0.6556, and the value was set as 1.3784 years. This value was calculated using the proportion of the relevant year band

the random number was associated with. In the example, the following formula would be used: 1+ [(0.4-0.2444)/(0.6556-0.2444)]=1.3784. The minimum time to diagnosis was arbitrarily assumed to be 3 months as it is believed unlikely that dementia is diagnosed immediately after the onset.

Time taken to receive a diagnosis was calculated in this manner for both incident AD cases and those who already had AD but were undiagnosed at the start of the model. It is acknowledged that the use of the data in Table 6.5 for those with undiagnosed AD could overestimate the time to diagnosis, as their onset could be earlier than the start of the model.

6.3.4.4. Pre-Institutionalisation & Institutionalisation

The institutionalisation state was defined as 'living in a residential home or a nursing home (not as short respite care) or in hospital on a long-term or permanent basis', as in the PenTAG model. For people with diagnosed AD, a state before institutionalisation was called 'pre-institutionalisation'.

Time to institutionalisation from the pre-institutionalisation state was estimated using an equation from an exponential survival regression analysis conducted by Bond et al. (2012).

For people who are not receiving a drug treatment, the time to institutionalisation was sampled from an exponential distribution with the rate parameter of:

$$\lambda = {1}/{\exp(4.928 + 0.00409 \times MMSE + 0.02139 \times Barthel\ ADL - 0.05735 \times Age)}$$

$where\ MMSE, Barthel\ ADL, and\ Age$ variables were the values at diagnosis. The effects of drug treatment on time to institutionalisation are detailed in Section 6.3.6.

Time to all-cause death from the pre-institutionalisation and institutionalisation states was also sampled from an exponential distribution with the rate parameter of:

$$\lambda = {1}/{\exp(4.322 + 0.00228 \times MMSE + 0.04173 \times Barthel\ ADL - 0.04875 \times Age)}$$

using the variables at diagnosis (Bond et al., 2012). The above equation was used for both populations receiving and not receiving a drug treatment as it was assumed that the treatment does not directly affect all-cause mortality, but does so only by improving MMSE and ADL scores.

At the institutionalisation event, time to death was updated subtracting the time spent before being institutionalised, i.e. (time to death – time to institutionalisation).

6.3.5. Disease progression

In the model, an individual's cognitive function (measured by MMSE), and functional status (measured by ADCS-ADL and Barthel ADL score) could be changed due to two reasons: the progression of the disease and drug treatment. Annual rates of decline in MMSE score over time due to disease progression were used to calculate a total change in MMSE over the time between events, based on an equation estimated from a piece-wise linear regression model conducted by Getsios et al. (2010) using CERAD data. Based on the changed MMSE value, ADCS-ADL and Barthel ADL scores were also updated. These updated values were used for the sampling of time to next event and QALY calculation.

Getsios et al. (2010) used an equation for the annual rate of change in the MMSE score since previous measurement as follows:

$$MMSE\ Change = 5.4663 - 0.4299PM_1 - 0.0042PM_2 + 0.1415PM_3 - 0.0791PrevRate + 0.0747Age + \delta_i$$

where $PM_1 = \min(PrevMMSE, 9)$, $PM_2 = \max(0, \min[PrevMMSE - 9,9])$ and $PM_3 = \max(0, \min[PrevMMSE - 18, 12])$. $PrevRate$ is the patient's last known annual rate of decline, Age patients' age at diagnosis, and δ_i a random intercept parameter.

This equation provides a different slope for different ranges of MMSE score, and was reproduced in the model for this thesis for three ranges of MMSE score as follows:

If $PrevMMSE \leq 9$,

$$MMSE\ change = 5.4663 - 0.4299PrevMMSE - 0.0791PrevRate + 0.0747Age + \delta_i$$

If $9 < PrevMMSE \leq 18$,

$$MMSE\ change = 1.6350 - 0.0042PrevMMSE - 0.0791PrevRate + 0.0747Age + \delta_i$$

If $18 < PrevMMSE \leq 30$,

$$MMSE\ change = -0.9876 + 0.1415PrevMMSE - 0.0791PrevRate + 0.0747Age + \delta_i$$

If an updated MMSE score exceeded the maximum score of 30, then it was replaced with 30. Based on the updated MMSE value, the ADCS-ADL score was sampled, and conditional on the

ADCS-ADL score, the deterministic mapping for Barthel score was applied as in Section 6.3.4.1. It was assumed that the values were independent of values in previous years. Changes in MMSE values due to drug treatments are detailed in the next section.

6.3.6. Effectiveness of drug treatment

Different time-to-event equations from those shown in Section 6.3.4.4 were used for drug treated cohort (Bond et al., 2012). For individuals on drug treatment, the average time to institutionalisation increased by $0.1032 \times \Delta MMSE + 0.0781 \times \Delta Barthel$ for mild-to-moderate patients (MMSE>15), and $0.0910 \times \Delta MMSE + 0.1159 \times \Delta Barthel$ for moderate-to-severe patients, where $\Delta MMSE$ and $\Delta Barthel$ are the treatment effects on the MMSE and Barthel scores. This was added to the mean of the exponential distribution in Section 6.3.4.4, and time to institutionalisation was sampled from the distribution with the updated event rate. No treatment effect on survival (time to death) was assumed as in the PenTAG model (see Section 6.3.3). Hence, the effectiveness of the drug treatment is manifested by an average delay in time to institutionalisation, and consequent slower decline in cognitive function. After the adjustment for the mean treatment effect, the ADCS-ADL and Barthel values were bounded within the possible range of the score (ADCS-ADL between 0 and 78; Barthel between 0 and 20).

The effect of treatments was measured by change in MMSE and ADL scores ($\Delta MMSE$ and $\Delta Barthel$). The results from meta-analyses conducted by Bond et al. (2012) are reproduced in Table 6.6. Annual changes in MMSE and Barthel ADL scores were sampled from Normal distributions fitted using the mean and confidence interval reported in Table 6.6, and applied to the baseline estimate of MMSE and ADL scores.

As the longest follow-up of the studies that were used to examine the effectiveness of drug treatment in Bond et al. (2012) was 6 months, it was assumed, as in Bond et al. (2012), that after 6 months, the MMSE and ADL scores of treated cohort declined at the same rate as those of untreated. To illustrate, Figure 6.3 shows the effect of drug treatment on the MMSE score. MMSE score declines at a slower rate for treated individuals compared with the untreated for the first 6 months after the treatment initiation, and the rate of decline for the treated is the same as that for the untreated after 6 months. Hence, a constant difference in MMSE score

between treated and untreated individuals was assumed from 6 months after treatment initiation, with all other things being equal. No bounce-back effect, where MMSE score goes back to the score which the individual would have had if he/she had not taken the drug from the beginning, was assumed as in Bond et al. (2012). It is noteworthy that although the same assumption as the PenTAG model was used due to the absence of data beyond 6 months, the 6-month treatment effect may not reflect the actual increase in MMSE and ADL scores among those receiving drugs for AD.

The treatment effect on MMSE and ADCS-ADL scores was assumed to last 6 months as reported in Bond et al. (2012) or until the treatment effect is sampled to discontinue, whichever is shorter. This was incorporated when sampling time to institutionalisation at the Pre-institutionalisation event.

Time to institutionalisation was sampled using the parameter adjusted for the treatment. If the earliest time to next event was shorter than time before treatment effects stop, then MMSE and ADCS-ADL, and Barthel scores were considered to be over-adjusted. Hence, these scores were re-adjusted so they can reflect the changes up to the next event time.

Table 6.6. Treatment effect at 6 months

Drug	6-month change in:	6-month estimate (95% CI)	Distribution for annual change used in the model	Source
Donepezil 10mg	MMSE	1.24 (0.81,1.66)	Normal (2.48, 0.42^2)	Meta analysis result in Bond et al. (2012)
	ADCS-ADL	2.02 (1.06, 3.28)	Normal (4.04, 1.12^2)	Bond et al. (2012): Average of estimates from galantamine (24mg) and rivastigmine (<=12 mg) due to lack of data
Memantine (15-20mg)	MMSE	0.70 (0.02, 1.38)	Normal (1.40, 0.694^2)	Reisberg et al. (2003)
	ADCS-ADL	1.41 (0.04, 2.78)	Normal (2.82, 1.4^2)	Reisberg et al. (2003), van Dyck et al. (2007)

Figure 6.3. Illustration of treatment effect
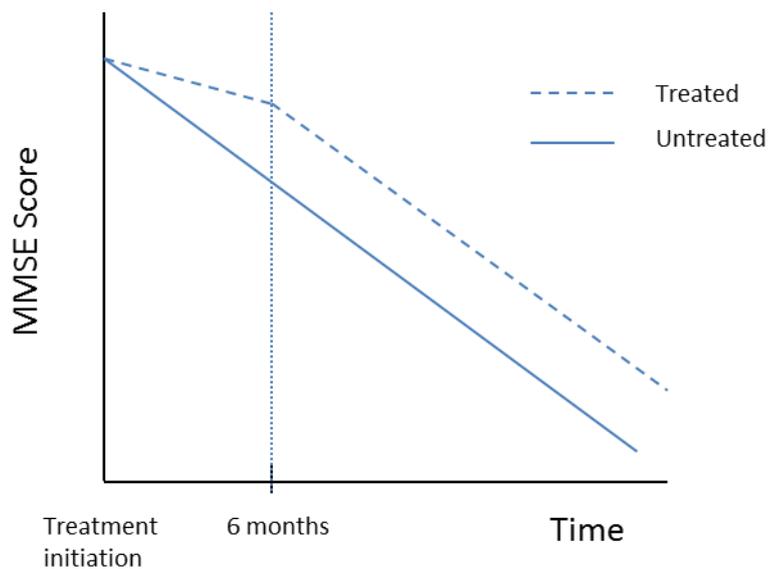
6.3.7. Treatment discontinuation

At diagnosis, it was assumed that all individuals diagnosed with AD initiate a drug treatment. They may discontinue the treatment, but reasons for discontinuation were not modelled. Using data from Bond et al. (2012) and Getsios et al. (2012), 4% (annual rate of 0.4899) of the total population were assumed to discontinue the treatment each month, meaning that almost all individuals no longer receive the treatment after 2 years of treatment. As with the 6-month period of treatment effect, no bounce-back effect was assumed upon treatment discontinuation, with MMSE score declining at the same rate as that of untreated people.

The same assumptions on treatment discontinuation as the PenTAG model (Bond et al. 2012) were used. In the PenTAG model, treatments with the any of the three cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) were assumed to stop once patients become institutionalised. In the model for this thesis, donepezil treatment was stopped if their MMSE fell below 10 or they entered an institution, as the treatment was licensed for mild-to-moderate AD. The model implicitly assumed that institutionalisation is equivalent to severe AD (MMSE <10): Bond et al. (2012) reported that the analysis of Wolstenholme et al. (2002) data suggested that entering institutionalisation is a good proxy for severe AD and also the current guidance recommends that patients be taken off those drugs at MMSE<10. No such assumption was made for memantaine, as the drug is licensed for moderate-to-severe AD.

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Hence, unless treatment is discontinued, memantine was assumed to continue to be taken by patients until they die (NB almost all individuals discontinue within 2 years of treatment).

6.3.8. Utility

Baseline utilities for people without AD were based on their age and gender using the values estimated by Ara and Brazier (2010) as reported in Chapter 4. The utility value at the age halfway between events was used as in the heart disease model.

If the person has AD, utility weights were based on the MMSE score. The EQ-5D values associated with MMSE score were reported in Jönsson et al. (2006) and were used as the base-case estimates of utility weights for people with AD (Table 6.7). The weights were dependent only on the MMSE score regardless of age or gender. The paper by Jönsson et al. (2006) was chosen by Bond et al. (2012) as it reported the utility values across the whole MMSE score range and because the utilities reported in the paper were not particularly different from those in other literature identified. Bond et al. (2012) obtained the standard deviation (SD) of these utility weights by assuming SD as $1/\sqrt{N}$, and these values were used in the model for this thesis. Institutionalised patients were assumed to have the utility weight used for people with MMSE <10 as in Bond et al. (2012).

Table 6.7. Utility weights used for Alzheimer's disease patients

MMSE score	Utility weights	PenTAG estimates of SD*
0-9	0.33	0.151
10-14	0.49	0.107
15-20	0.50	0.110
21-25	0.49	0.200
26-30	0.69	0.213

Source: Jönsson et al. (2006); * SD= $1/\sqrt{N}$ was assumed in Bond et al. (2012)

6.3.9. Costs

All individuals diagnosed with AD were assumed to incur costs (including those with MMSE >26). Three categories of costs were included in the model: 1) drug costs; 2) monthly costs of care (pre-institutionalised and institutionalised), and 3) six-monthly monitoring outpatients care for those on drug treatment. The same cost items as those included in the PenTAG model (Bond et al. 2012) were incorporated. The main sources of data for costs 2) and 3) in the model for this thesis were Unit Costs of Health and Social Care by Personal Social Services Research Unit (PSSRU)(Curtis, 2013), NHS Reference Costs (2008-2009), and BNF 67 (Joint Formulary Committee, 2014). Drug costs were taken from this BNF, and other costs were inflated to 2013 prices using the inflation indices for Hospital and Community Health Services (HCHS) reported in the Unit Costs of Health and Social Care (Curtis, 2013).

Individual-level costs of care were calculated by using the relationship between monthly cost and the time before the end of pre-institutionalisation provided in Bond et al. (2012). Equations for monthly costs were estimated from a linear mixed effects model based on the UK study by Wolstenholme et al. (2002). In the 'Pre-institutionalisation' event, patients with mild-to-moderate AD incurred the monthly healthcare costs of $2877 - 1122t + 194t^2 - 10.9t^3$, and moderate-to-severe AD patients incurred $3363 - 1117t + 191t^2 - 10.7t^3$, where t denoted years before the end of pre-institutionalisation (Bond et al., 2012). These equations reflect that the shorter the time before institutionalisation, the higher the monthly care cost. For all individuals at the pre-institutionalisation stage, these monthly costs were repeatedly calculated and summated until institutionalisation occurs by reducing t by one month at every calculation until $0 \le t < 1/12$. All time units were expressed in years.

For institutionalised individuals, the 2009 price of institutionalisation (£2,941) reported in Bond et al. (2012) was inflated to £3,184.43 (2013 price) using the 2012/13 inflation index of 1.083. Only 72% of this monthly cost was included in the model as the HTA model assumed that the 28% of institutionalised costs were privately funded (the proportion is likely to increase in the near future due to social care funding cuts; see Chapter 10). The NHS/PSS funded cost was therefore £2292.79. The monthly cost of institutionalisation is accrued until the patient moves to the dead state.

The costs of drugs used in the HTA report were updated using BNF 67 (Joint Formulary Committee, 2014). The monthly cost of donepezil (10mg/day) was £128.25 (4.28 x 30). For

memantine (10-20mg/day), a weighted average of daily costs for 10 mg (20% x £1.23) and 20mg (80% x £2.46) was calculated, which led to a daily cost of £2.22 and a monthly cost of £66.54. Drug costs were accumulated until moving to next event with discounting applied. The monthly costs were assumed to be incurred at the beginning of each monthly period.

No cost associated with death was included in the model. In the review conducted by Bond et al. (2012), no data on the NHS and PSS costs of carers of people with AD were identified. Similarly, no carer costs were included in the model.

6.4. Results

6.6.1. First order uncertainty and comparison with existing model results

As in Chapter 5, first-order uncertainty which can be decreased by increasing the number of simulated individuals was examined to identify the appropriate number of individuals to simulate. The mean results and uncertainty with varied number of simulated individuals ranging from 100 to 200,000 were examined (Figure 6.4).

Figure 6.4. First order uncertainty in relation to the number of patients simulated (age 45+)

a) Cost with drug treatment	
Undiscounted	Discounted

b) QALYs with drug treatment	
Undiscounted	Discounted

c) Incremental cost of drug treatment compared with no therapy

Undiscounted	Discounted

Incremental cost of drug therapy for AD

X-axis: Number of individuals simulated
Y-axis: Incremental Costs (£-10,000 to £10,000)

Incremental cost of drug therapy for AD

X-axis: Number of individuals simulated
Y-axis: Incremental D Costs (-£5,000 to £4,000)

d) Incremental QALYs of drug therapy compared with no therapy

Undiscounted	Discounted

Incremental QALYs of drug therapy for AD

X-axis: Number of individuals simulated
Y-axis: Incremental QALYs (-0.15000 to 0.20000)

Incremental QALYs of drug therapy for AD

X-axis: Number of individuals simulated
Y-axis: Incremental D QALYs (-0.08 to 0.06)

e) Cost per QALY gained – drug therapy vs. no drug therapy (jack-knife C.I.)

Undiscounted	Discounted

Cost per QALY of drug therapy for AD

X-axis: Number of individuals simulated
Y-axis: Cost per QALY gained (-£800,000 to £600,000)

Cost per QALY of drug therapy for AD (disc.)

X-axis: Number of patients simulated
Y-axis: Cost per QALY gained (-£600,000 to £400,000)

f) Incremental net monetary benefit (NMB) of drug therapy	
Undiscounted	Discounted
NMB of drug therapy for AD	NMB of drug therapy for AD (disc.)

The treatment was cost-saving compared with the no treatment option, and thus the drug treatment dominated no treatment option (i.e. costing less whilst producing more QALYs). However, the mean cost per QALY was not stable with an increasing number of modelled individuals as shown in Figure 6.4.

This pattern may be caused by the large proportion of the model population that cannot develop AD by assumption – the prevalence of AD amongst people aged under 65 years was assumed to be 0% whereas the model runs were from a population aged 45 years and older. As the base-case model assumes drug treatment does not directly affect mortality, the incremental life years were zero, if random variability was successfully eliminated. For patients without AD the simulated utility would be identical for those receiving and not receiving treatment, rendering the cost per QALY in this group to approach infinity (i.e. $\Delta C / \Delta E \rightarrow \infty$ as ΔE approaches zero).

In order to avoid the instability of cost per QALY due to the small values of incremental QALYs, the ratio-based measure was converted to incremental net monetary benefit (NMB) of the drug treatment using the willingness-to-pay threshold of £20,000 per QALY as shown in Figure 6.4 f). Incremental NMB was defined as $\lambda \cdot \Delta E - \Delta C$, where ΔE and ΔC are differences in effect and cost, respectively. Figure 6.4 f) shows that incremental NMB stabilises with the increasing number of simulated individuals.

In order to examine the level of uncertainty around cost per QALY gained, the model was run for a population simulated to have AD which would all be aged 65 years and over. Figure 6.5 shows the first-order uncertainty results from this model run. When only those already with AD were included, this significantly reduced the standard error around the mean cost per QALY.

When the population is restricted to people with AD aged 65 and over, incremental NMB stabilised with the lower number of simulated individuals than in Figure 6.4. Drug treatment was consistently cost-saving and the no treatment option was dominated for any number of simulated individuals over 10,000. Incremental NMB was around £1,000 with 50,000 and more simulated individuals.

Figure 6.5. First-order uncertainty only for **population aged 65 and over with AD**
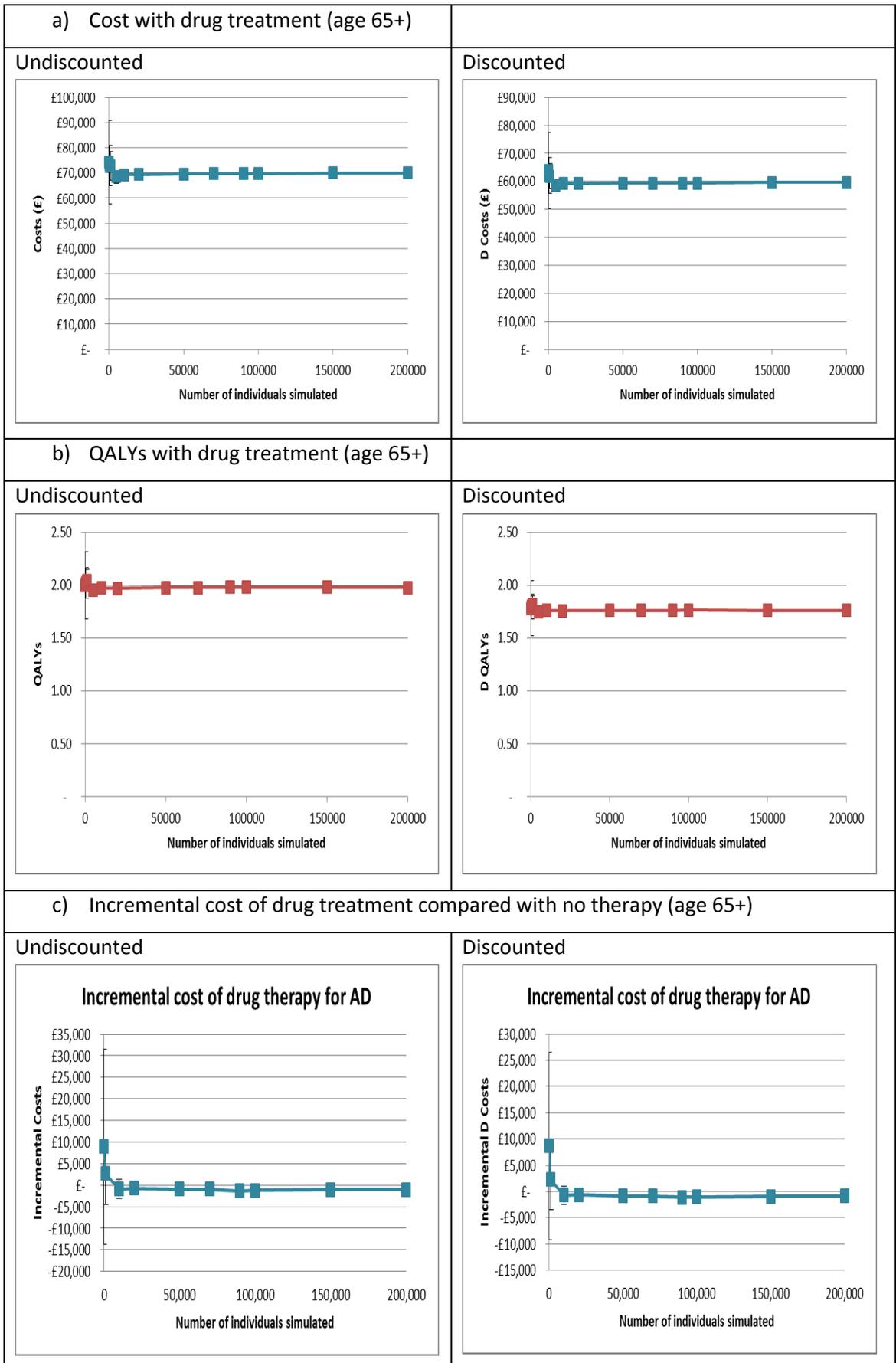
a) Cost with drug treatment (age 65+)

Undiscounted

Discounted

b) QALYs with drug treatment (age 65+)

Undiscounted

Discounted

c) Incremental cost of drug treatment compared with no therapy (age 65+)

Undiscounted

Discounted

d) Incremental QALYs of drug therapy compared with no therapy (Age 65+)

Undiscounted	Discounted

Incremental QALYs of drug therapy for AD
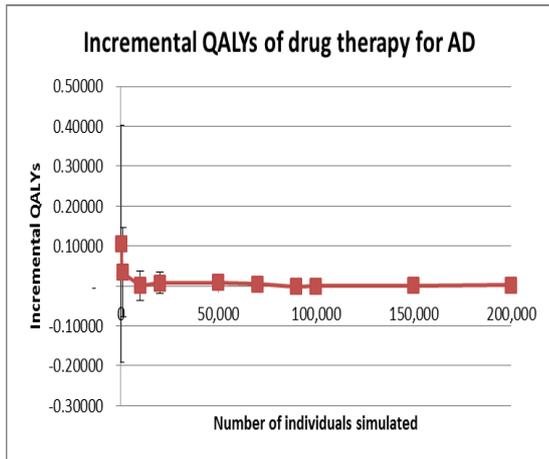
Incremental QALYs of drug therapy for AD
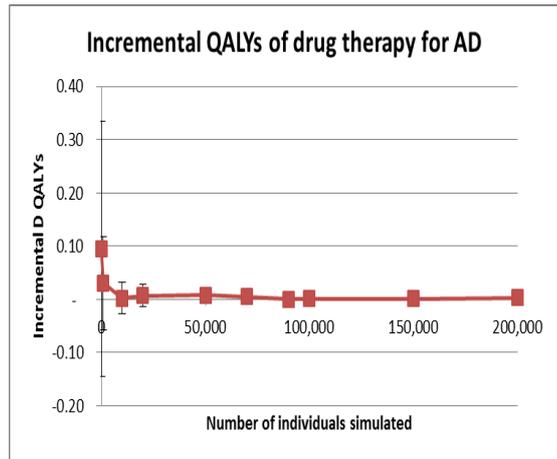
e) Cost per QALY gained – drug therapy vs. no drug therapy (jack-knife C.I.) (age 65+)

Undiscounted	Discounted

Cost per QALY of drug therapy for AD

Cost per QALY of drug therapy for AD (disc.)
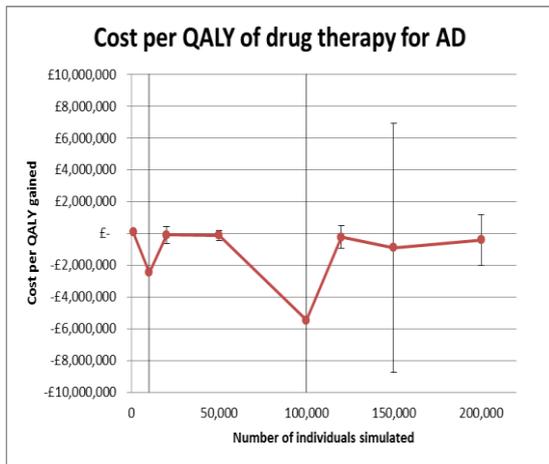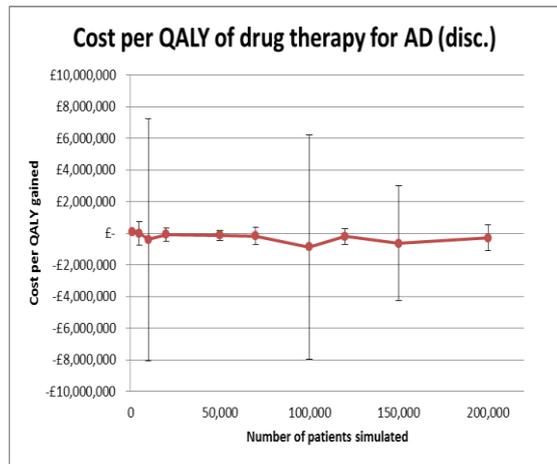
f) Incremental net monetary benefit (NMB) of drug therapy for population with AD aged 65 and over

Undiscounted	Discounted

NMB of drug therapy for AD (undisc.)

NMB of drug therapy for AD (disc.)
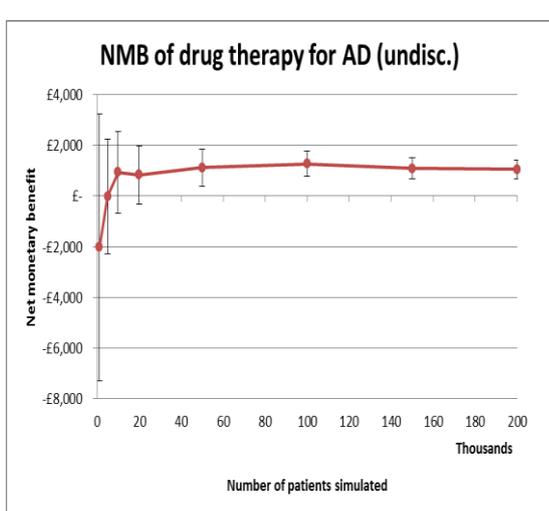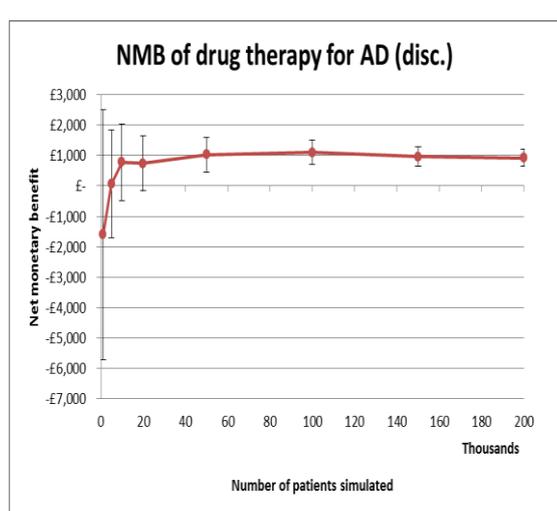
Although direct comparison could not be made due to differences in the default treatment assumptions, time horizon, and model population, for information the results for similar populations were compared to the results from Bond et al. (2012) in Table 6.8. The model results from population with AD aged 65 years and older were generally consistent with those from Bond et al. (2012). When compared with best supportive care (BSC), Bond et al. (2012) reported that donepezil saved £588 for 0.035 QALYs gained over 20 years horizon i.e. donepezil dominated BSC). On memantine, compared with BSC, 0.013 QALYs were gained for an extra cost of £405, leading to a cost per QALY of £32,100. In the model in this thesis, the donepezil treatment for mild to moderate AD and the memantine therapy for moderate to severe AD was cost-saving (£867) with 0.0029 QALYs gained compared with BSC (no treatment) (Table 6.8A).   As the population in the model by Bond et al. (2012) entered the model with diagnosed AD and no treatment costs were incurred without diagnosis, the costs from Bond et al. (2012) were higher compared with the results from the model in this thesis. When assuming an immediate diagnosis after the onset (Table 6.8B), the costs became closer to the level of cost reported in Bond et al. (2012). It is noteworthy that incremental QALYs from the model for this thesis were smaller than those from Bond et al. (2012) due to the difference in the assumed population between the models.

Table 6.8. Comparison of the model results with the results from Bond et al. (2012)

	A. Results for those aged 65+ with AD from the model in this thesis		B. Results for those aged 65+ with diagnosed AD from the model in this thesis		C. Base-case deterministic results in Bond et al. (2012)			
	Treatment (Donepezil + Memantine)	No treatment	Treatment (Donepezil + Memantine)	No treatment	Treatment (Donepezil)	No treatment (BSC)	Treatment (Memantine)	No treatment (BSC)
TDC	£ 59,592	£ 60,459	£ 68,220	£ 69,633	£69,624	£70,212	£78,528	£ 78,123
TDQ	1.978	1.975	1.505	1.498	1.619	1.584	1.227	1.215
Incremental cost of treatment	Cost-saving of £867 (undiscounted: cost saving of £1,006)		Cost-saving of £1,413 (undiscounted: cost saving of £1,579)		Cost-saving of £588		£405	
Incremental QALYs of treatment	0.0029 (undiscounted: 0.0025)		0.0071 (undiscounted: 0.0072)		0.035		0.013	

Based on N= 200,000 simulated individuals; TDC = total discounted cost; TDQ = total discounted QALYs.

Investigation into the simulated time to events for patients indicated that the random draws differed between individuals who received and did not receive intervention, even when the patient characteristics and parameters for distributions were the same. This was believed to be caused by the number of random draws in the intervention arm being greater than in the no treatment arm, and thus the random samples get misaligned for the same parameter between comparators. This could not be resolved within the time scale of the PhD, but it was considered it could be mitigated in terms of expectations of costs and QALYs by running a larger number of simulated individuals.

6.6.2. Base-case results

The base-case model results for the general population aged 45 years and older based on 200,000 simulated individuals produced lifetime costs and QALYs as shown in Table 6.9. The drug treatment dominated no treatment with the (discounted) cost saving of £14 and 0.001 QALY gain over a lifetime. Approximately, 24% individuals had AD at death. Average time to AD onset of the base year population who had AD at death was 19.8 years. The results for men and women aged 45 years at model initiation were also shown in Table 6.10.

Table 6.9. Base-case model results based on n=200,000 - Lifetime per-capita costs and QALYs for the general population aged 45 years and over

AD only model	Treatment (donepezil and memantine)	No treatment	Incremental values
Cost - Discounted	£4,582	£4,596	Treatment saves £14
QALYs - Discounted	10.642	10.641	0.001 QALYs
Cost	£8,845	£8,868	Treatment saves £23
QALYs	16.548	16.545	0.003 QALYs
Life years lived	21.653	21.650	

Table 6.10. Base-case model results for men and women aged 45 years at model initiation

(based on n=200,000 simulated individuals; with default treatment where applicable)

MEN	Discounted	Undiscounted
Cost	£ 2,381	£ 7,888
QALYs	15.916	27.828
Life years lived		34.053
WOMEN	Discounted	Undiscounted
Cost	£ 2,655	£ 9,620
QALYs	16.208	29.343
Life years lived		37.130

6.6.3. Annual cost projection results

Total annual costs for the treatment and management of AD were projected to increase from £4.87 billion in the base year and peak in 2037 at £6.92 billion (Figure 6.6 and Table 6.11).

Figure 6.6. Projected annual costs for the treatment and management of Alzheimer's disease
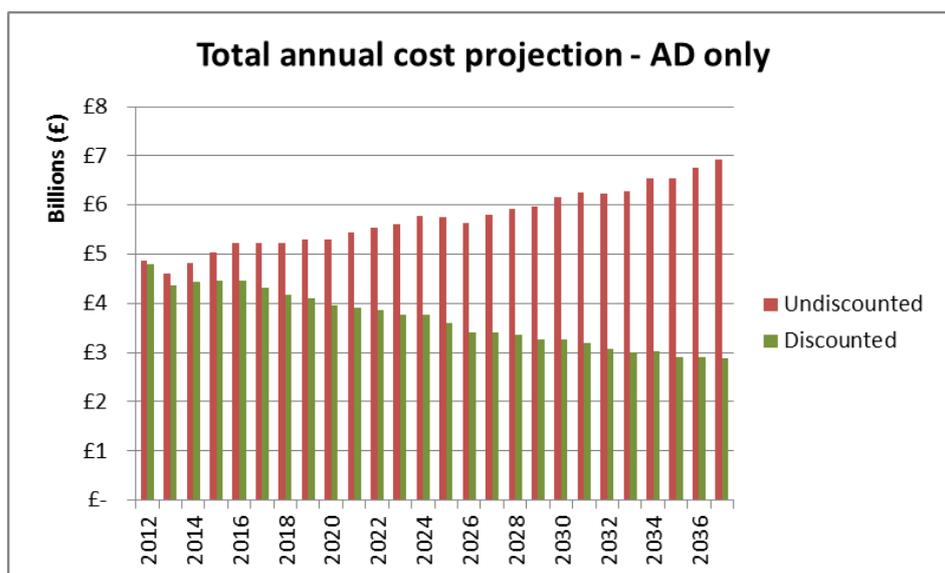
Table 6.11. Projected annual costs for 2012-2037 for the treatment and management of Alzheimer's disease

Year	Total cost (millions)		Total cost discounted to 2012 (millions)		Year	Total cost (millions)		Total cost discounted to 2012 (millions)	
2012	£	4,869	£	4,792	2025	£	5,747	£	3,613
2013	£	4,593	£	4,363	2026	£	5,632	£	3,420
2014	£	4,832	£	4,433	2027	£	5,795	£	3,400
2015	£	5,024	£	4,454	2028	£	5,918	£	3,354
2016	£	5,221	£	4,473	2029	£	5,969	£	3,269
2017	£	5,225	£	4,324	2030	£	6,161	£	3,260
2018	£	5,228	£	4,181	2031	£	6,265	£	3,204
2019	£	5,306	£	4,100	2032	£	6,237	£	3,081
2020	£	5,309	£	3,962	2033	£	6,282	£	2,998
2021	£	5,434	£	3,919	2034	£	6,553	£	3,022
2022	£	5,529	£	3,853	2035	£	6,542	£	2,915
2023	£	5,610	£	3,777	2036	£	6,745	£	2,903
2024	£	5,778	£	3,758	2037	£	6,923	£	2,879

The undiscounted cost for the base year (£4.9 billion) was higher than the next year (£4.6 billion), however the costs were projected to increase year-on-year thereafter. The difference between the year 1 and 2 costs was £275 million.

Investigation into the causes of the lower cost in year 2 than year 1 revealed this was due to: assumptions regarding drug treatment and mortality for people aged 90 years and over. Firstly, it was assumed that all individuals with diagnosed AD at time zero receive treatment at the model initiation, although some discontinue the drug treatment (4% per month), and incurring less cost in the subsequent years. The effect of this assumption was explored by running the model assuming no drug treatment for both populations with and without AD. The base year and second year costs projected were £4.9 billion and £4.8 billion, respectively, and the difference between Year 1 and 2 was reduced to £102 million (Figure 6.7a). As the costs for drug treatment for both Year 1 and 2 were not counted, this reduction in the difference cannot fully explain the difference between Year 1 and 2 costs. However, it could be said that the drug treatment assumption had some effect on total annual cost.

Secondly, it was considered that the mortality assumed for people aged 90 years and over could cause the drop in the second year cost. Costs associated with the management of AD are correlated with the age distribution of the population due to the strong association of AD prevalence with age. Due to the assumption on the age composition of the model population, people aged 100+ were included in the 90+ age group in the model, forming a heavy tail on the distribution for the total population. In order to see the effect of this assumption on the model results, the annual costs for the population aged 90 years and over were estimated and shown in Figure 6.7b). The annual cost of population aged 90+ in the base year decreased rapidly as the population depletes quickly due to the high mortality rate in this age group. The distribution of people aged 90 and over was constructed assuming a constant annual mortality rate. The mortality rate was taken from Death Statistics UK (2012) for females aged 90 years and over as described in Section 4.3.4. The undiscounted cost for Year 1 was £823 million (£811 discounted) and that for Year 2 was £559 million (£531 discounted). The difference between the first and second year undiscounted cost was approximately £264 million, which could explain the difference in the total annual costs.

Figure 6.7. Reasons for the difference in Year 1 and Year 2 costs

a) Annual costs with no drug treatment assumed	b) Annual costs for people aged 90 years and older

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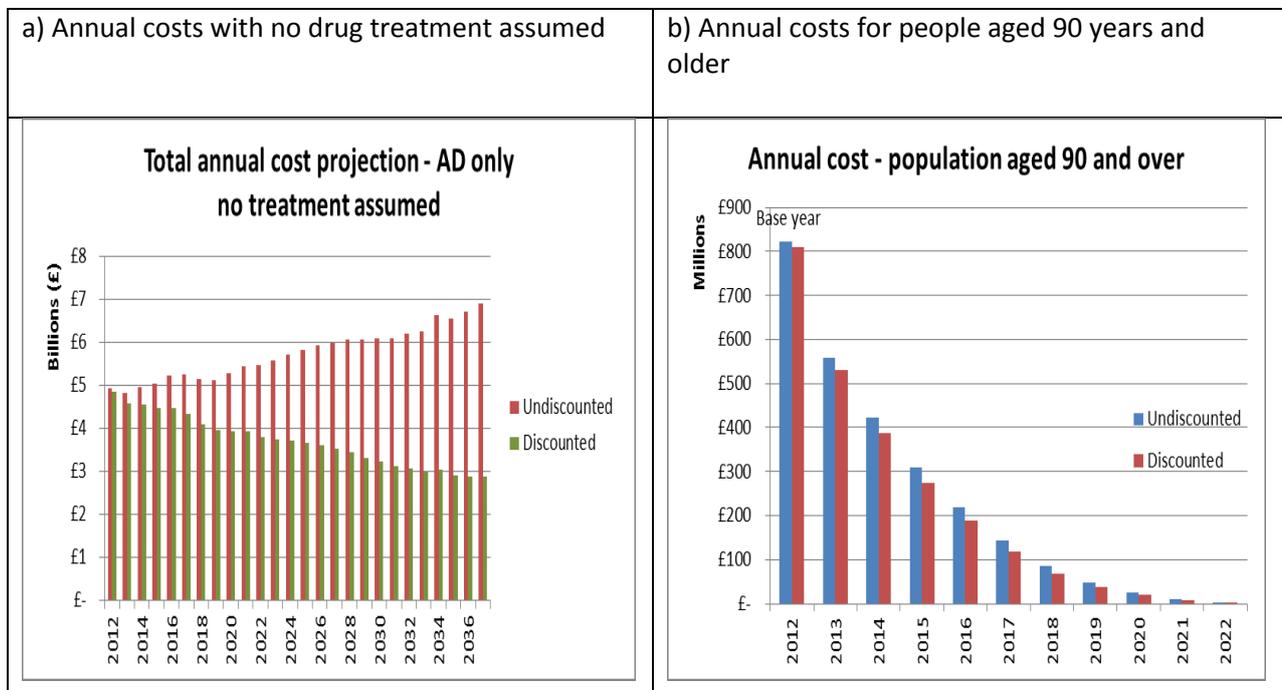
6.5. Discussion

The model in this chapter largely replicated the PenTAG model reported by Bond et al. (2012) with added events such as the onset and diagnosis of AD because the model was developed for the general population, not only for individuals already with AD. It also employed some data not used by Bond et al. (2012) and was constructed as a DES model.

A significant proportion of estimates used in the PenTAG model were based on the individual level data reported in Wolstenholme et al. (2002), which were therefore used in the model in this thesis. Although the use of the UK data might ensure the generalisability of the data to the UK setting, the model was based on rather old data (1988-1999) collected on a small sample (92 patients with AD). The mean follow-up of the study by Wolstenholme et al. (2002) was 40 months (range 1-132). Although it was not considered significantly short compared with other cohort studies, it was still questionable whether the estimates can be extrapolated to a lifetime horizon given the long-term nature of AD.

One of the important assumptions used in the model as well as in the PenTAG model was that when individuals discontinue treatment, their MMSE and ADL scores decline at the same rate as individuals who did not receive treatment. As Bond et al. (2012) noted, no evidence informing what would happen after the discontinuation of treatment was found. If these scores were assumed to revert to the values which would have occurred without treatment, the cost-effectiveness results would be less favourable to the drug treatment.

Furthermore, the trajectory of MMSE score was estimated based on the equation derived from a regression-based model in Getsios et al. (2010). This MMSE equation was estimated using US-based data from CERAD study. It is unclear how representative the US CERAD cohort is of UK individuals with AD.

The aforementioned limitations, nonetheless, are not existent only in the model for this thesis, but also in other models widely used. As the majority of the relationships between parameters for individuals with diagnosed AD were set up in the same way as in the PenTAG model, the limitations would also apply to the PenTAG model.

CHAPTER 7 INDIVIDUAL DISEASE MODEL 3 – MODELLING OSTEOPOROSIS

7.1. Background – Osteoporosis

Osteoporosis is a skeletal disease characterised by low bone mass and structural deterioration of bone tissue that causes bone fragility and increases susceptibility to fractures (Consensus development conference, 1991). Bone mineral density (BMD) is an important – albeit not the only – predictor for osteoporotic fracture. Since an accurate measurement of BMD became possible, a definitive diagnosis of osteoporosis can be made based on BMD. BMD measurements can be taken at different sites such as hip, spine and femoral neck, and are typically reported as a T-score, the number of standard deviations (SDs) from the average BMD of healthy young women. The World Health Organization (WHO) defined osteoporosis as having a T-score of -2.5 SDs or less (Kanis, 2007). A precursor to osteoporosis, osteopenia was defined by a T-score of less than -1 but higher than -2.5 SDs.

The risk of fracture steadily increases with age, especially for hip fracture whose incidence rises exponentially (Stevenson et al., 2005). Hence, population ageing is expected to considerably affect the economic burden from osteoporotic fractures. In England and Wales, for example, the cost of treating fractures was estimated in 2003 at £1.7 billion every year (Woolf and Akesson, 2003). A recent estimate in 2010 including fracture-related costs, cost of pharmacological fracture prevention and cost of long-term disability showed that the burden of osteoporosis in the UK amounts to €5.4 billion (approximately £3.9bn) (Hernlund et al., 2013). This is likely to further increase in the future due to the increase in both the number and proportion of older population (Kanis and Johnell, 2005).

7.2. Review of existing osteoporosis models

A recent systematic review of cost-effectiveness analysis models of interventions for screening and treating people with osteoporosis or osteopenia was identified (Müller et al., 2012). The review included studies in the Medline database published between January 2006 and November 2011. Müller et al. (2012) used a checklist developed by Philips et al. (2004) to assess the methodological quality of the included studies, and presented the number of positive and negative ratings across all dimensions of quality addressed in the checklist. In this thesis, only high-quality studies (n=6) with total points (i.e. the sum of positive (+1 point) and negative (-1 point) ratings based on Philips et al. (2004) checklist) being 12 or higher were reviewed.

Among the high-quality studies, Schousboe et al. (2007) constructed a cohort-based Markov model to evaluate the cost-effectiveness of bone densitometry followed by oral bisphosphonate therapy to prevent fractures for those with osteoporosis, compared with neither bone densitometry nor follow-up drug treatment. This study modelled osteoporosis in older men in contrast to the majority of the studies included in the review which reported results for women only, and showed bone densitometry followed by bisphosphonate therapy for those with osteoporosis may be cost-effective for men aged 65 years or older with a self-reported prior clinical fracture and for men aged 80 to 85 years with no prior fracture. However, the study that provided source data was conducted in the US. Another cohort model that scored high in the assessment by Müller et al. (2012) was also a Markov model with a 1-year cycle used to evaluate the cost-effectiveness of alendronate treatment in the UK setting (Kanis et al., 2008). This model had been extensively used to evaluate the cost-effectiveness of various drug treatments for osteoporosis and hormone replacement therapy in different settings (Borgstrom et al., 2006, Kanis et al., 2004b).

A microsimulation model by Stevenson et al. (2007) achieved the highest rating in the methodological quality assessment. The report by Stevenson et al. (2007) was commissioned by the NIHR Health Technology Assessment (HTA) programme and the model was an updated version of Sheffield Health Economic Model for Osteoporosis (SHEMO), which has been previously reported (Stevenson et al., 2005). In the model by Stevenson et al. (2007), individual patients passed through the model one at a time. The individual-patient approach allowed the full patient history including previous fractures and current residential status to be recorded

and used to determine the level of even risks in the next time period. One-year time intervals were used in this model.

In addition to the studies included in the Müller et al. (2012)'s review, other more recent HTA reports that were not available in the Medline database were searched within the NIHR Journals Library. The most recently published HTA report was a study by Stevenson et al. (2009) which was also based on the SHEMO model with updated parameter estimates and assumptions. It aimed to evaluate the clinical and cost-effectiveness of vitamin K in preventing fractures in postmenopausal women at high risk of fracture. Vitamin K therapy was compared with other licensed interventions such as bisphosphonates (alendronate and risedronate) and strontium ranelate. Due to As this model used recent data, has been applied extensively in the UK and the base model was assessed highly for methodological rigour in Müller et al. (2012), this model by Stevenson et al. (2009) was used as a basis of the model reported in this thesis.

7.3. Methods for osteoporosis modelling

7.3.1. Definition of osteoporosis used in the model

As in Kanis and Gluer (2000), osteoporosis was defined as having a T-score, measured at femoral neck, of -2.5 SDs below the mean of the female reference group (both for men and women). The same female reference group was chosen to define osteoporosis for both men and women as it has been shown that men and women have a similar fracture risk at a given level of absolute BMD measured (Langsetmo et al., 2010). Thus, men with a similar absolute BMD level would have a similar fracture risk to women.

As Stevenson et al. (2009) focussed on female population only, all parameter values used in their model were for women only. Wherever possible, secondary data sources reported by Stevenson et al. (2009) were sought to find equivalent data for men. Otherwise, alternative data sources were used or assumptions were made given that a dominant number of osteoporosis studies analysed only a female population.

7.3.2. Structure of the model used in this thesis

Stevenson et al. (2009) constructed a patient-based state-transition model with time slices of 1 year, in Microsoft Excel (Microsoft Corporation). The HTA model included four main fracture types (hip, vertebral, wrist and proximal humerus fractures); nursing home entry from hip fracture event; breast cancer; and coronary heart disease; and non-fracture related death events.

As in Stevenson et al. (2009), the main four fracture sites were assumed to include other relevant fractures. Hip fracture incorporated pelvis and other femoral fractures; proximal humerus fracture included tibia and fibula fracture; and wrist fracture included rib, sternum, clavicle and scapula fractures.

Breast cancer, which was technically included in the model by Stevenson et al. (2009), was not incorporated in this model. This had been included in earlier versions of the SHEMO models in order to evaluate oestrogen and raloxifene treatments which could affect the risk of breast cancer. However, both of these treatments were not considered in the model by Stevenson et al. (2009). For the assessment of osteoporosis treatments (see Section 7.3.8), effect on the incremental cost and QALY outcomes due to the removal of breast cancer is expected to be minor.

The model in this thesis was constructed on the platform of discrete event simulation (Figure 7.1). As no fixed time cycles were assumed, all transition probabilities reported in Stevenson et al. (2009) were converted to event rates, which are the instantaneous likelihood of event occurring per unit of time, unlike probabilities defined over a fixed period of time. Events included in the model for this thesis were the four fractures (hip, vertebral, wrist and proximal humerus fractures) including nursing home entry from hip fracture; death following fracture; and non-fracture related death. The initiation and discontinuation of a drug treatment were also included as qualifying events. It is noted that the model for this thesis included fractures occurring to both osteoporotic and non-osteoporotic populations, as in Stevenson et al. (2009).

Figure 7.1. Structure of the osteoporosis model
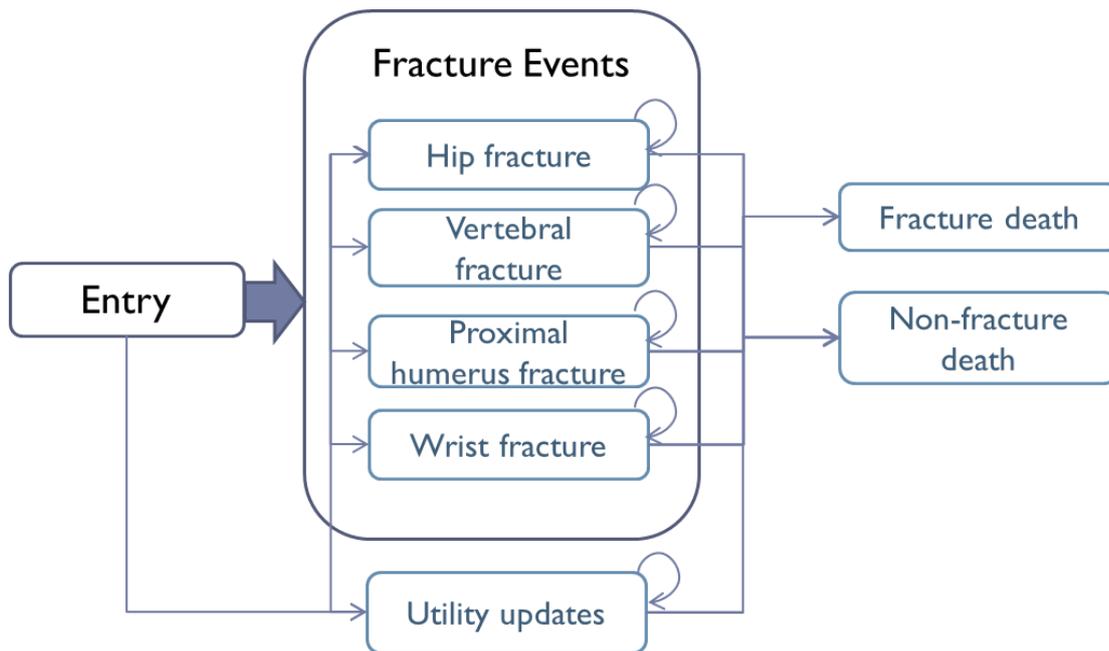
As in the heart disease model in Chapter 5, the 'utility cut off' event was included in the model in order to reflect that costs and utilities for the first year and subsequent years after a fracture could be different. This event activates a transient utility state where a different utility value is applied when there is no actual disease event. When more than one fracture event occurs within a year, the cut-off time point dividing the first year and subsequent years for one fracture would be greater than the time to the next fracture, leading to an overlap of the first-year periods. The logic was constructed so that the changes in utility respected both times of subsequent fractures and changes in utility after one year.

The discount rates used for the model were 3.5% per annum for both costs and utilities in accordance with the NICE recommendation. A lifetime horizon was adopted whilst the time horizon of the model by Stevenson et al. (2009) was a 10-year period with the model results subsequently adjusted to account for treatment benefits beyond the initial 10 years.

The UK general population aged 45 years and over was chosen for the base-case analysis as in the other disease models in Chapters 5 and 6. A summary of model assumptions is provided in Box 7.1 and is detailed in subsequent sections.

Box 7.1. Model assumptions

- Costs and utilities for the first year and subsequent years after a fracture are different.

- The Z-score of an individual is assumed to remain constant across time.

- The difference in average T-score between men and women for all age groups is assumed to be constant.

- The risk of having fracture following a previous fracture is assumed to be double that of a women without a previous fracture, as in Stevenson et al. (2009).

- Drug treatment is initiated when women and men have an osteoporotic fracture.

- The duration of the drug treatment was assumed to be 5 years. After the discontinuation of the 5-year treatment, the treatment would not be given to the same person again.

- The efficacy of the drug treatment wanes over a 5-year period after treatment discontinuation in a linear fashion.

- Nursing home stay is associated with lower utility. The same utility weight as that for institutionalised AD patients was used.

7.3.3. T-score, Z-score, and prevalence of osteoporosis at model entry

Z-score is defined as the number of SDs from the average BMD of people of the same age and sex as the patient, which is equivalent to the T-score of an individual minus the average T-score for that age and sex. The Z-score is assumed to follow standard Normal distribution: a person who is average has a Z-score of zero and is at the 50th percentile, and approximately a quarter of people have a Z-score of -0.68 or lower. In the model for this thesis, the Z-score was assumed to remain constant for an individual across time. It is noted that T-score would, however, change as the mean T-score differ by age.

The average T-score at the femoral neck for females was calculated using values at the mid-point of each age band derived from a linear relationship, $T - score = 2.0251 - (0.0512 \times Age\ in\ years)$, which was estimated from a UK population-based study by Holt et al. (2002).

Although the average T-scores were reported only for people aged 50 and over, the value for the age band of 45-49 was calculated backwards using the same linear relationship. The average T-score for the age band 85-89 were used for those aged 85 years and over.

The average UK T-scores were reported only for female population in Stevenson et al. (2009). The raw data from which the figures for female population were derived (Holt et al., 2002) could not be obtained for male population, hence the average difference between men and women in the population of the study by Holt et al. (2002) was applied to calculate the average T-scores for men (Table 7.1). The difference was calculated using T-scores measured at the femoral neck. A constant difference between men and women for all age groups was used. However, it is noted that this assumes that the same rates of deterioration in BMD for age groups and equal age distributions for men and women, an assumption that is uncertain.

The T-score of an individual was derived from the sum of the average T-score for the age group and sex of the person and the sampled Z score. Gradual deterioration of T-score on a continuous time scale or at regular time intervals was not recorded in the model. Instead, T-score was updated before every occasion where the current T-score could influence parameters of equations used to estimate time to next event, and consequently, costs and utility values. Prevalence of osteoporosis was determined when this T-score was lower than -2.5 SDs.

Table 7.1. Average T score for men and women in the UK by age band

Age in years (mid-point)	Average UK T score for women	Average UK T score for men*
45-49 (47.5)	-0.41	0.31
50-54 (52.5)	-0.66	0.06
55-59 (57.5)	-0.92	-0.20
60-64 (62.5)	-1.17	-0.45
65-69 (67.5)	-1.43	-0.71
70-74 (72.5)	-1.69	-0.97
75-79 (77.5)	-1.94	-1.22
80-84 (82.5)	-2.20	-1.48
85-89 (87.5)	-2.45	-1.73

*T-scores for men were calculated as T-scores for women +0.72 (the men-women difference in Holt et al. (2002))

7.3.4. History of previous osteoporotic fracture at model entry

Previous osteoporotic fracture could affect the risk of subsequent fractures and utility values.

Upon the entry to the model, a proportion of people with prevalent osteoporosis (T-score of -2.5 or lower) were assigned to have a history of previous osteoporotic fractures at different sites. As in Stevenson et al. (2009), 'severe osteoporosis' was used to describe osteoporosis patients with a prior fracture. The proportion of people with severe osteoporosis in the UK female population reported in Stevenson et al. (2009) was split into groups of people with fracture history at four different sites, using the distribution of fractures by age and gender.

The model for this thesis included fractures occurring to both osteoporotic and non-osteoporotic populations. However, this section concerns people with severe osteoporosis who have a history of fracture at model initiation: only osteoporotic fractures were considered.

Table 7.2 shows the proportion of women with severe osteoporosis. Stevenson et al. (2009) calculated the percentage of people with severe osteoporosis at each age using data from Kanis et al. (2000) on the incidence of fractures in men and women by fracture site. The ratio of people with severe osteoporosis to the total osteoporotic population was calculated for each age group using data reported in Stevenson et al. (2009) (Table 40, Appendix 7). As data on the proportion of people with severe osteoporosis was available only for the female population and the underlying calculations were not shown in Stevenson et al. (2009), it was assumed that the ratio of people with severe osteoporosis to people with osteoporosis is maintained for the male population and the ratio for the age band 75-79 was also used for people aged 80 years and over. Due to lack of data, it was also assumed that those aged 45-49 years did not have severe osteoporosis.

Table 7.2. Proportion of people with severe osteoporosis

Age	Proportion of women with osteoporosis (including severe) (A)	Proportion of women with severe osteoporosis (among all female population) (B)	Proportion of severe osteoporosis among osteoporotic population (B/A)*
50-54	3.29%	0.49%	14.89%
55-59	5.71%	2.4%	42.03%
60-64	9.18%	5.28%	57.52%
65-69	14.23%	9.46%	66.48%
70-74	20.9%	15.6%	74.64%
75-79	28.77%	22.4%	77.86%

*B/A was assumed to maintain for male population.

In order to assign a history of fracture at different sites to individuals with severe osteoporosis, distributions of four fracture sites were derived (Table 7.3). The distribution of fracture sites by age and sex was calculated by summing the proportions of fractures at different sites reported in Kanis et al. (2007) (Table 15; reproduced from Table 3 in Kanis et al. (2001)). The four sites of fractures incorporated other relevant fracture sites as in Stevenson et al. (2009) (see Section 7.3.5). Hip fracture included pelvis and other femoral fractures; proximal humerus fracture included tibia and fibula, and humeral shaft fractures; and wrist fracture incorporated distal forearm, rib, clavicle, scapula, and sternum fractures. In the model for this thesis, only one previous fracture per person with severe osteoporosis was assigned according to the distribution of fractures with the location of their previous fracture occurred based on data in

Table 7.3. The fracture site was randomly sampled from the distribution of fractures (proportions of each fracture sites were calculated to match 100% using the proportion of fractures at different sites reported in Kanis et al. (Kanis et al., 2001, Kanis et al., 2007).

Table 7.3. Distribution of fractures at model entry at different sites

Age	Women				Men			
	Hip	Vertebral	Proximal humerus	Wrist	Hip	Vertebral	Proximal humerus	Wrist
50-54	5.6%	15.1%	21.0%	58.2%	7.7%	21.9%	9.8%	60.6%
55-59	10.0%	12.7%	19.9%	57.4%	7.8%	9.1%	3.2%	79.9%
60-64	15.5%	19.2%	16.3%	49.1%	16.0%	20.3%	7.2%	56.5%
65-69	18.2%	16.4%	21.3%	44.0%	17.4%	12.1%	6.2%	64.3%
70-74	26.6%	20.0%	15.9%	37.5%	23.5%	19.9%	11.0%	45.6%
75-79	31.8%	17.3%	15.4%	35.6%	33.8%	19.5%	7.5%	39.2%

7.3.5. Fracture risks

The risks of fracture for the general population including people with and without osteoporosis were split into the baseline risks for a population with average BMD and no previous fracture and the risks for a more severe population. The risks for a population with high BMD were estimated assuming that risk reductions are made by the same factor as the risk increases, but in the opposite direction. This section first describes the risks for the general population, and moves onto how fracture risks were adjusted for low BMD, other relevant fracture sites, and previous fracture; and how the baseline risks for those with normal BMD and no previous fracture were calculated based on the population-level risks and the relative risks for high-risk populations.

Population level risks of the four main fractures

Both osteoporotic and non-osteoporotic populations are at risk of fracture. Hence, this section concerns total fracture risks. It is noted that, at model initiation, previous osteoporotic fracture

was assigned in order to incorporate the increased risk of future fracture for people with severe osteoporosis.

Stevenson et al. (2009) estimated the risks of fractures at four different sites by fitting an exponential regression to smooth the data taken from a large Scottish study by Singer et al. (1998). The estimated exponential survival function was used to extrapolate the incidence to those aged 50 years and under for the model in this thesis. The female population risks of fractures estimated from the study by Singer et al. (1998) are summarised in Table 7.4.

Table 7.4. Annual female population risks of fractures

Female population risk of fracture				
Age	Hip fracture	Vertebral fracture	Proximal fracture	Wrist fracture
45-50	0.0003	0.0009	0.0007	0.0031
50-55	0.0003	0.0009	0.0007	0.0031
55-60	0.0006	0.0013	0.0009	0.0036
60-65	0.0011	0.0019	0.0012	0.0043
65-70	0.002	0.0028	0.0015	0.0051
70-75	0.0038	0.004	0.002	0.0061
75-80	0.0073	0.0059	0.0026	0.0072
80-85	0.0138	0.0085	0.0035	0.0086
85-90	0.0262	0.0123	0.0046	0.0102

Adapted from Table 13 in Stevenson et al. (2009)

Increased risks of fracture incorporating sites other than the four

As in Stevenson et al. (2009), other fracture sites were incorporated into the four main fracture types. This was in order to use a meta-model that Stevenson et al. (2004) previously estimated. The meta-model was used to instantaneously calculate incremental costs and QALYs with a different parameter configuration in Stevenson et al. (2009). Hence, in order to use Stevenson et al. (2009) as the basis of the model in this thesis, the incidence of hip, vertebral, wrist and proximal humerus factures shown in Table 7.4 was adjusted to incorporate the incidence of fractures at other sites using multipliers reported in Table 7.5. The incidence of vertebral fractures was not increased as in Stevenson et al. (2009).

Table 7.5. The multipliers used to incorporate fractures at other sites

Age (years)	Increase in hip fracture incidence to incorporate pelvis and other femoral fractures	Increase in proximal humerus fracture incidence to incorporate tibia and fibula fractures	Increase in wrist fracture incidence to incorporate rib, sternum, clavicle and scapula fractures
45-50	1.26	1.87	1.63
50-55	1.26	1.87	1.63
55-60	1.25	1.75	1.33
60-65	1.23	1.63	1.17
65-70	1.22	1.51	1.14
70-75	1.2	1.39	1.24
75-80	1.19	1.27	1.48
80-85	1.17	1.15	1.86
85-90	1.17	1.15	1.86

Adapted from Table 14 in Stevenson et al. (2009)

Increased risks due to low BMD

The population risks of fracture were adjusted for BMD status. The increased probabilities of fracture associated with a Z score of -1 SD reported in Stevenson et al. (2009) were used (Table 7.6-7.7). The risk of hip fracture was adjusted using the data reported by Johnell et al. (2005). In Table 7.6, the increase factor for hip fracture in people aged 45-50 years was assumed to be the same as that in 50-55 year olds. For other fractures, a single factor was used for all ages and sexes based on the data reported by Marshall et al. (1996) (Table 7.7).

Table 7.6. Increased risk of hip fracture associated with a Z-score of -1 SD

Age	Increased risk of hip fracture
45-49	3.68
50-54	3.68
55-59	3.35
60-64	3.07
65-69	2.89
70-74	2.78
75-79	2.58
80-84	2.28
85-90	1.92

Table 7.7. Increased risk of fracture associated with a Z-score of -1 SD

	Increased risk of fracture per -Z score
Vertebral fracture	1.8
Proximal humerus fracture	1.6
Wrist fracture	1.4

The increased risk of fracture factor was used as the base raised to the power of the minus Z-score of the individual. For example, for a patient aged 67 years with a Z-score of -1.5 SDs, the risk of hip fracture is 4.91 times (=$2.89^{1.5}$) the general population risk. These values were used in the same way for those with positive Z-score. Hence, for those whose BMD is higher than the average of the same age and sex group, the fracture risks were reduced. For example, the risk of vertebral fracture for people with a Z score of +1.5 would be 41.4% (=$1.8^{(-1.5)}$) of the general population risk.

Increased risks after previous fracture

Previous fractures increase the risk of subsequent fractures. The incidence rate of fractures was adjusted for previous fracture history. Stevenson et al. (2009) used the results from Klotzbuecher et al. (2000) and the summary of the relative risks used in the model in this thesis is given in Table 7.8.

Table 7.8. The relative risk of subsequent fracture following an initial fracture

Previous fracture	Subsequent fractures			
	Hip	Vertebral	Proximal humerus	Wrist
Hip	2.3	2.5	1.9	1.4
Vertebral	2.3	4.4	1.8	1.4
Proximal humerus	2.0	1.9	1.9	1.8
Wrist	1.9	1.7	2.4	3.3

As in Stevenson et al. (2009), it was assumed that only the greatest risk adjustment would be applied for people who have history of fractures at two or more fractures. Hence, for example, if an individual had suffered a vertebral fracture previously, regardless of other fracture history, the RR adjustment for hip fracture and vertebral fracture would be 2.3 and 4.4, respectively.

Adjustments for the relative risks associated with BMD status and previous fracture were made to the general population probability (risk) of fracture. As the model adopts the DES structure, the adjusted probabilities were converted to event rates (hazards).

Baseline risks for people with average BMD and without previous fractures

Using the population-level risks of fracture including osteoporotic and non-osteoporotic populations and the relative risks associated with previous fracture and BMD, the baseline risks of fracture for people with average BMD and no previous fracture were estimated. The methodology reported in Stevenson et al. (2009) was followed to estimate the baseline risks of fracture for all age groups included in the model for this thesis (age 45 years and over). The assumptions and calculations were reported briefly in this section.

The population risks reported in Table 7.4 was split into risks for three groups: women with a T-score of less than -2.5 SDs and a previous fracture (Group A); women with a T-score of -2.5 SDs or less and without a previous fracture (Group B); and women with an average BMD (i.e. Z score of zero) and without a previous fracture (Group C). The risks in Group C were used as the baseline risks.

Then, the average population risks (in Table 7.4) could be expressed as a linear combination of the risks for Groups A, B, and C with the weights of percentages of people in the three Groups:

[Proportion of people in Group A (%) *Risk for Group A] +[Proportion of people in Group B (%) *Risk for Group B]+ [Proportion of people in Group C (%) *Risk for Group C]

This can be expanded with respect to the baseline risk for Group C:

[Proportion of people in Group A (%) *RR group A*Risk for Group C]+ [Proportion of people in Group B (%) *RR for Group B*Risk for Group C]+ [Proportion of people in Group C (%) *Risk for Group C]

This will allow the estimation of Group C risks.

Table 7.9 compares the T-score values of the average female population and of those with osteoporosis.

Table 7.9. T-score of the average female population and of those with osteoporosis

Age	Average T-score for the UK female population	Average T for patients with T-score <-2.5 SDs	Reduction in Z-score between osteoporotic women and those with average BMD
45-49	-0.41	-2.82*	2.41
50-54	-0.66	-2.82	2.16
55-59	-0.92	-2.72	1.80
60-64	-1.17	-2.78	1.61
65-69	-1.43	-2.84	1.41
70-74	-1.69	-3.00	1.31
75-79	-1.94	-2.97	1.03
80-84	-2.20	-2.97	0.77
85-89	-2.45	-2.97	0.52

*Assumed to be the same as the value for age group 50-55.

Using the data provided in Tables 7.6, 7.7 and 7.9, RRs associated with having low BMD with and without previous fracture were calculated (Table 7.10). It was assumed that the risk of fracture following a previous fracture is double that of a women without a previous fracture. Also, as data were available only for those aged 50 years and over in Stevenson et al. (2009), the model in this thesis assumed that the increased risk of fracture associated with a Z-score of -1 SD reported in Tables 7.6 and 7.7 are also applicable to the age group 45-50 years.

Using the linear combination shown above, the baseline risks for Group C were calculated. The results in Table 7.11 do not incorporate fractures at other associated sites.

Table 7.10. The relative risks of fracture for women with low bone mineral density with and without previous fracture

	Hip fracture		Vertebral fracture		Proximal fracture		Wrist fracture	
Age (years)	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
45-49	46.40	23.20	8.26	4.13	6.22	3.11	4.50	2.25
50-54	33.24	16.62	7.11	3.55	5.51	2.76	4.13	2.07
55-59	17.65	8.82	5.77	2.88	4.66	2.33	3.67	1.83
60-64	12.10	6.05	5.14	2.57	4.25	2.13	3.43	1.72
65-69	8.92	4.46	4.58	2.29	3.88	1.94	3.21	1.61
70-74	7.66	3.83	4.33	2.16	3.71	1.85	3.11	1.56
75-79	5.29	2.65	3.66	1.83	3.24	1.62	2.83	1.41
80-84	3.78	1.89	3.15	1.57	2.87	1.44	2.59	1.30
85-89	2.80	1.40	2.71	1.35	2.55	1.27	2.38	1.19

Table 7.11. Baseline risks of fracture for Group C (not incorporating fractures at other fracture sites)

Age (years)	Hip fracture	Vertebral fracture	Proximal humerus fracture	Wrist fracture
45-49	0.019%	0.083%	0.066%	0.299%
50-54	0.019%	0.082%	0.065%	0.297%
55-59	0.036%	0.110%	0.080%	0.330%
60-64	0.062%	0.148%	0.099%	0.372%
65-69	0.104%	0.200%	0.114%	0.412%
70-74	0.174%	0.253%	0.136%	0.449%
75-79	0.353%	0.358%	0.169%	0.502%
80-84	0.822%	0.560%	0.242%	0.625%
85-89	1.834%	0.875%	0.337%	0.772%

The increased risk multipliers to incorporate the incidence of fracture at other sites reported in Table 7.5 were applied to the baseline risks in Table 7.11, and these risks were converted to rates. The converted baseline event rates for the female population are provided in Table 7.12. For example, the risk of hip fracture incorporating fracture at other sites for women aged 65-70 years was calculated as 0.127%, by multiplying 0.104% (Table 7.11) by the increase factor of 1.22 (Table 7.5). This equated to an annual rate of 0.0013 (=-ln(1-0.127%)).

Table 7.12. Baseline incidence rates for female population with a Z-score of 0 SD and no previous fracture (annual incidence rates incorporating other fracture sites)

Age (years)	Hip fracture	Vertebral fracture	Proximal humerus fracture	Wrist fracture
45-49	0.0002	0.0008	0.0012	0.0049
50-54	0.0002	0.0008	0.0012	0.0048
55-59	0.0005	0.0011	0.0014	0.0044
60-64	0.0008	0.0015	0.0016	0.0044
65-69	0.0013	0.0020	0.0017	0.0047
70-74	0.0021	0.0025	0.0019	0.0056
75-79	0.0042	0.0036	0.0021	0.0075
80-84	0.0097	0.0056	0.0028	0.0117
85-89	0.0217	0.0088	0.0039	0.0145

In order to estimate the baseline fracture risks for men, the baseline incidence for female population was adjusted using incidence ratio of men to female population (Table 7.13). The incidence ratios of males to females for fractures at different sites were obtained by dividing the incidence of each fracture for male population by that for female population using data from Kanis et al. (2000). It was assumed that distal forearm fractures represent wrist fracture, and that the incidence ratio for the 45-49 age group was the same as that for 50-54 group.

Table 7.13. Incidence ratios of males to females (men/women)†

Age (years)	Incidence Ratio (men/women)			
	Hip	Vertebral	Proximal humerus	Wrist
45-49	1.43*	1.21*	0.52*	0.24*
50-54	1.43	1.21	0.52	0.24
55-59	1.55	0.75	0.24	0.33
60-64	0.37	0.75	0.47	0.25
65-69	0.65	0.55	0.26	0.41
70-74	0.54	0.64	0.54	0.10
75-79	0.48	0.56	0.28	0.17
80-84	0.70	0.80	0.40	0.21
85-89	0.46	0.73	0.45	0.23

†Calculated from Kanis et al. (2000); *Assumed the same as the value for age 50-54 group.

These incidence ratios were applied to the baseline fracture risks for the female population incorporating fracture at other sites to derive those for male population (Table 7.14). All other RR adjustments were applied in the same way as female population. For men aged 75-80 years, the baseline incidence of vertebral fracture was 0.0020 (=0.0036 (Table 7.12) × 0.5572 (Table 7.13)). This is equal to the annual probability of 0.0020 ($= 1 - e^{-0.0020}$). For men with a Z-score of -1.5 SDs, the annual probability of vertebral fracture increases by 2.415 (=$1.8^{1.5}$) times, resulting in 0.00482, which is equivalent to an incidence rate of 0.00483.

Table 7.14. Baseline incidence rates for male population with average BMD and no previous fracture

Age (years)	Hip fracture	Vertebral fracture	Proximal humerus fracture	Wrist fracture
45-49	0.0003	0.0010	0.0006	0.0012
50-54	0.0003	0.0010	0.0006	0.0012
55-59	0.0007	0.0008	0.0003	0.0015
60-64	0.0003	0.0011	0.0008	0.0011
65-69	0.0008	0.0011	0.0004	0.0019
70-74	0.0011	0.0016	0.0010	0.0005
75-79	0.0020	0.0020	0.0006	0.0013
80-84	0.0068	0.0045	0.0011	0.0025
85-89	0.0099	0.0064	0.0018	0.0034

The age-group specific incidence rates after adjustments for previous fracture and T-score were used to sample time to fracture at each site. Time to fracture was sampled using the technique described in Chapter 4, that is, when time to next age band was reached before the sampled time to fracture, the incidence rate was replaced by the incidence rate for the new age band and the time to the next age-band was assumed fracture free. The age-specific adjustment for the risk of hip fracture associated with a Z-score of -1 SD (Table 7.6) was applied in the same way. Hence, the incidence rate was increased if the time points when a change in age band was reached before the sampled time to next event.

The baseline fracture risks for the 45-49 age group were nearly identical to those for 50-54 group, as some values for the age group 45-49 years were assumed to be the same as those of the adjacent 50-54 group when calculating the baseline risks. However, it is noted that the final fracture risks for this group will be generally lower than those for the 50-54 years group due to the adjustments for previous fracture and T-score. For example, no history of previous fracture was assigned to those aged 45-49 years at the start of the model due to the unavailability of data.

7.3.6. Nursing home entry following hip fracture

It was assumed that only hip fracture (including pelvis or other femoral fractures) could result in entry into nursing home. The percentage of people who move from the community to a nursing home following a hip fracture calculated using data from the second East Anglian audit of hip fracture (Freeman et al., 2002) is shown in Table 7.15. As in the AD model, it was assumed that people who entered a nursing home will not return to community dwelling. The same percentages were applied to men.

Table 7.15. Percentage of people who move to a nursing home following a hip fracture

Age (years)	Percentage
50-59	0%
60-69	4%
70-79	4%
80-89	12%
90+	17%

7.3.7. Mortality

Mortality following fracture

Excess mortality after hip fracture was included in Stevenson et al. (2009). Mortality rates that were assumed attributable to hip fracture were estimated from data reported in the second East Anglian audit of hip fracture (Freeman et al., 2002). The percentage of hip fracture that was assumed to result directly in death reported in Stevenson et al. (2009) was used in the model for this thesis (Table 7.16). Although 90-day mortality rates were used for the estimation, it was assumed that these patients die immediately after hip fracture in the model. These values were assumed to be applicable for pelvis and other femoral fractures as in Stevenson et al. (2009).

Table 7.16. Percentage of hip fractures that result directly in mortality

Age (years)	Percentage of hip fractures that result directly in mortality by residential status	
	Community	Nursing home
<59	2%	0%
60-69	6%	0%
70-79	6%	13%
80-89	11%	22%
90+	16%	23%

The model for this thesis could not easily incorporate a hazard ratio (HR) for mortality following vertebral fracture as assumed in Stevenson et al. (2009) using a HR of 4.4 (95% CI 1.85 to 10.6). This was due to time to death sampled directly from discrete probability distributions derived from annual mortality rates (see Chapter 4), rather than from a parametric distribution with a rate parameter to which a HR could be applied. Hence, for simplicity, the time to non-disease death values were reduced by a factor of the rate ratios for the mortality of people with and without prevalent vertebral fracture (Table 7.17) estimated using data from a UK study (Jalava et al., 2003) in order to reflect the increased mortality following vertebral fracture. It was further assumed that vertebral fractures affect mortality only for one year after the fracture, so the reduced time-to-death was not applied if it was greater than one year. For example, if the remaining time to non-disease death was 12 years when a 65-year-old person had a vertebral fracture, time to death following the fracture could become 3 years (=12/4) using the ratio for the 60-69 age group, but as this was longer than 1 year, it was not used and the original time-to-death of 12 years was applied.

Table 7.17. Ratio of mortality rates of people with prevalent vertebral fracture to those without vertebral fracture

	Vertebral fracture			Proximal humerus fracture
Age (years)	≤59	60-69	≥70	
Rate ratio	6.67	4.00	3.75	2.00*

*Only 28% of time to deaths to which this factor was applied were used in the model; (Jalava et al., 2003, Kanis et al., 2004a);

In line with assumptions made by Stevenson et al. (2009), no increase in mortality from wrist fractures (incorporating rib, sternum, clavicle and scapula) was assumed. For proximal humerus fractures, it was assumed that the fractures will double the mortality and that 28% of deaths associated with humeral fractures are causally related (Kanis et al., 2004a). The increase in mortality was applied in the same way as that for vertebral fracture, assuming that fractures at proximal humerus increase mortality risk only in the first year.

Mortality due to other causes

In Stevenson et al. (2009), mortality rates for the general female population taken from 1999 interim life tables were adjusted to incorporate mortality associated with low BMD. A factor of 1.22 per SD decrease was applied to the probability of death for the general population (Browner et al., 1991). The data provided in Stevenson et al. (2009) reported summary probabilities for different age bands and for women only. The model for this thesis used data from interim life tables based on 2009-2011 data (Office for National Statistics, 2013b) and the distributions for time to death were constructed based on the mortality rates adjusted for low BMD for each yearly age and sex.

The same factor of 1.22 was used in the model for this thesis to adjust the mortality risks for low BMD assuming that the mortality for the general population is associated with the average T score for each age and sex group. The individual's risk of mortality was then calculated from their Z-score ($Average\ mortality\ risk \times 1.22^{(-z-score)}$).

All-cause mortality obtained from interim life tables was adjusted according to an individual's Z-score. To simplify the analyses, it was assumed that broad Z-score bands could be used rather than the exact Z-score of an individual. These Z-score bands were combined with age and gender to estimate mortality. These data are shown in Table 7.18 with the rates calculated using the mid-points of the Z-score ranges and each yearly age. Table 7.19 summarises the mortality rates of the general female population and those of women with a T-score of -2.5 SDs.

In models considering osteoporosis and another of the chosen diseases, the mortality rates associated with BMD replaced the distributions for time to non-disease death used in the

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other individual disease models. Therefore, time to non-disease death sampled in the all-disease linked model reflected the BMD status of all modelled individuals. Further distributions removing the estimated rate of cardiac death were calculated when a model linking osteoporosis and heart disease was used (mortality rates reported in Appendix 7.1 Table 7.18').

It is noted that the use of the distributions based on the ranges of Z-score could cause average life years from the model in this chapter to be different from those from the other disease models due to the difference in distributions for time to non-disease death. Also, the adjusted mortality rates in Table 7.18 extrapolated beyond the evidence adopted in Stevenson et al. (2009): studies have suggested that low BMD is associated with increased mortality. As the model by Stevenson et al. (2009) included only postmenopausal women with low BMD, only this assumption on the association between low BMD and mortality was used (Browner et al., 1991, Johansson et al., 1998). However, in order to maintain the total mortality across groups of population with different BMD levels, reduced mortality risk was assumed in the model for this thesis for those with BMD higher than average.

Whilst Z-scores have a symmetrical distribution centred on zero, the risk of death is associated with the Z-score in a non-linear fashion, which may result in differences in the sample means of time to non-disease death between the distributions based on Z-score and those based on age and sex only.

Table 7.18. Mortality rates due to causes other than fractures in association with BMD

Age	Z score = -2 SD (-2.5, -1.5)		Z score = -1 SD (-1.5, -0.5)		Z score = 0 SD (-0.5, 0.5) General population		Z score = 1 SD (0.5, 1.5)		Z score = 2 SD (1.5, 2.5)	
	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men
45	0.21%	0.33%	0.17%	0.27%	0.14%	0.22%	0.11%	0.18%	0.09%	0.15%
46	0.22%	0.35%	0.18%	0.29%	0.15%	0.23%	0.12%	0.19%	0.10%	0.16%
47	0.23%	0.36%	0.19%	0.29%	0.16%	0.24%	0.13%	0.20%	0.11%	0.16%
48	0.26%	0.40%	0.21%	0.33%	0.17%	0.27%	0.14%	0.22%	0.12%	0.18%
49	0.29%	0.43%	0.24%	0.35%	0.20%	0.29%	0.16%	0.24%	0.13%	0.20%
50	0.32%	0.46%	0.26%	0.38%	0.22%	0.31%	0.18%	0.25%	0.15%	0.21%
51	0.34%	0.53%	0.28%	0.43%	0.23%	0.36%	0.19%	0.29%	0.16%	0.24%
52	0.40%	0.60%	0.32%	0.49%	0.27%	0.40%	0.22%	0.33%	0.18%	0.27%
53	0.43%	0.64%	0.35%	0.53%	0.29%	0.43%	0.23%	0.35%	0.19%	0.29%
54	0.49%	0.69%	0.40%	0.56%	0.33%	0.46%	0.27%	0.38%	0.22%	0.31%
55	0.51%	0.78%	0.42%	0.64%	0.34%	0.52%	0.28%	0.43%	0.23%	0.35%
56	0.57%	0.88%	0.46%	0.72%	0.38%	0.59%	0.31%	0.48%	0.26%	0.40%
57	0.62%	0.93%	0.51%	0.76%	0.41%	0.63%	0.34%	0.51%	0.28%	0.42%
58	0.66%	1.04%	0.54%	0.85%	0.44%	0.70%	0.36%	0.57%	0.30%	0.47%
59	0.73%	1.11%	0.60%	0.91%	0.49%	0.75%	0.40%	0.61%	0.33%	0.50%
60	0.79%	1.24%	0.65%	1.01%	0.53%	0.83%	0.44%	0.68%	0.36%	0.56%
61	0.86%	1.32%	0.70%	1.08%	0.58%	0.89%	0.47%	0.73%	0.39%	0.59%
62	0.91%	1.41%	0.74%	1.16%	0.61%	0.95%	0.50%	0.78%	0.41%	0.64%
63	1.01%	1.56%	0.83%	1.28%	0.68%	1.05%	0.56%	0.86%	0.46%	0.70%
64	1.11%	1.71%	0.91%	1.40%	0.74%	1.15%	0.61%	0.94%	0.50%	0.77%
65	1.22%	1.88%	1.00%	1.54%	0.82%	1.26%	0.67%	1.04%	0.55%	0.85%
66	1.35%	2.11%	1.11%	1.73%	0.91%	1.42%	0.74%	1.16%	0.61%	0.95%
67	1.44%	2.28%	1.18%	1.87%	0.97%	1.53%	0.79%	1.25%	0.65%	1.03%
68	1.61%	2.56%	1.32%	2.10%	1.08%	1.72%	0.89%	1.41%	0.73%	1.16%
69	1.81%	2.83%	1.48%	2.32%	1.21%	1.90%	0.99%	1.56%	0.82%	1.28%
70	2.05%	3.13%	1.68%	2.56%	1.38%	2.10%	1.13%	1.72%	0.93%	1.41%
71	2.19%	3.44%	1.80%	2.82%	1.47%	2.31%	1.21%	1.89%	0.99%	1.55%
72	2.43%	3.80%	2.00%	3.11%	1.64%	2.55%	1.34%	2.09%	1.10%	1.71%
73	2.65%	4.15%	2.17%	3.40%	1.78%	2.79%	1.46%	2.29%	1.20%	1.87%
74	3.04%	4.60%	2.49%	3.77%	2.04%	3.09%	1.67%	2.53%	1.37%	2.08%
75	3.34%	5.03%	2.73%	4.13%	2.24%	3.38%	1.84%	2.77%	1.51%	2.27%
76	3.79%	5.71%	3.11%	4.68%	2.55%	3.83%	2.09%	3.14%	1.71%	2.58%
77	4.28%	6.23%	3.51%	5.11%	2.87%	4.19%	2.36%	3.43%	1.93%	2.81%
78	4.82%	6.99%	3.95%	5.73%	3.24%	4.69%	2.66%	3.85%	2.18%	3.15%

79	5.43%	7.78%	4.45%	6.38%	3.65%	5.23%	2.99%	4.29%	2.45%	3.51%
80	6.18%	8.82%	5.06%	7.23%	4.15%	5.92%	3.40%	4.86%	2.79%	3.98%
81	6.92%	9.85%	5.68%	8.08%	4.65%	6.62%	3.81%	5.43%	3.13%	4.45%
82	7.89%	11.03%	6.47%	9.04%	5.30%	7.41%	4.35%	6.07%	3.56%	4.98%
83	8.98%	12.16%	7.36%	9.97%	6.03%	8.17%	4.94%	6.70%	4.05%	5.49%
84	10.06%	13.66%	8.24%	11.20%	6.76%	9.18%	5.54%	7.52%	4.54%	6.17%
85	11.25%	15.24%	9.22%	12.49%	7.56%	10.24%	6.20%	8.39%	5.08%	6.88%
86	12.74%	16.76%	10.45%	13.74%	8.56%	11.26%	7.02%	9.23%	5.75%	7.56%
87	14.24%	18.87%	11.67%	15.47%	9.57%	12.68%	7.84%	10.39%	6.43%	8.52%
88	16.00%	20.91%	13.12%	17.14%	10.75%	14.05%	8.81%	11.51%	7.22%	9.44%
89	18.11%	23.85%	14.85%	19.55%	12.17%	16.02%	9.97%	13.14%	8.18%	10.77%
90	20.12%	24.64%	16.49%	20.20%	13.52%	16.55%	11.08%	13.57%	9.08%	11.12%
91	21.76%	26.47%	17.83%	21.70%	14.62%	17.79%	11.98%	14.58%	9.82%	11.95%
92	23.81%	28.04%	19.52%	22.98%	16.00%	18.84%	13.11%	15.44%	10.75%	12.66%
93	26.80%	31.84%	21.97%	26.10%	18.01%	21.39%	14.76%	17.53%	12.10%	14.37%
94	30.19%	35.21%	24.75%	28.86%	20.28%	23.66%	16.63%	19.39%	13.63%	15.89%
95	33.32%	38.28%	27.31%	31.38%	22.38%	25.72%	18.35%	21.08%	15.04%	17.28%
96	35.83%	40.99%	29.37%	33.60%	24.07%	27.54%	19.73%	22.57%	16.18%	18.50%
97	38.72%	44.23%	31.73%	36.26%	26.01%	29.72%	21.32%	24.36%	17.48%	19.97%
98	41.42%	47.22%	33.95%	38.70%	27.83%	31.73%	22.81%	26.00%	18.70%	21.31%
99	44.10%	48.83%	36.15%	40.03%	29.63%	32.81%	24.29%	26.89%	19.91%	22.04%
100	47.48%	52.00%	38.91%	42.62%	31.90%	34.94%	26.15%	28.64%	21.43%	23.47%

Table 7.19. Mortality rates due to causes other than fractures in the general population and in people at the threshold for osteoporosis

Age (years)	General population		Population with a T-score of -2.5 SDs	
	Women	Men	Women	Men
45	0.14%	0.22%	0.22%	0.40%
46	0.15%	0.23%	0.23%	0.42%
47	0.16%	0.24%	0.24%	0.42%
48	0.17%	0.27%	0.26%	0.47%
49	0.20%	0.29%	0.29%	0.50%
50	0.22%	0.31%	0.32%	0.53%
51	0.23%	0.36%	0.34%	0.60%
52	0.27%	0.40%	0.38%	0.67%
53	0.29%	0.43%	0.41%	0.71%
54	0.33%	0.46%	0.46%	0.75%
55	0.34%	0.52%	0.48%	0.84%
56	0.38%	0.59%	0.53%	0.94%
57	0.41%	0.63%	0.57%	0.99%
58	0.44%	0.70%	0.60%	1.09%
59	0.49%	0.75%	0.66%	1.15%
60	0.53%	0.83%	0.71%	1.27%
61	0.58%	0.89%	0.76%	1.34%
62	0.61%	0.95%	0.79%	1.42%
63	0.68%	1.05%	0.87%	1.56%
64	0.74%	1.15%	0.95%	1.69%
65	0.82%	1.26%	1.03%	1.84%
66	0.91%	1.42%	1.13%	2.04%
67	0.97%	1.53%	1.20%	2.18%
68	1.08%	1.72%	1.33%	2.43%
69	1.21%	1.90%	1.47%	2.66%
70	1.38%	2.10%	1.65%	2.91%
71	1.47%	2.31%	1.75%	3.16%
72	1.64%	2.55%	1.92%	3.46%

73	1.78%	2.79%	2.07%	3.75%
74	2.04%	3.09%	2.35%	4.11%
75	2.24%	3.38%	2.55%	4.45%
76	2.55%	3.83%	2.88%	4.99%
77	2.87%	4.19%	3.21%	5.40%
78	3.24%	4.69%	3.58%	5.99%
79	3.65%	5.23%	3.99%	6.60%
80	4.15%	5.92%	4.50%	7.41%
81	4.65%	6.62%	4.99%	8.19%
82	5.30%	7.41%	5.63%	9.07%
83	6.03%	8.17%	6.34%	9.91%
84	6.76%	9.18%	7.03%	11.02%
85	7.56%	10.24%	7.78%	12.17%
86	8.56%	11.26%	8.73%	13.24%
87	9.57%	12.68%	9.65%	14.76%
88	10.75%	14.05%	10.74%	16.19%
89	12.17%	16.02%	12.03%	18.28%
90	13.52%	16.55%	13.23%	18.69%
91	14.62%	17.79%	14.16%	19.88%
92	16.00%	18.84%	15.34%	20.85%
93	18.01%	21.39%	17.09%	23.43%
94	20.28%	23.66%	19.06%	25.65%
95	22.38%	25.72%	20.82%	27.61%
96	24.07%	27.54%	22.16%	29.26%
97	26.01%	29.72%	23.71%	31.25%
98	27.83%	31.73%	25.11%	33.02%
99	29.63%	32.81%	26.46%	33.81%
100	31.90%	34.94%	28.19%	35.64%

The general population death rates (accounting for BMD level) have not been adjusted for fracture-related death, similar to Stevenson et al. (2009). Hence, the non-disease adjusted mortality rates could be slight overestimates. In the model for this thesis, given that the rates of fracture-related death were applied only for one year after the fracture to a proportion whose death were assumed to be directly related to the fracture and a large proportion of the base-case population were low-risk people without osteoporosis, it was considered unlikely that using this non-disease adjusted mortality would change the model results significantly.

7.3.8. Default treatment and the effect and duration of the treatment

As in Stevenson et al. (2009), the default treatment assumed in this model was one of the second-generation bisphosphonates, 70mg alendronic acid taken once weekly.

The NICE Technology Appraisal (TA) 161 recommends bisphosphonates (alendronate, etidronate and risedronate) for the secondary prevention of fragility fractures in postmenopausal women who have osteoporosis and have had an osteoporotic fracture. NICE TA 160 relates to the primary prevention of osteoporotic fractures: alendronate is recommended as a first choice treatment for postmenopausal women who have had osteoporosis diagnosed but have not had a fracture. Both NICE TA 160 and 161 say that women aged 75 years and older may not need a BMD scan to have osteoporosis diagnosed. Since these TAs, the price of alendronate has drastically reduced (see Section 7.3.9), hence the decision on the use of alendronate may change upon review (ScHARR, 2015).

In this model, the primary assumption was that any men and women at high risk of osteoporotic fracture would receive alendronate. The high risk of osteoporotic fracture in this model meant having low BMD (T-score of -2.5 SDs or less) regardless of whether or not the individual had sustained an osteoporotic fracture, or was a postmenopausal woman. However, it was considered implausible to assume everyone who is osteoporotic in the population gets diagnosed and receives treatment as soon as their T-score reaches the threshold for osteoporosis or they experience menopause. Also, although women aged 75 years and older are not required to have a BMD scan to receive treatment, it is not probable that every woman aged 75 years or older would receive the treatment. NICE guidance states that a BMD scan is not required when the responsible clinician considers the scan to be clinically inappropriate or

infeasible, and the woman aged 75 years and older has one or more independent clinical risk factors for fracture such as low body mass index and untreated premature menopause, but did not previously had a BMD test. It is likely that only the women who have osteoporotic fracture or known risk factors would seek medical attention. Hence, in this model, it was assumed that the treatment initiates when women and men have an osteoporotic fracture. It is noted that some individuals were assumed to be receiving treatment when entering the model due to history of previous osteoporotic fracture (severe osteoporosis) with varying time left until treatment discontinuation. Although NICE TAs did not cover the use of alendronate in men, it was assumed that men would also start receiving the treatment when they have an osteoporotic fracture.

Reduction in fracture risks from the use of alendronate is shown in Table 7.20. The RRs were estimated from a random effects model detailed in Stevenson et al. (2009).

Table 7.20. Relative risks of fracture for alendronate treatment

Relative risks for the drug treatment (95% C.I)	
Hip fracture	0.72 (0.58-0.88)
Vertebral fracture	0.58 (0.50-0.67)
Other fractures	0.82 (0.74-0.90)

The risk reduction due to the drug treatment was assumed applicable to both men and women. The RRs were applied to the baseline probabilities (not rates) of fractures, and the probabilities were converted to incidence rates. Table 7.21 shows the annual rates of fractures for those on drug treatment, and these can be compared with Tables 7.12 and 7.14 (Baseline incidence rates for female and male population with average BMD and no previous fracture).

Table 7.21. Incidence rates of fracture for individuals receiving the drug treatment (RRs* applied)

Age (years)	Female				Male			
	Hip fracture	Vertebral fracture	Proximal Humerus fracture	Wrist fracture	Hip fracture	Vertebral fracture	Proximal Humerus fracture	Wrist fracture
45-50	0.0002	0.0005	0.0010	0.0040	0.0002	0.0006	0.0005	0.0010
50-55	0.0002	0.0005	0.0010	0.0040	0.0002	0.0006	0.0005	0.0010
55-60	0.0003	0.0006	0.0011	0.0036	0.0005	0.0005	0.0003	0.0012
60-65	0.0005	0.0009	0.0013	0.0036	0.0002	0.0006	0.0006	0.0009
65-70	0.0009	0.0012	0.0014	0.0039	0.0006	0.0006	0.0004	0.0016
70-75	0.0015	0.0015	0.0016	0.0046	0.0008	0.0009	0.0008	0.0005
75-80	0.0030	0.0021	0.0018	0.0061	0.0015	0.0012	0.0005	0.0010
80-85	0.0070	0.0033	0.0023	0.0096	0.0049	0.0026	0.0009	0.0021
85-90	0.0156	0.0051	0.0032	0.0118	0.0071	0.0037	0.0014	0.0028

*RR=relative risk

The duration of the drug treatment was assumed to be 5 years as in Stevenson et al. (2009). It was assumed that once an individual had previously received and discontinued the drug treatment after five years, the treatment would not be given to the same person again.

There were people who were already receiving the drug treatment at the entry to the model (i.e. either they were women aged 75 years and over or they were assigned a history of osteoporotic fracture at model time zero). Assuming this population had started receiving the drug treatment at a constant rate before model initiation, the duration of drug treatment left before discontinuation at the model entry was sampled from Uniform distribution with the lower bound of 0 and upper bound of 5 years.

The efficacy of the drug treatment was assumed, in accordance with Stevenson et al. (2009), to wane over a 5-year period after treatment discontinuation in a linear fashion. The relative risks of fracture for those on alendronate treatment in Table 7.20 increased in a linear manner since treatment cessation. Over the 5-year period, an RR was re-calculated in relation to time since treatment discontinuation at every yearly period from the time point where a new time to event is sampled.

When sampling time to a new fracture event, changes in fracture incidence rates due to changes in these RRs as efficacy waned and changes in age band were accounted for. The RR of fracture due to the efficacy of the drug waning was assumed to change annually. Change in 5-year age band and change in RR due to the waning of efficacy were acting as competing risks. Time to event was re-sampled when the rate of fracture changed.

As Stevenson et al. (2009) focussed on assessing the cost-effectiveness of vitamin K treatment, a compliance rate applied for those receiving weekly alendronate was not mentioned in the description of their economic model. However, it was suggested that the compliance rate for bisphosphonates was generally higher than that for vitamin K. The data used in Stevenson et al. (2009) to identify the compliance to the vitamin K treatment also reported persistence rates for alendronate: Lloyd Jones and Wilkinson (2006) reported that the evidence identified from randomised trials suggested that the percentage of patients persisting with daily alendronate was 88%-100% at year 1, and decreased to 72%-89% and 70%-89% at year 2 and 3, respectively. UK evidence from an un-randomised study (Biswas et al., 2003) reported the compliance rate of 75% with daily alendronate at one year. However, Lloyd Jones and Wilkinson (2006) suggested that the use of weekly rather than daily bisphosphonates regimens may improve persistence.

Lloyd Jones and Wilkinson (2006) described the UK prescription-event monitoring (PEM) studies of alendronate and risedronate as the most relevant evidence for compliance with oral bisphosphonate treatment in the UK (Barrera et al., 2005, Biswas et al., 2003). Hence, the base-case model for this thesis assumed 75% compliance at the time of treatment initiation. Sensitivity analyses included the assumption of 50% compliance rate. In accordance with the assumption in Stevenson et al. (2009), non-compliant patients were assumed to incur three months' cost of the drug treatment at the start of the treatment and receive no benefit.

On initiation of treatment, 25% of people eligible for drug therapy were randomly selected to be non-compliant. Once non-compliant, it was assumed that the individual does not re-initiate drug treatment when a new fracture occurs.

7.3.9. Costs of fractures and drug treatment

Table 7.22 summarises the cost of fracture events used in the model for this thesis. It was based on the calculation reported by Stevenson and Davis (2006). Healthcare Resource Groups (HRGs) data were used in the estimation of costs. Costs included: direct medical costs; home help; and nursing home costs. The costs were divided into first year costs and costs incurred in the subsequent years. The cost values reported in Stevenson et al. (2009) were inflated to 2012 price using the Hospital and Community Health Services (HCHS) inflation index (Curtis, 2013).

For hip fracture leading to nursing home admission, the monthly NHS cost of £2,293 as used in the AD model was applied in order to have consistency across individual disease models. This equates to the annual cost of £27,513, and was similar to the costs used in Stevenson et al. (2009) (£27,972-£28,777 when inflated to 2012 price).

As a cheaper generic version of alendronate became available, the cost of drug used in Stevenson et al. (2009) was replaced by the most recent price. The annual cost of alendronate was taken from the British National Formulary (Joint Formulary Committee, 2014), and was £28.21. Stevenson et al. (2009) used £51 for their analysis in accordance with the drug price of that time. The results of applying a higher cost were examined in Section 7.4. As previously mentioned, the cost of three months of drugs was applied for non-compliant population.

Table 7.22. Costs of fracture events by age and by first and subsequent years (£, 2012 price)

Age (years)	Cost of hip fracture (£)		Cost of hip fracture leading to nursing home admission (£)		Cost of death due to hip fracture (£)		Cost of vertebral fracture (£)		Cost of wrist fracture (£)		Cost of proximal humerus fracture (£)	
	First year	Subsequent years	First year	Subsequent years	First year	Subsequent years	First year	Subsequent years	First year	Subsequent years	First year	Subsequent years
50-54	6,762	-	37,797	27,972	9,526	-	2,776	244	954	-	2,798	-
55-59	6,762	-	37,797	27,972	9,526	-	2,776	244	1,078	-	2,656	-
60-64	6,762	-	37,797	27,972	9,526	-	2,776	244	1,173	-	2,493	-
65-69	7,629	-	38,674	28,374	9,526	-	2,776	244	1,193	-	2,305	-
70-74	8,013	-	39,021	28,777	9,526	-	3,277	244	1,698	-	3,045	-
75-80	8,013	-	39,021	28,777	9,526	-	3,277	244	1,487	-	2,678	-

7.3.10. Utilities

The utilities used in Stevenson et al. (2009) were also used in this model (Table 7.23). Utilities associated with the fractures at other sites incorporated in the main four were reported to be combined and matched with those for the four fracture sites. The utility multipliers were combined multiplicatively with the baseline utilities for the general population reported in Chapter 4.

Table 7.23. Utility multipliers used in the model

Fracture site	Utility multipliers in first year following fracture	Utility multipliers in subsequent years following fracture
Hip	0.792	0.813
Vertebrae (Spine)	0.626	0.909
Proximal humerus	0.794	Age Utility multipliers 45-54 years 0.949 55-59 years 0.952 60-64 years 0.955 65-69 years 0.958 70-74 years 0.960 75-79 years 0.963 80+ years 0.966
Wrist	0.977	1.000

Source: Kanis et al. (2004c)

Disutility associated with adverse events (AE) of bisphophnates was applied as in Stevenson et al. (2009). The model in Stevenson et al. (2009) adopted the same assumption used in Stevenson and Davis (2006). Bisphophonates were considered associated with an increased risk of upper gastro-intestinal (GI) problems, and the symptoms more likely to occur in the initial treatment month than in subsequent treatment months (Stevenson and Davis, 2006). The utility multiplier of 0.91 was applied for the first month since treatment initiation in order to incorporate the utility loss associated with GI problems (Groeneveld et al., 2001). As in

other events, this change caused the individual to move to the 'transient utility state'. When an individual was allocated to drug treatment at model entry due to a previous fracture, it was assumed that the disutility associated with treatment had already occurred.

It was assumed that the nursing home stay is associated with lower utility. For consistency, the utility weight used for institutionalised AD patients was also used. Stevenson et al. (2009) used a multiplier of 0.40, whilst the AD model used the absolute utility value of 0.33. As the utility of 0.33 was used as the final utility weight, not as a multiplier, it is not expected to be significantly different from applying the utility multiplier of 0.40.

7.4. Results from the osteoporosis only model

7.4.1. First order uncertainty and comparison with existing model results

First-order uncertainty was explored to identify the appropriate number of individuals to simulate (Figure 7.2). The mean results and uncertainty with varied number of simulated individuals ranging from 100 to 400,000 were examined. The error bars represent 95% confidence intervals around the mean. Incremental costs and QALYs approached to values near zero as the number of simulated individuals increased. Due to the small incremental values, the cost per QALY could fluctuate with a small change in incremental cost or QALYs. Instead, incremental net monetary benefit (NMB) was calculated and reported in Figure 7.2 e). The drug treatment dominated no treatment when 150,000-400,000 individuals were simulated with the NMB of £111-£627 when the willingness to pay threshold of £20,000 per QALY was assumed. The results for the general public started to stabilise when 100,000 or more individuals were run.

Although costs and QALYs stabilised quickly, considering the small values of incremental costs and QALYs, 400,000 individuals were simulated for the base case. With 400,000 individuals simulated and the threshold of £20,000, the NMB was £350 (undiscounted) and £252 (discounted).

Figure 7.2. First order uncertainty in relation to the number of patients simulated (**all population** aged 45 years and older)

d)	Incremental QALYs of drug therapy compared with no therapy	
Undiscounted		Discounted

Incremental QALYs of drug therapy for osteoporosis

Incremental QALYs of drug therapy for osteoporosis (disc)

e)	Net monetary benefit (with the willingness-to-pay threshold of £20,000)	
Undiscounted		Discounted

Net monetary benefit (NMB) of osteoporosis treatment

NMB of Osteoporosis therapy (disc.)
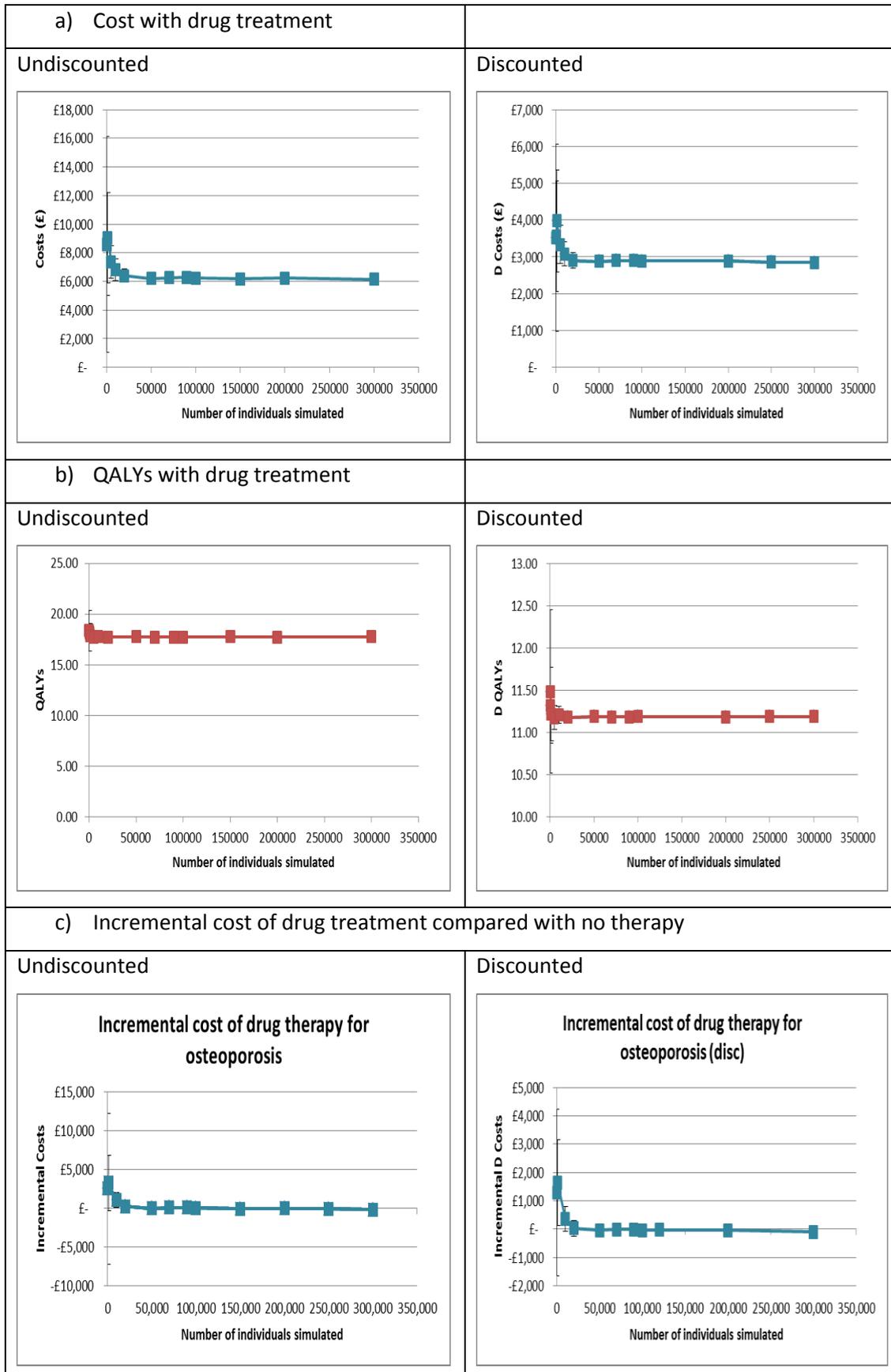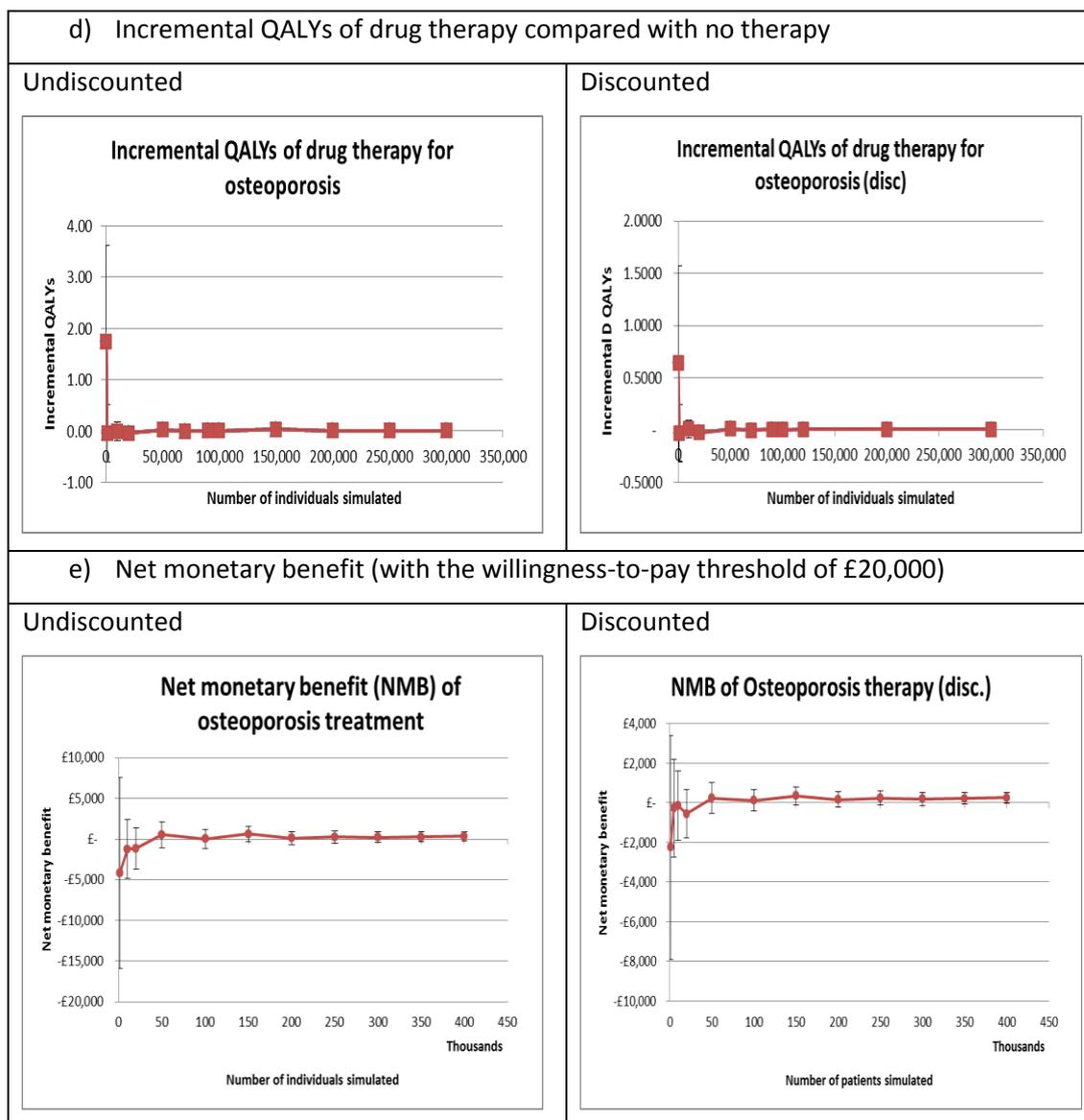
The model results were compared to those reported for weekly alendronate treatment alongside the vitamin K treatment results in the HTA report by Stevenson et al. (2009). Stevenson et al. (2009) reported results for women only by age group, T-score, and the presence of previous fracture. Tables 7.24-7.27 compare the results with those from the HTA report.

For comparison purposes, a narrower population was run with 100,000 individual patient simulations. The model population at entry was 75-year-old women with or without previous fracture. The cost of alendronate was increased to £51 to match with that used in Stevenson et al. (2009).

Results for women with no previous fracture

The results for women aged 75 years without a previous fracture were compared in Tables 7.24 and 7.25 for women with T-score of -3 SDs and -2.5 SDs, respectively, with those for alendronate treatment reported in Stevenson et al. (2009). Alendronate treatment dominated no treatment for women with a T-score of -3 SDs and -2.5 SDs. Compared the results where discount rates of 6% for costs and 1.5% with the HTA model results, alendronate treatment was more cost-saving with similar QALY gains for both T-score groups. Stevenson et al. (2009) adjusted the model outputs obtained using 6% annual discount rate for costs and 1.5% for utilities in retrospect to reflect interim changes in the NICE rates. The results using 6% and 1.5% discount rates with 50% compliance provided similar incremental costs and QALYs to those in the HTA report. The change in discount rates increased the incremental QALYs, but did not alter the results considerably. For women with a T-score of -2.5 SDs (Table 7.25), the drug treatment still dominated no treatment even when 50% compliance was assumed, whilst the results from Stevenson et al. (2009) showed a positive incremental cost.

Table 7.24. Comparison of cost-effectiveness results with those from Stevenson et al. (2009) for 75-year-old women with T-score of -3 SDs with no previous fracture assuming drug cost of £51

T score -3	Base-case assuming compliance of 75%			Base-case assuming compliance of 50%			Discount rates of 6% for cost and 1.5% for utility, assuming compliance of 50%			HTA Results†
	With treatment	No treatment	Incremental	With treatment	No treatment	Incremental	With treatment	No treatment	Incremental	Incremental
Cost	£ 12,429	£ 13,194	-£ 765	£ 12,486	£ 13,194	-£ 709	£ 12,486	£ 13,194	-£ 709	
Discounted Cost	£ 7,887	£ 8,380	-£ 494	£ 7,945	£ 8,380	-£ 436	£ 5,939	£ 6,252	-£ 314	-£ 140
QALYs	8.807	8.756	0.051	8.793	8.756	0.037	8.793	8.756	0.037	
Discounted QALYs	6.847	6.815	0.031	6.838	6.815	0.022	7.852	7.823	0.030	0.0402
Cost per QALY (£)			Dominating			Dominating			Dominating	Dominating

†Cost effectiveness of alendronate in women aged 75-79 years with a T-score of -3 SDs and no previous fracture from Stevenson et al. (2009)

Table 7.25. Comparison of cost-effectiveness results with those from Stevenson et al. (2009) for 75-year-old women with T-score of -2.5 SDs with no previous fracture assuming drug cost of £51

T score -2.5	Base-case assuming compliance of 75%			Base-case assuming compliance of 50%			Discount rates of 6% for cost and 1.5% for utility, assuming compliance of 50%			HTA Results†
	With treatment	No treatment	Incremental	With treatment	No treatment	Incremental	With treatment	No treatment	Incremental	Incremental
Cost	£ 8,640	£ 9,265	-£ 625	£ 8,577	£ 9,265	-£ 688	£ 8,577	£ 9,265	-£ 688	
Discounted Cost	£ 5,446	£ 5,840	-£ 394	£ 5,423	£ 5,840	-£ 416	£ 4,036	£ 4,335	-£ 299	£33.83
QALYs	9.034	9.003	0.031	9.026	9.003	0.023	9.026	9.003	0.023	
Discounted QALYs	6.987	6.968	0.019	6.983	6.968	0.014	8.042	8.023	0.019	0.0276
Cost per QALY (£)			Dominating			Dominating			Dominating	£ 1,226/QALY

†Cost effectiveness of alendronate in women aged 75-79 years with a T-score of -2.5 SDs and no previous fracture from Stevenson et al. (2009)

Results for women with previous fracture

The model results were compared with those reported in Stevenson et al. (2009) for women with previous fracture in Tables 7.26 and 7.27.

For women with a T-score of -3 SDs, the model for this thesis produced results with similar cost savings but lower QALY gains in comparison with the HTA results. For women with a T-score of -2.5 SDs, alendronate treatment was associated with smaller QALY gains, but larger cost savings than the HTA results. All results showed that the treatment dominated no treatment in line with the HTA results. When 50% compliance was assumed, the cost-saving and QALY gains associated with the drug treatment decreased, but did not alter overall conclusions concerning the dominance of the treatment.

Table 7.26. Comparison of cost-effectiveness results with those from Stevenson et al. (2009) for 75-year-old women with T-score of -3 SDs with a previous fracture assuming drug cost of £51

	Base-case assuming compliance of 75%			Results assuming compliance of 50%			Discount rates of 6% for cost and 1.5% for utility, assuming compliance of 50%			HTA Results†
T score -3	With treatment	No treatment	Incremental	With treatment	No treatment	Incremental	With treatment	No treatment	Incremental	Incremental
TC	£ 19,721	£ 20,393	-£ 671	£ 19,953	£ 20,393	-£ 440	£ 19,953	£ 20,393	-£ 440	
TDC	£ 12,818	£ 13,379	-£ 561	£ 13,005	£ 13,379	-£ 374	£ 9,886	£ 10,219	-£ 333	-£389
TQ	7.799	7.754	0.044	7.770	7.754	0.016	7.770	7.754	0.016	
TDQ	6.115	6.079	0.036	6.092	6.079	0.013	6.965	6.951	0.015	0.0609
Cost per QALY			Dominating			Dominating			Dominating	Dominating

†Cost effectiveness of alendronate in women aged 75-79 years with a T-score of -3 SDs and previous fracture from Stevenson et al. (2009)

Table 7.27. Comparison of cost-effectiveness results with those from Stevenson et al. (2009) for 75-year-old women with T-score of -2.5 SDs with a previous fracture assuming drug cost of £51

T score - 2.5	Base-case assuming compliance of 75%			Results assuming compliance of 50%			Discount rates of 6% for cost and 1.5% for utility, assuming compliance of 50%			HTA Results†
	With treatment	No treatment	Incremental	With treatment	No treatment	Incremental	With treatment	No treatment	Incremental	Incremental
Cost	£ 14,440	£ 14,894	-£ 454	£ 14,552	£ 14,894	-£ 342	£ 14,552	£ 14,894	-£ 342	
Discounted Cost	£ 9,356	£ 9,678	-£ 322	£ 9,422	£ 9,678	-£ 256	£ 7,133	£ 7,347	-£ 214	-£ 128
QALYs	8.077	8.038	0.039	8.063	8.038	0.025	8.063	8.038	0.025	
Discounted QALYs	6.292	6.259	0.033	6.280	6.259	0.020	7.206	7.183	0.023	0.0420
Cost per QALY (£)			Dominating			Dominating			Dominating	Dominating

†Cost effectiveness of alendronate in women aged 75-79 years with a T-score of -2.5 SDs and previous fracture from Stevenson et al. (2009)

The difference in the modelling method, such as a patient-based transition-state model alongside the use of a meta-model in Stevenson et al. (2009) and a DES model in this thesis, could cause the results to differ. However, when a similar model population was used, the model results in Tables 7.24-7.27 were not different to a great extent from those reported in Stevenson et al. (2009).

7.4.2. Base-case results for the general population

The base-case model with the UK general population aged 45 and over resulted in the cost and life years outcomes reported in Table 7.28. For the base year population of men and women aged 45 years and over, the lifetime costs per person were £2,847 (£6,151 when the value was undiscounted) with QALYs of 11.191 (17.759 when undiscounted). For the incoming cohorts aged 45 years, the costs were considerably lower for men than women given the higher prevalence of osteoporosis and life expectancy among women (Table 7.29). Compared with no treatment, alendronate treatment was less costly and more effective (Table 7.30), and dominated no treatment.

Table 7.28. Base-case results based on 400,000 simulated individuals for the general UK population aged 45 years and over with the default alendronate treatment

	Discounted	Undiscounted
Cost	£ 2,847	£ 6,151
QALYs	11.191	17.759
Life years		23.530

Table 7.29. Males and females aged 45 years at the start of the model (n=400,000) – with the default alendronate treatment

	Men		Women	
	Discounted	Undiscounted	Discounted	Undiscounted
Cost	£ 1,002	£ 3,274	£ 2,432	£ 8,824
QALYs	16.281	29.182	16.509	30.387
Life years		36.065		39.144

Table 7.30. Cost effectiveness of alendronate treatment following a fracture for population aged 45 years and older

Base-case	Discounted			Undiscounted		
	With treatment	No treatment	Incremental	With treatment	No treatment	Incremental
Cost	£ 2,847	£ 2,947	-£ 100	£ 6,151	£ 6,324	-£ 173
QALYs	11.1913	11.1837	0.0076	17.7593	17.7505	0.0088
Cost per QALY (£)			Dominating			Dominating

7.4.3. Annual cost projections

Total annual costs were projected to increase from £1.55 billion in 2012 to £4.91 billion in 2037 (Figure 7.3). Cohort annual costs per person from the base year population and new cohorts of 45 year olds were also given in Figure 7.4. The cohort annual costs for those aged 45 years showed stepped increases at 5-year intervals due to the increases in the estimates of fracture risks based on 5-year age bands. For those aged 45 years, most of the costs were incurred at the later stage of their life. As new 45-year-old cohorts enter the model every year, the total annual costs across all the yearly incoming cohorts will increase in the earlier years (the costs for 45-year olds at later years will come forward to earlier years after model initiation over time for the total population in Figure 7.4).

Figure 7.3. Projected total annual costs by the year 2037 for the treatment and management of osteoporosis for the base-year and incoming populations aged 45 years and over
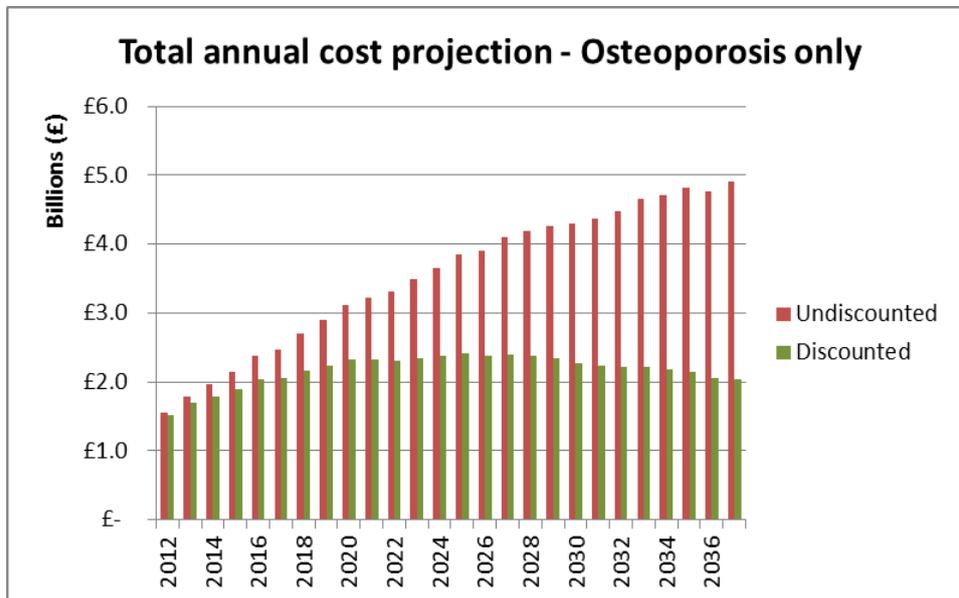
Figure 7.4. Cohort annual costs per person used to calculate the projected total annual costs
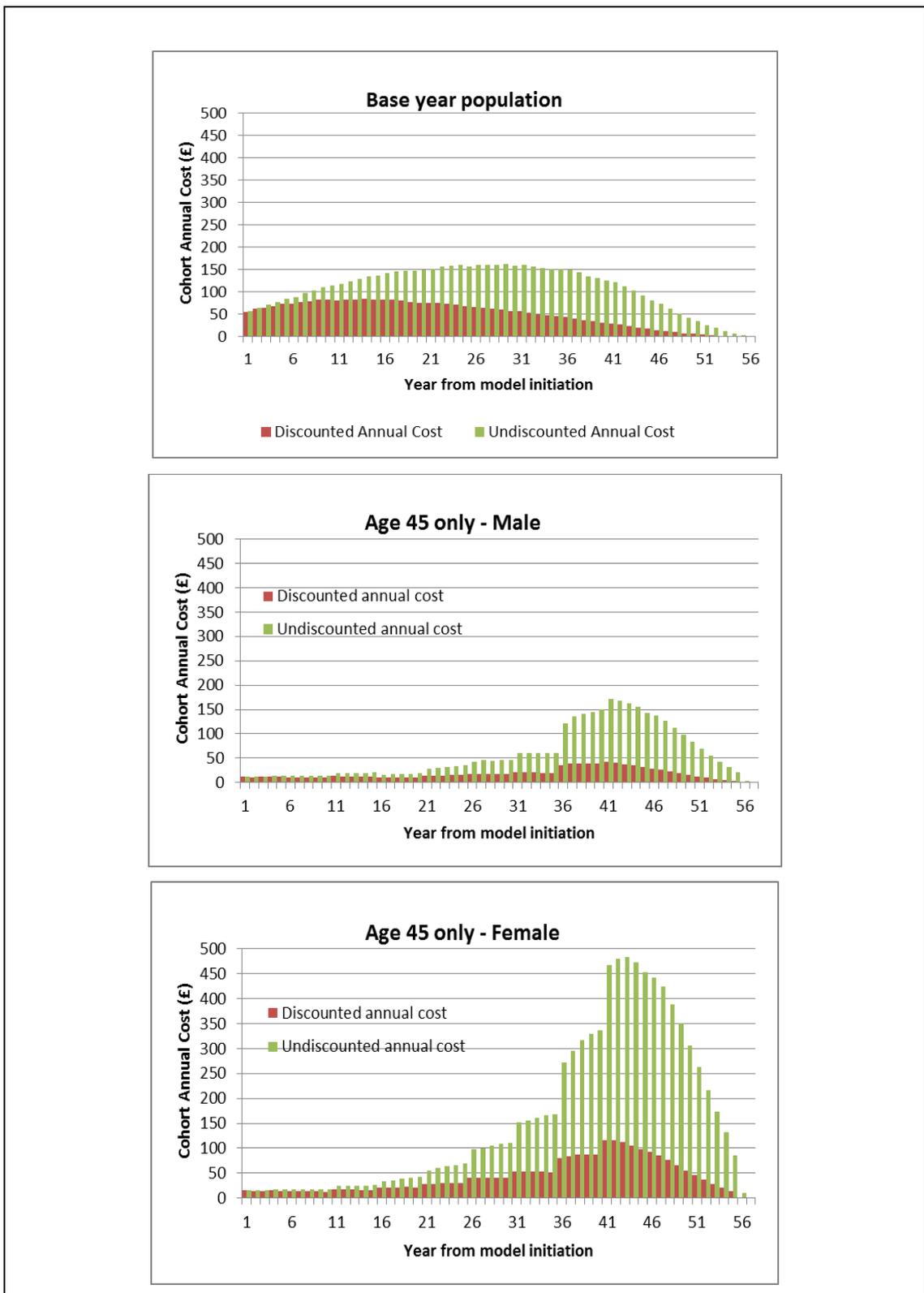
7.5. Discussion and Conclusion

Alendronate drug treatment following a fracture for the prevention of osteoporotic fracture for the general population aged 45 years and over as well as women aged 75 years with T-scores of -3 SDs and -2.5 SDs, dominated no treatment. As such, regardless of the willingness-to-pay threshold per QALY, the drug treatment is likely to be a cost-effective option for fracture prevention.

The total costs associated with treatment and management of osteoporosis was projected to increase over the projection horizon, reaching its peak at £4.9 billion in the farthest projection year of 2037.

However, it is noted that the model results are based on numerous assumptions which increases uncertainty, in particular, the inclusion of the male population and people with BMD higher than average unlike the model by Stevenson et al. (2009). When data were not available, the estimation of parameters for these groups was often based on assumptions. Although efforts were made to make plausible assumptions based on available evidence, the estimates may not accurately reflect the true values. For example, the average difference between men and women obtained from Holt et al. (2002) was applied to calculate the average T-scores for men (see Section 7.3.3). However, this implicitly assumes that the same rates of deterioration in BMD for age groups and equal age distributions for men and women. Also, for those whose BMD is higher than average, the non-fracture related mortality was reduced by the same factor as that used to increase mortality for those with low BMD.

Biases could be introduced in the process of estimating mortality rates based on mid-range values of Z-score. The same factor of 1.22 was used to adjust mortality for both people with low and high BMD in order to run a simulation for the general population as well as the diseased. Also, a standard Normal distribution was assumed for Z-score. If the model population aged 45 years and older does not have a symmetric distribution of Z-score as assumed, this can also introduce bias in the estimates. However, this was an extrapolation beyond available evidence, and was not considered to markedly influence the results.

CHAPTER 8   LINKING PAIRS OF DISEASES – CORRELATION BETWEEN DISEASES

8.1. Background

Individual disease models could be linked in two ways: one is where diseases were assumed independent and thus, the presence of one disease did not affect the risk of the others (denoted hereafter as 'independently linked model'); and the other where correlations between diseases were incorporated, which can reflect changes in risks associated with the presence of other diseases (denoted hereafter as 'correlated linked model'). A version of the linked model where all diseases were assumed independent was constructed in order to assess the reliability of results from the linked model.

This chapter develops further the method of model linkage introduced in Chapter 4. It describes correlations between the diseases that were incorporated in the linked model and how these correlations were implemented. It reports results from linked models where only two of the diseases were considered in order to evaluate the effect of the pairwise correlations implemented.

As described in Chapter 4, the order of the linkage was that the heart disease (HD) and Alzheimer's disease (AD) models were linked first, and then the osteoporosis model was added onto the HD-AD linked model. Hence, the results for the HD and AD pair will be reported from two models: the two-disease and three-disease linked models.

In the linked models, costs were additive and utilities were multiplicative across diseases. It is noted that if a patient in the model with correlated diseases has AD, the utility weights associated with AD were used as baseline utilities instead of the age- and sex-specific utility for the general population. This was due to Bond et al. (2012) having used the MMSE-based utilities as final utilities without multiplying them by age and sex based baseline utilities.

Targeted literature searches were conducted to identify data on correlations between the modelled diseases. Data were searched in the Medline and/or EMBASE databases using a combination of the disease names, the literature repository constructed for this thesis

(Chapter 3); and Google Scholar, and the method of snowballing was used to identify further literature from the papers identified from other sources. Where the impact of one disease (A) on another (B) was incorporated, the opposite direction of the correlation (the impact of B on A) was typically not included due to the potential risk of double-counting for a co-morbid population and the paucity of relevant data. In such cases, correlations regarding other disease events were prioritised for implementation in the model.

There were correlations that could be embedded in the model other than those described in this chapter. However, it was considered sufficient to incorporate some key correlations deemed important for the purpose of this thesis, thus demonstrating a proof-of-concept model. Researchers wishing to include further correlations may do so in their model using the method shown in this chapter. The following sections summarise correlations identified from the literature searches and incorporated in the model for each of the three pairs of diseases.

8.2. Correlation between Heart disease and Alzheimer's disease

Systematic searches for literature reporting the prevalence of AD and other co-existing conditions and the outcomes of treatment for patients with AD and other relevant conditions were conducted within the Medline and EMBASE databases. However, very few papers that could provide numerical data for populating the model were identified.

A small number of studies that discussed empirical data on the effect of one disease on another were identified from the literature search. As Maslow (2004) noted, studies mainly listed common co-existing conditions that were present in their study population only, or intentionally excluded people with AD who have other co-morbidities as the effect of other diseases could confound the effect of AD. Studies focussing on heart disease reported similar results.

The calculation methods described in this section were applied to other diseases.

8.2.1. Correlation of prevalence

The prevalence of HD among AD patients was considered higher than that of HD randomly allocated according to the prevalence within the general population. A number of studies have found that AD often co-exists with vascular conditions such as hypertension, hyper-cholesterolaemia, and diabetes mellitus (Maslow, 2004, Muqtadar et al., 2012, Barnes and Yaffe, 2011, Polidori et al., 2012, Sparks et al., 2000).

For instance, the US National Center for Health Statistics survey found that 82% of people in assisted living facilities where help is provided for daily activities such as bathing and dressing had one or more of dementia, hypertension, and heart disease (Figure 8.1) (The National Center for Health Statistics, 2010). 42% of the residents had Alzheimer's disease or other forms of dementia and 34% had heart disease. 14% of people had both dementia and heart disease and 9% of them had all three of the diseases. However, this survey was conducted within a specific population living in assisted living centres and the survey respondents were likely to be older than other study population.

Figure 8.1. Co-morbidities of residents in assisted living facilities
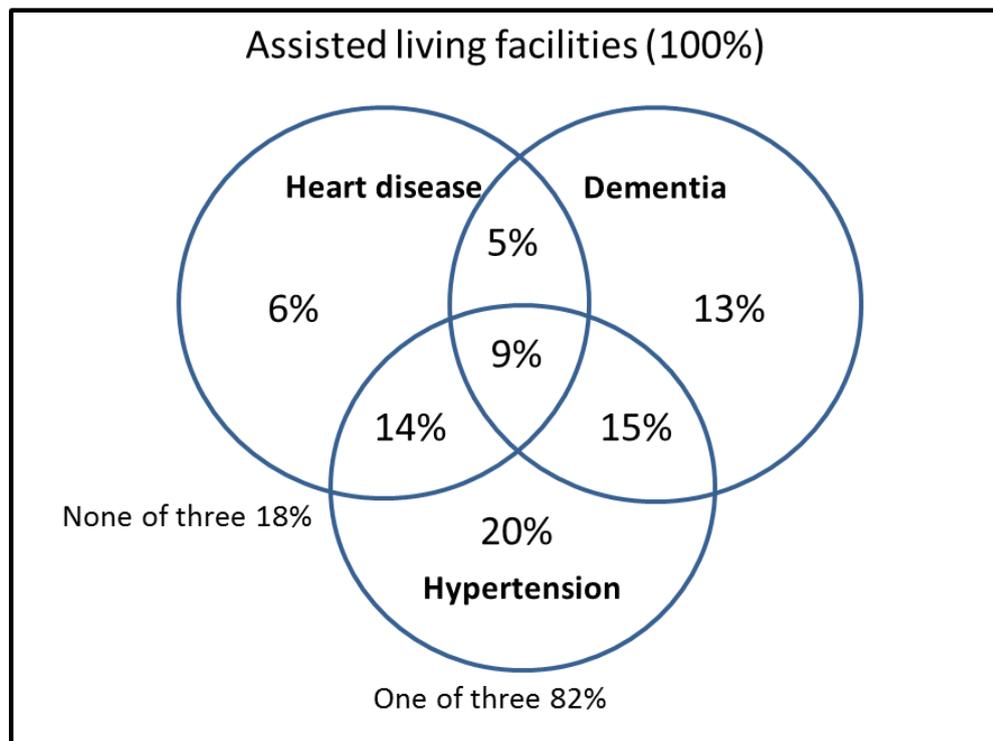
In order to incorporate the linkages between AD and HD with respect to the disease prevalence and incidence, the total prevalence of one disease was split into the prevalence of that disease for people with another disease and that for people without the disease, so that the total prevalence of people with a specific disease at model initiation match the sum of split prevalence values. For example, the total proportion of people who have AD at a specific point in time can be divided into the proportion of AD patients among people with heart disease and the proportion among people without HD.

For each age and sex group, the total prevalence of AD at a specific point in time, $P(AD = 1)$, can be seen as a weighted average of two conditional probabilities $P(AD = 1|HD = 1)$ and $P(AD = 1|HD = 0)$ as follows;

$$P(AD = 1) = P(AD = 1|HD = 1) \cdot P(HD = 1) + P(AD = 1|HD = 0) \cdot P(HD = 0)$$
[Eq. 8.1]

where AD and HD are binary variables taking the value of one when the disease is present and zero otherwise. Therefore, $P(AD = 1)$ and $P(HD = 1)$ are the prevalence of AD and HD, respectively. $P(AD = 1|HD = 1)$ denotes the probability of having AD conditional on the presence of HD, or the prevalence of AD among those with HD, and $P(HD = 1|AD = 1)$ the prevalence of HD among those with AD.

In the same way, the total prevalence of heart disease can be shown as:

$$P(HD = 1) = P(HD = 1|AD = 1) \cdot P(AD = 1) + P(HD = 1|AD = 0) \cdot P(AD = 0)$$
[Eq. 8.2]

Eq. 8.2 expresses the total prevalence of HD in terms of $P(HD = 1|AD = 1)$ and $P(HD = 1|AD = 0)$ using the value of AD prevalence, $P(AD = 1)$. However, Eq. 8.2 could not be used as the total prevalence of heart disease had to be partitioned among the cardiac events included in the model and data required for using Eq. 8.2 were not available from the literature searches. Hence, the prevalence of AD was split into the prevalence of AD for people with and without HD using Eq. 8.1.

Using Bayes' theorem, $P(AD = 1|HD = 1)$ in Eq. 8.1 was calculated as $P(AD = 1|HD = 1) = \frac{[P(HD=1|AD=1) \cdot P(AD=1)]}{P(HD=1)}$ **[Eq. 8.3]**. The relationship in Eq. 8.1 was used to back-calculate

$P(AD = 1 | HD = 0)$. The following sections describe why these were calculated in this manner and report the calculation results.

Regardless of which equation to use, the split should be the same as $P(HD = 1 | AD = 1)$ and $P(AD = 1 | HD = 1)$ represent the same coloured area in Figure 8.2 although the actual figures of the conditional probabilities differ depending on which disease status is assumed to be known.

Figure 8.2. Prevalence linkage between AD and heart disease
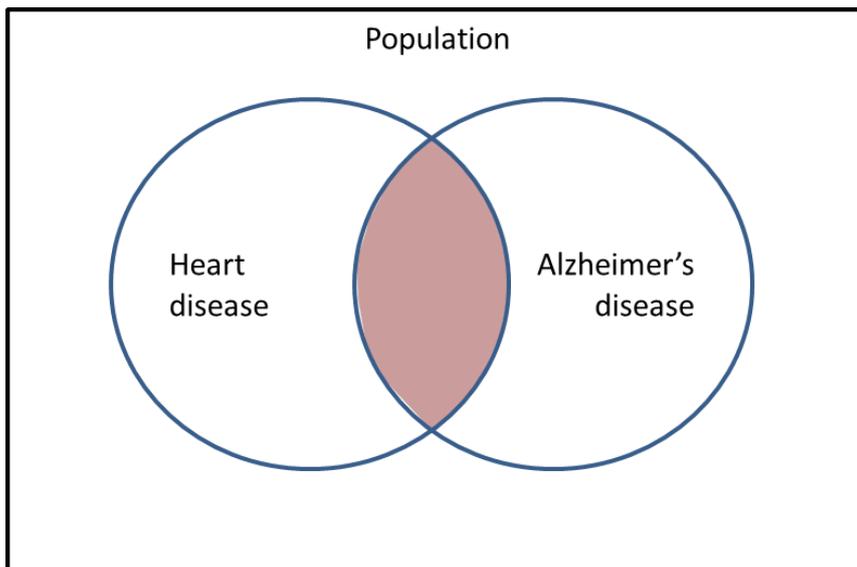
Prevalence of Alzheimer's disease among heart disease patients

The prevalence of AD among HD patients, $P(AD = 1|HD = 1)$ in Eq. 8.1, was explored. The Cardiovascular Health Study (CHS) is an observational population-based, longitudinal study of coronary heart disease and stroke in adults aged 65 years and older, mainly aimed to identify factors related to the onset and course of coronary heart disease and stroke (Fitzpatrick et al., 2004). However, AD prevalence was not reported in relation to the presence of heart disease or stroke.

More data on the prevalence of HD in AD patients, $P(HD = 1|AD = 1)$, than for the prevalence of AD in HD patients, were identified. The US Medicare Alzheimer's Disease Demonstration (MADD) study reported the prevalence of co-existing conditions in a large sample of people with dementia (Maslow, 2004). In the MADD study, conducted between 1989 and 1994, a considerable proportion of people had cardiovascular and cerebrovascular diseases: 47% had hypertension; 33% coronary heart disease; 28% congestive heart failure; and 25% stroke. A more recent study by the Alzheimer's Association reported that 30% of people with AD or other dementias also had coronary heart disease, 22% congestive heart failure, and 14% stroke using data from the National 20% Sample Medicare Fee-for-Service Beneficiaries for 2009 (Alzheimer's Association, 2013).

However, no UK data were found on the prevalence of co-morbid conditions among the population aged 65 years and over, although there were papers reporting relative incidence of AD in association with the presence of heart disease. Assuming that the prevalence of diseases that overlap in the older population is similar in the UK to the US population, the most recent data from the Alzheimer's Association was used in the calculation. As age- and sex-specific probabilities were not available, $P(HD = 1|AD = 1)$= 52% was used for people with a history of non-stroke cardiac conditions across all age and sex groups (Alzheimer's Association, 2013).

Prevalence of non-stroke cardiac disease

In the model for this thesis, the prevalence of stroke was not explicitly linked with the presence of AD. The existing literature has often focussed on non-stroke cardiovascular conditions in association with AD (Eriksson et al., 2010). It was considered that the association is unclear as studies often looked at vascular dementia, rather than AD, as the type of dementia that often occurs after stroke (Blom et al., 2014, Appel, 2007). Although vascular dementia often coexists with other types of dementia such as AD and the prevalence of stroke and other vascular risk factors is higher among people with AD as shown above (Alzheimer's Association, 2013, de la Torre, 2006), this linkage was not incorporated in the model in this thesis. However, as previous cardiac events influence rates of other cardiac events including stroke in the model, implementing correlations between AD and non-stroke cardiac conditions does indirectly affect the rates of stroke.

The prevalence of non-stroke cardiac events, denoted as $P(HD = 1)$ hereafter in this chapter, was obtained from simulated results from the heart disease model. This was due to the composite prevalence measure for only the non-stroke events included in the heart disease model – MI, angina, PAD, and revascularisation – being unavailable in the literature. In the HD model, these events were independently assigned according to the simulated prevalence of each HD event.

Prevalence of non-stroke HD in the base year (at model entry) by age and sex is shown in Table 8.1. As described earlier, the prevalence of AD for people aged 65 years and under was assumed to be zero, and thus the prevalence of HD was not split into people with and without AD for this age group.

Table 8.1. Prevalence of heart disease events included in the model by age and sex

	Prevalence of all heart disease events		Prevalence of non-stroke heart disease events	
Age	Men	Women	Men	Women
<65 years	0.12061	0.06452	0.10171	0.04953
65-69	0.34052	0.15917	0.28695	0.12559
70-74	0.36596	0.19145	0.31401	0.16154
75-79	0.48773	0.37097	0.40906	0.29194
80-84	0.48587	0.37356	0.39927	0.29204
85 and over	0.44709	0.36202	0.37302	0.28318

Calculation and calibration of the prevalence of Alzheimer's disease among heart disease patients

The results on $P(HD = 1|AD = 1)$ and $P(HD = 1)$ were combined to calculate $P(AD = 1|HD = 1)$ using Eq. 8.3, and $P(AD = 1|HD = 0)$ was also estimated using Eq. 8.1. The resulting prevalence of AD split into $P(AD = 1|HD = 1)$ and $P(AD = 1|HD = 0)$ is shown in Table 8.2. These values were used in the linked model as the prevalence of AD in relation to the presence of heart disease. The ratio $\frac{P(AD=1|HD=1)}{P(AD=1|HD=0)}$ varied with age group and sex as the prevalence of individual diseases, $P(HD = 1)$ and $P(AD = 1)$, differ between age and sex.

Table 8.2. Prevalence of AD divided into the prevalence for people with HD and that for people without HD (before calibration)

| | Prevalence of AD | | | | | |
| | People with HD ① | | People without HD ② | | Ratio (①/②) | |
Age	Men	Women	Men	Women	Men	Women
<65	0	0	0	0	NA	NA
65-69	0.018267	0.044718	0.006785	0.005929	2.69	7.54
70-74	0.036962	0.05099	0.015618	0.009068	2.37	5.62
75-79	0.051255	0.091056	0.032751	0.034654	1.57	2.63
80-84	0.095646	0.180764	0.058681	0.068831	1.63	2.63
85+	0.196727	0.363585	0.108037	0.132586	1.82	2.74

The prevalence of AD before and after applying the correlations were compared using the values sampled at the model entry in order to see whether the estimation method used for splitting prevalence produced similar results. The total prevalence of AD and the prevalence for people with and without HD are compared in Table 8.3. The prevalence values of AD with and without HD were combined for comparison with the total AD prevalence before splitting using 100,000 simulated individuals for each age group (in order to have enough numbers of simulated individuals in each age group). The absolute percentage differences ranged from 0.23% to 5.09% between the total population values and the split values of prevalence. The percentage difference was the largest for female population aged 70-74 years. The differences could be due to the use of the single estimate of $P(HD = 1|AD = 1)$ in Eq. 8.3 for all age groups and sex, which fails to reflect variation among different populations in the estimation equation.

Table 8.3. Comparison of simulated proportions of people with Alzheimer's disease (AD): between when the total prevalence of AD was used and when the prevalence of AD split into HD and non-HD groups was used

	Total prevalence of AD (before splitting)		Combined prevalence of AD using split prevalence values*		% Difference (compared with the total prevalence AD)	
Age	Men	Women	Men	Women	Men	Women
<65	0	0	0	0	0	0
65-69	0.0101	0.0108	**0.0098**	**0.0104**	-3.01%	-3.98%
70-74	0.0223	0.0158	**0.0232**	**0.0166**	3.88%	5.09%
75-79	0.0403	0.0511	**0.0387**	**0.0503**	-3.94%	-1.52%
80-84	0.0734	0.1015	**0.0732**	**0.1020**	-0.38%	0.44%
85+	0.1411	0.1980	**0.1451**	**0.1985**	2.79%	0.23%

*Based on the results of 100,000 simulated individuals for each age group.

Although the differences could be considered small, in order to start the model with the same population with respect to the total prevalence of AD, the prevalence of AD split for people with and without HD was calibrated to match the total prevalence. Based on the total prevalence values reported in Table 8.3, age- and sex-specific calibration multipliers were applied to the prevalence values for people with and without HD. These were calculated as the total prevalence divided by the combined prevalence using split values (Table 8.4).

Table 8.4. Calibration multipliers for prevalence of AD

Age	Men	Women
<65	1	1
65-69	1.031	1.041
70-74	0.963	0.952
75-79	1.041	1.015
80-84	1.004	0.996
85+	0.973	0.998

The calibrated prevalence after these multipliers were applied is shown in Table 8.5. The prevalence of AD reported in Table 8.5 was used in all models for this thesis where AD and heart disease were correlated. The split ratios remained the same as in Table 8.2 as the same multiplier was used to calibrate both for those with and without HD. Total prevalence obtained from running the model with the calibrated values in Table 8.5 was compared with that before splitting in Table 8.6. The percentage differences largely reduced after calibration, but were considered inconclusive as the differences increased for the age 75-79 and 80-84 groups, and females aged 85 and over. In order to examine the effect of the calibration at the population level, the numbers of people with AD across all age groups in the models before and after calibration were compared in Table 8.7 when 200,000 individuals aged 65 years and over were simulated for each model (the age distribution for people aged 65 and over was adapted from the ONS mid-2012 UK population estimates). The total numbers of people with AD among 200,000 simulated individuals from models with and without calibrated prevalence values were compared with that from the model where heart disease and AD were independently linked. The calibration reduced the difference between when the total AD prevalence was applied and when the split prevalence values were used from 0.50% to 0.24% for male population and from 1.89% to 1.18% for females.

There still existed differences in the number of people with AD after calibration due to Monte Carlo sampling error. Perfect calibration would have been possible if the calibration factors were calculated using the model results with the infinite number of runs for each age and sex group. In addition, if the infinite number of individuals were simulated in the perfectly calibrated model and the independently linked model for figures in Table 8.7, the differences would have been eliminated.

Table 8.5. Prevalence of AD split into the prevalence for people with HD and that for people without HD (after calibration) used in the model

	Prevalence of AD (after calibration)					
	People with HD ①		People without HD ②		Ratio (①/②)	
Age	Men	Women	Men	Women	Men	Women
<65	0	0	0	0	NA	NA
65-69	0.018834	0.046570	0.006996	0.006174	2.69	7.54
70-74	0.035583	0.048520	0.015035	0.008629	2.37	5.62
75-79	0.053356	0.092461	0.034094	0.035189	1.57	2.63
80-84	0.096015	0.179969	0.058907	0.068529	1.63	2.63
85+	0.191384	0.362735	0.105103	0.132276	1.82	2.74

Table 8.6. Comparison of proportions of simulated people with Alzheimer's disease (AD): between when the total prevalence of AD was used and when the prevalence of AD split into HD and non-HD groups was used

	Total prevalence of AD (before splitting)		Combined prevalence of AD using split prevalence values*		% Difference (compared with the total prevalence AD)	
Age	Men	Women	Men	Women	Men	Women
<65	0	0	0	0	0	0
65-69	0.0101	0.0108	**0.0103**	**0.0109**	1.87%	0.91%
70-74	0.0223	0.0158	**0.0225**	**0.0160**	0.94%	0.75%
75-79	0.0403	0.0511	**0.0420**	**0.0521**	4.07%	2.01%
80-84	0.0734	0.1015	**0.0743**	**0.1007**	1.18%	-0.82%
85+	0.1411	0.1980	**0.1414**	**0.1966**	0.20%	-0.69%

*Based on the results of 100,000 simulated individuals for each age group.

Table 8.7. Number of individuals with Alzheimer's disease (AD) before and after calibration compared with when total prevalence without correlations was applied

Number with AD when Total AD prevalence was used**		Number with AD when split prevalence values were used* (difference (n; %))			
Men	Women	Men	Women	Men	Women
		Before calibration		After calibration	
3378	6292	3395 (+17; +0.50%)	6411 (+119; 1.89%)	3386 (+8; 0.24%)	6366 (+74; +1.18%)

*Among 200,000 simulated individuals aged 65 years and older; **Results from the model where heart disease and AD were linked with independence between diseases assumed.

8.2.2. Correlation of incidence

The incidence of AD for the total population was split into that for a population with heart disease and for a population without heart disease. Heart disease was considered as a forerunner of AD and the onset of AD was earlier on average for those who have a history of heart disease with a hazard ratio of 1.3 (Newman et al., 2005).

In order to maintain the number of people with AD after the split, the incidence calculation was based on the prevalence of AD and HD. Eq. 8.1 was used as the basis of the calculation. However, it is noted that it could only approximate the incidence of AD as mortality rates and changes in mortality over time were ignored in the calculation.

When r is the baseline rate of AD incidence for people without HD per time unit t and HR is the hazard ratio for people with HD (assumed to be constant across age groups and >1), the incidence rates for people with and without HD can be expressed as rHR and r, respectively. The conditional prevalences $P(AD = 1|HD = 1)$ and $P(AD = 1|HD = 0)$ can be expressed with the incidence rate r and rHR using the relationship between probability and rate, $p = 1 - e^{-rt}$.

Eq. 8.1 reduces to:

$$[P(AD) - 1] = [P(HD) - 1] \cdot e^{-rt} - P(HD) \cdot e^{-r(HR)t} \qquad \textbf{[Eq. 8.4]}$$

As the values of $P(AD)$, $P(HD)$, t and HR could be obtained from the model or from the literature, Eq. 8.4. could be expressed in the the form of:

$$a + b^{cr} = d \cdot b^r$$

, where r is the rate parameter, $r \neq 0$, and known constants a, b, c, and d are $a = \frac{1}{P(HD=1)} - 1$, $b = e^t$, $c = 1 - HR$, and $d = \frac{1-P(AD=1)}{P(HD=1)}$.

However, there was no unique and exact (where no approximation was involved) solution for this exponential form: the rate was not a random variable but a fixed number in the equation, hence, differentiating both sides of any equation except an identity equation (an equation that is true for all values of the variables) would not make sense. Also, taking the natural logarithm of both sides does not solve the equation with respect to the parameter r as it would not remove the power of r due to the polynomial terms $a + b^{cr}$.

In addition, the definition of time t and prevalence in Eq. 8.4 made the incidence calculation intractable. Adopting the age bands used in Tables 8.5 and 8.6, $P(AD = 1)$ was the prevalence of AD newly developed since the previous age group (for all people with or without HD). As the prevalence of AD for people aged 65 years and under was zero, the time t in Eq. 8.4 was 5 years (or less than 5 years if mid-interval time points are used) for people in the 65-70 years age band. Equations for groups of higher age had to incorporate the prevalence for the population aged 65 years and under, and should be estimated sequentially from younger age groups to older.

Alternatively, incidence rates were approximated such that the total incidence of AD would match with a simple linear combination of incidence of AD with and without HD with the proportion (prevalence) of HD taken as the weights as in Eq. 8.5, where r represented the baseline incidence rate for people without HD and the rate for those with HD was calculated as rHR. The incidence rates of AD for people with and without HD are shown in Table 8.8.

[Eq. 8.5]

$$r = \frac{Total\ incidence\ of\ AD}{\{P(HD = 1) \cdot HR + [1 - P(HD = 1)]\}}$$

Table 8.8. Incidence of Alzheimer's disease (AD) for people with and without heart disease (HD)

	a) Total incidence of AD		b) Rate for people without HD		c) Rate for HD patients	
Age	Men	Women	Men	Women	Men	Women
<65	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000
65-69	0.004968	0.004536	0.004508	0.004329	0.005860	0.005628
70-74	0.010440	0.004392	0.009407	0.004153	0.012229	0.005399
75-79	0.010224	0.010656	0.008919	0.009589	0.011595	0.012466
80-84	0.012240	0.022464	0.010683	0.020200	0.013888	0.026260
85+	0.042048	0.051624	0.037075	0.046567	0.048198	0.060537

The prevalence and incidence of AD before and after applying the correlations were compared using the values sampled at the model entry in order to see whether the estimation method used for splitting prevalence and incidence produced similar results to the totals assuming independence between the diseases.

There were differences in the incidence rates with and without correlations applied as the method used was an approximation. When using the incidence rates for those with and without HD (Table 8.8), the average of time to AD onset sampled for individuals without AD at model initiation was approximately 1 year longer than that sampled from the independently linked model (39.8 years vs. 40.8 years, based on n=100,000), meaning that incorporating the correlation between AD and HD in the incidence of AD resulted in AD developing slightly more slowly compared with when no correlation was applied. They could not be perfectly matched as Eq. 8.5 was an approximation and Eq. 8.4 could not be solved with available data.

No numerical data were identified on the linkage between HD and AD in terms of the progression of the diseases. However, the correlations implemented with respect to prevalence and incidence indirectly influence the rate at which diseases progress.

8.2.3. Non-disease mortality

In the linked models where HD was included, non-disease death was non-cardiac death with age specific cardiac death rates subtracted from all-cause mortality rates. When AD is included in the linked model, no such subtraction was performed as it was assumed that AD would not affect non-disease mortality in the base case. As described in Chapter 6, a risk equation for sampling time to AD-related death from the pre-institutionalisation event was implemented as a competing risk in the AD model (see Chapter 6).

8.2.4. Costs

Papers on the cost of treating people with both AD and HD were not found from a Medline search (using the MESH terms 'Alzheimer's disease' AND 'Heart diseases', both with economics subheadings, limited to publications after 2000). However, there was some evidence showing that people with AD or other forms of dementia may incur higher cost for other co-existing diseases than people without dementia (Alzheimer's Association 2013; Maslow 2004). The US 2009 Medicare data showed that people with AD or dementia in addition to other co-existing conditions are more likely to be hospitalised than people with the same comorbid conditions but without AD or dementia (Alzheimer's Association 2013). However, equivalent UK studies could not be found.

In the model for this thesis, costs were assumed to be additive: if an individual has both AD and HD, it was assumed that the person incurs the cost for AD plus that for HD.

8.2.5. Utilities

Papers on the utility-based quality of life (QoL) values in relation to the co-existing AD and heart disease were not found from a Medline search (with search terms of 'Alzheimer's disease' AND 'Quality of Life', or 'Heart diseases' AND 'Quality of Life').

For those with both AD and HD, utility was assumed to be multiplicative. For patients with AD, the EQ-5D valuations of utilities based on cognitive function reported in Jönsson et al. (2006) were used as utility weights for patients with AD across all age and gender groups as used in

the model by Bond et al. (2012). If these patients were co-morbid with heart disease, the utilities associated with heart disease events were used as utility multipliers applied to the utility values for AD. If an individual had only heart disease, the utilities for heart disease were multiplied by the age and gender specific baseline utility values described in Chapter 4 (Ward et al., 2006, Ara and Brazier, 2010).

8.3. Correlation between Heart disease and Osteoporosis

Although there are a number of studies investigating possible correlations between osteoporosis and heart disease, the model in this thesis will focus specifically on correlations regarding hip fracture, and MI and stroke as these events are associated with the highest costs and utility effects. Wherever possible, estimates of correlation controlled for other factors such as age, sex, drinking and smoking status were used in the model.

8.3.1. Prevalent cardiovascular disease and fracture risks

Fracture risks are influenced by the presence of CVD. In a study that was a part of the Rochester Epidemiology Project, MI was associated with higher risk of all types of osteoporotic fracture (Gerber et al., 2011). Excess fracture risks after MI were found with the overall adjusted hazard ratio (HR) of 1.32 (95% CI 1.12-1.56) across all anatomic sites. Trends of the fracture incidence rates for three time-periods (1979-1989; 1990-1999; 2000-2006) were tested and an increase in fracture rates over time was found among MI patients. An HR of 1.66 for both men and women for hip fracture was used in the model, which was for the most recent time period (2000-2006). Data reported in Gerber et al. (2011) was used in the model as this study was based on a large sample size and similar ethnic group to that of the UK, and provided relatively recent data in the format suitable to be applied to the time-to-event distributions used in the model.

However, only a transient increase of fracture risks after MI was identified in the study. In the Gerber et al. (2011) study, the mean follow-up time was only 4 years, and the association between and MI and 5-year risk of osteoporotic fracture was reported. Also, in a large Danish case-control study including 124,655 fracture cases and 373,962 age and gender matched controls, a statistically significant increase in the risk of hip fracture was found only in the first 3 years after MI (Vestergaard et al., 2009). Following the more recent data reported in Gerber et al. (2011), HR was applied for five years after MI.

The incidence of hip fracture was split between that for those with MI and that for those without. All other risk adjustments associated with hip fracture (e.g. drug use, previous fracture, etc.) were applied taking these split incidence rates as baseline.

Using the prevalence of MI within the heart disease model, the total incidence of hip fracture was split between the incidence of hip fracture for patient who had an MI within 5 years and that for patients who did not have MI for the last 5 years. These were reported in Table 8.9 for those on no treatment (A) and on drug treatment for osteoporosis (B) where the RR of 72% for hip fracture was applied (see Chapter 7). Due to the low prevalence of MI among younger age groups, the baseline incidence for those without MI was similar to the total incidence including both groups with and without MI.

Table 8.9. Hip fracture incidence split between rates for those with MI and without MI

A. Hip fracture incidence with and without MI – No drug treatment

	Total incidence of hip fracture		Baseline rate r (without MI)		Rate for patients with MI	
Age	Men	Women	Men	Women	Men	Women
45-50	0.00030	0.00020	0.00030	0.00020	0.00049	0.00033
50-55	0.00030	0.00020	0.00030	0.00020	0.00049	0.00033
55-60	0.00070	0.00050	0.00067	0.00049	0.00112	0.00082
60-65	0.00030	0.00080	0.00029	0.00079	0.00048	0.00131
65-70	0.00080	0.00130	0.00073	0.00127	0.00121	0.00211
70-75	0.00110	0.00210	0.00100	0.00206	0.00167	0.00341
75-80	0.00200	0.00420	0.00180	0.00396	0.00299	0.00658
80-85	0.0068	0.0097	0.00613	0.00915	0.01017	0.01519
85+	0.0099	0.0217	0.00892	0.02047	0.01481	0.03398

B. Hip fracture incidence with and without MI – For individuals on drug treatment for osteoporosis

	Total incidence of hip fracture – on drug treatment		Baseline rate r (without MI)		Rate for patients with MI	
Age	Men	Women	Men	Women	Men	Women
45-50	0.00025	0.00018	0.00025	0.00017	0.00041	0.00029
50-55	0.00024	0.00017	0.00024	0.00017	0.00040	0.00028
55-60	0.00050	0.00033	0.00048	0.00032	0.00080	0.00054
60-65	0.00020	0.00055	0.00019	0.00054	0.00032	0.00090
65-70	0.00060	0.00092	0.00054	0.00090	0.00090	0.00149
70-75	0.00081	0.00150	0.00074	0.00147	0.00123	0.00244
75-80	0.00145	0.00303	0.00131	0.00286	0.00217	0.00475
80-85	0.00490	0.00695	0.00442	0.00656	0.00733	0.01088
85+	0.00713	0.01557	0.00643	0.01469	0.01067	0.02439

The incidence rates of hip fracture with and without a recent MI reported in Table 8.9 were used as the baseline event rates for hip fracture for the first 5 year period after MI. The relative risks associated with factors that can influence the event rates, such as low BMD and previous fracture, were applied onto these baseline rates. When sampling time to next hip fracture, these baseline incidence rates of hip fracture were updated when the sampled time to event was longer than the time before a change in age band, or the time left to a change in the drug efficacy due to the treatment fall time after discontinuation. Hence, all three time intervals for which different event rates are applied – time to 5 years after MI, time to next age band, and time to next efficacy change due to the fall time of treatment effect – were continuously compared with the sampled TTE value. When the sampled TTE value is longer than any of the three, the baseline incidence rates were changed accordingly and TTE was resampled. It was assumed that a previous MI at the initiation of the model does not affect the hip fracture risks (that is, it occurred more than 5 years ago).

8.3.2. Presence of osteoporosis and stroke risks

Osteoporosis and stroke share several risk factors, including age, smoking, low physical activity, and hypertension. Thus, low BMD and high stroke risk can be correlated. Some studies showed that low BMD or a history of fracture has an association with the incidence of stroke (Lui et al., 2003, Browner et al., 1993, Jørgensen et al., 2001). Jørgensen et al. (2001) examined the relationship, and found that women with BMD values in the lowest quartile had a higher risk of stroke than women with BMD values in the highest quartile (odds ratio= 4.8), and a linear trend over the quartiles was statistically significant. The OR for stroke increased 1.9 per SD (0.13 g/cm^2) reduction in BMD, and the association between low BMD and stroke in women remained significant when the analysis was adjusted for potential confounders. In men, no statistically significant difference in BMD between the stroke patients and their controls was found.

4024 American women aged 65 years or older were recruited in the Study of Osteoporotic Fractures, and found that low calcaneus BMD was associated with higher risk of stroke during a 2-year follow-up: per decrease of SD in calcaneus BMD (-0.09 g/cm^2), the incidence of stroke was 1.31-fold higher (HR 1.31, 95% CI 1.03-1.65) (Browner et al., 1993). Also, in a cohort of Swedish elderly men and women, low femoral neck BMD was associated with higher risk of stroke during a follow-up of 5.5 years (Nordstrom et al., 2010). However, a study showed that the existence of stroke history was not significant for the association with quartiles of percentage changes in BMD (prevalence of low BMD) (Lui et al., 2003).

Similarly, stroke risks were also often associated with a history of osteoporotic fracture. In a case-control study conducted in 8,404 patients (of whom 2101 were with hip fracture identified from a Taiwanese healthcare database called 'Longitudinal Health Insurance Database (LHID 2000)), a history of hip fracture was associated with a higher risk of having stroke during a 1-year follow up when adjusted for other cardiac diseases, diabetes, hypertension and hyperlipidemia (Kang et al., 2011). Using the same database, a more recent study covered a larger population (n=29,815 with 6013 hip fracture cases) and a longer data time frame (from 1996 to 2011) (Tsai et al., 2015). Although the effect of hip fracture over 5 year follow-up period was reported with an adjusted HR of 1.54 (95% CI 1.42-1.67), the highest effect was observed during the first year after hip fracture (HR 1.96, 95% 1.67-2.28). The first-year HR of 1.96 from the most recent data analysis was used in the model for one year after hip fracture.

For the first year of hip fracture, the total incidence of stroke was split into the incidence of stroke for those with a history of hip fracture and that without (Eq.8.6). The baseline incidence rate r was multiplied by hazard ratio (HR) associated with the presence of hip fracture history.

$$Total\ incidence\ of\ stroke = P(Hip = 1) \times (r \cdot HR) + [1 - P(Hip = 1)] \times r \quad \textbf{[Eq.8.6]}$$

, where $P(Hip = 1)$ is the prevalence of a recent (1 year) history of hip fracture, r denotes the baseline rate of event without hip fracture, and HR the hazard ratio associated with the presence of the history of hip fracture in the preceding year.

Due to the complex ways in which the total incidence of stroke was applied in the model where the rates were dependent on prior cardiac events (see Section 5.4.1), instead of directly calculating rates for people with and without previous hip fracture, a scale factor was calculated to be applied to all stroke incidence rates used in the first year after hip.

When Eq. 8.6 is rearranged with respect to r,

$$r = T \cdot \left[{}^{1}\!/_{P(Hip = 1) \cdot HR + [1 - P(Hip = 1)]} \right] = T \cdot A \quad \textbf{[Eq.8.7]}$$

, where T denotes the total incidence of stroke and A is

$\left[{}^{1}\!/_{P(Hip = 1) \cdot HR + [1 - P(Hip = 1)]} \right]$, the scale factor by which the total stroke incidence is adjusted.

Assuming the HR and the prevalence of hip fracture are constants, the baseline rate of stroke is the total incidence of stroke (without the split between people with and without hip fracture) multiplied by a constant A. Likewise, the scale factor for the incidence rate of stroke for people with a previous hip fracture within 1 year is $A \cdot HR$, as $r \cdot HR = T \cdot A \cdot HR$ from **Eq.8.7**.

The application of this scale factor does not affect the order of the maximum event rates applied in the heart disease model when comorbidities are found (see Section 5.3.2).

Due to the stochastic allocation of BMD and relationship between BMD and hip fracture prevalence, the simulated prevalence of hip fracture that was obtained directly from the model (as a result of running 100,000 individuals)were used to calculate the scale factors. The prevalence of hip fracture used for this calculation and the scale factor applied to the incidence of stroke whenever time to stroke was sampled are presented in Tables 8.10-8.11.

Table 8.10. Prevalence of hip fracture obtained from the simulation model (based on n=100,000 simulated individuals)

Prevalence of Hip fracture by age and sex		
Age	Men	Women
<55	0.0001	0.0001
55-59	0.0002	0.0018
60-64	0.0020	0.0090
65-69	0.0048	0.0194
70-74	0.0097	0.0423
75-79	0.0268	0.0784
80-84	0.0327	0.1292
85+	0.0664	0.1620

Table 8.11. Scale factors to be applied to the total incidence of stroke for the incorporation of correlation between hip fracture and stroke incidence

	Scale factor A for baseline rates (individuals without previous hip fracture)		Scale factor A*HR: (individuals with previous hip fracture)	
Age	MEN	WOMEN	MEN	WOMEN
<55	0.99995	0.99989	1.95990	1.95979
55-59	0.99985	0.99829	1.95971	1.95664
60-64	0.99804	0.99145	1.95616	1.94324
65-69	0.99540	0.98173	1.95099	1.92418
70-74	0.99081	0.96096	1.94199	1.88349
75-79	0.97494	0.92998	1.91089	1.82277
80-84	0.96957	0.88968	1.90036	1.74377
85+	0.94010	0.86541	1.84261	1.69621

The stroke event rates were adjusted using these scale factors for the first year after hip fracture in all cases where time to stroke is sampled by age at the time of sampling and sex (for individuals with and without hip fracture history). Once hip fracture occurs, a new time to stroke was sampled based on the updated rates at the hip fracture event in the osteoporosis model, which was compared with the time to next event values from the heart disease model. If the new time to stroke is shorter than other cardiac event times, then it replaced the earliest time to next heart disease event.

There were other studies that showed higher incident CVD events among those with osteoporosis or low BMD, or a history of osteoporotic fracture. In the placebo branch of the Multiple Outcomes of Raloxifene Evaluation (MORE) study, osteoporosis (T-score < − 2.5 at the spine or the femoral neck) was associated with a fivefold higher risk of cardiovascular events such as stroke and myocardial infarction (Tankó et al., 2005). In a group of 6,800 men and women (Multinational Monitoring of Trends and Determinants for Cardiovascular Diseases (MONICA) and Västerbotten Intervention Programme databases), low hip BMD was associated with higher risk of myocardial infarction (Wiklund et al., 2012). In men, this association remained significant after adjustment for confounders including cardiovascular risk factors. In the Framingham cohort, lower cortical mass of the second metacarpal was associated with a higher incidence of coronary heart disease in postmenopausal women but not in older men (Samelson et al., 2004). In the Health ABC (Health, Aging, and Body Composition) cohort, incident CVD was defined as the onset of coronary heart disease, cerebrovascular disease, PAD or carotid artery disease (Farhat et al., 2007). In this cohort, low hip BMD was associated with higher incidence of the above CVD in black, but not white, women. Contrastingly, low lumbar spine volumetric BMD was associated with higher CVD incidence in white, but not black, men. However, the higher incidence of other CVD events among population with osteoporosis or low BMD was not incorporated in the model for this thesis due to the various – hence, not comparable – modes of measurements by which correlations were shown, and the risk of double counting with the correlation between the prevalent CVD and the risk of fracture applied in the model.

8.3.3. Non-disease death in osteoporosis-linked model

In any linked models where osteoporosis was included, time to non-disease death was sampled as described in Chapters 4 and 7: the age- and sex-specific time-to-death distributions were further adjusted based on the Z-score of the individual. When the model includes both osteoporosis and heart disease, the mortality from cardiac causes were subtracted from the rates used to establish the time to non-disease death distributions in the osteoporosis-linked model (see Table 7.18' in Appendix 7.1 and Chapter 5, Section 'Non-disease mortality' section).

When osteoporosis is included in the model, multiple sets of non-disease death rates were established for ranges of Z-score (Table 7.18 in Chapter 7). In the model where HD and osteoporosis are linked, cardiac death rates were subtracted from these non-disease mortality rates based on Z-score (Table 7.18' in Appendix 7.1).

8.4. Correlation between Alzheimer's disease and Osteoporosis

8.4.1 Prevalent osteoporosis and the risk of Alzheimer's disease

A number of studies have demonstrated correlations between low BMD and the risk of AD (Chang et al., 2014b, Duthie et al., 2011, Tan et al., 2005). Tan et al. (Tan et al., 2005) examined whether low BMD in elderly individuals is associated with an increased incidence of AD. The relative risks for the relationship between age and sex-specific quartiles of BMD and the incidence of AD were reported for women and men adjusted for age, sex and other covariates such as smoking status, education, and apolipoprotein E ε4 status. The values for the lowest BMD quartile and the remaining quartiles of BMD measured at femoral neck adjusted for all covariates were used in the model in this thesis. The 'relative risks' reported in Tan et al. (2005) were considered to be hazard ratios given that Cox proportional hazard models were used within their statistical analyses and the paper discussed incidences of AD. The hazard ratios used were 2.04 (95% CI 1.11-3.75) for women and 1.33 (95% CI 0.46-3.86) for men. Although the value for men was not statistically significant, the central value was still used in the model. As all modelled individuals are assigned a Z-score which is an age and sex specific T-score, the lowest quartile of BMD was the 25th percentile of standard normal, that is, -0.67. Those whose Z-score is below -0.67 were assigned a higher incidence of AD than the remaining people.

The incidence rates split by BMD level were calculated using the same method as in Section 8.2 and are shown in Table 8.12.

Table 8.12. Splitting incidence of Alzheimer's disease into two groups: people with low BMD vs. people without low BMD

	Total incidence of AD		Baseline rate without low BMD (Quartiles 2-4)		Rate for patients with low BMD (Quartile 1)	
Age	Men	Women	Men	Women	Men	Women
<65	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000
65-69	0.004968	0.004536	0.004589	0.003600	0.006104	0.007344
70-74	0.010440	0.004392	0.009644	0.003486	0.012827	0.007111
75-79	0.010224	0.010656	0.009445	0.008457	0.012562	0.017253
80-84	0.012240	0.022464	0.011307	0.017829	0.015039	0.036370
85+	0.042048	0.051624	0.038843	0.040971	0.051662	0.083582

Incidence of Alzheimer's disease based on the prevalence of heart disease and osteoporosis

In order to fully account for correlations between the three diseases, the values in Table 8.12 were further divided between people with prevalent HD and with no prevalent HD using the incidence rates reported in Table 8.8 in Section 8.2.2 (incidence of AD split between people with HD and without HD). These can be compared with the total incidence of AD shown in Table 8.12 which was used in the individual AD model.

Table 8.13. Incidence of AD into four groups (with or without HD & with or without low BMD)

	Without heart disease				With heart disease			
	Incidence without low BMD (Quartiles 2-4)		Incidence with low BMD (Quartile 1)		Incidence without low BMD (Quartiles 2-4)		Incidence with low BMD (Quartile 1)	
Age	Men	Women	Men	Women	Men	Women	Men	Women
<65	0	0	0	0	0	0	0	0
65-69	0.00416	0.00344	0.00554	0.00701	0.00541	0.00447	0.00720	0.00911
70-74	0.00869	0.00330	0.01156	0.00672	0.01130	0.00428	0.01503	0.00874
75-79	0.00824	0.00761	0.01096	0.01553	0.01071	0.00989	0.01425	0.02018
80-84	0.00987	0.01603	0.01313	0.03270	0.01283	0.02084	0.01706	0.04252
85+	0.03425	0.03696	0.04555	0.07539	0.04452	0.04805	0.05922	0.09801

In the other direction, AD patients were more prone to osteoporosis and osteoporotic fractures. Weller and Schatzker (2004) found that osteoporosis was more prevalent among

nursing home residents with AD as opposed to those without AD. However, this was not incorporated in the model.

8.4.2. Costs, utilities and non-disease mortality

As in previous sections, costs were additive and utilities were multiplicative. Non-disease mortality rates were adjusted for Z-score.

8.5. Results from two-disease linked models

8.5.1. Single-disease results from the independently linked model

For the validation of the linked model results, results from the individual disease models were compared with those from the independently linked model where diseases outside of the comparison were assumed to have zero incidence.

All results in this section were obtained from the models for general UK population aged 45 years and older, and simulated individuals were assumed to receive default treatments (statin for HD; donepezil for mild-to-moderately severe AD and memantine for severe AD; and alendronate for osteoporosis) upon the onset of each disease. The same non-disease death distributions as those used in the individual disease model were applied in the linked model for this comparison. The HD and AD were linked first with osteoporosis subsequently added to the two-disease linked model, and thus results related to osteoporosis were obtained from a three-disease linked model.

Table 8.14 compares per-person results from each of the individual disease models with those from the independently linked models in which only the relevant diseases were considered.

For all diseases, the results from the independently linked model were similar to those from individual disease models with differences of less than 1% in most reported outcomes. These showed that the creation of linked models did not alter the results significantly, which indicated that this did not introduce coding errors.

Table 8.14. Comparison between independently linked models and individual disease models (% in brackets represents percentage differences from the individual disease model results)

1. Heart disease (HD) only (n=200,000)						
	Individual heart disease only model		HD-AD linked model where only HD was considered		Three disease linked model where only HD was considered	
	Discounted	Undiscounted	Discounted	Undiscounted	Discounted	Undiscounted
Cost	£ 8,091	£ 14,224	£ 8,123 (+0.39%)	£ 14,281 (+0.40%)	£ 8,108 (-0.21%)	£ 14,227 (-0.02%)
QALYs	9.249	13.843	9.218 (-0.33%)	13.791 (-0.37%)	9.241 (-0.09%)	13.833 (-0.07%)
Life years lived		21.319		21.256 (-0.30%)		21.313 (-0.03%)

2. Alzheimer's disease (AD) only (n=200,000)						
	Individual AD only model		HD-AD linked model where only AD was considered		Three disease linked model where only AD was considered	
	Discounted	Undiscounted	Discounted	Undiscounted	Discounted	Undiscounted
Cost	£ 4,582	£ 8,845	£ 4,599 (+0.38%)	£ 8,889 (+0.49%)	£ 4,586 (+0.09%)	£ 8,888 (+0.48%)
QALYs	10.642	16.548	10.650 (+0.07%)	16.548 (0.00%)	10.648 (+0.05%)	16.553 (+0.03%)
Life years lived		21.653		21.650 (-0.01%)		21.662 (+0.04%)

3. Osteoporosis only (n=400,000)						
	Individual osteoporosis only model		HD-AD linked model where only osteoporosis was considered		Three disease linked model where only osteoporosis was considered	
	Discounted	Undiscounted	Discounted	Undiscounted	Discounted	Undiscounted
Cost	£ 2,847	£ 6,151	NA	NA	£ 2,811 (-1.28%)	£ 6,075 (-1.23%)
QALYs	11.191	17.759	NA	NA	11.195 (+0.03%)	17.770 (+0.06%)
Life years lived		23.530		NA		23.541 (+0.05%)

8.5.2. Two-disease model results with and without correlations

This section reports lifetime per-capita results from the linked models in which only pairs of diseases were considered in order to see the results of incorporating the correlations described in this chapter. The three-disease linked model results will follow in Chapter 9 to fully examine the effect of model linkage and correlations in the larger model. For any pair of diseases which included osteoporosis, results were obtained from the three-disease linked model with the irrelevant disease not considered.

Table 8.15 shows costs and QALYs results for three pairs of diseases from the linked models with and without correlations with percentage changes compared with the results from the independently linked model. Across all pairwise results, 500,000 individuals aged 45 years and older were simulated.

Incorporating correlations between diseases did not alter results for the general population to a great degree in this model with the difference in costs and QALYs below 4% and 2%, respectively, compared with assuming independence between diseases. When only HD and AD are considered, the costs obtained from the independently linked model were smaller than the sum of costs from individual disease models, whilst QALYs and the average number of years lived were lower than the minimum of the individual disease model results (Table 8.16 (1)). In the model with correlations, the costs were lower compared with the results from the independently linked model when HD-AD and AD-osteoporosis pairs were considered, whilst the HD-osteoporosis only model produced slightly higher costs.

Table 8.15. Base-case results from the linked model where only two diseases were activated (n=500,000)

	Independently linked model		Correlated linked model	
	Discounted	Undiscounted	Discounted	Undiscounted
1. When Heart disease and Alzheimer's disease are considered				
Cost	£ 11,935 (£ 11,904)*	£ 21,229 (£ 21,185)*	£ 11,802 (-1.11%) (£11,909; +0.04%)*	£ 20,869 (-1.70%) (£21,067; -0.55%)*
QALYs	8.918 (8.910)*	13.144 (13.135)*	8.918 (0.00%) (8.914; +0.04%)*	13.154 (+0.07%) (13.141; +0.05%)*
Life years lived		20.301 (20.281)*		20.302 (+0.01%) (20.279; -0.01%)*
2. With Heart disease and Osteoporosis are considered				
Cost	£ 11,311	£ 21,080	£ 11,372 (+0.54%)	£ 21,235 (+0.74%)
QALYs	9.300	13.963	9.291 (-0.10%)	13.946 (-0.12%)
Life years lived		22.009		21.987 (-0.10%)
3. When Alzheimer's disease and osteoporosis are considered				
Cost	£ 7,183	£ 14,328	£ 6,989 (-2.71%)	£13,755 (-4.00%)
QALYs	10.751	16.741	10.755 (+0.04%)	16.767 (+0.15%)
Life years lived		22.341		22.359 (+0.08%)

%percentage in the brackets show the percentage difference compared with the independently linked model results.

*Numbers in brackets: results from the two-disease HD-AD linked model. Otherwise, results are from the three-disease linked models where only two of the diseases were activated.

Table 8.16. Summary of base-case results from individual disease models described in Chapters 5-7

	Sum of costs from individual disease models			
	(1) HD only and AD only models*	(2) HD only and osteoporosis only models*	(3) AD only and osteoporosis only models*	(4) Three individual disease models (HD, AD, and osteoporosis)
Cost - Discounted	£ 12,673	£ 10,938	£ 7,429	£ 15,520
Cost	£ 23,069	£ 20,374	£ 14,996	£ 29,220
	Minimum of QALYs/LYs from individual disease models			
QALYs - Discounted	9.249	9.249	10.642	9.249
QALYs	13.843	13.843	16.548	13.843
Life years lived	21.319	21.319	21.653	21.319

*Results from treatment arm; HD=heart disease, AD=Alzheimer's disease

The effect of correlations in models where patients were assumed to already have the diseases at model initiation was also explored. At model entry, individuals were assumed to have one of: a T-score of -2.5; Alzheimer's disease; or receiving statins for the secondary prevention of heart disease events. Results for those who already have a relevant disease are shown in Table 8.17. For comparison with the base-case results, the base-case population aged 45 years and over was simulated with one of the above disease status added as patient characteristics at model entry.

For patients assumed to be receiving statins for secondary prevention of heart disease events, the previous event history was assigned in the same manner as the secondary prevention population in Chapter 5. All individuals had only one previous heart disease event on a pro rata basis according to the ratio of prevalence of each event at the patient's age.

Compared with the base-case, the differences between the results from the independently linked model and the correlated linked model were generally larger when 100% prevalence was assumed for one of the diseases at model initiation. Costs were higher in the correlated linked model than in the independently linked model, when individuals enter the model with HD or osteoporosis.

Table 8.17. Two-disease model results for those *already with the diseases* at model initiation (n=500,000)

	Independently linked model		Correlated linked model*	
	Discounted	Undiscounted	Discounted	Undiscounted
1. Heart disease and Alzheimer's disease				
1-1) When all individuals have heart disease at model entry				
Cost	£ 20,388	£ 33,845	£ 21,111 (+3.54%)	£ 34,857 (+2.99%)
QALYs	7.768	11.451	7.697 (-0.90%)	11.326 (-1.10%)
Life years lived		20.109		19.905 (-1.01%)
1-2) When all individuals have Alzheimer's disease at model entry				
Cost	£ 95,015	£ 128,511	£ 94,886 (-0.14%)	£ 128,282 (-0.18%)
QALYs	2.545	3.106	2.545 (-0.03%)	3.105 (-0.04%)
Life years lived		7.687		7.683 (-0.06%)
2. Heart disease and Osteoporosis				
2-1) When all individuals have heart disease at model entry				
Cost	£ 20,178	£ 34,624	£ 20,183 (+0.02%)	£ 34,631 (+0.02%)
QALYs	8.119	12.204	8.102 (-0.21%)	12.168 (-0.29%)
Life years lived		21.843		21.783 (-0.28%)
2-2) When all individuals have osteoporosis at model entry				
Cost	£ 17,286	£ 35,390	£ 17,580 (+1.70%)	£ 36,001 (+1.73%)
QALYs	8.926	13.204	8.922 (-0.05%)	13.180 (-0.18%)
Life years lived		21.842		21.801 (-0.18%)
3. Alzheimer's disease and osteoporosis				
3-1) When all individuals have Alzheimer's disease at model entry				
Cost	£ 96,568	£ 132,279	£ 96,586 (+0.02%)	£ 132,286 (+0.01%)
QALYs	2.841	3.542	2.838 (-0.10%)	3.538 (-0.12%)
Life years lived		8.028		8.019 (-0.12%)
3-2) When all individuals have osteoporosis at model entry				
Cost	£ 12,502	£ 26,624	£ 13,067 (+4.53%)	£ 27,405 (+2.93%)
QALYs	10.310	15.747	10.206 (-1.01%)	15.508 (-1.52%)
Life years lived		22.161		21.844 (-1.43%)

Table 8.18 presents the projected annual costs of treating only two of the diseases considered in the model. The changes in the annual costs from incorporating correlations are given in Figure 8.3. Negative values meant the annual costs projected from the correlated linked model being lower than those from the independently linked model.

Table 8.18. Annual costs projected from the models where pairs of diseases were considered (£, millions)

	HD-AD only model		HD-osteoporosis only model		AD-osteoporosis only model	
Year	Model with independent diseases	Model with correlated diseases	Model with independent diseases	Model with correlated diseases	Model with independent diseases	Model with correlated diseases
2012	£14,136	£ 14,367	£11,218	£11,234	£6,417	£6,301
2013	£14,298	£ 14,313	£12,050	£12,132	£6,372	£6,229
2014	£15,045	£ 15,005	£12,773	£12,840	£6,661	£6,657
2015	£15,779	£ 15,616	£13,517	£13,514	£7,045	£7,108
2016	£16,356	£ 16,131	£14,180	£14,125	£7,420	£7,505
2017	£16,867	£ 16,813	£14,962	£14,961	£7,750	£7,836
2018	£17,385	£ 17,372	£15,681	£15,626	£7,911	£8,005
2019	£17,853	£ 17,717	£16,326	£16,283	£8,154	£8,254
2020	£18,296	£ 18,264	£16,806	£16,807	£8,427	£8,475
2021	£18,622	£ 18,807	£17,528	£17,420	£8,445	£8,631
2022	£18,821	£ 19,160	£18,170	£17,984	£8,677	£8,854
2023	£19,394	£ 19,542	£18,629	£18,471	£8,851	£8,869
2024	£19,953	£ 19,763	£19,081	£19,081	£8,985	£8,990
2025	£20,182	£ 20,054	£19,577	£19,624	£9,095	£9,071
2026	£20,473	£ 20,359	£19,960	£20,003	£9,291	£9,192
2027	£20,770	£ 20,512	£20,488	£20,453	£9,564	£9,424
2028	£21,072	£ 20,837	£20,803	£20,905	£9,659	£9,530
2029	£21,397	£ 21,019	£21,172	£21,254	£9,854	£9,714
2030	£21,627	£ 21,393	£21,566	£21,647	£10,214	£9,915
2031	£22,110	£ 21,743	£21,908	£22,051	£10,337	£9,960
2032	£22,352	£ 21,961	£22,379	£22,396	£10,383	£10,050
2033	£22,607	£ 22,167	£22,638	£22,751	£10,615	£10,162
2034	£22,899	£ 22,593	£22,850	£23,153	£11,098	£10,378
2035	£23,110	£ 22,891	£23,143	£23,427	£11,355	£10,579
2036	£23,360	£ 23,083	£23,456	£23,721	£11,390	£10,751
2037	£23,524	£ 23,322	£23,763	£23,996	£11,454	£10,931

The differences in annual costs were projected to widen over time with the costs from the correlated disease model results being lower. This may be due to the correlations associated with AD making individuals with AD more likely to develop the other diseases that increase mortality, and hence decreasing the number of people who get the costly institutional care in later stages of life.

Without such cost savings due to the correlation between AD and the other diseases, the model where only HD and osteoporosis were considered produced higher projected annual costs in later years with correlations incorporated than when using the results from the independently linked model. Also, as the presence of HD increases the incidence of fracture and vice versa, correlations between HD and osteoporosis would only increase the number of people with both HD and osteoporosis over time among those who survived the diseases in earlier years, which causes higher costs in later years.

Figure 8.3. Difference in projected annual costs after incorporating correlations in the model (Negative values mean the costs from the correlated linked model are lower than those from the independently linked model)

1) Heart disease and Alzheimer's disease only

2) Heart disease and osteoporosis only

3) Alzheimer's disease and osteoporosis only
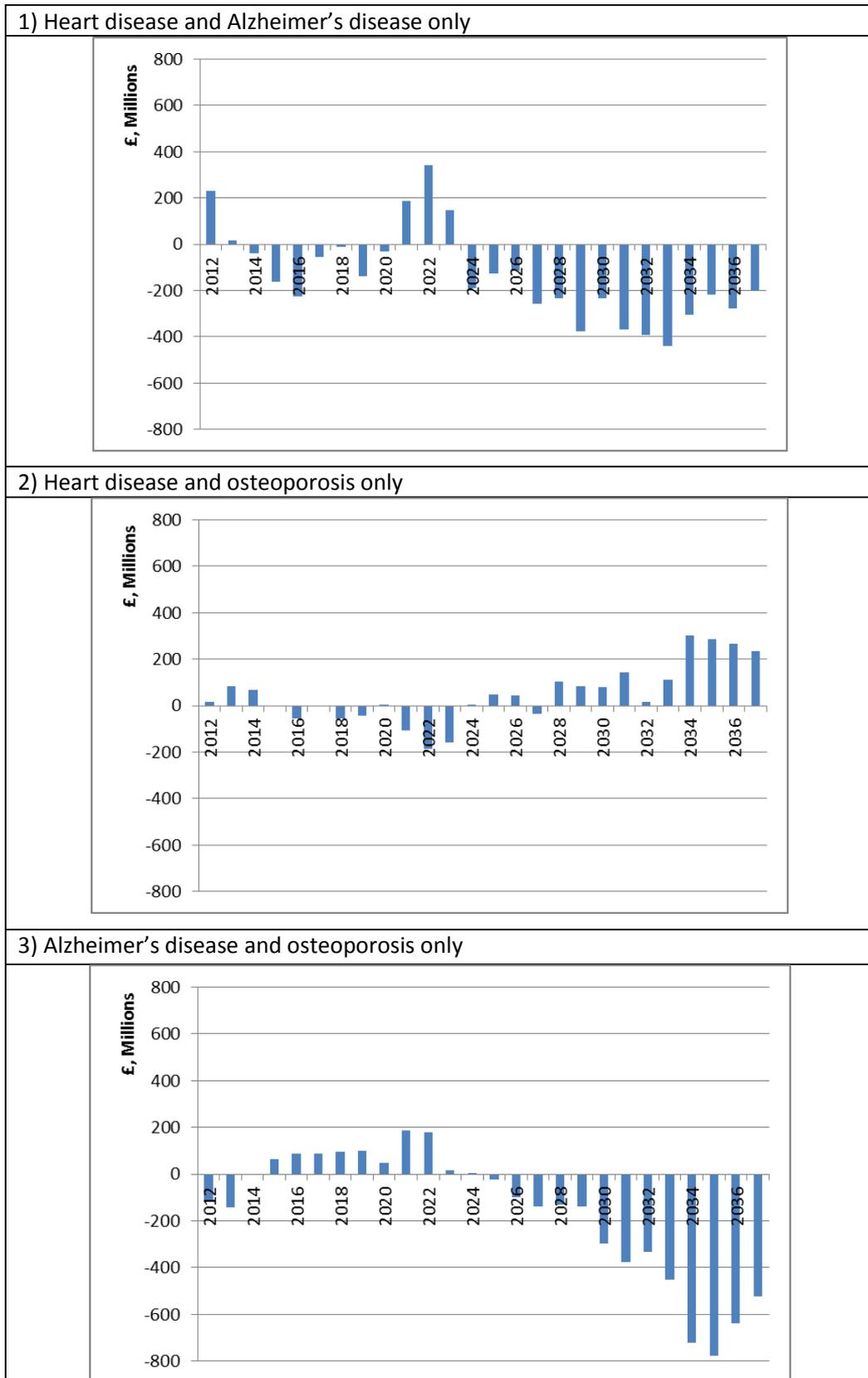
8.6. Discussion

The linked models where one disease was considered at a time showed similar results to those from individual disease models, indicating that the model linkage does not introduce significant inaccuracy compared with the single-disease model. Incorporating correlations between diseases into the linked model produced different costs and QALY results from those from the independently linked model, although the differences were small. The differences when running the model for people already with any of the diseases were larger.

It is noted that only some of the possible correlations between the included diseases were incorporated in the model as a proof-of-concept. Correlations were not incorporated for both directions of influence; for instance, the linked model reflects that individuals with low BMD have higher incidence of AD, but does not consider that prevalent or incident AD can accelerate the deterioration of BMD. Researchers wishing to explore further the impact of implementing correlations in the linked model may incorporate more correlations as exemplified in this chapter.

Chapter 9 will report results in more detail from the all-disease linked model including the cost-effectiveness of each intervention.

CHAPTER 9   RESULTS FROM THE ALL-DISEASE LINKED MODEL & SCENARIO ANALYSES

9.1. Base case results from the three disease linked model

This chapter presents the simulation results from the models where all the three diseases were linked. In the 'linked' model, an individual can experience events from any of the three diseases (HD, AD, and osteoporosis) within a single model (Chapter 4). There were two versions of the linked model: the model where the diseases were linked with correlations ('correlated linked model') and the model where the diseases were linked but assumed to be independent ('independently linked model'). The correlated linked model assigns disease history and event probabilities based on the status of the other diseases included in the model and patient characteristics such as age and sex (Chapter 8). The independently linked model does so, based only upon patient characteristics that are not necessarily related to the other diseases.

A set of scenario analyses to answer the main questions shown in Box 4.1 in Chapter 4 are also presented. All comparisons of results made in this chapter focussed more on costs rather than QALYs, with the projected annual costs taken as one of the main outcomes.

9.1.1. First-order uncertainty analyses

The first-order uncertainty associated with random variability around the mean incremental cost and QALYs, incremental net monetary benefit (NMB) and cost per QALY gained (CPQ) was examined using the results from the correlated linked model for the population aged 45 years and older. Incremental values were computed in comparison with no treatments for all three of the diseases. The standard errors of the mean results were estimated having varied the numbers of simulated individuals from 1,000 to 700,000. The jackknife 95% confidence interval for the mean CPQ and the NMB results with more than 400,000 simulated individuals were derived using R programming language (R version 3.2.1, © The R Foundation) due to limited capacity of the spreadsheet software. Jackknifing execution time for the data from

700,000 simulated individuals was 4.69 hours on an Intel ® Core ™ i5 CPU 2.30 GHz processor with 4.00 GB of RAM (3.54 hours for 600,000 data points).

As shown in Figure 9.1, incremental cost and QALYs stabilised when more than 200,000 individuals were simulated. The standard errors of the mean NMB and CPQ started to stabilise after running more than 500,000 simulated individuals. The chosen number of individuals to simulate was 700,000 for the base-case all-disease linked models (with and without correlations) in order to further reduce the variability of the results.

Figure 9.1. First order uncertainty in relation to the number of patients simulated in the all-disease linked model with correlations (base-year population aged 45 years and over)

1) Incremental cost (compared with none of the three treatments)	
Undiscounted	Discounted

2) Incremental QALYs (compared with none of the treatments for the three diseases)	
Undiscounted	Discounted

3) Cost per QALYs (95% jackknife confidence interval)	
Undiscounted	Discounted
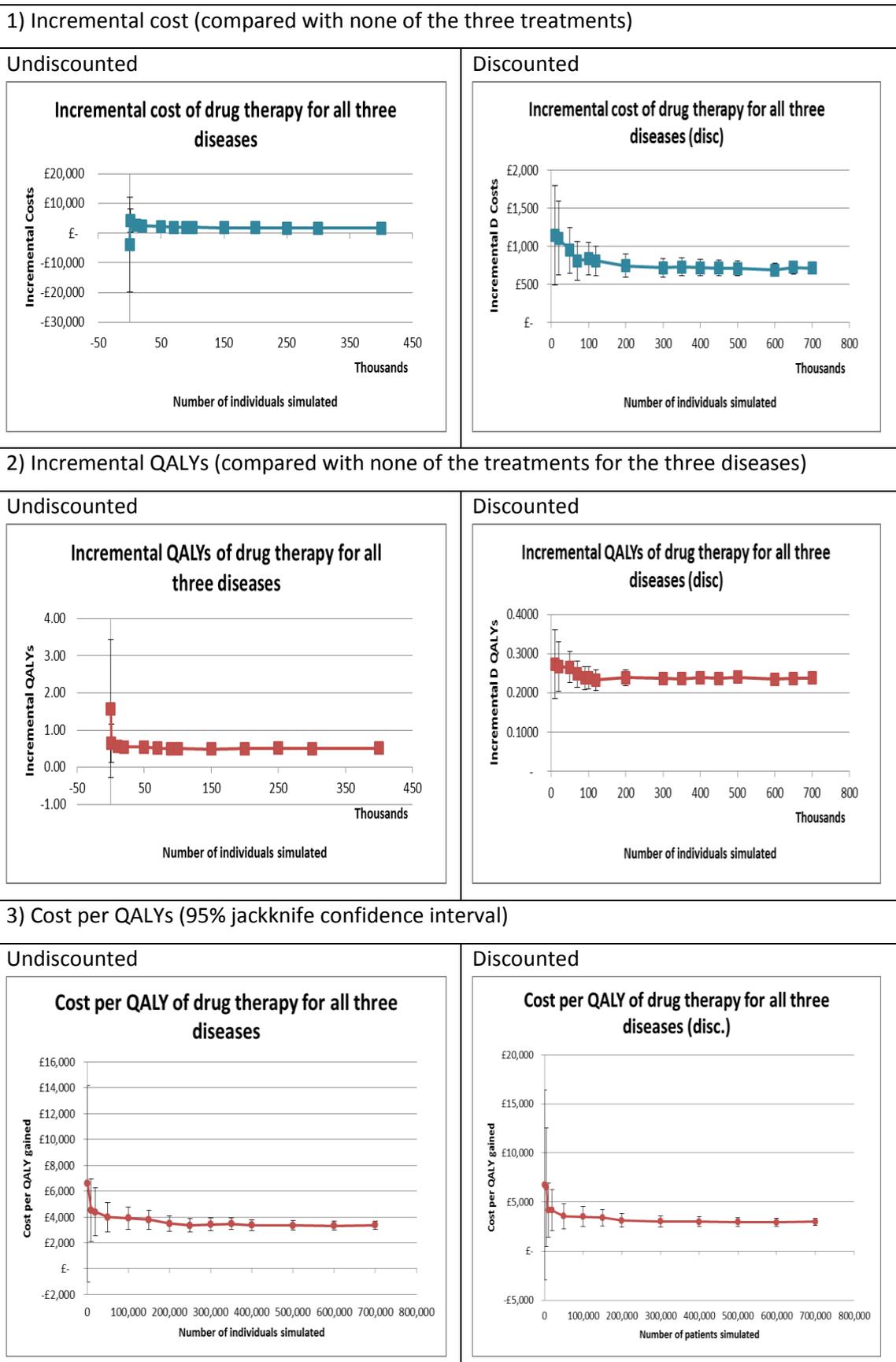
4) Net monetary benefit (£20,000 threshold)	
Undiscounted	Discounted
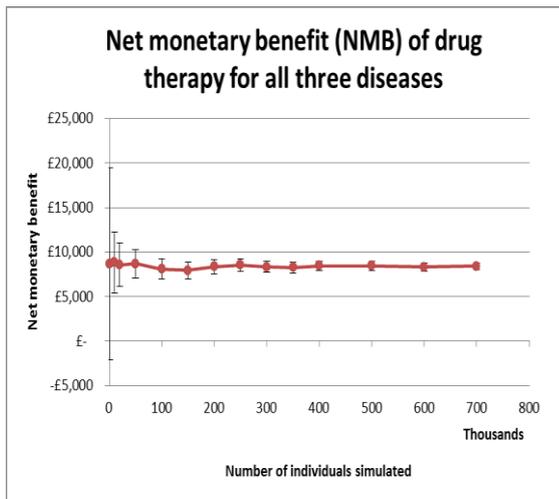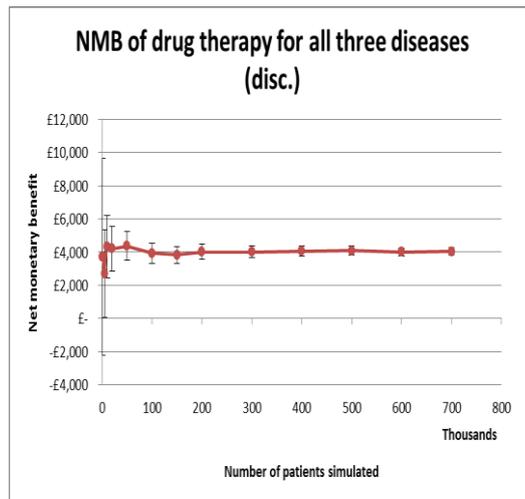
In the next sections, the base-case results from models with independent and correlated diseases will be compared in order to see the effect of incorporating correlations in the all-disease linked model. Also, the results from the independently linked model will be compared to examine the effect of multi-disease linkage on the per-capita cost, QALYs, life years and projected annual costs.

9.1.2. Base-case results from the linked model where diseases were assumed independent – Effect of linking the individual disease models

The base-case results from the independently linked model are given in Table 9.1. For the treatment arm results, the default treatments described in Chapters 5 - 7 were assumed to be used. For comparison, the results from the three individual disease models used to calculate the sum of the incremental cost and QALYs across the three disease models in Table 9.1 (see in Chapters 5 - 7) are presented in Table 9.2. Comparison of the results from the linked model with the sum of the results from the three individual disease models would indicate the effect of the model linkage on model outcomes. It is noted that the individual disease model results came from runs with different sized patient groups (700,000 for three disease model, 200,000 for HD; 200,000 for AD, and 400,000 for osteoporosis). However, this was not expected to influence the results which are reported per person.

The cost per QALY of the combined treatments for heart disease (HD), Alzheimer's disease (AD) and osteoporosis was £3,582 (£3,854 when undiscounted). The absolute costs from the independently linked model (Table 9.1) were slightly lower than the sum of the absolute costs from the three individual disease models (Table 9.2 – the sum of three treatment arm results being £15,520 when discounted and £29,220 when undiscounted; and the sum of no treatment results £15,112 when discounted and £28,389 when undiscounted). The absolute QALYs (Table 9.1 – 8.956 when discounted and 13.233 undiscounted) were lower than the minimum of the equivalent values from the three individual disease models, which were 9.249 (discounted) and 13.843 (undiscounted) from the HD only model (Table 9.2), as the population in the model including multiple diseases are sicker on average than those in single disease models.

The ICER of the combined treatments for the three diseases calculated as the sum of incremental costs divided by the sum of incremental QALYs in Table 9.2 (£1,458/QALY) was lower than the ICER estimated using the linked model results in Table 9.1 (£3,582/QALY) due to the higher incremental cost (£840) and lower incremental QALYs (0.234) from the linked model compared with the sum of the three individual disease model results (£408, 0.280). This shows that the estimates of the cost effectiveness of combined interventions derived from individual disease models can be substantially different from estimates derived from a model where multiple diseases are linked. This may be significant from a policy perspective as it can influence the ultimate adoption decisions relating to treatments.

Table 9.1. Per-capita results from the independently linked model based on n=700,000

	All disease linked model results			Individual disease models
	With all treatments*	None of the three treatments	Incremental values	Sum of incremental values across three individual models†
Cost - Discounted	£ 14,776	£ 13,936	£ 840	£ 408
QALYs - Discounted	8.956	8.722	0.234	0.280
Cost	£ 27,093	£ 25,179	£ 1,914	£ 831
QALYs	13.233	12.736	0.497	0.597
Life years lived	20.867	19.947	0.919	1.007
ICER – Discounted (£/QALY)			£ 3,582	£ 1,458
ICER (£/QALY)			£ 3,854	£ 1,391

*All the default treatments described in Chapter 5 - 7 were assumed to be available;

†See Table 9.2 for calculation.

Table 9.2. Summary of the results from the individual disease models from Chapters 5, 6, and 7 for comparison

	1) Heart disease only model			2) Alzheimer's disease only model			3) Osteoporosis only model			4) Sum of incremental values across 1)-3)
	Treatment	No treatment	Incremental values (A)	Treatment	No treatment	Incremental values (B)	Treatment	No treatment	Incremental values (C)	(A)+(B)+(C)
Cost - Discounted	£ 8,091	£ 7,569	£ 522	£4,582	£4,596	-£ 14	£ 2,847	£ 2,947	-£ 100	£ 408
QALYs - Discounted	9.249	8.978	0.271	10.642	10.641	0.001	11.191	11.184	0.008	0.280
Cost	£ 14,224	£ 13,197	£ 1,027	£8,845	£8,869	-£ 23	£ 6,151	£ 6,324	-£ 173	£ 831
QALYs	13.843	13.257	0.586	16.548	16.545	0.003	17.759	17.751	0.009	0.597
Life years lived	21.319	20.319	1.000	21.653	21.650	0.003	23.530	23.525	0.004	1.007
ICER – Discounted			£ 1,926 /QALY			Dominating			Dominating	£ 1,458 /QALY
ICER			£ 1,754 / QALY			Dominating			Dominating	£ 1,391 / QALY

HD: based on n=200,000; AD n=200,000; Osteoporosis n=400,000

As part of the base-case results from the independently linked model, the male and female cohorts of 45-year-olds that enter the population every year were simulated to incur £ 31,141 and £37,640, respectively, over their lifetime with 21.772 and 22.593 QALYs gained (Table 9.3). The equivalent figures when discounted were £13,057 and £14,308 and 13.335 and 13.557 QALYs. As in the other model results, the female population was estimated to incur a higher cost with longer life years. These figures were used to project future population-level costs of treating the three included diseases.

Table 9.3. Per-capita results from the linked model where diseases were assumed to be independent for the incoming cohorts of 45 year olds

	Male	Female
Cost – Discounted	£ 13,057	£ 14,308
QALYs - Discounted	13.335	13.557
Cost	£ 31,141	£ 37,640
QALYs	21.772	22.593
LY	32.660	35.079

Based on n=700,000 simulated individuals; All default treatments were assumed available.

Figure 9.2 shows graphically the cohort annual costs per person of the population aged 45 years and older in the base year and the new incoming cohorts of males and females aged 45 years in their entry year, and the total annual costs projected using the per-capita costs and the ONS population projection data (Office for National Statistics, 2013c). Per-capita cohort costs for 45-year-old males peaked earlier than those for females. The total annual costs were projected to increase from £15.90 billion in 2012 to £28.57 billion in 2037. Per-capita annual costs of the future incoming cohorts of male and female populations aged 45 years at model initiation (Figure 9.2a) did not change smoothly over time due to the stepped increase in cardiac death rates that were subtracted from the all-cause mortality in order to calculate non-disease death rates (see Chapter 5 Section 5.4.1). This was more prominent for female cohort due to their lower rates of disease-related mortality in HD and thus, a higher probability of the time to non-disease death (sampled from the distributions based on these stepped non-disease death rates) becoming their total life years.

Table 9.4 compares the projected annual cost results from the independently linked model with the sum of the three individual disease model results. The annual costs from the independently linked model were lower than the summed results with the cumulative difference estimated to amount to £16 billion (£7.8 billion when using discounted costs) over the period 2012-2037. This shows that the use of multi-disease models may have significant policy implications, impacting funding decisions about potential treatment interventions or influencing policy decisions about the prevention and treatment of relevant diseases. The difference in projected annual costs was estimated to be generally larger into the future years, whilst in earlier years of the projection horizon the differences showed irregular changes (Figure 9.3). Linked models do not double-count items such as the cost of institutionalisation. Hence, as individuals in the linked disease model age and more of them reach the age of 65 where AD prevalence becomes positive, those in the linked model can save more in later years on such costs overlapping between the three diseases. In earlier years, there is less potential for such savings, but more uncertainty due to different rates of cost accrual each year in the three individual disease models which result in an uneven increase in the sum of costs over time. Also, smaller differences are subject to more uncertainty in terms of the direction of savings as per-capita costs were scaled up to the population level.

Figure 9.2. Total population-level annual cost projections from the independently linked model

a) Per capita annual costs – total annual costs divided by the number of people at model initiation

Base year population

Age 45 only - Male

Age 45 only - Female
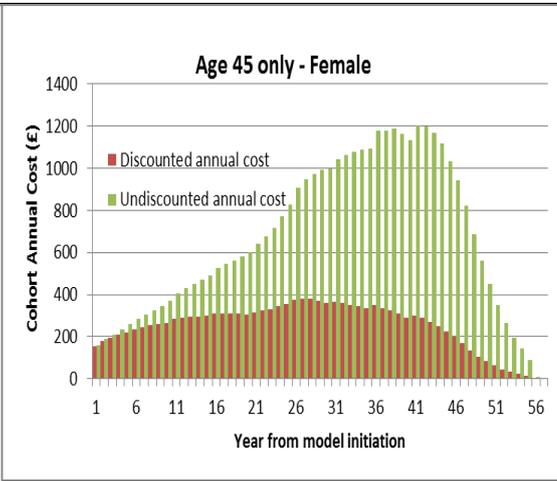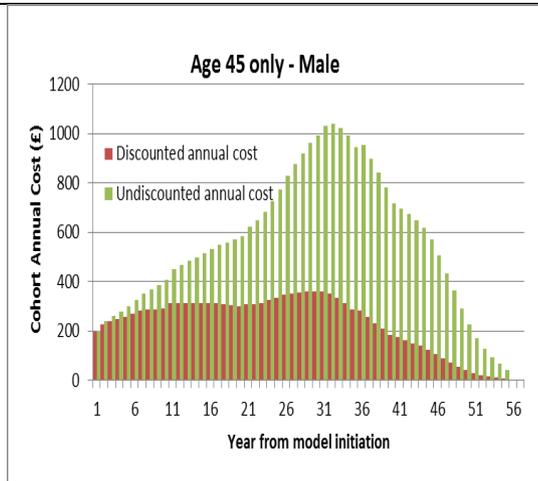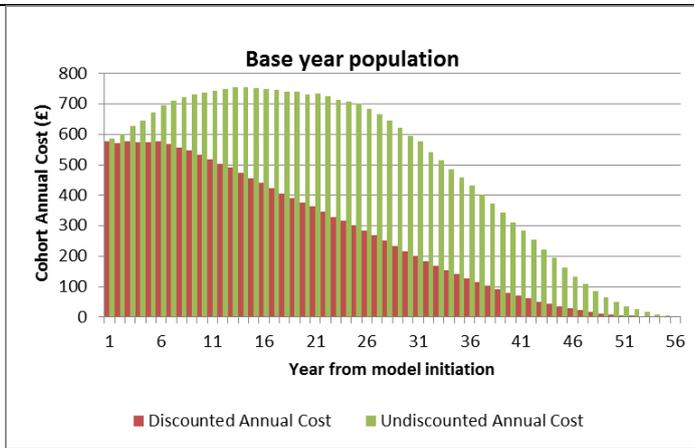
b) Total population level costs projected to the year 2037

Total annual cost projection - All diseases (independent diseases)
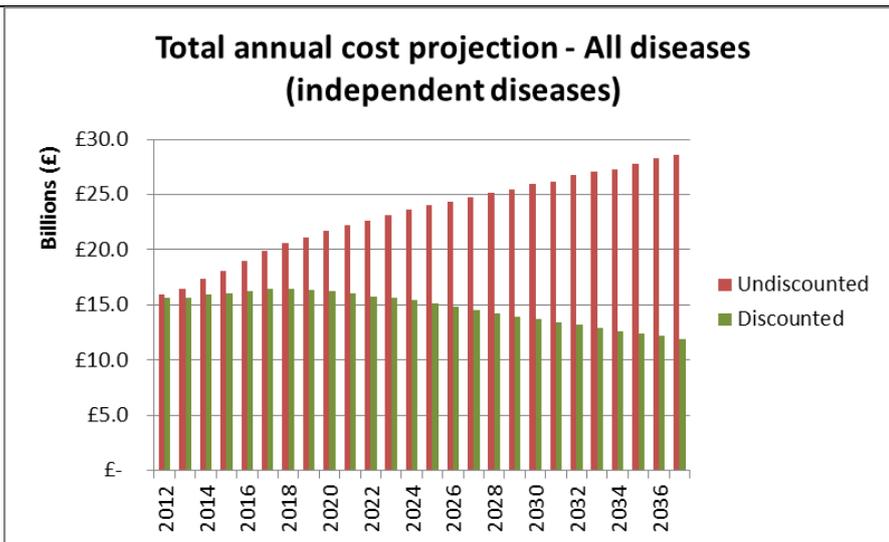
Table 9.4. Projected annual costs from the linked model where diseases were assumed independent in comparison with the sum of the individual disease model results

Year	Undiscounted costs			Discounted costs		
	Annual costs (£, millions) (1)	Sum of annual costs from three individual disease models (£, millions) (2)	Difference (£, millions) (1)-(2)	Annual costs (£, millions) (1)'	Sum of annual costs from three individual disease models (£, millions) (2)'	Difference (£, millions) (1)'-(2)'
2012	£ 15,905	£ 15,840	£ 65	£ 15,637	£ 15,574	£ 63
2013	£ 16,481	£ 16,323	£ 158	£ 15,652	£ 15,502	£ 150
2014	£ 17,365	£ 17,260	£ 104	£ 15,933	£ 15,837	£ 96
2015	£ 18,085	£ 18,147	- £ 62	£ 16,032	£ 16,088	-£ 56
2016	£ 18,973	£ 19,014	-£ 41	£ 16,250	£ 16,287	-£ 37
2017	£ 19,904	£ 19,583	£ 321	£ 16,472	£ 16,207	£ 265
2018	£ 20,616	£ 20,431	£ 186	£ 16,486	£ 16,336	£ 149
2019	£ 21,160	£ 20,968	£ 192	£ 16,348	£ 16,199	£ 149
2020	£ 21,746	£ 21,577	£ 170	£ 16,233	£ 16,106	£ 127
2021	£ 22,187	£ 22,224	-£ 37	£ 16,002	£ 16,028	-£ 26
2022	£ 22,619	£ 22,828	-£ 209	£ 15,762	£ 15,907	-£ 146
2023	£ 23,168	£ 23,453	-£ 285	£ 15,598	£ 15,791	-£ 192
2024	£ 23,689	£ 24,113	-£ 424	£ 15,410	£ 15,686	-£ 275
2025	£ 24,076	£ 24,763	-£ 687	£ 15,132	£ 15,564	-£ 431
2026	£ 24,398	£ 24,990	-£ 592	£ 14,816	£ 15,176	-£ 359
2027	£ 24,790	£ 25,743	-£ 953	£ 14,544	£ 15,104	-£ 559
2028	£ 25,168	£ 26,350	-£ 1,181	£ 14,268	£ 14,937	-£ 669
2029	£ 25,489	£ 26,732	-£ 1,243	£ 13,961	£ 14,642	-£ 682
2030	£ 25,933	£ 27,112	-£ 1,179	£ 13,724	£ 14,348	-£ 624
2031	£ 26,218	£ 27,645	-£ 1,427	£ 13,405	£ 14,134	-£ 730
2032	£ 26,790	£ 27,902	-£ 1,111	£ 13,235	£ 13,784	-£ 549
2033	£ 27,058	£ 28,464	-£ 1,406	£ 12,915	£ 13,586	-£ 671
2034	£ 27,308	£ 29,060	-£ 1,751	£ 12,594	£ 13,402	-£ 808
2035	£ 27,804	£ 29,377	-£ 1,573	£ 12,388	£ 13,090	-£ 701
2036	£ 28,276	£ 29,714	-£ 1,439	£ 12,173	£ 12,792	-£ 619
2037	£ 28,568	£ 30,176	-£ 1,608	£ 11,883	£ 12,552	-£ 669
Total (2012-2037)	£ 603,775	£ 619,788	-£ 16,013	£ 382,854	£390,659	-£7,805

Figure 9.3. Difference [(1)-(2)] between annual costs projected from the linked model with independent diseases (1) and the sum of annual costs from three individual disease models (2)*
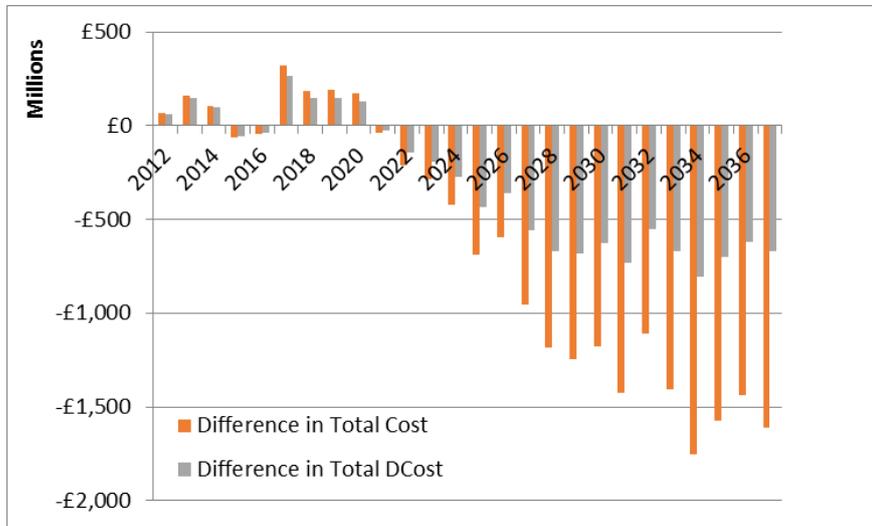
*Negative values denote lower costs from using the linked model with independent diseases.

Table 9.5 presents cost per QALY estimates of each intervention based on 700,000 simulated individuals when the other two interventions are available. The results differ from the results from the models where only one disease was considered which are reproduced in Table 9.2.

AD treatment produced lower QALYs with lower costs than no treatment whilst it was dominating no treatment in the individual AD model, although the absolute change in incremental QALYs between the two model results were very small and the results in Table 9.5 did not show face validity as it was considered implausible to have negative incremental QALYs for AD treatment. The results produced using a higher number of simulated individuals (n= 2,000,000) are shown in Table 9.6. With the 2 million individuals simulated, the AD treatment now dominated no treatment with a very small QALY gain.

Table 9.5. Cost-effectiveness of individual treatments from the all-disease linked model where diseases were assumed independent based on 700,000 simulated individuals

All disease linked model results	HD treatment		AD treatment		Osteoporosis treatment	
	No HD treatment*	Incremental values	No AD treatment*	Incremental values	No Osteo-porosis treatment*	Incremental values
Cost - Discounted	£ 13,815	£ 960	£ 14,800	-£ 24	£ 14,942	-£ 166
QALYs - Discounted	8.720	0.236	8.957	-0.001	8.954	0.002
Cost	£ 24,945	£ 2,148	£ 27,140	-£ 47	£ 27,391	-£ 298
QALYs	12.731	0.502	13.235	-0.003	13.230	0.003
Life years lived	19.939	0.928	20.870	-0.004	20.869	-0.003
ICER		**£ 4,277**		**£ 18,740†**		Dominating
ICER - Discounted		**£ 4,068**		**£ 32,549†**		

HD=heart disease; AD=Alzheimer's disease; *the other two treatments were assumed to be available; †Treatment with lower costs and lower QALYs.

Table 9.6. Cost-effectiveness of individual treatments from all-disease linked model where diseases were assumed independent based on 2,000,000 simulated individuals

	HD treatment		AD treatment		Osteoporosis treatment	
	No HD treatment*	Incremental values	No AD treatment*	Incremental values	No Osteo-porosis treatment*	Incremental values
Cost - Discounted	£ 13,798	£ 1,004	£ 14,819	-£ 18	£ 14,914	-£ 112
QALYs - Discounted	8.717	0.240	8.958	0.000	8.952	0.005
Cost	£ 24,918	£ 2,212	£ 27,168	-£ 38	£ 27,359	-£ 228
QALYs	12.727	0.508	13.235	0.000	13.227	0.008
Life years lived	19.933	0.938	20.869	0.002	20.861	0.009
ICER		£ 4,355		Dominating		Dominating
ICER - Discounted		£ 4,175				

HD=heart disease; AD=Alzheimer's disease;*the other two treatments were assumed to be available.

Further investigation of the model suggested that despite stability having been shown for the AD model in isolation, and in the linked model where all the diseases and relevant treatments were considered, this was not the case in the three-disease linked model when individual treatments were assessed. In the individual disease models, stability was defined as an adoption decision being robust. This allows the potential changes in costs and QALYs due to sampling error in a single disease model to remain considerably large in relation to other diseases, although the conclusions regarding adoption decision to be robust.

The size of incremental QALYs and costs per person from the three individual disease models presented in Chapters 5-7 are summarised in Table 9.7: it is seen that the effect of HD treatment is much larger than treatments for AD and osteoporosis. Hence, even though the results have been shown to be stable within individual disease models, the cost-effectiveness outcomes for individual treatments from the linked model where all three diseases were incorporated could be significantly altered should a change in the order of random numbers influence the simulated numbers of HD events.

Table 9.7. Incremental costs and QALYs of individual treatments from the individual disease models

	Individual heart disease model	Individual Alzheimer's disease model	Individual osteoporosis model
Incremental Cost - Discounted	£ 522	-£ 14	-£ 100
Incremental QALYs - Discounted	0.271	0.001	0.008

In the individual HD model (Chapter 5), the margin of error, defined as half-width of a confidence interval, around the mean incremental QALYs at 95% confidence level with 200,000 simulated individuals was 0.0288. In order to estimate the predicted margin of error of the mean incremental QALYs with the higher number of simulated individuals, the power regression model was used to fit a non-linear curve that decreases proportionally to $1/\sqrt{N}$.

The fitting results and the estimated errors using the fitted equation, which has an R^2 of 0.9999,

with varying numbers of simulated individuals are shown in Figure 9.4 and Table 9.8. The predicted margin of error in incremental QALYs for HD treatment with 700,000 individuals was 0.0155. With 10 million individuals simulated, this value (0.0042) was still large compared with the incremental QALYs associated with AD (0.001) and osteoporosis (0.008) treatments. As such, it is believed that the allocation of random numbers to simulate HD events is the probable cause of the lack of face validity in the results for the AD treatment. This shows that, in the case where the treatment of one disease has a much larger absolute impact on cost and QALYs than the impact of treatments for other diseases in a model where multiple diseases are linked, a very large number of individuals may need to be simulated for stable results for each of the three disease treatments.

Linked models incorporating interactions between diseases can produce more accurate results than individual disease models if sufficient individual patients are modelled. Whether this is feasible within the time scales of projects is likely to be dependent on the characteristics of the decision problem.

Figure 9.4. Power regression results for the margin of error (95% confidence level) in incremental discounted QALYs from the individual heart disease model
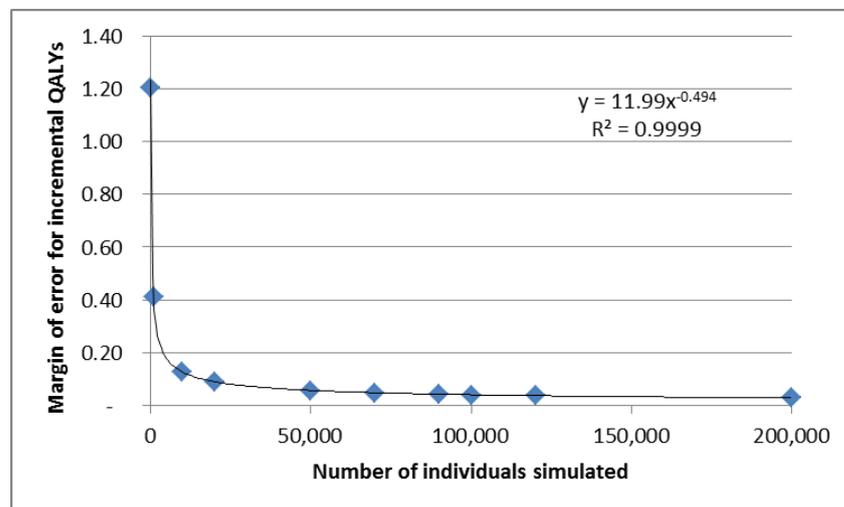
Table 9.8. Predicted margin of error for incremental discounted QALYs of heart disease treatment with increased number of simulated individuals

Number of simulated individuals	Margin of error of mean incremental QALYs (95% confidence level)
700,000	0.0155
2,000,000	0.0092
5,000,000	0.0059
10,000,000	0.0042
20,000,000	0.0030

In order to examine the effect of sampling error when all three treatments have a similar level of QALY gains, the scenarios in Table 9.9 were assumed: these are not meant to provide accurate evaluations of current treatments but to indicate that the results would be intuitive when QALY gains are comparable. For all three individual diseases, populations aged 65 years and older were simulated. Scenarios for larger QALY gains for AD and osteoporosis and reduced QALY gain for HD were explored. Table 9.9 shows the scenario assumptions applied to each of the three disease models in comparison with the base-case assumptions.

Table 9.9. Comparison of scenario assumptions and base-case assumptions

Base-case assumptions	Scenario assumptions
1. Heart disease model	
Relative risks were assumed to be 0.656, 0.754, 0.876, 0.59, 0.74, and 0.656 for MI, non-fatal stroke, fatal stroke, stable angina, fatal CHD, and non-cardiac death, respectively.	Relative risks of 0.98 for statin treatment were assumed for all events.
Utility values for MI, stroke and revascularisation were set to 0.76, 0.629, and 0.78, respectively.	Utility values for MI, stroke, and revascularisation were reduced to 0.5.
2. Alzheimer's disease model	
4% of monthly treatment discontinuation rate was assumed.	Lifetime treatment: No treatment discontinuation was assumed
6 months duration of treatment effect was assumed.	Lifetime treatment effect was assumed.
Utility value for institutionalised	Utility value for those institutionalised

individuals was 0.33.	was reduced to 0.1
The average annual improvements in MMSE score were 2.48 for donepezil and 1.4 for memantine per year.	Double treatment effect on MMSE score: the average improvements in MMSE score were set to 4.96 for donepezil and 2.8 for memantine per year.
Some individuals are institutionalised at model entry, and some patients are institutionalised immediately after diagnosis.	No individuals start at the institutionalisation state at model entry, nor get institutionalised immediately after the diagnosis (i.e. No individuals move to the institutionalisation event from the diagnosis event with zero time passed.)
3. Osteoporosis model	
Relative risks of fracture for alendronate treatment were set to 0.72, 0.58, and 0.82 for hip, vertebral, and other fractures, respectively.	Relative risks were assumed to be 0.33 for all fracture types.
5 years of treatment duration was assumed.	Lifetime treatment duration was assumed.

Table 9.10 compares incremental outcomes from the three individual disease models with those for each of the individual treatments from the linked model where the diseases were assumed independent. Under the hypothetical scenarios, a comparable magnitude of QALY gains across all three individual disease models (Table 9.10 Column a) was achieved. The margins of error around incremental costs and QALYs at 95% confidence level are shown in brackets.

Table 9.10 also repeats the analyses in Table 9.5, but under the scenarios in Table 9.9, assuming the diseases were independent. When none of the treatments have much larger impact on QALYs gained the linked model produced similar results to those from the individual disease models. This shows the robustness of the adoption decision within the linked model for individual treatments.

Table 9.10. Cost-effectiveness results under larger QALY gain scenarios for individual treatments from the individual disease models and the independently linked model

1. Heart disease				
	a. Individual heart disease model†	**b. Independently linked model (n=700,000)**		
	Incremental values (Margin of error) ‡	All treatments	No HD treatment*	Incremental values
DCost	£ 683 (£ 66)	£ 11,001	£ 10,201	£ 800
DQALYs	**0.0539 (0.0179)**	4.9232	4.8784	0.0448
TCost	£ 913 (£ 94)	£ 15,499	£ 14,380	£ 1,119
TQALYs	0.0875 (0.0267)	6.2589	6.1861	0.0728
ICER (disc.)	£ 12,665			£ 17,878
ICER	£ 10,433			£ 15,360

2. Alzheimer's disease (AD)				
	a. Individual AD model†	**b. Independently linked model (n=700,000)**		
	Incremental values (Margin of error) ‡	All treatments	No AD treatment*	Incremental values
DCost	-£ 4,551 (£ 93)	£ 11,001	£ 15,413	-£ 4,412
DQALYs	**0.0508 (0.0020)**	4.9232	4.8855	0.0377
TCost	-£ 6,319 (£ 130)	£ 15,499	£ 21,582	-£ 6,083
TQALYs	0.0688 (0.0028)	6.2589	6.2089	0.0500
ICER (disc.)	Dominating			Dominating
ICER	Dominating			Dominating

3. Osteoporosis				
	a. Individual osteoporosis model†	**b. Independently linked model (n=700,000)**		
	Incremental values (Margin of error) ‡	All treatments	No osteoporosis treatment*	Incremental values
DCost	-£ 1,186 (£ 74)	£ 11,001	£ 11,983	-£ 982
DQALYs	**0.0545 (0.0128)**	4.9232	4.8918	0.0314
TCost	-£ 1,856 (£ 123)	£ 15,499	£ 16,970	-£ 1,471
TQALYs	0.0900 (0.0204)	6.2589	6.2090	0.0499
ICER (disc.)	Dominating			Dominating
ICER	Dominating			Dominating

† Based on n=200,000 for HD and AD models; and n=400,000 for osteoporosis model, as in the base-case; ‡ Margin of error at 95% confidence level; *The other two default treatments were assumed to be available; D=discounted.

When all the individual disease models produce similar QALY gains (without any disease with a significantly larger impact) the impact of a change in the order of random numbers sampled for one disease on the incremental outcomes and cost-effectiveness of the other diseases can be much less influential. None of the margin of error estimates in Table 9.10 (0.0179, 0.0020, and 0.0128 for HD, AD, and osteoporosis models, respectively) will have a significant effect that changes the +/- signs of the values on the incremental QALY results from the linked model (0.0448, 0.0377, and 0.0314 for HD, AD, and osteoporosis treatments, respectively). Hence, when QALY gains are similar across all diseases, the results are less susceptible to sampling error from the other diseases. The base-case estimated very small QALY gains for AD and osteoporosis treatments which could fluctuate between positive and non-positive values due to the sampling error associated with the treatment for HD. In cases where QALY gains are similar, however, the proposed methods of linking individual disease models are likely to produce more accurate cost-effectiveness estimates for individual treatments.

9.1.3. Base-case results from the all-disease model with correlated diseases – Effect of correlations on the model outcomes

The base-case results from the model where the all diseases were linked with correlations are shown in Table 9.11. By incorporating correlations, disease status and event rates are influenced by the presence of the other diseases, which was deemed to better reflect population characteristics, rather than assuming independence between diseases. The general population per-person lifetime costs associated with the treatment of the three diseases were estimated to be £26,921 and £14,741 in undiscounted and discounted values, respectively. QALYs of 13.253 (undiscounted) and 8.962 (discounted) were estimated.

In comparison with no treatment for all three diseases, the combination of the three treatments was considered cost-effective with the discounted cost per QALY of £3,583 (£3,899/QALY when undiscounted). These were similar to the results from the independently linked model where the ICER of £3,854 (undiscounted) and £3,582 (discounted) per QALY were obtained.

Table 9.12 gives the results for male and female populations aged 45 years from the correlated linked model. As before, all default treatments were assumed to be used. In comparison to when diseases were assumed independent (Table 9.3), the costs are lower whilst the QALYs and life years were higher. This was due to positive correlations between diseases resulting in a greater number of disease-free people.

Table 9.11. Base-case results from the all-disease model with correlations based on n=700,000

All disease linked model (linked with correlations)	With all three treatments assumed	None of the three treatments	Incremental values
Cost - Discounted	£ 14,741	£ 13,894	£ 847
QALYs - Discounted	8.962	8.725	0.236
Cost	£ 26,921	£ 24,968	£ 1,953
QALYs	13.253	12.752	0.501
Life years lived	20.890	19.963	0.927
ICER - Discounted			£3,583/QALY
ICER			£ 3,899/QALY

Table 9.12. Simulation results from the correlated disease model for the incoming cohorts of 45 year olds (with all default treatments on)

All disease linked model (linked with correlations)	Males aged 45 years with all treatments assumed	Females aged 45 years with all treatments assumed
Cost - Discounted	£12,967	£14,207
QALYs - Discounted	13.333 QALYs	13.568 QALYs
Cost	£30,806	£37,223
QALYs	21.785 QALYs	22.640 QALYs
Life years lived	32.690	35.157

Figure 9.5 shows the total annual costs projected using the results from the correlated linked model and per-capita annual costs obtained from the model results. For the male and female populations aged 45 years at entry, per-capita costs peaked at later stages of life: around 30 years after model initiation for male population and 40 years for female population, which equate to ages of 75 and 85 years, respectively.

Table 9.13 gives the estimates of the projected annual costs. The undiscounted annual costs were projected to increase from £15.97 billion in 2012 to £28.30 billion in 2037. When compared with the results from the independently linked model, the differences in annual

costs varied over the projection horizon as costs were accrued at different rates in the two linked models. In general, the results from the correlated disease model suggested higher costs in the next 20 years, whilst the annual costs were estimated to be lower than those estimated from the independent disease model when projected further into the future (Table 9.14). This was believed to be caused by the higher prevalence of co-morbidities in the model with correlations between diseases resulting in high-cost populations with multiple diseases dying faster as the base-year population grow older, leading to lower costs in later time periods. It was considered that incorporating correlations between diseases would provide more realistic estimates of future expenditure than assuming independence between diseases. However, in this case study, simplifications were made in the estimation of correlated parameters, and thus the full effect of including correlations might not be captured.

Figure 9.5. Per-capita annual costs obtained from the correlated linked model

a) Per-capita (cohort) annual costs for base year population (age 45 and over, all gender)
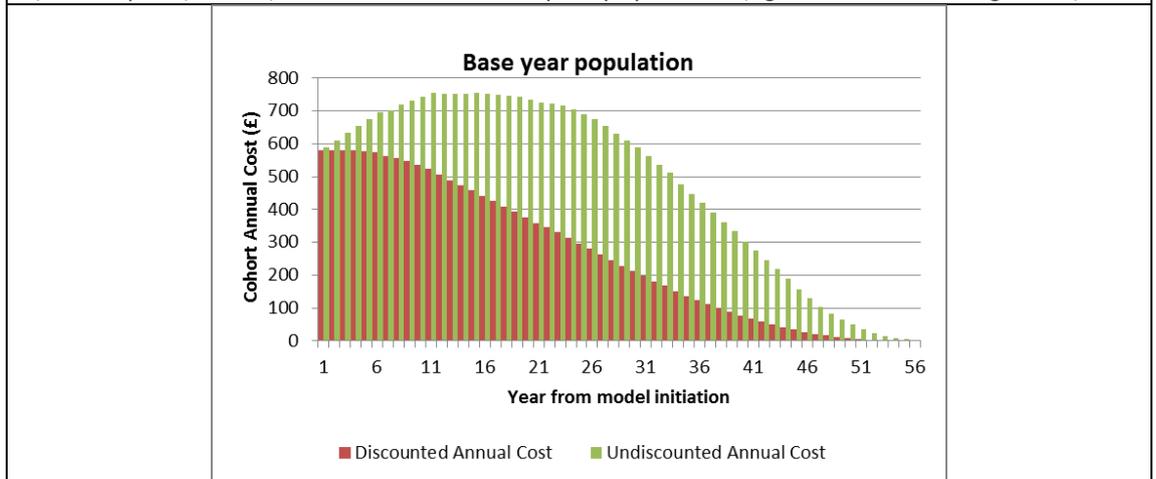
b) Per-capita (cohort) annual costs for male and female population aged 45 years at entry
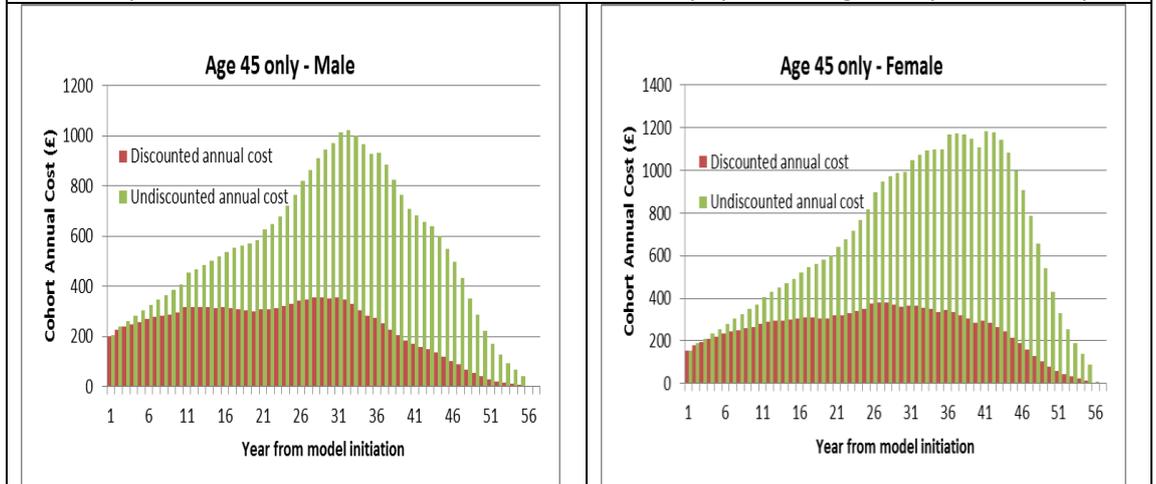
c) Total annual costs projected from the correlated linked model
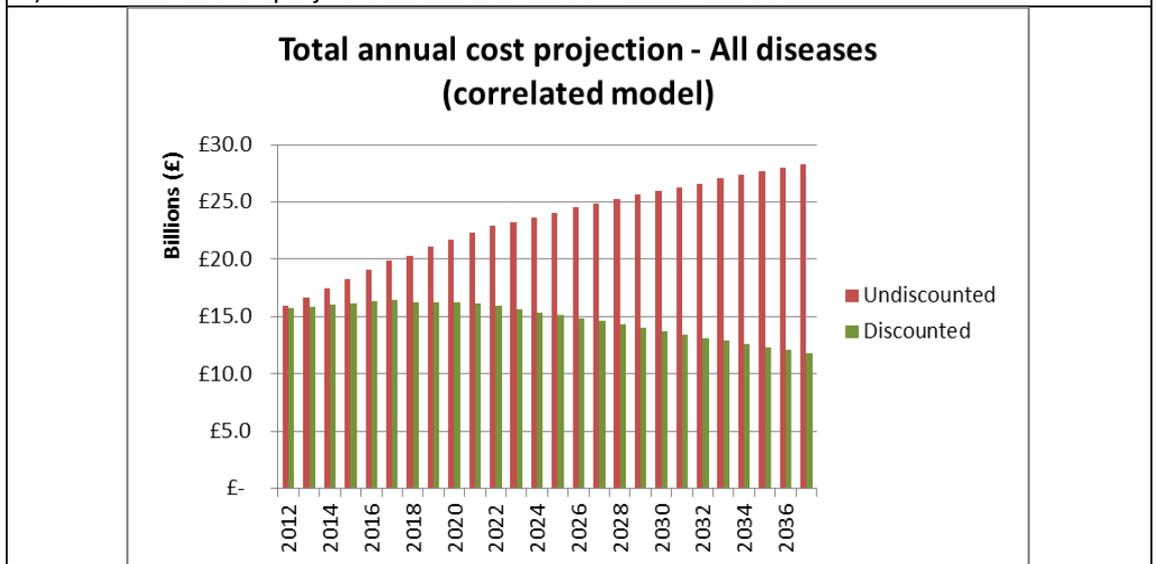
Table 9.13. Annual costs of treating the three diseases included projected using the results from the model with correlated diseases

Year	Annual costs – Undiscounted (£, millions)	Annual costs– Discounted (£, millions)
2012	£ 15,971	£ 15,701
2013	£ 16,689	£ 15,849
2014	£ 17,505	£ 16,062
2015	£ 18,263	£ 16,191
2016	£ 19,076	£ 16,338
2017	£ 19,891	£ 16,461
2018	£ 20,336	£ 16,262
2019	£ 21,097	£ 16,299
2020	£ 21,723	£ 16,215
2021	£ 22,359	£ 16,126
2022	£ 22,928	£ 15,977
2023	£ 23,219	£ 15,633
2024	£ 23,622	£ 15,366
2025	£ 24,049	£ 15,116
2026	£ 24,509	£ 14,883
2027	£ 24,895	£ 14,607
2028	£ 25,241	£ 14,309
2029	£ 25,650	£ 14,049
2030	£ 25,997	£ 13,757
2031	£ 26,283	£ 13,438
2032	£ 26,566	£ 13,124
2033	£ 27,032	£ 12,903
2034	£ 27,420	£ 12,645
2035	£ 27,721	£ 12,352
2036	£ 28,013	£ 12,060
2037	£ 28,297	£ 11,770
Total (2012-2037)	£ 604,349	£ 383,493

Table 9.14. Cumulative difference in annual costs between the results from the linked model with correlations and with independent diseases

Year	Difference from the independently linked model -Undiscounted* (£, millions)	Difference from the independently linked model -Discounted* (£, millions)
2012-2021	£ 487	£ 459
2022-2031	£ 842	£ 515
2032-2037	-£ 756	-£ 334
Sum over the projection horizon	£ 574	£ 639

*A positive number means that the costs were higher in the correlated model.

As in Section 9.1.2, the costs per QALYs for each of the three treatments are reported in Table 9.15. With correlations incorporated in the model, costs were lower by small magnitude although the QALYs and life years lived were higher compared with assuming independence between diseases. This was considered due to the co-morbidities being more concentrated on a narrower population when correlations were applied. This results in a wider population to be 'disease-free'.

However, there is still lack of face validity, when 700,000 individuals are simulated, as discussed in Section 9.1.2. The level of error in the mean incremental values of HD treatment could make a critical difference in the ICER of the AD and osteoporosis treatments when assessing the cost-effectiveness of individual treatments within the linked model. As such 2 million simulated individuals were run with the results shown in Table 9.16.

Table 9.15. Cost effectiveness of individual treatments using results from the all-disease model with correlations based on n=700,000 simulated individuals

	No HD treatment	Incremental values for HD treatment	No AD treatment	Incremental values for AD treatment	No Osteoporosis treatment	Incremental values for osteoporosis treatment
Cost - Discounted	£ 13,758	£ 983	£ 14,714	£ 27	£ 14,854	-£ 113
QALYs - Discounted	8.733	0.229	8.961	0.001	8.960	0.002
Cost	£ 24,743	£ 2,178	£ 26,869	£ 51	£ 27,144	-£ 223
QALYs	12.767	0.486	13.253	0.000	13.250	0.003
Life years lived	19.988	0.902	20.889	0.001	20.884	0.006
ICER - Discounted (£/QALY)		£ 4,297		£ 43,897		Treatment dominates
ICER (£/QALY)		£ 4,481		Dominated		Treatment dominates

HD=heart disease; AD=Alzheimer's disease.

Table 9.16. Cost effectiveness of individual treatments using results from the all-disease model with correlations based on n=2,000,000 simulated individuals

	No HD treatment	Incremental values for HD treatment	No AD treatment	Incremental values for AD treatment	No Osteoporosis treatment	Incremental values for osteoporosis treatment
Cost - Discounted	£ 13,791	£ 936	£ 14,742	-£ 15	£ 14,869	-£ 142
QALYs - Discounted	8.730	0.235	8.963	0.002	8.961	0.004
Cost	£ 24,803	£ 2,098	£ 26,927	-£ 26	£ 27,158	-£ 257
QALYs	12.761	0.498	13.254	0.004	13.251	0.008
Life years lived	19.982	0.914	20.891	0.005	20.887	0.009
ICER – Discounted (£/QALY)		£ 3,978		Treatment dominates		Treatment dominates
ICER (£/QALY)		£ 4,216		Treatment dominates		Treatment dominates

HD=heart disease; AD=Alzheimer's disease.

9.2. Population projection variants

In order to examine the effect of future population scenarios on the population-level costs, adjustments were made to the base-case projected population estimates. The base-case annual cost projections were carried out using the simulation model results and the Principal projection estimates for the UK from the 2012-based National Population Projections data published by ONS for the projection horizon of 2012-2037 (Office for National Statistics, 2013c). The ONS 'Principal projections' were performed under a pre-defined set of assumptions on fertility, mortality (life expectancy), and migration rates. Variant projections were produced based on a combination of assumptions on high or low levels of fertility, life expectancy and migration by the ONS. This section reports annual costs using these variant population projections.

The ONS 'High population projection' assumes high levels of increase in fertility, mortality and migration rates. This projection result would provide an indication of the upper bound of the population size, and thus of the total cost given the historic population trends.

The ONS 'Principal projection' assumed that completed family size for the UK would stabilise at 1.89 children per woman in the long-term. The high fertility variant assumes the long-term family sizes of 0.2 children per woman higher than the principal assumptions, which is 2.09 for the UK. Also, the principal projections assumed that rates of mortality improvement would converge to 1.2 % for most ages in mid-2037 and remain at 1.2 % each year thereafter. The high life expectancy variant assumed 2.4% improvement in annual rates of mortality in mid-2037 for most ages, which meant life expectancy at birth in mid-2037 to be 2.1 and 1.8 years higher for males and females, respectively. The principal assumption for net migration to the four countries of the UK combined was +165,000 each year. The high migration variant assumed long-term annual net migration to the UK to be 60,000 people higher, that is, +225,000.

In order to reflect the future time trends in birth, mortality, and migration rates assumed in the high population projection, annual costs using variant population projections were calculated differently from the base-case where it was assumed that the number of people in each cohort in the beginning of the entry year remained constant throughout the projection

horizon. Instead, yearly estimates of the projected number of people at each single year of age were combined in every projection year.

In the calculation described in Chapter 4, the total projected cost for a calendar year *j* was the sum of the costs for that year across all relevant cohorts, and the annual cost for cohort *i* and year *j* was the per-capita cost multiplied by the projected number of people in year *j* as below.

$$Total\ annual\ cost\ for\ year\ j = \sum_{i \in I} \left[Per\ capita\ cost_{ij} \times Number\ of\ people_{ij} \right]$$

, where I denotes the set of all cohorts assumed to have entered the model by year *j*.

The base-case assumed the constant numbers of people in cohorts with per-capita costs decreasing over time to take mortality into consideration. In contrast, the variant method explicitly allowed the population size, *Number of people* $_{ij}$, to decrease over time, so that the *Number of people* reflects the trends in mortality, migration, and fertility assumed in the variant population projections. The *Per capita cost* was calculated as the total annual cost from the model results divided by the number of people who are 'alive', or able to incur costs, within the model in year *j*. Without incorporating mortality and other population changes, per-capita cost increased over time as each cohort of population is likely to utilise more health services as they age.

Table 9.17 present the total annual costs projected under the higher population scenario from the correlated linked model. Under the high population scenario, the total population-level annual costs were projected to increase to £36.57 billion in 2037. The annual difference between the base-case and the high population estimate increased from £152 million in 2013 to £8.27 billion in 2037 with the cumulative difference estimated to near £80 billion over the 26-year horizon.

Table 9.17. Total annual costs - High population scenario

Year	Annual costs (£, millions)	Difference from base-case (£, millions)	Year	Annual costs (£, millions)	Difference from base-case (£, millions)
2012	£ 15,971	£ -	**2025**	£ 26,634	£ 2,585
2013	£ 16,840	£ 152	**2026**	£ 27,441	£ 2,932
2014	£ 17,762	£ 257	**2027**	£ 28,179	£ 3,285
2015	£ 18,637	£ 374	**2028**	£ 28,900	£ 3,659
2016	£ 19,582	£ 506	**2029**	£ 29,726	£ 4,076
2017	£ 20,549	£ 658	**2030**	£ 30,502	£ 4,505
2018	£ 21,145	£ 809	**2031**	£ 31,233	£ 4,950
2019	£ 22,105	£ 1,009	**2032**	£ 31,996	£ 5,430
2020	£ 22,936	£ 1,213	**2033**	£ 33,008	£ 5,976
2021	£ 23,812	£ 1,452	**2034**	£ 33,938	£ 6,518
2022	£ 24,639	£ 1,712	**2035**	£ 34,795	£ 7,074
2023	£ 25,195	£ 1,976	**2036**	£ 35,672	£ 7,659
2024	£ 25,890	£ 2,269	**2037**	£ 36,567	£ 8,270
			Total 2012-2037	£ 683,655	£ 79,306

The low population scenario assumed that the current life expectancy level is maintained over the projection horizon and the number of the incoming cohorts of 45 year olds after the base year would follow the figures estimated from the ONS projections assuming low life expectancy, birth rate, and migration.

As the base-case results were obtained assuming no changes in the mortality level at the base year over the projection period, the projected low population estimates were applied only to the new incoming cohorts of 45 year olds. Since the base-year population of 45 years or over at time zero forms the largest share of the model population, the results under the low population scenario showed relatively small differences from the base-case annual costs compared with the high population scenario results.

Table 9.18 shows the effect of assuming low population scenario for the new incoming cohorts of 45 year olds from year 1. As the new cohorts enter the model population on a yearly basis,

the difference between the base case and the low population results widens gradually over time. The assumed changes in the number of future cohorts of 45-year-olds were estimated to save £121 million in 2037 with the cumulative savings of £923 million over the projection period.

Table 9.18. Total annual costs - Low population scenario (£, millions)

Year	Annual costs (£, millions)	Difference from base-case (£, millions)	Year	Annual costs (£, millions)	Difference from base-case (£, millions)
2012	£ 15,971	£ -	**2025**	£ 24,025	-£ 24.8
2013	£ 16,689	-£ 0.0	**2026**	£ 24,481	-£ 28.5
2014	£ 17,505	-£ 0.1	**2027**	£ 24,862	-£ 32.8
2015	£ 18,263	-£ 0.2	**2028**	£ 25,202	-£ 38.4
2016	£ 19,076	-£ 0.4	**2029**	£ 25,606	-£ 43.9
2017	£ 19,890	-£ 0.7	**2030**	£ 25,947	-£ 50.1
2018	£ 20,328	-£ 8.1	**2031**	£ 26,226	-£ 57.1
2019	£ 21,087	-£ 10.0	**2032**	£ 26,501	-£ 64.9
2020	£ 21,711	-£ 11.7	**2033**	£ 26,958	-£ 74.1
2021	£ 22,346	-£ 13.7	**2034**	£ 27,336	-£ 84.2
2022	£ 22,912	-£ 15.9	**2035**	£ 27,626	-£ 95.2
2023	£ 23,201	-£ 18.5	**2036**	£ 27,905	-£ 107.5
2024	£ 23,600	-£ 21.4	**2037**	£ 28,176	-£ 121.2
			Total 2012-2037	£ 603,425	-£ 923

9.3. Scenario analyses

9.3.1. Hypothetical eradication of diseases

Box 4.1 in Chapter 4 summarises the key outcomes that were aimed to be derived from the linked disease model. Although unachievable, it is possible to ask how much could be saved by eradicating further events from one of the diseases; and also how many QALYs or life years could be produced. These questions were examined by comparing the results from the all-disease linked model and the results from models where only two diseases were set to be available. This was equivalent to zero incidence for eradication of further disease events with the current level of prevalence.

Adding osteoporosis into the linked model involved adjustments of probability distributions for time to non-disease death for the Z-score of individuals: these changes may introduce bias in the difference between the all-disease and all-but-osteoporosis model results, confounding the effect of eradicating osteoporosis. All results for the scenario of disease eradication were obtained from the model where the non-disease mortality based on the ranges of Z-score with CVD mortality subtracted was applied as used in the all-disease linked model, and 700,000 individuals were simulated in this section.

Table 9.19 shows the difference between the all-disease model results and the two-disease results with further events from one of the diseases eradicated. Eradicating further HD events included in the model was associated with an increase of 3.289 years of life, and was estimated to save a discounted cost of £ 4,382 and provide 2.053 more QALYs over a lifetime of an average individual from the population aged 45 and over in the base year (based on the results from models with correlations). Based on comparison between the results of the life time per-capita costs, eradicating further HD events was most cost-saving. The cost savings and the increase in QALYs when eradicating osteoporosis were the least among the three diseases.

Table 9.19. Hypothetical eradication of diseases – Comparison between the all-disease and the two-disease model results*

Difference between the all-disease model results and all-but-one disease model results			
I. Linked model with independent diseases assumed			
	1) Eradicating Heart Disease	**2) Eradicating Alzheimer's Disease**	**3) Eradicating osteoporosis**
Cost - Discounted	-£ 4,187	-£ 3,497	-£ 2,185
QALYs - Discounted	2.040	0.338	0.106
Cost	-£ 6,517	-£ 6,067	-£ 4,380
QALYs	4.288	0.722	0.239
Life years lived	3.246 years	1.130 years	0.147 years
II. Model linked with correlations			
	1) Eradicating Heart Disease	**2) Eradicating Alzheimer's Disease**	**3) Eradicating osteoporosis**
Cost - Discounted	-£ 4,382	-£ 3,380	-£ 2,199
QALYs - Discounted	2.053	0.330	0.112
Cost	-£ 6,965	-£ 5,713	-£ 4,389
QALYs	4.332	0.695	0.251
Life years lived	3.289 years	1.100 years	0.172 years

*Non-disease mortality distributions based on z-score with CVD mortality subtracted as in the all-disease model were used (see Chapter 7); Based on n=700,000 individuals

Table 9.20 presents population-level cost savings from eradicating each of the diseases. The projected annual costs over the 26-year horizon were compared with and without each of the diseases. Eradicating HD would save the most amongst the three diseases, with the cumulative savings over the projection horizon estimated to amount to £251 billion, compared with £119 billion and £77 billion from eradicating AD and osteoporosis, respectively. This shows the

burden of the three individual diseases within the linked model: heart disease is not only associated with the highest per-capita cost, but also the largest population-level spending.

Table 9.20. Projected cost savings from the hypothetical eradication of a disease (£, millions)*

	Projected cost savings from the eradication of:		
	Heart Disease	**Alzheimer's Disease**	**Osteoporosis**
2012 Base year	4,680	4,760	1,596
2013-2017	31,224	23,786	10,702
2018-2022	41,694	24,252	13,910
2023-2027	50,974	22,634	15,521
2028-2032	58,819	21,670	16,839
2033-2037	63,791	21,881	18,297
Cumulative savings in 2012-2037	**251,183**	**118,982**	**76,865**

*based on results from models with correlations between diseases incorporated
(undiscounted results)

9.3.2. Increase in treatment efficacy

This section tests which disease would benefit most from an improved intervention. This will give an indication of how much a healthcare system can expect to gain from focussing on the treatment of certain diseases. This section presents how much savings could be made when the efficacy of treatment for each one of the three diseases increases by 20%.

The results from the 20% efficacy increase scenario are compared with the base-case with the default treatment efficacy assumed. As this comparison involves changes in the efficacy of individual disease treatments within the three-disease model, the problem associated with the dominance of the HD treatment effect within the linked model and its impact on the effectiveness estimates of the other treatments applies as discussed in Section 9.1.2. Due to the large number of simulated patients required to achieve stable AD and osteoporosis outcomes in the linked model, the results for this scenario analysis were obtained from individual disease models reported in Chapters 5-7.

As the mechanism in which the drug treatment influences the progression of each of the three diseases differs, the application of the same 20% improvement in drug efficacy could mean a different impact on the incidence of associated events in individual diseases. For example, in the AD model (Chapter 6), donepezil and memantine can delay institutionalisation by helping slow the deterioration of, or improve cognitive function and functional ability of patients, whilst the statin treatment in the heart disease model (Chapter 5) directly reduces the incidence of disease events.

In order to avoid this inconsistency, 20% fewer events were uniformly assumed for all diseases. The following three hypotheses were tested:

> a) An improved treatment for Heart disease reduces 20% of previously simulated heart disease events.

> b) An improved treatment for Alzheimer's disease reduces 20% of previously simulated institutionalisations due to Alzheimer's disease.

> c) An improved treatment for Osteoporosis reduces 20% of previously simulated fractures.

As an example, if the RR was 0.7 initially, the RR with 20% increase in efficacy was adjusted to 0.56 (=0.7 x (1-0.2)), which will subsequently reduce the incidence of the event by 20% compared with the base-case.

This scenario of improved treatment efficacy illustrates how the model can be used to inform policy on potential interventions. The model can be used in various ways to explore the impact of potential changes in treatments and care delivery – for example, more people receiving home help resulting in less people needing institutional care, all people paying their own costs of institutional care and subsequent demand changes, or widely implementing tele-monitoring equipment and services – on the cost-effectiveness of interventions and on expenditure at the population level.

For the comparison of the increased efficacy scenario with the base-case, the number of simulated individuals required for stable cost-effectiveness estimates would be larger than in the base-case as both populations are on treatment with and without the adjustment for treatment efficacy and thus, are subject to the same sequence of random numbers. Individuals who do not experience disease events associated with the reduction in event rates would yield zero incremental costs and QALYs. In order to determine the number of individuals to simulate for each of the individual disease models, the mean incremental NMB of individual treatments with increased efficacy and the 95% confidence interval with varying numbers of simulated individuals are shown in Figure 9.6. Due to treatment dominance and associated negative incremental cost and QALYs values, results are shown for incremental NMB instead of cost per QALY.

Figure 9.6. First-order uncertainty for the comparison of the 20% increase in treatment efficacy scenario vs. base-case treatment efficacy (based on individual disease model results)
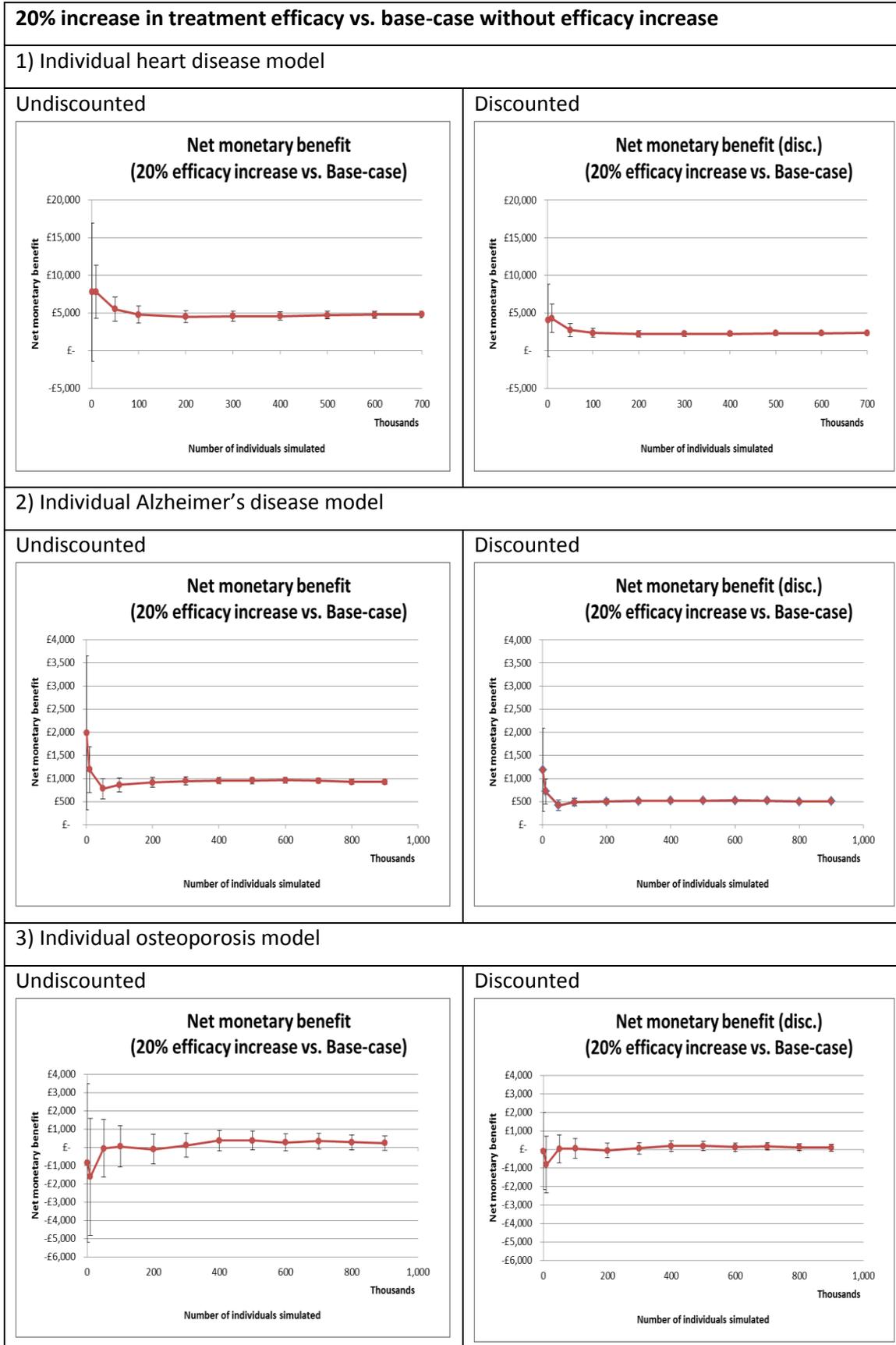
For the comparison of HD treatment with and without the efficacy adjustment, 500,000 individuals were chosen to be simulated in the heart disease model as incremental NMB (undiscounted) appeared stable for all values greater than 500,000 individuals. For AD, the number of individuals chosen to simulate was 700,000.

However, for osteoporosis model results, the level of error around NMB showed that the NMB outcomes did not stabilise with 900,000 simulated individuals. Due to the software limitation associated with the maximum size of individual patient data that could be saved, the margin of error with higher number of simulated individuals was estimated by fitting a power regression model. Based on the margin of error values calculated for up to 900,000 simulated individuals, the regression equation was estimated (Table 9.21 a), and the estimated equations were used to extrapolate the estimates for the margin of error with 1 million to 9 million simulated individuals (Table 9.21 b). For osteoporosis model, 5 million individuals were chosen to be simulated to ensure the 95% confidence interval of incremental NMB (discounted) falls in the positive range.

Table 9.21. Power regression results for the estimation of the margin of error for incremental net monetary benefit (incre. NMB) of osteoporosis treatment

a) Power regression results for discounted incre. NMB of osteoporosis treatment		b) Estimated margin of error	
$y = 41278x^{-0.388}$ $R^2 = 0.9637$		Number of individuals	Estimated margin of error (£)
		900,000	202
		1,000,000	194
		2,000,000	148
		3,000,000	127
		4,000,000	113
		5,000,000	104
		6,000,000	97
		7,000,000	91
		8,000,000	87
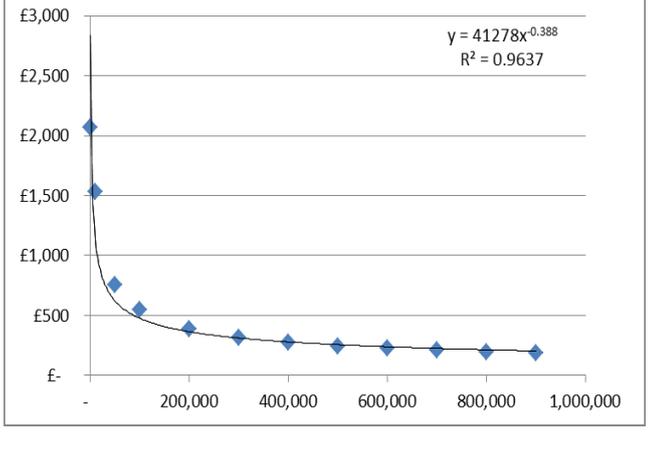
Table 9.22 presents the lifetime costs and QALYs obtained from individual disease models when assuming 20% reduction in disease events due to an increase in the efficacy of the three

treatments in comparison with the base-case where no efficacy adjustment was assumed. With 20% reduction in the occurrence of heart disease events (Table 9.22 (1)), individuals aged 45 years and over were estimated to live 0.4 years longer on average. With the efficacy increase, individuals gained 0.225 (undiscounted) and 0.107 (discounted) QALYs with lower lifetime costs by £199 (undiscounted) and £154 (discounted), compared with the base-case model results without the efficacy adjustment. Male population aged 45 years at model entry gained more life years and QALYs than females, whilst cost savings were larger for female population. The differences in incremental costs and QALYs between undiscounted and discounted values were larger for female population given the higher life expectancy. As heart disease generally develops at an earlier stage of life than Alzheimer's disease and osteoporosis, the effect of the increase in treatment efficacy could be reaped for a longer period of time than in the other diseases.

When assuming 20% reduction in institutionalisation events due to increase in the efficacy of the drug therapy for the treatment and management of AD (Table 9.22 (2)), per-capita cost saving was the largest among the three disease treatments with costs estimated to be lower than the base-case by £957 (undiscounted) and £520 (discounted). However, fewer institutionalisation events did not have much impact on life years and QALYs with incremental life years and QALYs estimated to be close to zero, as it was assumed that institutionalisation would not impact mortality and per-capita reduction in time in institutional care due to the improvement in treatment efficacy was not long enough to achieve noticeable QALY gain. Considering the monthly cost of institutionalisation, £2,293, the per-capita saving of £957 indicates that the duration for which QALY gain is generated due to avoided institutionalisation was less than 1 month on average for the base-case population. Table 9.22 (3) shows that the increase in the efficacy of alendronate would save £108 over a lifetime of an average individual from the population aged 45 years and over. The saving was larger for female population with the undiscounted lifetime saving of £224 per person. Life years lived and QALYs were also higher than the base-case without the efficacy adjustment.

Table 9.22. Effect of 20% reduction in disease events due to an increase in the efficacy of default treatments (based on results from individual disease models)

	Base-year population aged 45 years and over		Male aged 45 years at entry		Female aged 45 years at entry	
	20% reduction in disease events*	Increments compared with the base-case without efficacy adjustments	20% reduction in disease events*	Increments compared with the base-case without efficacy adjustments	20% reduction in disease events*	Increments compared with the base-case without efficacy adjustments
(1) Heart disease events reduction by 20% due to an increase in the efficacy of statin therapy						
Cost	£ 14,002	-£ 199	£ 20,629	-£ 478	£ 22,324	-£ 502
DCost	£ 7,934	-£ 154	£ 9,658	-£ 293	£ 9,675	-£ 300
QALYs	14.049	0.225	22.310	0.372	23.468	0.321
DQALYs	9.347	0.107	13.491	0.135	13.775	0.109
Life years	21.698	0.405	33.130	0.629	36.053	0.601
(2) Alzheimer's disease events (institutionalisation) reduction by 20% due to an increase in the efficacy of donepezil and memantine therapy						
Cost	£ 8,000	-£ 957	£ 6,856	-£ 1,050	£ 8,534	-£ 1239
DCost	£ 4,116	-£ 520	£ 2,067	-£ 319	£ 2,356	-£ 345
QALYs	16.553	0.000	27.889	0.000	29.380	0.002
DQALYs	10.650	0.000	15.938	0.000	16.218	0.000
Life years	21.660	-0.002	34.131	0.000	37.183	0.002
(3) Osteoporosis events (fracture) reduction by 20% due to an increase in the efficacy of alendronate therapy						
Cost	£ 5,957	-£ 108	£ 3,239	-£ 61	£ 8,705	-£ 224
DCost	£ 2,760	-£ 57	£ 995	-£ 17	£ 2,405	-£ 59
QALYs	17.753	0.009	29.199	0.003	30.388	0.011
DQALYs	11.189	0.004	16.288	0.001	16.509	0.003
Life years	23.517	0.008	36.083	0.002	39.140	0.007

*With all treatments assumed available; DCost=discounted cost; DQALYs=discounted QALYs.

Using the results in Table 9.22, the additional expenditures per person of the 20% improvement that would be permitted whilst maintaining an ICER of £20,000 per QALY – the incremental NMB per person compared with the base-case without the efficacy improvement – were calculated in Table 9.23. The highest expenditure could be additionally spent on the treatment of heart disease: at a willingness-to-pay threshold of £20,000 per QALY gained due to the additional treatment that would reduce 20% of the disease events, the incremental NMBs of the treatments for heart disease, AD and osteoporosis were £2,292, £517, and £143, respectively, on average over an individual's lifetime.

Assuming the other two treatment costs remain constant, these figures can be interpreted as the amount of resources that could be invested in an intervention reducing disease events by 20% for an average individual from the base-case population of men and women aged 45 years and over in the base year, while still achieving a cost per QALY of £20,000 when compared with the current treatment. The time on treatment was considered to calculate the additional cost per treatment year per person that could be charged (Table 9.24).

Table 9.23. Additional expenditure per person to maintain an ICER of £20,000 per QALY for the treatments with improved efficacy*

	a) Heart disease – 20% treatment efficacy increase	b) Alzheimer's disease – 20% treatment efficacy increase	c) Osteoporosis – 20% treatment efficacy increase
Undiscounted incremental values			
Cost**	-£199	-£ 957	-£ 108
QALYs gained	0.225	0.000	0.009
Incre. NMB†	£ 4,696	£ 951	£ 280
Discounted incremental values			
Disc. Cost**	-£154	-£ 520	-£ 57
Discounted. QALYs gained	0.107	0.000	0.004
Discounted incre. NMB†	£ 2,292	£ 517	£ 143

*Compared with the base-case results without efficacy improvement from individual disease models
**Negative values mean cost savings
†Incremental net monetary benefit (incre. NMB): the willingness-to-pay threshold of £20,000 per QALY gained due to additional treatments was assumed.

At the population level, if a government programme can guarantee a 20% reduction in heart disease events, £62 billion (discounted costs) can be spent on top of the default treatment for heart disease over the lifetime of the model population. The equivalent amounts that can be spent on the treatment and prevention of AD and osteoporosis are £14 billion and £4 billion over the lifetime of the base-year population.

For the annual treatment cost, the highest extra costs could be spent on the treatment of AD assuming the same estimated treatment duration as the base-case. If 20% fewer institutionalisation events can be guaranteed from an improved treatment, £7,631 per person per year can be additionally spent on treating an average individual from the population with AD. If a new heart disease treatment can guarantee the 20% reduction effect with the same average duration of treatment, this means an additional (discounted) cost of £293 per person per year can be spent on the treatment to have the ICER of £20,000 compared with the base-case treatment. For the treatment of osteoporosis, annual per-capita cost of £276 could be spent in addition to the default treatment cost.

Table 9.24. Cost savings made by the 20% reduction in event occurrence for the base-year population

	a) Heart disease – 20% treatment efficacy increase	b) Alzheimer's disease – 20% treatment efficacy increase	c) Osteoporosis – 20% treatment efficacy increase
Discounted values			
Cost to spend on population-level intervention over lifetime	£62.04 billion	£14.00 billion	£3.87 billion
Duration of treatment for the base-year population*	7.82 years	0.07 years	0.52 years
Additional cost per person per annum on treatment	£293	£7,631	£276

*Per person who entered the model, not per person who received the treatment.

For the total population including male and female populations aged 45 years at model entry, the efficacy change meant reduced yearly projected costs. With 20% reduction in heart disease events due to the increased treatment efficacy, the annual costs were lower with £17.82 billion in 2037 (Table 9.25). Yearly projected savings (undiscounted) due to the efficacy increase could exceed £500 million as shown in Figure 9.7a). Cost savings from 20% reduction in institutionalisation due to the increased efficacy of the treatment for AD were estimated to be larger than those from heart disease treatment, with the projected annual cost of £6.28 billion in 2037 (Table 9.25 and Figure 9.7b)). The annual cost savings were estimated to decrease over time as the entry population include people with diagnosed and undiagnosed AD, thus the larger population in earlier years is affected by the improved efficacy of AD treatment. The savings were generally larger in the next 10 years than in the rest of the projection horizon although there were savings in later years due to the ageing of the 45-year-old incoming cohorts (Figure 9.7b)). Compared with the base-case, the annual costs with 20% reduction in fracture events due to the increased efficacy of osteoporosis treatment were lower with £1.48 billion in 2012 and £4.71 billion in 2037 (Table 9.25). Figure 9.7c) shows that undiscounted yearly savings from improved osteoporosis treatment were lower than those from HD and AD treatments.

Cost savings projected in Figure 9.7 were shown as cost savings by 5-year band and cumulative savings over the projection horizon in Table 9.26. The largest cost savings compared with base case were projected to be obtained from the increased efficacy of treatment for AD, with a cumulative saving of over £16 billion over the 26-year horizon, followed by savings from the HD treatment (£10 billion) and the osteoporosis treatment (£1.7 billion). These results with 20% reduction in disease events assumed were not necessarily proportional to the population-level savings associated with the eradication of further disease events, as the 20% reduction in event probabilities due to improved treatment efficacy affects only the population on treatment, which depends on the duration of the treatment effect and the size of the population receiving the treatment in the three disease models. Also, unlike per-capita cost savings, annual cost savings could be affected by a difference in the rate at which costs accrue between the base-case model and the improved efficacy scenario model, as the yearly cost was multiplied by the projected number of people in the corresponding year.

Table 9.25. Comparison of annual costs projected under increased efficacy scenarios with the base-case

Year	Heart Disease		Alzheimer's Disease		Osteoporosis	
	Base-case (£, millions)	20% increase in HD treatment efficacy (£, millions)	Base-case (£, millions)	20% increase in AD treatment efficacy (£, millions)	Base-case (£, millions)	20% increase in Osteoporosis treatment efficacy (£, millions)
2012	9,489	9,119	4,879	3,946	1,564	1,476
2013	9,991	9,710	4,545	3,699	1,741	1,654
2014	10,461	10,234	4,668	3,850	1,956	1,854
2015	10,982	10,679	4,950	4,082	2,153	2,052
2016	11,409	11,161	5,103	4,303	2,370	2,272
2017	11,907	11,592	5,257	4,545	2,584	2,489
2018	12,526	12,090	5,335	4,651	2,780	2,695
2019	12,867	12,514	5,445	4,708	2,976	2,895
2020	13,211	12,907	5,430	4,818	3,151	3,054
2021	13,597	13,278	5,478	4,977	3,289	3,221
2022	14,094	13,646	5,603	5,131	3,423	3,350
2023	14,419	14,041	5,780	5,314	3,541	3,493
2024	14,685	14,384	5,874	5,380	3,633	3,614
2025	15,145	14,732	5,927	5,380	3,739	3,727
2026	15,485	15,101	5,883	5,402	3,839	3,828
2027	15,789	15,413	6,014	5,560	3,912	3,896
2028	16,100	15,666	6,071	5,658	4,005	3,987
2029	16,376	16,042	6,110	5,711	4,117	4,071
2030	16,668	16,225	6,287	5,700	4,224	4,158
2031	16,924	16,440	6,397	5,778	4,298	4,253
2032	17,145	16,766	6,437	5,889	4,413	4,347
2033	17,449	16,987	6,504	5,955	4,508	4,440
2034	17,677	17,148	6,663	6,049	4,603	4,544
2035	17,936	17,363	6,748	6,104	4,688	4,605
2036	18,113	17,611	6,904	6,158	4,740	4,644
2037	18,238	17,822	7,039	6,276	4,805	4,712
Total (2012-2037)	378,680	368,672	151,329	135,026	91,051	89,333

Figure 9.7. Projected annual cost savings from the increased efficacy of interventions in comparison with the base-case (£, millions)

a) Annual cost savings from 20% reduction in *heart disease* events due to an increase in heart disease treatment efficacy
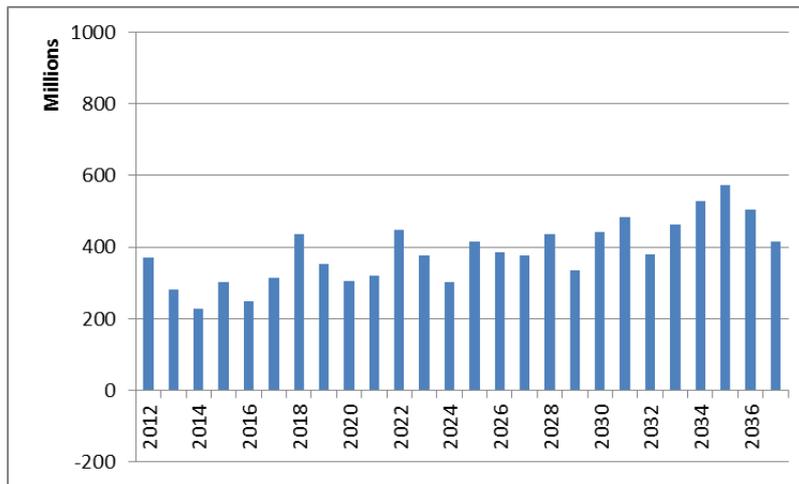
b) Annual cost savings from 20% reduction in *Alzheimer's disease* event (institutionalisation) due to an increase in treatment efficacy
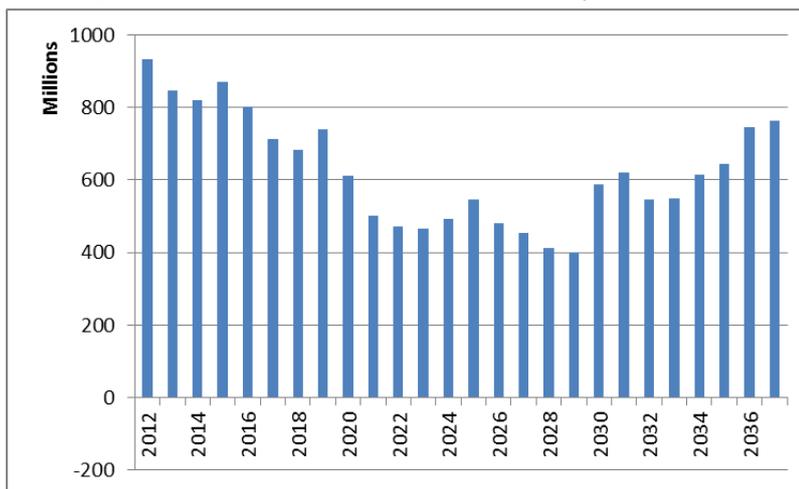
c) Annual cost savings from 20% reduction in osteoporosis events(fracture) increase in Osteoporosis treatment efficacy
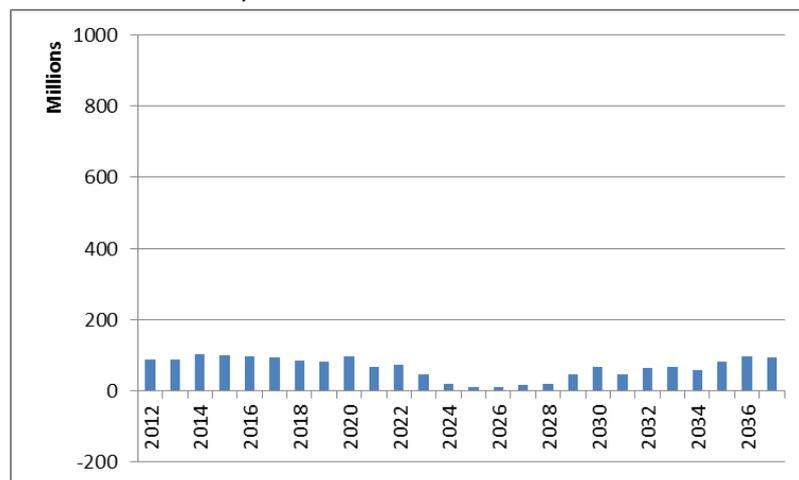
Table 9.26. Projected 5-year cost savings from the increase efficacy of interventions in comparison with the base-case, using results from individual disease models (£, millions)

	Projected cost savings from 20% reduction in events of:		
	Heart Disease	**Alzheimer's Disease**	**Osteoporosis**
2012 Base year	370	932	88
2013-2017	1,373	4,044	482
2018-2022	1,860	3,005	404
2023-2027	1,851	2,442	105
2028-2032	2,074	2,565	241
2033-2037	2,482	3,315	398
Cumulative savings in 2012-2037	10,009	16,303	1,718

9.4. Findings and Conclusion from the all-disease linked model

This chapter presented results obtained from the models where HD, AD and osteoporosis were linked with and without correlations.

The results showed that including multiple diseases with competing risks can alter the model outcomes such as the cost-effectiveness of interventions and future expenditure estimates compared with using results from multiple single-disease models. In the model for this thesis, when the results from the independently linked model were compared with the individual disease model results, the costs from the linked disease model were lower than the sum of the individual model results. Absolute QALYs from the linked model were also lower than the minimum of QALYs from the individual disease models. This indicates that different decisions on technology adoption could be reached when a model with multiple diseases linked is used. Also, the lower projected population-level costs when using the linked model compared with using individual disease models suggest that the estimation of future costs by summing costs

at the individual disease level may not be accurate, and thus funding decisions based on such estimates may not represent efficient allocation of resources.

However, although the linked model could produce stable ICERs for the three treatments combined, it was shown that when one disease has a much larger impact on costs and QALYs than the others, the sampling error around the treatment with larger impact could make a significant difference in the cost-effectiveness of the other individual treatments, which could lead to lack of face validity for the more minor diseases. The number of simulated patients sufficient to make the conclusions on adoption decisions stable within individual disease models may not be sufficient to make such claims in the model where multiple diseases are linked. In this case study, if the random numbers get misaligned between model runs due to different sequences of events, random error in HD events could markedly alter the ICERs for AD and osteoporosis treatments.

Including correlations could potentially change the cost-effectiveness of interventions. When correlations were implemented, absolute QALYs were higher than when the diseases were assumed independent due to the concentration of co-morbidities onto an already diseased population, resulting in lower QALY loss from an additional disease than the random allocation of diseases to the general population. When comparing all treatments with none of the three treatments in this case study, however, the ICERs for all three treatments combined were similar with and without incorporating correlations (£3,582/QALY when assuming independence between diseases; and £3,583/QALY when incorporating correlations). The projected annual costs were generally lower with correlated diseases in later time periods on the projection time horizon. Adding correlations was considered to have better reflected the relationship between multi-morbidities and mortality. However, it is noted that in this case study simplifications were made in terms of the estimation of correlated parameters, and thus the results may not capture the full effect of incorporating correlations.

In the scenario analyses, eradicating further HD events would provide the highest cost-saving and QALY gain amongst the three diseases, with the discounted cost-saving of £4,382 and 2.053 QALY gain based on the comparison between the lifetime per-capita costs. At the population level, the cost savings from eradicating HD amounted to £251 billion over the 26-year projection horizon.

The 20% reduction in event occurrence due to increased efficacy of treatments for the three diseases provided cost savings. These results were obtained from runs within individual

disease models due to the dominant size of the HD treatment effect within the linked model when assessing individual treatments. When considering the projected number of population over the 26-year projection horizon, the increase in efficacy of the AD treatment in reducing institutionalisation events could save the most among the three treatments with a cumulative saving of over £16 billion. Assuming the effect of 20% event reduction can be guaranteed and incorporating the results with the prevalence of the diseases and the average treatment duration, additional costs that could be spent on drug treatments per person were £293, £7,631, and £276 per annum for HD, AD, and osteoporosis, respectively. A population-level government programme that can guarantee the 20% event reduction can spend £62 billion, £14 billion and £4 billion on the treatment of HD, AD and osteoporosis, respectively, to obtain an ICER of £20,000 per QALY. The highest amount can be spent at the individual level on the AD treatment that can reduce institutionalisation by 20%. At the population level, however, the programme targeting HD is associated with the greatest gain in net monetary terms. Potentially, the model provides flexibility that enables policymakers to examine the impact of possible changes in the efficacy of interventions, delivery of care and funding methods on the projected costs and cost-effectiveness of interventions. However, the reader should note the caveat below.

Incorporating multiple diseases and correlations between them in a model can lead to different costs and health outcomes associated with the disease and estimates of future healthcare expenditure. In this case study, the cost-effectiveness of individual interventions could not be obtained from the linked model due to HD having a much larger impact on the model outcomes than the others. This may be mitigated by selecting a balanced set of diseases with similar cost and QALY outcomes for model linkage and using the model only to assess combined treatments that aim to tackle all diseases included in the model. Further research on better approaches to minimising this problem, in particular when incremental costs and QALYs are small in magnitude, would be beneficial.

CHAPTER 10   DISCUSSION

10. 1. Thesis summary and key implications

This final chapter comprises a summary of the key findings and implications of this thesis, a discussion of its limitations, an outline of the contributions to current knowledge made by this thesis as well as recommendations for future research priorities.

This thesis presented a methodology for modelling health and healthcare for an ageing population and estimating future healthcare expenditure at the disease level. It demonstrated a proof-of-concept model using three diseases of the older population: heart disease (HD); Alzheimer's disease (AD); and osteoporosis.

This PhD study included the following elements:

- A pragmatic method for searching literature in diffuse topic areas was developed.
- A freely-accessible literature repository containing papers on population ageing and healthcare expenditure was established.
- Multiple DES models for three diseases (HD, AD, and osteoporosis) were extended from existing HTA models, incorporating a range of methodological amendments necessary to model the general population, as opposed to only the prevalent cohorts of individuals.
- The individual disease models were linked in a single model by implementing a set of simple central routing logic in the model.
- Correlations between the diseases were incorporated in the linked model in order to fully examine the effect of linking correlated diseases on the model outcomes.
- Using the individual DES and linked models, the methods for projecting future healthcare expenditures were demonstrated. Population ageing and potential demographic changes were incorporated in the projection using external population projection data.
- An unanticipated finding related to the relative sizes of QALY gain between diseases that could affect the robustness of linked model results was identified.

Chapter 2 presented a pragmatic literature search method to identify relevant literature in the diffuse topic area of population ageing and healthcare demand. This approach identified 7,745 hits from 12 seed papers compared with over 29,000 hits from a broad search in Medline and over 21,000 hits in EMBASE. Moreover, the broad searches had lower sensitivity than the proposed approach identifying only 9 of 11 (10) seed papers available in Medline (EMBASE). The literature review in Chapter 3 reported the categorisation of the identified literature and a review of projection models. It also presented a literature repository containing 2,263 papers screened from the 7,745 papers with the categorisation results. Given the broad and diffuse nature of the literature on the topic, the repository is expected to provide a valuable resource for researchers wishing to quickly identify papers relevant to specific topics in this area. The review of models projecting future health and social care expenditure showed that the majority of the existing models adopt a macro-simulation approach in which aggregate levels of population and cost data are combined to estimate the total healthcare expenditure. Based on the examination of the existing models, Chapter 4 provided a rationale for the modelling approach chosen for this thesis.

The individual disease models described in Chapters 5 – 7 were based on existing models used within published health technology assessment (HTA) monographs identified from a brief review undertaken for each disease. New data were used if more up-to-date data equivalent to those used in HTA models are available and the models were modified if deemed appropriate to model different events from those included in the HTA models for the scope of the model or the implementation of a DES format. Instead of modelling diseased populations only, the model simulated individuals representative of the entire UK general population aged 45 years and over. A DES model structure was used throughout all individual disease models: time and patient characteristics updates were performed in the same order within the models to facilitate the linkage of the models. In all of the individual disease models, drug treatments were cost-effective assuming a £20,000 per QALY gained threshold used which was in line with the outcomes from the existing models. In all three diseases, the costs were projected to increase during the period of 2012 – 2037. When individual disease models are used, the highest annual costs among the three diseases were estimated to come from heart disease. The greatest proportional increase was for osteoporosis with the annual cost for treating and preventing osteoporosis projected to triple over the projection period 2012-2037 (from £1.55 billion in 2012 to £4.91 billion in 2037). For comparison, the annual costs for HD were expected to nearly double over the same period (£9.4 billion to £18.3 billion) and those for Alzheimer's disease to increase by 42% (£4.87 billion to £6.92 billion).

Chapter 8 described correlations between the diseases incorporated in this model reporting the results from models in which pairs of the three diseases were linked with and without the correlations subsumed. Chapter 9 reported the results from the all-disease linked model.

The key implication of the findings from the linked model is that the estimates of costs and (quality-adjusted) life years differ when multiple diseases are modelled within a single model in comparison with the summed results from single disease models. Consequently, the projected expenditure for healthcare services for the modelled diseases will also differ. In the case study presented in this thesis, the total annual costs of treating and managing HD, AD and osteoporosis from the independently linked model were lower than the sum of the costs from the three individual disease models. It implies that the use of the linked model can influence decisions on funding interventions for the prevention and treatment of diseases. When correlations between diseases were incorporated, the absolute costs were lower whilst the absolute QALYs and life years were higher due to a greater number of disease-free individuals due to the positive correlations identified. This indicates that the inclusion of correlations could alter the cost-effectiveness of interventions depending on the strength and direction of the correlations (positive or negative). Hence, policy decisions on the allocation and planning of healthcare resources based on the results from individual disease models can be different from those based on linked models with correlations incorporated.

It was found that when one disease has a much larger impact on costs and QALYs than the others included in the linked model despite all having clear adoption decisions, the sampling error around the effect of the treatment with higher impact could significantly influence the effect of the other individual treatments and create unintuitive results. In the model for this thesis, sampling error in HD events due to the misalignment of random numbers between model runs could make a considerable impact on the cost-effectiveness of AD and osteoporosis treatments which had small incremental costs and QALYs. However, in circumstances where QALY gains are similar across individual treatments, it is likely that the proposed methods of linking individual disease models produce more accurate cost-effectiveness estimates for the individual treatments.

Variants of population projections were also examined for their impact on the future healthcare expenditure. Population changes could significantly alter the future healthcare expenditure: in the higher population scenario with high levels of mortality improvement, fertility, and migration, the annual cost increase compared with the base-case was from £152

million in 2013 to £8.27 billion in 2037. The impact of the variants on Gross Domestic Product was not considered.

In exploring the impact of advances in treatment, the hypothetical eradication of further HD events (zero incidence rates) would save the most with the cumulative projected savings over the 2012-2037 period projected to amount to £251 billion, compared with £119 billion and £77 billion from eradicating AD and osteoporosis, respectively. The 20% reduction in institutionalisation due to the increase in the efficacy of the AD treatment would result in the highest cumulative saving of over £16 billion over the 26-year projection horizon, followed by savings from the treatment of HD (£10 billion) and osteoporosis (£1.7 billion). Combining the cost results with QALY gains, it was estimated that the highest amount of resources (£62 billion) can be spent on a population-level government programme that can guarantee a 20% reduction in HD event occurrence over the lifetime of the base-year population to achieve a value of £20,000 per QALY gained, followed by AD (£14 billion) and osteoporosis (£3.9 billion).

The existing cost projection models reviewed in Chapter 3 explored the implications of potential policy changes in their scenario analyses. For example, Hancock et al. (2003) reported projected costs of long-term care under a policy of free personal care, as well as under the current funding arrangements. The context of the analysis was that the Royal Commission on Long Term Care recommended a change to 'free' personal and nursing care whilst individuals in care homes continue to meet their accommodation and living costs according to their means test results (Royal Commission on Long Term Care, 1999). The government in England accepted many of the Royal Commission's recommendations including free nursing care, but not free personal care. However, as the Scottish government implemented a policy of free personal and nursing care, Hancock et al. (2003) examined the financial consequences of introducing free personal care in the entire UK. Also, analysts have used Future Elderly Model (FEM) to investigate the value of preventing expensive diseases among the elderly. For example, Goldman et al. (2009) examined the cost and health effects of reducing the key risk factors associated with heart disease, such as hypertension, smoking, obesity and diabetes. POHEM (Population Health Model) developed by Statistics Canada has also been extensively used to evaluate the effects of alternative health programmes, mainly with respect to the cost-effectiveness of interventions. For example, Berthelot et al. (2000) evaluated the cost-effectiveness of different chemotherapeutic therapies on patients with non-small-cell lung cancer, and Will et al. (2001) analysed the impact of reduced length of hospital stay following breast cancer surgery.

In addition to the scenarios explored in this thesis, it is believed that the model can be used flexibly and modified to examine the impact of potential changes in treatments, care delivery and funding methods for healthcare. For example, the impact of a reduced NHS contribution to institutional care (from the current 72%; see Chapter 6) for AD patients on the cost-effectiveness of AD treatment and future costs can be estimated. The use of the linked model can also help prioritise potential government programmes targeting the prevention and treatment of the diseases included in the model and can also be applied to other diseases. The modelling approach presented in this thesis makes possible various applications to explore the impact of such policy and intervention options, with some modifications such as linking additional risk factors to diseases, if needed.

The outcomes from the model in this thesis permit rigorous analyses in exploring the impact of potential changes in policy and treatments. Although not fully investigated in this thesis, the model can record the characteristics of all modelled individuals throughout the course of simulated events, and thus the distributional effect of policy changes can be examined. For example, groups of individuals affected by a policy change more than others can be identified, along with individual attributes strongly associated with reduction in healthcare utilisation after the implementation of a prevention programme. The model can incorporate more specific outcomes rather than only total costs and QALYs. For example, it can explore the average number of strokes over a lifetime in a population with previous hip fracture, and the proportion of individuals with low bone mineral density amongst those receiving institutional care.

10.2. Limitations

An unanticipated finding was that despite each disease having a clear adoption decision, this could be reversed in a linked model where the simulated number of patients is held at similar levels. When assessing the cost-effectiveness of individual disease treatments within the linked model, the size of treatment effect for HD dominated that for AD and osteoporosis. This thesis found that if random samples of variables associated with HD events are misaligned between treatment and no treatment arms, random error in incremental cost and QALYs of HD treatment could make a crucial difference in relatively small incremental outcomes of the other treatments included in the linked model.

The proof-of-concept model reported in this thesis was constructed to demonstrate the methodology of linking multiple single-disease models and incorporating correlations between the included diseases when estimating future healthcare expenditure. Future research based on this thesis could focus on the role of extensive probabilistic sensitivity analyses in linked models.

The diseases modelled in this PhD study were not exhaustive, however, the three diseases included were carefully chosen. There remains uncertainty in that the outcomes for the modelled diseases may not reflect the trends in future healthcare expenditure for other diseases of an ageing population, and the default treatments assumed currently may not be used in the future. However, this proof-of-concept model can be expanded and modified to include further diseases or/and other potential interventions.

In addition, given the large number of parameters included in the models, not all possible correlations between the parameters required for the three diseases could be addressed. Only a few selected correlations regarding the prevalence and incidence of the diseases that were deemed to influence utility and cost outcomes were considered, although the methods for estimating the correlated parameters were illustrated. Other correlations, such as the presence of AD possibly delaying the initiation of the preventative treatment for osteoporotic fractures, presumably due to barriers in seeking healthcare owing to a decline in cognitive function could exist (Chang et al., 2014a, Yaffe et al., 2012, Haasum et al., 2012). Furthermore, some of the correlations embedded in the model were approximations based on assumptions. This was due to the absence of appropriate estimation methods given the data available, and may have caused biases in the final model outcomes.

With respect to the modelling method, the use of the DES framework enabled the seamless linkage of the three disease models. There may be challenges in applying the method of model linkage presented in this thesis to other model forms, especially those with fixed time cycles. The application of the linkage method in other model structures has not been explored in this thesis.

In the model developed for this thesis, 'status quo' assumptions were applied including current treatment regimes and prices of healthcare. Moreover, epidemiological characteristics of the population regarding the prevalence and incidence of disease events were assumed throughout the projection horizon. The estimation of trend parameters using statistical models or via the examination of the existing literature for making informed assumptions could not be

performed within the time scale of this PhD given the large number of potential parameters that could influence the expenditure.

However, the existing literature suggests that there are many time trends that can potentially affect future healthcare expenditure. In addition to the changes in age composition over time, the prices of health and social care relative to other goods and services may increase over time. This would mean increases in unit costs of health and social care may exceed real GDP growth or average earning growth (Hancock et al., 2007a, Wittenberg et al., 2006). Healthcare is a labour-intensive sector and it is often considered that labour productivity does not grow as fast as productivity in other sectors of the economy. Nonetheless, in order to attract a highly-skilled workforce, wages in the healthcare sector may have to increase in line with the other sectors, which then makes healthcare relatively more expensive in the long term (van Elk et al., 2010). This problem of rising relative prices in the healthcare sector has been theoretically advocated (Baumol et al., 2012, Baumol and Bowen, 1966), and empirical evidence has shown that NHS pay inflation has been rising in line with that in the other sectors of the UK economy without a noticeable increase in labour productivity (Appleby, 2013). Nonetheless, the strength of the trend in the relative price of healthcare or whether it will continue is not clear.

The model reported in this thesis does not incorporate possible future trends in the prices of health and social care, but assumes that the current level of care costs are maintained in the future. The cost of drug interventions generally decreases over time due to patent expiry and availability of wider treatment options. This has not been incorporated in the model for this thesis and the intensity of treatments provided may change over time.

Technological progress can also contribute to growth in real spending on healthcare (Astolfi et al., 2012, Appleby, 2013). The availability of new health technologies and surgical methods can impose cost pressures, and a number of studies have identified technological changes as one of the dominant factors in the expenditure growth, which is estimated to account for 27-65% of health spending growth (Cutler, 1995, Smith et al., 2009, Newhouse, 1992, OECD, 2006). Increased life expectancy due to effective treatments could also add to future healthcare needs (Astolfi et al., 2012). As all individuals with a disease were assumed to receive the default treatment in 2015, the model results do not reflect the variety of treatment regimes that are adopted in real clinical practice. Technological breakthroughs that may significantly increase the cost of treatment but also increase life years or QALYs were not explored in the model, although this could be performed.

In relation to the availability of new technologies and emergence of surgical methods, patterns of healthcare utilisation may also change in the future. Schulz (2005: alternative scenarios) attempted to estimate trends in healthcare utilisation. However, due to the short period of data collection, trend analyses could not be undertaken. The country-specific data used by Schulz (2005) showed that increasing life expectancies are associated with higher utilisation of inpatient care. It is possible that life expectancy arising from the development of new technologies and treatment methods may lead to more hospital admissions. In this thesis, however, the current treatment regime was assumed throughout the projection period.

The structure of consumption may change in the long term towards a larger share of income spent on healthcare. Historical trends in the US and OECD countries have shown that as people get richer, the percentage of their income on healthcare increase more than that on food, clothing and shelter. This may drive the expenditure spent on healthcare over time (Fogel, 2008).

However, as parameter values were considered constant in this thesis, the impact of the potential trends in non-demographic factors mentioned above including those associated with the wider economy such as possible changes in consumption patterns and healthcare system reforms have not been examined.

As the existing HTA models and their data were used, some of the data used to populate the model were not up-to-date. Given the time scale of this PhD and the breadth of the data sources that could potentially be searched, new literature searches for all required data were not considered feasible.

Although the model results include variability among individual observations, probabilistic analyses which involve specifying probabilistic distributions for model parameters and sampling from these distributions using Monte Carlo simulation (Claxton et al., 2005) to handle uncertainty were not performed in the proof-of-concept model reported in this thesis. Also, uncertainty around the structure of the model was not examined. In the model for this thesis, time-to-event distributions and random numbers were used to represent variability across different individuals. However, parameters used to define the distributions were constants that do not vary, and parameter changes were made only when there are changes in: age band; disease status of the individual; or any other events that can affect the point estimates of these parameters. Hence, it is not known whether the uncertainty of some parameters might have had a significant impact on the model outcomes. This is an area for future research.

In order to conduct probabilistic sensitivity analyses (PSA) for this model, relevant evidence needs to be identified and synthesised to define probabilistic distributions to appropriately represent uncertainty around selected parameters. Also, significant model running time is expected: for example, the base-case model involving the three diseases required approximately one hour of running time, so 100 PSA runs would take five days. However, it is possible to reduce total run time by spreading the PSA runs across multiple computers.

10.3. Future research and recommendations

Future research

Due to the nature of this study incorporating the modelling of multiple diseases and the associated need for large amounts of data, a thorough review for each parameter could not be performed. Instead, secondary data used in published literature on the models of the diseases included in this PhD were sought and updated wherever possible. More up-to-date and detailed data (including data on the probabilistic distributions of parameters) and the inclusion of more relevant diseases and correlations between them need to be explored. Preferably, the use of individual patient data and corresponding appropriate statistical analyses of data collected in the relevant setting or country is recommended for a more accurate estimation of parameters to populate the model and thus, provide more reliable outcomes.

Also, further research on treatment costs and utility estimates for comorbid populations would improve the accuracy of estimates from multi-disease models. As shown in this thesis, total and incremental costs may differ when incorporating diseases incurring overlapping costs such as the cost of institutional care from Alzheimer's disease and fracture. Hence, linking multiple diseases can result in changes in the cost-effectiveness estimate of an intervention. Utilities were assumed to be multiplicative in the model for this thesis, which may over- or under-estimate the actual utilities of people with comorbidities. No agreement has been reached regarding the best approach to estimate utility values for people with comorbid conditions. However, there have been a growing number of studies estimating EQ-5D utility values for comorbid populations such as Ara and Brazier (2012) using the Health Survey for England data; and Sullivan and Ghushchyan (2016) for diabetes-related comorbidities.

A valuable extension of the model reported in this thesis would be the linkage of DES models for further diseases additional to those incorporated in this thesis. Using this model, it would be possible to assess a broader range of potential policies and interventions and examine the impact of the correlations between the diseases on the healthcare expenditure at the population level. However, care must be taken to ensure such diseases have the central estimate of incremental QALYs greater than the standard error in other diseases, or if this is the case, that a sufficient number of individuals are simulated. It is also noted that adding any new disease would require an amendment in non-disease mortality by subtracting mortality rates associated with the additional disease.

In order to inform realistic options for policies and interventions, future research is recommended to define specific sets of scenarios that may be implemented in real settings. In addition to this, further applications are possible, such as diverse sub-group analyses using the individual attributes assigned, and the examination of the impact of hypothetical changes in the population composition, strength of correlations between diseases, availability of improved technologies and policy options on future health and healthcare. In the current political context where it is often suggested that radical policy shifts are necessary in order to contain future health and social care costs, the model could be used to explore the potential impact of such changes on public expenditure (Committee of Public Accounts, 2015).

Further research on projecting long term trends in parameters that influence the outcomes of interest, such as those regarding health status, treatment efficacy, and population changes are expected to greatly improve the findings reported in this thesis. Identifying more detailed and up-to-date data sources should precede and will facilitate the projection.

Last but not least, uncertainty around the model results can be explored in future research by undertaking an extensive probabilistic sensitivity analysis. This will aid handling uncertainty when making decisions on alternative treatments and policy options.

Recommendations for modellers

Practical recommendations for modellers include:

- In the linked model, at all events, the values of time to all other events that can occur next should be specified in order to prevent potential errors that may arise when changes are made to the model. For example, although it was modelled that fatal stroke cannot occur immediately after the PAD event, time to fatal stroke should be specified at the PAD event. Otherwise, in the linked model where all the most recent time-to-event values are compared, fatal stroke may be simulated at an incorrect time point.

- Variables that can be updated after time to earliest disease event across all included diseases should be updated only once at a central routing point for efficiency. For example, time points where utility weights change due to the split between the first and subsequent years of events and where adverse events associated with treatment initiation are processed may be updated at the central routing point, without the need for including them at every event.

- Correlations between diseases can be implemented in various ways within the model. Care should be taken to apply correlations in intended directions (event A influencing event B or event B influencing event A).

- Especially at model entry, individual characteristics should be carefully ordered, due to the included correlations. If variable A depends on the status of variable B, then variable B should be specified first. When multiple diseases are linked, this may require careful consideration as a large number of variables representing individual characteristics can be involved.

- Individual disease models should be constructed to have a similar order in which time variables are updated to make model linkage easier. For example, if all variables regarding time to change in treatment efficacy (such as time to treatment discontinuation, and time since treatment discontinuation for the calculation of efficacy fall time) are updated immediately after the time to next event is determined in one model, all the other models should have the same time update structure as this.

The proposed method of linking diseases can be communicated to healthcare decision-makers and stakeholders by focussing on its intuitive logic of event occurrences rather than its background calculations. Decision makers may have neither the technical expertise nor motivation for understanding the underlying calculations and coding methods. Hence, the method can be explained as a mechanism through which the existing single-disease models

are expanded to incorporate other disease events where the central routing point serves as a bridge connecting the wider range of the included disease events. Graphical representation of the outputs of the model would be desirable, rather than trying to communicate the technicalities that are behind the method. Most bespoke DES software provides an intuitive interface with static or animated graphics showing patient movements. Within other generic software, similar graphics can be created manually. It is also possible to show a sequence of events occurring to a particular individual with comorbidities as an example, with the patient characteristics and disease history displayed alongside cost and QALY outcomes.

10.4. Conclusions

This thesis estimated future healthcare expenditure at the individual disease level. The patient-level models linked with correlations can provide more detailed and potentially more accurate results than a crude summation of costs projected from multiple individual disease models.

In summary, the key contributions of this PhD include the following:

- This study provided a modelling framework that has the potential to be flexibly modified or expanded to incorporate other disease areas and examine further outcomes of analysts' interest for the assessment of policy and intervention options and the estimation of future healthcare expenditure.

- The proof-of-concept model developed for this thesis illustrated that model linkage is feasible by implementing a simple routing logic.

- The analysis of hypothetical scenarios such as which disease would save the most if an additional treatment reduces disease events by 20% illustrated that this model could be used to inform decisions on healthcare resource allocations and the assessment of potential policy or interventions.

- The analysis of the linked model identified an unanticipated problem in combining multiple diseases in a single model. In the model for this thesis, the sampling error around incremental QALYs for HD treatment could make a significant impact on the cost-effectiveness of AD and osteoporosis treatments.

- Using the model, the impact of policy changes, for example, switching delivery of services to alternative sectors or increasing private co-payments, on total population health and care costs over time, can potentially be explored.

- A pragmatic literature search method which can be used for literature within diffuse topic areas was developed.

- A literature repository for future researchers to explore the existing literature in the diffuse topic area of ageing and healthcare expenditure was created.

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APPENDICES

Appendix 2.1: Exploratory Searches

MEDLINE search statements

(Ovid MEDLINE(R) <1948 to November Week 3 2011>) (Accessed on 01Dec.2011)

Medline search 1

1   Health Care Costs/ (22464)

2   *Aged/ (19896)

3   *Aging/ (105913)

4   Health Expenditures/ (12037)

5   "Costs and Cost Analysis"/ or "Cost of Illness"/ or "Delivery of Health Care"/ (108834)

6   1 or 4 or 5 (135093)

7   2 or 3 (125271)

8   6 and 7 (**729**)

Medline search 2

1   Aging/ (174887)

2   Aged/ (2073048)

3   1 or 2 (2186829)

4   *Health Expenditures/ or *"Costs and Cost Analysis"/ or *"Cost of Illness"/ or *"Delivery of Health Care"/ (50948)

5   *Health Care Costs/ (9550)

6   4 or 5 (58918)

7   3 and 6 (**7578**)

Medline search 3

1   Health Care Costs/ (22464)

2   Health Expenditures/ (12037)

3   Aging/ (174887)

4   Aged/ (2073048)

5   limit 4 to ("all aged (65 and over)" or "aged (80 and over)") (2073048)

6   limit 3 to ("all aged (65 and over)" or "aged (80 and over)") (61588)

7   Population Dynamics/ (37800)

8   5 or 6 or 7 (2108924)

9   "Delivery of Health Care"/ (56747)

10   "Health Services Needs and Demand"/ (36772)

11   Health Services for the Aged/ (13998)

12   1 or 2 or 9 or 10 or 11 (132873)

13   8 and 12 (**29673**)

Medline search 4

1   Health Care Costs/ (22464)

2   *"Health Services Needs and Demand"/ (13743)

3   "proximity to death".mp. (62)

4   older.ab,ti. (206812)

5   elder$.ab,ti. (151750)

6   *Aged/ (19896)

7   Population Dynamics/sn, td [Statistics & Numerical Data, Trends] (6)

8   "Delivery of Health Care"/ec, lj, ma, mt, og, st, sn, sd, td, ut [Economics, Legislation &
Jurisprudence, Manpower, Methods, Organization & Administration, Standards, Statistics &
Numerical Data, Supply & Distribution, Trends, Utilization] (30876)

9   Health Expenditures/ec, lj, sn, sd, td [Economics, Legislation & Jurisprudence, Statistics &
Numerical Data, Supply & Distribution, Trends] (5538)

10   ag?ing.ab,ti. (110062)

11   3 or 4 or 5 or 6 or 7 or 10 (421010)

12   1 or 2 or 8 or 9 (69587)

13   11 and 12 (**4442**)

Medline search 5

1   ag?ing.ab,ti. (110062)

2   Aged/ (2073048)

3   "proximity to death".mp. (62)

4   older.ab,ti. (206812)

5   *Aging/ (105913)

6   *Population Dynamics/ (7246)

7   Health Care Costs/ (22464)

8   Health Policy/ (44086)

9   Health Expenditures/ (12037)

10   "Health Services Needs and Demand"/ (36772)

11   "Delivery of Health Care"/ (56747)

12   Hospitals/ut [Utilization] (2819)

13   Long-Term Care/ut [Utilization] (325)

14   7 or 8 or 9 or 10 or 11 or 12 or 13 (161216)

15   1 or 2 or 3 or 4 or 5 or 6 (2268361)

16   14 and 15 (**22771**)

Medline search 6

1   ag?ing.ab,ti. (110062)

2   "proximity to death".mp. (62)

3   older.ab,ti. (206812)

4   *Aging/ (105913)

5   *Population Dynamics/ (7246)

6   Health Care Costs/ (22464)

7   Health Policy/ (44086)

8   Health Expenditures/ (12037)

9   "Health Services Needs and Demand"/ (36772)

10   "Delivery of Health Care"/ (56747)

11   Hospitals/ut [Utilization] (2819)

12   Long-Term Care/ut [Utilization] (325)

13   6 or 7 or 8 or 9 or 10 or 11 or 12 (161216)

14   1 or 2 or 3 or 4 or 5 (353046)

15   13 and 14 (**6408**)

Medline search 7

1   ag?ing.ab,ti. (110062)

2   "proximity to death".mp. (62)

3   older.ab,ti. (206812)

4   *Aging/ (105913)

5   *Population Dynamics/ (7246)

6   Health Care Costs/ (22464)

7   Health Policy/ (44086)

8   Health Expenditures/ (12037)

9   Hospitals/ut [Utilization] (2819)

10   Long-Term Care/ut [Utilization] (325)

11   1 or 2 or 3 or 4 or 5 (353046)

12   *"Health Services Needs and Demand"/ (13743)

13   "Delivery of Health Care"/ec, lj, ma, mt, og, sn, sd, td, ut [Economics, Legislation &
Jurisprudence, Manpower, Methods, Organization & Administration, Statistics & Numerical Data,
Supply & Distribution, Trends, Utilization] (26948)

14   6 or 7 or 8 or 9 or 10 or 12 or 13 (113344)

15   11 and 14 (**4361**)

Medline search 8

1   ag?ing.ab,ti. (110062)

2   "proximity to death".mp. (62)

3   older.ab,ti. (206812)

4   *Aging/ (105913)

5   *Population Dynamics/ (7246)

6   Health Care Costs/ (22464)

7   Health Policy/ (44086)

8   Health Expenditures/ (12037)

9   Hospitals/ut [Utilization] (2819)

10   Long-Term Care/ut [Utilization] (325)

11   *"Health Services Needs and Demand"/ (13743)

12   "Delivery of Health Care"/ec, lj, ma, mt, og, sn, sd, td, ut [Economics, Legislation &
Jurisprudence, Manpower, Methods, Organization & Administration, Statistics & Numerical Data,
Supply & Distribution, Trends, Utilization] (26948)

13   6 or 7 or 8 or 9 or 10 or 11 or 12 (113344)

14   *Longevity/ (6638)

15   1 or 2 or 3 or 4 or 5 or 14 (357004)

16   13 and 15 (**4391**)

Medline search 9

1   ag?ing.ab,ti. (110062)

2   "proximity to death".mp. (62)

3   older.ab,ti. (206812)

4   *Aging/ (105913)

5   *Population Dynamics/ (7246)

6   Health Care Costs/ (22464)

7   Health Policy/ (44086)

8   Health Expenditures/ (12037)

9   Hospitals/ut [Utilization] (2819)

10   Long-Term Care/ut [Utilization] (325)

11   *"Health Services Needs and Demand"/ (13743)

12   "Delivery of Health Care"/ec, lj, ma, mt, og, sn, sd, td, ut [Economics, Legislation &
Jurisprudence, Manpower, Methods, Organization & Administration, Statistics & Numerical Data,
Supply & Distribution, Trends, Utilization] (26948)

13   6 or 7 or 8 or 9 or 10 or 11 or 12 (113344)

14   *Longevity/ (6638)

15   1 or 2 or 3 or 4 or 5 or 14 (357004)

16   *Aged/ or *Health Services for the Aged/ (30660)

17   15 or 16 (378103)

18   13 and 17 (**5585**)

Medline search 10

1   "proximity to death".mp. (62)

2   older.ab,ti. (206812)

3   *Aging/ (105913)

4   *Population Dynamics/ (7246)

5   Health Care Costs/ (22464)

6   Health Expenditures/ (12037)

7   "Health Services Needs and Demand"/ (36772)

8   "Delivery of Health Care"/ (56747)

9   Hospitals/ut [Utilization] (2819)

10   Long-Term Care/ut [Utilization] (325)

11   Life Expectancy/ (12612)

12   *Longevity/ (6638)

13   *"Health Services Needs and Demand"/ (13743)

14   "Delivery of Health Care"/ec, lj, ma, mt, og, st, sn, sd, td, ut [Economics, Legislation & Jurisprudence, Manpower, Methods, Organization & Administration, Standards, Statistics & Numerical Data, Supply & Distribution, Trends, Utilization] (30876)

15   ag?ing.ab,ti. (110062)

16   1 or 2 or 3 or 4 or 11 or 12 or 15 (366616)

17   5 or 6 or 9 or 10 or 13 or 14 (77808)

18   16 and 17 (**4188**)

Medline search 11

1   "proximity to death".mp. (62)

2   older.ab,ti. (206812)

3   *Aging/ (105913)

4   *Population Dynamics/ (7246)

5   Health Care Costs/ (22464)

6   Health Expenditures/ (12037)

7   "Health Services Needs and Demand"/ (36772)

8   "Delivery of Health Care"/ (56747)

9   Hospitals/ut [Utilization] (2819)

10   Long-Term Care/ut [Utilization] (325)

11   Life Expectancy/ (12612)

12   *Longevity/ (6638)

15   ag?ing.ab,ti. (110062)

16   1 or 2 or 3 or 4 or 11 or 12 or 15 (366616)

20   5 or 6 or 7 or 8 or 9 or 10 (123795)

21   16 and 20 (**6445**)

Medline search 12

1   "proximity to death".mp. (62)

2   Health Care Costs/ (22464)

3   Hospitals/ut [Utilization] (2819)

4   Long-Term Care/ut [Utilization] (325)

5   *"Health Services Needs and Demand"/ (13743)

6   older.ab,ti. (206812)

7   elder$.ab,ti. (151750)

8   *Aged/ (19896)

9   Population Dynamics/sn, td [Statistics & Numerical Data, Trends] (6)

10   "Delivery of Health Care"/ec, lj, ma, mt, og, st, sn, sd, td, ut [Economics, Legislation & Jurisprudence, Manpower, Methods, Organization & Administration, Standards, Statistics & Numerical Data, Supply & Distribution, Trends, Utilization] (30876)

11   Health Expenditures/ec, lj, sn, sd, td [Economics, Legislation & Jurisprudence, Statistics & Numerical Data, Supply & Distribution, Trends] (5538)

12   *Aging/ (105913)

13   ag?ing.ab,ti. (110062)

14   1 or 6 or 7 or 8 or 9 or 12 or 13 (462108)

15   2 or 3 or 4 or 5 or 10 or 11 (72478)

16   14 and 15 (**4804**)

Medline search 13

1   "proximity to death".mp. (62)

2   Health Care Costs/ (22464)

3   Hospitals/ut [Utilization] (2819)

4   Long-Term Care/ut [Utilization] (325)

5   *"Health Services Needs and Demand"/ (13743)

6   older.ab,ti. (206812)

7   elder$.ab,ti. (151750)

8   *Aged/ (19896)

9   Population Dynamics/sn, td [Statistics & Numerical Data, Trends] (6)

10   "Delivery of Health Care"/ec, lj, ma, mt, og, st, sn, sd, td, ut [Economics, Legislation & Jurisprudence, Manpower, Methods, Organization & Administration, Standards, Statistics & Numerical Data, Supply & Distribution, Trends, Utilization] (30876)

11   Health Expenditures/ec, lj, sn, sd, td [Economics, Legislation & Jurisprudence, Statistics & Numerical Data, Supply & Distribution, Trends] (5538)

12   *Aging/ (105913)

13   ag?ing.ab,ti. (110062)

14   Life Expectancy/ (12612)

15   *Longevity/ (6638)

16   1 or 6 or 7 or 8 or 9 or 12 or 13 or 14 or 15 (475218)

17   2 or 3 or 4 or 5 or 10 or 11 (72478)

18   16 and 17 (**5330**)

Medline search 14

1   "proximity to death".mp. (62)

2   older.ab,ti. (206812)

3   elder$.ab,ti. (151750)

4   *Aged/ (19896)

5   Population Dynamics/sn, td [Statistics & Numerical Data, Trends] (6)

6   *Aging/ (105913)

7   ag?ing.ab,ti. (110062)

8   1 or 2 or 3 or 4 or 5 or 6 or 7 (462108)

9   Health Care Costs/ (22464)

10   Health Expenditures/ (12037)

11   "Health Services Needs and Demand"/ (36772)

12   "Delivery of Health Care"/ (56747)

13   Hospitals/ut [Utilization] (2819)

14   Long-Term Care/ut [Utilization] (325)

15   Life Expectancy/ (12612)

16   *Longevity/ (6638)

17   9 or 10 or 11 or 12 or 13 or 14 (123795)

18   8 or 15 or 16 (475218)

19   17 and 18 (**8873**)

Medline search 15

1   "proximity to death".mp. (62)

2   older.ab,ti. (206812)

3   elder$.ab,ti. (151750)

4   *Aged/ (19896)

5   Population Dynamics/sn, td [Statistics & Numerical Data, Trends] (6)

6   *Aging/ (105913)

7   ag?ing.ab,ti. (110062)

8   1 or 2 or 3 or 4 or 5 or 6 or 7 (462108)

9   Health Care Costs/ (22464)

10   Health Expenditures/ (12037)

11   Hospitals/ut [Utilization] (2819)

12   Long-Term Care/ut [Utilization] (325)

13   Life Expectancy/ (12612)

14   *Longevity/ (6638)

15   *"Health Services Needs and Demand"/ (13743)

16   "Delivery of Health Care"/ec, lj, ma, mt, og, st, sn, sd, td, ut [Economics, Legislation & Jurisprudence, Manpower, Methods, Organization & Administration, Standards, Statistics & Numerical Data, Supply & Distribution, Trends, Utilization] (30876)

17   9 or 10 or 11 or 12 or 15 or 16 (77808)

18   8 or 13 or 14 (475218)

19   17 and 18 (**5770**)

Medline search 16

1   "proximity to death".mp. (62)

2   older.ab,ti. (206812)

3   *Aging/ (105913)

4   *Population Dynamics/ (7246)

5   Life Expectancy/ (12612)

6   *Longevity/ (6638)

7   ag?ing.ab,ti. (110062)

8   1 or 2 or 3 or 4 or 5 or 6 or 7 (366616)

9   Health Care Costs/ (22464)

10   Hospitals/ut [Utilization] (2819)

11   Long-Term Care/ut [Utilization] (325)

12   *"Health Services Needs and Demand"/ (13743)

13   "Delivery of Health Care"/ec, lj, ma, mt, og, st, sn, sd, td, ut [Economics, Legislation & Jurisprudence, Manpower, Methods, Organization & Administration, Standards, Statistics & Numerical Data, Supply & Distribution, Trends, Utilization] (30876)

14   Health Expenditures/ec, lj, sn, sd, td [Economics, Legislation & Jurisprudence, Statistics & Numerical Data, Supply & Distribution, Trends] (5538)

15   9 or 10 or 11 or 12 or 13 or 14 (72478)

16   8 and 15 (**3860**)

Medline search 17

1   "proximity to death".mp. (62)

2   older.ab,ti. (206812)

3   elder$.ab,ti. (151750)

4   *Aged/ (19896)

5   *Aging/ (105913)

6   ag?ing.ab,ti. (110062)

7   Life Expectancy/ (12612)

8   *Longevity/ (6638)

9   Health Care Costs/ (22464)

10   Hospitals/ut [Utilization] (2819)

11   Long-Term Care/ut [Utilization] (325)

12   *"Health Services Needs and Demand"/ (13743)

13   "Delivery of Health Care"/ec, lj, ma, mt, og, st, sn, sd, td, ut [Economics, Legislation & Jurisprudence, Manpower, Methods, Organization & Administration, Standards, Statistics & Numerical Data, Supply & Distribution, Trends, Utilization] (30876)

14   *Population Dynamics/ (7246)

15   1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 14 (480888)

16   Health Expenditures/ec, lj, sn, sd, td [Economics, Legislation & Jurisprudence, Statistics & Numerical Data, Supply & Distribution, Trends] (5538)

17   9 or 10 or 11 or 12 or 13 or 16 (72478)

18   15 and 17 (**5442**)

Complementary MEDLINE search

1   Health Expenditures/ (12037)

2   Forecasting/ (65850)

3   1 and 2 (**613**)

EMBASE search results

Table 1. EMBASE search results (Access Date: 01 Dec. 2011; Database: Embase <1980 to 2011 Week 47>)

No.	Search details	Sample papers												Number of hits	Number of sample papers included (sensitivity)	Percentage of the sample paper among the papers retrieved (precision)
		Zweifel et al. 1999	Lloyd-Sherlock 2000	Spillman and Lubitz 2000	Reinhardt 2003	Schulz et al. 2004	Seshamani and Gray 2004	Borger et al. 2006	Payne et al. 2007	Werblow et al. 2007	Hakkinen et al. 2008	Palankaraya and Yong 2009	Caley and Sidhu 2011			
	Availability:	√	√	√	√	√	√	√	√	√	√	NA	NA	Max. = 10		
1	Broad ageing term search	√	√	√	√	√	√	x	√	√	√	NA	NA	21087	9 (90%)	0.04%
2	Combine Search 1 with "health care cost" using AND	√	x	√	√	x	√	x	√	√	√	NA	NA	11824	7 (70%)	0.06%
3	Title and abstract search with limiters applied	√	x	√	√	x	√	x	√	√	√	NA	NA	5248	7 (70%)	0.13%
4	As Search 3 but with narrower HC terms	√	x	√	√	x	√	x	√	√	√	NA	NA	6031	7 (70%)	0.12%
5	Broader ageing terms & focused	√	x	√	x	x	√	x	√	√	√	NA	NA	1343	6 (60%)	0.45%

No.	Search details	Sample papers												Number of hits	Number of sample papers included (sensitivity)	Percentage of the sample paper among the papers retrieved (precision)
		Zweifel et al. 1999	Lloyd-Sherlock 2000	Spillman and Lubitz 2000	Reinhardt 2003	Schulz et al. 2004	Seshamani and Gray 2004	Borger et al. 2006	Payne et al. 2007	Werblow et al. 2007	Hakkinen et al. 2008	Palankaraya and Yong 2009	Caley and Sidhu 2011			
Availability:		√	√	√	√	√	√	√	√	√	√	NA	NA	Max. = 10		
	"*health care cost" only for HC terms															
6	Ageing terms from Search 5 combined with much broader HC terms	√	x	√	√	√	√	x	√	√	√	NA	NA	10213	8 (80%)	0.08%
7	As Search 6 but with broader HC terms added (including *health care policy)	√	√	√	x	√	√	x	√	√	√	NA	NA	12881	8 (80%)	0.06%
8	As Search 6, but no 'Elder' term & with 'health policy' term added	√	√	x	√	√	√	x	√	√	√	NA	NA	9739	8 (80%)	0.08%

No.	Search details	Zweifel et al. 1999	Lloyd-Sherlock 2000	Spillman and Lubitz 2000	Reinhardt 2003	Schulz et al. 2004	Seshamani and Gray 2004	Borger et al. 2006	Payne et al. 2007	Werblow et al. 2007	Hakkinen et al. 2008	Palankaraya and Yong 2009	Caley and Sidhu 2011	Number of hits	Number of sample papers included (sensitivity)	Percentage of the sample paper among the papers retrieved (precision)
							Sample papers									
	Availability:	√	√	√	√	√	√	√	√	√	√	NA	NA		Max. = 10	
9	As Search 6, but no 'health policy and health service' term and with 'Longevity' added	√	√	√	x	√	√	x	√	√	√	NA	NA	8587	8 (80%)	0.09%
10	The same age terms as Search 9 but no 'health policy' broader cost terms	√	√	√	√	√	√	x	√	√	√	NA	NA	11351	9 (90%)	0.08%
11	As Search 10, but no 'older' term & with narrower HC terms added	√	√	√	√	√	√	x	√	√	√	NA	NA	3584	9 (90%)	0.25%

√: Included; X: Not included; NA: Not available in the database.

EMBASE search statements

EMBASE <1980 to 2011 Week 47> (Accessed on 01 Dec 2011)

EMBASE search 1

1   aged/ (1894973)

2   *aging/ (80604)

3   1 or 2 (1939177)

4   "health care cost"/ (103416)

5   health care delivery/ (109691)

6   health care financing/ (10624)

7   health care need/ (15425)

8   4 or 5 or 6 or 7 (220998)

9   3 and 8 (**21087**)

EMBASE search 2

1   aged/ (1894973)

2   *aging/ (80604)

3   1 or 2 (1939177)

4   "health care cost"/ (103416)

5   3 and 4 (**11824**)

EMBASE search 3

1   "health care cost"/ (103416)

2   health care delivery/ (109691)

3   health care financing/ (10624)

4   health care need/ (15425)

5   1 or 2 or 3 or 4 (220998)

6   ag?ing.ti,ab,kw. (131566)

7   older.ti,ab,kw. (241970)

8   elder$.ti,ab,kw. (190237)

9   6 or 7 or 8 (493848)

10   5 and 9 (11346)

11   limit 10 to (human and english language and aged <65+ years>) (**5248**)

EMBASE search 4

1   "health care cost"/ (103416)

2   ag?ing.ti,ab,kw. (131566)

3   older.ti,ab,kw. (241970)

4   elder$.ti,ab,kw. (190237)

5   2 or 3 or 4 (493848)

6   1 and 5 (**6031**)

EMBASE search 5

1   *"health care cost"/ (23189)

2   *aging/ (80604)

3   ag?ing.ti,ab,kw. (131566)

4   older.ti,ab,kw. (241970)

5   elder$.ti,ab,kw. (190237)

6   2 or 3 or 4 or 5 (517676)

7   1 and 6 (**1343**)

EMBASE search 6

1   "health care cost"/ (103416)

2   health care need/ (15425)

3   *aging/ (80604)

4   ag?ing.ti,ab,kw. (131566)

5   older.ti,ab,kw. (241970)

6   elder$.ti,ab,kw. (190237)

7   health care utilization/ (30309)

8   3 or 4 or 5 or 6 (517676)

9   1 or 2 or 7 (139384)

10   8 and 9 (**10213**)

EMBASE search 7

1   "health care financing"/ (10624)

2   *"health care cost"/ (23189)

3   health care need/ (15425)

4   "health care facilities and services"/ (365)

5   *aging/ (80604)

6   health care utilization/ (30309)

7   long term care/ (75092)

8   ag?ing.ti,ab. (127541)

9   older.ti,ab. (241697)

10   elder$.ti,ab,kw. (190237)

11   5 or 8 or 9 or 10 (515846)

12   1 or 2 or 3 or 4 or 6 or 7 (148361)

13   11 and 12 (**12881**)

EMBASE search 8

1   "health care cost"/ (103416)

2   health care policy/ (119016)

3   health care need/ (15425)

4   *aging/ (80604)

5   health care utilization/ (30309)

6   ag?ing.ti,ab. (127541)

7   older.ti,ab. (241697)

8   *population dynamics/ (9052)

9   4 or 6 or 7 or 8 (387246)

10   1 or 2 or 3 or 5 (242328)

11   9 and 10 (**9739**)

EMBASE search 9

1   "health care financing"/ (10624)

2   *"health care cost"/ (23189)

3   health care need/ (15425)

4   "health care facilities and services"/ (365)

5   *aging/ (80604)

6   health care utilization/ (30309)

7   long term care/ (75092)

8   1 or 2 or 3 or 4 or 6 or 7 (148361)

9   ag?ing.ti,ab. (127541)

10   older.ti,ab. (241697)

11   *population dynamics/ (9052)

12   longevity/ (13859)

13   5 or 9 or 10 or 11 or 12 (396390)

14   8 and 13 (**8587**)

EMBASE search 10

1   "health care financing"/ (10624)

2   "health care cost"/ (103416)

3   health care need/ (15425)

4   *aging/ (80604)

5   health care utilization/ (30309)

6   long term care/ (75092)

7   ag?ing.ti,ab. (127541)

8   older.ti,ab. (241697)

9   *population dynamics/ (9052)

10   longevity/ (13859)

11   4 or 7 or 8 or 9 or 10 (396390)

12   1 or 2 or 3 or 5 or 6 (218366)

13   11 and 12 (**11351**)

EMBASE search 11

1   "health care financing"/ (10624)

2   "health care cost"/ (103416)

3   health care need/ (15425)

4   *aging/ (80604)

5   health care utilization/ (30309)

6   long term care/ (75092)

7   ag?ing.ti,ab. (127541)

8   *population dynamics/ (9052)

9   longevity/ (13859)

10   4 or 7 or 8 or 9 (182117)

11   1 or 2 or 3 or 5 or 6 (218366)

12   10 and 11 (**3584**)

Complementary EMBASE search

1   *"health care cost"/ (23189)

2   forecasting/ (35943)

3   1 and 2 (**566**)

EconLit <1961 to October 2011> searches

Search 1

Broad search

3   older.ti,ab. (4628)

4   elder$.ti,ab. (2797)

5   long term care.mp. [mp=heading words, abstract, title, country as subject] (603)

10   "health?care expenditure".mp. [mp=heading words, abstract, title, country as subject] (29)

11   "health?care demand".mp. [mp=heading words, abstract, title, country as subject] (2)

12   "health?care utili?ation".mp. [mp=heading words, abstract, title, country as subject] (38)

22   ag?ing.ti,ab,kw. (3309)

23   health?care.ti,ab,kw. (4891)

30   health.ti,ab,kw. (26182)

31   hospital$.ti,ab,kw. (4295)

32   3 or 4 or 22 (9621)

33   5 or 10 or 11 or 12 or 23 or 30 or 31 (29769)

34   32 and 33 (**2248**)

Search 2

Narrow search

19   ag?ing.ti,ab,kw. (3309)

20   health?care.ti,ab,kw. (4891)

35   19 and 20 (**159**)

Search 3

19   ag?ing.ti,ab,kw. (3309)

37   demography.ti,ab,kw. (973)

38   population.ti,ab,kw. (25187)

20   health?care.ti,ab,kw. (4891)

27   health.ti,ab,kw. (26182)

28   hospital$.ti,ab,kw. (4295)

39   19 or 37 or 38 (27416)

40   20 or 27 or 28 (29395)

41   39 and 40 (**3471**)

Search 4 (Accessed on 13 Dec. 2011)

1   ag?ing.ti,ab,kw. (3320)

2   health?care.ti,ab,kw. (4908)

3   hospital$.ti,ab,kw. (4303)

4   demograph$.ti,ab,kw. (10948)

5   "long term care".mp. [mp=heading words, abstract, title, country as subject] (603)

6   longevity.mp. [mp=heading words, abstract, title, country as subject] (911)

7   1 or 4 or 6 (14120)

8   2 or 3 or 5 (9004)

9   7 and 8 (**542**)

ASSIA (1987-) searches (accessed on 30/11/2011)

Search 1: Narrow search

su.EXACT("Health costs" OR "Health services" OR "Long term care" OR "Health policy" OR "Expenditure") AND su.EXACT("Ageing" OR "Elderly people" OR "Demographic change" OR "Population") **752** results

Search 2: Broader search

 (su.EXACT("Ageing" OR "Elderly people" OR "Demographic change" OR "Population") OR AB,TI(ag?ing)) AND su.Exact("health care utilization" OR "health care costs" OR "health care needs" OR "Health costs" OR "Health services" OR "Long term care" OR "Health policy" OR "Expenditure") **764** results

Table 2. EconLit <1961 to October 2011>, ASSIA(1987-current), and CINAHL (1982-) search results

No.	Search details	Zweifel et al. 1999	Lloyd-Sherlock 2000	Spillman and Lubitz 2000	Reinhardt 2003	Schulz et al. 2004	Seshamani and Gray 2004	Borger et al. 2006	Payne et al. 2007	Werblow et al. 2007	Hakkinen et al. 2008	Palangkaraya and Yong 2009	Caley and Sidhu 2011	Number of hits	Number of seed papers identified (coverage)	Access Date
							Seed Papers									
EconLit availability:		Yes	No	No	No	No	Yes	No	No	Yes	Yes	Yes	No		Max.=5	
1	Broad title, abstract, keyword search	√	NA	NA	NA	NA	√	NA	NA	√	√	√	NA	**2248**	5/5 (100%)	21/11/11
2	Narrow search	√	NA	NA	NA	NA	√	NA	NA	√	√	√	NA	**159**	5/5 (100%)	21/11/11
3	Population & demography added to ageing terms	√	NA	NA	NA	NA	√	NA	NA	√	√	√	NA	**3471**	5/5 (100%)	21/11/11
4	Refined from Search 3 including 'long-term care' and 'longevity'	√	NA	NA	NA	NA	√	NA	NA	√	√	√	NA	**542**	5/5 (100%)	13/12/11
ASSIA availability:		Yes	Yes	No	No	No	Yes	No	Yes	Yes	No	No	Yes		Max.=6	
1	Narrow search	√	√	NA	NA	NA	√	NA	√	√	NA	NA	√	**752**	6/6 (100%)	30/11/11
2	Broad search	√	√	NA	NA	NA	√	NA	√	√	NA	NA	√	**764**	6/6 (100%)	30/11/11
CINAHL availability:		No	No	No	No	Yes	No	No	No	Yes	No	No	Yes		Max.=3	
1	Complementary search similar to Medline Search 16	NA	NA	NA	NA	√	NA	NA	NA	√	NA	NA	√	**1334**	3/3 (100%)	30/11/11

√: Included; X: Not included; NA: Not available in the database

Appendix 2.2: Final search results

<u>MEDLINE</u> (accessed on: 19 January 2012)

Database: Ovid MEDLINE(R) <1946 to January Week 2 2012>

1   "proximity to death".mp. (64)

2   older.ab,ti. (200935)

3   *Aging/ (101582)

4   *Population Dynamics/ (7148)

5   Life Expectancy/ (12347)

6   *Longevity/ (6274)

7   ag?ing.ab,ti. (105283)

8   1 or 2 or 3 or 4 or 5 or 6 or 7 (354785)

9   Health Care Costs/ (22138)

10   Hospitals/ut [Utilization] (2816)

11   Long-Term Care/ut [Utilization] (323)

12   *"Health Services Needs and Demand"/ (13692)

13   "Delivery of Health Care"/ec, lj, ma, mt, og, st, sn, sd, td, ut [Economics, Legislation &
Jurisprudence, Manpower, Methods, Organization & Administration, Standards, Statistics &
Numerical Data, Supply & Distribution, Trends, Utilization] (30683)

14   Health Expenditures/ec, lj, sn, sd, td [Economics, Legislation & Jurisprudence, Statistics &
Numerical Data, Supply & Distribution, Trends] (5469)

15   9 or 10 or 11 or 12 or 13 or 14 (71870)

16   8 and 15 (**3814**)

17   Health Expenditures/ (11889)

18   Forecasting/ (64816)

19   17 and 18 (603)

20   16 or 19 (**4353**)

21   limit 20 to (english language and humans) (**3731**)

<u>EMBASE</u> (accessed on 19 Jan 2012)

Database: Embase <1980 to 2012 Week 02>

1   "health care financing"/ (10664)

2   "health care cost"/ (104506)

3   health care need/ (15605)

4   *aging/ (81282)

5   health care utilization/ (30700)

6   long term care/ (75858)

7   ag?ing.ti,ab. (129066)

8   *population dynamics/ (9077)

9   longevity/ (14032)

10   4 or 7 or 8 or 9 (184007)

11   1 or 2 or 3 or 5 or 6 (220647)

12   10 and 11 (**3624**)

13   *"health care cost"/ (23366)

14   forecasting/ (36029)

15   13 and 14 (**567**)

16   12 or 15 (**4153**)

17   limit 16 to (human and english language) (**3052**)

<u>EconLit</u> (accessed on 19 January 2012)

Database: Econlit <1961 to December 2011>

1   ag?ing.ti,ab,kw. (3354)

2   health?care.ti,ab,kw. (4953)

3   hospital$.ti,ab,kw. (4347)

4   demograph$.ti,ab,kw. (11067)

5   "long term care".mp. [mp=heading words, abstract, title, country as subject] (608)

6   longevity.mp. [mp=heading words, abstract, title, country as subject] (932)

7   1 or 4 or 6 (14285)

8   2 or 3 or 5 (9086)

9   7 and 8 (**549**)

<u>ASSIA (1987-)</u> (accessed on 19 January 2012)

(su.EXACT("Ageing" OR "Elderly people" OR "Demographic change" OR "Population") OR AB,TI(ag?ing)) AND su.Exact("health care utilization" OR "health care costs" OR "health care needs" OR "Health costs" OR "Health services" OR "Long term care" OR "Health policy" OR "Expenditure")

757* results (*Represents the approximate result count without duplicates)

Appendix 3.1. Review of Projection Models

Table 1. Summary of Statistical/Econometric models

Name/developer of the model	Main objective	Projection outcomes	Time horizon	Method	Country	Key factors included	Key assumptions	Key datasets	Main scenarios	Conclusions
Bhattacharya et al. (2004): NBER (National Bureau of Economic Research) and RAND model	To project the future Medicare costs	Future per-capita Medicare cost	2000-2030	Stat modelling (regression-based forecasting model); However, cost projections are based on cell-based method combining the age-gender-disability profiles of Medicare costs from the previous section with our forecasts of population in each age-gender-disability cell to produce forecasts of Medicare costs.	US			Medicare Current Beneficiary Survey (MCBS) and National Health Interview Study (NHIS)	1. Base: Age-prevalence profile changes based on trends in the MCBS; 2. Constant: Age-prevalence profile fixed based on initial year; 3. Manton et al (1997): Age-prevalence profile changes based on trends in NLTCS from 1989-1994; 4. Manton and Gu (2001): Age-prevalence proffle changes based on trends in NLTCS from	Per-capita Medicare costs will decline for the next 15-20 years; this finding is in accordance with recent declines in disability among the elderly. By 2020, however, percapita costs begin to rise as a result of growth in disability among the young old. As these young-old cohorts age, per-capita costs will continue to grow. Total costs may well remain relatively flat until 2010 and then begin to rise as per-capita costs will cease to decline rapidly enough to offset the influx of new elderly people. As a result of growth in per-capita costs, total costs will then begin to grow at an accelerating rate.

Study	Objective	Outcome	Period	Method	Country	Variables	Assumptions	Data	Scenarios	Conclusions
										1994-1999
Breyer and Felder (2006)	To estimate the impact of both age and time-to-death on health care expenditures; To estimate what the expenditures in 2002 would have been if the demographic composition corresponded to the predictions for certain future dates;	Per-capita health expenditures of Social Health Insurance	2002-2050	Regression analysis (two-part model), age–expenditure profiles for men and women, each separated by survival status, are estimated.	Germany	Age, gender, survival status.	Everything but the age structure remains constant at year 2002 levels	Swiss sickness fund 1999 claims data	1. Only age structure changes; 2. Age structure and medical technology changes;	Explicitly accounting for costs in the last years of life leads to a downward correction of the demographic impact on per-capita expenditures as compared to a calculation on the basis of crude age-specific health expenditures; the impact of medical progress on health care expenditures is much larger than the impact of ageing so that taking this factor into account diminishes the relative importance of the error in the calculation of the demographic effect even further; Given the tremendous increase in expenditures over the next decades, the transition to uniform per-capita premiums may be a necessary step to at least partially uncouple health care financing from demography.
Centers for Medicare and Medicaid (CMS)/Office of Actuary model CMS (2001, 2009, 2011) - Heffler et al. 2002, 2003; Smith et al. 1999	To project US healthcare spending on personal care, Medicare and Medicaid	Total national health expenditures	10 years	Statistical/Actuarial models (NHE projection model is an econometric model that is estimated based on the historical National Health Expenditures; Actuarial projections for Medicare and Medicaid spending and projections for macroeconomic variables are included as exogenous variables)	US	Macroeconomic variables (economic growth and inflation), disposable personal income, relative medical price inflation, etc.	Based on historical data; Set of macroeconomic assumptions	Board of Trustees report; National Health Interview Survey (NHIS); Current Population Survey (CPS);		Depends on the application;

ENEPRI/AHEAD - Christiansen et al. (2006)	To investigate the relationship between ageing and the development in the aggregate healthcare expenditure in EU countries on a macroeconomic level.	More of a paper examining factors that may influence healthcare spending; Total HCE per capita for the next 10 years;	10 years	Statistical modelling (regression and time-series analysis)	EU	Various demand, supply, and institutional factors		OECD/WHO, EUROSTAT		The 10-year expenditure forecast show varying speeds during the 2004-2014 period. Expenditure is expected to increase but to a varying extent.
ENEPRI/AHEAD project - Khoman and Weale – Builds on Christiansen et. al (2006)	To project health care expenditure in order to assess the impact of ageing on future spending levels and to re-estimate it in a form which is convenient for incorporation into a spreadsheet model.	Total health care expenditure per capita		Stat modelling (fixed effects panel regression estimated by Generalised Least Squares)	EU	Economic variables; Demographic variables; Health care system variables;		Panel dataset that covers 13 of the old EU member states (1980 - 2003)		A variety of variables seems to influence health spending- and the influence of factors such as the share of the public sector in the total could easily be omitted from more mechanical calculations.Institutional variables are of great importance. (e.g. Finland having limited its health spending over the last ten years or so by means of institutional change); Total spending on health is significantly and positively related to the share of health spending paid for by the public sector.
Hashimoto et al. (2010)	To examine the impact of aging, time to death, survivorship, and use of LTC on medical care expenditure for people aged 65 and above in Japan	Probability of service use; the amount of expenditure conditional on the use of the service;		Stat modelling (two part model); Individual model (related to Polder et al. (2006), but still the model is different);	Japan	Survival status and age		Japanese public medical insurance data covering outpatient and inpatient medical services that cover the cost of physicians, hospitals, drugs, laboratory examinations, dental care, and surgical equipment		Findings are similar to those of Polder, et al. (2006); Elderly survivors require less spending on medical care compared to decedents, and survivors' medical costs did not differ across age categories.

Lowthian et al. 2011	To measure the growth in emergency ambulance use across metropolitan Melbourne since 1995, to measure the impact of population growth and ageing on these services, and to forecast demand for these services in 2015	Emergency ambulance use	1995–2015	Stat modelling: Log-linear regression modelled the main effects and interactions of sex and age, and of age and time on the logarithm of the transportation rate while controlling for the introduction of a referral service (The future numbers of transportations were calculated by multiplying predicted rates by projected population estimates).	AUS	Age and gender		Emergency transportation data by Ambulance Victoria	Projections based on conservative assumptions of fertility, life expectancy and migration	Transportation rate increases were only partly accounted for by changes in population size and age and sex distribution. The rate of transportation for all ages increased by 75% over the 14 years studied (95% CI, 62%–89%). Patients aged 85 years were eight times (incident rate ratio, 7.9 [95% CI, 7.6–8.3]) as likely to be transported as those aged 45– 69 years. Demand by people aged 85 years will continue to accelerate in the future. The study showed that introduction of a referral service reduced the rate of transportations but did not slow the steady increase over time.
OECD econometric analysis (Antioch et al. model) - Not a projection study Antioch (1997, 1999); Gerdtham et al. (1993); Oxley and MacFarlan (1994); Hagemann and Nicoletti (1989)	To estimate total and components of hospital expenditure in OECD countries; To discuss the various policy options for better achievement of health policy goals within the context of strained budgets	Overall Expenditure; Ambulatory Care; In-patient Care Expenditure; Pharmaceutical; Factors underlying past and future spending pressures;		Statistical modelling (regression and time-series analysis)	OECD countries	Efficiency and Effectiveness of Health-care Supply		OECD Health Data (1993)		
Powers et al. (2005)	To evaluate several statistical modelling approaches in predicting	Total annual health costs; Pharmacy costs;	2001-2003 (retrospective validat	Stat modelling (linear models) Two-year longitudinal analysis; Individual Stat model: several multivariate econometric	US	Age/gender/pharmacy cost/PHD category	Assumptions required to run the specified statistical models.	Integrated medical and pharmacy insurance claims data from a >600,000 participant state employer		The Pharmacy Health Dimensions (a pharmacy-based risk index) derived solely from pharmacy claims data can be used to predict future total health costs. Using PHD with a simple OLS model may provide similar predictive accuracy in

	prospective total annual health costs (medical plus pharmacy) of health plan participants using Pharmacy Health Dimensions (PHD).		ion)	approaches were explored. OLS, log-transformed regression, two-part models					comparison to more advanced econometric models.
van Elk et al. (2009) – ENEPRI/AHEAD	To give an up to date overview of the literature on health care expenditures & to contribute to the existing literature by investigating the in an empirical analysis using an error-correction model	Health care expenditure per capita; total healthcare expenditure;		Stat modelling (panel time-series, seemingly unrelated regression (SUR) model)	EU			Impact of several factors on health care expenditures was investigated	the increasing price of health care helps to explain the increase in real health care expenditures. However, the use of health care in volume terms is negatively affected by the increasing price. This effect seems to be stronger in periods of cost containment policy. the increasing price of health care helps to explain the increase in real health care expenditures. However, the use of health care in volume terms is negatively affected by the increasing price. This effect seems to be stronger in periods of cost containment policy.
Wang (2009)	To forecast short-term growth of health expenditure; To investigate whether the current equity market captures useful information on the growth of future health care	Total healthcare expenditure	Short term (1 year) predic tabilit y	Stat modelling (random walk, AR(1), AR(2); Stock returns model)	US	Stock returns, asset prices, GDP growth; (Not many factors included)		US annual observations of real personal health care expenditure (HEALTH) and its three major components: hospital care (HPCARE), durable medical equipment (MEDEQ) and prescription drugs (DRUG).	The market performances of three health care related industry portfolios, the aggregate health sector, health services and durable medical equipment,	The random walk model performs quite well in forecasting all four expenditure variables; Model incorporating HCEGRTH and one-period lagged RETURN performs best for HEALTH among the six competitors, implying that the one-period lagged stock returns contain useful information for forecasting current period total personal health care expenditure;

	expenditure								have some predictive power for their corresponding health expenditure components at a one-year horizon.	
Zhao et al. (2001, 2005)	T o examine and evaluate models that use inpatient encounter data and outpatient pharmacy claims data to predict future health care expenditures.	Individual model;		Stat modelling (regression)	US	Historical drug expenditure of enrollees and diagnostics data;		1997 and 1998 MEDSTAT Market Scan ® Research Database	NA	Models using both drug and diagnostic data best predicted subsequent-year total health care costs (highest R2 = 0.168 versus 0.116 and 0.146 for models based on drug or diagnostic data alone, respectively); Drug costs were far more predictable than total or non-pharmacy cost.

Table 2. Summary of macro-simulation models

Name/developer of the model	Main objective	Projection outcomes	Time horizon	Method	Country	Key factors included	Key assumptions	Key datasets	Main scenarios	Conclusions
Alberta diabetes model (Lau et al. 2011)	To predict the prevalence and costs of diabetes from 2008 to 2035 in Alberta	Diabetes prevalence, total physician costs, emergency department costs and hospital costs	2008-2035	Macro modelling (Life table method); Life table model similar to dynamic multi-state approach (new incident cases are added and deaths are subtracted; to estimate prevalence and cost of care, etc.	Canada	Disease incidence, prevalence, mortality; Migration;	incidence will continue to increase for an additional 8 years (2008 to 2015) and mortality rates will continue to decrease for the same period, based on trends in the preceding decade (1995 to 2007).	Alberta Diabetes Surveillance System (ADSS)		Total healthcare costs for diabetes in Alberta in 2035 were predicted to be $2.27 billion, a 237% increase from 2007. The category with the greatest increase in costs is predicted to be total physician costs, with a rise of 253%
Batljan and Lagergren (2004)	To make projections of future inpatient/outpatient health care demand showing how demographic development may influence health care demand in Sweden	Inpatient and outpatient costs in terms of remaining years of life	2000 - 2030	Macro modelling (the number of people given age group and gender with 0, 1, 2, 3, 4, 5, 6+ years left to live * previous cost estimates—given age group, gender and remaining years = total inpatient/outpatient cost per gender, age and remaining years of life)	Sweden	Age, gender, remaining years of life	postponement of morbidity hypothesis (i.e. connection between the decline in mortality and the improvement in health)	Data from Skane region (The National Board of Health and Welfare 2002)	NA	The high per capita cost of those with few years left to live; the less than 1% of population with zero remaining years of life account for circa 11% of the total annual expenditure for inpatient care; The increase in health care demand in the period 2000–2030 arrived at, by means of our method, is circa 37% lower than estimates done with a simple demographical extrapolation;

Begg et al. (2008)	To introduce a large body of work that explores the modelling of expenditure on health services per person living with major causes of disease or injury as a valid basis for conclusions regarding future health expenditure in Australia;	Total health expenditure	2002-2032	Macro-simulation (Separate projections were calculated for important health conditions by type of expenditure (hospital care, medical services, pharmaceuticals, aged care homes and other health services))	US	Expected changes in the number of affected cases, the proportion of cases treated, the volume of health services per treated case and excess health price inflation	Background paper for the UN World Economic Social Survey (2007)		Total health expenditure in Australia will grow by 0.5% greater than growth in the economy, to 10.8% of GDP in 2032–33. Population ageing will account for 32.3% of this growth; and non-demographic factors (excess price inflation, treatment proportion and volume per case) a further 36.5%.
Boyle et al. (2010): Burden of diabetes	To provide contemporary, realistic estimates of the growth of the national diabetes burden; a formal projection of costs is beyond the scope of this analysis;	National burden of diabetes	2010-2050	Individual model; Currently Macro-modelling with Hare et al.; Disease-specific (diabetes); a series of dynamic models that consisted; of systems of difference equations in time; (three-, four-, and five-state models); GAUSS software; More of a health projection model;	US	The time-varying transition matrix that differentially allotted population into states of normal glucose tolerance, prediabetes, and undiagnosed diabetes/diagnosed diabetes;	1. people cannot move from diabetes to nondiabetes; 2. the relative risks of death for the two diabetes states versus the no diabetes state are constant over time, i.e. no time variation; 3. the transition rates to diagnosed or undiagnosed diabetes for nondiabetics are constant multiples of	US Census Bureau and the Centers for Disease Control and Prevention (CDC)		All four model scenarios indicate at least a doubling, and in some cases an even greater increase, in the number of people with diagnosed diabetes from 2010 through 2050.

							the transition rate to diagnosed diabetes for undiagnosed diabetics.			
Caley and Sidhu (2011)	To describe a methodology that can be easily applied to estimating future healthcare costs using routinely available data that takes into account both increases in costs in the years before death and morbidity compression	Global healthcare demand	2006-2031	Macro model (indiv)	UK	Time to death	Compression or expansion of morbidity	Department of Health data; Office for National Statistics data;	i) Compression /Expansion of morbidity, and ii) Proximity to death taken into account,	Models with different assumptions resulted in markedly different estimates of future costs. The increases in healthcare costs in the final years of life and morbidity compression/expansion are fundamental and have a large effect on costs.
CBO - the Congressional Budget Office's (CBO's) long-term model, CBOLT	The model developed over 2001-2009 is used to analyse the budgetary and distributional effects of the Social Security programme and other federal policies and programmes, to evaluate potential reforms to federal entitlement programmes, and to quantify the nation's long-term fiscal challenges.	National long term care expenditures (Medicare, Medicaid, Private Long-Term Care Insurance, Out of Pocket, Other Payer)	Long term 75 year projectio ns	CBOLT itself is a microsimulation model which can generate distributional outcomes, however, projections of health-care spending were made at an aggregated level in its actuarial section (macro-simulation)	US	Excess health cost growth; economic growth; age composition of the population				Various scenario analyses are available using the micro-simulation model; Distribution effects can be examined

Colombier and Weber (2011)	To examine the impact of population ageing on healthcare expenditure	Health and long-term care expenditure	2004-2050	HC expenditures are decomposed by age groups, gender and services, i.e. LTC and HC. The decomposition of HC expenditures results in four different expenditure profiles. These profiles encompass the per capita expenditure of men and women by age group for HC and LTC.	Switzerland	Age; Proximity to death; Medical progress;	No policy change is taken into account; real wage growth corresponds to labour productivity growth of the economy; productivity growth (v) to be equal to 1%			
COMPACCS model (Angus et al. 2000)	To estimate the future demand for critical care and pulmonary services	Demand and supply of intensivists (demand as physician-per-population ratios)		The three major components of the model are • Population projections by age,42 sex, and metropolitan/non-metropolitan location; • Projected insurance distribution by insurance type, age, sex, metropolitan/nonmetropolitan location; and • Detailed physician-to-population ratios.	US		The COMPACCS study starts with the assumption that in the base year (1997) intensivist supply and demand are in equilibrium.			COMPACCS estimated a shortage in the number of available intensivist hours of care equal to 22 percent of demand by 2020 and 35 percent by 2030.16 In their analysis, the shortage became more severe if the demand for intensivist care was extended to a greater proportion of ICU patients. Alternative scenarios modeling changes in the variables affecting demand for critical care services, including greater managed care penetration, had little impact on this shortage.

Desai et al. (2008)	To project the demand for older people's services over the next 5 years, and calculate the impact this would have on the service provision required; to test the effectiveness of different interventions	Future demand for older people's services (numbers of initial contacts, numbers of service recipients, numbers of care packages, etc.)	2006-2011	Macro-modelling (System Dynamics (SD) simulation model (NOT a micro-modelling)); Individual model;	UK	Age of clients; whether client's initial referral is from an acute NHS setting or elsewhere; Whether the client was initially assessed as having a critical or substandtial level of need;	Due to the frequent movements of clients, age-group changing was not incorporated in the demand side model;		Influences' were changed to test different scenarios; Changes in rate of client inflow; Population increases/decreases;	As anticipated the numbers requiring care will increase over the next 5 years, particularly among clients aged over 85. The effects of two possible interventions were explored and demonstrate that providing care to critical clients only will reduce the numbers receiving care. However, a decrease in the number of substantial clients does not lead to the same percentage decrease in the number of care packages.
DG-ECFIN Ageing Reports - European Commission (EC)	To provide objective, reliable and comparable information on possible challenges to fiscal sustainability of EU countries in relation to population ageing.	Aggregate health and long term care expenditure, and other public expenditures.	up to 2060	Macro-simulation	EU	Macro-economic: labour productivity and potential economic growth; new technologies and medical progress; institutional features of the health system;		EUROPOP	Scenarios added to the 2009 report: Non-demographic determinants scenario: using econometric estimates; ii) Decomposed indexation scenario: input specific indexation (unit cost)	Limited growth in total population size together with a growing proportion of elderly will lead to ever higher demand for healthcare; Developments in medical technology will require further investment, but may pay off over the medium and long term; Persisting high discrepancies in healthcare provision across EU states will exert additional pressure on public expenditure in countries offering the narrowest and incomplete coverage to their citizens.

| ENEPRI - AIM (semi-aggregate model) - Ferraresi & Monticone (2009 - ENEPRI No. 62); Soede et al. (2004) | To project public expenditure on pensions and other social benefits, and produce a sustainability indicator (Not necessarily project healthcare expenditure, but may inform the projection methods) | Aggregate projections of social protection expenditures; Semi-aggregate projections of income sources by age class and gender; an indicator of the pension system sustainability | up to 2050 | Semi-aggregate approach (some features of the multistate approach as well as the aggregate models); Social projection expenditures were computed as the project of the number of recipients times the average amoung of each benefit. | EU | Stylised parameterisation of national economic and institutional features; | Conservative assumptions regarding future migration flows; Interest rate (short term real) 2% for all countries and all periods; Debt to GDP ratio Constant for the whole projection period; All income sources/average benefit in each category are assumed to grow for each age/gender class according to labour productivity; | ECHP and SHARE; Europop 2004 | i. Lisbon scenario (unrealistic): 70% for total employment, 60% for female employment; 50% for middle-aged (55-64) employment; Sensitivity analysis on demographic projections; Sensitivity analysis on old-age benefits level; | the increase in social spending is evident in many countries. The increase in employment and the recent reforms are at least partially able to offset the rise in public pensions expenditure. |

ENEPRI AGIR project (Westerhout and Pellikaan 2005)	To assess the implications of population ageing for acute healthcare, LTC, and public pension expenditure for 15 EU countries;	Age-specific prevalence rates, average length of hospital stay, average number of contacts with a doctor;		Macro-simulation	EU	Time trend of age profile of health expenditure included;		Main projection by DIW (German Institute for Economic Research); EU- EPC Eurostat datasets for population figures; Utilisation data from ECHP (European Community Household Panel);		
ESRI's HERMES model of the Irish economy (Layte et al. 2009)	To apply the demographics projections from HERMES to the patterns of healthcare utilisation and growth trends;	Overall population changes; Acute public hospital services; GP utilisation; Outpatient services; Long-term health and social care services;	2006-2021	Macro-simulation; HERMES - population projection model;	Ireland	Population health status; Technological change in health care; Changing demand; the availability and supply of care; Health care policy;	The rate of improvement in mortality will slow down to a long-run average rate of 1.5 per cent; Age-specific fertility rates change at an equal rate for each age group, which preserves this pattern.Patterns of referral between hospital networks do not change;	Hospital In-Patient Enquiry System data;		While there are undoubtedly benefits to an integrated model of health care provision as proposed by the HSE, reducing the over-reliance on hospitals inherent in the Irish health care system will be a challenge not only for the acute public hospital sector but for the health care system as a whole.

Feenstra/ Struijs (multi-state life table method) (earlier model: Feenstra et al.)	to estimate expected increase in stroke/COPD patients in the Netherlands;	The future burden of stroke in the Netherlands in terms of the incidence, prevalence, and potential years of life lost (PYLLs);	1995-2015 (COPD); 2000-2020 (Stroke)	Macro-modelling (dynamic multi-state life table method); prevalence projections were combined with age-specific information on the use of health care in physical units and the unit costs of care; Transition probabilities, Markov property;	The Netherlands	trends in 2 major risk factors for stroke, ie, hypertension and smoking;	Cost projections assumed constant prices and constant treatment patterns; Markov property: conditional on sex, age, and risk factor class, the model states 1 year ahead are independent of the past model states; Conditional independence: Conditional on the risk factor class, disease incidence and mortality rates are assumed to be mutually independent;	GP registration data; Data provided by the Foundation for Smoking and Health; The Dutch 1993 cost of illness study; The Dutch Ministry of Health data;	Struijs et al. (2005): i) A demographic scenario, in which the future prevalence depends only on demographic changes. ii) A hypertension scenario, in which the incidence rates depend on past trends in the prevalence of hypertension. iii) A smoking scenario, in which incidence rates depend on the trend in smoking prevalence. iii) A combined hypertension and smoking scenario	For the medium term, the increase in prevalence is marginally explained by expected changes in smoking behavior and changes in the prevalence of hypertension. Despite the conclusion that a large part of the increase in stroke/COPD patients is inevitable, the authors believe more attention should be paid to primary prevention and successful efforts to reduce smoking in society as a whole can reduce prevalence substantially in the long run.

Fox et al. (2001)	To estimate the current and projected economic burden of caring for community resident and institutionalised people with Alzheimer disease in California	Disease-specific (Alzheimers disease)	2000-2040	Macro model	US	Per capita costs of care and the number of people with AD only	10% AD prevalence rate for people aged 65+;		None	With projected increases in the number of persons at risk of developing AD in California, the economic impact of the disease in the future will be substantial. The amount of informal care provided is not significantly affected by the level of formal care received
Gerdtham (1993)	To estimate the impact of population ageing in Sweden	Healthcare expenditure	1985-2005	Macro modelling (+other statistical analyses); Individual model (not related to the OECD statistical analysis);	Sweden	Age structure				The impact of changing population age structure on health spending has been modest.
Hare et al. 2009 model	1. the number and age distribution of potential clients and Age dependent entry rates are then applied to determine the number of potential clients at each state; 2. Transitions between client groups and exits from the model are computed.	The number of clients of each age group for eight different home care and community care services		Macro modelling (deterministic multi-state model: between macro and micro?)	Canada			British Columbia model		

IIASA social security model (MacKellar et al. 2004)	To investigate economic impacts of demographic trends and structures, and associated uncertainties, in a globally consistent macroeconomic framework; To study linkages between population dynamics, the macro-economy, the pension and healthcare systems and intergenerational distribution;	HCE is not the main projection outcome;		Stat modelling (Economic demographic growth model (stock-flow model)): The model is built within the macro-economic framework using production function, etc. It tracks income, expenditure, and assets of each single-year cohort as it ages. (HC module & LTC module); Uses the partial equilibrium approach to obtain the model estimates.	Japan	Capital, production, labour force and employment,	HC/LTC as part of social expenditure			The relative robustness to changes in demographic assumptions indicates that among the many sources of uncertainty regarding the impact of population aging on Japan, uncertain demography probably ranks rather low.
Iwamoto & Fukui (2009)	To provide long-term outlook of social security financing problem in Japan; To examine the effect of social security system reforms;	Future social security costs (including pension, healthcare, welfare, and long term care)	2005-2105	First, per capita health care costs by age group were proportionally adjusted so that the national aggregate of the costs matches the figure reported in the Medical Information Analysis System (MEDIAS). The national aggregate of the health care costs was calculated as the product of population and per capita costs by age group. Similarly, the rescaled age-cost profile was used to project future health care costs.	Japan	Age only	LTC: Per capita long-term care costs by age group would increase 1.2% faster than wages;	Medical Information Analysis System (MEDIAS); FY2004 National Medical Expenditure (MHLW); Monthly Reports of Long-Term Care Benefits provided by MHLW;	Policy simulations: a balanced budget scheme (pay-as-you-go scheme) & prefunding scheme to equalise the intergenerational burden;	The introduction of a 'funded' insurance system may be worth discussing to correct the intergenerational inequality in burdens; Simulations using updated population projections show that the insurance premium would raise the peak premium. However, the premium increase during the transition to the pre-funded system would be small, indicating the system change would absorb some of the risks from demographic fluctuations.

Joyce et al. (2003)		GP services only		Macro-simulation (Method used in Denton et al. 2000)	AUS	Trends in service use		Health Insurance Commission on GP services; Australian Bureau of Statistics (ABS 2000, 2001, 2002)	
Karlsson et al. 2006; Rickayzen and Walsh 2002;	To estimate future costs for long term care for older people in the UK	Long term care costs	2000-2050	Macro-simulation (Based on multi-state disability projection model)	UK LTC model	Prevalence of disability;	Current patterns of informal care provision do not change in the future; Prices of LTC services increase in line with general earnings; Trends in dependency and demography are the main drivers of LTC expenditure;	Various sets of assumptions on trends in healthy life expectancy data (mortality, disability rate, etc.)	The demand for long-term care will start to increase considerably about 10 years from now, and reach a peak somewhere after 2040. The most important increase will be in informal care, since the number of older recipients is projected to increase from 2.2 million today to 3.0 million in 2050.
Kildemoes et al. (2010)	To develop a method for projecting the impact of ageing and changing drug utilization patterns on future drug expenditure	Drug expenditure only	2006-2015	Macro modelling (semi-Markov model); Similar to multi-state model; Individual model;	Denmark	Age and gender, changing drug utilisation patterns		1. Extrapolation of the historical trends observed during 2000-2005; 2. Parameters fixed at 2005 values.	Increasing treatment prevalences with three cardiovascular drug categories are likely to pose substantial burden on future healthcare resources. Yet, treatment incidence is likely to depend upon decisions internal to the healthcare system (e.g. guidelines).

VHA LTC Planning Model (Version 2.2); LTC Policy Model (Version 3.1) – Kinosian et al. (2007)	To describe the projected use for long-term-care services through 2012	Long term care service use 2002-2013, Nursing home use for enrolled veterans, Medicaid home and community based (HCBS) use;	2012	The projection took the cell-specific rate and applied it to the age/gender/marital status/disability class–specific enrolled veteran population projected for that year to produce the ADC for nursing home and HCBS use;	US	age/gender/marital status/disability class	the decline in disability from the 2002 level is at the same rate as the observed mortality decline—approximately 0.6% per year.	Veterans Health Administration (VHA); For service use rates from the 1999 National Long-Term Care Survey and the 2000 National Health Interview Survey		Projected use for long-term-care services will grow substantially over the next decade, by 22% and 24% for nursing home and HCBS services, respectively.
Lagergren (2005) - ASIM III-model	To provide estimates on the amount of public long term care services provided per age group, gender, marital status and degree of disability both retrospectively for the period 1985-2000 and prospectively according to the same terms for the period 2000-2030.	Total annual long term care costs; Number of persons per level of services.	2000–2030	Macro modelling; (the ASIM III-model consists of two parts: a retrospective part and a prospective part. The model involves a sub-division of the Swedish population 65 years and above into subgroups according to age, gender, civil status and degree of illness. The number of persons that receive public LTC services for each subgroup. Then, multiply the estimated number of persons each year with the respective proportion of persons receiving services on the respective levels in the year 2000 as calculated in the retrospective part of the model.	Sweden	age, gender, civil status (with or without spouse, and degree of ill-health	Health trends will remain up to the year 2030; the proportion of persons, per age group, gender, civil status and degree of ill-health, receiving services on the respective levels remains unchanged at the year 2000 level.	SNAC (Swedish National Study on Ageing and Care); Swedish National Survey of Living Conditions (ULF) - for prevalence of ill-health;	continued positive ill-health trends until 2010/2020; constant prevalence of ill-health	The wide range of results produced by alternative assumptions show that an effective preventive health policy aimed at the older persons is crucial. (In the most pessimistic scenario D the projected cost increase in fixed prices during the period amounts to 69%—in the most optimistic scenario 0 the cost increase stays at 25%.)

Lee and Miller (2002)	To quantify uncertainty in forecasts of health expenditures			Macro-simulation (simple accounting model: the sum of the number of people in a given health status times the annual spending associated with that status)	US	Age, time to death	Assume that the schedule of spending by time until death has a fixed shape, and that the level of spending by time until death is determined by multiplying this fixed schedule by a shifting index of spending			Medicare expenditures are currently 2.2 percent ofGDPin the United States. We project them to rise to 8 percent of GDP by 2075. There is substantial uncertainty about the future course of mortality decline. Demographic uncertainty has very little effect on the probability bounds for the forecast for the first forty years or so; only uncertainty about spending-per-beneficiary matters over this period.
Madsen, Serup-Hansen Danish model – Serup-Hansen et al (2002); Madsen et al (2002); Polder et al (2006)	To project future costs of hospital in-patient care and primary healthcare services in Denmark.	Future costs of hospital in-patient care and primary healthcare services	1995-2020	Macro modelling (cohort components method to project demographic changes); Total costs for a given age-group = averate cost per person per year for this group multiplied by the number of persons within the group (macro-method);	Denmark/ The Netherlan ds		Constant average costs of use of primary health care services during the period 1995–2020;			Madsen et al. (2002): Ageing as well as costs in the last year of life appear to have almost no effect on future costs of primary health care services. Hence, the future costs of primary care providers (but excluding drugs, nursing homes, etc.) appear to be determined largely by population size and not by ageing. A rather different conclusion in Serup-Hansen et al. (2002) is that: The high costs in the last year of life does matter in projections of future costs of hospital in-patient care and primary care services. Furthermore, ageing per se seems to have considerable impact.

Martini and Garrett (2007) model	HC demand projection		2000-2050	Macro-simulation (Cell-based: MPC-specific age and gender per capita cost rates using cross-sectional data for 2002–2003 and projects U.S. changes by MPC due to aging) *Major Practice Categories	US	Age and sex		MEPS	total U.S. per capita costs due to aging from 2000 to 2050 are projected to increase 18 percent (0.3 percent annually), the impact by MPC ranges from a 55 percent increase in kidney disorders to a 12 percent decrease in pregnancy and infertility care. Over 80 percent of the increase in total per capita cost will result from just seven of the 22 total MPCs.
Mendelson and Schwartz (1993)	To estimate the effect of demographic changes on past and future costs using existing secondary data and a series of models;	Annual % contribution of ageing and population growth to the rise in costs	1990-2005	Simple macro model		Macro model by age group only	The relative expense of treating each age group, observed in 1987, will remain constant over time.	Health Care Financing Administration (HCFA)	In the acute care sector, aging and population growth accounted for roughly 20 percent of the real rise in costs; in long-term care, roughly 35 percent. There has been a steady reduction in the contribution of aging and population growth (taken together) to the rise in costs in both the acute care and long-term care sectors between 1975 and 1990.

New Zealand MoH model – Frizelle (2005); Ministry of Health, New Zealand (2004);	To develop projections of health expenditure over the next 50 years; To examine whether improvements in health status can offset the impact of population ageing;	Total healthcare expenditure	2002-2051	Macro-simulation (cell-based): the model simulates the NZ population (disaggregated by age and sex) over 2002-2051. The model consists of 'population' component and 'cost' component; Individual model	New Zealand	Age, gender, health status, mortality, disability, growth in coverage and prices, growth in GDP per worker;	Central assumptions: Government expenditure as a proportion of GDP increases by 50% from 6.2% to 9.2%;			Under 'central' assumptions · % GDP spent on health will increase from 6% to 9%. · Older people's share of health expenditure will increase from 40% to 63%, yet the ratio of spending on the average older versus younger person will decrease (by approximately 25%). · Growth in coverage and prices, not population ageing, will continue to be the key driver of health expenditure. · However, ageing will increase upward pressure on spending (especially from about 2026). · Yet relative compression of morbidity (if it can be achieved) will reduce lifetime healthcare costs and so ease ageing pressure on health spending, constraining total health expenditure growth (by up to 30% of what it would otherwise have been).

OECD & EU-EPC (Dang et al. 2001) Dang et al. 2001; Economic Policy Committee of the EU (2000); EU EPC (2001, 2003); Bains and Oxley (2004);	To project age-related public spending; To run projections of public expenditure on health and long term care in order to assess the impact of ageing populations on future expenditure levels; International comparison of future expenditures;	Aggregate health and long term care expenditure, and future burden for public finances.	2000-2050	Macro-simulation (EPC (2001): Age- and sex-related expenditure profiles were matched to demographic projections for future years); Most recent estimates of per-capita health costs by age group were multiplied by the number of individuals in each age group in 2000 (base year))	EU, OECD countries	Age and sex; (Not modelled are diffusion of medical technology, relative prices for medical inputs, the intensity of care and concentration of health expenditures at the end of life)	No detailed account of modelling methods; (EPC 2001) Cost assumptions - 1. per-capita expenditures grow at the same rate as GDP per capita, 2. per-capita expenditures grow at the same rate as GDP per worker.	Member states' own.		(EPC 2001) Total HC & LTC increase in expenditure in % of GDP: +1.8-+2.5 (UK), +2.2-+2.7 (EU); Main conclusion: the impact of ageing on public expenditure onm health and long term care is likely to be significant. The consequences of demographic changes in terms of increase public expenditure would range from 1.7 to 3.9 % points of GDP. The largest part of this increase would come from expenditures on LTC.
Polder et al. (2002): Dutch projections	To describe the age pattern of health care costs, to analyse the age-specific cost changes and to project future healthcare costs in an ageing population	National healthcare costs projections (acute care, long-term care)	2015	Macro modelling	EU (The Netherlands)	Age and sex only	Age-specific 1988-1994 trends in acute and long term care costs persist in future decades.	Cost of illness data from the Ministry of Health, Netherlands; Probability distributions of key variables were derived from sector-specific registries and sample surveys	No scenario analyses	The share of the elderly in total healthcare costs will increase. Ageing as well as technological and epidemiological changes reinforce the age pattern in HCE. The influence of HC policy seems to be relatively large, larger in LTC than in acute care.

Polder et al. (2006) - Cohort component model	(1) To estimate health care costs in the last year of life in the Netherlands; (2) to describe age patterns and differences between causes of death for men and women; (3) To compare cost profiles of decedents and survivors; and (4) to use these figures in projections of future health expenditure.	Healthcare costs in the last year of life	1999-2020	Macro modelling (cohort components method): We used life tables (Siegel & Swanson, 2004) for the Dutch population (Statistics Netherlands, 2005) to estimate expected lifetime health care costs from birth until death according to mortality rates in 1999 and 2020. Using population forecasts of Statistics Netherlands (de Jong, 2003) in a simple cohort-component method	The Netherlands	Time to death; Population growth; Changing size of birth cohorts, mainly the ageing baby-boom generation; Changing mortality resulting in higher life expectancy and higher health expenditure for survivors;		Health insurance data representing 13.4% of the whole Dutch population.	11.1% of total expenditure of the included health services is estimated to be assigned to people in their last year of life. In a model in which lifetime expected costs comprised different estimates for the last year of life and all other years, the estimated growth rate of health expenditure is substantially lower compared to standard projection methods (9.3% for total expenditure, 13.0% for per capita expenditure and 25.8% if only the effect of increased longevity and postponement of death were taken into account). Future expenditures are affected by a lot of other factors.
PSSRU Long Term Care model for older people (Wittenberg 2006, other PSSRU papers) Comas-Herrera et al (2001, 2003, 2006, 2007, 2011); (PSSRU1)	To make projections of the future numbers of disabled older people, the likely level of demand for LTC services and disability benefits for older people, the costs associated with meeting this demand and the social care workforce required. To study long term care finance	Numbers of disabled older people, likely level of demand and disability benefits, costs of meeting demand.	Up to 2040 or 2050	Macro-simulation (the model divides the population into 1000 cells)	UK	Disability level;	Constant ratio of single/married people living alone to single/married people living with their children or others; Prevalence rates of disability by age and gender remain unchanged; the	2001/2 General Household Survey; PSSRU surveys of residential care;	Trends in functional disability; Availability of informal care; Future patterns of care; Unit costs development	The numbers of disabled older people requiring LTC will rise significantly; Projections are sensitive to assumptions; Policy makers need to plan for uncertainty in future demand for LTC; Need to promote measures likely to reduce disability in old age; A substantial expansion of non-residential services will be required.

	(funded by the UK Department of Health)					proportions of people receiving informal care, formal services, residential care, and disability benefits remain constant; Health and social care unit costs rise by 2% per year in real terms;		

| PSSRU Social care projection model for younger adults Wittenberg et al (2008); Snell et al.(2011) | To make projections of the future numbers of disabled younger adults and the likely level of demand for LTC services and disability benefits for younger adults; | Numbers of disabled younger adults; Numbers of service recipients; Public expenditure on social services for younger adults; Numbers of staff providing social care for younger adults; | 2005-2041 | Macro-simulation (an adapted version of PSSRU LTC model for older people) | UK | Disability; Unit cost of care; | Similar to the model used in Wittenberg et al (2006) for older adults; Marital status rates for physically disabled younger adults change in line with ONS 2008-based marital status and cohabitation projections (ONS, 2010), while those for learning disabled people remain constant; The supply of formal care will adjust to match demand; The real unit costs of social services and of ILF payments remain unchanged to 2015 and rise by 2% per year in real terms thereafter; | Family Resource Survey (1996/7); Emerson et al. (2005) for disability prevalence; Tribal Secta data provided by Department of Health, UK; PSS Expenditure data (2005/6) for unit costs; (Updated data were used for Snell et al. (2011) study); | Changes in assumptions on overall number of people aged 18-64, prevalence of disability, unit costs of services, and funding scenarios | The updated study by Snell et al. (2011) showed that the number of learning disabled youner people would rise by 32.2% and the number of physically and sonsorily impaired younger people would risd by 7.5% between 2010-2030 ; Net expenditure on social care (net of user contributions) is projected to rise by 66.6% from £6.8 bn. to £11.3 bn between 2010-2030; The sensitivity analysis demonstrated the projections are sensitive to changes in those assumptions. This meant that the projections should not be regarded as forecasts of the future. The projections are not the total costs to society of long-term care for younger adults. That would require inclusion of the costs of a wider range of services to a wider range of public agencies and service users and the opportunity costs of informal care. Also, no allowance has been made for changes in public expectations about the quality, range or level of care. |

Reuben et al. (1993)	To estimate the number of full-time-equivalent (FTE) physicians and geriatricians needed to provide medical care	Physician supply based on service utilisation estimates (in terms of ambulatory care, nursing home visits, and hospital visits per year)	2000-2030	Macro modelling (Individual model): The model stratifies the population into two subgroups: institutionalised and non-institutionalised, and these were sub-divided by age and functional status.	US		Economic growth;	1985 National Ambulatory Care Survey (NAMCS), 1986 Medicare Data Tapes, 1984 National Health Interview Supplement on Aging (NHIS-SOA), AND 1985 National Nursing Home Study (NNHS).	Scenario 1: Moderate economic growth similar to the 1970s; Scenario 2: hard times, Scenario 3: steady growth 5% per year.	Assuming moderate growth similar to the 1970s, a 39% increase in the total number of physician FTEs was projected by 2000. The total FTE geriatricians needed for year 2000 ranged from 1577 (Scenario 2) to 4176 (Scenario 3). The range of the estimates suggest that economic forces play a substantial (but not dominant) role in the adquacy of physician supply. Population changes may be the major factor determining the manpower requirements for medical care of the aged
Rice et al. 1983 (U.S. Department of Health and Human Services)	To examine the range of possible consequences for the health sector of an increasingly older American population	Projected number of persons with limitation of activity; Projections of physician visits, hospital days of care, and nursing home residents;	1983-2003	Macro modelling (cohort components method): The projection method used was the standard cohort-component approach in which separate assumptions are made for future levels of the demographic components—births, migration, and deaths. For this projection method, each age group, or cohort, is followed through successive calendar years. Each age group is survived from one calendar year to the next by applying survival probabilities.	US		Age-specific rates of health services utilization are assumed to be constant throughout the projection period	US Government data	Mortality assumptions	The aging of the population has a much greater impact on nursing home residents than on days of hospital care or physician visits. The amount spent on physicians' services is projected to increase 30 to 37 percent, from $36 billion in 1978 to between $47 and $50 billion in 2003. However, little change will occur in the age distribution of expenditures, with people between 20 and 64 years of age accounting for more than 60 percent of the total. The implications of the aging of the population in the years ahead for

									social institutions, including the health care delivery system, should be considered in policy planning. The U.S. population will grow more elderly and the need for health care facilities may well increase.
Roos et al. (1998)	To examine changes in the physician supply and assess the availability of physicians relative to population growth and ageing	Physician supply based on service utilisation estimates		Macro modelling (Individual model)	Canada			Canadian Institute for Health Information (CIHI)		
Russell 1981	To project the use of medical care forward and backward (1950-2050), to show the importance of the chang- ing age structure of the population for medical sector.		1950 - 2050	Macro-simulation (Use rates for each age-sex group were multiplied by the population-actual or projected-in that group for each year, and summed to estimate total use.)	US		A slow but steady decline in mortality rates was assumed; Current differences in use by age and sex continue (fixed rates of use by age and sex);	National Center for Health Statistics (NCHS) survey;		Age structure is more important for nursing home care than for hospital care; Changes in the age structure of the population have been and will continue to be important for institutional care, but not for outpatient visits to physicians or dentists.
Schneider and Guralnik (1990)	To project future costs for Medicare, nursing homes, dementia, and hip fractures.	Medicare expenses; Nursing home costs; Dementia and hip fracture costs	1987-2040	Simple macro model	US					

Schofield and Earnest (2006)	To develop models of future demand for hospital care and examine the sensitivity of the results to model assumptions	Demand for public hospital bed-days	2005-2050	Macro-simulation (CELL-BASED)	AUS	Age and population growth; Non-demographic factors (policy changes, new treatment approaches, and new technologies)		Australisan Institute of Health and Welfare (AIHW); Australian Bureau of Statistics (ABS);	Future population growth at the rate projected by ABS;	Between 2005 and 2050, the demand for hospital bed-days was projected to almost double, to about 30 million bed-days in 2050. There will be a need for additional staff. It seems the majority of the efficiency gains to be made from policies such as early discharge and same-day treatment have already been obtained. Plans to ensure future hospital needs of the ageing population are met are needed now.
Schulz, Leidl, Konig (2004) - the example of Germany	To show the impact of the isolated ageing effect on the use of hospital and long term care in Germany	Total number of hospital days; Number of long term care recipients;	1998-2050	Macro modelling	Germany	Time to death; Functional disability; Informal care availability; Socio-economic characteristics;	Utilisation rates were held constant over time;	German Institute for Economic Research; Diagnosis statistics from Federal Statistical Office; Utilisation data from Busse et al. 2002 (a German sickness fund)	Constant/increasing life expectancy; With/Without split between survivors and decedents;	Although demographic impact on the healthcare system is often discussed in terms of cost and financial consdquences, the study shows that significant policy issues may emerge on the side of care itself. The impact of demographic chage on LTC is likely to be much stronger and more difficult to cope with, and it is difficult to increase the supply. Health policy must consider strategies in the care sectors themselves, and measures to reduce actual demand.

SIMPOP model (part of MAP2030 project) Jagger et al. (2011)	To examine how trends and treatments in multiple chronic conditions might impact on disability and the future demand for LTC	The number of older people with disability; age-specific disability and disease prevalence;	2010 - 2030	Macro-simulation: SIMPOP projects the number of older people with disability from two-year transition probabilities to and from disability and to death derived from the MRC Cognitive Function and Ageing Study (MRC CFAS) and then applied to the 1992 mid-year England and Wales revised population estimates;	UK	Changing patterns of chronic disability;	Given the paucity of data on the impact of interventions on morbidity, a 5% change in the transition probabilities to onset of disability and to death was assumed;	MRC CFAS	1. Central health ('status quo') scenario: Age-specific prevalence/incidence remain at 2006 levels, 2. Improving population health scenario: decline in risk factors (10% decrease in disability onset for arthritis, stroke, CHD and mild CI from 2012; 3. Continuation of current trends scenario: Current obesity trends of 1–2% increase annually.	Population ageing will result in an increasing trend in disability prevalence and a substantial increase of almost one million in the numbers of older people needing LTC, many of these being the very old with multiple diseases; More effective treatments and greater use of assistive technology are allowing older people to remain independent; Efforts should be made on prevention and slowing down the progression to disability;

Strunk et al. (2006)	To predict how changes in the age distribution of the U.S. population will affect the future use of hospital inpatient services; Hospital care demand	Hospital inpatient services	2005-2015	Macro-simulation	US		Utilisation rate helt constant over time;	National Center for Health Statistics (NCHS), National Hospital Ambulatory Medical Care Survey (NHAMCS) and National Survey of Ambulatory Surgery (NSAS).		Between 2005-2015, per person inpatient resource use will increase by 7.6 percent because of aging, or 0.74 percent per year. However, aging still accounts for a relatively small portion of the growth in hospital spending projected for the next decade: only 11.8 % of the total increase. Changing technology is a much larger factor in changes in treatment than population aging. The effect of aging effect on use of inpatient serviceswill be small, but it will have a larger impact on use by patients with certain types of medical conditions that are more concentrated among the elderly.
The Whole Systems Partnership (2011) End of life care cohort model	To provide simulations of the likely end of life care needs for a selected population; To frame discussions between strategic partners about the implications and alternatives in implementing the National Strategy for End of Life Care;	the number of people whose end of life care needs will follow one of five trajectories of illness; Numbers of hospital admissions that will be saved from the implementation of the National EoLC		Dynamic systems model (using iThink) Stock and flow approach;	UK					Depends on the application

		Strategy							
Tuulonen et al. (2009)	(i) to create a structural simulation model capable of predicting the future need and cost of eyecare services in Finland; and (ii) to test and rank different policy alternatives for access to care and the required physician workforce	the number of cataract operations, glaucoma visits, screening of diabeties, AMD visits and PDT (photodynamic therapy) treatments;	2005-2040	Macro-modelling (System Dynamics (SD) simulation model (NOT a micro-modelling)); Individual model;	Finland	Five age groups;		The estimated demand for cataract surgery without and with the implementation of the national criteria of cataract surgery; different numbers of glaucoma visits in public sector; Different frequencies of diabetes screening;	The results of this modelling study indicate that policy initiatives, such as defining criteria for access to care, can have substantial implications on the demand for care and waiting times whereas the effect of ageing alone was relatively small. Measures to control several other factors – such as the adoption and price level of new technologies, treatments and practice patterns – will be at least equally important in order to restrain healthcare costs effectively.
US CBO Long term budget outlook Manchester and Schwabish (2010); CBO (1999, 2005, 2007, 2008, 2012)	To examine the implications of a continuation of current federal law, rather than to make a prediction of the future.	PROJECTIONS OF NATIONAL LONG-TERM CARE EXPENDITURES FOR THE ELDERLY (Medicare, Medicaid, Private Long-Term Care Insurance, Out of Pocket, Other Payer)	Long term 75 year projections	Macro-simulation (combine estimates of the elderly population with per capita expenditures for long-term care, classified by disability category and type of payer); CBO combines an assumption about excess cost growth in the spending on health care with projections of the growth and aging of the population and of the growth in per capita GDP.	US		The population projections assume that current trends in disability among the elderly will continue until 2040, with the prevalence of disability declining, on average, by 1.1 percent a year (CBO 1999); private	Congressional Budget Office calculations based on data from the Lewin Group and the Center for Demographic Studies at Duke University.	CBO's (2007)baseline budget projections for 2008 to 2017 assume no change in current federal law; an alternative scenario that assumes a change in federal law to prevent the reductions that would otherwise	The ageing of the US population would account for a modest fraction of the growth that CBO projects.

							insurance spending for long-term care will rise during the 2000-2020 period; (CBO2008) CBO assumed that even in the absence of changes in federal law, rates of spending growth in the Medicare and Medicaid programs would probably moderate to some degree. Historical excess cost growth rate will continue in the future.		occur in the fees that Medicare allows for physicians' services	

Warshawsky (1994)	To answer the question of 'Can the steady increases in health care expenditures as a share of GDP projected by widely cited actuarial models be rationalized by a macroeconomic model with sensible parameters and specification?'	Health care expenditures as a share of gross domestic product (GDP)	1990 - 2065	Actuarial and macroeconomic approaches	US	Actuarial analysis: demographic forecast, GDP projection (implicitly employing numerous other forecasts, including those of the labour force participation rate, the unemployment rate, the inflation rate, the rate of productivity growth;	Forecasts of Healthcare inflation: i) from simple regression analysis & ii) "structural" forecast based on HCFA assumptions (based on earnings of health care providers and non-labour inputs of hospital)	The most conservative assumptions: robust economic growth, improved demographic trends, or a significant moderation in the rate of health care price inflation;	Both models unanimously project a continued increase in the ratio of health care expenditures to GDP. The model projects the health care sector will consume 25%-50% of national output by 2065. In the macroeconomic model, the increasing use of capital goods in the health care sector explains the observed rise in relative prices. Moreover, this "capital deepening" implies that a relatively modest fraction of the labour force is employed in health care and that the rest of the economy is increasingly starved for capital, resulting in a declining standard of living. Projected expenditures show questionable sustainability of HC funding; serious and immediate structural reform is critical;

Weinberg (1995)	To examine the impact of demographic change upon the need for acute medical beds to the year 2000 in a district hospital using a Monte Carlo simulation;	Individual model; Hospital care only; Change in bed numbers needed in the year 2000;	1993 - 2000	Macro modelling (Monte Carlo simulation): Cell-based method, while the Monte Carlo technique has been used; computer-generated 'patients' were admitted to 'beds' for the period of their age-specific length of stay before being 'discharged'; Service utilisation variables were sampled from probability distributions, apart from that, the population has been stratefied by age.	UK	Daily number of admissions, the age of the admission and the age-specific length of stay	Current admission rates and length of stay will be maintained in the year 2000	Minimum Data Set (District Health Authority)	Two different population projections used: Regional Health Authority (1989) and County Council projections based on 1991 Census	No significant differences between the bed requirements under the current starting conditions and the modelled starting conditions for the year 2000; Reducing all lengths of stay by one day reduced the mean bed requirement by more than the critical number (significant at Scheffe's test).
WHO Long term care future tool-kit (2002)	to give policy makers and stakeholders a tool to help investigate the future of LTC in their country and find new directions for effective health policy	Demand & supply: the number of disabled across demographic categories, the numbers of Informal and Formal LTC workers. Disability Prevalence, Dependency Ratio.		No detailed account of the method used; As in other WHO models, would be macro modelling	Worldwide	Supply Factors: Family Structure, Social Capital, Economic Factors, Informal Caregiver Supply and Support; Demand factors: Technologies, Environment, Social Risks, Personal Lifestyles.	The toolkit is not designed to make specific future forecasts for LTC; rather it uses quantitative forecasts as the starting off point for further investigation of LTC.	UN Population projections.	1. The stabilization and gradual improvement of the economic system, 2. Hostile climate events, poor economic growth, and internal conflict, 3. a strong compression of morbidity (scenarios adjustable within the tool)	Depends on the application.

Table 3. Summary of micro-simulation models

Name/developer of the model	Main objective	Projection outcomes	Time horizon	Method	Country	Key factors included	Key assumptions (Important)	Key datasets	Main scenarios	Conclusions
Basu and Gupta Basu and Gupta (2008)	To explore the future utilisation of physicians in terms of full-time equivalent in Nova Scotia to the year of 2025 by 4 general types of medical disciplines.	Physician service use; Effect of population ageing on future demand for physicians	2000-2025	Micro-simulation (estimating future demand for physicians); Individual model;	Canada					
Cahow (2004) - PhD thesis	To estimate the demand for long term care	Nursing home care only	2005-2025	Use of statistical analyses to estimate transition probabilities, then micro-simulation)	US					

Davis et al. (2010) New Zealand model	To assess micro-simulation for testing policy options under demographic ageing	Patients visits to GP;	2002-2021	Micro-simulation	NZ	Morbidity and disability trajectories, availability of family and community support, intensity of practitioner behaviour;	Various sets of assumptions on utilisation rates, GP behaviour, health status, etc.	New Zealand Health Survey (1996/7 and 2002/3), a national survey of ambulatory care in New Zealand (2001/2), and the Australian National Health Survey (1995)	(a) profile of morbidity and disability associated with demographic ageing, as reflected in contrasting predictions of expansion and compression; (b) "healthy ageing", as reflected in the potential of family and community capacity to assist in coping (autonomy, dependency, intermediate); (c) the impact of changes in health service delivery, such as, technology and changes in practitioner repertoires.	Limited change in system demand on a 'pure' demographic model, although substantially more on scenario analysis of projections of morbidity burden and tractitioner behaviour; Micro-simulation models can contribute to addressing 'what if?' scenarios and realistic extrapolation into the future.
Dormont et al. (2006) French model	To estimate the future healthcare expenditure			Micro-simulation model (statistically expressed in the paper, but individuals were stochastically modelled, hence micro-modelling); Econometric/ Statistical analyses;	France			a survey (Sante′ Protection Sociale) conducted by IRDES (Institute for Research and Information in Health Economics,		

								Paris)		
DYNASIM (Dynamic Simulation of Income Model) Zedlewski & McBride (1992); Zedlewski et al. (1990) (book);	To serve as a framework for integrating economic and sociological research on micro entities, forecasting, policy analysis, investigation of the implications of socioeconomic change, and generation of individual and family histories	Demographic Events, Education, Location, Labour force events, Social security eligibility and benefits, Health status/disabilities;	1990-2030	Micro-simulation	US	Individual characteristics;		1973 Current Population Survey (CPS)		Demographics, health, and income trends will interact to increase the demand for nursing-home care faster than many now realize. Whereas the number of elderly will increase by 100 to 125 percent by 2030, the number requiring nursing-home care will triple during the same period. The need to find alternative long-term care financing arrangements will be acute
Gallagher et al. (2010) Monte Carlo simulation & Linear programming – Harper et al. (2012);	to explore the required skill-mix of the dental team to meet future need and demand of older people in England to 2028 utilising operational research methods, and examine a range of future scenarios.	NHS clinical supply hours	to 2028	MC simulation & linear programming together with Powell's Intermediate Care workforce model; Added optimisation functionality (i.e. Linear program to optimise skill-mix and predict workforce requirements); Demand and supply data were fed into an optimisation model to provide recommendations on the composition of the optimal	UK	the contribution of clinical dental technicians	Department of Health (2004). Report of the primary care dental workforce review; NHS Education for Scotland, ISD Scotland (2004). Workforce planning for dentistry in Scotland; NHS Scotland (2006).		5 different scenarios on varying staff competencies and skill-mix ('a gental evolution', 'no skill-mix', 'skill-mix revolution', etc.)	For the whole population, the current shortfall is estimated at 3,812 NHS WTE dental staff in 2005 and the shortfall is expected to peak in 2008, with a shortage of 4,018 NHS WTE dental staff forecast. By 2018 the shortfall is expected to reduce to 1,781 dental staff and by 2028 the shortfall is expected to have disappeared altogether with a surplus of 2,354 dental staff projected (due to the planned expansion of dentist and hygienist/therapist training places and the increase in the percentage of time that dental staff devote to treating older people). The model suggests that with widening skill-mix, dental care professionals can play a major role in building dental care capacity for older people in future. Policy makers need to explore the challenges and benefits of implementing the optimal skill-

				workforce.						mix workforce against the feasibility.
Lubitz et al. (2003)	To estimate the expenditure for healthcare	Expected Expenditures for Health Care from 70 Years of Age until Death According to Self-Reported Health at the Age of 70		Compound method (**multistate life-table methods** and micro-simulation. Then, linked annual health care expenditures with transitions between health states; Age-specific, first-order Markov transition probabilities were estimated with the use of a multivariate hazard model, and Health-expenditure matrixes were structured in a similar manner to the transition matrixes.	US			Medicare Current Beneficiary Survey		
POHEM, Statistics Canada	To model diseases and risk factors in which the basic unit of analysis is the individual person; to estimate lifetime costs of diseases or assess health technologies	Life-time costs of healthcare;		Micro-simulation	Canada					

PSSRU CARESIM-LTC model (linked) (PSSRU3) Hancock et al (2003, 2007); Malley et al. (2006); Wanless social care review (2006); Leung et al. (2007) - macro model only	To examine the effect of a range of options for paying for long term care.	Future long term care costs by sources of finance	2005-2051	Linkage between micro- and macro-simulation models	UK	Net income; household type; Disability level;	Health and social care unit costs rise by 2% per year in real terms; the supply of formal care will adjust to match demand and demand will be no more constrained by supply in the future	ELSA (English Longitudinal Survey Ageing); Department of Health GHS (General Household Survey);	alternative long-term care funding regimes (e.g. free personal care,	The results show that even without any possible demand effects, a policy of free personal care would lead to a substantial increase in the number of older people receiving some publicly-funded home care. The complexity of long-term care funding in the UK makes it difficult to gauge the current and projected future costs and distributional effects of such reforms without the kind of analysis presented here. An important conclusion of the present paper is that analysis of this kind is essential if informed judgements about policy options are to be made.
PSSRU dynamic micro-simulation (DMS) model (PSSRU4) Forder and Fernandez (2009, 2011 (Age UK doc.), 2012); Fernandez and Forder (2011); Fernandez and Forder (2010)	To explore the consequences of alternative policy reforms, the effect of funding systems on the possible draw-down of assets by service users.	Uptake rates of social security benefits; Assets and income; Amount of service and support any individual person uses in the care system; Levels of need;	2009-2025	Micro-simulation	UK		Developed from an earlier static model for Wanless review (2006)	BHPS (British Household Panel Survey); ELSA;		The current funding system is unfair on people that save, it is stigmatising and open to fraud. It is in stark contrast with universal access philosophy of the NHS. People above the asset ceiling – i.e. who have savings but would not be regarded as particularly wealthy by many – are more likely to experience disproportionately high levels of unmet need and more rapid draw-down of assets, according to the model.
RAND COMPARE model - Eibner (2009); Eibner et al. (2010, 2011)	To predict the effect of a range of policy/reforms; To project potential behavioural changes of individuals and firms in the US	Behaviour changes; Distributional impact of policy		Micro-simulation	US					

RAND Future Elderly Model (FEM) Goldman et al. (2004, 2008)	To project the future Medicare costs under the current and alternative health status and healthcare environment	Per capita and total medical expenditures; Health status of the future elderly;	2000-2030	Micro-simulation (three models are integrated: cost model, transition model, and rejuvenation model)	US	Age, gender, ethnicity, education, geographical area of residence, smoking status, etc.	i) Future individuals with a given set of health conditions receive the same medical care as individuals in the MCBS: Costs assume a level of treatment and technology as it existed in the 1990s; ii) 1998 unit prices continue throughout our forecast period; iii) the elderly do not migrate across Census region borders as they age;	Medicare Current Beneficiary Survey (MCBS)	Potential breakthrough technologies (e.g. cancer vaccines, anti-ageing compounds); changes in lifestyle and the health care system	Under the baseline scenario, the Medicare expenditures are $176 billion in 2000, $192 billion in 2005, $212 billion in 2010, $240 billion in 2015, $279 billion in 2020, $321 billion in 2025, and $360 billion in 2030. Breakthroughs in medical technologies or changes in risk factors change the health status transitions and the cost projections. The simulation shows that it makes sense for Medicare to provide services to people who are younger than 65 years old and who are not yet in the Medicare program, because they will be healthier later when they do enroll in Medicare, which will reduce the total expenditures for Medicare. The health and expenditures of the future elderly could be dramatically affected by better detection of subclinical disease or early clinical disease. Primary prevention may be effective in reducing the future expenditures.

Swedish SESIM III model - Klevmarken and Lindgren (2008)	To evaluate Swedish system for financing of pension, healthcare, etc.	Life time events including income, retirement, health events, etc.	1999-	Micro-simulation model	Sweden	Demography, inter-generational transfer, education, housing, labour market/status, tax and pension system, etc.		LINDA panel data; HINK/HEK; GEOSWEDE;		Depends on the application;
van Meijgaard et al. (2009) www.health-forecasting.org;	To primarily simulate individuals' lifetime histories and future health status of the population, and personal medical expenditure alongside.	Health status of the future population; Future lifetime medical expenditures	By 2025	Micro-simulation (comprehensive population health-forecasting model: The California Health Forecasting Model)	US	Obesity (Body Mass Index); Ethnicity; Exercise level;		Medical Expenditures Panel Survey.		The health forecasting model provides a strong rationale for current action, and support many specific interventions, policies, and programmes that can improve health of population in the long term.

Appendix 7.1

Table 7.18'. Mortality rates due to causes other than fractures in association with BMD not incorporating cardiac deaths

Age	Z score = -2 (-2.5, -1.5)		Z score = -1 (-1.5, -0.5)		Z score (-0.5, 0.5) General population		Z score = 1 (0.5, 1.5)		Z score = 2 (1.5, 2.5)	
	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men
45	0.19%	0.27%	0.15%	0.21%	0.12%	0.16%	0.10%	0.12%	0.08%	0.09%
46	0.21%	0.29%	0.17%	0.22%	0.13%	0.17%	0.11%	0.13%	0.08%	0.09%
47	0.22%	0.29%	0.17%	0.23%	0.14%	0.18%	0.11%	0.13%	0.09%	0.10%
48	0.24%	0.34%	0.20%	0.27%	0.16%	0.21%	0.13%	0.16%	0.10%	0.12%
49	0.28%	0.37%	0.22%	0.29%	0.18%	0.23%	0.14%	0.17%	0.11%	0.13%
50	0.30%	0.40%	0.25%	0.32%	0.20%	0.25%	0.16%	0.19%	0.13%	0.14%
51	0.33%	0.47%	0.26%	0.37%	0.21%	0.29%	0.17%	0.23%	0.14%	0.18%
52	0.38%	0.53%	0.31%	0.42%	0.25%	0.34%	0.20%	0.26%	0.16%	0.21%
53	0.41%	0.58%	0.33%	0.46%	0.27%	0.37%	0.22%	0.29%	0.17%	0.23%
54	0.47%	0.62%	0.38%	0.50%	0.31%	0.40%	0.25%	0.31%	0.20%	0.25%
55	0.45%	0.61%	0.36%	0.47%	0.28%	0.35%	0.22%	0.26%	0.17%	0.18%
56	0.51%	0.71%	0.41%	0.55%	0.32%	0.42%	0.25%	0.31%	0.20%	0.22%
57	0.56%	0.76%	0.45%	0.59%	0.36%	0.45%	0.28%	0.34%	0.22%	0.25%
58	0.60%	0.87%	0.48%	0.68%	0.38%	0.53%	0.30%	0.40%	0.24%	0.30%
59	0.67%	0.94%	0.54%	0.74%	0.43%	0.57%	0.35%	0.44%	0.27%	0.33%
60	0.74%	1.07%	0.59%	0.84%	0.48%	0.66%	0.38%	0.51%	0.30%	0.39%
61	0.80%	1.15%	0.65%	0.91%	0.52%	0.71%	0.41%	0.55%	0.33%	0.42%
62	0.85%	1.24%	0.69%	0.98%	0.55%	0.78%	0.44%	0.60%	0.35%	0.47%
63	0.95%	1.39%	0.77%	1.11%	0.62%	0.88%	0.50%	0.69%	0.40%	0.53%
64	1.05%	1.54%	0.85%	1.23%	0.69%	0.98%	0.55%	0.77%	0.44%	0.60%
65	1.02%	1.45%	0.80%	1.12%	0.62%	0.84%	0.47%	0.61%	0.35%	0.42%
66	1.15%	1.68%	0.91%	1.30%	0.71%	0.99%	0.54%	0.73%	0.41%	0.52%
67	1.24%	1.85%	0.98%	1.44%	0.77%	1.10%	0.59%	0.83%	0.45%	0.60%
68	1.41%	2.13%	1.12%	1.67%	0.89%	1.29%	0.69%	0.98%	0.53%	0.73%
69	1.61%	2.40%	1.28%	1.89%	1.01%	1.47%	0.80%	1.13%	0.62%	0.85%
70	1.85%	2.70%	1.48%	2.14%	1.18%	1.67%	0.93%	1.29%	0.73%	0.98%
71	1.99%	3.01%	1.60%	2.39%	1.27%	1.88%	1.01%	1.46%	0.79%	1.12%
72	2.23%	3.37%	1.80%	2.69%	1.44%	2.12%	1.14%	1.66%	0.90%	1.29%

73	2.45%	3.72%	1.97%	2.98%	1.58%	2.36%	1.26%	1.86%	1.00%	1.45%
74	2.84%	4.17%	2.29%	3.34%	1.84%	2.66%	1.47%	2.11%	1.17%	1.65%
75	2.47%	3.71%	1.87%	2.81%	1.38%	2.06%	0.97%	1.45%	0.64%	0.95%
76	2.93%	4.39%	2.25%	3.36%	1.69%	2.52%	1.23%	1.82%	0.85%	1.26%
77	3.41%	4.92%	2.64%	3.79%	2.01%	2.87%	1.49%	2.11%	1.07%	1.50%
78	3.96%	5.67%	3.09%	4.41%	2.38%	3.38%	1.79%	2.53%	1.32%	1.84%
79	4.57%	6.46%	3.59%	5.06%	2.79%	3.91%	2.13%	2.97%	1.59%	2.19%
80	5.31%	7.50%	4.20%	5.91%	3.29%	4.60%	2.54%	3.54%	1.93%	2.66%
81	6.06%	8.54%	4.81%	6.76%	3.79%	5.30%	2.95%	4.11%	2.26%	3.13%
82	7.03%	9.71%	5.61%	7.72%	4.44%	6.09%	3.49%	4.75%	2.70%	3.66%
83	8.11%	10.84%	6.50%	8.65%	5.17%	6.85%	4.08%	5.38%	3.19%	4.17%
84	9.20%	12.34%	7.38%	9.88%	5.90%	7.86%	4.68%	6.20%	3.68%	4.85%
85	7.69%	11.15%	5.66%	8.40%	4.00%	6.15%	2.64%	4.30%	1.52%	2.79%
86	9.19%	12.66%	6.89%	9.64%	5.00%	7.16%	3.46%	5.13%	2.19%	3.47%
87	10.68%	14.77%	8.11%	11.37%	6.01%	8.58%	4.28%	6.30%	2.87%	4.42%
88	12.44%	16.81%	9.56%	13.04%	7.19%	9.95%	5.25%	7.42%	3.67%	5.34%
89	14.55%	19.76%	11.29%	15.46%	8.61%	11.93%	6.42%	9.04%	4.62%	6.67%
90	16.56%	20.54%	12.93%	16.10%	9.96%	12.46%	7.52%	9.47%	5.52%	7.03%
91	18.20%	22.38%	14.28%	17.61%	11.06%	13.69%	8.42%	10.48%	6.26%	7.86%
92	20.26%	23.94%	15.96%	18.89%	12.44%	14.74%	9.56%	11.35%	7.19%	8.56%
93	23.25%	27.75%	18.41%	22.00%	14.45%	17.30%	11.20%	13.44%	8.54%	10.28%
94	26.63%	31.12%	21.19%	24.77%	16.73%	19.56%	13.07%	15.30%	10.07%	11.80%
95	29.76%	34.19%	23.75%	27.29%	18.83%	21.63%	14.79%	16.99%	11.48%	13.19%
96	32.28%	36.89%	25.81%	29.50%	20.52%	23.44%	16.18%	18.48%	12.62%	14.41%
97	35.16%	40.14%	28.18%	32.16%	22.45%	25.62%	17.76%	20.26%	13.92%	15.87%
98	37.87%	43.12%	30.40%	34.61%	24.27%	27.63%	19.25%	21.91%	15.14%	17.22%
99	40.55%	44.74%	32.59%	35.93%	26.07%	28.71%	20.73%	22.80%	16.35%	17.95%
100	43.92%	47.91%	35.36%	38.53%	28.34%	30.84%	22.59%	24.54%	17.87%	19.38%