

Cost-effectiveness of air pollution
control: Improving quantification
methods and estimating QALY gains
and health care resource impacts in
England

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Abstract

This thesis is about the economic evaluation of interventions for air pollution control. It is structured around three major components. First, a critical analysis of current methods for health impact quantification in the environmental health literature. Second, the development of a Markov model of the health impacts of long-term exposure to air pollution, using the quality-adjusted life year as health metric, in order to evaluate the cost-effectiveness of reducing air pollution in England. Third, evidence synthesis and COPD incidence estimation by severity stage, in order to parameterize the model developed.

I demonstrate that the current approach to quantifying the health benefits from air pollution reduction leads to substantially biased estimates. By ignoring interactions between morbidity and mortality impacts, including differential susceptibility to risk by health status, it overestimates the change in morbidity cases and underestimates life expectancy effects. I also show that current European guidelines for uncertainty analysis in assessments of air pollution control interventions underestimate decision uncertainty and may misguide air quality strategies.

My Markov model fully captures, for the first time, the lifetime impact of air pollution exposure on individuals' quality and length of life, and identifies the joint health care budget impact of a reduction in chronic morbidity and premature death. Air quality improvement has important health implications. In London, investing up to £500 million to reduce fine particulate concentrations by $1 \mu\text{g}/\text{m}^3$ (i.e. by 7%) is highly likely to be cost-effective, whether the investment is funded by the NHS or through taxation. If this improvement were to cost more than that, however, funding through taxation is more likely to be cost-effective than funding via the NHS, since consumer willingness to pay for a QALY is higher than the estimated NHS expenditure required to deliver one QALY. The optimal level of pollution reduction, as well as the decision about whether and for how long to delay investments, is therefore expected to depend on the source of financing.

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Preface

On completion of my Baccalaureat, I hesitated between Medical and Business studies and finally opted for the latter, driven by the perspective to travel around the world and work abroad. I was seventeen back then...

The highroad for entry to leading Business schools in France is through two or three years of “classes preparatoires” which pave the way for the competitive entry exams to each school. The preparation consists of fast-paced intensive learning of a range of subjects such as: maths, programming, history, philosophy, languages, in short, everything but business studies. It is also characterised by a particular teaching approach where getting negative marks and being told that you are “as thick as clotted cream” is not uncommon, but solely designed to spur excitement towards learning more and working even harder. I guess it worked for me as, at the time, I felt I had never learned so much in all my life. The working methods which I acquired during those two years of preparation proved to be precious throughout the entire course of my academic studies.

After completing my business studies, I settled for a committed job in the city of London as admittedly, over the years I had compromised on my wish to travel the world. Whilst the position was stimulating, I soon realised deep down that I had no real enthusiasm for what I was doing, although this would take up a great amount of my time and energy.

At that point I began to think seriously about something I had always felt a great concern for: our natural environment, but yet until then, had not really considered orienting my career towards. So after two years in asset management I enrolled on the MSc in Environmental Economics at the University of York. I am glad I dared to take this step.

In the course of familiarising with the concept of ecosystem services, I became very interested in the economic implications of the linkages between our natural environment and human health. This PhD thesis is the result of my desire to nurture this interest. It focuses on one particular aspect: the air we breathe. I hope however, to have the opportunity in the future to work on many other interconnections between our health and natural ecosystems and the economic benefits of rebuilding or maintaining these relationships, especially in a context where due to man-made global warming the Earth's climate is set to change at an increasing pace.

I wish to thank my parents for supporting my decisions and for being there for me, during moments of doubt and frustration. Most importantly, I wish to thank my partner Daniele who strongly encouraged me to re-orient my career and shared with me both the exciting and difficult moments of this PhD.

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Undertaking this PhD gave me the fantastic opportunity to discover the discipline of health economics and to meet inspiring and supportive people in the Centre for Health Economics at the University of York, among whom my supervisor Richard Cookson, one member of my Thesis Advisory Panel, Karl Claxton and the members of TEEHTA, Claire McKenna in particular.

Richard, I wish to thank you for accompanying me during my PhD by providing guidance, commenting on drafts and spending generous amounts of time pointing out how to improve my academic writing but also, by showing trust in me and my work. Claire, I wish to thank you for always listening to my many questions and for providing helpful advice. I am also very grateful to Professors Karl Claxton and Piran White, who constituted my Thesis Advisory Panel, for their helpful guidance and comments throughout my PhD.

Author's declaration

All the work contained in this thesis is original. This work has not previously been presented for an award at this, or any other university. All sources are acknowledged as references.

Chapter 1

Introduction

Environmental threats, in a broad sense, are estimated to be responsible for 23% of premature deaths globally (Prüss-Üstün & Corvalán, 2006). My PhD research aims to support decision-making pertaining to the evaluation of environmental health interventions (EHI), which are government interventions designed to improve population health by reducing environmental hazards. This thesis draws from quantification techniques used in the health economics literature, in order to address a number of methodological challenges associated with the quantification of health benefits and costs of EHIs and proposes a complementary approach to the economic evaluation of this type of interventions.

To achieve this objective, I chose to focus on EHIs of outdoor air pollution control. This choice was underpinned by the following three rationales. First, outdoor air pollution is ubiquitous, i.e. everybody is exposed to it to some extent. As a result, it is a major driver of ill-health globally, ranking as the 9th risk factor out of a total of 43 by attributable burden of disease for the year 2010 (Lim et al., 2012). Whilst the greatest health burden is borne by countries in East and South Asia, which are typically characterised with high concentrations of air pollutants, outdoor air pollution remains an important public health issue in developed countries, insofar as no safe level of air pollution has been identified. In England, which is the focus of this thesis, chronic exposure to current levels of air pollution was recently estimated to be

responsible for 25,000 premature deaths annually (Gowers et al., 2014).

Second, the costs of abating air pollution are considerable. For instance, in the US, the Environmental Protection Agency estimated that the annual costs of the National Ambient Air Quality Standards exceeded \$ 80 billion annually (US EPA, 1999). This puts decision-makers under great pressure to assess whether further air quality efforts are worthwhile, and bestow particular economic importance to improvements in the validity and accuracy of estimates of the health benefits associated with air pollution control.

Third, quantification of health impacts associated with a reduction in population exposure to an given environmental hazard requires quantitative evidence of associations between exposure and health effects. The health impacts of exposure to outdoor air pollution have been intensively quantified by epidemiological studies (Medina et al., 2013). Interventions of air pollution control are therefore perfect candidates to support the analysis and development of an alternative approach to economic evaluation of EHIs. Whilst outdoor air pollution is constituted by a mixture of pollutants, particulate matter is considered to adversely affect population health more than any other air pollutant (WHO, 2014) and accordingly, this thesis focuses on fine particulate air pollution ($PM_{2.5}$).

My research contributes to knowledge pertaining to the economic evaluation of air pollution control interventions in several ways: (i) by evaluating and identifying two major limitations associated with the traditionally used method to health benefit quantification, including its impact on predictions' validity; (ii) by developing an approach based on Markov modelling that fully captures, for the first time, air pollution's joint impact on quality and length of life and on health care costs; (iii) by performing systematic searches and statistical analyses of the epidemiological evidence base pertaining to a selected set of health endpoints and (iv) by developing an approach to address both underdiagnosis and late diagnosis issues that characterise chronic obstructive pulmonary disease, so that the public health benefits of reducing the risk of developing this disease as a result of air quality efforts are correctly quantified; (v) by providing estimates of impacts that inform decision-making about the

UK air quality strategy.

This thesis is structured as follows. Chapter 2 reviews the literature relevant to the economic evaluation of air pollution control interventions. It is structured in three parts pertaining to: (i) the epidemiological evidence base, with a focus on study design and statistical approaches to effect estimation; (ii) decision-making tools used in the environment and health policy fields and their respective theoretical underpinnings; (iii) the methodology to quantify health benefit and valuations approaches currently used in economic evaluations of air pollution control interventions.

Chapter 3 pertains to the first essential step to policy evaluation: impact quantification. This chapter is addressed to the wide audience of health impact assessment practitioners for environmental policies. It focuses on the limitations associated with the current approach to quantification, where morbidity and mortality are quantified separately and argues for a simultaneous quantification of impacts using Markov modelling.

Chapter 4 relies on the simultaneous approach to quantification advocated in Chapter 3 and develops a Markov Model to refine the understanding of air pollution control benefits. It assesses life expectancy gains but also improvements in quality of life, using the quality-adjusted life year (QALY) as health metric, and evaluates the total health care budget impact of a decrease in both morbidity and premature mortality. This is the first study to fully capture particulate air pollution's influence on the individual's baseline quality of life, life expectancy and level of susceptibility to adverse effects, which are crucial to perform a cost per QALY analysis of air pollution control interventions.

Chapters 5 and 6 aim at characterising parameter uncertainty pertaining to the estimation of the health benefits and health care resource impacts of air pollution control. The obtained parameters are fed into the Markov model developed in Chapter 4. Chapter 5 develops a coherent probabilistic framework to estimate the age-specific annual probability of being diagnosed at a given stage of COPD and applies it to the general population of England. Chapter 6 performs a systematic review and two meta-analyses of the association between long-term exposure to particulate air pollution and respectively all-cause mortality and lung cancer.

Chapter 7 presents the results from the application of the model developed in Chapter 4 to the UK, in order to support the UK air pollution strategy. It evaluates the cost-effectiveness of air pollution reduction in London, whether such an intervention would be funded by the NHS or via general taxation.

Finally, Chapter 8 concludes the thesis. Its aims are fourfold: (i) to restate the overall structure of the thesis; (ii) to underline the contributions of the work undertaken; (iii) to highlight its limitations and (iv) to outline some avenues for further research.

Chapter 2

Review of literature

2.1 The adverse health effects of outdoor air pollution

2.1.1 Outdoor air pollution: background

Air pollution results from the release in the atmosphere of a mixture of: (i) gases and vapour-phase compounds, such as nitrogen oxides (NO_x), sulphur dioxide (SO_2), ammonia (NH_3), volatile organic compounds and (ii) particulate matter, which is a mixture of liquid and solid compounds (Brook et al., 2010). These compounds are either emitted directly in the atmosphere or result from the atmospheric interaction of primary air pollutants with sunlight and water vapour. Particulate matter for instance, is constituted both by directly emitted elemental and organic carbon and by secondarily formed pollutants resulting from chemical reactions between SO_2 , NO_x , NH_3 and organic gases in the atmosphere (US EPA, 2012).

Air pollution is mostly the by-product of human activity (WHO, 2014). Primary air pollutants are essentially generated by fossil fuel combustion for power generation and transportation, but also result from various industrial processes (e.g. cement plants, smelters, paper and still mills) as well as road

dust, fertiliser use, livestock farming and biomass and waste burning (US EPA, 2012).

The awareness of the deleterious health impacts of air pollution at population level, and not only as a cause of occupational disease, started to grow in the 20th century, following a series of acute episodes of air pollution when unfavourable weather conditions increased the concentrations of air pollutants emitted from nearby factories (Jun, 2009). In particular, the upsurge in death rates in the Meuse valley (Belgium) during a 4-day long sulphuric fog in December 1930 (Firkey, 1936) and the increase in death rates and respiratory symptoms in Monongahela valley (Pennsylvania) during a short episode of heavy smog in 1948 (Schrenk et al., 1949) provided the first pieces of evidence on the potential toxicity of air pollution at community level. These events were followed by London's great smog in December 1952, which is estimated to have led to 3,000 premature deaths in the three weeks following the event and to 12,000 premature deaths until a year later (Bell & Davis, 2001). This series of acute air pollution episodes greatly contributed in arousing awareness of the harmful effects of air pollution and spurred governments in enacting the first national pieces of air pollution legislation, e.g. UK Clean Air Acts of 1956 and 1968, US Clean Air Act of 1970 which introduced the first National Ambient Air Quality Standards.

Much of the epidemiological effort on identifying the health risk posed by air pollution has focused on particulate matter (PM). Particulates are constituted by hundreds of chemicals and greatly vary in size and shape (US EPA, 2012). They are classified in terms of their aerodynamic diameter range. The three size fractions are PM_{10} , i.e. particles less or equal to $10 \mu m$ in diameter; $PM_{2.5}$, i.e. particles less or equal to $2.5 \mu m$ in diameter and $PM_{0.1}$, i.e. particles less or equal to $0.1 \mu m$ in diameter. PM_{10} are commonly referred to as coarse particles, $PM_{2.5}$ as fine particles and $PM_{0.1}$ as ultra fine particles.

The effect of particles less or equal to $10 \mu m$ in diameter have been intensively investigated since they cannot be filtered by the nose and upper airways and thus, penetrate into the respiratory system, while the fine fraction also pass into the blood stream (Marchwinska-Wyrwal et al., 2011). $PM_{2.5}$ are expected to be more harmful than PM_{10} since they have a longer life period,

penetrate deeper into the human organism as well as into indoor environments and carry more toxic compounds, e.g. sulphates, nitrates, acids, metals (Pope III & Dockery, 2006). While $PM_{0.1}$ are expected to be the most harmful, due to the lack of monitoring of these particulates, to date the evidence base for this pollutant is essentially based on laboratory-based toxicological studies.

2.1.2 Epidemiological studies: challenges and design typology

Challenges

Statistical analysis for causal inference of air pollution health effects in human is challenging for two main reasons. First, since controlled randomisation of individuals to air pollution exposure is possible only under very strict and limiting conditions, statistical analysis is overwhelmingly based on observational studies. The latter require extensive covariates adjustment and sophisticated modelling techniques to control for factors that may confound the association between air pollution exposure and health effect, where the choice of confounding variables will depend on study design (Dominici et al., 2003). Second, exposure measurement error appears inevitable as individual exposure to air pollution exposure is typically proxied by levels of ambient concentrations. Although exposure misclassification is not expected to pose a threat to studies' internal validity as participants should theoretically have an equal likelihood to be assigned an inaccurate estimate of exposure, it affects studies' statistical power and can lead to imprecise estimates of health effects (Raaschou-Nielsen et al., 2013).

The choice of epidemiological study design is motivated by the time-scale of exposure to be investigated, namely short-term or long-term i.e. cumulative. The latter determines the temporality of the health effect to be estimated: acute or chronic and the source of variation in air pollution exposure

to be exploited: temporal and/or spatial. In practice four main types of epidemiological study designs have been used to build evidence of air pollution effects: time series, case-crossover, cross-sectional studies and cohort studies. The health outcomes investigated by the first epidemiological studies were typically death and hospitalisations. In recent years, however, continuous outcomes such as changes in lung function (Eisner et al., 2010) and in levels of coronary atherosclerosis (Adar et al., 2013) for instance, have also been investigated. Study design and the nature of health outcome investigated (e.g. binary or continuous) drive the choice of statistical method for data analysis.

Studies of short-term changes in pollution

Time-series and case-crossover studies measure the change in daily counts of deaths and rare morbidity events (e.g. hospitalisations) over a time window of a few days, following a short-term peak in pollutants concentrations.

Time-series associate daily population-averaged exposure levels to count of health outcomes, where the bias from data aggregation is expected to be small if health effects are small and the frequency of disease outcome is low (Wakefield & Salway, 2001). Whilst the statistical designs of the earliest time-series were simple with count data being modelled using Poisson regression, adequate control for time-dependent covariates (e.g. seasonality, weather) increasingly became a primary concern. Since the mid-1990's, generalised additive models using non parametric smoothing have been extensively used to control for natural time-dependent fluctuations in mortality that would confound estimates of air pollution adverse effect (Pope III & Dockery, 2006).

The case crossover design consists in matching individuals' exposures at time of death/morbid event with exposures during one or more control periods in a retrospective case-control design, where each case represents his/her own control. It exploits the individual's variation in exposure over time using conditional logistic regression. Unlike time-series, case crossover studies control for seasonality and temporal trends in mortality by design through carefully chosen control periods, rather than by statistical modelling with smooth func-

tions (Dominici et al., 2003). Since the case-crossover design relies on events at the individual level, as opposed to population-averaged counts of events, it may be useful to investigate individual-level effect modification or susceptibility. The main drawback of this design, however, is that results can be sensitive to the choice of periods used as controls (Pope III & Dockery, 2006).

Studies of long-term cumulative exposure

Whilst information about the acute health effects of pollution peaks is important, the understanding of the cumulative impact of long-term air pollution is key to evaluate air pollution public health burden. The analysis of health impacts from long-term exposure to air pollution typically exploits spatial variation in exposure between geographical areas over time. Two main types of study design have been used by epidemiologists to study both binary and continuous health outcomes associated with cumulative exposure to air pollution: cross-sectional studies and cohort studies.

Cross-sectional studies associate data on individuals health status (e.g. disease prevalence) and pollution concentration levels measured at a single point in time. Whilst these studies are informative, they proxy long-term pollution exposure with actual air pollution concentrations (Brunebreef & Holgate, 2002) and oversimplify long term impacts (Sunyer, 2001). Consequently, although cohort studies are expensive and time consuming, they are considered the best source of epidemiological evidence of the long effects of exposure to pollution (Pope III & Dockery, 2006)

Cohort studies associate long-term exposure with health outcomes by exploiting cumulative variation in individuals' exposure between geographical locations. Prospective cohort studies are preferred for their ability to control for individual risk factors measured at enrolment, such as age, smoking history including passive smoking, occupational exposure to pollutants, drinking habits, diet, BMI and so forth. Unlike cross-sectional studies, cohort studies consist in following individuals over time to measure the time to adverse health event. The statistical analysis of time-to-event typically relies on the

Cox proportional hazard model, with the baseline hazard function being stratified by sex, age and, in the US, race. In addition to adjusting for individual risk factors, controls for area-specific potential confounding factors has been increasingly performed, although they do not seem to significantly alter estimates of effect (Krewski et al., 2009; Crouse et al., 2012).

As mentioned earlier, exposure measurement error is inherent in using estimates of exposure based on measures of pollutant concentrations captured by fixed monitors. To obtain finer spatial contrasts in exposure, most cohort studies use geographic information systems-based statistical methods to account for small-scale spatial variations in pollution concentrations. These methods, which fall into three categories: (i) interpolation methods, (ii) land use regression models or (iii) dispersion modelling are described in Chapter 6.

Natural experiment studies

The body of epidemiological evidence on the health effects of air pollution exposure is also built on natural experiments using a before/after study design and, when a control group is available, a difference in differences approach. In addition to a number of studies of unplanned events such as strikes (Pope III, 1996; Pope III et al., 2007; Parker et al., 2008), planned interventions resulting in either abrupt or progressive changes in air pollution concentrations have been intensively investigated.

Studies of planned actions are commonly referred to as “accountability studies”. They aim to identify one or more causal effects in the “accountability chain” that links regulatory actions to various policy-relevant outcomes. The causal chain has at least five sequential stages: (1) regulatory action or any other planned action, (2) change in air pollutants emissions levels, (3) change in ambient air quality, (4) change in exposure/dose, (5) human health response (HEI, 2003). Most accountability studies however, have focused on the linkages between (3) the change in ambient air quality and (5) human health (van Erp & Cohen, 2009).

As underlined by the reviews of van Erp & Cohen (2009); Bell et al. (2011);

Giles et al. (2011) and van Erp et al. (2012), very diverse past interventions of outdoor air pollution reduction have been analysed. Examples of intervention include: (i) emission restrictions in cities hosting Olympic games (Friedman et al., 2001; Lin et al., 2011); (ii) local regulations such as the ban on domestic coal use in Dublin in 1990 (Clancy et al., 2002) or restrictions on fuel sulphur-content in Hong Kong in 1990 (Hedley et al., 2002); (iii) the introduction of measures to decrease traffic congestion (Currie & Walker, 2011; Kelly et al., 2011); (iv) national policies such as the Clean Air Act in the US (US EPA, 1997, 1999, 2011).

Retrospective analyses of past interventions of air pollution control are often confronted with issues such as potential unmeasured confounding by others health stressors than pollution, the choice of appropriate time period before/after intervention and of control groups and limited data availability on both air quality and health outcomes (van Erp et al., 2012). A recent study of the impact of the congestion charging scheme on air quality in London (Kelly et al., 2011) further underlines such challenges. Investigators found it extremely difficult to attribute changes in air pollution concentrations to the congestion charge as other traffic interventions were implemented in parallel to its introduction.

Nevertheless, natural experiment studies do provide compelling evidence about the actual health benefits associated with past decrements in air pollution and valuable information regarding the decrease in health risk over time. For instance, the ban on domestic coal use in Dublin in 1990, was found to result in a $36 \mu\text{g}/\text{m}^3$ (70%) decline in black smoke (a former measure of PM). This was associated with a significant decrease in cardiovascular deaths (-10.3%, 95%CI -12.6 - 8%) and respiratory deaths (-15.5%, 95%CI -19.1 - 11.6%) in the first year after the ban (Clancy et al., 2002). Importantly, no rebound in cardio-pulmonary mortality was observed in the subsequent years. With regards to infant health, Currie & Walker (2011) found that the introduction of an electronic toll collection in the northeastern states of the US (E-ZPass), which led to a sustained reduction in traffic congestion, was associated with reduced premature birth (by 6.4 - 8.6%) and low birth weight (by 7 - 9.3%) in babies of mothers living within 2 kilometers from a toll plaza,

relative to babies of mothers living 2-10 km from a toll.

2.1.3 Epidemiological evidence: a selection of key findings

Preliminaries

Whilst there remains numerous uncertainties, epidemiological studies performed over the last decades have enabled to shed light on a number of adverse health impacts associated with exposure to air pollutants, particulate pollution in particular. This section discusses some key results from a selection of studies, in order to give a flavour of the range of mortality and morbidity effects associated with respectively acute and chronic exposure to particulate matter. Thorough reviews of epidemiological evidence and suspected mechanistic pathways may be found in Anderson et al. (2012); Spirić et al. (2012); Brook et al. (2010); US EPA (2009, 2004b).

Although a number of epidemiological studies have investigated the health effects of air pollution exposure on children, especially with regard to lung development - see Shannon et al. (2004) and Eisner et al. (2010) for a review - most studies have focused on adults. Nevertheless, more recently, epidemiological studies investigated air pollution impacts on fetal health and found association with low birth weight, premature birth and even a greater risk of autism (Pedersen et al., 2013; Raz et al., 2014).

Measure of excess risk

The effect of air pollution exposure on health is typically measured as a relative risk (RR), a hazard ratio (HR), or less commonly, as an odds ratio (OR). A ratio equal to 1 means that there is no association between hazard

exposure and adverse event. The RR is the ratio of risks, i.e. of probabilities, of adverse health event among the exposed and non-exposed group. For time-to-event data, HRs are a more appropriate measure as they are derived from instantaneous event rates in each group, conditional on survival at time t . Studies using the logistic regression to analyse data, such as case crossover studies typically express results with odds ratios. The latter are ratios of the probability of event occurrence and the probability of non-occurrence of event. Since odds and probabilities are related, where $Odd = Pr/(1-Pr)$, the relative risk is a function of the odd ratio and of the probability of event occurrence in the unexposed group Pr_0 , such that $RR = OR/(1 - Pr_0 + Pr_0OR)$. If $Pr_0 \leq 10\%$ and OR value is comprised between 0.5 and 2.5, the OR is quasi equivalent to a RR (Sistrom & Garvan, 2004).

Evidence from studies of short-term exposure

Since the 1990's, more than 100 single-cities daily time series and case cross-over studies exploiting relatively small changes in daily levels of air pollution have been carried out (Pope III & Dockery, 2006). The results of many of these studies have been pooled in meta-analyses, e.g. Levy et al. (2000); Steib et al. (2003), to improve the accuracy of effect estimates. Furthermore, in order to address potential city selection bias, multi-city daily time-series were conducted, the largest and most notorious ones being the National Morbidity Mortality and Air Pollution Study (NMMAPS) in the US and Air Pollution and Health (APHEA) in Europe. Further description and discussion of these studies can be found in Brunebreef & Holgate (2002).

Overall evidence from studies of short-term exposure of air pollution suggests that a $10 \mu g/m^3$ increase of ambient concentrations of PM_{10} and $PM_{2.5}$ in the preceding 1 to 5 days before event, is associated with an increase in mortality by 0.4% to 1% and does not support the hypothesis of a threshold to health effects (Brook et al., 2010). In this context, a threshold refers to a level of air pollutant concentration, below which no health impact is found. As underlined by Pope III & Dockery (2006), given that relatively small in-

crements in air pollution over a few days is unlikely to lead to a large increase in daily mortality, the fact that studies of short-term exposure consistently found a small but significantly positive effect at relatively low concentrations is impressive. In addition, numerous time-series and case crossover studies consistently found that short-term elevations in particulate pollution were associated with respiratory and cardio-vascular hospital admissions (US EPA, 2004b; Mustafic et al., 2012).

Evidence from studies of long-term exposure

Mortality:

The two most prominent prospective cohort studies of mortality, which have been extensively reanalysed under the lead of the Health Effects Institute and which follow-up duration has been extended several times are: the Harvard Six Cities (HSC) cohort and the American Cancer Society (ACS) cohort. The HSC cohort was constituted by 8,096 white adults aged between 25 and 74 years at enrolment, who were randomly sampled between 1974 and 1977 from six US cities characterised with large spatial contrasts of air pollution. The first study of the HSC cohort (Dockery et al., 1993) had 14-16 years of follow-up whereas the latest extended analysis (Lepeule et al., 2012) relied on a follow-up period of 33 years. The ACS cohort was based on the ACS Cancer Prevention Study II (CPS II), an on-going prospective study of mortality based on 1.2 million of adults aged at least 30 years old (with at least one family member aged 45 years or more) who voluntarily enrolled in 1982. Risk factor data from CPS II was linked with ambient $PM_{2.5}$ concentrations for 359,000 subjects from 61 metropolitan areas for the period 1979-1983 and for 500,000 subjects from 116 metropolitan areas for the period 1999-2000. The latest analysis of the ACS study has a follow-up of 18 years (Krewski et al., 2009).

Many other cohort studies of mortality were conducted both in the US and in other parts of the world (Canada, Europe, China). The complete list and a description of such studies is presented in Chapter 6. These studies overwhelmingly suggest that concentrations of $PM_{2.5}$ are significantly associated

with an excess risk of premature mortality, in particular from cardiovascular, pulmonary and lung cancer causes. For instance, based on the latest extended analysis of the ACS cohort, Krewski et al. (2009) reported that a $10 \mu\text{g}/\text{m}^3$ increment of $PM_{2.5}$ is associated with a 6% (95% CI of HR: 1.04 - 1.08) increase in all-cause mortality, a 24% (95% CI of HR: 1.19 - 1.29) increase in death from ischaemic heart disease and a 13% (95% CI of HR: 1.06 - 1.23) increase in death from lung cancer.

In general, risk estimates from cohort studies of mortality are an order of magnitude higher than effect estimates from studies of short-term exposure to air pollution. This is an important finding as it contradicts with the hypothesis of short-term harvesting, according to which air pollution would solely impact the frailest individuals by bringing their deaths only a few days forward. Indeed, if harvesting explained most of air pollution effect, then impacts on death rates in the long run would be negligible, which is clearly not the case (Pope III & Dockery, 2006).

Extended analyses of cohort studies and repeated cross-sectional analyses have also provided an opportunity to evaluate the change in health risk associated with long term changes in air pollution. Pope III et al. (2009) found that reductions in particulate pollution across various US counties over a two-decade period (1980s and 1990s) were associated with half to a full year increase in life expectancy, after controlling for changes in socio-economic, demographic, and proxy smoking variables. The observed changes in life expectancy appeared consistent with indirect estimates based on cohort studies results. Laden et al. (2006); Schwartz et al. (2008) exploited the fact that concentrations during the extended follow-up period of the Harvard Six Cities cohort were lower than during initial analysis. Their studies suggested that the excess mortality risk of air pollution was essentially associated with exposures as short as one to two years before event and thus, were relatively quickly reversible.

Finally, epidemiological studies also found that, at particulate concentration levels present in developed countries (e.g. between 5 and $35 \mu\text{g}/\text{m}^3$), health effects increase linearly with increments in exposure and no threshold below which there would be no adverse effect on health was found (Pope III et al., 2011; Lepeule et al., 2012; Crouse et al., 2012).

Morbidity:

Cohort studies were also used to investigate the impact of air pollution on the development of chronic respiratory and cardiovascular conditions. For instance, Abbey et al. (1995) used data from the Health and Adventist and Smog Study (ASHMOG) to look at the development of new cases of chronic bronchitis associated with $PM_{2.5}$ exposure (RR of 1.81, 95%CI: 0.98 - 3.25 per $45 \mu g/m^3$ increment in $PM_{2.5}$). Miller et al. (2007) exploited data from the Women's Health Initiative to analyse the effect of air pollution exposure on the risk of first cardiovascular events for menopausal women (HR of 1.24, 95%CI: 1.09 - 1.41 per $10 \mu g/m^3$ increment in $PM_{2.5}$). In the US, the Multi-Ethnic Study of Atherosclerosis and Air pollution (MESA-Air) was launched in 2004 in order to investigate the progression of cardiovascular disease associated with air pollution exposure over a 10-year period. In 2008, the European Study of Cohorts for Air Pollution Effects (ESCAPE), involving more than 30 cohorts of studies across Europe, was launched with a view to investigate the relationship between long-term exposure to PM and NO_2 , with several morbidity health endpoints.

The relatively few cohort studies of morbidity have been complemented by a number of cross-sectional studies. For instance, Zemp et al. (1999) relied on the Swiss study on air Pollution and lung disease in adults (SAPALINDA) to investigate the association between long term exposure to PM_{10} (proxied by PM_{10} data for the year 1993) and the prevalence of reported respiratory symptoms across eight areas in Switzerland characterised with differing levels of air pollution. The authors found that an $10 \mu g/m^3$ increment in average annual level of PM_{10} concentration was associated with an OR of 1.33 (95% CI: 1.14 - 1.55) for breathlessness day or night. Schikowski et al. (2005) used consecutive cross-sectional studies performed between 1985 and 1994 in seven areas of Germany as part of the Study on the Influence of Air pollution on Lung function, Inflammation and Ageing (SALIA) to assess the role of air pollution on the development of chronic obstructive pulmonary disease among 55 year old women and found a OR of 1.33 (95%CI: 1.03 - 1.72) associated with a $7 \mu g/m^3$ increment in five years mean of PM_{10} .

2.1.4 Epidemiological evidence: main conclusions

The adverse effects of outdoor air pollution in health have been documented since the early 20th century and have led to the first major regulatory interventions of air pollution control by the second half of the 20th century. Although the body of epidemiological evidence is extensively underpinned by observational studies, study designs and statistical approaches to data analysis have been greatly refined and adverse effects on the cardio-respiratory systems have consistently been found across studies. This strongly supports the hypothesis that exposure to air pollution causes adverse health effects.

Whilst the effects of acute exposure were the focus of the first wave of epidemiological studies, which relied on time-series and case crossover designs, over the last decades, large-scale expensive cohort studies have been conducted to investigate the effects from long-term cumulative exposure. Findings from cohort studies of mortality, which have primarily focused on adults of the general population: (i) contradict the hypothesis of short-term harvesting, according to which air pollution would solely impact the frailest individuals by bringing their deaths a few days forward; (ii) support the hypothesis that at concentrations prevailing in developed countries, health effects increase linearly with increase in exposure; (iii) suggest the absence of a concentration threshold below which there would be no health effect.

Finally, as underlined by section 2.1.3, which aimed at providing a brief overview of the range of health effects associated with both acute and long-term exposure to air pollution, the body of epidemiological evidence keeps on growing. This bestows particular importance on systematic reviews and meta-analyses of epidemiological findings, in order to ensure that decision-making pertaining to air quality targets is based on all available relevant evidence.

2.2 Evaluating air pollution control interventions: theoretical background

2.2.1 Interventions' key characteristics

In light of epidemiological findings mentioned in section 2.1.3, and of the fact that air pollution exposure is ubiquitous, interventions of air pollution control clearly represent public health interventions (Reisnik & Zeldin, 2005). Whilst possibilities of adapting to air pollution such as locating densely populated areas away from busy roads should not be neglected (Giles et al., 2011), owing to the high dispersion of air pollutants, abating emissions appears to be the key response to the environmental health threat of outdoor air pollution.

Pollution results from the release in the environment of a pollutant load that, by far, exceeds the waste assimilative capacities of natural ecosystems. Air pollution abatement will therefore also improve ecosystems' health, for instance by reducing the deposition of acidic particles and polycyclic organic matter, which damage trees, lakes and their aquatic life (US EPA, 2004a). Consequently interventions of air pollution control overlap with environmental policies, which aim to protect public health against the harmful effects of environmental degradation and prevent, reduce or mitigate the negative effects of human activities on ecosystems (McCornick, 2001).

Improving air quality is costly. In the US, for instance, the EPA estimated that nationwide pollution abatement costs were in the range of about \$80 billion per year (US EPA, 1999). Typically interventions of air pollution control are expected to be associated with a high up-front costs. For example, the UK Department of Transport recently pledged to commit a minimum of £200 million to support the early market for ultra low emission vehicles, in order to help achieve London's ultra low emission zone (Department for Transport, 2014).

This substantial use of scarce resources requires to assess whether further efforts in decreasing air pollution are expected to be worthwhile if compared

with other courses of action such as “business as usual”. The comparative analysis of costs and consequences of alternative actions, with view to support the choice between competing uses of scarce resources, constitutes an economic evaluation (Drummond et al., 2005).

However, should actions taken to reduce outdoor air pollution be evaluated as public health interventions or as environmental interventions? In light of the overlap between these two types of interventions, the economic evaluation of air pollution control somewhat lies at the intersection of environmental economics and health economics. The two disciplines, however, have been developed for different decision contexts and as a result, have differing theoretical foundations.

2.2.2 Differing decision contexts

Environmental interventions

Goods and services derived from natural ecosystems, such as clean air, often have no property rights attached to them and their misuse and resulting damages to third parties cannot be compensated by a market transaction (Freeman et al., 1984). Environmental policies are generally designed to correct for such market failures since if left uncorrected, they may lead to socially harmful over-exploitation and degradation of natural resources, as illustrated by Hardin (1968)’s “Tragedy of the Commons”. The latter involved herdsmen using a common pasture for grazing their cattle. Individually, the herdsmen would have no incentive to prevent overgrazing since they would not themselves benefit from holding back their own cattle. However, the collective impact of their self-interested strategies proved disastrous to their community in the long run.

Pollution, like any other uncompensated externality, creates a wedge be-

tween the private costs and the social costs of production and consumption and ultimately, a loss of social welfare (Pigou, 1920). Some economists, argued that externalities could be internalized via bargaining over pollution rights between polluters and their victims (Coase, 1960). However, air pollution victims are typically too large in number and too different in terms of income and geography to be able to organise themselves as a single agent for bargaining. Therefore it is now widely acknowledged that government intervention for pollution-control is a necessity (Mendelsohn, 2002; Ostrom, 2003).

Environmental interventions generally aim to internalize the external costs of pollution into private costs. This can be done via command and control polices, such as air pollution targets, quotas and bans or market based policies, such as Pigouvian taxes or tradeable pollution permits. As a consequence, EHIs of air pollution are typically regulatory interventions whose costs are expected to primarily fall on the polluter.

The objective of the economic evaluation of environmental policies is to assess policies' efficiency in addressing externalities, by evaluating whether their social benefits are worth seeking given their social opportunity cost embedded in the best possible alternative use of resources (Boardman et al., 2006). There are two good reasons to suppose that the socially optimal level of air pollution is above zero: (1) pollution controls typically have non-zero opportunity costs and (2) natural ecosystems typically provide waste-sink services that can cope with a certain level of pollution (Turner et al., 1994). Therefore, economic evaluations of pollution-control EHIs also aim to inform questions pertaining to the optimal scale of pollution-control programmes, whereby the socially optimal level of pollution is reached when the marginal abatement cost equals its marginal benefit.

Public health interventions

The World Health Organisation defines public health as: “all organized measures to prevent disease, promote health, and prolong life among the population as a whole” (WHO, 2015). The scope of public health interventions

is extremely broad, including for instance vaccination, occupational safety, healthy-behaviour promotion and their impacts typically go beyond health care budgets. Nevertheless, presumably due to historic links between medical and public health services, public health evaluations have often been carried out using a health care evaluation paradigm (Wanless, 2004; McDaid & Needle, 2009).

Public expenditure on health care is generally designed as an alternative to market provision, rather than as a way of regulating market provision to correct for market failure. It is typically justified as a way of addressing equity concerns (e.g. difficulties that the poor and the sick would face in buying health insurance) and market failures due to informational asymmetries.

The fact that relevant public sector entities are endowed with a budget to achieve health implicitly suggests that population health is a worthwhile output, and that the role of economic evaluation is to identify the most cost-effective way to produce it. From this point of view, that however is not shared by all (Pauly, 1995), economic evaluations of health care programmes do not seek to maximise social welfare but aim to optimally allocate a pre-determined health care budget across competing programmes (Gold et al., 1996; Drummond et al., 2005).

2.2.3 Decision-support tools

Cost Benefit Analysis

Different objectives require different decision-support tools. Assessing whether an environmental policy achieves a socially optimum level of pollution control requires to compare, at the margin, the present value of all benefits and costs accruing to society. As a consequence, the economic evaluations of environmental policies have extensively relied on the cost-benefit analysis (CBA)

framework.

CBA values all opportunity costs and benefits using the common money metric. In welfare economics, a good is considered valuable insofar as it generates utility to some individuals who, assuming the traditional axioms of consumers preferences (completeness, reflexivity and transitivity), will be willing to trade consumption for it. Therefore individuals' preferences for goods are revealed in the market-place by their willingness to pay (WTP) for them and the appropriate social value of a programme's benefits is the sum total of individuals' WTP for it (Boardman et al., 2006). Alternatively, especially in the context of a reduction in the good or service to be valued, individual's preferences can be revealed by individuals' "willingness to accept" the loss of benefits against compensation.

CBA is grounded in neoclassical welfare economic theory. It is often justified in terms of the Kaldor-Hicks compensation test, from which the potential Pareto efficiency rule was derived as a decision rule for accepting policies. The Kaldor-Hicks criterion suggests that a policy represents a potential Pareto improvement, and thus will increase efficiency, as long as those who will win from the implementation of a policy could potentially compensate those who will lose, while still being better-off (Boardman et al., 2006). An alternative justification for CBA is in terms of a utilitarian social welfare function (SWF) representing a social objective of maximising the sum total of individual welfare. Either way, the basic idea is that a policy should be adopted as long as its net social benefits are positive.

Cost Effectiveness Analysis

Economic evaluations of public health interventions and health care technologies have commonly relied on cost-effectiveness analysis (CEA), which consists in comparing the incremental costs of an intervention to its incremental health benefits. CEA is commonly considered from a social decision making point of view, as a tool to maximize an explicit societal objective, such as maximizing the present value of population health, subject to an exogenous

budget constraint (Paulden & Claxton, 2012). For public health, such approach is exemplified by WHO's CHOICE ¹ initiative, which is intended to support the allocation of limited resources across public health interventions. Consequently, health outcomes are commonly combined into a single composite index, such as disability-adjusted life years (DALYs) or quality-adjusted life years (QALYs), in order to compare the cost-effectiveness of competing interventions and support resource allocation (Drummond et al., 2005).

QALY and DALY encapsulate morbidity and mortality effects in one single indicator by multiplying life expectancy estimates with health-related quality of life weights that characterise health states or disability conditions (Gold et al., 2002). The DALY was developed to compare the health burden of diseases or risk factors globally. Whilst the DALY has also been recommended for economic evaluations of public health interventions in low- and middle-income countries (Gates foundation' reference case, NICE International (2014)), the QALY has been routinely used for economic evaluations of public health interventions and health care technologies in high income countries (Drummond et al., 2005; ISPOR, 2013). The QALY will therefore be the focus of the present thesis, which relies throughout on a UK case study.

Computation of the QALY requires two elements. The first is quality of life weights associated with a particular health condition. By convention, health-related quality of life weights (HRQoL) are anchored on a interval scale from 1 (perfect health) to 0 (death) and health states considered to be worse than dead have a negative value. Several methods may be used to obtain the HRQoL scores of health-related quality of life. The three main approaches are: (i) visual analogue scales, where individuals rank in a line the various health states representing the health-related quality of life continuum; (ii) time trade-off, where individuals have to choose between living a certain period of time with a given health condition versus living a shorter period of time but in a improved state of health; (iii) standard gamble, where individuals are required to choose between living a given health state or living in a better health state with a particular risk of death (Gold et al., 2002). To compute a QALY, disease duration is multiplied by its attached HRQoL score, so that living

¹CHOosing Interventions that are Cost-Effective

with a condition associated with quality weight x for T years amounts to Tx QALYs. The QALY therefore assumes linear substitution between quality and quantity of life and has interval scale properties such that, for example, a gain from 0.2 to 0.5 is equally valuable as a gain from 0.6 to 0.9. (Gold et al., 2002).

Finally, it should be underlined that QALY-based CEA was initially referred to as cost-utility analysis. However since CUA can be seen as a type of CEA (Drummond et al., 2005), nowadays most authors do not specify the distinction between the two. Accordingly, this thesis solely uses the term CEA.

2.2.4 Monetizing health benefits

In a CBA framework

Individuals' WTP to obtain a good such as clean air, or alternatively to avoid damages such as pollution, is an estimate of the change in consumer surplus measured by the Hicksian demand function (Boardman et al., 2006). For instance, the WTP for better air quality or for improved health represents the income that could be taken from a person so that her utility would get back to its level before the improvement (equivalent variation). Since neither health nor environmental services are traded in markets, their WTP value (or shadow price) can be either revealed through consumers' trade-offs in surrogate markets (e.g. via hedonic pricing methodology) or elicited through contingent valuation or choice modelling surveys, which involve hypothetical scenarios.

For health risk, the risk-wage trade-offs observable in the labour market have been extensively researched in hedonic models in order to derive a value of statistical life (VSL) from wage premiums for risks of death by occupational accident. VSL corresponds to individuals' aggregated WTP for a small change in survival probabilities (Chestnut & de Civita, 2009). VSL values, however, appear to be context specific and their estimates vary greatly (Drummond

et al., 2005). Recent meta-analyses found mean VSL values ranging from respectively \$ 2.8 million (Miller, 2000) to \$ 6.7 million (Viscusi & Aldy, 2003). This wide range of VSL values partially stems from the difficulty to control for workers' lack of full information or cognitive bias regarding job risk, self-selection according to differing levels of risk aversion and labour markets imperfections such as unions' bargaining powers (Boardman et al., 2006).

In this context, although they are potentially prone to bias associated with the use of hypothetical scenarios, contingent valuation studies (which focus on the non-market good as a whole) and choice experiments (which focus on specific attributes of the non-market good), provide a complementary source of valuation for specific improvements in health. These stated-preferences methods however, do also exhibit huge variation in estimates. Further discussion on the strengths and weaknesses of revealed and stated preferences can be found in Fujiwara & Campbell (2011).

Alternatively, when there is not enough information to derive a demand function for a good, there exists a set of another techniques, which do not aim to measure true changes in social welfare but still provide useful information for CBA. These techniques, referred to as damage or production-function approaches, rely on observable market information and include replacement cost, averted expenditure and cost-of-illness studies. Whilst cost of illness studies can encompass direct medical costs (physician service, hospital care and drugs) and productivity costs (loss workdays), they do not account for the value of pain and psychological suffering, quality of life impacts (e.g. restricted lifestyle) and typically ignore caretakers expenditures. Therefore, they are expected to understate the true changes in social welfare (Bell et al., 2008).

In a CEA framework

The use of a composite health index such as the QALY is sufficient to compare the cost-effectiveness of health care technologies, based on their incremental cost effectiveness ratio (ICER), e.g. $\pounds x/QALY$. However, in order to drive investment or dis-investment decisions, health care technologies' cost-

effectiveness performances need to be compared against a benchmark, known as cost-effectiveness threshold or cut-off value. The application of a decision-rule, whereby a health care technology costing more than the agreed cut-off value for every QALY it delivers should not be funded, effectively consists in applying a monetary value to health (Phelps & Mushlin, 1991).

According to the social-decision making perspective, the value of health is revealed by the health care budget constraint, which represents the health displaced by a given investment (Claxton et al., 2006). The NHS budget constraint can be seen as a partial expression of a latent social welfare function, and its shadow price corresponds to how much society is willing to pay for health that is generated by a collectively funded health care system (Claxton et al., 2007). In the UK, NICE uses a cost-effectiveness threshold range of £20,000 - 30,000 per QALY gained for health care technology assessments (NICE, 2013). However, recent empirical work suggests £13,000/QALY may be a more correct benchmark (Claxton et al., 2013).

As an alternative to this supply-sided approach to health valuation, a branch of health economics has applied welfare economic methods to obtain WTP values for a QALY, a recent review of which can be found in Ryen & Svensson (2014).

Ultimately, the choice of source of money value to monetize QALY impacts in CEA should be driven by the opportunity cost of intervention. If the latter is borne by the NHS, then the money value of a QALY should be informed by the cost-effectiveness of the health care to be displaced by the investment, as embedded in the budget constraint (Claxton et al., 2007). By contrast, if the intervention is funded by raising new tax revenue, private consumption will be displaced and thus, the source of valuation should be the utility loss of foregone private consumption that is equivalent to the willingness to pay for a QALY (Ryen & Svensson, 2014).

Value judgments embedded in the choice of monetization approach

There appears to be two main ways of valuing health benefits in economic

evaluation: either by relying on the budget constraint of the health care system (supply-sided approach) or by relying on consumers' willingness to trade consumption for health that is revealed or elicited by their trade-offs in surrogate or hypothetical markets (demand-sided approach). While the former assumes that the health care budget is optimally defined by a socially-legitimate authority. The latter is too underpinned by value judgments.

There are indeed a number of issues pertaining to the application of standard welfare economic theory as a source of societal value of outcomes. Firstly, as aggregated WTP is dependant on society's wealth distribution, if costs and benefits are borne by people in different wealth groups associated with differing marginal utilities of money, the application of the potential Pareto principle could lower aggregate utility (Boardman et al., 2006). This issue can however, be addressed by using a common general population value for benefits or by deriving distributional weights from the elasticity of marginal utility, e.g. by expressing the marginal utility of each quantile of the income distribution as a percentage of the average marginal utility, thus moving towards a social welfare justification of CBA (Fleurbaey et al., 2013).

Secondly, the economic axioms of rationality that define individuals as utility-maximisers have repeatedly been shown to be often violated by a large body of work in experimental economics. Furthermore, even if the assumption of individuals' transitive preferences were not violated, (Arrow, 1951) demonstrated that the aggregation of two or more individuals' preferences between three or more alternatives may fail to maintain an transitive social ordering of options.

Finally, the necessary conditions for achieving a first-best Pareto optimum are generally not fulfilled in some sectors of the economy due to second-best distortions, such as uncorrected externalities, monopolistic power etc. In such case, the theory of second-best asserts that seeking first-best Pareto optimality may reduce social welfare instead of increasing it, especially if there is insufficient information about the degree and direction of the divergence of the second-best optimum (Ng, 2004).

Whilst these limitations do not suggest the need to forsake welfare economic theory and its application altogether, they highlight that, just as the claim of

optimality of public agencies' existing budget allocations is rooted on social value judgements, so too are welfarist prescriptions for social choice (Claxton et al., 2007). In other words, valuing health in terms of its consumption value (collective WTP) or at the shadow price of the budget constraint imposed on the health care system, inevitably implies social value judgments.

2.3 Economic evaluations of interventions of air pollution control

2.3.1 *Ex-ante* accountability studies

In addition to the large number of retrospective evaluations of past interventions of air pollution control (section 2.1.2), the health effects associated with hypothetical policies of air pollution reduction have also been intensively evaluated. These *ex-ante* modelling studies are also qualified as accountability studies. Examples include impact analyses of complying with WHO guidelines in Hong Kong (Hedley et al., 2008), of reducing emissions from the industry and power sector in the Yangtze Delta River in China (Zhou et al., 2010), of curbing urban transit bus emissions in the US (Cohen et al., 2003) and so forth.

Unlike retrospective accountability studies, which focus on estimating the actual levels of reduction in pollutant air concentrations and associated health effects, *ex-ante* accountability studies of proposed interventions commonly include an economic evaluation as they aim to spur or justify regulatory action (Hunt, 2011).

Ex-ante accountability studies of proposed national environmental regulations are referred to as regulatory impact assessments. The latter are required in most OECD countries for major regulatory initiatives and typically con-

sist of a CBA (Scapecchi, 2008). As a result, the literature on economic evaluations of air pollution control essentially consists of CBAs of proposed air-quality targets and sector-specific emission control measures at national or inter-governmental level. In Europe, a CBA was conducted to analyse pollution control scenarios as part of the Clean Air for Europe (CAFE) programme (Holland et al., 2005b) and the European Environment Agency assessed the impact on Europe’s air quality of a selection of measures targeting the transport and energy sectors (Kuenen et al., 2010). In the US, the Environmental Protection Agency has performed CBAs of environmental policies since President Reagan’s 1981 order. In particular, it conducted CBAs for planned amendments to the 1990 Clean Air Act (US EPA, 1999, 2011) and for proposed revisions to the National Ambient Air Quality Standards for Particulate Matter (US EPA, 2006, 2012).

Although, in a CBA framework, the health benefits of air pollution control are expected to be considered alongside wider economic impacts including on ecosystems health and associated benefits (e.g. crop yields), most of these impacts are commonly too difficult to monetize, and are instead considered qualitatively in a separate analysis. Consequently, similarly to evaluations of public health interventions, *ex-ante* studies of air pollution control are primarily centred on health benefits. Productivity gains associated with health benefits are, however, also considered in some regulatory impact assessments in terms of reduced loss of working days and/or restricted activity days.

2.3.2 Method to quantify health impacts

Key principles

Ex-ante accountability studies of proposed interventions of air pollution control follow the health impact assessment (HIA) approach to perform projections of expected health benefits. HIA is defined as “a combination of procedures, methods and tools used to evaluate the potential health effects of a policy, programme or project.” (WHO, 1999). Since HIA may also rely on qualitative evidence, quantitative evaluation of impacts is also referred to as quantitative risk assessment (QRA) in the HIA literature.

Projections of health effects in HIA are based on a set of health impact functions, which are parameterised with results from epidemiological studies. The health impact function combines separately for each health endpoint of interest: (i) the size of the potentially affected population; (ii) the baseline endpoint incidence rate; (iii) the change in the concentration of outdoor air pollutant and (iv) the change in incidence of health endpoint per unit change in ambient concentration of outdoor air pollutant, also known as the coefficient of the concentration-response function.

Health effects in HIA are commonly expressed in attributable cases of selected morbidity or mortality endpoints, e.g. premature death, hospitalisation etc, without any aggregation of impacts in a summary metric (Briggs, 2008).

Impact computation

The functional form of a health impact function will depend on the statistical model used to analyse epidemiological data. For air pollution, a log-linear relationship is typically used to model the incidence rate of health endpoint y , for air pollution concentration x :

$$\log(y) = \beta x + \log(\alpha)$$

where β is the slope coefficient of the concentration-response function and α is the background incidence rate of endpoint y under no pollution.

The change in y , $\Delta y = y - y_0$ associated with a change in pollution $\Delta x = x - x_0$, can be therefore obtained as follows:

$$\begin{aligned}\log(y) - \log(y_0) &= \log(\alpha) - \log(\alpha) + \beta(x - x_0) \\ \frac{y}{y_0} &= \exp(\beta(x - x_0)) \\ \frac{y}{y_0} - 1 &= \exp(\beta(x - x_0)) - 1\end{aligned}$$

$$\Delta y = y_0(\exp(\beta\Delta x) - 1) \tag{2.1}$$

Whilst epidemiological studies estimate β , i.e. the slope coefficient of the concentration-response function, as mentioned in section 2.1.3, they typically report risk estimates (RE). The latter are ratios of risks (RR) or rates (HR) or of odds (OR) of experiencing an adverse health effect, for a given change in pollutant concentration levels x . For PM concentrations, typically RE are computed for $\Delta_x = 10\mu g/m^3$.

It is straightforward to show that under a log-linear functional form, $RE_{\Delta_x} = \exp(\beta\Delta x)$. For instance, if we use the specification of the Cox proportional hazard which is used to analyse time to event data in cohort studies (see section 2.1.2), we can model the hazard function of individual i over time as:

$$h_i(t) = h_0(t) \exp\left(\beta x_i + \sum_{i,j} \gamma_j z_{i,j}\right)$$

with $h_0(t)$ representing the baseline hazard function which is left unspecified, x representing the average cumulative level of exposure to pollution, β the dose-response coefficient, z_j representing confounding variables and γ_j their related regression coefficients.

Now, if we consider two individuals i and i' who are similar in all respect excepted in their level of cumulative level of exposure to pollution x_i and x'_i ,

the ratio of their hazards can be expressed as:

$$\begin{aligned}
 RE_{\Delta x} &= \frac{h_i(t)}{h'_i(t)} \\
 RE_{\Delta x} &= \frac{h_0(t) \exp(\beta x_i + c)}{h_0(t) \exp(\beta x'_i + c)} \quad \text{with } c = \sum_{i,j} \gamma_j z_{i,j} = \sum_{i',j} \gamma_j z_{i',j}
 \end{aligned}$$

Simplifying for $h_0(t)$, we obtain:

$$\begin{aligned}
 RE_{\Delta x} &= \exp(\beta(x_i - x'_i)) \\
 RE_{\Delta x} &= \exp(\beta \Delta x)
 \end{aligned}$$

Equation 2.1 can therefore be rewritten as:

$$\Delta y = y_0(RE_{\Delta x} - 1) \tag{2.2}$$

Where $(RE_{\Delta x} - 1)$ is also referred to as the % change in incidence of health endpoint y_0 for a Δx increment/decrement in air pollution.

It should be underlined that linearity in health effects in response to a change in air pollution exposure, as indicated by equations 2.1 and 2.2 has been repeatedly found solely in studies conducted in developed countries, i.e. with PM concentrations ranging between 5 to 35 $\mu g/m^3$ (see section 2.1.3). Attempts to extrapolate the shape of concentrations-response functions for concentrations far beyond those observed in North America and Western Europe were performed by Pope III et al. (2011) and Burnett et al. (2014), based on studies of health effects from active and passive smoking and household use of solid cooking fuel. Pope III et al. (2011)' results, which suggest a steeper increase in risk at low exposure levels than at higher concentrations (supra-linear function), were used in the 2010 Global Burden of Disease study (Lim et al., 2012).

2.3.3 Economic evaluations in practice

A 3-step process

Economic evaluations of *ex-ante* accountability studies of proposed interventions of air pollution control consist of three core steps. The latter have been systematised by some softwares, such as Benefits Mapping and Analysis Program (BenMAP) from Abt Associates, which is used by the US EPA for the assessment of air pollution control policies (US EPA, 2006, 2011, 2012). In the UK, the Department for Environment Food and Rural Affairs (DEFRA) refers to this 3-step approach as the “full-impact pathway” (DEFRA, 2013).

Step 1:

The first step involves the modelling of the change in air pollution concentrations to which the target population is exposed, based on the expected change in emissions associated with policy scenarios. This typically requires sophisticated GIS-based dispersion modelling tools, e.g. CMAQ, RAINS etc. An extensive description of such tools and of the algorithms underpinning them may be found in Yerramilli et al. (2011).

Step 2:

The second step consists of a quantitative health impact assessment, using the method to impact computation described above. Typically effects are computed per year, by applying epidemiological risk estimates to annual background rates of endpoint incidence. The most comprehensive regulatory impact assessments of proposed interventions of particulate air pollution control consider the following health endpoints: (1) premature deaths (or life expectancy impacts see section 2.3.4), (2) chronic bronchitis, (3) hospital admissions for cardio-pulmonary causes, (4) upper and lower respiratory symptoms, (5) asthma exacerbations and (6) restricted activity days. For Europe, the

World Health Organisation (WHO) has recently compiled a report of recommended coefficients of concentration-response function for each of these health endpoints, as part of the HRAPIE ² project (WHO, 2013).

Most regulatory analyses place particular emphasis on mortality effects, as recommended by WHO (2013). The latter are estimated based on risk estimates from cohort studies of long-term exposure, which capture the effects from both short-term peaks and long-term background exposure to pollution (Künzli et al., 2001). As mentioned in section 2.1.3, cohort studies of air pollution have investigated the mortality effects of long-term air pollution exposure on both all natural causes of death and specific causes of death. However, in order to avoid under-estimating the overall mortality burden (see Chapter 3 for further details), WHO recommends to use all-causes of death risk estimates in evaluations of air pollution control interventions (WHO, 2013).

In contrast to mortality impacts, with the exception of chronic bronchitis, morbid endpoints are typically considered only for acute exposure, i.e short-term peak in pollution above daily recommendation measures. It follows that, although the reduction in life expectancy associated with the development of chronic conditions associated with long-term exposure is expected to be captured in overall the mortality effect (Künzli et al., 2001), long-term quality of life impacts are completely ignored.

Step 3:

In a third step, in accordance with welfare theory roots of CBA which is the preferred decision tool of regulatory impact assessments (see section 2.3.1), the attributable change in each health endpoint is monetized using WTP (VSL) values for relevant health risk reduction. When WTP values do not exist, for instance for hospital admissions, cost of illness estimates are used. However as mentioned in section 2.2.4, since cost of illness estimates do not account for quality of life impacts from restricted lifestyle, pain and psychological suffering, their use is equivalent to setting quality of life impacts to zero.

It is worth highlighting that in most studies, mortality benefits drive the overall benefits (WHO, 2013). This is not surprising given that: (i) mortality

²Health Risks of Air Pollution In Europe.

impacts are the primary focus of such analyses; (ii) morbidity effects are commonly monetized using cost of illness estimates which as mentioned in section 2.2.4, do not account for quality of life impacts from restricted lifestyle, pain and psychological suffering.

As mentioned in section 2.2.4, WTP values for health risk reduction, be it revealed or stated, vary greatly. This results in substantial differences in governments' recommended values for monetizing health impacts. For instance, Scapecchi (2008)'s comparison of recommended values (mean estimates, expressed in 2006 \$) for monetizing mortality impacts from PM exposure showed that the VSL estimates for the US and Canada were much higher (respectively \$ 7,4 and 6 million) than those recommended at EU level (\$ 1,8 million). In the UK, the DEFRA-commissioned study of Chilton et al. (2004) suggested a VSL of about \$ 6 million.

Example: DEFRA's damage costs

Based on this 3-step impact pathway approach, in the UK, DEFRA produced standardised damage costs estimates per tonne of pollutant emitted (DEFRA, 2011, 2015), in order to support the evaluation of small-scale proposals (below £50 million).

The health endpoints and the magnitude of effects considered in damage costs computations are in line with recommendations from the UK Committee on the Medical Effects of Air Pollutants (COMEAP), which independently advises the government on matters concerning the health effects of air pollutants. For particulate matter, the health endpoints included are: (i) mortality effects associated with chronic exposure and (ii) hospital admissions for cardio-respiratory causes following acute exposure, i.e. following a short-term peak in pollutants concentrations over a few days (DEFRA, 2013).

Health impacts were computed for different densities of population e.g. "Central London", "Urban medium" or "Rural" and monetized based on WTP values or cost of illness estimates. For instance, according to DEFRA's damage costs calculator, an annual reduction of one tonne of PM emission in central

London is expected to yield an annual gain of £2.4 million (in 2015 prices). By contrast, the same reduction in a small rural area would be expected to provide an annual monetized benefit of £375,000 (in 2015 prices).

Dealing with uncertainty

In addition to considering uncertainties inherent to the modelling of air pollution concentrations, many large scale *ex-ante* studies consider uncertainty in key parameters, typically concentration-response coefficients and VSL/WTP values, via probabilistic sensitivity analysis (PSA). This consists in fitting a probability distribution to each uncertain input parameter, where uncertainty is indicated by the 95% confidence interval, and to propagate joint parameter uncertainty in total aggregated benefits via Monte Carlo simulations. The latter are readily integrated in software packages such as previously mentioned BenMAP or @RISK (Palissade Corporation).

If one takes into account the nature of the data used for estimating parameters as well as parameters' logical bounds, only a few distributions remain that are appropriate candidates for a given type of parameter (Briggs et al., 2006). Typically, the beta and Dirichlet distributions will be appropriate to model transition probabilities derived from respectively binomial and multinomial data, whereas the gamma distribution will be appropriate for costs and dis-utilities and the log-normal distribution will be adequate for relative risks (Briggs et al., 2006). By contrast the use of the triangular distribution, which simply requires a maximum, a minimum and a mode, has been largely discouraged since it is not statistically related to the estimation process of the data and thus, very difficult to parametrize correctly (Briggs et al., 2006).

Interestingly, probabilistic sensitivity analyses in past evaluations of air pollution control have departed from the above recommendations, which may bring their quality into question. For instance, the US EPA fitted triangular distributions to model utility parameters and WTP values in past regulatory analyses of air pollution control policies (US EPA, 2006, 2012). For the CBAs

of Clean Air for Europe (Holland et al., 2005b) and Revisions of the E.U. Gothenburg Protocol (Holland et al., 2011), triangular distributions were fitted to baseline incidence rates of health endpoints.

It should be underlined that recently published European guidelines for uncertainty analysis in health impact assessment and cost benefit analysis of air pollution control policies (Holland, 2014) do not suggest to rule out the triangular distribution. On the contrary, they recommend to use the latter for background mortality and morbid endpoint incidence rates as well as for risk estimates when “there is great confidence in central estimates but adoption of a normal distribution would imply that ranges were based on more data than is the case” (pp 41). Alternatively, guidelines suggest to chose among two other distributions for risk estimates. The normal distribution is recommended in the case of a higher probability of values towards the range midpoint than towards its extremes, whereas the uniform distribution is recommended when all values in the range are thought to be of equal probability. Uncertainty pertaining to WTP values for mortality risk reduction are recommended to be dealt with in univariate sensitivity analysis.

2.3.4 Controversies in impact quantification

Years of life lost (YLL) vs. counts of premature deaths

A major controversy in impact quantification pertained to whether premature deaths should be differentiated based on the amount of remaining life expectancy. This question is of particular relevance for interventions of air pollution control since their benefits are not expected to fall equally between age-groups. Indeed, although Krewski et al. (2000) and Pope III et al. (2002) found that the excess risk of mortality associated with air pollution exposure is almost uniform with age, as baseline mortality rates strongly increase with

age, the absolute number of air pollution-related premature deaths is expected to fall disproportionately among the elderly population.

A common argument against measuring benefits in counts of avoided premature deaths is that such approach would wrongly make air pollution control compare on a equal footing with, for instance, improvements in traffic safety, although the two are expected to vary an order of magnitude in terms of amount of life gained per person (McMichael et al., 1998; Rabl, 2003). The importance to consider the loss of life expectancy instead of the number of premature deaths to measure air pollution health impact is summarised in Bellander (2001)’s remark that “excess deaths are deaths that occur earlier than expected. The important question is how much earlier?” (pp 69).

Nowadays, while the number of avoided premature deaths remains in use to measure mortality impacts, it is now commonly considered alongside life expectancy effects, i.e. years of life gained (Hunt, 2011; WHO, 2013). However, the debate as to how to value reductions in mortality risk either as statistical lives (VSL) or alternatively, as statistical life years (VOLY) remains open, mainly because of the absence of consensus on the age-dependency of VSL (Hubbell, 2006; Chestnut & de Civita, 2009). During some time, the US EPA applied a 37% discount to the value of statistical live of individuals above 70. However, after public outcry at this “senior discount”, the US EPA dropped age difference in VSL in 2003.

Quality-adjustment to life year gains

Another important controversy pertains to whether a quality adjustment should be applied to gains in life expectancy (Hubbell, 2006). One obvious rationale for the application of HRQoL weight to life year gains is measurement accuracy. Indeed, as previously mentioned, it is now largely agreed that potential health gains should reflect that death can only be postponed but not avoided, i.e. that what matters is life expectancy effects. In the same line of thought, it can be argued that when evaluating the extra years of life to be gained from air pollution reduction, one should take into account that individ-

uals benefiting from air pollution reduction may not be in perfect health.

The discussion about the use of quality-adjusted life years (QALY) to assess air pollution control started about a decade ago. It stemmed from the US Office of Management and Budget's decision that both a CBA and CEA should be undertaken for policies expected to greatly impact public health and safety (US OMB, 2003) and from the US Institute of Medicine's recommendation that "Regulatory CEAs that integrate morbidity and mortality impacts should use the QALY to represent net health effects" (US Institute of Medicine, 2006) (pp 161).

The controversy about the use of QALY to assess air pollution control was greatly fuelled by Harris (1987)'s double jeopardy argument, which states that allocating a restricted budget based on a QALY-maximizing approach would systematically discriminate against those who have a low quality of life and small life expectancy due to preexisting health conditions. Whilst the double-jeopardy argument does not apply for interventions that improve quality of life, provided recipients have the same life expectancy, it is true that life-lengthening interventions will maximise QALY gains if they are targeted to individuals with the highest quality of life and/or life expectancy (Singer, 1995). In other words, the return on investment in postponing the deaths of ill or disabled people is lower than the return on investment in extending the lives of healthy people. However, it has been forcefully argued that this finding is not unfair or unjust, but merely results from the application of the most rational approach to maximize population health from available scarce resources (Singer, 1995; Claxton & Culyer, 2006).

Interestingly, although the QALY has been widely used in economic evaluations of public health interventions and health care technologies (Drummond et al., 2005), the issue of double-jeopardy appears to have represented a hurdle to the political acceptance of QALY in the evaluation of environmental policies, especially in the US. As remarked by Singer (1995), what seemed to stir controversy is not so much to discriminate recipients of a potential intervention based on their remaining life-expectancy, and thus their age, but based on differences in their baseline quality of life, as reflected by their health condition.

This led the US EPA to propose an innovative approach to measuring the impacts of air pollution reduction on quality and length of life. The agency decided to use a double-baseline of quality adjustment scores to compute separately the gain in quality of life from reduction in morbidity and the gain in non-quality adjusted life years. For instance, in its analysis of revisions of PM National Ambient Air Quality Standards, the agency used a HRQoL score of 0.95 as baseline for the general population when computing quality of life decrements associated with the incidence of chronic bronchitis and myocardial infarction due to PM exposure but in parallel, it used a HRQoL score of 1 as baseline when computing life expectancy effects (US EPA, 2006).

This double baseline of HRQoL weights however, no longer satisfies the linear substitution between quality and length of life that characterises the QALY. The resulting health measure is therefore no longer a QALY but a Morbidity Inclusive Life Year (MILY). The main issue with the MILY is that it cannot support the comparison of air quality policies with other public health interventions. In addition, to date, there has not been any attempt at valuing a MILY or to provide a cut-off value for MILY-based cost-effectiveness assessment. This is problematic since, as mentioned earlier, to support decision-making about resource allocation, consequences need to be monetized in one way or another in order to be compared with costs (Drummond et al., 2005). Finally, the construction of the MILY somehow presents a lack of consistency. Indeed while life year gains are adjusted with a HRQoL of 1, which implies perfect health, they are computed based on the life expectancy for the general population, which itself reflects the population prevalence of chronic conditions. Based on these considerations, the MILY does not appear adequate to support the evaluation of air pollution control interventions.

2.4 Conclusions

2.4.1 Context: decision frameworks

By pertaining to both the fields of public health and environmental economics, the economic evaluation of air pollution control interventions lies at the intersection of two disciplines which, due to the specificity of their decision contexts, are rooted on different theoretical frameworks and use different decision tools. The evaluation of environmental policies traditionally relies on CBA, which is grounded in welfare economics and seeks economic efficiency. By contrast, the evaluation of public health interventions has typically followed the health care evaluation paradigm rooted in decision science, where CEA is used to allocate constrained resources with view to satisfy most efficiently an explicit societal objective.

Whilst the two intellectual traditions are different, their decision tools do share a common ground in practice. Firstly, although economic evaluations of air pollution control traditionally rely on WTP-based CBA, similarly to public health evaluations, they are primarily centred on health benefits. Secondly, both CBA and CEA involve monetization of health output, either in terms of collective WTP or at the shadow price of the budget constraint imposed on the health care system, and either approach to valuation inevitably relies on social value judgments.

2.4.2 Research gaps

This review contributed to identify several limitations associated with the current approach to quantifying the health benefits of air pollution control and the uncertainty surrounding the cost-effectiveness of such interventions.

First economic evaluations of air pollution control rely on the HIA method to health impact quantification where the change in each health endpoint at-

tributable to the intervention under assessment is computed separately and the total aggregated effect is obtained via monetization. Such an approach ignores any interactional effects between morbidity and mortality impacts. This is expected to be a source of inaccuracy in impact estimates since morbidity and mortality do interact in a number of ways. In particular, morbidity may affect baseline life expectancy but also susceptibility, i.e. physiological reaction, to air pollution exposure.

Second, the morbidity effects considered are primarily associated with acute exposure and are commonly monetized using cost-of illness estimates which, given that they do not encompass any disutility effects, are equivalent to attributing a zero value to quality of life impacts. It follows that the long-term quality of life impacts associated with the development of chronic cardio-respiratory conditions have been largely ignored so far.

Third, in a context where the application of a quality-adjustment to life year gains from environmental policies has long been controversial, the most elaborated approach to encompassing quality of life effects alongside life expectancy impacts from air pollution reduction (US EPA's MILY) is inappropriate to support resource allocation.

Fourth, whilst economic evaluations of air pollution control interventions have placed substantial emphasis on dealing with parameter uncertainty, its impact on decision uncertainty, i.e. whether an intervention is cost-effective or not, and the value of reducing parameter uncertainty have not been evaluated yet. In addition, current European guidelines to probabilistic sensitivity analysis may need to be challenged.

2.4.3 Role of decision analytical modelling

The four limitations previously identified suggest that there is potentially substantial value in rethinking the current method to evaluating air pollution control interventions, by drawing on health modelling techniques and frameworks for characterising decision uncertainty currently used in health

care decision-making.

To construct a decision model that accurately reflects all the relevant costs and outcomes associated with competing interventions, it can be useful to consider a conceptual model before implementing the chosen modelling approach. Conceptual modelling can be broken down in two sequential steps: problem-oriented modelling and design-oriented modelling (Tappenden, 2012)

Problem-oriented modelling aims to embrace the complexity of the decision-problem and of the overall system in which it exists (Tappenden, 2012). For example, in order to assess interventions aimed at tackling obesity in the UK, the Foresight Project developed a series of causal loop models that mapped the interplay of a large numbers of causal factors (e.g. physical activity, diet, genetic make-up) within the wider cultural, environmental and social contexts (Vandenbroeck et al., 2007). In the case of air pollution, such analysis would for instance, underline the productivity effects related to work absences associated with exacerbations during acute exposure. In addition, potential linkages with physical activity may need to be considered, whereby air pollution may reduce individuals' willingness to undertake outdoor exercise, depending on their perception of air pollution as a health risk and their level of discomfort associated with exposure.

Design-oriented modelling subsequently sets boundaries to the depth of the analysis and considers alternative credible model structures based on considerations of feasibility, that are themselves based on evidence requirements and resources available in terms of person-time, expertise and so forth (Tappenden, 2012). The main benefit of undertaking this two-stage conceptual modelling is to provide a benchmark against which the appropriateness of the simplified structure of the final model may be evaluated in a transparent and accountable manner.

2.4.4 Reflecting uncertainty in decisions

Finally, it should be underlined that at the core of model development lies the intertwined concepts of choice as well as uncertainty. Indeed, in implementing a chosen model structure, assumptions are taken which require value judgements. In addition the evidence base may be uncertain. It is important to reflect any uncertainty in the evidence - referred to as parameter uncertainty - and assumptions - referred to as structural uncertainty - and explore how these may impact the decision.

Structural uncertainty stems from the fact that it is not possible to know for sure *ex-ante* whether the choices underpinning the structure of the hard implemented model (e.g. selection of relevant impacts, of appropriate simplifications) are right or wrong, i.e. whether they will substantially affect the model's capacity to usefully inform the decision problem (Tappenden, 2012).

Parameter uncertainty, which was discussed in section 2.3.3, also depends on a string of modelling choices, including but not restricting to deciding which parameters are relevant and which source of evidence should characterise them (Tappenden, 2012). Such choices will be a particular focus on this thesis which, following an assessment of currently available evidence, will undertake the estimation of a subset of parameters required to parameterise the model of the health effects from air pollution exposure.

Importantly, the consequences of parameter and structural uncertainty are intrinsically linked since the structure of the model will determine the relationship of parameters between one another and their relative influence on final outcomes.

Chapter 3

Quantitative impact assessment: why morbidity and mortality impacts need to be simultaneously considered

3.1 Introduction

This chapter challenges the current approach to quantification in health impact assessment of environmental health interventions, such as air pollution control.

Health impact assessments aim to predict the effects of projects, programmes or policies - hereafter also referred to as interventions - on population health and health inequalities. They are widely used to inform environmental policy and other public policies outside the health care sector and are championed by the World Health Organisation under the rubric of “Healthy Public Policy”, which calls for explicit consideration of health and equity matters in all policy areas (WHO, 1986; Kemm, 2001).

To achieve this objective, health impact assessments are expected to provide

predictions that are valid (Veerman et al., 2007; Bathia & Seto, 2011) and that add value to the decision-making process pertaining to the design and/or implementation of interventions (Davenport et al., 2006; Kemm, 2001). This is often best done through quantitative risk assessment (QRA), which provides a more precise description of impacts and their magnitude and also supports economic evaluation, which is a key input to decision-making (Veerman et al., 2005; Fehr et al., 2012).

QRA has often been carried out to evaluate interventions that affect health by modifying exposure to environmental risk factors, air pollution in particular (Medina et al., 2013). As mentioned in Chapter 2, the quantification method consists in applying, for each health endpoint, a health impact function that links together: (i) the relevant epidemiological risk estimate, (ii) incidence data and (iii) the change in risk factor exposure and its distribution within the target population (O’Connell & Hurley, 2009; Bathia & Seto, 2011; Medina et al., 2013). This provides the change in number of cases of a selection of morbidity and mortality endpoints, attributable to the intervention under evaluation. For instance, in the assessments of large-scale programmes of air pollution control, such as Clear Air for Europe (Holland et al., 2005a), Revisions of the E.U. Gothenburg Protocol (Holland et al., 2011) and Revisions to the US National Ambient Air Quality Standards for particulate matter (USEPA 2006; USEPA 2009), commonly reported health impacts included numbers of premature deaths and/or of life years lost, counts of cardio-respiratory hospital admissions, numbers of cases of chronic bronchitis and so forth.

Morbidity and mortality are, however, known to interact in a number of ways. In particular, a chronically sick person is expected to have a shorter life expectancy than a healthy person. Additionally, morbidity can influence individuals’ susceptibility to the harmful effects of environmental hazards.

The objective of this chapter is twofold: it aims (i) to demonstrate the importance of encompassing interactions between morbidity and mortality impacts in QRA of environmental health interventions; and (ii) to show how to handle these interactions via simultaneous quantification of effects using Markov modelling, which is used extensively to support decision-making in the health care sector. This work is based on the example of outdoor air pol-

lution that is one of the environmental risk factors for which health effects have been most intensively quantified over the recent years (Medina et al., 2013). Study findings, however, are expected to apply to any environmental risk factor associated with both morbidity and mortality effects.

The work consists of four main components. First, I briefly recall the current approach to QRA, which has been described in greater detail in Chapter 2 and is hereafter referred to as the “separate” approach. Second, I identify limitations associated with the latter and advocate simultaneous quantification of morbidity and mortality impacts. Third, I outline two approaches to applying the Markov modelling technique to QRA. Fourth, I illustrate the advantages of the simultaneous approach to quantification, based on an illustrative intervention of air pollution reduction in London.

3.2 Traditional approach to QRA: the separate approach

The change in annual number of cases of health endpoint y that is attributable to an intervention that modifies the exposure of a target population of size N to environmental hazard h is obtained by the following health impact function, assuming a log-linear concentration-response function:

$$\Delta y = y_0(RE_{\Delta h} - 1)N \quad (3.1)$$

where:

Δh represents the change in exposure to hazard h ;

Δy represents the change in annual incidence of endpoint y ;

y_0 is the annual incidence rate of endpoint y at hazard levels h_0 ;

$RE_{\Delta h}$ is the ratio of risk of experiencing endpoint y in the group exposed to Δh compared to the unexposed group.

The application of static health impact functions to quantify health impacts over a given period of time is however especially problematic when applied to quantify a change in mortality risk since death can be postponed but not permanently avoided. It has indeed been forcefully argued that what matters is not the number of attributable premature deaths, but time to death advancement (McMichael et al., 1998; Künzli et al., 2001; Brunekreef et al., 2007).

As a result, life expectancy impacts have been increasingly considered alongside premature deaths in QRA (O’Connell & Hurley, 2009). They are computed using the life-table method, which consists of comparing survival curves calculated from annual probabilities of death accumulated over time. The modification of age and gender-specific probabilities of death by the relevant mortality risk estimates allows one to derive a modified survival curve that can be compared against the baseline survival curve (Miller & Hurley, 2003). The weighted area between the two curves, with weights representing the age and sex distribution of the target population, is the average life expectancy impact associated with the change in risk factor exposure (Rabl, 2003).

Whilst the life-table method greatly improves upon health impact functions with regards to the quantification of life expectancy impacts, there remains a second and different set of issues that arise when morbidity and mortality impacts are quantified separately, which is the focus of this chapter.

3.3 Two key limitations of the separate approach

3.3.1 Overestimation of the change in morbidity cases

There is a straightforward interaction between morbidity and mortality effects: the longer people live, the more likely they are to experience additional morbidity events, and conversely if their life expectancy is shortened.

Understandably it is not common practice to exhaustively account for the potential morbidity impacts associated with a change in mortality risk in a given target population. However, if a risk factor is associated with adverse impacts on both mortality and a selection of morbid conditions, the described interactional effect implies that the true change in number of cases of morbid endpoints of interest, net of the mortality impact, will always be lower than the “crude” change computed separately from the mortality effect.

We shall examine this relationship using the example of outdoor air pollution that is positively associated with a greater risk of dying prematurely from all-causes and of developing chronic conditions such as chronic bronchitis (Anderson et al., 2012; US EPA, 2009). Under a decrement in exposure to air pollution, the crude decrease in number of cases of chronic bronchitis, resulting from a reduced risk to develop this disease, is expected to be partly compensated by additional cases of chronic bronchitis taking place during the extended length of life enjoyed by individuals of the target population. Conversely, under an increment in air pollution exposure, the crude increase in cases of chronic bronchitis is expected to be partly compensated by the shortening of an individual’s average lifespan, during which they can develop this disease.

The magnitude of the overestimation bias in the change in cases of morbid endpoint y under the separate approach will be determined by the interaction between three main factors: (i) the target population’s baseline probability of developing condition y , i.e. disease incidence; (ii) the relative magnitude of the risk factor’s impact on the risk of death and on the risk of developing condition y ; (iii) the analysis time-horizon. Indeed the longer the time-horizon, the more mortality impacts will matter when assessing the morbidity effects associated with a given intervention. The overestimation bias is therefore difficult to estimate *a priori*. However, modelling results based on a case study of air pollution reduction in London over a time horizon of 60 years, presented in section 3.5, shows that it can be substantial.

3.3.2 Limited ability to characterise the distribution of life expectancy impacts

By causal pathways

The computation of an intervention's impact on life expectancy separately from morbidity effects has two main limitations. The first pertains to the limited ability to identify the contribution of each morbid endpoints, i.e. each causal pathway, to the overall life expectancy impact.

Whilst cause-specific mortality risk estimates can help address this problem, their use is typically not recommended for health economic evaluation as it may lead to an under-estimation of the total mortality burden (WHO, 2013). Indeed, the effect of a severe disease on lifespan usually goes beyond death from this particular disease and includes an overall weakening of the general health condition, e.g. co-morbidities, that may lead to premature death from other causes. These premature deaths may not be captured by the narrower focus of cause-specific risk estimates. Second, the validity of cause-specific mortality risk estimates may be adversely affected by misclassification of causes of death in mortality registration. Background national statistics on all-cause mortality are therefore expected to be of greater precision than cause-specific death rates (Mathers et al., 2005). Finally, at least in the case of air pollution, cause-specific risk estimates are deemed more appropriate for meta-analysis, which is key to incorporate all relevant evidence and to decrease parameter uncertainty (WHO, 2013).

Between health-stratified population subgroups

Second, the life expectancy impact attributable to interactions between the presence of pre-existing morbid conditions, i.e. health status, and hazard exposure cannot be identified. Morbidity indeed typically affects mortality in

two main ways. Firstly, it can increase the individual's baseline probability of death. For instance, subjects with chronic obstructive respiratory disease, especially in the severe or very severe stages of the disease, have a higher probability of death (Mannino et al., 2006). Secondly, it can enhance individuals' predisposition to experience adverse effects associated with hazard exposure, hereafter referred to as greater susceptibility to exposure. For instance, survivors of a myocardial infarction were found to have a higher excess risk of death associated with air pollution exposure than individuals of the general population (Zanobetti & Schwartz, 2007).

A potential approach to encompassing interactions between health status and mortality may be to: (i) split the target population into subgroups whose health state has a known influence on baseline mortality risk and/or susceptibility to risk factor's adverse effects and (ii) apply the life-table method to each subgroup. However, in addition to being cumbersome, when assessing air pollution control interventions, such an approach would be incomplete and underestimate health benefits. Indeed, air pollution not only affects people differently according to their health status but, as it increases the risk of developing chronic conditions, also impacts upon the risk on entering each susceptibility-stratified subgroup. Consequently, simply applying the life-table method to each subgroup would fail to capture air pollution's influence on individuals' health distribution over time, and its interaction with health-related differential susceptibility. As a result, such an approach would underestimate total health benefits.

Reasons why the distribution of impacts matters

The ability to characterise the distribution of life expectancy impacts is extremely pertinent to implementing the concept of Healthy Public Policy. The latter indeed embraces concerns for both health and equity and places a particular emphasis on distributional analysis (WHO, 1999, 2005, 2008).

Firstly, combining knowledge of the distribution of life expectancy impacts by causal pathway and between population subgroups stratified by health sta-

tus, with evidence on social gradients in health outcomes (O'Neill et al., 2003) is key to finely characterise the distribution of health effects across socio-economic subgroups. It is therefore a crucial component of health inequality analysis.

Secondly, knowledge of impact distribution is paramount to the construction of summary measures of population health (SMPH), which require to adjust life expectancy estimates with health- or disability-related quality of life weights (Gold et al., 2002). Although SMPH are not used widely in health impact assessments (Briggs, 2008), they were suggested as a complementary metric to support resource prioritisation (Veerman et al., 2005).

Thirdly, instead of simply adding numbers of cases of morbid events, understanding the impact of morbid events on individuals' baseline probability of death as well as on their susceptibility to suffer from further adverse effects, helps provide an much more accurate picture of the morbidity health burden attributable to a given environmental health hazard.

Finally, distributional information is also pertinent to economic analyses, which are often performed for regulatory assessments. For instance, extending the life of a person with a medical condition or extending the time period during which a person remains healthy is expected to have opposite impacts on health care budgets.

3.4 Simultaneous quantification of health impacts using Markov modelling

3.4.1 Markov modelling: Description

The argumentation developed in section 3.3 makes a case for accounting for morbidity and mortality interactions, via simultaneous quantification of

these impacts. This can be performed using Markov models, which have a long history of use in medical decision-making and health care technology assessment (Sonnerberg & Beck, 1993; Briggs et al., 2006).

Markov models simulate the incidence of health events over the individual's lifetime via pathways to and from a set of mutually exclusive and exhaustive health states, such as "healthy", "diseased", "dead". The use of an absorbing state, i.e. a state that cannot be left once entered such as "dead", makes the Markov process finite (Sonnerberg & Beck, 1993).

The main strength of Markov models is to consider all relevant health effects simultaneously and thus to capture interactions between impacts. In addition, Markov models are especially suitable to QRA as they are dynamic projections tools. As such, unlike static health impact functions, they can allow for dynamics in population demographics as well as in the pattern of change in health risk, where the latter may vary by age and/or calendar time after intervention implementation. Whilst life-tables also allow for such dynamics, they can only evaluate life expectancy impacts. Furthermore, Markov models are particularly suited to model health effects that can repeat over time for a same individual as is often the case for morbidity effects, such as hospitalisations (Sonnerberg & Beck, 1993).

In a Markov model, pathways between health states are parameterised by probabilities of transiting between states, called transition probabilities (TP). Whilst Markov processes are continuous, they are typically evaluated using a discrete time approximation by expressing TP for a discrete time period known as a cycle, where the sum of cycles represents the time horizon for effect quantification.

Each TP represents the probability of transiting to a particular state of the model during a cycle, conditional on being in a given health state at the beginning of the cycle. This allows to differentiate an individual's probability of experiencing future health events according to his/her current health status. TPs are also typically stratified by age and gender and expressed as a function of numbers of cycles elapsed to reflect the time-dependency of health events (Briggs & Sculpher, 1998).

To estimate the total change in population health associated with an in-

intervention that increases or reduces population exposure to an environmental hazard such as air pollution, the Markov model structure should be composed of two arms: a “Baseline” arm, populated with baseline TP and (ii) an “Intervention” arm for which, similarly to a health impact function, baseline TP are multiplied with relevant epidemiological risk estimates, scaled to the expected change in hazard. For a decrement in hazard exposure, scaled risk estimates are hereafter referred to as risk reduction estimates (RRE) throughout the thesis.

Each arm of the model should then be evaluated across all cycles, either via first order Monte Carlo simulation which follows the unique pathways taken by a large number of individuals, or via cohort simulation where a cohort of individuals are followed altogether throughout the model (Briggs & Sculpher, 1998). At the end of all cycles, one can obtain the total life years spent by each individual, or by the overall cohort, in each health state of the model, along with the total count of health events experienced. Comparison of results for each arm provides the intervention’s attributable change in counts of health events and in total life years spent in each health state.

3.4.2 Applying Markov modelling to QRA

Modelling approach

Two main approaches to applying Markov modelling in QRA are presented below. They essentially differ in the scope of morbidity-mortality interactions encompassed and thus, in the way life expectancy impacts are modelled. The choice between the two approaches should be driven by the nature and availability of epidemiological data, as well as by the potential presence of policy-focus on some disease or susceptible populations subgroups.

- Full modelling of morbidity-mortality interactions:

A first approach consists in modelling the full range of diseases that are associated with hazard exposure and/or that enhance individuals' susceptibility to adverse health events. In this case, the life expectancy impact of a change in hazard exposure is fully mediated via the change in the risks of entering health states that represent life-shortening diseases and/or susceptibility-enhancing conditions. The mortality risk of individuals who do not enter those health states is therefore unchanged under an increment or decrement in hazard exposure.

Although this “full modelling” approach best characterises the distribution of life expectancy impacts by morbidity pathways and between population subgroups, it requires a good knowledge of the range of morbid impacts associated with the risk factor of interest. It is therefore quite resource intensive and may not be adequate if gaps in epidemiological evidence are known to be large.

- Focused modelling of morbidity-mortality interactions:

The second approach, hereafter referred to as “focused modelling”, consists in focusing on a restricted set of life-shortening and/or susceptibility-enhancing morbid condition(s) that are most strongly supported by epidemiological evidence, or that are of particular policy interest.

Importantly, in this case, the mortality effect of hazard exposure - if the latter is associated with all-cause mortality - will typically need to be modelled via all the model pathways, such that both the individuals who enter the disease state(s) and those who do not, face a change in death risk (with potentially differing magnitude) under exposure change.

Whilst the modelling of health impacts is easier to implement under the “focused modelling” approach, for model parameterisation to be accurate, the risk estimate of mortality associated with hazard exposure may need to be adjusted. Indeed, the Markov model structure implies that individuals who do not enter the disease state X , cannot die from cause x . Therefore, to be coherent and to avoid potential double-counting of life expectancy effects, the risk estimate of mortality that applies to the probability of death of those individuals who are not in state “ X ” should pertain to all other causes of death

than cause x . Whilst the required information may not be available from the epidemiological literature, a mean estimate of excess risk can be derived using the risk estimate of all-cause mortality and the risk estimate of mortality from cause x . A method to do so is presented in Appendix A.

Model structure

To assess the overall life expectancy impact of an intervention that modifies population exposure to a risk factor, only one “Intervention” arm, fitted with all relevant and appropriately scaled risk estimates is required (i.e. arm I_4 of Figure 3.1 in section 3.5.1).

However, disentangling health effects by morbidity pathways and across population subgroups requires additional “Intervention” arms, where risk estimates apply only on selected transition paths (e.g. arms I_1, I_2, I_3 of Figure 3.1 in section 3.5.1). To identify the health effect attributable to the change in the risk of a particular health event, inter-arms comparisons should involve two arms that solely differ on the basis of that particular risk being modified.

3.5 Illustration

3.5.1 Description and method

This section illustrates how Markov modelling-based simultaneous quantification of morbidity and mortality impacts can address the previously outlined limitations of the traditional “separate” approach to QRA. It is based on an illustrative intervention that is expected to decrease immediately and permanently concentrations of fine particulate air pollution ($PM_{2.5}$) by $1\mu g/m^3$ in London.

For illustrative purposes, quantification of the whole range of health effects associated with $PM_{2.5}$ exposure (Anderson et al., 2012; Brook et al., 2010; US EPA, 2009) was out of scope. Consequently, the “focused modelling” approach described in section 3.4.2, focusing on coronary heart disease (CHD) - ICD I20-25 - as a chronic morbid endpoint alongside all-cause mortality impacts, was followed to model the health benefits of air pollution reduction.

The model, which is illustrated in Figure 3.1, uses a simple 3-state structure: “Without CHD”, “With CHD”, “Dead”. This implies that, for a given age and gender, health status is defined as having CHD or not. This structure was duplicated four times such that the “Baseline” arm could be compared against four “Intervention” arms I_1 to I_4 , which differ according to the transition paths to which risk reduction estimates apply.

- Arm I_1 only accounts for the reduced risk of developing CHD;
- Arm I_2 only accounts for the reduced risk of premature mortality among individuals without CHD;
- Arm I_3 encompasses simultaneously the reduced risk of developing CHD and the reduced risk of premature mortality among individuals without CHD;
- Arm I_4 accounts simultaneously for the reduction in all risks of health events affected by the intervention: (i) the risk of developing CHD, (ii) the risk of death among individuals without CHD and (iii) the risk of death among individuals with CHD.

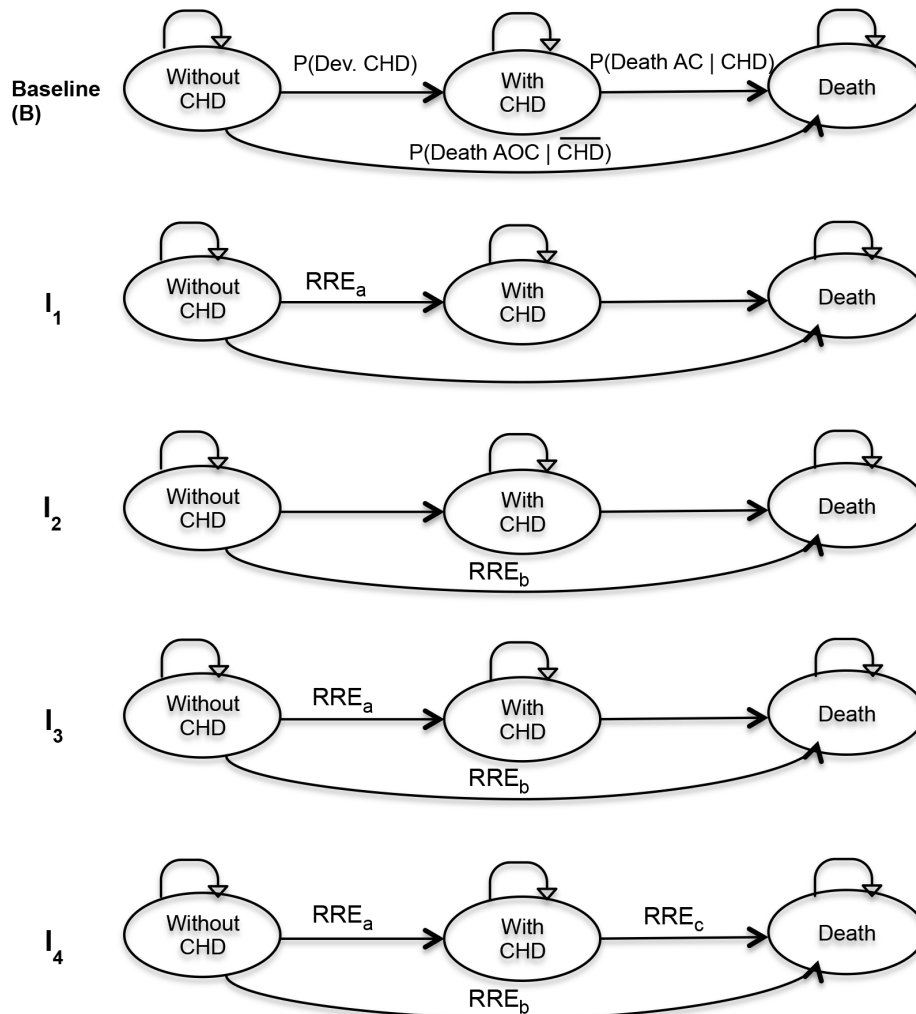


Figure 3.1: Diagram of 5-arm Markov model developed for evaluating the illustrative intervention.

Abbreviations: AOC = all other causes; AC = all causes; CHD = coronary heart disease, $\overline{\text{CHD}}$ = without CHD, Dev. = developing. Each oval represents a Markov state and full arrows indicate allowed transitions between them.

Risk reduction estimates RRE_a , RRE_b , RRE_c are epidemiological risk estimates scaled to a $1\mu\text{g}/\text{m}^3$ decrement in $\text{PM}_{2.5}$ concentrations and are defined in Table 3.2. RRE_a applies to $P(\text{Dev. CHD})$, RRE_b to $P(\text{Death}_{\text{AOC}} | \overline{\text{CHD}})$ and RRE_c to $P(\text{Death}_{\text{AC}} | \text{CHD})$.

Table 3.1 describes the various inter-arms comparisons that were performed to disentangle life expectancy impacts attributable to the reduction in each risk. It underlines how modelling results address the two limitations of the “separate” approach outlined in section 3.3.

Arms compared	Inter-arms comparisons’ output
Correct estimation of the change in morbidity cases (section 3.1.)	
$(B - I_3)$	Avoided CHD cases under the simultaneous approach to quantification ⁽¹⁾
$(B - I_1)$	Avoided CHD cases under the separate approach to quantification
$(I_1 - I_3)$	Overvaluation bias associated with the separate approach
Distributional analysis of life expectancy impacts (section 3.2.)	
$(I_3 - I_2)$	Life year (LY) gain due to reduced risk of developing CHD
$(I_2 - B)$	LY gain due to reduced mortality risk in individuals “Without CHD”
$(I_4 - I_3)$	LY gain due to reduced mortality risk in individuals “With CHD”
Intervention’s total life expectancy impact in the target population $(I_3 - I_2) + (I_2 - B) + (I_4 - I_3) = (I_4 - B)$	

Table 3.1: Inter-arms comparisons: limitations addressed and modelling output.

⁽¹⁾ In the present case, since CHD is chronic, comparing the baseline arm (B) against arm I_4 or arm I_3 provides exactly the same number of avoided CHD cases.

The target population was defined as the currently alive population of London aged 40 to 90 years (2011 census) followed until they reached 100 years or died. As a result, the analysis time horizon is 60 years. The modelling parameters, which consist of risk reduction estimates, death probabilities and CHD incidence and prevalence are detailed in Table 3.2. Since: (i) the present study focuses on the expected morbidity and mortality impacts and (ii) the structure of each arm of the model is linear, a deterministic analysis relying on the mean values of each parameter was performed. The model was evaluated in Matlab.

Name	Definition ⁽¹⁾	Source	Mean values ⁽²⁾ $\Delta_{PM_{2.5}} = -1\mu g/m^3$
$P(Dev.CHD)$	cycle 0 CHD Prevalence cycle 1-60 CHD Incidence	UK GPRD ⁽³⁾	N.A.
$P(Death_{AOC \overline{CHD}})$	Probability of death from all other causes than CHD, if without CHD	Own computations based on death rates in England (ONS, 20131) and hazard ratios of excess death from CHD provided by (Whiteley et al., 2005)	N.A.
$P(Death_{AC CHD})$	Probability of death from all causes, if with CHD	(Whiteley et al., 2005)	
RRE_a	$RR_{Dev.CHD}$	Gan et al. (2011)	0.988
RRE_b	$HR_{DeathAOC \overline{CHD}}$	Own computations (see Appendix A)	0.995
RRE_c ⁽⁴⁾	age ≤ 64 $HR_{DeathAC}$ age ≥ 65 $HR_{DeathAC CHD}$	Pope III et al. (2002) Zanobetti and Schwartz 2007	0.994 0.971

Table 3.2: Modelling parameters for parameterisation of the 5-arm model.

Abbreviations: AOC = all other causes; AC = all causes; CHD = coronary heart disease, \overline{CHD} = without CHD, Dev. = developing.

⁽¹⁾ All probabilities are expressed for a one-year period. They are stratified by one-year age group and gender. To be combined with risk reduction estimates (RRE), transition probabilities were converted into rates and the resulting product was converted back to probabilities to parametrize intervention arms. RRE values unconditional on health status hold for the general population.

⁽²⁾ Mean risk estimates rescaled to a $1\mu g/m^3$ decrement in $PM_{2.5}$ concentration. Rescaling method and original values provided in the epidemiological literature are presented in Appendix B.

⁽³⁾ Obtained from open-access model DYNAMO-HIA.

⁽⁴⁾ $HR_{DeathAC|CHD}$, which captures CHD-subgroup's specific susceptibility to $PM_{2.5}$ mortality effect, only applies to individuals with CHD aged 65 and above in order to be in line with Zanobetti & Schwartz (2007)'s study population.

3.5.2 Results

The results are presented for each gender and 1-year age group of the currently alive London adult population, over the 60 years modelling period. Percentage values given are population-weighted.

Overestimation bias in quantification of avoided CHD cases

Figure 3.2 contrasts the numbers of avoided cases of CHD under pollution decrement obtained by the separate approach (results represented by the full-line curve) as opposed to the simultaneous approach (results represented by the dotted curve). The comparison of those results - which is equivalent to directly comparing arm I_1 against arm I_3 - shows the impact of extending individuals' life expectancy, simultaneously to reducing their risk of developing CHD, on the total number of CHD cases expected to be avoided in the target population.

The interactional effect between the morbidity and mortality impacts of air pollution reduction is the strongest for younger age-groups, who are those who enjoy the reduction in mortality risk for the longest period, i.e. who have the largest life expectancy gain. As a result, the size of the bias in counts of CHD cases associated with the separate approach is the largest among younger age-groups and slowly decreases as a function of age. An implication of this finding is that the longer the time horizon of analysis, the greater the bias in quantification of morbid cases will be, as differences accumulate over time. Across all age-groups and a time horizon of 60 years, the bias is not negligible: under the separate approach, counts of avoided CHD cases is overestimated by about one fifth for each gender.

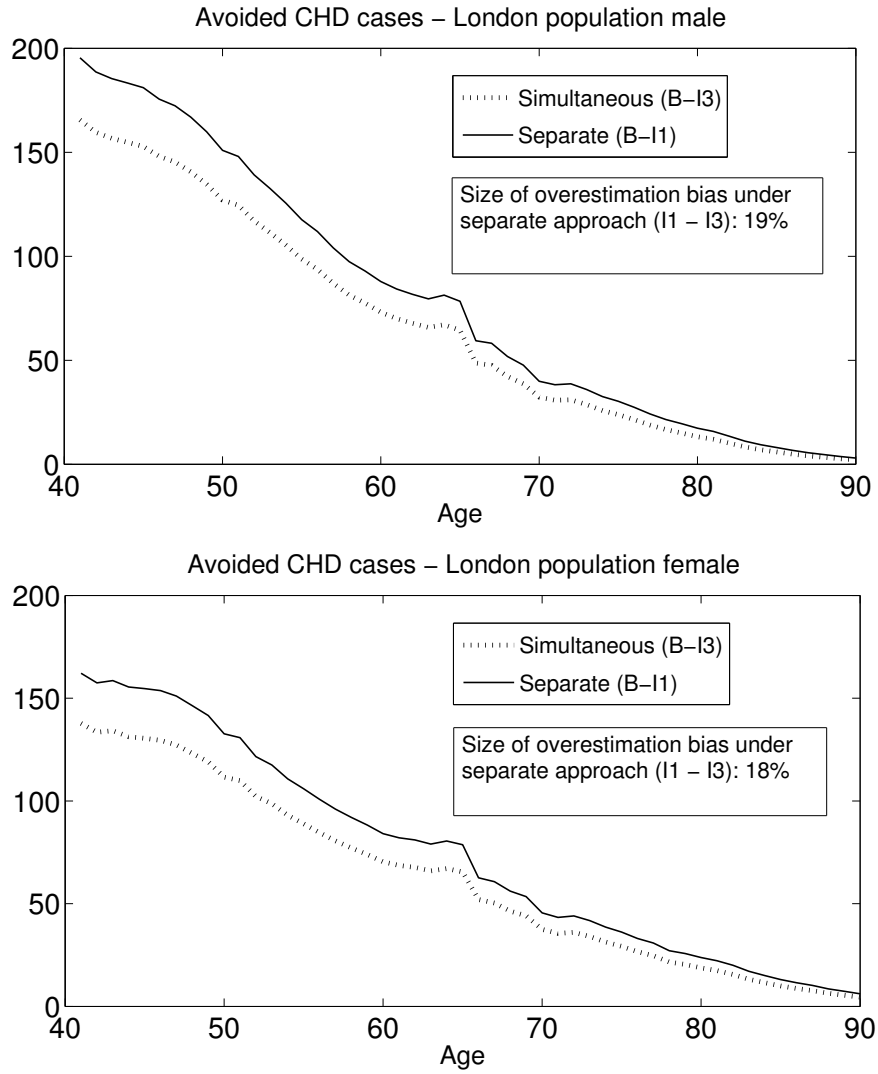


Figure 3.2: Number of avoided CHD cases in current London population under the separate and the simultaneous approaches to quantification.

Abbreviations: B, I_1 and I_3 stand for “Baseline” and “Intervention” arms I_1 and I_3 , as represented in Figure 3.1.

Distributional analysis of life expectancy impacts by causal pathways and between health-stratified population subgroups

Figure 3.3 illustrates how simultaneous quantification of morbidity and mortality impacts can characterise the distribution of life expectancy impacts by causal pathways and between population subgroups stratified by demographics and health status, presently defined by the presence of the CHD condition or not. In line with the fact that life expectancy gains are cumulative over a lifetime, the younger age groups gain the most from the intervention. The small irregularities in the pyramidal distribution of life year (LY) gains solely mirror the peculiarities of London’s population distribution (see Appendix C).

Figure 3.3 was obtained by performing three inter-arms comparisons defined in the lower-section of Table 1. It provides three main modelling insights. Firstly, individuals “With CHD”, i.e. those who had CHD at baseline or who developed it in their remaining lifetime, are expected to reap about a quarter of the intervention’s total LY gain (respectively 25% and 23% of total LY gain accruing to males and females populations across all ages). It should be underlined that this finding reflects epidemiological evidence that individuals with CHD aged above 65 years old are more susceptible to air pollution adverse effects than the rest of the general population (see section 3.5.1).

Secondly, about a fifth of the intervention’s total LY gain steams from reducing the risk of CHD incidence (respectively 22% and 16% of total LY gain accruing to males and females populations across all ages). A corollary of these two findings is that the CHD pathway is expected to be a major driver of the intervention’s overall life expectancy impact. Indeed, respectively 47% and 39% of the intervention’s total LY gain accruing to male and female populations is generated by preventing or decelerating the development of CHD and/or by staying alive longer once suffering from it.

Thirdly, the relative contribution of each risk reduction to total LY gain strongly depends on age and gender. For instance, the LY gain associated with a reduced risk of CHD incidence accounts for 26% of the total LY gain accruing to individuals aged 40 as opposed to 10% of the total LY gain accruing

to individuals aged 75. Indeed, as individuals get older, their probability of already having developed CHD before intervention implementation becomes greater and moreover, their risk of developing other life-shortening diseases than CHD becomes more prevalent. Finally, gender differences pertaining to the share of LY gain attributable to the CHD pathway corroborate results of Figure 3.2, where the absolute numbers of avoided CHD cases is lower for females than males. It is explained by the lower baseline incidence of CHD in females before menopause.

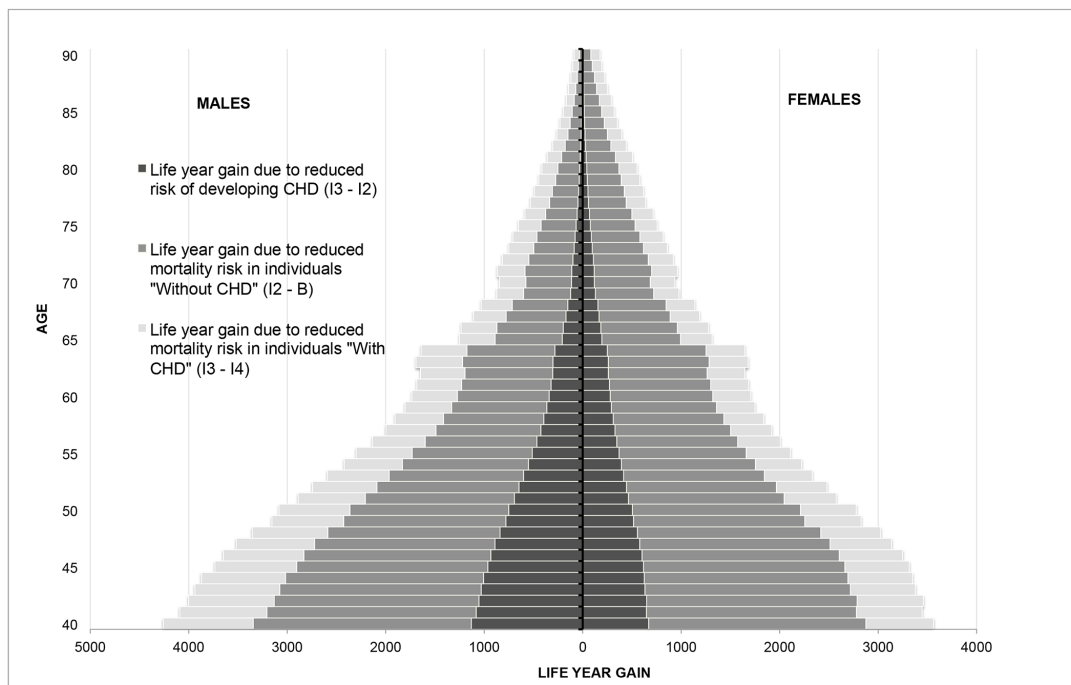


Figure 3.3: Distribution of the intervention's life year (LY) gain by causal pathway and between age-gender- and health status-stratified subgroups.

3.6 Discussion

The present work challenges the traditionally used approach to quantification in health impact assessments of environmental interventions such as air pollution control regulations, where morbidity and mortality impacts are quantified separately. It demonstrated that, by ignoring interactions between morbidity and mortality impacts, this “separate” approach undermines the validity of health predictions and cannot provide policy-relevant information pertaining to the distribution of life expectancy impacts.

As illustrated with a case study of air pollution reduction in London, the simultaneous quantification approach has two major benefits. First, it provides a correct estimate of the intervention-related change in cases of morbid endpoints in the target population, rather than systematically overestimating this impact. The size of the overestimation bias associated with the “separate” approach will depend on several factors, in particular the relative magnitude of the risk factor’s impact on mortality and morbidity risks. Over long time horizons, as typically used in HIA of air pollution control interventions, the bias may be substantial. Over a 60-year time horizon for instance, the “separate” approach was found to lead to an overestimation by one fifth of the number of CHD cases expected to be avoided following pollution abatement in London.

Secondly, by encompassing interactions between health effects, including health-related differential susceptibility to hazard exposure, the simultaneous quantification approach can characterise the distribution of life expectancy effects by causal pathways and across population subgroups stratified with different levels of health. This more refined understanding of the distribution of health effects is expected to have a least three main applications. First, in a context where the reduction of health inequalities is viewed as an essential component of the implementation of Healthy Public Policy (WHO, 1999, 2005, 2008), such distributional information, when combined with evidence of social gradients on health, can support health inequality analysis. Second, it is crucial to the computation of summary measures of population health, which require

to adjust life expectancy estimates by health (or disability)-related quality of life weights. Whilst not widely used in HIA, these measures allow to compare the performance of diverse interventions and provide an accurate picture of morbidity on length and quality of life, thus going beyond simple adding up of numbers of cases. Finally, encompassing interactions between health effects as also particularly relevant for budget impact analysis especially with regards to health care resource use.

Markov models were suggested as a quantification tool to perform simultaneous quantification of morbidity and mortality impacts in quantitative health impact assessments. In addition to capturing interactions between health effects, which was the focus of this chapter, it is worth underlining that Markov modelling also allows for dynamics in population demographics and health risks over time. Consequently it addresses the static feature of health impact functions, which are currently used to quantify morbidity impacts.

Markov models are also particularly suited to model repeating health effects as well as to attach costs and utilities to health states in order to compute summary measures of population health, such as QALYs and DALYs. As a result, they have been used extensively for decision-making in the health care sector. By contrast, to the exception of recently developed Markov-based generic software DYNAMO HIA (Lhachimi et al., 2012), Markov models have very little history of use in health impact assessments of environmental health interventions. A potential reason for the limited application of Markov models in quantitative health impact assessment may be their greater complexity than the current tools of the separate approach i.e. health impacts functions and life-tables. In this respect, the “focused modelling” approach illustrated in this chapter appears particularly attractive.

Notwithstanding the level of refinement in the quantification of predicted health impacts, it is worth stressing that quantitative risk assessment, be it performed under the “separate” or the presently advocated simultaneous approach, is underpinned by a set of assumptions which impact on predictive validity should always be considered. In particular it is assumed that epidemiological results from various studies are applicable to the target population of the intervention under assessment (Bathia & Seto, 2011). It should however

be noted that, by taking into account individuals' heterogeneity in susceptibility to health effects as a result of their health status, the simultaneous approach may help reduce extrapolation of epidemiological findings. Finally, whilst input parameters to quantification (e.g. mortality and disease incidence statistics) are typically assumed to be stable over time, secular trends, be it purely contextual or induced by the interventions themselves, may further widen the gap between predictions and reality (Bathia & Seto, 2011).

3.7 Conclusion

In a context where health impact assessment has become a major component of the implementation of Healthy Public Policy, the present work challenges the current approach to impact quantification, which assesses morbidity and mortality impacts separately. Two main limitations pertaining to predictions' validity and informational content were identified. To address these limitations, a simultaneous approach to quantification that captures interactions between impacts was advocated. Markov modelling was selected to implement the simultaneous approach and to illustrate its superiority, a simple 3-state Markov Model was constructed to evaluate an illustrative intervention of air pollution reduction in London. By improving predictions' validity and policy-relevant informational content, the simultaneous modelling approach to quantitative risk assessment in HIA is expected to help contribute to public health protection more effectively.

Chapter 4

A Markov modelling approach to the estimation of QALY gain and health care costs impacts of air pollution control

4.1 Introduction

Chapter 3 demonstrated that the current approach to quantitative health impact assessment of environmental health interventions such as air pollution reduction presents two important limitations: by quantifying morbidity and mortality impacts separately, it undermines predictive validity and cannot characterise the distribution of life expectancy impacts by causal pathways and among population subgroups with different levels of health. A simultaneous approach to quantification, that captures interactions between morbidity and mortality health effects, was therefore advocated.

Markov models were selected to apply this approach to quantitative health impact assessment, owing to their numerous attractive features. More specifically, since they were developed to represent stochastic processes, Markov mod-

els are particularly suited to modelling the dynamic progression of diseases and their interactions with health events, such as death, in a given target population. Additionally, they also allow for dynamics in population demographics and in the pattern of change in health risk associated with an intervention, thus addressing the static feature of commonly used health impacts functions.

As mentioned in Chapter 2, the morbidity effects considered in evaluations of air pollution control interventions are primarily associated with acute pollution exposure. Consequently, the long-term quality of life impacts associated with a reduction in chronic morbidity, following a sustained decrement in background air pollution, are typically ignored. However, in light of increasing political attention to strategies to improve air quality (Medina et al., 2013), it is of particular interest to refine the understanding of the long-term health benefits of such interventions, by evaluating quality of life gains alongside life expectancy effects.

The health metric designed to encompass impacts on both quality and length of life dimensions is the quality-adjusted life years (QALY). Although the QALY has been rarely used in HIA (Briggs, 2008), its use has been advocated for assessments of environmental health interventions in order to support resource prioritisation (Ponce et al., 2001; US Institute of Medicine, 2006). In particular, as the QALY routinely supports health care resources allocation (Drummond et al., 2005), its use in the assessment of air pollution control interventions would allow policy-makers to compare the latter with health care interventions, for which cost-effectiveness decision rules are in place.

Constructing a QALY requires the application of a quality-adjustment to life year gains using health-related quality of life (HRQoL) weights. However, as mentioned in Chapter 2, adjusting life years gains for quality of life has been controversial and past attempts at doing it have been simplistic. In this context, this piece of work aims to demonstrate that the Markov-modelling based simultaneous approach to quantification presented in Chapter 3 represents a step forward for QALY-based cost-effectiveness assessments of air pollution control.

The aims of this chapter are threefold: (i) to review existing attempts at estimating the QALY gain of air pollution control and to outline the advan-

tages of the Markov-modelling based simultaneous approach to perform such analysis (ii) to analyse and translate the rich body of epidemiological evidence on the adverse health effects of long-term exposure to fine particulate air pollution ($PM_{2.5}$) into chronic conditions associated with known effects on life expectancy and quality of life; (iii) to construct a Markov model that captures the main characteristics of the chronic conditions identified and that relies on the latest most relevant epidemiological evidence, as was feasible at the time of project realisation. This implies that the risk estimates that will parameterise the model will be more up to date than the estimates used in Chapter 3.

The underpinning objective is to apply the developed model to quantify the QALY gain and health care cost impact of reducing $PM_{2.5}$ concentrations in England and Wales and London, in order to support the UK air quality strategy. The present chapter however, solely focuses on the construction and parameterisation of the model. Estimation of a subset of key parameters required to parameterise the model will be dealt with separately in Chapters 5 and 6. Modelling findings will be presented and discussed in Chapter 7.

4.2 Benefits of the simultaneous approach to quantification in QALY analysis

4.2.1 Limitations of past QALY analyses

The QALY is obtained by multiplying the period of time spent in a given health state by health-related quality of life (HRQoL) weights associated with that state (Gold et al., 2002). There are two related elements to take into account when assessing the QALY gain of air pollution reduction. First, the lower the baseline quality of life and/or remaining lifespan of targeted individuals are, the smaller the QALY gain from postponing their deaths will be.

Second, epidemiological evidence suggests that air pollution is associated with both premature mortality and the development of chronic cardio-respiratory conditions (Anderson et al., 2012). A subset of population individuals affected by a poor health condition and thus, a low quality of life and a short life expectancy, is therefore attributable to cumulative exposure to air pollution.

Ignoring air pollution's influence on individuals' quality of life and life expectancies at baseline, i.e. under current pollution levels, will consequently greatly underestimate the QALY gain of air pollution control. Although this issue has been acknowledged (Hubbell, 2006), it has not been adequately addressed. Using the life-table method, Coyle et al. (2003) simply applied HRQoL weights for the general population to life year gains from a lower risk of premature mortality and completely ignored quality of life gains associated with reduced morbidity. Cohen et al. (2003) used a similar method but assumed that all the individuals who would die prematurely from air pollution suffered from a preexisting coronary or respiratory condition without however, accounting for air pollution's role in driving a subset of them to such health state. Such an approach further contributed to underestimating the QALY gain of air pollution control.

Whilst Hubbell (2006) partly accounted for air pollution's impact on quality of life via the development of chronic bronchitis, he did not use the resulting level of quality of life as a baseline to adjust life years gains from decreased mortality risk. This use of a double baseline of HRQoL weights to assess respectively morbidity and mortality effects, as was done by the US EPA to create the MILY (see Chapter 2), no longer allows a linear substitution between quality and quantity of life and thus, clearly departs from the QALY.

A second major limitation shared by all the above-mentioned studies - and by all past HIAs of air pollution control interventions in general - is that no study has accounted for the fact that individuals suffering from a compromised health condition have been found to be more susceptible to air pollution exposure than the general population (Zanobetti et al., 2008; Zanobetti & Schwartz, 2007; Tonne & Wilkinson, 2013). As argued and illustrated in Chapter 3, health-related differing susceptibility to air pollution drives the distribution of adverse impacts among population subgroups stratified by health status.

Such a knowledge is crucial to accurately adjust life expectancy estimates with HRQoL weights and ignoring it, as was done by past QALY analyses of air pollution control interventions, is expected to lead to inaccuracy in impact estimates.

4.2.2 Advantages of the simultaneous approach

The two major limitations of past QALY analyses stem from the fact that they relied on the traditional “separate” approach to impact quantification in HIA that was criticised in Chapter 3. These limitations can be addressed by encompassing interactions between morbidity and mortality impacts via the simultaneous approach to impact quantification, using Markov modelling as a quantification tool.

Markov modelling consists in following individuals’ health condition over time by simulating their trajectories to and from a set of mutually exclusive and exhaustive health states. It provides two core advantages to QALY analysis. First, individuals’ quality of life and life expectancies are no longer treated as exogenous parameters. Instead, they are endogenously determined as a function of individuals’ current health states, where air pollution influence in driving them to their respective states of health is fully accounted for. Second, individuals’ change in susceptibility to air pollution exposure over time, as a consequence of a degraded health condition that may, or may not, be associated with air pollution exposure is encompassed. Thanks to these two features, the lifetime impact of air pollution exposure on individuals’ quality and length of life is fully captured.

In addition, from an economic perspective, the proposed approach can quantify both the health care savings from a reduced occurrence of morbidity events, as well as the health care costs from extending the lives of individuals with chronic medical conditions. As a consequence, the total health care budget impact of reducing air pollution can be evaluated.

4.3 Modelling the QALY and health care costs impacts of air pollution exposure

4.3.1 Preliminaries

Chapter 2 discussed the importance of undertaking conceptual modelling (problem-oriented and design-oriented), in order to produce a benchmark against which to assess the credibility of the final model to be implemented. In this analysis a conceptual model has not been formally implemented, however elements that are relevant to the construction of a conceptual model are considered in sections 4.3.2 to 4.3.4 and section 4.4.2.

4.3.2 System boundaries: scope of analysis

As mentioned in Chapter 2, the impacts associated with air pollution exposure go beyond the increase in morbidity and mortality cases directly related to exposure but include productivity effects due to work absences following acute effects and potentially, wider effects on physical activity outdoors for those living in urban areas.

Nevertheless, the core objective of the present work is to apply for the first time, the Markov modelling technique to quantify the quality of life effects associated with the development of adverse health conditions under air pollution exposure. Consequently, the scope of impacts considered as relevant for the present analysis was restricted to direct effects on morbidity and mortality and associated health care costs.

4.3.3 Relevant health effects

Chapter 2 underlined two main categories of health effects which are related to the timing of exposure: acute effects associated with short-term peaks in pollution exposure versus chronic conditions developed as a result of sustained exposure.

The present analysis aims to quantify the impact on life expectancy, quality of life and health care resources of sustainably reducing $PM_{2.5}$ concentrations over the individual's remaining lifetime. Given such timescale, only chronic health effects were considered relevant. Whilst the life expectancy impacts associated with acute exposure are encompassed in risk estimates of excess mortality from cumulative exposure (Künzli et al., 2001), this choice implies that quality of life effects from morbid events triggered by acute exposure, such as respiratory exacerbations, are therefore not presently taken into account. Short-term quality of life effects from exacerbations are however, not expected to drive quality of life impacts over a lifetime.

4.3.4 Target population for the intervention

Air pollution has been found to affect individuals in every stage of life: (i) *in utero*, whereby maternal exposure to air pollution exposure has been associated with an excess risk of low birth weight in babies (Dadvand et al., 2013) and most recently, with a greater odds of developing autism (Raz et al., 2014); (ii) during childhood in particular by affecting children's lungs development (Eisner et al., 2010; Shannon et al., 2004) and (iii) in adulthood, whereby the sick and elderly have been identified as susceptible subgroups (Peled, 2011; US EPA, 2009).

The latest findings with regards to impacts *in utero* are however, extremely recent and may need further validation. Children are expected to be particularly susceptible to air pollution impacts due to more time spent outdoors, a higher air intake per body weight and bodies in developmental phase (Shannon

et al., 2004; US EPA, 2009; Peled, 2011). However, evidence of effects in children primarily pertains to respiratory exacerbations following acute exposure, which are outside the present scope of analysis, or to subclinical respiratory conditions (such as reduced lung growth), which are not well characterised with incidence and prevalence statistics.

On these grounds, the present analysis focuses on chronic health impacts experienced in adulthood. Importantly, since chronic respiratory impacts in adults partly derive from the worsening over time of subclinical conditions developed since childhood (Eisner et al., 2010; Peled, 2011), the long-term damaging impact of PM exposure on children’s lung development should to some extent, be encompassed in the analysis.

4.3.5 Inclusion/exclusion of relevant chronic health impacts in adults

As mentioned in Chapter 2, evidence requirements represent a key component of the feasibility assessment when considering alternative credible model structures. In the present case, the documented morbidity effects of particulate matter (PM) exposure had to be translated into well-defined chronic conditions for which population prevalence, incidence and survival statistics, as well as HRQoL scores and health care cost data, were available.

Epidemiological studies suggest a positive association between long-term exposure to fine particulate air pollution and incidence of myocardial infarction (Lipsett et al., 2011; Puett et al., 2009), coronary revascularization (Miller et al., 2007) and acute and sub-acute forms of coronary heart disease (Cesaroni et al., 2014), in individuals of the general population without heart disease at enrolment. In addition, further evidence suggests exposure to PM is also related to early stages of heart diseases by increasing coronary atherosclerosis (Adar et al., 2013; Künzli et al., 2010; Allen et al., 2009). Whilst long-term exposure to PM exposure has also been associated with stroke (Miller et al., 2007), to date the epidemiological evidence supporting such an association remains weak (Brook et al., 2010). Based on this body of evidence and con-

straints in terms of required data, the cardiovascular impacts of air pollution exposure were modelled using coronary heart disease (CHD) - ICD-10 I20-I25 - as health endpoint.

A number of studies have also shown positive associations between PM exposure and respiratory symptoms (Schindler et al., 2009; Zemp et al., 1999), including those of chronic bronchitis (Abbey et al., 1995) or lung function decrements (Downs et al., 2007), all of which are associated with chronic obstructive pulmonary disease (COPD). Although the body of evidence linking PM exposure and COPD development remains incomplete (Schikowski et al., 2013), such association is likely as reduced pulmonary growth in childhood and adolescence - for which the link with PM exposure is now established - increases the incidence of COPD later in life (Eisner et al., 2010). The COPD disease pathway (ICD-10 J40-J44) was therefore chosen to model the chronic respiratory impacts of PM exposure.

Lung cancer (ICD-C33-34), which has repeatedly been found to be associated with chronic PM exposure (Hamra et al., 2014), was considered as a third morbidity endpoint.

The life shortening impact of particulate air pollution exposure was modelled using mortality risk estimates for all causes of death, as recommended by WHO (2013) for health impact assessments (HIA) of air pollution control interventions. However, unlike past HIAs and QALY analyses of air pollution control, the mortality risk estimates used in the present analysis are stratified by health status. Indeed, although epidemiological research on health-related susceptibility to air pollution remains limited, it is generally recognised that individuals who are already in a compromised health condition are expected to suffer a disproportionate share of air pollution mortality burden than healthier individuals (Peled, 2011; US EPA, 2009). More especially, a few studies found that individuals with a chronic respiratory or cardiac condition are at a greater risk of a pollution-related death (from all causes) than the general population (Zanobetti & Schwartz, 2007; Zanobetti et al., 2008; Tonne & Wilkinson, 2013).

To conclude, the health impacts of a sustained decrement in exposure to particulate air pollution were modelled by assessing the reduction in the risks of developing COPD, CHD and lung cancer and in the risk of death from all

causes, while allowing for greater susceptibility to premature death in individuals suffering from COPD and CHD.

4.4 Model structure

4.4.1 Markov models: key features

Markov models were previously described in Chapter 3. They have two key structural components: (i) mutually exclusive and exhaustive health states and (ii) transition probabilities (TP) which, in discrete time approximation, are expressed for a cycle. TP represent the probability of transiting to a particular state of the model during a cycle, conditional on being in a given health state at end of the previous cycle. They are typically stratified by age and gender and expressed as a function of the number of cycles elapsed, to reflect the time-dependency of health events.

Additionally, Markov models are based on the Markovian assumption that knowledge of the past development of the Markov process is redundant for predicting its future development as only the present matters (Kulkarni, 2011). In other words, only the knowledge of the state in which the individual is at the end of cycle “c-1” is necessary to predict his/her probability to transit to other states during cycle “c”. When this assumption appears unrealistic, for instance when survival is a function of the time spent with a condition, tunnel states, which are health states in which individuals can only spend one cycle, can be introduced into the model to allow TP to depend on previous health history.

4.4.2 Disease pathways

The model was built around three disease pathways - one for each chronic morbid condition defined in section 4.3.5 - alongside the states “dead” and “healthy”, where the latter represents a health state exempt of any of the three conditions. As the analysis timeframe is the individual’s lifetime, the cycle period was set to one year. Due to data gaps pertaining to co-morbidity risks, the model assumed competitive risk between the three diseases pathways. In other words, an individual cannot suffer from two conditions at the same time. By ignoring co-morbidity effects, the estimates of health benefits from air pollution reduction are therefore expected to be slightly conservative. This will be further discussed in Chapter 8. In addition, each disease pathway was underpinned by the following structural assumptions:

COPD

As health care cost, quality of life decrements and survival probabilities greatly depend on the level of airflow obstruction, the COPD pathway was structured around the four severity stages: GOLD 1 to GOLD 4, defined by the Global initiative for chronic Obstructive Lung Disease (GOLD, 2014). Although COPD is treatable, it is not reversible and slowly worsens over time. Moreover, the disease is often diagnosed in late stages (GOLD, 2014). To reflect these characteristics, the COPD pathway was designed as unidirectional - i.e. without allowed transitions back to “healthy” or to a less severe state - and upon entry into the disease pathway, no jump of severity stage was allowed. By contrast, to reflect the reality of late diagnosis, transitions from the state “healthy” to the first three severity levels of the disease were allowed (see Figure 4.1). Further justifications of the structure of the COPD pathway is provided in Chapter 5.

Unlike the majority of existing population models of COPD (Najafzadeh et al., 2012; Hoogendoorn et al., 2011, 2005) that are centred around smoking as disease risk factor, the present model does not account for exacerbations of the disease, i.e. a worsening of symptoms for a few days. The reason is that

the impact of air pollution on COPD exacerbations is expected to be solely related to acute exposure, whereas the present model focuses on the chronic health effects associated with long-term exposure.

CHD

Although CHD also has different levels of severity that will influence quality of life and life expectancy, in the absence of a widely accepted classification by severity stages, the CHD disease pathway was composed of only one state. The CHD pathway was also designed as unidirectional, since CHD is a chronic condition that requires long-lasting disease management.

Lung cancer

Lung cancer is one of the deadliest cancers, from which most individuals die in the first years of the disease (ONS, 2011). Whilst 5-year lung cancer survivors remain at risk of cancer recurrence, most recurrences (about 80%) occur about two years after surgical resection (Maeda et al., 2010). Consequently, it was assumed that after five years spent alive with the condition, individuals would transit back to the state “healthy”, from where they would face the same risks of adverse health events and enjoy the same quality of life as individuals of the general population of same age and gender. To capture the time dependence of survival probabilities in lung cancer patients, the disease pathway was structured around five tunnel states. Each five state enables to differentiate lung cancer patients whether they have been suffering from the disease for respectively one, two, three, four and five years.

Figure 4.1 represents the Markov model structure, built around the three disease pathways, as a state transition diagram. Ovals represent health states and arrows represent the allowed transitions between them.

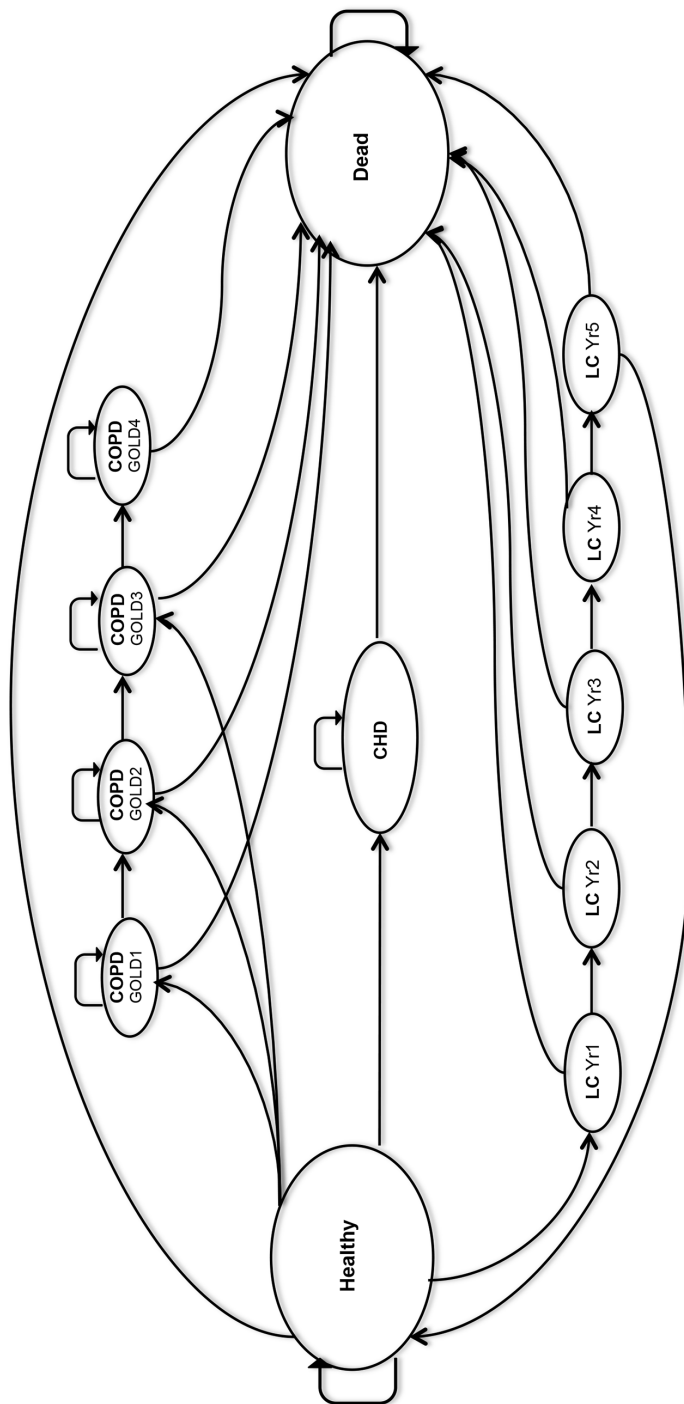


Figure 4.1: Model's structure around the three disease pathways.

Abbreviations: COPD = chronic obstructive pulmonary disease; CHD = coronary heart disease; lung cancer = lung cancer. Ovals represent health states and arrows, allowed transition between them.

4.4.3 Intervention arm and risk reduction estimates

Building from Chapter 3

As explained in Chapter 3, to evaluate an intervention such as air pollution reduction, the model requires: a “baseline” arm populated with baseline TP to be compared against (ii) an “intervention” arm for which, similarly to a health impact function, baseline TP are combined with risk reduction estimates (RRE). The latter are epidemiological risk estimates scaled to the intervention-related exposure decrement. Since TP are non-linear function of time, the multiplication of TP with RRE is carried out on the transition rate scale. Adjusted transition rates are then converted back to probabilities to parameterise the intervention arm.

Chapter 3 presented two approaches to the application of Markov modelling methodology to quantitative risk assessment, which differ in the scope of the morbidity-mortality interactions encompassed and in the way life expectancy impacts are modelled. Like the “full-modelling approach”, the present model aims at encompassing thoroughly the chronic morbidity effects associated with long-term PM exposure and their impacts on life-expectancy, including their influence on individuals’ susceptibility to dying prematurely due to PM exposure. However, since air pollution has been associated with a positive excess risk of all-cause mortality, a lower risk of death under pollution decrement was also applied to those “healthy” individuals who did not enter any disease pathway. Importantly, as advocated in Chapter 3 when describing the “focused” modelling approach, to avoid double-counting of life expectancy effects, the change in mortality risk for those “healthy” individuals exclusively pertains to all the other causes of death than the ones modelled (see parameter RRE_g in Table 4.1).

Finally, as the present objective is to assess the total QALY and health care resource impacts of reducing particulate air pollution, as opposed to disentangling impacts by causal pathways and population subgroups as was done in

Chapter 3, only one intervention arm fitted with all relevant and appropriately scaled risk estimates was built.

Risk estimates: sources and application

Although the model is to be applied to evaluate an intervention of air pollution control in the UK, risk estimates were taken from studies performed in various developed countries, mainly in North America and Europe, with only one risk estimate derived from a UK study (Tonne & Wilkinson, 2013). However, this is unlikely to be a major limitation since developed countries are characterised with a similar range of $PM_{2.5}$ concentrations - ranging from about 5 to 35 $\mu g/m^3$ - across which linearity in health impacts and absence of threshold to effects has repeatedly been found (Lepeule et al., 2012; Crouse et al., 2012; Krewski et al., 2009). These characteristics of the dose-response function have two implications. Within the above concentrations range: (i) estimates of health effects for a different level of pollution reduction may be obtained by simple proportional scaling of results obtained per one unit decrement in ambient $PM_{2.5}$ concentrations; (ii) RRE can be derived from risk estimates, that are typically expressed for $\Delta_{PM_{2.5}} = +10\mu g/m^3$, using simple logarithmic multiplicative scaling (see Appendix C of Chapter 3).

In an effort to encompass all existing relevant evidence and to decrease parameter uncertainty, risk estimates were preferably sourced from meta-analyses. In light of the number of studies pertaining to all-cause mortality and lung cancer development or mortality published in recent years, it was decided to carry out a systematic review of such studies and two meta-analyses. This was performed separately in Chapter 6.

To limit extrapolation of epidemiological findings, application of risk estimates in the model sought, to the extent that it was feasible, to be in line with study subjects' main characteristics in terms of age and/or health condition. For instance, the only available piece of evidence on the excess risk of death associated with PM exposure in COPD patients is based on individuals aged above 65 years old, identified using hospital discharge data (Zanobetti et al.,

2008). As the risk of hospital admission for COPD greatly increases with disease severity, the study's risk estimate was applied only to those individuals aged 65 and above if they were in GOLD 3 or 4 states. In other words, it was conservatively assumed that individuals with COPD in stages 1 and 2 or in stages 3 and 4 but aged below 65 faced the same PM-related excess risk of mortality as the general population. Similarly, the PM-related excess risk of mortality in individuals with CHD was informed by a study from Tonne & Wilkinson (2013), based on patients above 25 years of age admitted to hospital following acute coronary syndrome (ACS). ACS reflects a more severe health condition than CHD as a whole. Since the risk of ACS linearly increases with age (Simms et al., 2012), Tonne & Wilkinson (2013)'s risk estimate was only applied to individuals suffering from CHD if they were aged 75 or above. Individuals with CHD aged below 75 were therefore conservatively assumed to face the same PM-related excess risk of mortality as the general population.

Table 4.1 links baseline transition probabilities with relevant risk reduction estimates expressed for a $1 \mu\text{g}/\text{m}^3$ decrement in $PM_{2.5}$ concentrations. As lung cancer is very deadly, the impact of $PM_{2.5}$ exposure on the lung cancer pathway was restricted to disease development, i.e. no further PM-related excess risk of death applied to individuals suffering from lung cancer.

Figure 4.2 represents the model's intervention arm, with RRE associated with various transition paths. Dotted arrows represent RRE-adjusted transitions, i.e. transitions for which the underlying risk of event is reduced under pollution reduction, whereas full arrows represent transitions for which the underlying risk of event is assumed to be unchanged under the intervention.

Parameter Name	Transition Probability $P_{X,Y}$	Pop. age	Risk Reduction Estimates (RRE)		
			Risk Estimates		Mean (95%CI) $\Delta_{PM_{2.5}} = -1\mu g/m^3$
			Definition	Source	
RREa	$P_{H,COPDi}$ <small>i=GOLD1,..., 3</small>	All	$OR_{Dev.COPD}^{(a)}$	Schikowski et al. (2014)	0.988 (0.918-1.065)
RREb	$P_{H,CHD}$	All	$HR_{Dev.CHD}$	Cesaroni et al. (2014)	0.976 (0.949-1.004)
RREc	$P_{H,LC}$	All	$HR_{Dev.LC}$	see Chapter 6 ^(b)	0.985 (0.980-0.991)
RREd	$P_{COPDi,D}$ <small>i=GOLD1,...,2</small>	All	$HR_{DeathAC}$	see Chapter 6	0.993 (0.991-0.995)
RREe	$P_{COPDi,D}$ <small>i=GOLD3,...,4</small>	< 65	$HR_{DeathAC}$	see Chapter 6	0.993 (0.991-0.995)
		≥ 65	$HR_{DeathAC COPD}$	Zanobetti et al. (2008) ^(c)	0.980 (0.976-0.984)
RREf	$P_{CHD,D}$	< 75	$HR_{DeathAC}$	see Chapter 6	0.993 (0.991-0.995)
		≥ 75	$HR_{DeathAC CHD}$	Tonne & Wilkinson (2013)	0.982 (0.968-0.996)
RREg	$P_{H,D}$	All	$HR_{DeathAOC H}$	Pope III et al. (2002)	0.999 (0.994-1.005)

Table 4.1: Risk reduction estimates for intervention arm.

Abbreviations: $P_{X,Y}$: age and gender-specific annual probability of developing disease/ experiencing event “Y”, conditional on being in health state “X”; Dev. = developing; COPD = chronic obstructive pulmonary disease; CHD = coronary heart disease; LC = lung cancer; H=healthy; D= dead; HR=hazard ratio; $HR_{Y|X}$: hazard ratio of event “Y” in population with health condition “X”; OR= odd ratio; AC= all causes; AOC = all other causes.

^(a) When events are rare, i.e. with a probability of event occurrence in the unexposed group less than 10%, which is the case of COPD, OR can be considered equivalent to RR (Sistrom & Garvan, 2004).

^(b) In order to be in line with the most recent published work of Hamra et al. (2014), the pooled estimate of the excess risk of lung cancer associated with $PM_{2.5}$ exposure used to parameterise the present model was taken from sensitivity analysis run 3 in Chapter 6, as presented in Figure 6.7.

^(c) Results based on PM_{10} data.

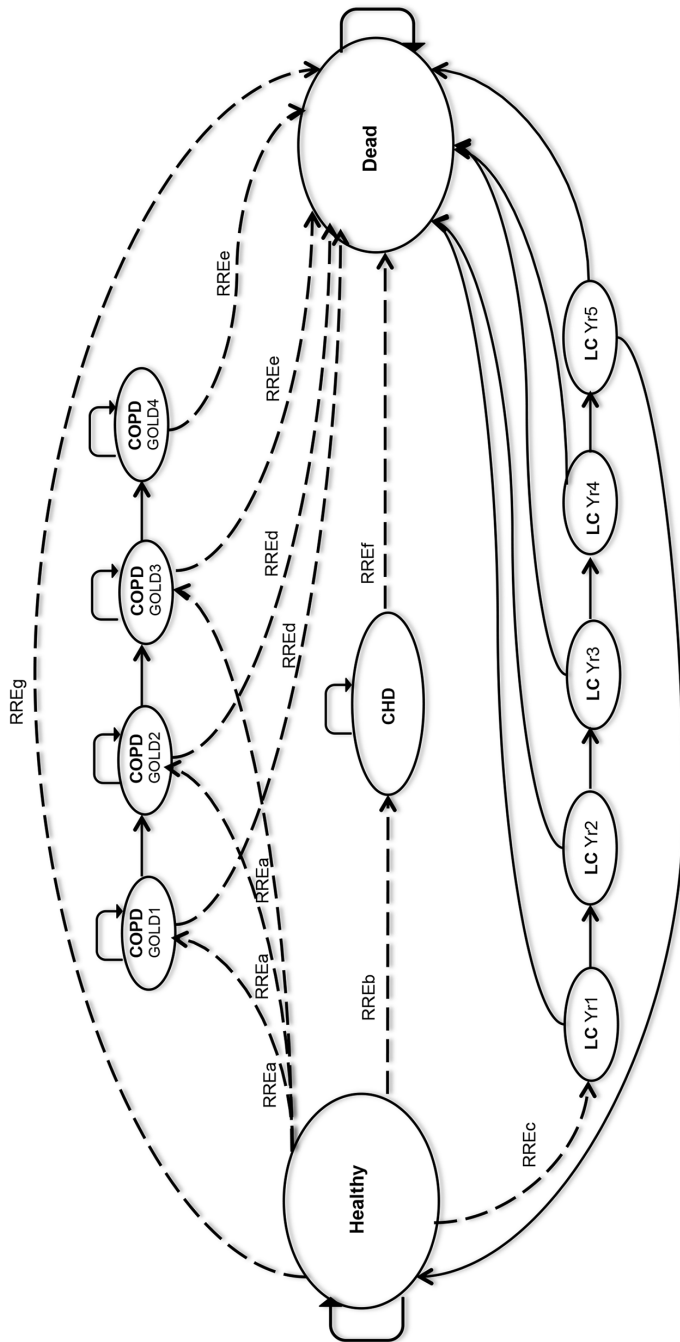


Figure 4.2: Diagram of the model's intervention arm.

Abbreviations: COPD = chronic obstructive pulmonary disease; CHD = coronary heart disease; LC = lung cancer; Yr = year. Risk reduction estimates $RRE_{a, \dots, g}$ are defined in Table 1 and apply to transitions represented by dotted arrows. Full arrows represent transitions unchanged by the intervention.

4.5 Parameterising the model for UK case study

4.5.1 Case study definition

The model was developed in order to evaluate an intervention that would lead to a sustained $1\mu\text{g}/\text{m}^3$ reduction in mean annual population-weighted concentrations of $PM_{2.5}$ in England and Wales and in London. This would represent a 9% and 7% reduction in the annual average concentrations in respectively England and Wales ($11\mu\text{g}/\text{m}^3$ as at 2008, COMEAP 2010) and London ($14.3\mu\text{g}/\text{m}^3$ as at 2008, COMEAP 2010).

This amount of pollution reduction was chosen for two reasons. First, it is in line with the UK Air Quality Strategy's target to reduce $PM_{2.5}$ concentrations at all locations and more especially, to achieve a 15% reduction in $PM_{2.5}$ levels at all urban locations by 2020 (DEFRA, 2012). Second, as mentioned in section 4.4.3, estimates of health effects for other reduction levels may be obtained to a very good approximation by proportional scaling of the estimates obtained for a $1\mu\text{g}/\text{m}^3$ reduction.

The lag between exposure decrement and health risk reduction, known as cessation lag, was assumed to follow the 20-year distributed lag developed and currently used by the US EPA for its assessment of air pollution control strategies. The latter assumes that 30% of the risk reduction takes place in year 1, an additional 12.5% every year between year 2 to year 5 and the final 20% reduction is phased in gradually over year 6 to year 20 (US EPA, 2010). This assumption was followed in past HIAs of air pollution reduction in the UK (Miller, 2010; COMEAP, 2010). Whilst the US EPA's distributed lag was carefully reviewed by the agency's science advisory board, it remains nevertheless highly hypothetical due to the large uncertainty surrounding dynamics in risk reduction following exposure change (Walton, 2010). The sensitivity of results to the structure of the cessation lag will be assessed in sensitivity analyses.

Pollution decrement under the intervention was assumed to be immediate.

While this is unlikely to be realistic, this choice was underpinned by the fact that the structure of the cessation lag is already largely uncertain.

The target populations of England and Wales and London were defined as the current adult population aged 40 to 90. Whilst WHO (2013) recently recommended to apply mortality risk estimates to adults aged 30 and over, the restriction to individuals aged 40 and above was driven by the availability of routine disease incidence and prevalence statistics (COPD in particular). Since the risk of mortality below 40 remains low, this restriction is not expected to lead to a substantial underestimation of the health benefits of air pollution control.

Individuals were followed until death with a cut-off at 100 years old, as disease and mortality statistics are typically no longer available beyond this age. This implies that subjects entering the model at age 40 were followed for a maximum of 60 years, whereas subjects entering the model at age 90 were followed for a maximum of 10 years. The two target populations were not augmented by future generations as doing so would have required additional assumptions pertaining to future births and would not provide an obvious cut-off point for ending the follow-up. Instead, results can be scaled, if necessary, to different population numbers. The analysis time horizon is therefore of 60 years.

For comparability with health care interventions, a discount rate of 3.5% was applied to health care costs and QALY gains, in line with guidelines for England and Wales expressed by the National Institute for health and Care Excellence (NICE, 2013). The sensitivity of results to alternative discounting structures will however, be assessed.

The model was structured around a yearly cycle length (see section 4.4.2) and individuals were assumed to move between health states at mid-cycle. It should nevertheless be underlined that for incremental analyses, as is the present case, the use of half cycle corrections should have only a small effect on results (Briggs & Sculpher, 1998).

All the assumptions defining the case study are summarised in Table 4.2.

Intervention	$PM_{2.5}$ reduction	$-1\mu g/m^3$ of mean ambient concentrations
	Location	(i) England and Wales (ii) London only
	Timing	Immediate and sustained reduction
	Lag to health effect	US EPA's 20-year distributed lag
Population	Scope	All currently alive adults aged 40 to 90
	Follow-up	Until death or 100 years old
Analysis	Time horizon	60 years
	Discount rate	3.5%
	Cycle length	One-year with half-cycle correction

Table 4.2: Assumptions underpinning the case study.

4.5.2 Population modelling

Modelling of currently alive adults aged 40 to 90 years old, was based on a total of 102 age and gender-specific cohorts of 1,000 individuals each (51 one-year age groups for each gender). Results for each age and gender-specific cohort were then scaled to the numbers of individuals of same age and gender living in respectively England and Wales and London, as informed by the 2011 census. The model was built and evaluated using the software MATLAB.

4.5.3 Transition Probabilities (TP)

Data were sourced for England and Wales or alternatively the UK (i.e. no London-specific data were used). Disease prevalence statistics, which represent the proportion of the population with a disease at a given point in time, were used to distribute each of the 102 cohorts into the model's health states at cycle 0, in order to reflect the target populations' level of health. Annual disease

incidence statistics, which represent the 1-year probability of developing a disease, informed cohorts' transitions from the state "healthy" to each disease state during each yearly cycle.

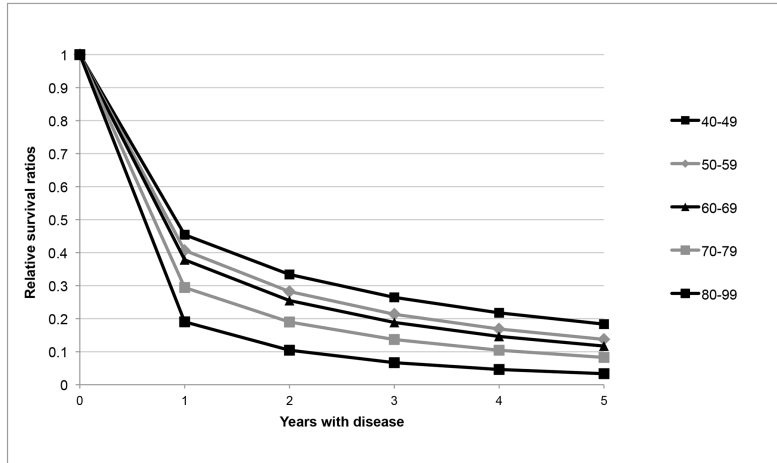
For CHD and lung cancer, incidence and prevalence data provided by the UK Clinical Practice Research Datalink were obtained from the open-access model DYNAMO-HIA.¹ Disease progression parameters for the COPD pathway were obtained by combining annual progression probabilities stratified by smoking status provided by Atsou et al. (2011) with data on the distribution of COPD patients in England by smoking status from Shahab et al. (2006). This approach was justified by the lack of strong evidence to date suggesting that smoking may impact upon individuals' biological response to air pollution exposure (Laurent et al., 2007). COPD prevalence statistics by GOLD stages and 10 year age-group were provided by the UK Department of Health (2010). However, due to data gaps, the incidence of COPD, or more precisely the probability of being diagnosed at the different stages of the disease, had to be estimated. Estimation of diagnosis probabilities was performed separately in Chapter 5.

Mortality TP were computed using mortality rate data from the UK Office for National Statistics (ONS, 2011) and reflect the assumption of competitive risk. The probability of death associated with the CHD pathway - i.e. the probability of dying from all other causes than COPD or lung cancer conditional on having CHD - was computed by applying hazard ratios of excess death associated with CHD provided by Whiteley et al. (2005) to the baseline mortality rates of individuals of the general population who do not suffer from CHD nor COPD nor lung cancer. The latter were obtained from life-table computation using ONS data on mortality rates and causes of death. Similarly, the probabilities of death associated with the COPD pathway were computed using GOLD-stratified hazard ratios of excess mortality in COPD patients estimated by Mannino et al. (2006) .

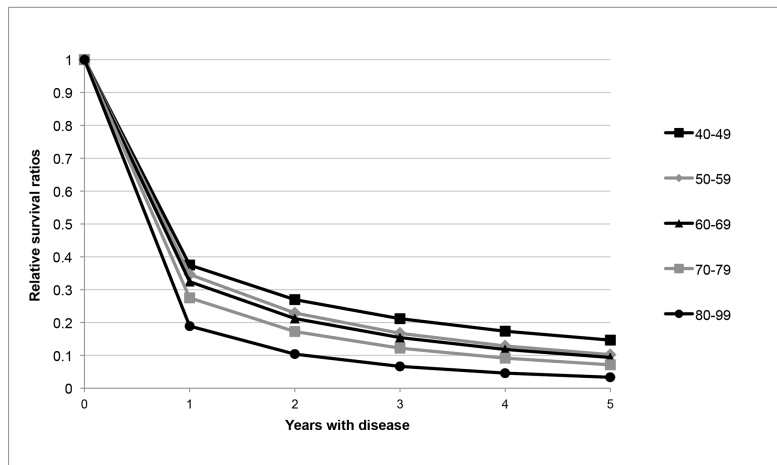
The probabilities of death in lung cancer patients were derived based on age and gender-specific ratios of relative survival at 1 and 5 years since diagnosis

¹DYNAMO-HIA is a European Union-funded generic open-access interface, developed to facilitate health impact assessments in Europe (Lhachimi et al., 2012). It contains country-level incidence and prevalence data for a number of common diseases such as CHD and lung cancer.

(ONS, 2011). The latter are ratios of: (i) the observed survival from all causes of death among subjects with lung cancer and (ii) the expected survival in a comparator group of subjects without lung cancer, matched on relevant covariates (Nelson et al., 2008). Estimation of relative survival ratios at the other time points (i.e. at 2, 3 and 4 years) was carried out by fitting a Weibull function to the survival data. Mean results are presented for each gender in Figure 4.3. Annual probabilities of survival in lung cancer patients after one to five years since diagnosis were then obtained by multiplying relative survival ratios by the expected probability of survival in subjects without lung cancer (nor COPD or CHD due to the competitive risk assumption).



(a) Females.



(b) Males.

Figure 4.3: Estimated relative survival ratios from lung cancer at 2, 3 and 4 years, by gender and age-group, using survival data at 1 and 5 years from ONS and LSTM.

4.5.4 HRQoL weights

The EuroQol five dimensional instrument (EQ-5D), which is the most commonly used HRQoL metric for cost-effectiveness analysis (De Smedt et al., 2014) and the preferred measure of the National Institute for health and Care Excellence (NICE, 2013), was chosen to express the quality of life associated to each health state.

Age and gender-specific HRQoL scores experienced by “healthy” individuals, i.e. individuals without COPD, CHD or lung cancer, were obtained from

Kind et al. (1999). These values were elicited from a representative sample of the English population who considered themselves to be generally healthy.

HRQoL scores associated with each condition are presented in Table 4.3 (left-hand side). To reduce parameter uncertainty, scores for COPD and lung cancer were sourced from meta-analyses (Pickard et al., 2008; Sturza, 2010) while CHD scores were based on a large patient population (n=7,242) as part of the EUROASPIRE III study (De Smedt et al., 2014). For lung cancer, the HRQoL score was based on results for non-small cell cancer, which accounts for about 90% of all cases of cancer in England (Riaz et al., 2012). The final HRQoL score for lung cancer was obtained by weighting HRQoL results for metastatic and non-metastatic non-small cell cancer by respectively 75% and 25%, based on the fact that in England, 75% of non-small cell cancers are detected at an advanced stage (NHSC, 2010).

Incorporation of HRQoL weights into the model combined two approaches. As HRQoL values associated with the CHD condition provided by De Smedt et al. (2014) were stratified by age-groups, a HRQoL decrement was applied to individuals in the CHD pathway, as a proportion of the HRQoL experienced by the general population, for a given age range and gender. This approach however, was not deemed suitable for the lung cancer and COPD pathways due to absence of information on the average age of patients from which HRQoL scores were obtained for these two conditions. Instead, HRQoL scores reported for patient populations were directly applied to subjects in the COPD and lung cancer pathways, while ensuring they were upper-bounded by the HRQoL scores of the general population for the same age and gender. The impact of age on HRQoL associated with COPD was however, indirectly encompassed via the use of HRQoL scores stratified by disease severity (4 GOLD stages), since the distribution of disease prevalence by severity stages is strongly determined by age (UK Department of Health, 2010). It is worth reminding that, given the model structure, after a period of five years, HRQoL scores of lung cancer survivors returned to the age and gender-matched scores of the general population.

4.5.5 Health care costs

“Healthy” individuals were assumed not to generate any health care cost, the implications of which will be discussed in Chapter 8. The average annual health care cost per patient in each condition is provided in Table 4.3 (right-hand side). Costs were inflated to 2013 prices, based on the hospital and community services’ inflation index for the UK NHS (PSSRU, 2013). In the absence of UK specific data, COPD costs stratified by GOLD stage were based on a Swedish study (Jansson et al., 2013).

Like for COPD, the costs of CHD also depend on disease severity as the latter drives the choice of appropriate medical treatment and treatment duration. However, for the reasons exposed in section 4.4.2, the condition was not modelled by severity levels. Consequently, the average annual cost of a CHD patient was obtained by scaling the total annual cost of CHD in the UK (£1.8 billion as of 2009, Nichols et al., 2012), to the number of CHD patients registered in the UK the same year ($n= 2,330,277$, British Heart Foundation, 2010). Whilst the obtained annual cost per patient is low (£836), it was applied from condition onset until death. The annual cost of a lung cancer patient was provided by the National Cancer Research Institute (NCRI, 2012), based on patients who have been diagnosed with cancer and are still alive (this includes newly diagnosed individuals and individuals with stable disease being followed-up).

		HRQoL scores (EQ-5D)		Mean annual cost / patient (2013 prices)
	Age	Severity	Value (SE)	
COPD	All	GOLD 1	0.74 (0.064)	£249
		GOLD 2	0.74 (0.043)	£951
		GOLD 3	0.69 (0.046)	£2,033
		GOLD 4	0.61 (0.084)	£4,943
	source: Pickard et al. (2008)			source: Jansson et al. (2013) ^(a)
CHD	≤ 40	All	0.85 (0.069)	£836
	50-69		0.80 (0.079)	
	≥ 70		0.73 (0.059)	
	source: De Smedt et al. (2014)			source: Nichols et al. (2012) and British Heart Foundation (2010)
Lung cancer	All	Non-metastatic	0.85 (0.074)	£9,283
		Metastatic	0.57 (0.067)	
	source: Sturza (2010)			source: NCRI (2012)

Table 4.3: Condition-specific HRQOL and health care costs.

^(a) Converted in GBP using the average EUR/ GBP exchange rate for 2013.

4.6 Sensitivity analyses

4.6.1 Propagating parameter uncertainty

Joint-uncertainty in parameters can be handled probabilistically by assigning distributions to all parameters, based on their characteristics (Briggs et al., 2006) and performing Monte Carlo simulations (10,000 draws).

A log-normal distribution was fitted to each of the epidemiological risk estimate constituting the intervention-effect (see Figure 4.2) as well as to the excess risk of death associated with each condition.

As no information was available on the variance around disease incidence,

an interval of $\pm 25\%$ around mean estimates was used as an estimate of variation around the incidence of COPD (for each severity stage) and CHD. Such an approach is in line with current recommendations for uncertainty analysis in health impact assessment and cost benefit analysis of air pollution control interventions in Europe (Holland, 2014). For lung cancer, however, as under-diagnosis or mis-diagnosis of the disease is much more unlikely than for COPD or CHD, a estimated variation of $\pm 5\%$ around the mean was used. Instead of fitting a triangular distribution to incidence data (which inform the transitions from the state “Healthy to each disease state), the Pert distribution, which is a special case of the beta distribution, was used. Like the triangular distribution, the Pert distribution is parameterised with a mode and a minimum and maximum value but it produces a smooth distribution that progressively puts greater weight on the most likely value and can provide a close fit to the normal distribution.

Beta and gamma distributions were fitted to respectively HRQoL weights and HRQoL decrements and a gamma distribution was fitted to health care costs. In the absence of information on the variance around health care costs associated with CHD and lung cancer, it was assumed that the standard error equaled to half of the mean, as has been done in past economic evaluations (Briggs et al., 2002).

4.6.2 Sensitivity scenarios

Sensitivity of results pertaining to: (i) dynamics in health risk reduction following pollution reduction and (ii) the discount rate will be analysed.

Walton (2010)’s thorough review of empirical evidence from cohort, intervention and smoking cessation studies stressed on the level of uncertainty about patterns of health risk reduction following exposure decrement. The US EPA considered Rösli et al. (2005)’s exponential decay model as an alternative to the 20-year distributed lag described in section 4.5.1. However, results were found to be very sensitive to the choice of time constant for the model and it

is not clear which source of evidence should inform this parameter (U.S. EPA - Science Advisory Board and Health Effects Subcommittee, 2009). Exponential decay will therefore not be considered in the present sensitivity analysis of time lag. Instead, the two following scenarios, summarised in Table 4.4, will be evaluated. Scenario “No CL” assumes the absence of a cessation lag, and thus represents an upper bound to the possible health benefits associated with the intervention. (ii) As the smoking cessation literature suggests that lung cancer risk may decrease more slowly than cardiovascular death risk (Walton, 2010; Rabl, 2003), scenario “Mixed CL” assumes that the decrease in lung cancer risk is progressive over 40 years, while the change in risks of other health effects is assumed to follow the US EPA’s 20 year distributed time lag.

For analysis of investments with pay-offs accruing over time-horizons above 50 years, the UK treasury suggests to use staged discount rates (Lowe, 2008). The two staged discounting structures proposed by the UK treasury, which are described in Table 4.4, will be used in sensitivity analysis.

Scenario	Cessation lag (CL)	Discounting
Base case	20-year distributed lag ^(a)	3.5% p.a.
Mixed CL	Lung cancer: progressive reduction over 40 years ^(b) Other health impacts: 20-year distributed lag ^(a)	3.5% p.a.
No CL	Immediate effect	3.5% p.a.
Staged discounting 1	20-year distributed lag ^(a)	Year 1 to 30: 3.5% p.a. Year 31 to 60: 3% p.a.
Staged discounting 2 ^(c)	20-year distributed lag ^(a)	Year 1 to 30: 3% p.a. Year 31 to 60: 2.57% p.a.

Table 4.4: Scenarios of sensitivity analysis against base case.

^(a) 30% of risk reduction in year 1, an additional 12.5% every year between year 2 to year 5 and the final 20% being phased in gradually over year 6 to year 20.

^(b) i.e. a cumulative decrease in risk at a rate of 2.5% every year.

^(c) Excludes the element of pure social time preference.

4.7 Conclusion

Whilst the understanding of air pollution impacts on length and quality of life is expected to be of particular interest to policy-makers, so far all past attempts at measuring the QALY gain from air pollution reduction have been simplistic and inaccurate. In this chapter, it was argued that the Markov-based simultaneous approach presented in Chapter 3 would enable, for the first time, to fully capture air pollution's joint impact on quality and length of life by encompassing air pollution's influence on population individuals' baseline

quality of life, life expectancy and level of susceptibility to adverse effects. A Markov model structured around three disease pathways, for which there is robust epidemiological evidence of association with long-term exposure to fine particulate pollution, namely chronic obstructive pulmonary disease, coronary heart disease and lung cancer, was therefore developed.

This chapter focused on the core steps to model construction and parameterisation and underlined two distinct data gaps for parameterisation, which will be addressed in the following two chapters. Chapter 5 develops a framework to estimate the annual probability of being diagnosed at a given stage of COPD and applies it to the general population of England. Chapter 6 performs a systematic review and two meta-analyses of the association between long-term exposure to particulate air pollution and respectively all-cause mortality and lung cancer. Modelling results will be presented in Chapter 7. The limitations of the presently developed model will be discussed in Chapter 8.

Chapter 5

Estimation of COPD incidence in England by severity stages

5.1 Introduction

In order to estimate the QALY gain and health care resource impact of air pollution control in the UK, Chapter 4 developed a Markov model structured around three disease pathways: CHD, lung cancer and COPD. The latter is a slowly progressive disease of airflow obstruction.

The transition probabilities that parameterise the model are informed by mortality and disease incidence (i.e. diagnostic) statistics for England and Wales. In the case of COPD however, available incidence data suffers from bias as the disease is largely underdiagnosed, especially in its milder stages. In England, up to 80% of adults above 30 affected by spirometry-defined COPD were found to report no respiratory diagnosis (Shahab et al., 2006). Consequently, using primary care data on COPD incidence to parameterise the model developed in Chapter 4, would seriously underestimate the total pool of individuals who would benefit from a reduction in the risk of developing COPD following air quality improvement.

An estimation of the underlying, i.e. “true”, prevalence of COPD by severity stage in England was, however, carried out by the UK Department of Health

(2010). The present objective is therefore to develop a coherent probabilistic framework to estimate the probability of COPD diagnosis in the English population at different severity stages of the disease, by exploiting existing estimates of underlying prevalence and linkages between disease prevalence, incidence, survival and progression.

The chapter is structured alongside the following sections. In section 2, I expand upon the key characteristics of COPD and its implications for cost-effectiveness analysis of preventive interventions such as air pollution control. In section 3, I outline the linkages between prevalence and incidence, I describe the approach used by the UK Department of Health to estimate the underlying prevalence of COPD in England and I further justify the structure of the COPD disease pathway of the model built in Chapter 4. In section 4, I first describe an incidence estimation model proposed by Podgor & Leske (1986) for a single-stage chronic disease and, in a second step, I extend this model to a multi-stage setting by allowing for disease severity progression and survival stratified by severity level. In section 6, I apply the developed framework to estimate the probabilities of COPD diagnosis in England by severity stage. In sections 6 and 7, I present and discuss the results.

5.2 COPD: Key characteristics and implications for cost-effectiveness analysis of preventive interventions

5.2.1 Key characteristics

Disease description and classification

COPD is a lung disease of progressive airflow obstruction or limitation, which is not fully reversible and typically worsen slowly over time (GOLD, 2014). There is clear evidence that health care cost (Jansson et al., 2013), quality of life decrements (Pickard et al., 2008) and mortality risk (Mannino et al., 2006) in COPD patients greatly depend on their levels of airflow obstruction.

Since anatomical and clinical symptoms may vary between patients, diagnosis of COPD is internationally defined by airflow obstruction. The latter is measured by a set of spirometric criteria, namely forced expiratory flow in 1 second (FEV_1) and forced vital capacity (FVC), i.e forced emptying capacity of the lungs. The American Thoracic Society, the European Respiratory Society, the National Institute for health and Care Excellence in England and the Global Initiative for Obstructive Lung Disease (GOLD) define COPD as a reduced FEV_1/FVC ratio strictly lower than 70% (Celli et al., 2004; NICE, 2010; GOLD, 2014).

Sub-classification of the disease is based on a third measure known as $FEV_1\%$, which is the ratio of measured FEV_1 against predicted FEV_1 , based on age, height and gender. In conjunction to a FEV_1/FVC ratio lower than 70%, a $FEV_1\%$ greater than 80% defines “mild” COPD¹, a $FEV_1\%$ between 50% and 79% defines “moderate” COPD, a $FEV_1\%$ between 30% and 49% defines “severe” COPD and a $FEV_1\%$ lower than 30% defines “very severe” COPD. “Mild”, “moderate”, “severe” and “very severe” stages are also referred to as GOLD1, GOLD2, GOLD3 and GOLD4.

Finally, in order to solely account for persistent airflow limitation, there is global agreement that all spirometric measures should always be taken post administration of a bronchodilator, i.e. a drug that help alleviate symptoms of airflow limitation (Celli et al., 2004; NICE, 2010; GOLD, 2014).

¹In contrast to the American Thoracic Society, the European Respiratory Society and GOLD, NICE recommends that symptoms should also be present to confirm diagnosis of the mild stage of the disease (NICE, 2010).

Substantial underdiagnosis

In England, based on cross-sectional data on population respiratory health obtained from the Health Survey for England (HSE) in 2001, Shahab et al. (2006) found that 80% of individuals aged 30 and over affected by spirometry-defined COPD reported no respiratory diagnosis.

As the analysis of HSE respiratory data collected in 2010 used a different methodology to compute COPD prevalence statistics than in 2001, it is not possible to evaluate with precision whether COPD underdiagnosis has decreased over time in England. Indeed, instead of using the fixed ratio of $FEV_1/FVC < 70\%$, in HSE 2010, COPD was defined based on the lower limit of normal (LLN) values of the FEV_1/FVC ratio, with the bottom 5% classified as abnormal. Whilst each criteria has its pro and cons, LLN values are highly dependant on reference equations to compare the distribution of FEV_1/FVC values and no scientific evidence to date supports LLN over the fixed ratio of $FEV_1/FVC < 70\%$ as best criteria to define COPD (GOLD, 2014).

Nevertheless, analysis of HSE results for the year 2010 greatly confirmed the magnitude of disease underdiagnosis, whereby less than a third (28% of males and 27% of females) of individuals with probable airflow limitation reported a doctor-diagnosis of COPD (Aresu et al., 2011).

Late diagnosis

While COPD is underdiagnosed as a whole, underdiagnosis is less pronounced for individuals in the severe and very severe stages of the disease (GOLD, 2014). In England, Shahab et al. (2006) reported that 50% of individuals found to be in the severe and very severe stages of the disease² were not diagnosed, whereas across all severity stages underdiagnosis reached 80%. Indeed, as symptoms worsen alongside disease progression, the disease is more

²as indicated by their spirometric results collected as part of HSE 2001.

likely to be detected at an advanced stage. Based on HSE (2001) data, the UK Department of Health (2010) estimated that in England, 95% of the total underlying (i.e. “true”) cases of GOLD stage 1 were underdiagnosed, as opposed to 79% for stage 2, 60% for stage 3 and only 7% for stage 4.

5.2.2 Implications for cost-effectiveness analysis

The key characteristics of the COPD disease have three major implications for the cost-effectiveness analysis of preventive interventions such as air pollution control.

First, as health care cost, quality of life decrements and mortality risk greatly depend on the level of airflow obstruction, in order to evaluate most accurately the impact of an intervention that contribute to alleviate the health burden of COPD, one should account for the various levels of disease severity and the speed of disease progression.

Second, since the probabilities to transition between health states are typically informed by diagnostic statistics (also referred to as incidence) underdiagnosis will threaten the accuracy of modelling results. More precisely, disease underdiagnosis will underestimate the population’s baseline risk of developing COPD, and thus the total population health gain associated with an intervention that reduces the risk of developing COPD or mitigates its consequences. Total population health gain is typically irrelevant when assessing whether a health care technology is cost-effective or not, since the focus of interest is on the ratio of the incremental cost and health benefit per patient. By contrast, it is of particular importance when evaluating the cost-effectiveness of an intervention characterised by a large fixed investment cost, as is typically the case of interventions of air pollution reduction. For these interventions, disease underdiagnosis will underestimate total population health gain and thus, the probability of the intervention to be cost-effective.

Third, if the underlying risk of developing the first stage of COPD is un-

known, despite COPD being a progressive disease, one should account for late diagnosis in order to avoid underestimating the total population of subjects with COPD. Late diagnosis is accounted for by allowing for transitions from the “healthy” state to any stages of the disease. Such an approach was followed by Hoogendoorn et al. (2005, 2011) when constructing a Markov model of COPD applied to the Dutch population, although the rationale for doing so was not stated.

5.3 Addressing challenges associated with the modelling of COPD

5.3.1 Linking incidence with prevalence

Relationship between incidence, prevalence and survival

Disease prevalence represents the proportion of the population with a disease at a given point in time, whereas incidence represents the risk of developing the disease during a given time period. In a group of individuals in steady state, prevalence and incidence are linked insofar as prevalence is the product of incidence and disease duration (Gordis, 2004).

In the case where a disease is treatable but not fully curable, as is the case of COPD, the only parameter that influences disease duration is disease survival, i.e. the probability of death conditional on having the disease. It follows that, under appropriate assumptions, prevalence statistics can be used in combination with survival data to estimate disease incidence, i.e. the probability of being diagnosed with the disease.

Estimates of underlying COPD prevalence in England

The UK Department of Health (2010) computed estimates of the underlying (i.e. true) numbers of COPD cases in the population, by GOLD severity stage and 10-year age-groups, for the year 2009 using population projections for year 2009. Estimates were based on lung function measurements gathered from HSE (2001), which at the time³, provided the most up-to date spirometry results on the respiratory health of the English population.

HSE (2001) methodology was described in Prior et al. (2003). Briefly, in 2001, 74% (n = 9,373) of households identified via multi-stage probability sampling agreed to take part to the health survey. From these cooperating households, 15,647 adults (89% of total adults) were interviewed and 12,404 adults (71% of total adults) saw a nurse who took lung function measures from 11,611 participants, where the most technically satisfactory blow out of five attempts was selected

As spirometry measurements from HSE (2001) were performed before bronchodilator use, in line with current guidelines for COPD diagnosis (see section 5.2.1) the UK Department of Health (2010) adjusted the data so that only the prevalence of persistent airflow limitation would be captured. This adjustment for bronchodilator use, known as “post-bronchodilator adjustment”, was performed using data provided by Perez-Padilla et al. (2007). Based on a cluster sampling of adults representative of five Latin American cities, the authors reported that using spirometric measurements after bronchodilator use, reduced the overall prevalence of airflow obstruction by 35%. Post-bronchodilator adjustment of raw prevalence estimates for England was based on the assumption that the bronchodilator effect was independent of age and impacted only the raw prevalence of mild and moderate stages of the disease.

³Whilst HSE cross-sectional studies are carried out on annual basis, survey focus on specific health issues such as lack of physical activity, cardiovascular disease or respiratory conditions varies from year to year.

5.3.2 Encompassing COPD characteristics into a Markov model structure

COPD characteristics were captured in the structure of the COPD disease pathway of the model developed in Chapter 4 in the following fashion:

- (1) COPD was modelled via the GOLD states - numbered 1 to 4 - of disease severity, which are equivalently referred to as mild, moderate, severe and very severe states.
- (2) Individuals were allowed to enter the COPD disease pathway at several stages of disease severity in order to allow for “late diagnosis”, as recommended in sections 5.2.2 and 5.3.1.
- (3) Since COPD is a chronic and irreversible disease, the probability to fully recover from it, or to move to a less severe state, was considered to be null. Additionally since COPD is a slowly progressing disease it was assumed that, once individuals entered the COPD disease pathway, they could not jump a severity stage of the disease, e.g. move directly from stage 1 to stage 3. These two assumptions are in line with existing Markov models of natural history of COPD (Hoogendoorn et al., 2005, 2011; Menn et al., 2012; Najafzadeh et al., 2012).

The resulting structure of the COPD disease pathway of the model developed in Chapter 4 is represented in Figure 5.1. Its parameterisation requires three sets of probabilities, pertaining to respectively:

- (1) Mortality conditional on health status, i.e. transitions from each four GOLD states to the “dead” state noted $P_{1,D}, P_{2,D}, P_{3,D}, P_{4,D}$ and from the “healthy” state to the “dead” state noted $P_{H,D}$;
- (2) Disease progression, i.e. transitions between severity states noted $P_{1,2}, P_{2,3}, P_{3,4}$;
- (3) Disease diagnosis/incidence, i.e. transition from the “healthy” state to each GOLD state of severity noted $P_{H,1}, P_{H,2}, P_{H,3}, P_{H,4}$.

The probabilities of disease diagnosis: $P_{H,i}, i = 1, \dots, 4$ are the focus of the present study and are underlined in light grey in Figure 5.1.

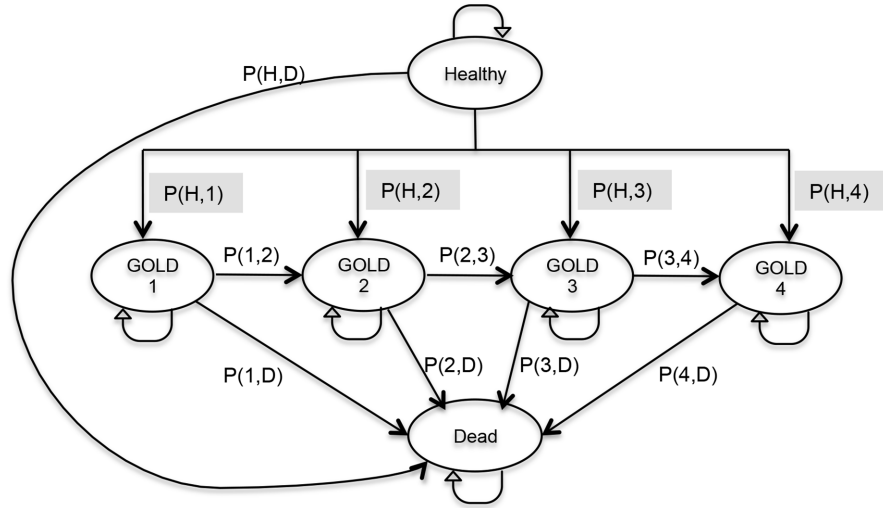


Figure 5.1: Markov model structure of COPD pathway and required parameters.

5.4 Incidence estimation in multi-stage chronic diseases

5.4.1 Podgor and Leske (1986)'s framework for a single-stage chronic disease

As mentioned in section 5.3.1, in a population in steady state, there is an intuitive relationship between incidence and prevalence. Additionally, assuming the disease is stable over time, one can treat the age-dimension of prevalence as a time dimension, whereby static age-specific prevalence represents the individual's probability of having the disease once reaching a certain age.

Relying on the two assumptions of: (1) stable population, i.e. population with stable age composition and (2) stable epidemic, Podgor & Leske (1986) outlined the relationship between incidence, prevalence and mortality for an irreversible one-stage chronic disease characterised by differential mortality. This relationship was modelled via a 3-state closed unidirectional system, whereby individuals of a population of size N were either healthy (H),

infected by the irreversible disease (I) or dead (D).

The authors defined the number of “infected” people of age $a + t$ in the population as the sum of: (i) the number of individuals who were healthy at age a times the joint-probability P_{HI} that they became infected during the t -year period and survived and (ii) the number of individuals who were already infected at age a times the probability P_{II} that they survived during the t -year period, given that they were infected. Similarly, the number of “healthy” people of age $a + t$ in the population was defined as the number of people who were healthy at age a times the joint probability P_{HH} that they did not become infected nor died during the t -year period. These two relationships are expressed by equations 5.1 and 5.2:

$$N_{a+t}\Pi_{a+t} = N_a(1 - \Pi_a)P_{HI} + N_a\Pi_aP_{II} \quad (5.1)$$

$$N_{a+t}(1 - \Pi_{a+t}) = N_a(1 - \Pi_a)P_{HH} \quad (5.2)$$

Where N_{a+t} and N_a represent the total number of alive individuals of age $a + t$ and a at any point in time in the system and Π_{a+t} and Π_a represent the static prevalence of the disease among population individuals of age $a + t$ and a .

Combining equations 5.1 and 5.2 eliminates the population parameters and provides a single equation with one unknown P_{HI} (5.3).

$$(1 - \Pi_a)\Pi_{a+t}\frac{P_{HH}}{(1 - \Pi_{a+t})} = \Pi_aP_{II} + (1 - \Pi_a)P_{HI} \quad (5.3)$$

P_{HI} represents the joint probability of developing the disease and surviving during the t -year period given that one is infected, whereas the parameter of interest is the probability of becoming infected among the total at-risk population. To derive this parameter, Podgor & Leske (1986) expressed the joint-probabilities P_{HH} , P_{HI} and the conditional probability P_{II} as a function of the rates of mortality among respectively those infected and those healthy and of the rate of disease incidence, assuming that rates followed independent exponential distributions. Solving for the rate of disease incidence however, required a rather sophisticated and computationally-intensive method (Newton-Raphson method).

5.4.2 Extension of Podgor and Leske (1986)'s framework to a k -stage chronic disease

For COPD, the modelling of the relationship between prevalence, incidence and mortality also need to account for disease progression and the impact of disease severity on survival. Podgor & Leske (1986)'s model was therefore extended to a k -stage chronic disease.

To reduce the computational burden associated with probabilities estimation, the extension of Podgor & Leske (1986)'s model was carried out in a discrete time setting. Importantly the extension of the model is also underpinned by the two assumptions of stable population and stable epidemic.

The modelling of the relationship between incidence, prevalence, survival and disease progression was based on the structural assumptions described in section 5.3.2. In particular, whilst individuals were allowed to enter the disease pathway in any state to reflect late diagnosis, once diagnosed with the disease it was assumed that, during each t -year period they could either: (i) stay in the disease state they were in or (ii) progress to the next severe state or (iii) die. The t -year probabilities to transit between severity states i are therefore of the form $P_{i,i+1}$.

To extend the model in a discrete-time setting, P_{HI} , P_{HH} and P_{II} were expressed in terms of t -year transition probabilities, where $P_{X,Y}$ denotes the probability of transiting to state Y during a t -year period conditional on being in state X at age a . It follows that for $i = 1, \dots, k$ representing disease stages:

$$P_{HH} = (1 - P_{H,i})(1 - P_{H,D})$$

$$P_{HI} = P_{H,i}(1 - P_{i,D})$$

$$P_{II} = (1 - P_{i,D})$$

In a stable population with stable disease, the total number of people aged $a + t$ who are in stage i of the disease at any point in time is the sum of: (i) individuals who were healthy at age a and got diagnosed with COPD in stage i during the t -year period and survived, (ii) individuals who were in stage i at age a and did not move to the next severe stage nor died during the t -year

period and (iii) individuals who were in stage $i - 1$ at age a and moved to stage i and survived during the t -year period. This relationship is expressed in equation 5.4, using notations for population size and disease prevalence introduced in section 5.4.1.

$$\begin{aligned}
N_{a+t}\Pi_{i,a+t} &= N_a\left(1 - \sum_{i=1}^k \Pi_{i,a}\right)P_{H,i}(1 - P_{i,D}) \\
&\quad + N_a\Pi_{i,a}(1 - P_{i,i+1})(1 - P_{i,D}) \\
&\quad + N_a\Pi_{i-1,a}P_{i-1,i}(1 - P_{i,D})
\end{aligned} \tag{5.4}$$

For $i=1$, equation 5.4 simplifies to:

$$N_{a+t}\Pi_{i,a+t} = N_a\left(1 - \sum_{i=1}^k \Pi_{i,a}\right)P_{H,i}(1 - P_{i,D}) + N_a\Pi_{i,a}(1 - P_{i,i+1})(1 - P_{i,D})$$

For $i=k$, equation 5.4 equals to:

$$N_{a+t}\Pi_{i,a+t} = N_a\left(1 - \sum_{i=1}^k \Pi_{i,a}\right)P_{H,i}(1 - P_{i,D}) + N_a\Pi_{i,a}(1 - P_{i,D}) + N_a\Pi_{i-1,a}P_{i-1,i}(1 - P_{i,D})$$

Similarly, the number of people aged $a + t$ who are healthy at any point in time is simply the sum of individuals who were healthy at age a and did not develop the disease nor died during the t -year period.

$$N_{a+t}(1 - \Pi_{i,a+t}) = N_a\left(1 - \sum_{i=1}^k \Pi_{i,a}\right)\left(1 - \sum_{i=1}^k P_{H,i}\right)(1 - P_{H,D}) \tag{5.5}$$

Combining equations 5.4 and 5.5 to eliminate the population size parameters N_{a+t} and N_a would however, generate an equation with two unknowns: $P_{H,i}$ and $\sum_{i=1}^k P_{H,i}$. To address this issue, the total size of the population of age $a + t$ was expressed as a function of: (i) the total size of the population of age a and (ii) the probabilities of survival for individuals of age a conditional

on their health status :

$$N_{a+t} = N_a \left(1 - \sum_{i=1}^k \Pi_{i,a}\right) (1 - P_{H,D}) + N_a \sum_{i=1}^k \Pi_{i,a} (1 - P_{i,D}) \quad (5.6)$$

Substituting the expression for N_{a+t} into equation 5.5 enabled to express the t-year probabilities for individuals of age a to transit within the closed-system from the state “healthy” to the each i disease state (i.e. $P_{H,i, i=1,\dots,k}$) as a function of:

- (i) t-year death probabilities conditional on health status: $P_{i,D, i=1,\dots,k}$, $P_{H,D}$
- (ii) t-year probabilities of transiting to the next more severe state: $P_{i,i+1, i=1,\dots,k-1}$
- (iii) disease prevalence by severity stage for t-year age-groups: $\Pi_{i,a}$, $\Pi_{i,a+t}$

For $i=2,\dots,k-1$:

$$P_{H,i} = \frac{\Pi_{i,a+t} \left[\left(1 - \sum_{i=1}^k \Pi_{i,a}\right) (1 - P_{H,D}) + \sum_{i=1}^k \Pi_{i,a} (1 - P_{i,D}) \right] - \Pi_{i,a} (1 - P_{i,D}) (1 - P_{i,i+1})}{\left(1 - \sum_{i=1}^k \Pi_{i,a}\right) (1 - P_{i,D})} - \frac{\Pi_{i-1,a} (1 - P_{i,D}) (1 - P_{i-1,i})}{\left(1 - \sum_{i=1}^k \Pi_{i,a}\right) (1 - P_{i,D})} \quad (5.7)$$

For $i=1$:

$$P_{H,i} = \frac{\Pi_{i,a+t} \left[\left(1 - \sum_{i=1}^k \Pi_{i,a}\right) (1 - P_{H,D}) + \sum_{i=1}^k \Pi_{i,a} (1 - P_{i,D}) \right] - \Pi_{i,a} (1 - P_{i,D}) (1 - P_{i,i+1})}{\left(1 - \sum_{i=1}^k \Pi_{i,a}\right) (1 - P_{i,D})} \quad (5.8)$$

For $i=k$:

$$P_{H,i} = \frac{\Pi_{i,a+t} \left[\left(1 - \sum_{i=1}^k \Pi_{i,a}\right) (1 - P_{H,D}) + \sum_{i=1}^k \Pi_{i,a} (1 - P_{i,D}) \right] - \Pi_{i,a} (1 - P_{i,D})}{\left(1 - \sum_{i=1}^k \Pi_{i,a}\right) (1 - P_{i,D})} - \frac{\Pi_{i-1,a} (1 - P_{i,D}) (1 - P_{i-1,i})}{\left(1 - \sum_{i=1}^k \Pi_{i,a}\right) (1 - P_{i,D})} \quad (5.9)$$

5.5 Estimating COPD diagnosis probabilities by severity stage in England

5.5.1 General approach

The framework was applied to the case of COPD in England, in order to estimate the age-specific t -year probabilities of being diagnosed at each stage i of the disease, where $i = \text{GOLD 1}, \dots, \text{GOLD 4}$.

In line with the cycle length chosen for the model developed in Chapter 4, the t -year period was set to a year. Since the framework considers age as a time dimension (see section 5.4.2), the period for which diagnostic probabilities were computed needed to match with the size of the age-groups for which prevalence data was expressed. Implementation of the framework therefore required three input parameters:

- (i) Annual probabilities of death conditional on health status;
- (ii) Annual probabilities to progress to the next more severe disease stage;
- (iii) COPD prevalence by severity stage stratified by one-year age-groups.

5.5.2 Input parameter 1: mortality data

The probability of dying if “healthy”, i.e. if without COPD, ($P_{H,D}$) was computed using life table analysis.

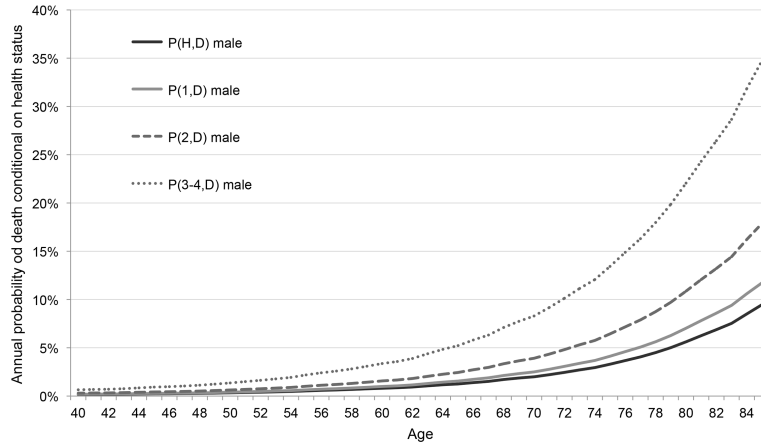
Information on the excess mortality risk in COPD patients was provided by Mannino et al. (2006) based on a cohort study of 15,440 American subjects followed up for 11 years. Hazard ratios, adjusted for age, sex, smoking status, body mass index, pack-years of smoking, race and educational level, were stratified by GOLD severity stage but also, by the presence of respiratory symptoms. Mortality hazard ratios, stratified by GOLD severity stage only,

were derived by combining Mannino et al. (2006)'s ratios with the proportions of COPD patients experiencing symptoms in each severity stage, as reported in the study. The obtained hazard ratios were then applied to age and gender-specific annual death rates in the general population of England (ONS, 2011) and resulting mortality rates stratified by GOLD severity stage were converted into 1-year transition probabilities using equation 5.10:

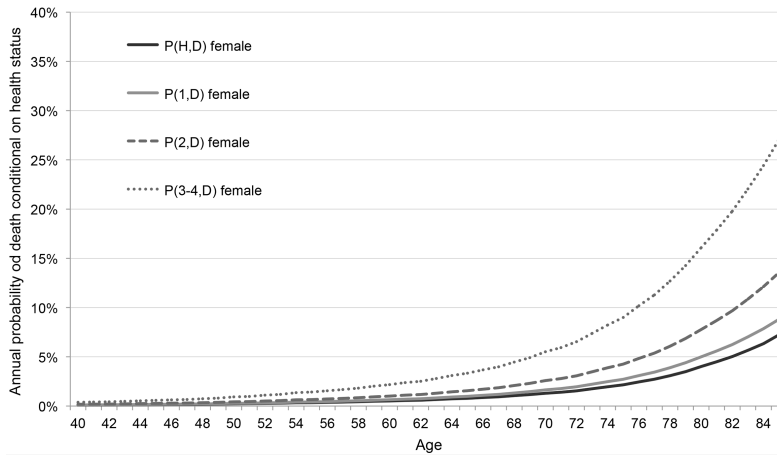
$$P = 1 - \exp^{-rt}, \text{ where } r \text{ is the annual event rate and } t \text{ is a one-year period} \quad (5.10)$$

Since hazard ratios of mortality provided by Mannino et al. (2006) were computed for stages 3 and 4 altogether, age and gender-specific probabilities of death conditional on being in GOLD 3 or in GOLD 4 were assumed to be similar.

Figure 5.2 depicts age and gender-specific probabilities of death conditional on health status. It underlines how the risk of death changes as one moves to a more severe disease stage.



(a) Males death probabilities.



(b) Females death probabilities.

Figure 5.2: Input parameter 1: Annual probabilities of death conditional on health status.

Abbreviations: H= healthy; D= dead. Numbers 1 to 4 stand for each GOLD severity stages of COPD.

5.5.3 Input parameter 2: data on severity progression

The annual probabilities to gradually transit from a severity stage to the next were computed by Atsou et al. (2011) for individuals aged 40 and above, as a function of age and smoking status. To compute these transition probabilities, the authors combined two data sources. The first consisted of rates of

progression from the mild to moderate and moderate to severe stages of COPD by age and smoking status, provided by the analysis of the Framingham Heart Study cohort from Massachusetts, US. In brief, study participants who had spirometry data available (n= 583 at baseline) were categorized according to GOLD stages at the beginning and at the end of 12 years of follow-up, in order to estimate progression rates between severity stages (Lee et al., 2006). The second data source was transition probabilities from moderate to severe and severe to very severe stages by smoking status, but not age nor gender, reported by Hoogendoorn et al. (2005) for the Dutch population.

As there is currently little evidence supporting a difference in biological response to air pollution exposure based on smoking habits, disease progression probabilities were computed for the overall COPD patient population in England. To do so, Atsou et al. (2011)'s age-specific annual transition probabilities stratified by smoking status were combined with the distribution of COPD patients in England by smoking status provided by Shahab et al. (2006). Unlike death probabilities, disease progression probabilities were not stratified by gender.

Figure 5.3 represents the annual probabilities of progressing to a more severe stage. It is worth noting that the speed of transition from stage 1 to 2 is slower than the speed of transition from stage 2 to 3 or from stage 3 to 4 and that all progression probabilities are a positive function of age.

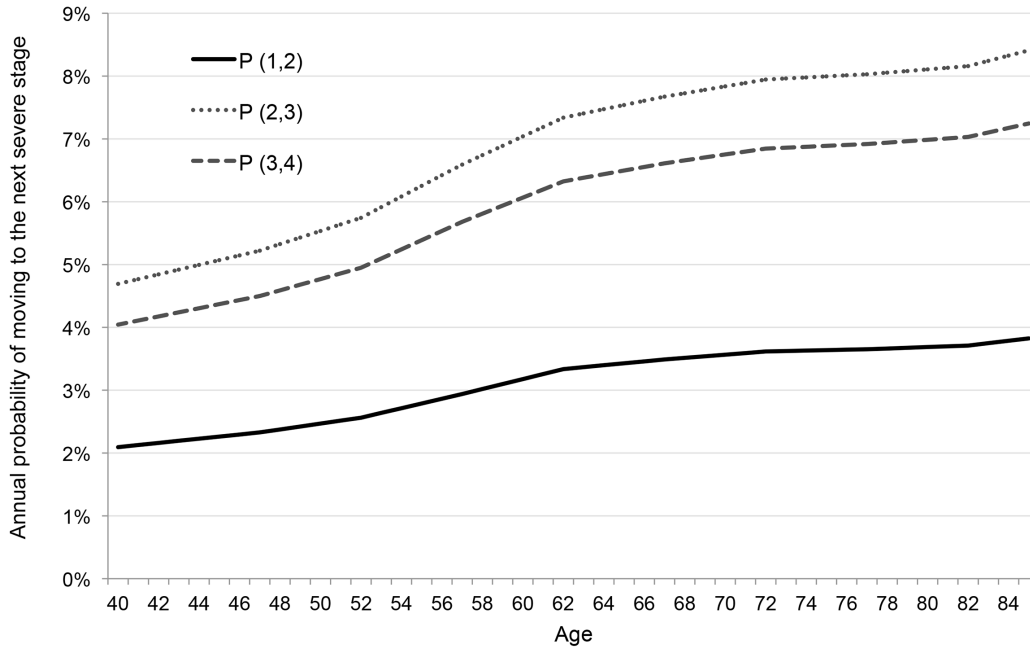


Figure 5.3: Input parameter 2: Annual probabilities to progress to the next severe stage of COPD.

Abbreviations: Numbers 1 to 4 stand for GOLD severity stages.

5.5.4 Input parameter 3: Prevalence data

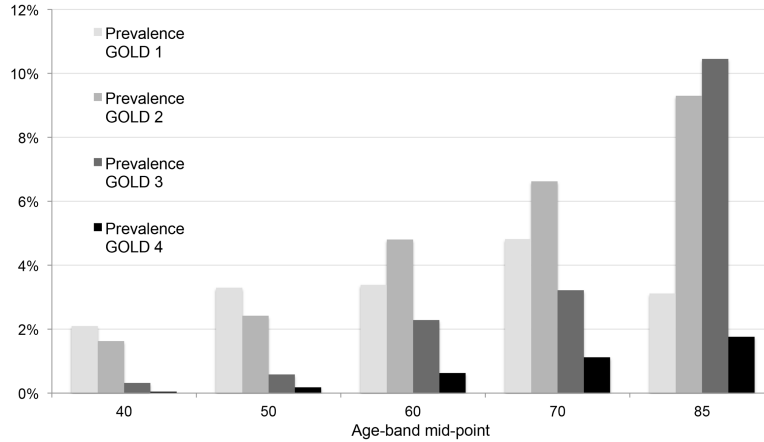
The UK Department of Health (2010) provided estimates of numbers of underlying cases of COPD by GOLD stage for 10 year age-bands: 35-44; 45-54; 55-64; 65-74 and 75+ for the year 2009. The following three manipulations were performed to the data, so that it could be used as input parameter to the probabilistic framework developed.

First, the estimated numbers of underlying COPD cases by GOLD severity stages were compared with population data (2011 census) for England. This enabled us to compute the distribution of the underlying COPD prevalence in England by disease severity for 10 year age-bands. Whilst the UK Department of Health (2010)'s estimates were based on population projections for the year 2009, the use of population census numbers as of year 2011 is not expected to have any major impact on obtained prevalence results.

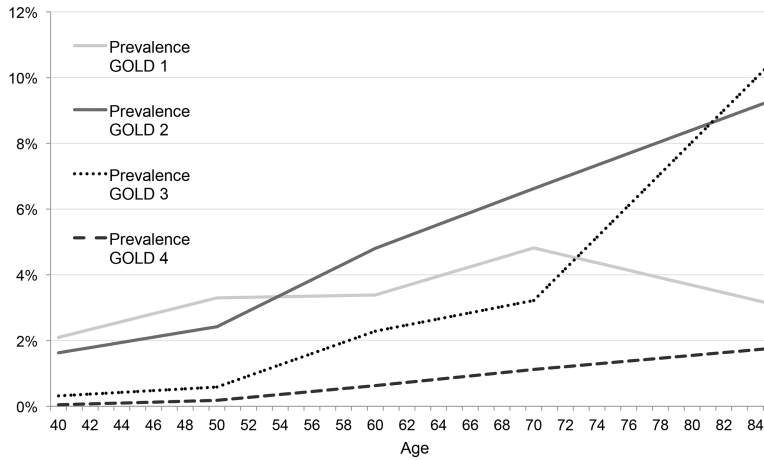
Second, as the assumption that the prevalence was uniform across each 10

year age-groups seemed unrealistic, the estimated prevalence was assumed to represent the point prevalence at age-group mid-point. For example, prevalence for the age-group 35-44 was assumed to represent prevalence at age 40 and so forth. Additionally, in the absence of further information, the last age-group “75+” was defined as age group 75-94 with mid-point 85 years old. The resulting estimates of underlying COPD prevalence by severity stage, at each age-band mid-point, is represented in Figure 5.4a.

Third, disease prevalence was estimated for one-year age-groups by performing a linear extrapolation between each age-band mid-point. Linear extrapolation results are presented in Figure 5.4b.



(a) COPD underlying prevalence by GOLD severity stage at each age group mid-point.



(b) COPD underlying prevalence by one-year age-groups obtained via linear extrapolation.

Figure 5.4: Input parameter 3: underlying prevalence of COPD in the general population in England, by age and GOLD severity stages, computed using numbers of COPD cases estimated by the UK Department of Health (2010).

Figure 5.4a shows that the underlying prevalence of COPD in the population, across all severity stages, is an increasing function of age. About 4% of individuals of the general population aged 40 are expected to be with COPD, as opposed to 11% of those aged 60, 16% of those aged 70 and 25% of those aged 85. The distribution of prevalence by severity stages is also strongly determined by age, reflecting the fact that COPD is a non-reversible progressive

disease. Indeed, up to age 50, individuals with COPD are typically expected to be in stages 1 or 2 whereas, in older individuals, stage 3 becomes increasingly prevalent and represents most of COPD cases in individuals aged 85.

Whilst there are clear age-trends in the estimated underlying prevalence of COPD, its distribution by severity stages and age nevertheless exhibits some variations. This resulted in kinked prevalence curves by one-year age-groups, as shown in Figure 5.4b. Indeed whilst the prevalence of stage 2 increases steadily as a function of age, the prevalence of stage 3 mostly increases between ages 50 and 60 and, to an even greater extent, between ages 70 and 85. Additionally, in contrast to the prevalence of stage 2 and 3, the prevalence of stage 1 is expected to be relatively stable over age-groups, varying from a minimum of 2% of the general population at age 40 to a maximum of 5% at age 70. The decrease in prevalence of stage 1 between the ages of 70 and 85 suggests that: (i) most individuals aged above 70 are expected to have progressed to more severe stages or to have died (ii) those who get diagnosed at that age are expected to be diagnosed in more advanced stages. Finally it is worth underlining that even at a very old age, stage 4 represents only a very small proportion of the total numbers of COPD cases.

5.6 Results

5.6.1 Results interpretation

$P_{H,i}, i=1,\dots,4$, represent the annual probabilities for the general population of England of being diagnosed with a given stage of COPD, as implied by the underlying prevalence of COPD and the relationship between disease incidence, prevalence, progression and survival.

Diagnostic probabilities are also referred to as the annual incidence of COPD. They are expressed in numbers of annual cases of the disease, by

severity stage, per 1,000 individuals of the general population without prior COPD diagnosis. As only the conditional probabilities of death were stratified by gender, results were very similar across gender and the simple average across both genders is presented.

5.6.2 Diagnosis/incidence probabilities by severity stage

GOLD stages 1 and 2 incidence

Figure 5.5 shows the expected annual numbers of cases of GOLD 1 and 2 per one-year age-group. In line with the previously described curves of age-specific prevalence by severity stage (see Figure 5.4b), the annual number of cases of GOLD 2 increases rather steadily among older age-groups whilst the number of cases of GOLD 1 remains within a small range of 1 to 4 cases per 1,000 persons per year. There appears to be a small substitution effect between the incidence of stage 1 and stage 2 around the ages of 50 and 60, which may reflect estimation error induced by the combination of diverse data sources.

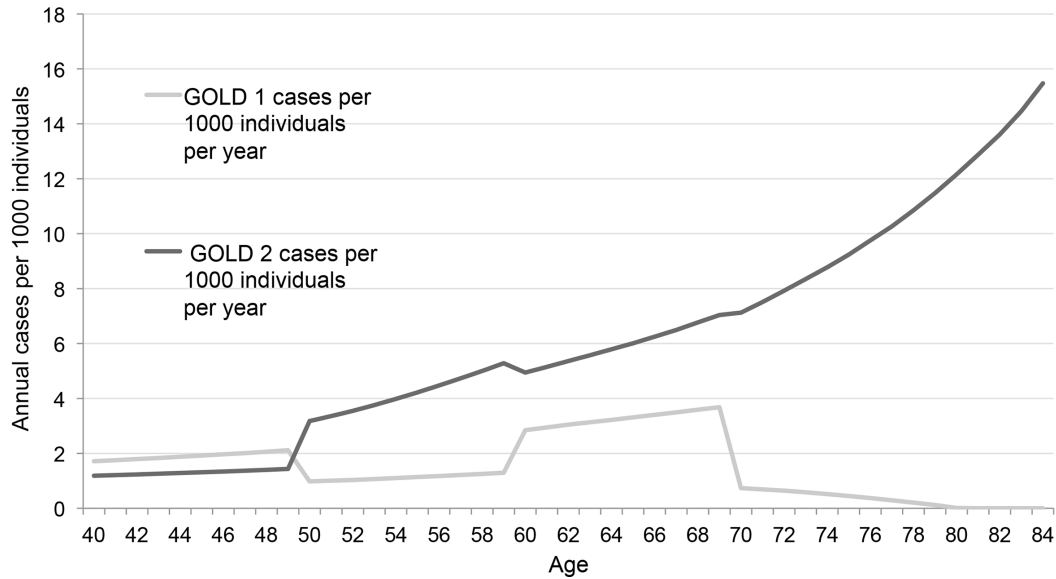


Figure 5.5: Estimated annual cases of COPD GOLD 1 and GOLD 2 per 1,000 individuals of the general population, by 1-year age groups.

GOLD 3 incidence

The 1-year probabilities of being diagnosed in stage 3 without previous diagnostic of the disease were slightly negative (in the order of - 1 case per 10,000 individuals) for individuals aged 40 to 50 and 60 to 70. This is expected to be the result of the combined effect of a small rate of prevalence increase between this age points (see Figure 5.4b) and a relatively fast rate of transition between stages 2 to 3 (see Figure 5.3).

In an attempt to provide stable estimates of age-specific probabilities of being diagnosed in GOLD stage 3, the analysis was re-conducted for 5-year time-intervals, based on estimates of underlying prevalence at age 40, 45, 55, 65, 70, 75, 80, 85. Survival and disease progression probabilities were expressed for a 5-year period by taking the average of 1-year probabilities constituting each 5-year age-intervals (e.g. 40-44; 45-50 and so forth) and transforming the obtained results to 5-year probabilities based on equation 5.11, assuming

a constant rate of incidence over each 5-year intervals.

$$P_t = 1 - (1 - P_1)^t \quad (5.11)$$

5-year $P_{H,3}$, for each age-group, were then transformed back to 1-year probabilities using equation 5.12.

$$P_1 = 1 - (1 - P_t)^{1/t} \quad (5.12)$$

In order to assess whether performing the analysis using 5-year intervals would introduce an important loss of accuracy in the estimation of $P_{H,3}$, a similar approach was applied to compute cumulative 5-year $P_{H,1}$ and $P_{H,2}$ and transform them back to 1-year $P_{H,1}$ and $P_{H,2}$ assuming a constant rate of incidence within 5-year age-groups. 1-year $P_{H,1}$ and $P_{H,2}$ estimated using 5-year intervals were of relatively similar magnitude than 1-year $P_{H,1}$ and $P_{H,2}$ estimated using 1-year intervals, which suggests that the loss of accuracy was limited.

Figure 5.6 represents the estimated annual incidence of GOLD 3 cases for each 5-year age-groups, expressed in annual numbers of GOLD 3 cases per 1,000 individuals. For comparison purposes, Figure 5.6 also shows the annual numbers of GOLD 1 and 2 cases per 1,000 individuals for the same 5-year age-groups. Results could not be calculated for the last age group (80-85) due to the lack of information on the prevalence for the next age group (85-90), which is required for the estimation process (see equation 5.7).

Figure 5.6 shows that the expected annual number of cases of GOLD 3 in the general population shoots up from age 65 onwards. This finding is in accordance with prevalence trends, where between ages 70 and 85, stage 3 replaces stage 2 as the most likely disease stage of individuals with COPD, and with the fact that diagnosis of COPD in old age groups tend to be in more advanced stages of the disease (UK Department of Health, 2010). It is nevertheless worth underlying that, even in the oldest age groups, the estimated incidence of new cases of GOLD 3 in the general population is lower than 2% per year.

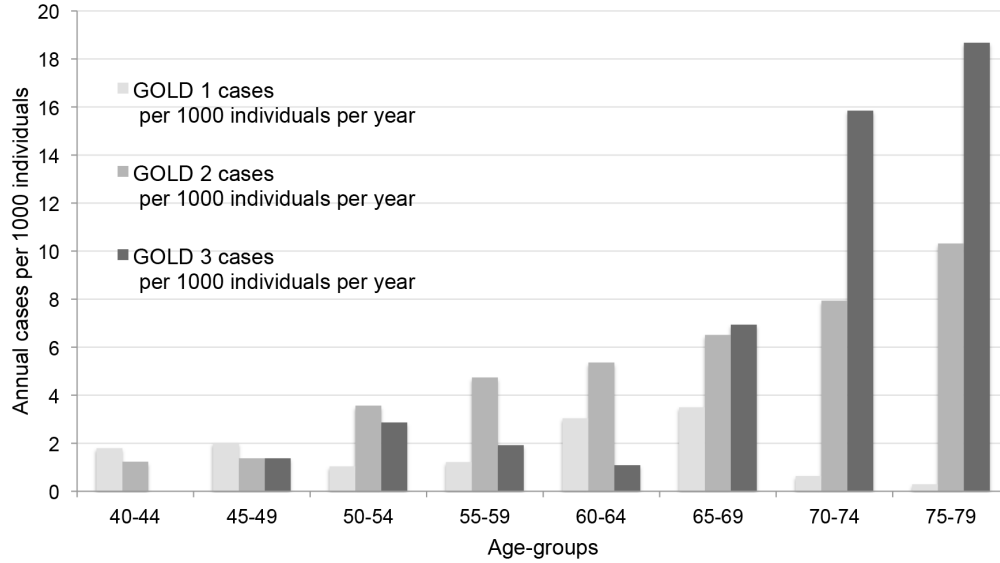


Figure 5.6: Estimated annual cases of GOLD 1, GOLD 2 and GOLD 3 COPD per 1,000 individuals of the general population, by 5-year age groups.

GOLD 4 incidence

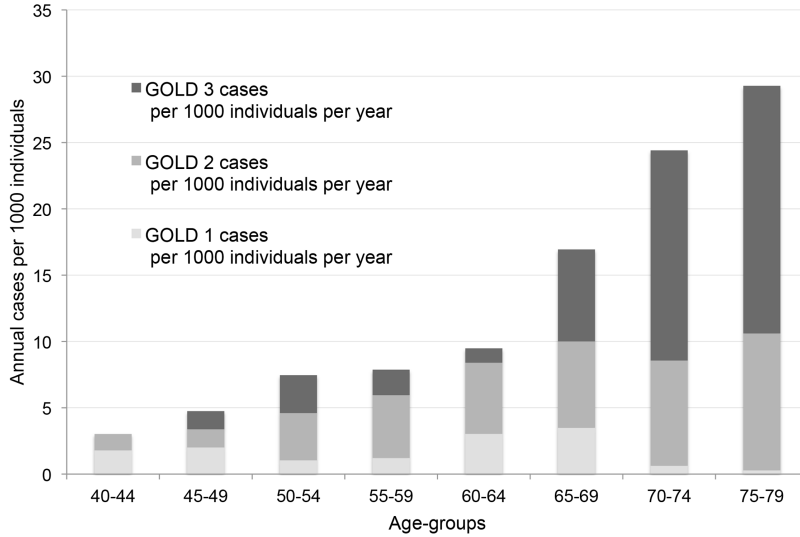
1-year $P_{H,4}$ based on 1-year intervals were quasi all negatives while 1-year $P_{H,4}$ computed using 5-year intervals were very small (in the order of 1 to 7 out of 10,000 individuals) with some age-intervals taking negative values. These results are not surprising given the very low prevalence of GOLD 4 (see Figure 5.4) and the possibility for individuals to progress from previous stages to stage 4 (see Figure 5.3). They support the assumption that the worst severity stage at which an individual of the general population of England can be diagnosed with the disease for the first time is stage 3. Consequently, it is hereafter assumed that in England $P_{H,4} = 0$.

5.6.3 Distribution of annual incidence by severity stage

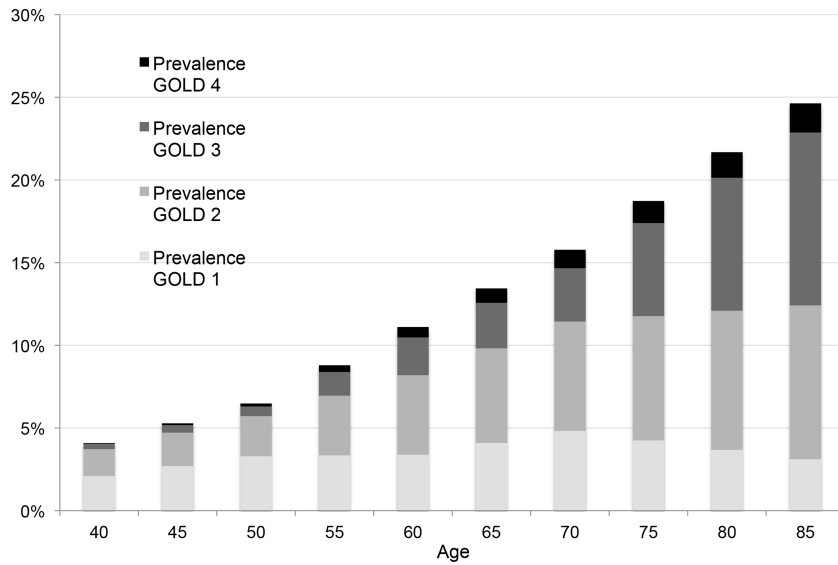
Figure 5.7 compares: (A) the presently estimated distribution of COPD incidence by severity stage, expressed in annual cases per 1,000 individuals of the general population with (B) the distribution by severity stage of the underlying prevalence of COPD estimated by the UK Department of Health (2010), which was used as input parameter to the present framework.

Figure 5.7 provides two main insights. First, like prevalence, the estimated incidence of COPD is expected to be a positive function of age. Indeed, the total annual number of COPD cases across all stages, per 1,000 individuals of the general population in age-group 75-79, is about 10 times as much as the number of cases in age-group 40-44.

Second, the age-specific distribution of incidence by severity stage is in accordance with the age-trends that characterise underlying prevalence estimates outlined in section 5.5.4. For instance, until the age of 49, individuals diagnosed with COPD are most likely to be diagnosed in stage 1. This is line with the fact that up to age 50, most individuals with COPD are in stage 1. Similarly, from age 50 up to age 64, individuals diagnosed with COPD are most likely to be diagnosed in stage 2, while after the age of 70, most new diagnoses are expected to pertain to stage 3. This is in accordance with the fact that up to the age of 70, most individuals with COPD are in stage 2, whereas as from the age of 80, most individuals with COPD are in stage 3. These findings suggest that the estimation method was sound.



(a) Distribution of presently estimated age-specific annual COPD incidence by GOLD severity stage.



(b) Distribution of COPD underlying prevalence by GOLD severity stage at age-group mid-point *Source: UK Department of Health (2010).*

Figure 5.7: Distribution of estimated incidence and underlying prevalence of COPD by GOLD severity stage and age.

5.6.4 Estimated incidence versus GP registrations-based incidence

Figure 5.6.4 compares the presently estimated “true” annual incidence of COPD across all stages, against registered incidence data from the UK British General Practice Research Database (GPRD)⁴. Comparison is performed across all four disease stages since GPRD data is not provided by severity stage.

Figure 5.6.4 shows that the difference in incidence results is very high among young age-groups, with the ratio “estimated incidence” over “GPRD data” being equal to 7 in age group 40-44. This ratio then decreases with age such that, for individuals aged 65 and over, presently estimated incidence is about 3 times greater than recorded incidence in general practices.

Whilst these results appear credible given the extent to which COPD is currently underdiagnosed (see section 5.2.1), their validity is difficult to assess due to the lack of information on the magnitude of disease underdiagnosis by age. Nevertheless, in line with the fact that stages 1 and 2 are the most underdiagnosed stages of the disease and that these stages are mostly prevalent among young individuals (UK Department of Health, 2010), it appears coherent that the discrepancy between the presently estimated incidence and GP registrations is the greatest for the youngest age-groups.

⁴UK GPRD data (2007) available from EU-funded open-access model DYNAMO HIA (<http://www.dynamo-hia.eu/>)

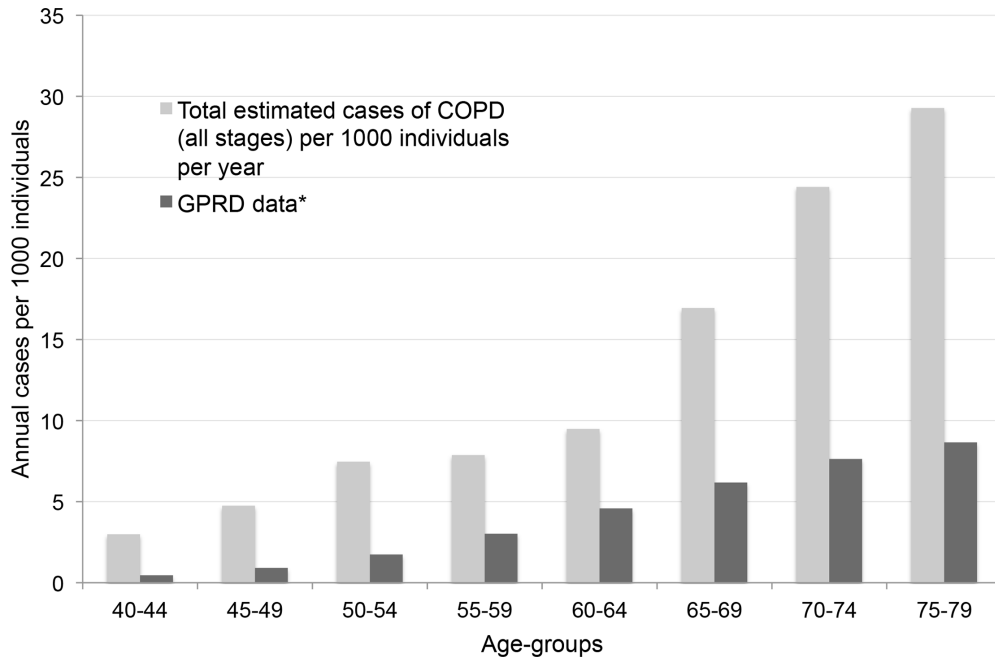


Figure 5.8: Estimated annual cases of COPD across all severity stages versus primary care records ⁽¹⁾.

⁽¹⁾ GPRD data for year 2007, obtained from EU-funded open-access model DYNAMO HIA.

5.7 Conclusions

5.7.1 Limitations

Model validation

Whilst diagnostic/incidence estimates are in line with expectations, ideally the developed framework should be validated, for instance by estimating the incidence implied by GP-recorded prevalence data and comparing the obtained result with GP recorded- incidence. Unfortunately this was not feasible since available primary care data on COPD registrations is not provided by severity stages.

The obtained distribution of age-specific annual incidence of COPD by severity stages could not be compared with estimated incidence data for other countries. Indeed, although Hoogendoorn et al. (2005, 2011) allowed population individuals to transit from the state “healthy” to each severity stages (as opposed to a single allowed transition from the state “healthy” to stage 1, as commonly assumed in other models of natural history of COPD), they assumed that the severity distributions of prevalence and incidence were the same across all age-groups. As both underlying prevalence estimates from the UK Department of Health (2010) and the presently estimated incidence are strongly determined by age, a comparison with Hoogendoorn et al. (2005, 2011) data hardly appears appropriate.

Model inputs and assumptions

Firstly, the reliability of the results crucially depends on the validity of input data and in particular, on the estimates of underlying prevalence of COPD in England provided by the UK Department of Health (2010). Additionally, parameters of disease progression and survival were obtained by combining different data sources and in particular results from studies performed on COPD patients in the US. Differences in health care management between the US and UK may however, influence survival and disease progression outcomes. More generally, the use of input parameters derived from various data sources is expected to have introduced some estimation error in output results. Moreover, as both prevalence data and disease transition parameters were not provided with confidence intervals, uncertainty around incidence estimates could not be estimated.

Secondly, the framework is underpinned by the assumption that both the population and the disease epidemic are stable. While the assumption of stable population could be relaxed, but at the expense of greatly complicating the framework, the assumption of a stable epidemic was required in order to estimate incidence based on results from a single cross-sectional survey.

Finally, in order to substantially reduce the computational burden, the

framework was developed and solved in a discrete time setting, although disease development, worsening and death are continuous processes. In order to reduce the approximation error, the length of intervals for which probabilities were estimated was set to a year, which appears a reasonable approximation given that COPD is a slowly progressive disease. However, as explained in section 5.6.2, in order to obtain stable estimates of stage 3 incidence, the latter were computed using a 5-year period. Whilst the annual incidence of GOLD stages 1 and 2 obtained by using respectively 1-year and 5-year time intervals was found to be of similar magnitude, inevitably the greater the time-period, the larger the approximation.

5.7.2 Implication for cost-effectiveness analysis

This chapter provided a coherent framework to estimate the age-specific annual probability of being diagnosed at a given stage of COPD, implied by the underlying population prevalence of COPD estimated at a single point in time and its relationship with disease incidence, progression and survival.

By addressing the issue of underdiagnosis reflected in primary care data (i.e GP-recorded incidence of the disease), the present estimates of COPD incidence will enable to model more accurately the total population health benefits of preventive interventions such as air pollution control that reduce the risk of developing COPD and COPD patients' risk of suffering from further adverse effects.

The framework was applied to the case of England, in order to parameterise the model of air pollution impacts developed in Chapter 4. However, since COPD under-diagnosis is a global issue (GOLD, 2014), the framework could be applied to estimate COPD incidence by severity stages in other countries, provided data on the underlying population prevalence of the disease are available.

It may be argued that only diagnosed cases should be taken into account

when assessing the intervention's impact on health care budget. However, the stages that are the most underdiagnosed, i.e. for which the difference between recorded and presently estimated "underlying" incidence is the greatest, are GOLD stages 1 and 2, which are the least expensive stages of the disease (Jansson et al., 2013). Secondly, estimates of underlying prevalence provided by the UK Department of Health (2010) aimed to capture the prevalence of persistent airflow limitation only, thanks to post-bronchodilator adjustment (see section 5.3.1). It is therefore likely that those undiagnosed individuals may nevertheless seek health care to treat their symptoms. Obviously as the health care cost associated with these undiagnosed individuals cannot be related to the COPD burden, it is not possible to verify this assumption (Hoogendoorn et al., 2005).

Chapter 6

Systematic review and meta-analysis of studies of the association between long-term exposure to $PM_{2.5}$ and all-cause mortality and lung cancer incidence or mortality

6.1 Introduction

Mortality in adults of the general population has been one of the health outcomes most intensively investigated in epidemiological studies of air pollution. A systematic review and meta-analysis of epidemiological studies of the association between long term exposure to particulate air pollution (PM) and mortality, published between 1950 and 2007, was performed by Chen et al. (2008). However, since publication of this piece of work, additional relevant epidemiological studies have been released, including results from the extended

follow-up of two main cohorts in the US: Harvard Six Cities and the American Cancer Study (see Chapter 2).

The objective of this chapter is therefore to help characterise uncertainty in the evidence base used to populate the model developed in Chapter 4, by systematically searching for and synthesising the evidence relevant to the excess risk of mortality associated with chronic air pollution exposure. More specifically, Chen et al. (2008)'s systematic review and meta-analysis will be extended for the period 2008-2014, focusing on studies of the association between long term exposure to particulate air pollution and: (i) all-cause mortality and (ii) lung cancer incidence or mortality, in adults of the general population.

Pooled risk estimates will be used to parameterise several distinct paths of the Markov model of the health impacts of air pollution exposure developed in Chapter 4. First, as mentioned in Chapter 4, individuals with COPD or CHD, who did not meet specific severity and age conditions, were assumed to have the same pre-disposition to dying prematurely due to PM exposure as individuals of the general population. As a result, the pooled risk estimate of all-cause mortality will be used to model the excess risk of mortality in: (i) COPD patients of all ages in GOLD stages 1 and 2 (i.e. RRE_d in Table 4.1 of Chapter 4); (ii) COPD patients in GOLD stages 3 and 4 aged below 65 years old (i.e. RRE_e for age < 65 in Table 4.1); (iii) CHD patients aged below 75 years old (i.e. RRE_f for age < 75 in Table 4.1). It should be underlined that the pooled risk estimate of all-cause mortality will not be applied to "healthy" individuals as the latter are assumed to die from all other causes of death than CHD, COPD or lung cancer.

Second, the pooled risk estimate of the association between PM exposure and lung cancer incidence or mortality will be used to model the excess risk of developing lung cancer in the general population (i.e. RRE_c in Table 1 and Figure 1 of chapter 4). Indeed, owing to the very high case-fatality rate for lung cancer, where the net survival rate at 5-year for adults in England is 9.5% (ONS, 2011), mortality and incidence are comparable indicators of the association between lung cancer and PM exposure and studies informing either incidence or mortality can be considered altogether.

The chapter is structured alongside three sections. Section 2 focuses on the

systematic search. It details the search strategy, the screening results and the key characteristics of the studies identified as relevant. Section 3 consists of the meta-analysis work. It also provides an assessment of potential sources of bias and describes the choice of statistical approaches to pooling effect estimates. Section 4 discusses and concludes.

6.2 Systematic review

6.2.1 Search protocol and strategy

Since Chen et al. (2008)'s search spanned between 1950 and December 2007, the present systematic search was run from January 2008 to present (April 2014). It was performed using PubMed and Embase databases, which were the same databases used by Chen et al. (2008).

The search was framed around four main inclusion criteria, described in Table 6.1.

No particular age restrictions were imposed on the studies subjects, to the exception of the exclusion of studies based on elderly populations, presently defined as studies based on adults aged above 65. Additionally, in the absence of conclusive evidence to date pertaining to gender-related differential susceptibility to air pollution exposure, both gender-specific and all-genders studies were included.

While the model developed in Chapter 4 focused on the health effects of fine particulate pollution, i.e. $PM_{2.5}$, to avoid being over-restrictive, the search initially considered studies pertaining to both fine and coarse particulate pollution. For the same reason, the search protocol did not include any restriction on studies' geographical location. However, since linearity in health impacts

Population	Adults of the general population - no focus on elderly subjects - no occupational studies
Intervention	Change in long-term exposure to particulate air pollution (PM) - Both $PM_{2.5}$ and PM_{10} were initially considered - Measure of change in PM concentrations: $\mu g/m^3$ or quantile ^(a)
Outcomes	- All-cause mortality - Lung cancer mortality - Lung cancer incidence
Study design	Cohort studies
Search period	Jan. 2008 to April 2014

Table 6.1: Inclusion criteria for search protocol.

^(a) For statistical analysis, all study estimates will be converted to represent the change in health risk per $10\mu g/m^3$ increment in PM exposure, which is the unit of measure commonly used in epidemiological studies of air pollution.

in response to a change in PM exposure has been validated only in studies conducted in developed countries (Krewski et al., 2009; Cesaroni et al., 2013; Lepeule et al., 2012), study location will be later considered in the analysis of the pool of studies identified as relevant.

The selection of health outcomes was based on the parameterisation needs of the model developed in Chapter 4 and the choice of study design was determined by the nature of the intervention and the type of health outcomes. Cohort studies, which link mortality data with long-term cumulative exposure variables and subject-specific covariates, were selected as the best suited study design.

Finally, in order to minimise the risk of missing relevant studies, the search strategy was broadened in the following fashion. First, even though studies of traffic pollution typically focus on NO_2 , search terms included “Vehicle emissions” or “Traffic” in case such studies would also consider the effect of particulate matter alongside NO_2 . Second, medical subject headings (MeSH) terms “Cardiovascular Disease/mortality” and “Respiration Disorders Disease/mortality” were added into the Pubmed query, as some studies sometimes also include all-cause mortality as secondary outcome.

The detailed search queries performed for each database are provided in Appendix D. Repeated assessment of the validity of the devised queries was

performed by checking whether they successfully captured publications that were known to be relevant.

6.2.2 Systematic search results

Queries in Embase and PubMed, run for the period January 2008 to April 2014, led to the identification of 275 publications in total (including duplicates): 139 articles in PubMed and 136 articles in Embase.

The study selection process is summarised in Figure 6.1. A first screening based on title and abstract excluded 231 studies which did not meet the inclusion criteria or were duplicates, thus leaving 44 distinct publications for full-review. Among these remaining 44 publications, two were based on the same cohort (the California Teachers study). In such case, in line with Chen et al. (2008), only the paper associated with the longest follow-up and/or the largest population study size was selected. In addition, 8 publications were reviews of literature that did not provide original results. Finally, another 15 publications were excluded based on inclusion criteria. Results were either: (i) not based on PM as air pollutant, (ii) based on occupational exposure or on specific populations subgroups, (iii) not derived from a cohort study (1 case-control study).

Out of the pool of 20 remaining publications identified as relevant following full-review, one (Beelen et al., 2008) was already included in Chen et al. (2008)'s review. As the majority of publications pertained to the health effects of $PM_{2.5}$ exposure, which tend to be associated with greater adverse health effects than PM_{10} , it was decided to focus solely on studies of the impact of $PM_{2.5}$ exposure, in order to ensure a greater homogeneity in effect estimates. This led to the exclusion of five studies on PM_{10} . Ultimately, the search therefore led to the identification of 14 publications.

For the period 1950-2007, Chen et al. (2008) had identified 8 publications on the association between long-term exposure to $PM_{2.5}$ and all-cause or lung-cancer mortality. Three of these studies had been “updated” by studies based on the same cohort but with longer follow-up and/or population size; two did not apply to the general adult population; and one (Naess et al., 2007) provided estimates which could not be reliably converted per $10 \mu g/m^3$ increment of $PM_{2.5}$. The two remaining relevant publications identified by the authors (for

the period 1950 - Dec. 2007) were combined with the 14 ones identified by the present search for the period 2008-2014, providing a final pool of 16 relevant publications.

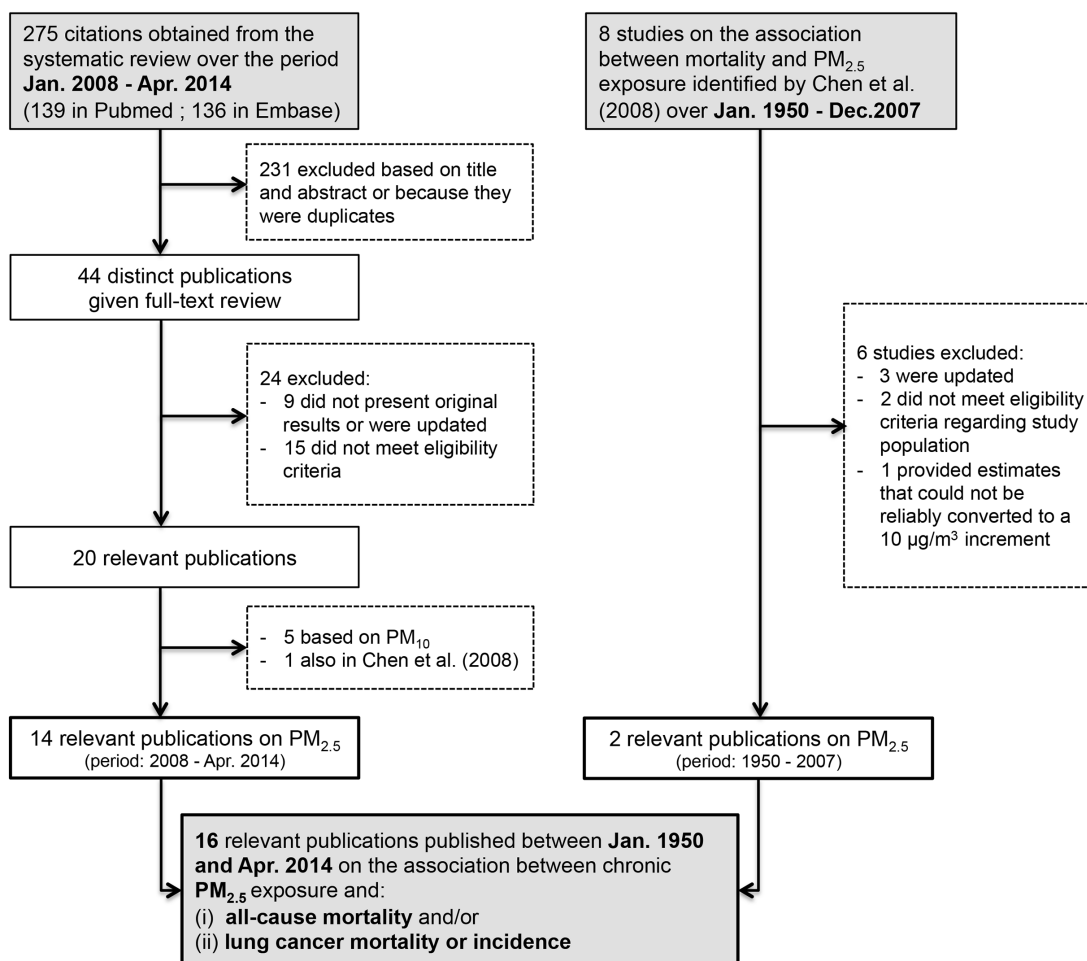


Figure 6.1: Flow diagram of search strategy and selection process.

6.2.3 Identification of the set of relevant risk estimates

One publication (Krewski et al., 2009) provided results for three cohorts: the American Cancer Study (ACS) national (full cohort) and two derived sub-cohorts in Los Angeles and New York, for which air pollution assessment and attribution were different from the national study. Therefore, the 16 publications identified through the search provided results from 18 distinct studies. Many of these studies investigated both all-cause and lung cancer mortality as health endpoints, which gave a total of 15 risk estimates for all-cause mortality and 13 estimates for lung-cancer mortality or incidence.

The ACS national (full cohort) provided results for two time periods of exposure, respectively 1979-1983 and 1999-2000 (same follow-up length). Since the risk estimates computed using the most recent exposure period were based on the largest population size (488,370 study participants, as opposed to 342,521 participants for the older period of exposure), they were selected to represent ACS national study results. However, since results pertaining to lung cancer mortality significantly varied between the two time periods of exposure (see Table 6.2), it was decided to use the risk estimate based on the 1979-1983 exposure period in sensitivity analysis.

6.2.4 Key characteristics of relevant studies

Preliminaries

Table 6.2 provides a summary of the key characteristics of the 18 distinct studies, which results were provided by the 16 publications identified as relevant to the present research question. In this section, studies are referred to by their cohort name, with corresponding author information being provided in Table 6.2.

All studies measured the strength of the pollution-mortality association using hazard ratios, to the exception of Beelen et al. (2014) and Jerrett et al. (2013) which used relative risks. However, since for rare events such as death, rates and probabilities are very similar, combining these two measures of effect in a meta-analysis was considered acceptable. Such an approach was also followed by Chen et al. (2008).

Methodological differences between studies essentially pertained to: study follow-up, spatial and temporal assignment of long-term cumulative exposure to study subjects and adjustment for confounding.

Study follow-up

Whilst most studies were based on population follow-up greater than 10 years, follow-up nevertheless varied greatly between studies. For instance, the latest analyses of the Harvard Six Cities and American Cancer Society cohorts relied on a population follow-up of respectively 36 and 18 years, as opposed to 5 years for the English cohort for instance.

Temporal assignment of cumulative exposure

In most studies, exposure was assessed and assigned to subjects solely for a period of the follow-up, with three studies using 1 to 3-year moving average of exposure prior to event. In two studies (ASHMOG and Japanese cohorts) the exposure period was respectively 5 and 10 years before enrolment. The difference in the temporal resolution of $PM_{2.5}$ exposure between studies reflects limited systematic monitoring of fine particulate concentrations until the late 90's in many countries, as well as the lack of evidence on critical time-windows of exposure. Whilst some studies suggest that the last few years of exposure prior to event are the ones most strongly associated with mortality (Lepeule et al., 2012; Puett et al., 2009; Schwartz et al., 2008), the identification of the

most influential time windows of exposure has typically proven to be difficult, due to too small spatio-temporal variations in concentrations.

Spatial assessment and assignment of cumulative exposure

Precision in effects estimation requires sufficient spatial variation in subjects' cumulative exposure over time. This is harder to obtain when exposure is assigned to individuals at a coarse scale (Dominici et al., 2003). Consequently, whilst a few studies used the mean of concentrations in the city of residence at enrolment (e.g. ACS full cohort; Harvard Six Cities) or at the nearest monitor (e.g. Japanese and US truckers cohorts), most studies used geographic information systems (GIS)-based statistical methods to account for small-scale spatial variations in pollution concentrations and obtain finer spatial contrasts in exposure.

These methods, which can be classified as interpolation methods, land use regression models or dispersion modelling are described in Jerrett et al. (2005). Briefly, statistical interpolation produces estimates of pollution concentrations at un-sampled sites by exploiting spatial dependence in the data (kriging method) or by relying on deterministic or geometric algorithms such as inverse distance weighting. By contrast, land use regression models regress pollution monitoring data obtained from a small number of sampling locations on an exogenous set of variables (e.g. traffic, land use, altitude), in order to predict pollution concentrations at other sites. Finally, dispersion models differ from the first two methods as they rely on monitoring measurements only for model calibration and validation, i.e. not as input data. Dispersion models generate estimates of pollutant concentrations based on data on pollutants emissions, meteorological conditions and topography, assuming these parameters are governed by deterministic processes.

Although each method has its pros and cons, land use regression models (used in 8 of the selected studies) have been found to outperform interpolation methods (used in 3 of the selected studies) (Hoek et al., 2008). The main drawbacks of interpolation methods is that they are mechanistic, they require

a relatively dense sampling network to avoid large estimation errors and they assume that variation is spatially homogenous (Jerrett et al., 2005). The few studies that have compared land use regression models with dispersion modelling do not suggest that one technique is dominated by the other, rather that the main strength of dispersion modelling is to assess source-specific concentrations of pollutants (Hoek et al., 2008).

Nevertheless, notwithstanding the complexity and refinement of these modelling approaches to exposure assessment, outdoor concentrations are solely a proxy for individual-level exposure, which is the underlying variable of interest. Exposure misclassification using outdoor concentrations is therefore inevitable due to individual-level differences in time-activity patterns, air exchange rate of outdoor pollutants at home, accommodation type, i.e. high-rise or low-floor buildings, and so forth (Briggs, 2005; Hoek et al., 2008). Whilst exposure misclassification is generally expected to be non-differential (i.e. study participants have an equal likelihood to be assigned an inaccurate estimate), which limits the risk of spurious associations, it adversely affects precision in effect estimation (Raaschou-Nielsen et al., 2013).

Adjustment for confounding

Given the nature of the data, i.e. time to event, all studies used the Cox proportional hazard model, which links the log of the relative risk to pollution concentrations. A few studies, namely ACS national, city-scale and regional sub-cohorts and the Canadian cohort included a random-effect component into the Cox proportional hazard model, in order to account for spatial clustering of data at neighbourhood level, i.e. confounding by spatially-varying contextual factors that are correlated with air pollution.

Studies differed in their adjustment for confounding by lifestyle factors, smoking in particular. The large majority of studies (15 out of the 18 included studies) used a set of individual-level covariates to adjust risk estimates for many risk factors such as diet, body mass index (BMI), active and passive smoking, alcohol consumption, along with socio-economic status. Neverthe-

less, three studies, namely the Rome, Canada and US truckers cohorts, solely relied on socio-economic status to adjust for lifestyle.

Although there is accumulated evidence on social patterns in smoking and diet, socio-economic status is only an imperfect measure for lifestyle risk factors and residual confounding may be an issue if these risk factors are correlated with air pollution concentrations. All four studies assessed potential correlation between $PM_{2.5}$ concentration estimates and smoking prevalence, using health survey samples or cohort subsets for which information on smoking was available. In the Rome, Oslo and US truckers cohorts, no such association was found, which suggests that smoking was an unlikely residual confounder in these studies. In the Rome cohort, adjustment for smoking and diet-related co-morbidities (chronic obstructive pulmonary disease and hypertensive heart disease) that were recorded on hospital discharges yielded similar or stronger associations between air pollution exposure and mortality and the inclusion of smoking habits for a subset of participants ($n = 7,845$) did not modify the size of associations.

For the Canadian cohort, analysis by Villeneuve et al. (2011) using estimates of Crouse et al. (2012) found an inverse association between $PM_{2.5}$ estimates and the prevalence of smokers and certain categories of BMI. This is consistent with the fact that in Canada, individuals with higher socio-economic status tend to live in more polluted areas. Effect estimates of the association between $PM_{2.5}$ and mortality in this cohort increased in magnitude after adjustment for individual-level socio-economic variables, which suggests that residual confounding by lifestyle factors may have led to an underestimation of the air pollution-mortality effect (Crouse et al., 2012).

Study population

Whilst studies were conducted in geographically-diverse populations, they were all based in developed countries (12 in North America, 5 in Europe and 1 in Japan).

Study populations had different age and gender composition, with five stud-

ies being gender-specific. Participants also had different socio-economic status, with some studies being based on selected population subgroups such as male truckers as opposed to female teachers or health professionals.

Finally, studies greatly differed in sample size. Of the 18 included studies, two had above 1 million participants, six had between 1 million and 100,000 participants; five had between 100,000 and 50,000 participants and five had below 50,000 participants.

Intervention

Although the levels of $PM_{2.5}$ concentrations to which study participants were exposed differed, they are within a rather narrow range (between 5 to $40 \mu g/m^3$). This range is in line with concentration levels at which linearity in impacts and the absence of threshold to effects have repeatedly been found (Krewski et al., 2009; Crouse et al., 2012; Lepeule et al., 2012; Cesaroni et al., 2013). The small difference in concentration between studies is therefore not expected to be problematic with regards to the pooling of risk estimates.

Particulate pollution, however, is a mixture of liquid and solid compounds emitted by varying sources such as fossil-fuel combustion, industrial processes, road dust, biomass burning. It is therefore likely that cohort participants have been exposed to a different mixture of particulates associated with different levels of toxicity. Nevertheless due to: (i) the lack of evidence on the relative toxicity of particulate components and (ii) ignorance of the particulate mix of concentrations in each study, this issue could not be addressed.

	Cohort name [Area]	Latest analysis					$PM_{2.5}$ exposure					HR (95% CI) ^(a)	
		Authors	Study population	Direct adjust. for smoking	Follow up	Mean conc. (SD or min-max)	Time period	Assessment	Spatial scale	All-cause	Lung cancer		
1	American Cancer Society [US]	Krewski et al. (2009)	488,370 adults > 30 yr old, both genders 342,521 adults > 30 yr old, both genders	Yes	1982-2000 1982-2000	14 (3) 21 (4)	1999-2000 1979-1983	Monitors (mean) Monitors (mean)	City City	1.06 (1.04-1.08) 1.05 (1.04-1.06)	1.14 (1.06-1.23) 1.09 (1.03-1.15)		
2	ACS [California]	Jerrett et al. (2013)	73,711 adults > 30 yr old, both genders	Yes	1982-2000	14 (4-25)	1998-2000	LUR	Address	1.06 (1.003-1.12)	N.A.		
3	ACS [Los-Angeles]	Krewski et al. (2009)	22,905 adults > 30 yr old, both genders	Yes	1982-2000	(9-27)	1999-2001	LUR	Zip code	1.14 (1.03-1.27)	1.39 (0.96-2.01)		
4	ACS [New York]	Krewski et al. (2009)	43,930 adults > 30 yr old, both genders	Yes	1982-2000	14 (3)	2000	LUR	Zip code	0.97 (0.82-1.13)	0.72 (0.26-1.31)		
5	ACS Non-smokers [US]	Turner et al. (2011)	188,699 lifelong never smokers > 30 yr old, both genders	Yes	1982-2008	13(4)	1979-83 and 1999-2000	Monitors (mean)	City	N.A.	1.19 (0.97-1.47)		
6	ASHMOG [US]	McDonnell et al. (2000)	3,769 lifelong 7th day adventists > 27 yr old, both genders	Yes	1977-1992	27(4-44)	1973-1977	Interpolation	Address	1.09 (0.98-1.21)	1.39 (0.79-2.46)		
7	California teachers study [US]	Lipsett et al. (2011)	73,489 female teachers > 20 yr old	Yes	1977-2005	16 (3-28)	1999-2005	Interpolation	Address	1.01 (0.95-1.09)	0.95 (0.70-1.28)		

Table 6.2: Summary of relevant studies identified.

	Cohort name [Area]	Latest analysis					$PM_{2.5}$ exposure					HR (95% CI) ^(a)	
		Authors	Study population	Direct adjust. for smoking	Follow up	Mean conc. (SD or min-max)	Time period	Assessment	Spatial scale	All-cause	Lung cancer		
8	Canadian national cohort	Crouse et al. (2012)	2.1 million Canadian > 25 yr old	No	1999-2001	9 (2-19)	2001-2006	monitors, satellite data	Enumeration areas	1.10 (1.05-1.15)	N.A.		
9	English cohort	Carey et al. (2013)	830,842 adults, 40-89 yr old, both genders	Yes	2003-2007	13 (9-20)	2002	Dispersion mod.	Address	1.13 (1.00-1.27)	1.13 (0.9-1.36)		
10	ESCAPE [Europe]	Beelen et al. (2014)	322,159 adults > 30 yr old from 12 European countries, both genders	Yes	14 yr (mean)	8(1) to 31(2)	2008-2011	LUR	Address	1.13 (1.01-1.25)	N.A.		
11	ESCAPE [Europe] (LC incidence)	Raaschou-Nielsen et al. (2013)	273,836 adults > 30 yr old from 8 European countries, both genders	Yes	13 yr (mean)	7(1) to 31(2)	2008-2011	LUR	Address	N.A	1.40 (0.92-2.13)		
12	Harvard Six Cities [US]	Lepeule et al. (2012)	8,096 adults, 25-74 yr old from 6 US cities, both genders	Yes	1974-2009	16 (11-24)	1-3 yr moving average	Monitors (mean)	City	1.14 (1.07-1.22)	1.37 (1.07-1.75)		
13	Health professional study [US]	Puett et al. (2011)	17,545 highly educated men, 40-75 yr old	Yes	1989-2003	18 (3)	1 yr moving average	LUR	Address	0.86 (0.71-1.01)	N.A.		
14	Japanese cohort	Katanoda et al. (2011)	65,520 adults > 30 yr old from 6 areas in Japan	Yes	1983-1993	17-42	1974-1983	Monitor (closest)	Address	N.A.	1.23 (1.09-1.38)		

TABLE 6.2. Summary of relevant studies identified (*continued*).

	Cohort name [Area]	Latest analysis					$PM_{2.5}$ exposure				HR (95% CI) ^(a)	
		Authors	Study population	Direct adjust. for smoking	Follow up	Mean conc. (SD or min-max)	Time period	Assessment	Spatial scale	All-cause	Lung cancer	
15	NLCSAIR [Netherlands]	Beelen et al. (2008)	120,852 adults, 55-69 years old, both gender	Yes	1987-1996	28 (23-37)	1987-1996	LUR and interpolation	Address	1.06 (0.97-1.16)	1.06 (0.82-1.38)	
16	Nurses health study [US]	Puett et al. (2009)	66,250 women from northeastern metropolitan areas > 30 yr old	Yes	1992-2002	14 (6-27)	1 yr moving average	LUR	Address	1.26 (1.02-1.54)	N.A.	
17	Rome cohort	Cesaroni et al. (2013)	1,265,058 adults > 30 yr old	No	2001-2010	23 (7-32)	1996-2010 (using 2005 data)	Dispersion mod.	Address	1.04 (1.03-1.05)	1.05 (1.01-1.10)	
18	US truckers cohort	Hart et al. (2011)	53,814 men > 15 yr old	No	1985-2000	14 (4)	2000	Monitor (closest)	Address	1.10 (1.02-1.18)	1.05 (0.88-1.26)	

TABLE 6.2. Summary of relevant studies identified (*continued*)

^(a) All HR are expressed for $\Delta PM_{2.5} = +10\mu g/m^3$.

6.3 Meta-analysis

6.3.1 Statistical framework

Two conceptual approaches

Meta-analysis consists in pooling risk estimates from individual studies by computing a weighted average of effect estimates, using the inverse of estimates' variance as weights. This allows to give more weight to the more precise studies, with view to maximise the precision of the pooled effect estimate. Mathematically,

$$\bar{\theta} = \frac{\sum_{i=1}^k w_i \theta_i}{\sum_{i=1}^k w_i} \quad \text{with } w_i = \frac{1}{v_i} \quad (6.1)$$

with $\bar{\theta}$ being the pooled estimate and θ_i and v_i representing study-specific mean effect and variance.

The variance of the pooled estimate is the reciprocal of the sum of study-specific weights w_i , i.e.

$$Var(\theta) = \frac{1}{\sum_{i=1}^k w_i} \quad (6.2)$$

There are two conceptually different approaches to performing a meta-analysis known as the fixed-effect model (FE) or the random-effect model (RE). The FE model assumes that each study generates an estimate of a common true treatment / intervention effect, subject to sampling error known as within-study variation. By contrast, the RE model recognises that studies are heterogeneous in some respect (e.g. they were drawn from populations that differed from each other), with such differences having an impact on their estimated treatment effect (Borenstein et al., 2009). As a result, each study is assumed to provide a study-specific treatment effect. This introduces another source of sampling error in the pooled risk estimate known as between-studies

variance (τ^2). Whilst study-specific effect estimates are not identical, they are assumed to come from a common distribution - typically taken as the normal distribution - that is centred at the pooled estimate.

The choice of conceptual approach to pooling each risk estimate has strong implications on the computation of the pooled estimate. Under the FE model, the pooled estimate is assumed to provide information about the best estimate of effect. Consequently, studies with the greatest precision, i.e. with the lowest within-study variance, will be attributed a much higher weight than the least accurate studies and will therefore strongly influence the value of the pooled estimate. By contrast, under the RE approach, the pooled estimate represents the average intervention effect across different study populations (Borenstein et al., 2009). This shifts the focus of interest from the estimation of a common effect to the characterisation of the distribution of effects across studies.

Computation-wise, although effect estimates are weighted by the inverse of their variance in both models, under the RE-model the variance includes within-studies and between-studies variance (Sutton et al., 2000). Denoting σ_i within-study variance, we obtain the following expressions for study-specific variance:

$$v_i = \sigma_i \quad \text{under the FE model and } v_i = \sigma_i + \tau^2 \quad \text{under the RE model} \quad (6.3)$$

Replacing for v_i , we obtain the following expressions for study-specific weights:

$$w_i = \frac{1}{\sigma_i} \quad \text{under the FE model and } w_i = \frac{1}{(\sigma_i + \tau^2)} \quad \text{under the RE model} \quad (6.4)$$

The inclusion of between-study variance in the RE model has three consequences. First, the weights assigned to each study will tend to be more balanced under the RE model than the FE model. Second, since the variance of the pooled estimate is the reciprocal of the sum of study weights (see equation (2)), in the presence of between-studies variation, the confidence interval of the RE-pooled estimate will be larger than the confidence interval around

the FE-pooled estimate. Third, in line with equations 6.1 to 6.4, if τ^2 equals to zero, FE and RE models will yield identical results.

Choice of random effect as conceptual model

The studies identified by the present systematic review and those selected from Chen et al. (2008)'s review were chosen for their similarities in terms of study population, intervention, health outcomes and study design. Nevertheless, as described in section 2.3., studies exhibit some level of heterogeneity especially with regards their methodology. Therefore, whilst studies are considered similar enough for the pooling of their effect estimates to be pertinent, their heterogeneity should be taken into account to avoid pooled estimates and their confidence intervals to be misleading. The RE model was therefore preferred.

Interpretation of random effect estimation results in decision modelling

Whilst the random effect model is advocated to incorporate heterogeneity between studies, the use of random effect meta-analysis results to populate cost-effectiveness decision models, is open to a number of possible interpretations about the source of heterogeneity between studies and how the target setting of the intervention under assessment may potentially differ from the ones in the studies included in the meta-analysis. (Welton et al., 2015). The expression of “target setting” presently refers to population characteristics, intervention definition etc.

Typically, the mean of the random effect distribution is interpreted as the true effect to be observed in the future. This assumes that the decision target setting is equal to the average setting of the included studies and that the pooled estimate is an estimate of the true underlying intervention effect (D) that has been observed under noisy conditions resulting from random measurement errors (with the bias across studies being centred on zero) (Ades et al.,

2005; Welton et al., 2015).

Although this common approach was followed when parameterising the model developed in Chapter 4, it is worth noting that alternative methods have been suggested to characterise decision uncertainty stemming from variation in intervention effect. Importantly, this source of decision uncertainty should be distinguished from parameter uncertainty as it cannot be reduced by further information.

In the case where the target setting for the decision is assumed to be similar to the ones in the studies included in the meta-analysis. Ades et al. (2005), suggested to rely on the predictive distribution of the intervention effect in a new study. Whilst the predictive distribution will be centred on the mean of the random effect distribution (i.e. RE pooled estimate), its variance will be larger as it accounts for uncertainty in parameters (D and τ^2), as well as in study setting (Welton et al., 2015), namely:

$$d_{predicted} \sim N(D, \tau^2) \quad (6.5)$$

with D being the true underlying effect and τ^2 the between-study variance in treatment effect.

Alternatively, if the decision target setting is expected to be made up of all the various target settings of the different studies included in the meta-analysis, it may be argued that there is not a single effect size but a distribution of effect sizes. In this case, quantification of the net benefit of intervention would ideally require to take the expectation of net benefit over the entire random effect distribution of intervention effect (Ades et al., 2005; Welton et al., 2015).

6.3.2 Checking for potential sources of bias

Publication bias

Before embarking on the meta-analysis, the potential existence of a publi-

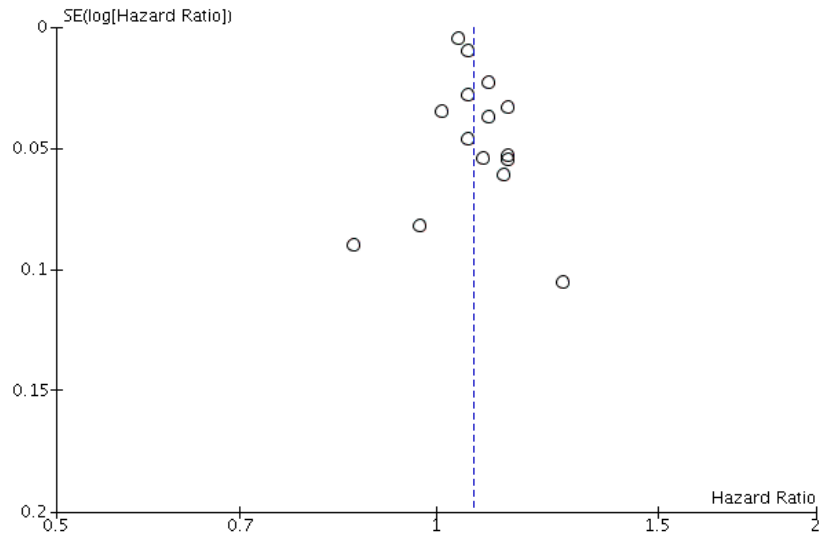
cation bias, which arises when studies reporting non-significant results are less likely to be published, was assessed. The main consequence of publication bias in meta-analysis is to produce an over-estimate of the pooled estimate and/or a too-narrowed confidence interval (Sterne et al., 2008).

The presence of a publication bias seems *a-priori* unlikely for epidemiological studies of air pollution, as both the absence or presence of health effects from exposure to fine particulate is policy-relevant. Nevertheless, a quick visual check for bias was performed by creating funnel plots. The latter are scatter plots of studies' effect estimates against their precision (i.e. standard error) on a reversed scale, such that the most accurate estimates are located at the top of the graph whereas the least accurate ones spread more widely at the bottom of the graph.

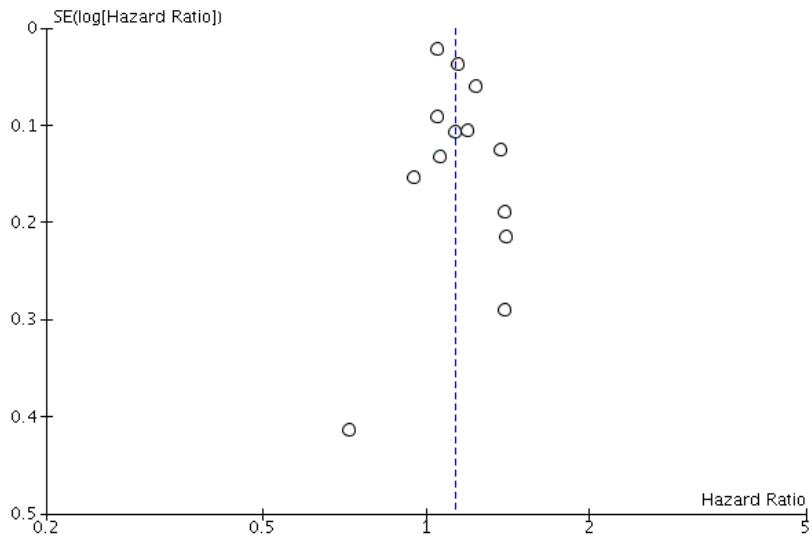
Funnel plots were created for the studies pertaining to respectively all-cause mortality and lung-cancer incidence or mortality, using the freely available software Revman 5.2 from the Cochrane Collaboration¹. Output results are provided in Figure 6.2. Since the outcome measure was a hazard ratio, the funnel plots were computed on the log scale, so that effects of the same magnitude but on different directions are equidistant from unity (Deeks et al., 2008).

In the absence of publication bias, the plots are expected to look like a symmetrical inverted funnel, with the dotted line at its centre representing the mean effect estimate. This appears to be the case for studies of all-cause mortality and lung-cancer incidence or mortality. It should nevertheless be underlined that the funnel plot is only an informal visual test for publication bias that may need to be completed by formal statistical tests such as the Rank correlation test (Sutton et al., 2000). In the present case, this does not appear necessary, as the symmetry in the funnel plots supports the *a-priori* expectation that there is no particular bias affecting the publication of studies on the association between chronic fine particulate pollution exposure and mortality.

¹<http://tech.cochrane.org/revman>.



(a) All-cause mortality.



(b) Lung cancer incidence or mortality.

Figure 6.2: Funnel plots of studies of the association between long-term exposure to $PM_{2.5}$ and (A) all-cause mortality and (B) lung-cancer incidence or mortality.

Small-study bias

The presence of small-study bias, which arises when effect size estimates from small studies are systematically different from the ones of larger studies (Deeks et al., 2008), was also investigated. Small-study bias is especially problematic when using the RE model, which puts more weight on small studies than the FE model in order to characterise the distribution of effects. Table 6.2, however, indicates that findings based on small or medium-size study populations are clearly not systematically different than results from larger cohorts and small-study bias can therefore be ruled out.

6.3.3 All-cause mortality: results

Main results

Results were obtained using the software Revman 5.2. from the Cochrane Collaboration. A forest plot in Figure 6.3 summarises meta-analysis results from the pooling of effect estimates provided by the 15 studies identified as relevant (see Table 6.2 for further description). In a forest plot, each study point estimate is marked by a square that is proportional in size to the weight given to the study, whereas confidence intervals are represented by horizontal lines. The pooled result is represented by a diamond shape that is centred on the value of the pooled estimate with the width of the diamond depicting the 95% confidence interval.

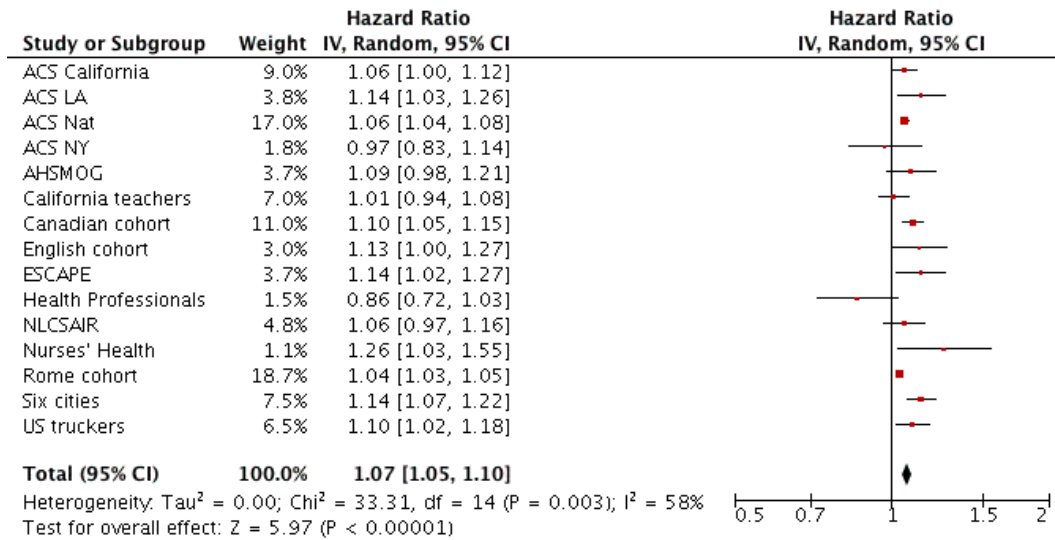


Figure 6.3: Meta-analysis of the association between long-term exposure to $PM_{2.5}$ and all-cause mortality (Random effect model - hazard ratio per 10 $\mu g/m^3$).

The random-effect pooled estimate is 1.07 with a 95% confidence interval: 1.05 - 1.10. The latter appears uncentered solely due to figures rounding (figures with more decimals are 1.0713 (1.0473 - 1.0958)). As indicated by its 95% confidence interval, the pooled estimate is statistical significant. This is corroborated by the very small p-value associated to the Z-test for the presence of an overall effect, where the Z-statistic is defined as:

$$Z = \frac{\bar{\theta}}{SE(\bar{\theta})} \text{ and follows a normal distribution under the null hypothesis.}$$

A visual inspection of the forest plot shows the absence of confidence interval overlap between the Health Professional and Nurses' Health studies. This suggests the presence of between study heterogeneity and is confirmed by the value of the chi-square (χ^2) statistic. The χ^2 statistic represents the total variance: it is the weighted sum of the square deviations of each study's effect estimates from the pooled estimate, weighted by the inverse of each study variance. Using similar notations to section 6.3.1, the expression for the χ^2

statistic is:

$$\chi^2 = \sum_{i=1}^k w_i(\theta_i - \bar{\theta})^2$$

Under the null hypothesis of no study heterogeneity, which is equivalent to assuming that each k study estimated the same underlying effect, the statistic should follow the χ^2 distribution with $(k-1)$ degree of freedom. As indicated by the very small p-value in Figure 6.3, the null hypothesis of no study heterogeneity is rejected. This test is however, known to have too much power in the presence of many studies and alternatively, too little power when only a few studies are pooled.

A simpler way to assess the presence of heterogeneity is to compare the value of the χ^2 statistic with its degrees of freedom, which represent the expected value of the χ^2 statistic if the only source of variance were within-study variation (Borenstein et al., 2009). In the present case, the χ^2 -statistic equals 33, which is clearly much higher than its degrees of freedom (df) equal to 14. This “excess variance” ($\chi^2 - df$) is due to between-study variation, i.e. heterogeneity.

Even with strict inclusion criteria, some level of study heterogeneity appears inevitable. As a result, it has often been argued that the focus of interest should not be on the presence of heterogeneity or not but on how much heterogeneity there is (Higgins et al., 2003). This can be assessed by scaling the “excess variance” by the total variance, which is referred to as the I^2 statistic:

$$I^2 = \max\left[\left(\frac{\chi^2 - df}{\chi^2}\right)100\%, 0\right]$$

In the present case, I^2 equals 58%. This means that heterogeneity between-studies explains about 58% of the variability in individual effect estimates, where the rest is the result of sampling error. Whilst there are no clear-cut guideline on how to interpret the value of the I^2 -statistic, a 58% value may be interpreted as moderate heterogeneity between studies (Higgins & Green, 2011).

Finally, it is worth noting that the computation of τ^2 , i.e. the between-studies variance, and the I^2 -statistic are related. However, while τ^2 is also

based on the “excess variance” ($\chi^2 - df$), it not scaled by the total variance but by a factor that is a function of within-studies variance. In the present case, despite positive excess variance, the value of τ^2 appears very small. The reason is that given the level of inaccuracy in a number of studies i.e. sampling error, one would anyway expect the effect size to vary across studies. In other words the variance between studies appears to be essentially explained by the variance within studies (Borenstein et al., 2009).

Sub-group analysis

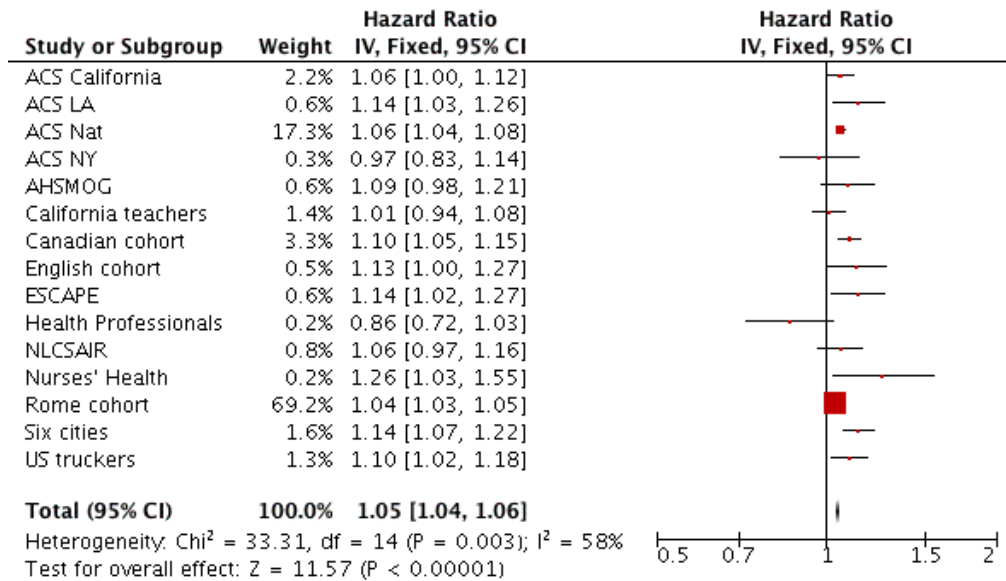
As there were too few gender-specific results (5 in total) to perform a sub-group analysis stratified by gender, alternatively effect estimates of studies based on respectively: (i) both genders or males only and (ii) both genders or females only were pooled separately. Results are presented in Appendix E. The three males studies (ASHMOG, Health Professional and US truckers cohorts, see Table 6.2) only account for a combined 12% of the total weight assigned to studies pertaining to both genders or males. Similarly, the two females studies (California teachers and Nurses’ Health cohorts, see Table 6.2) only account for a combined 9% of the total weight assigned to studies pertaining to both genders or females. As a consequence, the pooled estimate obtained for each subgroup is equal to the one computed by pooling all 15 available estimates.

Sensitivity analysis

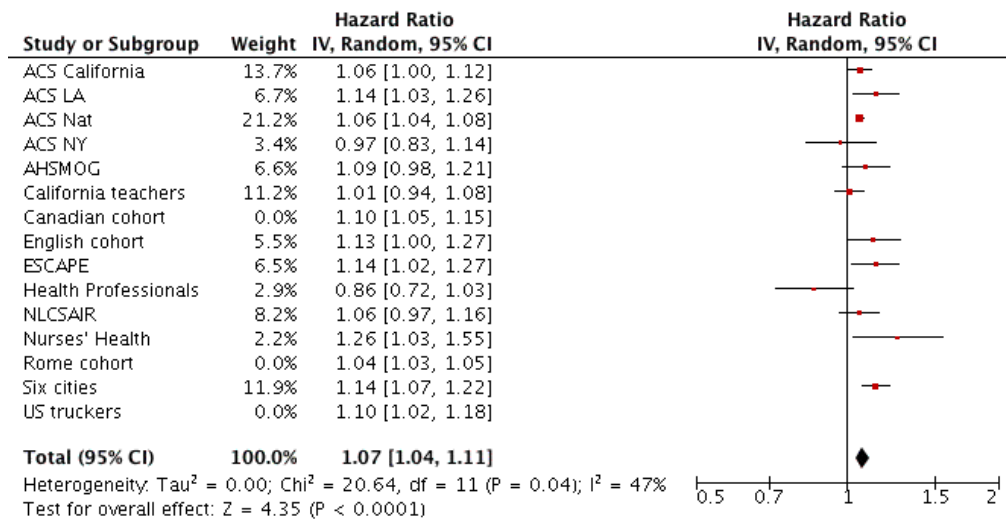
Whilst the presence of moderate study heterogeneity as indicated by the test statistics supports the choice of the random effect model, analysis under a fixed-effect model was run, in order to assess the impact of a change of statistical modelling assumption on the pooled estimate. Results are presented in Figure 6.4a. The weight assigned to the Rome cohort increased from 18.5% under the RE model to about 70% under the FE model. As a result, the FE-pooled risk estimate is extensively drawn towards the effect size estimated in

the Rome study and equal 1.05 with 95% CI: 1.04 - 1.06. Ignoring between-studies heterogeneity would therefore misleadingly suggest a much greater confidence in the precision of the mean of the distribution of effects.

Secondly, although positive residual confounding by smoking in the studies which did not directly control for this risk factor at individual-level seems unlikely (see section 2.3.1.), a sensitivity analysis was run (RE model) by excluding the studies which adjusted for lifestyle solely via socio-economic status. This led to the exclusion of results from three studies: Rome, Canada and US Truckers cohorts (see Table 6.2). Results are shown in Figure 6.4b. Whilst the pooled estimate remains the same, its confidence interval is wider since the Rome and Canada cohorts, excluded in this sensitivity run, provide rather precise estimates of effect.



(a) Results under fixed-effect model.



(b) Excluding studies with no direct adjustment for smoking (RE model).

Figure 6.4: Sensitivity-analysis for meta-analysis results for all-cause-mortality (hazard ratio per $10 \mu\text{g}/\text{m}^3$).

6.3.4 Lung-cancer incidence or mortality: results

Main results

Although most of the effect size estimates for lung cancer mortality were drawn from the same cohorts that provided estimates for all-cause mortality, they have much wider confidence intervals than estimates for all-cause mortality. This stems from the fact that statistical power is not solely determined by sample size but also by the number of participants experiencing the event of interest (Higgins & Green, 2011). In each cohort, counts of lung cancer deaths were obviously smaller than counts of total deaths, hence the lower precision in effect estimation. Similarly, although the only risk estimate for lung cancer incidence was based on a meta-analysis of results from 14 cohorts in Europe (ESCAPE study), its standard error is nevertheless very large (95% CI: 0.92 - 2.13).

Meta-analysis results are presented in Figure 6.5. Pooling of estimates from the 13 studies identified as relevant yielded a RE-pooled estimate of 1.13 with 95% CI: 1.07 - 1.20, which is statistically significant. It is worth noting that this estimate is of greater magnitude than the pooled estimate for all-cause mortality (1.07, 95%CI: 1.05 - 1.10), though the uncertainty about the centre of the distribution of effects is much greater. Between-studies heterogeneity is smaller than for studies of all-cause mortality (I^2 equal to 34%) but remain moderate, thus confirming the adequacy of the random effect model.

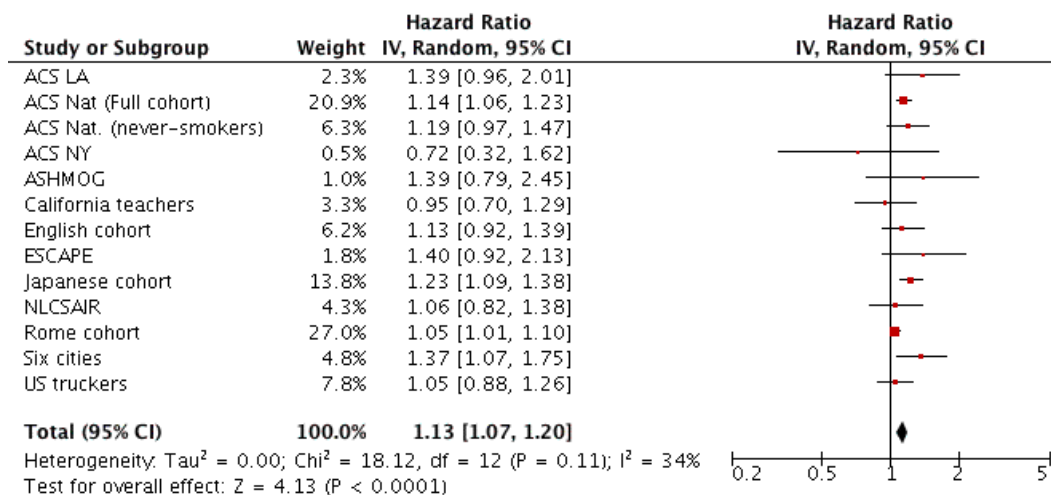
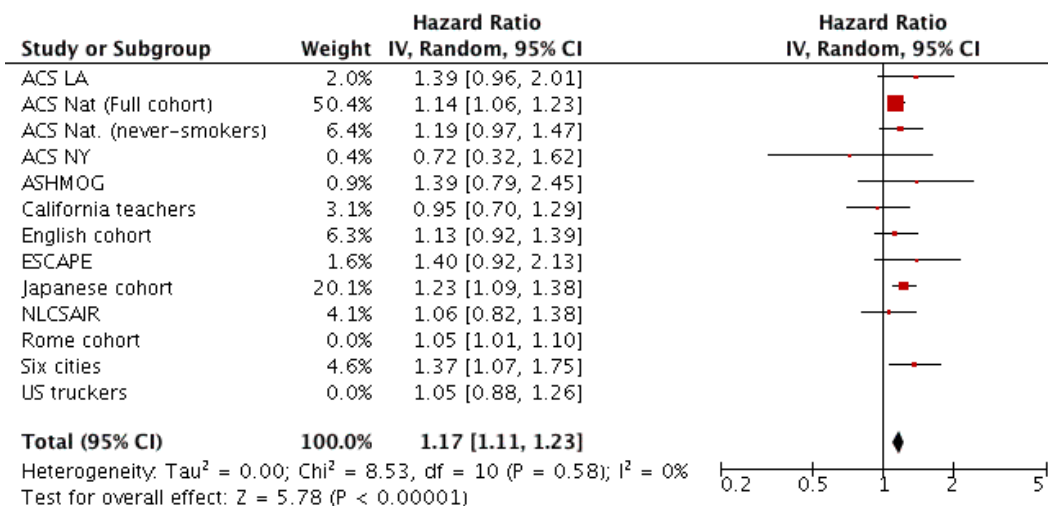


Figure 6.5: Meta-analysis of the association between long-term exposure to $PM_{2.5}$ and lung-cancer incidence or mortality. (Random effect model - hazard ratio per 10 $\mu g/m^3$).

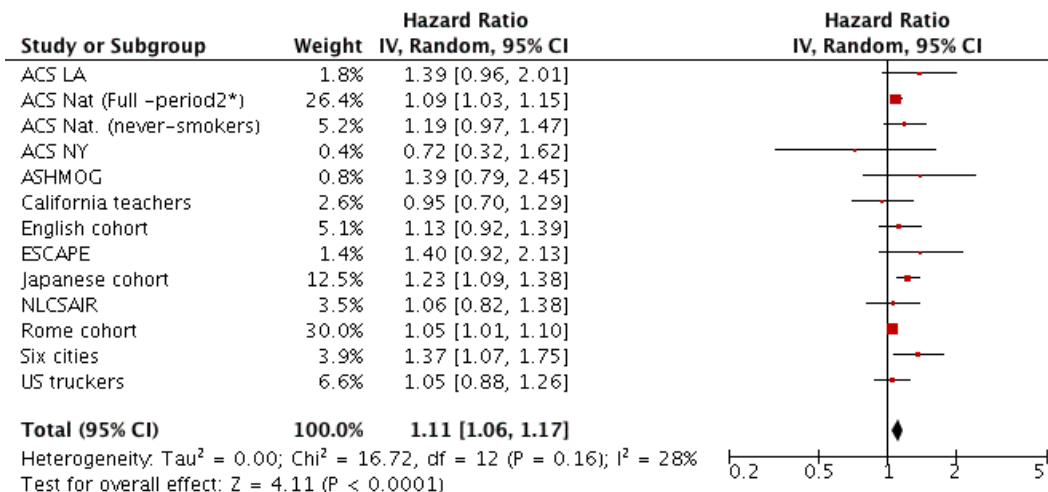
Sensitivity analysis

Two sensitivity analyses were performed. The first sensitivity run consisted in excluding studies without direct adjustment for smoking, as was previously done for all-cause mortality. This resulted in the exclusion of two studies: Rome and US truckers cohorts, which led to an increase in the pooled estimate to 1.17 with 95% CI: 1.11-1.23 (see Figure 6.6a).

The second sensitivity run consisted in using the risk estimate from the ACS national study (full cohort) that was estimated based on PM exposure for the period 1979-1983, as opposed to the period 1999-2000. This sensitivity run was justified by the fact that the weight assigned to this study in main analysis is large (21%, see Figure 6.5). Since the excess risk of lung cancer mortality estimated based on the oldest period of PM exposure is lower than the one estimated based on the most recent exposure data, its use would yield a slightly lower pooled estimate: 1.11 with 95% CI: 1.06-1.17 (see Figure 6.6b).



(a) Excluding studies with no direct adjustment for smoking.



(b) Using ACS national (full cohort) risk estimate based on 1979-1983 years of PM_{2.5} exposure.

Figure 6.6: Sensitivity-analysis for meta-analysis results for lung-cancer (Random effect model - Pooled hazard ratio per 10 μg/m³).

* Years of PM_{2.5} exposure: 1979-1983.

6.4 Discussion

6.4.1 Main findings

A total of 18 studies, published from 1950 until April 2014, have been identified as relevant for informing the association between chronic exposure to $PM_{2.5}$ and respectively all-cause mortality and lung cancer incidence or mortality. Mean effect estimates and 95% confidence intervals obtained by pooling study-specific results using the random-effect model are respectively: 1.07 (1.05 - 1.10) for all-cause mortality and 1.13 (1.07 -1.20) for lung cancer incidence or mortality.

Moderate heterogeneity was found between studies, which justifies the use of the random effect model. Several sources of between-studies heterogeneity were identified including: (i) varying approaches to spatio-temporal assessment and assignment of exposure ; (ii) differences in study-population age, gender and socio-economic status mix and (ii) expected differences in particulates' chemical composition and toxicity. A meta-regression of the pooled estimate against study characteristics was however, not performed for the following two reasons. First, performing these analyses requires a sufficient number of studies, with a suggested minimum of ten estimates per characteristic modelled (Higgins & Green, 2011), which were not available from the present pool of studies. Second, since studies are not randomised across potential effect-modifiers, their findings are problematic to interpret (Deeks et al., 2008).

6.4.2 Comparison with work published most recently

The present results, which take into account the most recent evidence published until end of April 2014 are consistent with those previously obtained by Chen et al. (2008) for the period 1950-2007. The authors reported random

effect-pooled estimates of respectively 1.06 (1.03 - 1.10) for all-cause mortality and 1.15 (1.06 - 1.24) for lung cancer incidence or mortality.

Since the start and completion of this piece of work, two meta-analyses on the association between $PM_{2.5}$ exposure and respectively all-cause mortality (Hoek et al., 2013) and lung cancer incidence or mortality (Hamra et al., 2014) were published (in May 2013 and September 2014 respectively).

Hoek et al. (2013) reported a random effect-pooled estimate of 1.06 (1.04 - 1.08) for all cause mortality, which is very similar to the present findings. The authors however, only included studies published until January 2013 and as a consequence, did not encompass results from three cohort studies: ESCAPE, English cohort and ACS California sub-cohort (see Table 6.2). In addition, the authors encompassed in their scope studies based on elderly populations (Zeger et al., 2008; Enstrom, 2005), which may further explain the slight difference with the present result.

Hamra et al. (2014) reported a random effect-pooled estimate of 1.09 (1.04 - 1.14) for lung cancer incidence or mortality, which is smaller than the present pooled estimate. After careful analysis, it appeared the difference in estimates was driven by two factors. First, Hamra et al. (2014) used the risk estimate from the American Cancer Society (ACS) national full cohort based on PM exposure for the years 1979-1982. By contrast, the present analysis relied on results based on the 1999-2000 exposure period, which included 42% more study participants (see section 6.2.3). Unfortunately, Hamra et al. (2014) did not justify their choice of exposure period. Sensitivity analysis using the risk estimate based on the 1979-1982 period of PM exposure yielded a slightly lower pooled estimate (1.11 - 95% CI: 1.06 - 1.17, see section 6.3.4), which is more in line with Hamra et al. (2014)'s findings.

Second, Hamra et al. (2014) included a result from a cohort study in China (Cao et al., 2011). This study was excluded from the pool of relevant studies in the present analysis as it did not provide a risk estimate for particulate air pollution exposure but only for total suspended particle (TSP). While Hamra et al. (2014) had similar inclusion criteria and clearly stated that they excluded studies which did not provide quantitative estimates for particulate matter, they apparently made an exception for this study - without justification - and

converted the risk estimate for TSP to a risk estimate of $PM_{2.5}$ applying a 3:1 ratio. This led to an estimate of 1.07 (95% CI: 1.0 - 1.07). Due to a relatively small standard error, the weight attributed to the Chinese study in Hamra et al. (2014)'s meta-analysis was high (21%).

In order to assess the impact of these two factors on the pooled risk estimate for lung cancer mortality or incidence, a third sensitivity scenario was run by (i) using the risk estimate from the ACS national full cohort based on PM exposure for the years 1979-1982 and (ii) adding results from Cao et al. (2011)'s study. Results are presented in Figure 6.7. In this scenario, the pooled estimate and its 95% CI exactly match with Hamra et al. (2014)'s findings.

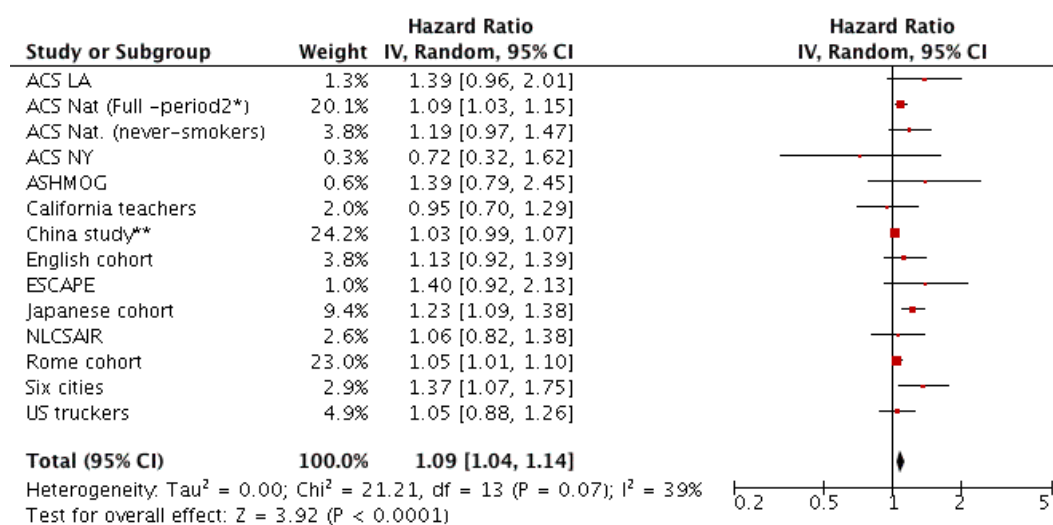


Figure 6.7: Sensitivity-analysis for meta-analysis results for lung-cancer using Hamra et al. (2014)'s study scope. (Random effect model - hazard ratio per $10 \mu g/m^3$).

6.5 Conclusion

A systematic review and two meta-analyses of the association between long-term exposure to fine particulate matter ($PM_{2.5}$) and respectively all-cause mortality and lung cancer incidence or mortality were performed. These quantitative analyses update past work done by Chen et al. (2008), by including all the relevant evidence published over the last seven years. These results are important for public health practitioners and policy-makers who need to assess air pollution control interventions based on all existing evidence.

Present results are consistent with two meta-analyses published after completion of this work: Hoek et al. (2013) and Hamra et al. (2014). For lung cancer incidence or mortality, the difference between the presently obtained pooled estimate and Hamra et al. (2014)'s results appears to be driven by two unjustified choices made by the authors and does not put into question the quality of the present work. Nevertheless, since Hamra et al. (2014) results were published, they will be used to parameterise the model built in Chapter 4. By contrast, the presently obtained pooled estimate for all-cause mortality, which closely matches with Hoek et al. (2013)' estimate, but includes most up to date evidence and excludes studies on elderly subjects, will be used to parameterise the model of the health effects of pollution exposure.

Chapter 7

QALY gain, health care resources impact and cost-effectiveness of air pollution control in England and London

7.1 Introduction

Chapter 4 developed a Markov model of the health effects of air pollution exposure, in order to fully capture air pollution's joint effect on quality and length of life as well as to assess the total health care budget impact of a reduction in air pollution. The model required a number of parameters, a subset of which were estimated in Chapters 5 and 6.

This chapter presents the results from the application of the developed model to the UK case study detailed in Chapter 4. The intervention underpinning the case study, hereafter referred to as “the intervention”, consists of an immediate and sustained $1\mu g/m^3$ decrease in population-weighted mean $PM_{2.5}$ concentrations in England and Wales and London. This is expected to represent a decrease by respectively 9% and 7% in current average concen-

trations. Section 2 provides the total expected health gain and health care cost impact associated with the intervention, as well as the distribution of outcomes by age and gender. Section 3 focuses on uncertainty surrounding outcomes and also evaluates results' sensitivity to the choice of discount rate and to dynamics in risk reduction. Section 4 compares the developed Markov model with the simple life-table approach currently used in health impact assessment (HIA) and contrasts estimates of un-discounted life expectancy gain with results from past HIAs. Based on case study results, section 5 evaluates the cost-effectiveness of reducing air pollution in London, whether such an intervention would be funded by the NHS or through general taxation.

7.2 Total mean health gain, health care cost impact and associated monetary benefit

7.2.1 Mean outcomes across each target population

Reducing mean $PM_{2.5}$ concentrations by $1\mu g/m^3$ is expected to generate more than 60,000 QALYs in London and 540,000 QALYs in England and Wales, among adult individuals currently aged 40 and above over their remaining lifetime, discounting at 3.5% p.a.

The total (i.e. net) health care resource impact of the intervention, which corresponds to the health care costs from extending the lives of individuals with a chronic cardio-respiratory condition, net of the health care savings from a reduction in cases of CHD, COPD and lung cancer, is slightly cost increasing. It accounts for respectively £24 million in London and £263 million in England and Wales. It should be reminded that extending the lives of "healthy" individuals (i.e. individuals without COPD, CHD or lung cancer) is assumed not to generate any health care cost and that the intervention

is not expected to impact upon the life expectancy of individuals with lung cancer (see sections 4.4.3 and 4.5.5 of Chapter 4). Total QALY gain and health care cost impact under deterministic analysis were slightly lower than under probabilistic analysis by respectively 1.2% and 2.3%.

7.2.2 Total expected monetary benefit

Valuing QALY gain

As discussed in Chapter 2, the approach to monetizing health gain should be determined by who will bear the cost of the intervention. If the intervention of air pollution control is funded by the NHS, which has a fixed and fully allocated budget, the money value of a QALY should represent the cost-effectiveness of the services to be displaced by the investment (Claxton et al., 2007). Whilst NICE officially uses a value of £20,000 to £30,000 to assess the cost-effectiveness of health care technologies (NICE, 2013), recent efforts to empirically estimate the shadow price of the NHS budget constraint suggest £13,000 as best estimate (Claxton et al., 2013).

However, if air pollution control is expected to be funded by raising new tax revenue, it will displace private consumption, as opposed to health care services from the NHS. In this context, health gain should be monetized based on the consumption value of a QALY (Ryen & Svensson, 2014). The Department of Health in the UK recommends to use a willingness to pay (WTP) value of a QALY of £60,000 in 2009 prices (Glover & Henderson, 2010). Additionally, Ryen & Svensson (2014)'s recent global review of WTP values for a QALY found a trimmed mean estimate of €74,159 (2010 prices), with most estimates coming from European and US studies. The authors, however, underlined that estimates vary widely due to differences in methodology (i.e. revealed vs. elicited method) and perspectives (societal vs. individual) but also, due to non-proportionality in WTP with regards to the change in QALYs and non

equivalent valuation of quality and length of life in practice.

Whilst the sensitivity of cost-effectiveness results to the money value of health will be evaluated in section 7.5, the following values will be used to monetize QALY impacts:

(i) From the “NHS perspective”, i.e. if the NHS were paying for the intervention, the empirically-based value of £13,000 (Claxton et al., 2013) will be used to monetize a QALY.

(ii) From the “private consumption perspective”, i.e. if the intervention were funded by raising taxes, the value of £65,000/QALY will be used. This value approximately corresponds to the two above cited values of £60,000 and €74,159 (converted to GBP at the average exchange rate for 2010), when inflated to 2013 prices.

Valuing health care resource impacts

Health care costs (savings) to the NHS can be expressed as QALY losses (gains) using the estimate of the shadow price of the NHS budget constraint, presently assumed to equal £13,000/QALY. From the private consumption perspective, these “QALY equivalent” will be monetized using the consumption value of a QALY (i.e. £65,000/QALY). This implies that NHS resources are presently assumed to be worth five times (65/13) their amount of taxes.

The sum of QALY gain and QALY loss (gain) equivalent from health care resource impacts will hereafter be referred to as net QALY gain. Net QALY gain results will only be presented for the total target population, as allocating the consequences of the intervention’s health care cost impact between age- and gender-stratified population subgroups is outside the scope of the present work.

Expected monetary benefit

Table 7.1 provides outcomes summary results, for each target population and from both payers' perspectives. Based on an estimate of £13,00/QALY as the shadow price of the NHS budget constraint, the QALY loss equivalent resulting from net health care costs accounts for solely 2.8% and 3.7% of the health benefits in respectively London and England and Wales. As the consumption value of health is five times higher than the estimated NHS expenditure required to deliver one QALY, and the net health care resource impact is small, the total monetary benefit of the intervention to private payers is about five times higher than to the NHS. For London for instance, total benefits are valued £4 billion from the private consumption perspective, as opposed to £800 million from the NHS perspective.

	Total gain ^(a)	
	London	England & Wales
Target population size ^(b)	3,215,975	27,273,400
QALY gain	63,293	541,217
Net health care costs ^(c)	£24 million	£263 million
QALY loss equivalent ^(d)	1,825	20,219
Net QALY gain	61,467	520,998
Total monetary benefit NHS perspective ^(d)	£799 million	£6,773 million
Total monetary benefit Private consumption perspective ^(e)	£3,995 million	£33,865 million

Table 7.1: Total net QALY gain and associated monetary benefit of reducing ambient $PM_{2.5}$ concentrations by $1\mu g/m^3$.

(a) 60-year time horizon, applying a discount rate of 3.5 % p.a.

(b) Currently alive adults aged 40 to 90 years old.

(c) Health care costs associated with extending the lives of individuals with a chronic cardio-respiratory condition net of savings from reduced cases of CHD, COPD and lung cancer.

(d) Using a value of £13,000/QALY as shadow price of the NHS' budget constraint.

(e) Using a value of £65,000/QALY as consumption value of a QALY.

7.2.3 Impact distribution by age and gender

At individual level

Figure 7.1a depicts the expected quality-adjusted life day (QALD) gain associated with the intervention, for each age and gender-stratified individual of the target population over his/her remaining lifetime. Whilst health gain is cumulative over a lifetime, the main beneficiaries of the intervention are not the youngest individuals but those aged around 65 years old. This result is mainly a consequence of discounting since, as the risk of experiencing adverse health events increases with age, young individuals are expected to benefit from the intervention much later in the future than older individuals. The sensitivity of the age-distribution of health gain to the choice of discounting rate will be investigated in section 7.3.2.

Figure 7.1a also shows the presence of a substantial gender-gap in health gain, in particular among young age groups, with the average QALD gain enjoyed by 40-year old men being nearly a third (28%) higher than the gain accruing to their female counterparts. This gap reflects gender-differences in baseline risks of adverse health events, whereby men aged between 40 to 70 in the UK are on average twice more likely to develop CHD and 60% more likely to die from all causes than women. By having a greater baseline risk of adverse health events than their female counterparts, young men are expected to benefit more - in absolute terms - than young women from a given decrease in risk. Whilst gender-differences in health risks do persist at older ages, there are smaller. Additionally, gender-differences in baseline health risks have another smaller opposite effect: by enjoying a greater life expectancy than men, women are expected to enjoy the intervention's benefit for a slightly longer time period than men. Consequently, in old age-groups, the gender-gap in health gain becomes relatively small.

Figure 7.1b represents the expected health care cost impact per individual (gender average) from a reduction in both morbidity and premature mortality

associated with the intervention. It shows that for individuals aged 53 and above, on average, the health care savings from reducing their lifetime risk of developing COPD, CHD and lung cancer are more than compensated by the health care costs associated with extending the lives of those with a chronic cardiac or respiratory condition.

As will be discussed in section 7.4.2, this finding reflects the expectation, based on current evidence (see section 4.4.3 of Chapter 4), that individuals with COPD or CHD - once they reach a given age and/or disease severity level - are more susceptible to air pollution exposure (i.e. suffer disproportionately) than individuals of the general population. Consequently, under pollution decrement, these individuals who are costly to the health care system, are expected to enjoy a greater lifespan extension (as a proportion of their baseline life expectancy) than “healthy” individuals.

At population level

Figure 7.2 and Figure 7.3 represent the age- and gender-specific distributions of respectively the expected QALY gain and the total net health care cost impact of the intervention for each target population.

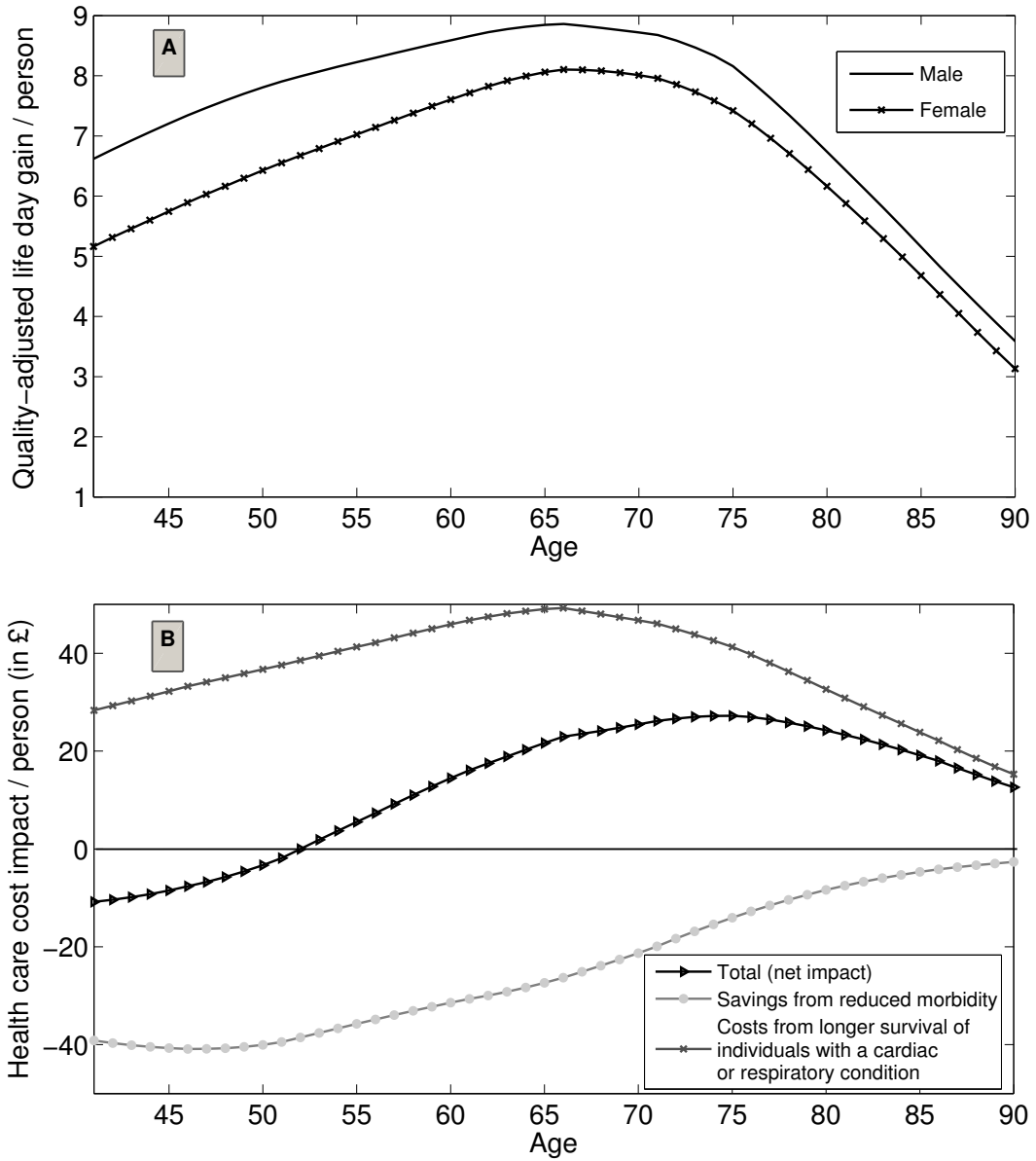
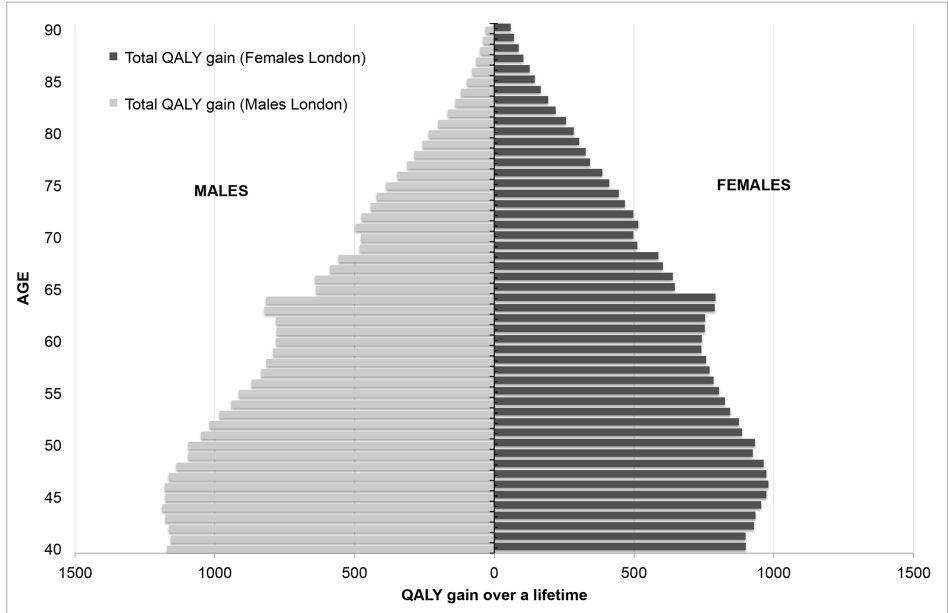
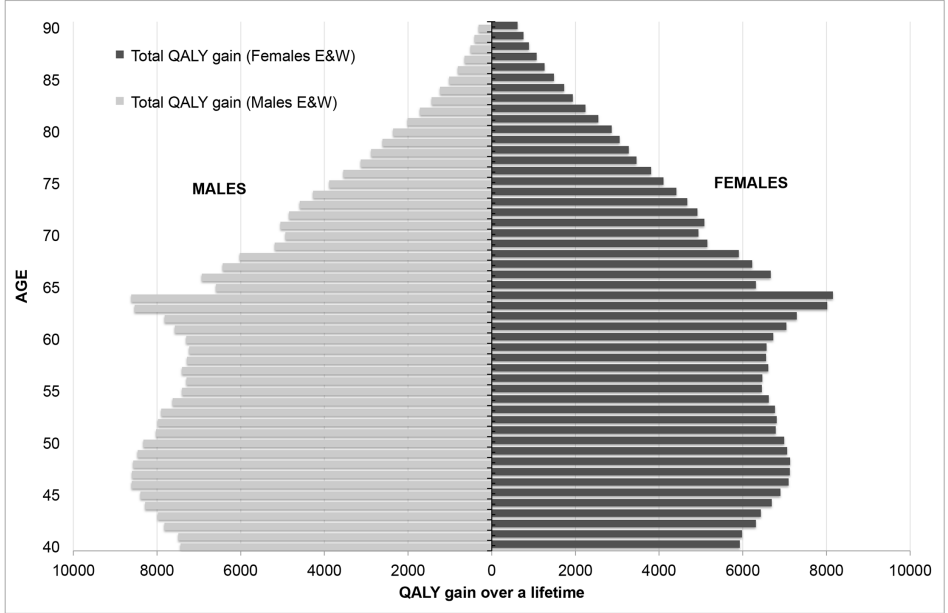


Figure 7.1: Intervention's average quality-adjusted life day gain (A) and health care cost impact (B) per person, stratified by age and gender.

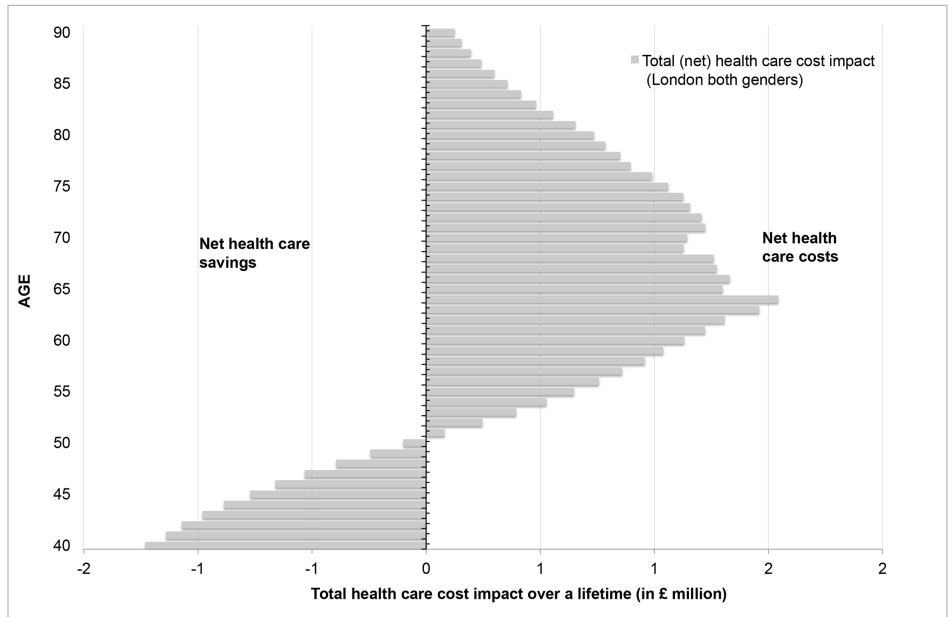


(a) London

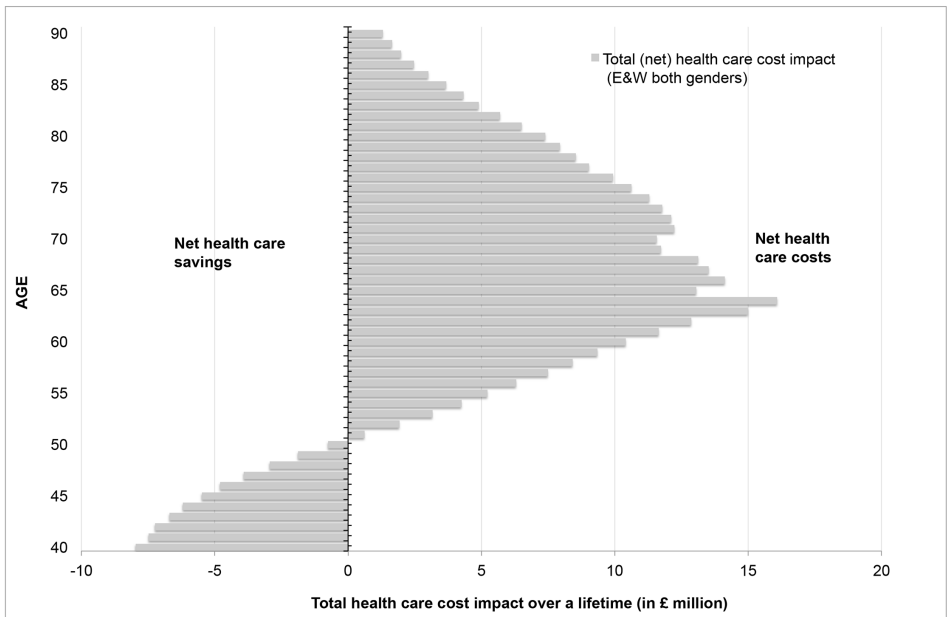


(b) England and Wales

Figure 7.2: Distribution of QALY gain by age and gender.



(a) London



(b) England and Wales

Figure 7.3: Distribution of total net health care cost impact by age and gender.

7.3 Uncertainty analysis

7.3.1 Outcomes distributions

Handling uncertainty in non statistically significant risk estimates

As was indicated in Table 4.1 in Chapter 4, out of the seven risk estimates used to parameterise the “intervention-effect”, three are not statistically significant at 5% significance level since they include the value of 1, i.e. “no effect”, in their 95% confidence interval. These three risk estimates are : $OR_{Dev.COPD}$; $HR_{Dev.CHD}$ and $HR_{DeathOAC|H}$, which were used to derive respectively RRE_a , RRE_b and RRE_g .

When carrying out Monte Carlo simulations, a random draw of a risk estimate value below 1, implies that air pollution reduction will increase the risk of adverse event. There is, however, general consensus that air pollution has deleterious effects on health and that reducing it cannot harm population health (Holland, 2014). On these grounds, recently released European guidelines for uncertainty analysis in HIA of interventions of air pollution reduction (HRAPIE group) recommend to adopt: “a range of +/-100% with a uniform distribution” for non statistically significant risk estimates (Holland, 2014) (pp 42).

The guidelines have the advantage of getting rid of the improbable possibility that reducing air pollution may damage public health. However, they are underpinned by the assumption that the mean effect size is true and that the variance was wrongly estimated, whilst no evidence supports this. Therefore, as will be further discussed in section 7.5, they potentially misleadingly reduce decision uncertainty. An alternative approach was therefore considered. It consists in truncating only the left-tail of the original distributions of non statistically significant risk estimates by assigning a value of 1 to randomly drawn values below 1. Truncating only the left-tail of risk estimates’ distribu-

tions, as opposed to truncating both tails as recommended by the guidelines, will to some extent shift risk estimates mean values and the mean of outcome measures to the right. On the other hand, this approach has the advantage of capturing all the information concerning the possible non implausible values that risk estimates can take.

Another alternative may be to simply get rid of all three non statistically significant risk estimates. However, the lack of statistical significance does not necessarily equate with true absence of effects and solely means that we failed to demonstrate effect for a given - arbitrary - significance level. In light of the overall body of evidence of positive association between air pollution and adverse effects on the cardio-respiratory system described in Chapters 2 and 4, ignoring existing evidence based on arbitrary rules of inference (Claxton, 1999) does not appear appropriate.

Table 7.2 summarises the three modelling approaches used to handle uncertainty in the three non statistically significant risk estimates. It should be underlined that A1 (no truncation) is the base case approach to computing mean estimates. Figure 7.4 compares the distributions of the three risk estimates obtained under each approach. As the magnitude of risk estimates is relatively small, for ease of comparison, results are provided for $\Delta_{PM2.5} = +10\mu g/m^3$, i.e. before rescaling as RRE for $\Delta_{PM2.5} = -1\mu g/m^3$.

Since A2 (guidelines) consists in truncating both tails of the original distributions of non statistically significant risk estimates, the distributions obtained under A2 remain centred around original mean values, but have a much smaller standard deviation. Under A3, truncating the left-tail of the original distributions of $HR_{Dev.CHD}$ and $HR_{DeathOAC|H}$ only slightly shifted their mean value. By contrast, as the left-tail of the original distribution of $OR_{Dev.COPD}$ reached quite below 1, the mean of the obtained distribution for this risk estimate noticeably shifted from 1.12 to 1.24.

Figure 7.4 clearly shows that by assigning a value of 1 to any draws of values below 1, as opposed to imposing 1 and “mean effect + 100%” as respectively the minimum and maximum values that risk estimates can take, A3 allows for a much larger possibility of no intervention effect than A2 with regards to

health events “Dev. COPD”, “Dev. CHD” and “Death from AOC”¹.

¹AOC stands for All Other Causes than COPD, CHD and lung cancer.

Modelling approach	Description
A1 ^(a)	Fit a log-normal distribution around original mean and standard error. Also referred to as: “No truncation”. It is the base case approach used for computing mean results.
A2	Fit a uniform distribution to a range of values bounded by mean +/-100%. Also referred to as: “Guidelines”.
A3	Fit a log-normal distribution around original mean and standard error but assign the value of 1 to random draws of values below 1. Also referred to as: “Left-tail truncation”.

Table 7.2: Modelling approaches used to assess uncertainty in non statistically significant risk estimates.

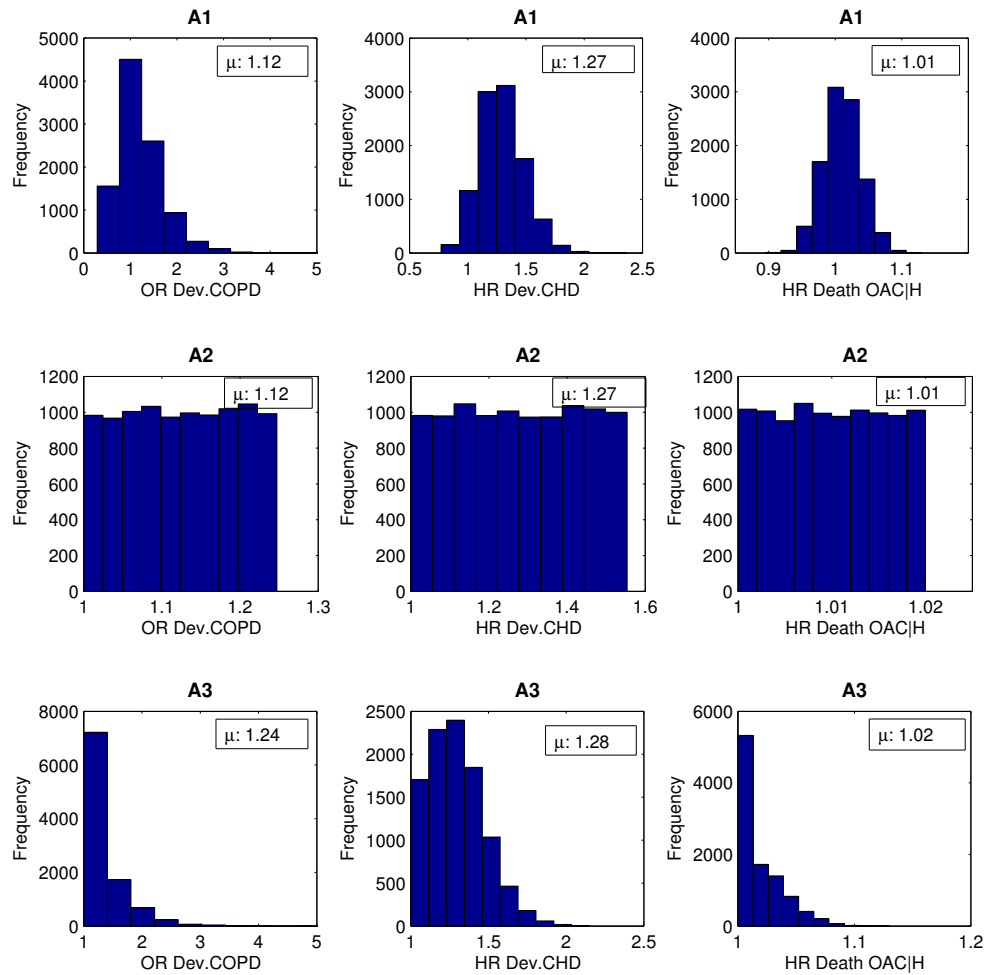


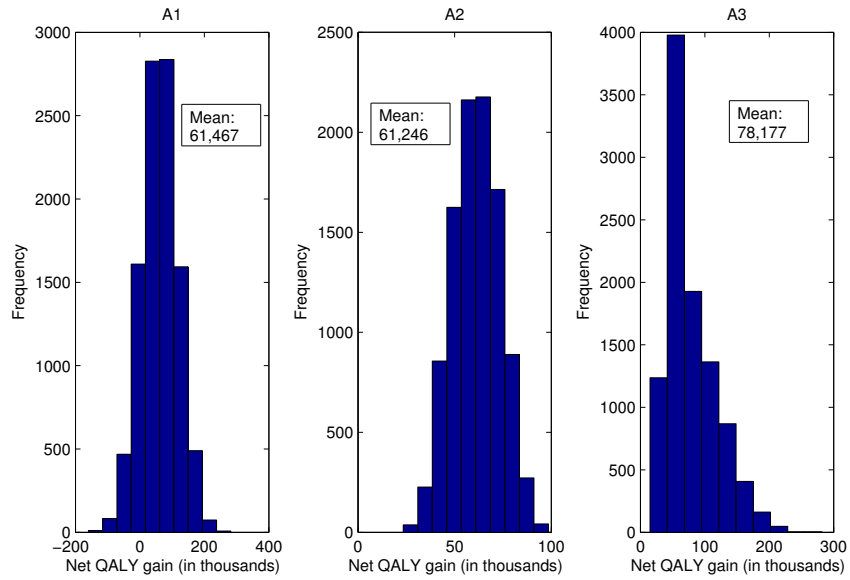
Figure 7.4: Distribution of risk estimates obtained under each modelling approach ($\Delta_{PM2.5} = +10\mu g/m^3$).

Obtained distributions of outcomes

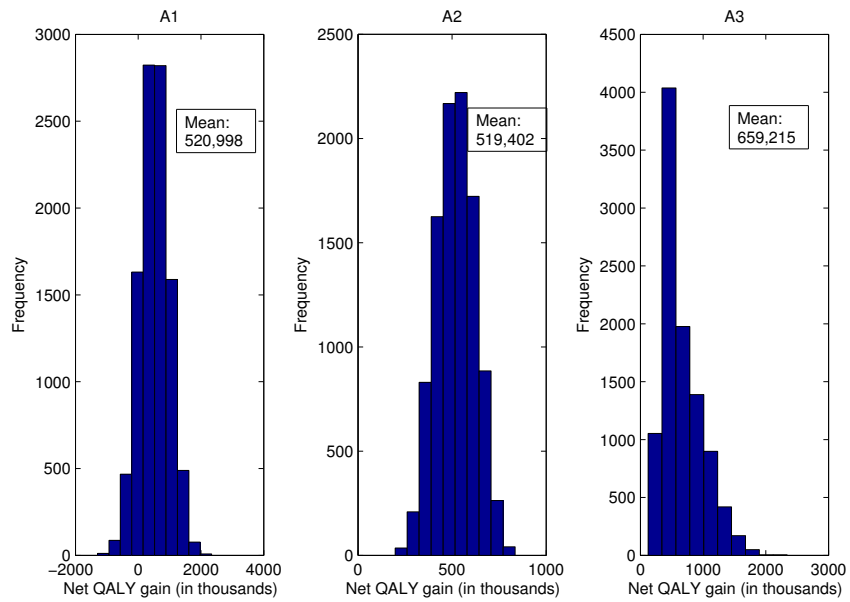
Figure 7.5 represents for each target population the distribution of net QALY gain obtained from Monte Carlo simulations, under each approach to handling uncertainty in non statistically significant risk estimates as defined in Table 7.2. As expected, the distribution of net QALY gain is the widest under A1 and the narrowest under A2.

Under A1, since the original distributions of non statistically significant risk estimates were left unmodified, the distribution of net QALY gain has a tail of negative values, which suggests that there is a non-negligible probability (about 10%) that reducing particulate air pollution could harm health.

As expected, mean outcomes under A2 and A1 are equal. By contrast, mean net QALY gain under A3 is about 25% greater (27.2% for London; 26.5% for England and Wales) than under A1 or A2. It is worth noting that about a quarter of the difference in net QALY gain between A3 and A1 or A2 is due to health care cost impacts. Indeed, under A3, on average the intervention is associated with net health care savings (£33 million for London and £195 million for England and Wales), as opposed to net health care costs under A1 or A2 (£24 million for London and £263 million for England and Wales). This reflects the fact that under A3, the intervention's capacity to reduce COPD incidence and thus, to reduce the health care cost burden of the disease, is expected to be stronger than under A1 or A2 (see Figure 7.4).



(a) London.



(b) England and Wales.

Figure 7.5: Distribution of net QALY gain by modelling approach.

A1: No truncation; A2: Guidelines; A3: Left-tail truncation.

7.3.2 Sensitivity analyses - cessation lag and discount rate

Table 7.3 and Table 7.4 report results of the analysis of the sensitivity of mean outcomes to dynamics in risk reduction, known as cessation lag, and discounting. Sensitivity scenarios were described in Table 4.4. of Chapter 4 and are briefly restated below. Mean estimates were obtained based on approach A1 (no truncation). Results are expressed in percentage change against base case results using net QALY gain as summary metric. The small difference in results between the two target populations essentially reflects their different age and gender structures, as previously underlined by Figures 7.2 and 7.3.

Cessation lag

The two scenarios pertaining to the dynamics of risk reduction assessed the effect of respectively:

- (i) no cessation lag (No CL), where the decrease in risk of all adverse health events under intervention applies fully from time 0;
- (ii) a mixed lag (Mixed CL), resulting from a mixture of the US EPA's 20-year distributed cessation lag with a lag specific to lung cancer, for which in light of evidence on smoking cessation, the decrease in risk is expected to be take place gradually over 40 years;

These two scenarios were assessed against the base case scenario which applies the US EPA's 20-year distributed lag to the reduction in all risks of adverse health events.

In order to assess the influence of the cessation lag independently from the discounting effect, differences in un-discounted life years gains were also reported in Table 7.3. Net QALY gain in the "No CL" scenario is 16% larger than in the base case scenario. By contrast, the difference in outcome between the base case and the "Mixed CL" scenario is small (3% difference), owing to the low baseline risk of developing lung cancer, relative to developing COPD or CHD. As expected, discounting amplifies results' sensitivity to the structure

of the cessation lag, whereby for each scenario comparison, the difference in net QALY gain is greater than the difference in un-discounted life year gain.

Figure 7.6 shows the impact of the cessation lag structure on the average QALD gain per person (gender-average) for each age group. The shorter the remaining life expectancy of individuals, the more their health gain is impacted by the cessation lag structure. Indeed, in the absence of a cessation lag, the average QALD gain of a 40-year old person would be 10% greater than in the base case scenario, whereas the average QALD gain of a 70- and a 80-year old person would be respectively 30% and 50% higher.

The comparison of QALD gain between the base case and “Mixed CL” scenarios provides a more subtle picture. Whilst the difference in health gain between the two scenarios initially grows with age, it slowly decreases as from age 70 since after this age, the risks of other adverse events are increasingly more prominent than the risk of lung cancer incidence. In other words, dynamics in lung cancer risk reduction have progressively less influence on the overall health gain among older age groups.

		Scenarios	
		No cessation lag	“Mixed” cessation lag
London	Net QALY gain	+ 15.9 %	- 3.1%
	LY gain	+ 9.0%	- 2.3%
England and Wales	Net QALY gain	+ 17.3 %	- 3.2%
	LY gain	+ 10.2%	- 2.3%

Table 7.3: Sensitivity of results to cessation lag

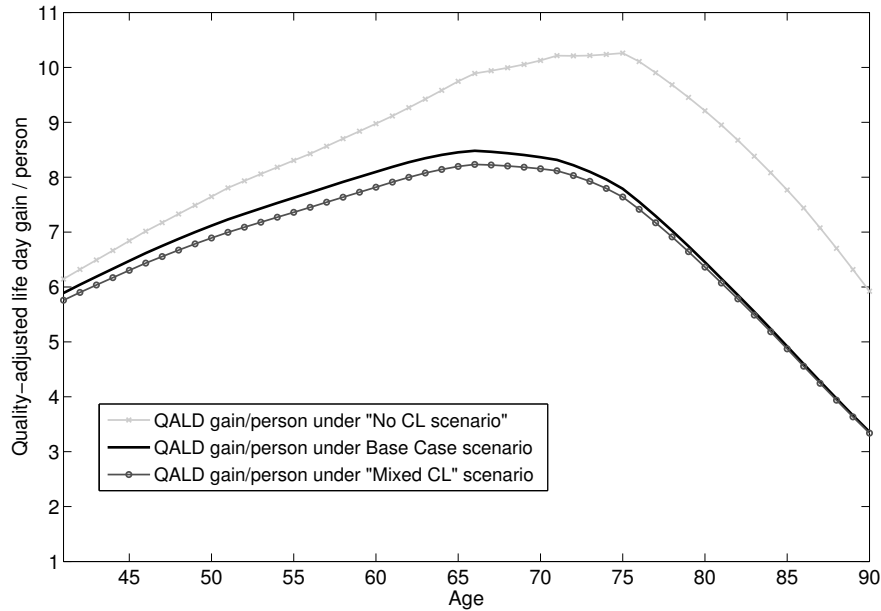


Figure 7.6: Impact of cessation lag structure on QALD gain per person

Discount rate

Two alternative scenarios of discounting based on recommendations from the UK treasury (Lowe, 2008) were used as an alternative to the base scenario, which applies a 3.5% discount rate p.a. In the “Staged discounting 1” scenario, a discount rate of 3.5% p.a. was applied in the first 30 years and a lower rate of 3% p.a. was applied from year 31 to 60. In the “Staged discounting 2” scenario, which excludes the element of pure social time preference, a discount rate of 3% p.a. was applied in the first 30 years and a rate of 2.57% p.a. was applied from year 31 to 60.

Decreasing the discount rate to 3% p.a. after the first 30 years would lead to an increase in total net QALY gain by about 7%, whereas decreasing the discount rate as from year 1 in “Staged discounting 2” would boost net QALY gain by about 20%. Results for London are slightly more sensitive to the choice of discount rate than results for England and Wales as the London population is slightly younger.

Figure 7.7 shows the impact of the choice of discounting structure on the

average QALD gain per person for each age group. The younger individuals are clearly the greatest beneficiaries of a lower rate of discounting. In the “Staged discounting 2” scenario for instance, individuals aged 40 would gain 35% more QALD than in the base case scenario, whereas individuals aged 60 would only benefit from 15% more health gain. Since the “Staged discounting 1” scenario consists in decreasing the discount rate after 30 years only, it would impact solely upon the health gain accruing to adults currently aged below 65.

		Scenarios	
		Staged discounting 1	Staged discounting 2
London	Net QALY gain	+ 6.9 %	+ 19.8%
England and Wales	Net QALY gain	+ 6.1%	+ 18.3%

Table 7.4: Sensitivity of results to the choice of discount rate.

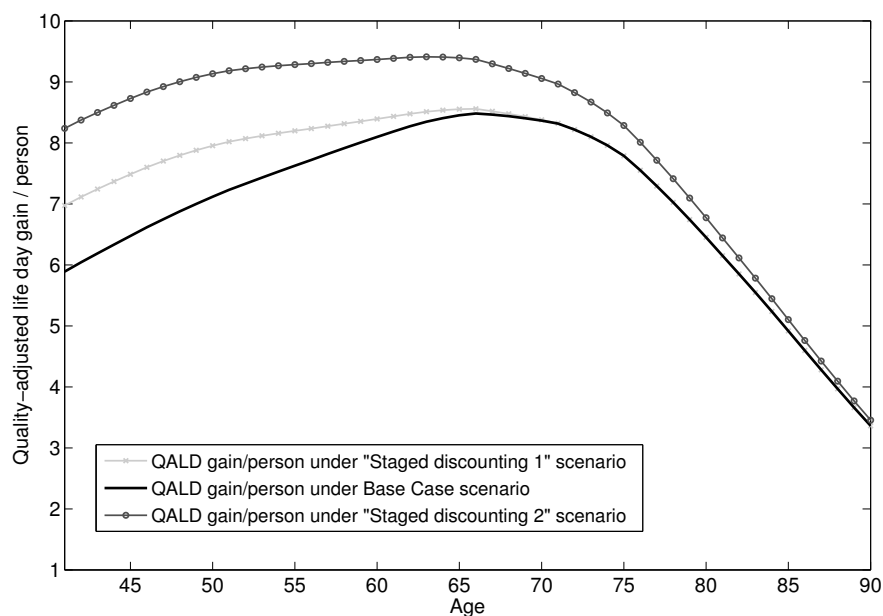


Figure 7.7: Impact of discounting structure on QALD gain per person

7.4 Comparative analysis

7.4.1 Comparison of methods: life-table vs. Markov modelling

As mentioned in Chapter 4 section 4.1, an alternative methodology used in past QALY analyses of air pollution control interventions consists in applying quality of life adjustments to life years gains computed using life-tables. In addition to the issue pertaining to the correct choice of HRQoL weights, it was argued that this approach would underestimate interventions' total QALY gain by failing to capture the quality of life gain associated with a reduction in chronic morbidity.

It was also argued that, by ignoring health-related differential susceptibility to air pollution exposure which drives the distribution of impacts among population subgroups stratified by health status, such a simplistic approach would not support an accurate estimation of QALY gains. On these grounds, it is of particular interest to compare the present QALY results, with estimates that would be obtained using the life-table approach.

The life-table method was described in Chapter 3. It consists in comparing survival curves, calculated from annual probabilities of death cumulated over time, under a pollution change as opposed to “business as usual”. The area between the two curves represents the average life expectancy impact associated with air pollution decrement (increment). Since it focuses only on life expectancy effects, the life-table can be represented as a Markov model with two health states: “Healthy” and “Dead”.

In order to compare the Markov model developed in Chapter 4 and the life-table approach, a 2-state model was constructed and parameterised with: (i) the age and gender-specific probabilities of death from all causes in the general population of England and Wales (ONS, 2011) and (ii) the risk estimates from all cause mortality estimated in Chapter 6 (i.e. RRE_d of Table 4.1). Life-table analysis based on this 2-state model was applied to the exact same case study presented in Chapter 4 (i.e. $1\mu\text{g}/\text{m}^3$ decrement in $PM_{2.5}$ concentrations; US

EPA cessation lag, 3.5% discount rate), using London as a target population.

Life years gain were then multiplied with age and gender-specific HRQoL weights for England provided by Kind et al. (1999). It should be underlined that these weights were elicited from a representative sample who considered themselves to be healthy. Applying those weights to life years gains computed from life-table analysis will therefore lead to a greater gain than would be obtained by using weights for the general population of England, in line with the underlying prevalence of chronic illnesses.

Since the life-table approach does not take into account health-related differential susceptibility, the comparison of QALY estimates generated by this method against the presently developed Markov model was based on two scenarios: (i) base case and (ii) a scenario that ignores health-related differential susceptibility, hereafter referred to as “No Diff. Susc.” scenario. In addition, as the life-table method cannot link costs to health outcomes except death, health care cost impacts were not considered in the present comparison.

The difference in mean QALY estimates for London (modelling approach A1) between the two methods is presented in Table 7.5 for each scenario.

	Markov modelling (MM)		Life-table (LT)	Difference	
	Base case	No Diff. Susc.		LT vs. MM (Base case)	LT vs. MM (No Diff. Susc.)
QALY gain (London)	63,293	41,457	38,463	-39%	-6 %

Table 7.5: Markov modelling vs. life-table approach.

Under the scenario of no differential susceptibility, the two methods provide relatively similar results. Nevertheless, in line with expectations, even by applying HRQoL weights that overestimate the true level of quality of life of the general population (since based on healthy subjects), the QALY gain estimated by the life-table approach is 6% lower than the one estimated by the present Markov model. This stems from the fact that, as argued in Chapter 4, the life-table approach does not encompass the quality of life gain from

reduced morbidity.

The principal finding however, is that health-related differential susceptibility to air pollution drives the difference in outcomes between the two methods. When encompassing health-related differential susceptibility (i.e. base case scenario), the total QALY for London obtained from the presently developed Markov model is 39% higher than the QALY obtained from life-table analysis.

It may be argued that the present model overestimates effects accruing to those who do not belong to susceptible population subgroups. This, however, appears to be unlikely. Indeed, the model is structured such that alive individuals may have either of the following four health status: (i) with CHD; (ii) with COPD; (iii) with lung cancer; (iv) healthy, i.e. without any of the three diseases. In light of the age and disease severity conditions that characterised the subjects in epidemiological studies informing differential susceptibility, the only population subgroups expected to suffer disproportionately from particulate air pollution (PM) exposure are: (i) individuals with CHD above 75 years old and (ii) individuals with COPD in stages 3 or 4 aged above 65 years old (see Chapter 4). This leaves: (i) individuals with CHD aged below 75; (ii) individuals with COPD in stage 1 or 2 (all ages) or in stages 3 and 4 aged below 65; (iii) individuals with lung cancer and (iv) “healthy” individuals, as remaining population subgroups. The first two of these subgroups are conservatively assumed to have the same susceptibility to air pollution as the general population. For the reasons explained in Chapter 4, no PM-related excess risk of death was applied to individuals with lung cancer.

Finally, the PM-related excess risk of mortality that was applied to “healthy” individuals pertains only to causes of death excluding cardio-respiratory and lung cancer causes. To check for the possibility of effects over-estimation in individuals of the general population, a sensitivity scenario where “healthy” individuals were assumed not to suffer from any excess mortality risk due to PM exposure (i.e. $HR_{DeathAOC|H} = 1$) was evaluated. This scenario was found to be associated with a small 4% decrease in net QALY gain, which confirms that the excess risk of mortality in “healthy” individuals does not drive the health gains associated with the intervention. It can therefore be concluded that it is unlikely that the present model overestimates effects.

Comparative analysis therefore shows that, ignoring the current body of epidemiological evidence on health-related differential susceptibility to air pollution (Zanobetti et al., 2008; Zanobetti & Schwartz, 2007; Tonne & Wilkinson, 2013), as is currently done when using the life-table approach, is expected to substantially underestimate the total health gain of air pollution control. Importantly, as will be further discussed in section 7.4.3, this finding is not relevant only for QALY analysis but also for life expectancy impact analysis as is traditionally performed in HIA.

Since air pollution not only affects people differently according to their health status, but also impacts upon the risk on entering health-related susceptible subgroups, the only possible approach to fully handling health-related differential susceptibility is via “simultaneous modelling” of impacts as advocated in Chapter 3. This finding therefore further demonstrates the inadequacy of the “separate” approach to quantification currently used in HIA.

7.4.2 Impact of CHD vs. COPD-related differential susceptibility

In order to identify which of CHD or COPD-related greater susceptibility to air pollution exposure drives the QALY gain and health care cost impacts of air pollution reduction, the scenarios of no CHD-related greater susceptibility and no COPD-related greater susceptibility were evaluated for London. Results are presented in Table 7.6, alongside results for the base case and the “No Diff. Susc.” scenarios.

Table 7.6 shows that CHD- and COPD-related greater pre-disposition to die prematurely due to PM exposure account for respectively 16% and 19% of the total QALY gain associated with the intervention in the base case scenario. It is worth noting that, by driving the distribution of life expectancy gain by population subgroups stratified by health status and thus, by level of cost to the health care system, health-related differential susceptibility also substantially influences the total health care cost impact of the intervention. In particular,

ignoring COPD-related differential susceptibility would lead to a net health care saving of £44 million, as opposed to a net health care cost of £24 million in the base case scenario. If both CHD and COPD-related susceptibility were ignored, the intervention would be expected to yield a net saving to the NHS of £55 million.

Therefore, the reduction in QALY gain in the “No Diff. Susc.” scenario (-34%) is partly compensated by health care resource savings. Overall, health-related differential susceptibility contributes to a quarter (26%) of the net QALY gain associated with the intervention in the base case scenario.

	Base case	No CHD-related Susc.	% diff.	No COPD related Susc.	% diff.	No Diff. Susc	% diff. (^a)
QALY gain	63,293	53,180	-16%	50,856	-19%	41,457	-34%
Total HC cost impact (in £m)	24	11	-53%	-44	-284%	-55	-329%
Net QALY gain	61,467	52,326	-15%	54,211	-12%	45,637	-26%

(^a) Percentages do not exactly sum up do your rounding.

Table 7.6: Results’ sensitivity to CHD- and COPD-related differential susceptibility.

7.4.3 Comparison with empirical estimates from past HIAs

Since this work represents the first attempt to measure the QALY impact of air pollution reduction in a UK setting, there are no relevant comparator from the empirical literature. By contrast, estimates of un-discounted life year (LY) gain are amenable to comparison with results from past HIAs of interventions of air pollution control. This metric as the advantage of being independent of any assumptions regarding the application of HRQoL weights and of the choice of discount rate.

The un-discounted life expectancy impact of reducing $PM_{2.5}$ concentrations in London was investigated as part of the European-funded Aphekom Project

(Pascal et al., 2013), as well as in a study commissioned by the Greater London Authority and carried out by Miller (2010). Evaluation of the effects of particulate air pollution on mortality in England and Wales was performed by the Health Protection Agency and communicated under the Committee on the Medical Effects of Air Pollutants report (COMEAP, 2010). All three studies relied on the life-table methodology and used the same risk estimate of all-cause mortality ($HR_{AC} = 1.06$ for $\Delta_{PM_{2.5}} = 10\mu g/m^3$ estimated by Pope III et al. (2002)).

As exemplified by the above cited-studies, there are at least three main ways of expressing life expectancy impacts in a given target population. “Total LY gain” depends on the size of the target population and the duration of its follow-up and therefore, is not adequate for comparing results between studies based on different target populations or follow-up duration, as is presently the case. The “average life expectancy gain per person of a target population” has the main advantage of being independent of the target population size and is typically computed over a person’s a lifetime. This metric will however, be influenced by the age structure of the target population whereby the younger the target population is, the greater the average LY gain per person will be. Finally, “life expectancy at birth or at a given age” has the advantage of being independent from both the size and the age-distribution of the target population.

Table 7.7 compares the mean estimates of life expectancy impacts provided by the presently developed Markov model (modelling approach A1) with results from past HIAs using: (i) average life expectancy gain per person of the target population and (ii) life expectancy at 30 or 40 as metrics. Since all three HIAs relied on the life-table method, they all ignored health-related differential susceptibility. Consequently, similarly to section 7.4.1, comparison was based on the base case and the “No Diff. Susc.” scenarios. When necessary, results were converted to a $1\mu g/m^3$ decrement in $PM_{2.5}$ concentrations and results’ sensitivity to the use of a cessation lag was taken into account.

This comparative analysis is mainly illustrative since the scope of target population between the HIAs and the present study is not exactly similar.

For instance Miller (2010) applied PM-related excess risk of mortality to all currently alive individuals, i.e. aged 1 to 100 years old, whereas as justified in Chapter 4, the present analysis focused on adults aged 40 to 90. The primary objective of this comparative analysis is therefore essentially to assess whether the direction and magnitude of the difference in results are in line with expectations. For instance, in light of the above discussion on the impact of the target population age structure on average gain estimates, the present results are expected to be lower than the ones from Miller (2010). Similarly, in the absence of discounting, present estimates of life expectancy gain at age 40 are expected to be slightly lower than estimates of life expectancy gain at age 30 provided by COMEAP (2010) and Pascal et al. (2013).

		Un-discounted life day gain/person for $\Delta PM_{2.5} = -1\mu g/m^3$				
Lag (a)		Past HIA results	Present results (Base case)	Diff.	Present results ("No Diff Susc")	Diff.
Young Adults	Yes	20 (age 30) COMEAP (2010) (b)	32.2 (age 40)	61%	22 (age 40)	10%
	No	24.2 (age 30) Pascal et al. (2013) (c)	33.1 (age 40)	37%	22.8 (age 40)	-6%
Average London popula- tion	Yes	19.3 (age 1-100) Miller (2010) (d)	25.8 (age 40-90)	33%	16.2 (age 40-90)	-16%

Table 7.7: Comparison of un-discounted life year gain estimates with results from past HIA studies.

(a) US EPA 20-year distributed cessation lag (US EPA, 2010).

(b) Whilst results were reported as life expectancy at birth for the 2008 birth cohort, risk estimates of mortality were only applied as from age 30.

(c) Reported results were 2.5 months gain /person aged 30 for $\Delta PM_{2.5} = -3.1\mu g/m^3$.

(d) Reported results were 405,659 life years gain for a target population composed of all currently alive individuals in London in 2008 (7,673,217 persons).

Table 7.7 provides two main findings. First, under the "No Diff. Susc." scenario, the difference between present estimates and results from Miller (2010) and Pascal et al. (2013) is in line with expectations, when one takes into account age differences in target population (present estimates are respectively

16% and 6% lower). Against expectations, presents results are higher than those provided by COMEAP (2010). The latter are, however, substantially lower (by 17%) than results from Pascal et al. (2013). Whilst these two studies differ in their application of a cessation lag, sensitivity analysis results reported in section 7.3.2 showed that the cessation lag has a relatively small impact on the health gain accruing to young individuals.

Second, base case results, which encompass health-related differential susceptibility are well above estimates from past HIAs. The difference between base case results and results from Pascal et al. (2013) and Miller (2010) is of similar magnitude than the difference found by comparing the life-table method and Markov modelling when using the QALY as health metric (see section 7.4.1). This finding further underlines that, even for life expectancy analysis, ignoring health-related differential susceptibility by relying on the “separate” approach to quantification, is expected to substantially underestimate the health gain from air pollution control.

7.5 Cost-effectiveness analysis of air pollution abatement in London

7.5.1 Preliminaries

Based on the modelled estimates of net QALY gain associated with a 1 μg decrement in $PM_{2.5}$ concentrations, this section aims to assess the cost-effectiveness of investments aimed at curbing fine particulate air pollution in London.

Section 7.3 underlined a number of sources of uncertainty surrounding the expected benefits of reducing air pollution. A major source of uncertainty

is uncertainty around parameter point estimates. Since it is highly improbable that air pollution reduction would harm health, cost-effectiveness analysis will be performed using the three different approaches to handling parameter uncertainty in the three non statistically significant risk estimates used in the model ($OR_{Dev.COPD}$, $HR_{Dev.CHD}$ and $HR_{DeathOAC|H}$), described in Table 7.2 of section 7.3.1. Briefly, A1= no truncation of original distributions of risk estimates; A2= guidelines (both tails truncation) and A3= left-tail truncation.

Secondly, the various possible views of the speed at which the risks of adverse events may decrease following pollution decrement, i.e. shape of cessation lag, represents a source of structural uncertainty. If the range and likelihood of possible scenarios of the cessation lag were known, cost-effectiveness evaluation could be performed by taking the expectations of net benefit across the joint-distribution of uncertain parameters and the likelihood of all possible scenarios of cessation lag (Claxton et al., 2012). However, the scenarios of cessation lag evaluated in section 7.3.2 were mainly illustrative, as the range and likelihood of possible lag scenarios remain largely uncertain. As a result, the present cost-effectiveness analysis will rely on the 20-year distributed lag (US EPA 2010) that was used in the base case scenario.

Whilst results are also sensitive to the choice of discount rate, this parameter does not qualify as a source of uncertainty but instead, as a choice that needs to be made by the decision-maker. The present cost-effectiveness analysis will rely on a 3.5% discount rate as used in the base case scenario.

In addition, results were found to be strongly influenced by health-related differential susceptibility to air pollution, whereby ignoring it would lead to a reduction in net QALY gain by one fourth (see section 7.4.2). Since the ability to capture health-related differential susceptibility is a key difference between the Markov-modelling based simultaneous approach to quantification advocated throughout this thesis and the “separate” approach currently used in HIA, cost-effective analysis will be evaluated for both the base case and the “No Diff. Susc.” scenarios. The objective is to assess whether consideration of health-related differential susceptibility may impact investment decisions in air pollution control.

Cost-effectiveness evaluation will be carried out from the two payers perspectives set out in section 7.2.2: (i) the NHS perspective, where the investment is assumed to fall on the NHS budget constraint and (ii) the private consumption (PC) perspective, where the investment is assumed to be funded by general taxation.

From the PC perspective, health care cost impacts are converted into QALY gain (loss) equivalent based on a fixed value of £13,000/QALY that is estimated to represent the NHS expenditure required to deliver one QALY (see section 7.2.2). By contrast, from the NHS perspective, health care costs impacts are converted to QALY equivalent based on the same rate at which QALY gains are monetized. The difference in the computation of the net monetary benefit (NMB) of intervention between the two perspectives is shown by equations 7.1 and 7.2 .

$$NMB_{NHS} = (QALY\ gain * k - HC\ costs) - I \quad (7.1)$$

$$NMB_{PC} = (QALY\ gain - \frac{HC\ costs}{13,000}) * v - I \quad (7.2)$$

where I stands for investment cost, k represents the value of health to the NHS and v represents the consumption value of health. When $v = k = 13,000$ both approaches are identical.

In line with the case study, cost-effectiveness will be evaluated for an intervention associated with an immediate and sustained $1\mu g/m^3$ decrement in population-weighted mean ambient $PM_{2.5}$ concentrations in London, which would represent a 7% decrease in current concentrations.

In order to assess the sensitivity of the cost-effectiveness performance of such an intervention to the size of investment required, three investment costs will be assessed: £100 million, £500 million and £1 billion. Investments are expected to be financed today as a lump-sum payment. Whilst these costs are hypothetical, they seem plausible when compared to government estimates for interventions aiming at reducing air pollution, though £1 billion is expected to be an upper estimate. For example, the UK Department of Transport recently

pledged to commit a minimum of £200 million to support the early market for ultra low emission vehicles, in order to help achieve London’s ultra low emission zone (Department for Transport, 2014).

It should be underlined that, as mentioned in Chapter 4, benefits are expected to scale linearly to further reduction in concentrations. Therefore, assuming an absence of economy or diseconomy of scale associated with a decrease in emissions, if the intervention costing £1 billion were to reduce $PM_{2.5}$ concentrations twofold with respect to the intervention costing £500 million, it would have the same probability of being cost-effective.

For each investment size, cost-effectiveness evaluation will be structured around the following questions:

- (i) “Is the intervention likely to be cost-effective?”;
- (ii) “When is the investment expected to break-even?”;
- (iii) “Is it recommended to wait for more information before going ahead?”.

7.5.2 Is the intervention likely to be cost-effective?

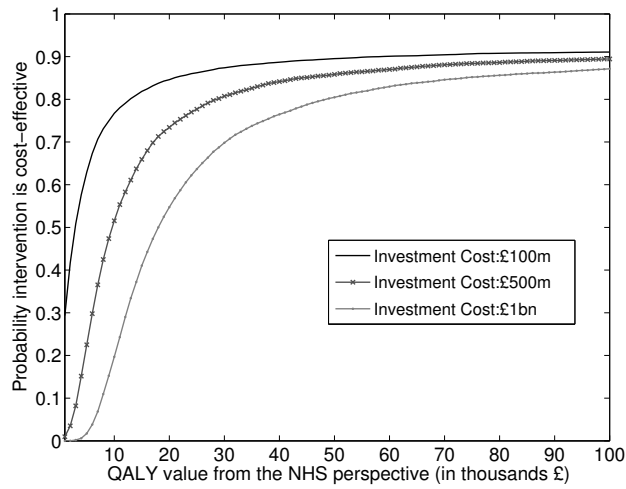
Cost-effectiveness probabilities and CEAC

For each random draw from the set of distributions fitted to uncertain parameters, hereafter denoted by the letter θ , the probability that each investment is cost-effective (i.e. $NMB \geq 0$) can be computed for a specific money value of a QALY. Expected cost-effectiveness probabilities for a given value of v or k are then found by averaging probabilities across the joint distribution of uncertain parameters (θ) and can be represented via a cost-effectiveness acceptability curve (CEAC) (Barton et al., 2008).

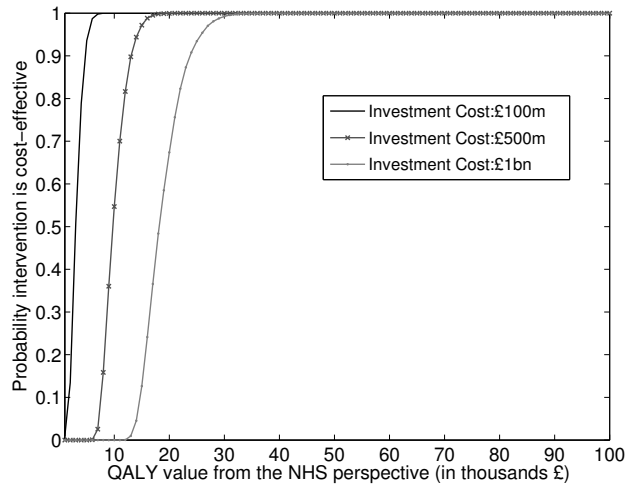
Although the values of $k = £13,000/QALY$ and $v = £65,000/QALY$ underpin the present cost-effectiveness analysis, it is of interest to assess the

sensitivity of cost-effectiveness results to the money value of health. Indeed, the WTP values for a QALY were found to vary greatly (Ryen & Svensson, 2014). In addition, whilst the shadow price of the NHS budget constraint has been estimated at £13,000/QALY (Claxton et al., 2013), NICE suggests a threshold value comprised between £20,000 and £30,000/QALY for cost-effectiveness assessment of health care technologies (NICE, 2013) and was found empirically, to use a threshold value around £40,000/QALY (Dakin et al., 2013).

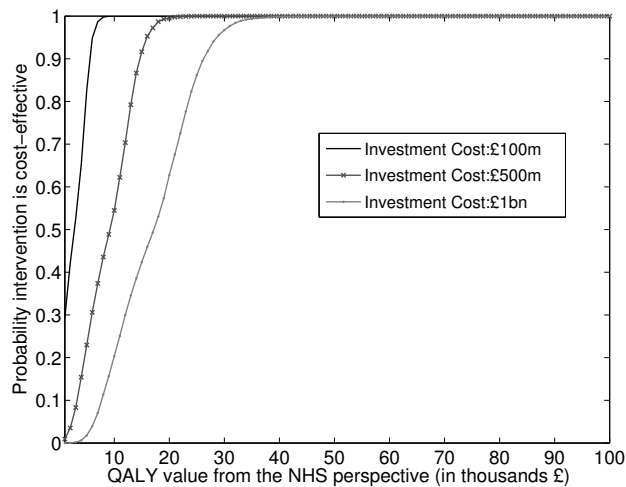
Figures 7.8 and 7.9 depict CEACs according to each approach to handling parameter uncertainty in non statistically-significant risk estimates (A1 to A3) from respectively the NHS and the PC perspective. CEACs pertaining to the “No Diff. Susc.” scenario are presented in Figures 7.10 and 7.11. In addition, Table 7.8 and Table 7.9 provide: (i) the expected NMB of investment and (ii) the probability that the investment is cost-effective $P_{INV}(CE)$ for $k = £13,000/QALY$ and $v = £65,000/QALY$ for respectively the base case and the “No Diff. Susc.” scenario.



(a) A1 "No truncation"

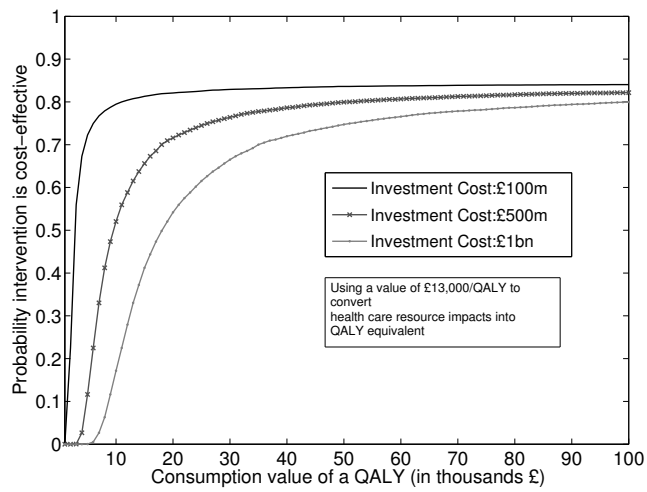


(b) A2 "Guidelines"

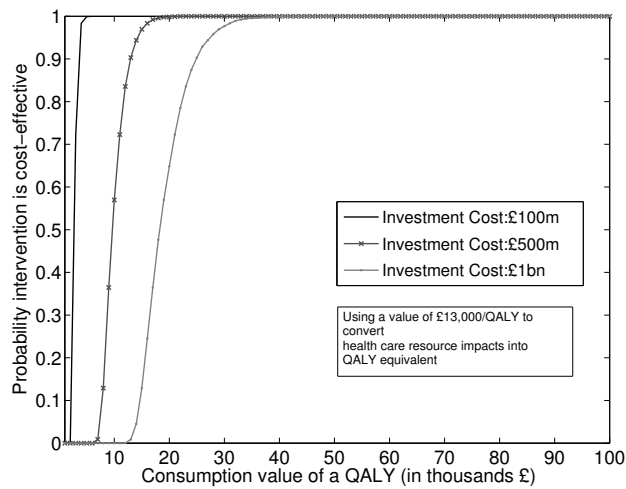


(c) A3 "Left-tail truncation"

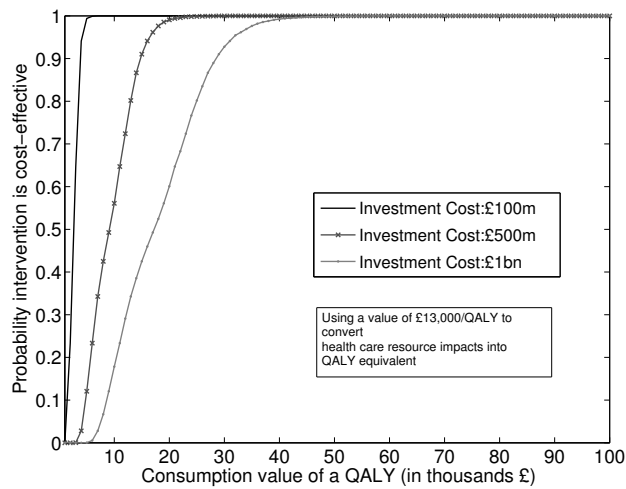
Figure 7.8: Probabilities that the intervention is cost-effective - Base case scenario - NHS perspective.



(a) A1 "No truncation"



(b) A2 "Guidelines"



(c) A3 "Left-tail truncation"

Figure 7.9: Probabilities that the intervention is cost-effective - Base case scenario - PC perspective.

		$k = \pounds 13,000/QALY$			$v = \pounds 65,000/QALY$		
		£100 m	£500 m	£1 bn	£100 m	£500 m	£1 bn
A1	$E_{\theta}(NMB)$ (in £m)	699	299	-201	3,895	3,495	2,995
	$P_{INV}(CE)$	0.81	0.64	0.37	0.84	0.81	0.77
A2	$E_{\theta}(NMB)$ (in £m)	696	296	-204	3,881	3,481	2,981
	$P_{INV}(CE)$	1	0.94	0.05	1	1	1
A3	$E_{\theta}(NMB)$ (in £m)	916	516	16	4,981	4,581	4,081
	$P_{INV}(CE)$	1	0.87	0.38	1	1	1

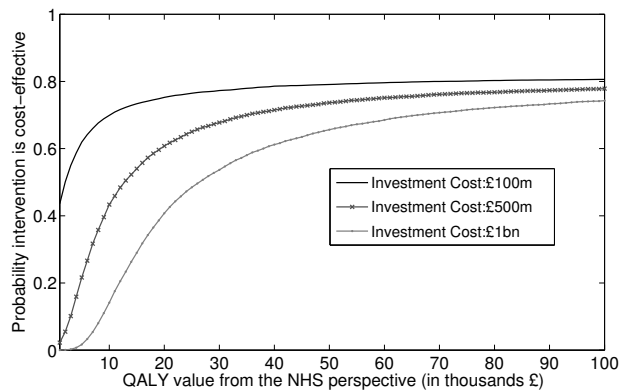
Table 7.8: Cost-effectiveness probabilities and expected net monetary benefit - Base case scenario.

A1= No truncation; A2= Guidelines; A3= Left-tail truncation.

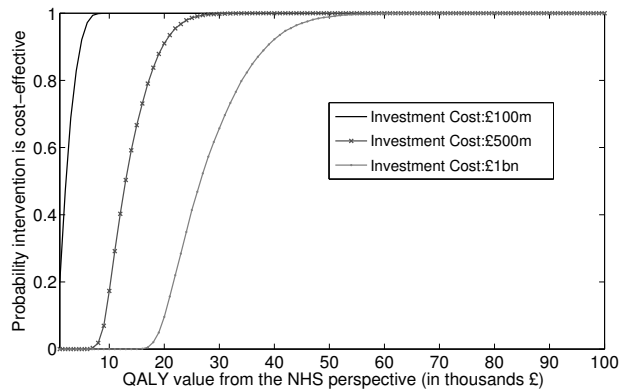
		$k = \pounds 13,000/QALY$			$v = \pounds 65,000/QALY$		
		£100 m	£500 m	£1 bn	£100 m	£500 m	£1 bn
A1	$E_{\theta}(NMB)$ (in £m)	493	93	-407	2,866	2,466	1,966
	$P_{INV}(CE)$	0.73	0.52	0.23	0.76	0.73	0.68
A2	$E_{\theta}(NMB)$ (in £m)	485	85	-414	2,827	2,427	1,927
	$P_{INV}(CE)$	1	0.60	0	1	1	1
A3	$E_{\theta}(NMB)$ (in £m)	697	297	-203	3,886	3,486	2,986
	$P_{INV}(CE)$	1	0.56	0.27	1	1	0.98

Table 7.9: Cost-effectiveness probabilities and expected net monetary benefit - No Diff. Susc. scenario.

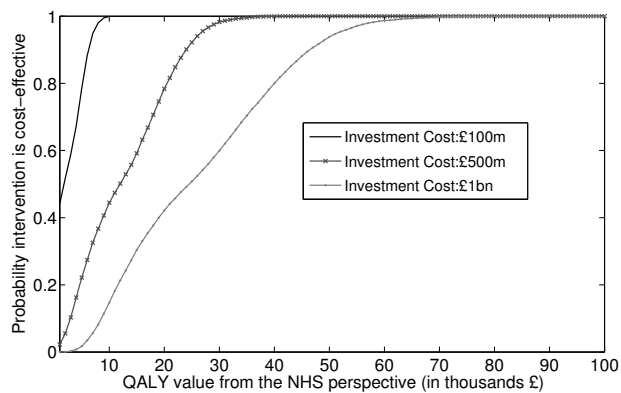
A1= No truncation; A2= Guidelines; A3= Left-tail truncation.



(a) A1 "No truncation"

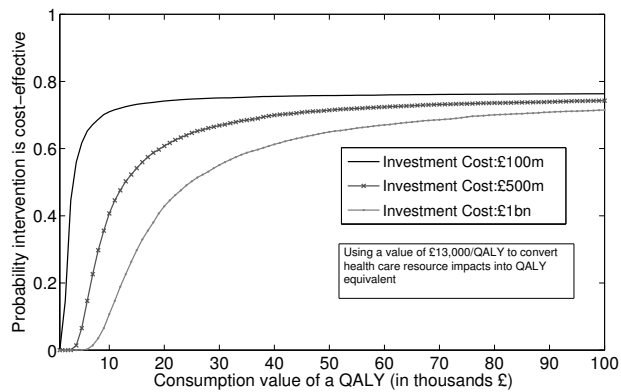


(b) A2 "Guidelines "

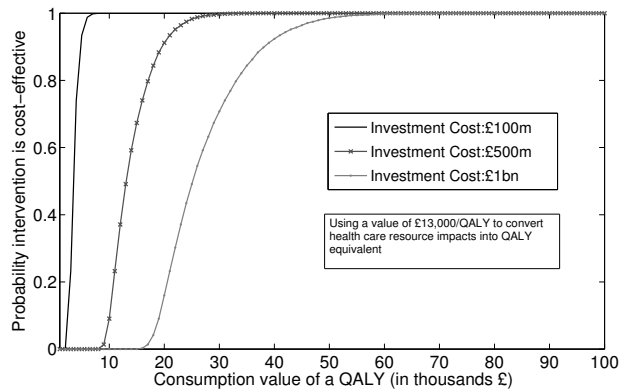


(c) A3 "Left-tail truncation"

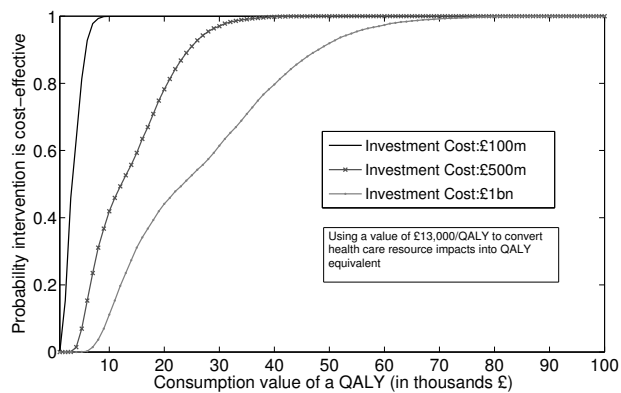
Figure 7.10: Probabilities that the intervention is cost-effective - No Diff. Susc. scenario - NHS perspective.



(a) A1 "No truncation"



(b) A2 "Guidelines"



(c) A3 "Left-tail truncation"

Figure 7.11: Probabilities that the intervention is cost-effective - No Diff. Susc. scenario - PC perspective.

Comparison of CEACs depicted in Figures 7.9 to 7.11 and of cost-effectiveness probabilities presented in Tables 7.8 and 7.9 provides three main insights.

Impact of modelling approach to parameter uncertainty (A1 to A3) on cost-effectiveness probabilities

Since under A1, the first decile of the distribution of net QALY gain is composed of negative values (see Figure 7.5), even when the value of health becomes very large, cost-effectiveness probabilities never reach the value of 1 and instead, have an asymptote around the value of 0.9. By contrast, since A2 and A3 reject the possibility that air pollution reduction may harm health, under both these approaches, the intervention only yields a positive net QALY gain and CEACs have an asymptote to 1.

By truncating both tails of the original distributions of non statistically significant risk estimates, approach A2 strongly reduces decision uncertainty, which translates in very steep CEACs. Indeed, for values of health below the value λ at which the investment (I) is expected to break-even (see equation 7.3), cost-effectiveness probabilities are near zero, thus implying that the probability of error associated with rejecting the investment is negligible. By contrast, as the value of health becomes greater than λ , cost-effectiveness probabilities quickly reach 1 (i.e. null probability of decision error).

$$\lambda = \frac{I}{E_{\theta}(MB)} \quad \text{where MB stands for monetary benefit.} \quad (7.3)$$

As was shown in Figure 7.4, A3 allows for a greater probability of no intervention-effect than A2, with regards to the health events “Dev. COPD”, “Dev. CHD” and “Death from AOC”. As a result, cost-effectiveness probabilities increase more progressively under A3 than under A2. This explains why, from the NHS perspective with $k = 13,000/QALY$, the guidelines (A2) suggest a lower probability of error if approving the £500 million investment (6%), than if one were solely to ignore non plausible risk estimate values (13%, see Table 7.8). Similarly, guidelines suggest a substantially lower probability of

error associated with the decision of rejecting the £1 billion investment than do approaches A1 or A3. Indeed, in this case, decision error equals to 5% under A2, as opposed to 37% under A1 and 38% under A3 (see Table 7.8). In conclusion, guidelines appear to systematically underestimate the probability of error associated with each decision option (namely invest or reject the investment). This limitation is less visible from the PC perspective, since even under A3 at $v = 65,000/QALY$, the probability of decision error is null.

Cost-effectiveness probabilities from the NHS vs. PC perspectives

From the PC perspective, as v increases above the value of 13,000, the conversion factor ($v/13,000$) at which health care costs (savings) are converted to QALY loss (gain) equivalent increases and as a result, more weight is put on health care resource impacts. However since the latter are small in comparison to health gain, the difference in cost-effectiveness probabilities between the two perspectives, when using the same value of health, is negligible.

Therefore, what drives the difference in cost-effectiveness performance between the two perspectives is essentially the choice of money value of health. Under A3, which unlike A1 rejects the possibility that air pollution reduction may cause harm but allows for greater uncertainty in outcomes than A2, cost-effectiveness probabilities for the £100 million, £500 million and £1 billion investments reach 1 for money values of a QALY equal to respectively £9,000, £23,000 and £40,000.

It follows that from the PC perspective assuming $v = 65,000/QALY$, the probability of investment decision error is null even for $I = £1$ billion. By contrast, from the NHS perspective with $k = £13,000$, cost-effectiveness probabilities under A3 equal to respectively 1 if $I = £100$ million; 0.87 if $I = £500$ million and 0.38 if $I = £1$ billion. In other words, whilst an intervention costing up to £500 million is highly likely to be cost-effective from both perspectives, the £1 billion would be expected to be cost-effective with high probability, only from the PC perspective.

The source of funding is therefore expected to have strong implications on

the optimal level of pollution reduction. Indeed, if the true cost of reducing ambient $PM_{2.5}$ concentrations by $1\mu g/m^3$ and $2\mu g/m^3$ were respectively £500 million and £1 billion (i.e. assuming no economy of scale), the optimal level of pollution reduction from the NHS perspective would be below $2\mu g/m^3$ whereas from the PC perspective, it would be above $2\mu g/m^3$.

Impact of ignoring health-related differential susceptibility on cost-effectiveness probabilities

First, under A1, CEACs have an asymptote to 0.8, as opposed to 0.9 for the base case. In other words, under current evidence, the minimum probability of error associated with each investment is 20%, as opposed to 10% under the base case.

Second, for investments above £100 million, cost-effectiveness probabilities increase much more progressively than in the base case scenario. Under A3, cost-effectiveness probabilities for the £500 million and £1 billion investments reach 1 for money values of a QALY equal to respectively £45,000 and £74,000, as opposed to respectively £23,000 and £40,000 in the base case scenario.

As a result, whilst ignoring evidence of health-related differential susceptibility to air pollution does not affect cost-effectiveness results from the PC perspective if $v = £65,000/QALY$ (assuming air pollution reduction cannot harm health), it strongly impacts upon the probability of decision error from the NHS perspective. As shown in Table 7.9, under A3 if $k = £13,000/QALY$, the probability of decision error associated with the £500 million investment equals to 44%, as opposed to 13% if health-related differential susceptibility were accounted for. From the NHS perspective, ignoring health-related differential susceptibility is therefore expected to lead to less ambitious and potentially sub-optimal strategies for improving air quality.

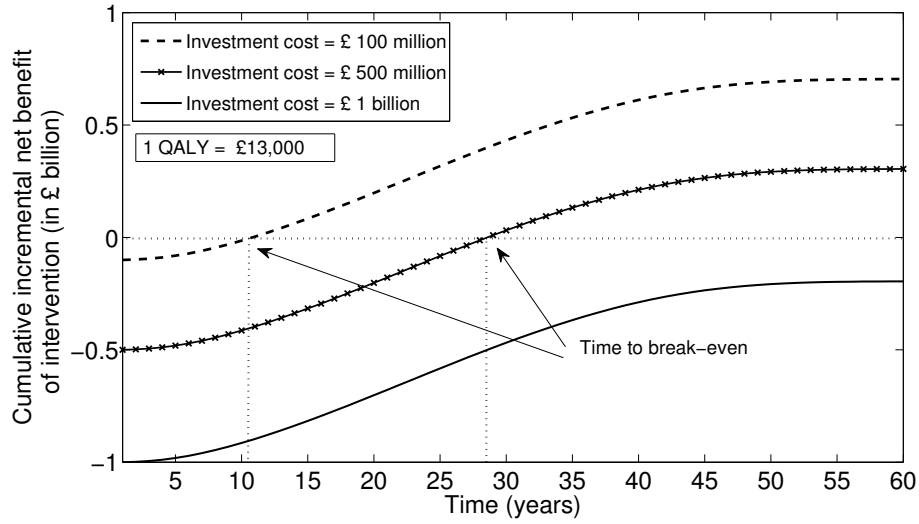
7.5.3 When is the investment expected to break-even?

The expected time to break-even is of particular interest when supporting decision-making with regards to investments characterised with a high upfront cost, such as air pollution control. First, it helps characterise the level of investment risk, whereby the sooner the expected time to break-even is, the lower the investment risk. Second, it helps identify the investments for which cost-effectiveness performance is expected to be sensitive to the size of the target population and the analysis time horizon. It indicates whether including benefits to future generations, and thus increasing the analysis time horizon, may substantially affect cost-effectiveness results up to a point where discounting would make future benefits negligible. A similar reasoning may be applied to assess cost-effectiveness results' sensitivity to discount rate. The shorter the time to break-even, the least cost-effectiveness results will be impacted by the discounting factor, and conversely for investments with a long time to break-even.

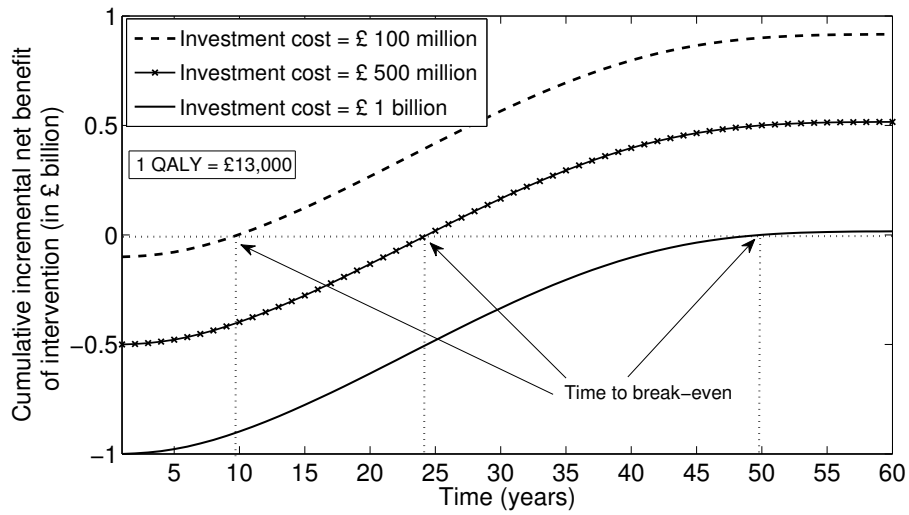
The expected time to break-even t^* is obtained by cumulating the discounted annual incremental net benefit from investment. It satisfies equation 7.4:

$$I_0 - \sum_{t=1}^{t^*} \frac{E_{\theta}(MB_t)}{(1+r)^t} = 0, \text{ where } I_0 \text{ stands for investment cost paid upfront} \quad (7.4)$$

Figures 7.12 and 7.13 show, from each perspective, interventions' expected time to break-even (t^*) under A1 and A3. It should be reminded that: (i) A1 was the base case approach used to compute mean outcomes estimates and that mean results under A1 and A2 are equal and (ii) total expected net QALY gain over the 60-year time horizon is 26% higher under A3 than under A1 (see section 7.3.1).

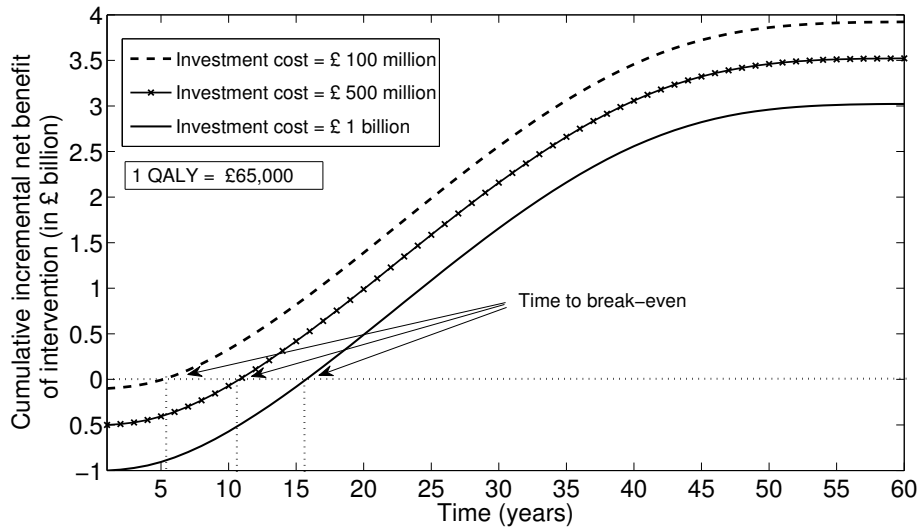


(a) A1 "No Truncation"

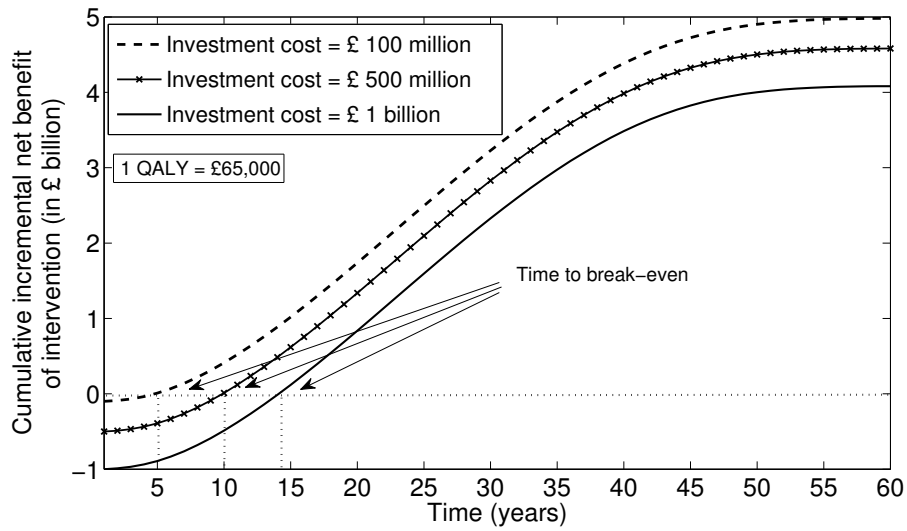


(b) A3 "Left-tail truncation"

Figure 7.12: Investments' expected time to break-even - NHS perspective - Base case scenario.



(a) A1 "No Truncation"



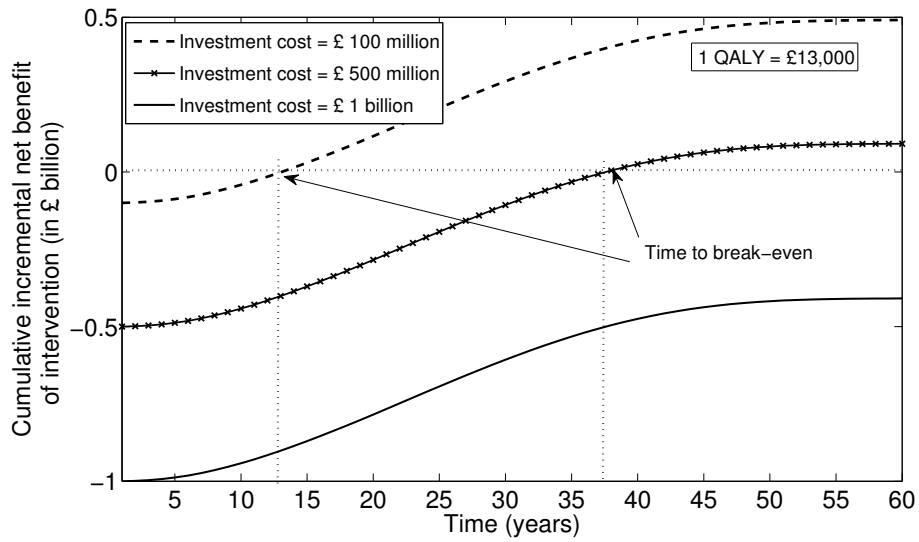
(b) A3 "Left-tail truncation"

Figure 7.13: Investments' expected time to break-even - PC perspective - Base case scenario.

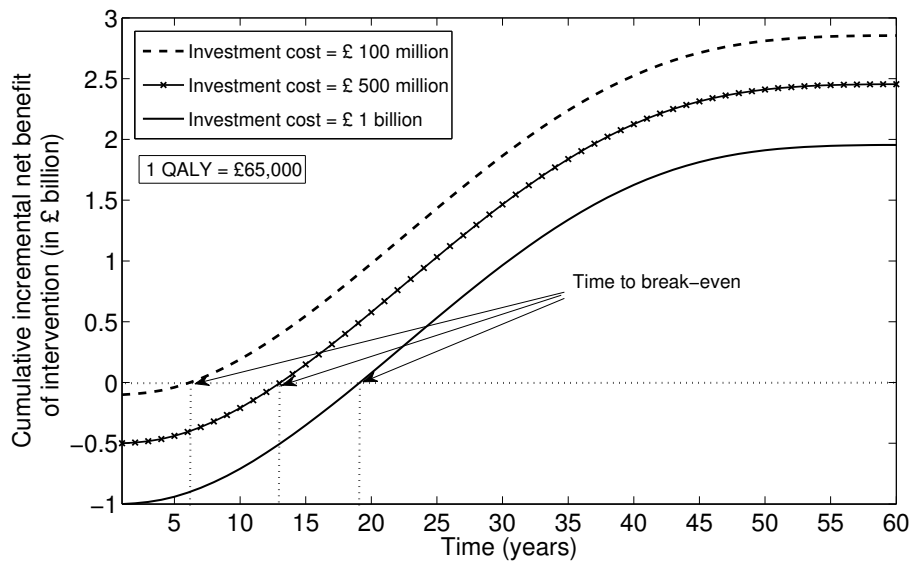
From the NHS perspective with $k = 13,000/QALY$, under A1, investments of £100 million and £500 million are expected to break-even after respectively 10 and 27 years whereas the £1 billion investment is expected to yield a net loss. Whilst the choice of modelling approach to parameter uncertainty does impact upon the total expected net QALY gain, it appears to have a relatively small impact on the expected time to break-even for investments up to £500 million. For instance, time to break-even for the £500 million investment is brought forward of only 3 years under A3. By contrast, the choice of modelling approach does make a substantial difference for the £1 billion investment since under A3, the latter breaks-even. Break-even however, is expected to happen only after 50 years. This suggests that for such a large investment, including benefits to future generations and/or reducing the discount rate is likely to substantially improve cost-effectiveness performance.

From the PC perspective with $v = 65,000/QALY$, under A1, an investment as large a £1 billion would break-even after solely 16 years (5 and 11 years for the £100 million and £500 million investments respectively) and time to break-even is only brought forward of a few years under A3. For each investment strategy, including benefits to future generations is therefore unlikely to significantly bring forward the expected time to break-even.

Figure 7.14 shows the impact of ignoring health-related differential susceptibility on the expected time to break-even from both perspectives, using approach A1 as a reference for comparative analysis with the base case scenario. The higher the investment cost, the greater the difference in time to break-even against the base case scenario. From the PC perspective, however, expected time to break-even would only be postponed for a few years.



(a) NHS perspective (A1)



(b) PC perspective (A1)

Figure 7.14: Investments' expected time to break-even - A1 "No truncation" - Both payers' perspectives - "No Diff. Susc." scenario.

7.5.4 Is more information required?

Necessary versus sufficient conditions for investment

The decision to invest should be made simultaneously to the decision of whether further research should be carried out (Claxton, 1999). Indeed, whilst a necessary condition for investment is that the expected NMB is greater than zero, a sufficient condition for investment typically cannot be solely based on cost-effectiveness rules. For instance, if adopting reduces the prospect of further research being conducted, a sufficient condition for investing needs to take into account the value of information that will be foregone (Griffin et al., 2011). In addition, if the investment is associated with irreversible costs, the loss to be incurred if the decision were to be reversed ought to be taken into account (Eckermann & Willan, 2008; Palmer & Smith, 2000).

Investments in air pollution control strategies are unlikely to affect further research, rather they could contribute to the body of epidemiological evidence as was done by past natural experiment studies. Air pollution control investments are however, expected to be largely irreversible.

If an investment is irreversible, further information only has value if one can delay the commitment (Eckermann & Willan, 2008). Consequently, in the present case, the two possible courses of action are:

- (i) Invest now (INV) or
- (ii) Delay commitment, i.e. Do Nothing (DN) and reassess the option to invest when research reports.

Deciding between these two options requires trading off the opportunity cost of delay, i.e NMB to be foregone by not investing now, with the expected benefit from waiting for more evidence to decrease decision uncertainty (Eckermann & Willan, 2008).

Expected value of perfect information

A starting point to evaluate the value of getting more evidence is to compute the expected maximum NMB, if all parameter uncertainty could be resolved, i.e. under perfect information. It is computed by identifying the option that yields the maximum net benefit, for each possible realisation of uncertainty and taking the average across all realisations (Griffin et al., 2011). Mathematically, the expected maximum NMB under perfect information can be expressed as:

$$E_{\theta} \max_j NMB(j, \theta) \quad (7.5)$$

where θ represents the set of all uncertain parameters and j denote decision options: delay i.e. do nothing (DN) or invest now (INV).

By subtracting to this maximum, the NMB associated with the option that generates, based on current evidence, the highest expected net benefit among all other possible options, one obtains the expected value of perfect information (EVPI) (Griffin et al., 2011). Mathematically, EVPI can be expressed as:

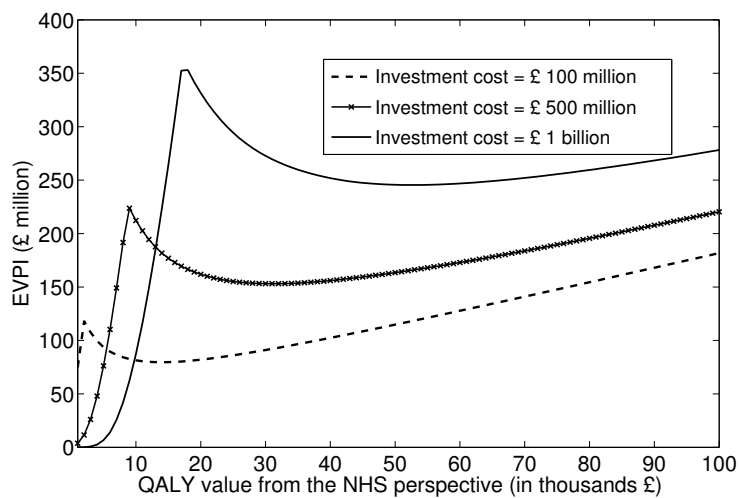
$$EVPI = E_{\theta} \max_j NMB(j, \theta) - \max_j E_{\theta} NMB(j, \theta) \quad \text{with } j = \text{DN, INV} \quad (7.6)$$

Since some uncertainty is irreducible and further information will not be available immediately, the EVPI provides an upper bound to the social value of undertaking further research. Consequently, the comparison of the maximum pay-off from further research with the expected cost of research provide a necessary condition for further research, i.e. the latter is potentially worthwhile only if EVPI exceeds the cost of research (Claxton, 1999).

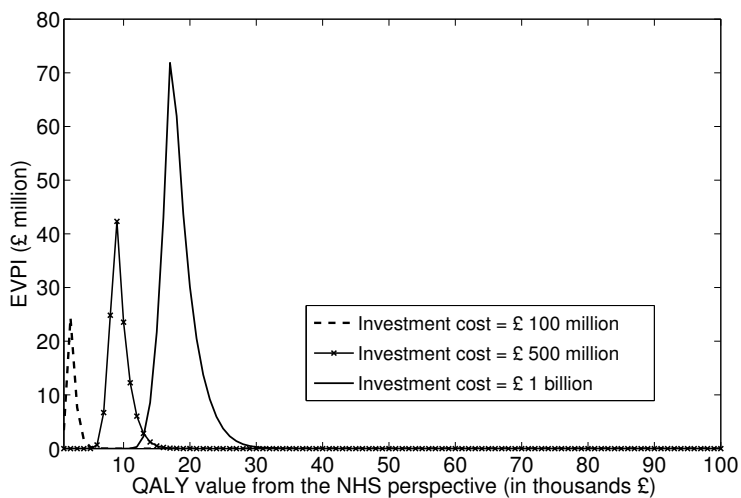
The EVPI depends upon the combination of two factors: (i) the probability of decision error, as previously depicted by the CEACs and (ii) the consequences of that wrong decision (Barton et al., 2008). The magnitude of the consequences of making an incorrect decision is clearly a positive function of the value of health. The probability that a wrong decision is being made will be the largest at the value of health λ at which the intervention is ex-

pected to break-even (see equation 7.3). Indeed for values of health below λ , one can be confident that the intervention will not be cost-effective and thus, the probability of error associated with “Do Nothing” will be low. Similarly, for values of health above λ , one can be confident that the intervention will be cost-effective and thus, the probability of error associated with “Invest now” will be low.

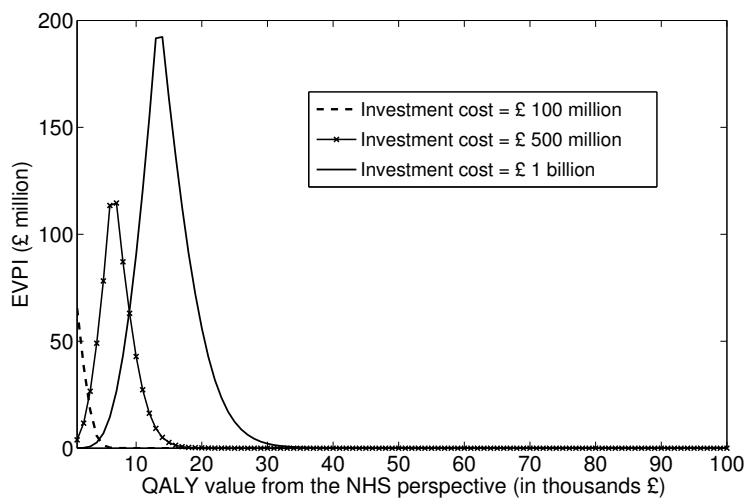
Figures 7.15 and 7.16 represent the curves of EVPI from both the NHS and the PC perspectives, according to each approach to handling uncertainty in non statistically significant risk estimates. It should be underlined that the present EVPI computations are based on the population and time-horizon that underpinned the previous benefit computations, i.e. all currently alive population aged 40 to 90 years followed until death.



(a) A1 "No Truncation"

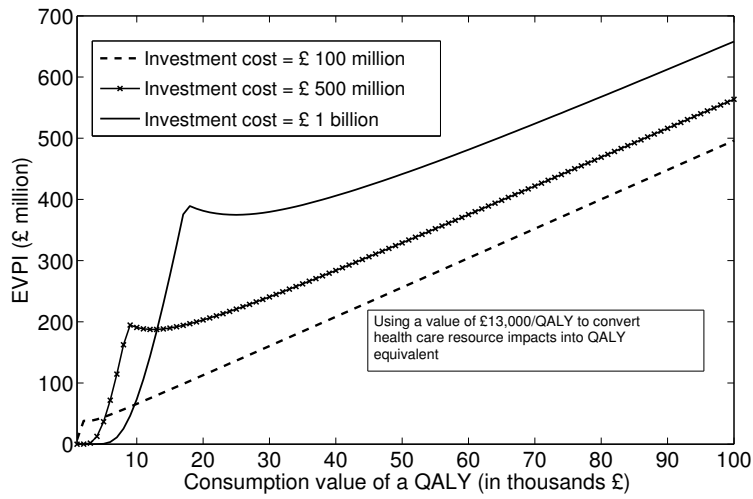


(b) A2 "Guidelines"

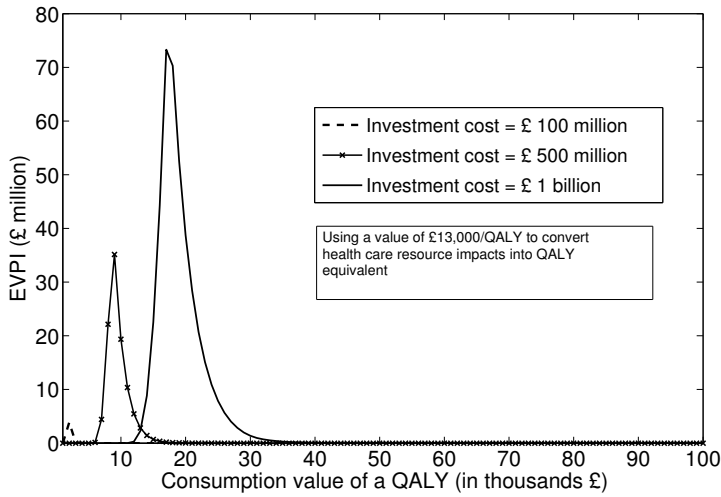


(c) A3 "Left-tail truncation"

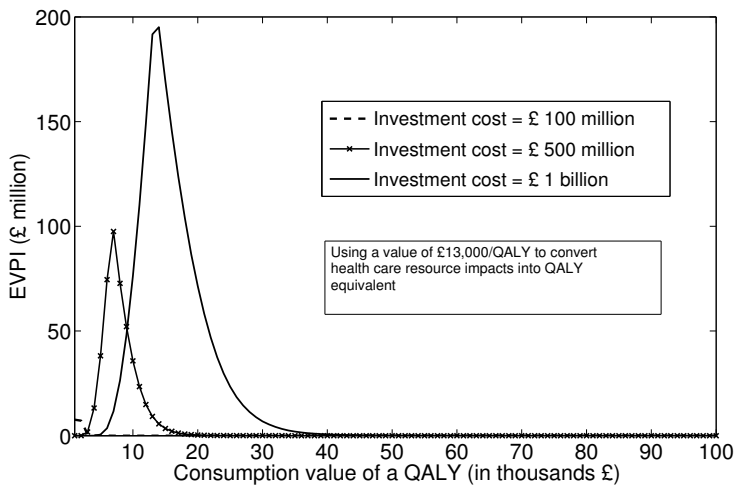
Figure 7.15: Expected Value of Perfect Information - Base case - NHS perspective.



(a) A1 "No Truncation"



(b) A2 "Guidelines"



(c) A3 "Left-tail truncation"

Figure 7.16: Expected Value of Perfect Information - Base case - PC perspective.

Comparison of EVPI results further underlines the impact of each modelling approach on decision uncertainty, as previously discussed in section 7.5.2. All EVPI curves exhibit a maxima at k or $v = \lambda$, where the probability of error is the largest. Under A1, however, as the value of health keeps on increasing, EVPI starts increasing again. The reason is that, based on current evidence, under A1, cost-effectiveness probabilities have an asymptote to 0.9 which reflects the view that air pollution reduction may harm health. Consequently, as the value of health increases, the combination of a non-null error probability with growing consequences of error leads to an increasing EVPI. By truncating both tails of the original distributions of non statistically significant risk estimates, A2 substantially reduces decision uncertainty and thus, the EVPI. Since decision uncertainty is greater under A3 than under A2 (due to a greater possibility of no intervention effect with regards to endpoints “Dev. COPD”, “Dev. CHD” and “Death from AOC”), the EVPI is larger under A3 than under A2. For instance, from the NHS perspective for $I = \text{£}500$ million, max EVPI equals to $\text{£}42$ million under A2, as opposed to $\text{£}115$ million under A3. It can also be noted that since $E_{\theta}(NMB)$ under A3 is greater than under A1 or A2, the value at which EVPI reaches a maximum is slightly lower under A3 than under A1 or A2.

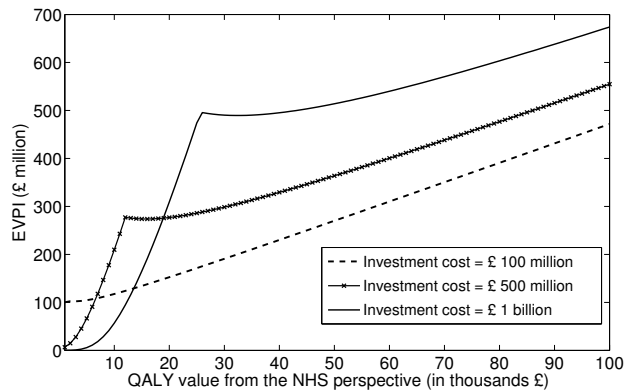
CEACs previously showed that, assuming air pollution reduction cannot harm public health, the decision error attached to each three investment is null for values of health above $\text{£}40,000/\text{QALY}$. Consequently, under A2 and A3, from the PC perspective, the EVPI associated with each investment equals to zero. By contrast, from the NHS perspective with $k = \text{£}13,000/\text{QALY}$, under A3, EVPI equals to respectively $\text{£}0$ for $I = \text{£}100$ million (cost-effectiveness probability = 1), $\text{£}9.2$ million for $I = \text{£}500$ million (cost-effectiveness probability = 0.87) and $\text{£}192$ for $I = \text{£}1$ billion (cost-effectiveness probability = 0.38).

Finally, whilst the difference in cost-effectiveness results between the PC and the NHS perspectives, for a same money value of health, is relatively small, EVPI curves from each perspective are slightly different under A1. The fall after the local maxima is smaller from the PC perspective than from the NHS perspective since, for values of $v \gg 13,000$, a substantial weight is put

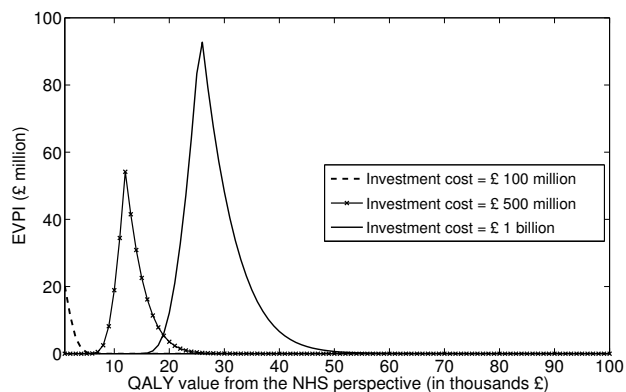
on health care cost impacts, which pushes up the consequences of error. This feature can barely be seen under A2 or A3 as the probability of error under these approaches quickly falls to zero, though not to the same speed.

Figures 7.17 and 7.18 show the EVPI curves associated with the “No Diff Susc” scenario. Both the value of health at which the EVPI reaches a maximum, and the magnitude of this maximum, are higher than in the base case scenario. In addition, since cost-effectiveness probabilities increase much more progressively than in the base case scenario, the EVPI decreases more slowly than in the base case scenario (under A2 and A3). This is especially flagrant for the £1 billion investment for which under A3, EVPI falls below £100,000 at a value of £72,000/QALY, as opposed to £39,000/QALY in the base case scenario.

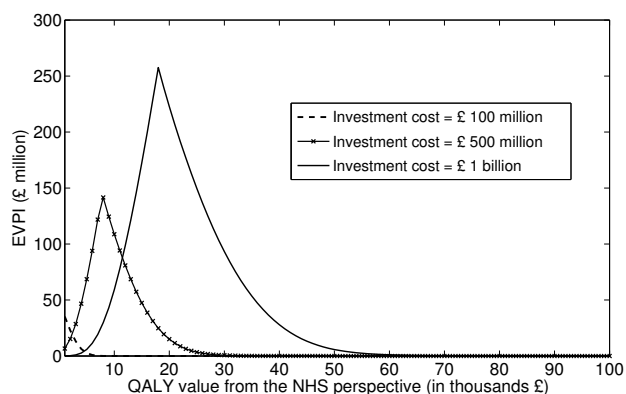
As mentioned in section 7.5.2, from the NHS perspective, ignoring evidence of health-related differential susceptibility strongly impacts upon the probability of error associated with the £500 million investment. As a result, the EVPI for this investment at $k = £13,000/QALY$ jumps to £60 million, as opposed to £4.7 million in the base case scenario. By contrast, since the probability of decision error from the PC perspective is unchanged in the “no Diff. Susc” scenario, the EVPI associated with each three investment strategies at $v = £65,000/QALY$ remains low (near zero for the £100 million and £500 million investments).



(a) A1 "No Truncation"

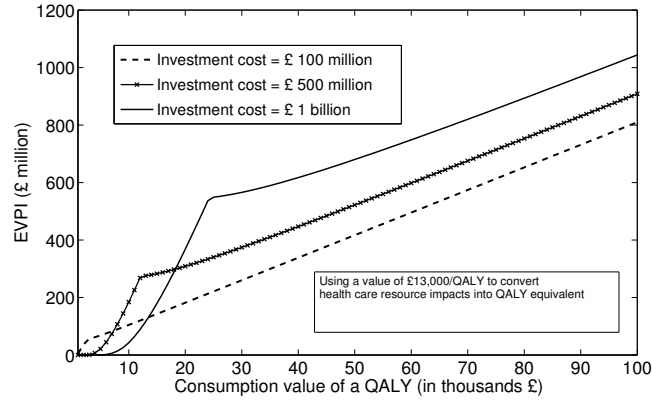


(b) A2 "Guidelines"

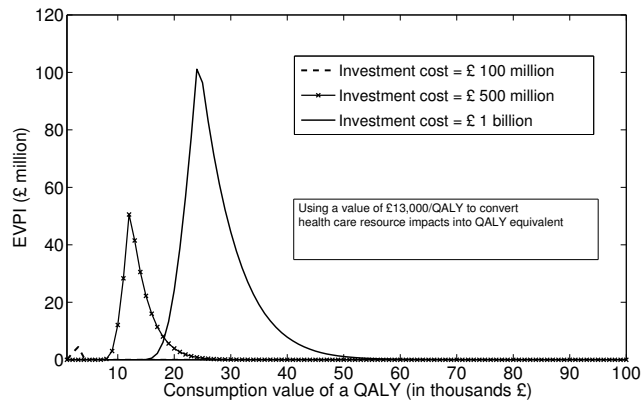


(c) A3 "Left-tail truncation"

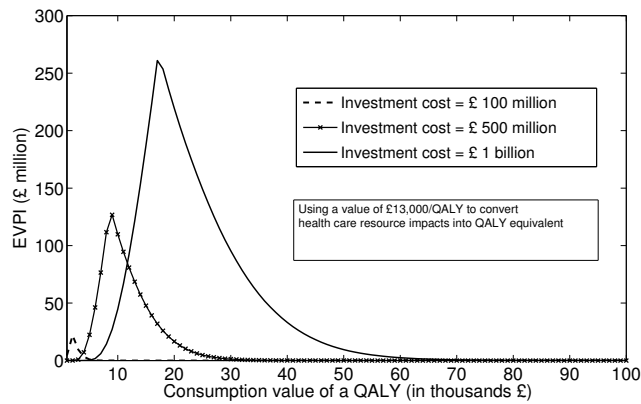
Figure 7.17: Expected Value of Perfect Information - "No Diff. Susc." scenario - NHS perspective.



(a) A1 "No Truncation"



(b) A2 "Guidelines"



(c) A3 "Left-tail truncation"

Figure 7.18: Expected Value of Perfect Information - "No Diff. Susc." scenario - PC perspective.

Sufficient conditions for approval and maximum investment delay

To decide which decision option is optimal, the pay-off associated with respectively “Invest now” or “Delay” (i.e. do nothing until further research reports) should be compared. The evaluation of the pay-off associated with delay requires an assessment of: (i) the likelihood that research will be performed (α) and (ii) the timing of when the research will report (τ) (Griffin et al., 2011).

If the decision maker had the remit and budget to commission research, α would be equal to one, τ would be known and the pay-off from delay should account for the cost of research (Griffin et al., 2011). In the present case, however, it is assumed that the decision maker does not have the remit to commission research and therefore, the expected pay-off requires an assessment of both α and τ .

The pay-off from delay can be calculated as the sum of NMB during time periods 0 to τ and τ to T , with T denoting the investment time horizon. Before time τ , the pay-off from delay corresponds to the expected NMB of doing nothing, which equals to zero. After time τ , the pay-off from delay is the sum of (i) the expected NMB of doing nothing weighted by the probability $(1 - \alpha)$ that research was not conducted and (ii) the expected maximum NMB under perfect information weighted by the probability α that research was conducted, assuming the latter resolved all uncertainty.

Mathematically, the pay-off from delay can be expressed as:

$$\begin{aligned} \pi_{DELAY} &= E_{\theta} \sum_{t=1}^{\tau} \frac{NMB_t(DN, \theta)}{(1+r)^t} + \dots \\ &+ (1+\alpha) E_{\theta} \sum_{t=\tau}^T \frac{NMB_t(DN, \theta)}{(1+r)^t} + \dots \\ &+ \alpha E_{\theta} \max_j \sum_{t=\tau}^T \frac{NMB_t(j, \theta)}{(1+r)^t} \quad \text{with } j=DN \text{ (do nothing), INV (invest now)} \end{aligned}$$

Since $E_{\theta} \sum_{t=1}^T \frac{NMB_t(DN, \theta)}{(1+r)^t} = 0$

$$\pi_{DELAY} = \alpha E_{\theta} \max_j \sum_{t=\tau}^T \frac{NMB_t(j, \theta)}{(1+r)^t} \quad \text{with } j=DN, INV \quad (7.7)$$

The pay-off from investing now is simply the expected NMB of the intervention:

$$\pi_{INV} = E_{\theta} \sum_{t=1}^T \frac{NMB_t(INV, \theta)}{(1+r)^t} \quad (7.8)$$

The value of the option to delay can be calculated as the difference between the pay-offs to delay and to invest now:

$$Option_{delay} = \pi_{DELAY}(\alpha, \tau) - \pi_{INV} \quad (7.9)$$

It is worth underlining that, if the intervention is expected to be cost-effective, when $\alpha = 1$ and $\tau = 0$, $Option_{delay} = EVPI$.

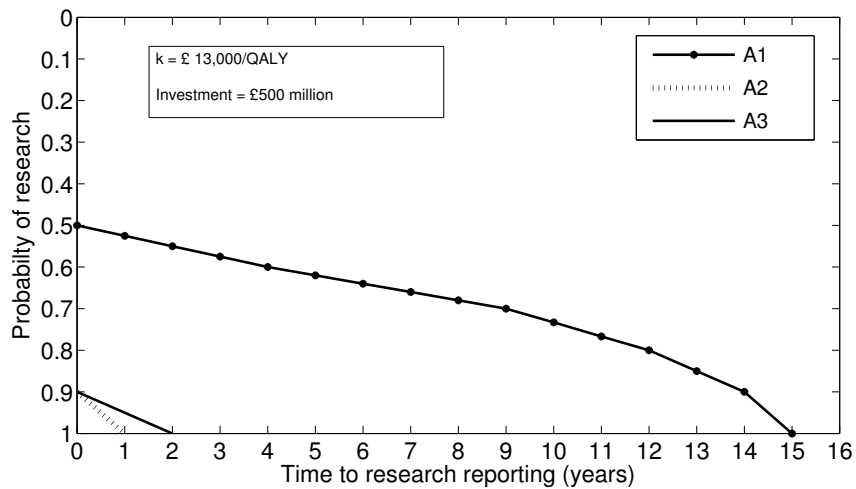
The pay-off from delay is computed by assuming that all uncertainty will be resolved at time τ , which is unrealistic. As a result, $Option_{delay} = 0$ provides a sufficient condition for investing now. Combinations of values of α and τ can be found for which $Option_{delay} = 0$ for each investment strategy. When represented in a graph, these combinations represent a boundary line, whereby any point to the North-East of this line represents a sufficient condition for approval (Griffin et al., 2011). Alternatively, since $Option_{delay} > 0$ provides a necessary condition for further research, for a given value of α , one can compute τ^* , the maximum time to delay the investment while waiting for research to report that satisfies $Option_{delay} > 0$.

τ^* values for all three investment costs under each modelling approach (A1 to A3) using $k = 13,000/QALY$ and $v = 65,000/QALY$ are reported in Table 7.10. When $Option_{delay}$ was strictly positive for several values of α , approval boundaries as a function of α and τ values were drawn. Figure 7.19 represents the approval boundaries from the NHS perspective, for investments of respectively £500 million and £1 billion.

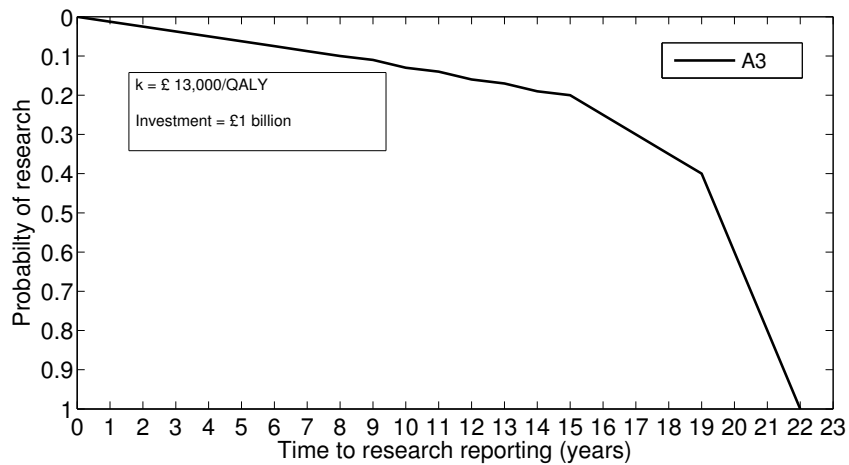
	NHS (k=13,000)			PC (v=65,000)		
INV	A1	A2	A3	A1	A2	A3
£100 m	2 yrs if $\alpha = 0.9$ 8 yrs if $\alpha = 1$	0	0	8 yrs if $\alpha = 1$	0	0
£500 m	see Figure 7.19a			2 yrs if $\alpha = 0.9$ 8 yrs if $\alpha = 1$	0	0
£1 bn	$E_{\theta}(NMB) < 0$		see Figure 7.19b	6 yrs if $\alpha = 0.9$; 10 yrs if $\alpha = 1$	0	0

Table 7.10: Maximum time to delay investment (τ^*) - Base case scenario.

A1= No truncation; A2= Guidelines; A3= Left-tail truncation.



(a) I = £500 million



(b) I = £1 billion

Figure 7.19: Approval boundaries - NHS perspective - Base case scenario.

A1= No truncation; A2= Guidelines; A3= Left-tail truncation. Any point to the North-East of the line represents a sufficient condition for approval.

As shown in the left-hand side of Table 7.10, from the PC perspective under approaches A2 and A3, $\tau^*=0$. In other words, the option to delay investments as large as £1 billion has no value. This is not surprising since, under A2 and A3, EVPI for each three investments at $v = \text{£}65,000/QALY$ equals to zero (see Figure 7.16). Even under A1 which, if one rules out that air pollution reduction could cause any harm, overestimates decision uncertainty delay would have value only if one were highly confident that research would be carried out ($\alpha \geq 0.9$) and report within a relatively short period.

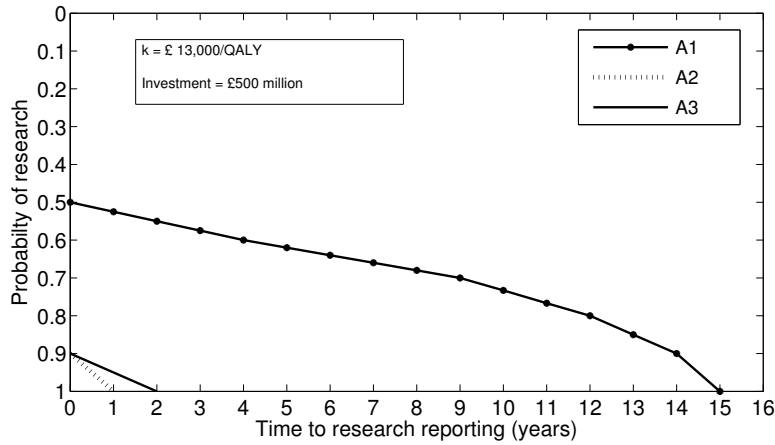
From the NHS perspective (right-hand side of Table 7.10), under the assumption that air pollution reduction cannot harm health (A2 and A3), delaying to gather further evidence has little value for investments costing up to £500 million. By contrast, for the £1 billion investment, delay appears to be valuable under A3, even given a low probability that research will be conducted. Indeed, under A3, if research were to be performed with a 50% probability and could resolve all uncertainty, it would be worth delaying the £1 billion investment up to 20 years.

Results for the “No Diff. Susc.” scenario are reported in Table 7.11. In line with EVPI results, ignoring health-related differential susceptibility has little impact on the option to delay from the PC perspective. By contrast, from the NHS perspective, ignoring health-related differential susceptibility would bestow more value to delay to collect further information, in particular for the £500 million investment. This is illustrated by Figure 7.20, which contrasts the sufficient conditions for approval of this investment under the “No Diff. Susc.” and the base case scenario.

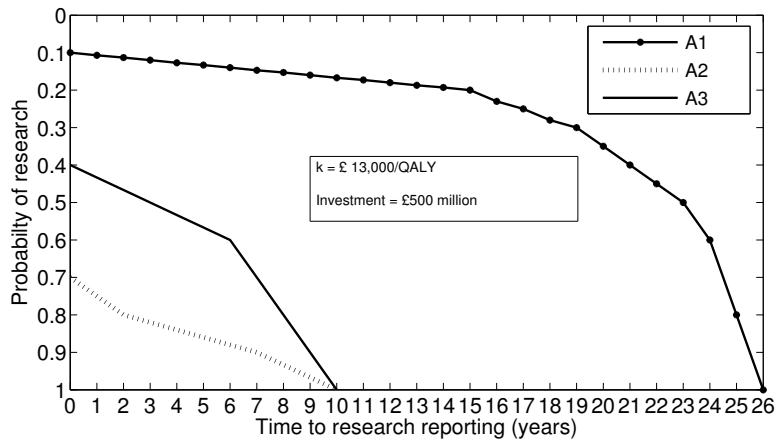
From the NHS perspective, under A3, ignoring health-related differential susceptibility would provide support for delaying the £500 million investment from 8 to 10 years if research were to be performed with a high probability ($\alpha \geq 0.8$), as opposed to maximum two year delay in the base case scenario. This suggests that if the NHS were paying for air pollution abatement, ignoring health-related differential susceptibility could lead to population health loss due to longer investment delay than optimal.

INV	NHS (k=13,000)			PC (v=65,000)		
	A1	A2	A3	A1	A2	A3
£100 m	4 yrs if $\alpha = 0.8$; 10 yrs if $\alpha = 0.9$; 13 yrs if $\alpha = 1$	0	0	8 yrs if $\alpha = 0.9$; 12 yrs if $\alpha = 1$	0	0
£500 m	see Figure 7.20b			4 yrs if $\alpha = 0.8$; 10 yrs if $\alpha = 0.9$; 13 yrs if $\alpha = 1$	0	0
£1 bn	$E_{\theta}(NMB) < 0$			4 yrs if $\alpha = 0.7$; 10 yrs if $\alpha = 0.8$; 13 yrs if $\alpha = 0.9$; 15 yrs if $\alpha = 1$	0	0

Table 7.11: Maximum time to delay investment (τ^*) - “No Diff. Susc.” scenario. A1= No truncation; A2= Guidelines; A3= Left-tail truncation.



(a) Base case scenario



(b) “No Diff. Susc.” scenario

Figure 7.20: Approval boundaries for $I = £500$ million - “No Diff. Susc.” vs. base case scenarios - NHS perspective.

A1= No truncation; A2= Guidelines; A3= Left-tail truncation.

Prioritizing research and informing future study design

In addition to providing an upper bound to the overall gain from delaying investment in order to collect further information, the value of information framework can also be used to prioritise further research. The first step to prioritisation is to identify the model parameters for which a reduction in uncertainty would have a substantial impact on decision uncertainty. This is performed by computing the expected value of perfect information associated to each uncertain parameter (or each subset of uncertain parameters): EVPPI.

Similarly to EVPI, the EVPPI is simply the difference in net benefit with perfect information versus current information about the set of uncertain parameter of interest (θ_I), which is a subset of all uncertain parameters θ . Computation of the expected net benefit with perfect information about θ_I requires two loops of probabilistic simulations. Indeed, one first needs to obtain the expectations of net benefit across the possible values that the remaining uncertain parameters (θ_R) can take conditional on knowing the value of (θ_I), in order to then take the expectation of these expected maximum net benefit over the distribution of θ_I (Ades et al., 2004). Mathematically:

$$EVPPI_{\theta_I} = E_{\theta_I} \max_j E_{\theta_R|\theta_I} NMB(j, \theta_I, \theta_R) - \max_j E_{\theta} NMB(j, \theta) \quad (7.10)$$

With $j=DN, INV$; θ_I = set of uncertain parameter of interest and θ_R is the complement set of remaining uncertain parameters such that $\theta = \theta_I + \theta_R$.

Like the EVPI, the EVPPI provides an upper-bound to the value of obtaining more information on θ_I and represents a necessary condition for further research, i.e. EVPPI needs to be greater than the cost of research. The latter will however, depend on the type and design of the study required to obtain additional information, e.g. cohort versus case-control study; sample size, follow-up duration and so forth. In this context, the expected value of sample information (EVSI) can be used to maximise the efficiency of study design.

The EVSI is the difference in expected net benefit after sample data D has been collected versus under current information (Ades et al., 2004). Similarly to EVPPI calculations, computations of the expected net benefit with sample data D contains a inner loop within the maximisation process. The first step consists in averaging over the posterior distribution of the net benefit of each intervention j , given the sample result D that informs the subset of uncertain parameters θ_I . The second step consists in taking the expectation of these expected maximum net benefit over the distribution of D . Mathematically, assuming that θ_I and θ_R are independent;

$$EVSI_D = E_D \max_j E_{(\theta_I|D), \theta_R} NMB(j, \theta_I, \theta_R) - \max_j E_{\theta} NMB(j, \theta) \quad (7.11)$$

For a given study design, sample results D will depend on sample size n . Based on this framework, one could therefore compute EVSI for various sample sizes n , in order to identify the optimal study size n^* (e.g. in the case of air pollution, the number of participants to enrol in a cohort study) that maximises the difference between $EVSI_{n^*}$ and the cost of research C_{n^*} . The difference between the EVSI and the cost of acquiring sample information is known as the expected net benefit of sample information (ENBS).

7.6 Results summary

The methodological contribution of the present study as well as its limitations will be discussed in Chapter 8, which provides an overall conclusion to the thesis. This section aims at outlining the key findings from the application of the model developed in Chapter 4 and its implications for the UK air quality strategy.

7.6.1 Main findings

Expected outcomes and their distributions

Reducing mean population-weighted $PM_{2.5}$ concentrations by about 7% in London and 9% in England and Wales ($1\mu g/m^3$ decrement) is expected to yield respectively 63,293 and 541,217 QALYs to adults aged 40 and above over their remaining lifetime, when discounting at 3.5% p.a. By reducing morbidity but also extending the lives of individuals with a chronic cardio-respiratory condition, the intervention is expected to increase health care costs (£24 million in London and £263 million in England and Wales). However, when converted to QALY loss equivalent at a value of £13,000/QALY, health care costs only account for 3% of total health benefits.

As a result, the intervention is expected to generate to the NHS a total of 61,467 net QALYs in London and 520,998 net QALYs in England and Wales. Based on a WTP value of a QALY of £65,000, which is in line with recommendations from the UK Department of Health (Glover & Henderson, 2010) and a recent review of WTP estimates (Ryen & Svensson, 2014), the intervention's total monetary benefit from the private consumption perspective amounts to £4 billion in London and £34 billion in England and Wales.

The distribution of outcomes obtained from Monte Carlo simulations depends on the approach chosen to handle uncertainty in three non statistically

significant risk estimates used to parameterise the “intervention-effect” (out of a total of 7 risk estimates). Three approaches were assessed: (A1) where parameters’ original distributions were left unchanged, which was the base case approach used to compute mean estimates; (A2) which follows European guidelines for uncertainty analysis in HIA of air pollution control and consisted in attributing a range of +/- 100% of mean effect and assuming equal likelihood within the assigned value range (Holland, 2014); (A3) where a value of 1 was assigned to any random draw value below 1 from risk estimates’ original distributions. By leaving unchanged the original distributions of non statistically significant risk estimates, A1 allows for the highly improbable possibility that air pollution could harm health. Consequently, under A1, the distribution of net QALY gain has a left-tail of negative values, whereas under A2 and A3 QALY gains are always positive. Whilst mean outcome results are equal under A1 and A2, they have a much smaller standard deviation under A2. Under A3, the mean of non statistically significant risk estimates is shifted to the right ($OR_{Dev.COPD}$ in particular), which pushes the expected net QALY gain by a quarter.

Cost-effectiveness analysis

Cost-effectiveness analysis was based on an intervention that reduces $PM_{2.5}$ concentrations in London by $1\mu g/m^3$ and which cost equals to respectively £100 million, £500 million or £1 billion, to be fully paid upfront. Cost-effectiveness was evaluated from two perspectives, whereby the investment cost would either (i) fall on the NHS budget constraint (NHS perspective) or (ii) be funded by general taxation (private consumption “PC” perspective). The analysis was underpinned by three questions.

(i) “Is the intervention likely to be cost-effective?”

Analysis showed that current European guidelines to uncertainty analysis in HIA of air pollution control interventions, that were followed in approach A2, systematically underestimate the probability of decision error. In contrast,

approach A3 offers the advantage of rejecting the highly improbable possibility that air pollution reduction may harm health while allowing for greater uncertainty in outcomes than A2.

The difference in investments' cost-effectiveness performances between the NHS and PC perspectives is essentially driven by the choice of the value of health. From both the PC and the NHS perspectives, an intervention costing up to £500 million is highly likely to be cost-effective (max probability of decision error equal to 13% under A3). By contrast the £1 billion investment is expected to be cost-effective with high probability from the PC perspective only. This shows that the source of funding is likely to influence the optimal level of air pollution reduction.

(ii) "When will the investment break-even?"

From the NHS perspective with $k = 13,000/QALY$, investments of £100 million and £500 million are expected to break-even after respectively 10 and 27 years under A1. For these investments, although the choice of modelling approach to parameter uncertainty (A1 to A3) impacts upon the total expected net QALY gain over the 60-year analysis time horizon, it has a relatively small impact on the expected time to break-even. By contrast, whilst the £1 billion investment is expected to yield a net loss under A1, it slightly breaks-even after 50 years under A3. For such a large investment, including benefits to future generations and/or reducing the discount rate is likely to substantially improve cost-effectiveness performance.

From the PC perspective with $v = 65,000/QALY$, an investment as large as £1 billion would break-even after solely 16 years under A1. Under A3, time to break-even is brought forward of a few years only.

(iii) "Is it recommended to wait for more information before going ahead?"

The comparison of EVPI results corroborates the finding that European guidelines underestimate decision uncertainty, whereby the EVPI for each three investment is much lower under A2 than under A3. For instance, for $I = £500$ million and $k = 13,000/QALY$, max EVPI equals £42 million under A2, as opposed to £115 million under A3.

Assuming that air pollution reduction cannot harm public health (A2 or A3), from the PC perspective with $v = 65,000/QALY$, the probability of decision error attached to each investment is null, and so is the EVPI. As a result, there is no value in delaying investments costing up to £1 billion. From the NHS perspective, whilst delaying to gather further evidence has little value for investments costing up to £500 million, under A3 delay appears valuable for the £1 billion investment, even given a low probability that research will be conducted. For instance, if research were to be performed with a 50% probability and could resolve all uncertainty, it would be worth delaying the £1 billion investment for up to 20 years to wait for research findings.

7.6.2 Sensitivity analyses

Discount rate and cessation lag

If the intervention's effect on the risk of adverse health effects would be immediate, i.e. no cessation lag, the intervention's total net QALY gain would increase by 16%. Applying a staged discount rate that excludes the element of pure time preference ("Staged discounting 2" scenario using 3 % p.a. in the first 30 years and 2.57% p.a. afterwards), would boost total net QALY gain by 20%. Cessation lag and discounting have opposite effects on the distribution of health gain across age -groups. Young individuals are clearly the greatest beneficiaries of a lower rate of discounting, whereas older individuals would benefit the most from an immediate reduction in the risks of adverse health events. In the "Staged discounting 2" scenario, individuals aged 40 would gain 35% more QALD than in the base case scenario, as opposed to only 15% additional gain for individuals aged 60. By contrast, an immediate reduction in health risks would increase the average QALD gain of an 80-year old person by 50%, as opposed to an increase by 30% for a 70-year old person and by 10% for a 40-year old person.

Health-related differential susceptibility

The present Markov-modelling based QALY estimates are 39% higher than estimates that would be obtained using the life-table method. The difference in results stems from Markov modelling’s capacity to capture health-related differential susceptibility to air pollution exposure and to a much lesser extent, quality of life gains from reduced morbidity. In the case of London, accounting for evidence of CHD and COPD-related greater pre-disposition to die prematurely due to PM exposure (Zanobetti et al., 2008; Zanobetti & Schwartz, 2007; Tonne & Wilkinson, 2013) represents a 34% difference in the expected QALY gain of air pollution control and a 26% difference in QALY gain net of health care cost impacts. Similarly, health-related differential susceptibility was found to explain most of the difference between present estimates of un-discounted life expectancy gain and results from past HIAs in a similar setting. It follows that, by ignoring interactions between morbidity and mortality mediated via health-related differential susceptibility to air pollution, the life-table method which underpins the “separate” approach to impact quantification currently used in HIA, substantially underestimates the total health gain of air pollution reduction.

From the PC perspective if $v = 65,000/QALY$, ignoring evidence of health-related differential susceptibility does not affect the probability of decision error nor the EVPI or the delay option value associated with each three investment strategies. By contrast, from the NHS perspective if $k = 13,000/QALY$, ignoring health-related differential susceptibility has a non negligible impact on cost-effectiveness probabilities for investments above £100 million. Under A3, the probability of error if the NHS makes the £500 million investment equals to 44% (as opposed to 13% in the base case scenario) and the EVPI jumps to £69 million (as opposed to £9.2 million in the base case scenario). In this context, if research were to be performed with a high probability, it may be optimal to delay the £500 million investment 8 to 10 years, as opposed to a maximum two-year delay in the base case scenario. Therefore, from the NHS perspective, ignoring health-related differential susceptibility may lead to population health loss by supporting a sub-optimal reduction in air pollution and/or extending the delay period of cost-effective investments.

Chapter 8

Conclusion

The present chapter concludes the thesis. Its aims are fourfold: (i) to restate the overall structure of the thesis; (ii) to underline the contributions of the work undertaken; (iii) to highlight its limitations and (iv) to outline some avenues for further research.

8.1 Thesis overview

Chapter 2 was a review that presented the body of epidemiological evidence on the health effects of air pollution exposure and highlighted several research opportunities in the economic evaluation of interventions of air pollution control, in particular with regards to the approach to quantifying health benefits.

Chapter 3 demonstrated that the current quantification approach traditionally used in health impact assessments (HIA) of environmental policies, where each health effect is computed separately, has major limitations. It advocated encompassing interactions between mortality and morbidity impacts, by quantifying effects simultaneously using Markov modelling as a quantification tool.

Chapter 4 described the construction and parameterisation of a Markov model of the health impacts associated with chronic exposure to particulate air pollution. The objective of this model was twofold: (i) to refine the un-

derstanding of air pollution adverse health effects by evaluating quality of life impacts alongside life expectancy effects using the QALY as health metric and (ii) to assess the total health care budget impact of air pollution control that would capture the joint impact of a reduction in chronic morbidity and premature death.

Chapters 5 and 6 consisted in estimating a subset of parameters required to parameterise the model developed in Chapter 4. Chapter 5 developed a probabilistic framework to estimate the age-specific probability of being diagnosed with COPD at different stages of the disease. In a context where COPD is severely underdiagnosed, the rationale for developing this framework was to estimate the true size of the population subgroup expected to benefit from a reduced risk of developing COPD following improvement in air quality.

Chapter 6 performed a systematic review and two meta-analyses of the risk estimates quantifying the association between long term exposure to fine particulate pollution and respectively all-cause mortality and lung cancer incidence or mortality. It aimed to encompass all relevant epidemiological evidence to date and to decrease parameter uncertainty.

Chapter 7 presented and analysed the QALY gain and health care resource impact associated with a sustained $1\mu\text{g}/\text{m}^3$ decrement in population-weighted mean $PM_{2.5}$ concentrations in respectively England and Wales and London. Based on these results, the cost-effectiveness of reducing particulate air pollution in London, whether such an intervention would be paid by the NHS or funded through general taxation, was evaluated for a range of three hypothetical investment costs.

8.2 Contributions

This thesis provides a number of methodological and empirical contributions to the economic evaluation of air pollution control.

8.2.1 Methodological contributions

Demonstration that the current approach to quantifying health benefits from air pollution reduction leads to substantially biased estimates.

The present work demonstrated that the approach to quantification currently used in HIA of environmental policies, where morbidity and mortality impacts are evaluated separately using static health impacts functions and the life-table method, seriously threatens the internal validity of estimates of health gain associated with air pollution control.

By ignoring interactions between morbidity and mortality effects, this “separate” approach was found to be associated with two major limitations. First, it systematically overestimates the change in number of morbidity cases associated with pollution increment or decrement. The size of the overestimation bias is not negligible, especially over long time-horizons as typically used in assessments of air pollution control interventions. Over a 60-year time horizon for instance, the “separate” approach was found to lead to an overestimation by one fifth of the number of CHD cases expected to be avoided following pollution abatement in London.

Second, the “separate” approach cannot characterise the distribution of impacts by causal pathways and between population subgroups stratified by their level of health. It is therefore inappropriate to support health care budget impact assessments and distributional analysis and also, to quantify health effects using summary measures of population health. This explains why the few past attempts at measuring the QALY gain from air pollution control either failed to encompass the quality of life gain from reduced chronic morbidity, or departed from the QALY by no longer allowing a linear substitution between quality and quantity of life.

More importantly, this second limitation was found to lead to a substantial underestimation of the life expectancy gain, be it quality-adjusted or not, from air pollution reduction. Indeed since the “separate” approach cannot charac-

terise the distribution of impacts by health-stratified population subgroups, it fails to encompass existing evidence that individuals with CHD and COPD, once they reach a certain age and/or severity level, are expected to face a greater excess risk of death under pollution exposure than individuals of the general population. This is problematic since the present analysis found that accounting for the current evidence of health-related differential susceptibility has a large impact on the expected health gain and health care cost impact of air pollution abatement. In the case of London, it represents a 34% difference in expected QALY gain and a 26% difference in expected QALY gain net of health care resource impacts.

Development of a Markov model that addresses all the limitations of the “separate approach” and represents a step forward to the cost-effectiveness analysis of air pollution control interventions

The thesis developed the first Markov model of health impacts from long-term exposure to air pollution that addresses all the limitations of the “separate approach”, by capturing interactional effects between morbidity and mortality impacts. The model indeed makes it possible to encompass for the first time: (i) air pollution’s influence on individuals’ quality of life and life expectancies at baseline and (ii) dynamics in individuals’ susceptibility to air pollution exposure as a consequence of a degraded health condition, be it related to cumulative air pollution exposure or not. Thanks to these two features, the model fully captures the lifetime impact of air pollution exposure on individuals’ quality and length of life. The model is also of particular relevance for health care budget impact analysis as it captures the joint budget impact of a reduction in both chronic morbidity and premature death. Consequently, the methodology proposed and the model developed are expected to represent a step forward to the cost-effectiveness analysis of air pollution control interventions.

The model follows adult individuals’ health trajectories over time from the states “healthy” to “dead” across three diseases that aim to represent the

overall body of epidemiological evidence on the cardio-respiratory effects of long-term exposure to particulate air pollution: chronic obstructive respiratory disease, coronary heart disease and lung cancer. Whilst the model was applied to a UK case study its structure, which accounts for COPD and lung cancer characteristics in terms of severity and survival pattern over time, as well as its thorough use of available epidemiological evidence could be easily replicated to quantify the health benefits of air pollution control elsewhere. In a context of increasing interest for the chronic morbidity impacts of long-term air pollution exposure, as exemplified by large-scale epidemiological projects such as ESCAPE¹ in Europe and MESA Air² in the US, the model developed in this thesis is expected to be of particular interest to HIA practitioners. It should nevertheless be reminded that the model is parameterised using risk estimates from epidemiological studies performed in developed countries, where linearity in health effects in response to a change in air pollution concentrations has been found. Application of the model to assess air pollution control interventions in developing countries should therefore take into account potential non linearity in effects, as suggested by existing attempts at extrapolating concentration-response functions at high concentration levels (Pope III et al., 2011; Burnett et al., 2014).

Demonstration that the current European guidelines for uncertainty analysis in HIA of air pollution control underestimate decision uncertainty

Notwithstanding the recommended use of a triangular distribution for a number of parameter (Holland, 2014), which in reality is difficult to parametrize correctly since it is not linked to the data estimation process (Briggs et al., 2006), current European guidelines³ to handling uncertainty in non statistically significant risk estimates of health effect were found to underestimate decision uncertainty.

Since it seems indeed implausible that curbing air pollution could harm

¹European Study of Cohorts for Air Pollution Effects.

²Multi-Ethnic Study of Atherosclerosis and Air Pollution.

³from the HRAPIE (Health Risks of Air Pollution In Europe) group.

health, in the case where the risk estimates used to compute the expected health benefits of air pollution reduction are non statistically significant, guidelines recommend to attribute a range of +/- 100% of mean effect and assuming equal likelihood within the assigned value range. In others words, they suggest to truncate both tails of the original distributions of parameters, thus assuming that their mean value was correctly estimated but not their variance.

In this thesis, these guidelines were contrasted with an alternative approach which truncated only the left-tail of original distributions, by assigning a value of 1 to any value below 1 randomly drawn from risk estimates' original distributions. Comparative analysis showed that the probability of decision error and thus, the EVPI and the option value to delay associated with investments in air pollution reduction, were systematically significantly lower when following the guidelines than under the alternative approach which solely ignored non-plausible risk estimate values. It follows that, by suggesting greater certainty in outcomes than is the case, current European guidelines for uncertainty analysis may misguide decision-making for air quality improvement.

Development of a framework to estimate COPD incidence by severity stages

The thesis developed a framework to estimate the age-specific annual probability of being diagnosed with COPD at a given severity stage, implied by the underlying population prevalence of the disease estimated at a single point in time and its relationship with disease incidence, progression and survival. By addressing the issue of underdiagnosis embedded in primary care data, this framework helps support the estimation of the total population health gain associated with a primary prevention intervention that would reduce the risk of developing COPD, or COPD patients' risk of suffering from further adverse effects. The framework was applied to the case of England in order to parameterise the model of air pollution impacts and to support cost-effectiveness evaluation of air pollution control in England and Wales and London. However, since COPD underdiagnosis is a global issue (GOLD, 2014), the framework could be applied to estimate COPD incidence by severity stages in other coun-

tries, provided data on the underlying prevalence of the disease is available.

8.2.2 Empirical contributions

Supporting the UK air quality strategy

In addition to showing that existing estimates of life expectancy gain from air quality improvement are likely to be seriously underestimated, and thus to lead to suboptimal levels of air pollution reduction, this thesis provides the first estimates of QALY gain and health care budget impact associated with particulate air pollution control in England and Wales and London. Estimates were computed for a unit decrement in $PM_{2.5}$ and can be linearly rescaled to a decrement of a different magnitude. These estimates which are summarised in section 6 of Chapter 7, alongside with the analysis of levels of uncertainty surrounding them, provide a concrete basis to support the UK air quality strategy.

More specifically, modelling results underline the strong public health implications of air pollution reduction. In London, reducing air concentrations of fine particulates by $1\mu g/m^3$ (i.e. by 7%) is expected to generate to the current population of adults aged above 40 more than 60,000 QALYs over their lifetime. As a result, investing up to £500 million to achieve this level of pollution reduction is highly likely to be cost-effective (less than 10% probability of decision error), whether the investment is funded by the NHS or through general taxation.

For larger investments, however, the source of money value of health embedded in the funding mechanism, namely NHS resources or general taxation, strongly influences cost-effectiveness results as consumer willingness to pay for a QALY is much higher than the estimated NHS expenditure required to deliver one QALY. It follows that the identification of the optimal level of

pollution reduction, as well as the decision about whether and for how long to delay investments to gather further evidence, is expected to depend on the choice of funding mechanism.

Evidence synthesis

At the time when the model was being developed, there was a gap in evidence synthesis pertaining to the association between long term exposure to fine particulate pollution and respectively all-cause mortality and lung cancer development. This gap was filled by the work of Chapter 6, which results were found to be consistent - or if a difference were found it could be fully explicated - with meta-analyses published after completion of the present work.

First estimates of underlying incidence of COPD by severity stage in England

Application of the framework developed in Chapter 5 to the case of England, provides the first estimates of the underlying incidence of COPD by GOLD severity stages in England. These estimates could be used to support economic evaluations of preventive interventions targeted at reducing the incidence of COPD in this country, or to support analyses of budget impact and population EVPI associated with health care technologies aimed at treating this disease.

8.3 Limitations

The Markov model of the health impacts of long-term exposure to particulate air pollution and its application to a UK case study, which are core components of this thesis, present a number of limitations.

First the model only builds on the linkages between concentration reduction and health impacts, whilst the chain of impacts from intervention to health effects is more complex. Indeed, reducing concentrations of air pollutants will typically require a portfolio of sector-specific interventions targeting various sources of emissions, e.g. transportation, industrial facilities, housing, which impact on concentrations over time will be uncertain. As a result, the total level of uncertainty surrounding the health and health care cost impacts of particulate air pollution abatement is presently underestimated.

Second, Chapter 7 placed particular emphasis on uncertainty analysis and in particular, on the value of reducing parameter uncertainty. However, as underlined in Chapter 2, the impact of parameter uncertainty on decision uncertainty is mediated by structural uncertainty, i.e. is conditional on the chosen structure of the model. Scenarios analysis was performed for three different approaches to handling risk estimates that were non statistically significant at the conventional 5% level and according to two approaches to encompassing health-related heterogeneity in susceptibility (namely by excluding or including existing evidence related to heterogeneity). Whilst scenarios analysis shows how cost-effectiveness results would change under different assumptions, it is important to underline that not all sources of structural uncertainty are represented in these scenarios. In particular, whilst it was argued that excluding evidence solely based on the conventional - but arbitrary - rules of statistical inference would lead to bias, as mentioned in Chapter 4, the body of epidemiological evidence on the association between air pollution exposure and COPD is currently incomplete (Schikowski et al., 2013). Therefore, ideally, the uncertainty as to whether to include or not COPD as relevant health endpoint should also be investigated. An approach to addressing this specific issue and more generally, to appropriately characterising structural uncertainty, will be discussed in section 8.4.

Third, the model applies to adult individuals and thus, ignores effects in children. It should, however, be underlined that documented adverse impacts in children tend to be subclinical (Shannon et al., 2004; US EPA, 2009; Peled, 2011). These impacts are therefore expected, to some extent, to be captured into a greater risk of developing chronic morbid conditions later in life. In-

deed, it is generally accepted for instance, that chronic respiratory impacts in adults partly derive from the worsening over time of subclinical conditions developed since childhood (Eisner et al., 2010). It follows that the excess risk of developing chronic morbid conditions at adult age may, at least in part, be a consequence of subclinical symptoms associated with exposure during childhood and/or adverse birth outcomes associated with exposure *in utero*. On these grounds, whilst focusing on chronic clinical conditions developed at adult age may not capture all potential benefits from air pollution reduction, it has the advantage of avoiding potential double counting of effects. It should also be noted that translating into QALY loss the adverse birth outcomes associated with air pollution exposure *in utero*, such as low birth weight and pre-term birth, would require a certain number of assumptions that would further contribute to uncertainty around outcomes.

Fourth, a source of uncertainty when assessing the impacts from pollution abatement pertains to the time profile of the reduction in risks of experiencing adverse effects following exposure decrement, which is known as the cessation lag. This model uses the 20-year distributed cessation lag developed by the US EPA, which assumes 30% of the risk reduction in year 1, an additional 12.5% every year between year 2 to year 5 and the final 20% of risk reduction being phased in gradually over year 6 to year 20 (US EPA, 2010). Although this lag was carefully elaborated in light of empirical evidence from cohort, natural experiments and smoking cessation studies, it remains largely uncertain (Walton, 2010). In addition, this lag was developed only to characterise dynamics in mortality risk reduction. Indeed so far morbidity impacts (to the exception of chronic bronchitis) have only been quantified with regards to acute exposure, for which the change in risk may be assumed to be immediate. Nevertheless, repeated cross-sectional analyses suggest that PM-related excess risks of morbid events are also expected to be reversible in a short to middle time-horizon following improvements in air quality (Downs et al., 2007; Schindler et al., 2009; Schikowski et al., 2010).

Fifth, whilst the model accounts for COPD and lung cancer characteristics in terms of severity levels and survival pattern over time, the CHD condition is modelled via a single state. As a result, the modelling of CHD-related greater

susceptibility to air pollution involved some level of extrapolation. Indeed, the study informing differential susceptibility associated with CHD (Tonne & Wilkinson, 2013) was based on patients aged 25 and above, who had an acute coronary event. This endpoint represents a more severe health condition than CHD as a whole. However, in light of evidence that the risk of acute coronary event is a positive function of age (Simms et al., 2012), the risk estimate estimated by Tonne & Wilkinson (2013) was only applied to individuals with CHD aged 75 or above, which considerably restricted the subset of susceptible individuals. The risk of potential overestimation of health benefits accruing to individuals with CHD is therefore expected to be limited.

Sixth, the model does not consider effects from acute exposure. Whilst the latter are irrelevant when considering life expectancy impacts (which are fully captured in the risk estimates of excess mortality from chronic exposure), acute effects are relevant for the quality of life dimension but also when assessing health care cost impacts. It follows that the incorporation of acute effects, such as asthma or COPD exacerbations for instance, would contribute to further improve the model.

Seventh, the model does not assign any health care costs to “healthy” individuals - i.e. those without CHD, COPD or lung cancer - although the latter will also cost to the health care system. Consequently, the health care costs associated with air pollution reduction are presently underestimated. Nevertheless it should be underlined that the health benefits of air pollution control are an order of magnitude higher than the QALY loss from health care cost impacts. Indeed, based on an estimate of £13,000 as the NHS expenditure required to deliver one QALY, the QALY loss resulting from net health care costs accounts for solely 2.8% and 3.7% of the health benefits in respectively London and England and Wales. As a result, the underestimation of health care cost impacts is unlikely to substantially affect the cost-effectiveness performance of interventions that improve air quality.

Eighth, the model is built on the assumption of competitive risk between disease pathways, which is partly challenged by the fact that COPD is a multi-component systemic disease that is associated with a greater risk of cardiovascular events and lung cancer (GOLD, 2014). However, since the model’s

estimates of un-discounted life years gain per person are in line with results from past HIAs (when ignoring health-related differential susceptibility), the assumption of competitive risk is not expected to have led to a substantial underestimation of the total life expectancy impact.

Ninth, this thesis and the model developed focus on particulate air pollution. Particulate matter results from the release of a number of pollutants and is therefore considered to be a good proxy for air quality (US EPA, 2012). In addition, it is estimated to adversely affect population health more than any other air pollutant (WHO, 2014). Nevertheless, effects from other air pollutants such as nitrogen dioxide, may also need to be considered when considering the benefits of improving air quality.

8.4 Further research

There are a number of avenues to extend the present work. First, it would be of particular interest to combine the presently developed model of the health impacts from air pollution exposure with dispersion modelling of air pollutants emissions. This would enable the overall uncertainty associated with each link of the chain of effects starting from the implementation of a specific intervention (e.g. low emissions zone, bus retrofitting) to final health impacts to be captured, as opposed to solely focusing on the uncertainty in health outcomes following a reduction in concentrations.

A second extension of the present work would be to apply a more structured approach to characterising structural uncertainty. Jackson et al. (2011) recommend to encompass all plausible structures of the model in a global model and to express them via additional model parameters. To inform these parameters, the authors suggest two alternatives. The first consists in relying on conventional methods used for choosing between statistical models, in order to derive weights to apply to the expected costs and benefits associated with each plausible model structure (for EVPI weights would have to be applied to each simulated value as opposed to the model-specific expected cost and

benefits across simulations). Akaike's Information Criterion (AIC) was suggested as a mean to derive those weights and is straightforward to apply if structural uncertainty pertains to the inclusion/exclusion of a parameter for which a p-value is available. The second alternative draws on expert elicitation, whereby experts' beliefs are translated into probability distributions for uncertain parameters.

In the presently developed model, a combination of both approaches may be applied with regards to the inclusion of: (i) COPD as relevant health endpoint and (ii) health-related heterogeneity in susceptibility to air pollution exposure. Indeed, both sources of uncertainty are informed by epidemiological risk estimates, based on which one can easily derive differences in AIC between a model structure that includes the effect of interest and one that excludes it. Deriving model weights based on a single study may, however, not always be the most appropriate, especially in the case of COPD where the overall body of evidence include a number of studies pertaining to related respiratory symptoms and subclinical conditions. In this case, AIC-based weights may be combined with prior expert opinion in a Bayesian framework.

Third, the present finding that the identification of the optimal level of pollution reduction and the decision to delay investments are expected to be driven by the source of financing could be further explored. In particular, in the present context of budget devolution whereby some NHS funds are to be transferred to local authorities (as is to be the case of Greater Manchester in April 2016), it would be of interest to investigate the impact on local air quality strategies associated with the use of local governments' budgets to fund investments in emission reduction. Alternatively, if the intervention were to be funded through taxation, cost-effectiveness analysis may be further refined by accounting for the deadweight loss of taxation, i.e. the economic loss resulting from inefficient activities undertaken as a result of tax introduction (Kay, 1980). A typical example of allocative inefficiency is the inefficient substitution of taxed paid work for untaxed leisure.

Fourth, a topic of particular relevance to "Healthy Public policy", which was only touched upon in Chapter 3, pertains to the distributional analysis of benefits of air pollution control among subgroups stratified by socio-economic

status and the associated impacts on socio-economic related health inequality. Three main factors are expected to drive the socio-economic distribution of impacts: (i) differential exposure, which is also linked to the issue of environmental justice when concentration levels are positively associated with levels of deprivation; (ii) the existence of a socio-economic gradient in health outcomes that impacts on individuals' baseline risks of experiencing adverse health events and (iii) differential susceptibility, i.e. systematic differences in relative risks between socio-economic subgroups for which however, existing epidemiological evidence to date remains inconclusive (Laurent et al., 2007). It should be underlined that accounting for differential exposure to air pollution by socio-economic status would require to link the presently developed model of health effects with dispersion modelling, as previously suggested.

Finally, an additional promising extension of the present work would consist in considering health effects in children (without double-counting), as well as wider societal effects than health care costs such as impacts on productivity, school absenteeism and pension costs. Air pollution is expected to impact productivity via two mechanisms: (i) premature exit of the job market due to the development of chronic illnesses and (ii) work loss days due to exacerbations of chronic morbid conditions following acute exposure. School absenteeism is expected to be essentially linked to acute exposure, e.g. asthma exacerbations. Consequently, in order to thoroughly encompass wider societal effects, health effects from acute exposure in both children and adults would need to be encompassed alongside effects from chronic exposure.

Appendices

Appendix A

Adjustment of mortality risk estimates

General method

The following method is proposed to estimate the excess risk of mortality from all other causes of death than cause x . The method is outlined for hazard ratios which are rate ratios.

The hazard ratio of all cause mortality, $HR_{\Delta h, Death_{AC}}$, is defined such that:

$$HR_{\Delta h, Death_{AC}} = \frac{h(t)_e(Death_{AC})}{h(t)_{ne}(Death_{AC})} \quad (A.1)$$

where $h(t)_e(Death_{AC})$ and $h(t)_{ne}(Death_{AC})$ denote the instantaneous mortality rate from all causes (AC) per period t in respectively the exposed and non-exposed groups and Δ_h is the difference in hazard exposure between the two groups.

Assuming death from cause x (denoted $Death_x$) and death from all other causes than x (denoted $Death_{AOC}$) are mutually exclusive events, we obtain:

$$HR_{\Delta h, Death_{AC}} = \frac{h(t)_e(Death_{AOC}) + h(t)_e(Death_x)}{h(t)_{ne}(Death_{AC})} \quad (A.2)$$

This implies that:

$$h(t)_e(Death_{AOC}) = HR_{\Delta h, Death_{AC}} h(t)_{ne}(Death_{AC}) - h(t)_e(Death_x) \quad (A.3)$$

where:

$$h(t)_e(Death_x) = HR_{\Delta h, Death_x} h(t)_{ne}(Death_x) \quad (A.4)$$

Dividing expression A.3 by $h(t)_{ne}(Death_{AOC})$ yields:

$$HR_{\Delta h, Death_{AOC}} = HR_{\Delta h, Death_{AC}} \frac{h(t)_{ne}(Death_{AC})}{h(t)_{ne}(Death_{AOC})} - HR_{\Delta h, Death_x} \frac{h(t)_{ne}(Death_x)}{h(t)_{ne}(Death_{AOC})} \quad (A.5)$$

Therefore, the hazard ratio of mortality from all other causes than x , can be expressed as a function of:

- (i) the hazard ratio of mortality from all causes;
- (ii) the hazard ratio of mortality from cause x ;
- (iii) death rates (death from x , death from AOC , death from AC) in the non-exposed group, which may be proxied by baseline mortality rates in the target population of the intervention under assessment.

Adjustment for evaluating the case study

One parameter required for the modelling was the hazard ratio (HR) of mortality from all causes of death than CHD. The adjustment was performed using:

- 1- The central value of hazard ratios of: (i) mortality from all-cause and (ii) mortality from CHD from Pope III et al. (2002).
- 2- Population-weighted average annual rates of death in the population of England aged 40 and above, provided by the UK Office for National Statistics.

Plugging-in the corresponding values into equation A.5, we obtain:

$$HR_{\Delta_h, DeathAOC|\overline{CHD}} = 1.07 \frac{0.000330}{0.000278} + 1.11 \frac{0.000052}{0.000278} = 1.05 \quad (\text{A.6})$$

where Δ_h represents an increment in $PM_{2.5}$ concentrations by $10\mu g/m^3$ and AOC stands for all other causes of death than CHD.

(For $\Delta_h = -1\mu g/m^3$, $HR_{\Delta_h, DeathAOC|\overline{CHD}} = 0.995$ - see section C)

Appendix B

Risk estimates: original values and rescaling

Rescaling of risk estimates (RE) to a decrement in $PM_{2.5}$ concentration of $1\mu g/m^3$ was performed using logarithmic multiplicative scaling, based on the fact that risk estimates were obtained using log-linear statistical models. As shown in Chapter 2, this implies that :

$$\begin{aligned} RE_{\Delta PM_{2.5}} &= \exp(\beta \times \Delta_{PM_{2.5}}) \\ \Rightarrow RE_{\Delta PM_{2.5}=-1\mu g/m^3} &= (RE_{\Delta PM_{2.5}=x\mu g/m^3})^{\frac{-1}{x}} \end{aligned}$$

The original values of risk estimates taken from the epidemiological literature are provided in Table B.1.

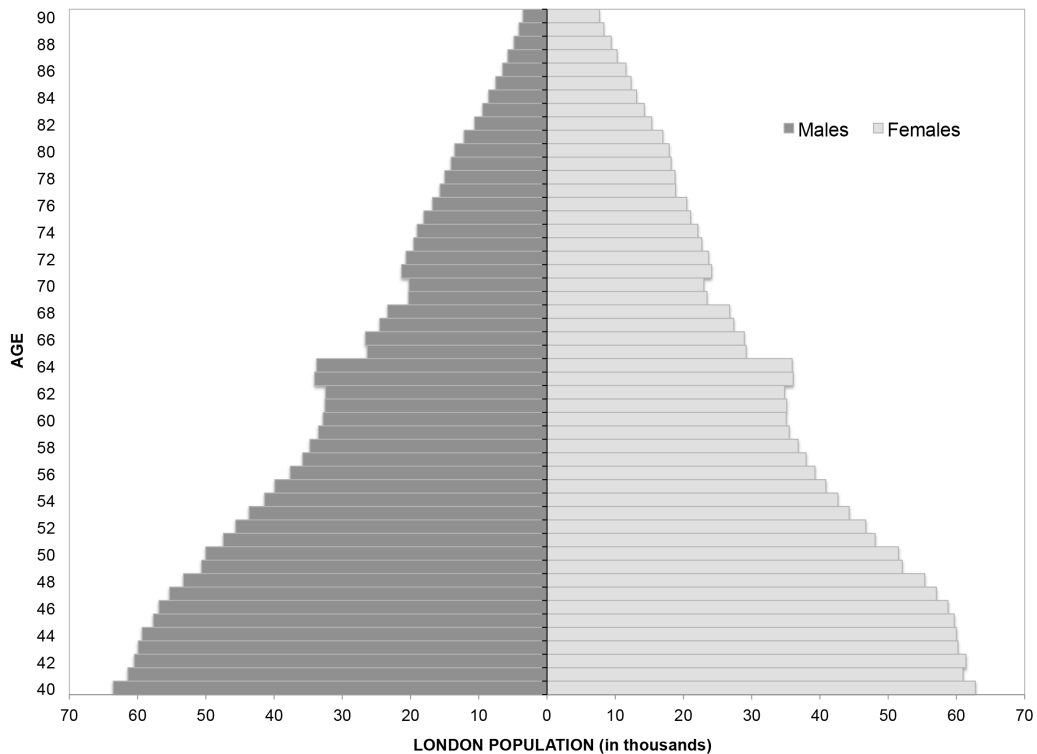
Parameter	Source	Values (95% CI)	$\Delta_{PM_{2.5}}$
$RR_{Dev.CHD}$	Gan et al. (2011)	1.02(1.0 – 1.05)	$+1.38\mu g/m^3$
$HR_{DeathAC}$	Pope III et al. (2002)	1.06(1.02 – 1.11)	$+10\mu g/m^3$
$HR_{DeathAC CHD}$	Zanobetti and Schwartz (2007) ^(a)	1.34(1.27 – 1.52)	$+10\mu g/m^3$

Table B.1: Risk estimates original values.

^(a) Study population was individuals aged 65 years old and above.

Appendix C

Distribution of London adult population (40+) by age groups and gender



Distribution of London adult population (40+) by age groups and gender, based on 2011 census.

Appendix D

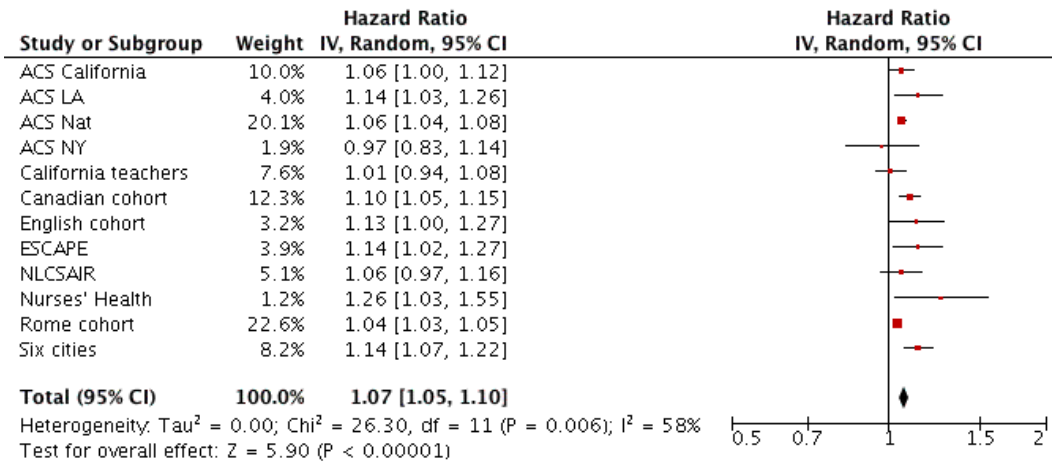
Systematic search: database queries

Search	Query	Items found
#6 = #1 AND #2 AND #3 AND #4 AND #5	Search (((((((((((Inhalation Exposure[MeSH Terms]) OR Risk Factors[MeSH Terms]) OR Environmental Exposure[MeSH Terms]) OR Urban Population[MeSH Terms]) OR Cities[MeSH Terms]) OR Urban Health[MeSH Terms]) OR Outdoor[Title/Abstract]) OR Urban[Title/Abstract]) OR Ambient[Title/Abstract]) OR Traffic[Title/Abstract]) AND ("2008/01/01"[PDat] : "2014/12/31"[PDat]) AND Humans[Mesh]) AND (((("Air Pollutants/toxicity"[Mesh]) OR ("Air Pollutants/adverse effects"[Mesh]) OR "Air Pollution/adverse effects"[Mesh]) OR "Environmental Exposure/adverse effects"[Mesh]) OR "Inhalation Exposure/adverse effects"[Mesh]) AND ("2008/01/01"[PDat] : "2014/12/31"[PDat]) AND Humans[Mesh]) AND (((((((Follow-up Studies[MeSH Terms]) OR Cohort Studies[MeSH Terms]) OR Retrospective Studies[MeSH Terms]) OR Prospective Studies[MeSH Terms]) OR Proportional Hazards Models[MeSH Terms]) OR Cohort[Title/Abstract]) OR Follow-up[Title/Abstract]) AND ("2008/01/01"[PDat] : "2014/12/31"[PDat]) AND Humans[Mesh]) AND (((("Cause of Death"[Mesh]) OR "Mortality"[Mesh]) OR "Cardiovascular Diseases/mortality"[Mesh]) OR "Respiration Disorders/mortality"[Mesh]) OR "Lung Diseases/mortality"[Mesh]) OR "Lung Neoplasms"[Mesh]) AND ("2008/01/01"[PDat] : "2014/12/31"[PDat]) AND Humans[Mesh]) AND (((((((Particulate Matter[MeSH Terms]) OR Particle Size[MeSH Terms]) OR Vehicle Emissions[MeSH Terms]) OR PM10[Title/Abstract]) OR PM2.5[Title/Abstract]) AND ("2008/01/01"[PDat] : "2014/12/31"[PDat]) AND Humans[Mesh])	139
#5	Search (((Particulate Matter[MeSH Terms]) OR Particle Size[MeSH Terms]) OR Vehicle Emissions[MeSH Terms]) OR PM10[Title/Abstract]) OR PM2.5[Title/Abstract] Filters: Publication date from 2008/01/01 to 2014/12/31; Humans	14501
#4	Search (((("Cause of Death"[Mesh]) OR "Mortality"[Mesh]) OR "Cardiovascular Diseases/mortality"[Mesh]) OR "Respiration Disorders/mortality"[Mesh]) OR "Lung Diseases/mortality"[Mesh]) OR "Lung Neoplasms"[Mesh] Filters: Publication date from 2008/01/01 to 2014/12/31; Humans	137848
#3	Search (((((((Follow-up Studies[MeSH Terms]) OR Cohort Studies[MeSH Terms]) OR Retrospective Studies[MeSH Terms]) OR Prospective Studies[MeSH Terms]) OR Proportional Hazards Models[MeSH Terms]) OR Cohort[Title/Abstract]) OR Follow-up[Title/Abstract] Filters: Publication date from 2008/01/01 to 2014/12/31; Humans	557025
#2	Search (((("Air Pollutants/toxicity"[Mesh]) OR ("Air Pollutants/adverse effects"[Mesh]) OR "Air Pollution/adverse effects"[Mesh]) OR "Environmental Exposure/adverse effects"[Mesh]) OR "Inhalation Exposure/adverse effects"[Mesh] Filters: Publication date from 2008/01/01 to 2014/12/31; Humans	14506
#1	Search (((((((((((Inhalation Exposure[MeSH Terms]) OR Risk Factors[MeSH Terms]) OR Environmental Exposure[MeSH Terms]) OR Urban Population[MeSH Terms]) OR Cities[MeSH Terms]) OR Urban Health[MeSH Terms]) OR Outdoor[Title/Abstract]) OR Urban[Title/Abstract]) OR Ambient[Title/Abstract]) OR Traffic[Title/Abstract] Filters: Publication date from 2008/01/01 to 2014/12/31; Humans	272957

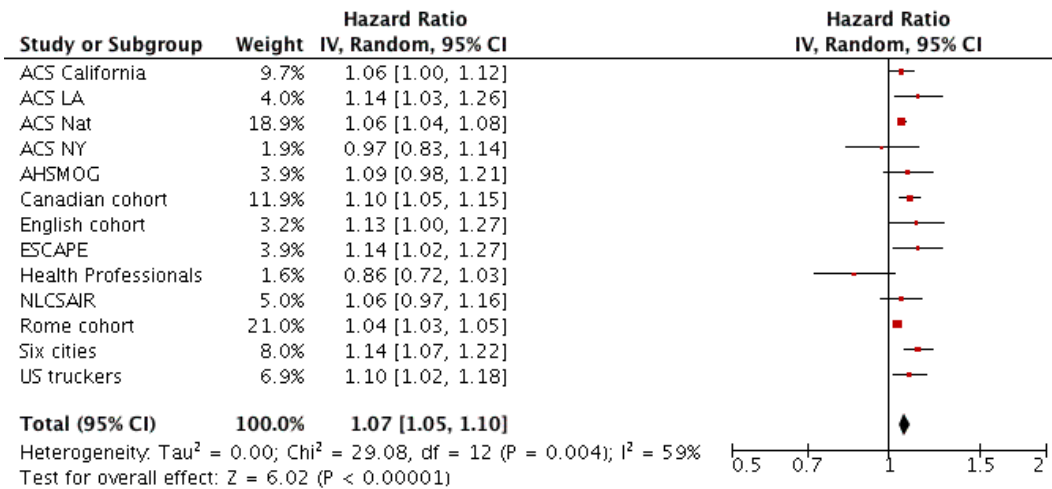
Figure D.1: Pubmed search query. Data 26/04/2014.

Select	#	Searches	Results	Search Type
<input type="radio"/>	1	(air pollution or air pollutant or particulate matter or particulate pollution).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	65195	Advanced
<input type="radio"/>	2	(urban area or outdoor or outside or ambient air or traffic or proximity).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	231408	Advanced
<input type="radio"/>	3	(lung cancer or lung carcinoma or lung neoplasm or lung disease or chronic lung disease).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	244064	Advanced
<input type="radio"/>	4	(death or cause of death or mortality).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1110553	Advanced
<input type="radio"/>	5	3 or 4	1308045	Advanced
<input type="radio"/>	6	(chronic or long-term or cohort).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1617654	Advanced
<input type="radio"/>	7	1 and 2 and 5 and 6	852	Advanced
<input checked="" type="radio"/>	8	limit 7 to (human and english language and yr="2008 -Current" and article and (adult <18 to 64 years> or aged <65+ years>))	136	Advanced

Figure D.2: Embase search query. Data 26/04/2014.



(a) Studies focusing on females or both gender

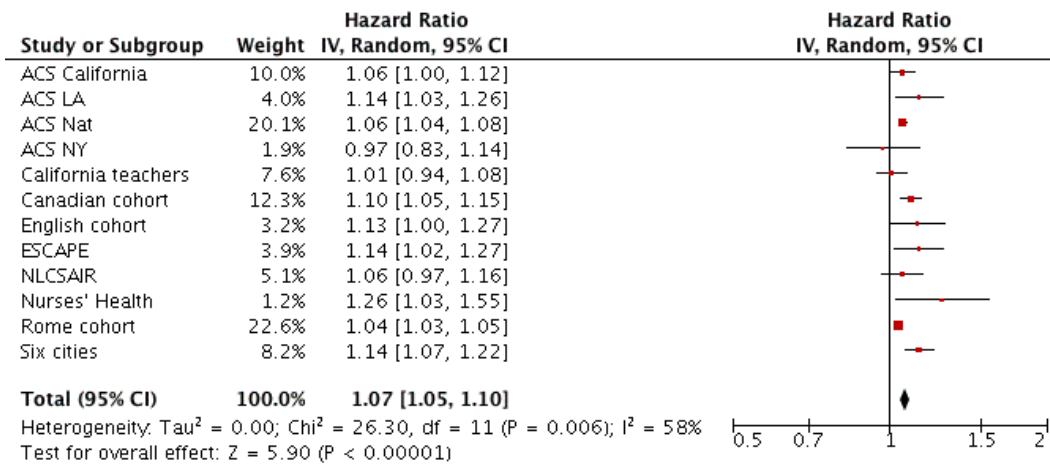


(b) Studies focusing on males or both gender

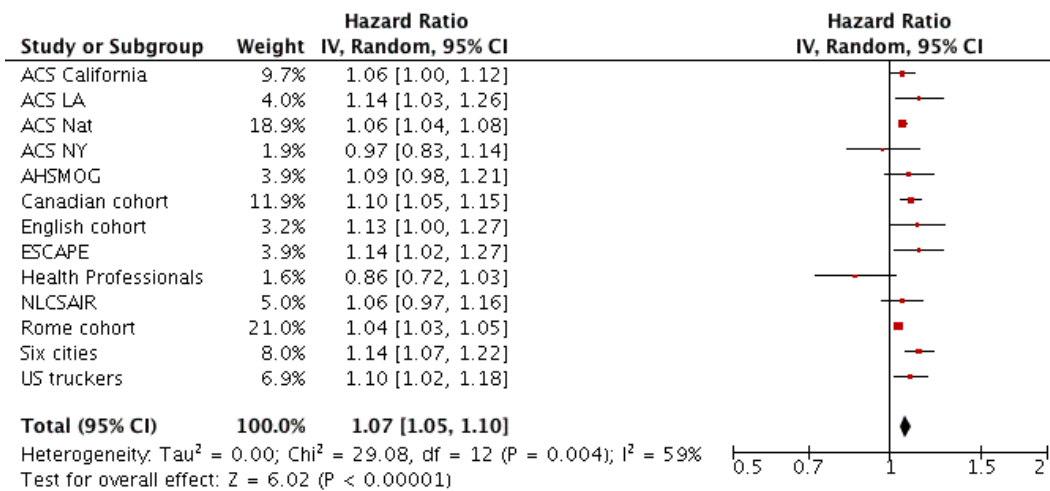
Figure D.3: Sub-group analysis by gender for the association between long-term exposure to $PM_{2.5}$ and all-cause mortality (Random effect model - Pooled hazard ratio per 10 $\mu g/m^3$).

Appendix E

Meta-analysis: sub-group analysis by gender



(a) Studies focusing on females or both gender



(b) Studies focusing on males or both gender

Figure E.1: Sub-group analysis by gender for the association between long-term exposure to $PM_{2.5}$ and all-cause mortality (Random effect model - Pooled hazard ratio per $10 \mu g/m^3$).

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