Quantification of Mortality and Hospital Admissions Associated with Ground-level Ozone

A report by the Committee on the Medical Effects of Air Pollutants

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Foreword

Summertime ozone exposure represents a substantial health risk to the UK population. As a secondary pollutant, ozone is highly sensitive to anthropogenic and natural precursor emissions as well as prevailing atmospheric conditions and is likely to be influenced by climate change. Current assessments on mortality/morbidity burdens in the UK are based on short-term exposure coefficients initially proposed by the Committee on the Medical Effects of Air Pollutants (COMEAP) in 1998 and updated by the World Health Organization (WHO) in 2004. As annual mean ozone concentrations are increasing in some urban areas in the UK, Public Health England asked COMEAP to reconsider the quantification of health effects linked with ozone, in preparation for the 2nd National Climate Change Risk Assessment to be presented in Parliament in early 2017.

With a suggested reporting deadline of mid-2015, COMEAP formed a working group to undertake this task. I am extremely grateful to its members, who chaired by Dr Heather Walton, performed this task in a matter of months and produced several draft reports for COMEAP and the secretariat to consider.

The report makes several important conclusions about the short-term health effects of ozone. Unsurprisingly, given the short timeline in place, the working group identified several areas which could not be resolved. A number of these arose because the evidence base is still insufficient to allow a reliable conclusion to be drawn at this time. Helpfully, the report highlights these gaps and deficiencies and makes recommendations for future research.

Ground-level ozone remains one of the most pervasive ambient pollutants, not only affecting human health, but also food production and the environment. However, as has been highlighted in this report, important gaps in our knowledge remain and uncertainties exist. With climate change potentially influencing availability of ozone precursor gases, as well as climatic conditions that favour its formation, it is now crucial to improve our understanding of the health impacts of this strongly oxidising ambient pollutant.

Professor Frank Kelly

Chair of the Committee on the Medical Effects of Air Pollutants

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Executive Summary

A Key points

a This report was prepared to feed into the evidence base for the 2nd National Climate Change Risk Assessment. It is a combination of (i) recommendations and (ii) suggestions of a strategy for research to develop these recommendations further over time

b There is sufficient evidence to recommend quantification of the impacts of short-term exposure to daily maximum 8-hour running mean ozone on all-cause mortality, respiratory hospital admissions and, acknowledging more uncertainty, cardiovascular hospital admissions, in the core analysis of a health impact assessment. The evidence suggests it is reasonable to assume no threshold for any of the health endpoints considered here in a health impact assessment

c The recommendations given here are for the purpose of planned health impact assessment for current and future scenarios that do not cover other pollutants. Also, it is likely that correlations with other pollutants may continue to be similar in the future. Therefore, the use of a concentration-response function based on single-pollutant models was considered, on balance, to be the best option

d We have not considered (i) panel study evidence on effects of ozone on reduced lung function, as this effect is difficult to value in cost-benefit analysis; (ii) other respiratory symptoms, for which evidence is difficult to synthesise; or (iii) restricted activity days, which will be considered in a separate piece of work

e The evidence from all-year associations between long-term exposure to ozone and mortality is not convincing. There is limited evidence for an association between ozone concentrations during the warmer months of the year. Further work is required on the assumptions needed for health impact calculations (thresholds, effect modification, cessation lags and life table methods for applying risks for part of a year). We do not therefore recommend quantification of effects of long-term exposure to ozone and mortality at this stage. We recommend further work in order to develop quantification approaches for use in sensitivity analyses in the future

f Interpretation of evidence on ozone is complicated by changes in correlations between pollutants by season and possible interactions with temperature. A future research strategy to improve understanding is suggested

g The concentration-response coefficients recommended for quantification in core analysis are given below

Short-term exposure	
Health endpoint	**Concentration-response coefficient: % increase per 10 µg/m³ daily maximum 8-hour running mean ozone (95% confidence interval)**
All-cause mortality, all ages	0.34% (0.12, 0.56%)
Respiratory hospital admissions, all ages	0.75% (0.30, 1.20%)
Cardiovascular hospital admissions, all ages	0.11% (–0.06, 0.27%)
Long-term exposure	
Not recommended for quantification at this stage; pending further work	

B Introduction

Climate change has the potential to increase ground-level ozone concentrations and this needs to be taken into account when assessing the risks of climate change overall. The Committee on the Medical Effects of Air Pollutants (COMEAP) was requested by Public Health England to give an updated opinion on the quantification of health effects of ozone, for use in the 2nd National Climate Change Risk Assessment (CCRA2). COMEAP formed a working group which reviewed the available evidence on appropriate concentration-response functions and drafted this report. The report has been endorsed by COMEAP.

Broadly, the terms of reference request advice, with reference to quantification of health effects in the UK, on:

a Whether the evidence is sufficient to support quantification

b Concentration-response relationships for short-term exposure to ozone and mortality and hospital admissions, for application in the UK

c Concentration-response relationships for long-term exposure to ozone and mortality

d Issues affecting the interpretation and/or application of the above, such as independence from other pollutants, thresholds, interaction with temperature, effect modification, ozone metric and use or not of seasonal results

This report is a combination of (i) recommendations and (ii) suggestions of a strategy for research to develop these recommendations further over time. Our recommendations can also be used for purposes other than the CCRA2. The conclusions could change as a result of further work.

This report concentrates on ground-level ozone. This is not the only pollutant affected by climate change – further work is recommended on other pollutants.

The report is structured in three parts at different levels of detail. This summary presents our conclusions as responses to particular questions, with cross-references to paragraphs in the main report. The main report sets out the reasoning behind the conclusions. Finally, there is a series of appendices that give fuller technical details behind this reasoning.

C Effects of short-term exposure (Chapter 3)

Q1 For which health endpoints is there sufficient evidence of causal associations with short-term exposure to ambient concentrations of ozone for these endpoints to be quantified?

We concentrated on evidence from population-based epidemiological studies (important for health impact assessment), and focused on studies relating to the general population rather than susceptible groups.

We have not considered panel study evidence on the effect of ozone on reduced lung function, as this effect, while well established, is difficult to value in cost-benefit analysis. There is evidence from panel studies for associations between ozone and respiratory symptoms but it is difficult to systematically summarise and synthesise this evidence due to variation in the exact definitions of study populations and symptom descriptions. Restricted activity days are being considered as an outcome for quantification separately but the evidence base for ozone and restricted activity days is very small. Instead we have concentrated on time-series studies that are able to pick up more serious disease outcomes.

Within the time-series studies, we examined studies on broad health outcomes for all ages: all-cause mortality, cardiovascular hospital admissions and respiratory hospital admissions (Sections 3.1–3.5). Associations with all-cause mortality have been examined in a larger number of studies covering a larger number of locations. Quantifying cause-specific mortality in addition to all-cause mortality would result in double-counting.

For admissions, we again chose broad health outcomes for all ages (all respiratory and all cardiovascular admissions) as, for all ages, there are many more studies on the broader diagnoses.

Meta-analyses from a Department of Health funded systematic review (Atkinson *et al.,* 2014) gave positive associations with all-cause mortality, all ages for all three averaging times considered[1], although the lower confidence interval was marginally below zero for daily maximum 1-hour mean ozone. The all-cause mortality evidence was supported by evidence from a smaller number of studies for associations with both cardiovascular mortality and respiratory mortality.

For all respiratory admissions, for all ages, positive associations were again found for all three averaging times, although the lower confidence interval spanned zero for daily maximum 1-hour mean ozone. This was supported by evidence of positive associations with confidence intervals above zero for all respiratory admissions in adults (daily maximum 1-hour and 8-hour mean), and in children (8-hour mean ozone[2] but not daily maximum 1-hour mean). Positive associations were also found for common respiratory sub-diagnoses (eg asthma in adults, lower respiratory infection and chronic obstructive pulmonary disease or COPD).

1 Daily maximum 1-hour mean, daily 8-hour mean ozone and 24-hour mean ozone.

2 The term '8-hour mean ozone' is used here because the studies included both those using daily maximum 8 hour running mean ozone and, for example, the 10 am to 6 pm 8-hour mean (which may or may not be the daily maximum).

For all cardiovascular admissions, for all ages, the associations were positive but smaller than for respiratory admissions. The lower confidence interval was above zero for maximum 1-hour mean ozone but not for 8-hour mean ozone and there were no studies available for 24-hour mean ozone. There was a mixture of positive and negative associations for admissions for sub-diagnoses of cardiovascular disease, although it is possible that positive associations are masked by negative confounding by particles.

We did not consider the causality of the associations for all-cause mortality and respiratory hospital admissions in detail. This is already established, for example in reports from the US EPA (2013) and the WHO (2013). There is more debate concerning causality for ozone and cardiovascular admissions (COMEAP, 2006; Goodman *et al.,* 2014), and the time-series evidence is less clear for cardiovascular hospital admissions than for cardiovascular mortality. We therefore conducted a preliminary review of panel studies on cardiovascular outcomes (Section 3.3). No clear, strong or consistent associations were observed but a more comprehensive review is needed. Chamber study and toxicological evidence was not reviewed in detail but other organisations such as the US EPA have noted some preliminary evidence suggesting modulation of the autonomic nervous system and systemic inflammation as a result of exposure to ozone (Section 3.3). Overall, the panel study, chamber study and toxicological evidence supporting causality for ozone and cardiovascular outcomes is mixed and the number of studies is relatively small.

In summary, there is sufficient evidence of adverse effects of short-term exposure to ambient concentrations of ozone for all-cause mortality and for respiratory hospital admissions. While evidence for cardiovascular hospital admissions is not as strong, we consider that it is sufficient to include quantification of all-cause mortality, respiratory hospital admissions and cardiovascular hospital admissions in the core analysis of a health impact assessment.

Q2 Which ozone metric should be used for quantification of the health effects of short-term exposure to ozone? (Sections 2.1 and 3.5)

Daily mean, daily maximum 1-hour mean, and daily maximum 8-hour running mean have all been used but the last is the most commonly used in European studies quantifying the health impacts associated with short-term exposure to ozone. It is regarded as the most appropriate metric on health grounds and is the metric currently used in EU limit values and UK air quality objectives. The recommendation is therefore to use the daily maximum 8-hour running mean.

Q3 Should quantification of the health effects of short-term exposure to ozone be based on all-year or summer periods only?

The aim of health impact assessment is to provide as complete a picture of the impact on particular health outcomes as possible. Thus, quantification based on all-year periods is preferred (Section 3.1). Many time-series studies only consider ozone associations for the warm season (often just summer). However, as the evidence for a threshold is weak (Section 3.6) and high concentrations of 8-hour mean ozone may not be restricted to the summer (Section 2.4), the justification for only quantifying the effects of ozone for part of the year is not strong.

Q4 Which concentration-response coefficients should be used for quantification of short-term health effects (mortality and morbidity) from ozone exposure? (Sections 3.5.1–3.5.3 and 3.9)

Based on the systematic review and meta-analysis of time-series studies indexed to May 2011, the following concentration-response coefficients are recommended:

Table 1: Recommended concentration-response coefficients for quantification of short-term health effects

Health endpoint	Concentration-response coefficient: % increase per 10 µg/m³ daily maximum 8-hour running mean ozone (95% confidence interval)[3]
All-cause mortality, all ages (ICD 9 <800; ICD 10 A00–R99)	0.34% (0.12, 0.56%)
Respiratory hospital admissions, all ages (ICD 9 460–519; ICD 10 J00–J99) (emergency admissions)	0.75% (0.30, 1.20%)
Cardiovascular hospital admissions, all ages ICD 9 390–459; ICD 10 I00–I99) (emergency admissions)	0.11% (–0.06, 0.27%)

Q5 Is there convincing evidence for a threshold for effect for short-term exposure to ozone? (Section 3.6)

Among the studies reporting associations between daily maximum 8-hour running mean and all-cause mortality (for all ages and all year) and selected for meta-analysis, few looked for evidence of a threshold for effect and most found no convincing evidence for one. Studies not selected for meta-analysis, or published more recently, also rarely investigated this issue. One study found a threshold and two found both decreasing and increasing slopes over different concentration ranges. A study in the UK found evidence of a threshold in London but not elsewhere in the UK for the all-year relationship, although thresholds were found more widely in summer-only relationships.

Among the studies of associations between daily maximum 8-hour running mean and all-respiratory or all-cardiovascular hospital admissions (for all ages and all year) selected for meta-analysis, only one looked for evidence of a threshold and found little evidence. One study not selected for meta-analysis found evidence for a threshold for respiratory hospital admissions.

The evidence for a threshold from studies on other averaging times was not considered in detail here, as interpretation of the presence of a threshold may be complicated by several factors, including correlations with other pollutants, which may differ for different averaging times (Sections 2.4 and 3.6). The evidence for a threshold from these studies is not consistent (WHO, 2013).

In summary, there is currently no convincing evidence of a threshold for short-term exposure to daily maximum 8-hour running mean, or of a non-linear relationship at low concentrations.

3 For ground-level ozone at ambient conditions in the UK, 2 µg/m³ is equivalent to 1 ppb.

Therefore we do not recommend using a threshold for quantification for short-term effects in health impact assessment.

Q6 If a threshold for effect or cut-off/counter-factual for quantification is to be applied, at which value should this be set? (Section 3.6)

We do not recommend applying a threshold for effect for quantification. We also discussed potential cut-offs (counter-factuals) for quantification in burden calculations. We considered whether there were concentrations below which there was a lack of data for effects but the time-series studies showing effects do consider very low concentrations (Appendix 5). There seems little reason to recommend a counter-factual other than zero.

Q7 To what extent are the effects of ozone independent of those of particulate matter (PM) and other pollutants for relevant health outcomes? (Sections 3.1 and 3.5)

Correlations between ozone and other air pollutants can vary in both size and direction according to temperature, and may differ at high and low ozone concentrations. Although multi-pollutant model studies exist, there are many more studies which are based on single-pollutant models.

The concentration-response functions for ozone and all-cause mortality have been found to reflect the health effects of ozone and the health effects of other pollutants to a greater or lesser extent (Section 3.5.1). The recommendations in this report are for the purpose of planned health impact assessment for future scenarios that cover ozone only. Broadly speaking, correlations of ozone with other pollutants may continue to be similar in the future (Section 2.4). Therefore, the use of a concentration-response function based on single-pollutant models was considered, on balance, to be the best option.

There is some suggestion that the associations of daily maximum 8-hour running mean with respiratory hospital admissions are robust to adjustment for other pollutants (mainly particles). The degree to which the pooled estimate could be reflecting effects of other pollutants is unclear (Section 3.5.2).

None of the studies examining daily maximum 8-hour running mean and cardiovascular hospital admissions included in the meta-analysis considered associations in multi-pollutant models. Given some of the associations in single-pollutant models were negative, and ozone was negatively correlated with some other pollutants, we cannot rule out that there is a stronger association of ozone with cardiovascular hospital admissions than is seen in single-pollutant models (Section 3.5.3).

Q8 Is there evidence of effect modification by temperature? (Section 3.7)

There is limited evidence that short-term health effects of ozone are modified by temperature, in particular that health effects are exacerbated on hot days. However, a full review of the literature has not been carried out at this stage. This is a recommendation for future work in this area. Further investigation would need to account for changes in correlations of ozone

with other pollutants as temperature changes – these might explain greater apparent effects of ozone on higher temperature days.

D Effects of long-term exposure (Chapter 4)

Q9 Is there sufficient evidence of associations between long-term exposure to ambient concentrations of ozone and mortality? (Chapter 4)

A systematic review and quantitative assessment of the evidence from cohort studies suggested no association between long-term annual ozone concentrations and mortality derived from single-pollutant models, or from models incorporating $PM_{2.5}$, and therefore quantification is not recommended. Adverse associations between ozone concentrations and respiratory mortality during the warm season months have been observed but the evidence base is limited, subject to a range of uncertainties and derived only from the US.

Our review (Chapter 4 and Appendix 9) has also identified further areas for review (thresholds, effect modification and lags) and a need for further methodological development (Sections 4.2 and 4.3) which was not possible in the time available. Further work is recommended to develop quantification approaches for use in sensitivity analyses in the future –see points (l) to (n) below.

E Conclusions and further work (Chapter 5)

In this report, we have recommended updated concentration-response coefficients for calculating the health impacts of day-to-day variations in ambient ozone concentrations on mortality and hospital admissions. Further work would be needed to develop future recommendations for quantification of long-term exposure to ozone and mortality. The underlying atmospheric chemistry of ozone needed to interpret the epidemiological studies is discussed. Finally, a suggested research strategy has been set out that would improve recommendations for the quantification of the health effects of ozone in the context of climate change in the future.

The future research priorities identified include:

a Assessment of change in other pollutants, such as particulate matter, with climate change, including improvements in modelling

b Assessment of correlation patterns between ozone and other pollutants and how these change with temperature, season and pollutant concentrations

c Work to reduce exposure measurement error in epidemiological studies and/or to increase understanding of the error present and its implications

d Assessment of health effects within multi-pollutant models, including the full range of pollutants

e Consideration of how best to meta-analyse multi-pollutant model results

f Investigation of thresholds taking account of correlation patterns between pollutants and potential effect modification by temperature

g Systematic review of the evidence on effect modification of ozone associations by temperature

h A comprehensive review of panel studies on cardiovascular endpoints

i Development of panel studies that consider both respiratory and cardiovascular endpoints in the same study

j Development of chamber and toxicological studies investigating effects of ozone on cardiovascular endpoints

k Review of chamber study and toxicological evidence on cardiovascular effects

l Cohort studies designed to investigate the effects of long-term exposure to ozone, particularly in the general population, including examination of lags

m Identification of new studies that would change summary estimates of concentration-response relationships, particularly studies on long-term exposure to ozone

n Consideration of methodological approaches to life table analyses including dealing with concentration-response coefficients that apply only to some periods within the year

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Chapter 1
Introduction

Climate change has the potential to increase ground-level ozone concentrations and this needs to be taken into account in assessing the risks of climate change overall. Hence, assessment of the health risks from ozone was included in the first Climate Change Risk Assessment (CCRA) (Hames and Vardoulakis, 2012) and will be reviewed in the forthcoming second Climate Change Risk Assessment (CCRA2), to be published in 2017[4]. Current assessments of mortality/morbidity burdens of ozone in the UK (COMEAP, 1998; Heal *et al.,* 2013; Stedman and Kent, 2008) are based on short-term exposure coefficients proposed by the Committee on the Medical Effects of Air Pollutants (COMEAP) in 1998 and updated by the World Health Organization (WHO) in 2004 (COMEAP, 1998; WHO, 2004). Public Health England has now requested an updated opinion from COMEAP on appropriate concentration-response functions for use in the forthcoming CCRA2.

A working group on quantification of effects of ozone was formed with the terms of reference and membership attached as Appendices 1 and 2. Broadly, the terms of reference for the working group request advice, with reference to quantification of effects in the UK, on:

a Whether the evidence is sufficient to support quantification

b Concentration-response relationships for short-term exposure to ozone and mortality and hospital admissions

c Concentration-response relationships for long-term exposure to ozone and mortality

d Issues affecting the interpretation and/or application of the above, such as independence from other pollutants, thresholds, interaction with temperature, effect modification, ozone metric and use or not of seasonal results.

4 http://www.theccc.org.uk/tackling-climate-change/preparing-for-climate-change/climate-change-risk-assessment-2017/

Chapter 2
Approach

Due to the imminent deadline of mid-2015 for the submission of evidence to the 2nd Climate Change Risk Assessment (CCRA2), only a short amount of time was available for COMEAP's review and investigation. (The recommendations are needed before quantification work is started.) Previous work by others has been drawn upon and further work undertaken but areas remain that would benefit from further work in order to improve the basis for future recommendations (CCRAs recur over a 5-year cycle, as required by the Climate Change Act 2008). Therefore, this report is a combination of (i) targeted recommendations as well founded as possible in the time available and (ii) suggestions of a strategy for research to develop these recommendations further over time.

This report concentrates on ozone, for which there is evidence of positive associations with adverse health outcomes and evidence of causality (US EPA, 2013; WHO, 2013a). In considering key studies in detail we note that the epidemiological evidence is based on real-life situations where ozone is but one of many environmental risk factors/modifiers including temperature and other pollutants. Further, the inter-relationships between these factors vary in different situations. Thus, we considered the following in interpreting the epidemiological evidence:

a Study quality (eg study size, adjustment for confounders, methods)

b What were the exposure contrasts? (Ozone is a regional pollutant, and some studies may have a narrow exposure range, this may be less of an issue for time-series studies, as there is usually more day-to-day variation than spatial variation)

c What were the correlations with other pollutants? Could the effect of ozone be masked by negative confounding? Is the effect partly reflecting the effect of other pollutants?

d If multi-pollutant models were performed, was the effect estimate robust to adjustment for other pollutants? As pollutant correlations differ by season, estimates stratified by season (or temperature) may be of interest

e Could there be an effect but only above a certain threshold? This might be indicated by finding effects only in periods of the year with higher ozone concentrations (provided this is not due to positive correlation with particles or temperature), or finding effects for exposure metrics that capture peaks in ozone levels. More rarely, there are studies that examine thresholds directly, using specific statistical methods that do not assume linearity

f Is there evidence of effect modification (eg by temperature)?

The report starts with some background information on ozone exposure estimates and the relationship between ozone, temperature and other pollutants. This background informs the following discussions of the epidemiological evidence for both short- and long-term exposure and its interpretation. We include more discussion on the interpretation of possible cardiovascular effects as these are less well established than is the case for respiratory effects.

In this report, we use the term 'threshold' to refer to an ozone concentration below which there is evidence for no adverse health outcome (i.e. a threshold for the effect) and 'cut-off' to mean a concentration below which the evidence on the size of the effect is uncertain or missing (i.e. a cut-off for quantification).

2.1 Ozone exposure, trends and relationship with other environmental factors

Ozone is a secondary pollutant formed from reactions between chemical precursors in the presence of ultraviolet light. The concentration of ozone is also determined by the balance between these formation reactions and other physical and chemical processes that disperse or remove ozone from the atmosphere (Appendix 3). Globally, minimum daily 8-hour average concentrations start at less than 1 $\mu g/m^3$ and maximum concentrations reach more than 350 $\mu g/m^3$. Further details regarding the measurement and atmospheric chemistry of ozone are described elsewhere. This section is to give the background needed for interpretation of epidemiological evidence and the health impact assessment recommendations, i.e.

a Metrics used to describe ambient ozone levels – this will assist interpretation of ozone metrics used in epidemiological studies

b Range of ozone concentrations that the health impact assessment may need to consider, including trends over time

c Correlations between ozone and other pollutants and how these vary by season, ozone concentration and location (to aid in interpretation of epidemiological evidence)

d Relationship between temperature and ozone and its correlated pollutants

2.2 Ozone metrics

Long-term exposure to ozone is appropriately quantified by an annual or seasonal average, with application of a cut-off concentration or threshold (related to the health effects) if needed. In some instances, long-term averages have been quantified as averages of a variety of shorter-term metrics with some specifically designed to reflect peak concentrations of ozone, such as the average of daily maximum 1-hour ozone concentrations over the summer period for a number of years (eg Jerrett *et al.,* 2009). These latter variations place greater emphasis on repeated exposure to higher ozone concentrations than does a long-term average across all ozone concentrations. Short-term exposure to ozone is appropriately quantified by a daily concentration metric, which can be combined with daily health data for health impact assessments. Daily mean, daily maximum 1-hour mean and daily maximum 8-hour running mean have all been used but the last is the most common metric for European studies quantifying the health impacts associated with short-term exposure to ozone. The related metric of SOMO35 is an annual metric derived as the summation of the daily ozone

concentrations in excess of 35 ppb[5] (70 μg/m^3), where daily refers to the daily maximum 8-hour running mean[6]. The intrinsic exclusion of concentrations below 35 ppb within this metric means that its value is sensitive to the number and magnitude of high ozone days in a year.

For short-term exposure, it has been argued on health grounds that daily maximum 8-hour running mean ozone is the most appropriate metric (Rombout, 1986). For this reason, it is also the metric used in regulations. It would therefore be a good metric to use for quantification. Modelled output is generally available on an hourly basis, so conversion to a daily maximum 8-hour running mean is possible. It is important to note that epidemiological studies tend to use different averaging times in different countries and that the daily maximum 8-hour running mean is commonly used in European epidemiological studies.

We specifically focus on ozone for this work as it has been identified as one of the air pollutants which is most likely to be affected by climate change, since it is highly sensitive to atmospheric conditions (as well as to anthropogenic and natural emissions). The CCRA (Hames and Vardoulakis, 2012) listed summertime ozone exposure as one of the main health risks to the UK population, and attempted quantification as to the possible impacts of climate change on future health burdens in the UK.

While not part of the current investigation, we emphasise that climate change may influence the levels of other pollutants, in addition to ozone. For example, particulate matter (PM) is also subject to secondary processes and to influences of atmospheric dispersion and transport. For PM, meteorological factors are less important than for ozone, but we recommend further work on PM and climate change at a later date. Most time-series studies are based on ozone data from one or several representative monitoring stations over a number of years. In assessments of future health impacts, ozone metrics are estimated using modelling techniques that provide gridded concentrations. Long-term exposure studies are more likely to use modelling data to derive the exposure metric used in the concentration-response relationship but the modelling used in describing the health impact assessment scenarios may not be the same. We considered these as acceptable approximations provided the uncertainties are borne in mind.

We acknowledge that, as with other pollutants, the ambient ozone level – whether measured or modelled – may not represent personal exposure. This creates some uncertainty in the concentration-response relationships and in assessing health impacts in future scenarios. To some extent it does not matter if the measured/modelled ambient ozone levels act as surrogates for the distribution of personal exposure in the population in the same way as in the populations from which the concentration-response relationships are derived, and in the population of interest (here the UK population in the future). However, it can matter if:

a Exposure misclassification is sufficient to lead to serious underestimation of the size of a true effect of ozone on health in epidemiological studies

b Correlation between measured/modelled ambient ozone levels and the distribution of personal exposures is so poor that observed effects are more likely to be related to

5 For ground-level ozone at ambient conditions in the UK, 2 μg/m^3 is equivalent to 1 ppb.

6 35 ppb is subtracted from each daily concentration. If this results in a negative number, the number is set to zero. The set of daily differences are then summed over the year.

another pollutant (which is correlated with ozone and ozone levels better reflect personal exposures to the other pollutant in the population than to ozone)

c In the future, there is a significant change in the way that the ambient measured/modelled ozone levels act as a surrogate for personal exposure in the population

The issue of personal exposure and potential measurement error is discussed in more detail in Appendix 4. According to the US EPA (2013), "Exposure measurement error, which refers to the uncertainty associated with using exposure metrics to represent the actual exposure of an individual or population, can be an important contributor to variability in epidemiologic study results. Exposure error can under- or over-estimate epidemiologic associations between ambient pollutant concentrations and health outcomes by biasing effect estimates toward or away from the null, and tends to widen confidence intervals around those". The issues raised in the previous paragraph are difficult to resolve fully but may counterbalance each other to some extent. Point (a) above would mean the apparent ozone associations were too small; point (b) would mean the apparent ozone associations were not real and instead due to another pollutant (or partly due to another pollutant). These exposure misclassification issues are not unique to ozone, and are generally an accepted uncertainty in health impact assessment.

2.3 Range in ozone concentrations and trends over time

The epidemiological studies discussed in the later sections come from many different parts of the world with differing ranges in ozone concentrations. The range of concentrations in these studies is set out here, along with comments on predicted future ozone levels, in order to judge the degree of overlap.

The concentrations of ozone in the short-term exposure studies selected for meta-analysis[7] are described in Appendix 5. These show ranges for 8-hour mean ozone studies from a mean of 21.5 μg/m^3 in Delhi to a median of 184.2 μg/m^3 in Mexico City. Minimum concentrations ranged from 0.8 μg/m^3 in the West Midlands to 31.4 μg/m^3 in Mexico City. Maximum concentrations ranged from 124.3 μg/m^3 in Brisbane to 350.8 μg/m^3 in Mexico City.

The figures for the ranges of ozone concentrations in the long-term exposure studies depend on the metrics used. For instance, when a long-term metric was used by Carey *et al.* (2013), the assigned annual average concentration in 2002 for the study cohort in the UK was 51.7 μg/m^3 (range: 44.5–63.0 μg/m^3), with a variation of only 2 μg/m^3 among the regions (London, North and South). In the case that long-term averages have been quantified as averages of a variety of shorter-term metrics (eg Jerrett *et al.,* 2009), the average daily maximum ozone concentrations across the 96 metropolitan areas in USA, during the summer periods of 1997–2000 (1 April to 30 September) ranged from 66.6 μg/m^3 (33.3 ppb) to 208 μg/m^3 (104 ppb), with the highest concentrations recorded in Southern California and the lowest in the Pacific Northwest. The epidemiological findings for the different forms of metric are discussed later. They are described here simply for the purpose of comparison with future ozone levels.

7 A form of analysis that pools estimates of concentration-response functions from individual studies, weighted by their variance, to give an overall summary estimate.

The ozone concentrations stated above cover a wide range, and it is expected that both current and future UK ozone concentrations will be well within these ranges. A brief discussion of the likely implications of climate change for ozone concentrations is given in Appendices 3 and 6. Ozone is not emitted directly into the atmosphere, but is formed by chemical reactions in the atmosphere and depends on concentrations of precursor chemicals (such as NO_X and VOCs) and atmospheric conditions. This makes predictions of ozone concentrations very difficult over medium to long timescales. Day to day, seasonal and inter-annual variations in ozone may also be very large. It is likely that anthropogenic emissions over Europe will influence changes in ozone levels more than changes in meteorology and climate over the next few decades, although changes in these atmospheric factors will also play a role.

2.4 Correlations with other pollutants

Understanding correlations between ozone and other pollutants is important for interpreting the epidemiological studies and their application in health impact assessment. Correlations between pollutants in specific short-term exposure epidemiological study locations and the implications of these for interpreting the results are discussed in Appendix 5. Of note, these correlations vary in both size and direction according to whether ozone concentrations are low or high. This observation has implications for interpretation of the shape of concentration-response functions from single-pollutant models– particularly if non-linear shapes are observed. The correlations also change according to temperature, which must be considered when interpreting seasonal results and predicting changes of concentration-response functions following temperature increases in the future. The nature of these correlations may change as temperature alters with climate change.

To demonstrate this point further, a limited analysis of currently available monitoring data has been conducted to illustrate variation in correlations between ambient ozone concentrations and $PM_{2.5}$ and NO_2 concentrations in the UK. Full results of these analyses are presented in Appendix 6.

Figure 1 shows a negative correlation between ozone concentrations (daily maximum 8-hour running mean) and $PM_{2.5}$ concentrations (daily mean) at the London North Kensington (urban background) monitoring station in 2013 on low ozone concentration days – less than 70 $\mu g/m^3$ (35 ppb). There is a weaker positive correlation for high ozone concentration days – greater than or equal to 70 $\mu g/m^3$. When all days are taken together there is a weaker negative correlation than for low ozone days. Similar behaviour was found for the correlations between ozone and NO_2 at this monitoring station.

Appendix 6 also includes examples of similar analyses for the Harwell (in south east England) and Edinburgh monitoring stations. Days have been divided into winter and summer months and low and high temperature days in addition to the low and high ozone days. Negative correlations between ozone and $PM_{2.5}$ and between ozone and NO_2 are generally found for any of the low ozone, winter or low temperature categories. Strata (temperature, season or ozone level), within which positive correlations of ozone with NO_2 or with $PM_{2.5}$ are seen, vary with location.

This type of analysis can provide useful insights into the correlation patterns of ozone concentrations with the concentrations of other air pollutants. However, a systematic analysis of a larger dataset would provide more robust conclusions. Results from chemistry transport models may also provide useful insights.

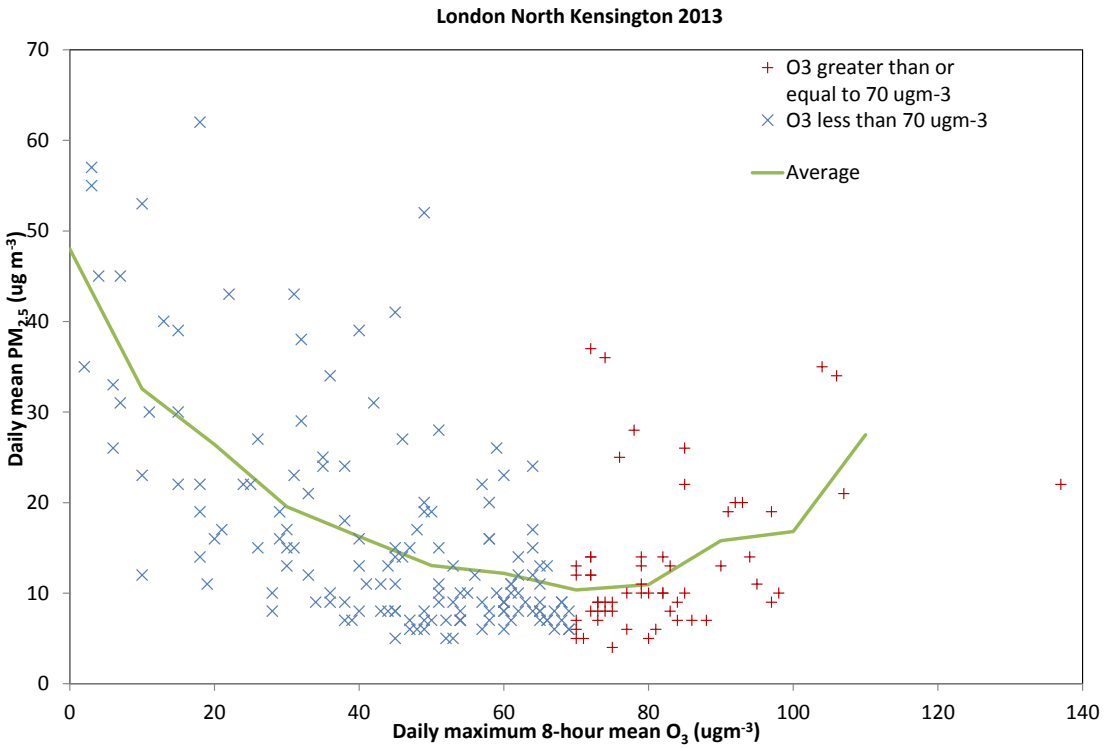


Figure 1: Ozone (O_3) and $PM_{2.5}$ concentrations for the London North Kensington monitoring station in 2013, classified into low and high ozone days

It cannot be stated with any confidence how correlations between different pollutants may change in the future compared with the present day. As described in Appendix 3, concentrations of ozone (and other air pollutants) are dependent on many factors that are directly or indirectly affected by aspects of climate change, including the particular mixtures and global behaviour of air pollutant emissions that drive climate change. However, very broadly speaking it may be anticipated that current trends and correlations between air pollutants in the UK will continue.

The current trend in the UK is for an increase in the levels of background ozone, derived from increasing levels of methane, CH_4 (and of carbon monoxide, CO) throughout the northern hemisphere. Declining NO_X emissions in urban areas also contribute to an increase in average background ozone in these locations as the reaction between NO and ozone is rapid. However, there has been a decline in the magnitude of short-term episodes of high ozone levels, because of a general decline in the emissions of both reactive volatile organic compounds (VOC) and NO_X in the UK and the rest of Europe (AQEG, 2009).

An important consequence of these changes is that the annual distribution of surface ozone concentrations in the UK has become more evenly spread throughout the year. If the full range of ozone concentrations is considered, and if it is assumed that it is the cumulative exposure to ozone that matters for long-term effects, then the contribution to cumulative exposure to ozone[8] is fairly even across the four seasons. If only concentrations above 35 ppb (70 µg/m^3) are considered, the

8 Studies of long-term exposure to ozone may use various averaging times, usually of a year or more.

contribution to cumulative exposure to ozone during the spring months (March, April and May) is currently twice as great as the contribution from the summer months (June, July and August). In the northern UK the proportion of cumulative exposure of ozone above 35 ppb derived during the spring months is approximately one-third greater than in the southern UK (Malley *et al.,* 2015). Historically, the majority of cumulative ozone exposure in the UK was associated with the summer months, but now contributions to cumulative exposure to ozone are associated with a range of temperatures throughout the year and with different patterns of co-pollutants throughout the year.

2.5 Ozone and temperature

Ozone concentrations (eg daily maximum 1-hour or 8-hour mean concentrations) tend to be more highly positively correlated with daily maximum 1-hour temperature above low to mid temperatures (22–25°C), although the amount of solar radiation and, to some extent, the prevailing wind conditions that tend to be associated with these temperatures are likely to be the cause of these correlations, rather than an effect of temperature itself. The limited analyses carried out for this report (presented in Appendix 3) show this at above 22°C.

Chapter 3
Health effects of ozone – short-term exposure

The sections below consider (i) the broad evidence for or against quantification from an epidemiological (time-series studies) perspective for all averaging times, (ii) other evidence bearing on causality and (iii) selection of a coefficient from a detailed examination of the evidence on 8-hour mean ozone.

3.1 Evidence for quantification

There are many studies of the effects of short-term exposure to ozone (US EPA, 2013; WHO, 2013a). We concentrate on epidemiological studies here as they study populations, although some other types of studies are briefly discussed in Sections 3.2 and 3.3. We concentrate also on studies relating to the general population rather than susceptible groups[9] as these are more widely applicable.

We have not considered panel studies in terms of quantification. Evidence from panel studies on ozone and reduced lung function is well established (Anderson *et al.,* 2007; US EPA, 2013; WHO, 2013a), but difficult to value for cost-benefit analysis, as it is difficult to generalise the clinical implications of a specific small change in lung function. There is evidence from panel studies of associations between ozone and respiratory symptoms (US EPA, 2013; WHO, 2013a) but this is hard to meta-analyse due to variation in the exact definitions of study populations and symptom descriptions. We consider panel study evidence on cardiovascular effects in Section 3.3 below and in Appendix 7, in the context of investigating causality rather than quantification. Restricted activity days are being considered as an outcome for quantification separately but in any case the evidence base is very small (Ostro and Rothschild, 1989). Instead we have concentrated on time-series studies that are able to examine more serious disease outcomes.

We examined studies on broad health outcomes for all ages and all year: all-cause mortality, cardiovascular hospital admissions and respiratory hospital admissions to consider whether to quantify and, if so, to identify potential concentration-response functions for quantification. We concentrated on evidence for all ages as it is most applicable for the general population, with some reference to other age groups in considering the broad evidence for quantification. We considered

9 The general population includes susceptible groups of course. It is more that use of a coefficient from a study in a susceptible group in quantification requires knowledge of the numbers of that susceptible group in the population using exactly the same definition. This is often unavailable. In addition, it is unclear how to combine these studies with general population studies, of which there is a greater number.

all-cause mortality rather than cause-specific mortality as associations with all-cause mortality were examined in a larger number of cities. Quantifying these effects in addition to all-cause mortality would result in double-counting.

For hospital admissions, we chose to analyse broad health outcomes ('all respiratory' and 'all cardiovascular') for all ages and all year to cover the breadth of the evidence on health impacts, rather than using a combination of health impacts that was incomplete (eg asthma in children in the summer and COPD in the elderly rather than all respiratory admissions, for all ages and all year). While there is the potential for 'diluting' the size of the effect by including respiratory outcomes that are unaffected, there are many more studies on broad outcomes.

The Department of Health commissioned work led by St George's, University of London, to provide a systematic review of time-series studies on air pollutants (Atkinson *et al.,* 2014) including a chapter on ozone (Walton *et al.,* 2014).

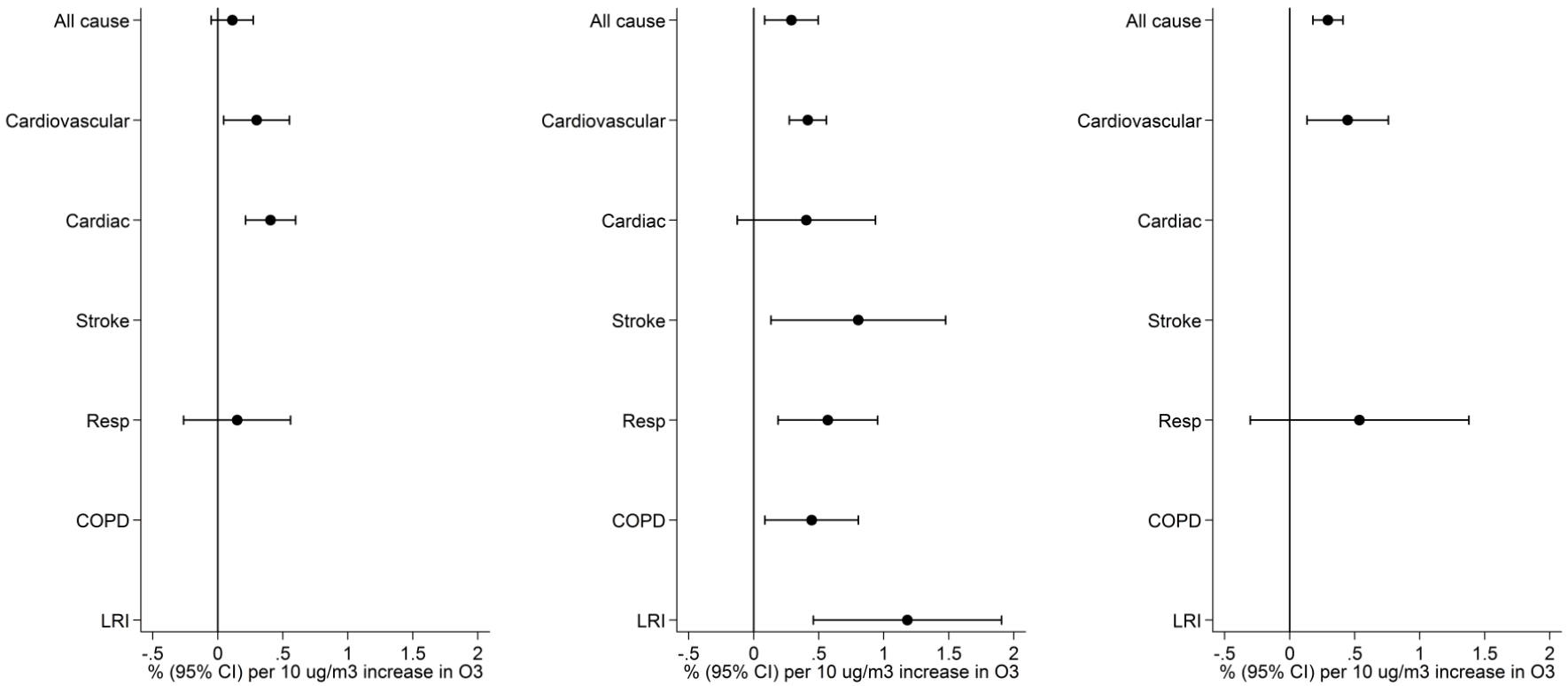
This work was commissioned to aid COMEAP and its working group to update concentration-response functions for the different pollutants. The work is the most recent quantitative meta-analysis of ozone associations (literature search from May 2011) and covers a range of outcomes and averaging times. We have therefore used this work to guide our recommendations on quantifying the effects of short-term exposure to ozone.

In the work commissioned by the Department of Health, time-series studies indexed in medical databases to May 2011 were identified using search terms relating to study design, outcome and pollutant. After screening studies against quality criteria, the estimates were further sifted according to an *a priori* protocol to select an estimate for a specific lag and to select only one estimate per city (as estimates from the same city are not statistically independent).

We did not choose to interconvert the averaging times as the conversion ratios vary by location (Anderson and Bell, 2010) but took note of results from studies using other averaging times in considering the general question of whether quantification is appropriate. The ozone metrics are closely correlated, particularly for daily maximum 8-hour running mean ozone and daily maximum 1-hour mean ozone. However, in comparing epidemiological study results for different averaging times, pooled results come from a different set of studies, often from different regions of the world (Walton *et al.,* 2014). Thus, it is not really possible to identify the 'best' metric from the epidemiological studies.

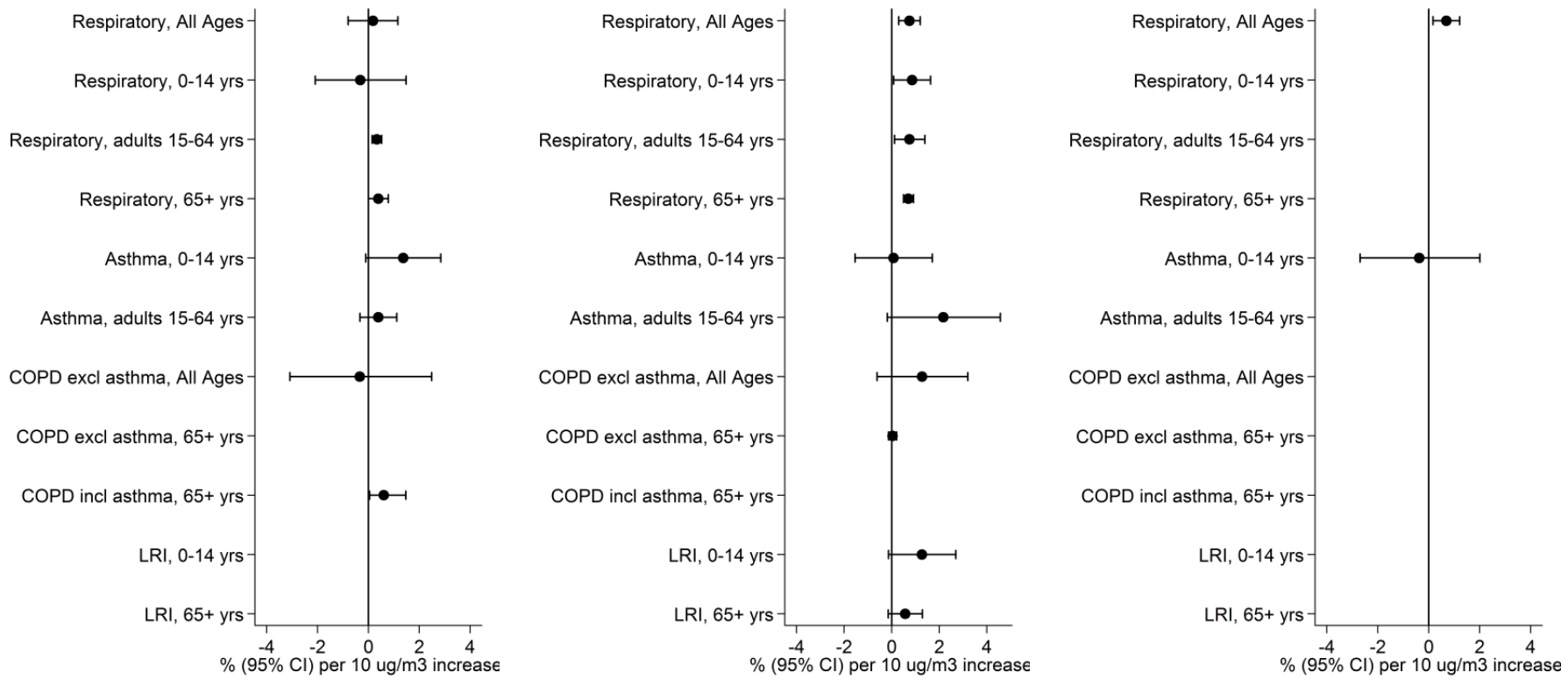
As shown in Figure 2, the meta-analyses from the systematic review gave positive associations with lower confidence intervals above zero for daily 8-hour and 24-hour mean ozone and all-cause mortality. The association with daily maximum 1-hour mean ozone was positive with the lower confidence interval only marginally below zero. The all-cause mortality evidence was supported by evidence for associations with all cardiovascular mortality (positive with lower confidence intervals above zero for all three averaging times) and all respiratory mortality (positive for all three averaging times, with a lower confidence interval above zero for 8-hour mean ozone).

As shown in Figure 3, the meta-analyses for all respiratory admissions, all ages, gave positive associations with lower confidence intervals above zero for both daily 8-hour and 24-hour mean, although the confidence intervals spanned zero for daily maximum 1-hour mean ozone. This was supported by evidence of positive associations with confidence intervals above zero for specific age groups for 8-hour mean ozone, although the evidence was mixed for daily maximum 1-hour mean



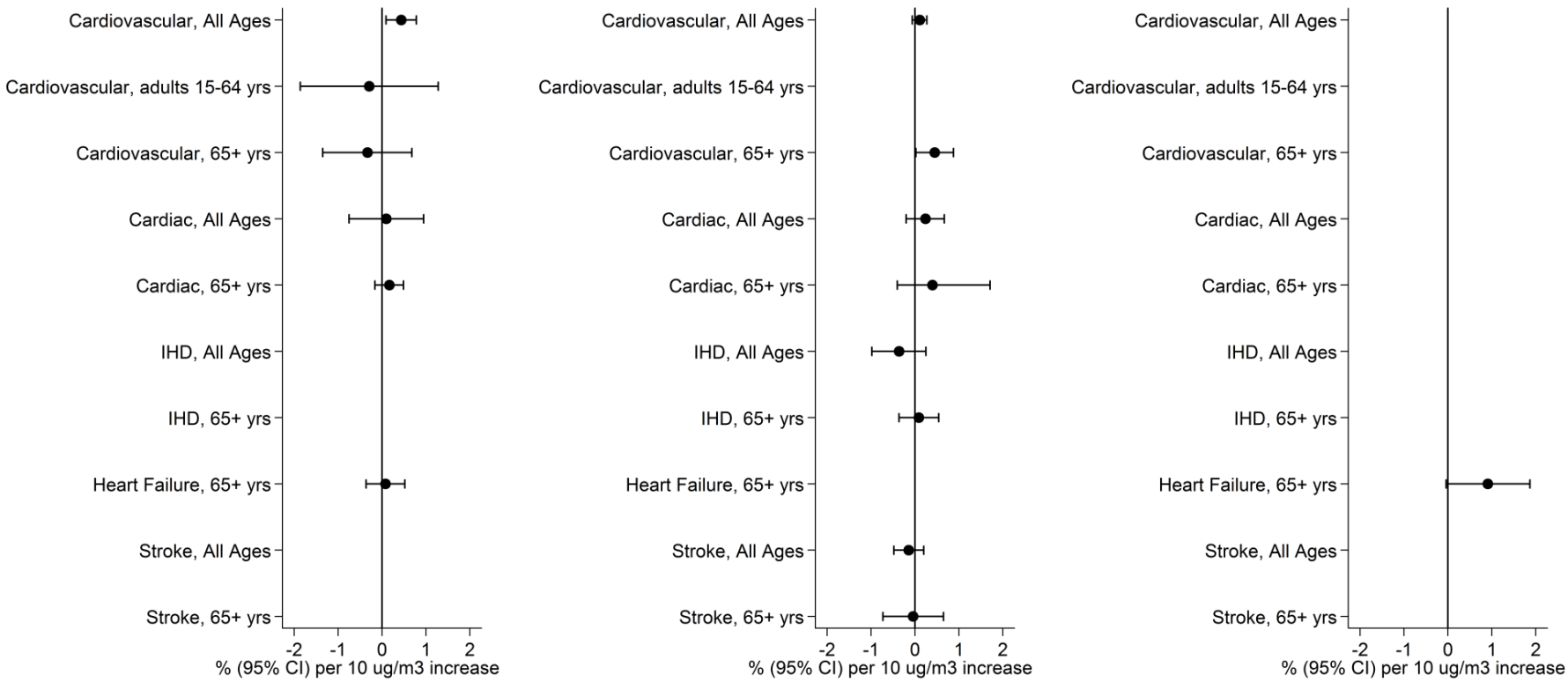
(a) 1-hour average ozone and mortality (b) 8-hour average ozone and mortality (c) 24-hour average ozone and mortality

Figure 2: Pooled summary estimates for time-series studies of ozone and all-cause and cause-specific mortality



(a) 1-hour average (b) 8-hour average (c) 24-hour average ozone

Figure 3: Time-series associations of ozone with respiratory admissions



(a) 1-hour average (b) 8-hour average (c) 24-hour average ozone

Figure 4: Time-series associations of ozone with cardiovascular admissions

ozone and absent for 24-hour mean ozone. Associations with specific sub-diagnoses were usually positive, although confidence intervals often spanned zero.

Figure 4 shows that the association of 8-hour mean ozone with cardiovascular hospital admissions was weaker (smaller with a lower confidence interval just below zero) than for respiratory hospital admissions. On the other hand, the summary estimate from the meta-analysis of associations between cardiovascular hospital admissions and daily maximum 1-hour mean ozone exposure, while still small, had a lower confidence interval above zero. There were no studies for 24-hour mean ozone and all cardiovascular admissions, for all ages. The evidence was also weaker for admissions for sub-diagnoses of cardiovascular disease than for sub-diagnoses of respiratory admissions, with a mixture of positive and negative associations.

The above broad description of the evidence has been based on single-pollutant model evidence. The systematic review commissioned by the Department of Health did not cover multi-pollutant model results. These are considered in detail later (Section 3.5) for the 8-hour mean ozone studies selected for meta-analysis, with discussion of information from studies not selected for meta-analysis and from reviews and multi-city studies for other averaging times. Broadly, there is some evidence for confounding by other pollutants in the all-cause mortality studies but it is not consistent in direction, and the ozone mortality risks estimates are regarded as independent of PM. Associations with respiratory hospital admissions seem to be relatively robust to adjustment for PM and other pollutants. Multi-pollutant model analysis of associations of ozone with cardiovascular admissions is very rarely performed, but there is an example where the estimate switched from negative to positive on adjustment for PM_{10}. This needs to be borne in mind in interpreting the negative associations for sub-diagnoses of cardiovascular admissions discussed above.

3.2 Other evidence on causality – mortality and respiratory hospital admissions

We have not considered the evidence on causality for all-cause mortality and respiratory hospital admissions in detail as it is already well established. The evidence on causality for cardiovascular hospital admissions is considered in a separate section (Section 3.3).

The associations between short-term exposure to ozone and all-cause mortality are generally accepted to be causal (US EPA, 2013; WHO, 2013a). The evidence for associations with all-cause mortality evidence is supported by evidence for positive associations with lower confidence intervals above zero in meta-analyses of studies of 8-hour mean ozone and both respiratory and cardiovascular mortality (Walton *et al.,* 2014)[10].

The causality of associations with respiratory admissions is supported by the fact that expert bodies have generally accepted a causal role for ozone in associations with respiratory endpoints when conducting health impact assessments (US EPA, 2013; WHO, 2013a). Overall, US EPA (2013) concludes that "recent epidemiologic studies affirm that respiratory morbidity and mortality associations are stronger during the warm/summer months and remain relatively robust after

10 Associations were also positive for 1-hour average and 24-hour average ozone and all respiratory or all cardiovascular mortality, although the confidence intervals spanned zero for the all respiratory mortality associations (Walton *et al.*, 2014).

adjustment for co-pollutants. The recent evidence integrated across toxicological, controlled human exposure, and epidemiologic studies, along with the total body of evidence evaluated in previous AQCDs (Air Quality Criteria Documents), is sufficient to conclude that there is a causal relationship between short-term O_3 exposure and respiratory health effects". WHO (2013a) noted that toxicological data from animal and human exposure studies provided ample support for the short-term effects of ozone on a range of pulmonary health-relevant endpoints and that new findings from a range of experimental animal models, including primates, provide evidence of chronic injury and long-term structural changes of the airway in animals exposed for prolonged periods to ozone and to ozone and allergens combined. These recent expert opinions update an extensive earlier literature on respiratory mechanisms underlying the effects of ozone (Mudway and Kelly, 2000).

The causality of associations with respiratory hospital admissions is also supported by coherence with results for respiratory mortality and with results for those specific respiratory outcomes that had sufficient studies for meta-analysis ['COPD including asthma' (daily maximum 1-hour mean) and lower respiratory infections (8-hour mean)] (Walton *et al.,* 2014). It is also supported by the results of panel studies (Anderson *et al.,* 2007). In the latter review the evidence from mainly US panel studies for effects of ozone on lung function was stronger than for other pollutants.

3.3 Causality with particular reference to short-term exposure to ozone and cardiovascular outcomes

This section concentrates on causality for cardiovascular outcomes. This has been less well discussed in previous reports and the stronger evidence for associations with cardiovascular mortality compared with cardiovascular hospital admissions merits more detailed consideration.

We have chosen to look at panel studies in more detail than the toxicological and chamber study evidence. Panel studies, in common with time-series studies, examine real populations with real life exposures, but provide a different perspective with more detailed individual level information and use of intermediate endpoints along a postulated mechanistic pathway. We searched for panel studies that examined both respiratory and cardiovascular endpoints within the same participants, as this could assist in interpretation of the differing results for time-series studies of respiratory and cardiovascular hospital admissions.

Panel studies, in which information on health and ozone exposure is collected from the same individuals repeatedly over a period of time, have been conducted. No studies were found that studied both respiratory and cardiovascular endpoints. Panel studies of respiratory outcomes have previously been reviewed (Anderson *et al.,* 2007; US EPA, 2013; WHO, 2013a), so we concentrated on panel studies with cardiovascular endpoints. The vast majority of such studies are likely to have been identified as part of a recently published, industry funded, extensive, systematic review of short-term exposure to ozone and cardiovascular effects conducted by Goodman *et al.* (2014). The panel studies identified in that review which scored highly on a quality metric generated by the authors have been reviewed (Appendix 7).

Most of the reviewed studies have been conducted in those with a high risk of cardiac events (the elderly, those with established coronary artery disease, and those who have implantable cardioverters and diabetics). Outcomes of interest have been cardiac arrhythmias, heart rate variability (HRV), other electrocardiographic features and biomarkers. Different ozone exposure metrics have been used. The studies show some limited evidence for an association of cardiac arrhythmias with ozone exposure (Anderson *et al.,* 2010; Bartell *et al.,* 2013; Dockery *et al.,* 2005) and

one good quality study suggests increased ozone exposure is associated with lower blood pressure (Hoffmann *et al.,* 2012). Of note, one London based study examined cardiac arrhythmias in adults with cardioverters for a period of about 3 years, suggesting an increase in arrhythmias with increasing ozone (relative risk 1.014, 95% CI 0.955, 1.076 per increase of 10 μg/m^3) (Anderson *et al.,* 2010).

However, from this preliminary review there are no clear, strong or consistent associations observed. A more comprehensive review of all panel studies, with reconsideration of the quality metrics for the study, including meta-analysis of results (if possible) and assessment of publication bias is required. This could usefully be conducted in relation to cardiac arrhythmias and HRV where there appear to be more studies, many of which are small and show small, but non-significant ($p > 0.05$) associations.

Chamber study and toxicological evidence is also relevant to the full breadth of evidence on whether associations between ozone and cardiovascular outcomes are likely to be causal. There was insufficient time for us to consider this in detail as part of the current exercise but we recommend further review of this evidence. In the meantime, we summarise views from other organisations such as the US EPA and the WHO, below.

Controlled human exposure studies have shown increases and decreases in high frequency HRV following relatively low [120 ppb (240 μg/m^3) during rest] and high [300 ppb (600 μg/m^3) with exercise] ozone exposures, respectively (US EPA, 2013). The WHO Review of Evidence on Health Aspects of Air Pollution – (REVIHAAP) Project report considered that the results from controlled human studies were ambiguous (WHO, 2013a).

The US EPA states that animal toxicology studies, although limited in number, suggest that short-term ozone exposure induces vascular oxidative stress and release of proinflammatory mediators, alters heart rate (HR) and heart rate variability (HRV), and disrupts the regulation of the pulmonary endothelin system (US EPA, 2013). It was noted that the changes in cardiac function observed in animal and human studies provided preliminary evidence for ozone-induced modulation of the autonomic nervous system through the activation of neural reflexes in the lung. Controlled human exposure studies also support the animal toxicology studies by demonstrating ozone-induced effects on blood biomarkers of systemic inflammation and oxidative stress as well as changes in biomarkers suggestive of a prothrombogenic response to ozone.

The overall view of the US EPA on cardiovascular effects of ozone (O_3) is "animal toxicological studies demonstrate O_3-induced cardiovascular effects, and support the strong body of evidence indicating O_3-induced cardiovascular mortality. Animal toxicological and controlled human exposure studies provide evidence for biologically plausible mechanisms underlying these O_3-induced cardiovascular effects. However, a lack of coherence with epidemiologic studies of cardiovascular morbidity remains an important uncertainty. Taken together, the overall body of evidence across disciplines is sufficient to conclude that there is likely to be a causal relationship between relevant short-term exposures to O_3 and cardiovascular effects".

REVIHAAP considered that the toxicological data from animal and human exposure studies provided ample support for the short-term effects of ozone on a range of pulmonary and vascular health-relevant endpoints (WHO, 2013a).

This overview of the panel, chamber and toxicology evidence on effects of ozone on the cardiovascular system provides some support for causality but the evidence is mixed and the numbers of studies available are often small.

As noted above (Section 3.1), stronger evidence for associations with cardiovascular mortality was found, in contrast to the weaker evidence for an association between 8-hour mean ozone and cardiovascular hospital admissions. A masking of the effect on cardiovascular hospital admissions, but not cardiovascular mortality, would require either a greater effect of ozone on cardiovascular mortality than cardiovascular admissions (for which some theories, such as an effect on tachyarrhythmias leading to sudden death, can be put forward), or for a negatively correlated pollutant to have a greater effect on cardiovascular admissions than cardiovascular mortality. It should also be noted that the process of defining the disease to be assigned the relevant ICD code differs for mortality and admissions – admissions are coded according to the immediate cause of the admission but mortality is coded according to the underlying cause.

3.4 Conclusions on whether to quantify

The above overview of the qualitative results of the time-series studies, and brief description of some issues relating to causality, led us to conclude that we should recommend quantification in core analysis for all-cause mortality and respiratory hospital admissions. There was more debate regarding cardiovascular admissions. While the lower confidence interval spanned zero in the association with 8-hour mean ozone, this was not the case for maximum 1-hour mean ozone. It is possible that the lower confidence interval spanning zero for 8-hour mean ozone and the negative associations with sub-diagnoses of cardiovascular admissions are due to negative confounding by particles being more apparent for smaller associations. There was some support for causality from panel, chamber and toxicology studies, although the evidence was mixed, and some coherence with evidence on cardiovascular mortality. On balance, we concluded that ozone and cardiovascular admissions should also be included in core analysis, acknowledging the somewhat greater uncertainty.

3.5 Selection of coefficients

The following sections consider selection of coefficients. As explained in Section 2.2, the studies considered in this report and the meta-analysis are those based on daily maximum 8-hour running mean ozone. The short-term exposure studies use a mixture of daily maximum 8-hour running mean, other 8-hour metrics, such as daily 8-hour average ozone from 10–6 pm and examples where the exact form of the 8-hour average is unclear. These studies were considered together in pooling studies for meta-analysis. These metrics are unlikely to differ significantly in the numerical value of the ozone concentration, or the nature of correlations with other pollutants. We therefore chose to express our final recommendations in terms of daily maximum 8-hour running mean, i.e. the metric as formally defined in regulations and as used in several of the important studies.

In discussing selection of coefficients, we first examined the results of single-pollutant models (for which there are many more studies) and we then described the effect of multi-pollutant adjustment in those studies included in the single-pollutant meta-analysis. This latter step was to understand how much of the effect in the single-pollutant models is reflecting ozone itself and how much that of other pollutants, in the context of what that means for the size of the coefficient. Appendix 5 contains details of the single-pollutant estimates contributing to the meta-analytical results in addition to information, where available, on the ozone concentration ranges, correlations between pollutants and results of multi-pollutant models.

3.5.1 Short-term exposure to 8-hour mean ozone and all-cause mortality

In the separate Department of Health funded work, ten estimates for 8-hour mean ozone and all-cause mortality, for all ages and all year, were identified for meta-analysis. These comprised eight single-city studies and two multi-city studies covering nineteen and four cities (31 cities in total) (references are given in Appendix 5). The pooled estimate from the meta-analysis was a 0.34% (95% CI 0.12, 0.56%) increase in all-cause mortality per 10 μg/m^3 increase in daily maximum 8-hour running mean. There was considerable heterogeneity between the estimates[11] contributing to the summary estimate (I^2 74.6%) but no evidence of small study bias. The concentration-response function in an earlier meta-analysis (WHO, 2004) was similar – 0.3% (95% CI 0.1, 0.4%) – and this has been used in several European health impact assessments (eg Hurley *et al.,* 2005).

The multi-pollutant model results are discussed in Appendix 5. In summary, the pooled single-pollutant estimate for 8-hour mean ozone and all-cause mortality includes studies which indicate that other pollutants contribute to the size of the effect. The degree to which this is the case is hard to summarise in quantitative terms (eg in a meta-analysis) because:

a Several studies do not provide multi-pollutant model results

b Of those that do, multi-pollutant models are often examined only for some of the pollutants analysed in the study

c Different studies may use different averaging times for the adjustment pollutant

d Even where the same adjustment pollutant has been used, the effect of the adjustment will be different according to the correlation pattern between pollutants, which can also differ by season

e Differences in measurement errors between pollutants (WHO, 2013b) can lead to those pollutants with less measurement error (but in truth weaker effects) coming through more strongly

Bearing the above in mind, the following points can be noted:

a When effect estimates for ozone were adjusted for NO_2 (Gryparis *et al.,* 2004; HEI Public Health and Air Pollution in Asia Program, 2010)[12], the estimate was always reduced in magnitude and was no longer statistically significant, although the latter may be due to fewer days with measurements of both pollutants rather than absence of an effect

b Studies which adjusted for ambient PM did not always use the same metric for PM. The effect of adjustment varied from:

(i) stability to adjustment (Katsouyanni *et al.,* 2009; Peng *et al.,* 2013, European cities)[13]; (Simpson *et al.,* 1997)

11 The meta-analysis was done in two stages – single-city estimates were pooled by WHO region and then these pooled single-city estimates were combined with estimates from multi-city studies, which also have a regional focus. Thus, variation by WHO region may contribute to the heterogeneity.

12 This HEI report contained information on multi-pollutant models in the individual studies contributing to the meta-analysis of four cities reported in Wong *et al.* (2008).

13 For 1-hour average ozone all year, but using the Gryparis *et al.* (2004) dataset. The multiple cities included give this finding substantial weight and it is for an all-year estimate.

(ii) reduction of the estimate to null (Borja-Aburto *et al.,* 1997; Wong *et al.,* 2010, Hong Kong)

(iii) reductions in the magnitude of the estimate (Gryparis *et al.,* 2004, summer; Wong *et al.,* 2010, Shanghai, Wuhan, Bangkok)

(iv) increases in the estimate (Peters *et al.,* 2009; Gryparis *et al.,* 2004, winter)

c There was only one example with adjustment for CO alone and this increased the estimate substantially (Gryparis *et al.,* 2004)

d The association in Hong *et al.* (1999) increased to become less negative with an upper confidence interval above zero on adjustment for CO, NO_2, SO_2 and PM_{10}

e The effects of adjustment for other pollutants could vary by season and by stratification by temperature. Again, this is probably due to different correlation patterns and to the concentrations of ozone relative to those of the other pollutants

The US EPA (2013) concluded that "overall, across studies, the potential impact of PM indices on O_3-mortality risk estimates tended to be much smaller than the variation in O_3-mortality risk estimates across cities suggesting that O_3 effects are independent of the relationship between PM and mortality. However, interpretation of the potential confounding effects of PM on O_3-mortality risk estimates requires caution". No concluding remarks were made concerning potential confounding by other pollutants. The WHO (2013a) noted that the associations between daily maximum 1-hour ozone and all-cause mortality reported in the APHENA study (Katsouyanni *et al.,* 2009; Peng *et al.,* 2013) were robust to adjustment for PM_{10}.

In conclusion, the concentration-response function for ozone and all-cause mortality is reflecting the effects of both ozone and other pollutants to a greater or lesser extent. The recommendations in this report are for the purpose of planned health impact assessment for future scenarios that do not cover other pollutants. Also, broadly speaking, correlations with other pollutants may continue to be similar in the future (Section 2.4). Therefore, the use of a concentration-response function based on single-pollutant models, for which there are many more estimates, was considered, on balance, to be the best option.

In summary, we recommend a concentration-response function of a **0.34% (95% confidence interval 0.12, 0.56%)** increase in all-cause mortality per 10 $\mu g/m^3$ increase in maximum 8-hour running mean ozone from the meta-analysis of single-pollutant model estimates for all ages and all year. Whether this should be implemented with or without a threshold is discussed in Section 3.6.

3.5.2 Short-term exposure to 8-hour mean ozone and respiratory hospital admissions

The pooled estimate of associations between 8-hour mean ozone and respiratory hospital admissions, for all ages and all year, was a positive and statistically significant (0.75%, 95% CI 0.30, 1.20) increase in respiratory hospital admissions per 10 $\mu g/m^3$ increase in 8-hour mean ozone. This was based on ten estimates from twelve cities (nine single-city studies and one multi-city study). There was substantial heterogeneity between the estimates contributing to the summary estimate (I^2 82.8%) but no small study bias (Walton *et al.,* 2014).

As with all-cause mortality, not all studies included multi-pollutant models. Of the ten studies, four included multi-pollutant models adjusted for other pollutants (Appendix 5). One adjusted for

several pollutants at once and found a very large increase in the effect estimate (Jayaraman *et al.,* 2008) but adjusting for multiple correlated pollutants may produce unstable estimates. This depends on the strength of the correlations and the missing data. Two others also found increases on adjustment for PM_{10} (Middleton *et al.,* 2008; Chang *et al.,* 2002). A study in Brisbane (Petroeschevsky *et al.,* 2001) adjusted for high levels of TSP (total suspended particles measured by light scattering) or SO_2 and found some reduction in the estimate. The reduced estimate remained statistically significant after adjustment for high SO_2 and just lost significance on adjustment for TSP. Some studies present information on correlations with other pollutants even if they do not include multi-pollutant model results. Several of these correlations are negative (Appendix 5).

The US EPA (2013) has concluded that ozone effect estimates for respiratory-related hospital admissions and hospital emergency department visits are relatively robust to the inclusion of PM and gaseous pollutants in two-pollutant models. The REVIHAAP review reached similar conclusions regarding PM_{10}, although the WHO (2013a) discussion concentrated on the APHENA study (Katsouyanni *et al.,* 2009; Peng *et al.,* 2013), which was limited to studying associations of respiratory admissions in those aged over 65 years.

In summary, there is some suggestion that the associations with respiratory hospital admissions are robust to adjustment for other pollutants (mainly particles) but there are no studies examining adjustment for NO_2 or CO alone. The latter two seemed important for all-cause mortality. The degree to which the pooled estimate could be reflecting effects of other pollutants is unclear.

In conclusion, we recommend a concentration-response function of a **0.75% (95% confidence interval 0.30, 1.20%)** increase in respiratory hospital admissions per 10 $\mu g/m^3$ increase in maximum 8-hour running mean ozone from the meta-analysis of single-pollutant model estimates for all ages and all year. Whether this should be implemented with or without a threshold is discussed in Section 3.6.

3.5.3 Short-term exposure to 8-hour mean ozone and cardiovascular hospital admissions

The systematic review mentioned previously (Atkinson *et al.,* 2014; Walton *et al.,* 2014) found only weak evidence for an effect on cardiovascular hospital admissions (Appendix 5), although effects were found on cardiovascular mortality (Section 3.1). Based on eight studies covering 17 cities, a pooled estimate of a 0.11% (95% CI –0.06, 0.27%) increase in cardiovascular hospital admissions per 10 $\mu g/m^3$ change in 8-hour mean ozone for all ages was found, i.e. the likely range includes the possibility of no effect. There was no evidence of heterogeneity or of publication bias.

Unfortunately, none of the studies contributing to the pooled estimate examined multi-pollutant models. Researchers tend to apply multi-pollutant models to test if a positive and statistically significant effect is maintained after adjustment for other pollutants. There is much less awareness that adjustment for a pollutant that is negatively correlated with ozone could reveal an association that was not previously apparent. Some studies provided information on correlations between ozone and other pollutants (Appendix 5). These showed many negative correlations and we cannot exclude the possibility that a masked association between ozone and cardiovascular admissions is present.

The US EPA (2013) made no clear statement regarding 'independence' of observed short-term ozone effects on cardiovascular outcomes. The WHO (2013a) included a table summarising results from the APHENA study (Katsouyanni *et al.,* 2009; Peng *et al.,* 2013) that showed that the negative,

non-significant association between daily 1-hour maximum ozone and cardiac hospital admissions in the elderly became positive and statistically significant on adjustment for PM_{10}.

The recommended concentration-response function is a **0.11% (95% confidence interval –0.06, 0.27%)** increase in all cardiovascular hospital admissions per 10 $\mu g/m^3$ increase in daily maximum 8-hour running mean ozone from the meta-analysis of single-pollutant model estimates for all ages and all year. Whether this should be implemented with or without a threshold is discussed in Section 3.6.

As stated above this estimate may be an underestimate, but there are no multi-pollutant models from which to derive a concentration-response function. We discussed previously (Section 3.3), at least briefly, other types of evidence on ozone and cardiovascular disease and recommend further work on this.

3.6 Thresholds for short-term exposure to ozone

Previous sections have discussed the overall literature on associations between 8-hour average ozone and mortality or hospital admissions. The estimates quoted in time-series studies are usually based on an assumption of linearity with a relative risk of 1 (no association) at the lowest ozone concentration in the dataset[14]. There is, however, a natural question as to whether these associations do in fact extend down to the lowest ozone concentrations as predicted under assumptions of linearity. This issue needs to be addressed in separate analyses specifically for the purpose. This is often not done. Where studies do examine whether or not there is a threshold, the results can be complicated to interpret. We outline some of these general issues of interpretation below, before examining whether or not a threshold should be used in health impact assessments.

One issue is that data points become sparser at lower ozone concentrations. This means that the confidence intervals around the concentration-response function widen at lower (and higher) concentrations. It can thus be difficult to be sure of the exact shape of the concentration-response function at lower levels.

In determining whether or not health effects at low concentrations are plausible, it is worth bearing in mind that thresholds from epidemiological studies are identified at the population rather than the individual level. This is because the exposure metric used in the epidemiological study acts as an indicator for the distribution of personal exposures in the population. Brauer *et al.* (2002) demonstrated, using simulations that defined individual thresholds, that surrogate metrics that are not highly correlated with personal exposures obscure the presence of thresholds in epidemiological studies, while surrogate metrics that are highly correlated with personal exposures can accurately reflect underlying personal thresholds. However, personal thresholds are usually unknown so it is the population level threshold that is investigated for potential use in health impact assessments of effects on populations.

[14] The coefficients are per unit increment and under the assumption of linearity apply irrespective of the reference concentration. To illustrate the shape of the concentration-response function, we can choose a reference value (mean ozone, minimum) and calculate the risks relative to this baseline.

Studies do not generally test for thresholds in the knowledge of all the different factors that vary at the same time as ozone concentrations. A plot of ozone concentrations against the relevant health effect, or the use of better statistical methods to examine thresholds, might appear to be sufficient to indicate whether or not there was a threshold for ozone. In fact, other factors that may also be linked to the relevant health effect vary across the range of ozone concentrations. Furthermore, as discussed in Section 2.4 and Appendix 6, these correlations vary in both size and direction according to whether ozone concentrations are low or high.

The points in the previous paragraph are illustrated in Figure 5.

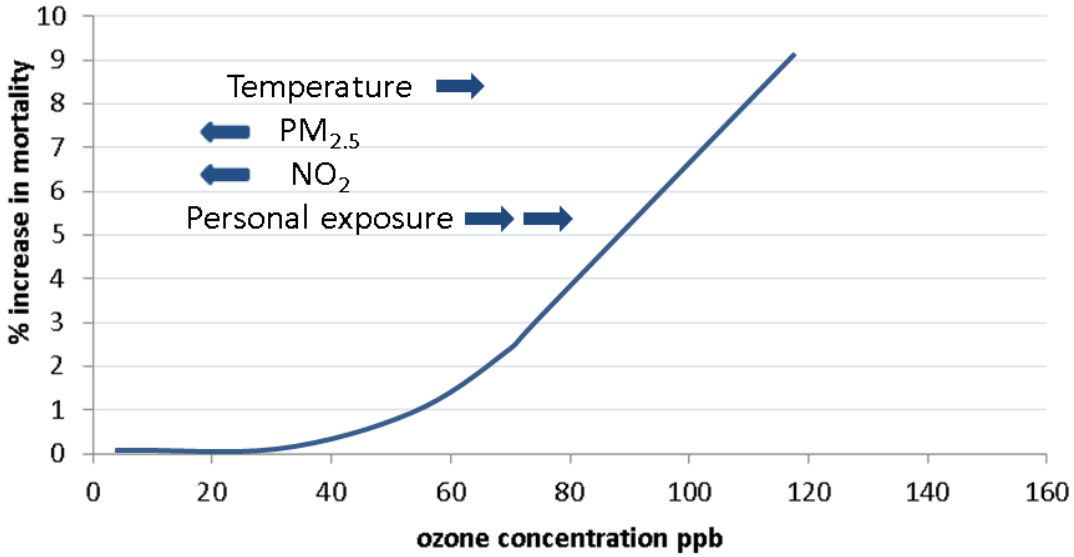


Figure 5: Hypothetical shape of concentration-response function for single-pollutant model of ozone association with mortality

Thus, as ozone concentrations decrease, towards the left-hand side of the graph, $PM_{2.5}$ concentrations, for example, may increase. If the apparent relationship between ozone and mortality in a single-pollutant model seemed to flatten as concentrations decreased, this could be the result of the decreasing 'true' effect of ozone-related mortality (unconfounded by particles) being cancelled out by an increase in $PM_{2.5}$-related mortality.

On the other hand, a steeper slope in the single-pollutant model ozone relationship as concentrations increased could be the result of positive correlations with $PM_{2.5}$ during photochemical episodes, leading to both $PM_{2.5}$-related and 'true' ozone-related mortality increasing together. Alternatively, or in addition, as temperature increases tend to correlate with ozone concentration increases, effect modification of the ozone relationship with mortality by temperature (if present) could be increasing (single-pollutant model ozone relationships are already controlled for temperature) – effect modification of ozone associations by temperature is discussed in Section 3.7. Also, personal exposure could be increasing as people spend more time out of doors and/or open windows.

The net effect of these interrelated factors on the shape of a single-pollutant model concentration-response curve will depend on the relative strengths of the relationships between the effects of these other factors (between each of them and between them and ozone). These aspects are not usually

investigated, and our main recommendation refers to a single-pollutant model, so Section 3.7 considers the evidence for or against thresholds for single-pollutant models. The issues above need to be borne in mind in interpreting the results.

Appendix 8 goes through the studies contributing to the single-pollutant pooled estimates outlining any information available on the shape of the concentration-response relationship. Only a minority of studies considered this. For all-cause mortality, one study suggested a threshold of around 23 ppb (46 μg/m^3), estimated from a graph (Hong *et al.,* 1999) but none of the other studies within the meta-analysis that examined thresholds could exclude linearity (Gryparis *et al.,* 2004[15]; Wong *et al.,* 2008).

Appendix 8 also includes details of a wider search for studies for 8-hour mean ozone and all-cause mortality (for all ages and all year) that investigated thresholds. This identified some earlier studies that had been superseded in the meta-analysis by more recent studies in the same city and some studies published since the literature cut-off for the meta-analysis. Anderson *et al.* (1996) found evidence for a threshold at around 50 ppb (100 μg/m^3); Galan Labaca *et al.* (1999) found an increase at low doses, a decrease at intermediate concentrations and then a rise again at higher concentrations, and Pascal *et al.* (2012) found a similar pattern with an increase to 50 μg/m^3 and a decrease to 100 μg/m^3 before rising again. Yang *et al.* (2012) found an essentially linear monotonic increase in log mortality risk with 8-hour mean ozone concentration. However, the study of most interest was a recent one in the UK that specifically aimed to look at thresholds in detail (Atkinson *et al.,* 2012).

Atkinson *et al.* (2012) examined the relationship between 8-hour mean ozone and all-cause mortality in five urban and five rural areas of the UK. For the all-year relationship, there was little evidence of non-linear relationships apart from for London, where a threshold of 65 μg/m^3 (95% CI 58, 83) was found. The concentration-response relationship above this threshold was 1.33% per 10 μg/m^3 (95% CI 0.8, 1.86%). Seasonal analyses showed evidence of thresholds in the summer for both urban and rural areas. This needs to be borne in mind but for the purpose of this report we are concentrating on all-year relationships. In addition, since the evidence for a threshold for effect was only found in London, and London was included in the multi-city pooled analyses for APHEA (Gryparis *et al.,* 2004) and APHENA (Katsouyanni *et al.,* 2009), which do not show strong evidence for a threshold, we do not recommend the use of a threshold for health impact assessment of all-cause mortality.

For 8-hour mean ozone and all respiratory hospital admissions, for all ages and all year, Atkinson *et al.* (1999) was the only study within the meta-analysis to investigate thresholds, concluding that the relationship was approximately linear with little evidence of a threshold. An earlier study by Ponce de Leon (1996), also in London, found a threshold around 50 ppb (100 μg/m^3) but this was only presented graphically. Both studies used bubble plots that are only an approximate way to investigate thresholds. We do not therefore suggest a sensitivity analysis using a threshold for quantification of respiratory hospital admissions.

For 8-hour mean ozone and all cardiovascular hospital admissions, for all ages and all year, Atkinson *et al.* (1999) was, as with respiratory hospital admissions, the only study within the meta-analysis to investigate thresholds, concluding again that the relationship was approximately linear with little

[15] The threshold investigation in Gryparis *et al.* (2004) was for the summer only but Katsouyanni *et al.* (2009) using the same dataset but for daily 1-hour maximum ozone, found no evidence for a threshold for the all-year period.

evidence of a threshold. No other studies were available. There is therefore no basis on which to suggest an analysis using a threshold for quantification of cardiovascular hospital admissions.

A wider range of studies was considered in the REVIHAAP report (WHO, 2013a; see the extract in Appendix 8). This included other outcomes and averaging times than those covered here. It was concluded that the evidence was not consistent and that, where a threshold had been observed, it was likely to be below 45 ppb (90 μg/m^3). (Only one study suggested a threshold for associations with all-cause mortality as high as 45 ppb as a 3-day weighted mean and then only in some cases – Stylianou and Nicolich, 2009.)

In the Health Risks of Air Pollution in Europe – (HRAPIE) project the WHO (2013b) recommends using a cut-off at 35 ppb (70 μg/m^3) to reflect greater confidence in a significant relationship above 35 ppb. However, HRAPIE emphasised that the coefficients were based on the whole range of ozone concentrations and that effects below 35 ppb were ignored rather than considered to be zero. The cut-off at 35 ppb is not based on specific evidence from any particular study.

In summary, of the studies investigating thresholds, most studies do not find strong evidence of non-linearity. Given the complexities of correlations with other factors potentially affecting the shape of the relationship, the findings may vary by location, and possibly with future climate change. We conclude that it is appropriate for the analyses for the 2nd Climate Change Risk Assessment to assume no threshold in all regions of the UK.

3.7 Counter-factuals for burden calculations

In burden calculations there is a need to define the reference scenario (counter-factual) with which the overall effect of total concentrations of ozone will be compared. This could be a threshold for effect, if it were concluded there was one. If there is concern about extrapolating beyond the range of the data, another option is to define the counter-factual at the low end or at the minimum concentration in the studies used to define the concentration-response coefficients. In the case of the time-series studies on ozone, the range of concentrations in the studies providing estimates for pooling in the meta-analysis goes down to very low levels (Appendix 5). The range of studies pooled for the different health outcomes includes places with minimum concentrations as low as 1.5 ppb (3 μg/m^3) (Brisbane, all-cause mortality study; Paris, all respiratory admissions study) or even 0.4 ppb (0.8 μg/m^3) (West Midlands, all cardiovascular admissions study). This means that extrapolation down to zero is not going far outside the range of the data at all. We therefore consider that there is no need to define a counter-factual other than zero.

3.8 Effect modification by temperature

In the process of reviewing papers for other parts of this report, we identified several time-series papers suggesting effect modification of the ozone and all-cause mortality association by temperature, with larger associations at higher temperatures (Atkinson *et al.,* 2012; Jhun *et al.,* 2014; Pascal *et al.,* 2012; Pattenden *et al.,* 2010; Wilson *et al.,* 2014). However, a systematic review of this evidence is needed. In addition, since correlation between ozone and other pollutants changes with temperature, this needs to be taken into account in interpreting results on effect modification by temperature. The results we have seen so far have been on mortality but possible effect modification by temperature of associations between ozone and other health outcomes also needs to be reviewed.

3.9 Summary of recommendations on concentration-response functions for short-term exposure to 8-hour mean ozone

Bringing all the evidence together from the sections on associations between ozone and all-cause mortality, all respiratory hospital admissions and all cardiovascular hospital admissions, our recommendation is to quantify the impacts of daily maximum 8-hour running mean ozone on all-cause mortality, all-respiratory admissions and all-cardiovascular admissions, using the concentration-response functions in Table 2 below.

Table 2: Recommended all-year concentration-response functions for maximum 8-hour running mean ozone and mortality or hospital admissions for use in UK health impact assessment

Outcome	ICD codes	Age group	Concentration-response function: % increase per 10 µg/m³ maximum 8-hour running mean ozone	95% confidence interval	Threshold ?
All-cause mortality	ICD 9 <800; ICD 10 A00–R99	All ages	0.34%	0.12, 0.56%	No
All respiratory emergency hospital admissions	ICD 9 460–519; ICD 10 J00–J99	All ages	0.75%	0.30, 1.20%	No
All cardiovascular emergency hospital admissions	ICD 9 390–459; ICD 10 I00–I99	All ages	0.11%	–0.06, 0.27%	No

Chapter 4
Health effects of ozone – long-term exposure

4.1 Introduction

In its update of the 2006 Air Quality Criteria Document (AQCD), the US EPA concluded that there was evidence suggestive of an association between long-term ozone concentrations and respiratory mortality but limited support for an association with total and cardiopulmonary mortality (US EPA, 2013), a view endorsed by the comprehensive review of the evidence in support of the revision of the EU's air quality policies (WHO, 2013a). Both reviews presented a narrative assessment of the evidence, and excluded results from recent large cohort studies in the UK (Carey *et al.,* 2013) and the USA (Jerrett *et al.,* 2013) that were published too late for inclusion.

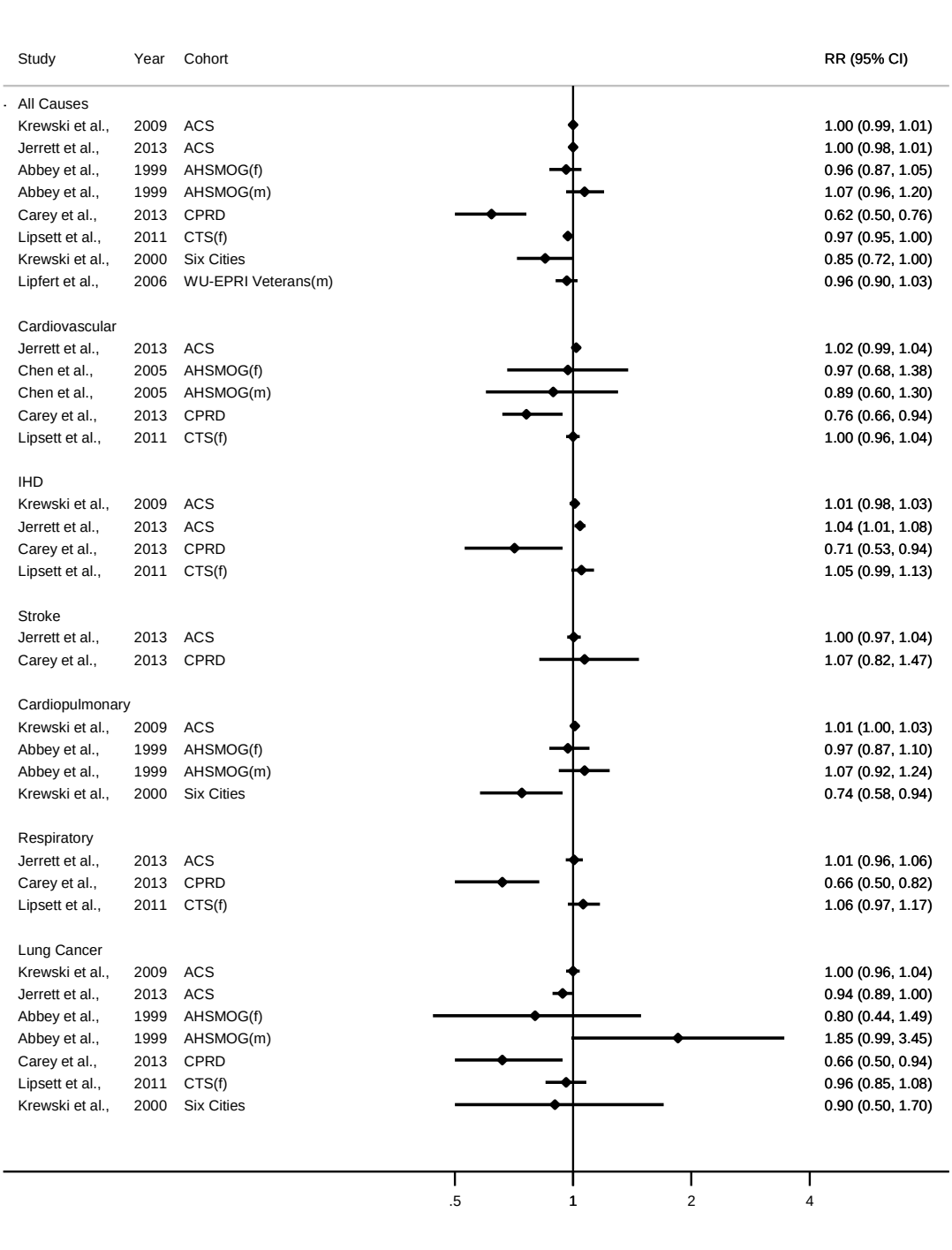
Analyses presented in Appendix 9 build upon this previous work by conducting a quantitative assessment of the evidence from cohort studies. Suitable studies published in peer-reviewed journals and indexed in Embase to August 2014 were identified via a search string using terms relating to study design, pollutant and health outcome. A sifting process identified those studies providing quantitative estimates of the associations between long-term average concentrations of ozone and mortality. These data were used to calculate standardised effect estimates expressed as hazard ratios (HR)[16] with associated 95% confidence intervals per 10 ppb (20 μg/m^3) increase in ozone concentration.

The evidence presented in this quantitative review did not provide support for an association between long-term annual ozone concentrations and mortality derived from single-pollutant models (Figure 6) or from models incorporating $PM_{2.5}$ (Figure 7) and therefore quantification is not recommended.

However, the evidence is suggestive of adverse associations between ozone concentrations and all-cause mortality during the warmer months of the year and from studies using peak ozone metrics, although the evidence base is limited to studies in the USA (Figure 8). There was a range of positive and negative associations for cause-specific mortality. The recent narrative review for WHO (2013a) and subsequent quantification exercise (WHO, 2013b) recommended quantification for respiratory mortality based upon warm season ozone concentrations as an alternative to quantification of effects from short-term exposure to ozone. The study of the American Cancer Society (ACS) cohort by Jerrett *et al.* (2009) provides the most appropriate concentration-response function for quantification because of its wider applicability to the general population (compared to the California Teachers Study (CTS) study (Lipsett *et al.,* 2011) which focused on female teachers in California). This

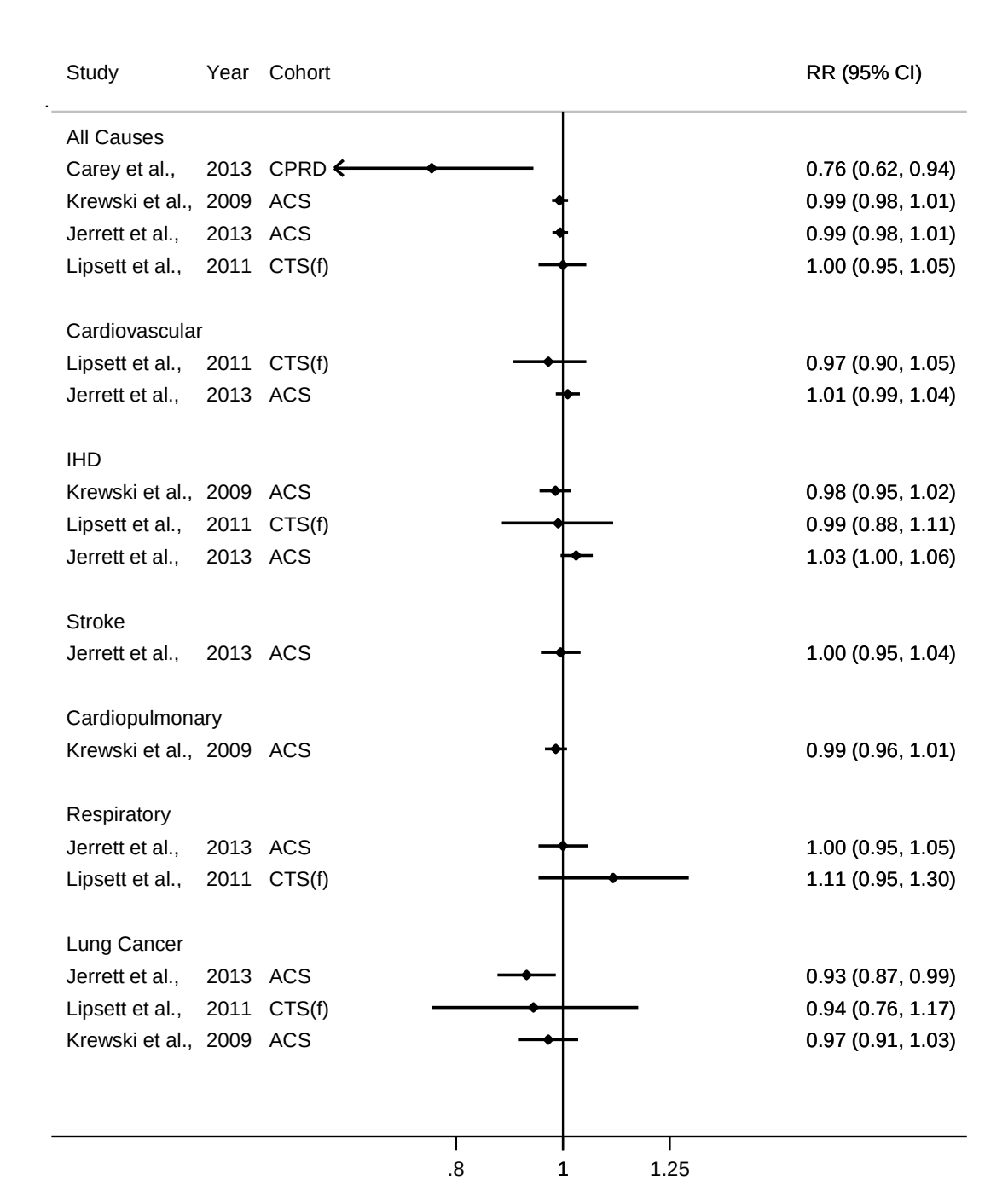
16 A hazard ratio of, for example, 1.029 for a 10 ppb increase can be expressed as a 2.9% increase in age-specific mortality rates by subtracting 1 and multiplying by 100.

coefficient for respiratory mortality in subjects aged 30+ years was based upon mean daily 1-hour ozone concentrations during the summer months (April–September) and derived from a single-pollutant model. It was robust to adjustment for $PM_{2.5}$. Its use in quantification was recommended in the HRAPIE project (WHO, 2013b).



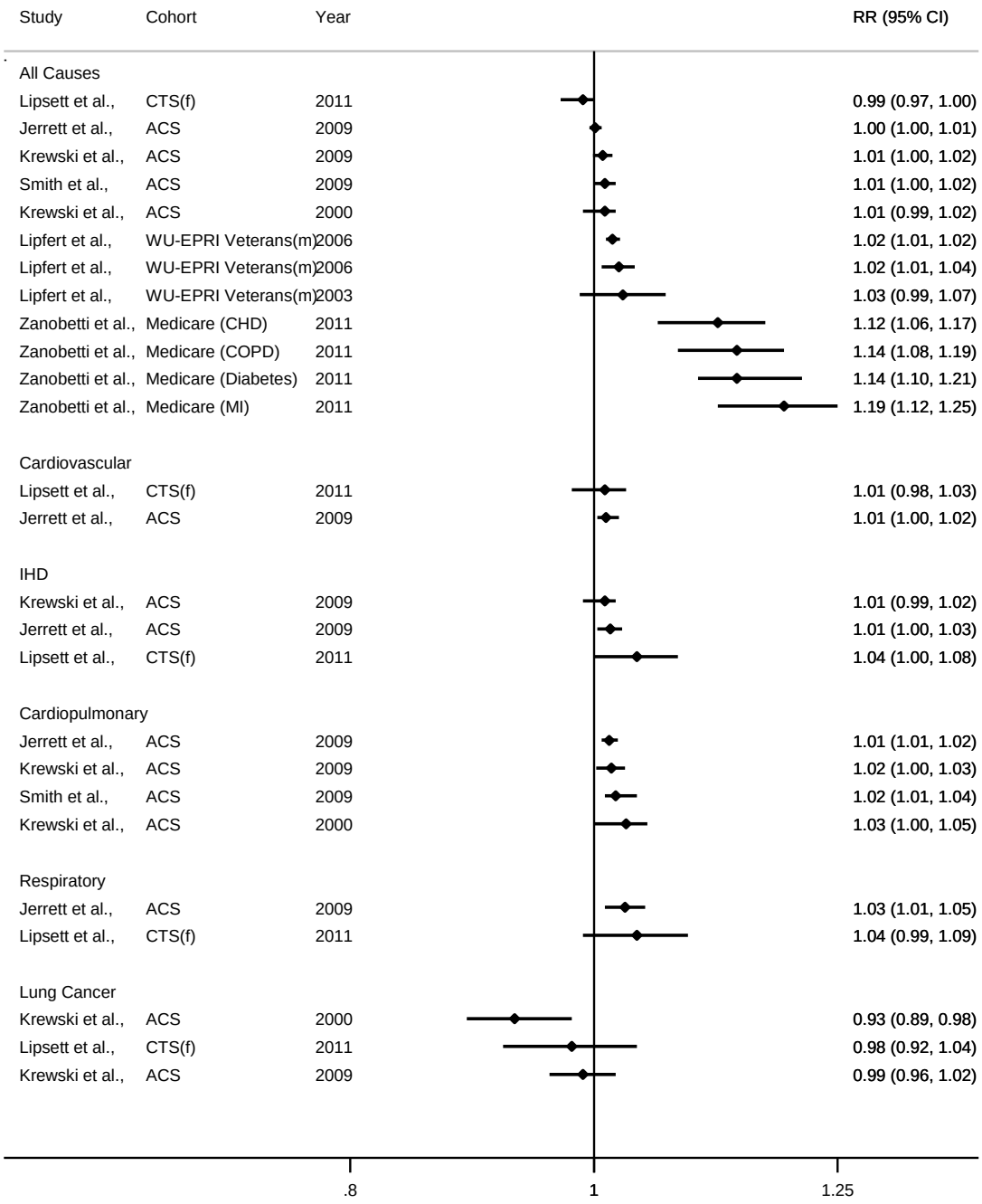
Cohort: Adventist Health Study of Smog (AHSMOG); California Teachers Study (CTS); Washington University-EPRI Veterans (WU-EPRI Veterans); American Cancer Society Cancer Prevention Study II (ACS CPS-II); cohort constructed from Clinical Practice Research Datalink (CPRD); cohort constructed from Medicare database (Medicare). (f) all subjects female; (m) all subjects male

Figure 6: Relative risk (95% CI) of death from a given cause per 10 ppb (20 µg/m³) increase in long-term exposure to ozone



Cohort: Adventist Health Study of Smog (AHSMOG); California Teachers Study (CTS); Washington University-EPRI Veterans (WU-EPRI Veterans); American Cancer Society Cancer Prevention Study II (ACS CPS-II); cohort constructed from Clinical Practice Research Datalink (CPRD); cohort constructed from Medicare database (Medicare). Krewski (2009) Los Angeles only. (f) all subjects female; (m) all subjects male

Figure 7: Relative risk (95% CI) of death from a given cause per 10 ppb (20 µg/m^3) increase in long-term ozone exposure, adjusted for long-term exposure to $PM_{2.5}$



Cohort: Adventist Health Study of Smog (AHSMOG); California Teachers Study (CTS); Washington University-EPRI Veterans (WU-EPRI Veterans); American Cancer Society Cancer Prevention Study II (ACS CPS-II); cohort constructed from Clinical Practice Research Datalink (CPRD); cohort constructed from Medicare database (Medicare). (f) all subjects female; (m) all subjects male; (CHF) prior diagnosis of CHF; (COPD) prior diagnosis of COPD; (Diabetes) prior diagnosis of diabetes; (MI) prior diagnosis of MI.

Figure 8: Relative risk (95% CI) of death from a given cause per 10 ppb (20 µg/m^3) increase in long-term warm-season ozone exposure

Therefore, as a sensitivity analysis (to a health impact assessment using evidence from short-term exposure studies), a health impact calculation could be considered, using the result for respiratory mortality and warm season (April–September) mean ozone derived from the single-pollutant model from Jerrett *et al.* (2009): hazard ratio (HR) of 1.029 (1.010, 1.048) per 10 ppb increment in mean daily 1-hour maximum ozone[17]. However, given the importance of this work, we should mention that there are substantial uncertainties regarding the suitability of the ACS result:

a There was evidence that the HR was modified by area-average temperature

b Transferability of the result from a study in a US population to a UK population

c Reservations about the Jerrett *et al.* (2009) study noted by Boogaard *et al.* (2014) and summarised as follows:

(i) it incorporated 23 years of ozone concentrations (1977–2000) but only 2 years of $PM_{2.5}$ data (1999 and 2000), due to lack of data availability. Given that both ozone and $PM_{2.5}$ levels decreased significantly over the years 1977–2000, the ozone concentrations included higher levels observed in the past compared to the lower $PM_{2.5}$ values observed recently. This leads to a situation where confounding by $PM_{2.5}$ is not adequately controlled

(ii) while the metric for ozone was the daily maximum hourly levels in the summer, the metric to assess potential confounding by $PM_{2.5}$ was the annual average. This uneven approach maximised the potential to observe an association between ozone and mortality and minimised the potential for $PM_{2.5}$ to confound the ozone association. The authors appear to recognise this implication in the discussion, where they state "it is likely that we have underestimated the effect of $PM_{2.5}$ in our analysis"

(iii) Jerrett *et al.* (2009) did not consider confounding by SO_2, a pollutant that had previously demonstrated a stronger mortality association than $PM_{2.5}$ in the ACS cohort (Krewski *et al.,* 2000)

Furthermore, any such recommendation for quantification would need to be accompanied by other, more general statements expressing the substantial uncertainties regarding the evidence base for an association between long-term exposure to ozone and respiratory mortality:

a Evidence base linking long-term exposure to ozone and mortality is limited – only a small number of studies/cohorts have assessed associations and most of these are in the USA

b Few cohorts are national and representative of the general population

c Categories of mortality vary between studies limiting the scope for quantitative meta-analysis to derive summary concentration-response functions

d Evidence from the UK suggesting a negative association between annual ozone concentrations and respiratory mortality

[17] Health impact assessment is a full assessment of a policy change or a scenario change (eg due to climate change) of several pollutants and outcomes. A sensitivity analysis is a 'what if' analysis around the total health impacts to see how the total would change if, for example, uncertain additional outcomes were true.

4.2 Other methodological issues

For the specific purpose of the 2nd Climate Change Risk Assessment, we also needed to consider the inputs and methodologies needed to do such an impact calculation at this time. Impact calculations for long-term exposure to $PM_{2.5}$ using life tables are based on assuming that effects on mortality are spread evenly throughout the year. The methodology and inputs could be adapted to deal with a (postulated) summer-only effect but only after more extensive discussion. The differences in the 'ozone season' between the USA and the UK should be considered. There is little information available to define an appropriate lag between exposure and effect and assuming it is the same as for $PM_{2.5}$ may not be appropriate for a summer-only effect. Finally, for an effect of long-term exposure incorporated into an impact calculation for a specified year in the future, modelling is needed not only for that specific year but also for intervening years in order to take into account both lagged effects from previous years and the shifts in size and age structure of the population as a result of long-term effects in previous years.

4.3 Summary of recommendations on concentration-response functions for long-term exposure to ozone

In summary, quantification of the associations between long-term ozone concentrations and mortality is not recommended. Although the limited evidence base could be acknowledged in a sensitivity analysis (a 'what-if' scenario[18]), the additional uncertainties in the assumptions needed for the health impact calculations (thresholds, effect modification, cessation lags and life table methods for applying risks for part of a year) led us to decide against recommending quantification, particularly given the tight timescale within the context of the CCRA2. We recommend further work in order to develop quantification approaches for use in sensitivity analyses in the future.

18 To consider how much difference it would make to an overall health impact assessment if this uncertain evidence were to be confirmed.

Chapter 5
Future research

5.1 General

This report has concentrated on ground-level ozone. This is not the only pollutant affected by climate change – further work is recommended on other pollutants. Simulations of potential future mixtures of air pollutants and accompanying meteorological variables rely on process-based atmospheric chemistry transport models. These models must simulate at sufficient spatial and temporal resolution accurately to capture the chemistry and transport processes and require the development of necessary input data.

A better understanding of personal exposure to ozone and its relationship to measured and modelled ozone would improve exposure assignment within population-based studies. This, and comparison with similar work on other pollutants, would improve interpretation of multi-pollutant models.

5.2 Time-series studies and related issues

Choosing broad health outcomes for health impact assessment is a reasonable approach to quantification but if some more specific outcomes are strongly affected and others are not, it might be more appropriate to choose more specific outcomes in the future. Further time-series studies on sub-diagnoses and age groups and meta-analyses of a wider range of outcomes would be needed to determine whether this was the case.

There is a need for maintenance of relevant literature databases and active surveillance of the research literature to identify studies that can change/inform overall pooled concentration-response functions.

Several papers in the literature only present multi-pollutant models if they find 'positive and significant' associations, to check if the association is robust to adjustment. However, negative associations may be masking a positive relationship, particularly in the presence of known negative correlations with other pollutants. Future studies should investigate whether negative confounding by other pollutants is present. This is particularly important for the associations with cardiovascular admissions.

The APHEA2 study found marked changes in the associations between 8-hour mean ozone and all-cause mortality after adjustment for NO_2 and CO. Future studies should investigate multi-pollutant models accounting for gaseous pollutants.

Greater numbers of reported multi-pollutant model associations would make meta-analyses of adjusted estimates more feasible. However, methodological issues would need to be considered as to how best to do this and how to take account of difficulties in interpretation of multi-pollutant model results when pollutants are measured with different degrees of measurement error.

Understanding correlation patterns between ozone and other pollutants, and how these change with temperature, season and pollutant concentrations, is important for interpreting the epidemiology. Preliminary analysis of these patterns was presented here but a systematic analysis of a larger dataset should provide more robust conclusions. Results from chemistry transport models may also provide useful insights.

Many time-series studies do not investigate thresholds and those that do usually use single-pollutant models. This report has set out in hypothetical terms how the shape of the concentration-response relationship is likely to be influenced by changing correlation patterns with other pollutants by temperature and season as ozone concentrations change. Effect modification by temperature and personal exposure may also change as ambient ozone concentrations change, perhaps providing reasons for thresholds observed. There is a need to investigate threshold relationships in multi-pollutant models, personal exposure to ozone by season/weather and effect modification by temperature. Simulations may help to illustrate the inter-relationships between these factors.

Effect modification of associations between ozone and health effects by temperature may be particularly important in the context of climate change. We recommend a systematic review of the evidence on factors, including temperature, which may modify associations of ozone with health effects.

The evidence that we have seen so far on effect modification by temperature does not take into consideration changes in correlations between pollutants by temperature. Changes in confounding by other pollutants as temperature changes need to be investigated as a possible alternative or contributing explanation to the results seen.

5.3 Causality of cardiovascular effects

Panel studies or chamber studies that examine both respiratory and cardiovascular endpoints within the same study would be of interest to inform the debate as to whether the apparent difference between the greater effect of ozone on respiratory admissions compared with cardiovascular admissions is real.

A more comprehensive review of all panel studies, with consideration of whether to amend the quality metrics for the studies compared with those in Goodman *et al.* (2014), including meta-analysis of results (if possible) and assessment of publication bias is required. This could usefully be conducted in relation to cardiac arrhythmias and heart rate variability where there appear to be more studies, many of which are small and show small, but non-significant ($p > 0.05$) associations.

There was insufficient time in the current exercise to review the chamber study and toxicological evidence, particularly that on cardiovascular effects. We recommend further review of this evidence and further studies on cardiovascular endpoints.

5.4 Long-term exposure to ozone

The need for maintenance of relevant literature databases and active surveillance of the research literature to identify studies that can change pooled meta-analytical estimates for response functions also applies to long-term exposure studies, particularly as there are very few studies for meta-analysis. Further cohort studies specifically designed to investigate the effects of long-term exposure to ozone in the general population are needed.

Concentration-response functions are not the only input needed to calculate the effects of long-term exposure to ozone. There is also a need for recommendations regarding the lag between reduction in exposure and reduction in effect – there is very little information on this. While it could be assumed that the same lags apply as for $PM_{2.5}$, the observation that effects from long-term exposure to ozone mainly apply to respiratory mortality and to the warm season, suggests the lags might well be different. More research on this is needed, potentially including re-analysis of current studies.

There is also a need to think through the approach and input data required for life table calculations were these to be required for, say, an April to September only coefficient. The unit for such life table calculations would need to be 6 months rather than a year, or shifted from calendar years to April-to-March years so that effects did not precede April to September exposures. Health impact calculations of long-term exposure to ozone also need modelling of ozone concentrations to be available for several years in the future as exposure in earlier years affects the size and age structure of the population affected by ozone concentrations in later years.

5.5 Conclusions

This report has recommended updated concentration-response coefficients for calculating the health impacts of day-to-day variations in ambient ozone concentrations on mortality and hospital admissions. While it was not possible to make a recommendation regarding quantification of mortality associated with long-term exposure to ozone at this stage, the further work needed to reconsider this in future has been set out. In addition, the need for a good understanding of the complexities of the atmospheric chemistry of ozone when interpreting the epidemiological results has been discussed. Finally, a research strategy has been suggested to improve recommendations for the quantification of the health effects of ozone in the context of climate change in the future.

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Appendix 1
Terms of reference for the COMEAP Working Group on Quantification of Effects of Ozone on Health: short-term coefficients and long-term exposure and mortality in the United Kingdom

A1.1 Aim

To develop a draft report for consideration by COMEAP, giving recommendations for concentration-response functions for the quantification of key aspects (i.e. based on strong evidence and/or likely to have a noticeable effect) of the health effects of ozone. The report should also include information to guide the correct application of the concentration-response functions in quantifying health impacts and recommendations for further work to improve quantification of the health effects of ozone in the future.

A1.2 Background

Ground-level ozone is a climate-sensitive and climate-altering pollutant and as such needs to be included in the second national Climate Change Risk Assessment (CCRA2) (Hames and Vardoulakis, 2012; IPCC, 2014; Vardoulakis and Heaviside, 2012). The CCRA2 does not require any specific calculations, but will rely upon published papers estimating the burden of ozone on mortality and morbidity in the UK and the impact of climate change on this burden over time. Current assessments on mortality/morbidity burdens in the UK are based on short-term exposure coefficients proposed by the WHO and COMEAP in 2004 and 1998 (COMEAP, 1998; Heal *et al.,* 2013; Stedman and Kent, 2008; WHO, 2004). Recent work carried out on behalf of the Adaptation Sub-Committee of the Committee on Climate Change indicates that annual mean ozone concentrations are increasing in some urban areas in the UK. It is anticipated that this work will be completed in time for the COMEAP recommendations to be included in the CCRA2, which will cover literature up until (or shortly after) mid-2015. It may also feed into subsequent quantification work. The CCRA2 will be presented in Parliament in early 2017 (the previous CCRA was presented in 2012).

A1.3 Issues to be addressed

There are a number of areas to consider in order to improve understanding of the health effects of ozone, associated with both short- and long-term exposure.

Short-term exposure effects

Currently, the short-term coefficients used in quantification (and related burden estimates) are dated, and do not reflect developments in the literature since QUARK/COMEAP last gave recommendations on this topic in 1998. Work may include:

a Recommendations on health endpoints (eg all-cause or cause-specific mortality, respiratory hospital admissions, cardiovascular hospital admissions, minor restricted activity days (RADs))

b Recommendation on the metric for short-term exposure to ozone (eg daily maximum of 8-hour running mean) and for period of assessment (all year or summer only)

c Recommendations for the appropriate concentration-response coefficient for quantification of mortality and hospital admissions associated with short-term exposure to ozone

d Discussion on the use of a threshold and, if so, what the threshold should be

e A view on the extent to which the effects of ozone are additional to or independent of those of PM and other pollutants for relevant health outcomes

f A view on effect modification by temperature

g Recommendations for quantification or sensitivity analyses of mortality/morbidity (health endpoints, coefficients, threshold and temperature dependency) associated with short-term exposure to ozone

Long-term exposure effects

The health effects of long-term exposure to ozone have not been quantified in the UK – although effects on COPD mortality have been included in the global burden of disease study by Lim *et al.* (2012) – so some review of recent evidence for long-term effects or recommendations for a coefficient may be required, particularly since the REVIHAAP report (WHO, 2013a) was published. In particular:

a The view on hazard related to long-term exposure to ozone – taking into account recent evidence reviewed in REVIHAAP, and the national English cohort study (Carey *et al.,* 2013) – and, if quantification of effects in the UK is recommended, even for sensitivity analysis

b Recommendations on health endpoints to be included (eg respiratory mortality)

c Recommendation on the metric for long-term exposure to ozone (eg annual mean) and for period of assessment (all year or summer only)

d Possible threshold, or effect modification by temperature – taking into account results from Jerrett *et al.* (2009)

e A discussion on the methodology involved in estimating long-term health burdens/impacts as opposed to short-term burdens/impacts

f A view on likely extent of overlap between long and short-term effects (eg whether or not it is valid to sum mortality estimates)

It is not envisaged that the work will cover long-term exposure to ozone and morbidity on this occasion.

Given the time constraints, the preferred approach may be to revisit the REVIHAAP and HRAPIE reports (WHO, 2013a,b) and either endorse/modify their conclusions, taking into account that the COMEAP recommendations are for application in the UK, not to the EU as a whole.

A1.4 Scope of the work

Provide advice on the evidence linking short- and long-term exposures to ozone with specific health endpoints, and on aspects that will need to be taken into account when considering quantification. It is suggested that the considerations of COMEAP and its working group are largely based on recent authoritative reviews by WHO (REVIHAAP and HRAPIE) supplemented by the Department of Health funded meta-analysis of short-term exposures undertaken by St George's, University of London (Atkinson *et al.,* 2014) and existing UK studies (Carey *et al.,* 2013).

It is anticipated that detailed recommendations for quantification (eg coefficients for specific health endpoints and thresholds) will be proposed.

A1.5 Resources

Once COMEAP has given a view on hazard, a COMEAP working group on ozone may be formed to consider approaches to quantification. Sani Dimitroulopoulou, Clare Heaviside and Sotiris Vardoulakis (PHE Air Pollution and Climate Change Group) will be the main secretariat leads preparing papers and coordinating discussion at COMEAP meetings. Heather Walton will chair the working group.

A1.6 Timescales

The first meeting of the COMEAP Working Group on Quantification of Effects of Ozone on Health will be in mid-July 2014, with regular follow-up meetings organised by the APCC group (the frequency of meetings will be decided at the first working group meeting). There will be a discussion item on ozone at the COMEAP meeting in November 2014, covering discussion of hazard and initial indications of recommendations for quantification. The working group will further develop recommendations for quantification leading to a draft report discussed at the COMEAP meeting in March 2015 and the final report agreed at the COMEAP meeting in June 2015.

A1.7 Deliverables

A COMEAP report, including recommendations for quantification, is anticipated by September 2015.

A1.8 References

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Appendix 2
Membership lists

Membership of the Committee on the Medical Effects of Air Pollutants

Chair

Professor Frank J Kelly BSc PhD FRSA

Members

Professor H Ross Anderson MD MSc FFPHM FRCP FMedSci (*until June 2003*)

Dr Richard Atkinson BSc MSc PhD PG Cert HE

Professor Alan R Boobis OBE PhD CBiol FSB FBTS

Dr Nicola Carslaw BSc MSc PhD

Ms Ruth Chambers MA MSc

Dr Beth Conlan BSc MSc PhD

Professor Jonathan Grigg BSc MBBS MRCP MD FRCPCH

Professor Roy Harrison OBE PhD DSc CChem FRSC FRMetS HonFFOM HonMFPH

Dr Mike Holland BSc PhD

Mr J Fintan Hurley MA

Professor Debbie Jarvis MBBS MRCP MD FFPH

Dr Jeremy Langrish BA MA MB BCh MRCP PhD

Professor Robert L Maynard CBE FRCP FRCPath FFOM

Dr Brian G Miller BSc PhD CStat

Dr Alison Searl BSc(Hons) PhD MEnvS

Mr John Stedman BA

Dr Heather Walton BSc DPhil

Professor Paul Wilkinson BA BM BCh MSc MFPHM FRCP

Secretariat

Dr Sotiris Vardoulakis BSc MSc PhD

Ms Alison Gowers BSc MSc

Miss Inga Mills BSc MSc

Dr Karen Exley BSc MSc PhD

Dr Sani Dimitroulopoulou BSc PhD

Dr Sarah Robertson BSc PhD

Membership of the COMEAP Working Group on Quantification of Effects of Ozone on Health

Chair	Dr Heather Walton BSc DPhil
Members	Dr Richard Atkinson BSc MSc PhD
	Dr Nicola Carslaw BSc MSc PhD
	Dr Mathew Heal MA DPhil CChem
	Prof Debbie Jarvis MBBS MRCP MD FFPH
	Mr John Stedman BA
Secretariat	Dr Sani Dimitroulopoulou BSc PhD (Scientific)
	Dr Clare Heaviside BEng(Hons) MSc PhD (Scientific)
	Dr Sotiris Vardoulakis BSc MSc PhD (Scientific)

Appendix 3
Future ozone concentrations

Mat Heal

A3.1 Drivers of ozone concentration

Ozone is not emitted directly into the atmosphere but is formed by chemical reactions within the atmosphere. Some ozone is present naturally in the lower atmosphere from ozone brought down from the stratosphere. Model estimates suggest an average pre-industrial level of ozone of around 20 ppb (40 μg/m^3). Increased levels of ground-level ozone arise from additional photochemically initiated reactions involving other 'precursor' species emitted into the air from human activities. The most important of these precursors are methane (CH_4) and carbon monoxide (CO), which have lifetimes of weeks to years and which, with emissions of nitrogen oxides (NO_X = NO + NO_2), have contributed to an increase in the general hemispheric 'background' of ozone, and volatile organic compounds (VOC) which influence ozone formation on a regional and local scale. When NO_X emissions are high, such as in urban areas, the rate of production of ozone is suppressed. Reaction with the hydroperoxy radical (HO_2), ultimately derived from photolysis of water vapour destroys ozone, although this only becomes the dominant chemical process in remote areas. The majority of net loss of ozone from the lower atmosphere occurs by deposition to the surface, particularly to vegetation.

Meteorology also substantially impacts on ozone levels via its influences on, for example, the rates of chemical reactions, rate of deposition of ozone to the surface, emissions of biogenic VOC, boundary-layer depth, stagnating air pollution episodes and long-range atmospheric transport.

All these processes give rise to diurnal variability and seasonality in ozone levels, superimposed on which can be episodes of high ozone of a few days' duration.

A3.2 Ozone quantification metrics

Long-term exposure to ozone is appropriately quantified by an annual or seasonal average, with application of a cut-off concentration or threshold (related to the health effects), if needed. In some instances, long-term averages have been quantified as averages of a variety of shorter-term metrics with some specifically designed to reflect peak concentrations of ozone, such as the average of daily maximum 1-hour ozone concentrations over the summer period for a number of years (eg Jerrett *et al.,* 2009). These variations place greater emphasis on repeated exposure to higher ozone concentrations than does a long-term average across all ozone concentrations. Short-term exposure to ozone is appropriately quantified by a daily concentration metric, which can be combined with daily health data for health impact assessments. Daily mean, daily maximum 1-hour mean and daily maximum 8-hour running mean have all been used but the last is the most common metric for European studies quantifying the health impacts associated with short-term exposure to ozone. The related metric of SOMO35 is an annual metric derived as the summation of the daily ozone

concentrations in excess of 35 ppb (70 μg/m^3), where daily again refers to the daily maximum 8-hour running mean[19]. The intrinsic exclusion of concentrations below 35 ppb (70 μg/m^3) within this metric means that its value is sensitive to the number and magnitude of high ozone days in a year.

A3.3 Emissions and climate change impacts on future ozone

The most important influence on levels of ozone over Europe on the timescale of a few decades will be the magnitudes of anthropogenic emissions of the precursor CH_4, VOC and NO_X gases (Coleman *et al.,* 2013; Fang *et al.,* 2013; Hedegaard *et al.,* 2013). Increases in global CH_4 emissions, regardless of where these occur, will lead to increased background ozone. On the other hand, continued European reductions in emissions of VOC and NO_X will lead to reductions in production of ozone on the regional scale, except where a locality is currently in a strongly VOC-limited (NO_X-saturated) regime, eg urban areas in north west Europe, where reductions in anthropogenic NO_X may initially result in higher levels of ozone before the benefits of continued NO_X reductions in lowering ozone become dominant.

However, since meteorology and climate are also determinants of ozone concentrations at any given location and time, then any future changes to climate (which will necessarily also include changes to meteorology) will have an impact on human health from ozone exposure. This is discussed in more detail in the following text, but it is important to note the following points. First, natural variations between years in meteorology cause both long-term (annual and seasonal) and short-term episodic values of ozone concentrations to vary from year to year. A practical consequence of this is the need for simulations over many years to draw out trends in both present-day and future projections of air quality. Second, future climate changes are largely caused by changes in air pollutant emissions (of CH_4, VOC and NO_X, primary PM, etc, as well as of CO_2), and these changes in emissions also drive changes in future ozone concentrations. It is therefore difficult (and potentially irrelevant) to address the question of how changes in climate and meteorology in isolation may affect ambient ozone since the changes in ozone are also driven by the changes in emissions that change the climate. Third, some processes influencing ozone concentrations occur on short (minutes) timescales (eg chemical reactions near sources of NO) which can lead to strong spatial gradients in ozone, particularly in urban areas, that the coarse spatial-resolution of many models may not adequately simulate.

The climate impacts directly or indirectly on many processes that determine the concentrations of ozone at a particular location and time (Jacob and Winner, 2009; Fiore *et al.,* 2012). Some identified climate-mediated influences on ozone include those related to:

a Emission fluxes of ozone precursors, eg biogenic VOC from vegetation (in particular, isoprene, and α- and β-pinene), evaporation of anthropogenic VOC, NO_X from soil and from lightning, CH_4 from wetlands, and NO_X, CO and VOC from wild fires

b Atmospheric chemistry, eg via changes in temperature and atmospheric water vapour content

19 35 ppb (70 μg/m^3) is subtracted from each daily concentration. If this results in a negative number, the number is set to zero. The set of daily differences are then summed over the year.

c Atmospheric dispersion and transport, eg boundary layer ventilation, convective mixing, storm tracks, prevalence of anticyclonic blocking highs, precipitation and stratosphere-troposphere exchange

d Loss of ozone by dry deposition to vegetation, which depends on soil moisture content and CO_2 concentrations

Furthermore, climate change may also influence future anthropogenic emissions of ozone precursors indirectly through mitigation and adaptation responses such as reduced energy demand for space heating in winter but greater energy demand for air-conditioning in summer.

Current understanding is that the greatest uncertainties in simulated ozone pertinent to the impact of climate change specifically are (i) uncertainty in ozone precursor emissions from climate-sensitive biogenic sources (Doherty *et al.,* 2013; Guenther *et al.,* 2012; Langner *et al.,* 2012) and (ii) in parameterisations of ozone dry deposition especially under drought conditions (Emberson *et al.,* 2013). Biogenic VOC emissions from vegetation, NO_X from soil, and CH_4 from wetlands all generally increase as the climate warms; however, countering increases from higher temperatures, there is evidence that increases in CO_2 levels lead to a physiological response of reduced biogenic VOC emissions (Arneth *et al.,* 2010). Under dry soil conditions the stomata of vegetation are almost completely closed because plants are conserving water, so loss of ozone by dry deposition decreases and ozone levels increase (Andersson and Engardt, 2010; Vieno *et al.,* 2010).

Climate change may also affect ground-level ozone through changes in atmospheric transport and mixing processes, from small scales (eg boundary layer ventilation and convection), through synoptic scales (eg location of storm tracks and prevalence of anticyclonic blocking highs), up to planetary scales (eg increases in the Brewer-Dobson circulation, together with shifts in modes of climate variability such as the North Atlantic Oscillation). Changes in these processes may affect both annual- and seasonal-average ground-level ozone as well as ozone episodes.

At present, climate model projections provide inconsistent results on the impact of climate change on mixing depth, with increases and decreases in different regions. In particular, Murazaki and Hess (2006), using the same climate model at different resolutions, noted different trends in mixing depth with climate change.

Doherty *et al.* (2013) reported that shifts in atmospheric transport patterns associated with inter-hemispheric transport are unlikely to have a major role in influencing spatial patterns of annual-mean ozone due to climate change, while Glotfelty *et al.* (2014) reported that climate change may enhance intercontinental transport of air pollution from East Asia, leading to a simulated increase in global average ozone mixing ratio of around 0.8 ppb (1.6 $\mu g/m^3$) by 2050 compared with 2001.

Changes in long-range atmospheric transport patterns may well be important when considering changes in high percentiles or in daily maximum 8-hour ground-level ozone (Langner *et al.,* 2012). Import of polluted air from continental Europe to the UK can be a significant component of ground-level ozone in the UK, particularly during air pollution episodes (Vieno *et al.,* 2010). Therefore, changes in this aspect of synoptic (long-range) transport, as well as climate-mediated changes in continental European ozone, will be important for ozone in the UK. At present there is little consensus in model simulations on future trends for the 'blocking highs' which can influence import of ozone into the UK and stagnation events (Masato *et al.,* 2013).

For those climate-mediated processes included in model simulations to date, global model studies indicate that, very broadly, the net impact of climate change on ground-level ozone is generally a decrease in remote (low NO_X) areas (over oceans or well away from anthropogenic emissions), but an increase in some densely populated (high NO_X) areas (Wu *et al.,* 2008). In remote areas, the higher water vapour content in warmer air leads to a decreased ozone lifetime via the reaction with HO_2 (which is ultimately derived from water vapour). Over populated land areas, with higher NO_X, higher temperatures increase climate-sensitive biogenic isoprene and soil NO_X emissions, and increase chemical reaction rates, eg increasing the decomposition of peroxyacetyl nitrate (PAN, a major NO_X reservoir species and ozone precursor).

However, the overall net ozone change in the future depends very sensitively on the world geographical region and climate change scenario being considered (Fiore *et al.,* 2012). Over northern Europe (including the UK), model simulations using the most pessimistic climate change scenarios (which include projections of changes in anthropogenic ozone precursor emissions) give a net increase in ground-level ozone, whilst less pessimistic climate change scenarios project a net decrease (Lei *et al.,* 2012; Wild *et al.,* 2012; Young *et al.,* 2013). For example, Wild *et al.* (2012) calculated estimates of changes in annual mean ozone between 2000 and 2050 averaged over Europe that were negative (−2 to −4.7 ppb; –4 to –9.4 μg/m^3) for all climate RCPs (representative concentration pathways) except for RCP8.5 (+0.3 ppb; +0.6 μg/m^3) which has the largest increase in CH_4. By 2100, European annual multi-model mean ground-level ozone changes between +2 ppb (+4 μg/m^3) for RCP8.5 and −15 ppb (–30 μg/m^3) for RCP2.6 were estimated (Fiore *et al.,* 2012). (The other two RCPs also give decreases in multi-model annual ozone over Europe in 2100.) Young *et al.* (2013), in the recent Atmospheric Chemistry and Climate Model Intercomparison Project (ACCMIP) of 15 GCMs (global circulation models), indicate annual mean ozone increases of >10 ppb (>20 μg/m^3) over Europe under RCP8.5 in 2100 compared to 2000. Similarly, Lacressonniere *et al.* (2014) showed an increase in ozone in north-western Europe under RCP8.5 (to 2050) and a decrease in southern Europe. As noted above, net ozone change under climate change depends on the future magnitudes of emissions of the different relevant anthropogenic precursors within that climate. The four RCPs developed for 5th Assessment Report (AR5) of the Intergovernmental Panel on Climate Change (IPCC) assumed substantial reductions in ozone precursor emissions, except for CH_4 in RCP8.5 which doubles relative to the year 2000. It is this large increase in projected CH_4 that drives the increases for annual mean ozone under RCP8.5. In this respect, the RCPs provide a strong contrast to the former IPCC SRES (Special Report on Emissions Scenarios) in regard to their projections for emissions relevant to air quality; the RCP scenarios were primarily developed to encompass a range of long-term (end of century) climate outcomes and do not cover the range of possible shorter-term air quality emissions trajectories (Colette *et al.,* 2012). Two global energy assessments (GEA) air quality scenarios were subsequently developed to provide climate responses broadly comparable to RCP2.6 and RCP8.5 in terms of radiative forcing. Using these emissions scenarios with six regional and global CTMs, Colette *et al.* (2012) found increases in 2030 in ensemble-median annual mean ozone in NO_X-saturated areas of around 5–10 ppb (10–20 μg/m^3) which includes most UK cities, accompanied by decreases in ozone in southern Europe. This highlights the importance of considering VOC as well as NO_X controls for ozone reductions. It is also important to recognise that the coarse spatial resolution of many global models, combined with ensemble averaging, may not capture effects of ozone removal through reaction with NO in NO_x-saturated areas (Heal *et al.,* 2013). Previous work to calculate health burdens due to ozone for 2003 and for various emissions scenarios in 2030 by Heal *et al.* (2013) has used output from the EMEP4UK model at 5 km resolution across the UK.

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Appendix 4
Personal exposure to ozone

Sani Dimitroulopoulou

Epidemiological studies estimate the effects of air pollution on human health, based on the assumption that outdoor air pollutant levels are an acceptable surrogate for population exposure. However, the health impacts of air pollutants are likely to be more directly related to personal exposure of individuals than to ambient concentrations. Furthermore, for a given ambient pollutant concentration at any time, there will be a wide range of personal exposures within the population, due to variation in indoor and outdoor location, indoor sources and people's activity. In Western Europe and North America, people typically spend 80–90% of their time in indoor environments and especially in the home (ECA, 2003; McCurdy *et al.,* 2000; Torfs *et al.,* 2008).

This appendix provides initially a short introduction to personal exposure modelling, which is based on the concept of the microenvironment. The application of this concept to the ozone exposure assessment carried out by the US EPA (2014) is presented. The importance of considering the indoor environment in exposure estimates and the implications for epidemiological studies are finally discussed based on the relationships of indoor/outdoor ozone levels and the personal exposure/ambient concentrations reported in the literature.

A4.1 Exposure modelling

Personal exposure modelling simulates the movement of individuals through time and space and estimates their exposure to a given pollutant while being in a variety of locations, including indoor and outdoor locations. A key concept in exposure modelling is the *microenvironment*, which is defined as a generic location with homogeneous pollutant concentrations where people spend time; so this refers to the immediate surroundings of an individual at a particular time (Duan, 1982).

For personal exposure assessment, two types of models are needed: (i) microenvironmental models, to simulate time-series of pollutant concentrations in different microenvironments and (ii) modelling of daily activity patterns, to indicate the corresponding movement of individuals exposed, between these microenvironments, through time (NRC, 1991).

The pollutant concentrations in indoor microenvironments are affected by outdoor concentrations, built environment factors (i.e. infiltration and ventilation rates) and pollutant characteristics (decay and deposition rates).

The activity patterns of individuals, which have been found to vary by age, are important to determine their exposure. Variation in ozone levels among various microenvironments means that an individual's exposure is influenced by the time spent in each microenvironment as well as the level of activity. In the USA, according to Klepeis *et al.* (2001), the working population spend the least time

outdoors, while the school-age population spend the most time outdoors. The elderly (aged 65 and over) spend somewhat more time outdoors than adults aged 18–64, with a greater fraction of time spent outdoors at a residence. Children aged 0–4 also spend most of their outdoor time in a residential outdoor location. Thus, personal exposure is affected by time-activity patterns, time-averaged or activity-specific breathing rates among varying sexes and/or life stages and microenvironmental concentrations of air pollutants.

The exposure modelling can be either deterministic or probabilistic. The deterministic approach implies the use of single values for the above input parameters (Dimitroulopoulou *et al.,* 2001). On the other hand, the advantage of the probabilistic exposure modelling is the ability to account for variability in exposure by representing the input parameters of both microenvironmental modelling and activity profiles as statistical distributions (eg Dimitroulopoulou *et al.,* 2006; US EPA, 2014).

A4.2 US EPA (2014) ozone exposure assessment

The US EPA (2014) uses a modelling framework to assess exposures to ozone and the associated risks to human populations. This consists of:

a the Air Pollution Exposure model (APEX) (US EPA, 2012), which is used to simulate personal exposure and to estimate risks that rely upon personal exposure estimates

b the environmental Benefits Mapping and Analysis Program (BenMAP), which is used to simulate population level risks and impacts for endpoints, which are associated with changes in ambient air quality, based on the results of epidemiological studies (US EPA, 2013a)

The overall characterisation of risk draws from the results of the exposure assessment and both types of risk assessment (i.e. based on personal exposure and population exposure). The two modelling approaches are independent of each other. In this appendix, we focus on the personal exposure APEX modelling, which employs the concept of microenvironment.

The ozone personal exposure assessment provides estimates of exposures for people residing in 15 urban study areas in the USA. Exposures were calculated using 2006 to 2010 spatially interpolated hourly ambient monitoring ozone data, in order to reasonably capture year-to-year variability in ambient concentrations and meteorology and include most of the high concentration events occurring in each area. The wide range of air quality data across several years allows for more realistic estimates of a range of exposures, rather than using a single year of air quality data.

The population groups considered in the assessment are: (i) all school-age children (ages 5–18), (ii) asthmatic school-age children (ages 5–18), (iii) asthmatic adults (ages 19–95), and (iv) all older adults (ages 65–95). The strong emphasis on children, asthmatics and older adults is driven by the fact that these are important at-risk groups (US EPA, 2014).

APEX simulates the movement of individuals through time and space and estimates their exposure to ozone while occupying indoor, outdoor and in-vehicle microenvironments (28 modelled microenvironments). The importance of modelling indoor microenvironments (eg homes, offices and schools) is underscored by research indicating that personal exposure measurements of ozone may not be well correlated with ambient measurements, and indoor concentrations are usually much lower than ambient concentrations (US EPA, 2013b). Mass balance modelling was used to estimate

ozone concentrations in all indoor microenvironments, considering probabilistic distributions of outdoor temperature dependency (where data were available), building ventilation rates (air exchange) and chemical decay rates.

A4.3 Indoor/outdoor ozone relationships

The importance of considering the microenvironment approach in exposure estimates is apparent from the relationship of indoor/outdoor ozone levels, as discussed below.

Outdoor ozone concentrations vary spatially due to reactions with other atmospheric species. For instance, on or near busy roads, ozone concentrations are decreased due to the reaction with NO to form NO_2. On the contrary, pollutants such as CO and NO_X show significantly higher concentrations at the roadside than several hundred metres away (Karner *et al.,* 2010; Vardoulakis *et al.,* 2011). Thus, correlations between ozone and traffic-related pollutants are moderately to strongly negative, with the most strongly negative correlations observed for NO_2 (–0.5 to –0.9) (Vardoulakis *et al.,* 2011). Policies to reduce NO_X levels from traffic may lead to an increase in ozone levels near busy roads. Over spatial scales of a few kilometres and away from roads, ozone is formed as a secondary pollutant and can be more homogeneous, while over scales of tens of kilometres and downwind of an urban area, additional atmospheric processing can result in higher concentrations downwind of an urban area. The temporal variation of ozone also results in higher concentrations during daytime in urban background areas; higher concentrations in the afternoon and evening compared to early morning at busy roads, and higher ozone concentrations during summer than in winter (eg Gentner *et al.,* 2013; Vieno *et al.,* 2010).

Indoor concentrations are usually substantially lower than the outdoor concentrations unless indoor sources are present (eg in the case of offices, where ozone is emitted from photocopiers and printers). Studies have shown that ozone is deposited on to internal surfaces (eg Weschler, 2000), as well as being removed by reactions with terpenes (emitted from consumer products and building materials) to produce strong airway irritants (Weschler, 2006; Wolkoff *et al.,* 1999; 2000).

In the absence of indoor sources, the indoor to outdoor ratio is greatly affected by the building ventilation rates. Thus, in rooms with open windows, the indoor-outdoor (I/O) ratio may approach the value of 1.0. Several studies summarised in US EPA (2014) show that I/O ratios are typically in the range of 0.1 to 0.4, with some evidence for higher ratios during the ozone season when concentrations are higher.

A4.4 Personal exposure/ambient concentration relationship

Personal exposure is moderately correlated with ambient ozone concentration, as indicated by studies reporting correlations generally in the range of 0.3–0.8 and reviewed by the US EPA (2013b). Correlations between personal exposures to ozone and corresponding ambient concentrations are more variable when hourly values are used compared to 24-hour or longer averages. Correlations in outdoor microenvironments ($r = 0.7–0.9$) are much higher than those in residential indoor ($r = 0.1$) or other indoor ($r = 0.3–0.4$) microenvironments. Some studies report substantially lower personal exposure to ambient ozone concentration correlations, partly due to low air exchange rate and indoor ozone concentrations below the sampler detection limit, conditions often encountered during winter. Low correlations may also occur for individuals or populations spending substantial time indoors.

The ratio between personal exposure and ambient ozone concentration varies widely depending on activity patterns, housing characteristics, and season, with higher personal/ambient ratios generally observed with increasing time spent outside, higher air exchange rates, and in seasons other than winter. Personal/ambient ratios are typically 0.1–0.3, although individuals who may spend substantial time outdoors (eg outdoor workers) may have higher ratios (0.5–0.9) (US EPA, 2013b).

A4.5 Implications for epidemiological studies

From the above, it may be concluded that the wide spatial and temporal variations in ambient ozone concentrations result in uncertainty in exposure estimates and contribute to exposure measurement error in epidemiological studies.

Furthermore, apart from the ambient levels, the factors that influence personal ozone exposure include the indoor ozone exposure, which is affected by outdoor ozone levels, built environment characteristics, meteorology and activity patterns. Therefore, the use of ambient ozone concentration as a surrogate for personal ozone exposure may result in exposure misclassification in epidemiological studies.

Exposure measurement error mainly refers to the uncertainty, which is associated with exposure metrics, to represent the actual exposure of an individual or population. Short-term, time-series studies assess the daily health status of a large population over several years, by estimating their daily exposure using a short monitoring interval (hours to days). In these studies, the ozone concentrations measured at fixed monitoring stations and averaged over community level, are typically used as a surrogate for individual or population exposure.

According to the US EPA (2013b), this exposure measurement error can be an important contributor to variability in epidemiologic study results. It can underestimate or overestimate epidemiological associations between ambient pollutant concentrations and health outcomes, by biasing effect estimates and widening confidence intervals around those estimates. As it is also stated, exposure misclassification can tend to obscure the presence of potential thresholds for health effects. The importance of exposure misclassification varies with study design and depends on the spatial and temporal aspects of the design.

There are relatively few indoor ozone sources; as a result, personal ozone exposure is mainly affected by ambient ozone levels, which are, however, greatly reduced in the case of low ventilation conditions (i.e. closed windows). Even in microenvironments where indoor exposure is substantial, (eg in the case of offices with photocopiers and printing machines), this indoor exposure is unlikely to be correlated with ambient ozone exposure. US EPA (2013b) concludes that since personal exposure to ambient ozone is a fraction of the ambient ozone concentration, it should be noted that effect estimates calculated based on personal exposure rather than ambient concentration will be increased in proportion to the ratio of ambient concentration to personal exposure. So, daily fluctuations in this ratio can widen the confidence intervals in the ozone effect estimate.

Another factor that may influence epidemiological results is the tendency for susceptible people to avoid outdoor exposure on high ozone days, by reducing time spent outdoors. Activity pattern has a substantial effect on personal exposure to ozone, with time spent outdoors contributing to increased exposure. This behaviour has been predominantly observed among children, older adults and people with respiratory problems (eg Bresnahan *et al.,* 1997; McDermott *et al.,* 2006; Neidell M and Kinney, 2010; Semenza *et al.,* 2008).

A4.6 References

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Appendix 5
Single and multi-pollutant models in short-term exposure studies (all-cause mortality, respiratory and cardiovascular hospital admissions)

Heather Walton

The Department of Health commissioned work led by St George's, University of London, to provide a systematic review of time-series studies on air pollutants including ozone. The report of this project has been peer reviewed and the final version submitted to the Department of Health (Atkinson *et al.,* 2014a). The ozone chapter of the report contains full details (Walton *et al.,* 2014).

One purpose of commissioning this work was to aid COMEAP and its working group in updating concentration-response functions for the different pollutants. The work is the most recent quantitative meta-analysis (literature search since May 2011) that covers a full range of outcomes and averaging times. We have therefore used this work to guide our recommendations on quantifying the effects of short-term exposure to ozone.

The main report explains the reasons for focussing on 8-hour average ozone[20] and on broad health outcomes for all ages: all-cause mortality, cardiovascular hospital admissions and respiratory hospital admissions in terms of investigating potential concentration-response functions for quantification. This appendix therefore covers these outcomes.

The methodology for the ozone meta-analysis follows that used for the $PM_{2.5}$ meta-analysis that has already been published (Atkinson *et al.,* 2014b). After sifting for quality the estimates were further sifted according to an *a priori* protocol to select an estimate for a specific lag and to select only one estimate per city (as estimates from the same city are not statistically independent). The resulting studies and estimates are shown in the sections below.

The sections below also contain information, where available, on the ozone concentration ranges, correlations between pollutants and results of multi-pollutant models. The aim is to understand how much of the effect in the single-pollutant models is reflecting ozone itself and how much the effects of the other pollutants. It may not be possible to fully represent this quantitatively due to the fact that not all studies with single-pollutant models also consider multi-pollutant models, and those that do use different metrics and do not necessarily investigate adjustment for each of the pollutants other than ozone.

20 The studies use a mixture of daily maximum 8-hour running mean, other 8-hour metrics such as daily 8-hour average ozone from 10–6 pm and examples where the exact form of the 8-hour average is unclear.

A5.1 All-cause mortality

The relevant estimates for 8-hour average ozone, all-cause mortality for all ages are shown in Table A5.1. The pooled estimate was a 0.34% (95% CI 0.12, 0.56%) increase in mortality per 10 μg/m^3 increase in ozone. There was considerable heterogeneity (I^2 74.6%). The contributing estimates are presented in a forest plot (Figure A5.1)[21].

Table A5.2 shows the information on multi-pollutant models. Of the ten studies included, only three had information from multi-pollutant models. Borja-Aburto *et al.* (1997) found that the single-pollutant model result for ozone was almost entirely reflecting effects of total suspended particles (TSP) rather than ozone. On the other hand, the single-pollutant model result was increased on adjustment for ultrafine particle (0.01–0.1 μm) number count (Peters *et al.,* 2009). This probably reflects negative confounding by ultrafine particles at low ozone concentrations. However, the confidence intervals were wide (spanning zero) (probably due to fewer days having both ozone and ultrafine particle measurements) and the weight of the single-pollutant estimate in the meta-analysis was low. Hong *et al.* (1999) controlled for four pollutants (CO, NO_2, SO_2 and PM_{10}) and found the effect became less negative with an upper confidence interval that was now positive but the confidence intervals were extremely wide. However, in addition to these findings there is indirect information on some of the other studies (Tables A5.4–A5.10).

The APHEA2 (Air Pollution and Health – a European Approach) study (Gryparis *et al.,* 2004) included extensive analyses by season. Thus, although there are no multi-pollutant model results equivalent to the all-year single-pollutant estimate, there are multi-pollutant model results by season (Table A5.5). The summer estimates all remain significant after adjustment for other pollutants but the extent to which the effects of other pollutants appear to be contributing varies by pollutant. The single pollutant summer estimate is more or less unaffected by adjustment for SO_2, only slightly reduced on adjustment for PM_{10}, more obviously reduced by adjustment for NO_2 and actually increased on adjustment for CO. This is in line with the correlations in Table A5.4, where, for example, there are negative correlations with CO in several cities, even in the summer. The increase in the estimate on adjustment for CO is even more marked in the winter and increases in the estimate also occur on adjustment with several other pollutants in the winter (negative correlations between ozone and other pollutants occur for more pollutants and for more cities in the winter). The increased estimates are still not statistically significant, with the notable exception of the estimate adjusted for CO. Adjustment for NO_2 also reduces the estimate to some extent in the winter. These interesting results illustrate the complexities of judging the size of an independent effect of ozone when the estimate can be both reduced and increased on adjustment for other pollutants.

There is also information on multi-pollutant models from the APHEA2 study for all-year estimates but for 1-hour average rather than 8-hour average ozone. As these ozone metrics are closely correlated, this should still be informative. These multi-pollutant models were reported in the Europe dataset for the APHENA (Air Pollution and Health – a European and North American Approach) study (Katsouyanni *et al.,* 2009) which was essentially the same dataset as in Gryparis *et al.* (2004). The single-pollutant model results were stable to adjustment for PM_{10}, sometimes increasing slightly, sometimes decreasing slightly according to the model. Only ozone and PM_{10} were examined in this study.

21 It should be noted that the x–axis on the figure is 1000 x ln RR which approximates to percentage change per 10 μg/m^3 as given in the table.

O3 - All Cause Mortality, All season, All ages, 8 Hour Average

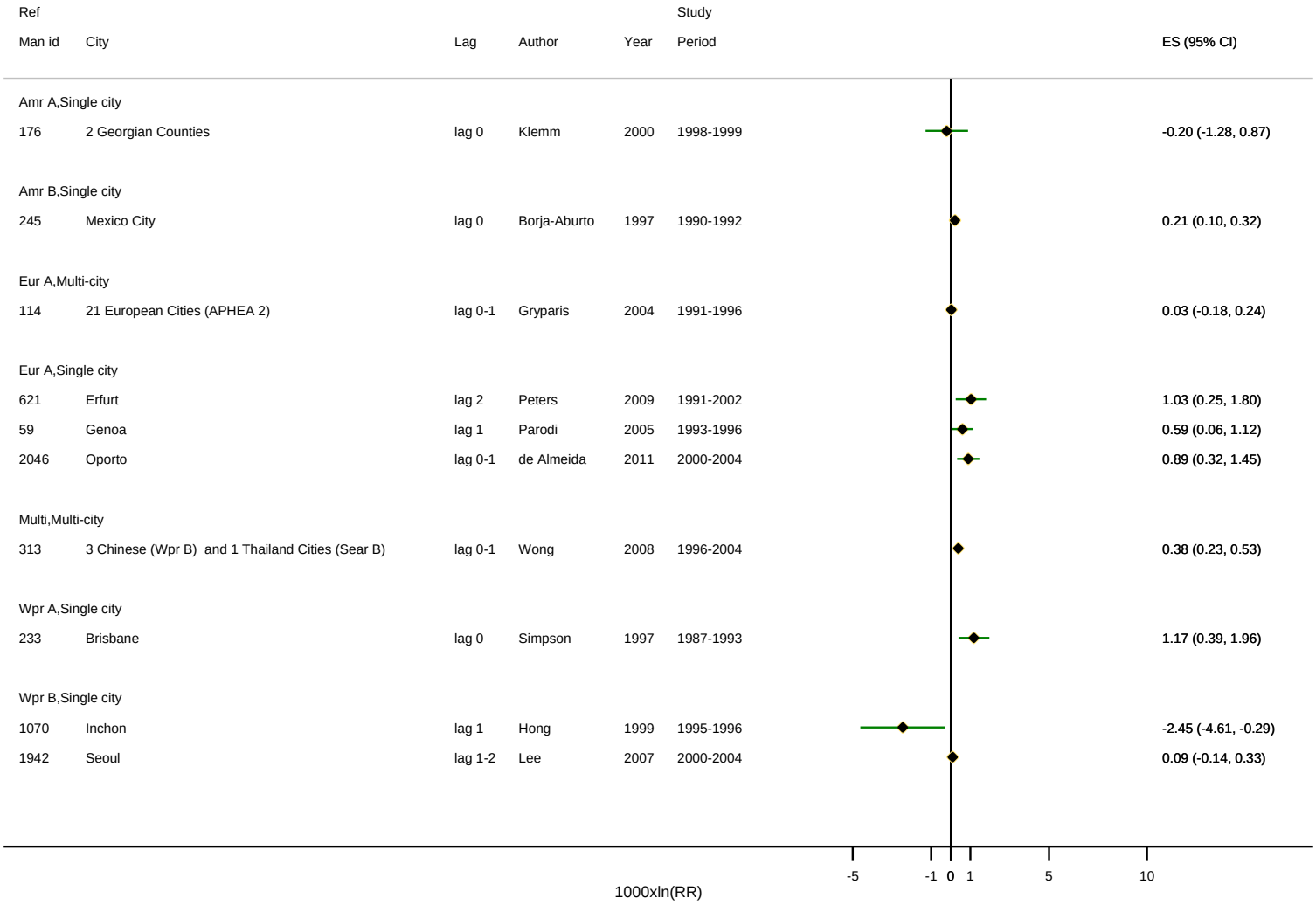

Figure A5.1: Ozone – All-cause mortality, for all seasons and all ages – 8-hour average

Table A5.1: 8-hour average ozone and all-cause mortality – single-pollutant models from studies used for pooled estimate

WHO region	Study location	Author/name	Study period	Concentration range Mean, min, max µg/m³	Lag	Estimate (single-pollutant model) % change per 10 µg/m³ 8-hour average ozone	Weight in regional single city meta-analysis	Pooled single city regional estimate	Weight in overall single city meta-analysis
AmrA	2 Georgian counties	Klemm (2000)	1998–1999	89.2, 6.9, 256.2	0	–0.20 (–1.27, 0.87)			4%
Amr B	Mexico city	Borja-Aburto (1997)	1990–1992	184.2 (median), 31.4, 350.8	0	0.21 (0.10, 0.32)			26%
Eur A	21 (19, 8 h) European cities (APHEA2)	Gryparis (2004)	1991–1996	See Table A5.3	0–1	0.03 (–0.18, 0.24)			22%
Eur A	Erfurt	Peters (2009)	1991–2002	IQR 43.8	2	1.03 (0.25, 1.82)	20%	0.79 (0.44, 1.14)	16%
Eur A	Genoa	Parodi (2005)	1993–1996	Mean 79.2, SD 45.3	1	0.59 (0.06, 1.13)	43%		
Eur A	Oporto	De Almeida (2011)	2000–2004	73, 6, 250	0–1	0.89 (0.32, 1.46)	37%		
WprB/ SEAR B	3 Chinese cities/1Thai city	Wong (2008)	1996–2004	Shanghai 63.3, 5.3, 251.3 Wuhan 85.7, 1, 258.5 Hong Kong 36.9. –8.2[a], 196.6 Bangkok 59.4, 8.2, 180.6	0–1	0.38 (0.23, 0.53)			25%
WprA	Brisbane	Simpson (1997)	1987–1993	35.5, 3.3, 124.3	0	1.18 (0.39, 1.98)			6%
WprB	Inchon	Hong (1999)	1995–1996	25.3, 3.6, 66.1	1	–2.42 (–4.50,–0.29)	41%	–0.94 (–3.34, 1.52)	1%
WprB	Seoul	Lee (2007)	2000–2004	Mean 52.6 SD 28.9	1–2	0.10 (–0.14, 0.33)	59%		
Pooled estimate (multi-city studies plus single-city studies pooled by region (n = 7) 0.34 (0.12, 0.56) % change per 10 µg/m³, I^2 74.6% (heterogeneity across the pooled single-city regional estimates and the multi-city estimates) [a] negative values occur in the centred data when the deviations of the original values from the individual station mean are greater than the overall means of all stations									

Table A5.2: Multi-pollutant models from the same studies/averaging times compared with single-pollutant model results from the studies in Table A5.1 (all-cause mortality)

WHO region	Study location	Author/name/	Study period	Single- or multi-pollutant model?	Lag	Estimate (single-pollutant model) % change per 10 µg/m³ 8-hour average ozone	Weight in regional single city meta-analysis[a]	Weight in overall single city meta-analysis[a]
Amr B	Mexico city	Borja-Aburto (1997)	1990–1992	Single	0	0.21 (0.10, 0.32)		26%
				With TSP	0	–0.01 (–0.24, 0.23)		
Eur A	21 European cities (19, for 8 h) (APHEA2)	Gryparis (2004)	1991–1996	Single	0–1	0.03 (–0.18, 0.24)		22%
				n/a but available by season (Table A5.5)/ all year 1-h average (Table A5.6)				
Eur A	Erfurt	Peters (2009)	1991–2002	Single	2	1.03 (0.25, 1.82)	20%	16%
				With ultrafine NC (0.01–0.1)	2	1.08 (–0.3, 2.49)		
WprB/ SEAR B	3 Chinese cities/1 Thai city	Wong (2008) (PAPA study)	1996–2004	Single	0–1	0.38 (0.23, 0.53)		25%
				n/a for multi-city estimate, single cities see Table A5.8				
WprA	Brisbane	Simpson (1997)	1987–1993	Single	0	1.18 (0.39, 1.98)		6%
				n/a but for 1-h average, see Table A5.10				
WprB	Inchon	Hong (1999)	1995–1996	Single	1	–2.42 (–4.50,–0.29)	41%	1%
				CO, NO_2,SO_2, PM_{10}	1	–1.88 (–4.26, 0.55)		

[a] Percentages do not add up to 100 as only studies that examined multi-pollutant models are shown in this table.

Table A5.3: Ozone concentrations for cities (Gryparis *et al.*, 2004)

City	Study period	Summer period				Winter period			
		Median		90th %ile		Median		90th %ile	
		1 hour (µg/m³)	8 hour (µg/m³)	1 hour (µg/m³)	8 hour (µg/m³)	1 hour (µg/m³)	8 hour (µg/m³)	1 hour (µg/m³)	8 hour (µg/m³)
Athens	1/92-12/96	109	90	150	118	57	44	88	69
Barcelona	1/91-12/96	90	75	121	100	49	33	79	60
Basel	1/90-12/95	87	74	135	118	35	24	68	58
Birmingham	1/92-12/96	66	52	93	78	47	36	69	61
Budapest	1/92-12/95	108	97	144	131	56	49	88	78
Erfurt	1/91-12/95	94	-	152	-	48	-	77	-
Geneva	1/90-12/95	92	78	141	120	35	24	66	50
Helsinki	1/93-12/96	66	58	90	81	50	44	68	62
Ljubljana	1/92-12/96	107	54	166	90	39	12	84	39
London	1/92-12/96	53	41	88	72	32	21	55	44
Lyon	1/93-12/97	87	65	140	110	40	19	63	42
Madrid	1/92-12/95	75	59	111	91	31	20	58	42
Milan	1/90-12/96	85	66	143	119	11	8	40	26
Netherlands	1/90-12/95	83	74	140	121	48	38	71	62
Paris	1/91-12/96	56	44	107	91	22	13	43	31
Prague	2/92-12/96	107	91	168	147	57	41	85	71
Rome	1/92-12/96	59	30	110	57	24	11	48	25
Stockholm	1/90-12/96	75	69	100	92	53	48	69	64
Tel-Aviv	1/91-12/96	44	-	62	-	26	-	44	-
Teplice	1/90-12/97	75	66	119	106	31	24	66	53
Torino	1/90-12/96	117	99	173	154	34	23	84	63
Valencia	1/94-12/96	72	58	95	77	44	31	65	49
Zurich	1/90-12/95	92	79	141	124	37	24	66	54

Table A5.4: Correlations (by season, 1-hour average) (Reprinted from Gryparis *et al.* (2004) with permission of the American Thoracic Society. Copyright © 2015 American Thoracic Society. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society)

TABLE 1. DESCRIPTIVE DATA ON THE STUDY PERIOD, POPULATION, OUTCOME (TOTAL, CARDIOVASCULAR DISEASE, RESPIRATORY DAILY NUMBER OF DEATHS), AND EXPOSURE (SEASONAL MAXIMUM DAILY 1- AND 8-HOUR OZONE)

						Ozone ($\mu g/m^3$)							
						Summer Period				Winter Period			
						Median		90th Percentile		Median		90th Percentile	
City	Study Period	Population × 1,000	Mean No. of Total Deaths per Day	Mean No. of CVD Deaths per Day	Mean No. of Respiratory Deaths per Day	1 Hour	8 Hour	1 Hour	8 Hour	1 Hour	8 Hour	1 Hour	8 Hour
Athens	1/92–12/96	3,073	73	36	5	109	90	150	118	57	44	88	69
Barcelona	1/91–12/96	1,644	40	16	3	90	75	121	100	49	33	79	60
Basel	1/90–12/95	360	9	4	1	87	74	135	118	35	24	68	58
Birmingham	1/92–12/96	2,300	61	28	9	66	52	93	78	47	36	69	61
Budapest	1/92–12/95	1,931	80	40	3	108	97	144	131	56	49	88	78
Erfurt	1/91–12/95	216	6	—	—	94	—	152	—	48	—	77	—
Geneva	1/90–12/95	317	6	2	0	92	78	141	120	35	24	66	50
Helsinki	1/93–12/96	828	18	9	1	66	58	90	81	50	44	68	62
Ljubljana	1/92–12/96	322	7	3	0	107	54	166	90	39	12	84	39
London	1/92–12/96	6,905	169	71	29	53	41	88	72	32	21	55	44
Lyon	1/93–12/97	416	9	3	1	87	65	140	110	40	19	63	42
Madrid	1/92–12/95	3,012	61	22	6	75	59	111	91	31	20	58	42
Milan	1/90–12/96	1,343	29	11	2	85	66	143	119	11	8	40	26
Netherlands	1/90–12/95	16,000	347	143	31	83	74	140	121	48	38	71	62
Paris	1/91–12/96	6,700	124	38	9	56	44	107	91	22	13	43	31
Prague	2/92–12/96	1,213	38	22	1	107	91	168	147	57	41	85	71
Rome	1/92–12/96	2,775	56	23	3	59	30	110	57	24	11	48	25
Stockholm	1/90–12/96	1,126	30	15	3	75	69	100	92	53	48	69	64
Tel-Aviv	1/91–12/96	1,141	27	12	2	44	—	62	—	26	—	44	—
Teplice	1/90–12/97	625	18	8	1	75	66	119	106	31	24	66	53
Torino	1/90–12/96	926	21	9	1	117	99	173	154	34	23	84	63
Valencia	1/94–12/96	753	16	6	2	72	58	95	77	44	31	65	49
Zurich	1/90–12/95	540	13	6	1	92	79	141	124	37	24	66	54

Definition of abbreviation: CVD = cardiovascular disease.

Table A5.4: Correlations (by season, 1-hour average) (Reprinted from Gryparis *et al.* (2004) with permission of the American Thoracic Society. Copyright © 2015 American Thoracic Society. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society)

Table E1: Seasonal ratio of 1-hour to 8-hour ozone and seasonal correlations between 1-hour ozone and other pollutants.

	Ratio		Correlations							
	Ozone 1-hour/ 8-hours		CO		SO_2		NO_2 1-hour		PM_{10}	
City	Winter	Summer	Winter	Summer	Winter	Summer	Winter	Summer	Winter	Summer
Athens	1.32	1.25	-0.09	0.00	-0.19	0.08	0.41	0.35	0.06	0.30
Barcelona	1.42	1.23	-0.34	0.08	-0.06	0.04	0.27	0.42	0.08	0.13
Basel	1.34	1.17	-0.60	0.00	-0.34	0.14	0.05	0.37	-0.49	0.46
Birmingham	1.26	1.21	-0.47	-0.06	-0.49	-0.01	-0.29	0.44	-0.55	0.31
Budapest	1.16	1.11	-0.05	0.04	-0.36	0.27	0.11	0.48	0.02	0.50
Erfurt	-	-	-	-	-0.27	0.12	0.02	0.45	-0.35	0.36
Geneva	1.41	1.20	-0.35	-0.09	-0.35	-0.05	0.13	0.56	-0.30	0.44
Helsinki	1.13	1.14	-0.35	-0.38	-0.34	-0.10	0.15	0.13	0.10	0.35
Ljubljana	2.51	1.96	-0.25	-0.15	-0.14	0.12	0.11	0.32	-	-
London	1.36	1.28	-0.52	0.06	-0.50	0.38	-0.31	0.51	-0.54	0.52
Lyon	1.80	1.37	-0.26	-0.21	-0.30	0.17	0.07	0.30	-0.28	0.31
Madrid	1.49	1.27	-	-	-0.35	0.00	-0.15	0.44	-0.40	0.22
Milan	1.45	1.28	-0.23	-0.46	-0.31	-0.35	0.01	0.21	-0.08	0.02
Netherlands	1.31	1.17	-0.58	0.11	-0.46	0.31	-0.32	0.37	-0.51	0.51
Paris	1.50	1.24	-	-	-0.52	-0.08	0.06	0.45	-0.43	0.06
Prague	1.36	1.16	-0.11	0.01	-0.11	0.01	0.16	0.46	0.03	0.37
Rome	2.05	1.95	-0.49	-0.39	-0.33	-0.22	0.25	0.04	0.10	0.14
Stockholm	1.10	1.11	-0.38	-0.02	-0.22	0.16	1.09	0.24	0.27	0.68
Tel-Aviv	-	-	-	-	-0.47	-0.18	-	-	-0.07	-0.10
Teplice	1.28	1.13	-0.16	0.25	-0.37	-0.22	-0.01	0.38	-0.25	0.21
Torino	1.42	1.17	-0.29	-0.36	-0.30	-0.33	0.11	0.30	0.00	0.12
Valencia	1.38	1.25	-0.32	0.04	-0.19	0.12	-0.29	-0.26	-	-
Zurich	1.36	1.17	-0.42	-0.04	-0.31	-0.16	0.11	0.54	-0.40	0.39

Table A5.5: Multi-pollutant models (by season) (Reprinted from Gryparis A, *et al.* (2004) with permission of the American Thoracic Society. Copyright © 2015 American Thoracic Society. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society)

TABLE 2. POOLED* ESTIMATES FOR THE INCREASE IN THE TOTAL DAILY NUMBER OF DEATHS ASSOCIATED WITH 1- AND 8-HOUR OZONE INCREASES OF 10-μg/m³ (AVERAGE OF LAGS 0 AND 1) ADJUSTING ALTERNATIVELY FOR OTHER POLLUTANTS IN TWO POLLUTANT MODELS

Other Pollutant (Number of Cities)†		Ozone (*h*)	Summer Period Increase % (*95% CI*)		Winter Period Increase % (*95% CI*)	
			FE Model	RE Model	FE Model	RE Model
None	(21)	1	0.33 (0.24, 0.45)	0.33 (0.17, 0.52)	0.08 (−0.09, 0.18)	0.09 (−0.25, 0.28)
	(21)	8	0.34 (0.27, 0.50)	0.31 (0.17, 0.52)	0.13 (−0.03, 0.29)	0.12 (−0.12, 0.37)
SO_2	(21)	1	0.34 (0.26, 0.46)	0.33 (0.18, 0.50)	0.22 (0.07, 0.36)	0.23 (−0.02, 0.47)
	(21)	8	0.33 (0.22, 0.47)	0.31 (0.13, 0.51)	0.28 (0.10, 0.45)	0.29 (−0.01, 0.55)
NO_2	(21)	1	0.22 (0.14, 0.35)	0.24 (0.09, 0.40)	0.09 (−0.09, 0.20)	0.07 (−0.19, 0.30)
	(21)	8	0.23 (0.12, 0.38)	0.23 (0.07, 0.41)	0.12 (−0.04, 0.29)	0.07 (−0.20, 0.39)
PM_{10}	(19)	1	0.25 (0.16, 0.40)	0.27 (0.10, 0.47)	0.27 (0.09, 0.41)	0.21 (−0.07, 0.48)
	(19)	8	0.25 (0.13, 0.40)	0.27 (0.08, 0.49)	0.35 (0.12, 0.51)	0.22 (−0.08, 0.51)
CO	(19)	1	0.44 (0.33, 0.56)	0.43 (0.30, 0.58)	0.22 (0.06, 0.38)	0.25 (0.02, 0.48)
	(19)	8	0.44 (0.30, 0.57)	0.44 (0.29, 0.59)	0.28 (0.08, 0.46)	0.34 (0.04, 0.59)

Definition of abbreviations: CI = confidence interval; FE = fixed effects; PM_{10} = particulate matter with aerodynamic diameter less than 10 μm; RE = random effects.

*The combined estimates were calculated using a multivariate second-stage regression program.

† Without Erfurt and Tel-Aviv for ozone 1 hour.

The PAPA (Public Health and Air Pollution in Asia) study (Wong *et al.,* 2008) did not provide a pooled multi-pollutant model result but did examine multi-pollutant models in the individual cities in the associated Health Effects Institute report Parts 1–5 (Kan *et al.,* 2010; Qian *et al.,* 2010; Vichit-Vadakan *et al.,* 2010; Wong *et al.,* 2010a,b). Negative correlations were less common in this dataset of tropical cities (Table A5.7). Adjustment for NO_2 made the most difference in the multi-pollutant models (Table A5.8) but adjustment for PM_{10}, and sometimes SO_2, also made a difference. The results for Wuhan (Qian *et al.,* 2010) are interesting in that they also stratified by temperature. At high temperatures, while the estimates were still reduced they remained significant, with the exception of the estimate adjusted for NO_2 which was marginally insignificant. The degree to which this is relevant to a future climate in the UK needs further discussion but it can be noted that Wuhan does not have a maritime climate.

The study by Simpson *et al.* (1997) does not provide multi-pollutant model results for 8-hour average ozone but does for 1-hour average ozone adjusted for bsp[22]. The correlation with bsp was small but positive (Table A5.9). Adjustment for bsp reduced the estimate slightly but the association remained positive and statistically significant (Table A5.10).

22 Particles measured by light scattering (nephelometry).

Table A5.6: Multi-pollutant models (APHENA; all year, 1-hour average) (Reprinted with permission from Katsouyanni *et al.*, 2009)

Table 14. Europe: Percentage Change in All-Cause Mortality per 10-μg/m^3 Increase in O_3

Seasonality Control	Average of Lags 0–1		Lag 1		Distributed Lags	
	Penalized Splines % (95% CI)	Natural Splines % (95% CI)	Penalized Splines % (95% CI)	Natural Splines % (95% CI)	Penalized Splines % (95% CI)	Natural Splines % (95% CI)
O_3 Results						
All ages						
3 *df*/year	−0.02 (−0.18, 0.14)	0.13 (0.00, 0.26)	0.02 (−0.10, 0.14)	0.14 (0.06, 0.22)	0.06 (−0.12, 0.24)	0.18 (0.02, 0.35)
8 *df*/year	0.18 (0.07, 0.30)	0.17 (0.05, 0.28)	0.17 (0.09, 0.25)	0.13 (0.05, 0.21)	0.25 (0.10, 0.40)	0.21 (0.06, 0.37)
12 *df*/year	0.17 (0.04, 0.30)	0.12 (−0.02, 0.26)	0.16 (0.08, 0.24)	0.10 (0.01, 0.20)	0.24 (0.09, 0.39)	0.17 (0.02, 0.33)
PACF	0.10 (−0.02, 0.22)	0.12 (−0.01, 0.24)	0.09 (0.01, 0.17)	0.09 (0.01, 0.17)	0.14 (−0.01, 0.29)	0.16 (0.01, 0.31)
≥ 75 Years						
3 *df*/year	−0.09 (−0.30, 0.11)	0.09 (−0.10, 0.27)	−0.02 (−0.17, 0.13)	0.10 (−0.03, 0.23)	−0.04 (−0.27, 0.20)	0.08 (−0.16, 0.31)
8 *df*/year	0.12 (−0.02, 0.26)	0.11 (−0.05, 0.26)	0.14 (0.04, 0.24)	0.10 (−0.02, 0.21)	0.17 (−0.03, 0.37)	0.11 (−0.10, 0.31)
12 *df*/year	0.11 (−0.04, 0.26)	0.07 (−0.12, 0.25)	0.13 (0.02, 0.24)	0.08 (−0.06, 0.21)	0.15 (−0.04, 0.34)	0.05 (−0.15, 0.27)
PACF	0.00 (−0.17, 0.17)	0.11 (−0.07, 0.30)	0.04 (−0.09, 0.16)	0.07 (−0.07, 0.21)	0.11 (−0.07, 0.29)	0.09 (−0.11, 0.29)
< 75 Years						
3 *df*/year	0.13 (−0.02, 0.29)	0.25 (0.10, 0.40)	0.13 (0.03, 0.24)	0.22 (0.11, 0.33)	0.22 (0.00, 0.44)	0.33 (0.11, 0.56)
8 *df*/year	0.25 (0.10, 0.40)	0.29 (0.14, 0.44)	0.18 (0.07, 0.29)	0.20 (0.08, 0.32)	0.37 (0.14, 0.59)	0.35 (0.12, 0.57)
12 *df*/year	0.23 (0.06, 0.40)	0.27 (0.12, 0.42)	0.17 (0.06, 0.28)	0.18 (0.06, 0.30)	0.36 (0.14, 0.59)	0.33 (0.10, 0.55)
PACF	0.15 (−0.03, 0.32)	0.22 (0.07, 0.37)	0.15 (0.04, 0.26)	0.18 (0.07, 0.29)	0.24 (0.02, 0.47)	0.29 (0.07, 0.52)
Controlling for PM_{10}						
All ages						
3 *df*/year	0.03 (−0.14, 0.19)	0.15 (0.00, 0.30)	0.07 (−0.05, 0.20)	0.17 (0.07, 0.27)		
8 *df*/year	0.21 (0.10, 0.31)	0.18 (0.07, 0.29)	0.19 (0.10, 0.28)	0.16 (0.06, 0.25)		
12 *df*/year	0.17 (0.07, 0.28)	0.10 (−0.01, 0.21)	0.16 (0.08, 0.25)	0.09 (0.00, 0.18)		
PACF	0.09 (−0.01, 0.19)	0.11 (−0.02, 0.23)	0.09 (0.00, 0.18)	0.10 (0.02, 0.19)		
≥ 75 Years						
3 *df*/year	−0.01 (−0.20, 0.18)	0.13 (−0.03, 0.30)	0.06 (−0.09, 0.21)	0.15 (0.02, 0.29)		
8 *df*/year	0.14 (0.00, 0.27)	0.10 (−0.04, 0.24)	0.16 (0.05, 0.28)	0.12 (0.00, 0.23)		
12 *df*/year	0.10 (−0.04, 0.23)	0.02 (−0.15, 0.19)	0.13 (0.02, 0.25)	0.06 (−0.08, 0.19)		
PACF	0.00 (−0.14, 0.14)	0.08 (−0.09, 0.26)	0.05 (−0.07, 0.16)	0.10 (−0.03, 0.23)		
< 75 Years						
3 *df*/year	0.15 (−0.05, 0.36)	0.23 (0.02, 0.44)	0.16 (0.02, 0.31)	0.24 (0.11, 0.37)		
8 *df*/year	0.31 (0.14, 0.47)	0.30 (0.12, 0.47)	0.24 (0.12, 0.37)	0.23 (0.10, 0.36)		
12 *df*/year	0.31 (0.15, 0.47)	0.25 (0.09, 0.42)	0.23 (0.10, 0.36)	0.18 (0.04, 0.31)		
PACF	0.15 (−0.05, 0.34)	0.24 (0.06, 0.42)	0.19 (0.06, 0.31)	0.22 (0.09, 0.34)		

Table A5.7: Correlations between pollutants from PAPA studies

	Concentration range O_3 Mean, min, max µg/m³	Correlation with PM_{10}	Correlation with SO_2	Correlation with NO_2	Correlation with temperature	Correlation with relative humidity
Shanghai	63.3, 5.3, 251.3	0.19	0.14	0.01	0.48	–0.35
Wuhan	85.7, 1, 258.5	0.09	0.16	0.20	Not given	Not given
Hong Kong (correlation range across stations)	36.9. –8.2[a], 196.6	0.44 to 0.55	–0.25 to 0.15	–0.07 to 0.41	Not given	Not given
Bangkok	59.4, 8.2, 180.6	0.55	0.18	0.62	Not given	Not given

Table A5.8: Multi-pollutant and single-pollutant models from cities contributing to multi-city PAPA study estimate in Table A5.1 (all-cause mortality) % change per 10 µg/m³ 8-hour average ozone

	O_3 single-pollutant	With PM_{10}	With SO_2	With NO_2
Shanghai	**0.31 (0.04, 0.58)**	0.19 (–0.08, 0.47)	0.21 (–0.06, 0.49)	0.13 (–0.15, 0.69)
Wuhan	0.29 (–0.05, 0.63)	0.24 (–0.10, 0.58)	0.16 (–0.19, 0.50)	0.10 (–0.24, 0.44)
	Stratified by temp * † Low 0.68 (–0.83, 2.21)	Stratified by temp * Low 0.52 (–0.98, 2.04)	Stratified by temp * Low 0.38 (–1.12, 1.90)	Stratified by temp * Low 0.33 (–1.16, 1.85)
	Normal 0.19 (–0.15, 0.54)	Normal 0.16 (–0.18, 0.50)	Normal 0.06 (–0.29, 0.41)	Normal 0.02 (–0.33, 0.36)
	High **1.41 (0.23, 2.61)**	High **1.20 (0.02, 2.39)**	High **1.25 (0.07, 2.44)**	High 1.10 (–0.07, 2.29)
Hong Kong (multi-pollutant models in graph)	0.34 (0.02, 0.66)	Attenuated to null (Part 5)‡	Stable to adjustment (Part 5)	Attenuated to null (Part 5)
Bangkok	**0.6 (0.3, 0.9)**	0.2 (–0.2, 0.5)	Stable to adjustment (Part 5)	Substantially reduced (Part 5)

* Mean temperature Low 2.2, Normal 18.0, High 33.1°C
† P-value for interaction 0.049 single-pollutant model. Other pollutants were low on high temperature days
‡ Part 5 refers to the HEI report by Wong (2010b)

Table A5.9: Correlations between pollutants in Brisbane (Simpson *et al.*, 1997)

Season	Concentration range 8 hr O_3 Mean, min, max µg/m³	Correlation with bsp	Correlation with SO_2	Correlation with NO_2 (24 hour)	Correlation with temperature (min)	Correlation with temperature (max)	Correlation with relative humidity
All year	35.5, 3.3, 124.3	0.224	–0.106	0.042	0.059	0.375	–0.336
Summer	39.6, 5.3, 124.3	0.424	0.005	0.333	–0.21	0.281	–0.304
Winter	31.6, 3.3, 111.5	0.192	–0.182	0.036	–0.105	0.333	–0.338
Data also available for 1 hour O_3, and correlations 1 hour and 8 hr O_3 with 1 horr NO_2							

Table A5.10: Multi-pollutant and single-pollutant models from Brisbane (Simpson *et al.*, 1997) (1-hour average) (all-cause mortality) % change per 10 µg/m³

	O_3 single-pollutant 1-hour average	With bsp
Brisbane	**0.79 (0.30, 1.28)**	**0.71 (0.12, 1.31)**
Interaction 1 hour O_3 and bsp not significant.		

In summary, the pooled single-pollutant estimate for 8-hour average ozone and all-cause mortality is derived from studies which indicate that other pollutants are contributing to the size of the effect. The degree to which this is true is hard to summarise in quantitative terms because:

a Several studies do not provide multi-pollutant model results

b Of those that do, multi-pollutant models are often examined only for some of the pollutants analysed in the study

c Even where the same adjustment pollutant has been used, the effect of the adjustment will be different according to the correlation pattern between pollutants, which can also differ by season

d In general, multi-pollutant models can be affected by differential measurement error between pollutants (WHO, 2013), with pollutants with less measurement error coming through more strongly

Bearing the above in mind, the following points can be noted:

a Where results adjusted for NO_2 were available, the estimate was always reduced and was no longer statistically significant (although the reduction in the estimate is more important than the presence or absence of statistical significance which can be due to smaller numbers of days with measurements of both pollutants)

b Adjustment for particles, where available, did not always use the same metric. The effect of adjustment varied including stability to adjustment, reducing the estimate to null, smaller reductions to the estimate and even increasing the estimate. This probably depends on the correlation pattern between ozone and the specific particle metrics in the study location

c There was only one example with adjustment for CO alone but this increased the estimate substantially

d The effects of adjustment for other pollutants could vary by season and by stratification by temperature. This is again probably due to different correlation patterns and also to the concentrations of ozone relative to those of the other pollutants

In conclusion, the single-pollutant model concentration-response function for ozone is reflecting both ozone and other pollutants to a greater or lesser extent and adjustment may both increase and decrease the estimate. The investigation of multi-pollutant model results is not sufficiently comprehensive to pool the results and the appropriate way to do this is not obvious. An effect of ozone is plausible (see other sections). Multi-pollutant model results have their own uncertainties and there are more single-pollutant than multi-pollutant model results available. Application of a single-pollutant model ozone concentration-response relationship in health impact assessment will need to acknowledge the uncertainties regarding the exact size of the estimate.

A5.2 Cardiovascular admissions

The main report discusses the findings, for 8-hour mean ozone, of effects on cardiovascular mortality but not cardiovascular admissions (Table A5.11). A pooled estimate of a 0.11% (–0.06, 0.27) increase in cardiovascular admissions all ages was found but this was not statistically significant. There was no heterogeneity. The data are presented as a forest plot in Figure A5.2. A positive association with confidence intervals above zero was found for 1-hour mean ozone.

One of the key issues in discussing this finding is whether the weak evidence on cardiovascular admissions is a result of a true lack of an effect, or whether negative confounding is masking an effect. It could be asked why this should particularly be the case for cardiovascular admissions and not for other outcomes. There could be an explanation if there was a real effect of ozone on cardiovascular admissions but it was small relative to the effect of particles on cardiovascular admissions, for example. If ozone has a stronger effect on respiratory admissions than cardiovascular admissions then the implications of negative correlations with other pollutants could be less important for respiratory admissions, eg it could affect the size but not the direction of the effect. Conversely, the pollutants with which ozone is negatively correlated could have greater effects on cardiovascular than respiratory admissions. A lack of masking of the effect on cardiovascular admissions, but not cardiovascular mortality, would require either a greater effect of ozone on cardiovascular mortality than cardiovascular admissions (for which some theories can be put forward), or for a negatively correlated pollutant to have a greater effect on cardiovascular admissions than cardiovascular mortality.

Unfortunately, none of the studies selected to derive the pooled estimate analysed results using multi-pollutant models. Article authors tend to apply multi-pollutant models to test if a positive and statistically significant effect is maintained after adjustment for other pollutants. There is much less awareness of the fact that adjustment for a pollutant that is negatively correlated with ozone could reveal an association that was not previously apparent. Some studies did provide information on correlations between ozone and other pollutants (Table A5.12). This did show many negative correlations so the possibility of a masked association between ozone and cardiovascular admissions remains.

Table A5.11: 8-hour average ozone and all cardiovascular admissions – single-pollutant models from studies used for pooled estimate

WHO region	Study location	Author/name/	Study period	Concentration range Mean, min, max µg/m³	Lag	Estimate (single-pollutant model) % change per 10 µg/m³ 8-hour average ozone	Weight in regional single city meta-analysis	Pooled single city regional estimate	Weight in overall single city meta-analysis
Eur A	8 French cities	Larrieu (2007)	1998–2003	Range of summer means 68.4–106.1*	0–1	0.00 (–0.30, 0.30)			30%
Eur A	Valencia	Ballester (2001)	1994–1996	45.9, 10.2, 125	2	–0.95 (–2.90, 1.04)	4.9%	0.19 (–0.26, 0.65)	13.3%
Eur A	London	Atkinson (1999)	1992–1994	34.3, 3.7, 156.6	2	0.45 (0.04, 0.87)	51.7%		
Eur A	West Midlands	Anderson (2001)	1994–1996	47, 0.8, 176.2	0–1	0.02 (–0.48, 0.51)	43.4%		
Wpr A	Brisbane	Petroeschevsky (2001)	1987–1994	37.2, 3.3, 126.8	3	–0.65 (–1.46, 0.16)	49.7%	–0.19 (–1.09, 0.73)	3.3%
Wpr A	Perth	Hinwood (2006)	1992–1998	50.8, 10th %ile 37.0, 90th %ile 66.8	3	0.28 (–0.53, 1.08)	50.3%		
WprB	3 Taiwanese cities	Chang (2002)	1997–1999	*74.2, 9.8, 189.3*	3	0.45 (–0.20, 1.11)			6.4%
WprB	Hong Kong	Thach (2010)	1996–2002	Mean 36.9, SD 23	0–1	0.12 (–0.12, 0.36)			47%
Pooled estimate (multi-city studies plus single-city studies pooled by region (n = 5) 0.11 (–0.06, 0.27) % change per 10 µg/m³ I^2 0% (heterogeneity across the pooled single-city regional estimates and the multi-city estimates) * While only summer means were given in the pollutant concentration table, there was no indication that the concentration-response function was for the summer only									

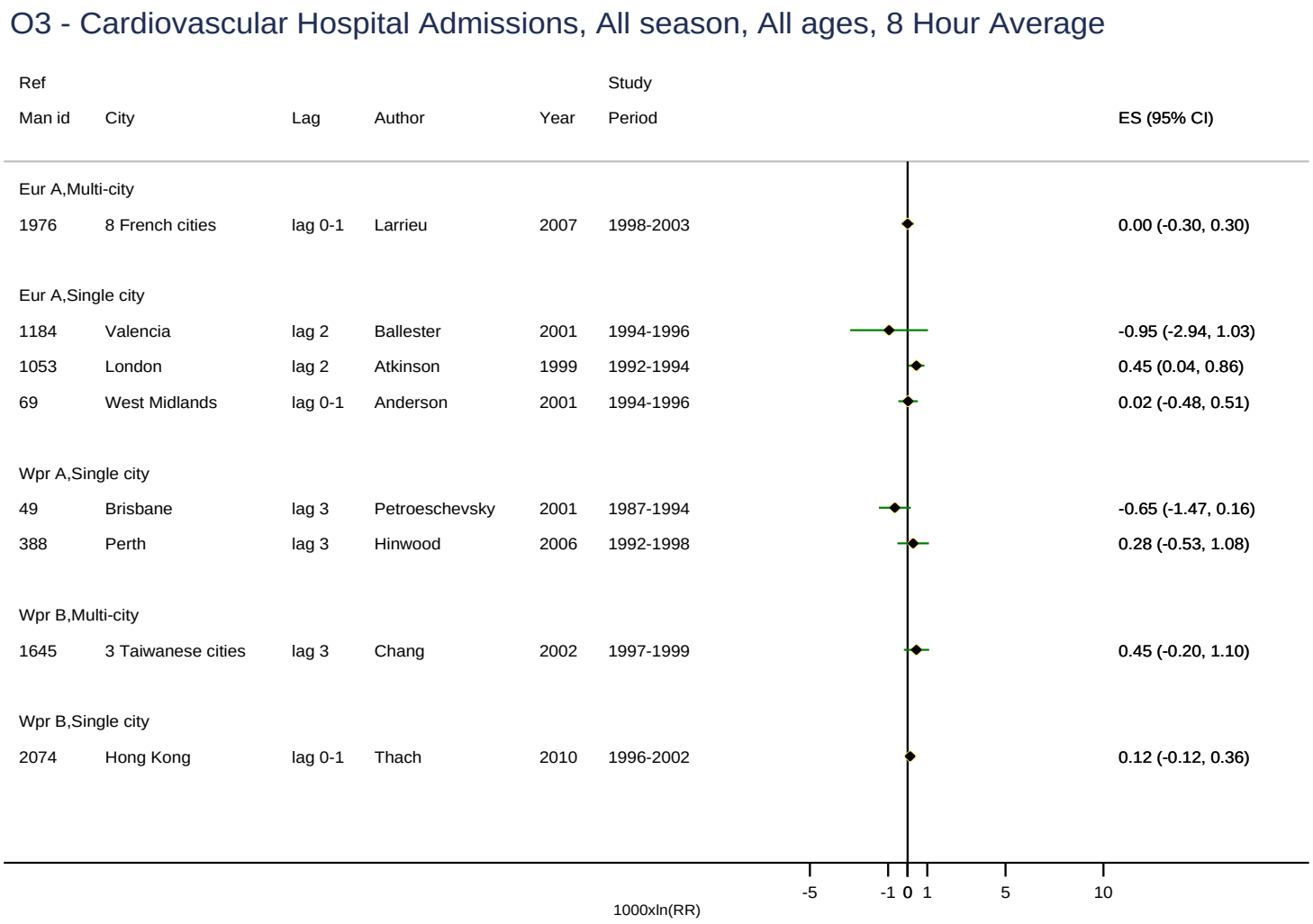

Figure A5.2: Ozone – cardiovascular hospital admissions, for all seasons and all ages – 8-hour average

Table A5.12: Correlations between pollutants from studies in Table A5.11 (all cardiovascular admissions) (where available)

	Concentration range O_3 Mean, min, max µg/m³	Correlation with PM_{10}	Correlation with $PM_{2.5}$	Correlation with $PM_{10-2.5}$	Correlation with black smoke	Correlation with SO_4^{2-}	Correlation with NO_2	Correlation with SO_2	Correlation with CO	Correlation with temp/humidity
Valencia	45.9, 10.2, 125				–0.57		–0.1	–0.35	–0.26	0.45/–0.1
London	34.3, 3.7, 156.6	Negative (weak positive in summer)					Negative (weak positive in summer)	Negative (weak positive in summer)	Negative (weak positive in summer)	
West Midlands	47, 0.8, 176.2	–0.06	–0.11	0.19	–0.35	0.00	0.08	–0.22	–0.29	0.44/–0.59
Perth	50.8, 10th %ile 37.0, 90th %ile 66.8	0.01 (bsp)	0.16				–0.06		0.00	0.2/–0.12
3 Taiwanese cities	*74.2, 9.8, 189.3*	0.55					0.36/0.45 (24 h/1 h)	0.49		

A5.3 Respiratory admissions

The association between 8-hour average ozone and respiratory hospital admissions is positive and statistically significant. There was substantial heterogeneity (I^2 82.8%). The forest plot is presented in Figure A5.3.

As with all-cause mortality, not all studies included multi-pollutant models. Of the ten studies, four included multi-pollutant models adjusted for other pollutants (Table A5.16). One adjusted for several pollutants at once and found a very large increase, but it is unclear whether adjusting for several pollutants at once results in a stable estimate. Two others also found increases on adjustment for PM_{10}. The study in Brisbane adjusted for high levels of bsp or SO_2 and found some reduction in the estimate which remained statistically significant on adjustment for high SO_2 and just lost significance on adjustment for bsp. Some studies present information on correlations with other pollutants even if they do not include multi-pollutant model results. Several of these correlations are negative (Table A5.15).

In summary, there is some suggestion that the associations with respiratory hospital admissions are robust to adjustment for other pollutants (mainly particles) but there are no studies examining adjustment for NO_2 or CO alone. The latter two seemed important for all-cause mortality.

Table A5.13: 8-hour average ozone and all respiratory admissions – single-pollutant models from studies used for pooled estimate

WHO region	Study location	Author/name/	Study period	Concentration range Mean, min, max µg/m³	Lag	Estimate (single-pollutant model) % change per 10 µg/m³ 8-hour average ozone	Weight in regional single city meta-analysis	Pooled single city regional estimate	Weight in overall single city meta-analysis
Eur A	Nicosia	Middleton (2008)	1995–2004	See Table A5.14	2	0.36 (–0.88, 1.62)	25.1%	0.14 (–0.22, 0.51)	26.9%
Eur A	Paris	Dab (1996)	1987–1992	27.7, 5th %ile 3.0, 99th %ile 110	0	0.24 (–0.25, 0.73)	27.0%		
Eur A	Rome	Fusco (2001)	1995–1997	27, 25th %ile 13.3, 75th %ile 37.2	1	0.87 (–0.17, 1.93)	7.4%		
Eur A	London	Atkinson (1999)	1992–1994	34.3, 3.7, 156.6	1	0.23 (–0.20, 0.67)	30.3%		
Eur A	West Midlands	Anderson (2001)	1994–1996	47, 0.8, 176.2	0–1	–0.42 (–0.95, 0.10)	10.1%		
Sear D	Delhi	Jayaraman (2008)	2004–2005	21.5, 10, 50	5	3.30 (1.90, 4.72)			8.0%
Wpr A	Brisbane	Petroeschevsky (2001)	1987–1994	37.2, 3.3, 126.8	2	1.14 (0.15, 2.15)	49.9%	0.07 (–2.01, 2.18)	4.0%
Wpr A	Perth	Hinwood (2006)	1992–1998	50.8, 10th %ile 37.0, 90th %ile 66.8	1	–1.00 (–1.94, –0.04)	50.1%		
WprB	3 Taiwanese cities	Chang (2002)	1997–1999	*74.2, 9.8, 189.3*	3	0.65 (0.45, 0.85)			30.9%
WprB	Hong Kong	Thach (2010)	1996–2002	Mean 36.9, SD 23	0–1	0.81 (0.58, 1.04)			30.3%
Pooled estimate (multi-city studies plus single-city studies pooled by region (n = 5) 0.75 (0.30, 1.20) % change per 10 µg/m³ I^2 82.8% (heterogeneity across the pooled single-city regional estimates and the multi-city estimates)									

Table A5.14: Ozone concentrations in Nicosia (Reproduced from Middleton *et al.*, 2008)

B. Levels of air pollutants, shown separately for cold and warm months[3]

		Number of Days (% of total days)[4]	Mean	SD	Min	5%	Median	95%	Max
Nicosia Central									
PM_{10} 24-hour average (µg/m³)	Cold	1553 (85.7%)	57.6	52.5	5.0	20.0	50.8	103.0	1370.6
	Warm	1664 (90.4%)	53.4	30.7	18.4	32.0	50.5	77.6	933.5
O_3 8-hour MA max (ppb)	Cold	1514 (83.6%)	28.7	12.6	3.7	9.9	27.5	50.2	63.6
	Warm	1692 (92.0%)	44.4	10.3	7.8	24.4	46.1	58.8	71.1
Ayia Marina[5]									
PM_{10} 24-hour average (µg/m³)	Cold	918 (84.5%)	25.9	28.0	6.3	9.3	19.0	62.3	553.2
	Warm	903 (81.8%)	35.7	40.5	8.1	16.0	30.9	58.9	952.4
O_3 8-hour MA max (ppb)	Cold	1155 (80.1%)	45.7	6.8	30.2	35.1	44.6	58.4	71.0
	Warm	1247 (84.7%)	54.9	8.2	28.9	40.6	55.2	68.1	78.7

O3 - All Respiratory Hospital Admissions, All season, All ages, 8 Hour Average

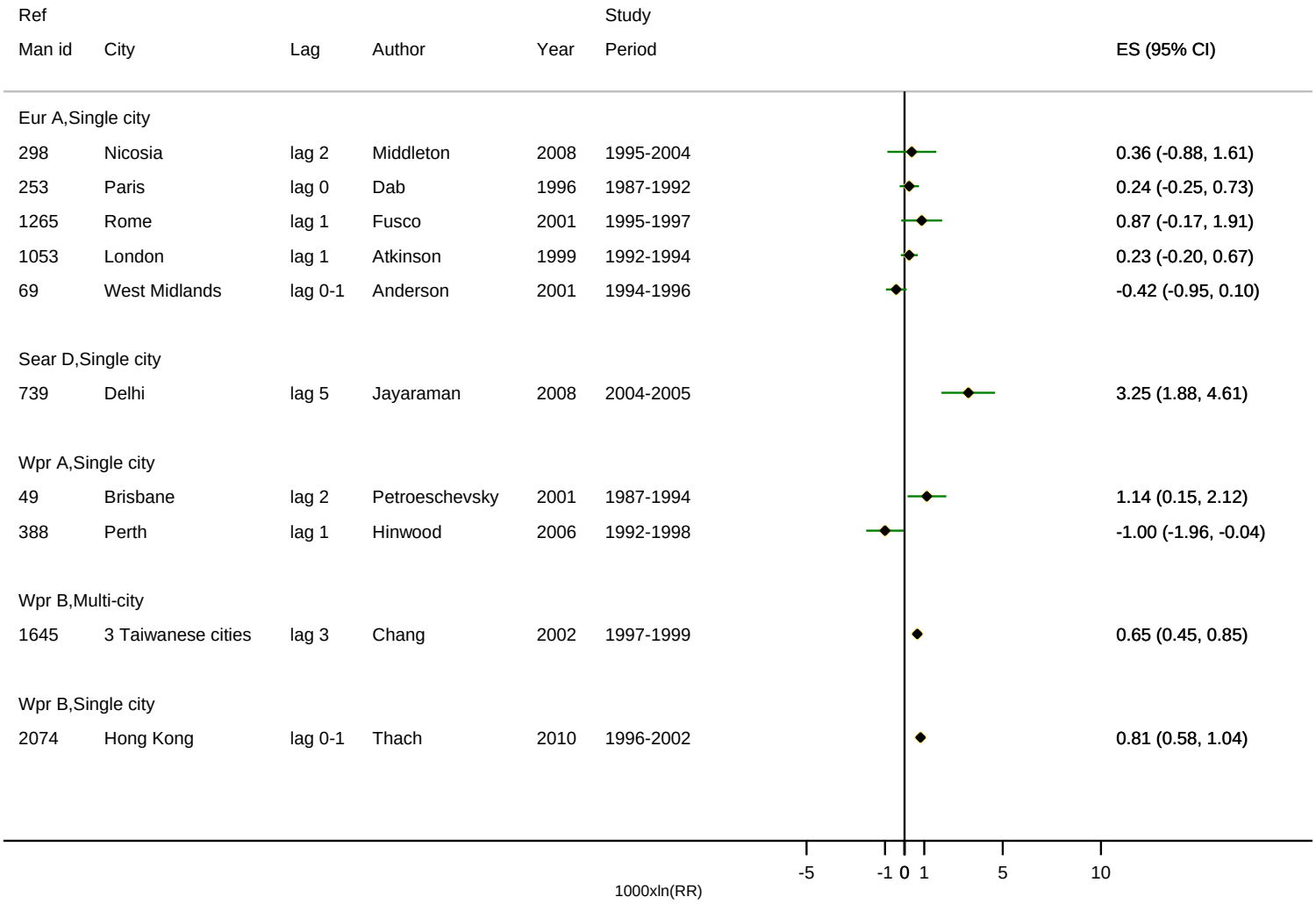

Figure A5.3: O3 – All respiratory hospital admissions, for all seasons and all ages, 8-hour average

Table A5.15: Correlations between pollutants from studies in Table A5.13 (all respiratory admissions) (where available)

	Concentration range O_3 Mean, min, max µg/m³	Correlation with PM_{10}	Correlation with $PM_{2.5}$	Correlation with $PM_{10-2.5}$	Correlation with black smoke	Correlation with SO_4^{2-}	Correlation with NO_2	Correlation with SO_2	Correlation with CO	Correlation with temp/humidity
Rome	27, 25th %ile 13.3, 75th %ile 37.2	–0.01					0.19	–0.35	–0.57	0.68/–0.55
London	34.3, 3.7, 156.6	Negative (weak positive in summer)					Negative (weak positive in summer)	Negative (weak positive in summer)	Negative (weak positive in summer)	
West Midlands	47, 0.8, 176.2	–0.06	–0.11	0.19	–0.35	0.00	0.08	–0.22	–0.29	0.44/–0.59
Delhi	21.5, 10, 50	0.273 (SPM)	0.299 (RSPM)				–0.137	–0.042	0.063	0.507/–0.548
Perth	50.8, 10th %ile 37.0, 90th %ile 66.8	0.01 (bsp)	0.16				–0.06		0.00	0.2/–0.12
3 Taiwanese cities	*74.2, 9.8, 189.3*	0.55					0.36/0.45 (24 h/1 h)	0.49		

SPM suspended particulate matter, RSPM respirable suspended particulate matter, bsp particles measured by light scattering (nephelometry)

Table A5.16: Multi-pollutant models from the same studies/averaging times compared with single-pollutant model results from studies in Table A5.13 (all respiratory admissions)

WHO region	Study location	Author/name/	Study period	Single or multi-pollutant model?	Lag	Estimate (single-pollutant model) % change per 10 µg/m³ 8-hour average ozone	Weight in regional single city meta-analysis*	Weight in overall single city meta-analysis*
Eur A	Nicosia	Middleton (2008)	1995–2004	Single	2	0.36 (–0.88, 1.62)	25.1%	26.9%
				With PM_{10} (in graph)	2	Increased slightly, remains non-significant		
Sear D	Delhi	Jayaraman (2008)	2004–2005	Single	5	3.30 (1.90, 4.72)		8.0%
				Adjusted for NO_2, CO, SO_2, SPM, RSPM	5	24.4 (16.9, 32.38)		
Wpr A	Brisbane	Petroeschevsky (2001)	1987–1994	Single	2	1.14 (0.15, 2.15)	49.9%	4.0%
				Adjusted for high bsp	2	1.05 (–0.1, 2.20)		
				Adjusted for high SO_2	2	1.09 (0.05, 2.15)		
WprB	3 Taiwanese cities	Chang (2002)	1997–1999	Single	3	0.65 (0.45, 0.85)		30.9%
				Adjusted for PM_{10}		Increased on adjustment		

* Percentages do not add up to 100 as only studies that examined multi-pollutant models are shown in this table.

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Appendix 6
Correlations of ozone concentrations in the UK with the concentration of other pollutants of relevance to health impact assessment

John Stedman

A6.1 Introduction

The COMEAP Working Group on Quantification of Effects of Ozone on Health has requested that some analysis of the correlations of ambient ozone concentrations with other pollutants and temperature be undertaken in order to provide background information to aid interpretation of its work on the quantification of effects of ozone on health. This appendix summarises the results of that specifically requested analysis using recent monitoring data.

A6.2 Methods

Three monitoring stations have been selected in order to cover a range of different situations:

a London North Kensington (Urban Background, south east England) 2013 data

b Harwell (Rural Background, south east England) 2012 data

c Edinburgh St Leonards (Urban Background, central Scotland) 2013 data

The magnitude of local sources of NO_X, NO_2 and primary PM decreases in the order London > Edinburgh > Harwell. The magnitude of the contribution from regional (largely secondary) PM decreases in the order London = Harwell > Edinburgh.

Daily data for the following air pollutant metrics have been extracted from http://uk-air.defra.gov.uk/:

a Daily maximum 8-hour running mean ozone concentration

b Daily mean NO_2 concentration

c Daily mean $PM_{2.5}$ concentration (by FDMS)

d Daily mean isoprene concentration

e Daily mean temperature (modelled value for the station)

f Daily maximum temperature (modelled value for the station)

Isoprene data from the London Eltham station were used for the London North Kensington analysis and isoprene data from the Auchencorth Moss station were used for the Edinburgh St Leonards analysis. 2012 monitoring data were used in preference to 2013 for the Harwell station due to low data capture in 2013.

Analysis was restricted to the subset of days at each station with valid data for all pollutants and modelled temperature, except at Harwell where low data capture for isoprene meant that isoprene could not be included in the correlation analysis.

Correlation coefficients between the different parameters were calculated for the full dataset at each station and also for three alternative ways of dividing the data into two groups that might be expected to show distinct characteristics:

a Days with daily maximum 8-hour running mean ozone concentration greater than or equal to 70 μg/m^3 versus days with daily maximum 8-hour running mean ozone concentration less than 70 μg/m^3. This concentration was chosen as a value reasonably representative of the annual mean hemispheric background concentration. This value is also often taken as a cut-off below which health impacts of ozone are not quantified. This value also corresponds to an approximate minimum in the $PM_{2.5}$ concentration when plotted as a scatter plot against daily maximum 8-hour running mean ozone concentration for the datasets examined here

b The warm months of April, May, June, July, August and September versus the cold months of January, February, March, October, November and December. Examination of the time series of daily maximum 8-hour running mean ozone concentrations confirmed that the highest ozone concentrations were largely confined to the warm period and the lowest values were largely confined to the cold period at London North Kensington and Harwell. The pattern was less clear at Edinburgh St Leonards

c Days with a maximum temperature of greater than or equal to 22°C versus days with a maximum temperature of less than 22°C. Examination of scatter plots of daily maximum of 8-hour running mean ozone concentration versus maximum daily temperature confirmed that the positive correlation of ozone with temperature was confined to days above about 20–22°C. 22°C was chosen as a cut-off point rather than 20°C as it led to higher positive correlations between ozone and NO_2 and between ozone and $PM_{2.5}$ than 20°C at London North Kensington and Edinburgh St Leonards

A6.3 Results

Table A6.1 shows the Pearson correlation coefficients between daily maximum 8-hour running mean ozone concentration and the other metrics.

London North Kensington

London North Kensington (London) shows a negative correlation between ozone and NO_2 and between ozone and $PM_{2.5}$ for all days. This negative correlation is stronger for low ozone (daily maximum 8-hour running mean ozone concentration less than 70 μg/m^3) days. There is a weak positive correlation between ozone and NO_2 and ozone and $PM_{2.5}$ for high ozone (daily maximum 8-hour running mean ozone concentration greater than or equal to 70 μg/m^3) days. There is no

correlation with NO_2 or $PM_{2.5}$ for summer days, the negative correlation is stronger for winter days than for all days. The positive correlation of ozone with NO_2 and with $PM_{2.5}$ is stronger for high temperature (daily maximum temperature greater than or equal to 22°C) days than for high ozone days.

Harwell

Harwell shows weaker negative correlations with NO_2 and with $PM_{2.5}$ for all days than London. The positive correlation of ozone with NO_2 and of ozone with $PM_{2.5}$ for high ozone days is stronger than for London and is stronger with $PM_{2.5}$ than with NO_2. The negative correlations are stronger for low ozone days than for all days, which is similar to London. There is a positive correlation of ozone with $PM_{2.5}$ for summer days, which is in contrast to the lack of correlation for London. The positive correlation with $PM_{2.5}$ is even stronger for high temperature days but the low number of days in this category should be noted.

Table A6.1: Correlation coefficients (values ≥ to a magnitude of 0.50 in bold)

London North Kensington 2013

	All days	Ozone ≥70	Ozone <70	Summer	Winter	Temp ≥ 22°C	Temp < 22°C
NO_2	**–0.54**	0.21	**–0.68**	–0.12	**–0.71**	0.27	**–0.68**
$PM_{2.5}$	–0.42	0.37	**–0.63**	–0.03	**–0.66**	0.49	**–0.58**
Isoprene	0.44	**0.62**	0.22	0.39	–0.40	**0.66**	–0.26
Average temp	**0.50**	**0.52**	0.38	0.18	0.06	0.46	0.32
Max temp	**0.55**	**0.55**	0.39	0.32	–0.04	**0.63**	0.37
Count	208	58	150	137	71	59	149

Harwell 2012

	All days	Ozone ≥70	Ozone <70	Summer	Winter	Temp ≥ 22°C	Temp < 22°C
NO_2	–0.27	0.43	**–0.76**	0.36	**–0.63**	0.48	**–0.63**
$PM_{2.5}$	–0.19	**0.51**	**–0.63**	**0.70**	–0.49	**0.80**	–0.49
Isoprene	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Average temp	**0.51**	**0.59**	0.39	0.17	0.43	0.06	0.43
Max temp	**0.54**	**0.67**	0.35	0.38	0.42	**0.61**	0.42
Count	180	63	117	67	113	17	163

Edinburgh St Leonards 2013

	All days	Ozone ≥70	Ozone <70	Summer	Winter	Temp ≥ 22°C	Temp < 22°C
NO_2	**–0.59**	–0.09	**–0.65**	–0.33	**–0.79**	0.13	**–0.61**
$PM_{2.5}$	–0.17	–0.05	–0.36	0.02	–0.29	**0.68**	–0.18
Isoprene	–0.10	–0.19	0.01	–0.17	–0.11	–0.05	–0.15
Average temp	–0.17	–0.32	0.17	**–0.59**	0.08	–0.44	–0.16
Max temp	–0.17	–0.25	0.12	**–0.54**	–0.02	–0.13	–0.17
Count	294	96	198	148	143	14	280

Edinburgh St Leonards

Edinburgh St Leonards (Edinburgh) shows weaker all-days negative correlations between ozone and $PM_{2.5}$ than London but similar all-days correlations for ozone and NO_2. There is no correlation between ozone and NO_2 or between ozone and $PM_{2.5}$ for high ozone days. There is a positive correlation between ozone and $PM_{2.5}$ but not between ozone and NO_2 on high temperature days but the low number of days in this category should be noted.

Negative correlations

Overall, any of the low ozone, winter or low temperature categories have a strong negative correlation between ozone and NO_2 and between ozone and $PM_{2.5}$ except for the weak negative correlations between ozone and $PM_{2.5}$ for Edinburgh.

Positive correlations

The categories leading to positive correlations of ozone with NO_2 or with $PM_{2.5}$ vary with location. Harwell shows positive correlations for high ozone days, summer days and high temperature days, while London shows positive correlations for high ozone days and high temperature days but not for summer days and Edinburgh only shows a strong positive correlation for high temperature days.

Figures A6.1 to A6.6 show scatter plots of the concentrations of ozone with NO_2 and ozone and $PM_{2.5}$ in London for the different categories of days. Figures A6.7 to A6.12 and Figures A6.13 to A6.18 show scatter plots for Harwell and Edinburgh.

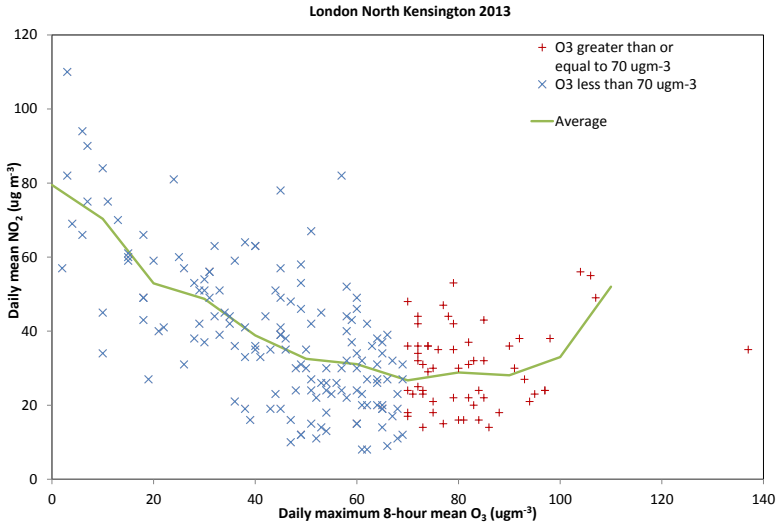
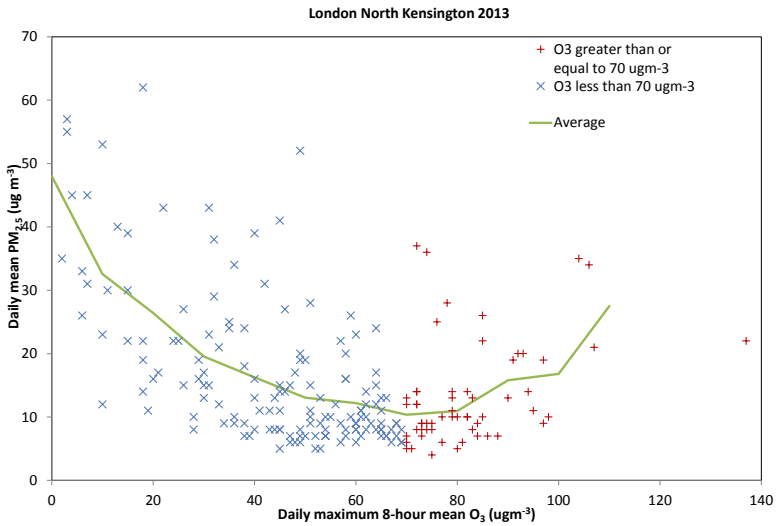


Figure A6.1



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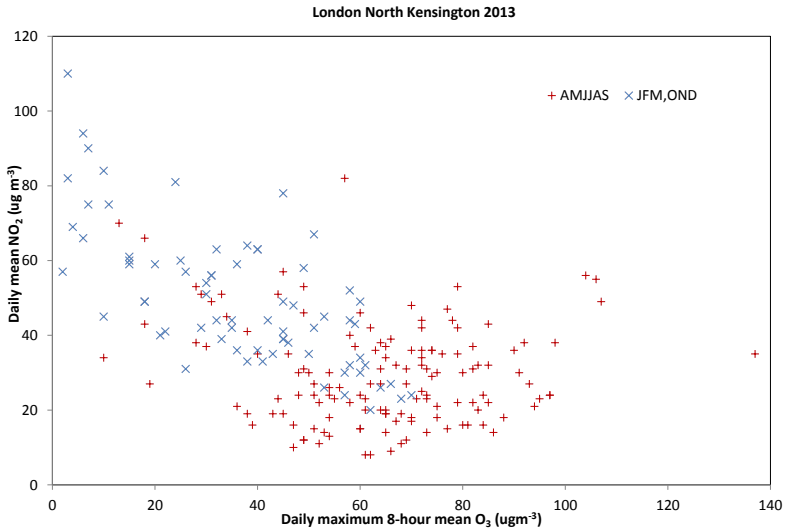

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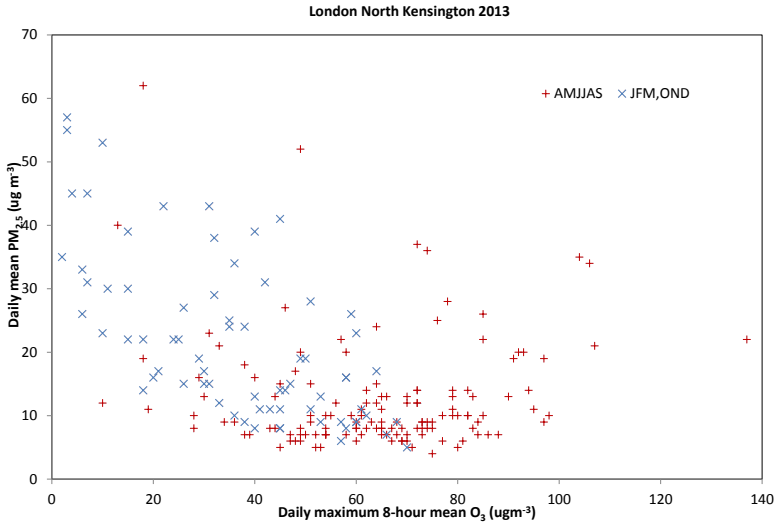

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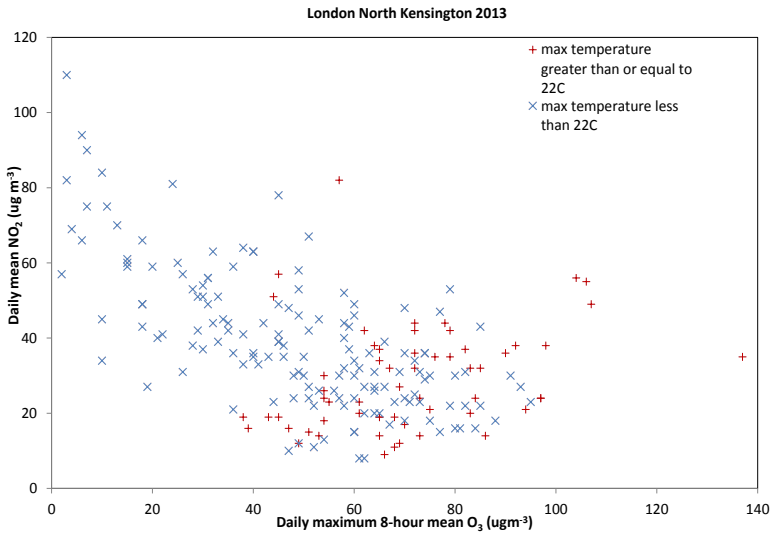

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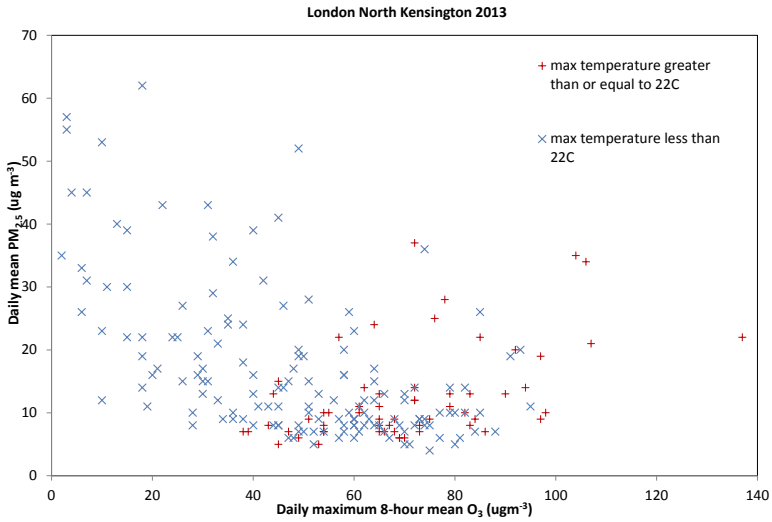

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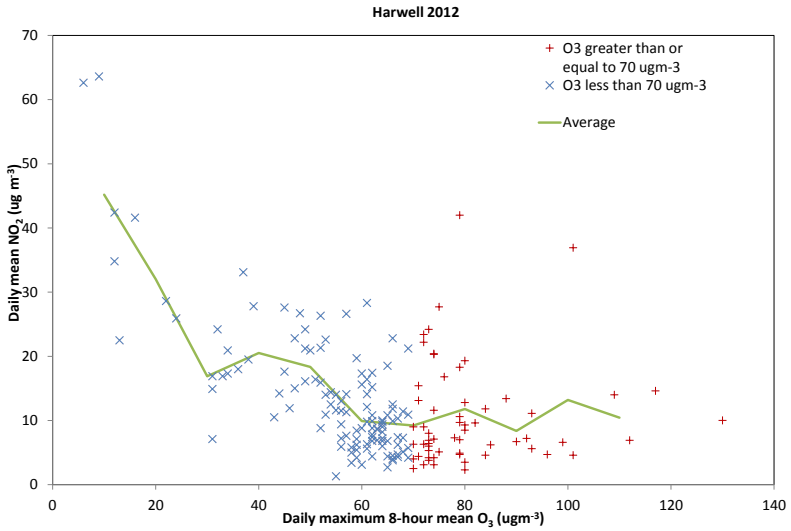

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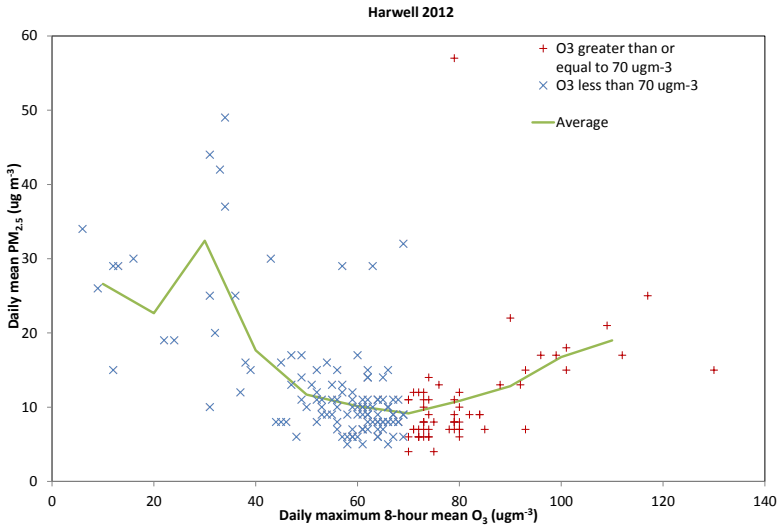

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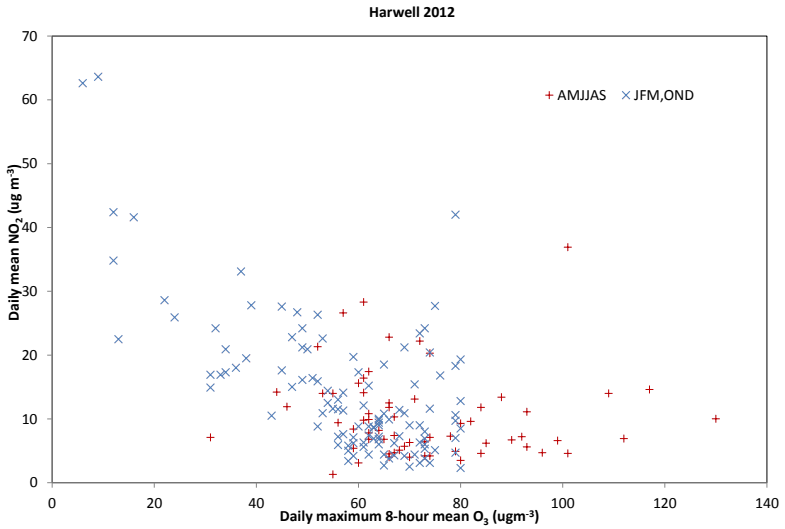

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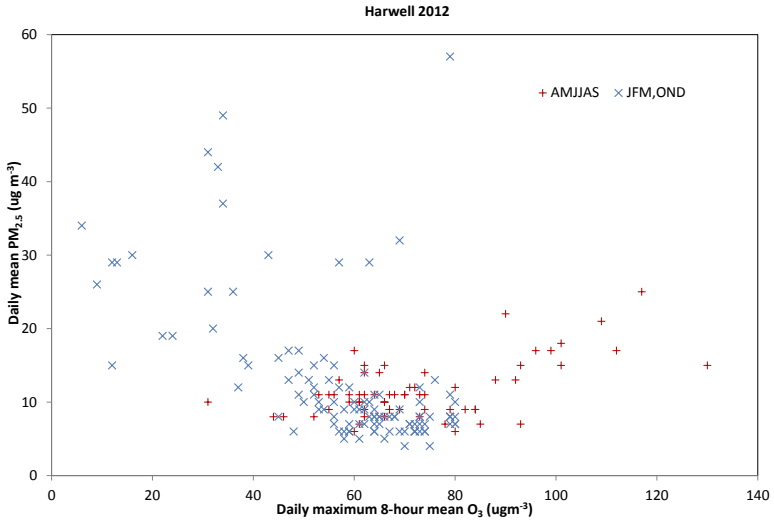

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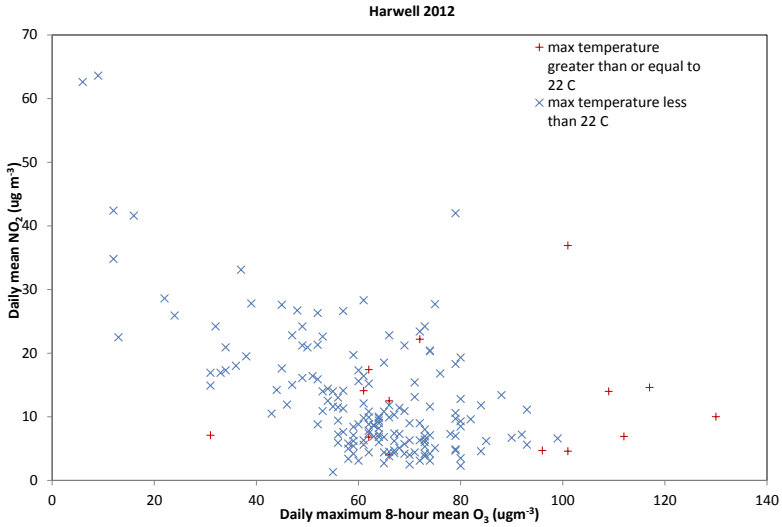

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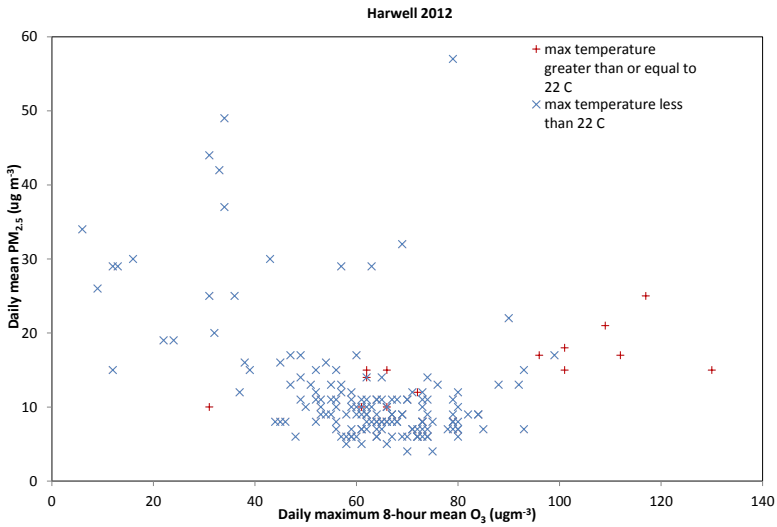

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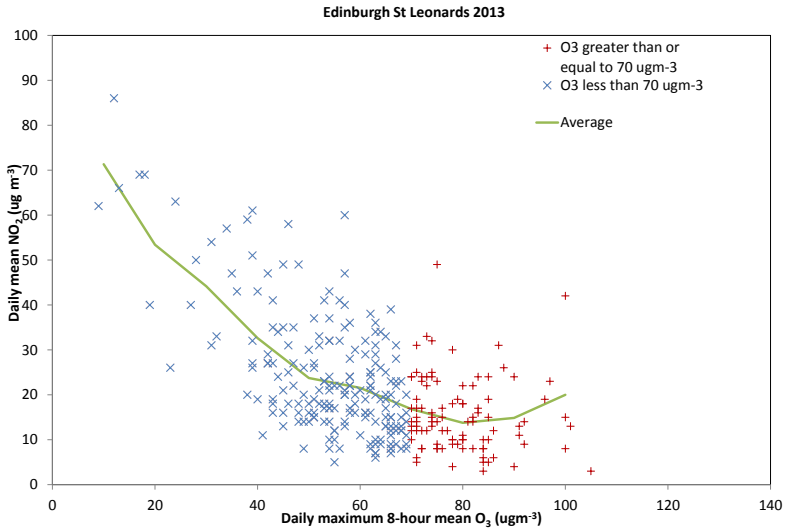

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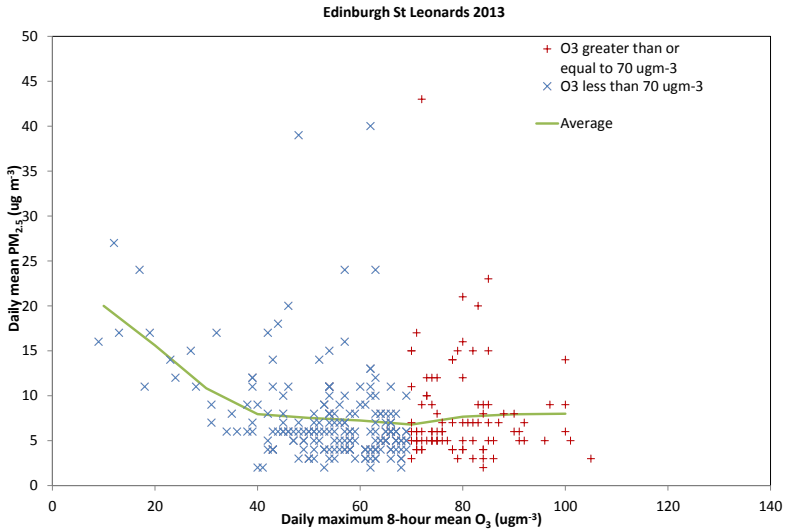

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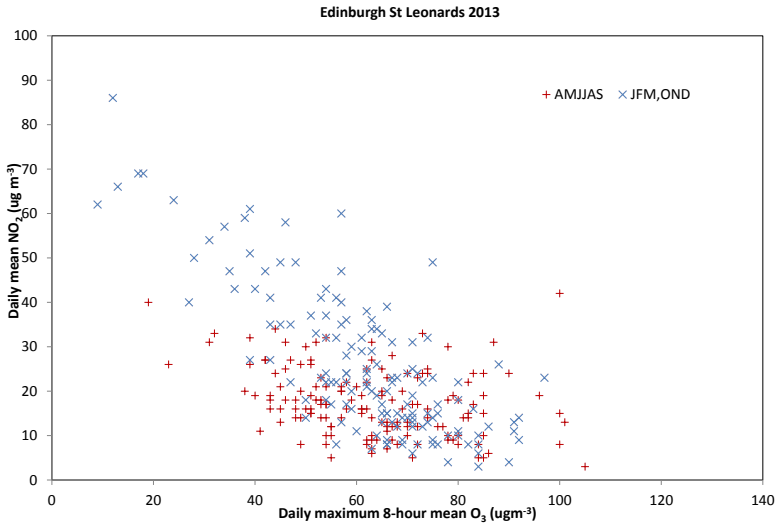

Figure A6.15

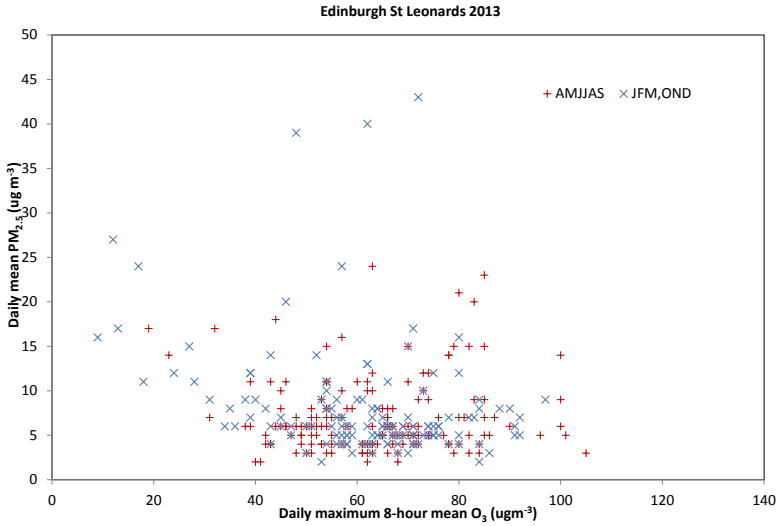

Figure A6.16

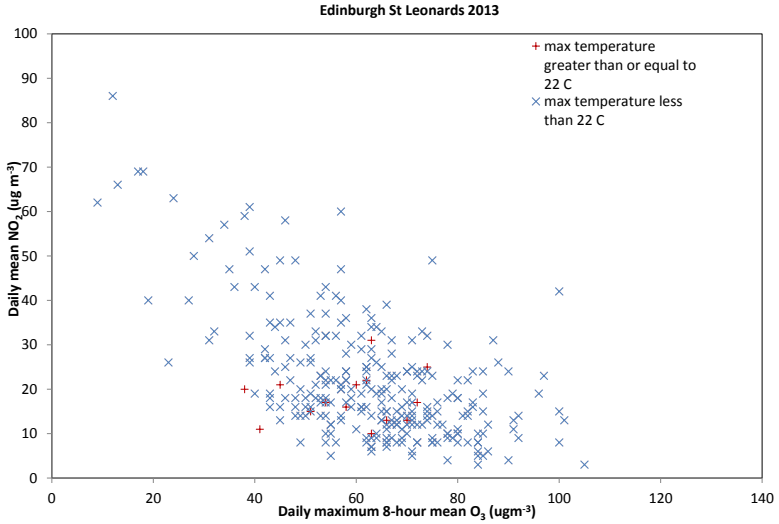

Figure A6.17

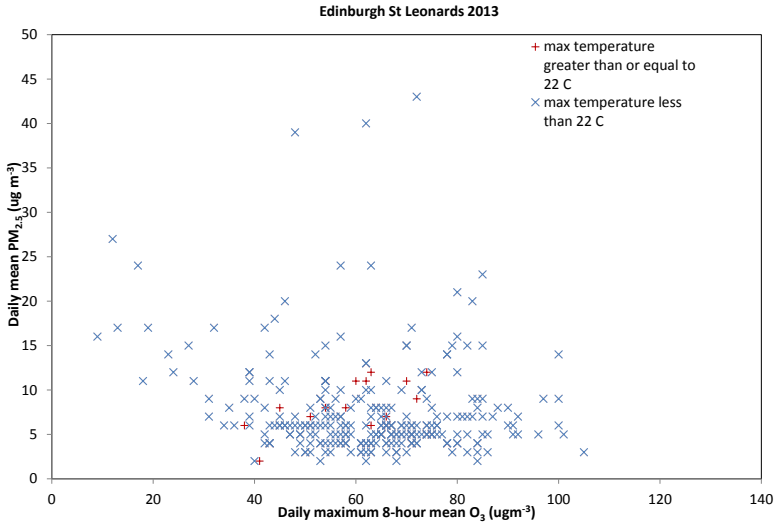

Figure A6.18

Appendix 7
Cardiovascular admissions, panel study evidence

Debbie Jarvis

A7.1 Previous reviews of panel studies

In 2007, a Department of Health commissioned report on 'Quantitative systematic review of short-term associations between ambient air pollution (particulate matter, ozone, nitrogen dioxide, sulphur dioxide and carbon monoxide), and mortality and morbidity' was published (Anderson *et al.,* 2007). The extensive review included assessment of panel studies that considered health effects of ozone (57 relevant papers identified). Most were from USA and Europe, most had used 1-hour or 8-hour averaging times and the three main outcomes were measures of lung function, respiratory symptoms and asthma medication. Twenty-seven studies were said to report 'other' outcomes – these may refer to cardiovascular (CV) outcomes but, to date, we have not verified this. In the report only four groupings met the criteria for meta-analysis; they were all studies of children, related to lung function and considered 1-hour ozone exposure. The authors reported consistent associations of higher ozone concentrations and lower lung function, with effects on forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) being similar. No further comment or assessment of cardiovascular related outcomes was made.

In 2014, an industry-funded (American Petroleum Institute) extensive systematic review of short-term (<30 days) exposure and cardiovascular effects was published (Goodman *et al.,* 2014). Literature searches using appropriate terms were conducted in PubMed and Scopus (January 2006 to November 2013) and added to those previously identified by the US EPA in the 2006 Air Quality Criteria Document (US EPA, 2006) and in US EPA work on ozone and CV effects that was available at the time (US EPA, 2013a,b). The general approach used should identify all relevant panel studies up to November 2013 but without a further extensive review this cannot be verified. Overall, the review identified:

a 33 epidemiology studies on cardiovascular mortality

b 20 studies on myocardial infarction

c 26 on heart rate variability (or related markers)

d 20 studies on arrhythmia

e 11 studies on blood pressure

f 13 studies on CV biomarkers

Panel studies are most likely for the latter four groups.

Quality criteria were applied. In summary, these were as follows:

a Study design – longitudinal or case crossover scored 1 (time series and cross-sectional 0)

b Sample – geographically well-defined area or sample of geographically well-defined area scored 1 (others 0)

c Study size –longitudinal and panel studies with >100 measures and >50 participants scored 1 (smaller studies 0)

d Outcome assessment – outcome assessed by physician/trained field worker, automatic devices/multiple measures scored 1 (hospital records/health registries 0)

e Exposure measurement – personal or residential monitors to account for indoor and outdoor levels scored 1 (central monitor within 10 km of home 0, central monitor greater than 10km –1)

f Statistical modelling – if included bi or multi-pollutant models scored 1 (0 single pollutant only, -1 if 'poor' statistical methods)

g Confounders – for case-crossover – accounted for time varying individual risk factors (eg physical activity, stress); for longitudinal included at least one of season, day of week, holidays, flu epidemics, and other individual factors or pre-existing conditions scored 1

h Sensitivity – if different lags, different statistical models scored 1

Within current resources, it was not possible to review all the identified studies. A summary of studies that, using these criteria, had a score of four or above was conducted. Components of the quality scores of these reports, as considered by Goodman *et al.* (2014) are shown in Table A7.1.

Table A7.1: Quality scores applied to studies in Goodman *et al.* (2014)

	Design	Selection bias	Study size	Outcome assessment	Exposure assessment	Statistical modelling	Control for confounders	Sensitivity analyses	Total
Anderson *et al.* (2010)	1	0	1	1	0	0	0	1	4
Bartell *et al.* (2013)	1	–1	1	1	0	0	1	1	4
Dockery *et al.* (2005)	1	–1	1	1	–1	1	1	1	4
Zanobetti *et al.* (2010)	1	0	0	1	–1	1	1	1	4
Delfino *et al.* (2010)	1	–1	1	1	1	0	1	1	5
Hoffmann *et al.* (2012)	1	0	1	1	–1	1	1	1	5
Brüske *et al.* (2011)	1	0	1	1	0	0	1	1	5

Anderson *et al.* (2010) studied 705 patients in London with implantable cardioverter defibrillators (average of 1200 days of observations, 5462 activations) and, using a case crossover design, observed positive but non-significant associations between activations and 8-hour average ozone exposure (RR 1.014, 95% CI 0.955, 1.076 per 10 μg/m^3). Analyses included assessment of up to 5-day lags and included control (but not stratification) for temperature. The report included a summary of all studies examining associations of activations of implantable cardioverter defibrillators and pollution exposure up to 2010 (a further nine). Of these, two studies from the same research group in Boston reported significant associations with ozone (Rich *et al.,* 2005, 2006); both were identified in the Goodman *et al.* (2014) review and quality scored as 2 and 3, respectively.

Bartell *et al.* (2013) studied 50 non-smokers with coronary artery disease (CAD) over the age of 71 years with an ambulatory electrocardiogram (up to 235 hours per participant). Over half the group had a documented history of myocardial infarction (MI), most were hypertensive and all had raised cholesterol levels. Ozone [24-hour average 27.1 ppb (54.2 μg/m^3)], interquartile range (IQR) 17.4 ppb (34.8 μg/m^3), was associated with daily ventricular tachycardias (VTs) – the association was most marked when ozone was considered as a daily or a 3-day average.

Association of ventricular tachycardia with ozone exposure (per IQR) (Bartell *et al.,* 2013)

Daytime 8-hour average	RR 1.37	95% CI 0.98, 1.91
Night-time 8-hour average	RR 1.13	95% CI 0.74, 1.70
24-hour average	**RR 1.60**	**95% CI 1.12, 2.30**
3-day average	**RR 2.95**	**95% CI 1.29, 6.74**
5-day average ozone	RR 0.93	95% CI 0.10, 8.16

For the longer averaged exposures, associations were most marked for night-time, compared to daytime, VTs (p for interaction 24-hour average ozone p=0.004, 3-day average ozone p = 0.082, 5-day average ozone p=0.010). Multi-pollutant models were not considered – associations with daily VTs were observed for $PM_{2.5}$, black carbon, elemental carbon, organic carbon, primary organic carbon, and secondary organic carbon (24-hour average).

Dockery *et al.* (2005) studied 195 people with cardioverters (it should be noted this is one of the nine studies alluded to in Anderson *et al.,* 2010). There was some evidence that 'any arrhythmia' was associated with 24-hour average ozone at a 1-day lag. Effect estimates tended to be greater for ventricular (VA), rather than supra-ventricular arrhythmias (SVA), but when 2-day means were used as the exposure metric the opposite was true. Multipollutant models were examined for '2-day means', although ozone effects were not significant for this metric. Ozone effect estimates (for 2-day means) remained unchanged after adjustment for other pollutants. When the patient group was limited to a geographical region in which exposure assessment was likely to be best (i.e. closest to central monitor), positive associations were seen for 2-day mean ozone level with SVAs (OR 1.79, 95% CI 1.12, 2.85; p for interaction for difference of effect for VA compared to SVA <0.001). Stratification by severity (based on ejection fraction) suggested 2-day mean ozone was associated with SVA in those with more severe disease (OR 1.22, 95% CI 1.01, 1.47%; p for interaction <0.001). Those with more episodes overall seemed to have the strongest associations with 2-day mean ozone for SVAs.

Associations of 'any arrhythmia' per IQR Increase (16 ppb; 32 µg/m³) in ozone (Dockery *et al.*, 2005)

(92 patients, 764 episode-days)

0-day lag	OR 1.02	95% CI 0.88, 1.20
1 day	**OR 1.16**	**95% CI 1.00, 1.34 (p = 0.051)**
2 days	OR 0.99	95% CI 0.86, 1.14
3 days	OR 0.93	95% CI 0.81, 1.07
5-day	OR 0.98	95% CI 0.79, 1.22

Zanobetti *et al.* (2010) studied 46 patients aged 43–75 years who had had recent percutaneous angiography. On four occasions during the year after treatment participants wore a 24-hour electrocardiogram monitor. There were decreases in root mean square of the successive differences (r-MSSD, an index of vagally mediated cardiac control) for all averaging times of ozone, with a 2.1% (95% CI –3.5, –0.6%) decrease for an IQR increase (19 ppb; 38 µg/m³) for 2-hour average ozone and a 3.4% (95% CI –5.2, –1.5%) decrease for an IQR increase (13 ppb; 26 µg/m³) in the 5-day moving average of ozone. High frequency (HF, another measure of vagal tone) was not associated with ozone. Associations with 72-hour mean ozone were tested in two pollutant models (one adjusting for $PM_{2.5}$ and the other for black carbon); these are interpreted by the authors as showing ozone and $PM_{2.5}$ had independent effects on HF (but they are in opposite directions). Looking at Figure 3 in the Zanobetti *et al.* (2010) paper – and then subsequently at Table 4 of the same paper, there is a suggestion that significant ($p<0.05$) effect estimates of the association of r-MSSD with 72-hour ozone levels become non-significant and of lesser magnitude after adjustment for $PM_{2.5}$.

Delfino *et al.* (2010) studied 64 elderly (mean age 84 years) patients with CAD for 10 days of hourly waking ambulatory blood pressure (BP) monitoring (n = 6539 total measurements). Ozone was reported as not being associated with blood pressure. This was stated rather than demonstrated, even though associations with other pollutants were reported.

Hoffmann *et al.* (2012) studied 70 subjects with type 2 diabetes mellitus and measured BP and pulse wave velocity (PWV) on up to five occasions a fortnight apart. Decreases in systolic, diastolic and central mean blood pressure were seen with increased 5-day mean ozone, after adjustment for season, age, sex, BMI, and years of diabetes and 5-day mean $PM_{2.5}$ (estimated relative change per IQR –13.3 ppb; systolic blood pressure –4.0% 95% CI –6.6, –1.4%; diastolic pressure –2.0% 95% CI –4.2, 0.2%; central mean –2.8% 95% CI –5.2, –0.3%). The changes in systolic blood pressure are shown in Figure A7.1.

Bruske *et al.* (2011) studied changes in lipoprotein-associated phospholipase A2 (Lp-PLA2) and changes in ozone. Lp-PLA2 is an enzyme produced by monocytes and macrophages, T cells, and mast cells, and Lp-PLA2 mass or activity has been associated with CAD and stroke. Lp-PLA2 may be directly involved in the causal pathway of plaque inflammation and the formation of rupture-prone plaques. Two-hundred patients who had had an MI were recruited. Up to six repeated clinical examinations were scheduled every 4–6 weeks between May 2003 and March 2004. The association of ozone with Lp-PLA2 was different to that observed for the other pollutants, showing a marked increase at lag 0 with a maximum percentage change of 2.34, 95% CI 0.15, 4.54 per IQR change in 8-hour average ozone. Other pollutants, tended to show decreases at lags of 0 and 1 days and show positive associations at lags of 4 and 5 days (PM_{10}, $PM_{2.5}$, CO and NO_2). The authors reported that

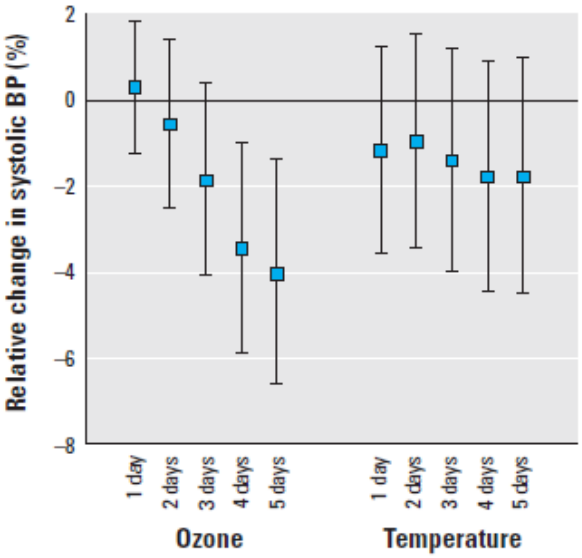

Figure 2. Estimated relative change (and 95% CI) of SBP related to short-term increases of ozone and temperature, per IQR of the exposure metric. Estimates adjusted for each other and for $PM_{2.5}$ (5-day mean), season, age, sex, BMI, and years of diabetes.

Figure A7.1: Estimated relative changes in systolic blood pressure (Reproduced from Hoffmann *et al.*, 2012)

"The immediate positive association with ozone suggests a different physiological mechanism, if associations represent causal effects".

No relevant studies published since November 2013 were identified on a preliminary search – it is possible that more extensive searching may locate more.

A7.2 Summary

Panel studies on short-term effects of ozone on cardiovascular status have been conducted, largely in those who are susceptible to cardiac events. Studies that might be considered to be of good quality (compared with others) show some limited evidence of associations of ozone with arrhythmias. However, from this preliminary review there is no clear, strong or consistent association and a more comprehensive review of panel studies, including assessment of scope for meta-analysing results and assessing publication bias – particularly with relation to cardiac arrhythmias and heart rate variability – may allow a more definitive report to be made.

A7.3 References

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Bartell SM, Longhurst J, Tjoa T, Sioutas C, Delfino RJ (2013) Particulate air pollution, ambulatory heart rate variability, and cardiac arrhythmia in retirement community residents with coronary artery disease. Environ Health Perspect; 121: 1135-41.

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Dockery D, Luttmann-Gibson H, Rich D, *et al.* (2005) Particulate Air Pollution and Nonfatal Cardiac Events. Part II: Association of Air Pollution with Confirmed Arrythmias Recorded by Implanted Defibrillators. Report No. 124.

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Rich DQ, Mittleman MA, Link MS, *et al.* (2006) Increased risk of paroxysmal atrial fibrillation episodes associated with acute increases in ambient air pollution. Environ Health Perspect; 114: 120-23.

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Appendix 8
Thresholds in short-term exposure studies

Heather Walton

A8.1 Short-term exposure to ozone and all-cause mortality, respiratory and cardiovascular hospital admissions – shape of concentration-response relationship

Each section of this appendix first looks at the information (where available) on the shape of the concentration-response relationship in the studies used to provide pooled estimates for short-term exposure to 8-hour average ozone and all-cause mortality, and for ozone and respiratory and cardiovascular hospital admissions.

It is acknowledged that there are other studies that may have examined this issue in the following categories:

a Studies that met some but not all of the sifting criteria for the meta-analysis, eg not all studies from the same city are included

b Studies published after the literature search cut-off of May 2011

c Studies for other averaging times and related outcomes, eg sub-diagnoses of cardiovascular and respiratory disease

The section on each health outcome considers studies in categories (a) and (b) more briefly at the end. Information from other averaging times is occasionally considered, particularly when closely related to 8-hour average ozone datasets. It should be noted that as correlation patterns between pollutants may differ for different averaging times, the interpretation of a possible threshold in a single-pollutant model is difficult to transfer from one averaging time to another. A similar point applies to results for all year, compared with separate seasons.

A8.2 All-cause mortality (8-hour average ozone, for all ages and all year)

Studies selected for meta-analysis

Many of the studies of ozone and all-cause mortality in Table A5.1 (Appendix 5) do not contain any information on the shape of concentration-response relationships.

The PAPA study (Wong *et al.,* 2008) looked at the shape of the concentration-response relationship in each of the constituent cities. These are shown in Figure A8.1.

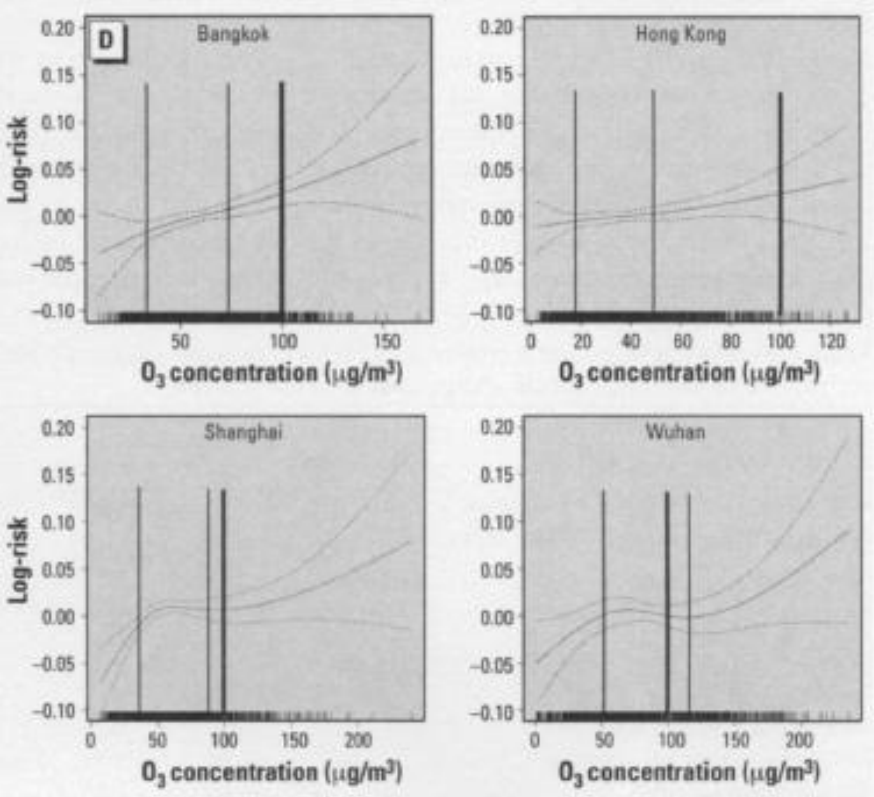

Figure A8.1: Shape of the concentration-response relationship (PAPA study; Reproduced from *Environmental Health Perspectives* (Hong *et al.*, 2008))

The heavy lines show the WHO guideline and the thinner lines show the interquartile range of ozone concentrations. The authors of Wong *et al.* (2008) note, in describing the curves for all pollutants, that most of the concentration-response curves are linear within the interquartile range. In addition, tests for non-linearity showed that linearity could not be rejected at the 5% level for most of the associations. In the Health Effects Institute report for the same study (HEI Public Health and Air Pollution in Asia Program, 2010), the report sections on the individual cities indicated that the test for linearity could not be rejected for all-cause mortality all ages in Shanghai, Wuhan, Hong Kong and Bangkok.

It should be noted that the 'cut-off' of 35 ppb (70 μg/m^3) used in Europe is well within the interquartile range in these cities. The interquartile range in Hong Kong is from 19.2–50.8 μg/m^3 (9.6–25.4 ppb), i.e. well below 35 ppb (70 μg/m^3) and it still shows a linear relationship.

The shape of the concentration-response relationship has been considered in the APHEA dataset but for the summer only (Gryparis *et al.,* 2004). This showed no indication of a threshold (Figure A8.2).

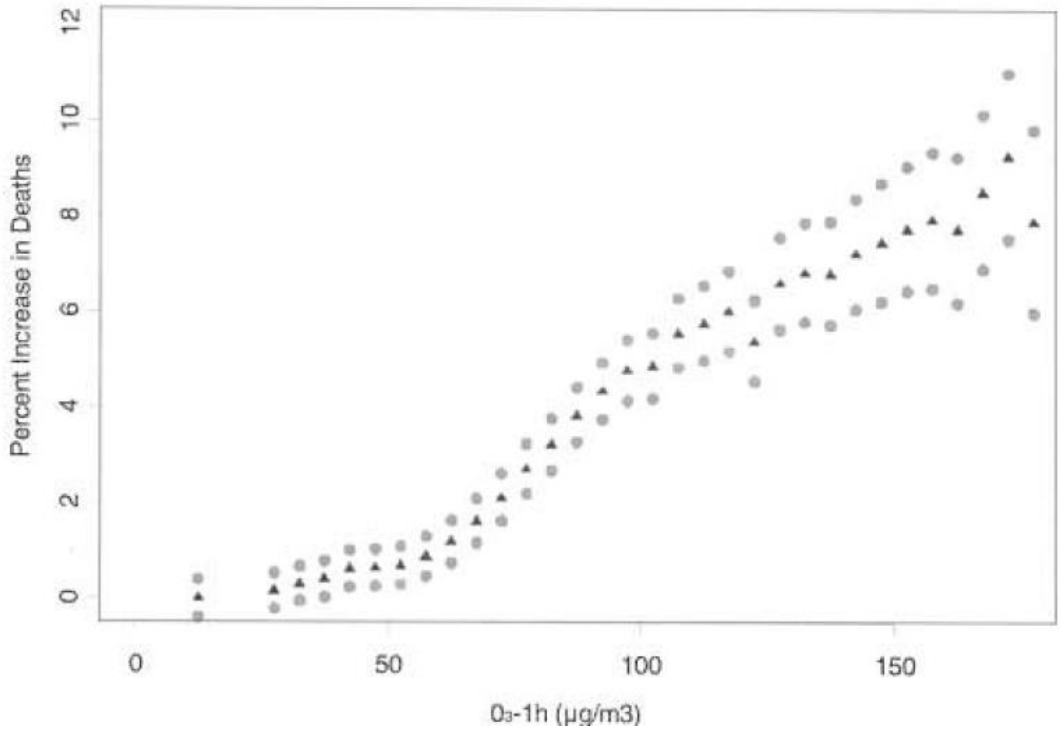

Figure A8.2: Concentration-response relationship for daily maximum 1-hour average ozone, summer only (Reprinted from Gryparis A, et al. (2004) with permission of the American Thoracic Society. Copyright © 2015 American Thoracic Society. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society)

The APHENA study examined the issue of thresholds further in the same dataset but for all year. This was based on daily maximum 1-hour average ozone. A whole series of models were fitted in different cities, each assuming thresholds increasing sequentially in increments of 5 µg/m^3. Each threshold model involved subtracting the hypothetical threshold concentration from all other concentrations and setting all resulting negative responses to zero. For example, for a threshold of 20 µg/m^3 any concentration less than 20 µg/m^3 would become zero and any concentration above 20 µg/m^3 would be scaled by subtracting 20 µg/m^3. The fit of the data to this proposed model was then examined. The mean deviance from the fitted model was then considered across cities. A minimum deviance would be expected at a specified threshold value, if this was a good fit.

Figure A8.3 indicates that the data did not support the hypothesis of a threshold (where a minimum at a specified threshold in the middle of the graph would have been expected). This was also true in the summer.

Hong *et al.* (1999) plotted the log of the relative risks against ozone concentrations for a lag of 1 day (the same lag as that used for the estimate in the meta-analysis). The slope declined to a minimum at 23 ppb (46 µg/m^3) before rising steeply but with wider confidence intervals (Figure A8.4, right). In contrast, for a 5-day moving average, the slope rose between 5 and 10 ppb (10 and 20 µg/m^3) and fell above 10 ppb (20 µg/m^3).

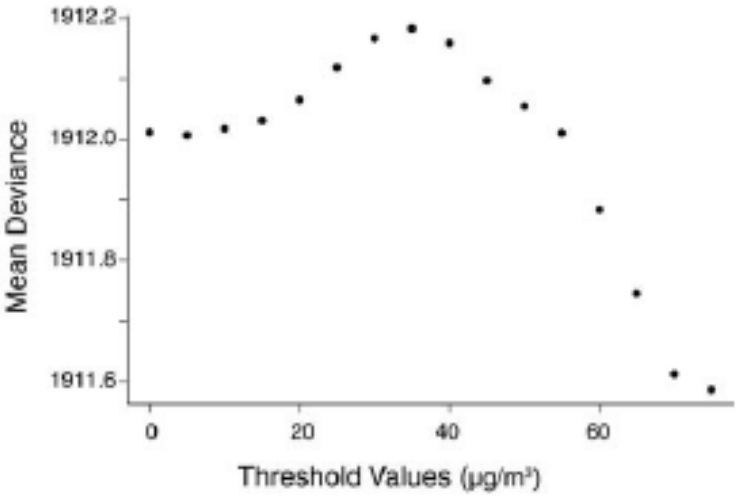

Figure 23. Europe (all ages): Plots of threshold values versus mean deviance of the fitted models for O_3 (lag 1) and all-cause mortality in the European cities.

Figure A8.3: Plot of threshold values versus mean deviance of fitted threshold models for European cities for daily maximum 1-hour average ozone, lag 1, and all-cause mortality for all ages (Reprinted with permission from Katsouyanni *et al.*, 2009)

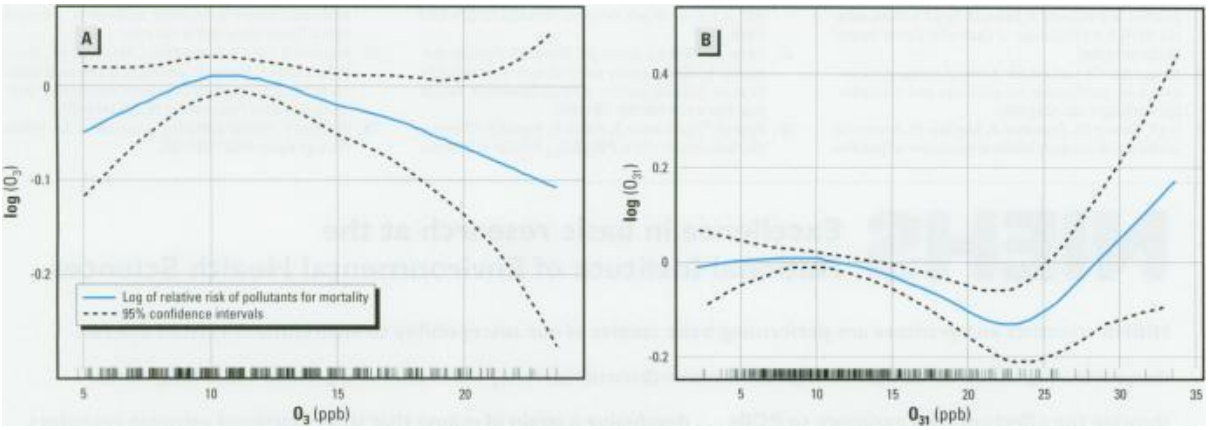

Figure A8.4: Graphic analysis of relationship of ozone concentrations for (A) the 5-day moving average of ozone concentrations (O_3) and (B) the previous day's ozone concentrations (O_{31}) with daily mortality by generalised additive model using loess function after controlling time trends, season and weather variables' (Reproduced from *Environmental Health Perspectives* (Hong *et al.*, 1999))

Other studies not selected for meta-analysis

Not all studies of 8-hour average ozone and all-cause mortality, for all ages and all year, were included in the meta-analysis, as explained in Section A8.1. Other studies were identified from several sources:

a past COMEAP secretariat work that examined studies on associations between 8-hour average ozone and mortality published before 2003 to check for evidence for or against a threshold (COMEAP, 2002)

b a literature search in PubMed on 'ozone AND (linear or threshold) AND mortality'

c citation searches for Atkinson *et al.* (2012), Bell *et al.* (2006); Pattenden *et al.* (2010) and Powell *et al.* (2012).

Previous COMEAP Secretariat work (studies before 2003)

The previous COMEAP secretariat work identified four studies that investigated thresholds among studies before 2003 on associations between 8-hour average ozone and all-cause mortality. One of these, Hong *et al.* (1999), is described above as it is one of the studies selected for the recent meta-analysis. The remaining three described below have been superseded by more recent studies in the meta-analysis but still provide useful information on thresholds.

Anderson *et al.* (1996) found an increase above about 50 ppb (100 μg/m^3) in a bubble plot plotting ozone concentrations against predicted death counts in London. Galan Labaca *et al.* (1999) found an increase at low doses, a decrease at intermediate concentrations and then a rise again at higher concentrations in Madrid. Wong *et al.* (2001) found a steady increase in log mortality risk with increasing ozone concentrations in the cool season and a steady decrease in the warm season in Hong Kong (where rain storms occur frequently in the warm season meaning median ozone concentrations are lower than in the cool season).

Literature search and citation searches on thresholds and mortality – study identification

The literature search identified 91 studies of which 12 were relevant to investigating thresholds in time-series studies on mortality, after sifting to identify time-series studies and then checking papers published since 2002. Four of these were publications from the PAPA study, the results from which are already described above through the summary publication Wong *et al.* (2008). Katsouyanni *et al.* (2009) was another study identified that has also already been described. Bell *et al.* (2006), Moolgavkar *et al.* (2013) and Goldberg *et al.* (2013) used data from the USA, the USA and Canada, respectively, but were related to 24-hour average not 8-hour average ozone. Stylianou and Nicolich (2009) examined several models in USA cities using a 3-day weighted mean. The study by Kim *et al.* (2004) related to 1-hour average ozone but is described below as a study that carefully considered the shape of the relationship by season and in both one- and two-pollutant models.

The remaining three studies (Pattenden *et al.,* 2010*;* Atkinson *et al.,* 2012; Yang *et al.,* 2012) were for 8-hour average ozone. They were not included in the meta-analysis as Pattenden *et al.* (2010) was for the summer only and the other two studies were published after the cut-off for the literature search of May 2011. One was of particular interest as it was for 8-hour average ozone for all year, based in the UK and focused on examining the evidence for thresholds (Atkinson *et al.,* 2012). These three studies are also described below.

The literature search was supplemented with a direct citation search and a related citation search for Bell *et al.* (2006) which identified a total of 212 studies, accounting for duplicates. Of these, 15 were time-series studies investigating the presence or absence of a threshold. Nine had already been identified in the literature search above, three were further PAPA publications and one was a publication based on the APHENA study already discussed above. Two new studies were identified. Powell *et al.* (2012) was based on 24-hour average ozone and was for respiratory not all-cause mortality. The final identified study by Pascal *et al.* (2012) is discussed below.

Citation searches on Pattenden *et al.* (2010), Powell *et al.* (2012) and Atkinson *et al.* (2012) did not identify any new studies examining thresholds that had not already been picked up.

Literature search and citation searches – description of key studies on thresholds and mortality

Kim *et al.* (2004) found, for associations with daily 1-hour maximum ozone and mortality, that threshold models were the best fit for all year and for the summer. The relationship was linear in spring and autumn and there was no relationship in the winter (with an increase, a decrease and another increase in the slope). The threshold was estimated as 28 ppb (56 μg/m^3) in the all-year single-pollutant model with a steeper slope above the threshold than the slope for the linear model. Adjustment for each of CO, PM_{10}, SO_2 and NO_2 had little effect on the slope above the threshold or the value of the threshold. Analogous results were found in the summer. It would have been interesting to see the effect of adjustment for other pollutants in the other seasons but this was not presented. The authors note that for an all-year calculation, the threshold model would give a smaller health impact given the number of days below the threshold. However, for the summer the health impact would be bigger as there are fewer days below the threshold, and more days when the slope is steeper.

Yang *et al.* (2012) in a study in Suzhou, China, found that the concentration-response curve of log mortality risk against 8-hour average ozone concentrations was essentially linear, with a monotonic increase in risk with concentration.

Pascal *et al.* (2012) in a study in 9 French cities found a rise in the percentage increase in mortality rate to 50 μg/m^3 8-hour average ozone, a decrease to 100 μg/m^3 and then a further rise.

Pattenden *et al.* (2010), while only analysing data from the summer (as the focus was on ozone-heat interactions), is of interest because all models accounted for levels of PM_{10}. There was no adjustment for other pollutants. Effects in London are highlighted in the description of the results due to the London all-year findings in Atkinson *et al.* (2012) below. The threshold identified was 65 μg/m^3 across 15 British conurbations including London, with the p-value for the threshold model $p < 0.01$ compared with $p = 0.01$. The mean rate ratio for ozone was increased on hot days, although the interaction was only significant in London. This was a model that was controlled for mean temperature (this was a better fit in London). With control for maximum temperature instead, the ozone association in the linear model was reduced to null. The threshold determined was much higher at 130 μg/m^3, the ozone association above this value was positive with a lower confidence interval just under 1. In London, the association above this threshold was positive, larger and had a lower confidence interval above 1. Even in the model adjusting for maximum temperature where the basic model result was null, there was still some evidence of an ozone-heat interaction, the ozone effects again being significantly higher on high temperature days in London.

Atkinson *et al.* (2012) examined the relationship between 8-hour average ozone and all-cause mortality in five urban and five rural areas of the UK. For the all-year relationship, there was little evidence of non-linear relationships apart from for London, where a threshold of 65 μg/m^3 (95% CI 58, 83) was found. The concentration-response relationship above this threshold was 1.33% per 10 μg/m^3 (95% CI 0.8, 1.86%).

Seasonal analyses in Atkinson *et al.* (2012) showed evidence of thresholds in the summer for both urban and rural areas. For those associations that were positive, thresholds ranged from 38 to 64 μg/m^3 in urban areas and 53 to 87 μg/m^3 in rural areas. The threshold in London was very similar to the all-year threshold at 64 rather than 65 μg/m^3. In interpreting these results it should be noted that the study also found evidence of effect modification by temperature, when this was examined in detail for London in the summer. No relationship was found below 20°C.

In urban areas, in the linear model, adjustment for PM_{10} attenuated the relationship in autumn and winter but not in the spring or summer. The effect of adjustment for PM_{10} was not examined in the threshold model and PM_{10} concentration data were not available in rural areas. The paper acknowledges a need to investigate adjustment for other pollutants, although the data were not available. From data in London, it was noted that high ozone days were also days with high secondary particulates (particularly nitrates) and low nitrogen dioxide, carbon monoxide, particle number concentrations and chlorides.

In summary, Atkinson *et al.* (2012) concluded that the preponderance of evidence suggested adverse effects at low concentrations, with the notable exception of London. It was suggested that the results were interpreted with caution, given the sensitivity analyses investigating effect modification by temperature and adjustment for PM_{10}. It was noted that future studies may benefit from more sophisticated modelling of meteorological and atmospheric parameters.

This section has considered a series of studies in the UK investigating thresholds in the relationship between 8-hour average ozone and all-cause mortality, with several in London. Anderson *et al.* (1996) suggested a threshold at 50 ppb (100 μg/m^3) for the years 1987–1992. Gryparis *et al.* (2004) (summer only) and Katsouyanni *et al.* (2009) (maximum 1-hour average) both included data from London and Birmingham for the years 1992–1996 and found no evidence of a threshold in an analysis combined with other APHEA2 European cities. Pattenden *et al.* (2010) used summer only data from 1993–2003 in a study of 15 British conurbations and identified an overall threshold of 65 μg/m^3 when controlling for mean temperature. Finally, Atkinson *et al.* (2012) using data from 1993–2006 did not generally find thresholds for all-year data, apart from a threshold of 65 μg/m^3 in London. (Thresholds were found in summer-only data.) Of these, Atkinson *et al.* (2012) is the most recent, uses the largest number of years of data and was specifically aimed at investigating thresholds.

A8.3 Cardiovascular admissions (8-hour average ozone, for all ages and all year)

Studies selected for meta-analysis

Atkinson *et al.* (1999) was the only study of those in Table A5.11 in Appendix 5 to examine the shape of the concentration-response relationship. The results were presented as bubble plots. The summary across all pollutants was that the relationships were "approximately linear with little evidence of a threshold". Possible non-linearity was mentioned for NO_2 but not for any other pollutants.

The following sources were checked for studies not included in the meta-analysis:

a past COMEAP secretariat work that examined studies on associations between 8-hour average ozone and admissions published before 2003 to check for evidence for or against a threshold (COMEAP, 2002)

b a literature search in PubMed on 'ozone AND (linear or threshold) AND admissions'

Previous COMEAP secretariat work (studies before 2003) did not identify any studies for 8-hour average ozone, for all ages and all year, that investigated thresholds in studies of all cardiovascular admissions.

The literature search generated 45 articles. Of these, 17 were time-series studies on air pollution and admissions published in 2003 or later. These were further sifted to exclude studies that were not for all ages and not for 'all respiratory' or 'all cardiovascular' diagnoses. Studies of other pollutants but not ozone and studies on susceptible subgroups were also excluded. The only study remaining after this sift was a study in Madrid (Linares and Diaz, 2010). However, this study used 24-hour average ozone and used groups stratified by concentration for cause-specific admissions. (It did note a quadratic relationship for the full range of 24-hour average ozone concentrations, with a minimum at 65 $\mu g/m^3$, when analysing all-cause admissions.)

As there was only one study that investigated the issue, it is not possible to come to an overall conclusion about a possible threshold for any relationship between 8-hour average ozone and all cardiovascular admissions, for all ages and all year.

A8.4 Respiratory admissions

Atkinson *et al.* (1999) also produced bubble plots for the relationship of ozone with respiratory hospital admissions. The text that "The summary across all pollutants was that the relationships were approximately linear with little evidence of a threshold" applied to respiratory as well as cardiovascular hospital admissions.

As with cardiovascular hospital admissions, this was again the only study to examine the shape of the concentration-response relationship for ozone and respiratory hospital admissions.

An earlier study by Ponce de Leon (1996), also in London, found a threshold around 50 ppb (100 $\mu g/m^3$) but this was only presented graphically. The literature search described above did not identify any further studies examining 8-hour average ozone and all respiratory admissions, for all ages.

Both the identified studies used bubble plots that are only an approximate way to investigate thresholds and came to different conclusions. It is thus hard to come to any overall conclusion about a possible threshold for any relationship between 8-hour average ozone and all respiratory admissions, for all ages and all year.

A8.5 WHO reviews

The WHO REVIHAAP project (WHO, 2013a) considered a wider literature (not just the studies of 8-hour average ozone as discussed above). The relevant extract from this report is attached at the end of this appendix. This found mixed results. It concluded that the evidence was not consistent

and that, where a threshold had been observed, it was likely to be below 45 ppb (90 μg/m^3) (only one study suggested a threshold as high as 45 ppb and then only in some cases).

The HRAPIE project (WHO, 2013b) (extract attached) recommends using a cut-off at 35 ppb (70 μg/m^3) to reflect greater confidence in a significant relationship above 35 ppb. However, it is emphasised that the coefficients were based on the whole range of ozone concentrations and that effects below 35 ppb (70 μg/m^3) were ignored rather than considered to be zero.

A8.6 Conclusions

Overall, for 8-hour average ozone, all-cause mortality, for all ages and all year, the data are mixed but there is strong evidence from two multi-city studies (Wong *et al.,* 2008; Katsouyanni *et al.,* 2009) suggesting no threshold for the relationship between 8-hour average ozone and all-cause mortality for all ages and all year. Although Atkinson *et al.* (2012) generally found no threshold in the all-year data, a threshold was found in London. It also needs to be borne in mind that the all-year findings may represent a composite of both linear and non-linear results in different seasons and that interpretation of identification of apparent thresholds may be complicated by both effect modification by temperature and confounding by other pollutants changing with ozone concentration. There is insufficient evidence for 8-hour average ozone, and either all respiratory or all cardiovascular admissions, for all ages and all year, to come to conclusions as to the presence or absence of a threshold.

A8.7 References

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REVIHAAP extract (WHO, 2013a)

Question B2

What new health evidence has been published in relation to the evidence or likeliness of a threshold below which impacts are not expected?

Answer

Epidemiological studies reporting an effect of long-term exposure to ozone on mortality do not, in general, provide data that permit the firm identification of a threshold for the effects of long-term exposure to ozone.

Recent experimental exposures of healthy human volunteers to ozone at concentrations of 120 $\mu g/m^3$ (60 ppb) have shown impaired lung function and inflammation, relative to clean air controls, but thus far only in healthy young adults exposed for prolonged periods (6.6 hours), with exercise. These conditions are unlikely to reflect fully the range of exposures experienced in the general population and the real world combinations of susceptibility and exposure. The effects of ozone on lung function and inflammation have been reported for real world situations, most notably in summer camp studies at lower concentrations, less than 110 $\mu g/m^3$ (55 ppb), as an 8-hour average. It has been argued that the responses at these lower levels may be due to subpopulations with greater susceptibilities or to additional effects of other stressors, such as other pollutants. The evidence from epidemiological studies for a threshold for short-term exposure is inconsistent with some large, multicity studies that reported little evidence of a threshold down to near background ozone concentrations, whereas other short-term studies suggest a threshold between 20 $\mu g/m^3$ and 90 $\mu g/m^3$ (10 ppb and 45 ppb) (daily maximum 1-hour). In summary, the evidence for a threshold for short-term exposure is not consistent, but where a threshold is observed, it is likely to lie below 90 $\mu g/m^3$ (45 ppb) (maximum 1 hour).

Rationale

Epidemiological studies of long-term exposure

The studies that suggest that long-term exposure has an effect on mortality do not in general provide data to examine the support for a threshold. For respiratory mortality, there was limited evidence that a threshold model improved model fit (Jerrett et al., 2009a). In several studies of long-term exposure, mean concentrations for summer months or peak ozone seem to give stronger associations (Lipfert et al., 2006; Krewski et al., 2009), possibly indicating that the highest exposure levels are important.

Epidemiological studies of short-term exposure

A small number of time-series studies have specifically considered the threshold issue (Hoek et al., 1997; Kim et al., 2004; Gryparis et al., 2004; Ito, De Leon & Lippmann, 2005; Bell, Peng & Dominici, 2006). A variety of methodological approaches have been used. The most comprehensive analysis was carried out by Bell & Dominici (2008) using data from 98 urban communities in the United States for the period 1987–2000. They investigated the concentration–response function for ozone and mortality using a variety of methods, including: (a) a linear approach; (b) a subset approach (limiting the analyses to days with ozone concentrations below a predetermined value only; (c) a so-called hockey stick threshold model (assuming the regression coefficient is 0 below the hypothesized threshold

HRAPIE extract (WHO, 2013b)

For the cost–effectiveness analysis, the HRAPIE experts recommended a cut-off concentration of 35 ppb (70 µg/m^3) to reflect greater confidence in the significant relationship above 35 ppb. An additional argument is the availability of O_3 models that can estimate the sum of means over 35 ppb with greater reliability than concentrations below 35 ppb. Owing to uncertainty regarding the presence of a threshold for O_3 effects, additional effort to estimate the impacts of O_3 in concentrations above 10 ppb, which is the lowest concentration observed in monitoring stations in Europe (using the sum of means over 10 ppb), would also be justified. In such additional analysis, the same risk coefficients should be used as with the sum of means over 35 ppb.

It should be noted that the coefficients in the APHENA study were based on the whole range of observed O_3 concentrations, including levels below 35 ppb. No assumption of "no effect" of the lower levels of O_3 is thus made in the impact calculations. Rather, any such impacts are ignored in the cost–effectiveness analysis. While this approach should not affect comparison of various policies reducing peaks of O_3, the effect of this assumption should be tested in the cost–benefit analysis.

Appendix 9
Quantification of long-term effects of ozone

Richard Atkinson

The associations between long-term exposure to air pollution and the risks of adverse health events have been investigated using cohort studies, an epidemiological design exploiting spatial differences in average air pollution concentrations and incident health events. The most common outcome studied in air pollution cohort studies is mortality. Long-term exposure to air pollution for cohort members is typically characterised by average (over months/years) pollution concentrations determined from monitoring stations or from air pollution dispersion or land use regression models. A statistical procedure (survival analysis) links pollution concentrations to the risk of death accounting for other potential explanatory variables such as age, smoking history and socioeconomic status.

Recent reviews of the evidence for adverse health effects associated with long-term exposure to ozone have concluded that the evidence supporting an association is mixed. The 2005 global update to the WHO air quality guidelines (WHO, 2006) found support only for a short-term association between ozone and mortality. In its update of the 2006 Air Quality Criteria Document, the US EPA concluded that there was evidence suggestive of an association with respiratory mortality but limited support for an association with total and cardiopulmonary mortality (US EPA, 2013) (a view endorsed by the comprehensive review of the evidence in support of the revision of the EU's air quality policies (WHO, 2013a). Both reviews presented a narrative assessment of the evidence and excluded results from recent large cohort studies in the UK (Carey *et al.,* 2013) and the USA (Jerrett *et al.,* 2013).

A narrative assessment of the evidence in the REVIHAAP report (WHO, 2013a) as well as in the individual studies by Jerrett *et al.* (2009, 2013), together with an outline of the concentration-response functions adopted in the HRAPIE exercise (WHO, 2013b), were presented to COMEAP in 2014 (COMEAP/2014/03). The analysis presented here builds upon this previous work in conducting a systematic review and quantitative assessment of the evidence from cohort studies. Suitable studies published in peer-reviewed journals and indexed in Embase to August 2014 (no start date specified) were identified via a search string using terms relating to study design, pollutant and health outcome. Citations of a number of key papers were also used to identify any relevant studies not selected from the Embase search. A sifting process identified (from study titles, abstracts and the full paper) those studies providing quantitative estimates of the effects of ozone on mortality.

Study details were entered into a STATA (STATA/SE 10. StataCorp Texas) dataset and included citation information and details of the cohort and effect estimates. These data were used to calculate standardised effect estimates expressed as hazard ratios (HR) with associated 95% confidence intervals per 10 ppb (20 $\mu g/m^3$) increase in ozone concentration. The STATA program 'metan' was used to produce forest plots showing HRs, 95% confidence intervals and study descriptors.

Seventeen publications from seven cohorts presented results for ozone and mortality. Two cohorts were broadly population samples and five were based upon selected population subgroups. The majority of cohorts and publications were from the USA with the American Cancer Society Cancer Prevention Study II (ACS CPS II) cohort analysed in six separate publications.

Standardised effect estimates for all-cause and cause-specific mortality are shown in the forest plot in Figure A9.1. There was little evidence to suggest a relationship between long-term annual ozone concentrations and the risk of death from all-cause, cardiovascular or respiratory disease.

Four cohorts (American Cancer Society Cancer Prevention Study II (ACS CPS-II), Washington University-EPRI Veterans (WU-EPRI Veterans), California Teachers Study (CTS) and a cohort constructed from the Medicare database (Medicare) also reported results for ozone concentrations during the warm 'season' or from peak ozone measures (Figure A9.2), but the evidence base is dominated by analyses of the ACS CPS II cohort (four publications). HRs for all-cause mortality in the ACS CPS II cohort were close to unity but generally more convincing for cardiopulmonary and respiratory causes of death, HRs in the range 1.01–1.04 with lower confidence intervals close to 1. A study of Medicaid enrollees with pre-existing diabetes, respiratory or cardiovascular diseases reported substantially larger HRs in the range 1.12–1.14.

Long-term annual ozone concentrations and death from a range of diseases adjusted for concentrations of fine particles ($PM_{2.5}$, mass of particles with a median aerodynamic diameter less than 2.5 μm) were studied in three cohorts (Figure A9.3). The evidence base was too limited to draw conclusions regarding the independence of the ozone associations from $PM_{2.5}$.

The evidence presented in this quantitative review does not provide support for an association between long-term annual ozone concentrations and mortality derived from single-pollutant models and from models incorporating $PM_{2.5}$. While the evidence suggests small, adverse associations between ozone concentrations during the warm season months and cause-specific mortality, the evidence base is restricted to two US cohorts only, one of which is limited to a specific population subgroup.

The recent narrative review for WHO (2013a) and subsequent quantification exercise (WHO, 2013b) recommended adopting the coefficient from the study of the ACS cohort by Jerrett *et al.* (2009). This coefficient for respiratory mortality in subjects aged 30+ years was based upon mean daily 1-hour ozone concentrations during the summer months (April–September) and derived from a single-pollutant model. Its use in quantification was recommended in the HRAPIE project (WHO, 2013b) as an alternative to quantification of effects from short-term exposure to ozone on mortality.

In contrast, the analysis of 100,000 female participants in the CTS (Lipsett *et al.,* 2011) included both annual and summer-only ozone estimates based upon residential address and derived from inverse distance weighted pollution surfaces. Respiratory mortality effect estimates for the two ozone metrics were comparable; 1.06 versus 1.04 per 10 ppb (20 $\mu g/m^3$) increment in ozone, respectively.

As a supplementary analysis (to an health impact assessment using evidence from short-term exposure studies), a health impact calculation could be undertaken using the result for respiratory mortality and summer mean ozone derived from the single-pollutant model from Jerrett *et al.* (2009): HR = 1.029 (1.010, 1.048) per 10 ppb (20 $\mu g/m^3$) increment in the mean of daily maximum 1-hour ozone concentrations. The following points are noted: (i) this result was robust to adjustment for MSA (US metropolitan statistical areas) annual average temperature; (ii) there was limited evidence

that a threshold model specification improved model fit as compared with a non-threshold linear model ($p = 0.06$); and (iii) the evidence for a stronger association using warm season ozone measures compared to all-year measures is further supported by analyses of cardiopulmonary mortality from the ACS (Krewski *et al.,* 2009) where stronger associations were observed in the warm season, 1.03 (1.02, 1.04) versus all year 1.01 (1.00, 1.03), each per 10 ppb (20 $\mu g/m^3$) increment in average ozone concentrations.

However, there are also substantial uncertainties regarding the suitability of the ACS result:

a There was evidence that the HR was modified by area average temperature

b Transferability of the result from a study in a US population to a UK population

c Reservations about the Jerrett *et al.* (2009) study noted by Boogaard *et al.* (2014) and summarised as follows:

(i) it incorporated 23 years of ozone concentrations (1977 to 2000) but only 2 years of $PM_{2.5}$ data (1999-2000), due to lack of data availability. Given that both ozone and $PM_{2.5}$ levels decreased significantly over the years 1977–2000, the ozone concentrations included higher levels observed in the past compared to the lower $PM_{2.5}$ values observed recently. This leads to a situation where confounding by $PM_{2.5}$ is not adequately controlled

(ii) while the metric for ozone was the daily maximum hourly levels in the summer, the metric to assess potential confounding by $PM_{2.5}$ was the annual average. This uneven approach maximised the potential to observe an association between ozone and mortality and minimised the potential for $PM_{2.5}$ to confound the ozone association. The authors appear to recognise this implication in the discussion, where they state "it is likely that we have underestimated the effect of $PM_{2.5}$ in our analysis"

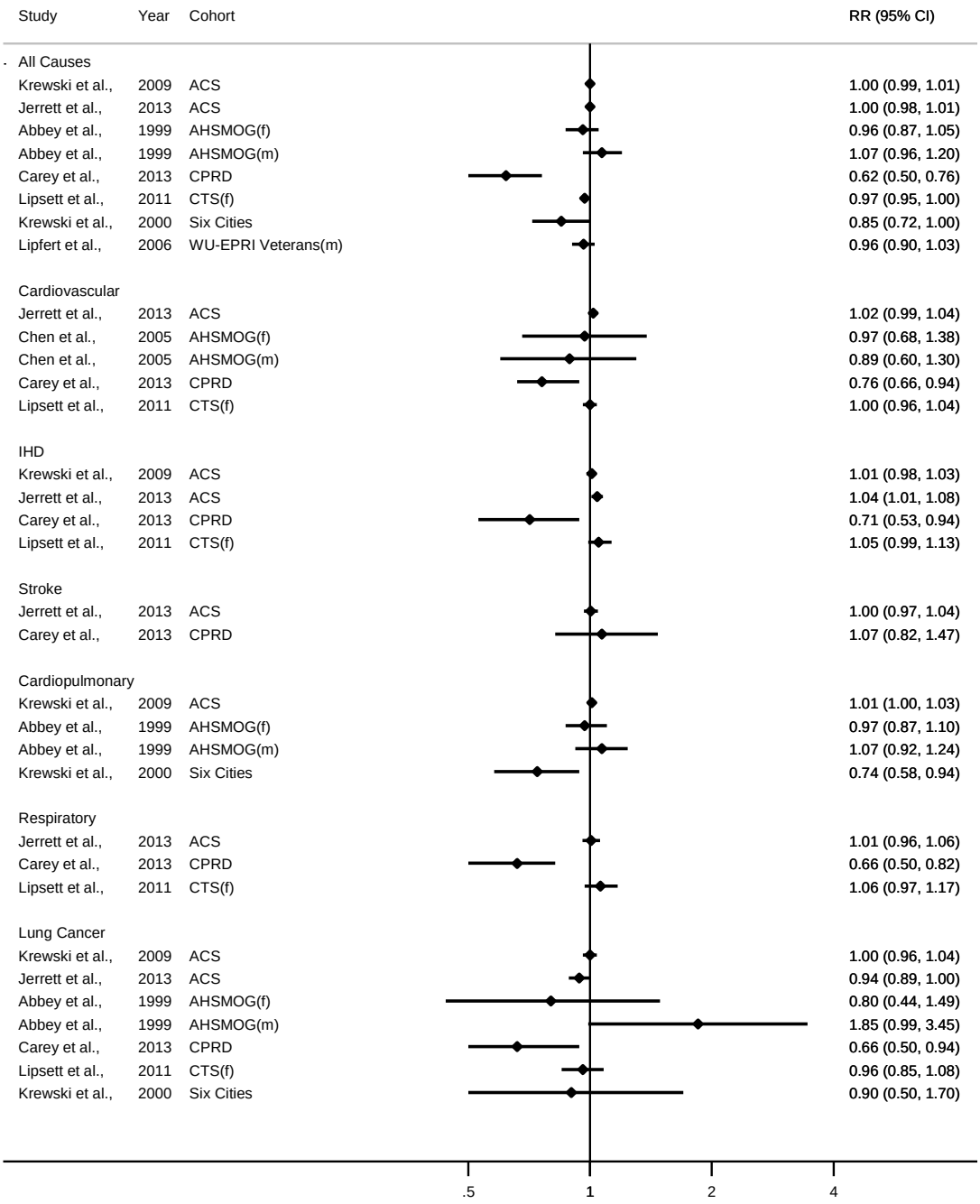
(iii) Jerrett *et al.* (2009) did not consider confounding by SO_2, a pollutant that had previously demonstrated a stronger mortality association than $PM_{2.5}$ in the ACS cohort (Krewski *et al.,* 2000)

Furthermore, any such recommendation for quantification would need to be accompanied by other, more general statements expressing the substantial uncertainties regarding the evidence base for an association between long-term exposure to ozone and respiratory mortality: (i) the evidence base linking long-term exposure to ozone and mortality is limited – only a small number of studies/cohorts have assessed associations and most of these are in the USA; (ii) few cohorts are national and representative of the general population; (iii) categories of mortality studied vary between studies limiting the scope for quantitative meta-analysis to derive summary concentration-response functions; and (iv) the evidence from the UK suggesting a negative association between annual ozone concentrations and respiratory mortality.

For the purpose of the 2nd Climate Change Risk Assessment, consideration is also needed for the inputs and methodologies needed to do such an impact calculation. Impact calculations for long-term exposure to pollutants using life tables are based on the assumption that effects on mortality are spread evenly throughout the year. The methodology and inputs could be adapted to deal with a (postulated) summer-only effect but this would require a significant amount of time to complete. Also, there is little information available to define an appropriate lag between exposure and effect. Finally, for an effect of long-term exposure incorporated into an impact calculation for a specified year in the future, modelling is needed not only for that specific year but also for intervening years in

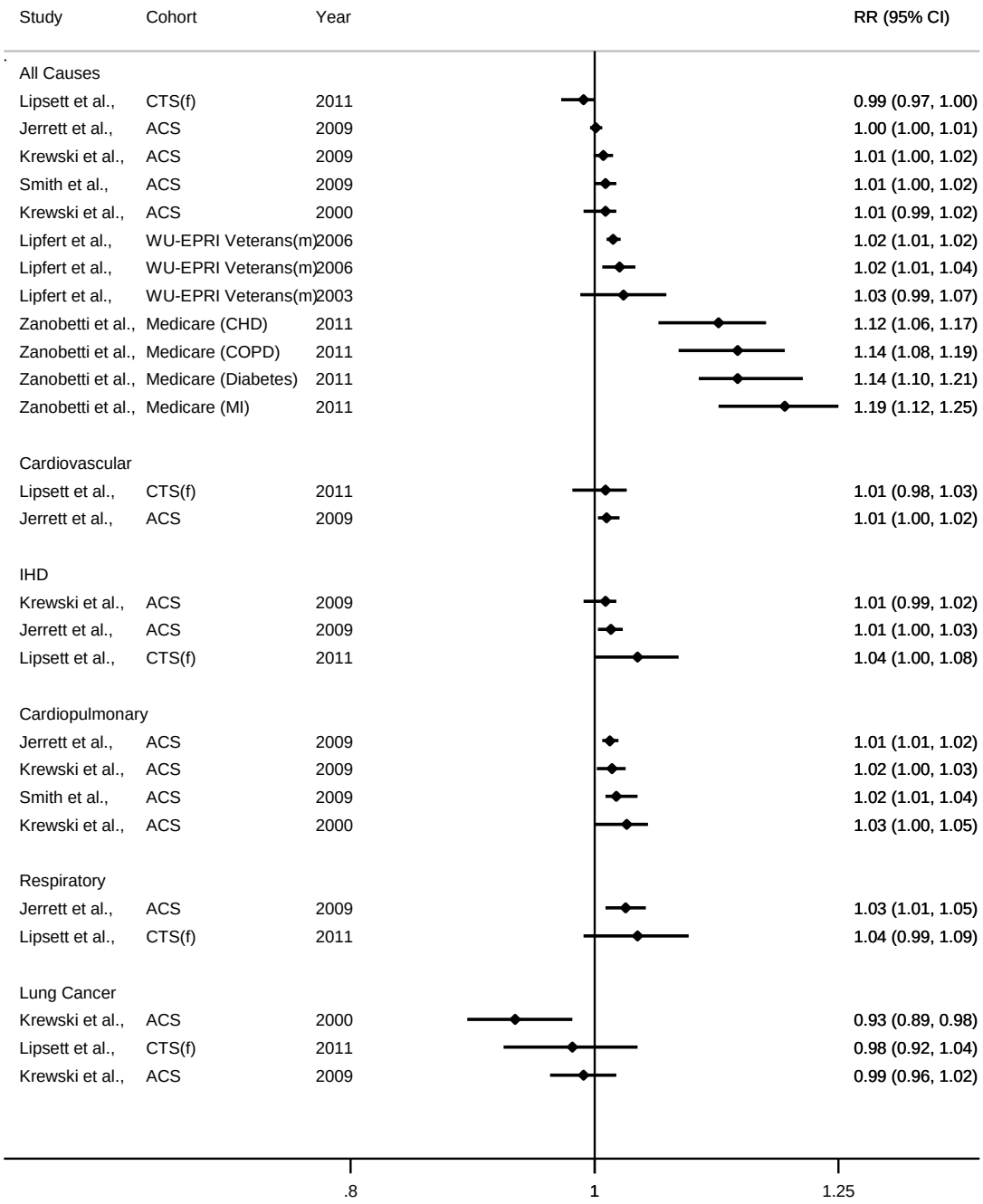
order to take into account both lagged effects from previous years and the shifts in size and age structure of the population as a result of long-term effects in previous years.

In summary, quantification of the associations between long-term ozone concentrations and mortality is not recommended. The combination of the limited evidence base and the uncertainties in the assumptions needed for the health impact calculations (thresholds, effect modification, cessation lags and life table methods for applying risks for part of a year), led us to decide against recommending quantification particularly given the tight timescale within the context of the 2nd Climate Change Risk Assessment. We recommend further work in order to develop quantification approaches for use in sensitivity analyses in the future.



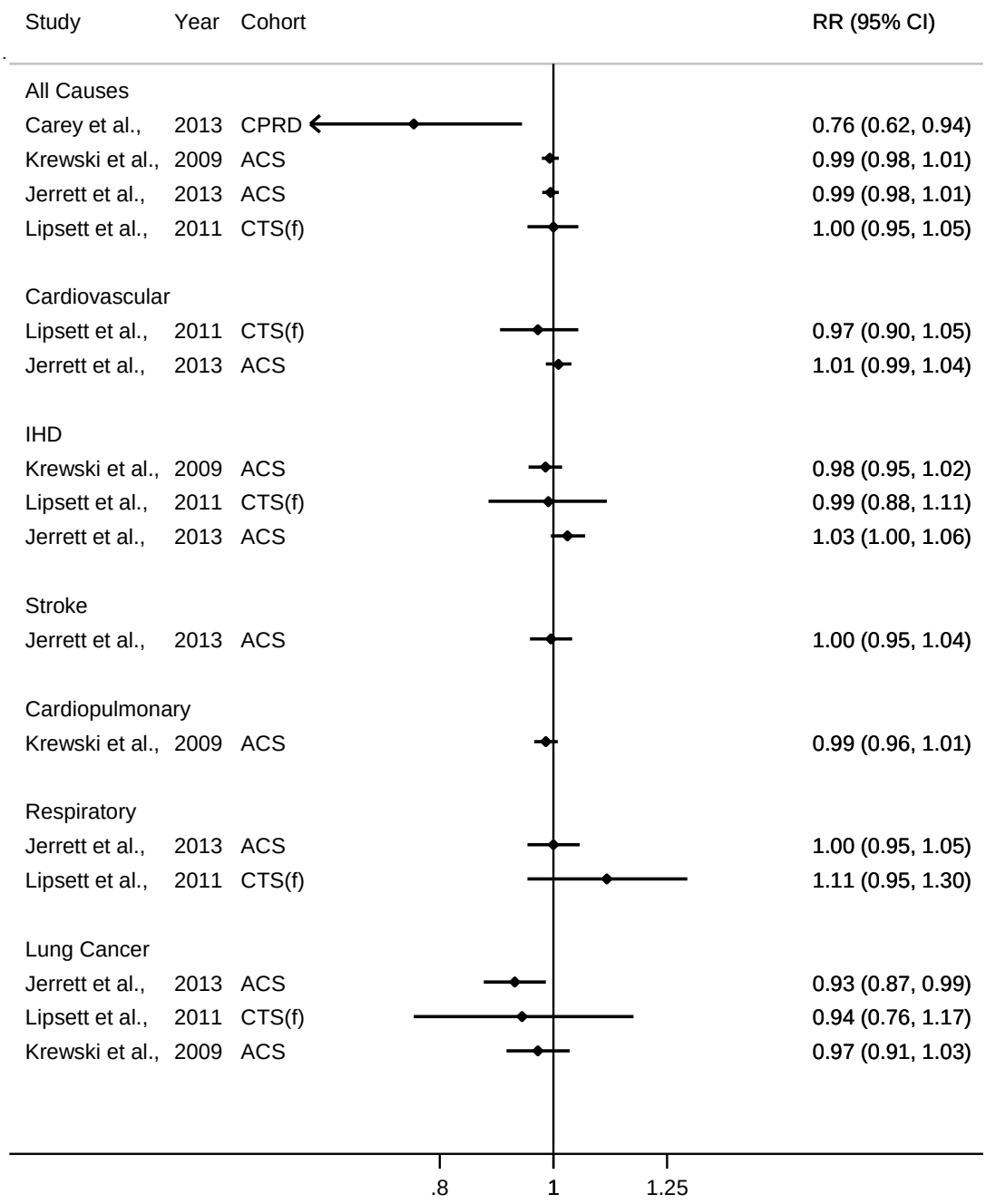
Cohort: Adventist Health Study of Smog (AHSMOG); California Teachers Study (CTS); Washington University-EPRI Veterans (WU-EPRI Veterans); American Cancer Society Cancer Prevention Study II (ACS CPS-II); cohort constructed from Clinical Practice Research Datalink (CPRD); cohort constructed from Medicare database (Medicare).
(f) all subjects female; (m) all subjects male

Figure A9.1: Relative risk (95% CI) of death from a given cause per 10 ppb (20 µg/m³) increase in long-term exposure to ozone



Cohort: Adventist Health Study of Smog (AHSMOG); California Teachers Study (CTS); Washington University-EPRI Veterans (WU-EPRI Veterans); American Cancer Society Cancer Prevention Study II (ACS CPS-II); cohort constructed from Clinical Practice Research Datalink (CPRD); cohort constructed from Medicare database (Medicare).
(f) all subjects female; (m) all subjects male; (CHF) prior diagnosis of CHF; (COPD) prior diagnosis of COPD; (Diabetes) prior diagnosis of diabetes; (MI) prior diagnosis of MI.

Figure A9.2: Relative risk (95% CI) of death from a given cause per 10 ppb (20 µg/m³) increase in long-term warm-season ozone exposure



Cohort: Adventist Health Study of Smog (AHSMOG); California Teachers Study (CTS); Washington University-EPRI Veterans (WU-EPRI Veterans); American Cancer Society Cancer Prevention Study II (ACS CPS-II); cohort constructed from Clinical Practice Research Datalink (CPRD); cohort constructed from Medicare database (Medicare). Krewski 2009 Los Angeles only
(f) all subjects female; (m) all subjects male

Figure A9.3: Relative risk (95% CI) of death from a given cause per 10 ppb (20 µg/m^3) increase in long-term ozone exposure, adjusted for long-term exposure to $PM_{2.5}$

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