Long-term exposure to ambient ozone and mortality: a quantitative systematic review and meta-analysis of evidence from cohort studies

R W Atkinson, B K Butland, C Dimitroulopoulou, M R Heal, J R Stedman, N Carslaw, D Jarvis, C Heaviside, S Vardoulakis, H Walton, H R Anderson

ABSTRACT

Objectives: While there is good evidence for associations between short-term exposure to ozone and a range of adverse health outcomes, the evidence from narrative reviews for long-term exposure is suggestive of associations with respiratory mortality only. We conducted a systematic, quantitative evaluation of the evidence from cohort studies, reporting associations between long-term exposure to ozone and mortality.

Methods: Cohort studies published in peer-reviewed journals indexed in EMBASE and MEDLINE to September 2015 and PubMed to October 2015 and cited in reviews/key publications were identified via search strings using terms relating to study design, pollutant and health outcome. Study details and estimate information were extracted and used to calculate standardised effect estimates expressed as HRs per 10 ppb increment in long-term ozone concentrations.

Results: 14 publications from 8 cohorts presented results for ozone and all-cause and cause-specific mortality. We found no evidence of associations between long-term annual O₃ concentrations and the risk of death from all causes, cardiovascular or respiratory diseases, or lung cancer. 4 cohorts assessed ozone concentrations measured during the warm season. Summary HRs for cardiovascular and respiratory causes of death derived from 3 cohorts were 1.01 (95% CI 1.00 to 1.02) and 1.03 (95% CI 1.01 to 1.05) per 10 ppb, respectively.

Conclusions: Our quantitative review revealed a paucity of independent studies regarding the associations between long-term exposure to ozone and mortality. The potential impact of climate change and increasing anthropogenic emissions of ozone precursors on ozone levels worldwide suggests further studies of the long-term effects of exposure to high ozone levels are warranted.

INTRODUCTION

Outdoor air pollution comprises a mixture of particles and gases and has been associated with a range of acute and chronic health effects. An important component of this mixture of pollutants is ozone (O₃), a gaseous pollutant formed by atmospheric chemical reactions involving nitrogen oxides (NOₓ) and volatile organic compound precursor gas emissions, and driven by solar radiation and temperature. Ozone is a highly reactive, oxidative gas and the concentrations of O₃ at a given time and place are also determined by the rate of loss through chemical reactions, the rate of surface deposition and long-range atmospheric transport processes which can vary with season and meteorological conditions. Climate change, as well as changes in anthropogenic emissions of O₃ precursors, is likely to have an effect on ground-level O₃ concentrations in the future.

The highly reactive nature of O₃ initiates oxidative stress when it enters the...
Epidemiological studies have demonstrated adverse associations between short-term exposure to O3 and human health including reduced respiratory function and increased hospital admissions and deaths from respiratory diseases. Associations between short-term exposure to O3 and cardiovascular mortality have also been reported; however, associations with cardiovascular morbidity are less convincing.

In contrast to the evidence from short-term exposure studies, the evidence for adverse health effects associated with long-term exposure to O3, that is, average exposure measured over years, is mixed. The 2005 global update to the WHO air quality guidelines did not find support for an association with mortality. In their update of the 2006 Air Quality Criteria Document, the US Environmental Protection Agency (EPA) concluded that there was evidence suggestive of an association with respiratory mortality but limited support for an association with total and cardiopulmonary mortality, a view endorsed by the comprehensive review of the evidence in support of the revision of the European Union’s (EU) air quality policies. While both of these reviews covered a wide range of possible health effects, both excluded recent large cohort studies in the UK and the USA. Furthermore, both reviews presented a narrative assessment of the evidence and did not attempt a quantitative evaluation of hazard or meta-analysis.

There is an important need to develop better concentration response functions that can be used in health impact assessments such as the Global Burden of Disease and for modelling the potential ozone impacts associated with climate change. In this review, we present a quantitative evaluation of the evidence from cohort studies published in the peer-reviewed literature to October 2015, reporting associations between long-term exposure to ozone and mortality. We also assess the evidence stratified by cause of death, during the ‘warm season’ and after adjustment for fine particle concentrations.

**MATERIALS AND METHODS**

**Systematic ascertainment of cohort studies**

Cohort studies published in peer-reviewed journals were identified from searches of EMBASE (between 1974 and week 40 2015) and MEDLINE (1946 to September week 4 2015) within Ovid. Three search strings, relating to study design, health outcome and pollutant were used without language restriction (provided in the online supplementary material). Studies identified in each search were combined and duplicates (241) removed within Ovid.

A screening process to identify cohort studies assessing associations between long-term exposure to ozone and mortality was applied to the remaining 277 records. This process used the study title and abstract to identify potential studies for which the full paper was downloaded and checked. Exclusion criteria related to: (1) article type, (2) study design, (3) outcome, (4) exposure, and (5) use of individual rather than ecological covariates and further details of these criteria are provided in the online supplementary material. A total of 255 records were deleted. The main reasons for removal were: conference abstracts/notes, reviews, not cohort design and no ozone data in study. The literature searching and screening was undertaken by BKB.

We also conducted a separate search of PubMed (6 October 2015), undertaken by RWA and using three similar search terms (provided in the online supplementary material). Studies identified in each PubMed search were downloaded to Reference Manager databases (2006 Thomson Reuters) which were then combined and duplicates identified and removed. Two publications, additional to those returned in the Ovid searches, were identified. One study was published subsequent to the Ovid search date, and the second was a reanalysis of an existing cohort with a focus on particulate matter. Finally, we included three known potentially relevant early publications. In total, 29 cohort studies were available for detailed evaluation to determine their inclusion in our review.

Each study was then further assessed against inclusion/exclusion criteria relating to covariate adjustment and provision of quantitative data to facilitate standardisation of hazard ratio (HR). Details of these exclusion/inclusion criteria are also given in the online supplementary material. Seven cohort studies did not include adjustment for key confounders (age, sex, body mass index, smoking and socioeconomic status) and were excluded. Five studies did not provide numerical values for HRs and associated 95% CIs together with the necessary data to enable standardisation of the HR (to an increment of 10 ppb). We do, however, note the qualitative findings from these studies. One study of respiratory mortality included contributory respiratory causes of death as well as underlying causes and was not included in our quantitative assessment of the evidence because of this non-standard definition of cause of death. Finally, two studies included duplicated data presented in other publications and were excluded. Hence, 14 studies met our inclusion/exclusion criteria and were included in our quantitative review. The process, together with the numbers of studies identified at each stage, is illustrated in figure 1.

**Data extraction and coding**

For each cohort study, the following details were extracted: (1) citation details (title, authors, date of publication, etc); (2) cohort details including study location (country/city), study population, follow-up period(s), confounder adjustment; (3) details of the effect estimates including diagnosis, unit of measurement, concentration range for HR, metric description (annual mean, etc), period of year for exposure assessment (either all-year or ‘warm season’ according to the
definition used in the original studies). These data were
used to characterise/describe each cohort and to calcu-
late standardised HRs and 95% confidence interval (CI)
expressed per 10 ppb increase in O₃ concentration.
Where necessary, estimates reported in µg/m³ were con-
verted to ppb using 1 ppb=2 µg/m³ at an ambient pres-
sure of 1 atm and a temperature of 25°C. This process
was undertaken by BKB and checked by RWA.

The STATA program ‘metan’ was used to produce forest
plots and to undertake random-effects meta-analysis
where three or more estimates from separate cohorts
were available for a specific cause of death. Where a
cohort was analysed more than once, the estimate from
the most recent study analysed, the largest sample size,
most recent exposure and follow-up periods was selected
for inclusion in the meta-analysis. This process ensured
the size and direction the HRs reported in the studies
did not influence their selection for meta-analysis, there-
fore limiting the potential for selection bias.

RESULTS
Our literature search identified 14 publications from
eight cohorts reporting HRs for ozone and mortality and
associated data to enable standardisation. Key character-
istics of each study are summarised in the online supple-
mentary material. Six cohorts focused on selected
population subgroups: Seventh Day Adventists
non-Hispanic white non-smokers (Adventist Health Study
of Smog; AHSMOG), white participants (six cities), male
veterans with diagnosed hypertension (Washington
University - Electric Power Research Institute Veterans
Cohort; WU-EPRI), and three selected occupation
cohorts: female teachers (California Teachers Study;
CTS), energy workers (Gazel) and Taiwanese civil ser-
vants. The American Cancer Society Cancer Prevention
Study II (ACS CPS II) cohort was comprised of mainly
friends, neighbours, acquaintances and relatives of volun-
teer recruiters. One study used administrative data to con-
struct a primary care cohort (CPRD). The majority of
cohorts (5/8) and publications (11/14) were from the USA with the ACS CPS II cohort analysed in five separate publications. In total, 12/14 studies assessed associations with all-cause mortality and 11/14 cause-specific mortality. Summer or peak O3 measures were assessed in 8/14 studies, and 8/14 studies reported associations adjusted for mass of particles with a median aerodynamic diameter <2.5 µm (PM_{2.5}).

**Figure 2** RR (95% CI) of death per 10 ppb increase in long-term exposure to ozone. ACS CPS II, American Cancer Society Cancer Prevention Study II; AHSMOG, Adventist Health Study of Smog; CTS, California Teachers Study; IHD, ischaemic heart disease; RR, relative risk; WU-EPRI, Washington University - Electric Power Research Institute Veterans Cohort.

All season

Standardised effect estimates, expressed as the HR (95% CI) per 10 ppb increase in O3, for all-cause and cause-specific mortality are shown in the forest plot in figure 2, and random-effects summary estimates are presented in table 1. We found no evidence of an association between long-term annual O3 concentrations and the risk of death from all causes. Meta-analysis of the seven
Adjustment for PM2.5 with a non-threshold linear model. The authors assessed the shape of the concentration response function and found no evidence that a threshold was used in any of the six cohorts. The HRs from the six cohorts gave a summary HR=0.96 (95% CI 0.92 to 1.00) per 10 ppb increase in O3 with evidence of heterogeneity (I²=81%). Similarly, we did not find evidence for associations between long-term annual O3 concentrations and deaths from cardiovascular, ischaemic heart disease (IHD), cardiopulmonary and respiratory diseases and lung cancer (table 1).

### Warm season
O3 concentrations during the ‘warm season’ (defined either as the period April to September or July to September or by selecting peak annual concentrations) were reported in the ACS CPS II, CTS, WU-EPRI and Gazel cohorts (figure 3). HRs for all-cause mortality were generally close to unity with 95% CI that encompassed unity. Associations for cardiopulmonary and respiratory causes of death were more convincing with HRs in the range 1.01–1.02 and 1.02–1.04, respectively, with lower confidence limits close to 1 other than for the French Gazel cohort. Summary HRs derived from meta-analysis of three or more cohorts (table 1) showed no association with all-cause mortality but positive associations with cause-specific mortality, respiratory in particular. The reanalysis of the ACS CPS II cohort by Jerrett et al.26 included almost 500,000 participants across the USA and reported a HR for respiratory mortality of 1.03 (95% CI 1.01 to 1.05) per 10 ppb increase in the average daily maximum 1 h ozone concentrations measured between April and September. They also considered the impact of adjusting for ambient temperature in 90 of the 96 metropolitan statistical areas and found no material difference in the O3 HR. Finally, the authors assessed the shape of the concentration–response function and found no evidence that a threshold model specification improved model fit when compared with a non-threshold linear model.

### Adjustment for PM2.5
O3 concentrations and death from a range of diseases adjusted for concentrations of fine particles (PM2.5) were studied in five cohorts (ACS CPS II, CTS, CPRD, WU-EPRI and Gazel) though the bulk of the evidence was from the ACS (figure 4). Results from these studies do not suggest a positive association between O3 and all-cause or cause-specific mortality, other than the single estimate for respiratory mortality from the ACS CPS II cohort.

### Qualitative studies
Four of the five studies that did not provide numerical data to enable the standardisation of the HR and CIs and hence inclusion in our quantitative review found no evidence of statistically significant associations with mortality.14 16 25 39 The fifth study reported elevated significant overall associations with mortality.

### DISCUSSION
This quantitative systematic review of the evidence for an association between long-term exposure to O3 and an increased risk of death identified a small literature base dominated by US studies and the ACS CPS II cohort in particular. We found no evidence of associations between long-term annual O3 concentrations and the risk of death. Studies that used O3 concentrations measured during the warmer months or peak ozone (95% centile of daily maximum 1 h ozone) as the exposure metric generally reported positive associations, especially with cardiopulmonary and respiratory mortality.

Previous reviews of the health effects of long-term exposure to O3 have provided narrative assessments of the cohort literature as part of comprehensive assessments of the epidemiological and toxicological evidence.1 6 Prueitt et al.40 utilised the studies identified in the EPA review as a basis for a weight of evidence analysis for long-term exposure to O3 and cardiovascular disease. Cohort studies published since earlier reviews7 8 were examined and revisions to previous concluding statements considered. Our focus on a quantitative

---

**Table 1 Meta-analytic summary estimates by cause of death**

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Study citation</th>
<th>Number of estimates</th>
<th>HR (95% CI)</th>
<th>I² (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All causes</td>
<td>9 15 29 30 34 36</td>
<td>7†</td>
<td>0.96 (0.92 to 1.00)</td>
<td>81</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>9 12 32 36</td>
<td>5†</td>
<td>0.98 (0.93 to 1.04)</td>
<td>55</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>9 29 36</td>
<td>3</td>
<td>1.00 (0.92 to 1.09)</td>
<td>72</td>
</tr>
<tr>
<td>Cardiopulmonary</td>
<td>15 29 30</td>
<td>4†</td>
<td>0.98 (0.90 to 1.07)</td>
<td>59</td>
</tr>
<tr>
<td>Respiratory</td>
<td>9 10 36</td>
<td>3</td>
<td>0.94 (0.81 to 1.10)</td>
<td>84</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>9 15 29 30 36</td>
<td>6†</td>
<td>0.95 (0.83 to 1.08)</td>
<td>55</td>
</tr>
<tr>
<td>Warm season/peak ozone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All causes</td>
<td>29 34 36 37</td>
<td>4</td>
<td>1.00 (0.99 to 1.02)</td>
<td>46</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>26 36 37</td>
<td>3</td>
<td>1.01 (1.00 to 1.02)</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory</td>
<td>26 36 37</td>
<td>3</td>
<td>1.03 (1.01 to 1.05)</td>
<td>0</td>
</tr>
</tbody>
</table>

HRs expressed per 10 ppb increase in O3.
*I² statistic.
†Separate estimates for male and female members of AHSNOG cohort; hence, number of cohorts is one less than the number of estimates in the meta-analysis.
analysis of all cohorts, irrespective of publication date, complements the narrative approach by: (1) facilitating an assessment of the number of cohorts, the number of published analyses and reanalyses as well as basic information such as participant characteristics and exposure estimation methods; (2) providing a graphical summary of all of the evidence (in the form of a forest plot) to enable a broad overview of the direction, magnitude and precision of all study findings; and (3) providing, where possible, summary HRs for use in health impact assessment exercises. Concentration response functions from cohort studies have been used previously in burden and impact calculations. A disadvantage of our quantitative approach is that it does not reflect the diversity between studies in the methods for estimating exposure to O₃, the definition of potential confounders and the
statistical models employed. However, the relatively small number of independent cohorts limits the scope for effect modification analysis with which to explore the relative impact of these important characteristics.

There is also a need for more details of the methods used to determine and assign exposure estimates and statistical models. Some studies used exposure metrics derived from averages, or percentile values, of daily 1 h concentrations and these may not be the most appropriate measure of lower (by definition) long-term average exposures to O₃. Studies using such metrics may actually be investigating associations with repeat exposures to the

---

**Figure 4** RR (95% CI) of death per 10 ppb increase in long-term ozone exposure, adjusted for long-term exposure to PM₂.₅. Note: For Krewski 2009, ozone increment assumed to be 10 ppb. ACS CPS II, American Cancer Society Cancer Prevention Study II; CTS, California Teachers Study; IHD, ischaemic heart disease; WU-EPRI, Washington University - Electric Power Research Institute Veterans Cohort; RR, relative risk; PM₂.₅, mass of particles with a median aerodynamic diameter less than 2.5 µm.
highest O₃ concentrations rather than investigating associations with long-term (ie, cumulative) exposure. However, cohort studies exploit spatial variation in individual exposure estimates and report HRs for an increment in the O₃ concentrations. Therefore, if the statistical model assumes a linear concentration response function (and most do), then the exact metric used is less important and estimates can be combined in a meta-analysis. However, the selected O₃ metrics (and the concentrations they represent) may be a source of heterogeneity in any meta-analysis if there is, in reality, a non-linear concentration response function. None-the-less, the exact definition of the exposure metric used in each analysis has an important bearing on the utility of study results in health impact assessment exercises where a concentration response function is applied to a change in pollution concentration.

Our review reveals the paucity of population-based cohorts from which to draw substantive conclusions about the health effects associated with the long-term exposure to O₃. One cohort comprised participants with pre-existing medical conditions, and others selected participants based on employment or specific participant characteristics. The ACS CPS II cohort utilised friends, neighbours, acquaintances and relatives of volunteers and is therefore unlikely to be representative of the US general population and the Six Cities cohort is restricted to white participants. Only the English cohort based on an administrative database of patients registered with general practitioners (which is almost universal in the UK) is population based. While studies in selected subgroups support hazard assessment, their findings have limited application in quantifying the risk in the general population. The use of large, linked administrative databases may enable a growth in the number of studies reporting results which are nationally representative. There is also a need for cohort studies outside of the USA in order to provide a broader evidence base across a range of O₃ concentrations and where relationships between O₃ and co-variables of temperature and other pollutants may be different. This contrasts sharply with the large volume of epidemiological evidence from time-series studies investigating associations from short-term exposure to O₃. This literature incorporates a wide range of health outcomes/diseases and from many regions of the world, including stratification by season. This evidence from short-term exposure studies worldwide does, however, provide support for the application of results from long-term exposure studies in locations with cohort evidence to regions without such evidence.

A number of publications using the ACS CPS II cohort have assessed associations between O₃ concentrations measured during the warmer months of the year and mortality and have reported positive associations with lower confidence limits very close to 1 (figure 3). Krewski et al reported results for O₃ measured both throughout the year and during April to September. They found stronger associations for cardiopulmonary mortality using measures of O₃ during the warmer months compared with all year (incorporating comparable confounder adjustment—ref. 29, table 3; 1.03 (95% CI 1.02 to 1.04) vs 1.01 (95% CI 1.00 to 1.03) respectively. Similarly, Lipfert et al reported a positive association between peak exposure (95% centile of daily maximum hourly ozone) and mortality but not with the annual mean. However, this pattern of associations was not observed in a similar comparison using the CTS cohort.

The reasons for the modest differences between HRs estimated using warm season and all year concentrations in the ACS CPS II study are not clear. One possibility is that exposure measurement error varies between seasons due to different patterns of human behaviour (eg, time spent outdoors or window opening). It may suggest a non-linear concentration response function with larger HRs during the higher ozone concentrations experienced during the warmer months compared with the cooler months of the year though we note that O₃ in the northern hemisphere can be high earlier in the year. However, the ranges of ozone exposures in the warm and all year periods were not that dissimilar, 11.7–56.4 vs 10.4–41.1 ppb, respectively, although means (30.2 vs 22.9), medians (30.7 vs 22.5) and variances (40.9 vs 21.5) differed substantially. An analysis of summer ozone concentrations using the ACS CPS II examined the shape of the concentration–response function and did not find evidence that a threshold model specification improved model fit over the linear, non-threshold model. Ozone production during summer episodes is closely related to temperature and solar radiation; hence, the question of whether or not ozone associations observed during the warmer months are independent of the effects of temperature requires investigation.

Jerritt et al in their analyses of summer ozone concentrations in the USA, found no evidence of confounding by temperature but did report a modifying effect of temperature on the ozone HRs.

Concentrations of ozone at a given time and place are determined not just by its photochemical production, but also the rate of chemical loss, the rate of surface deposition, and of long-range atmospheric transport which vary by season and meteorological conditions. Correlations with other pollutants, including NO₂ and particles, also vary by season. Therefore, studies of the health effects associated with long-term ozone concentrations should consider, if possible, the numerous complexities involved including (1) seasonal patterns of ozone production/loss; (2) whether relationships are driven by temperature; (3) the shape of the concentration response relationship; and (4) the impact of co-pollutants.

Climate impacts directly or indirectly on many processes that determine the concentrations of ozone at a particular location and time. Climate-mediated influences on ozone include those related to emission.
fluxes of ozone precursors, atmospheric chemistry, dispersion and transport, and loss of ozone by dry deposition to vegetation. Climate change may 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. Biogenic emissions of ozone precursors will also be influenced by climate change. For those climate-mediated processes included in model simulations to date, modelling studies indicate that, overall, the net mediated processes included in model simulations to behaviour changes arising from adaptive strategies. Biogenic emissions of ozone precursors will also be impact of climate change on surface ozone is generally a change will require further large, population-based burden estimation and evaluation of impacts of climate change will require further large, population-based cohorts utilising comparable ozone metrics.

**REFERENCES**

Long-term exposure to ambient ozone and mortality: a quantitative systematic review and meta-analysis of evidence from cohort studies

R W Atkinson, B K Butland, C Dimitroulopolou, M R Heal, J R Stedman, N Carslaw, D Jarvis, C Heaviside, S Vardoulakis, H Walton and H R Anderson

BMJ Open 2016 6:
doi: 10.1136/bmjopen-2015-009493

Updated information and services can be found at:
http://bmjopen.bmj.com/content/6/2/e009493

These include:

References
This article cites 36 articles, 2 of which you can access for free at:
http://bmjopen.bmj.com/content/6/2/e009493#BIBL

Open Access
This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections
Epidemiology (1436)
Public health (1445)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/