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

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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 standardized effect estimates expressed as hazard ratios (HR) per 10 ppb increment in long-term ozone concentrations.

Results

Fourteen 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 O_3 concentrations and the risk of death from all-causes, cardiovascular or respiratory diseases or lung cancer. Four 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, 1.02) and 1.03 (95% CI: 1.01, 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.

Strengths and limitations of this study

1. This is the first quantitative review and meta-analysis of cohort evidence for long-term exposure to ozone and a range of causes of death.
2. Fourteen publications from 8 cohorts were identified. The majority of cohorts were from the US and most of these focused on selected population sub-groups.
3. We found no evidence of associations between long-term annual O_3 concentrations and the risk of death. Studies that used O_3 concentrations measured during the warmer months as the exposure metric generally reported positive associations especially with respiratory mortality.
4. Climate change and increasing anthropogenic emissions of ozone precursors on ozone levels worldwide is likely to increase the population exposure to ozone. For the impact of these changes on mortality to be estimated further cohort studies in representative populations utilizing comparable ozone metrics are required.

INTRODUCTION

Outdoor air pollution comprises a mixture of particles and gases and has been associated with a range of acute and chronic health effects.(1) An important component of this mixture of pollutants is ozone (O_3), a gaseous pollutant formed by atmospheric chemical reactions involving nitrogen oxides (NO_x) and volatile organic compound (VOC) precursor gas emissions, and driven by solar radiation and temperature.(2;3) Ozone is a highly reactive, oxidative gas and the concentrations of O_3 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 O_3 precursors, is likely to have an effect on ground-level O_3 concentrations in the future.(4;5)

The highly reactive nature of O_3 initiates oxidative stress when it enters the respiratory tract (2). Epidemiological studies have demonstrated adverse associations between short-term exposure to O_3 and human health including reduced respiratory function and increased hospital admissions and deaths from respiratory diseases.(1;2) Associations between short-term exposure to O_3 and cardiovascular mortality have also been reported, however associations with cardiovascular morbidity are less convincing.(6)

In contrast to the evidence from short-term exposure studies, the evidence for adverse health effects associated with long-term exposure to O_3, i.e. average exposure measured over years, is mixed. The 2005 global update to the WHO air quality guidelines(7) did not find support for an association with mortality. In their update of the 2006 Air Quality Criteria Document(8), 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(6), a view endorsed by the comprehensive review of the evidence in support of the revision of the EU's air quality policies.(1) Whilst both of these reviews covered a wide range of possible health effects, both excluded recent large cohort studies in the UK(9) and the US.(10) 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(11) 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 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: a) article type; b) study design; c) outcome; d) exposure; and e) use of Individual rather than ecological covariates and further details of these criteria are provided in the Supplementary Material. A total of 253 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 and was undertaken by BB.

We also conducted a separate search of PubMed (6th October 2015), undertaken by RWA and using three similar search terms (provided in the Supplementary Material). Studies identified in each PubMed search were downloaded to Reference Manager databases (© 2014 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(12) and the second, a reanalysis of an existing cohort with a focus on particulate matter.(13) Finally, we included 3 known potentially relevant early publications.(14-16) 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 standardization of HRs. Details of these exclusion/inclusion criteria are also given in the Supplementary Material. Seven cohort studies did not include adjustment for key confounders (age, sex, body mass index, smoking and socio-economic status (SES) and were excluded.(17-23) Five studies(14;16;24-26) did not provide numerical values for hazard ratios (HR) and associated 95% confidence intervals together with the

necessary data to enable standardization of the HR (to an increment of 10 parts per billion (ppb)). We do however note the qualitative findings from these studies. One study of respiratory mortality(27) 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 mortality. Finally, two studies(13;28) duplicated data presented in other publications(15;29) and were excluded. Hence, 14 studies met our inclusion/exclusion criteria and were included in our quantitative review. (9;10;12;15;26;29-37) 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 characterize/describe each cohort and to calculate standardized HRs and 95% confidence intervals expressed per 10 ppb increase in O_3 concentration. Where necessary, estimates reported in $\mu g/m^3$ were converted to ppb using 1 ppb=2 $\mu g/m^3$ at an ambient pressure of 1 atmosphere and a temperature of 25 °C. This process was undertaken by BB and checked by RWA.

The STATA program 'metan' was used to produce forest plots and to undertake random-effects meta-analysis where 3 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 therefore limiting the potential for selection bias.

RESULTS

Our literature search identified 14 publications from 8 cohorts reporting HRs for ozone and mortality and associated data to enable standardization. Key characteristics of each study are summarized in the Supplementary Material. 6 cohorts focused on selected population subgroups: Seventh Day Adventists non-Hispanic white non-smokers (ASHMOG), white subjects (Six Cities), male veterans with diagnosed hypertension (WU-EPRI), and three selected occupation cohorts: female teachers

(CTS), energy workers (Gazel) and Taiwanese civil servants (TCS). The American Cancer Society Cancer Prevention Study II (ACS CPS II) cohort was comprised of mainly friends, neighbours, acquaintances and relatives of volunteer recruiters. One study used administrative data to construct a primary care cohort (CPRD). The majority of cohorts (5/8) and publications (11/14) were from the US with the ACS CPS II cohort analyzed in 5 separate publications. 12/14 studies assessed associations with all-cause mortality and 11/14 cause-specific mortality. Summer or peak O_3 measures were assessed in 8/14 studies and 8/14 studies reported associations adjusted for $PM_{2.5}$.

All season

Standardized effect estimates, expressed as the HR (95% confidence interval) per 10 ppb increase in O_3, 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 O_3 concentrations and the risk of death from all-causes. Meta-analysis of the 7 HRs from the 6 cohorts gave a summary HR = 0.96, (95% CI: 0.92, 1.00) per 10 ppb increase in O_3 with evidence of heterogeneity (I^2=81%). Similarly, we did not find evidence for associations between long-term annual O_3 concentrations and deaths from cardiovascular, IHD, cardiopulmonary and respiratory diseases and lung cancer (Table 1).

Table 1 Meta-analytic summary estimates by cause of death. Hazard ratios expressed per 10 ppb increase in O_3.

Cause of Death	Study Citation	Number of Estimates	Hazard Ratio (95% Confidence Interval)	I^2 (%)‡
All year				
All-Causes	(9;15;29;30;34;36)	7*	0.96 (0.92, 1.00)	81
Cardiovascular	(9;12;32;36)	5*	0.98 (0.93, 1.04)	55
IHD	(9;29;36)	3	1.00 (0.92, 1.09)	72
Cardiopulmonary	(15;29;30)	4*	0.98 (0.90, 1.07)	59
Respiratory	(9;10;36)	3	0.94 (0.81, 1.10)	84
Lung Cancer	(9;15;29;30;36)	6*	0.95 (0.83, 1.08)	55
Warm season/peak ozone				
All-Causes	(29;34;36;37)	4	1.00 (0.99, 1.02)	46
Cardiovascular	(26;36;37)	3	1.01 (1.00, 1.02)	0
Respiratory	(26;36;37)	3	1.03 (1.01, 1.05)	0

* includes separate estimates for male & female members of AHSMOG cohort, hence number of cohorts is 1 less that the number of estimates in the meta-analysis; ‡ I^2 statistic

Warm season

O_3 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 3 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 subjects across the US and reported a HR for respiratory mortality of 1.03 (95% CI: 1.01, 1.05)per 10 ppb increase in the average daily maximum 1 hour ozone concentrations measured between April-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 O_3 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 $PM_{2.5}$

O_3 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 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 O_3 and all cause or cause specific mortality, other than the single estimate for respiratory mortality from the ACS CPS II cohort.(26)

Qualitative studies

Four of the 5 studies that did not provide numerical data to enable the standardization of the HR and confidence intervals and hence inclusion in our quantitative review found no evidence of statistically significant associations with mortality.(14;16;25;38) The fifth study reported elevated significant overall associations with mortality.(24)

DISCUSSION

This quantitative systematic review of the evidence for an association between long-term exposure to O_3 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 O_3 concentrations and the risk of death. Studies that used O_3 concentrations measured during the

warmer months or peak ozone (95% percentile of daily maximum 1 hour 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 O_3 have provided narrative assessments of the cohort literature as part of comprehensive assessments of the epidemiological and toxicological evidence.(1;6) Prueitt and colleagues(39) utilized the studies identified in the EPA review as a basis for a weight of evidence analysis for long-term exposure to O_3 and cardiovascular disease. Cohort studies published since earlier reviews(7;8) were examined and revisions to previous concluding statements considered. Our focus on a quantitative 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 re-analyses as well as basic information such as subject 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 hazard ratios for use in health impact assessment exercises. Concentration response functions from cohort studies have been used previously in burden and impact calculations.(11;40) A disadvantage of our quantitative approach is that it does not reflect the diversity between studies in the methods for estimating exposure to O_3, 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 hour concentrations and these may not be the most appropriate measure of lower (by definition) long-term average exposures to O_3. Studies using such metrics may actually be investigating associations with repeat exposures to the highest O_3 concentrations rather than investigating associations with long-term (i.e. cumulative) exposure. However, cohort studies exploit spatial variation in individual exposure estimates and report hazard ratios for an increment in the O_3 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 O_3 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 O_3. One cohort comprised subjects with pre-existing medical conditions,(33) and others selected subjects based upon employment(12;36;37) or specific subject characteristics.(30) The ACS CPSII cohort utilized friends, neighbours, acquaintances and relatives of volunteers and is therefore unlikely to representative of the US general population and the Six Cities cohort is restricted to white subjects. Only the English cohort based upon an administrative database of patients registered with General Practitioners (which is almost universal in the UK) is population based. Whilst studies in selected sub-groups support hazard assessment, their findings have limited application in quantifying the risk in the general population. The use of large, linked administrative databases(9) 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 US in order to provide a broader evidence base across a range of O_3 concentrations and where relationships between O_3 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 O_3.(1) 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.(11)

A number of publications using the ACS CPS II cohort have assessed associations between O_3 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 and colleagues(29) reported results for O_3 measured both throughout the year and during April-September. They found stronger associations for cardiopulmonary mortality using measures of O_3 during the warmer months compared to all year (incorporating comparable confounder adjustment – Table 3(29); 1.03 (95%CI 1.02, 1.04) vs. 1.01 (95%CI 1.00, 1.03) respectively. Similarly, Lipfert and colleagues reported a positive association between peak exposure (95% percentile of daily maximum hourly ozone) and mortality but not with the annual mean.(33) However, this pattern of associations was not observed in a similar comparison using the CTS cohort.(36)

The reasons for the modest differences between HRs estimated using warm season and all year concentrations in the ACS study are not clear. One possibility is that exposure measurement error varies between seasons due to different patterns of human behaviour (e.g. time spent outdoors or window opening).(41) It may suggest a non-linear concentration response function with larger HRs during the higher ozone concentrations experienced during the warmer months compared to the cooler months of the year though we note that O_3 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.(29) An analysis of summer ozone concentrations using the ACS(26) 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. Jerrett et al.(26), in their analyses of summer ozone concentrations in the US, 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 NO_2 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.(42;43) 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(4;44) indicate that, overall, the net impact of climate change on surface ozone is generally a decrease in remote (low NO_x) areas, but an increase in some densely populated (high NO_x) areas.(45) Human exposure to ambient ozone may also be affected by behavioural changes arising from adaptive strategies.(46) Studies of long-term exposure to ozone may therefore have increasing relevance in the future if concentrations of ozone rise in densely populated urban areas.

Our quantitative review of the literature revealed a paucity of independent, population-based studies regarding the effects of long-term exposure to ozone on mortality. Furthermore, the evidence from outside the US was very limited. However, there is a suggestion of a modest, adverse association between long-term ozone concentrations measured during the warmer months of the year and cardiopulmonary and respiratory mortality. The need for concentration response functions for burden estimation and evaluation of impacts of climate change will require further large, population-based cohorts utilizing comparable ozone metrics.

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Figure Captions

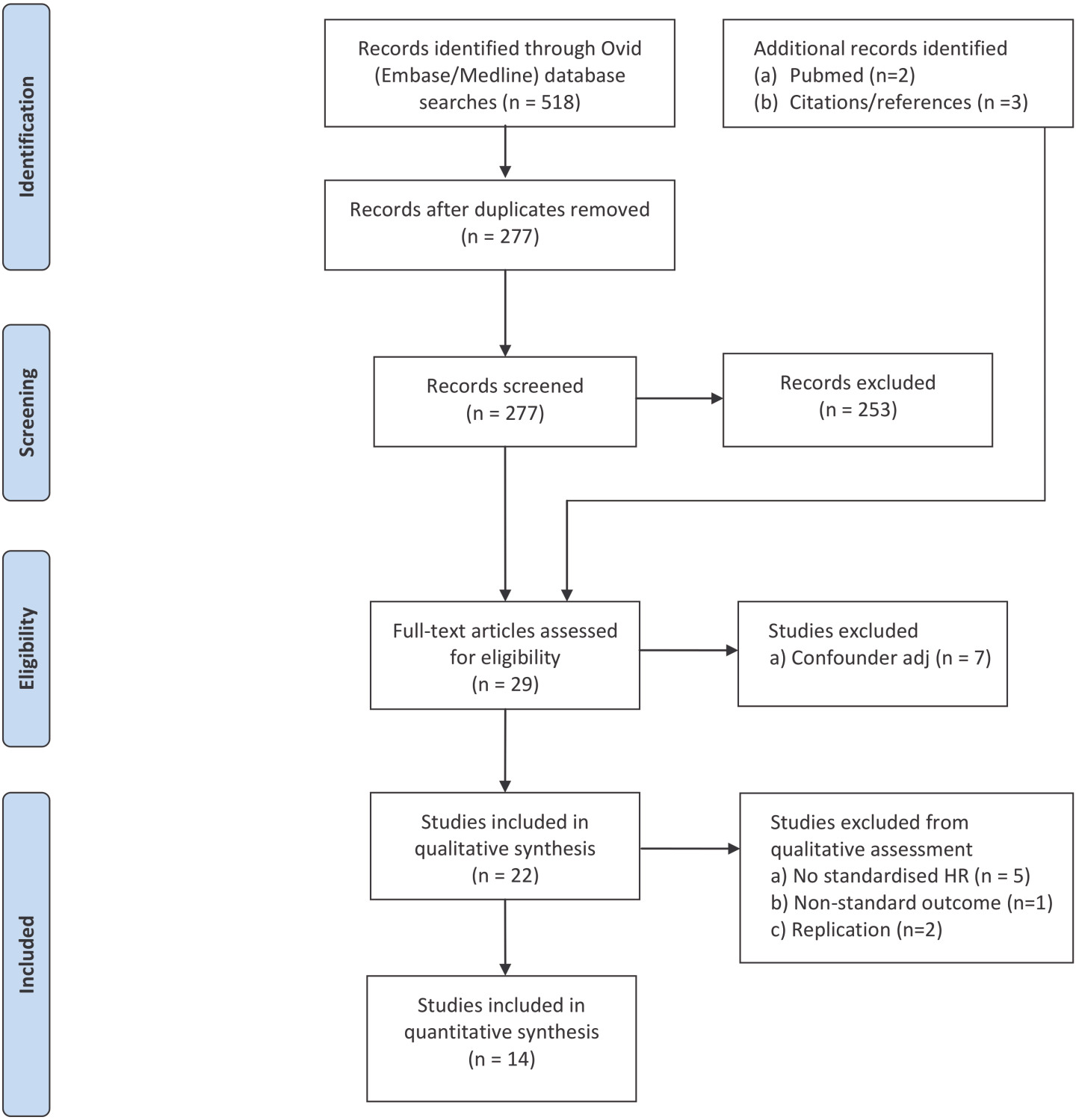
Figure 1 Overview of ascertainment of studies

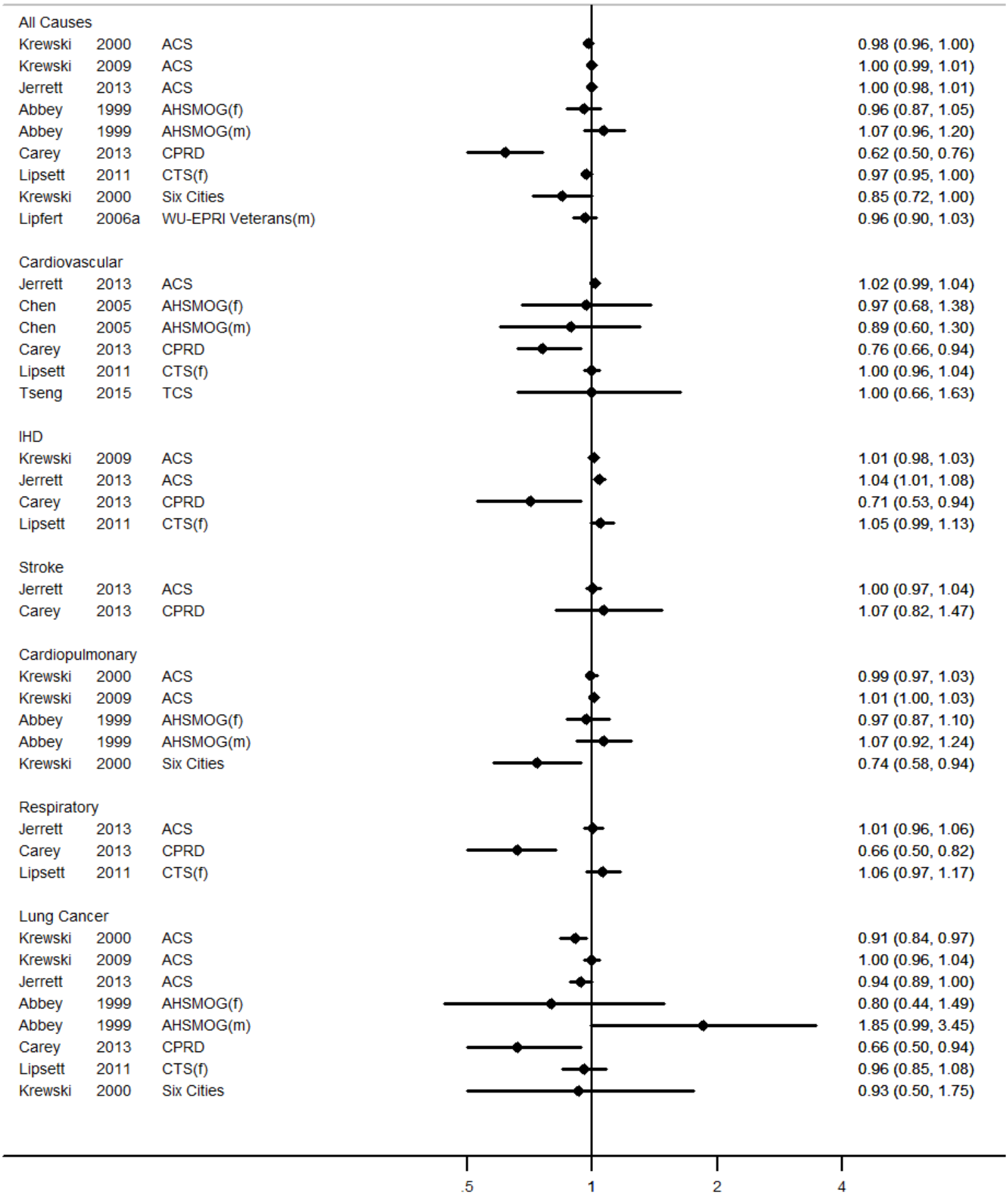
Figure 2: Relative Risk (95% CI) of death per 10 ppb increase in long-term exposure to ozone

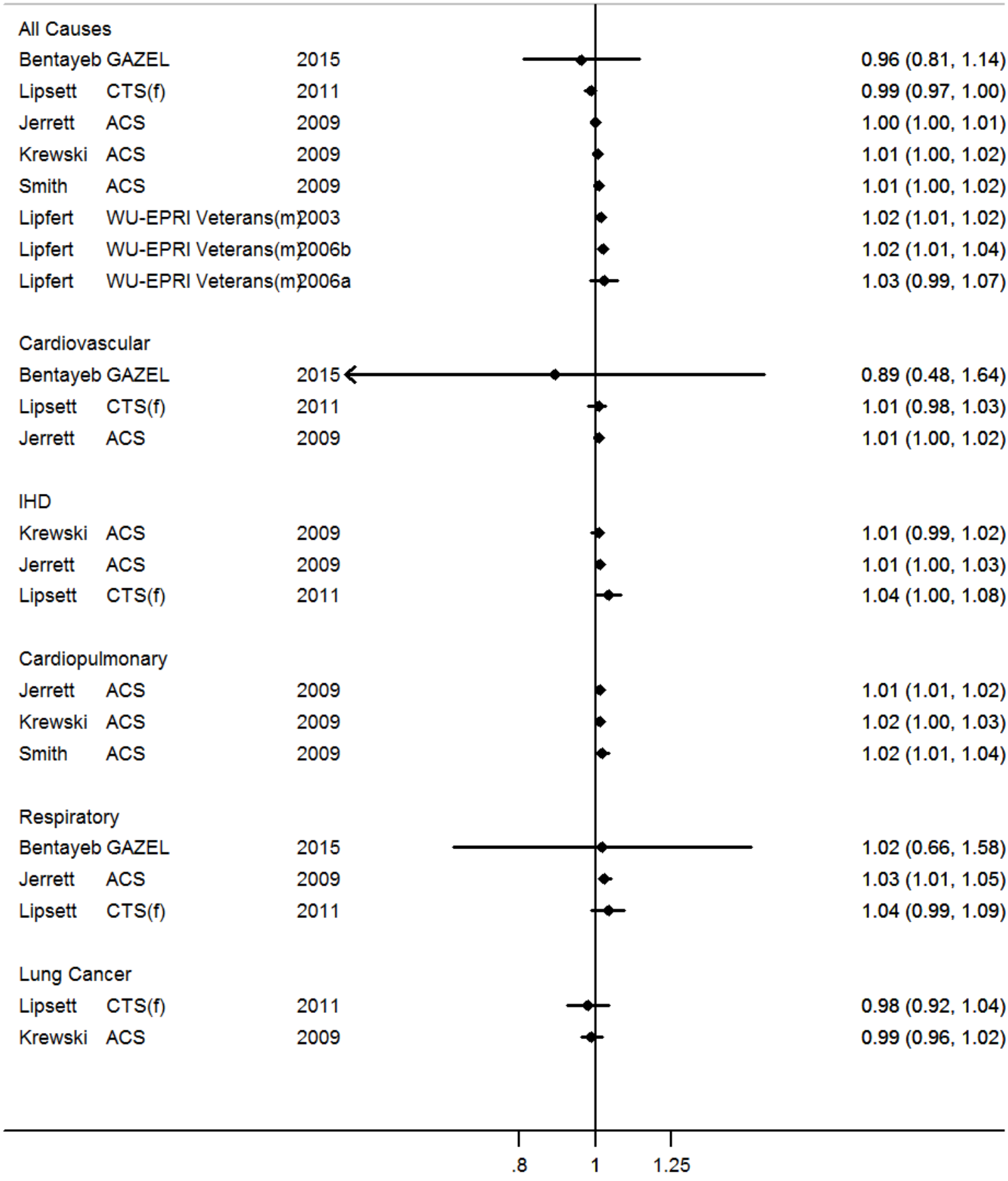
Figure 3: Relative Risk (95% CI) of death per 10 ppb increase in long-term 'warm-season' ozone exposure

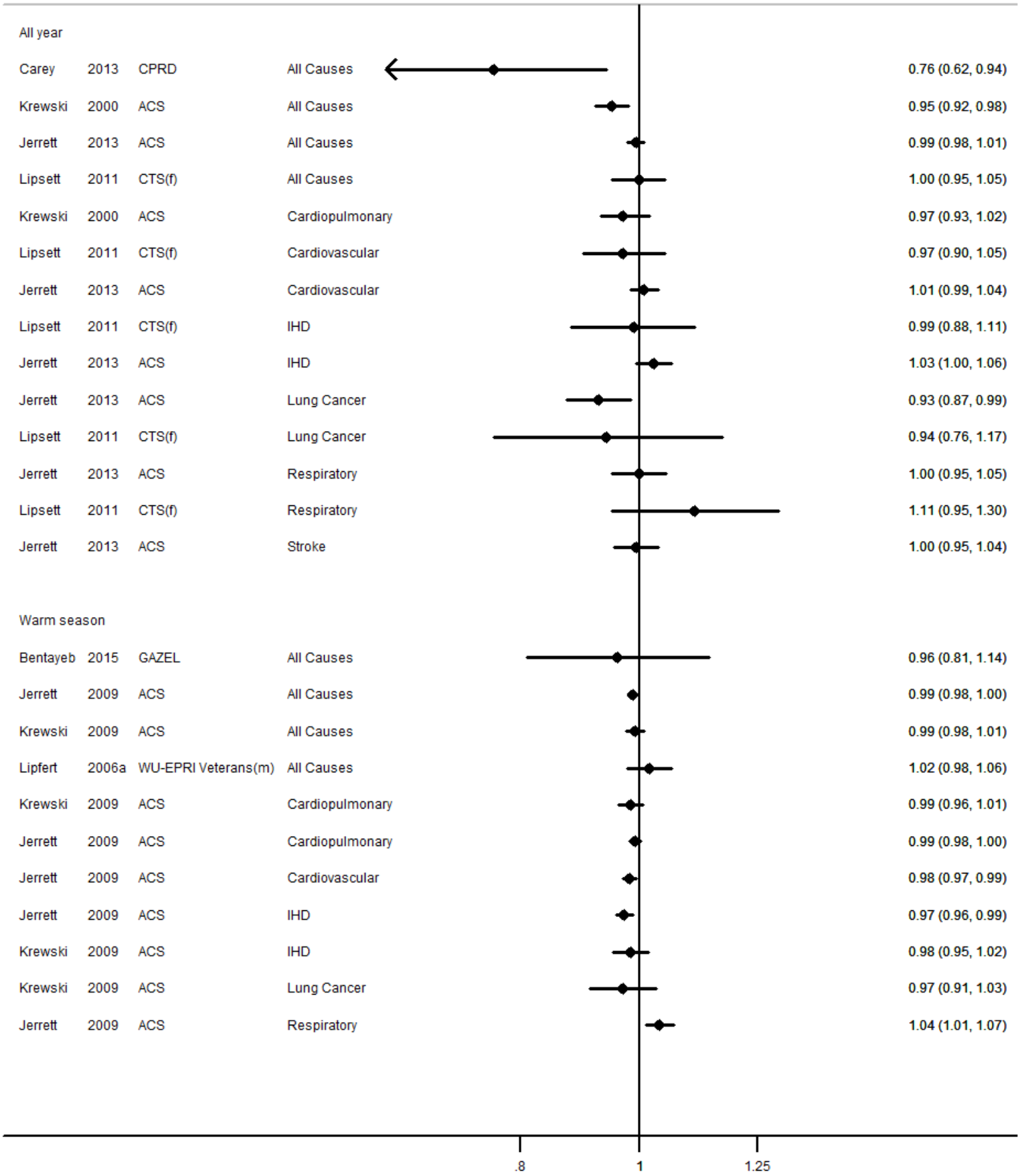
Figure 4: Relative Risk (95% CI) of death per 10 ppb increase in long-term ozone exposure, adjusted for long term-exposure to $PM_{2.5}$

Note: Krewski 2009 assumed per 10 ppb


Identification
Screening
Eligibility
Included
Records identified through Ovid (Embase/Medline) database searches (n = 518)
Additional records identified
(a) Pubmed (n=2)
(b) Citations/references (n =3)
Records after duplicates removed (n = 277)
Records screened (n = 277)
Records excluded (n = 253)
Full-text articles assessed for eligibility (n = 29)
Studies excluded
a) Confounder adj (n = 7)
Studies included in qualitative synthesis (n = 22)
Studies excluded from qualitative assessment
a) No standardised HR (n = 5)
b) Non-standard outcome (n=1)
c) Replication (n=2)
Studies included in quantitative synthesis (n = 14)


Study
Year
Cohort
RR (95% CI)
All Causes
Krewski 2000 ACS 0.98 (0.96, 1.00)
Krewski 2009 ACS 1.00 (0.99, 1.01)
Jerrett 2013 ACS 1.00 (0.98, 1.01)
Abbey 1999 AHSMOG(f) 0.96 (0.87, 1.05)
Abbey 1999 AHSMOG(m) 1.07 (0.96, 1.20)
Carey 2013 CPRD 0.62 (0.50, 0.76)
Lipsett 2011 CTS(f) 0.97 (0.95, 1.00)
Krewski 2000 Six Cities 0.85 (0.72, 1.00)
Lipfert 2006a WU-EPRI Veterans(m) 0.96 (0.90, 1.03)
Cardiovascular
Jerrett 2013 ACS 1.02 (0.99, 1.04)
Chen 2005 AHSMOG(f) 0.97 (0.68, 1.38)
Chen 2005 AHSMOG(m) 0.89 (0.60, 1.30)
Carey 2013 CPRD 0.76 (0.66, 0.94)
Lipsett 2011 CTS(f) 1.00 (0.96, 1.04)
Tseng 2015 TCS 1.00 (0.66, 1.63)
IHD
Krewski 2009 ACS 1.01 (0.98, 1.03)
Jerrett 2013 ACS 1.04 (1.01, 1.08)
Carey 2013 CPRD 0.71 (0.53, 0.94)
Lipsett 2011 CTS(f) 1.05 (0.99, 1.13)
Stroke
Jerrett 2013 ACS 1.00 (0.97, 1.04)
Carey 2013 CPRD 1.07 (0.82, 1.47)
Cardiopulmonary
Krewski 2000 ACS 0.99 (0.97, 1.03)
Krewski 2009 ACS 1.01 (1.00, 1.03)
Abbey 1999 AHSMOG(f) 0.97 (0.87, 1.10)
Abbey 1999 AHSMOG(m) 1.07 (0.92, 1.24)
Krewski 2000 Six Cities 0.74 (0.58, 0.94)
Respiratory
Jerrett 2013 ACS 1.01 (0.96, 1.06)
Carey 2013 CPRD 0.66 (0.50, 0.82)
Lipsett 2011 CTS(f) 1.06 (0.97, 1.17)
Lung Cancer
Krewski 2000 ACS 0.91 (0.84, 0.97)
Krewski 2009 ACS 1.00 (0.96, 1.04)
Jerrett 2013 ACS 0.94 (0.89, 1.00)
Abbey 1999 AHSMOG(f) 0.80 (0.44, 1.49)
Abbey 1999 AHSMOG(m) 1.85 (0.99, 3.45)
Carey 2013 CPRD 0.66 (0.50, 0.94)
Lipsett 2011 CTS(f) 0.96 (0.85, 1.08)
Krewski 2000 Six Cities 0.93 (0.50, 1.75)
.5
1
2
4


Study Cohort Year RR (95% CI)
All Causes
Bentayeb GAZEL 2015 0.96 (0.81, 1.14)
Lipsett CTS(f) 2011 0.99 (0.97, 1.00)
Jerrett ACS 2009 1.00 (1.00, 1.01)
Krewski ACS 2009 1.01 (1.00, 1.02)
Smith ACS 2009 1.01 (1.00, 1.02)
Lipfert WU-EPRI Veterans(m) 2003 1.02 (1.01, 1.02)
Lipfert WU-EPRI Veterans(m) 2006b 1.02 (1.01, 1.04)
Lipfert WU-EPRI Veterans(m) 2006a 1.03 (0.99, 1.07)
Cardiovascular
Bentayeb GAZEL 2015 0.89 (0.48, 1.64)
Lipsett CTS(f) 2011 1.01 (0.98, 1.03)
Jerrett ACS 2009 1.01 (1.00, 1.02)
IHD
Krewski ACS 2009 1.01 (0.99, 1.02)
Jerrett ACS 2009 1.01 (1.00, 1.03)
Lipsett CTS(f) 2011 1.04 (1.00, 1.08)
Cardiopulmonary
Jerrett ACS 2009 1.01 (1.01, 1.02)
Krewski ACS 2009 1.02 (1.00, 1.03)
Smith ACS 2009 1.02 (1.01, 1.04)
Respiratory
Bentayeb GAZEL 2015 1.02 (0.66, 1.58)
Jerrett ACS 2009 1.03 (1.01, 1.05)
Lipsett CTS(f) 2011 1.04 (0.99, 1.09)
Lung Cancer
Lipsett CTS(f) 2011 0.98 (0.92, 1.04)
Krewski ACS 2009 0.99 (0.96, 1.02)
.8
1
1.25


Study
Year
Cohort
Cause
RR (95% CI)
All year
Carey 2013 CPRD All Causes 0.76 (0.62, 0.94)
Krewski 2000 ACS All Causes 0.95 (0.92, 0.98)
Jerrett 2013 ACS All Causes 0.99 (0.98, 1.01)
Lipsett 2011 CTS(f) All Causes 1.00 (0.95, 1.05)
Krewski 2000 ACS Cardiopulmonary 0.97 (0.93, 1.02)
Lipsett 2011 CTS(f) Cardiovascular 0.97 (0.90, 1.05)
Jerrett 2013 ACS Cardiovascular 1.01 (0.99, 1.04)
Lipsett 2011 CTS(f) IHD 0.99 (0.88, 1.11)
Jerrett 2013 ACS IHD 1.03 (1.00, 1.06)
Jerrett 2013 ACS Lung Cancer 0.93 (0.87, 0.99)
Lipsett 2011 CTS(f) Lung Cancer 0.94 (0.76, 1.17)
Jerrett 2013 ACS Respiratory 1.00 (0.95, 1.05)
Lipsett 2011 CTS(f) Respiratory 1.11 (0.95, 1.30)
Jerrett 2013 ACS Stroke 1.00 (0.95, 1.04)
Warm season
Bentayeb 2015 GAZEL All Causes 0.96 (0.81, 1.14)
Jerrett 2009 ACS All Causes 0.99 (0.98, 1.00)
Krewski 2009 ACS All Causes 0.99 (0.98, 1.01)
Lipfert 2006a WU-EPRI Veterans(m) All Causes 1.02 (0.98, 1.06)
Krewski 2009 ACS Cardiopulmonary 0.99 (0.96, 1.01)
Jerrett 2009 ACS Cardiopulmonary 0.99 (0.98, 1.00)
Jerrett 2009 ACS Cardiovascular 0.98 (0.97, 0.99)
Jerrett 2009 ACS IHD 0.97 (0.96, 0.99)
Krewski 2009 ACS IHD 0.98 (0.95, 1.02)
Krewski 2009 ACS Lung Cancer 0.97 (0.91, 1.03)
Jerrett 2009 ACS Respiratory 1.04 (1.01, 1.07)
.8
1
1.25

Supplementary Material

Contents

1. Search terms used in OVID and PubMed searches

2. Inclusion/Exclusion criteria

3 Characteristics of cohorts selected for quantitative review

1. Search terms used in OVID and PubMed searches

OVID

1) “cohort” AND “mortality” AND “ozone”

2) “cohort” AND “mortality” AND “O3”

3) “cohort” AND “mortality” AND “long term” AND “air pollution”

PubMed

1) “cohort” AND “mortality” AND “ozone”

2) “cohort” AND “mortality” AND “O3”

3) “cohort” AND “mortality” AND “air pollution”

2. Inclusion/Exclusion criteria

a) Type of article: conference abstracts, conference papers, reviews (with no new study results), letters and notes were excluded.

b) Study Design: Prospective and retrospective cohort studies were included. Study designs excluded from the review were: nested case-control studies, time-series and case-crossover analyses; prevalence studies.

c) Outcome: Mortality. Studies of disease incidence were excluded.

d) Exposure: Long-term ozone.

e) Individual-level covariate data: studies without individual level data i.e. fully ecological covariates were excluded.

f) Covariate adjustment: individual level age, sex, body mass index and smoking and an individual level or ecological level marker of socio-economic status (e.g. education, income, deprivation index).

g) Standardisation: Studies included if they reported numeric values (i.e. not in graphical format) for the hazard ratio, pollutant concentration range used to calculate the HR and a measure of precision (standard error or confidence limit value).

3 Characteristics of cohorts selected for quantitative review

Cohort/ Country	Subject selection	Age (years)	Publication	n	Follow-up period	Exposure period	Exposure scale	Exposure Metric	Covariate Adjustment
Six Cities USA	Random sample from white subjects in six communities	25-74	Krewski 2000	8,111	1974-1989	1977-1985	Monitor, City mean	All year, Mean	Age, sex, BMI, smoking, alcohol, education, marital status
ACS CPS II USA	Friends & neighbors of ACS volunteers	30+	Krewski 2000	552,138 (295,223 with $PM_{2.5}$)	1982-1989	1980	Monitor City (117) mean	All year Cool season (Oct-Mar) Warm season (Apr-Sept) Daily max 1-hr	Age, sex, BMI, smoking, alcohol, education, marital status, occupational exposure to air toxics
			Krewski 2009	531,826	1982-2000	1980	Monitor MSA (118) mean	All year Warm season (Apr-Sept) Mean	Individual: age, sex, BMI, smoking, race, education, marital status, alcohol, diet, PM occupational exposure Ecological: air conditioning, education, ethnicity, income, unemployment, income disparity & poverty

				22,905 Los Angeles	1982-2000	2000	Monitor Interpolation using universal kriging to 267 ZCAs	All year Average of 4 highest 8-hour means	As for main analyses except poverty replaced by population
			Jerrett 2009	448,850	1982-2000	1977-2000	Monitor MSA (96) mean	Warm season (Apr-Sept) Daily max 1-hr	Individual: age, sex, BMI, education, race, smoking, diet, marital status, occupational PM, alcohol. Ecological: air conditioning, education, ethnicity, income unemployment, income disparity & poverty
			Smith 2009	352,242	1982-2000	1980	Monitor MSA (66) mean	Warm season (Apr-Sept) Mean	As for Jerrett 2009
			Jerrett 2013	73,711	1982-2000	1988-2002	Monitor <50km (262 sites) IDW estimate to individual	All year Mean	Individual: 42 variables similar to Krewski 2009. Ecological: unemployment, poverty, income disparity & ethnicity.
ASHMOG USA	Seventh Day Adventists, white, non-Hispanic non-smokers	27-95	Abbey 1999	4,060 (f) 2,278 (m)	1977-1992	Time varying, 1973-1992	Monitor<50km Interpolation to ZIP code	All year Mean & 8-hr mean	Age, sex, smoking, BMI, education, occupational pollutants as appropriate

			Chen 2005	2,090 (f) 1,149 (m)	1976-1998	Time varying, 1973-1998	Monitor <50km Interpolation to ZIP code	All year Mean	Age, sex, BMI, education, meat consumption,
WU-EPRI USA	Male veterans with hypertension	Mean (SD) 51 (12)	Lipfert 2003	54,292 (m)	1976-1996	1982-1988	Monitor County mean	All year 95th percentile	Age, race, smoking, BMI, SBP, 'selected ecological covariates'
			Lipfert 2006a	Not given (subset with PM)	1997-2001	1999-2001	Monitor County mean	All year 24-hr, 95thpercentile (Daily max 1-hr)	As for Lipfert 2003
			Lipfert 2006b	25,736 (m)	1989-2001	1989-1996	Monitor County mean	All year 95thpercentile (Daily max 1-hr)	As for Lipfert 2003
CTS USA	Female teachers	30+	Lipsett 2011	101,784 (f)	1997-2005	Time varying, 1996-2005	Monitor <20km IDW estimate to individual	All year Mean	Individual: Age, race, smoking, BMI, marital status, alcohol, physical activity, diet, menopausal status, hormone therapy use, family history of MI or stroke, blood pressure medication, aspirin use. Ecological: income, income inequality, education, population size,

									racial composition, unemployment.
CPRD England	GP Practices participating in CPRD	40-89	Carey 2013	824,654	2003-2007	2002	Monitor Interpolation to 1km^2	All year Mean	Age, sex, BMI, smoking, area-level socio-economic status (income)
Gazel France	EDF-GDF workers	Mean (SD) 43.7 (3.5)	Bentayeb 2015	20,327	1989-2013 (1989-2010 or cause-specific mortality)	1989	CTM 2km resolution zipcode of residential address	Summer mean daily max 8-hr	Individual: Age, sex, BMI, marital status, education, occupational level, smoking status, alcohol intake, region of residence. Ecological: deprivation index income, mean temperature, principal road network, population density.
TCS Taiwan	Civil servants in Greater Taipei area	Mean (SD) 39.7 (10.8) to 42.5 (10.5)	Tseng 2015	43,227	1992-2008	2000-2008	Monitor data: district level	All year mean	Age, sex, marital status, income, smoking, alcohol, BMI, education