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Long-term concentrations of nitrogen dioxide and mortality: a meta-analysis of cohort studies

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ABSTRACT

Background

Concentrations of outdoor nitrogen dioxide (NO_2) have been associated with increased mortality. Hazard ratios (HRs) from cohort studies are used to assess population health impact and burden. We undertook meta-analyses to derive concentration-response functions suitable for such evaluations and assessed sensitivity of the summary estimates to study selection based upon a range of cohort characteristics.

Methods

We searched Medline, Embase, Web of Science and existing reviews for cohort studies published to October 2016 reporting HRs for NO_2 and mortality. Meta-analytic summary estimates were calculated using fixed/random-effects models. Potential effect modification by a number of study and cohort characteristics was assessed using sub-group meta-analysis.

Results

Forty-eight articles analysing 28 cohorts were identified. Meta-analysis of HRs found positive associations between NO_2 and all-cause[1.02 (95% CI: 1.01, 1.03); prediction interval (PI): (0.99, 1.06) per 10μg/m^3 increment in NO_2], cardiovascular (1.03 (95% CI: 1.02,1.05); PI: (0.98, 1.08)) , respiratory (1.04 (95% CI: 1.01,1.05); PI: (0.97, 1.11))and lung cancer mortality (1.05 (95% CI: 1.02,1.08); PI: (0.94, 1.17)) with evidence of substantial heterogeneity between studies. In subgroup analysis, summary HRs varied by age at cohort entry, spatial resolution of pollution estimates and adjustment for smoking and BMI at the individual level; for some sub-groups the HR was close to unity, with lower confidence limits below 1.

Conclusions

Given the many uncertainties inherent in the assessment of this evidence base and the sensitivity of health impact calculations to small changes in the magnitude of the HRs, calculation of the impact on health of policies to reduce long-term exposure to NO_2 should utilize prediction intervals and report ranges of impact rather than focusing upon point estimates.

INTRODUCTION

Epidemiological studies have reported associations between long-term concentrations (typically averaged over a year or more) of outdoor air pollution and a range of health endpoints. Outdoor air pollution comprises a mixture of particles and gases, emitted directly from the combustion of fossil fuels or formed from secondary chemical reactions in the air. The evidence for ambient particulate matter monitored as $PM_{2.5}$ (mass per m^3 of particles of aerodynamic diameter generally less than 2.5µm) has been extensively reviewed and judged sufficient to infer a causal, adverse effect on a range of health outcomes.[1,2]

Nitrogen dioxide (NO_2) is a respiratory toxicant gas which in outdoor air is derived primarily from the oxidation of nitric oxide (NO). In urban areas, the predominant source of NO and NO_2, as well as carbon particles, carbon monoxide and other pollutants, is motor vehicle exhaust. A growing number of cohort studies have exploited spatial variability in long-term NO_2 concentrations estimated using pollution models based upon the interpolation of monitoring data, land use regression (LUR) or dispersion models[3] to investigate associations with mortality or disease incidence. Recent systematic reviews and meta-analyses have assessed the evidence from cohort studies published to 2013/2014 and reported associations between NO_2 concentrations and mortality from all-cause, cardiovascular and respiratory diseases[4,5] and lung cancer[6]. An assessment of the evidence for oxides of nitrogen conducted by the US Environmental Protection Agency (EPA) Integrated Science Assessment[7] including toxicological and epidemiological evidence across a wide range of health endpoints concluded that "the evidence is suggestive of, but not sufficient to infer, a causal relationship between long-term exposure to NO_2 and mortality among adults." This extensive review included cohort studies published up to 2014 but did not undertake meta-analyses nor attempt to establish concentration response functions for use in health impact calculations. A similar conclusion was reached by Health Canada following their review.[8]

Summary risk estimates (hazard ratios (HRs)) from meta-analyses of cohort studies are used in policy evaluations to assess the health impact and burden of current, and future, pollutant concentrations.[9] These calculations usually apply to the general population of a defined geographical area and the results are often widely reported/discussed in the mainstream media outlets. In air pollution epidemiology, HRs are generally small (close to 1) indicating low individual risk. However, because of the ubiquitous nature of ambient air pollution and the very large populations exposed, small HRs can translate into important, and substantial, consequences for health at the population level. The

process used to derive the summary HRs, including decisions on included studies, appropriate analytical model, assessment of heterogeneity and effect modification are therefore important.

In this study we undertook a systematic search of the literature to identify cohort studies examining the association between long-term concentrations of NO_2 and mortality. We used stratified meta-analyses to assess the sensitivity of summary HRs to the selection of studies with different cohort and study characteristics and considered the implications for the selection of concentration-response functions (CRFs) for use in health impact assessment (HIA) in a general population. We also calculated prediction intervals and considered their relevance for HIA exercises. Our study updates previous reviews by including studies published to October 2016 and incorporating a wider range of causes of death.

METHODS

To identify publications reporting results from cohort studies of NO_2 and mortality we conducted a broad search of the online medical databases supplemented with citation searches of recently published literature reviews.

Search strategy

The search string "cohort & ('no2' or 'nitrogen dioxide' or 'air pollution') & mortality" was applied to: a) Ovid Medline (R) without Revisions for the period 1996 to October Week 2 2016 and Embase for the period 1996 to 2016 Week 42; b) Web of Science (1970 to October 2016); and c) Pubmed (1966 to October 2016). We also searched citations in 5 review articles.[4-6,10,11] Studies identified in each search were combined and duplicates removed leaving 959 studies to be assessed.

Inclusion/exclusion criteria

Studies were screened by study title and abstract. Inclusion criteria were: 1) cohort studies including individual-level covariate information; and 2) a 'long-term' exposure metric for NO_2, i.e. annual or multi-year averages. Exclusion criteria were: 1) conference abstracts, conference papers, notes, editorials and letters; 2) cross-sectional, case-control and nested case-control study designs; 3) mean daily or monthly NO_2 exposure metrics (short-term exposure (time series) studies); and 4) study population selected because of close proximity to a specific pollution sources (e.g. waste incinerators). After applying these inclusion/exclusion criteria, 73 studies remained and were subject to full text review.

Suitability of these studies for inclusion in the quantitative assessment was assessed as follows: studies were excluded if: 1) they reported results for NO_X rather than NO_2 (n=5); 2) replicated results from previous publications (n=7); or 3) did not provide quantitative HRs together with a measure of precision (standard errors or 95% confidence intervals) and adequate information to enable standardisation of the HR per 10μg/m^3 increase in NO_2 (n=13). 48 studies remained from which data characterising the outcome, HR and other relevant information were extracted. Figure 1 summarizes the literature search and study assessment.

Data extraction and coding

Cohort and estimate level information were extracted from each paper and entered into an EXCEL database. These data included cohort name, country, cohort description, date of enrolment of cohort members, age at enrolment, number of subjects, follow-up period, exposure period and exposure assessment method (measured/modelled). The level of covariate adjustment was also recorded including individual-level age, sex, smoking and BMI and level of adjustment for a marker of socioeconomic status (e.g. education level, income etc.) at either the individual or ecological level. All HRs were standardised to 10μg/m^3 increase in NO_2. Where the units used in the original study were ppb, a conversion factor of 1.88μg/m^3 per 1ppb was used (assuming 25°C and 1013mb atmospheric pressure).

Meta-analysis

Where studies reported results for various follow-up periods for the same cohort, we selected studies using the most recent follow-up period. If results for the same outcomes were available for the full cohort and a subset, we used results from the full cohort unless these results were considered to be out of date (e.g. statistical analysis, exposure assessment, date of last follow-up). Two studies from the same cohort were only included if they provided results for different outcomes.

Analyses were conducted in STATA Version 12 (StataCorp. 2011). All studies reported HRs together with 95% confidence intervals. Therefore estimates of the standard error were derived using each limit value and the two estimates averaged. Forest plots were used to display study information and HRs graphically. Articles used different terms to describe causes of death and were grouped together for meta-analysis according to terms and ICD codes where available (eTable 1,). Meta-analytic summary estimates were calculated using fixed and random effects models using the

program 'metan' in STATA. Heterogeneity was assessed using the I^2 statistic. Prediction intervals were calculated when heterogeneity was identified.[12] Small study bias was assessed using Begg[13] and Egger[14] tests and the Trim and Fill procedure[15].

A series of stratified analyses assessed potential effect modification by both cohort and study characteristics. Cohort characteristics included: 1) study population - general population cohorts *vs*. cohorts using subjects with pre-existing disease; and 2) age at recruitment, cohorts based upon adults across a wide age range at recruitment *vs.* cohorts in selected ages at cohort entry. As the focus of our investigation was the identification of CRFs for use in HIA, we selected cohorts conducted in the general population and without narrow age restriction at cohort entry for further stratified analyses by study characteristics. These included: 1) adjustment for individual measures of BMI and smoking *vs.* no adjustment or use of area-level estimates of BMI and / or smoking; and 2) use of LUR models to estimate residential NO_2 concentrations *vs.* area-based concentration estimates. Our assessment of differences between strata was based upon the sizes of the respective summary HRs and the statistical significance of differences between HRs in the subgroup analyses derived using the method of Altman and Bland.[16]

RESULTS

The 48 articles identified in the review analysed 28 cohorts (including the ESCAPE study comprising 22 separate cohorts)[17-64]. eTable 2 provides a description of each article/cohort including cohort size and geographical location, subject characteristics, exposure assessment and control for key individual confounders. Cohorts were studied in Europe (13 plus the ESCAPE consortium of cohorts), North America (10), Taiwan (1), China (2) and Japan (2).

HRs for NO_2 and all-cause mortality were reported in 32 studies (22 cohorts including ESCAPE) and cause-specific mortality in 41 studies (24 cohorts including ESCAPE).

All-cause mortality

Of the 32 studies reporting results for all-cause mortality (eFigure 1), 11 studies, selected according to our *a priori* algorithm, were excluded from the meta-analyses: 3 studies [38,40,53] because their results were included in the ESCAPE meta-analysis[20] and 8 studies as the same cohorts were analysed in other publications included in our review[26,31,41,43,46,47,62,64]. In one article[42], results for two cohorts were reported – the HR for the ACS CPS II cohort reported in this study was not used, the

more recent re-analyses of the ACS CPS II cohort[60] selected instead. Following these exclusions, results from 20 separate cohorts (including the ESCAPE consortium of 22 individual cohorts) reported results for NO_2 and all-cause mortality. In the fixed-effects meta-analysis (eFigure 2a), three large administrative cohorts[25,30,35] and the ACS study[60] accounted for 80% and 11% of the weight respectively. Meta-analysis indicated a high level of heterogeneity between study HRs (I^2=84%). The random-effects summary HR was 1.02 (95% CI: 1.01, 1.03; prediction interval (PI): 0.99 to 1.06) per 10μg/m^3 increment in NO_2 (Table 1 and eFigure 2b). Begg and Egger tests for small study bias returned P-values of 0.3 and 0.9 respectively. Application of the trim and fill technique indicated the need to impute 2 additional study estimates to adjust for small study bias assuming a fixed-random effects model although the adjusted HR (and 95% CI) remained unchanged.

Five studies investigated associations with mortality in cohorts selected on the basis of pre-existing disease: survivors of stroke[50], CHD[55], Acute Coronary Syndrome[58]; attendees at respiratory clinic[44] and hypertensive US veterans[48] (eFigure 3). Meta-analysis of these studies gave a summary HR of 1.04 per 10μg/m^3 increment in NO_2 compared to 1.02 for the 15 cohorts recruiting subjects from the general population (Table 1).

Eleven of the 15 cohorts recruited adults within a broad age range and 4 cohorts limited recruitment to narrower age ranges: 35-50[22], 55-69 years[23], 25-59 years[34] and 65-84 years of age[61] (eFigure 4). A stratified meta-analysis indicated a substantial, statistically significant (P=0.04) difference in the summary HRs between cohorts recruiting adults over a broad age range compared to cohorts restricting age at entry, 1.02 *vs.* 1.08 per 10μg/m^3 increment in NO_2 respectively (Table 1).

For the 11 cohorts that recruited adults within a broad age range , Figure 2 shows the cohort specific HRs and meta-analytic summary estimates stratified by A) level of covariate adjustment i.e. those controlling for required confounding factors including individual BMI and smoking status and those that did not; B) the spatial resolution of the estimated NO_2 concentrations i.e. LUR models predicting concentrations at subjects' residential addresses *vs.* estimates for larger geographical areas derived from models or interpolation of data from monitoring stations; and C) ordered by study mean/median NO_2 concentration. HRs from studies that controlled for individual measures of BMI and smoking were more variable and less precise than HRs from studies lacking this level of covariate adjustment. Summary HRs for the two sub-groups are presented in Table 1 and indicate a larger summary HR for studies without control for individual measures of BMI and smoking compared to studies that did (1.03 *vs.* 1.00 per 10μg/m^3 increment in NO_2, a difference that was

statistically significant (P=0.03)). Studies that used estimated area-level concentrations of NO_2 were more variable and less precise than studies that used LUR-based residential concentration estimates and when meta-analysed gave a smaller summary HR (1.00) compared to studies using residential LUR estimates (1.03). Three administrative cohorts constructed from national registries rather than recruitment of individuals accounted for 3/4 studies that did not adjust for individual-level BMI and smoking and 3/6 studies that used residential concentration estimates from LUR models. When ordered by study mean/median NO_2 concentration (Figure 2C) there was a suggestion of a downward trend in the size of the HR as study mean NO_2 concentrations increased. Meta-regression confirmed this impression though the trend was not statistically significant (data not shown).

Cause specific mortality

Cardiovascular

Twenty-two studies reported results for cardiovascular mortality (eFigure 5). Two studies[53,56] were excluded from the meta-analyses as their results were included in the ESCAPE meta-analysis[21] and 4 studies were excluded as the same cohorts were analysed in other publications included in our review[19,31,43,62]. One study from China[63] reported a (precisely estimated) HR in excess of 2.4 per 10μg/m^3 increment in NO_2. The authors were cautious about the validity of this extreme finding in the Shenyang cohort and therefore the study was excluded from further analyses.

The random-effects summary HR for the remaining 15 studies was 1.03 (95% CI: 1.02, 1.05; PI: 0.98, 1.08) per 10μg/m^3 increment in NO_2 (Table 2). Heterogeneity between study estimates was high (83%). No evidence of small study bias was detected (data not shown). After exclusion of the age-restricted cohorts, larger summary HRs were observed in studies with limited age ranges at cohort enrolment (vs broader age ranges); in cohorts without individual adjustment for BMI and smoking (vs studies with individual adjustment) and in studies using residential LUR estimates (compared to area-level concentrations of NO_2), though none of the comparisons achieved statistical significance (Table 2).

Respiratory

Of the 17 studies report HRs for respiratory mortality (eFigure 21), 4 were excluded from the meta-analysis (included in the ESCAPE study[40]; analysed in other publications included in the review[31,62]; and the Chinese Shenyang cohort study[33] which reported a HR of 2.97 per 10μg/m^3 increment in NO_2). The random effects summary HR (13 studies) was 1.04 (95% CI: 1.01, 1.05; PI: 0.97, 1.11) per 10μg/m^3 increment in NO_2. Heterogeneity between study estimates was high (I^2=75%). Following

exclusion of the two age-restricted cohorts, larger summary HRs were observed in cohorts without individual adjustment for BMI and smoking (vs studies with individual adjustment) and in studies using area-level concentrations of NO_2 (compared to residential LUR estimates), though neither of the comparisons achieved statistical significance (Table 2).

Lung cancer

Twenty studies reported results for lung cancer mortality (eFigure 33). Four studies, selected according to our *a priori* algorithm, were excluded as the same cohorts were analysed in other publications included in the review.[42,43,46,62]. In the fixed-effects meta-analysis, two large administrative cohorts[30,35] and the ACS study[60] accounted for over 80% of the weight. Heterogeneity between study HRs was high (I^2=88%). The random-effects summary HR for the 16 studies was 1.05 (95% CI: 1.02, 1.08; PI: 0.94, 1.17) per 10µg/m^3 increment in NO_2 (Table 2). There was no evidence of publication bias. After exclusion of the age-restricted cohorts, larger summary HRs were observed in studies with limited age ranges at cohort enrollment (vs broader age ranges) and in cohorts without individual adjustment for BMI and smoking (vs studies with individual adjustment) though neither of these comparisons achieved statistical significance (Table 2). Stratification by spatial resolution of the estimated NO_2 concentrations suggested little difference in the respective summary HRs (Table 2 & eFigure 37).

Other causes

Sufficient studies were available for meta-analysis for CHD (12), cerebrovascular (7) and COPD (8) after exclusions. Details of exclusions are given in the supplementary material and results are presented in Table 3. Summary HRs for CHD and COPD were 1.04 and 1.03 respectively but close to 1 for cerebrovascular mortality. Heterogeneity was also present except for COPD. For CHD, a larger summary HR was observed for cohorts with individual measures of BMI or smoking compared to those without. A larger summary HR was also observed in studies using estimates of residential vs. small area NO_2 concentrations for CHD but reversed for COPD.

Four studies (3 from Japan and 1 from England) analysing three cohorts reported HRs for pneumonia mortality and NO_2 (eFigure 32). The meta-analytic summary HR was 1.08 (95% CI: 1.06, 1.10) with no evidence of heterogeneity (I^2=0%). For brain cancer and diabetes there were insufficient studies for meta-analysis. Two studies[30,54] in two cohorts (Can CHEC and DCH) reported HRs for diabetes-associated mortality of 1.03 (95% CI: 1.00, 1.06) and 1.31 (95% CI: 0.98, 1.76) per 10µg/m^3 increment

in NO_2 respectively, and a single study based on data from the ACS[51] reported a hazard ratio for brain cancer mortality of 0.93 (95% CI: 0.89, 0.98) per 10μg/m^3 increment in NO_2.

DISCUSSION

Our study identified 48 articles reporting results for all-cause and cause specific mortality from 28 cohorts. The majority of the cohorts were in North America and Europe with only a few cohorts in Asia. Concentrations of NO_2 were positively associated with all-cause mortality as well as mortality from cardiovascular and respiratory diseases and lung cancer. Summary hazard ratios were generally in the range 1.02-1.5 per 10μg/m^3 with lower confidence limits above 1. There was substantial heterogeneity between HRs for all categories of death except COPD and pneumonia mortality. There was evidence of effect modification by subject age range at cohort recruitment and control for individual measures of smoking and BMI. Studies using cohorts comprising subjects with pre-existing respiratory and cardiovascular disease tended to report higher HRs the studies in the general population.

Our study adds to previous quantitative reviews by incorporating studies published to October 2016 and a wider range of cause-specific mortality. A review in 2014[4] included studies of NO_2 and NO_X published between 2004 and January 2013 but was restricted to studies (n=23) which also included HRs for particles. Hoek et al.[5] also reviewed studies published to January 2013 reporting results for NO_2 and fine and coarse particles and carbon. Our study identified 20 cohort studies of NO_2 and mortality published during the period 2013 – October 2016, an indication of the growing evidence base, though a number of these more recent studies included re-analyses of existing cohorts. Only 7 of the 48 studies (5 separate cohorts) identified were outside of North America and Europe and illustrates the limited geographical spread of the current evidence base. None-the-less, the addition of new studies can facilitate meta-analysis of less common causes of death as well as incorporate results from updated cohorts incorporating longer follow-up periods, enhanced exposure estimation or inclusion of new variables in the analyses. Therefore, on-going review of studies remains appropriate.

Our summary HR for all-cause mortality (cohorts n=20) 1.02 (95% CI: 1.01, 1.03) per 10μg/m^3 increment in NO_2 was smaller than reported in Faustini et al[4] (n=12; 1.04 (95% CI: 1.02, 1.06)) and Hoek et al[5] (n=11; 1.06 (1.04, 1.08)). Because of the ubiquitous nature of ambient air pollution and the very large populations exposed, small HRs can translate into substantial consequences for health

at the population level. Hence, small variations in summary HRs can translate into important differences in population impact. The process used to derive the summary HRs needs therefore careful consideration.

The selection of study results for meta-analysis depends upon which studies are identified (which in turn depends upon the search strategy, review period, inclusion/exclusion criteria etc.) and the protocol for estimate selection and highlights the importance of preparing, *a priori,* an analytical protocol for study and estimate selection without reference to the direction and magnitude of the HRs. The choice of model, fixed or random, also needs consideration.[65] In a fixed effects model a single underlying HR is assumed whereas in a random effects model a distribution of HRs is assumed. For NO_2, a fixed effects model would seem to be an appropriate *a priori* choice: NO_2 does not vary in its composition from one location to another nor would one expect its toxicity to vary, unlike particulate matter. However, studies vary in many other respects including modelling of pollution concentrations, population characteristics and statistical model/confounders, suggesting a random effects is most appropriate. The two modelling approaches also differ in the assignment of study weights; a fixed effects model assigns weights based upon the precision of study estimates whereas a random effects model also incorporates between study variability. As a consequence, in a random effects model smaller studies are given larger weight in the meta-analysis. This may or may not be appropriate depending upon the characteristics of the studies. For example, smaller studies may have a greater range of individual confounders and possibly higher data quality than very large studies based upon large administrative databases with limited data on individual risk factors. In such a scenario the reweighting that can arise in a RE model may be appropriate.

In common with previous reviews[4,5] our study found high levels of heterogeneity between study HRs for almost all causes of death assessed. Heterogeneity is an indicator of the extent to which study estimates are sufficiently consistent to be summarized using a weighted average in a fixed-effects model. The presence of heterogeneity indicates that the variability between study estimates is too great to be explained by chance alone but it does not necessarily rule out a causal interpretation.[66] Large variations in study size (as here where sample sizes ranged from 2000+ to 7.5 million) can lead to an artificially high I^2 statistic, a measure of heterogeneity.[67] An investigation of the sources of this heterogeneity is needed to inform the interpretation of the evidence.[68] Such an investigation also prevents these issues becoming lost in the statistical summary[69] provided by a random-effects analysis[70]. The presence of high levels of heterogeneity between cohort estimates in our study is

therefore an important finding in its own right and should be incorporated into any assessment of the evidence.

We assessed a range of potential effect modifiers. We first compared HRs from studies in subjects with pre-existing disease *vs.* other cohorts. For all-cause mortality we observed a larger, less precise summary HR in subjects with pre-existing disease (1.04) *vs.* the rest (1.02). This comparison was limited however in two ways: 1) the small number of studies; and 2) such cohorts tend to be smaller and therefore carry little weight in any meta-analyses. Inclusion or otherwise in a meta-analysis should not be guided by a statistical assessment of differences between HRs, rather it should be determined by the purpose of the analysis – hazard identification or calculation of a concentration response function for input to a health impact calculation in the general population. To assess other potential effect modifiers we chose to exclude studies in subjects with pre-existing disease. Sensitivity analyses including these cohorts did not alter materially our findings (data not shown).

A small number of studies[22,23,34,61,62] used restricted age ranges for subjects at cohort entry limiting our ability to compare their results with cohorts including subjects with broad adult age ranges on entry. There was a tendency for cohorts restricting subjects' ages at cohort entry to report higher NO_2 HRs for all-cause, cardiovascular and respiratory mortality compared to cohorts with much broader age ranges upon entry. This observation, based upon a small number of studies, may be a chance finding. Alternatively, age at cohort entry may be correlated with smoking status, disease status, as well as NO_2 concentrations and proximity to traffic and further work is required to in order to better understand this potentially important effect modifier.

In recent years a number of studies have used administrative databases to construct retrospective cohorts.[24,25,30,35] 'Administrative' cohorts tend to use very large numbers of subjects with broad population coverage. They may lack individual measures of potential confounders, e.g. smoking status and BMI utilizing instead small area measures derived from other sources. Residual confounding is generally acknowledged as a potential weakness in these studies and investigators have attempted to evaluate this using statistical methods or survey data.[25,35] Our stratified meta-analyses, separating studies with individual measures of smoking status and BMI from those that did not, found smaller HRs in the former for all causes of death and with lower confidence limits below 1 for all causes of death except from CHD. A number of explanations for this finding are possible: 1) chance, the differences observed reflecting the results of studies that happen to be available at the time of the review; 2) other confounders, the two groups of studies give different results because of

differences between studies other than the BMI and smoking characterization; 3) measurement error related to different scales of measurement of confounders and exposure estimates; and 4) adjustment for these potential confounders at the small area level does not provide adequate control compared to that provided by individual measures. A sensitivity analyses using the English CPRD cohort (Carey, 2016, personal communication) found that adjustment for individual level smoking status and BMI after adjustment for a small area-level marker of socio economic status attenuated the HRs by a further 15%. The possibility remains, therefore, that studies unable to control for key individual confounders may be overstating the size of the association between long-term NO_2 and all-cause mortality

Meta-analysis stratified by the spatial resolution of the modelled NO_2 concentrations showed for all-cause and cardiovascular related deaths, a trend towards larger HRs for cohorts that used LUR models capable of estimating NO_2 concentrations at the subjects' residential address compared to other pollution models that estimated concentrations at a lower spatial resolution. This pattern was reversed for respiratory deaths. Such differences, though small, would have important implications for health impact assessments. LUR models are capable of revealing gradients in NO_2 concentrations that are missed by models that estimate concentrations for larger geographical areas. The improved precision of the estimate of a subject's long-term exposure to a pollutant is achieved by reducing both systematic and random measurement error in the exposure estimate. Random measurement error has long been acknowledged as a problem in epidemiological studies. If the *estimated* exposure can be expressed as a linear combination of the true exposure plus random error, that error is described as additive and "classical" but if the *true* exposure can be expressed as a linear combination of the estimated exposure plus random error, the error is described as additive and Berkson. Additive classical error leads on average to the underestimation of hazard ratios (bias towards the null), whereas Berkson error leads to wider confidence intervals due to reduced statistical power. Measurement error introduced by spatial smoothing behaves like Berkson error whereas error introduced by parameter estimation behaves like classical error.[71,72] Thus, even if greater spatial resolution in modelled NO_2 concentrations results in more precise exposure estimates (i.e. less measurement error) the effect on hazard ratio estimation will depend on whether it is the overall Berkson or the classical component of measurement error that is reduced.[71] Hence, it does not follow necessarily that LUR models will suffer less from bias towards the null than models with coarser spatial resolution. Of the 6 studies that used LUR models to estimate NO_2 concentrations (Figure 2B), 3 administrative cohorts dominated the meta-analysis (combined weight >69%). These 3 studies were also limited in their ability to control for individual measures of BMI and

smoking and accounted for over 94% of the weight in the meta-analysis of studies with limited control for confounders (Figure 2A) and therefore one should be cautious in the interpretation of these findings.

The calculation and use of prediction intervals in meta-analyses has been advocated.[12,67] In a random effects model, study HRs are assumed to follow a distribution. The 95% CI for the summary HR represents therefore the range within which the mean of this distribution lies. It does not convey the uncertainty in the HR from any one study. A prediction interval allows for the fact that the health effects of NO_2 may differ from one setting to another (for example due to the susceptibility of the underlying population; the assessment of NO_2 concentrations; the pollutant mixture; underlying disease prevalence; competing risk factors; model specification etc.). It provides an appropriate indication of the precision of the estimated HR in a future setting.[67] Given the sensitivity of health impact calculations to small changes in the magnitude of the HR and the imprecision inherent in any meta-analyses of HRs, subsequent impact calculations should utilize prediction intervals and report ranges of impact rather than focusing upon point estimates.

Evidence gathered from experimental studies in animals and human volunteers and from epidemiological studies employing biomarkers of effects of exposure to air pollutants, offers limited support for the assertion that long-term exposure to NO_2 is causally associated with an increase in risk of death.[7,8] Such evidence as there is for toxicological effects of NO_2 on mortality comes largely from studies of the association with short term exposure. These studies have, so far, provided no means of distinguishing the effects of NO_2 from those of PM: both might well act via the same mechanisms including the induction of increased levels of oxidative free radicals and inflammation. Evidence for effects on the cardiovascular system, for example effects on levels of clotting factors and on the rate of progression of arterial disease, is better developed for PM than for NO_2.

Only a small number of the studies identified in our review reported HRs for NO_2 adjusted for PM. In some studies the correlation between pollutants was high (>0.8) limiting their ability to disentangle associations between the pollutants and mortality. The difficulties in interpreting coefficients in multi-pollutant models has received attention.[73,74] These difficulties include: 1) correlation between pollutants (arising due to common sources and meteorological conditions) which can lead to unstable parameter estimation; 2) differential measurement error between pollutants which can lead to the 'transfer' of an association from the less well measured (but true) pollutant to the better measured (but incorrect) pollutant; and 3) statistical models which do not generally assess

interactions between pollutants in order to interpret correctly model main effects. Statistical methods for dealing with correlated predictors have been proposed as well as the use of combined pollutant estimates to be used in formulating a multi-pollutant approach to regulatory policy.[73,74] Given the current limited evidence base and the statistical issues described it remains infeasible to distinguish associations between NO_2 and mortality from those for PM, especially fine particles arising from vehicle exhaust.

Previous reviews of both the toxicological and epidemiological literature have concluded that the evidence was not sufficient to infer a causal relationship between long-term exposure to NO_2 and mortality.[7,8] In part this caution was due to a lack of consistency in study findings and concerns relating to potential confounding by co-pollutants especially particles in traffic exhaust. Our study confirms the need for continued caution in respect of causality particularly since the revised meta-analyses suggest HRs close to one, with the possibility of further attenuation if meta-analyses are restricted to studies with individual measures of BMI and smoking. The substantial heterogeneity between study results also weaken the argument for causality. Unlike particles where unit mass concentrations might vary between locations in size, composition and nature (primary/secondary), a unit mass concentration of NO_2 gas is the same everywhere. We therefore consider that as the evidence stands at present, the causal basis for estimating the burden of NO_2 on mortality and loss of life expectancy remains weak.

Our study found positive associations between long-term concentrations of NO_2 and risk of mortality from a range of diseases. However, there was substantial heterogeneity between estimates and evidence of differences in the magnitude and precision of HRs depending upon the degree of control for individual confounding factors and the spatial resolution of the NO_2 concentration estimates. This has important implications for the selection of HRs for use in health impact assessment calculations. Given the many uncertainties inherent in the assessment of this evidence base and the sensitivity of health impact calculations to small changes in the magnitude of the HR subsequent impact calculations should take account of these issues by utilizing prediction intervals and reporting ranges of impact rather than focusing upon a point estimate.

Figure Legend

Figure 1 Summary of literature search and study assessment.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009) Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Figure 2 A HRs for all-cause mortality stratified by level of adjustment for smoking and BMI; B HRs for all-cause mortality stratified by spatial resolution of NO_2 concentration estimates; C HRs for all-cause mortality ordered by study mean/median NO_2 concentrations

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Cohort stratification		No. of cohorts	HR (95% CI) per 10 µg/m^3	I^2 (%)	P-value[4]	Figure[5]
All cohorts			N = 32 (removed = 12)			e1
Cohorts excluding duplicates						
Selected cohorts[1]	Fixed	20	1.03 (1.02, 1.03)	84	NA	e2a
	Random		1.02 (1.01, 1.03) (0.99, 1.06)[6]			e2b
Stratification by cohort characteristics						
Pre existing disease	YES	5	1.04 (0.98, 1.10)	76	0.82	e3
	NO	15	1.02 (1.01, 1.03)	86		
Stratification by cohort characteristics excluding pre-existing disease cohorts						
Age-restricted[1,2]	YES	4	1.08 (1.02, 1.15)	79	0.04	e4
	NO	11	1.02 (1.01, 1.03)	88		
Stratification by study characteristics excluding pre-existing disease and age-restricted cohorts						
Individual BMI and smoking adjustment[1,2,3]	YES	7	1.00 (0.98, 1.03)	89	0.03	2a
	NO	4	1.03 (1.02, 1.04)	67		
Residential NO_2 exposure Estimates[1,2,3]	Yes	6	1.03 (1.02, 1.03)	68	0.19	2b
	No	5	1.00 (0.96, 1.04)	90		

Table 1 Summary hazard ratios (95% CI) for all-cause mortality without and with stratification by selected study characteristics.

Notes: 1 Excluding studies identified as previous/smaller analyses of the same cohort and cohorts included in ESCAPE; 2 Excluding pre-existing disease cohorts; 3 Excluding age-restricted cohorts; 4 P-value for differences between HRs in subgroup analyses; 5 Corresponding figure giving study information, HRs (95% CI); 6 Prediction Interval

Cohort stratification		Cardiovascular Mortality					Respiratory Mortality					Lung Cancer Mortality				
		No. of cohorts	HR (95% CI) per 10 µg/m^3	I^2 (%)	P-value[4]	Fig[5]	No. of cohorts	HR (95% CI) per 10 µg/m^3	I^2 (%)	P-value[4]	Fig[5]	No. of cohorts	HR (95% CI) per 10 µg/m^3	I^2 (%)	P-value[4]	Fig[5]
All cohorts			n = 22 (removed = 7)			e5		n = 17 (removed = 4)			e21		n = 20 (removed = 4)			e33
Cohorts after excluding duplicates																
All cohorts[1]	Fixed	15	1.03 (1.02, 1.03)	83	NA	e6a	13	1.03 (1.02,1.04)	75	NA	e22a	16	1.07 (1.06,1.08)	88	NA	e34a
	Random		1.03 (1.02, 1.05) (0.98, 1.08)[5]			e6b		1.04 (1.01,1.05) (0.97, 1.11)[6]			e22b		1.05 (1.02,1.08) (0.94, 1.17)[5]			e34b
Stratification by cohort characteristics																
Pre existing disease[1]	YES	1	NA	NA	NA	e7	1	NA	NA	NA	e23	0	NA	NA	NA	NA
	NO	14	1.03 (1.02, 1.04)	83			12	1.04 (1.01, 1.06)	77			16	1.05(1.02,1.08)	88		
Stratification by cohort characteristics excluding pre-existing disease cohorts																
Age-restricted[1,2]	YES	3	1.10 (0.93, 1.29)	90	0.41	e8	2	NA	NA	NA	e24	3	1.15 (0.92, 1.42)	81	0.68	e35
	NO	11	1.02 (1.01, 1.04)	81			10	1.03 (1.01, 1.05)	78			13	1.05 (1.02, 1.08)	90		
Stratification by study characteristics excluding pre-existing disease and age-restricted cohorts																
Key confounder adjustment[1,2,3]	YES	5	1.01 (0.99, 1.04)	68	0.50	e9	5	1.00 (0.95,1.06)	70	0.30	e25	6	1.02 (0.96, 1.08)	72	0.20	e36
	NO	6	1.03 (1.01, 1.04)	82			5	1.04 (1.01, 1.06)	85			7	1.06 (1.03, 1.10)	86		
Residential NO_2 exposure Estimates[1,2,3]	Yes	7	1.03 (1.01, 1.04)	87	0.15	e10	6	1.02 (1.01, 1.03)	0	0.57	e26	5	1.04 (1.00, 1.09)	96	0.77	e37
	No	4	1.01 (1.00, 1.03)	0			4	1.04 (0.98, 1.10)	83			8	1.05 (1.00, 1.11)	65		

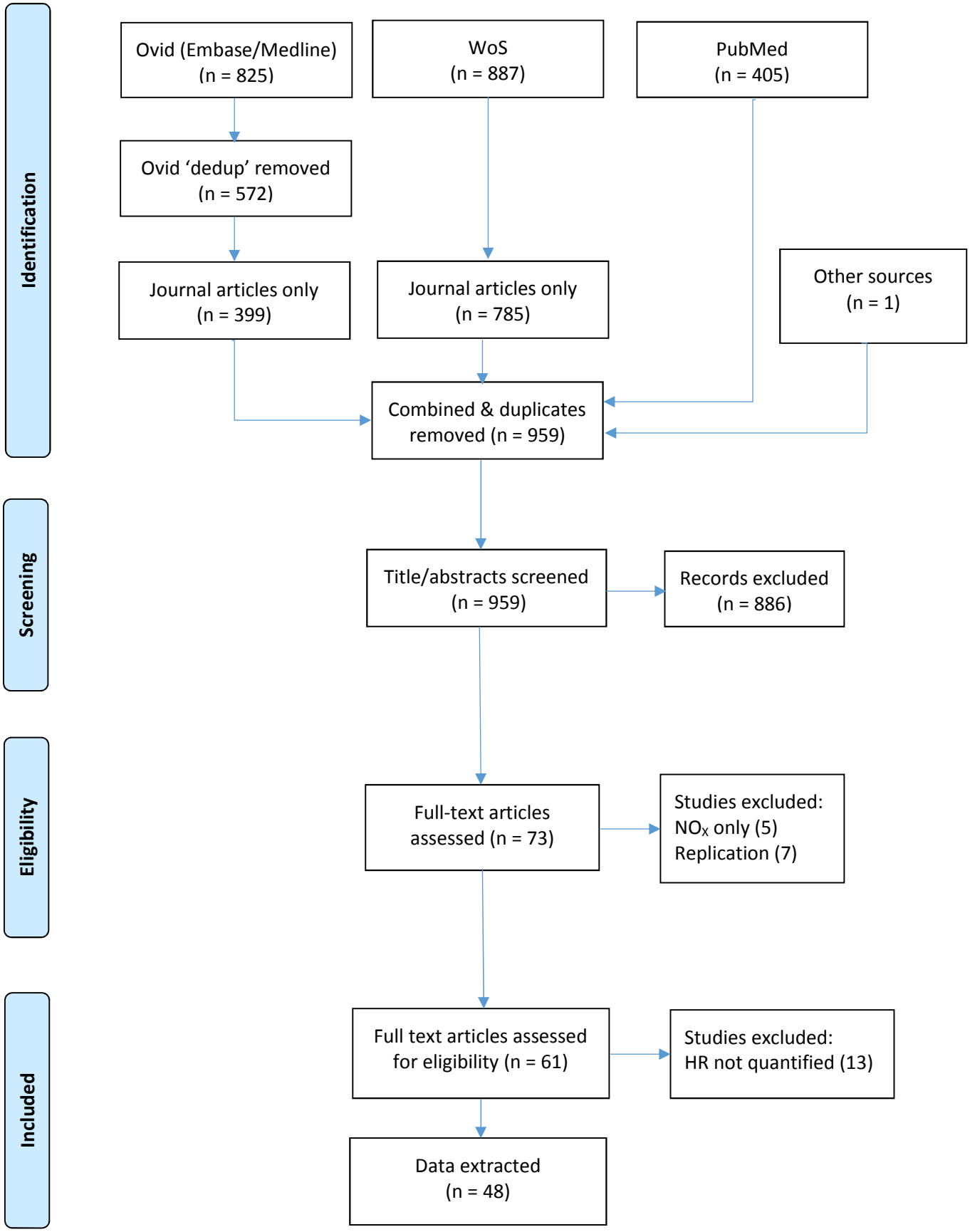
Table 2 Summary hazard ratios (95% CI) for cardiovascular, respiratory and lung cancer mortality, without and with stratification by selected cohort and study characteristics

Notes: 1 Excluding studies identified as previous/smaller analyses of the same cohort and cohorts included in ESCAPE meta-analysis; 2 Excluding pre-existing disease cohorts; 3 Excluding age-restricted cohorts; 4 P-value for differences between HRs in subgroup analyses; 5 Corresponding figure giving study information, HRs (95% CI); 6 Prediction Interval

Cohort - stratification		CHD Mortality					Cerebrovascular Mortality					COPD Mortality				
		No. of cohorts	HR (95% CI) per 10 µg/m^3	I^2 (%)	P-Value[4]	Fig[5]	No. of cohorts	HR (95% CI) per 10 µg/m^3	I^2 (%)	P-Value[4]	Fig[5]	No. of cohorts	HR (95% CI) per 10 µg/m^3	I^2 (%)	P-Value[4]	Fig[5]
All cohorts			n = 16 (removed n = 4)			e11		n = 11 (removed = 4)			e16		n = 9 (removed = 1)			e27
							Cohorts after excluding duplicates									
All cohorts[1]	Fixed	12	1.03 (1.03, 1.04)	71	NA	e12a	7	1.01 (1.00, 1.02)	64	NA	e17a	8	1.03 (1.01, 1.04)	0	NA	e28a
	Random		1.04 (1.02, 1.05) (0.99, 1.09)[5]			e12b		1.01 (0.98, 1.05) (0.93, 1.10)[6]			e17b		1.03 (1.01, 1.04) (1.01, 1.05)[5]			e28b
							- stratification by cohort characteristics									
Pre existing disease[1]	YES	0	NA	NA	NA	NA	0	NA	NA	NA	NA	0	NA	NA	NA	NA
	NO	12	1.04 (1.02, 1.05)	71			7	1.01 (0.98, 1.05)	64			8	1.03 (1.01, 1.04)	0		
							- stratification by cohort characteristics excluding pre-existing disease cohorts									
Age-restricted[1,2]	YES	2	NA	NA	NA	e13	2	NA	NA	NA	e18	1	NA	NA	NA	e29
	NO	10	1.03 (1.02, 1.05)	66			5	1.00 (0.99, 1.02)	0			7	1.03 (1.01, 1.04)	5		
							- stratification by study characteristics excluding pre-existing disease and age-restricted cohorts									
Key confounder adjustment[1,2,3]	YES	5	1.02 (1.01, 1.03)	3	0.01	e14	2	NA	NA	NA	e19	2	NA	NA	NA	e30
	NO	5	1.04 (1.03, 1.06)	13			3	1.01 (0.99, 1.02)	0			5	1.03 (1.02, 1.05	0		
Residential NO_2 exposure Estimates[1,2,3]	Yes	6	1.04 (1.03, 1.05)	9	0.05	e15	4	1.01 (0.99, 1.03)	0	NA	e20	4	1.02 (1.00, 1.04)	10	0.19	e31
	No	4	1.02 (1.00, 1.04)	24			1	NA	NA			3	1.04 (1.01, 1.07)	0		

Table 3 Summary Hazard ratios (95% CI) for cardiovascular, CHD, cerebrovascular and COPD mortality without and with stratification by selected cohort and study characteristics.

Notes: 1 Excluding studies identified as previous/smaller analyses of the same cohort and cohorts included in ESCAPE meta-analysis; 2 Excluding pre-existing disease cohorts; 3 Excluding age-restricted cohorts; 4 P-value for differences between HRs in subgroup analyses; 5 Corresponding figure giving study information, HRs (95% CI); 6 Prediction Interval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Screening
Eligibility
Included
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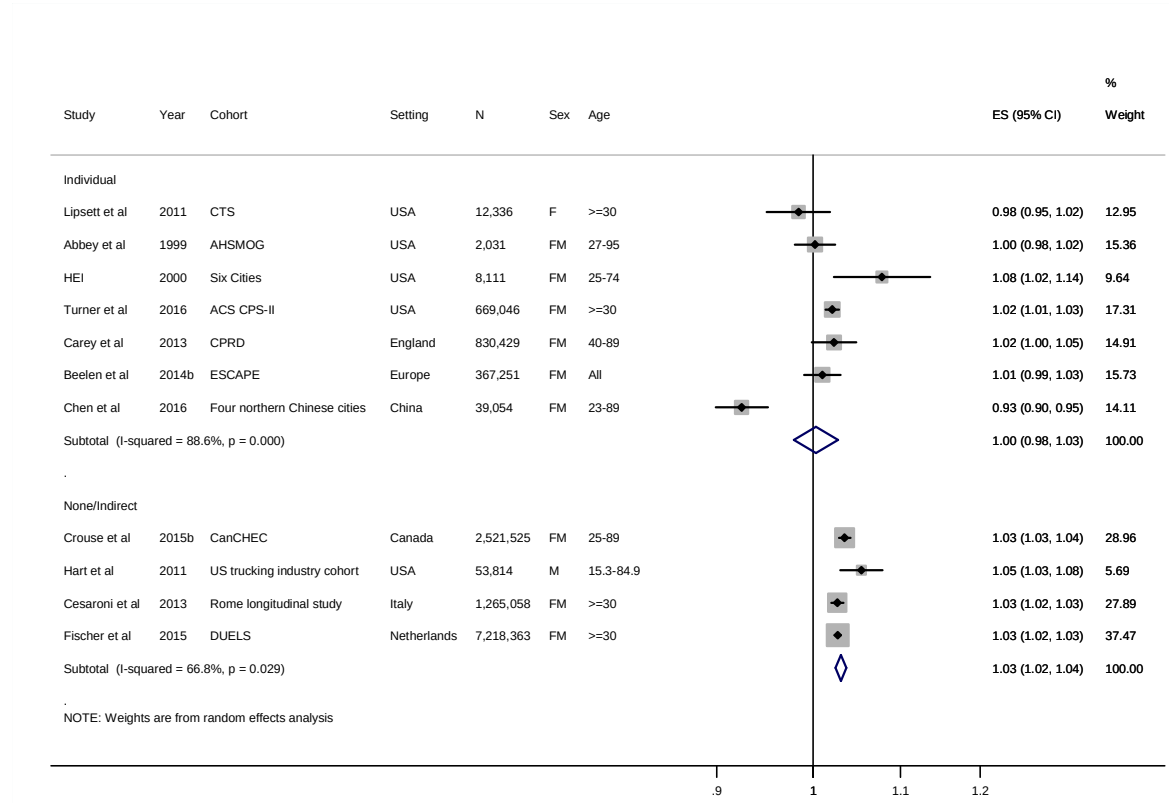
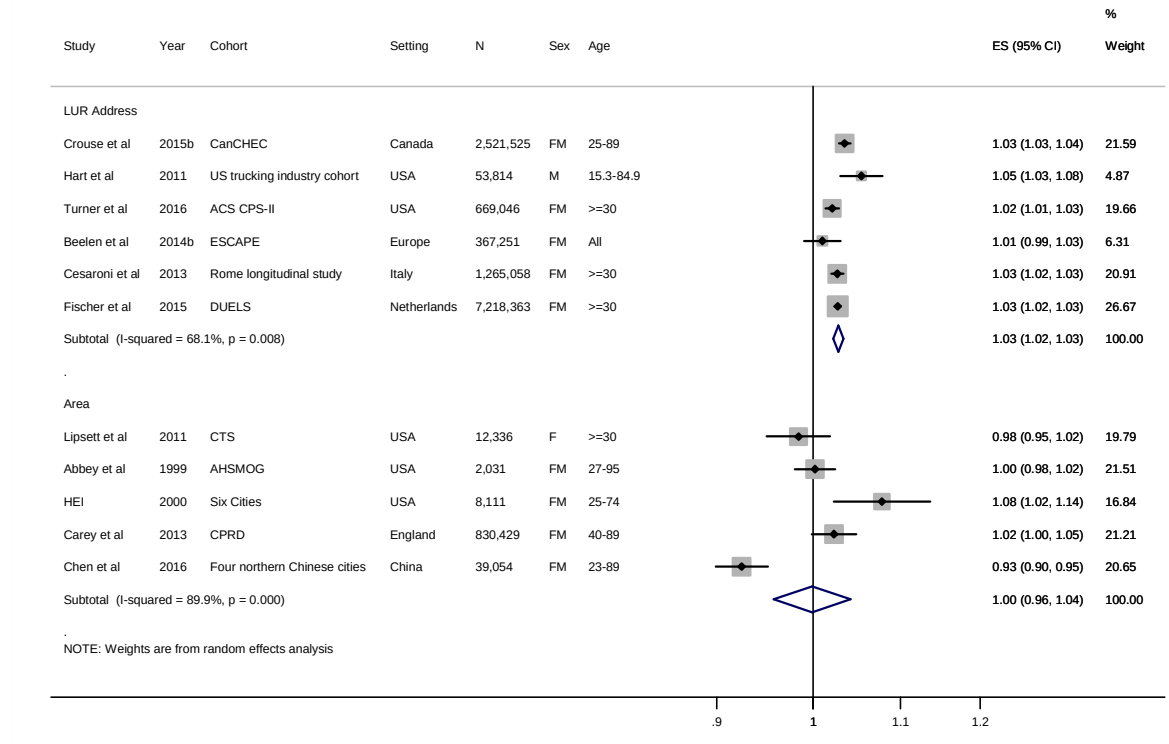
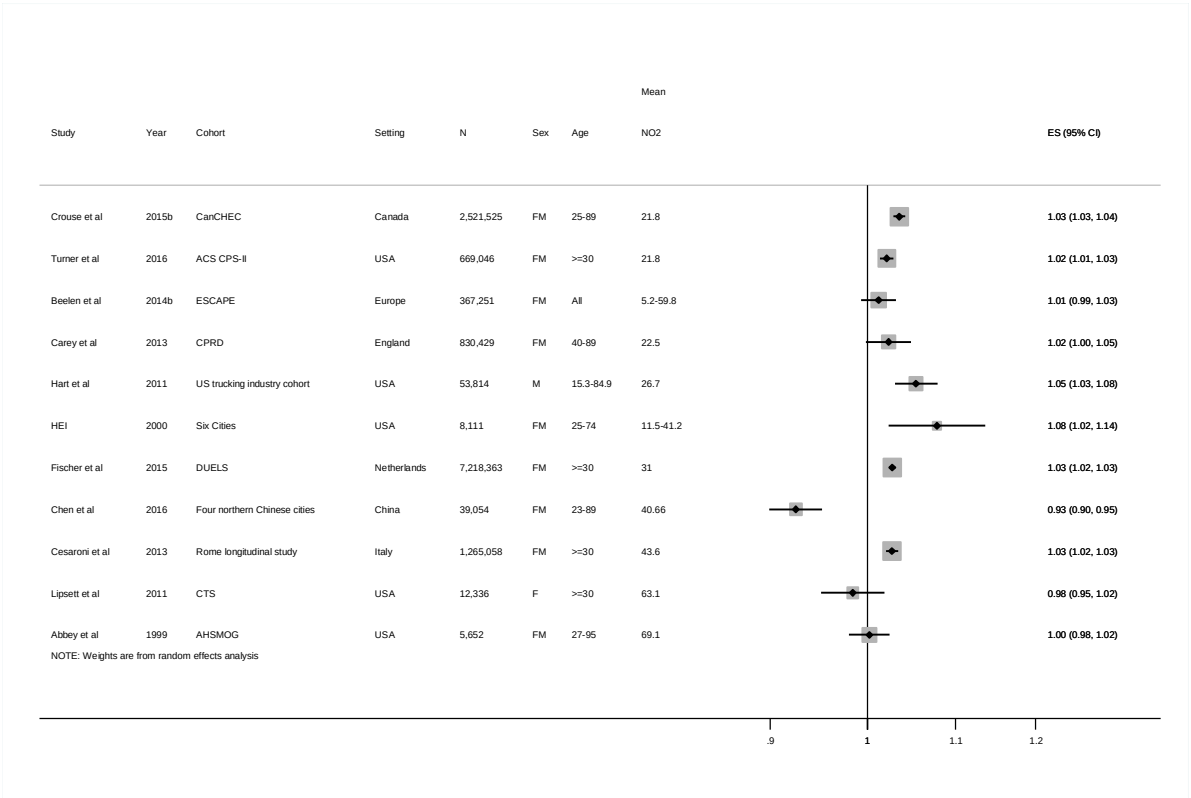
(n = 825)
WoS
(n = 887)
PubMed
(n = 405)
Ovid 'dedup' removed
(n = 572)
Journal articles only
(n = 399)
Journal articles only
(n = 785)
Other sources
(n = 1)
Combined & duplicates
removed (n = 959)
Title/abstracts screened
(n = 959)
Records excluded
(n = 886)
Full-text articles
assessed (n = 73)
Studies excluded:
NOx only (5)
Replication (7)
Full text articles assessed
for eligibility (n = 61)
Studies excluded:
HR not quantified (13)
Data extracted
(n = 48)


Study Year Cohort Setting N Sex Age ES (95% CI) % Weight
Individual
Lipsett et al 2011 CTS USA 12,336 F >=30 0.98 (0.95, 1.02) 12.95
Abbey et al 1999 AHSMOG USA 2,031 FM 27-95 1.00 (0.98, 1.02) 15.36
HEI 2000 Six Cities USA 8,111 FM 25-74 1.08 (1.02, 1.14) 9.64
Turner et al 2016 ACS CPS-II USA 669,046 FM >=30 1.02 (1.01, 1.03) 17.31
Carey et al 2013 CPRD England 830,429 FM 40-89 1.02 (1.00, 1.05) 14.91
Beelen et al 2014b ESCAPE Europe 367,251 FM All 1.01 (0.99, 1.03) 15.73
Chen et al 2016 Four northern Chinese cities China 39,054 FM 23-89 0.93 (0.90, 0.95) 14.11
Subtotal (I-squared = 88.6%, p = 0.000) 1.00 (0.98, 1.03) 100.00
None/Indirect
Crouse et al 2015b CanCHEC Canada 2,521,525 FM 25-89 1.03 (1.03, 1.04) 28.96
Hart et al 2011 US trucking industry cohort USA 53,814 M 15.3-84.9 1.05 (1.03, 1.08) 5.69
Cesaroni et al 2013 Rome longitudinal study Italy 1,265,058 FM >=30 1.03 (1.02, 1.03) 27.89
Fischer et al 2015 DUELS Netherlands 7,218,363 FM >=30 1.03 (1.02, 1.03) 37.47
Subtotal (I-squared = 66.8%, p = 0.029) 1.03 (1.02, 1.04) 100.00
NOTE: Weights are from random effects analysis
.9
1
1.1
1.2

A


Study Year Cohort Setting N Sex Age ES (95% CI) % Weight
LUR Address
Crouse et al 2015b CanCHEC Canada 2,521,525 FM 25-89 1.03 (1.03, 1.04) 21.59
Hart et al 2011 US trucking industry cohort USA 53,814 M 15.3-84.9 1.05 (1.03, 1.08) 4.87
Turner et al 2016 ACS CPS-II USA 669,046 FM >=30 1.02 (1.01, 1.03) 19.66
Beelen et al 2014b ESCAPE Europe 367,251 FM All 1.01 (0.99, 1.03) 6.31
Cesaroni et al 2013 Rome longitudinal study Italy 1,265,058 FM >=30 1.03 (1.02, 1.03) 20.91
Fischer et al 2015 DUELS Netherlands 7,218,363 FM >=30 1.03 (1.02, 1.03) 26.67
Subtotal (I-squared = 68.1%, p = 0.008) 1.03 (1.02, 1.03) 100.00
Area
Lipsett et al 2011 CTS USA 12,336 F >=30 0.98 (0.95, 1.02) 19.79
Abbey et al 1999 AHSMOG USA 2,031 FM 27-95 1.00 (0.98, 1.02) 21.51
HEI 2000 Six Cities USA 8,111 FM 25-74 1.08 (1.02, 1.14) 16.84
Carey et al 2013 CPRD England 830,429 FM 40-89 1.02 (1.00, 1.05) 21.21
Chen et al 2016 Four northern Chinese cities China 39,054 FM 23-89 0.93 (0.90, 0.95) 20.65
Subtotal (I-squared = 89.9%, p = 0.000) 1.00 (0.96, 1.04) 100.00
NOTE: Weights are from random effects analysis
.9
1
1.1
1.2

B


Study
Year
Cohort
Setting
N
Sex
Age
Mean NO2
ES (95% CI)
Crouse et al 2015b CanCHEC Canada 2,521,525 FM 25-89 21.8 1.03 (1.03, 1.04)
Turner et al 2016 ACS CPS-II USA 669,046 FM >=30 21.8 1.02 (1.01, 1.03)
Beelen et al 2014b ESCAPE Europe 367,251 FM All 5.2-59.8 1.01 (0.99, 1.03)
Carey et al 2013 CPRD England 830,429 FM 40-89 22.5 1.02 (1.00, 1.05)
Hart et al 2011 US trucking industry cohort USA 53,814 M 15.3-84.9 26.7 1.05 (1.03, 1.08)
HEI 2000 Six Cities USA 8,111 FM 25-74 11.5-41.2 1.08 (1.02, 1.14)
Fischer et al 2015 DUELS Netherlands 7,218,363 FM >=30 31 1.03 (1.02, 1.03)
Chen et al 2016 Four northern Chinese cities China 39,054 FM 23-89 40.66 0.93 (0.90, 0.95)
Cesaroni et al 2013 Rome longitudinal study Italy 1,265,058 FM >=30 43.6 1.03 (1.02, 1.03)
Lipsett et al 2011 CTS USA 12,336 F >=30 63.1 0.98 (0.95, 1.02)
Abbey et al 1999 AHSMOG USA 5,652 FM 27-95 69.1 1.00 (0.98, 1.02)
NOTE: Weights are from random effects analysis
.9
1
1.1
1.2

C

Supplementary Material

Contents

Details of studies excluded from meta-analysis for other causes or mortality (references refer to main manuscript)

CHD: Twelve studies were meta-analysed after exclusions of one study [53] included in ESCAPE [21] and 3 analysed in other publications [31, 43, 62].

Cerebrovascular: Seven studies were meta-analysed after exclusions of one study [53] included in ESCAPE [21]; one study reporting an abnormally high HR (>2.4) from the Shenyang Cohort [63] and 2 studies where the same cohorts were analysed in other publications [31, 62].

COPD: Only a single study [62] analysed in a subsequent publication was excluded.

eTable 1 Coding of categorise of cause of death

Mortality	Coded
All-causes	"All Causes" , "All Cause (after ACS)" , "All Causes (after stroke)" , "All causes" , "Natural Causes" , "Non Accidental"
Cardiovascular	"Cardiovascular" , "Circulatory"
Cerebrovascular	"Cerebrovascular"
CHD	"CHD" , "IHD"
Respiratory	"Respiratory" , "Pulmonary" , "Non-malignant Respiratory"
COPD	"COPD" , "COPD & allied conditions"
Pneumonia	"Pneumonia" , "Pneumonia & Influenza"
Lung cancer	"Lung Cancer" , "Trachea, bronchus and lung cancers"

eTable 2: Cohort and study characteristics (ordered by cohort/date of publication); citation numbers correspond with main paper

Cohort Name and brief description	Country	Enrolment (baseline)		Publication and Date	Number of Subjects	Follow-up Dates / Length	Exposure Period	Exposure assessment	Covariate adjustment includes#:	Mortality Cause
		Date	Age							
European Cohorts										
ESCAPE 22 population based cohorts from 13 European Countries	Europe	mainly 1990s	all ages	[20] Beelen R et al 2014b	367,251	Average 13.9 years	1 year Oct 2008-May 2011 with back-extrapolation to baseline	LUR + back-extrapolation: Address-level	Age, sex, smoking, BMI, occupational and educational factors	All-cause
				[21] Beelen R et al 2014a	367,383	Average 13.9 years	1 year Oct 2008-May 2011 with back-extrapolation to baseline	LUR + back-extrapolation: Address-level	Age, sex, smoking, BMI, occupational and educational factors	CV, CHD, MI, Cerebrovascular
				[32] Dimakopoulou K et al 2014	307,553 (16 cohorts)	16.3 to 18.6 years	Annual average (baseline)	LUR: Address-level	Age, sex, smoking, BMI, occupational and educational factors	Respiratory
Diet Cancer and Health cohort (DCH) Population based sample with no cancer history living in areas of Copenhagen and Aarhus.	Denmark	1993-1997	50-64	[53] Raaschou-Nielsen O et al 2012	52,061	to end 2009	1971 onwards: Annual mean exposure, time varying	DM: Address-level allowing for change of residence	Age, sex, smoking, BMI, employment status, length of school attendance	All-cause CV, CHD, Cerebrovascular
				[54] Raaschou-Nielsen O et al 2013	52,061	to end 2009	1971 onwards: Annual mean exposure, time varying	DM: Address-level allowing for change of residence	Age, sex, smoking, BMI, length of school attendance	Diabetes
				[18] Andersen ZI et al 2012	52,215	to June 27th 2006	1971 onwards: Annual mean exposure, time varying	DM: Address-level allowing for change of residence	Age, sex, smoking, BMI, educational level.	Fatal stroke (and sub-types)

				[57] Sorensen M et al 2014	51,569	1st July 1997 to 30th Nov 2009	1987-2009: 10-years exposure, time varying	DM: Address-level allowing for change of residence	Age, sex, smoking, BMI, length of school attendance	Fatal stroke
Clinical Practice Research Datalink (CPRD) Patients in GP practices participating in CPRD	England	2003	40-89	[24] Carey IM et al 2013	830,429	2003-2007	2002	DM: 1 km grid square-level	Age, sex, smoking, BMI, area-level income	All-cause, CV, CHD, MI, HF, Cerebrovascular, Stroke, Respiratory, COPD, Pneumonia, Lung Cancer
South London Stroke Register (SLSR) Patients in the South London Stroke Register who experienced their first ever stroke between 1995 and 2005.	England	1995-2005	Mean (SD) 70.4 (14.6)	[50] Maheswaren R et al 2010	3,320	to mid-2006	2002	Modelled: 20x20m grid level	Age, sex, smoking, social class but not BMI	All-cause
MINAP (Acute Coronary Syndrome survivors) Patients admitted to hospital in England and Wales with acute coronary syndrome and recorded in MINAP (Myocardial Ischaemia National Audit Project) who are still alive 28 days post admission.	England & Wales	2004-2007	Mean (SD) 68 (13) >25	[58] Tonne C et al 2013	154,204	3.7 years	2004-2010: Annual average, time varying	DM: 1km x 1km level	Age, sex, smoking, area-level income but not BMI	All-cause
	Greater London	2003-2007	>25	[64] Tonne C et al 2016	18,138	4.0 years	2003-2010	DM: 20m x 20m level	Age, area-level income deprivation, but not BMI. Smoking, and ethnicity in a sensitivity analysis after imputation of large number of missing values	All-cause

Pollution Atmosphérique et Affections Respiratoires Chroniques (PAARC) Adults from French family households resident in 24/18 areas of 7 Cities.	France	1974-1976	25-59	[34] Filleul L et al 2005	14,284	1974-2000	1974-1976 (August excluded)	Monitoring data: Area-level (areas 0.5 to 2.3 km in diameter)	Age, sex, smoking, BMI, educational level	All-cause, Cardio-pulmonary, Lung Cancer
GAZEL Cohort EDF-GDF workers	France	1989-2013	Mean (SD) 43.7 (3.5) 35-50	[22] Bentayeb et al, 2015	20,327	1989-2013	1989-2008	Chemistry Transport Model (resolution 2km) linked to ZIP code, allowing for change in residence	Age, sex, smoking, BMI, highest level of education, occupational level	All-cause, CV, Respiratory, Lung Cancer
German cohort Women sampled at random from cross-sectional studies conducted in North Rhine-Westphalia in the 1980s and 1990s.	Germany	1985-1994	50-59 (92% aged 53-55)	[38] Gehring U et al 2006	4,752	to May 2003	5-year average prior to baseline	Monitoring data: Area-level	Smoking, educational level but not BMI (all female cohort of similar age)	All-cause, Cardio-pulmonary
				[56] Schikowski T et al 2007	4,750	to May 2003	5-year average prior to baseline	Monitoring data: Area-level	Smoking, educational level but not BMI (all female cohort of similar age)	CV
				[40] Heinrich J et al 2013	4,752	to Oct 2008	1-year average (baseline)	Monitoring data: Nearest monitor to residence	Smoking, educational level but not BMI (all female cohort of similar age)	All-cause, Cardio-pulmonary Respiratory, Lung Cancer
CHD survivors cohort Population based cohort of CHD survivors (Rome)	Italy	1998-2000	35-84	[55] Rosenlund M et al 2008	6,513	29th day after event to end June 2005	1995/1996: Annual mean	LUR: Census block-level	Age, sex, area-based socioeconomic status but not smoking or BMI	All-cause

Rome longitudinal study Population based cohort of long-term (5+ years) residents of Rome.	Italy	2001	>=30	[25] Cesaroni G et al 2013	1,265,058	Oct 2001-Dec 2010	Oct 1996-Dec 2010: Cumulative mean exposure, time varying	LUR: Address-level allowing for change of residence	Age, sex, education, occupation but not smoking or BMI	All-cause, CV, CHD, Cerebrovascular, Respiratory, Lung Cancer
				[26] Cesaroni G et al 2012	684,204 (subset age 45-80 in 2001)	2001-2006	1995/1996: Annual mean	LUR: Address-level	Age, sex, education, occupation but not smoking or BMI	All-cause
Dutch Environmental Longitudinal Study DUELS Dutch inhabitants who had lived at the same address between 1/1/1999 and 1/1/2004	Nether-lands	2004	>=30	[35] Fisher PH et al 2015	7,218,363	2004-2010	2001	LUR: 100 x 100m level	Age, sex, standardised disposable household income but not smoking or BMI	All-cause, CV, Respiratory, Lung Cancer
Netherlands Cohort Study (NLCS-AIR) Subjects selected from 323 of the 714 municipalities of the Netherlands	Nether-lands	1986	55-69	[19] Beelen et al, 2009	117,528	1987-1996	1987-1996	LUR, Monitoring, GIS: Address-level (baseline address)	Age, sex, smoking, neighbourhood indicators of socioeconomic status but not BMI	CV, CHD, HF, Cerebrovascular, Cardiac Dysrhythmia
				[23] Brunekreef B et al 2009	117,528	1987-1996	1987-1996	LUR, Monitoring, GIS: Address-level (baseline address)	Age, sex, smoking, neighbourhood level and COROP area-level percentage of persons with high & low income but not BMI	All-cause, CV, Respiratory, Lung Cancer
				[41] Hoek et al 2002	Random sample: 4,492	Sept 1986-Oct 1994	1987-1990	LUR, Monitoring, GIS: Address-level (baseline address)	Age, sex, smoking, BMI, education, occupation	All-cause, Cardio-pulmonary
Oslo cohort Inhabitants of Oslo	Norway	1992	51-90	[52] Naess O et al 2007	143,842	1992-1998	1992-1995	DM: Neighbourhood level	Age, education, occupational class but not smoking or BMI	CV, COPD, Lung Cancer

									(sex-specific analyses)	
North American Cohorts										
Adventist Health Study on the Health Effects of Smog (AHSMOG) Sub-sample of the Adventist Health Survey. All subjects, Seventh Day Adventists, white, non-Hispanic and resident in California.	USA	1977	27-95	[28] Chen LH et al 2005	3,239 [1,149 M; 2090 F]	1977-1998	1973-1998: Annual mean, time varying (4-year window)	Monitor data: Interpolation to ZIP code centroid (<50km from monitor), allowing for change of residence	Age, sex, past smoking, BMI, years of education.	CHD
				[17] Abbey D et al 1999	5,652 [~3621 F; ~2031 M]	1977-1992	1973-1992: Cumulative monthly mean exposure, time varying	Monitor data: Interpolation to ZIP code centroid (<50km from monitor), allowing for change of residence	Age, sex, past smoking, BMI, years of education (sex-specific analyses)	All-cause, Cardio-pulmonary, Respiratory, Lung Cancer
American Cancer Society Prevention II Study (ACS CSP-II) Friends, neighbours, acquaintances of American Cancer Study (ACS) volunteers	USA	1982	>=30	[60] Turner et al, 2016	669,046	1982-2004	Annual average for 2006	LUR (~30 m): Address-level	Age, sex, smoking, BMI, occupational and educational factors	All-cause, CV, COPD, Diabetes, Lung Cancer
				[43] Jerrett M et al 2013	73,711 California	1982-2000	1988-2002	LUR: Address-level	Age, sex, smoking, BMI, occupational and educational factors.	All-cause, CV, CHD, Stroke, Respiratory, Lung Cancer
				[46] Krewski et al 2009	406,917	1982-2000	1980	Monitoring Data: MSA level	Age, sex, smoking, BMI, occupational and educational factors.	All-cause, Cardio-pulmonary, CHD, Lung Cancer
				[51] McKean-Cowen et al, 2009	527,123	1982-2000	1982-1998	Monitoring Data: MSA level	Age, sex, smoking, educational level but not BMI	Brain cancer

				[42] Krewski et al, 2000	552,138 (295,223 with $PM_{2.5}$)	1982-1989	1980	Monitoring data: City level	Age, sex, smoking, BMI, educational level	All-cause, Cardio-pulmonary, Lung Cancer
California Teachers Study (CTS) Prospective cohort of female public school professionals living in California.	USA	1995	>=30	[49] Lipset MJ et al 2011	12,336	June 1997-Dec 2005	June 1996-Dec 2005: Cumulative mean exposure, time varying	Monitor data & IDW: 250x250m grid level , allowing for change of residence	Age, smoking, BMI, ecological variables for income, education, unemployment	All-cause, CV, CHD, Cerebrovascular, Respiratory, Lung Cancer
Six Cities Random sample from white subjects in six communities	USA	1974-1977	25-74	[42] Krewski et al, 2000	8,111	1974-1989	1977-1985	Monitor data: City-level	Age, sex, smoking, BMI, education level	All-cause, Cardio-pulmonary, Lung Cancer
US trucking industry cohort Men employed in four trucking companies	USA	1985	15.3-84.9	[39] Hart JE et al 2011	53,814	1985-2000	1985-2000	LUR + spatial smoothing: Address-level	Age, years of work in each of 8 job groups but not smoking or BMI (all male cohort)	All-cause, CV, CHD, Respiratory, COPD, Lung Cancer
Washington University-EPRI Veterans cohort US male veterans with a diagnosis of hypertension	USA	1975-1976	Mean (SD) 51 (12)	[47] Lipfert et al 2006a	~15,200 survivors (1997)	1997-2001	1997-2001	Monitor data: County-level	Age, smoking, BMI, zip code and /or country-level education and income (male only cohort)	All-cause
				[48] Lipfert et al 2006b	28,635 survivors (1997)	1997-2001	1999-2001	Monitor data: County-level	Age, smoking, BMI, zip-code level: income, education and poverty status (male only cohort)	All-cause
Canadian Census Health and Environment Cohort (Can CHEC) Population based cohort of residents	Canada	1991	25-89	[31] Crouse DL et al 2015a	735,590 [10 cities]	Jun 1991-Dec 2006	1984-2006: Annual mean exposure, time varying (7-year moving window)	LUR: Post-code level allowing for change in residence	Age, sex, education, employment status, occupational classification, household income but no direct adjustment for smoking or BMI	All-cause, CV, CHD, Cerebrovascular, Respiratory

				[30] Crouse DL et al 2015b	2,521,525	Jun 1991-Dec 2006	1984-2006: Annual mean exposure, time varying (7-year moving window)	LUR: Post-code level allowing for change in residence	Age, sex, education, employment status, occupational classification, household income but no direct adjustment for smoking or BMI	All-cause, CV, CHD, Cerebrovascular, Respiratory, COPD, Diabetes, Lung Cancer
Ontario tax cohort Retrospective cohort study. Random sample from federal family income tax database of subjects living in 3 cities in Ontario.	Canada	1982-1986	35-85	[27] Chen H et al 2013	205,440	1982-2004	1982-2004: 3-year moving average, time varying	LUR: Post-code level allowing for change of residence	Age, sex, annual household income, but not smoking or BMI	CV, CHD, Cerebrovascular
Toronto respiratory cohort Subjects treated at a respiratory disease clinic in Toronto	Canada	1992-1999	Median (IQR) 60 (49-69)	[44] Jerrett M et al 2009	2,360	1992-2002	Average (Autumn 2002 and Spring 2004)	LUR: Address-level	Age, sex, smoking, BMI, EA-level deprivation index	All-cause, CV, Respiratory
Vacouver cohort Long-term (5+ years) residents of Metropolitan Vancouver with no CHD history.	Canada	1999	45-85	[37] Gan WQ et al 2011	452,735	1999-2002	1994-1998	LUR (10m): Address-level allowing for change of residence	Age, sex, neighbourhood socioeconomic status but not smoking or BMI	CHD
				[36] Gan WQ et al 2013	467,994	1999-2002	1994-1998	LUR: Address-level allowing for change of residence	Age, sex, neighbourhood socioeconomic status but not smoking or BMI	COPD

Chinese Cohorts										
Shenyang cohort Population based retrospective cohort of family members living in 5 urban districts of Shenyang city.	China	2009	35-103	[63] Zhang P et al 2011	9,941	1998-2009	1998-2009: Annual mean exposure, time varying	Monitoring data: District-level	Age, sex, smoking, BMI, educational level, personal income	CV, Cerebrovascular
				[33] Dong G-H et al 2012	9,941	1998-2009	1998-2009: Annual mean exposure, time varying	Monitoring data: District-level	Age, sex, smoking, BMI, educational level, household income	Respiratory
Four northern Chinese cities Random sample of neighbourhoods within 1km of a monitor.	China	1998	23-89	[29] Chen et al, 2016	39,054	1998-2009	1998-2009 Annual average, time varying OR 1998 annual average	Monitor data: nearest monitor <1km.	Age, sex, BMI, household income, occupation	All-cause, Lung Cancer
Japanese Cohorts										
Shizuoka elderly cohort Age-sex - stratification random sample of residents from 74 municipalities of Shizuoka	Japan	Dec 1999	65-84	[62] Yorifuji T et al 2010	13,444	Dec 1999-Mar 2006	Apr 2000-Mar 2006	LUR: Address-level	Age, sex, smoking, BMI, financial capability	All-cause, CV, CHD, Cerebrovascular, Cardio-pulmonary, Respiratory, COPD, Pneumonia, Lung Cancer

				[61] Yorifuji T et al 2013	13,412	Dec 1999-Jan 2009	Apr 1996-March 2009: Annual mean exposure, time varying	LUR: Address-level	Age, sex, smoking, BMI, financial capability	All-cause, CV, CHD, Cerebrovascular (and sub-types), Cardio-pulmonary, Respiratory, COPD, Pneumonia, Lung Cancer
3 Japanese Prefectures Subjects living in 6 areas in 3 prefectures	Japan	1983-1985	>=40	[45] Katanoda K et al 2011	63,520	10 years (max to Oct 1995)	1974-1983	Monitor data: area-level	Age, sex, smoking, health insurance type / occupational exposure, but not BMI	Respiratory, COPD, Pneumonia, Lung Cancer
Taiwanese Cohort										
TCS Civil servants in Greater Taipei area	Taiwan	1989-1992	Employed Mean (SD) 41.3 (10.5)	[59] Tseng et al, 2015	43,227	1992-2008	2000-2008	Monitor data: District-level	Age, sex, smoking, BMI, income, educational level	CV

¶ lung cancer and for female all natural causes not adjusted for BMI;

This is not meant to be a complete list of covariates but focusses only on a few "key" variables.

References

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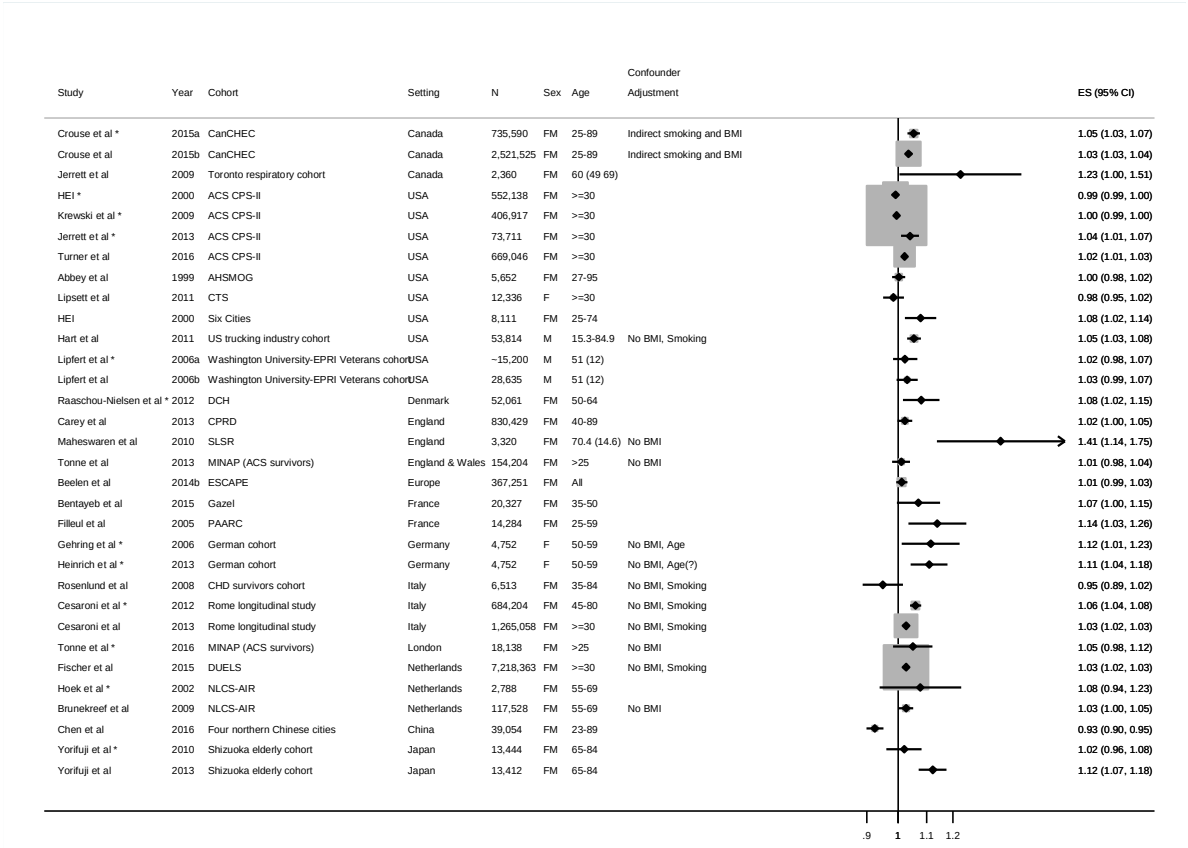
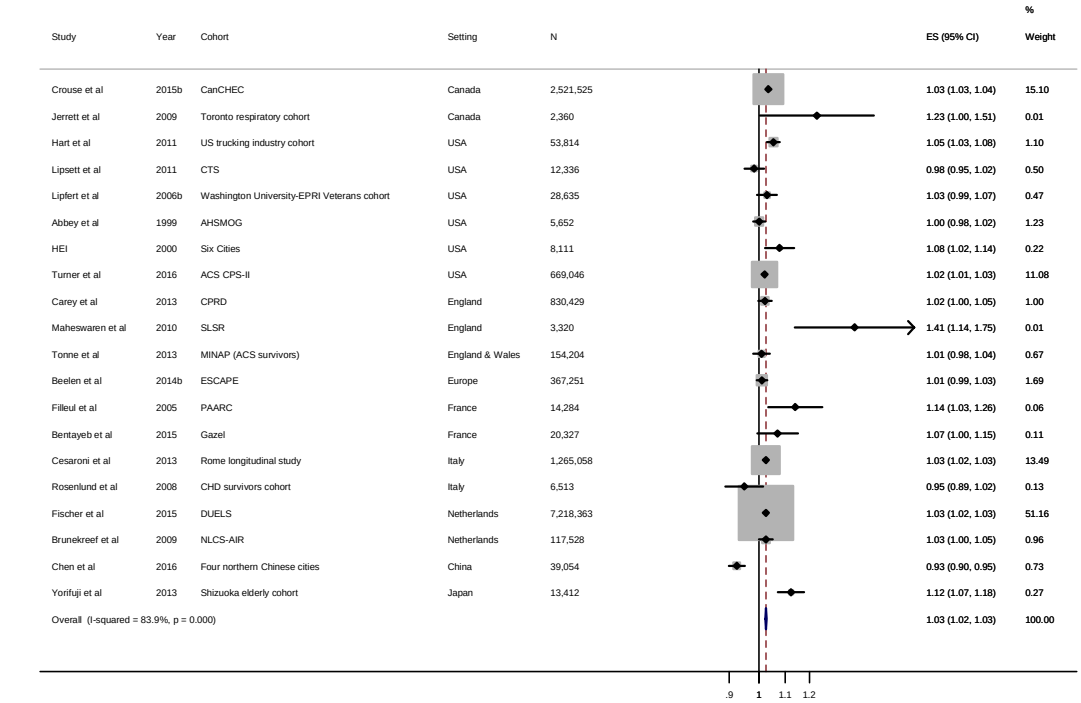
eFigure 1 All-cause mortality

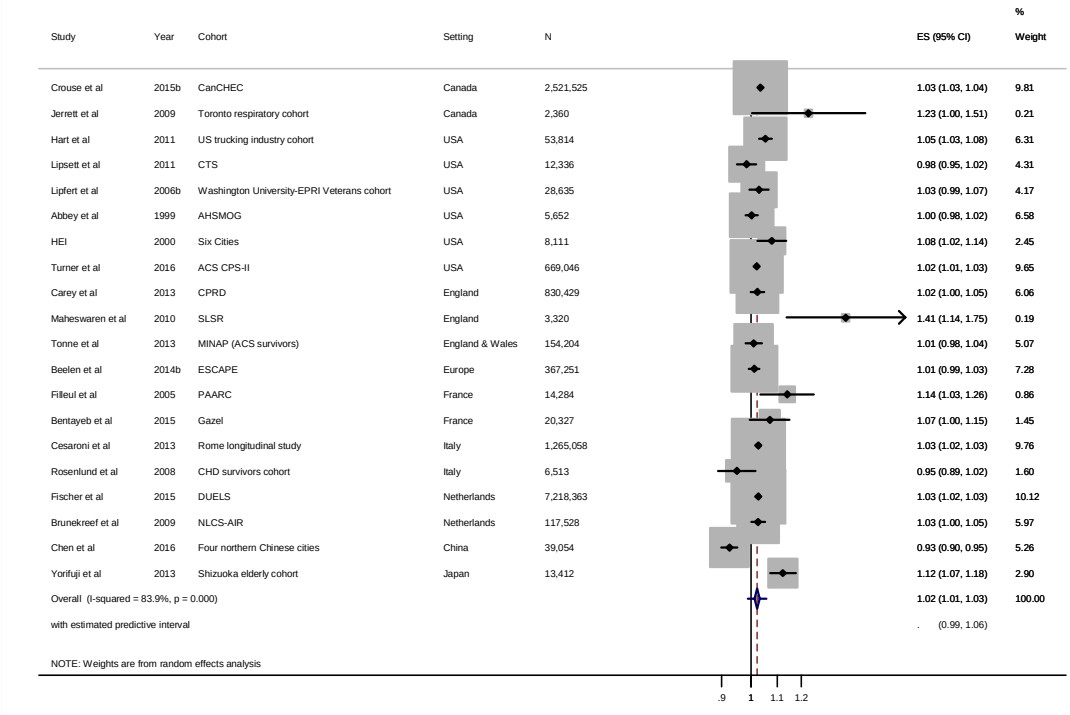


* indicates exclusion from meta-analysis. Refer to methods/results sections of manuscript.

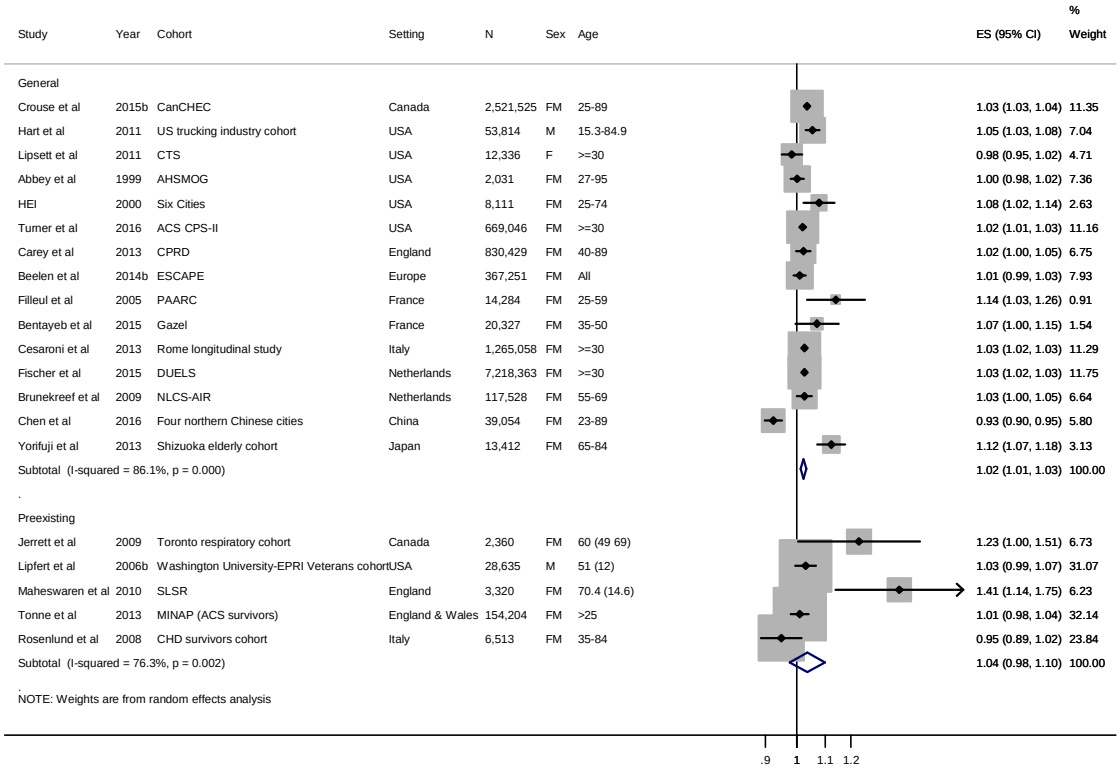
eFigure 2a All-cause mortality – fixed effects model



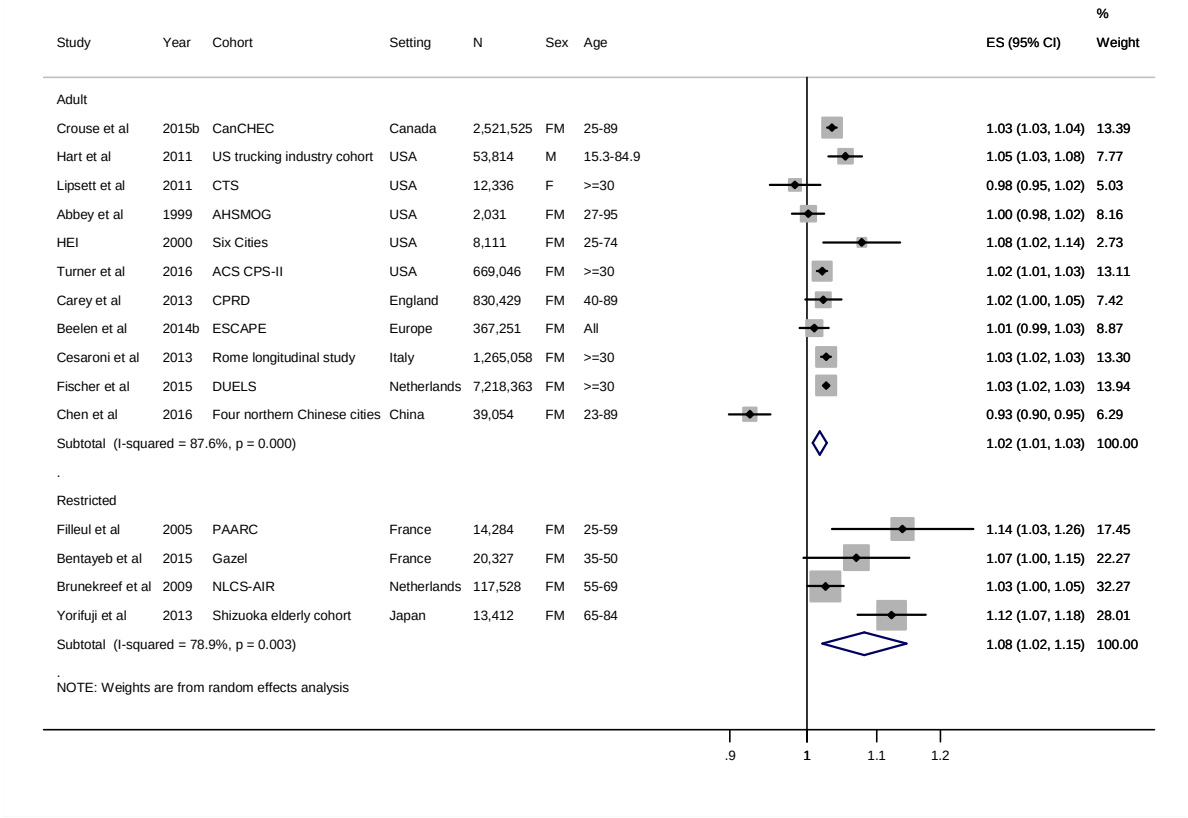
eFigure 2b All-cause mortality - random effects model



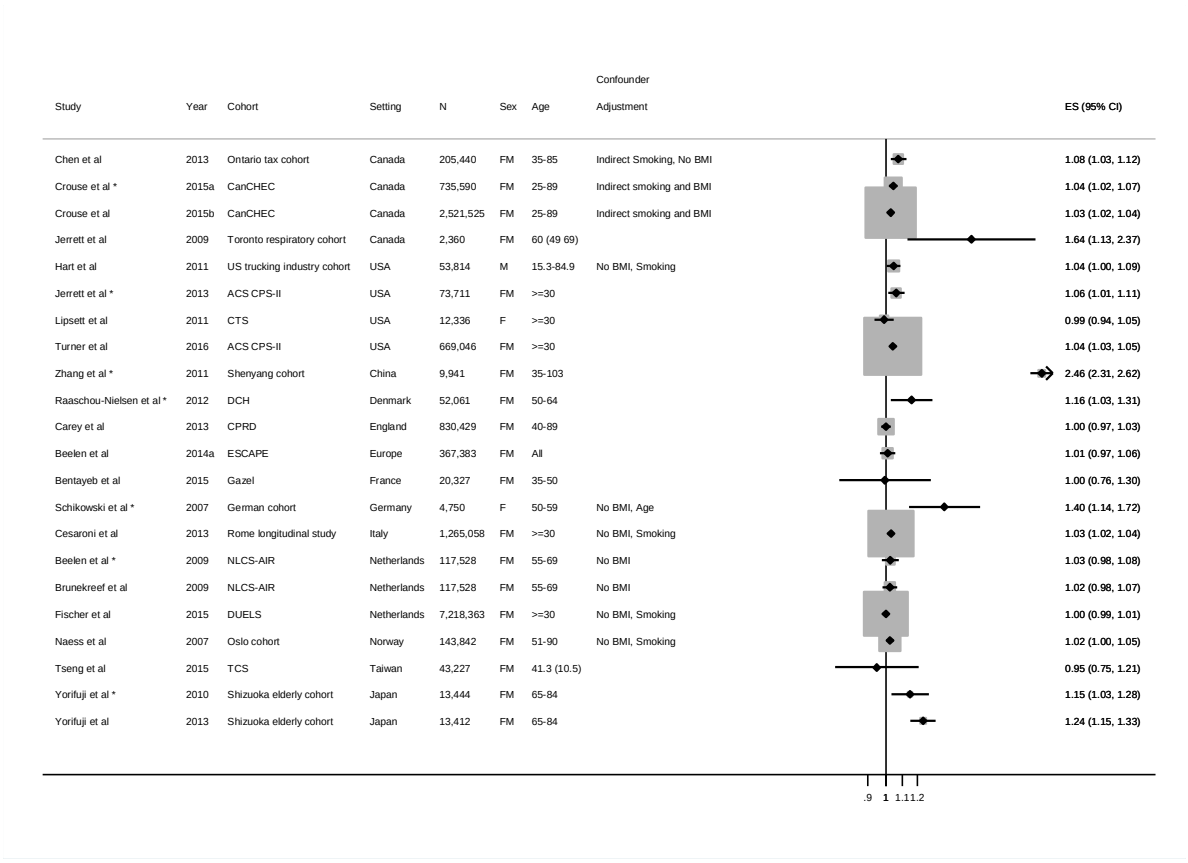
eFigure 3 All-cause mortality - stratification by pre-existing disease on recruitment



eFigure 4 All-cause mortality - stratification by age range at cohort recruitment

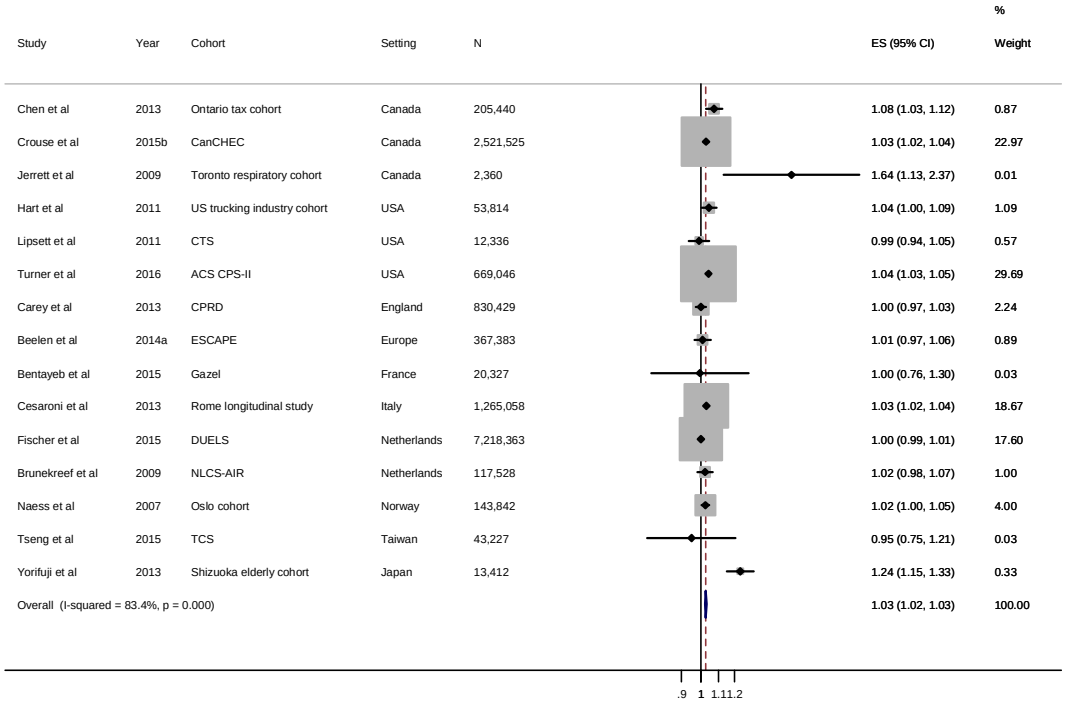


eFigure 5 Cardiovascular mortality

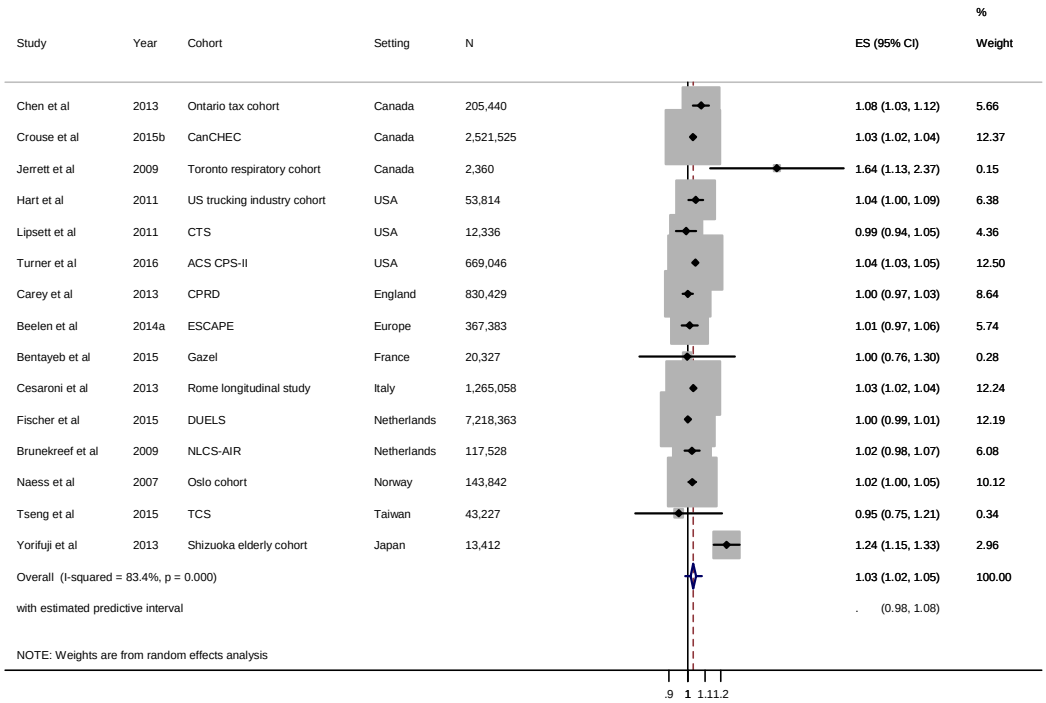


* indicates exclusion from meta-analysis. Refer to methods/results section of manuscript.

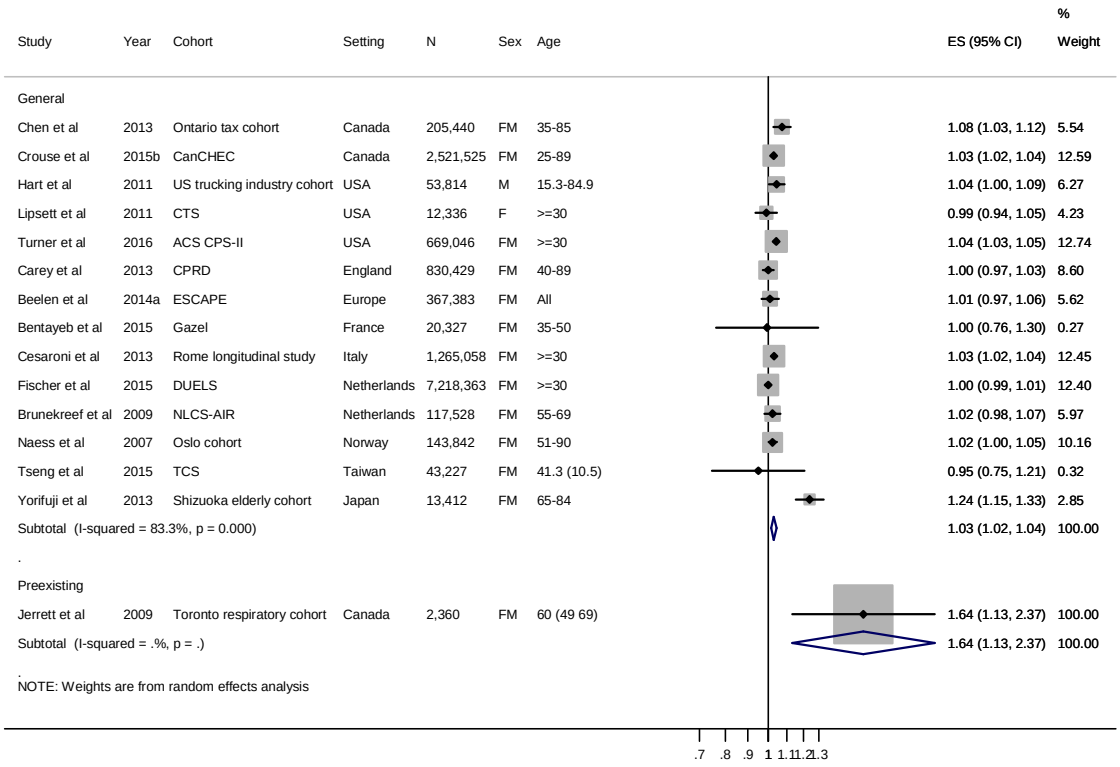
eFigure 6a Cardiovascular mortality – fixed effects model



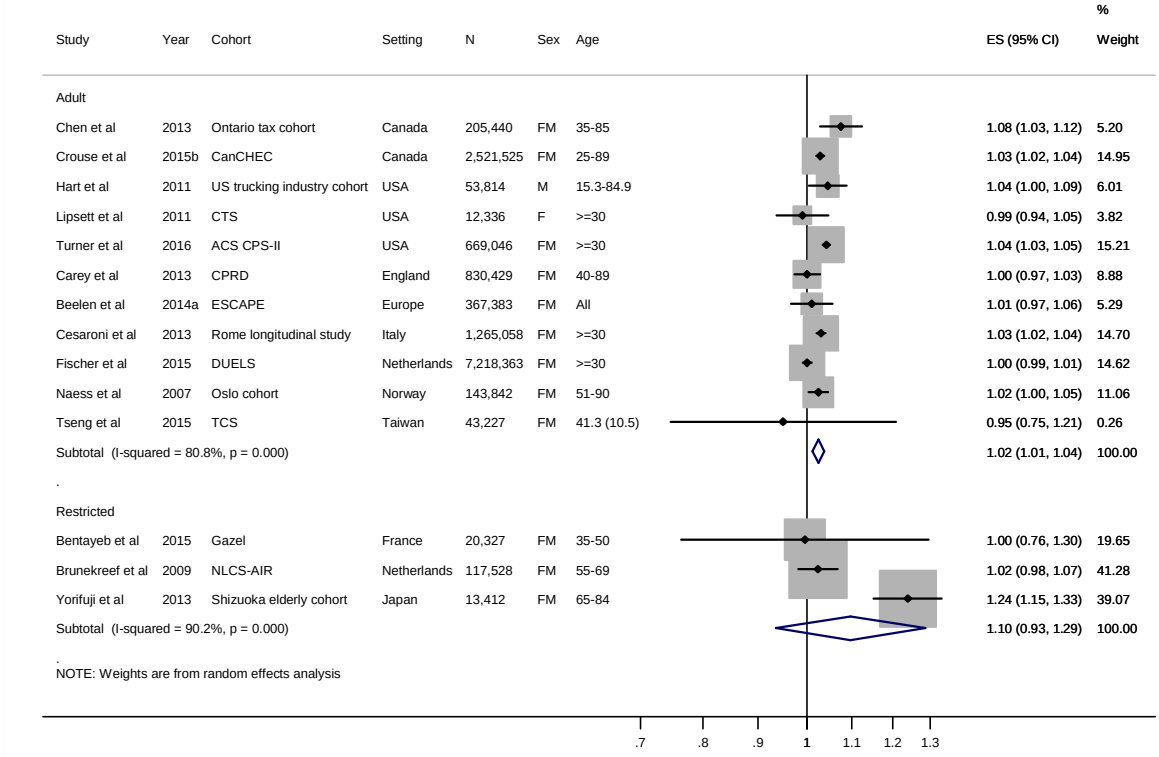
eFigure 6b Cardiovascular mortality – random effects model



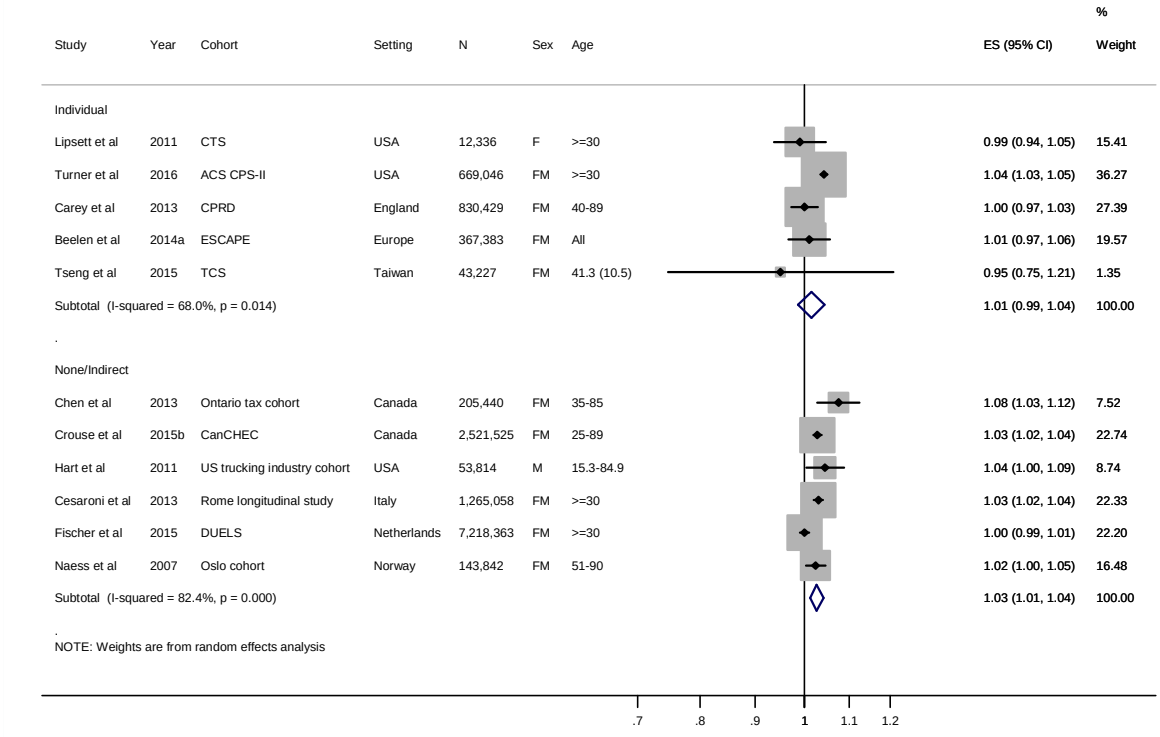
eFigure 7 Cardiovascular mortality - stratification by pre-existing disease on recruitment



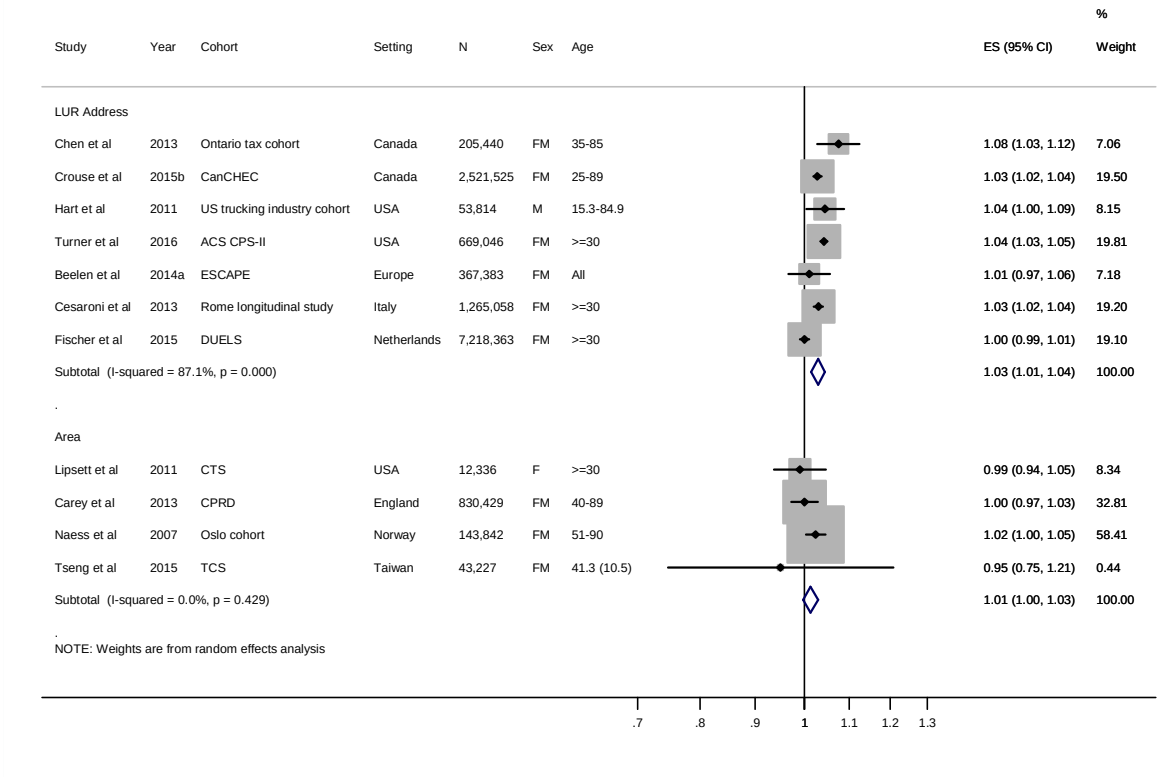
eFigure 8 Cardiovascular mortality - stratification by age range at cohort recruitment



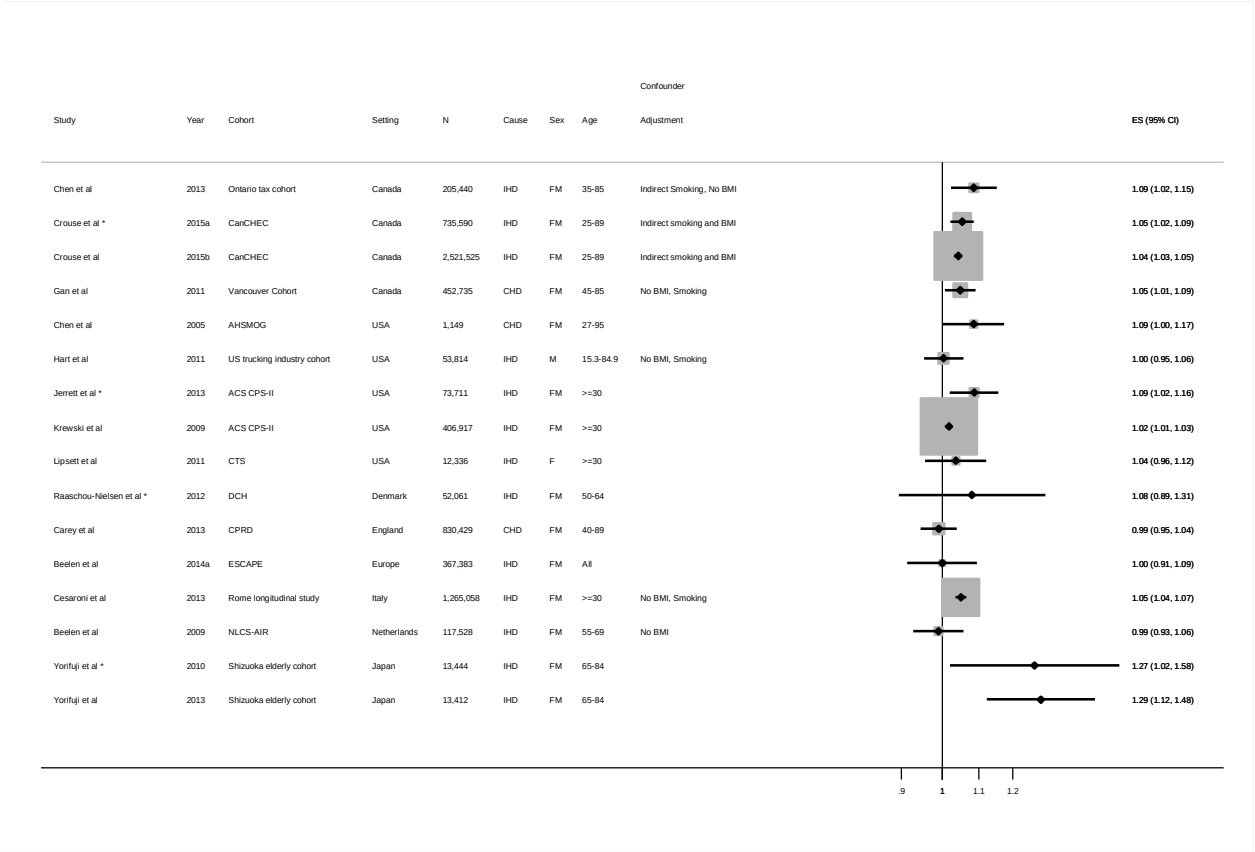
eFigure 9 Cardiovascular mortality - stratification by level of adjustment for smoking and BMI



eFigure 10 Cardiovascular mortality - stratification by spatial resolution of NO_2 concentration estimates

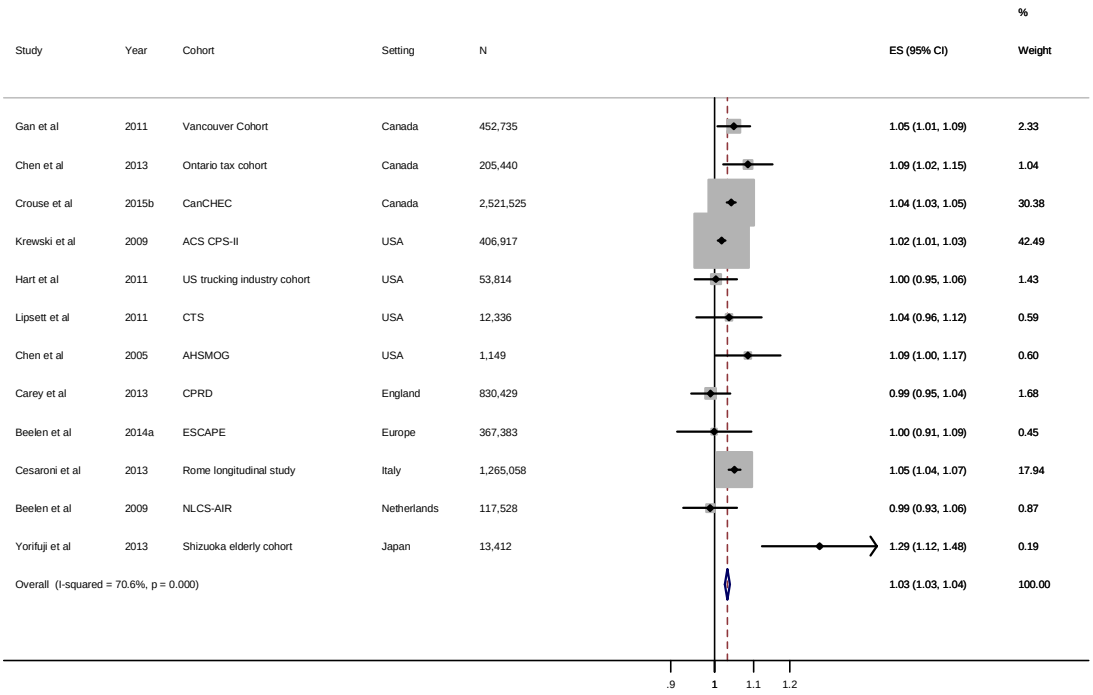


eFigure 11 CHD mortality

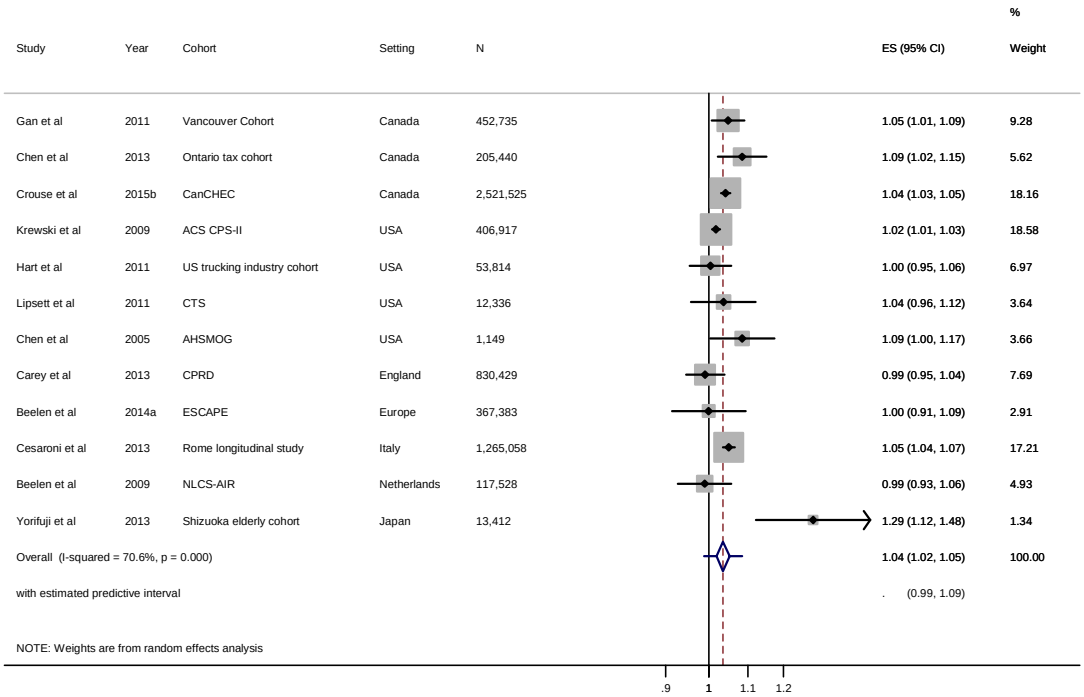


* indicates exclusion from meta-analysis. Refer to methods/results sections of manuscript.

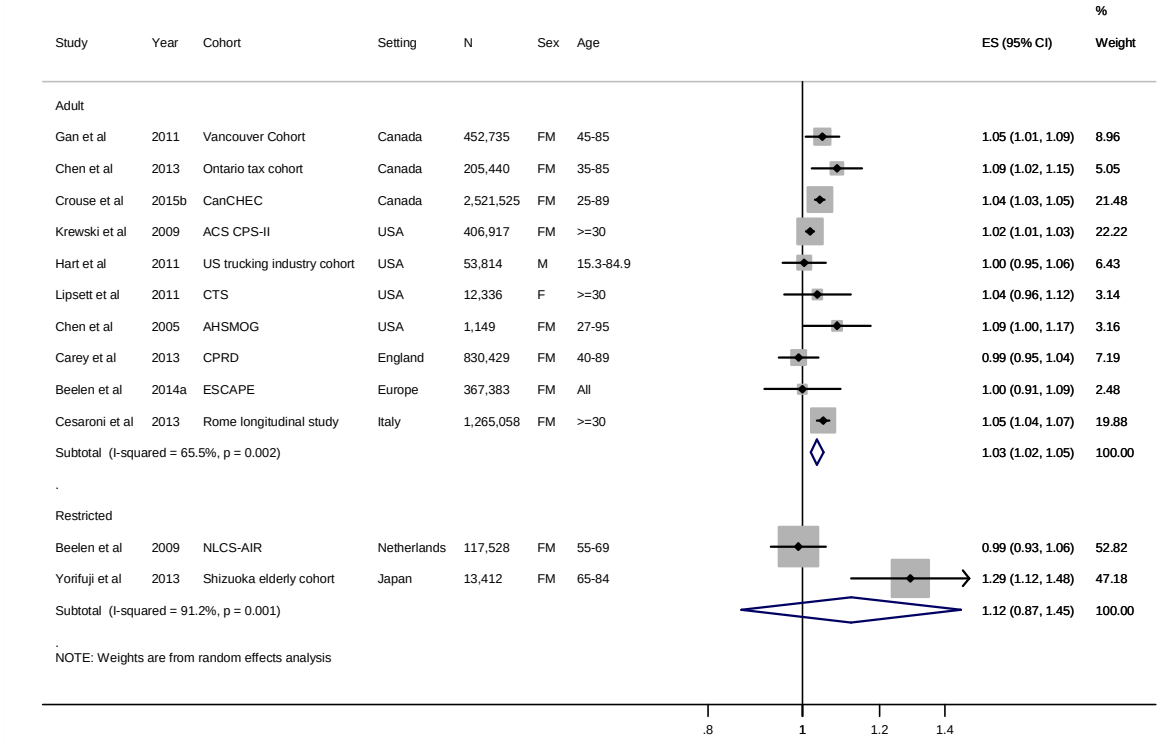
eFigure 12a CHD mortality - fixed effects model



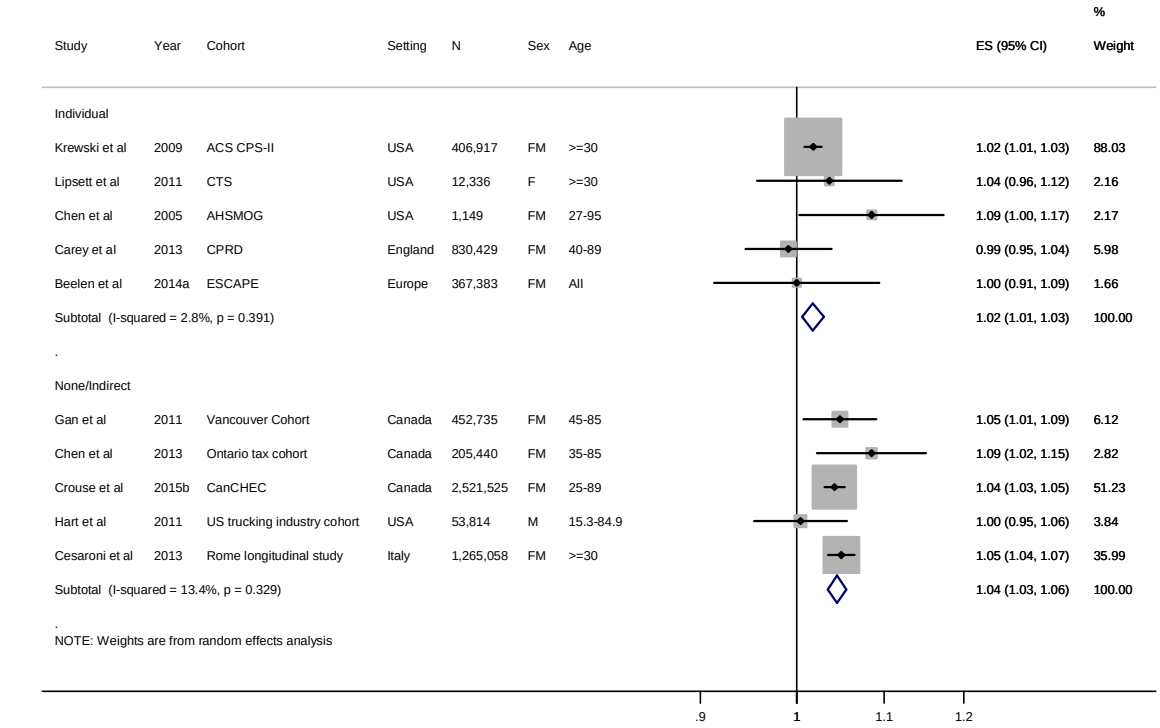
eFigure 12b CHD mortality - random effects model



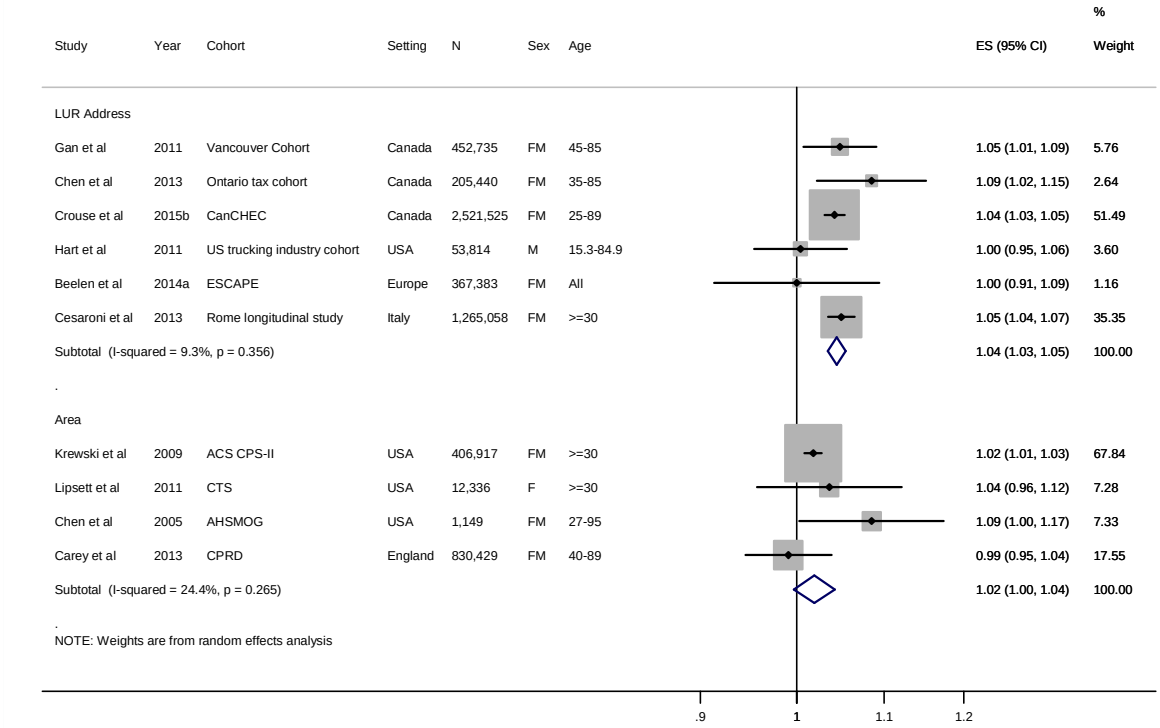
eFigure 13 CHD mortality - stratification by age range at cohort recruitment



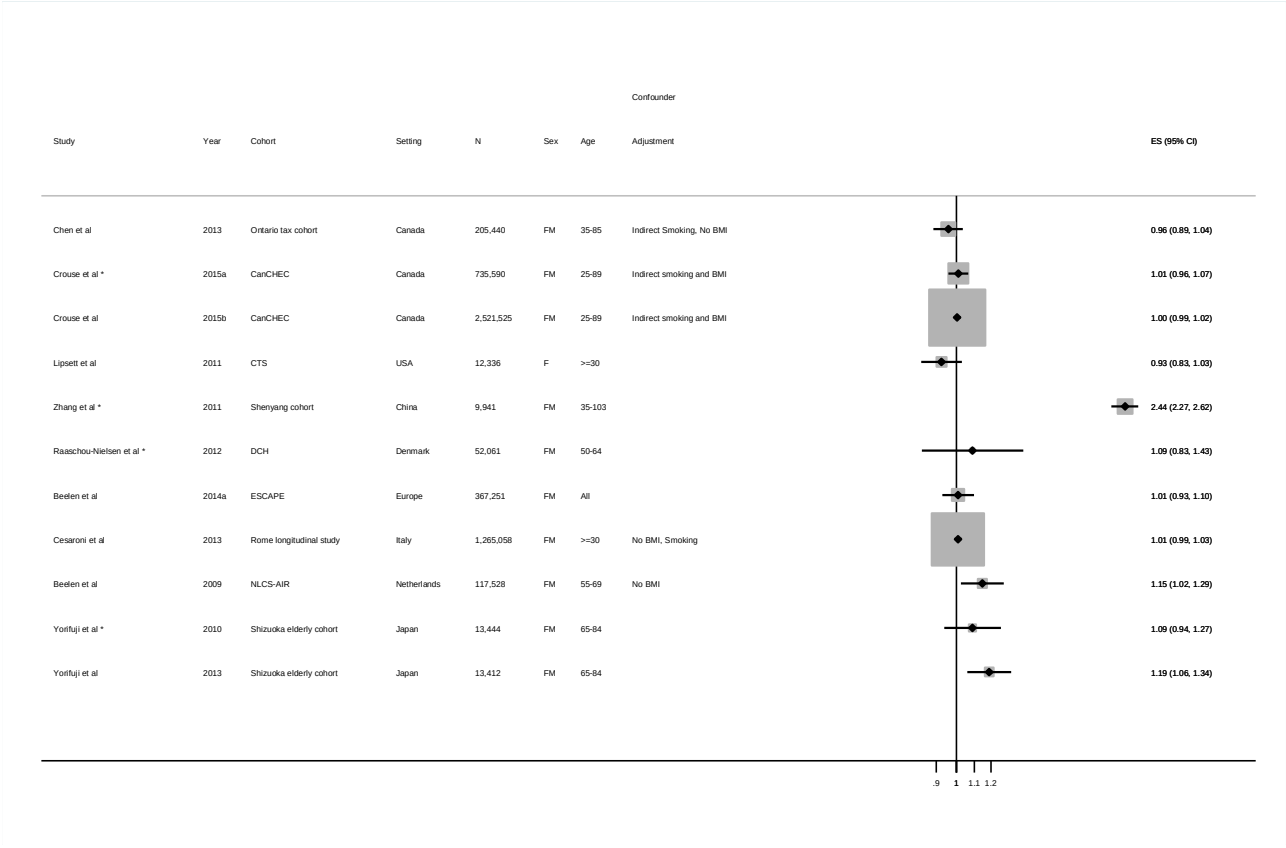
eFigure 14 CHD mortality - stratification by level of adjustment for smoking and BMIl



eFigure 15 CHD mortality - stratification by spatial resolution of NO_2 concentration estimates

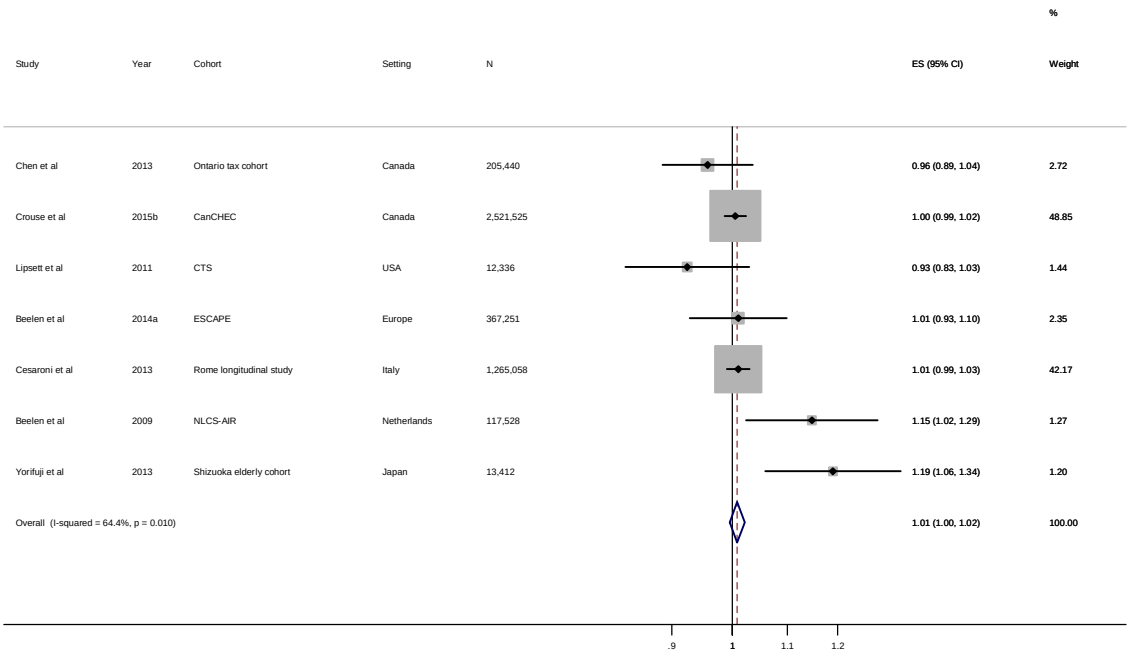


eFigure 16 Cerebrovascular mortality

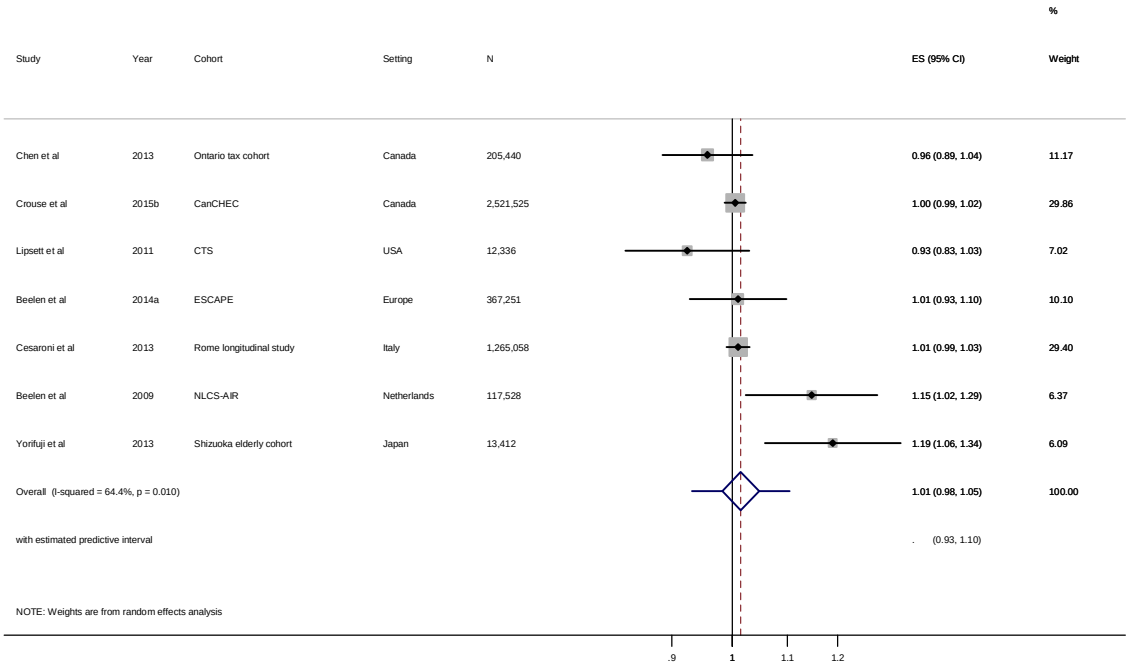


* indicates exclusion from meta-analysis. Refer to methods/results sections of manuscript.

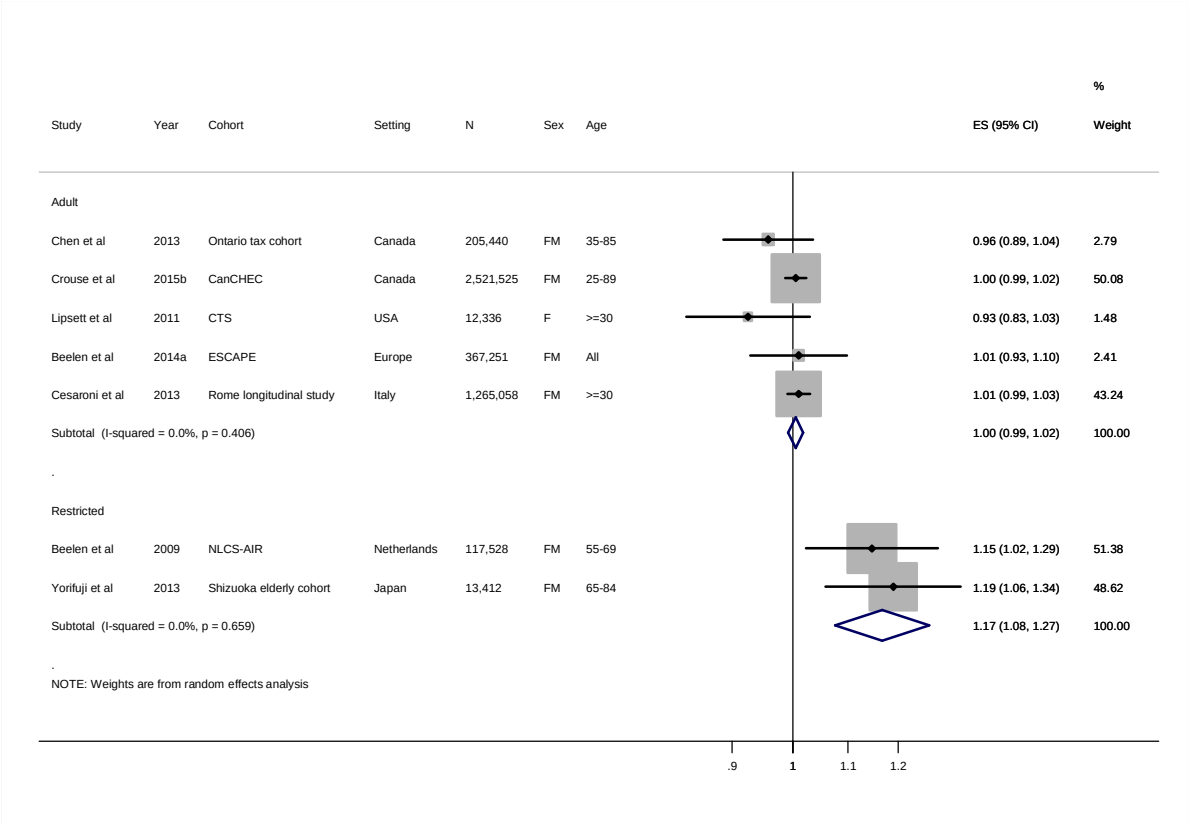
eFigure 17a Cerebrovascular mortality - fixed effects model



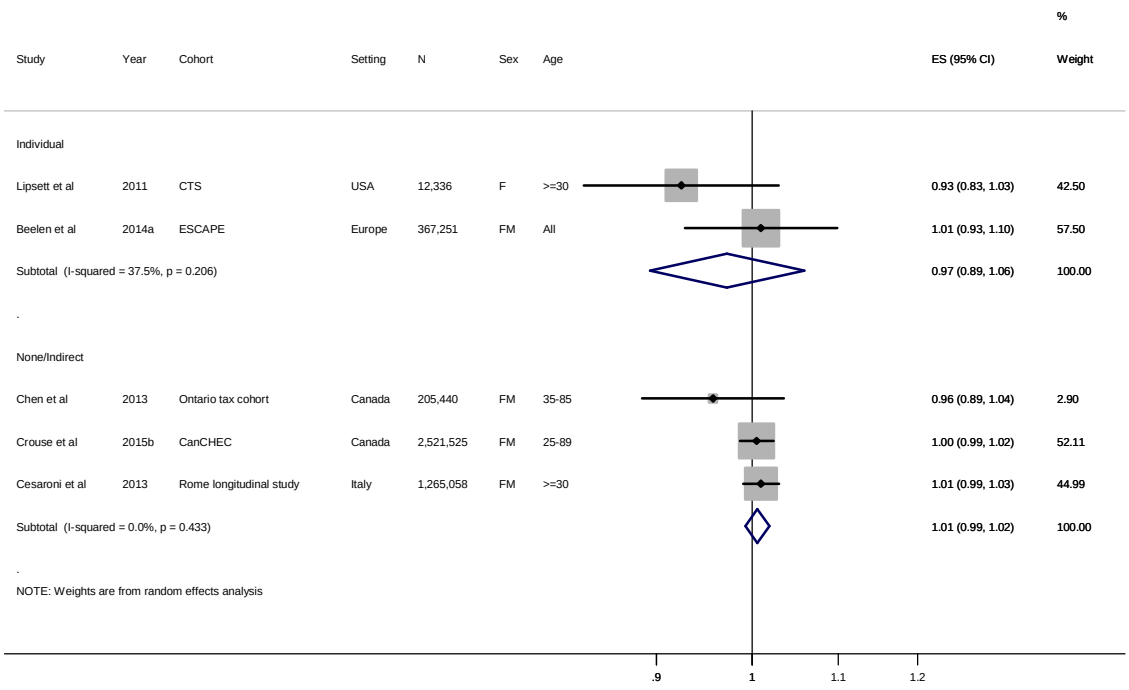
eFigure 17b Cerebrovascular mortality - random effects model



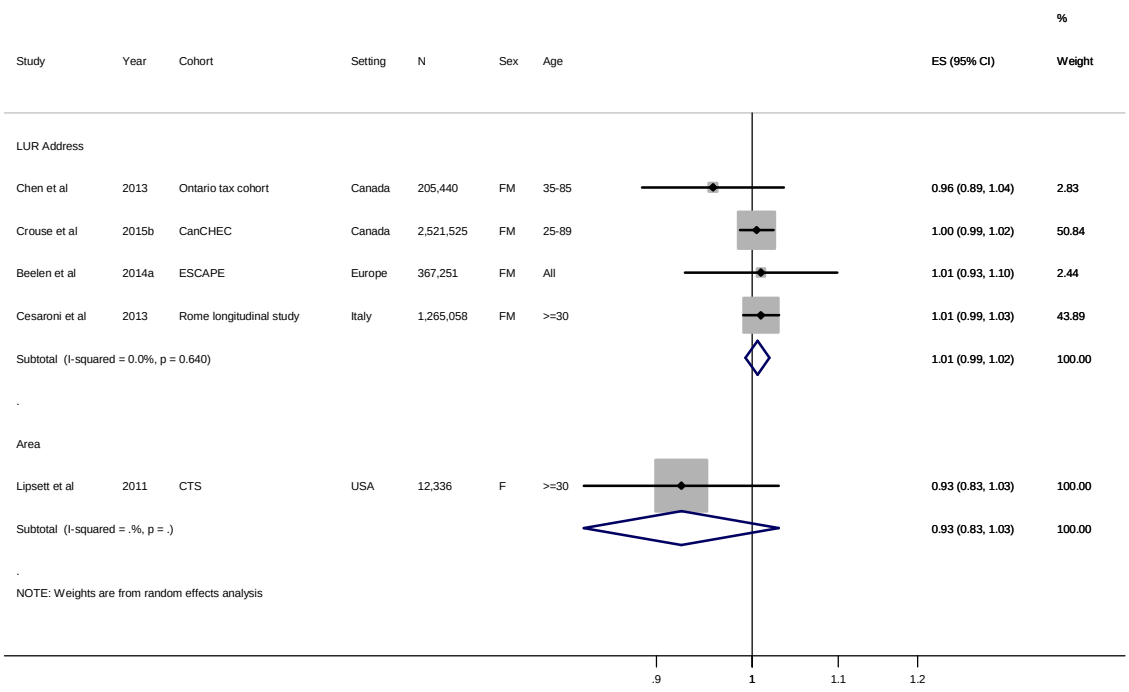
eFigure 18 Cerebrovascular mortality - stratification by age range at cohort recruitment



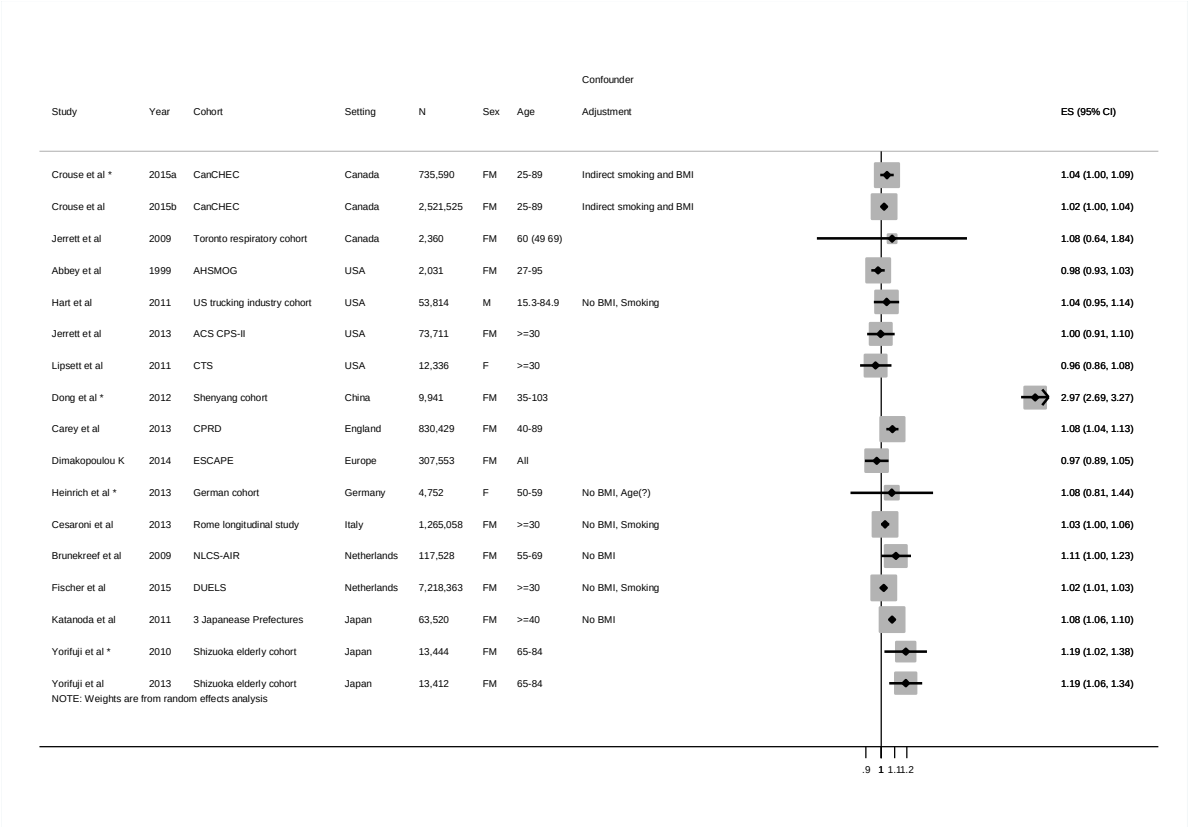
eFigure 19 Cerebrovascular mortality - stratification by level of adjustment for smoking and BMI



eFigure 20 Cerebrovascular mortality - stratification by spatial resolution of NO_2 concentration

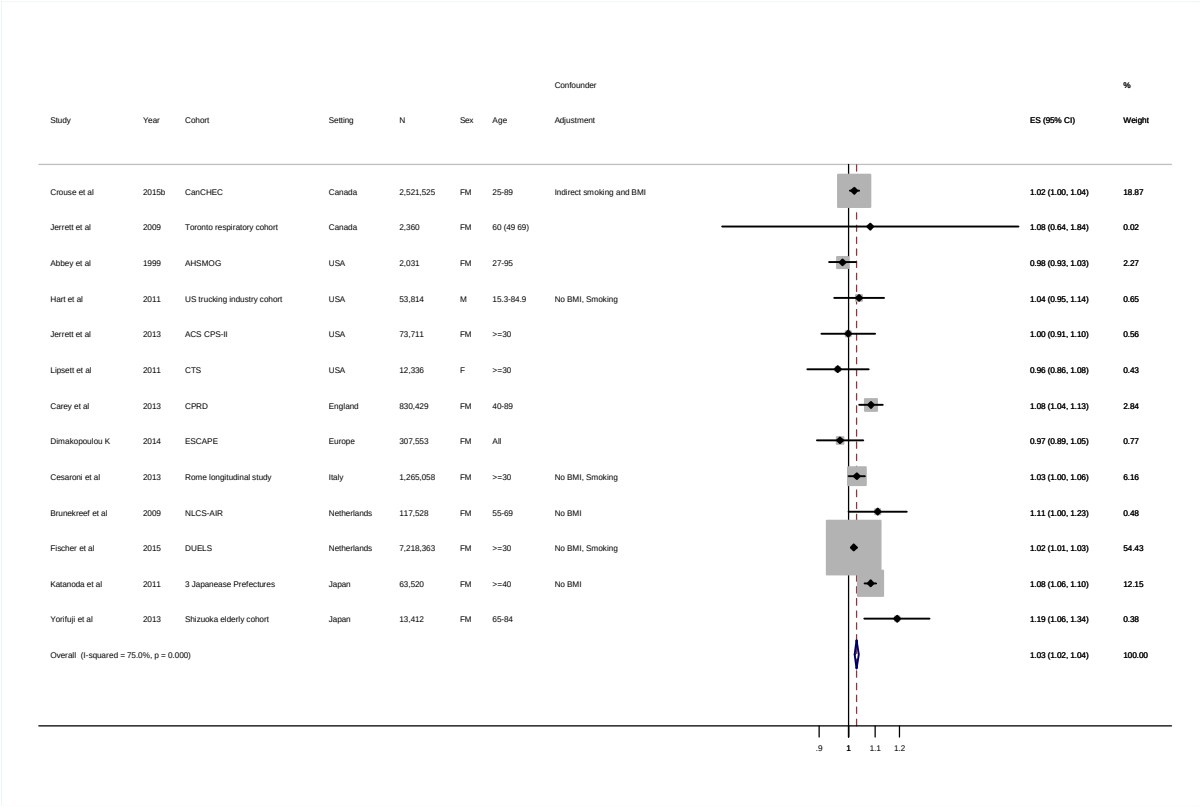


eFigure 21 Respiratory mortality

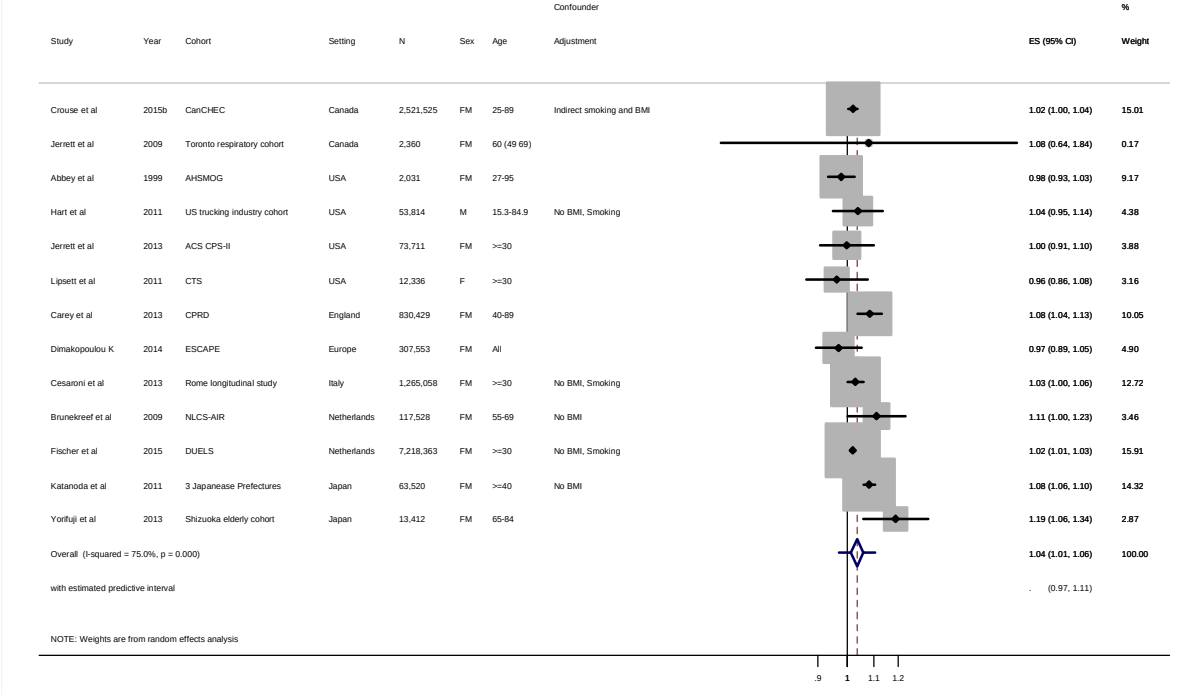


* indicates exclusion from meta-analysis. Refer to methods/results sections of manuscript.

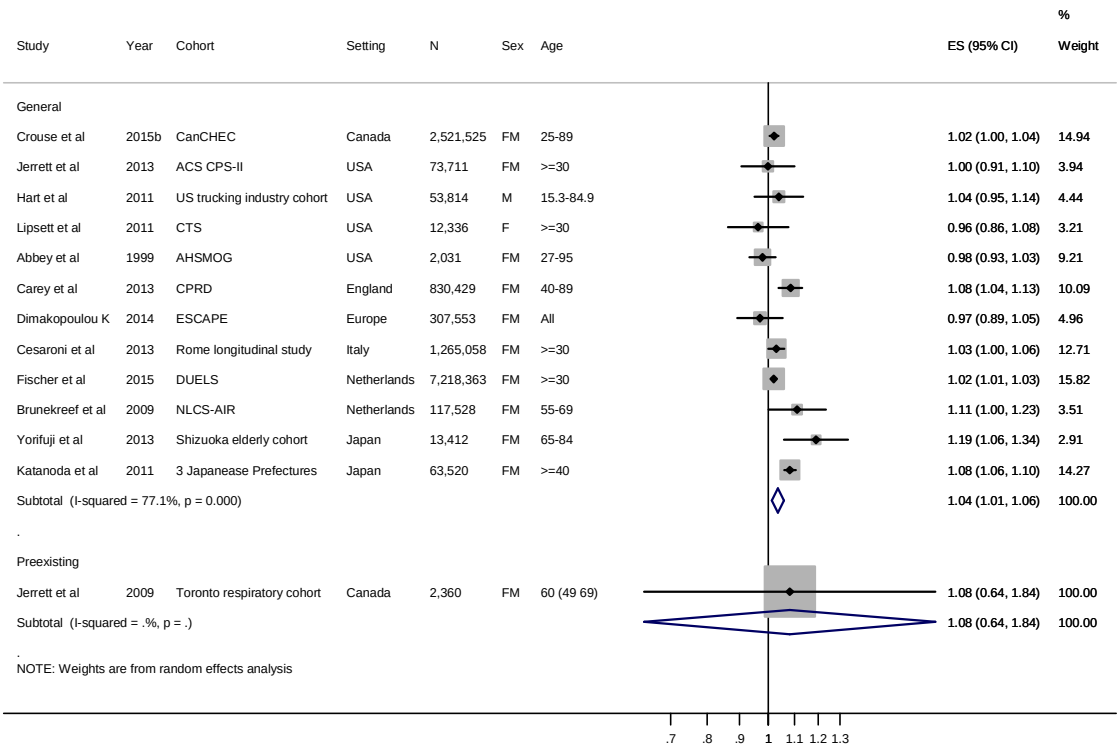
eFigure 22a Respiratory mortality - fixed effects model



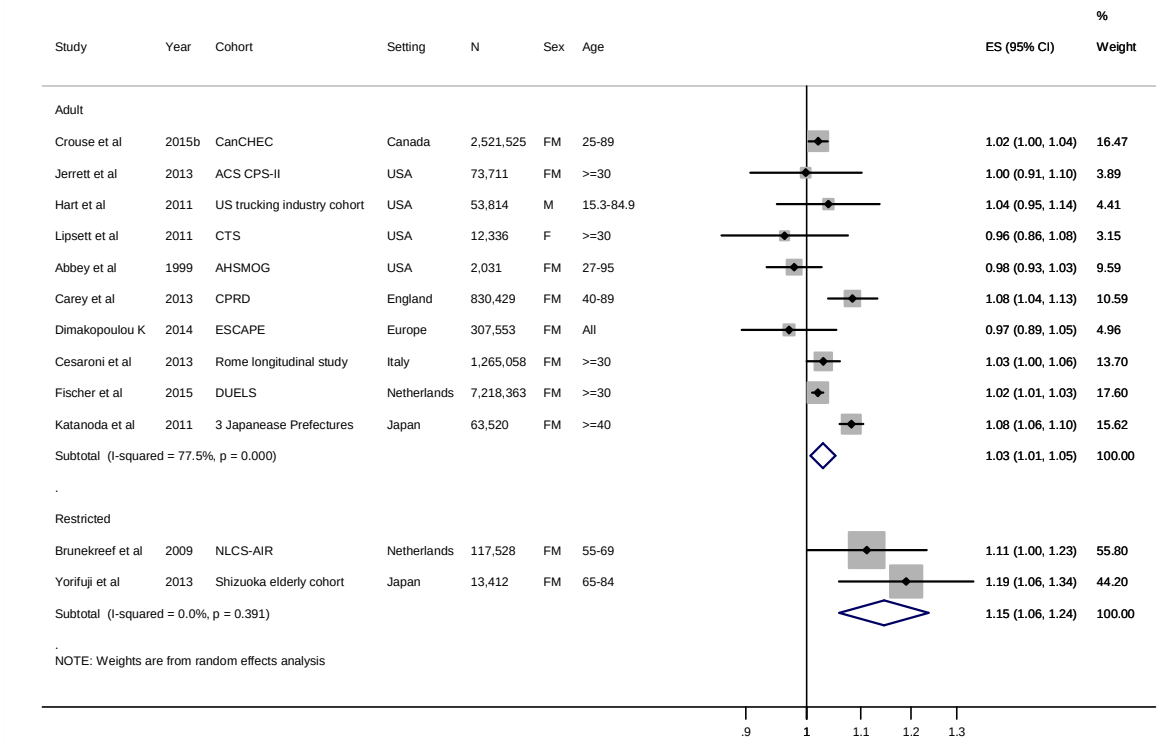
eFigure 22b Respiratory mortality - random effects model



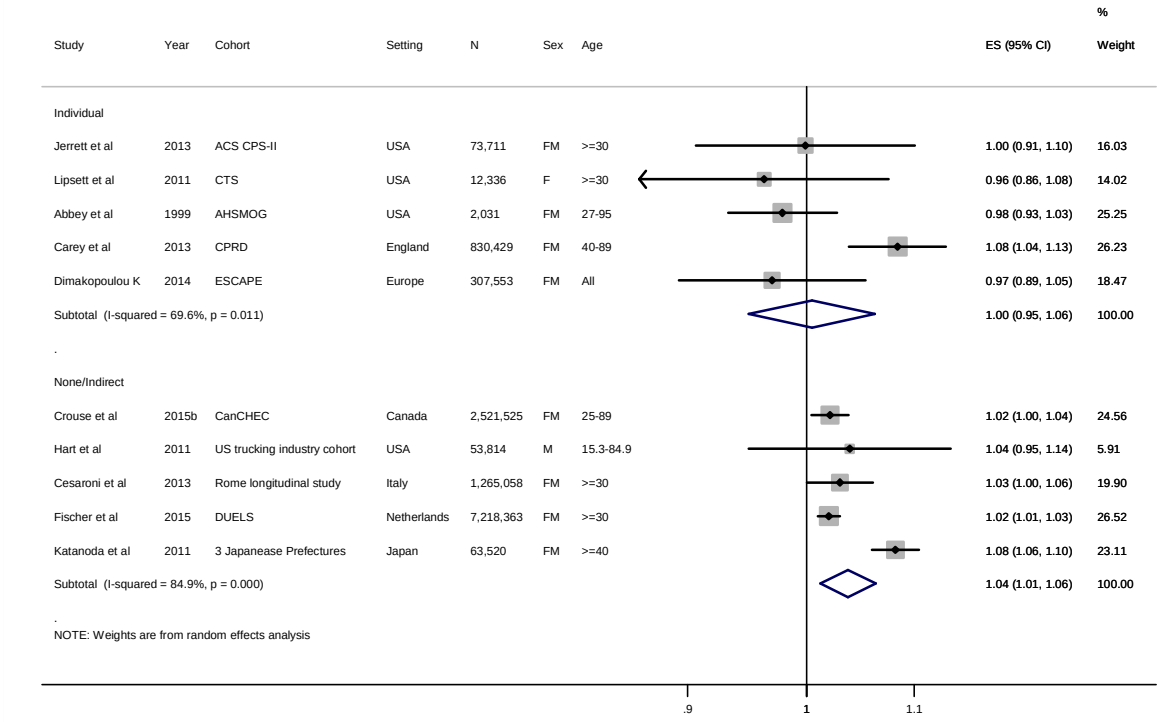
eFigure 23 Respiratory mortality - stratification by pre-existing disease



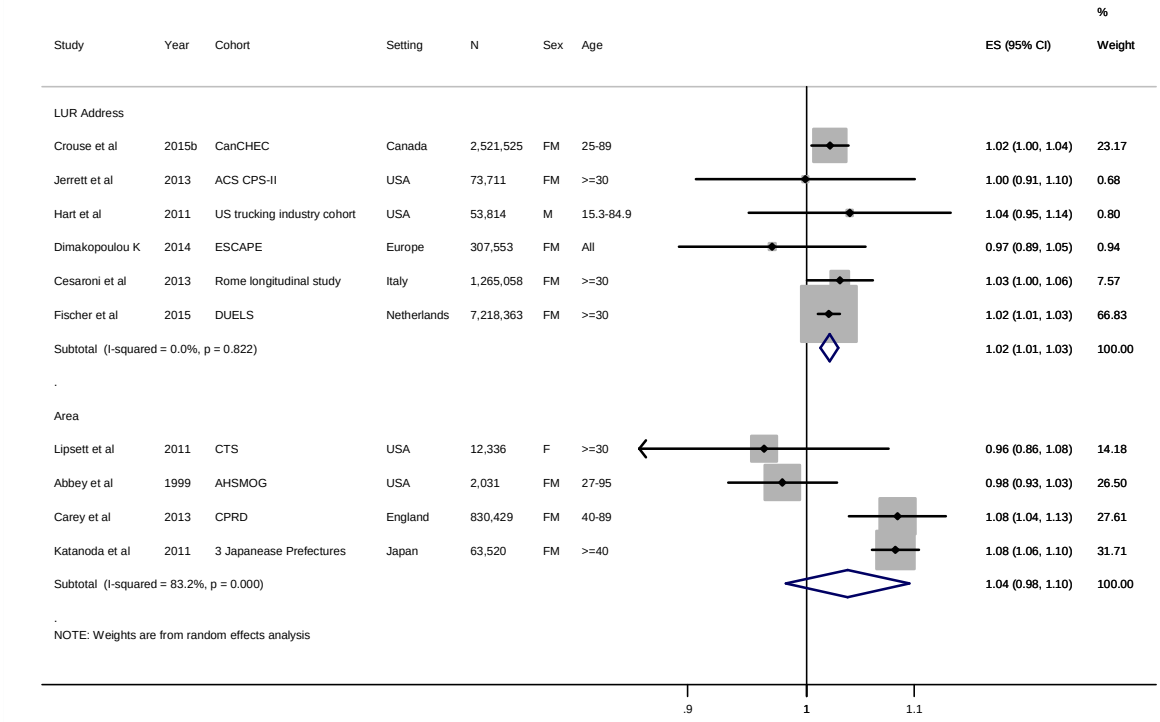
eFigure 24 Respiratory mortality - stratification by age range at cohort recruitment



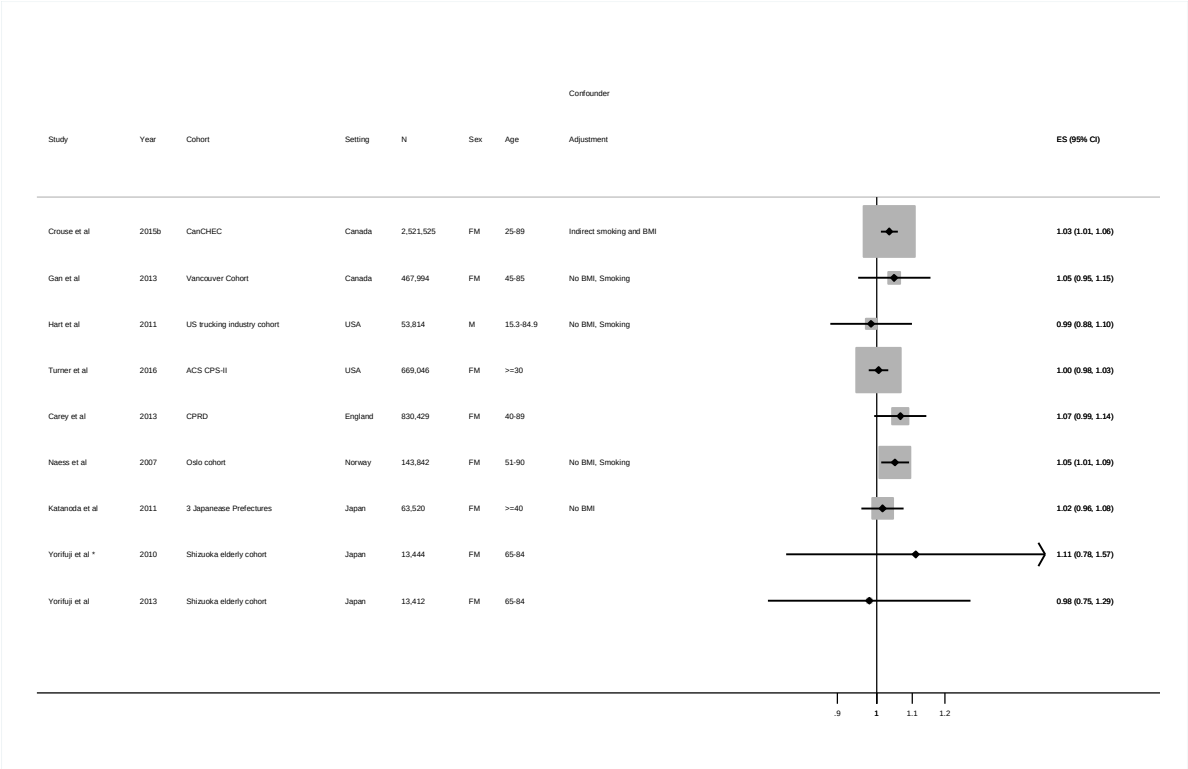
eFigure 25 Respiratory mortality - stratification by level of adjustment for smoking and BMI



eFigure 26 Respiratory mortality - stratification by spatial resolution of NO_2 concentration

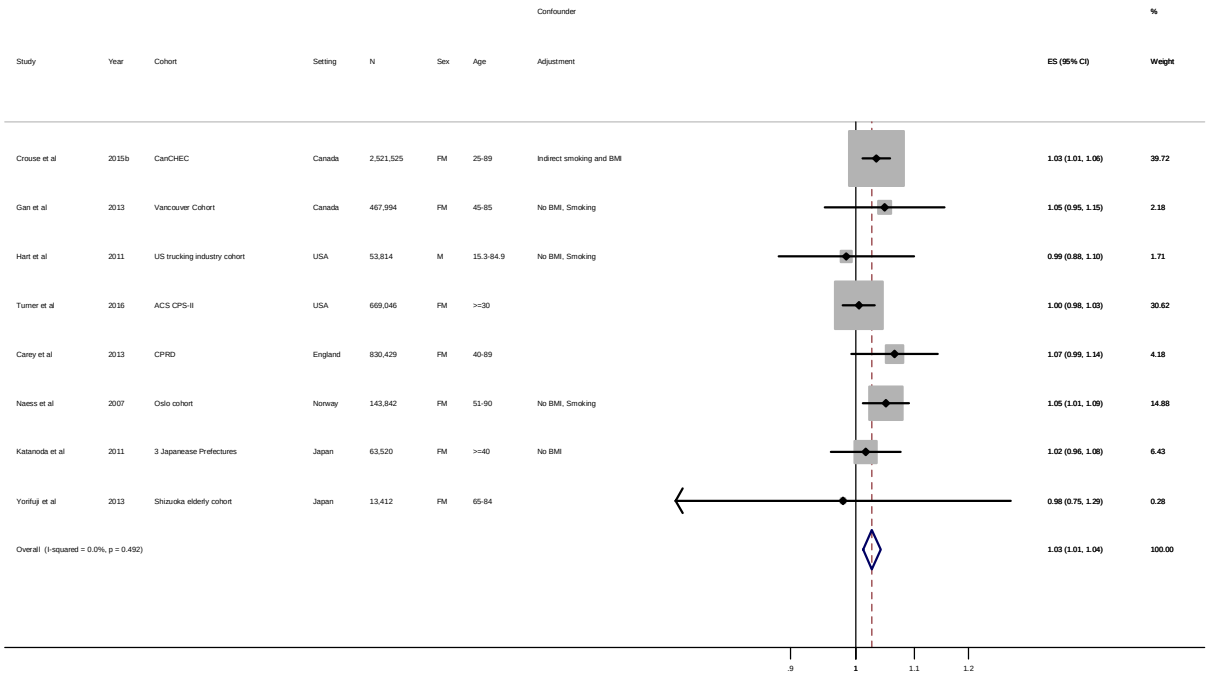


eFigure 27 COPD mortality

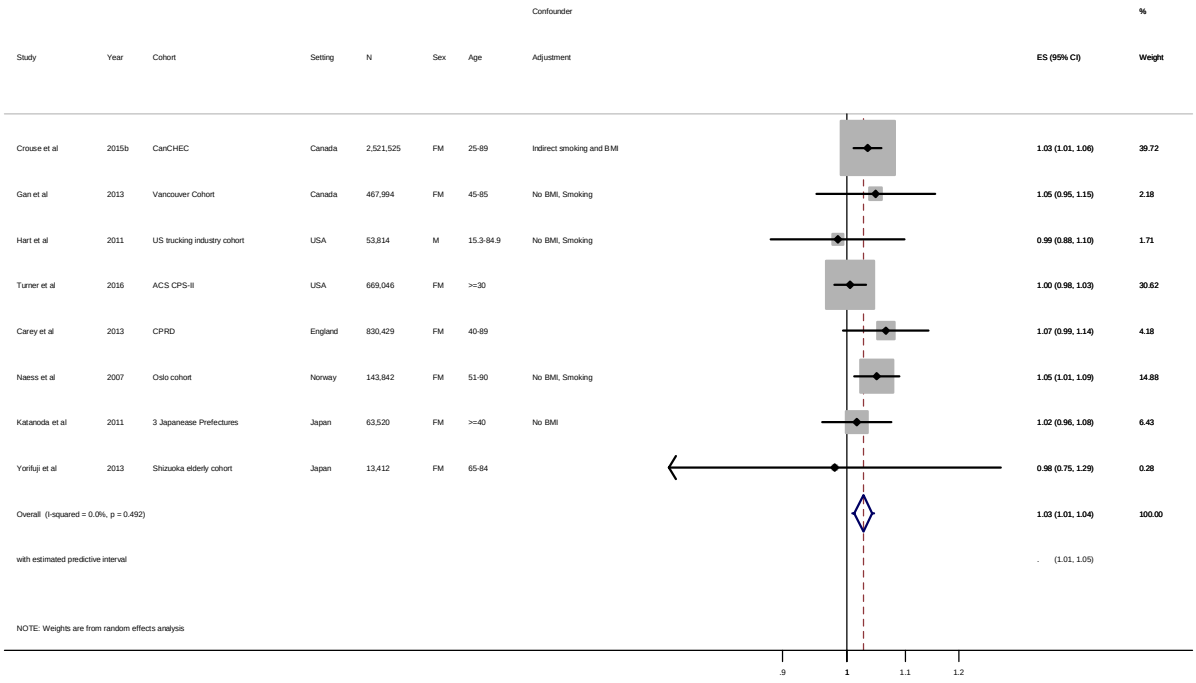


* indicates exclusion from meta-analysis. Refer to methods/results sections of manuscript.

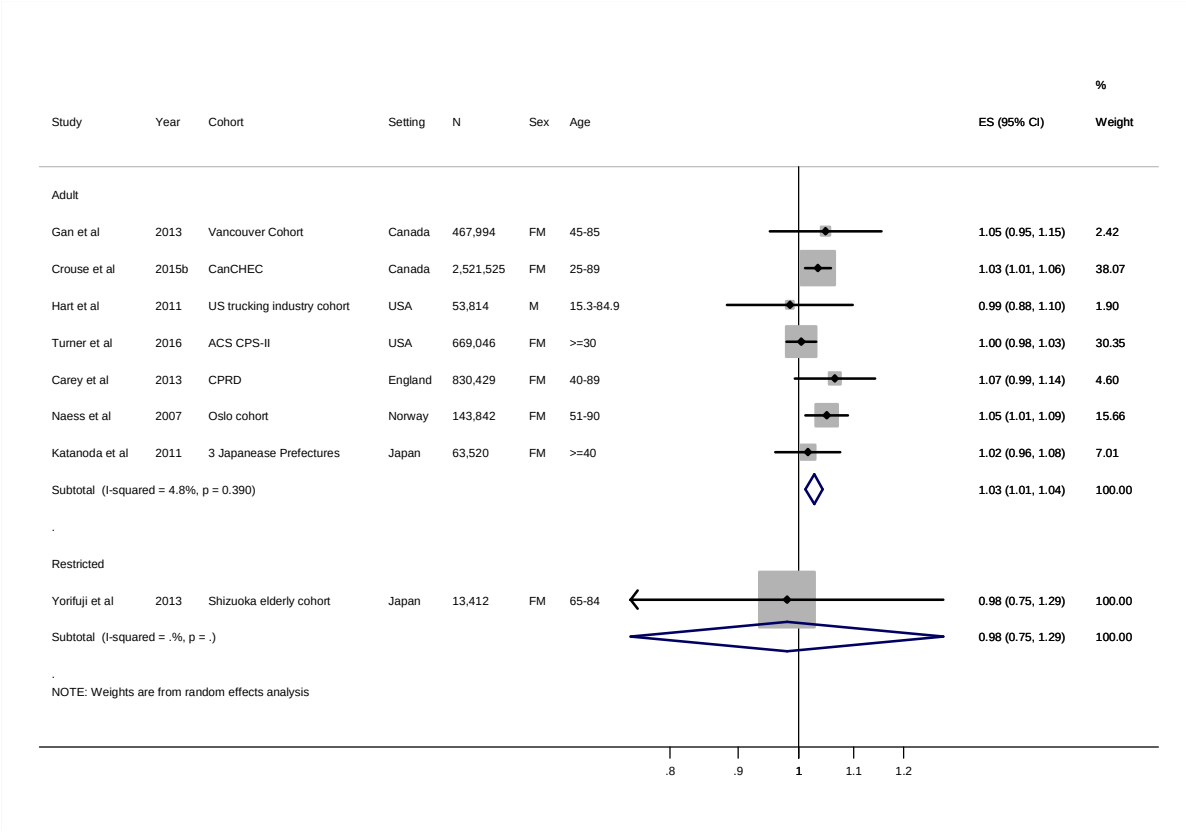
eFigure 28a COPD mortality - fixed effects model



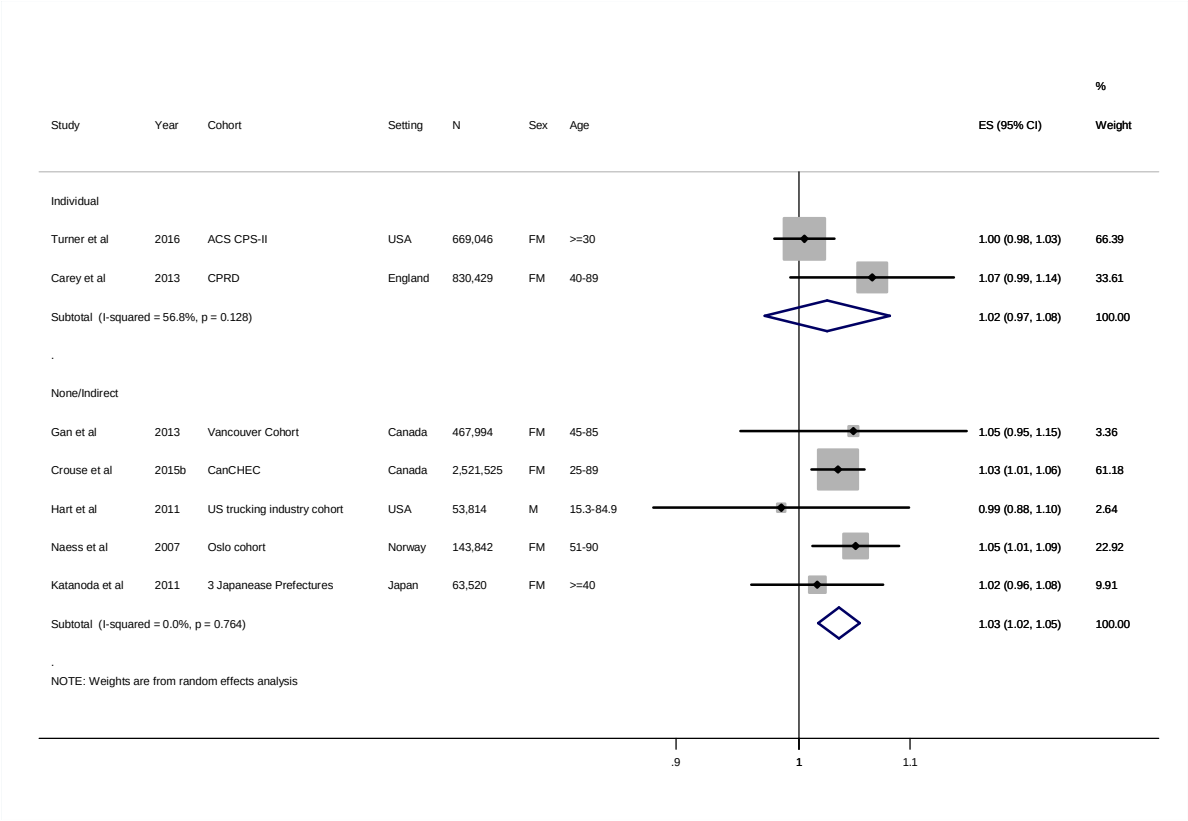
eFigure 28b COPD mortality - random effects model



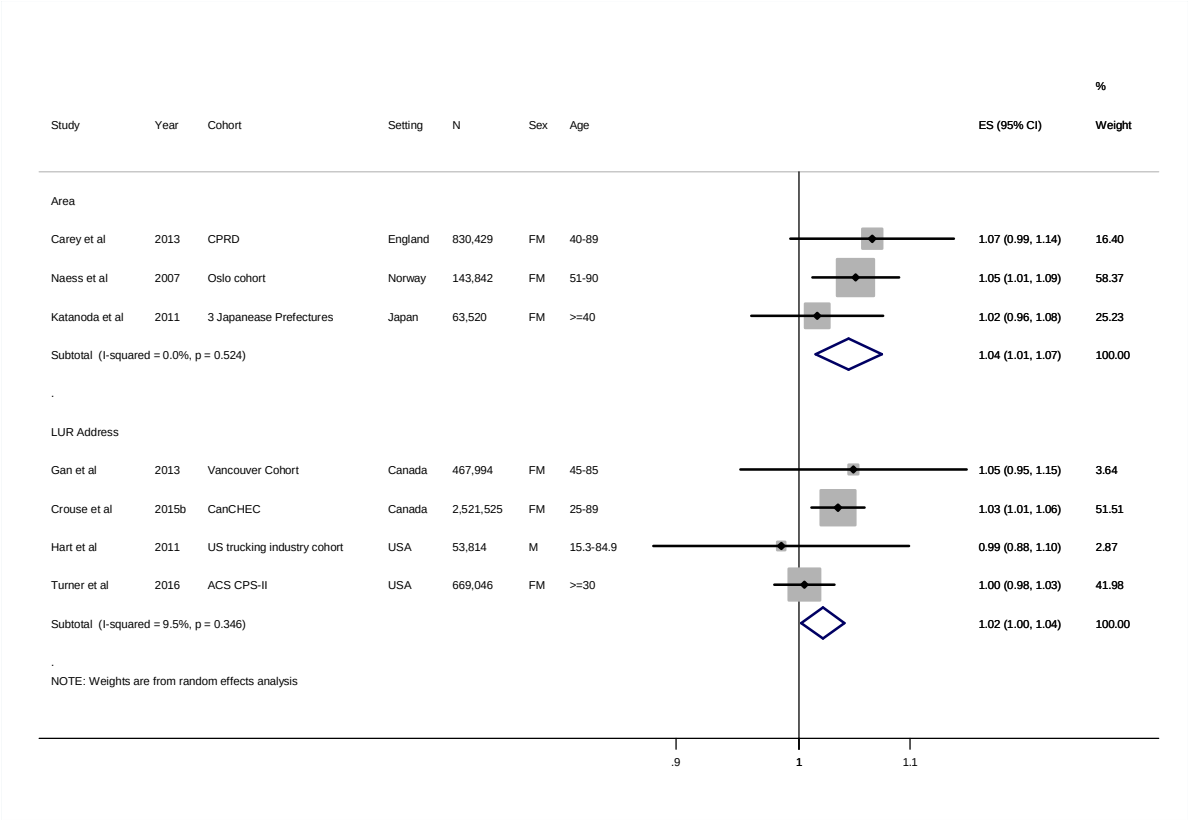
eFigure 29 COPD mortality - stratification by age range at cohort recruitment



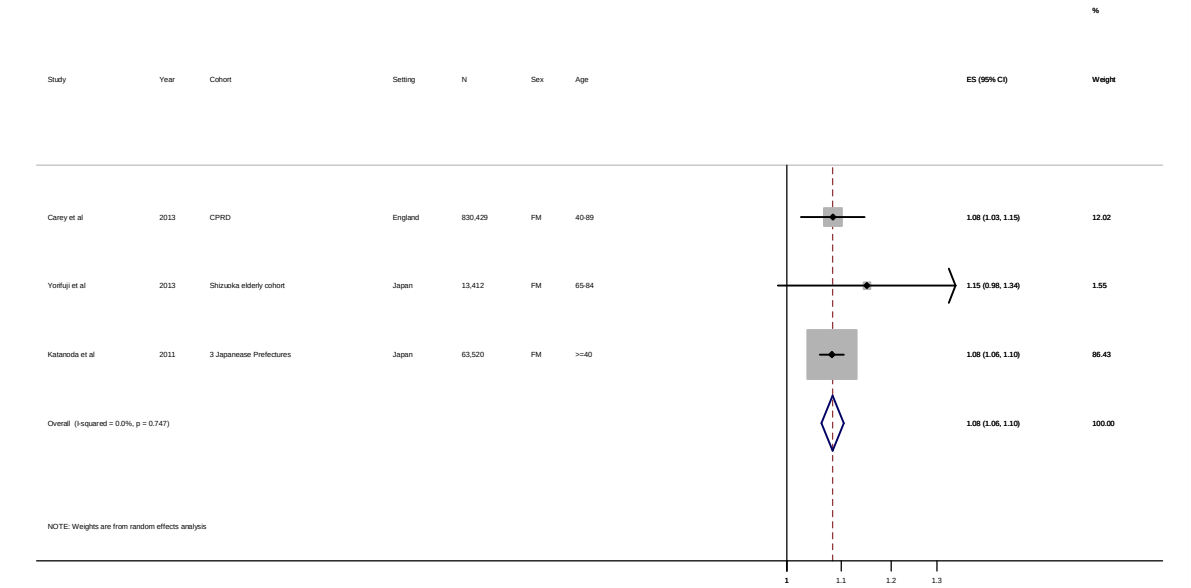
eFigure 30 COPD mortality - stratification by level of adjustment for smoking and BMI



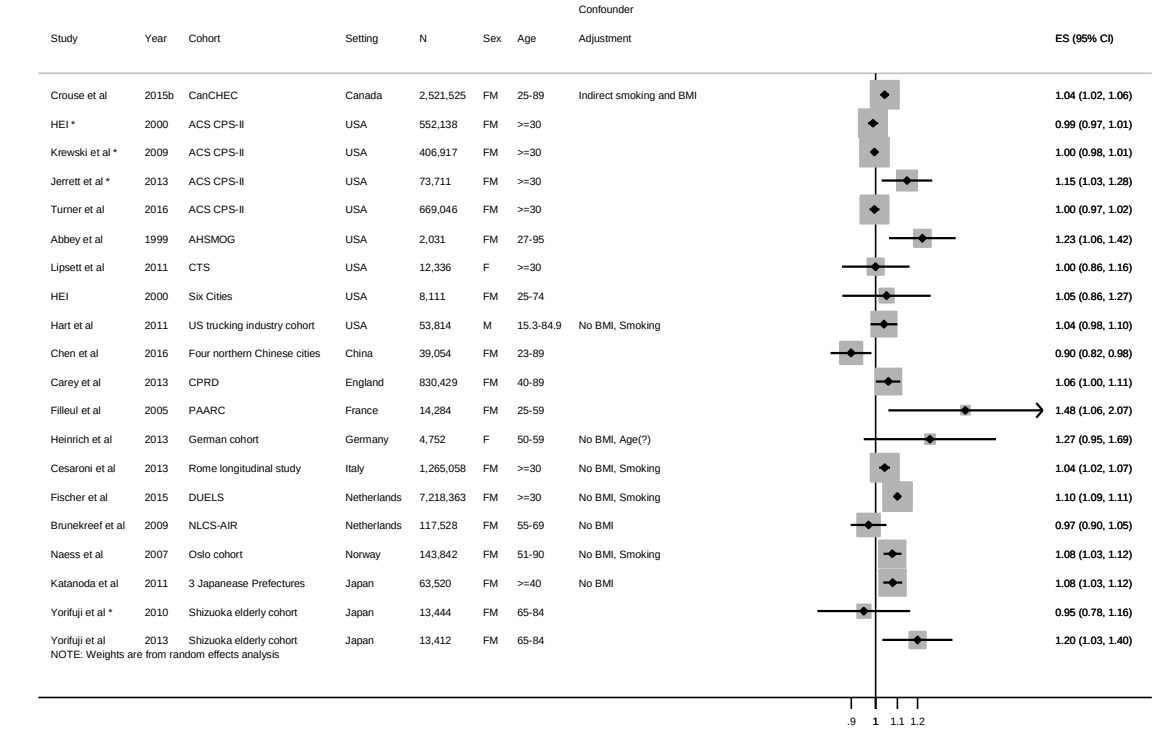
eFigure 31 COPD mortality - stratification by spatial resolution of NO_2 concentration



eFigure 32 Pneumonia mortality

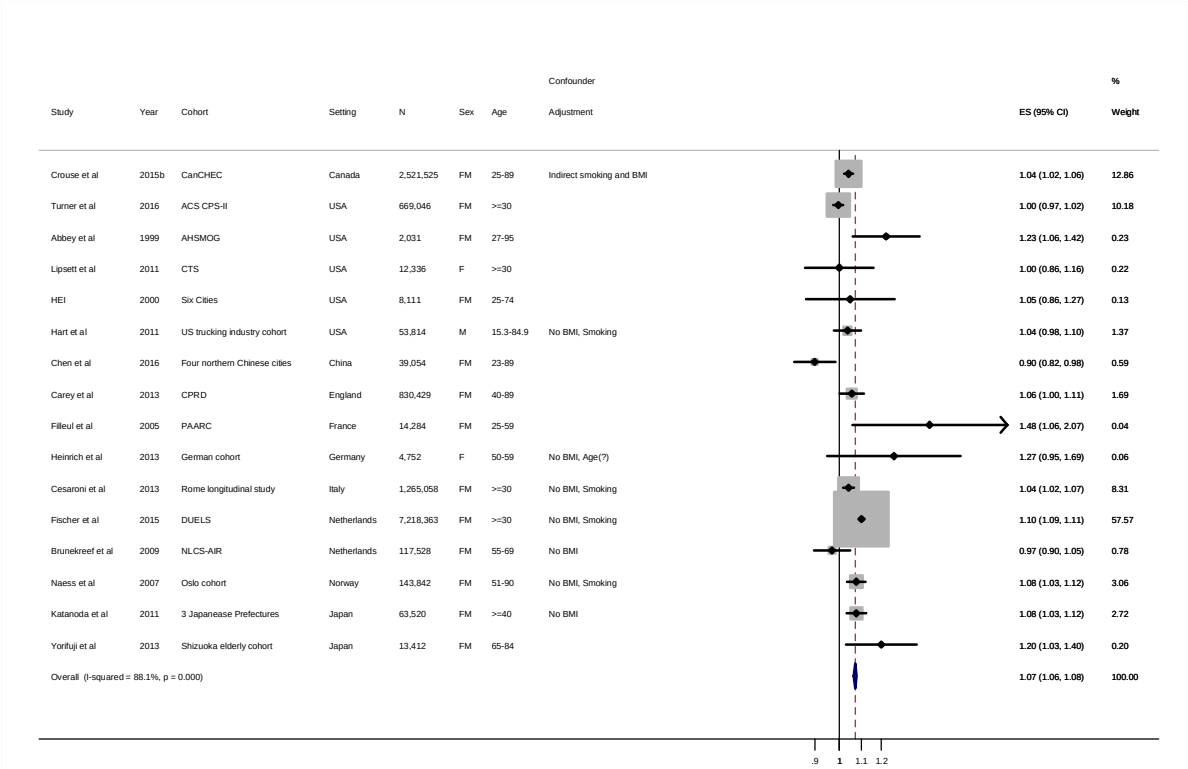


eFigure 33 Lung cancer mortality

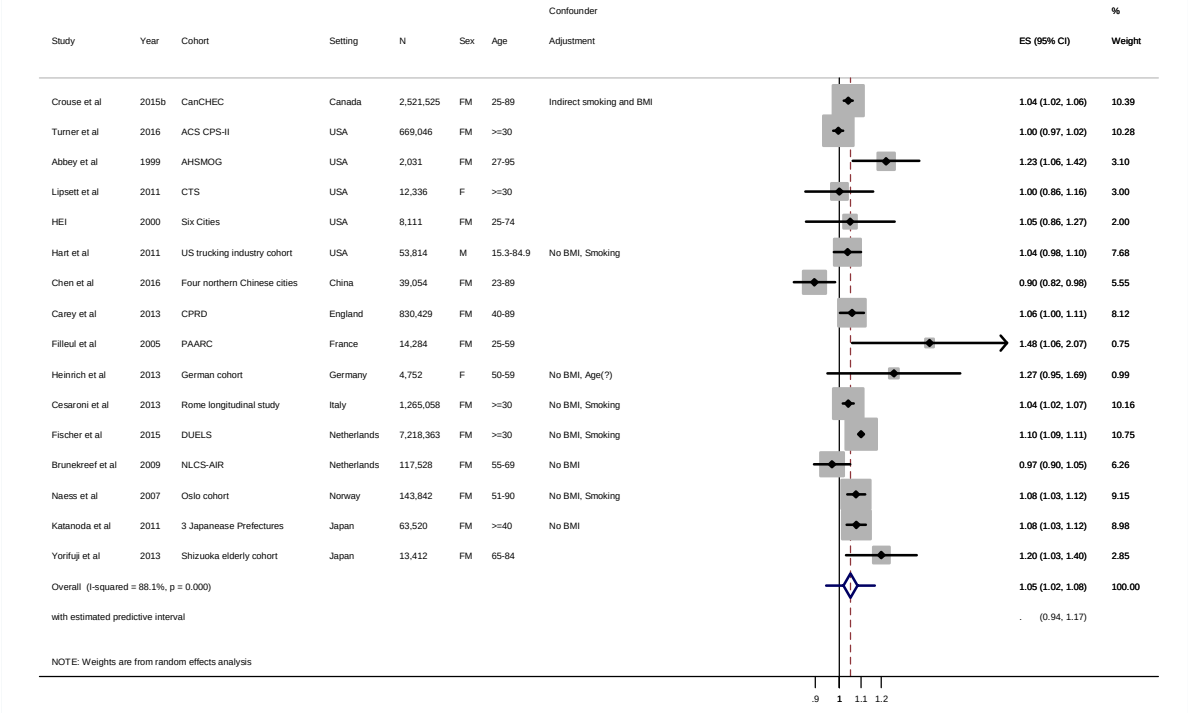


* indicates exclusion from meta-analysis. Refer to methods/results sections of manuscript.

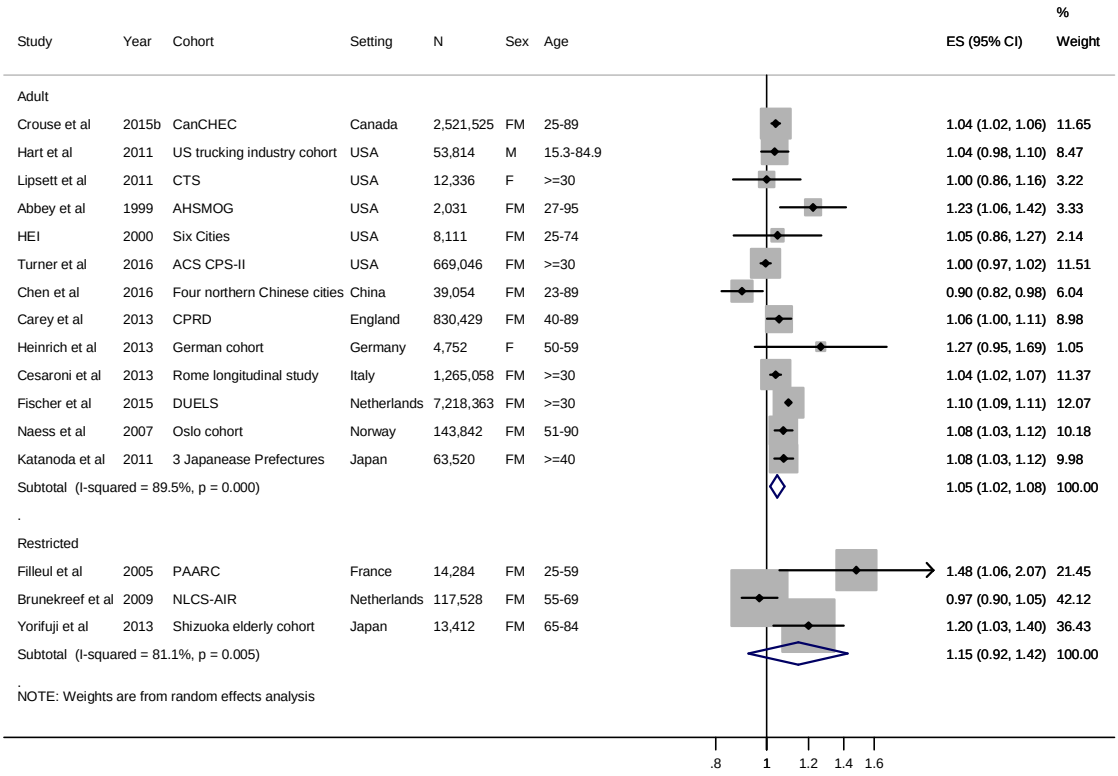
eFigure 34a Lung cancer mortality - fixed effects model



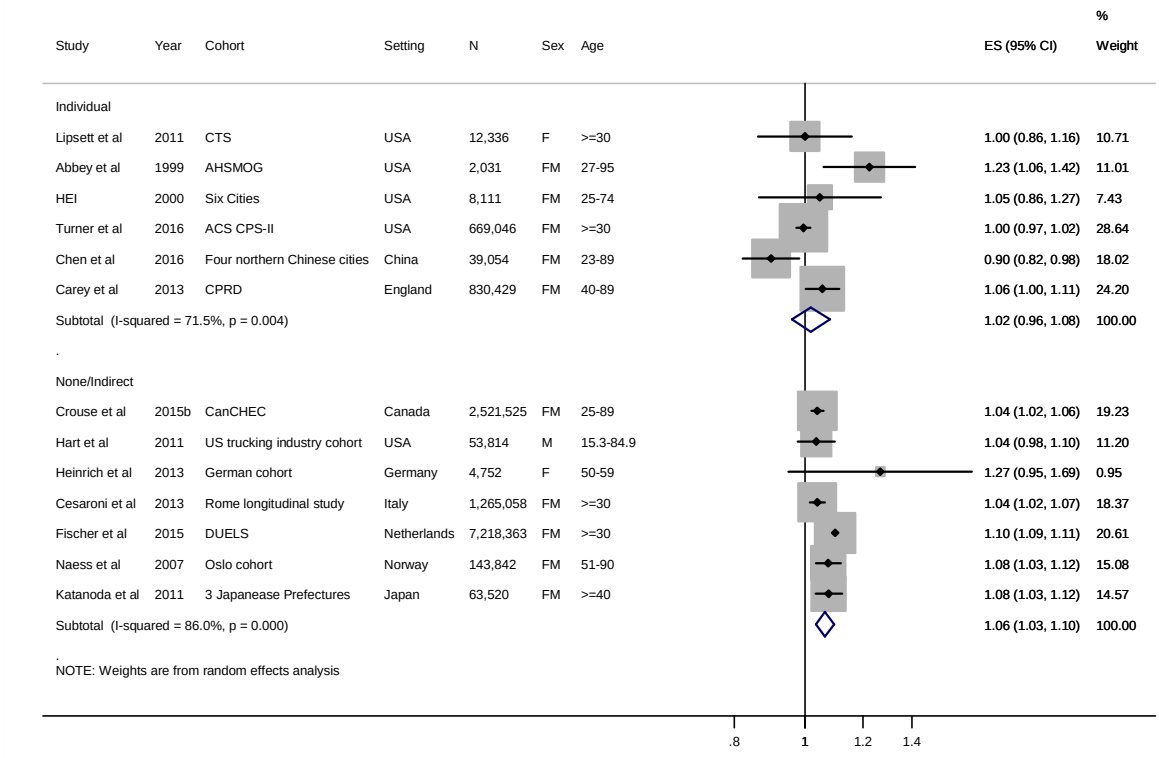
eFigure 34b Lung cancer mortality - random effects model



eFigure 35 Lung cancer mortality - stratification by age range at cohort recruitment



eFigure 36 Lung cancer mortality - stratification by level of adjustment for smoking and BMI



eFigure 37 Lung cancer mortality - stratification by spatial resolution of NO_2 concentration