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http://dx.doi.org/10.1289/ehp.1307711

Received: 29 September 2013
Accepted: 26 January 2015
Advance Publication: 27 January 2015

ERRATUM: After Advance Publication of this article, Perez et al. added Maria Foraster as a coauthor and corrected the misspelling of coauthor Damiano Baldassare to Damiano Baldassarre.
The authors regret the errors.

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Acknowledgments: The research leading to these results has received funding from the European Community's Seventh Framework Program (FP7/2007-2011) under grant agreement number: 211250. The Stockholm study was financed commonly by the Swedish Environmental Protection Agency, the Swedish Heart-Lung Foundation and the Swedish Council for Working Life and Social Research. The KORA research platform and the MONICA Augsburg studies were initiated and financed by the Helmholtz Zentrum München, German Research Center for

Environmental Health, which is funded by the German Federal Ministry of Education and Research and by the State of Bavaria.

REGICOR was supported by Marató 081632, Instituto de Salud Carlos III – ISCIII (FIS PI060258, ISCIII-RETIC 06/0018-FEDER-ERDF (Red RedIAPP)

We thank all study participants and the dedicated personnel of the Heinz Nixdorf Recall Study. We gratefully acknowledge the collaboration with K.-H. Jöckel, D. Grönemeyer, R. Seibel, K. Mann, L. Vollbracht, K. Lauterbach. We thank the North Rhine-Westphalia State Agency for Nature, Environment and Consumer Protection for providing road maps with traffic data and emission data from the reference sites for back-extrapolation. The study was supported by the Heinz Nixdorf Foundation [chairman: M. Nixdorf; former chairman: G. Schmidt (deceased)], the German Ministry of Education and Science, the German Research Foundation (DFG; projects JO-170/8-1, HO 3314/2-1, SI 236/8-1, and SI236/9-1).

Competing Financial Interests: No conflict of interest reported by authors.

Abstract

Background: In four European cohorts, we investigated the cross-sectional association between long-term exposure to air pollution and intima-media thickness of the common carotid artery (CIMT), a pre-clinical marker of atherosclerosis.

Methods: Individually assigned levels of NO_2, NO_x, $PM_{2.5}$, absorbance of $PM_{2.5}$ ($PM_{2.5abs}$), PM_{10}, PM_{coarse}, and two indicators of residential proximity to highly trafficked roads were obtained under a standard exposure protocol (European Study of Cohorts for Air Pollution effects-ESCAPE study) in the Stockholm area (Sweden), the Ausburg and Ruhr area (Germany) and the Girona area (Spain). We used linear regression and meta-analyses to examine the association between long-term exposure to air pollution and CIMT.

Results: The meta-analysis with 9183 individuals resulted in an estimated increase in CIMT (geometric mean) of 0.72% (95% Confidence Interval [CI]: -0.65%, 2.10%) per 5 $\mu g/m^3$ increase in $PM_{2.5}$ and 0.42% (95% CI: -0.46%, 1.30%) per $10^{-5}/m$ increase in $PM_{2.5abs}$. Living in proximity to high traffic was also positively but not significantly associated with CIMT. Meta-analytic estimates for other pollutants were inconsistent. Results were similar across different adjustment sets and sensitivity analyses. In an extended meta-analysis for $PM_{2.5}$ with three other previously published studies, a 0.78% (95% CI: -0.18%, 1.75%) increase in CIMT was estimated for a 5 $\mu g/m^3$ contrast in $PM_{2.5}$.

Conclusions: Using a standardized exposure and analytical protocol in four European cohorts, cross-sectional associations between CIMT and the eight ESCAPE markers of long-term residential air pollution exposure did not reach statistical significance. The additional meta-analysis of CIMT and $PM_{2.5}$ across all published studies also was positive but not significant.

Introduction

The cardiovascular effects of air pollution are well recognized (Brook et al. 2010), however the patho-physiological pathways by which long term air pollution may affect the cardiovascular system are not completely understood. Experimental and observational studies point to a link between inflammatory processes and the development of atherosclerosis (*i.e.,* atherogenesis) as one of the potential pathways (Libby et al. 2002). The hypothesis that air pollution contributes to atherogenesis through vascular damage due to oxidative stress and systemic inflammation has been supported by animal models (Araujo et al. 2008; Sun et al. 2005; Suwa et al. 2002).

Several epidemiological studies have addressed this hypothesis using measurements of carotid intima-media thickness (CIMT). Cross-sectional measurements of CIMT are an established marker of pre-clinical stages of atherosclerosis (Lorenz et al. 2012). CIMT is a particularly useful marker to investigate the atherogenic role of ambient air pollution, because it is not sensitive to short-term influences (Kunzli et al. 2011). Instead of the binary nature of cardiovascular events, CIMT describes the pre-clinical and clinical degree of the atherogenic state on a continuous scale. This is of relevance both from a biological perspective to investigate the etiology of the long-term process of atherogenesis and in the context of primary prevention.

So far, only three longitudinal studies in the United States have used CIMT measurements to test the hypothesis of an accelerated progression of CIMT among those with higher cumulative exposure to air pollution, two of which have reported positive associations (Adar et al. 2013; Kunzli et al. 2010; Wilker et al. 2013). These results suggest that chronic exposure to air pollution may accelerate injury to the vasculature. This may lead to a substantial shift in the age of the population at risk of suffering a cardiovascular outcome and may explain stronger associations of mortality based on long-term studies compared with time-series studies (Kunzli et al. 2011). A cross-sectional analysis in an adult population should reflect a differential atherogenic progression by an association between measured CIMT and long-term exposure to ambient air pollution.

The first cross-sectional study that tested this hypothesis used data from 798 participants in two clinical trials in Southern California and reported a 4.2% (95% confidence interval [95%CI]: -0.2%, 8.9%) larger CIMT with a 10 $\mu m/m^3$ increase in chronic exposure to $PM_{2.5}$ (Kunzli et al. 2005). Several others have also used CIMT data to explore this association (Adar et al. 2013; Bauer et al. 2010; Diez Roux et al. 2008; Erdogmus et al. 2006; Iannuzzi et al. 2010; Lenters et al. 2010; Rivera et al. 2013; Tonne et al. 2012; Wilker et al. 2013). However the size and direction of associations have varied across studies. In addition to differences in susceptibility or the specific composition or extent of exposures, these inconsistencies might also be a consequence of differences in population measurement of CIMT, statistical models, adjustment sets, or exposure assessment.

The ESCAPE project (European Study of Cohorts for Air Pollution Effects) made unprecedented efforts to standardize the selection, modelling, and assignment of markers of exposure to ambient air pollution, as well as health-related statistical protocols, in a total of 30 European cohorts. Recently published results of prospective analyses of several of these cohorts suggested that particulate matter air pollution contributes to the incidence of coronary events and lung cancer in Europe (Cesaroni et al. 2014; Raaschou-Nielsen et al. 2013). As part of the ESCAPE collaboration we brought together four established cohorts with available CIMT measurements in adults. The objective of this analysis was to investigate the cross-sectional association between CIMT and a set of markers of long term exposure to ambient air pollution.

Methods

Study population and CIMT data collection

Data from four on-going European cohort studies were used. IMPROVE-Stockholm (Stockholm, Sweden) is based on 60-year old adults at recruitment with increased risk for cardiovascular diseases (CVD). KORA (Augsburg, Germany), Heinz Nixdorf Recall (HNR, Ruhr Area, Germany) and REGICOR (Girona region, Spain) are population based cohorts (ages between 25 and 75 at baseline). CIMT was measured at least at one point in time between 1997 and 2009. B-mode ultrasound was used for CIMT measurement in all studies although sonographic protocols differed across studies. Details have been published elsewhere (Baldassarre et al. 2010; Bauer et al. 2009; de Groot et al. 2008; Kowall et al. 2012; Rivera et al. 2013). In brief, in all cohorts, images were obtained by trained sonographers of segments of the left and right common carotid artery at the far artery wall approximately 10 mm proximal to the bulb. In IMPROVE-Stockholm and REGICOR, additional scans were obtained of the carotid bulb, and of the internal carotid 10mm distal to the flow divider. While only one image with 45° transducer angle was taken per location for REGICOR and HNR, images at different angles were taken at each location in the other cohorts. CIMT measurement was conducted manually in HNR, in which a maximum of 10 manual CIMT measurements per subject and side were conducted at 0.1 cm intervals over a 1 cm segment. Manual tracing was conducted in REGICOR, but a dedicated scan application protocol was used for CIMT measurements in any given 1 cm of the artery segment. Automatic tracing and measurements were conducted in IMPROVE-Stockholm and KORA. CIMT measurements in HNR were conducted in plaque free areas only, whereas there was no specific protocol applied regarding plaques in other cohorts (i.e measurements may include plaques). Only in IMPROVE.-Stockholm presence of plaques were additionally recorded. Cohort population characteristics and CIMT measurements are summarized in Supplemental Material, “Description of cohorts and CIMT data collection”. For comparability with past studies, and to address differences in CIMT measurement protocols, we used the mean of all IMT measurements of the left and/or right common carotid (CCA) far wall made 10 mm proximal to the bulb as the common outcome for the present analysis. The four cohorts operate under approval of their respective ethical committees and all participants gave written informed consent at time of original cohort enrollment.

Exposure assessment

We made use of all standard markers of exposure to ambient air pollution developed by the standardized Land Use Regression models (LUR) of ESCAPE (Cyrys et al. 2012; Eeftens et al. 2012). This included different fractions of the particulate matter mass concentrations, $PM_{2.5}$, PM_{10}, the coarse fraction of PM (PM_{coarse}), absorbance of $PM_{2.5}$ ($PM_{2.5abs}$), estimates of nitrogen dioxide (NO_2) and oxides of nitrogen (NO_x). Two markers of local traffic density were also collected under a standard protocol. Estimates of background levels of NO_x, and NO_2 were also available.

Details of standardized ESCAPE protocols and methods used to develop exposure models and traffic markers for each of the four study areas are given elsewhere (Beelen et al. 2013; Eeftens et al. 2012). In brief, particulate matter (PM), NOx, and NO_2 were measured over two-week periods during three different seasons in 2008–2009 in all four study areas. Measurements were made at about 20 sites for PM and 40 sites for NOx and NO_2 for the IMPROVE-Stockholm, HNR, and KORA study areas, and at twice as many sites for the REGICOR study area. $PM_{2.5}$ and PM_{10} were collected on pre-weighted Teflon filters, and PM_{coarse} was obtained as their difference. $PM_{2.5abs}$ was measured on $PM_{2.5}$ filters. Each monitoring site was further characterized by a set of potential geographical predictors. Land Use Regression models (LUR) independently developed at each area were used to explain spatial variation at each measurement site, and the regression models obtained were then used to predict exposure concentrations at each cohort participant's baseline home address. NO_2 background LUR models were developed using a similar approach, but the LUR models were based only on regional and urban background sites and background predictors. The performance of the ESCAPE model was routinely tested across all ESCAPE cohorts (Beelen et al. 2013; Eeftens et al. 2012). This was done by first comparing the explained variance between measured and predicted values obtained in the final model at all measured sites (model R^2) and then by comparing measured values and predicted values at all measured sites for a model that was developed by excluding one measurement location at a time (leave-one-out-cross validation-LOOCV R^2).

The traffic indicators used in ESCAPE are traffic intensity on the nearest road (vehicles*day^{-1}) and traffic load on major roads in a 100-meter buffer, defined as the sum of traffic intensity multiplied by the length of all major road segments (vehicles*meters*day^{-1}). Individual indicators of exposure to traffic were derived from the most recent road networks for Europe and from locally available traffic intensity data (see Supplemental Material for detail description, "Exposure assessment method").

Statistical analysis

We used linear regression to estimate associations between the natural logarithm of CIMT and individually assigned measures of exposure. To independently estimate the effects of living near traffic, we adjusted analyses of traffic indicators for background NO_2 with associations estimated using exposures modelled as both continuous and categorical variables to facilitate interpretation.

Three pre-defined adjustment models were used for the main analysis, including a crude model (M1) and a model adjusted by age and gender only (M2). The third model (M3) was adjusted for gender, age and age^2, smoking status (current, ex, never/occasional), cigarette pack-years and pack-years^2, education level (low, middle, high), occupational status (employed/self-employed, unemployed, homemaker/housewife, retired), and body mass index (BMI and BMI^2). Covariate definitions were standardized across cohorts to the extent possible. Except for IMPROVE-Stockholm based on two more individuals in M1 and M2 than in M3, for other cohorts, models M1 to M3 were restricted to individuals with complete data for all covariates included in model M3.

For model M3, sub-group analysis was conducted using a set of predetermined variables, namely sex, age (< 60 or ≥ 60 years), BMI (< 30 or ≥ 30 kg/m^2), education (low, middle, or high), smoking status (current, ex, or never/occasional), having either diabetes, impaired fasting glucose (treatment with insulin, oral hypoglycaemic drugs or fasting blood glucose >110 mg/dL) (yes/no), use of antihypertensive medication (yes/no), and use of statins (yes/no). We also hypothesized that clusters of cardiovascular risk factors could interact with exposure to air pollution in complex ways. Therefore, we calculated the Framingham risk score (FRS) for developing a general cardiovascular disease in a 10-year period (Wilson et al. 1998) for each participant and evaluated for effect modification across three pre-defined levels of risk [low risk<10%, moderate risk (10-20%), and high risk>20%]. This stratification was also used to facilitate comparison between the older high-risk IMPROVE-Stockholm cohort and the three younger population-based cohorts, since we assumed that differences among the populations would be less pronounced within strata defined by FRS categories. We further evaluated differences in effects between long-term residents and short-term residents. Long-term residents were defined as subjects living at the same address ≥10 years. For the HNR study, residential history was not available for all participants and 5 years was the longest available cut-off. Thus HNR was excluded from this sub-analysis.

Three additional stepwise adjustment models were developed for sensitivity analyses. First, we additionally adjusted model M3 by physical activity (categorized as low, middle, or high, or according to metabolic equivalents, depending on availability), alcohol intake (categories of drinks per week), and wine consumption (model M4a). Model M4a was further adjusted for continuous levels of systolic blood pressure and high- and low-density lipoprotein (HDL and LDL) (model M4b). Model 5 was adjusted for covariates in model M4b plus anti-hypertensive and statin medication use (M5). All covariates were defined *a priori*.

We additionally assessed the sensitivity of results by using estimates of air pollution back-extrapolated to the year of the CIMT measurements; adjusting for long-term noise exposure in 5 dB categories of day-evening-night- noise (L_{DEN}) or night noise (L_{NIGHT}); and by accounting for potential clustering by area, because individuals living in same areas may share similar characteristics (e.g. socio-economical and environmental). ESCAPE exposure concentrations were developed with data collected between 2008 and 2009 that does not correspond to the year of CIMT measurement at each cohort. To adjust for possible differences in air pollution levels between time points and given the lack of historic LUR models to reconstruct historic spatial trends, individual exposures were back-extrapolated as follows: in each study region, available historic annual means (NO_2, NO_x, and PM_{10} only) from fixed site monitoring stations were used to calculate the ratio between the average annual concentrations for the period of interest in the past and the period of the ESCAPE measurement. Individual ESCAPE exposure for each study participant was then multiplied by this ratio. Detail of the back-extrapolated approach followed in ESCAPE has been described elsewhere (Cesaroni et al. 2012). While this approach was meant to capture the long-term general changes in urban background pollution, it did not account for potential spatial within-city individual exposure changes. Exposure to ambient noise was obtained from from the first round of noise mapping developed in the European Union (2007) following the 2002 EU directive that required that all member states produce every 5th year a noise map for major roads, major railways and major airports and for larger agglomeration (EC 2002). For controlling clustering by area, a maximum-likelihood random-effect model was used. Area level was represented by an indicator of the neighbourhood for IMPROVE-Stockholm and HNR, an indicator of municipality for REGICOR, and by a 5x5 km grid indicator for KORA.

Cohort specific results were meta-analysed for both fixed and random-effects and reported in Forest plots. The heterogeneity of effect estimates among studies was evaluated with the I^2 statistic (Higgins and Thompson 2002). In the absence of heterogeneity, results from fixed-effect models are reported when describing the results. In case of significant heterogeneity (p-value <0.1 or $I^2>50\%$), random-effects are reported instead (DerSimonian and Laird 1986). Because the meta-analyses were based on only four individual studies, we did not attempt to evaluate the influence of specific study characteristics on the summary estimates. Sub-group specific estimates were also meta-analysed. Differences in stratum-specific effect estimates were qualitatively evaluated, without any formal test of the interactions.

In an expanded meta-analysis, ESCAPE estimates for $PM_{2.5}$ were combined with estimates from other published cross-sectional studies that also used CIMT as outcome. We used a previous review to identify relevant studies (Rivera et al. 2013) and also searched PUBMED to identify any additional studies published online before September 2, 2013. Different combinations of the key words “intima media thickness”, “air pollution”, “fine particulate air pollution”, “progression”, and ”atherosclerosis” were used in the search strategy.

All statistical analyses were conducted using Stata (version 12.1, Stata Corp, College Station, Texas, USA). Results are presented for a pre-selected set of exposure contrasts that cover the variability of exposures observed across the ESCAPE project. The exposure contrasts for descriptive and categorical association analyses of traffic indicators were chosen to facilitate the interpretation of results throughout the ESCAPE project. For example, for traffic intensity at the nearest road we used a 5,000 vehicle per day contrast, which is approximately equal to the traffic density of many urban roads in Europe, and thus represents the effect of a doubling of the traffic intensity on a typical major road. The default alpha level for statistical significance was assumed as 0.05.

Results

A total of 9183 individuals were included in our study (based on a complete case analysis for model M3). Depending on the cohort, this represented 78% to 87% of the total cohort participants with both valid CIMT and air pollution measurements. A summary of common individual characteristics is provided in Table 1. Mean CIMT ranged from 0.68 mm (in HNR) to

0.85 mm (in IMPROVE-Stockholm and KORA). Because of selection for higher cardiovascular risk, IMPROVE-Stockholm participants were older and more likely to be diabetic, and had lower levels of HDL and higher blood pressure on average than participants in the other cohorts. In addition, although participants from IMPROVE-Stockholm were less likely to be current smokers, they were more likely to be former smokers. Reported use of lipid-lowering medication was considerably more prevalent in REGICOR than in any other cohort. Educational levels differed considerably across cohorts. For example, 8% of participants were classified as having low education in KORA compared with 51.4% in REGICOR.

The distribution of air pollution exposures by cohort is presented in Table 2. Mean levels of $PM_{2.5}$ varied between 7.2 and 18.4 ($\mu g/m^3$), between 0.6 and 2.1 ($10^{-5}/m$) for $PM_{2.5abs}$, between 14.7 and 30.8 ($\mu g/m^3$) for PM_{10}, between 6.2 and 15.6 ($\mu g/m^3$) for PM_{coarse}, between 10.4 and 32.5 ($\mu g/m^3$) for NO_2, and between 18.1 and 56.1 ($\mu g/m^3$) for NO_x. The lowest mean levels of pollutant exposures, except for PM_{coarse}, were estimated for participants in IMPROVE-Stockholm. Apart from $PM_{2.5}$, mean exposures, including the traffic indicators, were highest in REGICOR (Table 2). For REGICOR, less than 57% individuals lived in the lowest categories of traffic intensity and traffic load, while this percentage was above 65% for the other cohorts (Supplemental Material, Table S1). With a few exceptions, exposure contrasts, indicated by the interquartile ranges (IQR), were very small for PM in all cohorts (e.g. for $PM_{2.5}$ the IQR ranges between 1.1 and 1.7 $\mu g/m^3$) but rather large for NO_2 or NOx (e.g. for NO_2 the IQR ranges between 3.7 and 17.8 $\mu g/m^3$) (Table 2).

Patterns of correlations between pollutants varied considerably across cohorts (Supplemental Material, Table S2). For example the Spearman correlation coefficient (r) between $PM_{2.5}$ and

NO_2 was around 0.6 in IMPROVE-Stockholm, HNR and REGICOR, but only 0.38 in KORA. Similarly, a low r was observed between $PM_{2.5}$ and $PM_{2.5abs}$ in this cohort (0.44), although it was above 0.8 in others. Correlation coefficients between pollutants and traffic indicators were low to moderate (0.08-0.62). Previously published R^2 for model validation ranged across pollutants from 62% to 90% and from 51% to 87% for LOOCV R^2 (Supplemental Material, Table S2). The difference between model R^2 and LOOCV R^2 never exceeded 19% (percent point), below the 20% threshold usually interpreted as indication of potential model bias (Eeftens et al. 2012).

In cohort-specific analyses of long-term air pollution exposures and CIMT, there were no statistically significant positive associations based on adjusted models (models M2–M5) with the exception of positive associations with $PM_{2.5}$ in KORA and $PM_{2.5abs}$ in REGICOR (both for model M2 only) (Supplemental Material, Figure S1). In IMPROVE-Stockholm, a pattern of inverse associations was seen across all exposures, reaching statistical significance for PM_{10}, PM_{coarse}, NO_2, and NO_x (Supplemental Material, Figure S1A). Associations between traffic load and/or intensity were inconsistent between HNR and KORA and IMPROVE-Stockholm and REGICOR (Supplemental Material, Figure S1E and F). Only for the latter cohorts, estimates with traffic load reached statistical significance in model M3. For all pollutants, in general, results were robust to the different adjustment sets, although models M4a, M4b, and M5 were based on fewer participants due to missing covariate data.

Meta-analytic model M3 estimates of the association between CIMT and air pollution levels using ESCAPE cohort-specific estimates are presented in Figure 1A. Summary estimates across the four cohorts (N=9183) were positive but not statistically significant for $PM_{2.5}$ and $PM_{2.5abs}$. The combined fixed-effect estimates indicated a 0.72% (95%CI: –0.65%, 2.1%) increase in

CIMT (geometric mean) per 5 μg/m^3 increase in $PM_{2.5}$ and a 0.42% (95% CI: -0.46%, 1.30%) increase per 10^{-5}/m increase in $PM_{2.5abs}$. Summary estimates for the other pollutants (PM_{coarse}, PM_{10}, NO_2, and NO_x) were inverse but not statistically significant, though there was significant heterogeneity across the studies (I^2 >50% or p <0.1) in associations with all four pollutants. Estimates from combined analyses without IMPROVE-Stockholm, that showed a pattern of inverse significant results for these pollutants, did not change (result not shown) except for PM_{coarse} for which direction of effects changed although remained non statistically significant (0.37% [95%CI: -1.49%; 2.26%]).

We found positive but not statistically significant associations for traffic indicators (Figure 1B). For example, when considered on a continuous scale, we found a fixed-effect estimate of 0.29% (95% CI: -0.17%, 0.74%) higher CIMT (geometric mean) per 5,000 vehicles*day^{-1} in traffic intensity (over three cohorts only) and a 1.1% (95%CI: -0.56%, 2.7%) increase per 4,000,000 vehicles*day^{-1}*m^{-1} of traffic load (reported as random-effects because of significant heterogeneity). Estimates by categories of traffic markers were similarly positive but with some inconsistency across categories given the inhomogeneous distribution of traffic counts between cohorts. For example, for traffic load estimates were only generated for the third and fourth categories, and categorical associations for traffic intensity were positive for the second and fourth categories but null for the third (Supplemental Material, Table S3).

Meta-analytic estimates did not materially differ when adjusted for a random effect for neighborhood or when adjusted for noise (L_{den} or L_{night}, results not shown for the latter) (Supplemental Material, Table S4). Results remained similar when correcting exposures for historical trends (only available for NO_2, NO_x and PM_{10}).

Sub-group specific meta-analytic results are illustrated in Supplement Material, Figure S2 for three selected pollutants. Some differences in magnitude of stratum-specific associations are worth mentioning; associations appeared to be stronger in current smokers than in ex-smokers or nonsmokers (all pollutants); for NO_x, all sub-group meta-analysis remained inversely non-statistically significant; for $PM_{2.5}$, effects remained positive only for younger people, non-obese, non-diabetics, those with intermediate/higher education level, those using statin medication and with an intermediate FRS. Sex and hypertensive medication use did not materially modify the direction of the main effects, while and inverse association was observed for both long-term and short-term residents. For $PM_{2.5abs}$ inverse associations for males and those with low FRS were observed. Effects remained positive for both long-term and short-term residents.

We identified three studies reporting on a cross-sectional association between CIMT and $PM_{2.5}$ suitable to be included in an extended meta-analysis. Two studies were conducted on populations above 40 (Adar et al. 2013; Kunzli et al. 2010), while the other study population was 25 years on average (Lenters et al. 2010). Previously published results of HNR (Bauer et al. 2010) were not retained, because this cohort was included in the primary ESCAPE analysis. We used the most recent cross-sectional results reported for the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA) population (Adar et al. 2013). Given the very young age, we discarded one cross-sectional study of nonsmoking high-school students in the United States (Breton et al. 2012). Exposure assessment in Lenters et al (2010) was based on a similar LUR approach than ESCAPE, Künzli at al. (2010) used a geostatistical model to derive exposure assessment. MESA was based on a spatio-temporal model that also incorporated a component of LUR to predict concentrations at locations and times where measurements were not available (Cohen et al. 2009). In Künzli et al. (2010) and the MESA study, only measurements from the right common carotid were examined. Using results from models similar to our model M3, the extended meta-analytic estimate indicated a 0.78% (95%CI: -0.18%, 1.75%, p=0.11) difference in CIMT per 5 $\mu g/m^3$ contrast in $PM_{2.5}$ (Figure 2). For the population-weighted mean CIMT of 0.743 mm across the four ESCAPE cohorts, this result would correspond to a mean difference in CIMT of 5.8 µm with a 5 $\mu g/m^3$ increase in $PM_{2.5}$. No evidence for heterogeneity was observed (I^2 =0% or p=0.557).

Discussion

In a meta-analyses of four cross-sectional European studies we found positive but not statistically significant associations between CIMT and long-term estimates of residential exposure to several markers of air pollution, namely $PM_{2.5}$, $PM_{2.5abs,}$ traffic load within 100m of home, and traffic intensity at the nearest road. In contrast, inverse non-statistically significant associations were estimated for NO_2, NO_x, PM_{10} and PM_{coarse}. It is a major strength of ESCAPE that fully standardized sets of exposure metrics were derived to allow comparability across cohorts, that otherwise present substantial population heterogeneity. Other strengths of this study include assessment of a comprehensive set of pollutants, cohorts covering a wide range of exposures, large numbers of participants, common information about potential confounders, and comparability of health analysis methods.

Except for IMPROVE-Stockholm, our cohort-specific and combined ESCAPE estimates for $PM_{2.5}$ were within the range of other cross-sectional studies. A 5 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 2.1% (95%CI: -0.1%, 4.4%) higher CIMT among older adults in Los Angeles (Kunzli et al. 2005). A 0.47% (95%CI: -3.0%, 3.94%) increase of CIMT per 5 $\mu g/m^3$ $PM_{2.5}$ contrast was reported in the population based study “Atherosclerosis Risk in Young Adults” conducted in the Netherlands (Lenters et al. 2010). In Germany, associations between $PM_{2.5}$ and CIMT were slightly larger (4.1 % increase [95%CI: 1.7%, 6.5%]) per 4.2 $\mu g/m^3$ $PM_{2.5}$) based on an earlier analysis of the HNR Study using a different exposure model (Bauer et al. 2010). In MESA, a 5 $\mu g/m^3$ increase in $PM_{2.5}$ within cities was associated with a 0.2% (95%CI: -1.7%, 2.1%) increase in CIMT based on a model similar to our model adjustment M3. When these existing cross-sectional studies-except HNR to avoid including twice the same study population- and our ESCAPE estimates were combined the estimated difference in CIMT with a 5 $\mu g/m^3$ increase in $PM_{2.5}$ was <1%.

In addition to $PM_{2.5}$, our ESCAPE summary estimates were positive only for the set of standardized traffic indicators and $PM_{2.5abs}$. The literature does not provide comparable estimates to expand the meta-analysis to these markers. $PM_{2.5abs}$ is considered a better marker of traffic-related particles than $PM_{2.5}$, in part because of its larger spatial heterogeneity. Only one other study has used this indicator to evaluate the association between CIMT and long-term exposure to air pollution (Wilker et al. 2013). Despite a very different population (elderly men only), this study conducted in the Greater Boston Area reported that a spatially resolved estimate of the home outdoor 1-year average black carbon concentration was associated with a 1.1% higher CIMT (95%CI: 0.4%, 1.4%) per 0.26 $\mu g/m^3$ increase of this pollutant. Our results for PM_{10} were fairly inconsistent with those from a study based on 2348 participants of the Whitehall II cohort of British civil servants and from a past HNR study (Bauer et al. 2010; Tonne et al. 2012). Whitehall II reported a 5% difference (95%CI: 1.9%, 8.3%) for an IQR increase of 5.2 $\mu g/m^3$ PM_{10}. HNR reported a positive though not statistically significant association with PM_{10} (1.8 % change [95%CI: 0.6%, 4.3%] per 6.7 $\mu g/m^3$ of PM_{10}).

Our effect estimates were robust to several tests. The internal validation was good for the exposure models developed for our four cohorts. Adding covariates that may be on the causal pathway linking air pollution with atherosclerosis, such as blood pressure or medication to control blood pressure, did not substantially attenuate the coefficients. Associations also were not confounded by noise. Estimates were robust to adjustment for potential clustering by area, although the indicators used in the different cohorts represented different spatial dimensions, and residual confounding by area cannot be ruled out. We had no true long-term estimates of exposure, thus, the analyses rely on the assumption that current levels, as estimated in ESCAPE during 2008-2009, reflect long-term exposures before the CIMT measurement. However, the similarity of associations among long-term residents compared with the movers (Supplemental Material, Figure S2) suggests limited sensitivity. Studies investigating the validity of LUR modeled exposures also suggest that the ESCAPE modeled exposure reflects the spatial contrasts reasonably well over years (Cesaroni et al. 2012).

It has been hypothesised that long-term air pollution exposure could act through a pathophysiological pathway that leads to endothelial dysfunction and sub-clinical atherosclerosis (Brook and Rajagopalan 2010). In a study in Los Angeles, CIMT progression was estimated to be accelerated by 0.6 µm/y (95%CI:-0.1 µm/y, 1.4 µm/y) per 2.5 µg/m^3 of PM$_{2.5}$ (Kunzli et al. 2010). For the participants of the MESA population conducted in six cities across the US, a 5.0 µm/y (95%CI: 2.6 µm/y, 7.4 µm/y) faster progression of CIMT per 2.5 µg/m^3 of PM$_{2.5}$ was estimated (Adar et al. 2013). Atherosclerosis is the underlying cause for many cardiovascular outcomes. If air pollution accelerates atherosclerosis, the burden of air pollution may be larger than anticipated. By extension, a reduction of long-term exposure to air pollution may result in delays or reduction of this burden (Kunzli et al. 2011). It is possible that CIMT does not reflect the differential lifelong processes of atherosclerosis in different vascular beds and especially plaque formation in the carotid artery, which is more strongly related with clinical endpoints (Lorenz et al. 2012). Development of atherosclerosis, together with interactions with other biological pathways or added susceptibility to acute air pollution triggers, could help explain such large risk as well (Brook and Rajagopalan 2010).

Our study presents weaknesses which may in part explain the null findings. The cross-sectionally assessed CIMT may be the result of all cumulative past atherogenic and atheroprotective exposures, including, but not limited to air pollution (Kunzli et al. 2011). In addition, as exposure contrasts were rather limited within studies for most markers of exposure, statistical power to detect significant effects in such settings may face its limits. The protocols and methods to measure CIMT differed across cohorts, though all studies tested the internal validity of their CIMT measurement methods and protocols. For example, high intra- and inter –observed repeatability measures have been reported (Baldassarre et al. 2007; Bauer et al. 2009; Kowall et al. 2012; Rivera et al. 2013). Our study design did not permit comparisons of validity across studies. However the standardized analytical approach followed in ESCAPE aimed to minimize the possibility that large systematic bias has occurred.

The four studies had different designs and protocols for covariate assessments, thus, there were only limited options to more precisely operationalize some of these covariates in ways that would still be consistent across the studies. For example, socio-economic status (SES) could only be represented by three levels of education and unspecific occupational status in the minimum adjusted model (Model M3).

Current smokers had stronger risk estimates especially with $PM_{2.5}$ exposure.Others have hypothesized that the difference in the precision of CIMTs measurements or competing risks for CIMT progression in some susceptible populations can bias results (Adar et al. 2013; Rivera et al. 2013). The stratification by the FRS showed that when populations were made similar across cohorts, no modification existed. Thus modification by susceptibility factors such as smoking status could be interpreted here as an indication of some difference by location and may in part relate to the exposure modelling approach (see below).

Finally, non-systematic exposure misclassification is a potential cause of bias toward null findings. Two of our cohorts previously published estimates of cross-sectional associations between CIMT and pollution based on other exposure models, but using data from most of the same subjects (Bauer et al. 2010; Rivera et al. 2013). In REGICOR, individual exposure to NO_2 was estimated as the 10-year time-weighted average of assigned home outdoor concentrations. The local REGICOR LUR model was based on 562 NO_2 measurements in Girona town and the 10 surrounding communities where participants lived (Rivera et al. 2013). The difference in number of sampling sites between REGICOR LUR and ESCAPE LUR was due to the conceptual differences in the modelling designs. While REGICOR was aimed at capturing the small-scale variation between residential addresses of cohort members in a Mediterranean city with narrow street canyons, ESCAPE was based at capturing exposure to main emission sources in a standardized manner all across regions in Europe. Comparison of performance between the REGICOR and the ESCAPE LUR models has been evaluated elsewhere (de Nazelle et al. 2013). This study showed that models performed relatively similarly well at predicting their own measured concentrations but the ESCAPE model increasingly overpredicted the measurements of independent datasets at higher NO_2 levels. We found that for the same contrast of 10 $\mu g/m^3$ in exposure to NO_2, Rivera et al. reported a 0.22% (95%CI: -2.24%, 2.74%) coefficient for CIMT compared to a -0.18% (95%CI: -0.89%, 0.53%) in our study. It has also been shown that the number of predictors tested to develop the LUR and the number of measurements influence the model performance (Basagaña et al. 2012; Basagaña et al. 2013; Wang et al. 2012; Wang et al. 2013). This may have also contributed to some non-differential biases in the ESCAPE model. In HNR, past individual exposure to $PM_{2.5}$ was the average of daily concentrations of the 365 days before the examination day (Bauer et al. 2010). $PM_{2.5}$ individual exposures were predicted by a chemistry transport model coupled with daily data from monitoring stations (European Air Pollution Dispersion Model, EURAD-CTM). Again, the concepts of the exposure models differed between ESCAPE and the original HNR study, for which the EURAD-CMT exposure modelling was aimed at capturing urban background particulate matter concentrations (1 km^2 grid). Estimates reported by Bauer et al. correspond to a 4.9% (95%CI: 2.0%, 7.7%) difference in CIMT per 5 $\mu g/m^3$ $PM_{2.5}$, while our estimate was 0.57% (95%CI: -1.95%, 3.14%) for the same exposure contrast. There remains a need to better understand bias from the different exposure models and implications for interpreting and comparing findings from epidemiological studies.

In this meta-analysis of four cross-sectional European studies developed under standardized exposure and analytical protocols, we found no significant associations between CIMT and long-term estimates of residential exposure to eight pre-defined markers of air pollution, namely $PM_{2.5}$, $PM_{2.5abs}$, traffic load within 100m of home, and traffic intensity at the nearest road. This contrasts with the strong experimental evidence for an atherogenic role of ambient particulate matter (Araujo and Nel 2009; Sun et al. 2005; Suwa et al. 2002). Our meta-analytic estimate across all published studies for CIMT and $PM_{2.5}$ was suggestive but not statistically significant. Given the public health relevance of atherosclerosis, further studies are needed to clarify the quantitative association between markers of atherogenesis and long-term exposure to air pollution and both the cross-sectional level and the longitudinal progression of atherosclerosis.

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Table 1. Distribution of carotid intima-media thickness (CIMT), and selected baseline individual characteristics in the four cohort studies contributing to this ESCAPE analysis.

Characteristics	**Categories**	**IMPROVE-Stockholm**	**HNR**	**KORA**	**REGICOR**
N[a]		487	3759	2646	2291
Geographical location		Stockholm area (Sweden)	Ruhr Area (Germany)	Augsburg (Germany)	Girona area (Spain)
Year CIMT measurements		1997-1999	2001-2003	2006-2008	2007-2009
CIMT (mm)		0.85 ±0.16	0.68±0.13	0.85 ±0.14	0.70 ±0.15
Women (%)		50%	51%	52%	55%
Age (mean±SD)		66.8 ±0.38	59.7 ±7.8	55.8 ±13.0	58.5 ±12.2
Body Mass Index (mean±SD)		26.8 ± 4.1	27.9 ± 4.6	27.7 ± 4.8	26.8 ± 4.3
Educational level (%)					
	low	24.1%	10.9%	8.1%	51.4%
	middle	49.1%	55.3%	76.2%	28.6%
	high	26.1%	33.9%	15.8%	20%
Occupational status (%)					
	Employed/Self-employed	55.0%	40.3%	51.9%	52.9%
	Unemployed	10.1%	13.7%	2.0%	2.6%
	Homemaker/housewife	7.4%	39.7%	10.3%	13%
	Retired	27.5%	6.3%	35.9	31.5%
Smoking status (%)					
	Current	12.3%	23.2%	18.6%	16.4%
	Ex	41.3%	35.3%	38.7%	27%
	Never or occasional	46.4%	41.5%	42.6%	56.6%
Total pack-years in current/ex-smokers (mean±SD)		11.2 ± 15.5	15.63 ± 24.8	11.6 ±19.2	23.93 ±11.9
Wine drinks per week (mean±SD)		5.08 ±7.8	5.42 ±10.5	4.04 ±7.8	4.23 ±7.7
Physical activity in metabolic equivalents (mean±SD)		NA	1131 ±2110	NA	2009 ± 1926
Physical activity					
	Low	10.5%	NA	31.8%	NA
	Medium	54.4%	NA	44.0%	NA
	High	35.1%	NA	24.2%	NA
Low-density lipoprotein (LDL) (mg/dl)		139.1± 37.1	146.5 ± 36.2	136.3 ± 34.8	137.7 ± 31.8

Characteristics	Categories	IMPROVE-Stockholm	HNR	KORA	REGICOR
High-density lipoprotein (HDL) (mg/dl)		49.7 ± 14.7	57.9± 17.2	56.1 ± 14.5	54.7 ± 12.4
Diastolic blood pressure (mmHg)		84.8 ± 9.3	81.1 ± 10.7	75.1 ± 9.9	77.4 ± 10.1
Systolic blood pressure (mmHg)		149.8 ± 19.1	132.6± 20.6	122.2 ± 18.1	126.4 ± 18.7
Lipid-lowering medication (yes)		27.5%	10.3%	11.4%	39.3%
Diabetes[b] (yes)		16%	13.4%	7.4%	12.6%
Hypertensive medication (yes)		47.8%	35.6%	29.9%	24.0%

NA: Not available for the cohort.

[a] N based on complete case analysis for Model M3. [b] Defined as impaired fasting glucose (blood glucose level >110 mg/dl) or treatment with insulin or oral hypoglycemic drugs.

Table 2. Summary of cohort-specific individually assigned air pollutant and traffic exposure indicators.

Cohort	Pollutant indicator	Mean	±SD	min	median	max	IQR
IMPROVE-Stockholm (N=487)							
	$PM_{2.5}$ ($\mu g/m^3$)	7.2	±1.3	4.2	7.3	10.8	1.7
	$PM_{2.5abs}$ ($10^{-5}/m$)	0.6	±0.2	0.4	0.6	1.3	0.1
	PM_{coarse} ($\mu g/m^3$)	7.1	±3.0	0.7	7.4	20.3	3.0
	PM_{10} ($\mu g/m^3$)	14.7	±4.0	6.0	15.1	31.1	4.1
	NO_2 ($\mu g/m^3$)	10.4	±4.1	6.0	9.1	31.1	3.7
	NO_x ($\mu g/m^3$)	18.1	±8.9	11.4	14.6	73.3	6.0
	Traffic intensity at the nearest road ($veh*day^{-1}*10^{-4}$)	0.15	±0.33	0.02	0.05	2.9	0.05
	Traffic load within 100m on major roads ($veh*day^{-1}*m^{-1}*10^{-4}$)	54.2	±180.5	0	0	2620	0
HNR (N=3759)							
	$PM_{2.5}$ ($\mu g/m^3$)	18.4	±1.1	16.0	18.3	21.4	1.5
	$PM_{2.5abs}$($10^{-5}/m$)	1.6	±0.3	1.0	1.5	3.4	0.4
	PM_{coarse} ($\mu g/m^3$)	10.0	±1.8	0.8	10.1	15.0	1.9
	PM_{10} ($\mu g/m^3$)	27.8	±1.8	23.9	27.5	34.5	2.1
	NO_2 ($\mu g/m^3$)	30.3	±4.9	19.8	29.6	62.4	6.3
	NO_x ($\mu g/m^3$)	50.9	±11.9	24.3	49.7	120.0	16.3
	Traffic intensity at the nearest road ($veh*day^{-1}*10^{-4}$)	NA	NA	NA	NA	NA	NA
	Traffic load within 100m on major roads ($veh*day^{-1}*m^{-1}*10^{-4}$)	109.6	±221.0	0.0	0.0	2682	145.5
KORA (N=2646)							
	$PM_{2.5}$ ($\mu g/m^3$)	13.6	0.9	11.8	13.5	17.8	1.1
	$PM_{2.5abs}$ ($10^{-5}/m$)	1.7	0.2	1.3	1.7	2.6	0.2
	PM_{coarse} ($\mu g/m^3$)	6.2	1.1	4.1	6.1	12.6	1.2
	PM_{10} ($\mu g/m^3$)	20.4	2.4	14.8	20.5	30.7	3.2
	NO_2 ($\mu g/m^3$)	18.8	3.8	11.5	18.4	39.1	5.0
	NO_x ($\mu g/m^3$)	32.8	7.3	19.7	31.4	75.2	8.8
	Traffic intensity at the nearest road ($veh*day^{-1}*10^{-4}$)	0.16	±0.32	0.0	0.05	3.3	0
	Traffic load within 100m on major roads ($veh*day^{-1}*m^{-1}*10^{-4}$)	41.5	±103.7	0.0	0.0	1177	0
REGICOR (N=2291)							
	$PM_{2.5}$ ($\mu g/m^3$)	14.9	±1.6	9	14.9	21.3	1.3
	$PM_{2.5abs}$ ($10^{-5}/m$)	2.1	±0.7	1.1	2.0	4.5	0.8
	PM_{coarse} ($\mu g/m^3$)	15.6	±2.7	9.9	14.9	26.4	3.7
	PM_{10} ($\mu g/m^3$)	30.8	±4.9	20.8	30.1	47.2	5.8
	NO_2 ($\mu g/m^3$)	32.5	±12.0	10.1	33.0	78.7	17.8
	NO_x ($\mu g/m^3$)	56.1	±24.2	15.3	55.4	175.0	31.4
	Traffic intensity at the nearest road ($veh*day^{-1}*10^{-4}$)	0.34	±0.57	0.0	0.11	3.4	0.30
	Traffic load within 100m on major roads ($veh*day^{-1}*m^{-1}*10^{-4}$)	127.0	±199.5	00	0.0	1013	207.1

NA: Not available for the cohort.

Figure Legends

Figure 1. Forest plot of the percent difference in CIMT (geometric mean with 95% Confidence Intervals) for Model M3 for (A) ESCAPE air pollutants per standard contrast of exposure as indicated in the figure and (B) ESCAPE continuous traffic indicators with Traffic near: Traffic intensity at the nearest road per contrast of exposure of 5,000 veh*day^{-1} and Traffic load: Traffic load within 100m on major roads per contrast of exposure of 4,000,000 veh*day^{-1}*m^{-1}. Fixed (I-V subtotal) and random effects (D+L) shown. I-square: variation in estimated effects attributable to heterogeneity with % weight I-V as relative percent weight of each cohort (grey boxes). D+L: DerSimonian and Laird method. For IMPROVE-Stockholm arrow indicates direction of the effect estimate. Model M3 adjusted for: sex, age (centered), age^2, smoking status (3 categories), smoking pack years (centered), smoking pack-years^2, education level (3 categories), occupation status (4 categories), BMI (centered), BMI^2, indicator of city residence when applies.

Figure 2. Forest plot of the percent difference in CIMT (geometric mean with 95% Confidence Intervals) per 5 µg/m^3 PM$_{2.5}$ using the four ESCAPE cohort and previously published results. Fixed (I-V subtotal) and random effects (D+L) shown. I-square: variation in estimated effects attributable to heterogeneity with % weight I-V as relative percent weight of each cohort (grey boxes). D+L: DerSimonian and Laird method. For IMPROVE-Stockholm arrow indicates direction of the effect estimate. Estimates of ESCAPE cohorts based on Model M3 adjusted for: sex, age (centered), age^2, smoking status (3 categories), smoking pack years (centered), smoking pack-years^2, education level (3 categories), occupation status (4 categories), BMI (centered), BMI^2, indicator of city residence when applies. Other adjustment sets: Künzli et al, 1995 : sex, education, income, active and passive smoking, multivitamins, alcohol (Table 2)(Kunzli et al. 2005). Lenters et al, 2010: age, sex, pulse pressure, BMI, pack-years of smoking, parental smoking at home during childhood, alcohol intake, education, highest profession, diabetes, and percent of low and high income households in neighborhood (Table 2) (Lenters et al. 2010). Adar et al, 2013: sex, age ethnicity, education, neighborhood socio-economic score, adiposity, pack-years at baseline, and time varying smoking status (Table 2) (Adar et al. 2013).

Figure 1A.

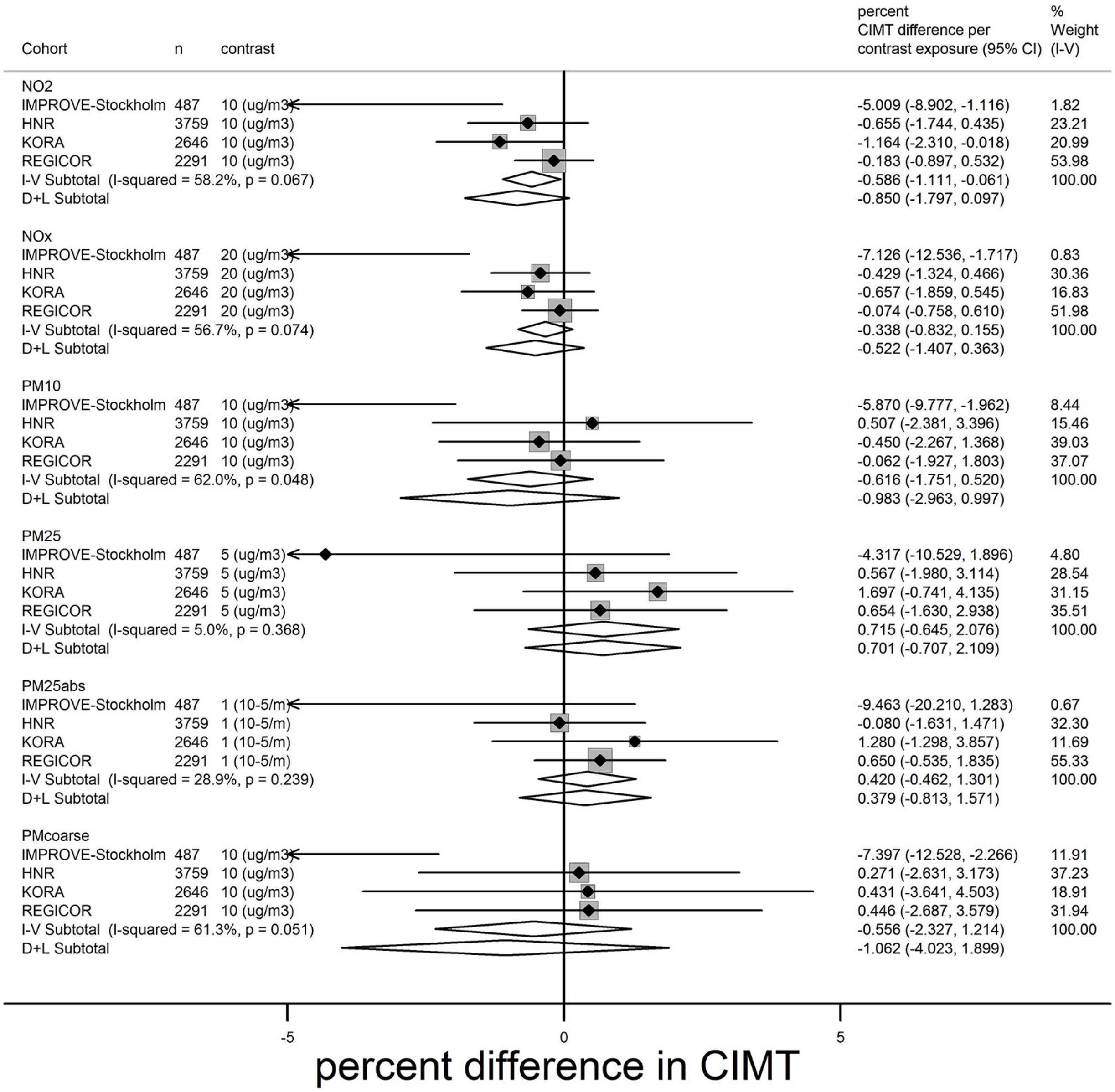

Cohort
n
contrast
percent
CIMT difference per
contrast exposure (95% CI)
%
Weight
(I-V)
NO2
IMPROVE-Stockholm 487 10 (ug/m3) -5.009 (-8.902, -1.116) 1.82
HNR 3759 10 (ug/m3) -0.655 (-1.744, 0.435) 23.21
KORA 2646 10 (ug/m3) -1.164 (-2.310, -0.018) 20.99
REGICOR 2291 10 (ug/m3) -0.183 (-0.897, 0.532) 53.98
I-V Subtotal (I-squared = 58.2%, p = 0.067) -0.586 (-1.111, -0.061) 100.00
D+L Subtotal -0.850 (-1.797, 0.097)
NOx
IMPROVE-Stockholm 487 20 (ug/m3) -7.126 (-12.536, -1.717) 0.83
HNR 3759 20 (ug/m3) -0.429 (-1.324, 0.466) 30.36
KORA 2646 20 (ug/m3) -0.657 (-1.859, 0.545) 16.83
REGICOR 2291 20 (ug/m3) -0.074 (-0.758, 0.610) 51.98
I-V Subtotal (I-squared = 56.7%, p = 0.074) -0.338 (-0.832, 0.155) 100.00
D+L Subtotal -0.522 (-1.407, 0.363)
PM10
IMPROVE-Stockholm 487 10 (ug/m3) -5.870 (-9.777, -1.962) 8.44
HNR 3759 10 (ug/m3) 0.507 (-2.381, 3.396) 15.46
KORA 2646 10 (ug/m3) -0.450 (-2.267, 1.368) 39.03
REGICOR 2291 10 (ug/m3) -0.062 (-1.927, 1.803) 37.07
I-V Subtotal (I-squared = 62.0%, p = 0.048) -0.616 (-1.751, 0.520) 100.00
D+L Subtotal -0.983 (-2.963, 0.997)
PM25
IMPROVE-Stockholm 487 5 (ug/m3) -4.317 (-10.529, 1.896) 4.80
HNR 3759 5 (ug/m3) 0.567 (-1.980, 3.114) 28.54
KORA 2646 5 (ug/m3) 1.697 (-0.741, 4.135) 31.15
REGICOR 2291 5 (ug/m3) 0.654 (-1.630, 2.938) 35.51
I-V Subtotal (I-squared = 5.0%, p = 0.368) 0.715 (-0.645, 2.076) 100.00
D+L Subtotal 0.701 (-0.707, 2.109)
PM25abs
IMPROVE-Stockholm 487 1 (10-5/m) -9.463 (-20.210, 1.283) 0.67
HNR 3759 1 (10-5/m) -0.080 (-1.631, 1.471) 32.30
KORA 2646 1 (10-5/m) 1.280 (-1.298, 3.857) 11.69
REGICOR 2291 1 (10-5/m) 0.650 (-0.535, 1.835) 55.33
I-V Subtotal (I-squared = 28.9%, p = 0.239) 0.420 (-0.462, 1.301) 100.00
D+L Subtotal 0.379 (-0.813, 1.571)
PMcoarse
IMPROVE-Stockholm 487 10 (ug/m3) -7.397 (-12.528, -2.266) 11.91
HNR 3759 10 (ug/m3) 0.271 (-2.631, 3.173) 37.23
KORA 2646 10 (ug/m3) 0.431 (-3.641, 4.503) 18.91
REGICOR 2291 10 (ug/m3) 0.446 (-2.687, 3.579) 31.94
I-V Subtotal (I-squared = 61.3%, p = 0.051) -0.556 (-2.327, 1.214) 100.00
D+L Subtotal -1.062 (-4.023, 1.899)
-5
0
5
percent difference in CIMT

Figure 1B.

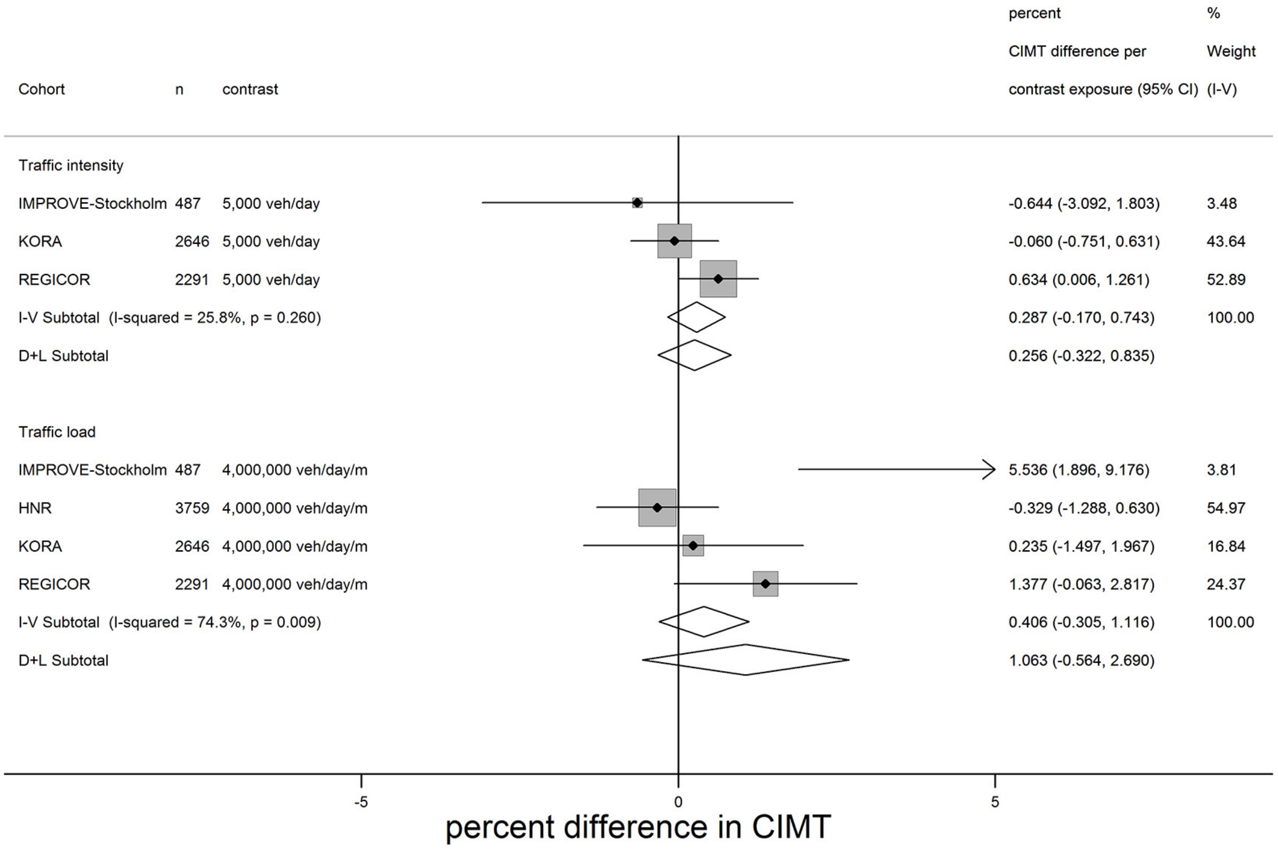
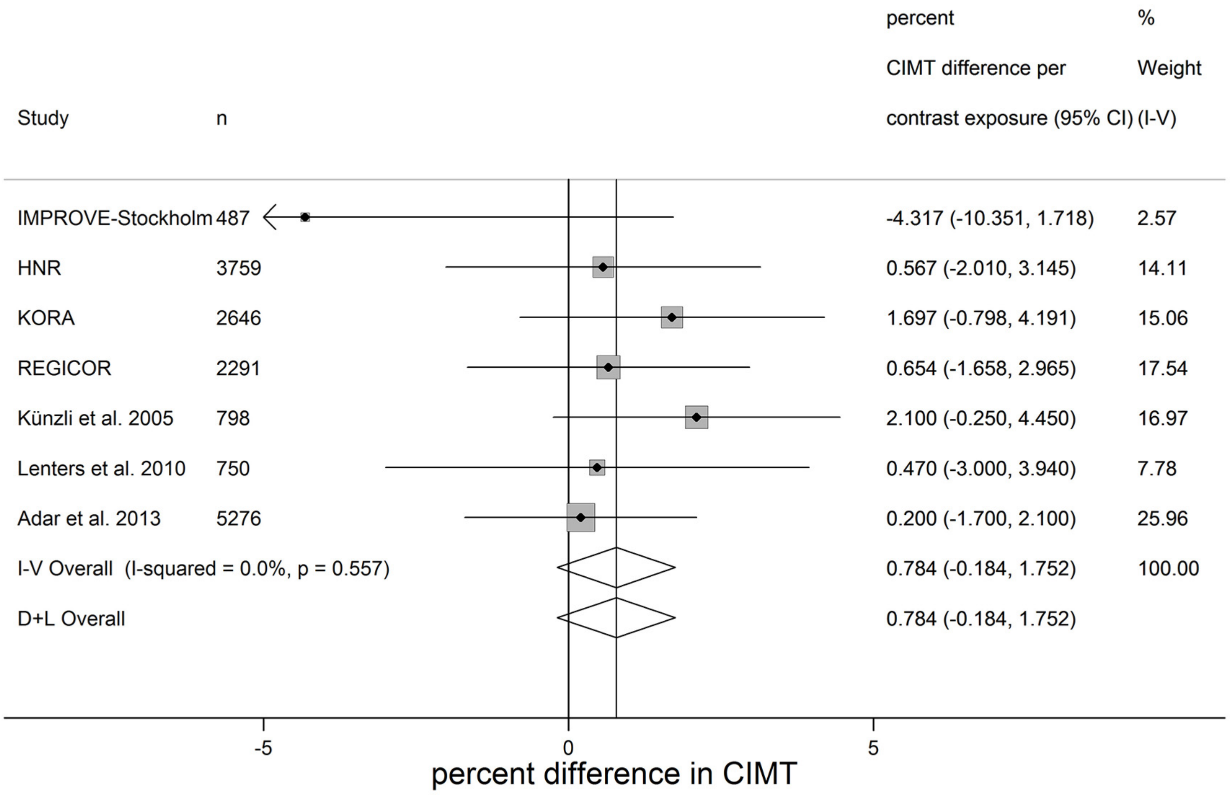

Cohort
n
contrast
percent
CIMT difference per
contrast exposure (95% CI)
%
Weight
(I-V)
Traffic intensity
IMPROVE-Stockholm 487 5,000 veh/day -0.644 (-3.092, 1.803) 3.48
KORA 2646 5,000 veh/day -0.060 (-0.751, 0.631) 43.64
REGICOR 2291 5,000 veh/day 0.634 (0.006, 1.261) 52.89
I-V Subtotal (I-squared = 25.8%, p = 0.260) 0.287 (-0.170, 0.743) 100.00
D+L Subtotal 0.256 (-0.322, 0.835)
Traffic load
IMPROVE-Stockholm 487 4,000,000 veh/day/m 5.536 (1.896, 9.176) 3.81
HNR 3759 4,000,000 veh/day/m -0.329 (-1.288, 0.630) 54.97
KORA 2646 4,000,000 veh/day/m 0.235 (-1.497, 1.967) 16.84
REGICOR 2291 4,000,000 veh/day/m 1.377 (-0.063, 2.817) 24.37
I-V Subtotal (I-squared = 74.3%, p = 0.009) 0.406 (-0.305, 1.116) 100.00
D+L Subtotal 1.063 (-0.564, 2.690)
-5
0
5
percent difference in CIMT

Figure 2.


Study
n
percent
CIMT difference per
contrast exposure (95% CI)
%
Weight
(I-V)
IMPROVE-Stockholm 487
-4.317 (-10.351, 1.718)
2.57
HNR
3759
0.567 (-2.010, 3.145)
14.11
KORA
2646
1.697 (-0.798, 4.191)
15.06
REGICOR
2291
0.654 (-1.658, 2.965)
17.54
Künzli et al. 2005
798
2.100 (-0.250, 4.450)
16.97
Lenters et al. 2010
750
0.470 (-3.000, 3.940)
7.78
Adar et al. 2013
5276
0.200 (-1.700, 2.100)
25.96
I-V Overall (I-squared = 0.0%, p = 0.557)
0.784 (-0.184, 1.752)
100.00
D+L Overall
0.784 (-0.184, 1.752)
-5
0
5
percent difference in CIMT