Association of Exposure to Particular Matter and Carotid Intima-Media Thickness: A Systematic Review and Meta-Analysis

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Abstract
Long time exposure to particulate matter has been linked to myocardial infarction, stroke and blood pressure, but its association with atherosclerosis is not clear. We did a systematic review and meta-analysis to assess whether particular matter has an effect on subclinical atherosclerosis measured by carotid intima-media thickness (CIMT).

Keywords: Air pollution; Particular matter; Carotid Intima-Media Thickness; Subclinical atherosclerosis; Meta-analysis

Introduction
The association between air pollution (especially particular matter) and cardiovascular disease (CVD) or their risk factors has been demonstrated by a great number of epidemiological and experimental studies [1-6]. Among the size fractions of particular matter, long term exposure to ambient and individual particular matter less than 2.5 µm in diameter (PM$_{2.5}$) is responsible for morbidity and mortality of cardiovascular events [7].

Atherosclerosis is a chronic process and mainly affects the aorta, coronary artery and cerebral artery, which often leads to serious consequences like lumen occlusion and plaque rupture. It is the major pathological process of heart disease and stroke. In western developed countries, atherosclerosis account for about 50% of all deaths [8-10]. Epidemiological studies have suggested that the degree of atherosclerosis can be measured by carotid intima-media thickness (CIMT) to forecast population’s future cardiovascular risk [11-13]. Several studies of long term exposure to particular matter (PM$_{2.5}$, PM$_{10}$) have shown that the higher particular matter concentrations were associated with increased CIMT. However, not all studies had found significant results, so the association between particular matter and CIMT is still uncertain. We therefore systematically reviewed the studies examining the effect of particular matter (PM$_{2.5}$, PM$_{10}$) on CIMT and quantify this effect.

Materials and Methods

Search strategy and eligibility criteria
We performed a comprehensive databases search in PubMed, Ovid Medline, Embase and CNKI using the key words as follows: "air pollution", "air pollutants", "particular matter", "PM$_{2.5}$", "PM$_{10}$", "meteorological factor", "carotid intima-media thickness", "Carotid atherosclerosis", "carotid IMT", "CIMT" and "subclinical atherosclerosis". The publication date of literatures was limited between 1948 and March 31, 2015. Literatures were included if they were population-based studies, which not only reported the association between particular matter (PM$_{2.5}$ or PM$_{10}$) and CIMT, but also provided original data for particular matter (PM$_{2.5}$ or PM$_{10}$) and carotid artery intima-media thickness. There were no language restrictions. We excluded duplicates, summaries, reviews, letters, commentaries and editorials, toxicological studies, case reports and case series. In this way we selected 13 studies meeting the inclusion criteria. However, 2 of these studies, which only presented the median value or the percentage change of CIMT, didn’t have adequate data for CIMT. We contacted authors for detail data and no answer was obtained, so the 2 studies were excluded and 11 studies were finally included in our meta-analyses (Figure 1).

Study selection
By screening all titles and abstracts potentially eligible studies were selected by two independent investigators (X.L. and H.L.). Then the eligibility of the study for the meta-analysis was picked out by reading the full text of the potentially eligible studies. If the two reviewers had disagreements, a third reviewer (R.L.) would help adjudicate conflicts.

Data extraction
On the basis of in-depth reading of all eligible literatures we extracted the useful data and enter it in an in advance designed standardized information table, which presented a comprehensive description of the study characteristics, including title, first author, journal publication year, study design, location and period, characteristics of the participants (age, sex, physical condition, sample size), measurement of CIMT, data analysis model, exposure measurement, effect measurement and confounding factors adjusted (age, sex, race, education, temperature, humidity and so on). Two reviewers (X.L. and H.L.) completed the operation of data extraction respectively and then compared. In case of conflict, a third reviewers (R.L.) was asked to judge and make a decision.

Statistical analysis
We transformed the value of CIMT with 95% CIs from each study for a standardized increment per 10 μg/m$^2$ in particular matter (PM$_{2.5}$, PM$_{10}$) and took it as our outcome. In addition, we hypothesized a linear relation between exposure and outcome because most studies used linear regression models. On account of different study design, geographical settings, methods of exposure and CIMT measurement, characteristics of participants and exposure duration, heterogeneity existed in the studies. Therefore, we used the random-effects model, which accounts for both within and between studies heterogeneity to pool the summary-effect estimates. According to the weight (1/SE$^2$) of each study account for the total, we calculated the overall effect. Standard I$^2$-statistic was applied to tests for heterogeneity in order

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to quantify inconsistencies between studies. I² values of 25% or less, 50% and 75% or more stand for low, moderate and high heterogeneity respectively.

We also did subgroup analyses stratifying studies performed by study design (cross-sectional VS longitudinal), sex (female vs male), education (low education vs high education), treatment (lipid-lowering treatment vs no lipid-lowering treatment). In addition, association between traffic proximity and CIMT was also assessed. To estimate the potential publication bias, funnel plots were constructed and we also tested them using the Egger regression test due to the limitations of funnel plot. Statistical analyses were conducted using Stata software (Stata Corp., College Station, Texas, USA). Statistical significance was taken as two-sided \( P<0.05 \) with the exception of the heterogeneity assessment, which was considered statistically significant at \( P<0.10 \).

Results

Literature search

104 initial records were retrieved by searching databases and 56 remained after removing duplicates. Then by screening the titles and abstracts, 35 articles were excluded, which were animal studies or not primary documents (review, letter). After that we read the full text of the remaining 21 studies and determined 13 of them were fulfilled the eligibility criteria. Whereas 2 studies did not present sufficient data for mean value of CIMT and authors did not respond to our e-mails \([14,15]\), 11 articles were finally eligibility of the review and meta-analysis (Figure 1).

Study characteristics

The characteristics of included studies are presented in the Table 1. Among the eligible studies, nine used cross-sectional design, one used longitudinal design, and another one used both study designs. Study locations were mainly (6 studies) USA, except that two studies (one of them including 4 cohorts) were Europe, one study was Canada and one was Taiwan. The sample size of participants ranged from 509 to 6256. The population of these studies was all adults and most of them were healthy. 4 studies selected the population from a same existing cohort, participant s of which aged from 45 to 84 and without preexisting clinically apparent cardiovascular disease. In addition, one study was conducted in young adults aged from 18 to 27.

Particular matter in 10 studies is PM_{2.5}, 1 study was PM_{10} and 3 studies were both. The concentrations of PM_{2.5} and PM_{10} were estimated in ambient or individual-level. Linear regression model was used to evaluate the association between air pollution and CIMT in most studied. The number of potential confounding factors included in the studies varied, most adjusted for age, sex, race/ethnicity, BMI, smoking status, education, and LDL-C in the results.

Analysis

The results from the random-effects meta-analysis of the relationship between exposure to PM\textsubscript{2.5} and CIMT are shown in Figure 2. When the concentration of PM\textsubscript{2.5} increased 10 \( \mu \)g/m\(^3\) in the evaluation of overall combination, its relationship with CIMT reached statistical significance (the increment of CIMT is 16.79 \( \mu \)m; 95% CI, 4.95-28.63 \( \mu \)m). The heterogeneity observed for 10 studies was small (\( I^2=67.6\% \)). When some of the eligible studies were pooled with additional adjustment for education and income, the summary estimate was attenuated to 16.68 \( \mu \)m (95% CI, 4.93-28.43 \( \mu \)m), results were not shown in the table.

There was no statistical evidence of publication bias in overall analyses. In Egger's test we got \( P=0.211 \). The subgroup analysis about PM\textsubscript{10} and CIMT was conducted by sex education lipid-lowering treatment and study design. Significant association between PM\textsubscript{10} and CIMT was found with female, the summary estimate of which was larger than overall analysis (64.42 \( \mu \)m; 95% CI, 38.44-90.39 \( \mu \)m). However, the association with male had no statistic significant. Similarly, in longitudinal study design a weak correlation between exposure to PM\textsubscript{10} and CIMT was represented (5.50 \( \mu \)m; 95% CI, 0.00-10.99 \( \mu \)m), comparing with no significant association in cross-sectional study design (22.60 \( \mu \)m; 95% CI, -8.39-53.60 \( \mu \)m). The subgroup analysis stratified by educational qualifications showed that people with low education had a larger effect than high education, whereas neither of them had statistic significant \([16]\). The pooled estimates of low education and high education were 31.80 \( \mu \)m (95% CI, -4.16-67.77 \( \mu \)m) and 14.46 \( \mu \)m (95% CI, -15.47-44.40 \( \mu \)m), respectively. When compared the effects based on whether receive the lipid-lowering treatment, we also found a difference. Participants with a lipid-lowering treatment showed an increase of CIMT with 43.57 \( \mu \)m (95% CI, -12.12-107.27 \( \mu \)m), whereas people had no lipid-lowering treatment was 24.74 \( \mu \)m (95% CI, -7.75-57.25 \( \mu \)m) (Figure 3).

Squares represent study-specific estimates (size of the square reflects the study-specific statistical weight); horizontal lines represent 95% confidence intervals (CIs); diamonds represent the total effect with corresponding 95% confidence interval (CIs). IMPROVE-Stockholm, HNR, KORA and REGICOR are four on-going European cohort analyzed by Perez et al. \([17]\).

Summary estimate for PM\textsubscript{10} is shown in Figure 4. When the concentration of PM\textsubscript{10} increased 10 \( \mu \)g/m\(^3\) in the evaluation of overall combination, the CIMT increment is 4.13 \( \mu \)m (95% CI, -5.79-14.04 \( \mu \)m), which was inverse in comparison with PM\textsubscript{2.5}, but not statistically significant, though there was significant heterogeneity across the studies (\( I^2=66.5\% \) or \( p=0.006 \)) in associations with PM\textsubscript{10}.

We also estimated the relationship between CIMT and traffic proximity \([18-26]\). For people living near the traffic incompatibilities were existent within and between different studies on the association between traffic proximity and the variation of CIMT compared with participants living away from major roadways.

| 104 records identified through database searching | 56 records after duplicates removed |
|-----------------------------------------------|-----------------------------------|
| 40 articles were possibly appropriate based on titles | 21 publications were potentially eligible |
| 13 studies were eligibility of the study for meta-analysis | 16 records excluded by screening the titles (animal studies or not primary documents) |
| 2 studies were eligibility of the study for meta-analysis | 19 studies excluded based on screening the abstract |
| 8 of full text articles excluded without sufficient data of CIMT | |

**Figure 1:** Flow chart of studies selection in the meta-analysis.
Table 1: Characteristics of studies that were eligible for this review and meta-analysis of associations between particular matter (PM$_{2.5}$, PM$_{10}$) and carotid intima-media thickness.

| Author [Ref. No.] | Location | Period    | Study design      | Sample size | Age (years) | Exposure measurement | Statistical analysis |
|--------------------|----------|-----------|-------------------|-------------|-------------|----------------------|---------------------|
| Su et al. [16]     | Taiwan   | 2009-2011 | cross-sectional   | 689         | 35-65       | Individual           | multiple linear regression model |
| Perez et al. [17]  | Europe   | 1997-2009 | cross-sectional   | 9183        | 42-68       | Individual           | linear regression model    |
| Kim et al. [18]    | USA      | 2000-2002 | cross-sectional   | 5488        | 45-84       | Individual           | multiple linear regression model |
| Gan et al. [19]    | Canada   | 2004-2011 | longitudinal      | 509         | 30-65       | Individual           | general linear regression model |
| Sun et al. [20]    | USA      | 2000-2002 | cross-sectional   | 6256        | 45-84       | Ambient              | multiple linear regression model |
| Adar et al. [21]   | USA      | 2000-2005 | cross-sectional   | 5660        | 45-84       | Individual           | longitudinal mixed model   |
| Breton et al. [22] | USA      | 2007-2009 | cross-sectional   | 768         | 18-27       | Ambient              | linear regression model    |
| Tonne et al. [23]  | Britain  | 2002-2006 | cross-sectional   | 2348        | 55-67       | Individual           | generalized linear regression model |
| Künnali et al. [24]| USA      | 1994-2006 | cross-sectional, longitudinal | 1483 | >30 | Ambient | linear regression model |
| Lelters et al. [25]| Netherlands | 1999-2000 | cross-sectional   | 745         | 45-84       | Individual           | multiple linear regression model |
| Künnali et al. [26]| USA      | 1998-2003 | cross-sectional   | 798         | >40         | Ambient              | linear regression model    |

Discussion

This study is the first meta-analysis to our knowledge to estimate the effects of exposure to particular matter (PM$_{2.5}$, PM$_{10}$) on CIMT, an accepted measure of the progression of atherosclerosis [27,28]. In overall estimation we observed a significant and positive association between PM$_{2.5}$ and CIMT. When compared with the overall analysis, subgroup analyses were associated with lower heterogeneity and had the same direction of estimated effect. Therefore, the association was robust.

Two studies we excluded due to no sufficient data for mean value of CIMT showed similar results. One is in Germany [14] Median CIMT of the 3,380 analyzed participants was 0.66 mm (interquartile range 0.16 mm). An interdecile range increase in PM(2.5) (4.2 μg/m$^3$), PM(10) (6.7 μg/m$^3$), and distance to high traffic (1,939 m) was associated with a 4.3% (95% confidence interval [CI]: 1.9% to 6.7%), 1.7% (95% CI: -0.7% to 4.1%), and 1.2% (95% CI: -0.2% to 2.6%) increase in CIMT, respectively; The other one is in the USA [15]: Intimal-medial thickness was weakly, positively associated with exposures to particulate matter <10 micron in aerodynamic diameter and <2.5 micron in aerodynamic diameter after controlling for age, sex, race/ethnicity, socioeconomic...
exposures to particular matter among people with different education [48]. Studies for Scandinavian indicated the discrepancy of personal air pollution have been demonstrated among disadvantaged groups proved this phenomenon. For example, higher concentrations of some and expose to multiple air pollutants. Many previous studies have people with lower education are more likely to live near busy roads pathways. Firstly, because of poor living conditions or occupation were limited to studies with participants receiving higher education. [34]. Hoffmann et al. [35] paper from the Heinz Nixdorf Study showed fine particulate matter exposure was associated with coronary artery calcification (CAC), which is related in relevant ways to CIMT. Wilker et al. [36] reported annual mean black carbon concentration was associated with CIMT in a population of elderly men. These findings support an association between long-term air pollution exposure and atherosclerosis. Many animal experiments also support the viewpoint that exposure to PM<sub>2.5</sub> may contribute to the process of atherosclerosis by potential mechanisms including bone marrow stimulation, release of monocytes and altered vasomotor tone [37-39]. Apolipoprotein E--/ mice expose to PM<sub>2.5</sub> had an effect on altered vasomotor tone, vascular inflammation and increase of aortic atherosclerosis [37]. In addition, animal experiments found other biologic mechanisms, which connect particulate matter exposure with the progress of atherosclerosis in a long-term period, were that exposure to particular matter may influence blood pressure, autonomic function and low density lipoprotein oxidation [40-44].

As shown in Figure 3, we found the size of the effect was larger in women. The result may suggest that sex can influence the association between PM<sub>2.5</sub> and CIMT. We hypothesize that one potential mechanism is based on the secretion of androgen. If male expose to cardiovascular risk factors such as particular matter dominate atherosclerosis, a smaller effect signal would be shown in the estimates among men. In addition, compared with young men, elderly men with less androgen have higher risk for atherosclerosis [26]. The other potential pathway is that females have slightly greater airway reactivity than males. Thus, compared with males we might find dose-response relations more easily in females [45]. Although some previous studies have also reported that particular matter had greater effect estimates in women than in men [45,46], the effect modification by sex remains unclear and further investigations are needed [47]. Our findings showed that the associations were slightly stronger when analyses were limited to studies with participants receiving higher education. As a measure of socioeconomic status (SES), individual education attainment may impact the health effects of particular matter in several pathways. Firstly, because of poor living conditions or occupation people with lower education are more likely to live near busy roads and expose to multiple air pollutants. Many previous studies have proved this phenomenon. For example, higher concentrations of some air pollution have been demonstrated among disadvantaged groups [48]. Studies for Scandinavian indicated the discrepancy of personal exposures to particular matter among people with different education and occupation [49,50]. Secondly, a majority of people receiving lower education have poor living conditions and don’t have ability to get enough nutrition, such as antioxidant polysaturated fatty acids and vitamins, which may protect against adverse effects of particular matter [51]. Thirdly, people with lower SES have a higher prevalence of preexisting diseases and usually receive inferior medical treatment for them, which leads to higher sensitivity of air pollution-related health hazards. Existing evidence have shown that lipid-lowering treatment may affect the association between PM<sub>2.5</sub> and CIMT. Some studies reported, that participants taking lipid-lowering medications at baseline represented stronger association between CIMT and PM<sub>2.5</sub> [24,26]. These results also agree with hyperlipidemic rabbits experiments estimating effects of PM on atherosclerosis [38,52]. In these rabbits relationship between the amount of PM contained in the alveolar macrophages and atherogenic reaction was found. However, the modification direction reported in other study was inconsistent, so the summary estimate of people with lipid-lowering treatment in our study was not significant and only slightly different from those without treatment. In order to illuminate the relevance of lipid and statin status, future researches can be conducted among cohorts with familial hypercholesteremia [53,54]. We also demonstrated longitudinal results have stronger association in contrast to cross-sectional study design. Moreover, when excluding cross-sectional studies, the relevance between PM<sub>2.5</sub> and CIMT had no statistical significance. Because in cross-sectional studies we measured CIMT at a single point in time per participant and associations are based on between-person contrasts, these effects may be more affected without controlling for person-level factors and intra-individual variability of CIMT than those in longitudinal studies, in which information derived from the same individual.

Living close to major roads may indicate high exposure to traffic-related exhaust emissions, such as ultrafine particles and other highly redox-active pollution especially diesel particles [55]. Nonetheless, the relation between CIMT or other atherosclerosis markers and traffic proximity were still unclear, as the findings of existing studies were inconsistent. In our meta-analysis 4 studies observed the relation between traffic and CIMT. Perez et al. [17] presented that living in proximity to high traffic was also positively but not significantly associated with CIMT. Künzli et al. [24] showed that with a 10 μg/m<sup>3</sup> increasing in PM<sub>2.5</sub> annual increase in CIMT was 2.5 μm (95% CI -0.3-5.4 μm), which had no significant. When living within 100 m traffic, annual CIMT increased 5.5 μm (95% CI 0.13-10.79 μm) compared with people living away from traffic. However, living within a highway (100 m) or within a major road (50 m) was related with a non-significant 1.6 μm (95% CI -0.15-3.42 μm) augment in CIMT per year. Lenters et al. [25] didn’t find consistent direction of association between traffic indicators (traffic proximity, traffic density) and CIMT. Similar results were also represented by Gan et al. [19]. Several other recent studies observing the associations of CIMT with biomass fuel [56] and traffic-related air pollution [57,58] showed statistic significant results. Rivera et al. [52] reported that exposure contrasts between the 5th and 95th percentiles for NO<sub>x</sub> (25 μg/m<sup>3</sup>), traffic intensity in the nearest street (15,000 vehicles/day), and traffic load within 100 m (7,200,000 vehicle-m/day) were related with 0.56% (95% CI -1.5, 2.6%), 2.32% (95% CI: 0.48, 4.17%), and 1.91% (95% CI: -0.24, 4.06%) percent difference in IMT, respectively. Whereas other scholars examined the association of long-term exposure to traffic with CIMT in children [58]. The results showed that children residing <100 meters from the nearest heavily trafficked road had mean and maximum CIMT increment of 15% and 11% compared to those living >200 meters away (P=0.0001). From the above, future researches should focus on the effects of traffic proximity on atherosclerosis. Furthermore, studies can also be conducted to find if CIMT is a necessary ideal marker to reflect adverse
effects of atherosclerosis related with particular matter.

The results for PM$_{10}$ presented by Perez et al. [17] 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. [33]; Tonne et al. [23]). Whitehall II reported a 5% change (95% CI, 1.9%, 8.3%) for an IQR increase of 5.2 μg/m$^3$ PM$_{10}$. HNR showed a positive but not statistically significant association with PM$_{10}$ (1.8% change [95% CI, 0.6%, 4.3%] per 6.7 μg/m$^3$ increase of PM$_{10}$).

Several potential limitations should be noted in our study. Firstly, heterogeneity due to distinction between individuals and between studies was found across all researches, such as publication year, location, study design, study period, characteristics of participants, PM$_{2.5}$ and PM$_{10}$ measurement, sample size, covariates in each study and many other single-pollutant of CIMT. As a result of which, the included protocols about measurement technique and analysis, the CIMT was assessed noninvasively by B-mode ultrasound imaging coupled with automatic data processing systems. However, the optimal site and used value are still uncertain [30]. Some studies utilized the value of mean CIMT of the right far common carotid wall. Other studies regarded the average of the largest IMT in the left and right carotid arteries as a person’s CIMT. Still one study used mean of all available maximum wall thicknesses. In addition, choosing to use the cross-sectional CIMT or progression of CIMT also make some differences. Thus heterogeneity exists in the measurement of CIMT. Health status of participants and medication use were other potential factors having effects on outcome. Different statistical methods have been used in the studies and inferences in our meta-analysis make it difficult for us to find other potential factors by further analysis. As a result of which, heterogeneity, publication bias and quality reduction for studies arose. Secondly, since few involved studies used “multipollution” model, we only preserved single-pollutant model in our study regardless of latent interactions between pollutants. Therefore, we can’t estimate the interaction of multipollution associated with CIMT. Thirdly, some potential confounding factors were shown by subgroup analysis and additional overall analysis, which assessed the pooled-effect after putting an additional adjustment for education and income in some included studies. Nonetheless, more confounding factors are not able to be represented by more stratified analysis due to the less number of studies and limited information they provide.

The major strength of our study is the comprehensive retrieval in multiple databases and without publication language limitation. Moreover, the studies involved in our meta-analysis most had a large, well-examined population-based sample, which derived from an existing cohort.

Our study provides further evidence that particular matter exposure may increases the risks of atherosclerosis as well as the morbidity and mortality of cardiovascular diseases. Almost all of studies included in our meta-analysis used linear regression model to estimate the relationship between particular matter (PM$_{2.5}$, PM$_{10}$) and CIMT. If the association is linear, it is of great value to reduce the concentration of PM$_{2.5}$ at all levels and can provide a basis for the government to issue regulations about decrease of particular matter emission. In view of the limited number of existing studies about association between particular matter and CIMT, more analogous studies should be conducted in the future to further verify the results. In addition, future research can also focus on distinguishing potential confounding factors that impact the effect of PM$_{10}$ and PM$_{2.5}$ on CIMT, such as noise, postmenopausal women, diabetics or physical exercises.

In conclusion, our results represented that an increase in PM$_{10}$ had a significant association with CIMT, which is a mark for subclinical atherosclerosis. In female the effect may be more obvious and statistic significant, while the relationship of the effect with education level and lipid-lowering treatment status was still unclear.

Methods

PubMed, Ovid Medline, Embase and NICK between 1948 and 31 March 2015 were searched by combining the keywords about exposure (air pollution, air pollutants, particular matter, PM$_{2.5}$ and PM$_{10}$) to the outcome related words (carotid intima-media thickness, Carotid atherosclerosis, carotid IMT, CIMT, subclinical atherosclerosis). Two independent researchers selected the eligible studies successively by screening titles, abstracts and by reviewing the full text of potentially qualified studies. Then descriptive and quantitative information was extracted from each included study. The random-effects model was applied in computing the change of carotid intima-media thickness (CIMT) and their corresponding 95% confidence interval (95% CI). The effect of potential confounding factors was assessed by stratified analysis and the impact of traffic proximity was also estimated.

Results

Findings of 56 identified studies, 11 articles satisfied the inclusion criteria. In overall analysis per increment of 10 μg/m$^3$ in PM$_{10}$ was positively associated with an increase of CIMT (16.79 μm; 95% CI, 4.95-28.63 μm). When the concentration of PM$_{2.5}$ increased 10 μg/m$^3$ in the evaluation of overall combination, the CIMT increment is 4.13 μm (95% CI, -5.79-14.04 μm). Results shown in subgroup analysis had reference value for comparing with those of the overall analysis. The impact of traffic proximity on CIMT was uncertain.

Conclusion

Exposure to PM$_{2.5}$ had a significant association with CIMT and for women the effect may be more obvious.

References

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