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Ambient particulate air pollution and circulating C-reactive protein level: A systematic review and meta-analysis

Qisijing Liu[a], Xuelin Gu[a], Furong Deng[a], Lina Mu[b], Andrea A. Baccarelli[c], Xinbiao Guo[a], Shaowei Wu[a,*]

[a] Department of Occupational and Environmental Health Sciences, School of Public Health, Peking University, Beijing, China
[b] Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo, The State University of New York, United States
[c] Department of Environmental Health Sciences, Columbia University Mailman School of Public Health, New York, NY, United States

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Particulate matter
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A B S T R A C T

Background: Ambient particulate air pollution is a major threat to the cardiovascular health of people. Inflammation is an important component of the pathophysiological process that links air pollution and cardiovascular disease (CVD). A classical marker of inflammation—C-reactive protein (CRP), has been recognized as an independent predictor of CVD risk. Exposure to ambient particulate matter (PM) may cause systemic inflammatory response but its association with CRP has been inconsistently reported.

Objectives: To estimate the potential effects of short-term and long-term exposures to ambient particulate air pollution on circulating CRP level based on previous epidemiological studies.

Methods: A systematic literature search of PubMed, Web of Science, Embase, and Scopus databases for publications up to January 2018 was conducted for studies reporting the association between ambient PM ($PM_{2.5}$ or PM_{10}, or both) and circulating CRP level. We performed a meta-analysis for the associations reported in individual studies using a random-effect model and evaluated the effect modification by major potential modifiers.

Results: This meta-analysis comprised data from 40 observational studies conducted on 244,681 participants. These included 32 (27 $PM_{2.5}$ studies and 13 PM_{10} studies) and 11 (9 $PM_{2.5}$ studies and 5 PM_{10} studies) studies that investigated the associations of CRP with short-term and long-term exposure to particulate air pollution, respectively. A 10 $\mu g/m^3$ increase in short-term exposure to $PM_{2.5}$ and PM_{10} was associated with increases of 0.83 % (95% CI: 0.30%, 1.37%) and 0.39% (95% CI: -0.04%, 0.82%) in CRP level, respectively, and a 10 $\mu g/m^3$ increase in long-term exposure to $PM_{2.5}$ and PM_{10} was associated with much higher increases of 18.01% (95% CI: 5.96%, 30.06%) and 5.61% (95% CI: 0.79%, 10.44%) in CRP level, respectively. The long-term exposure to particulate air pollution was more strongly associated with CRP level than short-term exposure and $PM_{2.5}$ had a greater effect on CRP level than PM_{10}.

Conclusion: Exposure to ambient particulate air pollution is associated with elevated circulating CRP level suggesting an activated systemic inflammatory state upon exposure, which may explain the association between particulate air pollution and CVD risk.

1. Introduction

A considerable amount of epidemiological evidence supports that ambient air pollution represents a serious threat to the health of people in recent decades and has been widely recognized as an important risk factor for the increased mortality and morbidity of CVD (Hoek et al., 2002; Katsouyanni et al., 1997; Samet et al., 2000). Exposure to one of the major ambient air pollutants, particulate matter (PM), can contribute substantially to both the onset of CVD and exacerbation of existing cardiovascular conditions (Dabass et al., 2016; Newby et al.,

Abbreviations: cardiovascular disease, (CVD); C-reactive protein, (CRP); particulate matter, (PM); high-sensitivity, CRP (hs-CRP); high-sensitivity enzyme-linked immunosorbent assay, (ELISA); National Heart Lung and Blood Institute, (NHLBI); standard deviation, (SD); interquartile range, (IQR); confidence intervals, (CIs); standard error, (SE); reactive oxygen species, (ROS)

* Corresponding author. Department of Occupational and Environmental Health Sciences, School of Public Health, Peking University, 38 Xueyuan Road, Haidian District, Beijing, China.
E-mail address: shaowei_wu@bjmu.edu.cn (S. Wu).

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2015). One of the most relevant underlying pathophysiological pathways involved in the air pollution-related cardiovascular outcomes is the activation of system inflammation upon exposure to ambient particulate air pollution.

PM is a complex mixture of particles from a wide variety of sources (Pope et al., 2009). The health impact of PM increases with decreasing particle size. PM with an aerodynamic diameter $\leq 2.5\,\mu m$ ($PM_{2.5}$) is capable to reach alveoli and deposit deeper in the lung while PM with an aerodynamic diameter $\leq 10\,\mu m$ (PM_{10}) is much larger and mostly stopped at the upper bronchi and it can stimulate pulmonary inflammation (Nemmar et al., 2002). Herein, we focus on a typical biomarker of inflammation—C-reactive protein (CRP), an acute-phase protein of hepatic origin that is also widely recognized as a biomarker for CVD to reflect the role of the ambient particles in causing systemic inflammation, thus influencing the cardiovascular outcome. CRP is a sensitive downstream systemic marker of inflammation. Its level remains very low among healthy individuals but rises to 10,000-fold during the acute phase when inflammation or major tissue damage occurs (Gabay and Kushner, 1999). Slight elevation in CRP level is associated with a high number of medical conditions such as atrial fibrillation, hypertension, moderate chronic obstructive pulmonary disease, and type 2 diabetes (Kushner et al., 2006).

Over a dozen prospective epidemiological studies demonstrated that the level of CRP is a strong predictor of future CVDs such as coronary heart disease, stroke, and peripheral artery disease, as well as secondary cardiovascular events including myocardial infarction, ischemic stroke and sudden cardiac death among CVD patients and also individuals with no prior history of CVD (Chen et al., 2017; Koenig et al., 1999; Ridker, 2003; Shrivastava et al., 2015). There is also evidence showing that CRP is a valid predictor of CVD risk even 20 years after the initial blood sample was obtained (Sakkinen et al., 2002). Traditional CRP detection methods such as nephelometry (detection range 1–10 mg/L) can only detect obvious inflammatory responses instead of subtle changes in CRP level (Kamath et al., 2015). In contrast, the measurement of high-sensitivity CRP (hs-CRP) using highly sensitive assay techniques such as immunonephelometry, immunoturbidimetry, high-sensitivity enzyme-linked immunosorbent assay (ELISA), and resonant acoustic profiling is more precise (detection range 0.01–10 mg/L). It is also a more sensitive way of measuring CRP than normal CRP (Kamath et al., 2015). This improved sensitivity makes hs-CRP suitable for detecting low-grade inflammation and determining CVD risk among seemingly healthy people. Results from a comprehensive meta-analysis suggested that risk ratios per three-fold higher of CRP were 1.37, 1.27, 1.55, and 1.54 for coronary heart disease, ischemic stroke, vascular mortality, and non-vascular mortality, respectively (The Emerging Risk Factors Collaboration‡, 2010).

Existing epidemiological studies reported inconsistent results regarding whether exposure to air pollution can lead to an elevation in circulating CRP. A previous systematic review published in 2012 stated that epidemiological studies among children reported generally consistent positive associations between exposure to particulate air pollution and CRP (Li et al., 2012). Whereas, this positive association between PM and CRP in adults could only be observed at higher peak levels of PM and no consistent result was found in adults with chronic inflammatory conditions (Li et al., 2012). However, this review did not include a quantitative analysis to summarise the changes in CRP level in association with PM exposure. Moreover, many new studies with larger sample sizes and improved exposure assessment have been published since 2012, strengthening the necessity of conducting a formal meta-analysis study. In this study, we focused on the associations between short/long-term exposures to both $PM_{2.5}$ and PM_{10} and circulating CRP level, and conducted a comprehensive meta-analysis to summarise the currently available study findings (till January 2018).

2. Methods

2.1. Search strategies

The studies were comprehensively examined using the same combination of keywords of exposure and health outcomes in the following databases: Science Direct (EMBASE) (all fields), PubMed (all fields), Web of Science (topic), and Scopus (article title, abstract and keywords) up to January 2018 (no start date specified). The studies included in this meta-analysis consisted of epidemiological studies that evaluated the association between ambient $PM_{2.5}$/PM_{10} and CRP/hs-CRP level. The search terms related to exposure were "air pollutants", "air pollution", "particulate matter", "PM", "$PM_{2.5}$", "PM_{10}", or "particles". The terms that described health outcomes were "high-sensitivity C-reactive protein", "high-sensitivity CRP", "hs-CRP", "hsCRP", "C-reactive protein", or "CRP".

2.2. Study selection criteria

We examined all abstracts, full texts, and supplementary materials of the identified records by inclusion and exclusion criteria. Eligible studies must have reported quantitative measurements such as percent change (%-change), beta coefficient (β), fold change or relative difference in the magnitude of the association between ambient PM and biomarker CRP level in human blood in adults. Specific exclusion criteria were listed in the supplementary material (see supplementary material).

2.3. Data extraction

Two investigators (Q. Liu and X. Gu) evaluated all records and data extractions independently. Initial screening was conducted by skimming through the titles, abstracts, and keywords against the inclusion and exclusion criteria. Full-text articles were reviewed for all potentially eligible records. Discrepancies were resolved by discussions between the two investigators. If consensus was not reached, decisions were made by the third investigator (S. Wu).

Data and study characteristics from all eligible studies were extracted and recorded including: (1) study reference, (2) study period, (3) study location (country), (4) participant characteristics (total number, age and disease status), (5) circulating hs-CRP/CRP level, (6) exposure level, (7) total number of observations (total number of blood samples obtained from the study population), (8) exposure ($PM_{2.5}$, PM_{10}) assessment methodology, (9) effect estimates and 95% Cis, (10) unit of the effect estimates, and (11) study design. For articles with missing information, we contacted the corresponding authors to obtain specific data. In this meta-analysis, the estimated effect of PM was categorised into estimated short-term effect (within days or several weeks) (Lee et al., 2017) and a long-term effect (more than 6 months) (Rodosthenous et al., 2018). During data extraction, study results from all available models and exposure metrics were extracted and recorded, including the results for the full study of population and subgroups. However, only the largest effect (either positive or negative) with the narrowest confidence interval among the short-term exposure and/or long-term exposure metrics from the full population analysis of each study was selected for the meta-analysis (Atkinson et al., 2014). If the study only reported subgroup results, then all subgroup data was included.

2.4. Quality assessment

Quality assessments of the included studies were also conducted by two independent investigators (Q. Liu, and X. Gu) and any controversy was solved through thorough discussions. Appraisal of the included studies was completed using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, as recommended by

the Cochrane Handbook (Higgins Julian PT, 2006). It is a set of 14 questions designed for the critical appraisal of the potential risk of bias ("Study Quality Assessment Tools | National Heart, Lung, and Blood Institute (NHLBI)," n.d.).

2.5. Statistical analysis

Percent changes were commonly used to quantify the association across all eligible studies included in this meta-analysis. Original effect estimates in included studies were reported per standard deviation (SD), interquartile range (IQR) or other specific unit change of the PM level, and they were converted and standardised into percent changes (%) and 95% CIs associated with a 10 μg/m^3 increase in PM exposure. Results reported in the format of relative difference were considered equivalent to percent change after multiplying the effect estimates by 100%. Antilog transformation was performed on the changes in log-transformed CRP level per unit increase of PM exposure before pooling together. Fold change of CRP was deducted by 1, then multiplied by 100% to transform to percent change. Our study also included regression coefficient results. Beta-coefficients from linear regression models (not log-transformed) were transformed back to percent changes in association with a 10 μg/m^3 increase in PM using the equation [β*10 ÷ M]*100%, where β was the regression coefficient and M was the mean of CRP level; 95% confidence intervals (CIs) were calculated as [(β ± 1.96*SE)*10 ÷ M]*100%, where SE was the standard error associated with the regression coefficient β (Yang et al., 2015).

Percent changes and 95% CIs of the circulating CRP/hs-CRP level associated with a 10 μg/m^3 increase in PM exposure collected or re-calculated from each included empirical study were pooled, and the pooled results were computed using Stata software version 12.0 (StataCorp., College Station, Texas). Heterogeneity among different studies and study subgroups was examined using Chi-square-based Cochrane Q statistic test and standard I^2 test. Pooled results were calculated using random-effect models if $I^2 > 50\%$, which indicated a substantial degree of heterogeneity across studies (Higgins, 2011).

In addition to adopting a random-effect model to examine the effect modification, the results were stratified into subgroups by study location (Asia or Europe or the USA), CRP assessment (CRP or hs-CRP), baseline CRP level (by clinical reference level), sample size (< 1000 or ≥1000), study quality (medium or high), pollution level (high or low according to WHO guidelines), exposure assessment (fixed sites or others), disease status of participants (general population or diseased population), study design (panel study, cross-sectional study, or others), and mean or median age, or age range (< 40 years or ≥40 years). Detailed categorising methods are shown in the supplementary material. When significant heterogeneity was identified, we conducted a meta-regression analysis to investigate if it was related to one or more characteristics of the studies using random effect restricted maximum likelihood model. We did not perform subgroup and meta-regression analyses for long-term effects of PM_{10} owing to too few studies.

The publication bias of included studies was examined using the symmetric plot as well as the Begg's test build in Stata statistical software. Sensitivity analysis was also performed by removing each study at a time to evaluate if the omission of any study would alter the significance of the pooled results.

3. Results

The literature search and eligible study selection procedure followed a comprehensive, pre-designed methodology, as shown in Fig. 1. Initial search resulted in a total of 6,181 records from four databases: Scopus (n = 1,804), Pubmed (n = 1,189), Embase (n = 1,694), and Web of Science (n = 1,494). After removing the duplicates and evaluating the records based on the inclusion and exclusion criteria, 49 articles fulfilled the criteria. Two reports (Rückerl et al., 2014, 2016) studied the same population during the same period and only the latest data from 2016 were included in this meta-analysis. Three reports (Hennig et al., 2014; Hoffmann et al., 2009; Viehmann et al., 2015) investigated the CRP changes associated with long-term exposure to PM_{10} and/or $PM_{2.5}$ of the same population from the Heinz Nixdorf Recall Study. Therefore, we only adopted the long-term association data from the latest study (Viehmann et al., 2015) according to our exclusion criteria. We also included the study by Hoffmann et al. (2009) in the final analysis for the short-term exposure to PM_{10} because this study investigated the short-term exposure effect of PM_{10} on CRP as well. We further excluded 7 records without effect estimates after contacting the authors, thus leaving 40 studies. Table S1 lists the descriptive characteristics of the included studies. Among these studies, 33 investigated the $PM_{2.5}$-CRP association (26 for short-term & 10 for long-term) and 18 studies investigated the PM_{10}-CRP association (13 for short-term & 5 for long-term) (Fig. 1, Table 1).

The meta-analysis showed that a 10 μg/m^3 increase in short-term exposure to ambient $PM_{2.5}$ was associated with a 0.83% increase in hs-CRP (95% CI: 0.30%, 1.37%) (Fig. 2, Table 1), revealing a significant positive but weak association. However, the association between the short-term exposure to PM_{10} and CRP level was insignificant (pooled percent change: 0.39%, 95% CI: −0.04%, 0.82%) (Fig. 2, Table 1). In contrast, the positive associations with CRP level were stronger for long-term exposures to $PM_{2.5}$ (18.01%, 95% CI: 5.96%, 30.06%) and PM_{10} (5.61%, 95% CI: 0.79%, 10.44%) than that for short-term exposures (Fig. 2, Table 1). Nevertheless, heterogeneity test results suggested a moderate to high level of heterogeneity among the effect estimates for all four PM-CRP associations (Table 1), particularly for the short-term exposure to $PM_{2.5}$ and CRP association (I^2 = 89.8%).

We performed subgroup analyses to offer insights into the sources of heterogeneity. PM was associated with increased circulating CRP level in most subgroups, but the heterogeneity remained at a moderate to high level (Table 2). There were no significant modification effects found for short-term exposure of PM_{10}. The meta-regression analysis identified multiple factors including CRP level (P = 0.02), study quality (P = 0.01), and study design (P = 0.08), which may help explain the heterogeneity for CRP level change associated with long-term exposure of $PM_{2.5}$. Only the study design (P = 0.03) was able to alter the effect of short-term exposure of $PM_{2.5}$ (Table S2).

Sensitivity analyses were performed to estimate the stability of the results by re-calculating the pooled percent changes after omitting one study each time. We found that the pooled percent changes in CRP per 10 μg/m^3 increase in short-term or long-term exposure to both $PM_{2.5}$ and PM_{10} showed no significant change and were not dominated by any single study, suggesting that the combined results were relatively stable and reliable (Table S3). Both plot symmetry and Begg's test results indicated that there was no publication bias among long-term studies.- Some evidence of publication bias was found for the short-term studies as indicated by a slight to mild asymmetric funnel plots (Fig. S1). Results of Beggs' test verified that the publication bias was insignificant (P > 0.05) (Table S4).

4. Discussion

So far, several prospective studies conducted among individuals with no prior history of CVD have demonstrated that CRP was a classical biomarker of inflammation and a strong predictor of future CVD events that is independent of age, smoking, blood cholesterol, blood pressure, and diabetes (Wilson et al., 1998). Our results demonstrated that both short-term and long-term exposures to ambient $PM_{2.5}$ and PM_{10} were positively associated with an increased level of CRP, suggesting that exposure to ambient PM may increase future CVD risk through the inflammatory pathway. A 10 μg/m^3 increase in short-term exposure to $PM_{2.5}$ and PM_{10} can lead to 0.83% and 0.39% increase in CRP level, respectively. A 10 μg/m^3 increase in long-term exposure to $PM_{2.5}$ and PM_{10} was associated with much higher increases of 18.01% and 5.61% in CRP level, respectively.

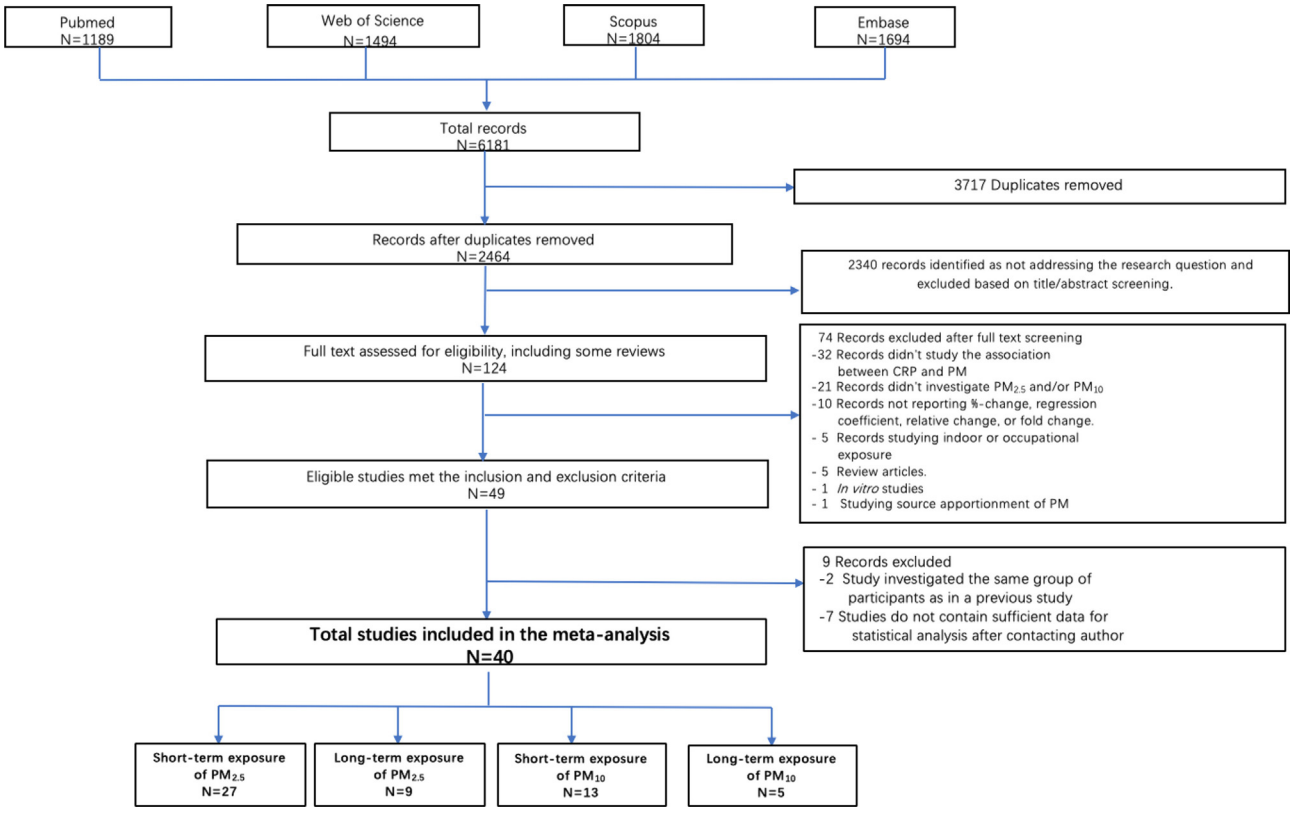

Fig. 1. Flow-chart of literature search for meta-analysis.

Table 1
Meta-analysis of percent change in CRP in association with a 10 μg/m^3 increase in ambient PM concentrations.

Overall analysis	Exposure	Pooled %-changes (95% CI)	Significance test (*P* value)	No. of effect estimates	No. of studies	Heterogeneity	
						P Value for Heterogeneity	I^2
PM2.5	Short-term	0.83 (0.30, 1.37)	0.002	31	27	< 0.001	89.8%
	Long-term	18.01 (5.96, 30.06)	0.003	9	9	< 0.001	79.5%
PM_{10}	Short-term	0.39 (−0.04, 0.82)	0.076	16	13	0.032	43.6%
	Long-term	5.61 (0.79, 10.44)	0.023	5	5	0.813	0.0%

CI: confidential interval.

Major pathophysiological pathways through which air pollution may promote the development of CVD include cardiac autonomic imbalance, increased oxidative stress, and inflammation. When a human body is exposed to particles (via respiratory tract, dermal or ocular contact), PM activates a complex cascade of cellular signaling networks, stimulates resultant reactive oxygen species (ROS) that depletes endogenous antioxidants, and causes a rise in the CRP level (Chen et al., 2016; Yan et al., 2016). CRP release can also be triggered by inflammatory cytokines including interleukin-6, interleukin-8, and tumour necrosis factor-alpha in the circulation system because of pulmonary inflammation after particle deposition (Veronesi et al., 1999; Jiménez et al., 2002; Nemmar et al., 2002). Low-grade systemic inflammation may precede incident cardiovascular events. Moreover, CRP not only acts as a marker of the systemic inflammation but also induces the cardiac outcomes. The elevation in CRP is expected to lead to the upregulation of adhesion molecules expression, increase in low-density lipoprotein-uptake, induction of complement activation, activation of macrophages, and secretion of tissue factor, which could further cause endothelial dysfunction and induce pro-coagulatory state leading to the development of adverse cardiac outcomes (Robson, 2008).

In vitro and *in vivo* evidence also supports that the PM-systemic inflammation pathway is biologically plausible (Ramage and Guy, 2004; Upadhyay et al., 2010; Vogel et al., 2005). *In vitro* studies quantified the particle-related CRP mRNA expression increases in Human Macrophage Cell Line U937 (Vogel et al., 2005) and A549 human lung cells (Ramage and Guy, 2004). There is also *in vivo* evidence showing a four-fold elevation in serum CRP after a high dose instillation of 1000 μg $PM_{2.5}$ in spontaneously hypertensive rats, indicating a potentially high risk for cardiovascular impairment (Upadhyay et al., 2010). Another *in vivo* study found that $PM_{2.5}$ alone can trigger the significant increase in CRP and lead to further inflammation and endothelial function injury in rats (Wang et al., 2013).

Growing evidence from epidemiological studies has shown that short-term exposure to ambient $PM_{2.5}$ and PM_{10} for hours to weeks can trigger acute adverse health effects including increased mortality and morbidity of CVD (Agusti, 2007; Brook et al., 2010; Dominici et al., 2006; Kim et al., 2012; Tecer et al., 2008). A longer-term exposure to PM for months to years was found to have a greater influence on the risk of cardiovascular mortality, even at a low concentration (Brook et al., 2010; Dominici et al., 2006; Sandhu et al., 2005). The results of our study agree with these findings and the magnitude of association was found to be much greater for long-term exposure than for short-term exposure in both $PM_{2.5}$ and PM_{10}. Most of the included studies

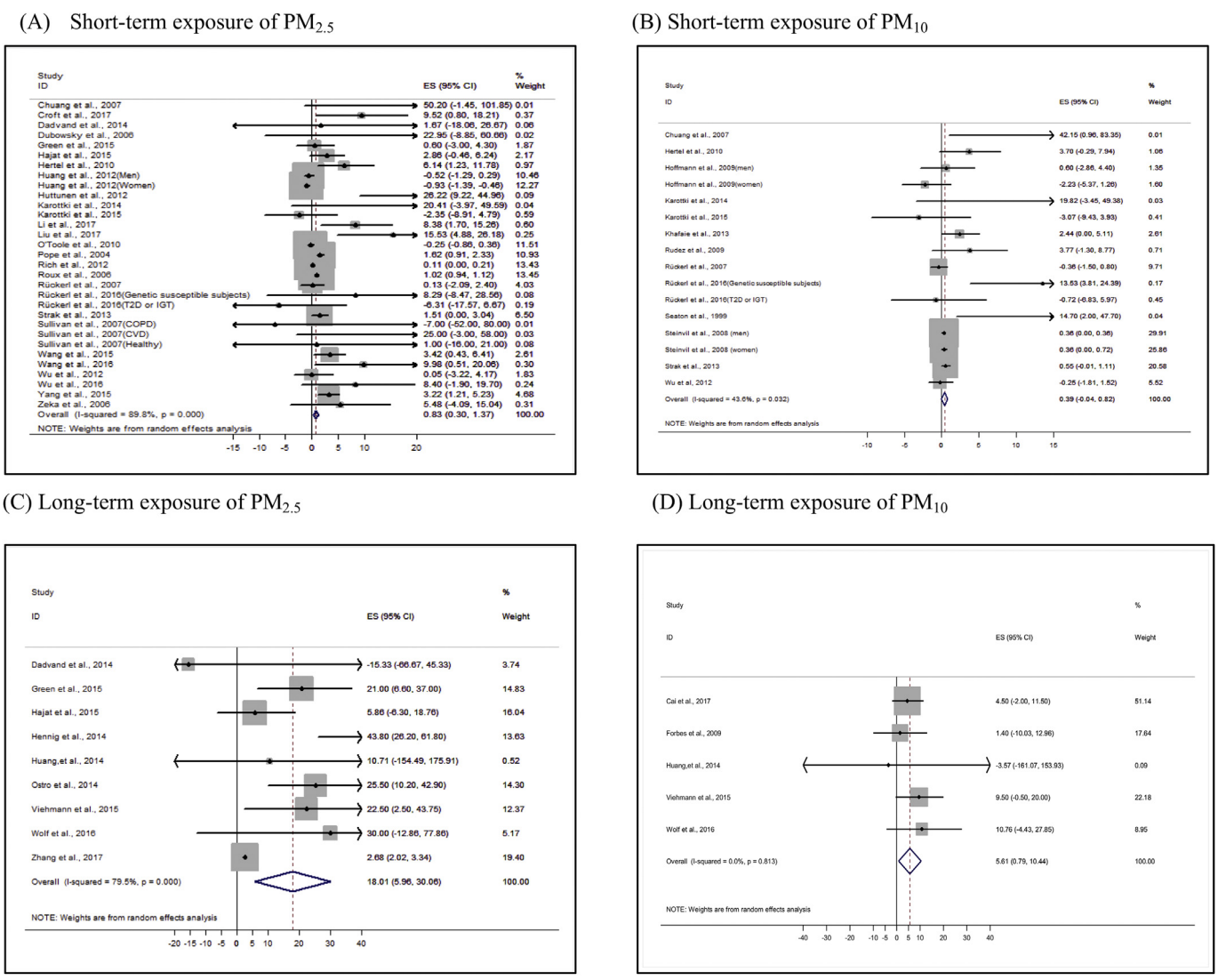

Fig. 2. Forest plot of the meta-analysis: (A) Pooled percent change (%) of CRP associated with a 10 μg/m^3 increase in long-term exposure to $PM_{2.5}$ (B) Pooled percent change (%) of CRP associated with a 10 μg/m^3 increase in short-term exposure to PM_{10} (C) Pooled percent change (%) of CRP associated with a 10 μg/m^3 increase in long-term exposure to $PM_{2.5}$ (D) Pooled percent change (%) of CRP associated with a 10 μg/m^3 increase in long-term exposure to PM_{10}. (Li et al., 2017b, Liu et al., 2017, Ostro et al., 2014, Pope et al., 2004, Rückerl et al., 2007, Wang et al., 2015, Wang et al., 2016, Wolf et al., 2016, Wu et al., 2016)

only investigated the short-term or long-term effects estimates in a single study. Only three studies investigated the health effects associated with both short-term and long-term exposures (Dadvand et al., 2014; Green et al., 2016; Hajat et al., 2015). These studies also found that long-term exposure was more strongly associated with increased inflammatory biomarkers than short-term exposure. We believe that the stronger estimated effects associated with long-term exposure can be explained by the cumulative damage over long durations. Similarly, hospitalization rates for CVD were also found to be more strongly associated with long-term $PM_{2.5}$ exposure than with short-term $PM_{2.5}$ exposure (Kloog et al., 2012). Therefore, we believe that improvements in long-term air quality can effectively reduce the incidence of CVD.

Moreover, we also demonstrated a more consistent association pattern with CRP for $PM_{2.5}$ than for PM_{10}, suggesting that $PM_{2.5}$ may be more capable of increasing CRP level than PM_{10}. Animal studies also demonstrated the adverse effects of smaller particles (Routledge and Ayres, 2005). Smaller particles have a larger surface area than larger particles and their porous surface allows for a higher number of toxic substances such as transition metals and a variety of organic chemicals to be absorbed and retained inside the particles, which subsequently cause the inflammatory status and an increase in CRP. (Valavanidis et al., 2008).

Moderate to high heterogeneity was identified in both overall meta-analysis and subgroup analysis, suggesting the existence of inherent differences between the studies. Subgroup analyses and meta-analyses were performed to evaluate the impact of multiple potential effect modifiers. We identified several potential modifiers such as study design, study quality, and CRP level that could partially explain the heterogeneity for changes in CRP in association with long-term exposure to $PM_{2.5}$ and only a study design can explain the heterogeneity of short-term exposure of $PM_{2.5}$.

Our study also found a positive association in exposure of PM level under the WHO guidelines. Therefore, we believe that there is no threshold concentration for ambient PM exposure because there is still a strong association between ambient PM on CRP level below the current WHO regulatory guidelines that could lead to increasing CVD risk. Cardiovascular mortality is the leading type of mortality due to air pollution (Lelieveld et al., 2019) and our result findings suggest that there is still room for the reduction of WHO guidelines to reduce the CVD mortality and morbidity attributed to ambient particulate pollution.

Subgroup analyses by exposure assessment method found a smaller

Table 2
Subgroup analysis of percent change in CRP in association with a 10 μg/m^3 increase in ambient PM concentration.

Subgroup	Exposure	Grouping criteria	Pooled %-changes (95% CI)	P value	No. of effect estimates	No. of studies	Heterogeneity	
							P Value for Heterogeneity	I^2
Study location								
PM2.5	Short-term	Asian	1.1 (−0.5, 2.7)	0.179	7	6	< 0.001	83.1%
		European	2.0 (−0.9, 4.8)	0.175	9	8	0.031	52.7%
		USA	0.9 (0.2, 1.5)	0.002	14	12	0.008	93.5%
	Long-term	Asian	2.7 (2.0, 3.4)	< 0.001	3	3	0.582	0.0%
		European	28.4 (9.3, 47.6)	0.004	4	4	0.154	42.9%
		USA	16.6 (4.3, 28.8)	0.008	3	3	0.122	52.5%
PM_{10}	Short-term	Asian	0.4 (0.0, 0.8)	0.048	5	4	0.135	43.0%
		European	0.6 (−0.8, 1.9)	0.394	11	9	0.034	48.9%
hs-CRP vs CRP								
$PM_{2.5}$	Short-term	CRP	2.6 (0.6, 4.5)	0.009	10	10	< 0.001	77.6%
		hs-CRP	0.6 (−0.0, 1.2)	0.062	20	16	< 0.001	92.4%
	Long-term	hs-CRP	–	–	10	10	–	–
PM_{10}	Short-term	CRP	4.7 (−16.6, 25.9)	0.667	2	2	0.100	63.1%
		hs-CRP	0.4 (−0.0, 0.8)	0.062	14	11	0.036	44.7%
Mean CRP level								
$PM_{2.5}$	Short-term	High-risk	3.4 (1.7, 5.0)	< 0.001	4	4	0.052	0.0%
		Moderate-risk	0.6 (−0.3, 1.6)	0.178	12	10	< 0.001	88.6%
		Low-risk	22.3 (13.6, 30.9)	0.000	12	10	< 0.001	94.7%
		NA	3.8 (−5.6, 13.1)	0.428	2	2	0.048	74.5%
	Long-term	High-risk	4.9 (−7.4, 17.1)	0.437	2	2	0.469	0.0%
		Moderate-risk	23.3 (12.6, 33.9)	< 0.001	7	7	0.062	49.9%
		Low-risk	2.7 (2.0, 3.3)	< 0.001	1	1	–	–
PM_{10}	Short-term	Average-risk	0.3 (0.0, 0.7)	0.046	10	7	0.131	34.6%
		Low-risk	2.5 (−2.0, 7.0)	0.279	5	5	0.088	50.6%
		NA	14.7 (−8.2, 37.6)	0.207	1	1	–	–
Pollution level								
$PM_{2.5}$	Short-term	High	0.2 (−1.2, 1.6)	0.765	6	6	0.001	74.5%
		Low	4.6 (0.8, 8.4)	0.017	21	17	0.001	65.2%
		NA	1.4 (−1.3, 4.1)	0.300	3	3	0.002	84.1%
	Long-term	High	2.7 (2.0, 3.4)	< 0.001	3	3	0.582	0.0%
		Low	21.8 (10.1, 33.5)	< 0.001	7	7	0.030	57.0%
PM_{10}	Short-term	High	0.3 (0.1, 0.6)	0.023	4	3	0.215	32.8%
		Low	1.1 (−0.8, 3.0)	0.251	10	8	0.017	55.4%
		NA	2.8 (−7.4, 13.0)	0.587	2	2	0.225	32.1%
Exposure assessment								
$PM_{2.5}$	Short-term	Fixed site	0.5 (−0.1, 1.1)	0.097	25	21	< 0.001	91.1%
		Others	2.6 (0.9, 4.2)	0.002	5	5	0.189	34.9%
	Long-term	Fixed site	13.5 (5.5, 21.5)	0.001	5	5	0.262	23.8%
		Others	19.1 (−3.3, 41.4)	0.094	5	5	< 0.001	84.5%
PM_{10}	Short-term	Fixed site	0.4 (−0.0, 0.8)	0.065	13	11	0.041	44.8%
		Others	0.5 (−2.8, 3.8)	0.761	3	2	0.087	59.1%
Age								
$PM_{2.5}$	Short-term	< 40	1.2 (−0.7, 3.1)	0.211	5	5	0.002	76.8%
PM_{10}		≥40	0.8 (0.2, 1.4)	0.014	25	21	< 0.001	91.2%
	Long-term	≥40	–	–	10	10	–	–
	Short-term	< 40	0.3 (−1.35, 2.0)	0.720	3	3	0.094	57.7%
	Long-term	≥40	0.4 (−0.1, 0.9)	0.143	13	10	0.041	44.7%
Quality of study								
$PM_{2.5}$	Short-term	High	1.2 (0.5, 1.8)	0.001	13	13	< 0.001	94.1%
		Medium	0.8 (−0.3, 1.9)	0.159	17	13	< 0.001	65.6%
	Long-term	High	4.9 (−0.0, 9.7)	0.051	5	5	0.263	0.0%
		Medium	28.9 (19.7, 38.1)	< 0.001	5	5	0.414	84.4%
PM_{10}	Short-term	High	0.4 (−0.5, 1.3)	0.375	7	7	0.160	35.1%
		Medium	0.4 (−0.2, 1.0)	0.185	9	6	0.027	53.8%
Sample size								
$PM_{2.5}$	Short-term	< 1000	1.4 (1.3, 2.5)	0.013	22	19	< 0.001	77.7%
		≥1000	0.8 (0.0, 1.6)	0.040	8	8	< 0.001	96.1%
	Long-term	< 1000	7.6 (−3.0, 18.2)	0.161	3	3	0.717	23.8%
		≥1000	19.5 (6.8, 32.1)	0.003	7	7	< 0.001	0.0%
PM_{10}	Short-term	< 1000	1.2 (−1.0, 3.4)	0.292	7	7	0.016)	61.7%
		≥1000	0.3 (0.0, 0.7)	0.046	9	7	0.228	24.2%
Study design								
$PM_{2.5}$	Short-term	Panel study	0.4 (−0.1, 1.0)	0.123	22	19	< 0.001	92.1%
		Cross-sectional study	4.3 (2.5, 6.0)	< 0.001	7	7	0.440	0.0%
		Others	1.5 (−0.0, 3.0)	0.052	1	1	–	–
	Long-term	Panel study	13.8 (4.9, 22.7)	0.002	4	4	0.154	42.9%
		Cross-sectional study	8.1 (−3.8, 19.9)	0.184	5	5	0.254	25.1%
		Others	43.8 (6.5, 26.1)	< 0.001	1	1	–	–
PM_{10}	Short-term	Panel study	2.3 (−1.8, 6.4)	0.265	7	6	0.019	60.4%
		Cross-sectional study	0.3 (−0.1, 0.7)	0.087	8	6	0.138	36.5%
		Others	0.6 (−0.0, 1.1)	0.054	1	1	–	–

(*continued on next page*)

Table 2 (*continued*)

Subgroup	Exposure	Grouping criteria	Pooled %-changes (95% CI)	P value	No. of effect estimates	No. of studies	Heterogeneity	
							P Value for Heterogeneity	I^2
Disease status								
$PM_{2.5}$	Short-term	General population	1.0 (0.2, 1.7)	0.014	16	16	< 0.001	84.0%
		Patients	3.3 (1.6, 5.0)	< 0.001	16	14	< 0.001	83.1%
	Long-term	General population	12.7 (3.4, 22.1)	0.007	7	7	0.018	60.9%
		Patients	2.6 (1.9, 3.3)	< 0.001	5	5	0.051	0.0%
PM_{10}	Short-term	General population	0.4 (0.0, 0.8)	0.034	12	5	0.016	33.1%
		Patients	1.9 (−1.2, 4.9)	0.231	5	10	0.228	64.2%

*Classification criteria: Mean CRP level (hs-CRP < 1 mg/L, CRP < 5 mg/L, represents low-risk group; 1 mg/L ≤ hs-CRP ≤ 3 mg/L, 5 mg/L ≤ hs-CRP ≤ 10 mg/L represents moderate-risk group; hs-CRP > 3 mg/L or CRP > 10 mg/L represents high-risk group); Pollution level (high: annual mean of $PM_{2.5}$ > 10 μg/m3 or 24 h mean of $PM_{2.5}$ > 25 μg/m3 or annual mean of PM_{10} > 20 μg/m3 or 24 h mean of PM_{10} > 50 μg/m3 vs low: PM level below the above threshold); Quality of study (High quality: score ≥ 11; Medium quality: score: 9 ≤ quality score < 11).

effect estimate of PM on CRP for studies using fixed-site monitoring data than for studies using other methods (models or personal exposure data from a short-term study), especially for long-term exposures of $PM_{2.5}$ (Table 2). PM exposure assessment method used in epidemiological studies usually depends on the study design and the fixed-site monitoring data is usually used in short-term studies, while land use regression or dispersion models are usually used in long-term studies. The utilisation of municipal monitoring data that lacks spatial variations may cause non-differential misclassification in individual exposure and underestimate the association, especially for long-term studies. Exposure data from statistical models (such as land use regression or dispersion model) is a better exposure assessment solution for long-term studies because it is spatially more detailed (Ostro et al., 2010). Short-term studies are more concerned on the temporal variation instead of spatial variation in exposure levels. Therefore, fixed-site monitoring data or personal exposure monitoring data are more suitable for short-term studies as it is temporally resolved. Nevertheless, the difference in the estimated effects for different PM assessment methods was subtle in our present study.

The reasons for the different effect estimates of PM on CRP for short-term studies using fixed-site monitoring data and other methods remain unclear. Investigating the exposure to PM constituents that have different potentials to induce toxicities could be informative for the identification of the source of heterogeneity observed in short-term studies (Pedersen et al., 2015) and may also be informative to explain the heterogeneity observed in long-term studies. However, the measurement of PM constituent exposure is difficult in long-term studies unless routine PM constituent monitoring is available over long durations.

Of all included studies, only three studies investigated the association of CRP with PM compositions such as transition metal components (iron, copper, and nickel) and ionic components (nitrate and sulfate), elemental carbon, and organic carbon (Chuang et al., 2007; Strak et al., 2013; Wu et al., 2012). Further epidemiologic studies are encouraged to study the association between chemical constituents of particles and CRP. It will not only help us understand the effects of PM on CRP and its underlying pathological mechanism but also benefit the policymakers to efficiently control the source of PM constituents and its adverse effects.

Moreover, we found that CRP has stronger associations with $PM_{2.5}$ and PM_{10} than hs-CRP. The difference in assay sensitivity could affect the result but the meta-regression analysis did not find it statistically significant. Additionally, we found that the association with exposure to PM appeared stronger among participants with lower CRP level than those with higher CRP level. This may be because the patients may take medication that has anti-inflammatory functions, such as statins, and thus weaken the potential effect of PM in the presence of inflammatory response. Therefore, the adverse effect of PM on population is more obvious among people with no sign of systemic inflammation than those with already elevated CRP level. Besides, we also found that the CRP increase associated with short-term exposure to PM appeared stronger in patients with chronic diseases. It is possible that a relatively healthier population has a stronger resistance toward abrupt PM exposure. In contrast, this association pattern reversed in terms of the long-term exposure of $PM_{2.5}$. However, the results of meta-regression did not reveal any significant differences for the subgroups of the population stratified according to disease status. Owing to the considerable heterogeneity observed in different subgroups, more future studies are needed to confirm these findings. Nevertheless, sensitivity analyses proved that our estimated effects for both $PM_{2.5}$ and PM_{10} on CRP were robust and stable. Therefore, our study findings are reliable.

This meta-analysis is strengthened by the comprehensive evaluation of existing studies. However, our study results may change owing to the exclusion of seven studies with unavailable effect estimates for meta-analysis after contacting the authors through emails (Bind et al., 2012; Dabass et al., 2018, 2016; Emmerechts et al., 2012; Hildebrandt et al., 2009; Li et al., 2017a; Mirowsky et al., 2015). Nevertheless, most studies on PM and CRP in the literature have been included in our meta-analysis, and the potential bias due to the excluded seven studies is unlikely to be substantial. According to our research, the number of long-term studies are much smaller than that of short-term studies, which may be owing to the difficulty to obtain higher-resolution exposure assessment data and high study costs over long-terms. Future studies on the cardiovascular effect of long-term PM exposure are encouraged to better clarify the underlying scientific questions.

In conclusion, our study results showed that exposure to PM was associated with increases in the levels of circulating CRP, which is a classical marker of inflammation. In addition, long-term exposure to PM was more strongly associated with increasing CRP level than short-term exposure. These results may help explain the increased CVD risk associated with exposure to PM as reported in previous epidemiological studies and may also add to the scientific basis for the health risk monitoring and disease prevention efforts related to ambient particulate air pollution.

Conflicts of interest

The authors declare that they have no competing financial interests.

Ethical approval

Ethical approval not required.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ijheh.2019.05.005.

References

Agusti, A., 2007. Systemic effects of chronic obstructive pulmonary disease: what we know and what we don't know (but should). Proc. Am. Thorac. Soc. 4, 522–525. https://doi.org/10.1513/pats.200701-004FM.

Atkinson, R.W., Kang, S., Anderson, H.R., Mills, I.C., Walton, H.A., 2014. Epidemiological time series studies of PM $_{2.5}$ and daily mortality and hospital admissions: a systematic review and meta-analysis. Thorax 69, 660–665. https://doi.org/10.1136/thoraxjnl-2013-204492.

Bind, M.-A., Baccarelli, A., Zanobetti, A., Tarantini, L., Suh, H., Vokonas, P., Schwartz, J., 2012. Air pollution and markers of coagulation, inflammation, and endothelial function. Epidemiology 23, 332–340. https://doi.org/10.1097/EDE.0b013e31824523f0.

Brook, R.D., Rajagopalan, S., Pope, C.A., Brook, J.R., Bhatnagar, A., Diez-Roux, A.V., Holguin, F., Hong, Y., Luepker, R.V., Mittleman, M.A., Peters, A., Siscovick, D., Smith, S.C., Whitsel, L., Kaufman, J.D., American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Council on Nutrition, Physical Activity and Metabolism, 2010. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. Circulation 121, 2331–2378. https://doi.org/10.1161/CIR.0b013e3181dbece1.

Chen, R., Hu, B., Liu, Y., Xu, J., Yang, G., Xu, D., Chen, C., 2016. Beyond PM2.5: the role of ultrafine particles on adverse health effects of air pollution. Biochim. Biophys. Acta Gen. Subj. 1860, 2844–2855. https://doi.org/10.1016/j.bbagen.2016.03.019.

Chen, S.-Y., Chan, C.-C., Su, T.-C., 2017. Particulate and gaseous pollutants on inflammation, thrombosis, and autonomic imbalance in subjects at risk for cardiovascular disease. Environ. Pollut. 223, 403–408. https://doi.org/10.1016/j.envpol.2017.01.037.

Chuang, K.-J., Chan, C.-C., Su, T.-C., Lee, C.-T., Tang, C.-S., 2007. The effect of urban air pollution on inflammation, oxidative stress, coagulation, and autonomic dysfunction in Young adults. Am. J. Respir. Crit. Care Med. 176, 370–376. https://doi.org/10.1164/rccm.200611-1627OC.

Dabass, A., Talbott, E.O., Rager, J.R., Marsh, G.M., Venkat, A., Holguin, F., Sharma, R.K., 2018. Systemic inflammatory markers associated with cardiovascular disease and acute and chronic exposure to fine particulate matter air pollution (PM 2.5) among US NHANES adults with metabolic syndrome. Environ. Res. 161, 485–491. https://doi.org/10.1016/j.envres.2017.11.042.

Dabass, A., Talbott, E.O., Venkat, A., Rager, J., Marsh, G.M., Sharma, R.K., Holguin, F., 2016. Association of exposure to particulate matter (PM2.5) air pollution and biomarkers of cardiovascular disease risk in adult NHANES participants (2001–2008). Int. J. Hyg Environ. Health 219, 301–310. https://doi.org/10.1016/j.ijheh.2015.12.002.

Dadvand, P., Nieuwenhuijsen, M.J., Agusti, A., de Batlle, J., Benet, M., Beelen, R., Cirach, M., Martinez, D., Hoek, G., Basagana, X., Ferrer, A., Ferrer, J., Rodriguez-Roisin, R., Sauleda, J., Guerra, S., Anto, J.M., Garcia-Aymerich, J., 2014. Air pollution and biomarkers of systemic inflammation and tissue repair in COPD patients. Eur. Respir. J. 44, 603–613. https://doi.org/10.1183/09031936.00168813.

Dominici, F., Peng, R.D., Bell, M.L., Pham, L., McDermott, A., Zeger, S.L., Samet, J.M., 2006. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. J. Am. Med. Assoc. 295, 1127. https://doi.org/10.1001/jama.295.10.1127.

Emmerechts, J., Jacob, L., Van Kerckhoven, S., Loyen, S., Mathieu, C., Fierens, F., Nemery, B., N, T.S., H, M.F., 2012. Air pollution-associated procoagulant changes: the role of circulating microvesicles. J. Thromb. Haemost. 10, 96–106. https://doi.org/10.1111/j.1538-7836.2011.04557.x.

Gabay, C., Kushner, I., 1999. Acute-phase proteins and other systemic responses to inflammation. N. Engl. J. Med. 340, 448–454. https://doi.org/10.1056/NEJM199902113400607.

Green, R., Broadwin, R., Malig, B., Basu, R., Gold, E.B., Qi, L., Sternfeld, B., Bromberger, J.T., Greendale, G.A., Kravitz, H.M., Tomey, K., Matthews, K., Derby, C.A., Jackson, E.A., Green, R., Ostro, B., 2016. Long- and short-term exposure to air pollution and inflammatory/hemostatic markers in midlife women. Epidemiology 27, 211–220. https://doi.org/10.1097/EDE.0000000000000421.

Hajat, A., Allison, M., Diez-Roux, A.V., Jenny, N.S., Jorgensen, N.W., Szpiro, A.A., Vedal, S., Kaufman, J.D., 2015. Long-term exposure to air pollution and markers of inflammation, coagulation, and endothelial activation: a repeat-measures analysis in the Multi-Ethnic Study of Atherosclerosis (MESA). Epidemiology 26, 310–320. https://doi.org/10.1097/EDE.0000000000000267.

Hennig, F., Fuks, K., Moebus, S., Weinmayr, G., Memmesheimer, M., Jakobs, H., Bröcker-Preuss, M., Führer-Sakel, D., Möhlenkamp, S., Erbel, R., Jöckel, K.-H., Hoffmann, B., 2014. Association between source-specific particulate matter air pollution and hs-CRP: local traffic and industrial emissions. Environ. Health Perspect. 122, 703–710. https://doi.org/10.1289/ehp.1307081.

Higgins, J.P.T., 2011. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration Version 5.1.0[updated March 2011. https://doi.org/10.3233/PRM-2010-0129.

Higgins Julian PT, G.S., 2006. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6.

Hildebrandt, K., Rückerl, R., Koenig, W., Schneider, A., Pitz, M., Heinrich, J., Marder, V., Frampton, M., Oberdörster, G., Wichmann, H.E., Peters, A., 2009. Short-term effects of air pollution: a panel study of blood markers in patients with chronic pulmonary disease. Part. Fibre Toxicol. 6, 25. https://doi.org/10.1186/1743-8977-6-25.

Hoek, G., Brunekreef, B., Goldbohm, S., Fischer, P., van den Brandt, P.A., 2002. Association between mortality and indicators of traffic-related air pollution in The Netherlands: a cohort study. Lancet 360, 1203–1209. https://doi.org/10.1016/S0140-6736(02)11280-3.

Hoffmann, B., Moebus, S., Dragano, N., Stang, A., Möhlenkamp, S., Schmermund, A., Memmesheimer, M., Bröcker-Preuss, M., Mann, K., Erbel, R., Jöckel, K.H., 2009. Chronic residential exposure to particulate matter air pollution and systemic inflammatory markers. Environ. Health Perspect. 117, 1302–1308. https://doi.org/10.1289/ehp.0800362.

Jiménez, L.A., Drost, E.M., Gilmour, P.S., Rahman, I., Antonicelli, F., Ritchie, H., MacNee, W., Donaldson, K., 2002. PM 10 -exposed macrophages stimulate a proinflammatory response in lung epithelial cells via TNF-α. Am. J. Physiol. Cell. Mol. Physiol 282, L237–L248. https://doi.org/10.1152/ajplung.00024.2001.

Kamath, D.Y., Xavier, D., Sigamani, A., Pais, P., 2015. High sensitivity C-reactive protein (hsCRP) & cardiovascular disease: an Indian perspective. Indian J. Med. Res 142 261–8. https://doi.org/10.4103/0971-5916.166582.

Katsouyanni, K., Touloumi, G., Spix, C., Schwartz, J., Balducci, F., Medina, S., Rossi, G., Wojtyniak, B., Sunyer, J., Bacharova, L., Schouten, J.P., Ponka, A., Anderson, H.R., 1997. Short-term effects of ambient sulphur dioxide and particulate matter on mortality in 12 European cities: results from time series data from the APHEA project. Air Pollution and Health: a European Approach. BMJ 314, 1658–1663.

Kim, S.-Y., Peel, J.L., Hannigan, M.P., Dutton, S.J., Sheppard, L., Clark, M.L., Vedal, S., 2012. The temporal lag structure of short-term associations of fine particulate matter chemical constituents and cardiovascular and respiratory hospitalizations. Environ. Health Perspect. 120, 1094–1099. https://doi.org/10.1289/ehp.1104721.

Kloog, I., Coull, B.A., Zanobetti, A., Koutrakis, P., Schwartz, J.D., 2012. Acute and chronic effects of particles on hospital admissions in new-england. PLoS One 7 e34664. https://doi.org/10.1371/journal.pone.0034664.

Koenig, W., Sund, M., Fröhlich, M., Fischer, H.G., Löwel, H., Döring, A., Hutchinson, W.L., Pepys, M.B., 1999. C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. Circulation 99, 237–242.

Kushner, I., Rzewnicki, D., Samols, D., 2006. What does minor elevation of C-reactive protein signify? Am. J. Med. 119, 166. e17-166.e28. https://doi.org/10.1016/j.amjmed.2005.06.057.

Lee, H., Myung, W., Kim, D.K., Kim, S.E., Kim, C.T., Kim, H., 2017. Short-term air pollution exposure aggravates Parkinson's disease in a population-based cohort. Sci. Rep. 7, 44741. https://doi.org/10.1038/srep44741.

Lelieveld, J., Klingmüller, K., Pozzer, A., Pöschl, U., Fnais, M., Daiber, A., Münzel, T., 2019. Cardiovascular disease burden from ambient air pollution in Europe reassessed using novel hazard ratio functions. Eur. Heart J. https://doi.org/10.1093/eurheartj/ehz135.

Li, H., Cai, J., Chen, R., Zhao, Z., Ying, Z., Wang, L., Chen, J., Hao, K., Kinney, P.L., Chen, H., Kan, H., 2017a. Particulate matter exposure and stress hormone levels. Circulation 136, 618–627. https://doi.org/10.1161/CIRCULATIONAHA.116.026796.

Li, W., Dorans, K.S., Wilker, E.H., Rice, M.B., Ljungman, P.L., Schwartz, J.D., Coull, B.A., Koutrakis, P., Gold, D.R., Keaney, J.F.J., Vasan, R.S., Benjamin, E.J., Mittleman, M.A., 2017b. Short-term exposure to ambient air pollution and biomarkers of systemic inflammation: the Framingham heart study. Arterioscler. Thromb. Vasc. Biol. 37, 1793–1800. https://doi.org/10.1161/ATVBAHA.117.309799.

Li, Y., Rittenhouse-Olson, K., Scheider, W.L., Mu, L., 2012. Effect of particulate matter air pollution on C-reactive protein: a review of epidemiologic studies. Rev. Environ. Health. https://doi.org/10.1515/reveh-2012-0012.

Liu, C., Cai, J., Qiao, L., Wang, H., Xu, W., Li, H., Zhao, Z., Chen, R., Kan, H., 2017. The acute effects of fine particulate matter constituents on blood inflammation and coagulation. Environ. Sci. Technol. 51, 8128–8137. https://doi.org/10.1021/acs.est.7b00312.

Mirowsky, J.E., Peltier, R.E., Lippmann, M., Thurston, G., Chen, L.-C., Neas, L., Diaz-Sanchez, D., Laumbach, R., Carter, J.D., Gordon, T., 2015. Repeated measures of inflammation, blood pressure, and heart rate variability associated with traffic exposures in healthy adults. Environ. Health (Nagpur) 14, 66. https://doi.org/10.1186/s12940-015-0049-0.

Nemmar, A., Hoet, P.H.M., Vanquickenborne, B., Dinsdale, D., Thomeer, M., Hoylaerts, M.F., Vanbilloen, H., Mortelmans, L., Nemery, B., 2002. Passage of inhaled particles into the blood circulation in humans. Circulation 105, 411–414. https://doi.org/10.1161/HC0402.104118.

Newby, D.E., Mannucci, P.M., Tell, G.S., Baccarelli, A.A., Brook, R.D., Donaldson, K., Forastiere, F., Franchini, M., Franco, O.H., Graham, I., Hoek, G., Hoffmann, B., Hoylaerts, M.F., Künzli, N., Mills, N., Pekkanen, J., Peters, A., Piepoli, M.F.,

Rajagopalan, S., Storey, R.F., ESC Working Group on Thrombosis, European Association for Cardiovascular Prevention and Rehabilitation, ESC Heart Failure Association, 2015. Expert position paper on air pollution and cardiovascular disease. Eur. Heart J. 36, 83–93. https://doi.org/10.1093/eurheartj/ehu458.

Ostro, B., Lipsett, M., Reynolds, P., Goldberg, D., Hertz, A., Garcia, C., Henderson, K.D., Bernstein, L., 2010. Long-term exposure to constituents of fine particulate air pollution and mortality: results from the California teachers study. Environ. Health Perspect. 118, 363–369. https://doi.org/10.1289/ehp.0901181.

Ostro, B., Malig, B., Broadwin, R., Basu, R., Gold, E.B., Bromberger, J.T., Derby, C., Feinstein, S., Greendale, G.A., Jackson, E.A., Kravitz, H.M., Matthews, K.A., Sternfeld, B., Tomey, K., Green, R.R., Green, R., 2014. Chronic PM2.5 exposure and inflammation: determining sensitive subgroups in mid-life women. Environ. Res. 132, 168–175. https://doi.org/10.1016/j.envres.2014.03.042.

Pedersen, M., Gehring, U., Beelen, R., Wang, M., Giorgis-Allemand, L., Andersen, A.-M.N., Basagaña, X., Bernard, C., Cirach, M., Forastiere, F., de Hoogh, K., Gražulevičvienė, R., Gruzieva, O., Hoek, G., Jedynska, A., Klümper, C., Kooter, I.M., Krämer, U., Kukkonen, J., Porta, D., Postma, D.S., Raaschou-Nielsen, O., van Rossem, L., Sunyer, J., Sørensen, M., Tsai, M.-Y., Vrijkotte, T.G.M., Wilhelm, M., Nieuwenhuijsen, M.J., Pershagen, G., Brunekreef, B., Kogevinas, M., Slama, R., 2015. Elemental constituents of particulate matter and newborn's size in eight european cohorts. Environ. Health Perspect. 124. https://doi.org/10.1289/ehp.1409546.

Pope, C.A., Ezzati, M., Dockery, D.W., 2009. Fine-particulate air pollution and life expectancy in the United States. N. Engl. J. Med. 360, 376–386. https://doi.org/10.1056/NEJMsa0805646.

Pope, C.A., Hansen, M.L., Long, R.W., Nielsen, K.R., Eatough, N.L., Wilson, W.E., Eatough, D.J., Eatough, D.J., 2004. Ambient particulate air pollution, heart rate variability, and blood markers of inflammation in a panel of elderly subjects. Environ. Health Perspect. 112, 339–345.

Ramage, L., Guy, K., 2004. Expression of C-reactive protein and heat-shock protein-70 in the lung epithelial cell line A549, in response to PM10 exposure. Inhal. Toxicol. 16, 447–452. https://doi.org/10.1080/08958370490439614.

Ridker, P.M., 2003. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation 107, 363–369. https://doi.org/10.1161/01.CIR.0000053730.47739.3C.

Robson, J., 2008. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Heart 94, 1331–1332. https://doi.org/10.1136/hrt.2008.150979.

Rodosthenous, R.S., Kloog, I., Colicino, E., Zhong, J., Herrera, L.A., Vokonas, P., Schwartz, J., Baccarelli, A.A., Prada, D., 2018. Extracellular vesicle-enriched microRNAs interact in the association between long-term particulate matter and blood pressure in elderly men. Environ. Res. 167, 640–649. https://doi.org/10.1016/j.envres.2018.09.002.

Routledge, H.C., Ayres, J.G., 2005. Air pollution and the heart. Occup. Med. (Chic. Ill) 55, 439–447. https://doi.org/10.1093/occmed/kqi136.

Rückerl, R., Greven, S., Ljungman, P., Aalto, P., Antoniades, C., Bellander, T., Berglind, N., Chrysohoou, C., Forastiere, F., Jacquemin, B., von Klot, S., Koenig, W., Küchenhoff, H., Lanki, T., Pekkanen, J., Perucci, C.A., Schneider, A., Sunyer, J., Peters, A., 2007. Air pollution and inflammation (Interleukin-6, C-reactive protein, fibrinogen) in myocardial infarction survivors. Environ. Health Perspect. 115, 1072–1080. https://doi.org/10.1289/ehp.10021.

Rückerl, R., Hampel, R., Breitner, S., Cyrys, J., Kraus, U., Carter, J., Dailey, L., Devlin, R.B., Diaz-Sanchez, D., Koenig, W., Phipps, R., Silbajoris, R., Soentgen, J., Soukup, J., Peters, A., Schneider, A., 2014. Associations between ambient air pollution and blood markers of inflammation and coagulation/fibrinolysis in susceptible populations. Environ. Int. 70, 32–49. https://doi.org/10.1016/j.envint.2014.05.013.

Rückerl, R., Schneider, A., Hampel, R., Breitner, S., Cyrys, J., Kraus, U., Gu, J., Soentgen, J., Koenig, W., Peters, A., 2016. Association of novel metrics of particulate matter with vascular markers of inflammation and coagulation in susceptible populations -results from a panel study. Environ. Res. 150, 337–347. https://doi.org/10.1016/j.envres.2016.05.037.

Sakkinen, P., Abbott, R.D., Curb, J.D., Rodriguez, B.L., Yano, K., Tracy, R.P., 2002. C-reactive protein and myocardial infarction. J. Clin. Epidemiol. 55, 445–451. https://doi.org/10.1016/S0895-4356(01)00502-9.

Samet, J.M., Dominici, F., Curriero, F.C., Coursac, I., Zeger, S.L., 2000. Fine particulate air pollution and mortality in 20 U.S. Cities, 1987–1994. N. Engl. J. Med. 343, 1742–1749. https://doi.org/10.1056/NEJM200012143432401.

Sandhu, R.S., Petroni, D.H., George, W.J., 2005. Ambient particulate matter, C-reactive protein, and coronary artery disease. Inhal. Toxicol. 17, 409–413. https://doi.org/10.1080/08958370590929538.

Shrivastava, A.K., Singh, H.V., Raizada, A., Singh, S.K., 2015. C-reactive protein, inflammation and coronary heart disease. Egypt. Hear. J. 67, 89–97. https://doi.org/10.1016/J.EHJ.2014.11.005.

Strak, M., Hoek, G., Godri, K.J., Gosens, I., Mudway, I.S., van Oerle, R., Spronk, H.M.H., Cassee, F.R., Lebret, E., Kelly, F.J., Harrison, R.M., Brunekreef, B., Steenhof, M., Janssen, N.A.H., 2013. Composition of PM affects acute vascular inflammatory and coagulative markers - the RAPTES project. PLoS One 8 e58944. https://doi.org/10.1371/journal.pone.0058944.

Study Quality Assessment Tools, National Heart, Lung, and Blood Institute (NHLBI) [WWW Document], n.d. URL https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools (accessed 6.9.18)..

Tecer, L.H., Alagha, O., Karaca, F., Tuncel, G., Eldes, N., 2008. Particulate matter ($PM_{2.5}$, $PM_{10\text{-}2.5}$, and PM_{10}) and children's hospital admissions for asthma and respiratory diseases: a bidirectional case-crossover study. J. Toxicol. Environ. Health Part A 71, 512–520. https://doi.org/10.1080/15287390801907459.

The Emerging Risk Factors Collaboration‡, 2010. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 375, 132–140. https://doi.org/10.1016/S0140-6736(09)61717-7.

Upadhyay, S., Ganguly, K., Stoeger, T., Semmler-Bhenke, M., Takenaka, S., Kreyling, W.G., Pitz, M., Reitmeir, P., Peters, A., Eickelberg, O., Wichmann, H.E., Schulz, H., 2010. Cardiovascular and inflammatory effects of intratracheally instilled ambient dust from Augsburg, Germany, in spontaneously hypertensive rats (SHRs). Part. Fibre Toxicol. 7, 27. https://doi.org/10.1186/1743-8977-7-27.

Valavanidis, A., Fiotakis, K., Vlachogianni, T., 2008. Airborne particulate matter and human health: toxicological assessment and importance of size and composition of particles for oxidative damage and carcinogenic mechanisms. J. Environ. Sci. Health Part C 26, 339–362. https://doi.org/10.1080/10590500802494538.

Veronesi, B., Oortgiesen, M., Carter, J.D., Devlin, R.B., 1999. Particulate matter initiates inflammatory cytokine release by activation of capsaicin and acid receptors in a human bronchial epithelial cell line. Toxicol. Appl. Pharmacol. 154, 106–115. https://doi.org/10.1006/taap.1998.8567.

Viehmann, A., Hertel, S., Fuks, K., Eisele, L., Moebus, S., Möhlenkamp, S., Nonnemacher, M., Jakobs, H., Erbel, R., Jöckel, K.H., Hoffmann, B., 2015. Long-term residential exposure to urban air pollution, and repeated measures of systemic blood markers of inflammation and coagulation. Occup. Environ. Med. 72, 656–663. https://doi.org/10.1136/oemed-2014-102800.

Vogel, C.F.A., Sciullo, E., Wong, P., Kuzmicky, P., Kado, N., Matsumura, F., 2005. Induction of proinflammatory cytokines and C-reactive protein in human macrophage cell line U937 exposed to air pollution particulates. Environ. Health Perspect. 113, 1536–1541.

Wang, C., Chen, R., Zhao, Z., Cai, J., Lu, J., Ha, S., Xu, X., Chen, X., Kan, H., 2015. Particulate air pollution and circulating biomarkers among type 2 diabetic mellitus patients: the roles of particle size and time windows of exposure. Environ. Res. 140, 112–118. https://doi.org/10.1016/j.envres.2015.03.026.

Wang, G., Jiang, R., Zhao, Z., Song, W., 2013. Effects of ozone and fine particulate matter (PM2.5) on rat system inflammation and cardiac function. Toxicol. Lett. 217, 23–33. https://doi.org/10.1016/j.toxlet.2012.11.009.

Wang, M., Utell, M.J., Schneider, A., Zareba, W., Frampton, M.W., Oakes, D., Hopke, P.K., Wiltshire, J., Kane, C., Peters, A., Breitner, S., Chalupa, D., Rich, D.Q., 2016. Does total antioxidant capacity modify adverse cardiac responses associated with ambient ultrafine, accumulation mode, and fine particles in patients undergoing cardiac rehabilitation? Environ. Res. 149, 15–22. https://doi.org/10.1016/j.envres.2016.04.031.

Wilson, P.W., D'Agostino, R.B., Levy, D., Belanger, A.M., Silbershatz, H., Kannel, W.B., 1998. Prediction of coronary heart disease using risk factor categories. Circulation 97, 1837–1847. https://doi.org/10.1161/01.CIR.97.18.1837.

Wolf, K., Popp, A., Schneider, A., Breitner, S., Hampel, R., Rathmann, W., Herder, C., Roden, M., Koenig, W., Meisinger, C., Peters, A., 2016. Association between long-term exposure to air pollution and biomarkers related to insulin resistance, subclinical inflammation, and adipokines. Diabetes 65, 3314–3326. https://doi.org/10.2337/db15-1567.

Wu, C.-F., Shen, F.-H., Li, Y.-R., Tsao, T.-M., Tsai, M.-J., Chen, C.-C., Hwang, J.-S., Hsu, S.H.-J., Chao, H., Chuang, K.-J., Chou, C.C.K., Wang, Y.-N., Ho, C.-C., Su, T.-C., 2016. Association of short-term exposure to fine particulate matter and nitrogen dioxide with acute cardiovascular effects. Sci. Total Environ. 569–570, 300–305. https://doi.org/10.1016/j.scitotenv.2016.06.084.

Wu, S., Deng, F., Wei, H., Huang, J., Wang, H., Shima, M., Wang, X., Qin, Y., Zheng, C., Hao, Y., Guo, X., 2012. Chemical constituents of ambient particulate air pollution and biomarkers of inflammation, coagulation and homocysteine in healthy adults: a prospective panel study. Part. Fibre Toxicol. 9, 49. https://doi.org/10.1186/1743-8977-9-49.

Yan, Z., Jin, Y., An, Z., Liu, Y., Samet, J.M., Wu, W., 2016. Inflammatory cell signaling following exposures to particulate matter and ozone. Biochim. Biophys. Acta Gen. Subj. 1860, 2826–2834. https://doi.org/10.1016/j.bbagen.2016.03.030.

Yang, T.-H., Masumi, S.-I., Weng, S.-P., Chen, H.-W., Chuang, H.-C., Chuang, K.-J., 2015. Personal exposure to particulate matter and inflammation among patients with periodontal disease. Sci. Total Environ. 502, 585–589. https://doi.org/10.1016/j.scitotenv.2014.09.081.