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Effect of particulate matter air pollution on C-reactive protein: a review of epidemiologic studies

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Abstract

Inflammatory response is implicated as a biologic mechanism that links particulate matter (PM) air pollution with health effects. C-reactive protein (CRP), an important acute-phase reactant with profound proinflammatory properties, is used clinically as an indicator of the presence and intensity of inflammation. In vitro and in vivo animal studies suggest that CRP levels increase in response to PM exposure, but there was no consistency in epidemiologic studies. Herein, a systematic review was conducted to examine the association between PM exposure and serum CRP levels in humans. Elevated CRP levels were consistently found among children, and CRP elevations were also observed among healthy adults, albeit requiring higher peak levels of PM exposure. PM-induced CRP responses were not consistently found in adults with chronic inflammatory conditions, perhaps because of the use of anti-inflammatory medications in this population. Of the eight examined randomized trials, only one trial with a longer intervention period supported the effect of PM exposure on CRP concentrations. To provide conclusive evidence, further epidemiologic studies are needed to better quantify the magnitude of CRP level changes in response to PM with well-defined study populations and better control of various confounding factors.

Keywords

air pollution; C-reactive protein; epidemiologic studies; inflammation; particulate matter

Introduction

Particulate matter (PM) air pollution is a suspended mixture of solid and liquid particles of various sizes, composition, and origin (1). PM is broadly categorized by aerodynamic properties because these properties are associated with chemical composition and sources of the PM and govern their deposition within the respiratory system (1). PM with aerodynamic diameter $< 10 \mu\text{m}$ (PM_{10}) derives predominantly from crushing and grinding processes, and most PM_{10} deposits in the extrathoracic and upper tracheobronchial regions (2, 3). Fine particles, or PM with aerodynamic diameter $< 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$), originate mostly from combustion sources, like vehicle emissions, coal burning, and industrial processes (2, 3). $\text{PM}_{2.5}$ can be inhaled more deeply into the lungs, with a portion depositing in the alveoli and entering the pulmonary circulation and presumably the systemic circulation (4). Ultrafine

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particles, or PM with aerodynamic diameter $< 0.1 \mu\text{m}$ ($\text{PM}_{0.1}$), primarily derive from vehicle emissions and may translocate from the alveoli to the circulatory system (3).

Compelling epidemiologic evidence indicates that elevated PM levels increase mortality and morbidity from cardiovascular diseases (CVD) (5, 6). For non-fatal events, an increase of $10 \mu\text{g}/\text{m}^3$ of PM has been associated with a 10 % – 24 % increase in the risk of a cardiovascular event (7 – 9). Every $10\text{-}\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentration was estimated to increase short-term daily cardiovascular death rates by approximately 1 %, whereas for chronic exposure, every $10\text{-}\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ was associated with a 10 % – 30 % elevation in cardiovascular deaths (3). In addition, exposure to PM has been associated with excess risk of several cancers, in particular, lung cancer. About 10 % of lung cancers can be attributable to ambient air pollution (10). Each $10\text{-}\mu\text{g}/\text{m}^3$ increase in ambient $\text{PM}_{2.5}$ concentrations was associated with an approximately 8 % increased risk of lung cancer mortality (11).

Inflammatory response is implicated as a possible biologic mechanism underlying PM exposure-related health events. Certain PM components, like metals and endotoxin, were found to possess proinflammatory properties (3, 12– 14). PM deposited in the alveoli of the lung can induce local inflammation, which may subsequently elicit a systemic inflammatory state (2, 6, 15– 17). Ultrafine and soluble constituents of PM can penetrate into the systemic circulation through the pulmonary capillary bed, and this directly leads to a systemic inflammatory cascade (2, 18). Acute-phase proteins are key markers of systemic inflammation (19). C-reactive protein (CRP) is the most sensitive acute-phase reactant and has profound proinflammatory properties. Serum CRP measurement has widespread clinical use because serum CRP reflects the presence and intensity of inflammation (20). CRP has been shown to predict incident myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death (21). CRP is also found within macrophages of atheromatous plaques, and it may have a direct effect on the development and aggravation of atherosclerosis (22). In addition to its role in the pathogenesis of CVD, there is also some evidence that elevated CRP levels are associated with cancer risk and poor prognosis, as well as the development of rheumatic diseases (23, 24).

Serum CRP concentration is usually low in normal individuals but can be up-regulated rapidly in response to injury, infection, and other inflammatory stimuli (25, 26). Several in vitro studies suggest that CRP levels increase in response to PM exposure (27 – 30). Most animal studies provide strong evidence that CRP levels increase after PM exposure (31 – 35). There is also some suggestive evidence that animal models of certain human diseases have different CRP responses to PM exposure. Significantly stronger PM-induced CRP responses were observed in spontaneously hypertensive rats, compared with rats with normal blood pressure (32, 33). In another study, serum CRP levels increased significantly in nondiabetic rats after $\text{PM}_{2.5}$ exposure, but increase of CRP levels in diabetic rats did not reach statistical significance (35). However, animals in some of the studies were exposed to PM through routes other than inhalation or through inhalation but in a very high dose. In two of these studies, animals were exposed by intratracheal instillation (34, 35). In the other three studies, animals were exposed through inhalation using very high doses of PM ($918\text{--}15,600 \mu\text{g}/\text{m}^3$), which is more than ten times higher than the ambient level (31 – 33). Moreover, interspecies extrapolation of findings from animals to humans is an issue. Therefore, epidemiologic studies are still necessary to make conclusions concerning the relationship of PM exposure to CRP levels.

Although many epidemiologic studies have been conducted to explore this possible association, the results are far from consistent, and a systematic review of epidemiologic evidence has not been published to date. The present article systematically assesses the

epidemiologic studies regarding serum CRP concentration changes in response to PM exposure and evaluates whether serum CRP can serve as a possible intermediate marker to indicate that systemic inflammation has been induced by PM exposure among humans. Further, we will examine whether PM differentially affects certain subpopulations.

Methods

A systematic literature review was conducted to examine the association between PM exposure and serum CRP levels in humans. PubMed, OVID Medline, and Web of Science databases were searched for epidemiologic studies with terms as follows: (1) outcome: C-reactive protein, CRP, or inflammation, (2) exposure: particulate matter, PM, or air pollution. Search results from “outcome” and “exposure” were combined. From the identified publications, we examined the reference lists to locate additional relevant studies. We restricted the search to studies conducted among human subjects and written in English. There was no publication date restriction of the included publications.

Data were extracted using a standardized form with a full description of the study characteristics (authors, publication year, study location and period, characteristics of study population, sample size, baseline CRP levels, measurement methods of CRP, PM aerodynamic diameter and peak levels, lag time between PM and CRP measures, main results of CRP levels in response to PM exposure). Where possible, CRP concentrations were expressed in milligrams per liter (mg/L) and PM measures in micrograms per cubic meters ($\mu\text{g}/\text{m}^3$). The studies were summarized based on their study designs (cross-sectional study, longitudinal study, and randomized crossover trial) and major characteristics of the study participants, especially their health status. Different study designs were defined based on the following criteria. A cross-sectional study is an observational study conducted in a defined population at one particular time and compares CRP concentrations among individuals with different PM exposure levels at one specific time. A longitudinal study is an observational study with multiple measurements of CRP among the same group of study participants over periods with different levels of PM. In randomized crossover trials, study participants are allocated into groups with a certain level of PM first and switched to another exposure level after a wash-out period. CRP concentrations are measured and compared upon completion of each exposure session.

We decided not to undertake a meta-analysis and provide quantitative summary measures because of the great heterogeneities across the reviewed studies in characteristics of study populations, laboratory methods to measure serum CRP concentrations, PM levels and properties, lag time between PM exposure and CRP measures, and statistical methods.

Results and discussion

A total of 44 publications that met the aforementioned selection criteria were included in this review. Results for the cross-sectional studies, longitudinal studies, and randomized trials are presented in Tables 1 – 3, respectively.

Cross-sectional studies

Table 1 summarizes results from 15 cross-sectional studies. We presented the results in children and adults separately because of their different susceptibilities to air pollution.

Cross-sectional studies in children

Significant positive associations between PM exposure and CRP concentration were found in all of the four cross-sectional studies conducted among children younger than 18 years. A

study conducted among 2094 Japanese children found that an increased CRP above the 90th percentile (1.4 mg/L) was significantly associated with 3-year mean levels of suspended particulate matter (SPM) [odds ratio (OR) = 1.49, 95% confidence interval (CI) 1.07 – 2.06] (36). A study of 374 children in Iran found that levels of PM₁₀ on the previous 7 days were significantly associated with CRP concentration ($p < 0.0001$) (37). Another two studies in Mexico examined the long-term effects of PM and found that children in heavily polluted Mexico City had significantly higher levels of blood CRP compared with those in the control city where air pollution level was low (38, 39).

Cross-sectional studies in adults

In contrast to studies in children, weaker associations were found in the cross-sectional studies conducted in adults, regardless of PM size, lag time of exposure, and smoking or health status of study participants. Three large-scale cross-sectional surveys were conducted to examine the effect of PM₁₀ on CRP level with lag time of 0 – 7 days, 28-day average, and 1-year average, but none of these three studies reported a positive response of CRP to different PM₁₀ exposure levels (40 – 43). Similar null results were found in four out of the five cross-sectional studies that focused on PM_{2.5}, although the effects of various lag time were examined (41, 44, 45). One study suggested a difference of 3.91 $\mu\text{g}/\text{m}^3$ in annual PM_{2.5} exposure was significantly associated with a 23.9 % increase of CRP in men, but the association lost significance after adjusting for daily PM_{2.5} level, which might indicate that daily variations in PM concentrations exerted a short-term effect on blood markers of inflammation (46).

In contrast to the largely null findings of the cross-sectional studies conducted among the randomly selected adults, one study conducted among adults with type 1 or 2 diabetes found that the 7-day mean of PM₁₀ was significantly associated with CRP changes (47).

Two cross-sectional studies compared CRP levels among women using different types of cooking fuels, with PM levels in households using traditional fuel about three times higher than those in the households that use clean fuel. In one study that found significantly higher levels of CRP among traditional users, subjects in the two groups were matched on age, years of cooking, and secondhand smoke exposure, and this study also has larger sample size (48). Another study that failed to detect any difference in CRP reported that there was a significant difference in age, years of cooking, and secondhand smoke exposure between the two groups, and a dried blood spot was used to measure CRP (49). The inconsistent findings of these two studies might stress the importance of controlling for confounders and using a more sensitive assay to measure CRP.

The stronger associations observed in children might relate to their higher susceptibility to the adverse effects of air pollutants than adults. This might be because children spend more time outdoors and have higher activity levels and lung volume per unit body weight, all of which can lead to an increased PM dose per lung surface area and greater adverse effects on the developing lungs and immune system (79). In addition, adults are more likely to have some medical inflammatory conditions and take anti-inflammatory medications, which may obscure the PM-induced CRP reactions.

Longitudinal studies

Table 2 shows results of 21 longitudinal studies, which includes 20 panel studies with repeated measures over a short period. We summarized the studies conducted among occupational and general populations separately. We further explored whether healthy adults and adults with different medical conditions had different CRP responses to the PM.

Longitudinal studies in occupational populations

Because the levels and composition of PM in occupational settings might differ from ambient PM, occupational studies were reviewed separately. Three occupational studies were identified, and all demonstrated significantly positive associations between PM exposure and CRP levels. The three studies all had very high peak levels of PM compared with ambient levels and great variations over the study period. In a panel of 37 steel production plant workers, CRP levels were found to have a significant positive correlation with levels of PM₁ (range 1.7 – 30.5 µg/m³) and coarse PM (range 71 – 1190 µg/m³) (50). The CRP levels increased by 17 % 2 days after working with welding, cutting, grinding, and in foundries in 73 subjects (PM_{2.5} range 20 – 1380 µg/m³; PM₁₀ range 150 – 1780 µg/m³) (51). Among 24 welders, the exposure to welding fumes was associated with an increase in CRP levels of 0.90 mg/L (95 % CI 0.17 – 1.64) 24 h after exposure (PM_{2.5} range 890 – 2440 µg/m³) (52).

These positive results suggested that the high PM exposure levels in the occupational setting might be able to induce synthesis of CRP, and the larger variations of PM levels could enable the detection of meaningful changes of CRP levels. In addition, because occupational populations are mostly likely to be healthy and less likely to use medications that might affect CRP levels, the effect of PM is more easily detected.

Longitudinal studies in healthy adults

We identified ten longitudinal studies conducted among healthy adults, in which most of the study participants were non-smokers. No consistent results were observed in these ten studies. We also examined whether the effects of PM on CRP levels were stronger among populations with higher levels of PM exposure. Because the PM levels in studies conducted among the general population were much lower than that in occupational studies, the values set by the US National Ambient Air Quality Standards (NAAQS) were used as the cut-off for high and low PM exposure.

For PM_{2.5}, four studies were conducted among non-smoking healthy adults with peak levels of PM_{2.5} higher than the NAAQS (24-h average PM_{2.5} 35 µg/m³). Three of these four studies supported a statistically significant or borderline significant association between PM_{2.5} exposure and blood CRP levels (53 – 55), and one did not support, such association (56). Null results were also reported in two other studies with peak exposure levels lower than the NAAQS (57, 58).

For PM₁₀, four longitudinal studies were conducted among healthy adults. One study with a high peak PM level (418 µg/m³), about three times that of the NAAQS (24-h average PM₁₀ of 150 µg/m³), found that the CRP levels increased significantly with increased previous 3-day mean PM₁₀ levels among 112 non-smoking elderly without cardiac diseases (59). Another panel study conducted over the period of the Beijing Olympic Games found that the fraction of the CRP above the detection limit value (0.3 mg/L) declined from 55 % in the pre-Olympic period (peak PM_{2.5} 219.1 µg/m³) to 46 % during the Olympic period (peak PM_{2.5} 171.4 µg/m³), and the fraction was lowest (36 %) in the post-Olympic period (peak PM_{2.5} 268.2 µg/m³) (60). Results were not consistent for the other two studies with lower peak PM₁₀ levels. One study found that CRP was significantly associated with 1- and 3-day average PM₁₀ levels (range for the 1-day average 29.5 – 83.4 µg/m³; range for the 3-day average 22.2 – 87.2 µg/m³) among 76 healthy young non-smokers (55). The other study suggested no relationship between PM₁₀ [interquartile range (IQR) 23.8 – 39.2, maximum 110.1 µg/m³] and CRP measurements with time lags from 1 to 4 days before blood sampling among 40 healthy adults, even in the analyses limited to non-smokers (61).

Another classic longitudinal study with a relatively high peak level of total suspended particles (TSP) (TSP range 7 – 176 $\mu\text{g}/\text{m}^3$), the original indicator for particulate air pollutants used before 1987, found that an increase of 26 $\mu\text{g}/\text{m}^3$ in TSP exposure raised the odds of having a CRP level above the 90th percentile by 50 % among 631 men free of CVD (62).

Despite the inconsistent findings among the healthy general population, there is suggestive evidence that higher PM levels during the observation period tended to induce stronger inflammatory responses. However, because the peak PM levels in the general population were much lower than occupational studies, the effects from PM were more likely to be outweighed by some other time-variant factors that might transiently alter CRP levels, like acute infections, medication use, and the inherent physiologic variability of CRP. These time-variant factors were not effectively controlled in most of the reviewed studies. Another limitation of these studies is the varied criteria used to define “healthy adults”. Most studies just excluded individuals with CVD, and some further excluded individuals with hypertension, diabetes, chronic obstructive pulmonary disease (COPD), and/or infectious diseases. Failure to exclude individuals with inflammatory conditions in some studies might also mask the relatively moderate effects from PM exposure.

Longitudinal studies in adults with chronic inflammatory conditions

PM-induced CRP responses are also inconsistent among adults with chronic inflammatory conditions, like CVD, COPD, diabetes, and obesity.

- **Adults with CVD:** Among adults with CVD, one study with a relatively high peak level of PM_{10} (74.5 $\mu\text{g}/\text{m}^3$) supported a positive relationship with CRP levels (63), whereas the other study with a relatively low peak level of PM_{10} (24.63 $\mu\text{g}/\text{m}^3$) did not (64). However, no clear pattern was observed for $\text{PM}_{2.5}$ among CVD patients. Only one study found a significant increase in CRP 2 days after relatively low level of PM exposure (peak $\text{PM}_{2.5}$ 27.4 $\mu\text{g}/\text{m}^3$) among ischemic heart disease patients (65). No statistically significant associations were found for the other three studies, despite the varied peak levels of $\text{PM}_{2.5}$ across studies (33.9, 66.77, and 83.7 $\mu\text{g}/\text{m}^3$, respectively) (57, 63, 64). Another study was conducted among a special group of CVD patients (i.e., myocardial infarction survivors), and no associations were found between $\text{PM}_{2.5}$ and PM_{10} with serum CRP levels from immediately preceding blood collection up to 4 days (66).
- **Adults with COPD:** No associations between PM exposure and CRP level were found in the two studies conducted among individuals with COPD (57, 67).
- **Adults with elements of metabolic syndrome:** The results from several longitudinal studies conducted among adults with certain other chronic inflammation conditions, including obesity, overweight, and/or diabetes, were also inconsistent, and no obvious patterns about the effect of PM levels on CRP measures were observed. For patients with diabetes, one study reported that the 5-day mean $\text{PM}_{2.5}$ level (peak level 28 $\mu\text{g}/\text{m}^3$) was significantly associated with elevated CRP levels (58), whereas two other studies did not support any relationship between $\text{PM}_{2.5}$ (peak level < 35 $\mu\text{g}/\text{m}^3$) and PM_{10} (peak level 133.0 $\mu\text{g}/\text{m}^3$) exposure and CRP concentration (68, 69). Two studies were conducted among overweight or obese individuals. No notable associations among 3-, 30-, or 60-day mean $\text{PM}_{2.5}$ levels (mean levels 33.4, 20.7, and 19.1 $\mu\text{g}/\text{m}^3$, respectively) and CRP were found among 115 overweight or obese women (70), whereas another study found that 5-day mean $\text{PM}_{2.5}$ (peak level 28 $\mu\text{g}/\text{m}^3$) was significantly associated with elevated CRP levels among 14 obese elderly, but not among 4 elderly with concurrent diabetes, obesity, and hypertension (58).

In summary, we did not find that adults with chronic inflammatory conditions had enhanced CRP responses to PM exposure. This is contrary to previous evidence that suggested that individuals with medical conditions associated with chronic inflammation might be more vulnerable to the inflammatory effects of PM (80) as well as previous animal studies that suggested different CRP responses among animals with hypertension and diabetes to the same dose of PM (32, 33, 35). One likely reason for the lack of association might relate to their high prevalence of lipid-lowering drugs use, particularly statins, which have been shown to reduce CRP synthesis, as well as their high likelihood of using other anti-inflammatory medications (81). Because few of the reviewed studies have controlled for medication use, a transient alteration of CRP levels associated with disease progression and medication use might overwhelm the effect of PM. The lack of controlling for the time-variant confounders may also explain why no obvious responses related to peak levels of PM were observed among adults with chronic inflammatory conditions.

Randomized crossover trials

The results for eight randomized crossover trials studying associations between PM exposure and CRP levels are presented in Table 3.

Only one randomized crossover trial with a relatively long intervention period found a significantly positive association between PM exposure and CRP levels. HEPA filters were installed in the main activity rooms and bedrooms of 45 healthy adults in consecutive 7-day periods, and the filtration reduced indoor fine particle concentrations by 60 % compared with the non-filtered period. A 32.6% (4.4 % – 60.9 %) decrease in CRP level was found through using HEPA filtration (71).

None of the other seven randomized crossover trials with shorter intervention period found significant associations between PM and CRP levels. Five out of the seven trials were conducted among healthy non-smokers, and the intervention periods varied from 1 to 48 h. CRP levels were not significantly different among 20 healthy subjects 5 h after exposure to control air or welding fumes for 1-h period (72). No increase in CRP was found among 13 healthy participants who were exposed to diesel exhaust for 2 h (73). Exposure to wood smoke or clean air in a chamber for 4 h on two separate occasions did not lead to a significant difference in serum CRP levels (74). No significant differences in CRP levels were observed after exposure to particle-rich or filtered air for 24 h in 29 subjects (75). Also, filtration of indoor air for 48 h in homes did not induce changes of CRP levels among 21 non-smoking couples compared with non-filtered air (76). The other two trials with null results were conducted among individuals with chronic inflammatory conditions. Serum CRP levels were largely unchanged 6 – 8 h after exposure to concentrated ambient fine and ultrafine particles or filtered air for 2 h in patients with stable coronary heart disease (77). Similar null results were found among 15 COPD patients who were exposed to diesel exhaust and filtered air for 1 h on two separate occasions (78).

The largely negative findings of the randomized trials, with the exception of one trial with a longer intervention period (7 days), might suggest that short exposure duration is not sufficient to induce a detectable inflammatory response. Another limitation of some experimental studies is that study participants in the trials were exposed to diesel exhaust, welding fume, or wood smoke, which might not reproduce PM in the natural ambient environment with regards to size and components.

Methodologic issues

Among the included studies, individualized PM exposure data were generally not available and using monitored PM data within certain geographic areas may not represent the actual

exposure levels for each individual, which could lead to exposure misclassification. If the exposure misclassification is non-differential, the possible associations between PM exposure and CRP levels were more likely to be biased toward null. However, the effects of differential misclassification can go in either direction and are dependent on the individual circumstances of the problem. The reviewed studies also differed in constituents of PM and lag time between PM exposure and CRP measures, which make summarizing the findings complicated. PM contains a broad range of toxic substances, including transition metals, organic compounds, and biologic fractions. Previous studies suggest that the components of PM exhibited temporal patterns and also varied across geographic locations (82, 83). The same concentration of PM with different components may have varied ability to induce biologic responses (84). However, among the reviewed studies, very few analyzed the components of collected PM. It will be more informative to explore the effects of individual components of PM in future studies. In addition, a variety of laboratory methods were used to measure CRP in the included studies, and the assays might have different sensitivities, which may partially explain the inconsistent results across studies and also the limited possibility of conducting a meta-analysis. Another issue is the relatively small sample size among some of the longitudinal studies and randomized trials. Most of the longitudinal studies had a sample size fewer than 100, and all the randomized trials had fewer than 50 participants. Therefore, we cannot exclude the possibility that some of the studies were underpowered in their ability to detect small effects, especially when there was modest change of PM levels over the follow-up period. Finally, yet importantly, some of the reviewed studies did not adequately control for potential confounders, like smoking, disease status, and medication use, which might mask the relatively moderate effects from PM exposure. For example, lipid-lowering drugs, particularly statins, have been shown to reduce CRP synthesis (81). Some of the included studies suggested a high prevalence of statin use among the participants with CVD (73 % – 88 %) (65, 66). Certain anti-inflammatory medications might also affect the levels of CRP (85). Further studies with better control of those time-variant variables might help to provide more conclusive evidence.

In this review, we focused on the change of CRP levels in response to PM exposure because serum CRP is a widely used clinical marker for systemic inflammation and the evidence linking CRP with different human diseases is more extensive and consistent. In addition, a substantial number of epidemiologic studies have been conducted to explore the possible relationship between PM exposure and CRP response, but there is no review article to summarize their findings to provide more confirmatory evidence. Despite the importance of systematically examining the effects of PM exposure on CRP levels, CRP is only one of the many possible biomarkers reflective of systemic inflammation, and it is possible for some other pathways not including CRP to lead to inflammatory responses. In future examinations, other proinflammatory markers, like interleukins 1, 6, and 8 and fibrinogen, need to be analyzed to better understand the underlying inflammatory pathways.

Conclusion

In this review article, children were found to have a greater susceptibility to the PM exposure-induced CRP response, and stronger responses were also observed among healthy adults with higher levels and greater variations of PM exposure. Only one randomized trial with a longer intervention period supported the possible effect of PM exposure on CRP. Further studies are needed to better quantify the magnitude of CRP level changes in response to PM among well-defined subgroups of individuals and with effective control of various confounding factors so as to substantiate whether altered CRP levels may play a role in the pathogenesis of PM exposure-induced human diseases.

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References

1. WHO. Health aspects of air pollution with particulate matter, ozone and nitrogen dioxide. WHO; Geneva: 2003.
2. Brook RD, Franklin B, Cascio W, Hong Y, Howard G, et al. Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. *Circulation*. 2004; 109:2655–71. [PubMed: 15173049]
3. Pope CA 3rd, Dockery DW. Health effects of fine particulate air pollution: lines that connect. *J Air Waste Manag Assoc*. 2006; 56:709–42. [PubMed: 16805397]
4. Sun Q, Hong X, Wold LE. Cardiovascular effects of ambient particulate air pollution exposure. *Circulation*. 2010; 121:2755–65. [PubMed: 20585020]
5. Brook RD, Rajagopalan S, Pope CA III, Brook JR, Bhatnagar A, et al. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation*. 2010; 121:2331–78. [PubMed: 20458016]
6. Kunzli N, Tager IB. Air pollution: from lung to heart. *Swiss Med Wkly*. 2005; 135:697–702. [PubMed: 16511705]
7. Brunekreef B, Beelen R, Hoek G, Schouten L, Bausch-Goldbohm S, et al. Effects of long-term exposure to traffic-related air pollution on respiratory and cardiovascular mortality in the Netherlands: the NLCS-AIR study. *Res Rep Health Eff Inst*. 2009; (139):5–71. discussion 73–89. [PubMed: 19554969]
8. Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med*. 2007; 356:447–58. [PubMed: 17267905]
9. Nevalainen J, Pekkanen J. The effect of particulate air pollution on life expectancy. *Sci Total Environ*. 1998; 217:137–41. [PubMed: 9695177]
10. Cohen AJ. Air pollution and lung cancer: what more do we need to know? *Thorax*. 2003; 58:1010–2. [PubMed: 14645959]
11. Pope CA 3rd, Burnett RT, Thun MJ, Calle EE, Krewski D, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *J Am Med Assoc*. 2002; 287:1132–41.
12. Behndig AF, Mudway IS, Brown JL, Stenfors N, Helleday R, et al. Airway antioxidant and inflammatory responses to diesel exhaust exposure in healthy humans. *Eur Respir J*. 2006; 27:359–65. [PubMed: 16452593]
13. Jacobs L, Nawrot TS, de Geus B, Meeusen R, Degraeuwe B, et al. Subclinical responses in healthy cyclists briefly exposed to traffic-related air pollution: an intervention study. *Environ Health*. 2010; 9:64. [PubMed: 20973949]
14. van Eeden SF, Tan WC, Suwa T, Mukae H, Terashima T, et al. Cytokines involved in the systemic inflammatory response induced by exposure to particulate matter air pollutants (PM(10)). *Am J Respir Crit Care Med*. 2001; 164:826–30. [PubMed: 11549540]
15. Driscoll KE, Carter JM, Hassenbein DG, Howard B. Cytokines and particle-induced inflammatory cell recruitment. *Environ Health Perspect*. 1997; 105(Suppl 5):1159–64. [PubMed: 9400717]
16. Sandhu RS, Petroni DH, George WJ. Ambient particulate matter, C-reactive protein, and coronary artery disease. *Inhal Toxicol*. 2005; 17:409–13. [PubMed: 16020037]
17. Polichetti G, Cocco S, Spinali A, Trimarco V, Nunziata A. Effects of particulate matter (PM(10), PM(2.5) and PM(1)) on the cardiovascular system. *Toxicology*. 2009; 261:1–8. [PubMed: 19379789]

18. Godleski JJ, Verrier RL, Koutrakis P, Catalano P, Coull B, et al. Mechanisms of morbidity and mortality from exposure to ambient air particles. *Res Rep Health Eff Inst.* 2000; 91:5–88. discussion 89–103. [PubMed: 10817681]
19. Mattoli S. Allergen-induced generation of mediators in the mucosa. *Environ Health Perspect.* 2001; 109(Suppl 4):553–7. [PubMed: 11544162]
20. Pope CA 3rd. Particulate air pollution, C-reactive protein, and cardiac risk. *Eur Heart J.* 2001; 22:1149–50. [PubMed: 11440485]
21. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation.* 2003; 107:363–9. [PubMed: 12551853]
22. Libby P. Inflammation in atherosclerosis. *Nature.* 2002; 420:868–74. [PubMed: 12490960]
23. Allin KH, Nordestgaard BG. Elevated C-reactive protein in the diagnosis, prognosis, and cause of cancer. *Crit Rev Clin Lab Sci.* 2011; 48:155–70. [PubMed: 22035340]
24. Rhodes B, Furnrohr BG, Vyse TJ. C-reactive protein in rheumatology: biology and genetics. *Nat Rev Rheumatol.* 2011; 7:282–9. [PubMed: 21468143]
25. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med.* 1999; 340:448–54. [PubMed: 9971870]
26. Szalai AJ, Agrawal A, Greenhough TJ, Volanakis JE. C-reactive protein: structural biology and host defense function. *Clin Chem Lab Med.* 1999; 37:265–70. [PubMed: 10353470]
27. Watterson TL, Hamilton B, Martin R, Coulombe RA Jr. Urban particulate matter causes ER stress and the unfolded protein response in human lung cells. *Toxicol Sci.* 2009; 112:111–22. [PubMed: 19675143]
28. Ramage L, Guy K. Expression of C-reactive protein and heat-shock protein-70 in the lung epithelial cell line A549, in response to PM10 exposure. *Inhal Toxicol.* 2004; 16:447–52. [PubMed: 15204760]
29. Ramage L, Proudfoot L, Guy K. Expression of C-reactive protein in human lung epithelial cells and upregulation by cytokines and carbon particles. *Inhal Toxicol.* 2004; 16:607–13. [PubMed: 16036753]
30. Vogel CF, Sciullo E, Wong P, Kuzmicky P, Kado N, et al. Induction of proinflammatory cytokines and C-reactive protein in human macrophage cell line U937 exposed to air pollution particulates. *Environ Health Perspect.* 2005; 113:1536–41. [PubMed: 16263508]
31. Niwa Y, Hiura Y, Sawamura H, Iwai N. Inhalation exposure to carbon black induces inflammatory response in rats. *Circ J.* 2008; 72:144–9. [PubMed: 18159116]
32. Rohr AC, Wagner JG, Morishita M, Kamal A, Keeler GJ, et al. Cardiopulmonary responses in spontaneously hypertensive and Wistar-Kyoto rats exposed to concentrated ambient particles from Detroit, Michigan. *Inhal Toxicol.* 2010; 22:522–33. [PubMed: 20384466]
33. Farraj AK, Haykal-Coates N, Winsett DW, Hazari MS, Carll AP, et al. Increased nonconducted P-wave arrhythmias after a single oil fly ash inhalation exposure in hypertensive rats. *Environ Health Perspect.* 2009; 117:709–15. [PubMed: 19479011]
34. Upadhyay S, Ganguly K, Stoeger T, Semmler-Bhenke M, Takenaka S, et al. Cardiovascular and inflammatory effects of intratracheally instilled ambient dust from Augsburg, Germany, in spontaneously hypertensive rats (SHRs). *Part Fibre Toxicol.* 2010; 7:27. [PubMed: 20920269]
35. Lei YC, Hwang JS, Chan CC, Lee CT, Cheng TJ. Enhanced oxidative stress and endothelial dysfunction in streptozotocin-diabetic rats exposed to fine particles. *Environ Res.* 2005; 99:335–43. [PubMed: 16307975]
36. Shima M. Air pollution and serum C-reactive protein concentration in children. *J Epidemiol.* 2007; 17:169–76. [PubMed: 17827864]
37. Kelishadi R, Mirghaffari N, Poursafa P, Gidding SS. Lifestyle and environmental factors associated with inflammation, oxidative stress and insulin resistance in children. *Atherosclerosis.* 2009; 203:311–9. [PubMed: 18692848]
38. Calderon-Garciduenas L, Villarreal-Calderon R, Valencia-Salazar G, Henríquez-Roldán C, Gutiérrez-Castrellón P, et al. Systemic inflammation, endothelial dysfunction, and activation in clinically healthy children exposed to air pollutants. *Inhal Toxicol.* 2008; 20:499–506. [PubMed: 18368620]

39. Calderon-Garciduenas L, Macías-Parra M, Hoffmann HJ, Valencia-Salazar G, Henríquez-Roldán C, et al. Immunotoxicity and environment: immunodysregulation and systemic inflammation in children. *Toxicol Pathol.* 2009; 37:161–9. [PubMed: 19171930]
40. Steinvil A, Kordova-Biezuner L, Shapira I, Berliner S, Rogowski O. Short-term exposure to air pollution and inflammation-sensitive biomarkers. *Environ Res.* 2008; 106:51–61. [PubMed: 17915210]
41. Hertel S, Viehmann A, Moebus S, Mann K, Bröcker-Preuss M, et al. Influence of short-term exposure to ultrafine and fine particles on systemic inflammation. *Eur J Epidemiol.* 2010; 25:581–92. [PubMed: 20559688]
42. Forbes LJ, Patel MD, Rudnicka AR, Cook DG, Bush T, et al. Chronic exposure to outdoor air pollution and markers of systemic inflammation. *Epidemiology.* 2009; 20:245–53. [PubMed: 19234416]
43. Tsai DH, Amyai N, Marques-Vidal P, Wang JL, Riediker M, et al. Effects of particulate matter on inflammatory markers in the general adult population. Part Fibre Toxicol. 2012; 9:24. [PubMed: 22769230]
44. Diez Roux AV, Auchincloss AH, Astor B, Barr RG, Cushman M, et al. Recent exposure to particulate matter and C-reactive protein concentration in the multi-ethnic study of atherosclerosis. *Am J Epidemiol.* 2006; 164:437–48. [PubMed: 16751260]
45. Zeka A, Sullivan JR, Vokonas PS, Sparrow D, Schwartz J, et al. Inflammatory markers and particulate air pollution: characterizing the pathway to disease. *Int J Epidemiol.* 2006; 35:1347–54. [PubMed: 16844771]
46. Hoffmann B, Moebus S, Dragano N, Stang A, Möhlenkamp S, et al. Chronic residential exposure to particulate matter air pollution and systemic inflammatory markers. *Environ Health Perspect.* 2009; 117:1302–8. [PubMed: 19672412]
47. Emmerechts J, Jacobs L, Van Kerckhoven S, Luyen S, Mathieu C, et al. Air pollution-associated procoagulant changes: the role of circulating microvesicles. *J Thromb Haemost.* 2012; 10:96–106. [PubMed: 22066779]
48. Dutta A, Ray MR, Banerjee A. Systemic inflammatory changes and increased oxidative stress in rural Indian women cooking with biomass fuels. *Toxicol Appl Pharmacol.* 2012; 261:255–62. [PubMed: 22521606]
49. Clark ML, Peel JL, Burch JB, Nelson TL, Robinson MM, et al. Impact of improved cookstoves on indoor air pollution and adverse health effects among Honduran women. *Int J Environ Health Res.* 2009; 19:357–68. [PubMed: 19626518]
50. Bonzini M, Tripodi A, Artoni A, Tarantini L, Marinelli B, et al. Effects of inhalable particulate matter on blood coagulation. *J Thromb Haemost.* 2010; 8:662–8. [PubMed: 19922434]
51. Ohlson CG, Berg P, Bryngelsson IL, Elihn K, Ngo Y, et al. Inflammatory markers and exposure to occupational air pollutants. *Inhal Toxicol.* 2010; 22:1083–90. [PubMed: 21029032]
52. Kim JY, Chen J-C, Boyce PD, Christiani DC. Exposure to welding fumes is associated with acute systemic inflammatory responses. *Occup Environ Med.* 2005; 62:157–63. [PubMed: 15723880]
53. Pope CA 3rd, Hansen ML, Long RW, Nielsen KR, Eatough NL, et al. Ambient particulate air pollution, heart rate variability, and blood markers of inflammation in a panel of elderly subjects. *Environ Health Perspect.* 2004; 112:339–45. [PubMed: 14998750]
54. Riediker M, Cascio WE, Griggs TR, Herbst MC, Bromberg PA, et al. Particulate matter exposure in cars is associated with cardiovascular effects in healthy young men. *Am J Respir Crit Care Med.* 2004; 169:934–40. [PubMed: 14962820]
55. Chuang KJ, Chan CC, Su TC, Lee CT, Tang CS, et al. The effect of urban air pollution on inflammation, oxidative stress, coagulation, and autonomic dysfunction in young adults. *Am J Respir Crit Care Med.* 2007; 176:370–6. [PubMed: 17463411]
56. O'Toole TE, Hellmann J, Wheat L, Haberzettl P, Lee J, et al. Episodic exposure to fine particulate air pollution decreases circulating levels of endothelial progenitor cells. *Circ Res.* 2010; 107:200–U65. [PubMed: 20595651]
57. Sullivan JH, Hubbard R, Liu SL, Shepherd K, Trenga CA, et al. A community study of the effect of particulate matter on blood measures of inflammation and thrombosis in an elderly population. *Environ Health.* 2007; 6:3. [PubMed: 17270049]

58. Dubowsky SD, Suh H, Schwartz J, Coull BA, Gold DR. Diabetes, obesity, and hypertension may enhance associations between air pollution and markers of systemic inflammation. *Environ Health Perspect.* 2006; 114:992–8. [PubMed: 16835049]
59. Seaton A, Soutar A, Crawford V, Elton R, McNerlan S, et al. Particulate air pollution and the blood. *Thorax.* 1999; 54:1027–32. [PubMed: 10525563]
60. Rich DQ, Kipen HM, Huang W, Wang G, Wang Y, et al. Association between changes in air pollution levels during the Beijing Olympics and biomarkers of inflammation and thrombosis in healthy young adults. *J Am Med Assoc.* 2012; 307:2068–78.
61. Rudez G, Janssen NA, Kilinc E, Leebeek FW, Gerlofs-Nijland ME, et al. Effects of ambient air pollution on hemostasis and inflammation. *Environ Health Perspect.* 2009; 117:995–1001. [PubMed: 19590696]
62. Peters A, Fröhlich M, Döring A, Immervoll T, Wichmann HE, et al. Particulate air pollution is associated with an acute phase response in men; results from the MONICA-Augsburg Study. *Eur Heart J.* 2001; 22:1198–204. [PubMed: 11440492]
63. Ruckerl R, Ibaldo-Mulli A, Koenig W, Schneider A, Woelke G, et al. Air pollution and markers of inflammation and coagulation in patients with coronary heart disease. *Am J Respir Crit Care Med.* 2006; 173:432–41. [PubMed: 16293802]
64. Delfino RJ, Staimer N, Tjoa T, Gillen DL, Polidori A, et al. Air pollution exposures and circulating biomarkers of effect in a susceptible population: clues to potential causal component mixtures and mechanisms. *Environ Health Perspect.* 2009; 117:1232–8. [PubMed: 19672402]
65. Huttunen K, Siponen T, Salonen I, Yli-Tuomi T, Aurela M, et al. Low-level exposure to ambient particulate matter is associated with systemic inflammation in ischemic heart disease patients. *Environ Res.* 2012; 116:44–51. [PubMed: 22541720]
66. Ruckerl R, Greven S, Ljungman P, Aalto P, Antoniadou C, et al. Air pollution and inflammation (interleukin-6, C-reactive protein, fibrinogen) in myocardial infarction survivors. *Environ Health Perspect.* 2007; 115:1072–80. [PubMed: 17637925]
67. Hildebrandt K, Ruckerl R, Koenig W, Schneider A, Pitz M, et al. Short-term effects of air pollution: a panel study of blood markers in patients with chronic pulmonary disease. *Part Fibre Toxicol.* 2009; 6:25. [PubMed: 19781092]
68. Schneider A, Neas LM, Graff DW, Herbst MC, Cascio WE, et al. Association of cardiac and vascular changes with ambient PM_{2.5} in diabetic individuals. *Part Fibre Toxicol.* 2010; 7:14. [PubMed: 20525188]
69. Liu L, Ruddy TD, Dalipaj M, Szyzskowicz M, You H, et al. Influence of personal exposure to particulate air pollution on cardiovascular physiology and biomarkers of inflammation and oxidative stress in subjects with diabetes. *J Occup Environ Med.* 2007; 49:258–65. [PubMed: 17351511]
70. Williams L, Ulrich CM, Larson T, Wener MH, Wood B, et al. Fine particulate matter (PM_{2.5}) Air pollution and immune status among women in the Seattle area. *Arch Environ Occup Health.* 2011; 66:155–65. [PubMed: 21864104]
71. Allen RW, Carlsten C, Karlen B, Leckie S, van Eeden S, et al. An air filter intervention study of endothelial function among healthy adults in a woodsmoke-impacted community. *Am J Respir Crit Care Med.* 2011; 183:1222–30. [PubMed: 21257787]
72. Scharrer E, Hessel H, Kronseder A, Guth W, Rolinski B, et al. Heart rate variability, hemostatic and acute inflammatory blood parameters in healthy adults after short-term exposure to welding fume. *Int Arch Occup Environ Health.* 2007; 80:265–72. [PubMed: 16791613]
73. Carlsten C, Kaufman JD, Peretz A, Trenga CA, Sheppard L, et al. Coagulation markers in healthy human subjects exposed to diesel exhaust. *Thromb Res.* 2007; 120:849–55. [PubMed: 17321570]
74. Barregard L, Sällsten G, Gustafson P, Andersson L, Johansson L, et al. Experimental exposure to wood-smoke particles in healthy humans: effects on markers of inflammation, coagulation, and lipid peroxidation. *Inhal Toxicol.* 2006; 18:845–53. [PubMed: 16864402]
75. Brauner EV, Möller P, Barregard L, Dragsted LO, Glasius M, et al. Exposure to ambient concentrations of particulate air pollution does not influence vascular function or inflammatory pathways in young healthy individuals. *Part Fibre Toxicol.* 2008; 5:1–9. [PubMed: 18269765]

76. Brauner EV, Forchhammer L, Møller P, Barregard L, Gunnarsen L, et al. Indoor particles affect vascular function in the aged: an air filtration-based intervention study. *Am J Respir Crit Care Med*. 2008; 177:419–25. [PubMed: 17932377]
77. Mills NL, Robinson SD, Fokkens PH, Leseman DL, Miller MR, et al. Exposure to concentrated ambient particles does not affect vascular function in patients with coronary heart disease. *Environ Health Perspect*. 2008; 116:709–15. [PubMed: 18560524]
78. Blomberg A, Törnqvist H, Desmyter L, Deneys V, Hermans C, et al. Exposure to diesel exhaust nanoparticles does not induce blood hypercoagulability in an at-risk population. *J Thromb Haemost*. 2005; 3:2103–5. [PubMed: 16102120]
79. Sacks JD, Wichers Stanek L, Luben TJ, Johns DO, Buckley BJ, et al. Particulate matter-induced health effects: who is susceptible? *Environ Health Perspect*. 2011; 119:446–54. [PubMed: 20961824]
80. Prescott GJ, Lee RJ, Cohen GR, Elton RA, Lee AJ, et al. Investigation of factors which might indicate susceptibility to particulate air pollution. *Occup Environ Med*. 2000; 57:53–7. [PubMed: 10711269]
81. Devaraj S, Siegel D, Jialal I. Statin therapy in metabolic syndrome and hypertension post-JUPITER: what is the value of CRP? *Curr Atheroscler Rep*. 2011; 13:31–42. [PubMed: 21046291]
82. Son JY, Lee J-T, Kim K-H, Jung K, Bell ML. Characterization of fine particulate matter and associations between particulate chemical constituents and mortality in Seoul, Korea. *Environ Health Perspect*. 2012; 120:872–8. [PubMed: 22440884]
83. Steenhof M, Gosens I, Strak M, Godri KJ, Hoek G, et al. In vitro toxicity of particulate matter (PM) collected at different sites in the Netherlands is associated with PM composition, size fraction and oxidative potential – the RAPTES project. *Part Fibre Toxicol*. 2011; 8:26. [PubMed: 21888644]
84. Ghio AJ, Devlin RB. Inflammatory lung injury after bronchial instillation of air pollution particles. *Am J Respir Crit Care Med*. 2001; 164:704–8. [PubMed: 11520740]
85. Bogaty P, Brophy JM, Noel M, Boyer L, Simard S, et al. Impact of prolonged cyclooxygenase-2 inhibition on inflammatory markers and endothelial function in patients with ischemic heart disease and raised C-reactive protein: a randomized placebo-controlled study. *Circulation*. 2004; 110:934–9. [PubMed: 15302800]

Table 1

Cross-sectional studies on associations between PM exposure and CRP levels.

Author	Study location and period	Study population	Sample size	CRP level, mg/L	CRP method	PM and peak levels, µg/m³	Lag time	Main results
Children								
Shima, M. 2007 (36)	Chiba Prefecture, Japan, 2001	School children, 6–12 years	2094	90th percentile (1.4)	Latex-enhanced immune-nephelometric assay (Dade Behring, Marburg, Germany)	SPM (42.7)	3-year mean	OR (95% CI) for CRP level above 90th percentile: (1.4 mg/L): 1.49(1.07–2.06) ^a
Kelishadi, R. 2009 (37)	Isfahan, Iran, 2004–2005	Non-smoking children, 10–18 years	374	Mean±SD: 1.1±0.2	Pars Azmoun assay (Eppendorf)	PM ₁₀ (191)	7-day mean	CRP change per unit of PM ₁₀ : β=1.5 (SE=0.2), p<0.0001 ^a
Calderon-Garciduenas L. 2008 (38)	Mexico City and Polotitlan (control area), Mexico	Healthy children in Mexico City: 8.8±0.2 years	Mexico City: 28	Mean±SD: 0.83±0.26	ELISA (R&D Systems, Inc., Minneapolis, MN, USA)	PM _{2.5} 25	Long-term	Children in Mexico City had significantly higher levels of CRP (p=0.001) ^a
		Healthy children in control city: 8.4±0.1 years	Control: 24	Mean±SD: 0.23±0.04	PM _{2.5} <15			
Calderon-Garciduenas L. 2009 (39)	Mexico City and Polotitlan (control area), Mexico	Healthy children in Mexico City: 9.8±1.7 years	Mexico City: 66	Mean±SD: 0.89±0.04	ELISA (Cell Sciences, Canton, MA, USA)	Mean±SD: PM _{2.5} , 35.89±0.93	Long-term	Children in Mexico City had significantly higher levels of CRP (p<0.001) ^a
		Healthy children in control city: 9.7±1.8 years	Control: 93	Mean±SD: 0.19±0.26	PM _{2.5} <15			
Adults								
Steinvil, A. 2008 (40)	Israel, 2003–2006	Non-smoking healthy individuals, 46±12 years	Men: 2203	Men: mean±SD: 1.5±2.8	hs-CRP, Behring BN II nephelometer (DADE Behring, Marburg, Germany)	PM ₁₀ : mean±SD, 64.5±100.8; median (IQR), 43.0 (33.1–60.7)	Men: CRP change (%) per IQR of PM ₁₀ (27.6 µg/m³)	
							–1 (–2 to 1)	0 day
							0 (–1 to 1)	1 day
							–1 (2–1)	2 days
							–1 (–2 to 0)	3 days
							0 (–1 to 1)	4 days
							0 (–1 to 2)	5 days
							1 (0–2)	6 days
							1 (0–1)	7 days
							–2 (–5 to 1)	7-day mean
Women: 1456				Women: mean±SD, 1.7±3.2				
							Women: CRP change (%) per IQR of PM ₁₀ (27.6 µg/m³)	
							0 (–2 to 2)	0 day

Author	Study location and period	Study population	Sample size	CRP level, mg/L	CRP method	PM and peak levels, µg/m³	Lag time	Main results
Hertel, S. 2010 (41)	Ruhr, Germany, 2000–2003	Randomly selected participants 45–75 years	3999	Mean±SD: 3.0±5.2	hs-CRP, automated nephelometer (BN-II, Dade-Behring Inc, Deerfield, USA)	PM ₁₀ (246.00)	1 day	0 (−1 to 2)
							2 days	1 (0–2)
							3 days	0 (−1 to 1)
							4 days	0 (−1 to 2)
							5 days	0 (−1 to 2)
							6 days	−1 (−3 to 1)
							7 days	0 (−2 to 1)
							7-day mean	1 (−2 to 4)
								CRP change (%) per IQR of PM ₁₀ (13.9 µg/m³)
							0 day	0.85 (−2.66 to 4.49)
Forbes, L.J. 2009 (42)	England, 1998 and 2003	Adults, >16 years	Year 1998: 9830 Year 2003: 7736	1998 Mean: male, 1.39; female, 1.67 2003 Mean: male, 1.48; female, 1.78	hs-CRP, N Latex CRP mono Immunoassay (Dade Behring, Germany)	PM ₁₀ (27.0)	1 day	−0.02 (−3.52 to 3.62)
							2 days	0.97 (−2.90 to 4.98)
							3 days	1.34 (−2.36 to 5.17)
							2-day mean	0.51 (−3.28 to 4.46)
							3-day mean	0.95 (−2.89 to 4.95)
							4-day mean	0.21 (−3.72 to 4.30)
							5-day mean	−0.18 (−4.27 to 4.08)
							6-day mean	−0.41 (−4.62 to 3.98)
							7-day mean	−1.28 (−5.45 to 3.07)
							14-day mean	−0.90 (−5.20 to 3.60)
Tsai, D.H. 2012 (43)	Lausanne, Switzerland, 2003–2006	Randomly selected participants, 35–75 years	6171	Median (IQR): 1.30 (0.60–2.70)	hs-CRP, immunoassay (Diagnostic Products Corporation, LA, CA, USA)	NA	21-day mean	1.13 (−3.86 to 6.38)
							28-day mean	5.16 (−0.41 to 11.04)
							1-year mean	CRP change per 1 µg/m³ of PM ₁₀
								Year 1998: −0.27 (−1.78 to 1.27) Year 2003: 0.66 (−1.07 to 2.42) CRP change per 10 µg/m³ of PM ₁₀ : ±0.002 (−0.017 to 0.013)

Author	Study location and period	Study population	Sample size	CRP level, mg/L	CRP method	PM and peak levels, µg/m ³	Lag time	Main results
Hertel, S. 2010 (41)	Ruhr, Germany, 2000–2003	Randomly selected participants, 45–75 years	3999	Mean±SD: 3.0±5.2	hs-CRP, automated nephelometer (Dade-Behring Inc, Deerfield, USA)	PM _{2.5} (187.10)	1 day	0.001 (−0.013 to 0.016)
							2 days	0.002 (−0.013 to 0.017)
							3 days	−0.001 (−0.015 to 0.014)
							4 days	0.002 (−0.013 to 0.017)
							5 days	0.003 (−0.011 to 0.018)
							6 days	0.002 (−0.012 to 0.017)
								CRP change (%) per IQR of PM _{2.5} (11.5 µg/m ³)
							0 day	1.66 (−1.82 to 5.26)
							1 day	0.74 (−2.64 to 4.24)
							2 days	1.03 (−2.85 to 5.06)
Diez Roux, A.V. 2006 (44)	Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Manhattan and Bronx, NY; St. Paul, MN, USA, 2000–2002	45–84 years, free of CVD	5634	Median (IQR): 1.84 (0.82–4.10)	Automated immunoanalyzer (Dade Behring, Inc., Deerfield, IL, USA)	PM _{2.5} Median (IQR)	3 days	2.03 (−1.67 to 5.87)
							2-day mean	1.00 (−2.66 to 4.80)
							3-day mean	1.57 (−2.13 to 5.42)
							4-day mean	0.70 (−3.17 to 4.71)
							5-day mean	0.23 (−3.84 to 4.47)
							6-day mean	−0.10 (−4.25 to 4.22)
							7-day mean	−0.72 (−4.67 to 3.39)
							14-day mean	0.05 (−4.06 to 4.33)
							21-day mean	2.17 (−2.65 to 7.22)
							28-day mean	7.06 (1.42 to 13.02) ^a
								CRP change (%) per 10 µg/m ³ of PM _{2.5}
							1-day mean	−1 (−4 to 1)
							2-day mean	−1 (−4 to 1)
							7-day mean	0 (−4 to 4)
							30-day mean	3 (−2 to 10)
							60-day mean	4 (−3 to 11)
								CRP change (%) per 8.5 µg/m ³ of PM _{2.5}
							2-day mean	−4.88 (−13.29 to 3.53)
Zeka, A. 2006 (45)	Boston, MA, USA, November 2000–December 2004	21–80 years	710	Mean±SD: 3.5±8.5; median (IQR): 1.7 (0.8–3.5)	Immunoturbidimetric assay (Roche Diagnostics, Indianapolis, IN, USA)	PM _{2.5} 90th percentile: 21.48		

Author	Study location and period	Study population	Sample size	CRP level, mg/L	CRP method	PM and peak levels, µg/m ³	Lag time	Main results
Hoffmann, B. 2009 (46)	Essen, Mülheim, and Bochum, Germany, 2000	Randomly selected participants, 45–75 years	Men: 2028	Men: median (IQR), 1.50 (2.40)	hs-CRP, automated nephelometer (Dade-Behring Inc., Deerfield, IL, USA)	PM _{2.5} (147)	7-day mean	–1.37 (–10.44 to 7.71)
							28-day mean	4.36 (–3.25 to 11.9)
								Men: CRP change (%) per 3.91 µg/m ³ of PM _{2.5}
							1-year mean	23.9 (4.1–47.4) ^a
							1-year mean	19.4 (–1.1 to 44.2) further adjust for daily exposure
								Women: CRP change (%) per 3.91 µg/m ³ of PM _{2.5}
			Women: 2004	Women: 1.50 (2.50)			1-year mean	–1.0 (–16.5 to 17.3)
							1-year mean	–2.0 (–18.5 to 17.9) further adjust for daily exposure
Emmerrechts, J. 2012 (47)	Leuven, Belgium, February–April 2010	Type 1 or 2 diabetic patients, age > 18 years	233	Mean±SD: 2.5±3.6	hs-CRP	PM ₁₀ (44.4)	7-day mean	CRP change (%) per 10 µg/m ³ of PM ₁₀ : 23% (5%–45%) ^a
Dutta, A. 2012 (48)	West Bengal, India, 2007–2010	Non-smoking healthy women, 22–44 years	Biomass users: 635	Mean±SD: 6.2±1.3	ELISA (IBL, Hamburg, Germany)	Mean±SD: PM ₁₀ , 275±93; PM _{2.5} , 158±64	NA	Biomass users had significantly higher levels of CRP (p<0.05) ^a
			Liquefied petroleum gas users: 452	Mean±SD: 1.9±0.7		Mean±SD: PM ₁₀ , 97±34; PM _{2.5} , 51±23		
Clark, M. L. 2009 (49)	Honduras, June–August 2005	Non-smoking women	Traditional stoves users: 38	Mean±SD: 3.3±4.8;	hs-CRP dried blood spot assay, ELISA (Hemagen Diagnostics, Inc, Columbia, MD, USA)	Mean±SD: PM _{2.5} 197.7±135.5;	8-h mean	Natural log-transformed CRP change per IQR of PM _{2.5} : –0.2 (–0.5 to 0.01)
			Improved stoves users: 41	Mean±SD: 5.2±4.0		Mean±SD: PM _{2.5} 73.6±34.0		

Results using moving average of PM levels were presented in the format of 3-, 5-, 7-day mean, etc.

^aStatistically significant results.

Longitudinal studies on associations between PM exposure and CRP levels.

Table 2

Author	Study location and period	Study population	Sample size	CRP level, mg/L	CRP method	PM and peak levels, µg/m ³	Lag time	Main results
Occupational population								
Bonzini, M. 2010 (50)	Brescia, Italy	Male workers in a steel production plant	37	Mean±SD: time 1, 1.5±1.6; time 2, 1.4±1.4	ELISA (HYPHEN BioMed, Neuville-Sur-Oise, France)	Coarse PM: 1190 PM ₁ : 30.5	3 days 3 days	CRP change per 1 µg/m ³ of coarse PM β=0.48 (SE=0.20), p=0.01 ^a CRP change per 1 µg/m ³ of PM ₁ β=0.59 (SE=0.27), p=0.03 ^a
Ohlson, C. G. 2010 (51)	NA	Welding, cutting, grinding workers, mean age 40 years	73	Preshift mean (median, range): 1.61 (1.19; 0.15–11.1)	LIATEST D-DI Diagnostica Stago	Mean (range): PM ₁₀ , 600 (150–1780); PM _{2.5} , 310 (20 to 1380)	1 day 2 days	Postshift mean (median, range) of CRP level: 1.60 (1.24; 0.15–9.4) 1.89 (1.14; 0.11–9.8), p=0.04 ^a
Kim, J. Y. 2005 (52)	Quincy, MA, USA, 2003–2004	24 welders and 13 controls at an apprentice welding school	37	Mean±SD: welders, 2.13±0.38; control, 2.79±0.60	Latex particle enhanced immunoturbidimetric assay (Roche Diagnostics Corporation, Indianapolis, IN, USA)	PM _{2.5} median (IQR): welders, 1690 (890–2440); controls, 40 (20 to 110)	4 days 24 h	1.69 (1.16; 0.09–9.0) CRP change due to welding fume exposure: 0.90 (0.17–1.64) ^a
Healthy adults								
Pope, C. A., 3rd 2004 (53)	Utah, USA, winter of 1999/2000 and summer 2000	Non-smoking elderly, 54–89 years, no serious diseases	88	Mean±SD: 5.0±6.0	Nephelometry (IMMAGE Immunochemistry Systems)	PM _{2.5} : 74	0 day 1 day 2 days 3 days	CRP change per 100 µg/m ³ of PM ₁₀ : regression coefficients (SE) 0.81 (0.18); p<0.01 ^a 0.33 (0.20); p<0.05 ^a 0.38 (0.20); p<0.05 ^a 0.64 (0.21); p<0.01 ^a
Riediker, M. 2004 (54)	North Carolina, USA, 2001	Healthy young non-smokers, 23–30 years	9	Mean±SD: 1.0±1.2	NA	PM _{2.5} : 54.4	14 h	CRP increased 31.9% per 10 µg/m ³ PM _{2.5} change (p=0.023) ^a
Chuang, K. J. 2007 (55)	Taiwan, April and June of 2004 or 2005	Healthy young non-smokers, 18–25 years	76	Mean±SD: 0.8±0.3	hs-CRP, chemiluminescent enzyme immunoassay (IMMULITE® hs-CRP, Diagnostic Products Corporation, CA, USA)	PM _{2.5} : 59.5	1 day 2 days 3 days	CRP change (%) per IQR of PM _{2.5} : 1 day, 32.7 µg/m ³ ; 2 days, 34.5 µg/m ³ ; 3 days, 26.0 µg/m ³ 90.2 (–10.2 to 190.1) 99.1 (–26.1 to 224.3) 100.4 (–2.9 to 203.7)

Author	Study location and period	Study population	Sample size	CRP level, mg/L	CRP method	PM and peak levels, $\mu\text{g}/\text{m}^3$	Lag time	Main results
O'Toole, T. E. 2010 (56)	Provo, UT, USA, January and early March of 2009	Healthy young non-smokers, 18–25 years	16	NA	NA	$\text{PM}_{2.5} > 80$	1 day	CRP change per $50 \mu\text{g}/\text{m}^3 \text{PM}_{2.5}$ (SE): -0.020 (0.025), $p=0.430$
Sullivan, J. H. 2007 (57)	Seattle, WA, USA, February 2000 and March 2002	Healthy non-smoking elderly, 55 years	9	Median (range): 3.0 (1.0–20)	hs-CRP, Dade-Behring radioimmunoassay	$\text{PM}_{2.5}$: 33.9	0 day 1 day	Log-transformed CRP change (%) per $10 \mu\text{g}/\text{m}^3$ of $\text{PM}_{2.5}$ -3 (-52 to 7) 1 (-15 to 19)
Dubowsky, S. D. 2006 (58)	St. Louis, MO, USA, March–June, 2002	Non-smoking elderly, 60 years	18	Median (range): 2.2 (0.25–41)	Immunoturbidimetric assay (Roche Diagnostics, Indianapolis, IN, USA)	$\text{PM}_{2.5}$: 28	5-day mean	CRP change (%) per IQR of $\text{PM}_{2.5}$ ($10.0 \mu\text{g}/\text{m}^3$): 12 (-25 to 67)
Seaton, A. 1999 (59)	Belfast and Edinburgh, UK, November 1996–April 1998	Non-current smokers, elderly, 60 years, no cardiac diseases	112	NA	Belfast by rate nephelometry	PM_{10} : 418	3 days	Log-transformed CRP change (%) per $100 \mu\text{g}/\text{m}^3$ of PM_{10} : 147 (20 to 477) ^a
Rich, D. Q. 2012 (60)	Beijing, China, June–October, 2008	Healthy young non-smokers: mean $\pm$ SD, 24.2 ± 2.1	125	NA	Immunonephelometric assay	$\text{PM}_{2.5}$ range: pre-Olympics, $24.4\text{--}219.1$; during Olympics, $14.6\text{--}171.4$; post-Olympics, $15.0\text{--}268.2$		Percentage of above detection limit values (0.3 mg/L): pre-Olympics, 55% ; during Olympics, 46% ; post-Olympics, 36%
Chuang, K. J. 2007 (55)	Taiwan, April and June of 2004 or 2005	Healthy young non-smokers, 18–25 years	76	Mean $\pm$ SD: 0.8 ± 0.3	hs-CRP, chemiluminescent enzyme immunoassay (IMMULITE® hs-CRP, Diagnostic Products Corporation, CA, USA)	PM_{10} : 87.2	1 day 2 days 3 days	CRP change (%) per IQR of PM_{10} : IQR 1 day, $20.4 \mu\text{g}/\text{m}^3$; 2 days, $25.2 \mu\text{g}/\text{m}^3$; 3 days, $20.0 \mu\text{g}/\text{m}^3$ 135.8 ($1.8\text{--}269.7$) ^a 108.2 (-10.9 to 227.3) 109.6 ($2.5\text{--}216.7$) ^a
Rudez, G. 2009 (61)	Rotterdam, the Netherlands, January 2005–December 2006	Healthy volunteers, 41 ± 15 years	40	Mean $\pm$ SD: 0.6 ± 1.2	In-house high-sensitivity ELISA (Dako, Glostrup, Denmark)	PM_{10} : 110.1	1–2 days 2–3 days 3–4 days	CRP change (%) per IQR of PM_{10} : $15.4 \mu\text{g}/\text{m}^3$ 1.9 (-5.6 to 9.4) 5.8 (-2.0 to 13.5) 3.4 (-6.2 to 12.9)
Peters, A. 2001 (62) ^b	Augsburg, Germany, 1985	Randomly selected men, free of CVD, 45–64 years, 68% non-smokers	631	Mean $\pm$ SD: 3.01 ± 5.20 ; median (IQR): 1.59 (0.70 to 3.63)	Sensitive immunoradiometric assay	TSP: 176	0 day 1 day 5-day mean 5-day mean	All participants: OR (95% CI) for CRP level above 90th percentile (5.7 mg/L) 1.33 ($1.09\text{--}1.63$) ^a 1.36 ($1.12\text{--}1.65$) ^a 1.46 ($1.17\text{--}1.82$) ^a Non-smokers: 1.37 ($1.04\text{--}1.79$) ^a
Adults with CVD								

Author	Study location and period	Study population	Sample size	CRP level, mg/L	CRP method	PM and peak levels, µg/m ³	Lag time	Main results
Ruckerl, R. 2006 (63)	Erfurt, Germany, winter of 2000/2001	Male with coronary heart disease (CHD), 51–76 years	57	Mean±SD: 3.7±6.5; median: 2.0; 90th percentile	hs-CRP, immunonephelometry (Dade Behring, Marburg, Germany)	PM _{0.01–0.1} : 34,294 n/cm ³	1 day	OR (95% CI) for CRP level above 90th percentile (8.5 mg/L)
							2 days	0.7 (0.5–1.2)
							3 days	1.2 (0.7–2.0)
							5-day mean	2.3 (1.3–3.8) ^a
							1 day	1.5 (0.9–2.6)
							2 days	1.1 (0.7–1.8)
							3 days	1.5 (0.9–2.5)
							5-day mean	1.2 (0.8–1.9)
							1 day	1.4 (0.9–2.3)
							2 days	1.2 (0.8–1.9)
Delfino, R. 2009 (64)	Los Angeles, CA, USA, 2005–2007	Non-smoking elderly with CAD, 65 years	60	Mean±SD: 2.43±3.18; median (range): 1.40 (0.25–26.8)	Zymutest, Hyphen BioMed, Neuville sur Oise, France	PM _{0.25} : 30.05	5-day mean	CRP change per IQR of PM _{0.25} (7.00 µg/m ³)
							1 day	2.0 (1.1–3.6) ^a
							3 days	2.2 (1.2–3.8) ^a
							5-day mean	2.0 (1.2–3.7) ^a
							1 day	0.57 (0.08–1.06) ^a
							3 days	0.75 (0.10–1.40) ^a
							5 days	0.29 (–0.44 to 1.02)
							PM _{0.25–2.5} : 66.77	CRP change per IQR of PM _{0.25–2.5} (10.58 µg/m ³)
							1 day	–0.18 (–0.38 to 0.02)
							3 days	–0.42 (–0.82 to –0.02)
5 days	–0.35 (–0.73 to 0.02)							
PM _{2.5–10} : 24.63	CRP change per IQR of PM _{2.5–10} (5.46 µg/m ³)							
1 day	0.25 (–0.06 to 0.56)							
3 days	4.31 (–0.05 to 0.91)							
5 days	0.02 (–0.34 to 0.37)							

Author	Study location and period	Study population	Sample size	CRP level, mg/L	CRP method	PM and peak levels, µg/m ³	Lag time	Main results					
Huttunen, K. 2012 (65)	Kotka, Finland, November 2005–May 2006	Non-smoking ischemic heart disease patients, 50–80 years	52	Mean±SD: 2.3±4.1	hs-CRP, immunoturbidimetric method			CRP change (%) per IQR of PM _{2.5} (6.45 µg/m ³)					
							0 day	2.89 (−6.87 to 13.67)					
							1 day	15.83 (4.68 to 28.17) ^a					
							2 days	16.91 (5.95 to 29.00) ^a					
							3 days	4.20 (−6.05 to 15.56)					
Sullivan, J.H. 2007 (57)	Seattle, WA, USA, February 2000 and March 2002	Non-smoking elderly with CVD, =55 years	23	Median (range): 2.0 (0.2–145)	hs-CRP, Dade-Behring radioimmunoassay		CRP change (%) per IQR of PM _{2.5–10} (5.37 µg/m ³)						
						0 day	−4.51 (−8.99 to 0.20)						
						1 day	1.25 (−3.99 to 6.77)						
						2 days	2.82 (−2.68 to 8.63)						
						3 days	3.51 (−5.30 to 13.14)						
							Log-transformed CRP change (%) per 10 µg/m ³ of PM _{2.5}						
						0 day	19 (−14 to 64)						
						1 day	25 (−3 to 58)						
						Ruckerl, R. 2007 (66)	Athens, Greece; Augsburg, Germany; Barcelona, Spain; Helsinki, Finland; Rome, Italy; and Stockholm, Sweden, May 2003–July 2004	Myocardial infarction survivors, 35–80 years	1003	Athens: 2.52 Augsburg: 2.26 Barcelona: 3.52 Helsinki: 1.98 Rome: 2.56 Stockholm: 2.86	Dade Behring Marburg GmbH, Marburg, Germany	PM _{2.5} : 62.7	CRP change (%) per IQR of PM _{2.5} ; 24 h, 10.99 µg/m ³ ; 5-day mean, 8.59 µg/m ³
												0 day	0.11 (−1.9 to 2.21)
1 day	−0.06 (−1.98 to 1.90)												
2 days	0.11 (−1.80 to 2.06)												
5-day mean	−0.13 (−2.15 to 1.92)												
	CRP change (%) per IQR of PM ₁₀ : 24 h, 17.37 µg/m ³ ; 5-day mean, 13.54 µg/m ³												
0 day	−0.71 (−2.75 to 1.37)												
1 day	−0.63 (−2.61 to 1.39)												
2 days	−1.42 (−4.23 to 1.47)												
5-day mean	−1.35 (−3.45 to 0.79)												
Adults with COPD													
Hildebrandt, K. 2009 (67)	Erfurt, Germany, 2001/2002	Male with COPD, 53.8±12.3 years	38	Mean±SD: 3.8±8.4; median: 1.6	hs-CRP, immunonephelometry (Dade Behring, Marburg, Germany)	PM ₁₀ : 57.3		CRP showed no significant associations with air pollutants					

Author	Study location and period	Study population	Sample size	CRP level, mg/L	CRP method	PM and peak levels, µg/m ³	Lag time	Main results
Sullivan, J. H. 2007 (57)	Seattle, WA, USA, February 2000 and March 2002	Non-smoking elderly with COPD, 55 years	16	Median (range): 6.0 (1.0–35)	hs-CRP, Dade-Behring radioimmunoassay	PM _{2.5} : 33.9		Log-transformed CRP change (%) per 10 µg/m ³ of PM _{2.5}
Adults with elements of metabolic syndrome	Dubowsky, S. D. 2006 (58)	Non-smoking elderly, 60 years	60	Median (range): 2.2 (0.25–41)	Immunoturbidimetric assay (Roche Diagnostics, Indianapolis, IN, USA)	PM _{2.5} : 28	0 day	–7 (–52 to 79)
							1 day	–31 (–66 to 42)
							5-day mean	CRP change (%) per IQR of PM _{2.5} (10.0 µg/m ³)
			Obese (14)					Obese: 48 (5.3–109) ^a
			Diabetes (8)					Diabetes: 74 (18–158) ^a
			Obesity, Diabetes, and Hypertension (4)					Obesity, diabetes, and hypertension: 12 (–25 to 67)
Schneider, A. 2010 (68)	Chapel Hill, NC, USA, November 2004 and December 2005	Type 2 diabetic patients, aged 48–78 years	22	NA	ELISA (Alpco Diagnostics, Salem, NH, USA)	PM _{2.5} < 35	1–4 days	CRP increased slightly, however, non-significantly, with a lag of 2 days
Liu, L. 2007 (69)	Windsor, Ontario, Canada	Diabetic patients, median age 47.0 (27.8–63.3)	25	Median (5th–95th percentile): 1.7 (0.4–11.7)	ELISA (Alpco, Windham, NH, USA)	PM ₁₀ median (5th–95th percentile): 25.5 (9.8–133.0)	1-day mean	CRP change per 10 µg/m ³ of PM ₁₀ : 0.11 (SE=0.07)
Williams, L. 2011 (70)	Seattle, WA, USA	Healthy, overweight, or obese, non-smoking women, aged 50–75 years	115	Mean±SD: 3.7±3.5	Behring Nephelometer II analyzer (Dade-Behring Diagnostics, Deerfield, IL, USA)	PM _{2.5} : 3-day mean, 33.4; 30-day mean, 20.7; 60-day mean, 19.1	3-day mean	CRP change (%) per 5.6 µg/m ³ of 3-day mean PM _{2.5} : 2 (–3 to 9)
							30-day mean	CRP change (%) per 3.9 µg/m ³ of 30-day mean PM _{2.5} : 2 (–6 to 10)
							60-day mean	CRP change (%) per 3.7 µg/m ³ of 60-day mean PM _{2.5} : 1 (–7 to 11)

Results using moving average of PM levels were presented in the format of 3-, 5-, 7-mean, etc.

^aStatistically significant results.

^bThis study used classic longitudinal study design.

Table 3

Randomized crossover trials on associations between PM exposure and CRP levels.

Author	Study location and period	Study population	Sample size	CRP level, mg/L	CRP method	PM and peak levels, $\mu\text{g}/\text{m}^3$	Lag time	Main results
Healthy adults								
Allen, R.W. 2011 (71)	Smithers, British Columbia, Canada, November 2008–April 2009	Healthy adults with no tobacco smoking in household (43.0 $\pm$ 9.9 years)	45	HEPA filtration on: 0.78 $\pm$ 0.74; HEPA filtration off: 1.00 $\pm$ 0.78	ELISA	Indoor HEPA filters: mean $\pm$ SD (4.6 $\pm$ 2.6 $\mu\text{g}/\text{m}^3$), no internal filters (11.2 $\pm$ 6.1 $\mu\text{g}/\text{m}^3$); each intervention period lasted 7 days	The end of each 7-day intervention period	HEPA filtration was associated with a 32.6% (4.4–60.9%) ^a decrease in CRP
Scharrer, E.H. 2007 (72)	NA	Healthy never-smoking volunteers, aged 29 $\pm$ 8 years	20	Median (IQR): welding fume, 2 (2–3); control, 3 (1–4)	NA	Welding fume for 1 h; median PM ₄ 3500 $\mu\text{g}/\text{m}^3$ (IQR 1400–6300 $\mu\text{g}/\text{m}^3$) or control air in office without high-level PM exposure; two sessions separated by 2 days	5 h	No statistically significant differences in the concentrations of CRP
Carlsten, C. 2007 (73)	NA	Healthy, non-smokers, 18–49 years	13	NA	Immunonephelometric assay (Dade Behring, Newark, DE, USA)	Three levels of diesel exhaust: 0 (filtered air, FA), 100 $\mu\text{g}/\text{m}^3$ (DE100) and 200 $\mu\text{g}/\text{m}^3$ (DE200) of particulate diesel exhaust; each exposure session lasted 2 h; different sessions separated by 2 weeks	22 h	Fold change (95% CI) from preexposure to postexposure in DE200 group: 1.01 (–1.29 to 1.25)
Barregard, L.G. 2006 (74)	Goteborg, Sweden	Healthy never-smoking adults, aged 20–56 years	13	Wood smoke: 0 h, 0.45 (0.34–1.46); 3 h, 0.44 (0.32–1.34); 24 h 0.44 (0.32–1.34); clean air, 0 h, 0.67 (0.37–2.37); 3 h, 0.64 (0.35–2.25); 24 h, 0.62 (0.32–2.05)	Modular equipment and reagents from Roche	Filtered indoor air: 14–27 $\mu\text{g}/\text{m}^3$; wood smoke: 243–279 $\mu\text{g}/\text{m}^3$; each intervention period lasted 4 h; two sessions separated by 1 week	3 h, 24 h	No statistically significant differences in concentrations of CRP
Brauner, E.V. 2008 (75)	Copenhagen, Denmark	Healthy non-smoking, volunteers, aged 20–40 years	29	Non-filtered: 6 h, 1.3 (1.1–1.5); 24 h, 1.4 (1.2–1.7); filtered 6 h, 1.5 (1.3–1.8); 24 h, 1.5 (1.2–1.7)	NA	Non-filtered chamber (NC); mean $\pm$ SD, 11,600 $\pm$ 5600 per cm^3 ; PM ₁₀ 24.3 $\pm$ 9.6 $\mu\text{g}/\text{m}^3$; PM _{2.5} 10.5 $\pm$ 4.8 $\mu\text{g}/\text{m}^3$; filtered chamber: NC 555 $\pm$ 1053 per cm^3 ; each intervention period lasted 24 h; two	NA	CRP change (%) relative to exposure to non-filtered air: –9.97 (–19.7 to 1.01)

Author	Study location and period	Study population	Sample size	CRP level, mg/L	CRP method	PM and peak levels, $\mu\text{g}/\text{m}^3$	Lag time	Main results
Brauner, E. V. 2008 (76)	Copenhagen, Denmark	21 healthy non-smoking couples, aged 60–75 years	42	Non-filtered air: 1.5 (1.3–1.9); particle-filtered air: 1.6 (1.4 to 1.9)	NA	Particle-filtered air: mean (95% CI) $\text{PM}_{10-2.5}$ 4.6 (3.5–6.0) $\mu\text{g}/\text{m}^3$; $\text{PM}_{2.5}$ 4.7 (3.9–5.7) $\mu\text{g}/\text{m}^3$; non-filtered air: $\text{PM}_{10-2.5}$ 9.4 (8.1–10.0) $\mu\text{g}/\text{m}^3$; $\text{PM}_{2.5}$ 12.6 (11.2–14.1) $\mu\text{g}/\text{m}^3$; each intervention period lasted 24 h	On the morning after each 48-h scenario	CRP change (%) relative to exposure to non-filtered air 2.0 (–10.4 to 16.1)
Adults with CVD								
Mills, N.L. 2008 (77)	Edinburgh, Scotland, UK	12 male with stable CHD, 12 healthy male non-smoking volunteers	24	NA	Highly sensitive immunonephelometric assay (Dade-Behring, Marburg, Germany)	Concentrated ambient fine and ultrafine particles (CAPs): mean $\pm$ SD, $190 \pm 37 \mu\text{g}/\text{m}^3$; filtered air, $0.5 \pm 0.4 \mu\text{g}/\text{m}^3$; each exposure session lasted 2 h; different sessions separated by 2 weeks	6–8 h	Serum CRP concentrations were unaltered by CAPs or air exposure at any time point
Adults with COPD								
Blomberg, A. 2005 (78)	NA	COPD patients, 15 ex-smokers, 56–72 years	15	NA	NA	Diesel exhaust (300 $\mu\text{g}/\text{m}^3$) and filtered air for 1 h	6 h, 24 h	No significant diesel exhaust-induced effect on CRP level changes

^aStatistically significant results.