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REVIEW

Systematic review of the effects of black carbon on cardiovascular disease among individuals with pre-existing disease

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Abstract
Objectives Recent interest has developed in understanding the health effects attributable to different components of particulate matter. This review evaluates the effects of black carbon (BC) on cardiovascular disease in individuals with pre-existing disease using evidence from epidemiologic and experimental studies.
Methods A systematic literature search was conducted to identify epidemiologic and experimental studies examining the relationship between BC and cardiovascular health effects in humans with pre-existing diseases. Nineteen epidemiologic and six experimental studies were included. Risk of bias was evaluated for each study.
Results Evidence across studies suggested ambient BC is associated with changes in subclinical cardiovascular health effects in individuals with diabetes and coronary artery disease (CAD). Limited evidence demonstrated that chronic respiratory disease does not modify the effect of BC on cardiovascular health.
Conclusions Results in these studies consistently demonstrated that diabetes is a risk factor for BC-related cardiovascular effects, including increased interleukin-6 and ECG parameters. Cardiovascular effects were associated with BC in individuals with CAD, but few comparisons to individuals without CAD were provided in the literature.

Keywords Air pollution · Cardiovascular disease · Susceptible populations · Black carbon · Elemental carbon

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Introduction

The health risks associated with ambient particulate matter (PM) are well established and have been documented in studies conducted around the world. For fine PM (aerodynamic diameter <2.5 μm; $PM_{2.5}$), these health effects include cardiovascular disease and mortality associated with both long- and short-term exposures. The World Health Organization (WHO) estimates that $PM_{2.5}$ accounts for 3 % of cardiovascular deaths worldwide (Cohen et al. 2005). Furthermore, certain populations with pre-existing disease are known to be at increased risk for PM-related health effects (Sacks et al. 2011).

Recently, interest has grown in understanding health effects associated with individual components of PM and determining if PM components are better predictors of health effects compared with PM mass (US EPA 2009). This is a plausible hypothesis given that PM composition varies across different geographical regions and regional differences are observed in PM-related health effects reported in a number of epidemiologic studies (Bell et al. 2007; US EPA 2009). The evidence for health effects of specific PM components includes a growing body of literature indicating effects associated with exposure to black carbon (BC) (US EPA 2012; Janssen et al. 2000), which is generally present in submicron particles emitted globally from a wide range of combustion-related sources including biomass burning, residential heating and cooking, industry, and transportation. In the United States, BC emissions are dominated by transportation (52 %; particularly from on-road and non-road diesel) and open biomass burning (35 %; including wildfires) (US EPA 2012). In general, the health effects associated with BC are similar to those of $PM_{2.5}$ (Janssen et al. 2000), which has been demonstrated in a previous review and meta-analysis (Janssen et al. 2011, 2012) where associations of mortality, hospital admissions, and emergency department visits with BC were consistent with those for $PM_{2.5}$ and PM_{10}. However, pre-existing disease is known to modify the association between $PM_{2.5}$ and cardiovascular disease, but this has not been evaluated for BC.

The objective of this systematic review was to evaluate cardiovascular health effects associated with ambient BC in individuals with pre-existing disease. This review focused on three different categories of pre-existing disease: (1) coronary artery disease [CAD; i.e., ischemic heart disease, myocardial infarction (MI), atherosclerosis] and coronary heart disease (CHD); (2) diabetes and metabolic syndrome; and (3) asthma and chronic obstructive pulmonary disease (COPD), which are highly prevalent in countries around the world (Anderson 2005; Tardif 2010; Wild et al. 2004).

Methods

Definition of black carbon and elemental carbon

There are a multitude of measurement techniques available to quantify concentrations of BC or BC analogs. The most commonly used techniques can be classified into two groups: optical methods and thermochemical methods. Optical methods measure light absorption which is proportional to the BC concentration. Thermochemical methods measure thermal evolution of carbon from a filter sample to quantify the elemental carbon (EC) concentration. BC and EC are strongly associated, although not identical due to their fundamentally different operational definitions (Arnott et al. 2005). While BC and EC have specific operational definitions, they are both indicators for carbon-rich combustion sources and are often used interchangeably in the literature. Therefore, BC and EC were simultaneously evaluated in this review. Soot is another term frequently used to describe the carbon-rich emissions resulting from incomplete combustion. However, because the definition of soot can vary and is often imprecise, we did not include studies of soot in this review.

In addition to epidemiologic studies on BC or EC, experimental studies were included in this review when the exposure was relevant to ambient BC or EC. Carbon black, a laboratory-derived model compound for diesel soot, has been used to exclusively evaluate the toxicity of EC, but the representativeness of these particles to ambiently derived BC or EC is unclear. Furthermore, few studies have investigated the effect of carbon black on cardiovascular health in individuals with pre-existing disease. Therefore, this review was expanded to include experimental studies for any PM source in which BC or EC were explicitly quantified. The set of experimental studies included in this review examined exposure to diesel particles due to its high EC mass fraction as well as CAPs derived from ambient air with a varying range of reported EC concentrations. A major limitation to these studies, however, is the inability to isolate any direct health effect resulting from EC exposure from the PM mixture.

Search strategy

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used for our stepwise systematic literature search (Moher et al. 2009). For epidemiologic studies (Fig. 1), the PubMed database was used to search for black carbon or elemental carbon, which yielded 1,288 records. Next, publications on cardiovascular health effects were identified in PubMed, resulting in 2,034,802 records (Online Resource). Overlap between these two searches returned 117 epidemiologic records. Nineteen studies were identified that included subjects with pre-existing disease: nine for diabetes or metabolic syndrome, ten for CAD or CHD, and two for asthma/COPD.

Experimental studies were identified using a similar approach (Fig. 2). The PubMed database was used to search for carbon black, diesel or concentrated ambient particles; 6,128 records were identified. Overlap between these records and 2,397,283 records resulting from a PubMed search for publications related to cardiovascular health effects yielded 421 experimental records (Online Resource). These records were categorized by exposure

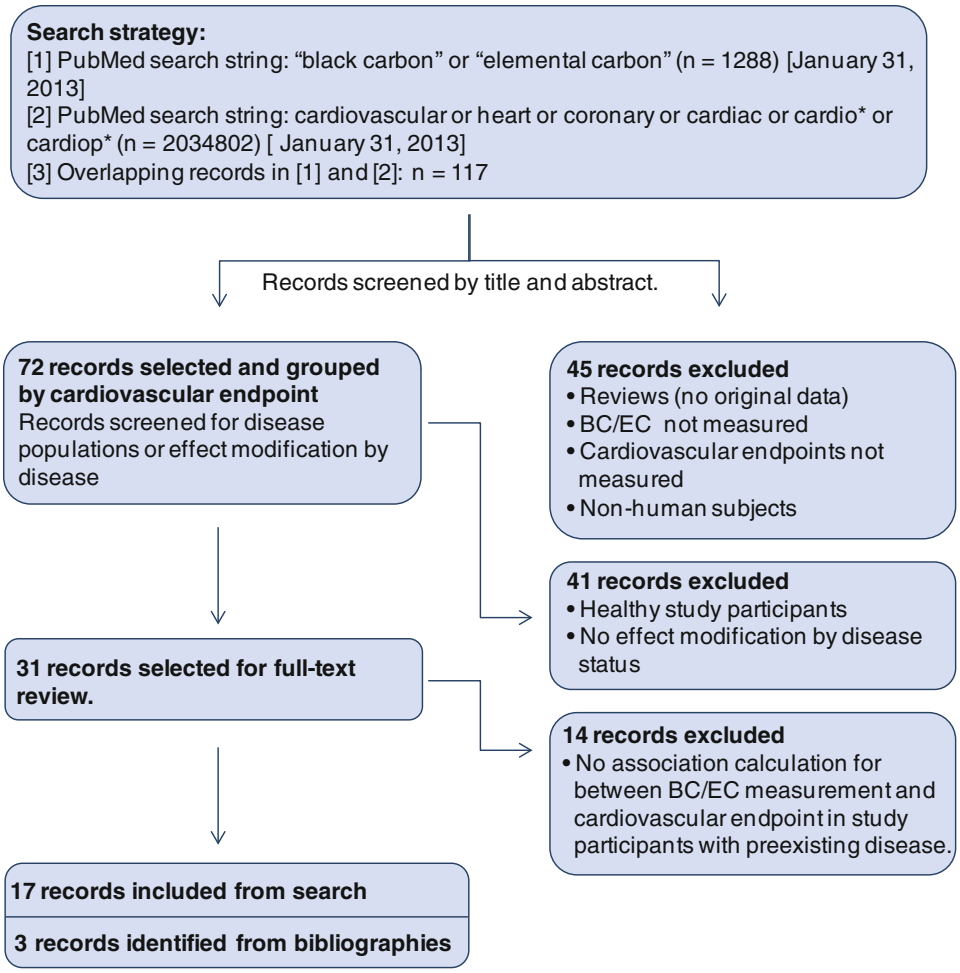

Fig. 1 PRIMSA flow diagram summarizing the systematic literature search and exclusion/inclusion criteria for epidemiologic studies

(i.e., carbon black, diesel, or CAPs) to facilitate further evaluation of exposure characterization and the study population. Diesel exhaust and CAPs records were screened and included only if they reported BC or EC measurements. Ultimately this review included one carbon black study, two diesel exhaust studies, and three CAPs studies.

Risk of bias evaluation

Studies meeting inclusion criteria were evaluated for risk of bias in results and study design. Published sources on systematic review were considered when developing a risk of bias framework for use in this review (Agency for Healthcare and Quality 2012; Higgins et al. 2011). Epidemiologic studies were evaluated for evidence of confounding bias, exposure misclassification, selection bias, detection bias, disease misclassification, and selective reporting. Experimental studies were evaluated for similar biases. Due to the controlled nature of these experiments, exposure bias in these studies assessed subject and research staff blinding and inclusion of appropriate controls. Additional information regarding these biases and the evaluation results for all studies are provided in the Online Resource.

Data extraction and synthesis

Upon selection of studies meeting inclusion criteria, study details and relevant results were extracted into tables and reviewed for verification by an additional author. Any inconsistencies between the two authors were discussed for clarification and agreement on final reporting. Results and trends were compared across studies for each pre-existing disease to identify similarities and inconsistencies in cardiovascular effects associated with BC.

Results

Risk of bias evaluation

The risk of bias framework developed for this review addressed relevant biases for this field of literature. In

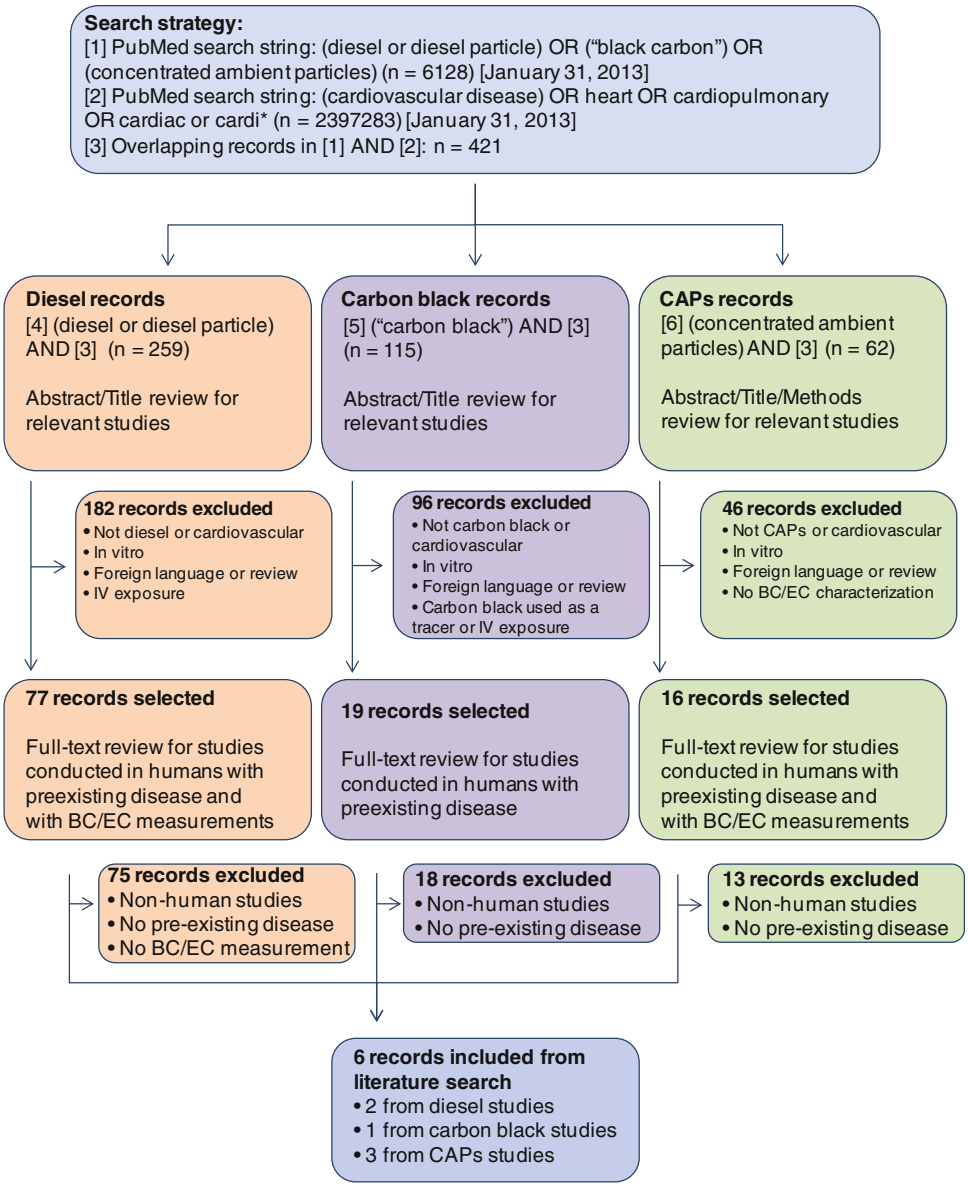

Fig. 2 PRIMSA flow diagram summarizing the systematic literature search and exclusion/inclusion criteria for experimental studies

general, low risk was assigned for the majority of studies and categories of bias (Fig. 3; Online Resource), which was anticipated given the nature of these studies; most were panel studies with individual-level data available for both BC exposure and cardiovascular effects while others included repeated measures, thus accounting for time-invariant, individual-level confounders. Additionally, cardiovascular effects were derived from electrocardiograph (ECG) readings or laboratory assays, rather than being self-reported or subjective. The variability in risk of bias assignment for exposure misclassification reflects the proximity of monitors to study subjects in epidemiologic studies; given the potential for spatial variability in BC concentrations and for removal of BC particles on infiltration indoors, low exposure misclassification risk was assigned only to studies incorporating indoor or personal exposure measurements (Delfino et al. 2008, 2009, 2010; Hsu et al. 2011; Jansen et al. 2005; Zanobetti et al. 2009). Two studies were assigned probably high exposure risk of bias for highly uncertain monitoring techniques (Dubowsky et al. 2006; von Klot et al. 2009). Selection bias also contributed a small amount of uncertainty due to subject attrition and potential healthy subject effects in recruitment, though this would likely shift the estimate towards the null. Selective reporting was identified in two studies that did not include quantitative results, but reported no association between health effects and BC exposure (Hsu et al. 2011; Jansen et al. 2005).

Bias across experimental studies was similarly low. Subject blinding was not attainable in all studies and some studies included few or no control exposures in healthy subjects or poorly designed clean-air controls.

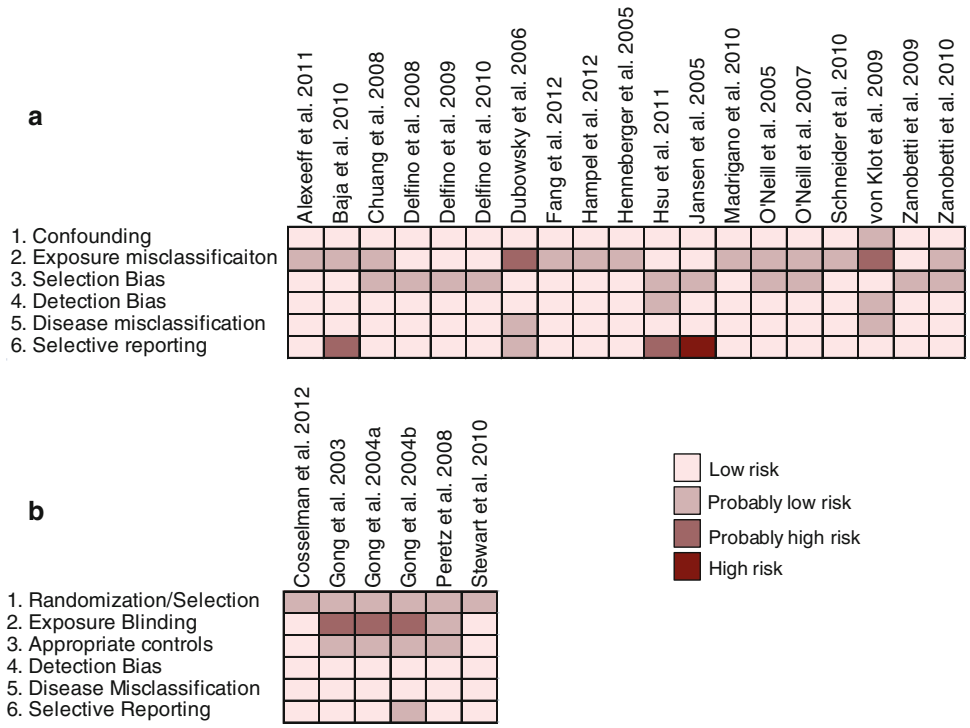

Fig. 3 Risk of bias evaluation for (**a**) epidemiologic studies and (**b**) experimental studies

Additionally, all experimental studies reported a randomized design but did not discuss methods used to randomize participants and exposures. Overall, bias was not a substantial concern in interpreting the data presented across studies.

Pre-existing diseases

Diabetes

Previously published evidence indicates that individuals with diabetes are at increased risk for PM-related cardiovascular disease (Brook et al. 2004; Zanobetti and Schwartz 2002). To evaluate risk related to ambient BC, we identified nine studies (Table 1) examining associations between BC and cardiovascular health effects in subjects with diabetes or examined effect measure modification by diabetes within a larger population. The majority of these epidemiologic studies observed increased risk for several cardiovascular effects with ambient BC exposure.

Among people with diabetes, positive associations have been reported for BC and heart rate variability (HRV) and ventricular repolarization, both of which may predict cardiac arrhythmia. Hampel et al. (2012) and Zanobetti et al. (2010) evaluated ECG recordings for measures of heart rate (HR) and HRV. In a panel of individuals with diabetes, a 0.9 % increase in HR was associated with BC concentrations as well as a 5.2 and 3.7 % decrease in the square root of the mean of the squared differences between adjacent normal RR intervals (rMSSD) and the standard deviation of normal-to-normal heart beat intervals (SDNN), respectively (Hampel et al. 2012). Although the trend in HR was inconsistent for different lag structures examined in the hours before cardiovascular effects were measured, measures of HRV (i.e., rMSSD and SDNN) were consistently reduced in all models. Zanobetti et al. (2010) reported similar findings, where individuals with diabetes had reduced rMSSD relative to BC concentrations compared to those without diabetes (9.1 vs. 3.2 %). There is also evidence that ventricular repolarization, as measured by the heart rate-corrected QT (QTc) interval, is modified by diabetes status; increases in QTc were consistently reported across lag structures (Baja et al. 2010). This trend was not observed in individuals without diabetes.

Changes in endothelial function, coagulation, and inflammation have also been associated with exposure to BC, and may be greater in individuals with diabetes. Flow-mediated dilation, a standard measure of endothelial function, decreased by 12.6 % with increasing concentrations of BC in subjects with diabetes, while no associations were observed in subjects without diabetes but having documented diabetic risk factors (O'Neill et al. 2005). Blood markers of coagulation and inflammation were measured in a cross-sectional study of individuals with diabetes, and increases in von Willebrand Factor (vWF) were weakly associated with BC at various lags; however, exposure to BC using individual lag days was strongly associated with soluble intracellular adhesion molecule-1 (sICAM-1) as well as vascular cellular adhesion molecule-

Table 1 Epidemiologic studies of cardiovascular health effects in subjects with pre-existing disease identified in the systematic literature review

Epidemiologic studies ($n = 19$)							
Study	Study details	Location	Health effect	Metric	Concentration (μg/m^3)	Exposure assessment	Selected effect estimates (95 % CI)
Diabetes ($n = 9$)							
Alexeeff et al. (2011)	Panel study $n = 642$ males (126, diabetes); 1999–2008	Boston, MA, US	Blood markers of inflammation and coagulation	BC	Mean ± SD (4-week avg): 0.42 ± 0.30; (8- and 12-week avg): 0.42 ± 0.29	Predicted daily outdoor residential concentrations from spatiotemporal land-use regression model generated from 82 city-wide monitors	Change in sICAM-1(%) per IQR (0.3 μg/m^3): 4.437 (1.803, 7.139), 4-week avg; 4.637 (1.747, 7.610), 8-week avg; 4.480 (1.482, 7.567), 12-week avg Change in sVCAM-1 (%) per IQR (0.3 μg/m^3): 5.720 (2.007, 9.567), 4-week avg; 4.999 (0.951, 9.209), 8-week avg
Baja et al. (2010)	Repeated measures study $n = 580$ males (133, diabetes) (926 total ECG readings); November 2000–December 2008	Boston, MA, US	Ventricular repolarization	BC	Mean ± SD (1-h avg during ECG): 1.08 ± 0.84 (1-h avg 10 h before ECG): 0.64 ± 0.51	Continuous measurements from outdoor central-site monitor	Change in mean QTc (msec) per IQR (0.55 μg/m^3, 10-h): 5.28 (0.67, 9.90), 4-h avg
Dubowsky et al. (2006)	Panel study $n = 44$ (8 diabetes, 26 samples)(14 obese, 41 samples) (36 hypertension, 108 samples); March–June 2002	St. Louis, MO, US	Blood markers of inflammation and coagulation	BC	Mean ± SD (24-h avg): 0.90 ± 0.28	Continuous measurements from outdoor central-site monitor	Change in CRP (%) per IQR (0.23 μg/m^3): 3 conditions present: 49 (16, 90), 5-day avg ≤2 conditions present: 9.0 (−3.8, 24), 5-day avg Change in IL-6 (%) per IQR (μg/m^3): 3 conditions present: 15 (−2.2, 35), 5-day avg ≤ 2 conditions present: −2.7 (−11, 6.2), 5-day avg
Fang et al. (2012)	Panel study $n = 580$ males (138 diabetes, 76 diabetes + CHD); 2000–2008	Boston, MA, US	Blood markers of inflammation and coagulation	BC	Mean, range (24-h avg): 0.39, 0.01–3.84	Predicted daily outdoor residential concentrations from spatiotemporal land-use regression model generated from > 80 city-wide sites	Change in blood markers (%) per IQR (0.36 μg/m^3): IL-6: 55.1 (16.7, 106.3), 3-day lag IL-8: 19.9 (5.3, 36.4), 4-day lag VEGF: 12.5 (−7.2, 36.5), 4-day lag IL-1β: 27.4 (0.9, 60.8), 3-day lag; 46.1 (18.8, 79.6), 4-day lag; 25.1 (6.4, 46.9), 5-day lag

Table 1 continued

Epidemiologic studies ($n = 19$)							
Study	Study details	Location	Health effect	Metric	Concentration (μg/m^3)	Exposure assessment	Selected effect estimates (95 % CI)
Hampel et al. (2012)	Panel study $n = 61$, diabetes March 2007–December 2008	Augsburg, Germany	HRV	BC	Mean ± SD (1-h avg): 1.8 ± 1.5	Hourly measurements from outdoor central-site monitor	Change in ECG parameters (%) per IQR (1.2 μg/m^3): HR: 0.9 (0.0, 1.8), 6-h lag rMSSD: −3.8 (−7.1, −0.5), 1-h lag; −5.2 (−9.8, −0.4), 6-h lag SDNN: −3.7 (−5.6, −1.8), 2 h
Madrigano et al. (2010)	Repeated measures study $n = 809$ males (383 of 1819 measurements from subjects with diabetes); 1999–2008	Boston, MA, US	Blood markers of inflammation and coagulation	BC	Mean ± SD (24-h avg): All Visits: 0.84 ± 0.44; Visit 1: 0.94 ± 0.47 Visit 2 0.77 ± 0.41; Visit 3 0.74 ± 0.37	Hourly measurements from outdoor central-site monitor	No diabetes effect of associations between BC and sVCAM-1
O'Neill et al. (2005)	Panel study $n = 270$ (227 diabetes); 1998–2002	Boston, MA, US	Endothelial dysfunction	BC	Mean ± SD (24-h avg): 1.0 ± 0.6	Continuous measurements from outdoor central-site monitor	Change in vascular reactivity (6-day avg) (%) per IQR[a]: Flow-mediated dilation −12.6 (−21.7, −2.4) No effect modification in nitroglycerin-mediated dilation
O'Neill et al. (2007)	Cross-sectional study $n = 55$ males, 37 females; diabetes; May 1998–December 2002	Boston, MA, US	Blood markers of inflammation and coagulation	BC	Mean ± SD (24-h avg): 1.1 ± 0.8	Daily measurements from outdoor central-site monitor	Change in blood markers (%) per IQR (0.6 μg/m^3): sICAM-1 (ng/ml): 5.84 (0.87, 11.05), 1-day avg sVCAM-1 (ng/ml): 27.51 (11.96, 45.21), 6-day avg No significant associations between BC and vWF
Zanobetti et al. (2010)	Panel study $n = 46$, CAD (11 diabetes), October 1999–January 2003	Boston, MA, US	HRV	BC	Median, IQR (3-day avg): 0.80, 0.48	Continuous measurements from outdoor central-site monitor	Change in RMSSD (%) per IQR (0.48 μg/m^3): −9.1 (−13.2, −4.9), 3-day avg

Table 1 continued

Epidemiologic studies ($n = 19$)							
Study	Study details	Location	Health effect	Metric	Concentration ($\mu g/m^3$)	Exposure assessment	Selected effect estimates (95 % CI)
Coronary artery disease (CAD) ($n = 10$)							
Chuang et al. (2008)	Repeated measures study $n = 48$, CAD; Dates of study not reported	Boston, MA, US	Myocardial ischemia	BC	Median, IQR (24-h avg): 0.79, 0.47; (12-h avg): 0.75, 0.55	Continuous measurements from outdoor central-site monitor	Relative risk for ST-segment depression $\geq$ 0.1 mm per IQR: 1.13 (0.94, 1.37), 12-h avg, IQR 0.55 $\mu g/m^3$ 1.50 (1.19, 1.89), 24-h avg, IQR 0.47 $\mu g/m^3$
Delfino et al. (2008)	Panel study, repeated measures $n = 29$, CAD (313 blood samples); 2005–2006	Los Angeles, CA, US	Blood markers of inflammation and coagulation	BC and EC	Mean $\pm$ SD (24-h avg): BC 2.00 $\pm$ 0.77, EC 1.61 $\pm$ 0.62 (Correlation between outdoor BC and EC: 0.92)	Hourly measurements from outdoor residential monitor	Change in CRP (ng/mL) per IQR (EC 0.92 $\mu g/m^3$, BC 0.96 $\mu g/m^3$): EC: 1526 (437, 2616), 9-day avg BC: 586 (77, 1094), 1-day avg Change in IL-6 (pg/mL) per IQR (EC 0.92 $\mu g/m^3$, BC 0.96 $\mu g/m^3$): EC: 0.31 (0.04, 0.58), 1-day avg; 0.48 (0.16, 0.80), 3-day avg; 1.14 (0.49, 1.78), 9-day avg BC: 0.48 (0.17, 0.79), 1-day avg; 0.42 (0.07, 0.78), 3-day avg Change in sTNFRII (pg/mL) per IQR (EC 0.92 $\mu g/m^3$, BC 0.96 $\mu g/m^3$): EC: 135 (27, 243), 1-day avg BC: 133 (13, 252), 3-day avg; 288 (53, 521), 9-day avg Change in P-selectin (ng/mL) per IQR (EC 0.92 $\mu g/m^3$, BC 0.96 $\mu g/m^3$): EC: 5.87 (0.98, 10.76), 9-day avg BC: 5.19 (2.20, 8.19), 1-day avg; 2.85 (0.47, 5.23), 3-day avg; 4.23 (1.75, 6.71), 9-day avg

Table 1 continued

Epidemiologic studies ($n = 19$)							
Study	Study details	Location	Health effect	Metric	Concentration (μg/m^3)	Exposure assessment	Selected effect estimates (95 % CI)
Delfino et al. (2009) (Continuation of Delfino et al. (2008))	Panel study $n = 60$, CAD (578 blood samples); 2005–2007	Los Angeles, CA, US	Blood markers of inflammation and coagulation	BC and EC	Mean ± SD (24-h avg): July-Oct: BC 1.59 ± 0.63, EC 1.45 ± 0.52; Oct-Feb: BC 1.76 ± 0.91, EC 1.55 ± 0.71 (Correlation between outdoor BC and EC: 0.89)	Hourly measurements from outdoor residential monitor	Change in IL-6 (pg/mL) per IQR (EC 0.87 μg/m^3): EC: 0.96 (0.43, 1.48), 9-day avg Change in P-selectin (ng/mL) per IQR (EC 0.87 μg/m^3): EC: 4.10 (1.58, 6.61), 5-day avg; 5.66 (1.22, 10.09), 9-day avg
Delfino et al. (2010)	Panel study $n = 64$, CAD (6539 BP measurements); 2005–2007	Los Angeles, CA, US	Blood pressure	BC	Mean ± SD (24-h avg): 1.67 ± 0.79	Hourly measurement from outdoor residential monitor	Increase in systolic BP (mm Hg) per IQR (1.02 μg/m^3): 2.06 (0.6, 3.52), 3-day avg 3.14 (0.57, 5.71), 5-day avg 5.28 (0.86, 9.69), 9-day avg Increase in diastolic BP (mm Hg) per IQR (1.02 μg/m^3): 1.27 (0.49, 2.06), 3-day avg 2.38 (0.99, 3.76), 5-day avg 4.18 (1.8, 6.55), 9-day avg
Fang et al. (2012)	Panel study $n = 580$ males (213 CHD, 76 diabetes + CHD); 2000–2008	Boston, MA, US	Blood markers of inflammation and coagulation	BC	Mean, range (24-h avg): 0.39, 0.01–3.84	Predicted daily outdoor residential concentrations from spatiotemporal land-use regression model generated from > 80 city-wide sites	Change in blood markers (%) per IQR (0.36 μg/m^3): IL-6: 25.6 (7.2, 47.1), 4-day lag TNF-α: 13.2 (1.9. 25.8), 4-day lag; 10.9 (1.0, 21.7), 5-day lag

Table 1 continued

Epidemiologic studies ($n = 19$)

Study	Study details	Location	Health effect	Metric	Concentration (μg/m^3)	Exposure assessment	Selected effect estimates (95 % CI)
Henneberger et al. (2005)	Panel study, repeated measures $n = 56$ males, CAD (625 ECG recording); October 2000–April 2001	Erfurt, Germany	Ventricular repolarization	EC	Mean ± SD (24-h avg): 2.6 ± 2.4	Hourly measurements from outdoor central-site monitor	T-wave amplitude (μV) per IQR (2.3 μg/m^3): 4.67 (−10.00, 0.67), 0–5 h lag Variability of T-wave complexity (%) per IQR (2.3 μg/m^3): 0.13 (0.00, 0.26), 0–5 h lag 0.16 (0.04, 0.29), 12–17 h lag 0.10 (−0.01, 0.22), 18–23 h lag 0.18 (0.03, 0.32), 0–23 h lag
Schneider et al. (2010)	Repeated measures study $n = 56$ males, CAD; October 2000–April 2001	Erfurt, Germany	HRV	EC	Mean ± SD (24-h avg): 2.3 ± 2.1	Hourly measurements from outdoor central-site monitor	Change in ECG parameters (%) per IQR (1.8 μg/m^3): rMSSD, 5-min reading: −7.2 (−12.0, −2.1), 1–23 h avg rMSSD, 24-h reading: −5.5 (−10.7, −0.1), 24–47 h avg pNN50, 24-h reading −13.8 (−26.6, −1.1), 24–47 h avg DC, 24-h reading: −9.1 (−15.4, −2.8), concurrent; −11.5 (−18.1, −4.9), 0–23 h avg; −10.4 (−17.3, −3.5), 24–47 h avg
von Klot et al. (2009)	Cohort study $n = 4096$, myocardial infarction; 1995, 1997, 1999, 2001, and 2003	Worcester, MA, US	Mortality	EC	Mean, range (1-year avg): 0.42, 0.05–.92	Predicted weekly outdoor residential concentrations from spatiotemporal land-use regression model generated from BC measurements in Boston, MA	Change in mortality after second year follow-up (%) per IQR (0.24 μg/m^3): 1.17 (1.04, 1.32), 30-day avg
Zanobetti et al. (2009)	Panel study $n = 48$, CAD; Dates of study not reported	Boston, MA	Ventricular repolarization	BC	Mean, IQR (6-h avg): Central-site: 0.72, 0.60; Outdoor: 0.5, 0.50; Indoor: 0.41, 0.41	Continuous measurements from outdoor central-site, outdoor residential, and indoor residential monitors	Change in T-wave alternans ≤ 26 μV (%) per 1.0 μg/m^3: 2.9 (1.5, 4.3), 6-h avg

Table 1 continued

Epidemiologic studies ($n = 19$)							
Study	Study details	Location	Health effect	Metric	Concentration (μg/m^3)	Exposure assessment	Selected effect estimates (95 % CI)
Zanobetti et al. (2010)	Panel study $n = 46$, CAD; October 1999–January 2003	Boston, MA	HRV	BC	Mean, IQR (3-day avg): 0.80, 0.48	Continuous measurements from outdoor, central-site monitor	Results presented graphically[b]
Asthma/COPD ($n = 2$)							
Hsu et al. (2011)	Panel study $n = 9$ (New York), 15 (Seattle), COPD; July 2000–January 2001	New York, NY and Seattle, WA	Heart rate	BC	Not reported	Daily measurements from outdoor central-site, indoor residential, and personal monitors	No associations were observed between BC and HR.
Jansen et al. (2005)	Panel study $n = 2$ males, 5 females, asthma $n = 5$ males, 5 females, COPD; 2002–2003	Seattle, WA	Blood pressure	BC	Mean, IQR (24-h avg): Outdoor: 2.01, 1.68; Indoor: 1.34, 1.12; Personal: 1.64, 2.05	Hourly measurement from outdoor central-site, outdoor residential, indoor residential and personal monitors	No associations were observed between BC and BP.

[a] IQR not reported

[b] Significant decreases in rMSSD and HF are reported for 30 min up to 5 days moving averages of BC

1 (sVCAM-1), with increases as large as 27.51 % per IQR increase in BC (O'Neill et al. 2007). Similar results were reported in a long-term exposure study; BC exposure (4–12 weeks) was associated with increases in these adhesion molecules in individuals with diabetes compared to those without (sICAM 4.437–4.637 %, sVCAM-1 4.999–5.720 %) (Alexeeff et al. 2011). In contrast, Madrigano et al. (2010) did not find any evidence for effect measure modification by diabetes status when examining associations between BC and sVCAM-1.

Two studies also evaluated associations between BC exposure and various inflammatory cytokines and proteins in individuals with diabetes. Fang et al. (2012) conducted a panel study and stratification of results by diabetes status resulted in a 55.1 % increase in interleukin-6 (IL-6) and a 19.9 % increase in IL-8 in association with an IQR increase in BC. A positive association between BC and IL-1β in subjects with diabetes was also observed and was somewhat consistent across individual lag days. Interestingly, there was an inverse relationship between BC measurements and IL-1β in individuals without diabetes (Fang et al. 2012). IL-6 and C-reactive protein (CRP) were also associated with BC exposure in subjects that were diabetic, hypertensive, and obese; when only two of these diagnoses were present, the association between BC and inflammatory markers was diminished (Dubowsky et al. 2006).

An experimental study found that inhalation of EC ultrafine particles (50 $\mu g/m^3$) for 2 h by subjects with type 2 diabetes at rest caused an increase in IL-6 and vWF (Stewart et al. 2010) (Table 2). These subjects also had a transient increase in platelet activation and conjugation with leukocytes following EC exposure, indicative of an increased pro-thrombotic environment. Other biomarkers of systemic inflammation (CRP), coagulation, or vascular activation such as ICAM-1 or VCAM-1 did not change following exposure.

Metabolic syndrome is a group of metabolic risk factors (such as obesity, high blood pressure, high cholesterol, and insulin resistance) that, when occurring together, increase the chance for future cardiovascular diseases such as type 2 diabetes and CAD. Two studies have exposed resting adults with and without metabolic syndrome to diesel exhaust (Cosselman et al. 2012; Peretz et al. 2008). Cosselman et al. (2012) reported an increase in systolic blood pressure, but not diastolic blood pressure or HR, following diesel exhaust inhalation (200 $\mu g/m^3$). However, pre-existing metabolic syndrome did not modify this result. Another study reported an increase in brachial artery diameter and plasma endothelin-1 (ET-1) levels following inhalation of diesel exhaust (200 $\mu g/m^3$) (Peretz et al. 2008). These effects were greater in healthy participants than those with metabolic syndrome. These studies suggest that having metabolic syndrome may not cause an individual to be more at risk for cardiovascular effects following diesel exhaust inhalation, and potentially BC as well.

Overall, the studies evaluated provide evidence indicating that individuals with diabetes are at increased risk for cardiovascular health effects in response to BC exposure. This conclusion is based on a number of studies that found larger effects in individuals with diabetes when compared to individuals without diabetes. Moreover, aside from Dubowsky et al. (2006), risk of bias was low or probably low across all studies evaluated, strengthening this conclusion.

Coronary artery disease and coronary heart disease

The systematic literature search identified 10 epidemiologic publications that examined the relationship between cardiovascular effects and BC in subjects with pre-existing CAD or CHD (Table 1). These studies observed decreased heart rate variability (HRV), modulation of cardiac electrophysiology measures, and increased systemic inflammation in subjects with pre-existing CAD. Few studies evaluated whether presence or absence of pre-existing CAD modified the risk for these responses following exposure to BC; however, one study does suggest that BC may have greater effects in people with pre-existing CAD (Fang et al. 2012).

Several studies evaluated associations between BC and blood markers of inflammation and coagulation. Delfino et al. (2008) conducted a panel study in 29 subjects (age $\geq$ 65 years) with diagnosed CAD during cool and warm temperatures. Positive associations were reported for CRP, IL-6, tumor necrosis factor receptor type II (TNFRII), and P-selectin with concentrations of BC, while no associations were observed for fibrinogen, IL-6 receptor, TNF-α, VCAM-1, and ICAM-1. A second year of data was added to this study as 31 subjects from two additional retirement communities were enrolled (Delfino et al. 2009). Associations between BC and IL-6 and P-selectin remained positive. The associations with CRP and TNF RII were more variable and less precise. Inflammatory and coagulatory markers were also evaluated in a seasonal context; associations were strongest during cooler months with more stagnant air while those for the warmer months were inconsistent. Fang et al. (2012) also observed a positive association between BC and IL-6; a 25.6 % increase was reported for subjects with CHD compared to a 4.2 % decrease in subjects without CHD, relative to an IQR increase in BC. Associations between TNF-α and BC were also modified by CHD (Table 1).

BC exposure has been associated with cardiophysiologic perturbations assessed by ECGs, including measures of HRV and ventricular repolarization. Decreases in

Table 2 Experimental studies of cardiovascular health effects in subjects with pre-existing disease identified in the systematic literature review

Experimental studies with quantified EC exposure ($n = 6$)						
Study	Study subjects (n = m/f)	Location	Exposure	Metric	Concentration ($\mu g/m^3$)	Health effects
Cosselman et al. (2012)	Metabolic syndrome ($n = 8/6$); Healthy ($n = 22/9$)	Seattle, WA, US	$PM_{2.5}$ diesel exhaust, 2 h at rest	EC	$PM_{2.5}$: 205.4 ± 5.4	Blood pressure and heart rate
Gong et al. (2003)	Asthma ($n = 6/6$); Healthy ($n = 6/6$)	Los Angeles, CA, US	$PM_{2.5}$ CAPs, 2 h with exercise	EC	EC in CAPs: 13 ± 7; EC in filtered air: 3.1 ± 3.9	ECG analysis (HR and HRV), Blood pressure, Respiratory function, Respiratory/Cardiovascular symptoms, biomarkers of systemic and respiratory inflammation and coagulation
Gong et al. (2004a)	Asthma ($n = 4/8$); Healthy ($n = 2/2$)	Los Angeles, CA, US	PM_{10} CAPSs, 2 h with exercise	EC	EC in CAPs: 2.9 ± 2.1	Respiratory/Cardiovascular symptoms, blood pressure, respiratory function, airway inflammation, ECG (HR and HRV)
Gong et al. (2004b)	COPD ($n = 8/5$); Healthy elderly ($n = 4/2$)	Los Angeles, CA, US	$PM_{2.5}$ CAPs, 2 h with exercise	EC	EC in CAPs: 12 ± 8; EC in filtered Air: 1.1 ± 1.0	ECG analysis (HR and HRV), Hematologic analyses, Blood pressure, Respiratory function, Respiratory/Cardiovascular symptoms, biomarkers of systemic and respiratory inflammation and coagulation
Peretz et al. (2008)	Metabolic syndrome ($n = 11/6$); Healthy ($n = 8/2$)	Seattle, WA, US	$PM_{2.5}$ diesel exhaust, 2 h. at rest	EC	$PM_{2.5}$: 101.53 and 205.33	Endothelial function, biomarkers of vascular tone, plasma catecholamines and metabolites
Stewart et al. (2010)	Diabetes ($n = 9/10$)	Rochester, NY, US	Carbon UFPs (count median diameter = 32 nm), 2 h at rest	EC	EC UFP (> 95 % EC): 50.7 ± 2.8	Biomarkers of systemic inflammation, vascular activation, and coagulation

measures of HRV including rMSSD and high-frequency domain (HF) were consistently associated with ambient BC concentrations in a panel of subjects with CAD. Effect estimates were greatest when exposure was assigned using 5-day moving averages; rMSSD and HF decreased by 4 and 16.7 %, respectively, per IQR increase in BC. Other statistical models controlling for indoor and traffic-related BC exposure also resulted in consistent reductions in rMSSD and HF, with traffic-related decreases in HF estimates reaching as much as 39 % (Zanobetti et al. 2010).

Positive associations between ambient and residential BC concentrations on ventricular repolarization have also been reported. T-wave alternans (TWA) were increased by as much as 2.9 % with increasing BC concentrations, and models controlling for time spent in traffic calculated increases as high as 6.12 % (Zanobetti et al. 2009). Associations between EC and T-wave parameters have also been reported by Henneberger et al. (2005), who conducted a panel study in individuals with CAD in East Germany. A 4.87 % decrease in T-wave amplitude was associated with increases in BC concentration while increases in the variability of T-wave complexity were consistently associated with BC concentrations during the first 24 h. Chuang et al. (2008) found consistent decreases in ST segment depression $\geq$0.1 mm related to BC exposure in a cohort of men diagnosed with CAD; exposure to BC was associated with a 1.5 % increase in relative risk for ST segment depression. These changes in electrocardiographic markers are indicative of myocardial ischemia or altered cardiac repolarization.

These effects may reflect subclinical cardiac disease and are closely related to cardiac arrhythmia, which can be a precursor to cardiovascular mortality. To date, few studies have examined the association between BC and mortality in populations with pre-existing disease. von Klot et al. (2009) identified patients with a discharge diagnosis of MI and used census information to determine the length of survival after discharge in relation to ambient EC concentrations. Associations were positive, although not statistically significant within 2 years of discharge; however, a 15 % increase in death 2 years after hospital discharge was associated with EC concentration.

Generally, data across these studies indicate that individuals with CAD or CHD experience cardiovascular effects in association with ambient BC exposure. With the exception of uncertainty in the EC monitoring technique used in the mortality study by von Klot et al. (2009), there was minimal concern regarding bias in this body of literature. There were no experimental studies identified for subjects with pre-existing CAD to support these observations. Additionally, only one study (Fang et al. 2012) allowed for comparison to subjects without CAD, which suggested increased risk for BC-related inflammation. Conclusions regarding increased risk for BC-related cardiovascular health effects among individuals with CAD or CHD are limited given the available evidence.

Asthma/COPD

The literature search identified two epidemiologic and three experimental studies that examined cardiovascular effects following exposure to BC in individuals with pre-existing asthma or COPD. One small panel study in Seattle, WA, reported no associations between BC and blood pressure in subjects with asthma or COPD, although quantitative data were not provided (Jansen et al. 2005). Another panel study found positive associations between EC exposure and HR in subjects with COPD during the summer in New York City, but negative associations in the winter (Hsu et al. 2011). Subjects with COPD were also evaluated in the summer and winter in Seattle, WA, but no trend or associations were reported between HR and EC concentration.

Two studies examined the effects of inhalation of CAPs derived from Los Angeles, CA in exercising subjects with and without asthma (Gong et al. 2003, 2004a) (Table 2). These studies differed in selection of particle size of the CAPs. Gong et al. (2004a) exposed volunteers with and without asthma to concentrated ambient coarse particles (CCP) with a mean EC concentration of 2.9 $\pm$ 2.1 $\mu g/m^3$ and reported decreased measures of HRV (SDNN and SDANN5) and increased HR; however, these effects were greater in healthy subjects than in subjects with asthma. It is important to note that EC is generally in the submicron particles, and CCP samples would not capture the majority of the ambient EC. Gong et al. (2003) exposed volunteers to CAPs in the $PM_{2.5}$ size range with a mean EC concentration of 13 $\pm$ 7 $\mu g/m^3$ and reported increased plasma ICAM-1 and IL-6, decreased LF/HF power ratio, decreased ST-AMD (composite ST voltage index), and changes in systolic blood pressure. Compared to healthy subjects, subjects with asthma had a greater increase in IL-6 and decrease in systolic blood pressure, whereas healthy subjects showed an increase in blood pressure. The authors also conducted an exposure–response analysis and found that higher EC concentration predicted a more negative change in ST-AMD measured 2 days after exposure, while higher EC predicted a more positive change in ST-AMD immediately post-exposure. The other cardiovascular changes (ICAM-1, IL-6, and LF/HF) were not associated with EC concentration changes. One study exposed exercising volunteers with and without COPD to CAPs in the $PM_{2.5}$ size range from Los Angeles, CA (Gong et al. 2004b). Subjects with COPD had a decrease in the incidence of ectopic heartbeats, whereas healthy subjects had a

decrease in HR and HRV, and an increase in plasma basophil counts following inhalation of CAPs.

Overall, these epidemiologic and experimental studies suggest that pre-existing asthma or COPD does not result in increased risk for cardiovascular effects following BC exposure, and experimental studies suggest that individuals with either asthma or COPD may be less responsive to BC exposure. The potential biases present in this body of literature slightly mitigate these conclusions; the experimental studies were unable to achieve complete exposure blinding due to sensory detection of exposure and the epidemiologic studies (Hsu et al. 2011; Jansen et al. 2005) only reported that the associations were not statistically significant, which preclude any identification of trends in BC-related cardiovascular effects that may be important across studies.

Discussion

The objective of this systematic review was to characterize the relationship between exposure to BC and cardiovascular effects among individuals with pre-existing disease. The cardiovascular health effects included were subclinical, including HRV, ventricular repolarization, and blood markers of coagulation and inflammation; no studies evaluated relationships between BC and hospital admissions or emergency department visits in populations with pre-existing disease.

Modification of cardiovascular effects by BC exposure in individuals with diabetes or CAD/CHD was observed across studies. The strongest evidence for increased risk of effects related to BC exposure was found for individuals with diabetes as most studies included a comparison to individuals without diabetes and reported larger effects in subjects with diabetes. Only one study of individuals with CAD stratified by disease status, thus limiting our understanding of increased risk modification by the presence of CAD. Few studies evaluated the cardiovascular effects associated with exposure to ambient BC in individuals with respiratory disease and evidence for an association was inconsistent. The results of these studies could not be analyzed using a meta-analysis since studies reported a wide variety of effects that could not be used to calculate a pooled average.

A weakness in interpreting evidence in this review is the limited generalizability. The large majority of studies analyzed data from subjects in the Boston metropolitan region. Of the nine studies informing risk to individuals with diabetes, only one was conducted outside of Boston (Augsburg, Germany) (Hampel et al. 2012). Five of the studies with CAD subjects were from Boston, while three were conducted in Los Angeles and two were conducted in East Germany. The ambient concentration and composition of PM is geographically heterogeneous, with variations due to unique PM sources in different locations. Thus, conclusions drawn from a body of evidence that is focused on one geographic area, in this case Boston, MA, may have limited generalizability to populations in other geographic locations. Furthermore, the majority of studies included only male subjects. Panels or cohorts that included females did not stratify by sex to elucidate differences among men and women.

In presenting evidence of health effects associated with ambient BC, conclusions were drawn for each pre-existing disease to identify at-risk populations, but it is also useful to look at cardiovascular health effects across studies of pre-existing disease in an attempt to understand which endpoints are most sensitive to ambient BC concentrations. In doing so, we observed that the proinflammatory cytokine, IL-6 was associated with ambient BC exposure in all epidemiologic studies, where it was measured and was also increased in individuals with asthma and diabetes exposed to CAPs and EC ultrafine particles, respectively. Despite being measured across multiple studies of pre-existing disease, associations between vWF, CRP, ICAM-1, and VCAM-1 were not consistent. However, associations of these biomarkers were consistently observed with multi-day averages (e.g., 6 days) and longer lags (e.g., 3–4 days), suggesting a more delayed response to ambient BC.

Another cardiovascular measure having consistent associations with BC was RMSSD, which estimates the short-term components of HRV. Although changes in RMSSD were not observed in subjects with asthma or COPD, decreases in RMSSD were consistently reported in epidemiologic studies including subjects with diabetes or CAD. Additionally, other measures of HRV (SDNN, LF/HF, and total power) were associated with BC in a subset of studies. HRV has been shown to be an independent predictor of mortality following an acute MI and consistently observed in patients with cardiac failure, potentially indicating a decrease in vagal activity to the heart and instability of the cardiac electrical system (Malik 1996). Similarly, various ECG parameters related to ventricular repolarization were also associated with BC. T-wave amplitude, T-wave complexity, T-wave alternans, and QT interval measurements were not replicated across studies, but a consistent trend was observed across ECG analyses calculated in individual studies. These alterations in HRV and repolarization parameters suggest that BC may be related to an imbalance between sympathetic and parasympathetic regulation of cardiac function, which is known to underlie more severe cardiovascular events such as arrhythmias. Moreover, in contrast to the trends in association of biomarkers with BC, these parameters had stronger associations with BC with shorter lags (0–23 h)

and hourly averages (6–48 h). Overall, studies included in this review demonstrated that inflammation (IL-6) and ECG measurements of HRV and ventricular repolarization were most sensitive to BC exposure, while blood markers of coagulation, HR, and blood pressure were not consistently modified by ambient BC across studies and pre-existing diseases.

We have examined effects of BC in populations with pre-existing disease because PM-induced health effects are greatest in these individuals. Additional observational and experimental lines of evidence not included in our qualitative analysis support our observations for association between BC and cardiovascular disease. A recently published epidemiologic review conducted a meta-analysis to evaluate the effects of BC particles (BCP) on mortality, hospital admissions, and emergency department visits for comparison with $PM_{2.5}$ and PM_{10} (Janssen et al. 2011). In contrast to our review, the definition of BCP in this analysis was broad and included measurement of black smoke in addition to BC and EC. Overall, there were limited data specific to cardiovascular disease, but effect estimates were significantly increased for all-cause mortality and hospital admissions for BCP and $PM_{2.5}$, and results from traffic abatement modeling suggested that BCP would be useful as an additional indicator for health effects related to air pollution. This study was part of a WHO report (2012) on the health effects of BC which also evaluated evidence from toxicological studies using carbon-rich exposure atmospheres. Due to the large variation in experimental exposures (EC ultrafine particles, diesel exhaust, CAPs, and combustion of biomass) compared to the limited number of relevant studies, effects of short-term exposure to pollutant mixtures containing BC could not be determined. This was the case for our review as well, despite differences in inclusion criteria with regard to study subjects and experimental exposures. Although measures of BC are uncommon in human studies, exposure to combustion-derived particles, namely diesel exhaust, has been shown to elicit extra-pulmonary health effects (Ghio et al. 2012) including exacerbation of exercise-induced ischemia as measured by ST-segment depression in individuals with a prior MI (Mills et al. 2007). The effects observed in epidemiologic studies have also been reported in experimental animal studies using pure carbon exposures. Moller et al. (2011) reviewed the literature and concluded that exposure to ambient particles and ultrafine carbon black was associated with vasomotor dysfunction and development of atherosclerotic plaques in animal models of cardiovascular disease (Niwa et al. 2007; Vesterdal et al. 2009). Additionally, multiple studies have demonstrated effects of carbon black exposure on HRV in various in vivo models of cardiovascular disease (Chang et al. 2007; Jia et al. 2012; Tankersley et al. 2004; Wellenius et al. 2002). While this is not a comprehensive summary of the literature, these observational and experimental studies provide coherence and biological plausibility for epidemiologic observations linking ambient BC to cardiovascular health effects.

Conclusions

This study evaluated populations potentially at increased risk of effects associated with exposure to BC. Evidence in these studies consistently demonstrated that diabetes is a risk factor for BC-related cardiovascular effects. Additionally, cardiovascular effects were associated with BC in individuals with coronary artery disease (CAD), but few comparisons to individuals without CAD were provided in the literature. Risk associated with exposure to ambient BC may be small compared to other risk factors for cardiovascular disease; however, these diseases account for large proportions of the population in developed countries and are rapidly increasing in developing nations (King et al. 1998; Neal et al. 2002). Thus, any increase in risk of cardiovascular disease associated with ambient BC is of significance in the context of public health.

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Conflict of interest The authors declare that they have no conflict of interest.

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