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A systematic review of cardiovascular responses associated with ambient black carbon and fine particulate matter

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Abstract

Background: Exposure to fine particulate matter ($PM_{2.5}$), an ambient air pollutant with mass-based standards promulgated under the Clean Air Act, and black carbon (BC), a common component of $PM_{2.5}$, are both associated with cardiovascular health effects.

Objectives: To elucidate whether BC is associated with distinct, or stronger, cardiovascular responses compared to $PM_{2.5}$, we conducted a systematic review. We evaluated the associations of short- and long-term BC, or the related component elemental carbon (EC), with cardiovascular endpoints including heart rate variability, heart rhythm, blood pressure and vascular function, ST segment depression, repolarization abnormalities, atherosclerosis and heart function, in the context of what is already known about $PM_{2.5}$.

Data sources: We conducted a stepwise systematic literature search of the PubMed, Web of Science and TOXLINE databases and applied Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines for reporting our results.

Study eligibility criteria: Studies reporting effect estimates for the association of quantitative measurements of ambient BC (or EC) and $PM_{2.5}$, with relevant cardiovascular endpoints (i.e.

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Financial interests' declaration

The authors declare that they have no actual or potential competing financial interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.02.027.

meeting inclusion criteria) were included in the review. Included studies were evaluated for risk of bias in study design and results.

Study appraisal and synthesis methods: Risk of bias evaluations assessed aspects of internal validity of study findings based on study design, conduct, and reporting to identify potential issues related to confounding or other biases. Study results are presented to facilitate comparison of the consistency of associations with $PM_{2.5}$ and BC within and across studies.

Results: Our results demonstrate similar associations for BC (or EC) and $PM_{2.5}$ with the cardiovascular endpoints examined. Across studies, associations for BC and $PM_{2.5}$ varied in their magnitude and precision, and confidence intervals were generally overlapping within studies. Where differences in the magnitude of the association between BC or EC and $PM_{2.5}$ within a study could be discerned, no consistent pattern across the studies examined was apparent.

Limitations: We were unable to assess the independence of the effect of BC, relative the effect of $PM_{2.5}$, on the cardiovascular system, nor was information available to understand the impact of differential exposure misclassification.

Conclusions: Overall, the evidence indicates that both BC (or EC) and $PM_{2.5}$ are associated with cardiovascular effects but the available evidence is not sufficient to distinguish the effect of BC (or EC) from that of $PM_{2.5}$ mass.

Keywords

Black carbon; Fine particulate matter; Cardiovascular effects

1. Introduction

National Ambient Air Quality Standards (NAAQS) are promulgated for a set of “criteria” pollutants, including particulate matter (PM). PM is a heterogeneous mixture of particles and liquid droplets, comprising multiple components (e.g., organics, acids, metals, crustal material) and size fractions. The mass of particles measured in ambient air with a nominal mean aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$) is one of the indicators used to determine compliance with the NAAQS. The choice of $PM_{2.5}$ mass as an indicator for the standard is underpinned by evidence from numerous studies linking ambient exposure to $PM_{2.5}$ with an array of cardiovascular effects, ranging from subtle subclinical measures (e.g., heart rate variability) to cardiovascular-related mortality (U.S. EPA, 2009).

Epidemiologic studies have found regional differences in the magnitude of the associations between $PM_{2.5}$ and health effects that are not fully explained by variations in the concentration of ambient $PM_{2.5}$ (U.S. EPA, 2009). Experimental studies focusing on individual components point to several components that may be highly toxic to the cardiovascular system motivating research designed to elucidate whether specific components of $PM_{2.5}$ could explain the heterogeneity in $PM_{2.5}$ risk estimates across the epidemiologic study findings (e.g., Baxter et al., 2012; Davis et al., 2011). The extent to which $PM_{2.5}$ mass is the preferred indicator, and whether, or not, a particular component is more closely associated with health effects is of interest to policymakers.

Like exposure to $PM_{2.5}$, exposure to black carbon (BC), a common component of $PM_{2.5}$ and a potentially important contributor to total $PM_{2.5}$ mass (Bell et al., 2007), is associated with cardiovascular effects (U.S. EPA, 2012). BC is generally present in submicron particles generated during combustion (e.g., transportation, biomass burning, residential heating and cooking, power plants, some industries). Although the evidence linking BC to subclinical cardiovascular endpoints is more limited than that for $PM_{2.5}$, BC is of interest from a health perspective because multiple studies report associations between combustion-related air pollution and health effects (U.S. EPA, 2009, 2012; WHO, 2012) and some research suggests that combustion-related particles may have a greater relative toxicity on a per mass basis than $PM_{2.5}$ (Janssen et al., 2011).

The U.S. EPA Integrated Science Assessment for PM (U.S. EPA, 2009) and the subsequent Report to Congress on Black Carbon (U.S. EPA, 2012) concluded that there was limited evidence to indicate BC or other sources and components would be a better predictor of health effects than $PM_{2.5}$, or that the associations between health effects and BC concentrations observed in epidemiologic studies are independent of the associations with $PM_{2.5}$. Reviews focusing on studies that applied source apportionment methods to examine health effects with source categories that include BC also substantiate the conclusion that, based on the current evidence, health effects are attributed to the mixture containing BC as opposed to any individual component such as BC (Stanek et al., 2011; Vedal et al., 2013; Thurston et al., 2016). By contrast, a report by the World Health Organization (WHO) concluded that BC is a better indicator of harmful PM exposure than mass concentration (WHO, 2012). The authors of the WHO report used increment-based, rather than interquartile range (IQR)-based standardization, which largely explained the different interpretations of evidence across reports (Luben et al., 2017).

The epidemiologic evidence linking BC to cardiovascular effects is expanding, and to our knowledge, has not been systematically reviewed. This systematic review aims to examine the strength and trends in the relationships between $PM_{2.5}$ and BC and selected cardiovascular endpoints. We build on the analysis of Luben et al. (2017) who conducted a systematic review to examine the extent to which the current evidence supported an independent effect of BC, separate from $PM_{2.5}$, on hospital admissions, emergency department visits, and mortality from cardiovascular causes. Luben et al. (2017) found exposures to both $PM_{2.5}$ and BC were positively associated with cardiovascular outcomes and that the associations for both $PM_{2.5}$ and BC were generally similar in magnitude. They further concluded that there was insufficient evidence to distinguish the observed effects of BC from those of $PM_{2.5}$. The current study applies similar methods to that of Luben et al. (2017), but focuses on changes in cardiovascular responses that can be measured prior to the manifestation of clinical disease. These endpoints can provide key evidence that supports the biological plausibility for air pollution exposure to affect the cardiovascular system and result in more severe (and more commonly studied) outcomes, like hospital admissions and mortality. Like Luben et al. (2017) our evaluation of BC-associated cardiovascular effects is considered in the context of what is already understood about the health effects of $PM_{2.5}$.

Several pathways by which short- and long-term exposure to $PM_{2.5}$ can lead to overt cardiovascular disease and mortality have been postulated (U.S. EPA, 2009; Brook et al.,

2010). Activation of the sensory nerves in the lung can lead to changes in heart rate, heart rate variability (HRV) and effects on vascular function followed by increased blood pressure, which is a risk factors for cardiovascular disease. In addition, exposure to $PM_{2.5}$ can result in pulmonary inflammation, which can then induce systemic inflammation. Circulating inflammatory cytokines can stimulate the liver to release additional proteins and coagulation factors that can alter hemostasis and increase the potential for thrombosis. In addition to its effect on hemostasis, systemic inflammation can induce vascular dysfunction leading to further plaque development and rupture of existing atherosclerotic plaques, obstruction of blood flow to the heart (i.e., ischemic heart disease), and decreased cardiac output (i.e., heart failure). Although the mechanism of toxicity for BC is not as well understood as that for $PM_{2.5}$, the plausibility that BC may affect the cardiovascular system through pathways involving inflammation and oxidative stress, leading to endothelial dysfunction has been demonstrated in some studies (Niranjan and Thakur, 2017). Thus, a systematic evaluation of the associations between BC (or EC) and $PM_{2.5}$ and cardiovascular endpoints on these pathways could elucidate whether the observed effects can be attributed to the mixture containing BC (i.e., $PM_{2.5}$) as opposed to individual components of $PM_{2.5}$, including BC.

This systematic review uses the following Population, Exposure, Comparison, Outcome, Study Design (PECOS) statement: In any population of adults (ages 18+), including subgroups of susceptible individuals (P), what is the association of BC or $PM_{2.5}$ (E) per unit ($\mu g/m^3$) increase equal to the interquartile range (C) with cardiovascular endpoints (i.e., heart rate (HR) and HRV, preclinical atherosclerosis, electrocardiogram (ECG) changes, and blood pressure) (O) observed in panel (for short-term exposure) or cohort (for long-term exposures) epidemiologic studies (S)?

2. Methods

2.1. Definition of black carbon and elemental carbon

This systematic review was developed as part of a series of manuscripts and its rationale as it relates to exposure metrics is described in detail elsewhere (Luben et al., 2017; Nichols et al., 2013). Briefly, both BC (a carbonaceous or “sooty” material) and elemental carbon (EC) are included in this systematic review with the understanding that they have fundamentally different operational definitions (Arnott et al., 2005) and are measured using different analytical techniques. EC is composed of carbon that is not bound to other elements and for which the natural carbon structure may or may not be preserved, while BC contains EC but refers generally to the dark, components of aerosols that absorb light (WHO, 2012; US EPA, 2012). The terms BC and EC are often used interchangeably in the epidemiologic literature because they are both indicators of carbon-rich combustion sources and are strongly correlated with each other when measured by filter-based methods (U.S. EPA, 2012; Arnott et al., 2005). Epidemiologic studies of less precisely defined carbonaceous materials such as soot and black smoke are not included in this review. When comparing associations with BC to those of $PM_{2.5}$ we scale to IQR increments because the use of a standard increment does not account for the fact that mass-based concentration of BC is often substantially lower than that of $PM_{2.5}$ and, thus, may not reflect real-world exposure to BC.

2.2. Search strategy

A comprehensive search of the scientific literature compiled in the PubMed, Web of Science and TOXLINE databases through December 31, 2017 was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Search strings, inclusion and exclusion criteria are summarized in Fig. 1. The initial PubMed search string was developed to identify publications on BC, EC and $PM_{2.5}$. The second PubMed search string was used to identify studies of cardiovascular health effects. The references were manually screened for relevance to the review (initially by author JN and updated by EFK). Titles and abstracts were subsequently screened using SWIFT-ActiveScreener (SWIFT-AS), a software application employing machine learning in real-time based on inclusions and exclusion screening decisions to predict relevant references (by EFK). Using this method, references were queued based on predicted relevance, until a 95% threshold was reached (Cohen et al., 2006; Howard et al., 2016). The full-text of the potentially relevant publications was reviewed against inclusion and exclusion criteria (by EFK) to identify studies for a subsequent risk of bias evaluation described below.

Except for the endpoints examined, study inclusion criteria listed below are similar to those described by Luben et al. (2017):

- Original peer-reviewed research article;
- Published in the English language;
- Quantitative measurement of BC or EC and $PM_{2.5}$ to characterize exposure to these pollutants in outdoor air;
- Associations of BC or EC and $PM_{2.5}$ concentrations with inter-mediate cardiovascular endpoints reported.

The cardiovascular endpoints typically measured in short-term exposure studies (hours to days) that were included in this review were indicators of autonomic nervous system tone (i.e., heart rate variability [HRV]), heart rhythm, blood pressure and vascular function, ST segment depression, and repolarization abnormalities. Cardiovascular endpoints evaluated in long-term exposure studies were HRV, atherosclerosis and heart function. The studies of short-term exposures are discussed separately from studies of long-term exposure (months to years).

2.3. Risk of bias evaluation

Epidemiologic 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 and Green, 2011; Rooney et al., 2014). Epidemiologic studies were evaluated by two study authors (EFK primary and AB or TJL secondary) for evidence of confounding bias, exposure misclassification, selection bias, detection bias, disease misclassification, and selective reporting. Discrepancies between authors were reconciled after the independent evaluations were completed. These study aspects could be rated as “high”, “probably high”, “probably low”, or “low” depending on the standardized evaluation criteria. In short, the

methods applied to the risk of bias evaluation were adapted from the Office of Health Assessment and Translation (OHAT) risk-of-bias tool described in Rooney et al. (2014) and modified for application to the observational studies included in this review. Specifically, questions pertaining to randomization, treatment allocation groups or blinding were not used. Rather, more general questions that applied to observational studies were used and additional criteria were developed to facilitate consistent evaluation of the studies (see Supplemental text and Table 1).

2.4. Data extraction and synthesis

Study details and relevant results from epidemiologic studies that met inclusion criteria were initially extracted (EFK) and validated by a second author (TJL). Inconsistencies between the two reviewers were discussed for clarification and agreement on final reporting. Epidemiologic studies of cardiovascular responses to air pollution often examine several sub-daily, daily or longer exposure periods in relation to the endpoint measured, which may be measured continuously, in real time (e.g., ECG or ICD recordings). Because the biologically relevant timing and duration of air pollution exposure on these intermediate endpoints is not certain, we selected effect estimates to maximize comparability across studies. If results for both sub-daily and daily exposures were presented, we selected results for the 24 h average exposure because the majority of the data on $PM_{2.5}$ exposures and health effects encompasses this averaging time. Otherwise, the longest duration sub-daily exposure metric was selected. If only associations with multi-day average exposures were reported, the shortest duration exposure metric was selected. Although exposures were lagged in some studies such that a defined period prior to the outcome measurement was not considered in the analysis, exposures measured concurrently relative to the outcome were preferentially selected if available. Effect estimates from fully adjusted models were extracted for display in forest plots to reflect an increase in exposure concentration equal to the IQR as reported in the study.

As noted previously, our evaluation of BC-associated health effects is considered in the context of what is already understood about the health effects of exposure to $PM_{2.5}$. The scientific evidence for long- and short-term exposure to ambient $PM_{2.5}$ was systematically synthesized and characterized in the Integrated Science Assessment for PM (U.S. EPA, 2009). The approach used in the Integrated Science Assessment (ISA) relies upon integration of the scientific evidence both within and across scientific disciplines (i.e. epidemiologic, experimental animal and controlled human exposure studies), and draws upon the Hill criteria for causation (Hill, 1965) emphasizing biological plausibility, consistency within lines of evidence, and coherence across lines of evidence to draw conclusions (Owens et al., 2017; U.S. EPA, 2015). Based on the application of this approach, the 2009 PM ISA concluded that there was a causal relationship between short- and long-term exposure to $PM_{2.5}$ and cardiovascular effects (U.S. EPA, 2009). Although the evidence base is more limited, we apply a similar approach to BC in this study, briefly characterizing the biological plausibility and the experimental evidence that informs coherence between the epidemiologic and experimental results. Our emphasis, however, is on elucidating the similarities and/or inconsistences of the results and discernable trends, both within and across the epidemiologic studies in order to consider whether BC is a more

strongly associated with cardiovascular responses than $PM_{2.5}$. Results presented in plots were ordered by type of population (i.e. healthy adults, older adults, pre-existing disease).

3. Results

3.1. Search strategy and risk of bias evaluation

The PRISMA search of the PubMed, Web of Science and TOXLINE databases returned 1167 records. Ninety of these records, plus an addition 6 records identified through manual screening, were selected for a full text review after screening the title and abstract, and 40 short-(< 30-day exposure) and 4 long-term exposure (months to years) epidemiologic studies were confirmed to meet the inclusion criteria defined by the PECOS statement after the full text review. These results are summarized in the PRISMA flow diagram in Fig. 1.

The risk of bias framework developed for this series of reviews addresses relevant biases encountered in the field of epidemiology. Overall, the risk of bias assigned to studies evaluated in this review was either “low” or “probably low” (Fig. 2). The methods and study designs applied by various investigators were similar across studies and study attributes that would constitute “high” or “probably high” risk of bias, were not identified. The majority of differences in risk of bias evaluations across studies stemmed from different exposure assessment methods. We distinguished methods that derived exposure estimates by averaging concentrations from centrally located monitors from those that better characterized spatial and temporal variability of PM2.5 and BC. Additional information regarding the specific questions used to evaluate these biases, criteria for assigning a risk of bias category, and the evaluation of results for all studies are provided in Supplemental materials (Risk of Bias Evaluation Summary and Supplemental Table 1.) Study design is also noted in the text of the supplement and in Supplemental Table 1.

3.2. Cardiovascular responses associated with short-term exposure to BC (or EC) and $PM_{2.5}$

3.2.1. Autonomic nervous system tone—HRV provides a noninvasive marker of cardiac autonomic nervous system tone. The variation in the intervals between heartbeats can be quantified in either the time domain or the frequency domain (TFESC and NASPE, 1996). Common time domain measures of HRV include the standard deviation of all normal to-normal intervals (SDNN, an index of total HRV), the root mean-square of successive differences (rMSSD, an index influenced mainly by the parasympathetic nervous system) and pNN50 (proportion of NN50 divided by the total number of NN (R-R) intervals). In the frequency domain, HRV is usually divided into the high frequency (HF [generally reflecting parasympathetic activity]) and low frequency (LF [generally reflecting sympathetic activity]) components, as well as the ratio of the LF to HF components (LFHFR) (TFESC and NASPE, 1996). Decreases in indices of HRV have been associated with increased risk of cardiovascular events in prospective cohort studies (La Rovere et al., 2003; Kikuya et al., 2000; Tsuji et al., 1994, 1996). Overall reduction in HRV is a powerful predictor of adverse cardiac events in individuals with pre-existing heart disease and the general population (Zulfiqar et al., 2010; La Rovere et al., 2003; Kleiger et al., 1987),

although it is recognized that acute changes in HRV in response to pollutant exposure may not be persistent (Rowan et al., 2007).

A total of 16 studies of short-term exposure to BC/EC or $PM_{2.5}$ with HRV meeting the inclusion criteria were identified for this review. Characteristics of the studies highlighted below and including Chen et al. (2017), Huang et al. (2013) and Schneider et al. (2010), are compiled in Supplemental Table 2. The most commonly reported metrics of HRV were SDNN, rMSSD, pNN50, LF, HF and LFHFR, but most studies did not present associations for each of these metrics. Study design varied with panel, repeated measures, prescribed exposures, and cross-sectional analyses available for inclusion in this review.

Plots comparing selected results from studies that present associations for BC/EC and $PM_{2.5}$ and time domain measures of HRV are presented in Fig. 3. Results are organized by type of population (i.e. health adults, pre-existing disease, and older adults). Overall, associations with BC/EC were similar to associations with $PM_{2.5}$ for most studies and HRV metrics. Where point estimates were less similar, confidence intervals were generally relatively wide and overlapping. An exception is Luttmann-Gibson et al. (2006) who reported a larger decrease in SDNN associated with $PM_{2.5}$. By contrast, Suh and Zanobetti (2010) examined the impact of differential exposure misclassification between $PM_{2.5}$ and BC reporting markedly stronger magnitude associations of personal exposure to BC with decreased SDNN (shown in Fig. 3) and relatively weak or null associations with 24-hour ambient exposure to BC or $PM_{2.5}$ (not shown in Fig. 3).

Results of several studies included in Supplemental Table 2 are not pictured in Fig. 3 because they could not be standardized to the IQR or were reported only in figures. Mirowsky et al. (2015) reported that decreased rMSSD was associated with EC but not $PM_{2.5}$ in their case cross-over study of healthy adults walking along roadways in New Jersey. Park et al. (2005) found both $PM_{2.5}$ and BC were associated with decreases in SDNN of similar magnitude with wide, largely overlapping confidence intervals. Zanobetti et al. (2010) presented figures showing that BC was associated with reduced SDNN while $PM_{2.5}$ was not associated with SDNN. Findings for HF were similar across $PM_{2.5}$ and BC for moving averages up to 2 h but only BC was associated with HF for longer moving averages in this study.

A generally similar pattern of results for frequency domain measure of HRV is apparent in Fig. 4. Luttmann-Gibson et al. (2006) and Huang et al. (2012) reported larger decreases of LF and HF, respectively, in association with $PM_{2.5}$ compared to BC. In a study using centrally located monitors to characterize exposure, Schwartz et al. (2005) reported a larger increase in LFHFR in association with EC compared to $PM_{2.5}$. Adar et al. (2007) measured exposure using real time monitors while study participants were riding a bus and observed a larger decrease in HF and LFHFR in association with BC than $PM_{2.5}$.

3.2.2. Heart rhythm abnormalities—Heart rhythm abnormalities or arrhythmias can originate in the upper (atria) or lower (ventricles) chambers of the heart and range in severity. Ectopy (supraventricular ectopy [SVE] and ventricular ectopy [VE]), or premature heartbeats, may indicate risk for severe arrhythmias. Atrial fibrillation (AF) is the most

common sustained arrhythmia and is associated with various forms of cardiovascular disease and mortality while ventricular arrhythmia (VA) is a well-known cause of sudden death (Laupacis et al., 1994; Prystowsky et al., 1996; Roy et al., 2009; Kannel et al., 1983). Arrhythmia is ascertained by examining output from implantable cardioverter defibrillator (ICD) devices or ECG recordings.

A total of 8 studies of heart rhythm abnormalities or arrhythmias meeting our inclusion criteria were identified. Findings from these studies are organized by type in Fig. 5 (and Supplemental Table 3, which includes the studies highlighted below and results for Rich et al. (2005), Rich et al. (2006a), Rich et al. (2006b) and Sarnat et al. (2006)). Overall, point estimates are similar for BC or EC and $PM_{2.5}$ and confidence intervals are overlapping in all of these studies. Most were repeated measures or case-crossover designs and all relied on central site monitors to estimate exposure to BC and $PM_{2.5}$. One notable exception is Zanobetti et al. (2014a, 2014b) in which authors estimated BC and $PM_{2.5}$ concentrations using methods to maximize spatial and temporal resolution. These authors found similar magnitude associations for 24 h average BC and $PM_{2.5}$ concentrations with arrhythmia episode. ICD discharge results for Rich et al. (2004), which were null for both BC and $PM_{2.5}$, are not included in Fig. 5 because quantitative results were not available.

3.2.3. Blood pressure and vascular function—The vascular endothelium plays a fundamental role in the maintenance of vascular tone and the regulation of blood pressure and blood flow. Studies of blood pressure report several metrics including systolic blood pressure (SBP), diastolic blood pressure (SBP), mean arterial pressure (MAP) and pulse pressure (PP). Endothelium dependent vascular reactivity is measured through a variety of clinical tests that ascertain the extent to which blood flow, vessel tone and diameter respond to hyperemia or nitroglycerin. The epidemiologic studies available to evaluate the association of BC and $PM_{2.5}$ with blood pressure included 14 studies. In addition, six studies of vascular reactivity endpoints including flow mediated dilation (FMD) or nitroglycerin (nitroglycerin mediated dilation [NMD]) reactive hyperemia index (RHI), and peripheral arterial tonometry (PAT) ratio were identified (Supplemental Table 4).

Associations of BC and $PM_{2.5}$ with SBP and DBP were not consistently observed across studies and, where associations were reported, confidence intervals for $PM_{2.5}$ and BC were generally overlapping (Chung et al., 2015; Brook et al., 2016; Lim et al., 2017; Weichenthal et al., 2014; Hoffmann et al., 2012; Kubesch et al., 2015; Lin et al., 2017; Wu et al., 2013). Although strong associations of both BC and $PM_{2.5}$ with FMD and NMD were observed by O'Neill et al. (2005) among diabetics, confidence intervals were overlapping. A study of healthy women cycling in high and low traffic routes did not provide evidence that $PM_{2.5}$ or BC were associated with changes in RHI (Weichenthal et al., 2014). Ljungman et al. (2014) reported associations of both BC and $PM_{2.5}$ with baseline pulse amplitude but not PAT ratio, with little evidence to support a difference between BC and $PM_{2.5}$ in this study.

There were some exceptions where differences in the magnitude of the association between BC and $PM_{2.5}$ could be discerned. Bind et al. (2016) reported a larger association of BC than $PM_{2.5}$ with SBP. Mirowsky et al. (2015) found larger changes in blood pressure (SBP, DBP, PP, MAP) in association with EC compared to $PM_{2.5}$ in their study of healthy adults

walking along roadways in New Jersey. Zhang et al. (2016) reported a somewhat larger magnitude association between BC and RHI than between $PM_{2.5}$ and RHI. Zanobetti et al. (2014a, 2014b) found a stronger magnitude association between ambient BC and NMD than between $PM_{2.5}$ and NMD. Associations of both pollutants with FMD were similar in magnitude but imprecise; however, Liu et al. (2009) reported significant associations of BC with SBP, DBP and BAD while $PM_{2.5}$ was only associated with DBP.

3.2.4. Ischemia and repolarization abnormalities—Seven studies of ST segment depression or repolarization abnormalities were identified for this review including those discussed below and including Baja et al. (2010) (Supplemental Table 5.) The ST segment of the ECG represents the interval between ventricular depolarization and repolarization and is often used as a nonspecific measure of myocardial ischemia. The QT interval and T Wave complexity provide ECG markers of ventricular repolarization. Prolongation and increased variability of the QT interval are associated with increased risk of life-threatening ventricular arrhythmias (Castro-Torres et al., 2015; Brook et al., 2004).

Chuang et al. (2008) and Gold et al. (2005) found small (0.02–0.08 mm) changes in ST segment depression in association with both BC and $PM_{2.5}$. Associations of similar magnitudes and with overlapping confidence intervals were also reported by Henneberger et al. (2005) who examined several repolarization abnormalities (i.e., QTc Interval, T wave complexity, T wave variability, T wave amplitude). Rich et al. (2016) conducted a factor analysis to reduce the number of ECG outcomes included in the analysis and focused on T wave complexity. These authors did not find consistent changes in T wave complexity across the Augsburg or Rochester panel studies. Zanobetti et al. (2009) reported a stronger association of T wave alternans ≥26 μV with BC than with $PM_{2.5}$. Overall, the limited number of studies evaluated point to an effect of both BC and $PM_{2.5}$ on ST segment depression while there was no consistent trend for the relationship of these pollutants with repolarizations abnormalities.

3.3. Cardiovascular responses associated with long-term exposure to BC (or EC) and $PM_{2.5}$

Four studies that examined the association between long-term exposure to BC and $PM_{2.5}$ with intermediate cardiovascular endpoints that met our inclusion criteria were identified (Supplemental Table 6). Kaufman et al. (2016) reported increased coronary artery calcification (CAC) progression during the follow-up period, in association with $PM_{2.5}$ but not in association with BC. These analyses of the Multi Ethnic Study of Atherosclerosis (MESA) cohort did not support an effect of either BC or $PM_{2.5}$ on increased carotid intima media thickness (cIMT). Similarly, Gan et al. (2014) reported little evidence of an effect of BC or $PM_{2.5}$ on cIMT progression (or progression of other measures of atherosclerosis, Supplemental Table 6). In another study, Yang et al. (2017) examined left ventricular structure and function in relation to long-term exposure to BC and $PM_{2.5}$. Although these analyses supported effects on left ventricular function assessed by ejection fraction and left atrial volume index (as well as additional metrics not included in Supplemental Table 5), the magnitude of the associations with BC and $PM_{2.5}$ were similar. Finally, Mordukhovich et al. (2015) reported associations of long-term exposure to BC and $PM_{2.5}$ with HRV (SDNN, LF,

HF, LFHFR) that were imprecise, often spanning the null value, with generally overlapping confidence intervals.

4. Discussion

As discussed previously, our evaluation of BC-associated health effects is considered in the context of what is already understood about the health effects of $PM_{2.5}$ with the objective of understanding whether or not BC (or EC), which are components of $PM_{2.5}$, have stronger associations with cardiovascular effects or distinct cardiovascular responses, compared to $PM_{2.5}$ as a whole. In addition, understanding the available evidence pertaining to the cardiovascular responses included in this review may elucidate the extent to which exposure to BC or EC and $PM_{2.5}$ perturb specific disease pathways and lead to various cardiovascular diseases. With these objectives in mind, we chose to standardize the estimates from each study to an increase in concentration equal to the IQR for each pollutant. Scaling to the IQR de-emphasizes the evaluation of the relative toxicity of BC (or EC) versus $PM_{2.5}$ in favor of an evaluation of observed associations due to real-world ambient exposures, where EC typically represents < 10% of $PM_{2.5}$ mass (Bell et al., 2007).

Application of PRISMA guidelines and systematic evaluation of risk of bias allowed us to avoid the selective inclusion of studies as well as to critically evaluate each of the included studies according to the same criteria. We used a combination of approaches including SWIFT-AS, which relies on machine learning to identify and predict relevant references, and manual screening of titles and abstracts to identify potentially relevant references. Overall, we observed very little difference across studies regarding risk of bias because the study designs and methods were similar (Supplemental Table 1). All the studies identified in the literature search were deemed of sufficient quality for inclusion in the review.

Specific study results were selected for extraction to maximize the number of studies that could be compared. For example, associations with the most common averaging time (i.e. concurrent 24-hour exposures) were selected if available. If 24-hour concurrent exposure was not examined in a particular study, the longest sub-daily or shortest daily lag was selected. As a result of this practical decision, we could not consider timing of exposure in our analysis, although multiple studies presented associations for multiple averaging and lag times. Despite some uncertainty, the evidence for short-term $PM_{2.5}$ exposure and cardiovascular effects generally supports an immediate effect in the range of lag 0 to 1 day, however (U.S. EPA, 2009).

A small number of the studies included in this review examined cardiovascular responses in healthy populations during prescribed exposures (e.g. riding a bike near a busy road or other source of exposure), while other studies examined cardiovascular responses in people with preexisting disease or among older adults. The heterogeneity of the populations studied may limit the generalizability of the specific studies and, in addition, limit the extent to which findings can be compared across studies. Hence, our emphasis is on comparison of findings within studies and across studies of similar populations.

The results of most studies included in our systematic review support a similar risk or overlapping confidence intervals for the associations of BC or EC and $PM_{2.5}$ with indicators of autonomic nervous system tone (i.e., heart rate variability), heart rhythm, blood pressure and vascular function, ST segment depression, repolarization abnormalities, atherosclerosis and heart function. Although there were some differences in the magnitude of the single pollutant associations across pollutants within studies, most noticeably in the studies of blood pressure and vascular function, no consistent pattern was discernable across the group of studies we evaluated. This finding is consistent with previous reviews focusing on hospital admissions and emergency department visits for cardiovascular disease (Luben et al., 2017) and populations with pre-existing disease (Nichols et al., 2013). Our results are also coherent with experimental studies of animals and humans that demonstrate effects on cardiovascular endpoints following exposures used to mimic ambient pollution such as concentrated ambient particles (CAPs) and diesel exhaust (Lippmann and Chen, 2009; Lippmann, 2009). For example, Gong et al. (2003) conducted a series of experimental studies in humans and found that CAPs exposures resulted in changes in HR and HRV. Campen et al. (2010) and Bai et al. (2011) reported diesel exhaust-related changes in metrics related to atherosclerosis in ApoE−/− mice.

To fully explore whether BC or EC are more closely associated with cardiovascular effects than $PM_{2.5}$, the extent to which the effect of each is statistically independent is an important consideration. Several experimental studies in humans, dogs, and rats included both $PM_{2.5}$ and BC or EC simultaneously in multiple regression models. This set of studies did not provide consistent evidence that changes in cardiovascular endpoints including heart rate variability and endothelial dysfunction were more consistently demonstrated following exposure to either $PM_{2.5}$ or BC/EC (Urch et al., 2004; Kamal et al., 2011; Gong et al., 2003, 2008; Clarke et al., 2000; Bartoli et al., 2009; Ghelfi et al., 2008).

This review identified a limited body of epidemiologic studies that were designed to examine whether associations observed with BC or EC were statistically independent of the effect of $PM_{2.5}$ or vice versa. For example, Huang et al. (2012) reported similar magnitude reductions in SDNN and LF in association with both $PM_{2.5}$ and BC. In two pollutant models these associations with $PM_{2.5}$ persisted after adjustment for BC. Lim et al. (2017) reported associations of EC that were adjusted for $PM_{2.5}$ mass, which were similar to the single pollutant associations, although less precise. Chuang et al. (2008) reported results from two-pollutant models showing attenuation in the association of ST segment depression with $PM_{2.5}$ while the association with BC remained after adjustment. Overall, no consistent pattern of results emerged from the evaluation of this set of studies.

There are complications involved with distinguishing the effects of $PM_{2.5}$ on health from those of its components. Mostofsky et al. (2012) noted that the use of two-pollutant models, such as those described above, may result in an over-adjustment or model convergence issues due to collinearity if pollutants are highly correlated. Most correlations between $PM_{2.5}$ and BC reported in short-term exposure studies were moderate to high (i.e., $r > 0.5$ in most studies reporting this parameter) suggesting the potential for confounding. The correlations in the limited number of long-term exposure studies included in this review

were more variable and reported correlations ranging from 0.13 (Gan et al., 2014) to 0.89 (Kaufman et al., 2016).

The potential for differential exposure measurement error (i.e. exposure measurement error that is different for $PM_{2.5}$ versus its components) also has implications for the interpretation of our findings. Studies using centrally located monitors for exposure assessment were assigned a risk of bias score of "probably low" in order to maintain consistency with the approach taken in our previous systematic review (Luben et al., 2017). However, it is known that BC concentrations are more spatially variable than $PM_{2.5}$ concentrations (Clougherty et al., 2008). Consequently, we recognize the potential for the exposure error for $PM_{2.5}$ to be different than the exposure error for BC/EC, particularly in studies that rely upon monitors located at various distances from subjects' homes or clinic locations to estimate exposure. In fact, it has been suggested that attenuation of the association between local pollutants such as BC and health effects in epidemiologic studies using centrally located monitors may be substantial (Dionisio et al., 2014).

Overall, the studies included in this review did not provide information needed to assess the use of centrally located monitors in a particular study was appropriate to characterize BC or EC exposure. Many studies reported the distance from the monitor to the medical clinic or participants' residence (Supplemental Tables 2–5) in an effort to provide some information about the extent to which the centrally located monitor was appropriate exposure metric, but the appropriate distance is not known. Link et al. (2013) conducted a sensitivity analysis limiting the analysis to participants residing within 26 km as opposed to farther from the monitoring station, reporting that the associations of $PM_{2.5}$ and BC with AF persisted but were less precise. Further, time activity patterns that determine exposure to ambient air pollutants were not examined in the studies included in this review.

Several studies applied methods designed to reduce exposure measurement error. Suh and Zanobetti (2010) examined the effect of exposure error by comparing the associations observed for HRV with EC, $PM_{2.5}$ and other pollutants depending on whether personal or ambient exposure metrics were used in the analysis. Authors report larger decreases across all HRV metrics with personal exposure to BC compared to ambient BC exposure. No similar pattern was observed for $PM_{2.5}$, and associations with $PM_{2.5}$ were generally weaker in magnitude than those for EC. Stronger magnitude associations between BC or EC and cardiovascular endpoints (compared to associations with $PM_{2.5}$) are not consistently observed in studies that employ exposure assessment methods designed to achieve greater characterization of the spatial variability of the pollutant concentrations (Adar et al., 2007; Mirowsky et al., 2015; Weichenthal et al., 2014; Weichenthal et al., 2011; Zanobetti et al., 2014a, 2014b).

5. Conclusion

Overall, we found generally similar magnitude associations of BC (or EC) and $PM_{2.5}$ with the cardiovascular endpoints examined in the majority of studies. The evidence did not suggest that BC would be a better indicator of cardiovascular effects than $PM_{2.5}$. Confidence intervals for the associations of BC (or EC) and $PM_{2.5}$ were overlapping in most studies.

Where differences in the magnitude of the single pollutant associations were observed across pollutants within a study, no consistent pattern was discernable across the literature as a whole. Although timing of exposure was an important consideration in many studies, we were limited in our ability to consider exposure lags. There was a general lack of consistency in the lags reported across studies and, consequently an insufficient number of results to compare. Further, only a limited number of studies attempted to distinguish the independent effect of BC or EC from that of $PM_{2.5}$ or examine the effect of exposure measurement error on their results. The interplay between these two factors can lead to possibly differential bias in the observed associations and future studies would benefit from applying methods designed to address these issues.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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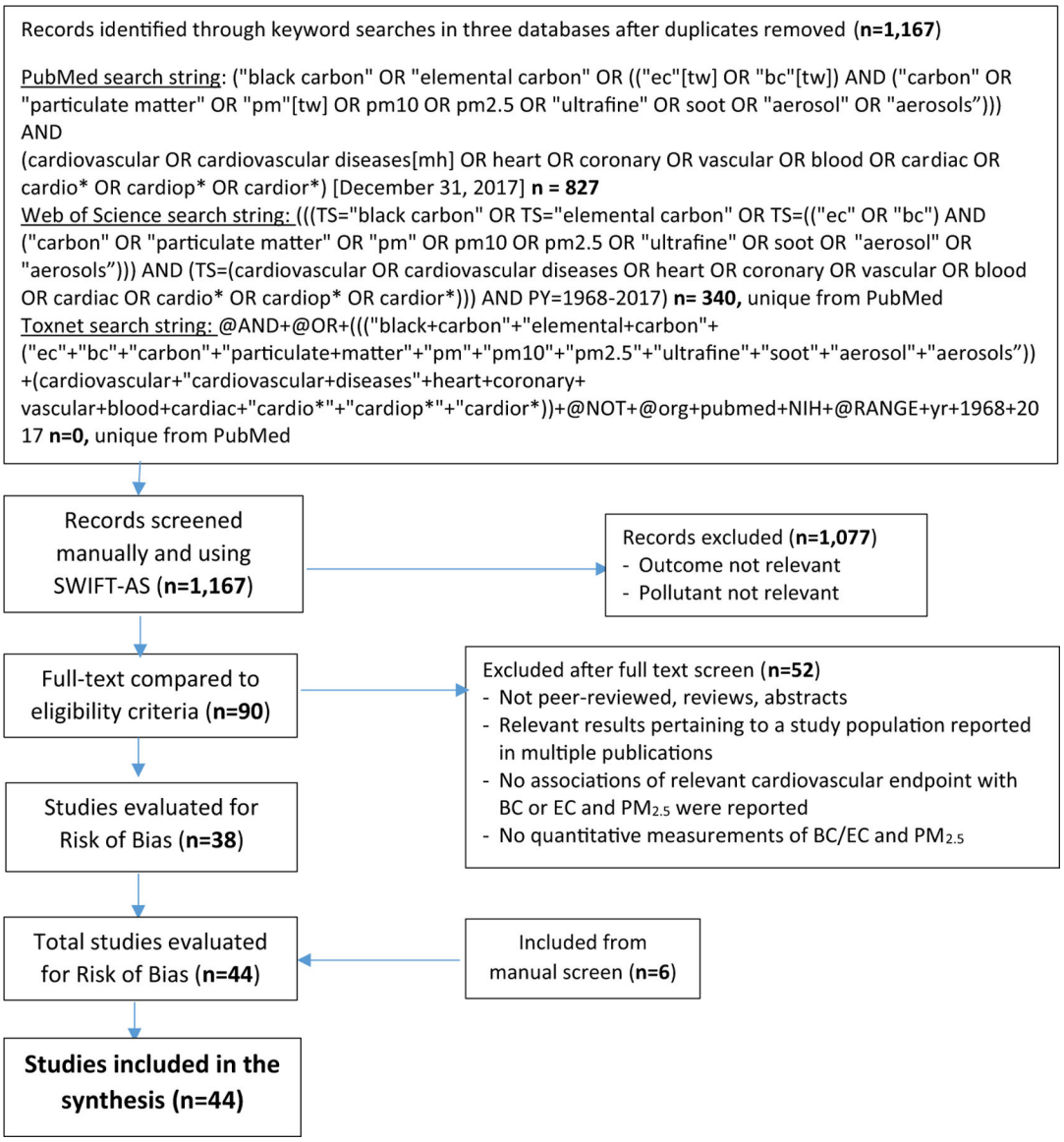

Fig. 1.

Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flow diagram summarizing the systematic literature search, inclusion and exclusion criteria for studies of cardiovascular responses included in this review. Note: mh = MeSH headings; n = number of records; tw = text words.

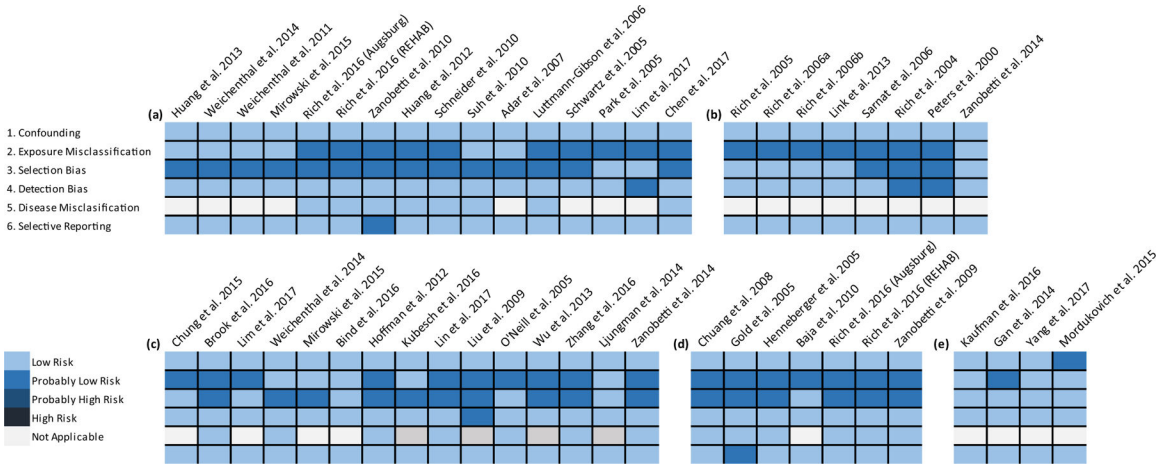

Fig. 2.

Risk of bias evaluation for epidemiologic studies of subclinical cardiovascular endpoints (a) Heart Rate Variability; (b) Arrhythmia; (c) Blood Pressure and Vascular Function; (d) Ischemia and Repolarization Abnormalities (e) Long-term Exposure. Note: Rich et al., 2016 report includes findings for the Augsburg Germany and REHAB (Rochester, NY) studies.

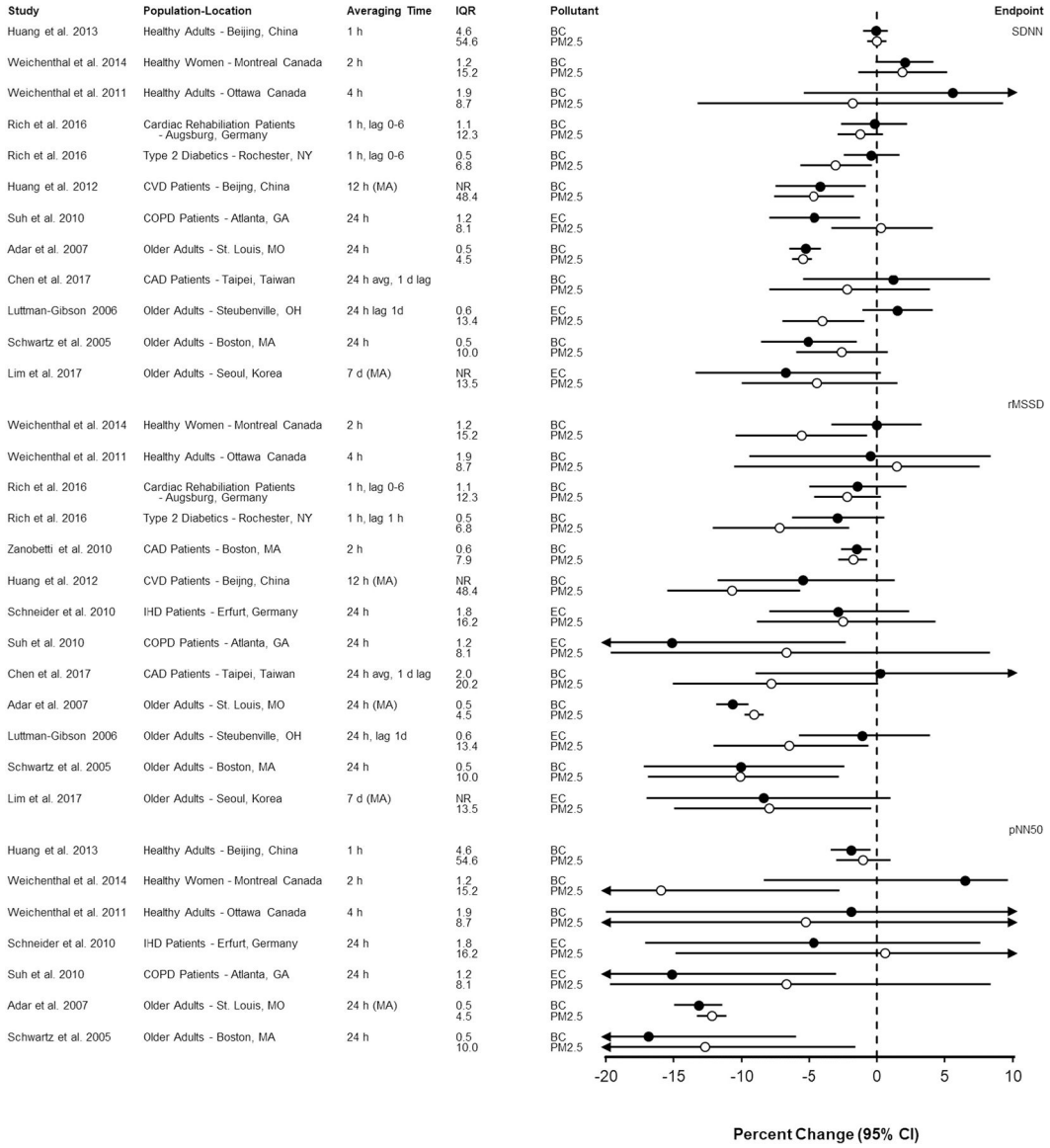

Fig. 3.

Association of short-term exposure to black carbon or elemental carbon (black circles) and particulate matter < 2.5 μm in diameter (open circles) with time domain measures of heart rate variability per interquartile range increase in mean (or median) pollutant concentration (in $\mu g/m^3$). Studies are organized by endpoint (SDNN, rMSSD, pNN50), population type (i.e., healthy, pre-existing disease, older adults) and averaging time (i.e., shortest averaging time first). Circles represent point estimates and horizontal lines represent 95% confidence intervals. BC = black carbon; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; d = day; EC = elemental carbon; h = hour; IQR = interquartile range; MA = moving average; pNN50 = proportion of successive NNs that differ by > 50 ms; rMSSD = root mean-square of successive differences; SD: standard deviation; SDNN = standard deviation of all normal to-normal intervals.

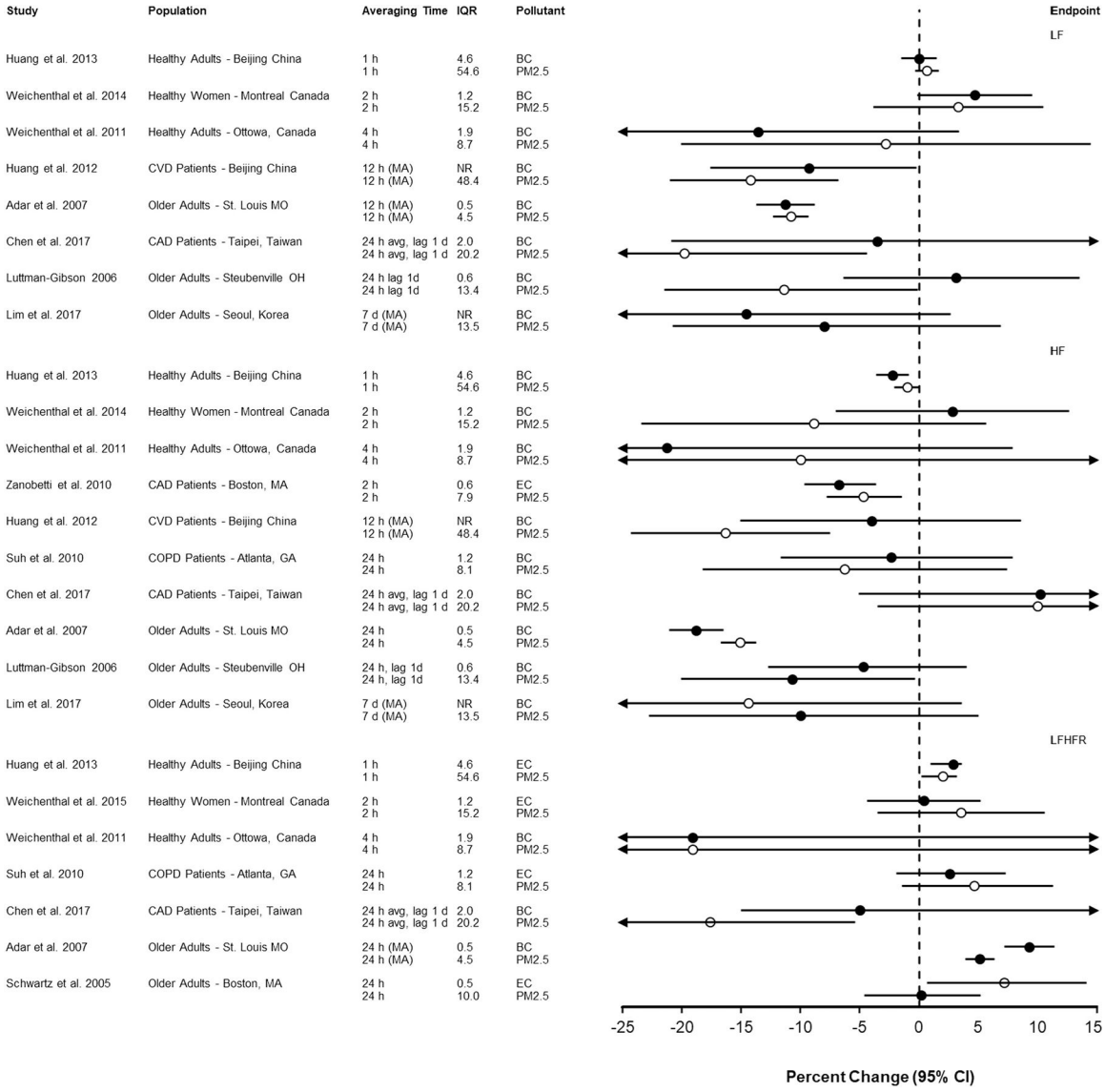

Fig. 4.

Association of short-term exposure to black carbon or elemental carbon (black circles) and particulate matter < 2.5 μm in diameter (open circles) with frequency domain measures of heart rate variability per interquartile range increase in mean (or median) pollutant concentration (in $\mu g/m^3$). Studies are organized by endpoint (LF, HF, LFHFR), population type (i.e., healthy, pre-existing disease, older adults) and averaging time. Circles represent point estimates and horizontal lines represent 95% confidence intervals. BC = black carbon; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; d = day; EC = elemental carbon; h = hour; HF = high frequency; IQR = interquartile range; LF = low frequency; LFHFR = low frequency high frequency ratio; MA = moving average.

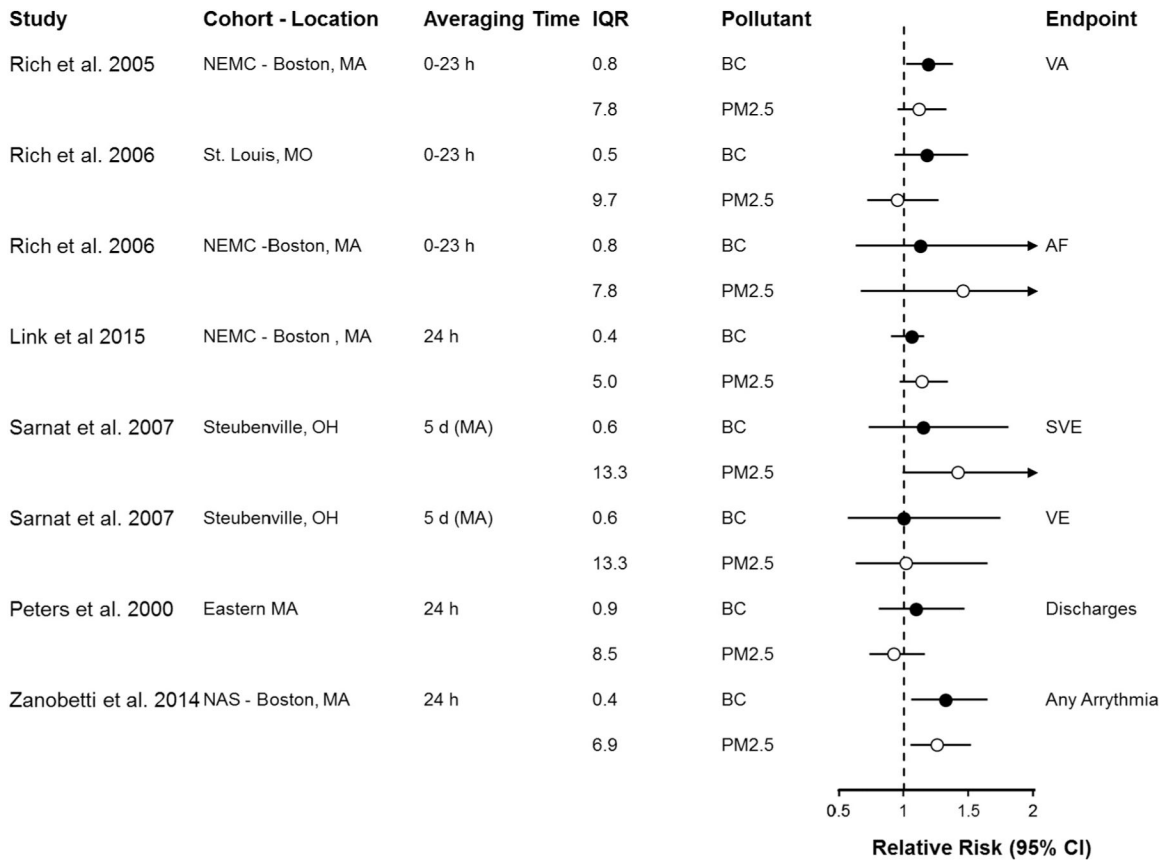

Fig. 5.

Association of short-term exposure to black carbon or elemental carbon (black circles) and particulate matter < 2.5 μm in diameter (open circles) with arrhythmia recorded on implantable cardioverter defibrillator or electrocardiogram, per interquartile range increase in mean (or median) pollutant concentration (in $\mu g/m^3$). Studies are organized by endpoint (VA, AF, SVE, discharges, any arrhythmia), population type (i.e., healthy, pre-existing disease, older adults) and averaging time. Circles represent point estimates and horizontal lines represent 95% confidence intervals. BC = black carbon; EC = elemental carbon; h = hour; IQR = interquartile range; MA = moving average; $PM_{2.5}$ = particulate matter < 2.5 μm in diameter; VA = ventricular arrhythmia; AF = atrial fibrillation; SVE = supraventricular ectopy; VE = ventricular ectopy.