EPA Public Access

Author manuscript

Environ Res. Author manuscript; available in PMC 2019 February 01.

About author manuscripts

Submit a manuscript

Published in final edited form as:

Environ Res. 2018 February ; 161: 144–152. doi:10.1016/j.envres.2017.11.008.

A cross-disciplinary evaluation of evidence for multipollutant effects on cardiovascular disease

Thomas J. Luben^{a,*}, Barbara J. Buckley^a, Molini M. Patel^a, Tina Stevens^b, Evan Coffman^{b,c}, Kristen M. Rappazzo^{a,b}, Elizabeth O. Owens^a, Erin P. Hines^a, Danielle Moore^b, Kyle Painter^b, Ryan Jones^a, Laura Datko-Williams^{b,d}, Adrien A. Wilkie^{b,e}, Meagan Madden^{b,f}, and Jennifer Richmond-Bryant^a

^aOffice of Research and Development, US EPA, RTP, NC, USA

^bOak Ridge Institute of Science and Education (ORISE) Research participant at the US EPA, RTP, NC, USA

^cOffice of Air and Radiation, US EPA, RTP, NC, USA

^dCROS NT, LLC, Chapel Hill, NC, USA

^eDepartment of Epidemiology, UNC Gillings School of Global Public Health, Chapel Hill, NC, USA

^fDevelopment Research Group, The World Bank, Washington, DC, USA

Abstract

Background—The current single-pollutant approach to regulating ambient air pollutants is effective at protecting public health, but efficiencies may be gained by addressing issues in a multipollutant context since multiple pollutants often have common sources and individuals are exposed to more than one pollutant at a time.

Objective—We performed a cross-disciplinary review of the effects of multipollutant exposures on cardiovascular effects.

Methods—A broad literature search for references including at least two criteria air pollutants (particulate matter [PM], ozone [O₃], oxides of nitrogen, sulfur oxides, carbon monoxide) was conducted. References were culled based on scientific discipline then searched for terms related to cardiovascular disease. Most multipollutant epidemiologic and experimental (i.e., controlled human exposure, animal toxicology) studies examined PM and O₃ together.

Discussion—Epidemiologic and experimental studies provide some evidence for O₃ concentration modifying the effect of PM, although PM did not modify O₃ risk estimates. Experimental studies of combined exposure to PM and O₃ provided evidence for additivity,

*Correspondence to: USPS Address: U.S. EPA, MD B243-01, RTP, NC 27711. luben.tom@epa.gov (T.J. Luben).

¹UPS, FEDEX & Other Delivery Address: U.S. EPA, MD B243-01, 4930 Old Page Rd, Durham, NC 27703.

Competing financial interests declaration

All actual or potential competing financial interests have been declared and the authors' freedom to design, conduct, interpret, and publish research is not compromised by any controlling sponsor as a condition of review and publication.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.envres.2017.11.008>

synergism, and/or antagonism depending on the specific health endpoint. Evidence for other pollutant pairs was more limited.

Conclusions—Overall, the evidence for multipollutant effects was often heterogeneous, and the limited number of studies inhibited making a conclusion about the nature of the relationship between pollutant combinations and cardiovascular disease.

Keywords

Air pollution; Particulate matter; Ozone; Multipollutant; Cardiovascular

1. Introduction

Under the Clean Air Act, EPA regulates six criteria pollutants [particulate matter (PM), ozone (O₃), nitrogen dioxide (NO₂), sulfur dioxide (SO₂), carbon monoxide (CO), and lead (Pb)] individually. Implementation of the National Ambient Air Quality Standards (NAAQS) has reduced annual average concentrations of criteria air pollutants by 28–87% from 1980 to 2013 (U.S. EPA, 2016b, 2017). However, several research groups have commented that single-pollutant regulation is inefficient because multiple pollutants often have common sources and individuals are not exposed to only one pollutant at a time (Dominici et al., 2010; Greenbaum and Shaikh, 2010; Hidy and Pennell, 2010; Johns et al., 2012; Mauderly et al., 2010; NRC, 2004). Generally speaking, a multipollutant regulatory approach might focus on how different air pollutant mixtures contribute to population-level exposures and identify which mixtures are most closely associated with particular health outcomes. Once relevant mixtures are identified, regulators could focus on the sources of those mixtures, transport and transformation of emissions from those sources, and relevant population exposures to those mixtures. While this approach is certainly complex, it will be more efficient by allowing for regulatory assessments to be conducted for a subset of relevant mixtures. For example, a case study that modeled scenarios to quantify health impacts of air pollution management strategies found larger reductions in both pollutant concentrations and cases of premature mortality attributable to PM with aerodynamic diameter $\leq 2.5 \mu\text{m}$ (PM_{2.5}) or O₃ exposure for multipollutant emission control strategies than for single-pollutant control strategies (i.e., reductions were greater than additive) (Wesson et al., 2010).

There are also uncertainties related to evaluating one air pollutant at a time, which may be one reason for the growing interest in health effects of multipollutant exposures in both epidemiologic and experimental (i.e., controlled human exposure, animal toxicological) studies. Epidemiologic studies may statistically adjust for the association of another air pollutant in multivariable copollutant models to discern a potential independent association for a single pollutant. However, inferences from such analyses may be uncertain as effect estimates can be inflated for pollutants measured with less error or can be unreliable if copollutants are highly correlated (Zeger et al., 2000). Single-pollutant analyses do not account for the possibility that exposure to multiple pollutants may have effects that are other than additive, (i.e., the combined influence of multiple pollutants represented by the sum of their independent effects). While multipollutant analyses do not reduce or eliminate residual confounding or the impacts of measurement error commonly attributed to single-

pollutant models, they allow for examination of the combined influence of multiple pollutants.

Several statistical methods have been applied or are being developed to examine the relationship between multipollutant exposures and health effects (Billionnet et al., 2012; Davalos et al., 2016). To date, experimental studies have evaluated *interactions*, effects of simultaneous exposure to two or more pollutants that differ from the summed effect of each exposure occurring alone (Vanderweele, 2009). These interaction effects may be antagonistic, an effect of simultaneous exposure to two or more pollutants that is lower in magnitude than the sum of the effect of the individual pollutants, or synergistic, an effect of simultaneous exposure to two or more pollutants that is greater than the sum of the effect of the individual pollutants (Mauderly, 1993; Mauderly and Samet, 2009). In epidemiologic studies, various multipollutant regression techniques are available to estimate *joint effects* by including additive or multiplicative interaction terms in the regression model. For example, Winquist et al. (2014) assessed the joint effect of combinations of air pollutants for asthma emergency department visits by calculating the effect of a specified change in each pollutant in the combination. Epidemiologic and experimental studies have also examined *effect measure modification*, where the effect of one pollutant varies by level of another (Howe et al., 2012; Vanderweele, 2009).

The objective of this review was to perform a cross-disciplinary evaluation of the multipollutant effects on health endpoints related to cardiovascular disease (CVD). In other words, the review entails integration of results from observational epidemiologic studies with experimental controlled human exposure and animal toxicological studies. The cross-disciplinary nature of this review allows us to integrate across the continuum of CVD endpoints, from biomarkers of inflammation and coagulation, sub-clinical markers of CVD, clinical endpoints including hospital admission and emergency department visits, and mortality, and aids in reducing uncertainties related to potential confounding, exposure misclassification, and differences across animal species that would be present if the review were limited to one scientific discipline. In this review, *multipollutant effects* were specified to include at least two criteria air pollutants evaluated for *interactions* (in experimental studies), *joint effects* (in epidemiologic studies), or *effect measure modification* (in experimental or epidemiologic studies). We identified studies reporting interactions, joint effects, and effect measure modification (which include data on concentrations of individual criteria air pollutants) which are more informative of multipollutant effects than studies of clusters, indices and whole atmosphere exposures, where information on concentrations of individual criteria pollutants are often not available. To be complete, we discuss studies of cluster, indices and whole atmosphere exposures in Section 3.7. We assessed the coherence of results from epidemiologic and experimental studies to strengthen inference about health effects due to multipollutant exposures.

2. Methods

We identified studies on multipollutant exposures and CVD-related effects published through December 31, 2015 using a stepwise systematic literature search that employed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

as illustrated in Fig. 1 and described in detail in the Supplemental Materials. The literature review began with a broad literature search for references including at least two criteria air pollutants among PM, O₃, oxides of nitrogen (NO_x), sulfur oxides (SO_x), and CO using an array of search terms (Supplemental Tables S1 and S2). The retrieved references were refined by applying an automatic topic classification algorithm to segregate references into epidemiologic or experimental study domains. The algorithm, trained by a set of known relevant seed references, had recall greater than 90% but lower precision (Supplemental Tables S3 and S4), meaning the bins captured most of the relevant references for the intended domain but also captured many references from other domains. Next, specific terms related to CVD (identified from (Gill et al., 2011)) were applied to the domain-specific bins (Supplemental Table S5). From those results, irrelevant references (i.e., non-criteria pollutants and non-CVD-related health effects) were excluded based on manually screening the title and, if necessary, reviewing the abstract. If we could not conclusively determine whether inclusion criteria were met from reviewing an abstract, we reviewed the reference's methods section. Epidemiologic studies were required to examine *joint effects* or *effect measure modification* for CVD in order to be included. Experimental studies were included if they examined CVD effects of (1) an individual air pollutant, (2) co-exposure to one or more additional air pollutants; and (3) a filtered air control in order to examine *interactions* or *effect measure modification*. Both simultaneous and sequential co-exposure scenarios were considered relevant. From this process, we identified 31 relevant epidemiologic studies and 15 relevant experimental studies.

Studies meeting inclusion criteria were evaluated for risk of bias in results and study design. Risk of bias evaluations assess some aspects of internal validity of study findings based on study design, conduct, and reporting, and can identify potential issues associated with chance, confounding, and other biases. The risk of bias evaluation is a way to characterize potential strengths and weaknesses of individual studies more transparently, and to characterize the body of evidence on which conclusions from this review will be based. Published sources on systematic review were considered when developing a risk of bias framework for use in this review (AHRQ, 2012; Higgins and Green, 2011). Epidemiologic studies were evaluated for evidence of risk of bias by answering six questions related to confounding bias, exposure misclassification, selection bias, detection bias, disease misclassification, and selective reporting. Controlled human exposure and animal toxicological studies were evaluated for evidence of risk of bias by answering six questions related to confounding bias, performance bias, selection bias, appropriate controls, detection bias and selective reporting. Specifically, we examined the extent to which potential confounders were accounted for in the study population, study design and exposure assessment, whether monitoring techniques were appropriate for the sample population, whether study sampling techniques were clearly described and included subject attrition, the extent to which study conditions were identical across study groups, whether research staff were blinded to exposure status, our confidence in the disease status of subjects reported in the studies, and whether all results were reported. In evaluating these six factors for risk of bias in each study, we assigned a “low”, “probably low”, “probably high”, or “high” risk of bias rating for each factor based on the answer to the question. The results of the risk of bias evaluation are presented in Fig. 2 and additional information is provided in Supplemental

Tables S6 and S7 regarding these biases, criteria for assigning a risk of bias category. These criteria are based on the National Toxicology Program's Office of Health Assessment and Translation risk-of-bias tool described in Rooney et al. (2014) and modified slightly to focus on aspects related to population-based epidemiologic and experimental health studies.

We evaluated and characterized each pair-wise interaction or joint effect available for criteria pollutants in the studies identified by the literature search. Among epidemiologic studies, short-term exposure periods (i.e., hours to weeks) and long-term exposure periods (i.e., months to years) were evaluated separately. Experimental studies mainly evaluated short-term exposure periods of either a few hours or a few days. However, one study involved a subchronic exposure period of several months. The results of epidemiologic and experimental studies were integrated for each possible combination of criteria pollutants included in the identified studies.

3. Results and discussion

The 31 epidemiologic and 15 experimental studies that met our inclusion criteria are listed by the pollutant combination(s) they examine in Table 1. Detailed study characteristics and results were extracted from each study and can be found in Tables S8 and S9 for epidemiologic and experimental studies, respectively. We provide broad overviews of the synthesized and integrated evidence for pollutant pairs and air pollutant mixtures in the following sections.

3.1. Particulate matter and ozone

Among the relevant multipollutant exposure studies, most examined short-term exposures to PM and O₃. In addition to evaluating multipollutant exposures, these studies often provide evidence that CVD effects are independently related to exposure to PM or O₃ in single pollutant models. Given the evidence for an independent effect of both PM and O₃ exposures on CVD endpoints, it is plausible that PM and O₃ could influence each other's effects. However, the U.S. EPA noted consistent evidence for O₃-associated CVD mortality but inconsistency for O₃-associated CVD morbidity indicated by hospital admissions, emergency department visits, and blood pressure changes. This may complicate interpretation of the results for PM-O₃ multipollutant effects. There are a few studies of long-term multipollutant PM and O₃ exposure. While there is ample evidence supporting a relationship between CVD effects and long-term PM_{2.5} exposure (U.S. EPA, 2009), there is relative uncertainty in the evidence for a relationship with longterm O₃ exposure (U.S. EPA, 2009, 2013).

Generally, studies of multipollutant exposure to PM and O₃ report heterogeneous results and do not demonstrate coherence across scientific disciplines, CVD health effects, or time periods of exposure. Across epidemiologic studies, the CVD events included measures of blood pressure, heart-rate variability (HRV), microvascular changes, and hospital admissions or mortality due to cardiovascular conditions. Experimental studies conducted in humans and animals evaluated several non-specific markers and early biological effects (e.g., heart rate, HRV, myocardial repolarization, arterial elastance) that may or may not lead to the type of CVD events evaluated in epidemiologic studies. Results of experimental studies

demonstrated synergistic, antagonistic, or no overall interactive effect of PM and O₃ when evaluated on an additive scale. Several studies were conducted in human subjects using essentially the same study design involving a 2-h exposure to PM_{2.5} CAPs (concentrated ambient particles) which were collected in Toronto. Acute exposure to PM+O₃ had a synergistic effect on diastolic blood pressure in one study (Fakhri et al., 2009) but not in another (Brook et al., 2009). Results suggested antagonism for a measure of parasympathetic tone (Fakhri et al., 2009), and synergism for two measures of myocardial repolarization (Sivagangabalan et al., 2011). The other experimental studies were conducted in healthy animals or animal models of disease, and involved acute or subchronic exposure to CAPs, diesel exhaust particles and carbon black. They provide evidence for both synergistic and antagonistic effects on blood pressure, myocardial repolarization, cardiac function, and expression of aortic genes (Farraj et al., 2015; Kurhanewicz et al., 2014; Wagner et al., 2014; Tankersley et al., 2013; Kodavanti et al., 2011). Although no consistent pattern of results emerges from these experimental studies in humans and animals, it is not unexpected given the differences in endpoints examined and/or differences in study design. Similarly, epidemiologic studies of joint effects for both short- and long-term exposure to PM and O₃ do not provide evidence for a greater combined effect (Bob et al., 2013; Kalantzi et al., 2011; Crouse et al., 2015; Jerrett et al., 2013). While epidemiologic studies do not provide clear evidence of joint effects, there is some evidence for effect measure modification. Three epidemiologic studies observed larger risk estimates for PM with aerodynamic diameter 10 µm (PM₁₀) when O₃ concentrations were higher. Conversely, experimental studies show that O₃ exposure dampened the effects of PM on IL-6 and on a measure of HRV (Fakhri et al., 2009; Urch et al., 2010). Risk estimates for CVD hospital admissions or mortality and exposure to O₃ are not consistently modified by PM concentration (Hong et al., 2002; Wong et al., 1999; Ponka et al., 1998). In contrast, Weichenthal et al. (2014) observed that personal exposure to O₃ had larger associations with HRV on days with higher PM_{2.5} concentrations.

The body of evidence available to evaluate the effects of multipollutant exposure to PM and O₃ on CVD effects has several limitations. Epidemiologic studies often estimate PM exposure by ambient PM₁₀ or PM_{2.5} concentrations, while experimental studies often use surrogates (e.g., CAPs, diesel exhaust particles, carbon black) for exposure to ambient PM. The variability in the size fraction/composition of PM used in these studies may explain some of the heterogeneity in the results. Similarly, the wide range of CVD effects evaluated in this limited number of studies (biomarkers, subclinical effects, counts of hospital admissions, and mortality due to any CVD) and differences in whether healthy animals or animal models of disease were used in experimental studies, make it difficult to assess coherence for any period of exposure (e.g., short-term, subchronic, long-term) or specific CVD effect and to reconcile evidence for early biologic effects that could lead to more severe CVD effects.

3.2. Particulate matter and carbon monoxide

Few studies examined multipollutant effects of PM and CO. The ability of short-term CO and PM_{2.5} exposure to lead to CVD outcomes is well-established (U.S. EPA, 2010). As described below and examined in epidemiologic and experimental studies, multipollutant effects are not clearly indicated for CO with PM_{2.5} or PM₁₀.

In a rat model of myocardial infarction, acute exposure to PM_{2.5} CAPs collected in Boston, MA had opposite effects on two separate arrhythmic responses (Wellenius et al., 2004, 2006). Simultaneous exposure to CO attenuated the effect of PM on the supraventricular arrhythmia rate, but not the frequency of ventricular premature beats. In an epidemiologic study, PM_{2.5} and CO were examined for associations with out-of-hospital cardiac arrest during wildfires in Melbourne, Australia (Dennekamp et al., 2015), but inference about joint effects is weak because analyses were stratified on number of hours people experienced wildfire smoke rather than concentrations of the copollutant. Other studies observed no consistent combined effect of elevated PM₁₀ and CO concentrations on CVD effects effect measure modification observed with PM₁₀ associations on high CO days only in Seoul, Korea (Hong et al., 2002), and a strong joint effect between PM₁₀ and CO observed on a Greek peninsula (Kalantzi et al., 2011).

Overall, the few epidemiologic studies of multipollutant effects of PM and CO represent a mix of effect measure modification (Dennekamp et al., 2015; Hong et al., 2002) or joint effects analyses (Kalantzi et al., 2011) while the experimental studies reported different effects on arrhythmic responses (Wellenius et al., 2004, 2006). Epidemiologic and experimental studies examined arrhythmia, cardiovascular hospital admissions or cardiovascular mortality and exposure to either PM₁₀, PM_{2.5}, or PM_{2.5} CAPs making it difficult to assess coherence or consistency across studies.

3.3. Ozone and carbon monoxide

Recent assessments provide evidence that short-term exposure to CO or O₃ individually are related to CVD outcomes (U.S. EPA, 2010, 2013). Two available epidemiologic studies evaluating the combined effect of CO and O₃ observed associations with CO or O₃ in single-pollutant analyses but have contrasting results regarding a stronger association when concentrations of both CO and O₃ are elevated (Samoli et al., 2007; Kalantzi et al., 2011). Inference about multipollutant effects is weak from both studies because of potential differential exposure measurement error for CO and O₃, the stratification by O₃ concentrations at the city level in the multicity European study (Samoli et al., 2007), or the inadequately described method to analyze joint effects in the Greek Peninsula study (Kalantzi et al., 2011).

3.4. Particulate matter and nitrogen dioxide

Information on the multipollutant effects of PM and NO₂ is provided by several epidemiologic studies and one controlled human exposure study. While there is abundant evidence for the relationship between PM_{2.5} exposure and CVD endpoints (U.S. EPA, 2009), there is some uncertainty as to whether NO₂ exposure has an effect on CVD endpoints independent from other traffic-related pollutants such as ultrafine particles, CO, elemental carbon/black carbon, and PM_{2.5} (U.S. EPA, 2016a). This may complicate interpretation of the results for PM-NO₂ multipollutant effects.

Evidence integrated from epidemiologic and experimental studies does not provide a clear indication of multipollutant effects of exposure to PM and NO₂. Among epidemiologic studies, CVD hospital admissions and mortality increase with joint increases in short- and

long-term PM and NO₂ concentrations (Kalantzi et al., 2011), although the elevated risk estimates for long-term concentrations do not indicate joint increases (Crouse et al., 2015; Jerrett et al., 2013). Epidemiologic evidence shows that higher long-term NO₂ concentrations modify the effect of O₃ and PM_{2.5} on CVD hospital admissions (Bobb et al., 2013) but does not show NO₂ or PM₁₀ to modify each other's association with CVD hospital admissions (Wong et al., 1999; Yu et al., 2013) or stroke mortality (Hong et al., 2002) in a consistent manner. Adding to the uncertainty in drawing inferences from epidemiologic studies is the potential differential measurement error in PM and NO₂ exposure estimates. Similarly, a controlled human exposure study (Huang et al., 2012) of PM_{2.5} CAPs collected in Chapel Hill, NC and NO₂ shows both synergistic and antagonistic effects of the combined exposure (evaluated on an additive scale) for an array of endpoints including blood markers, measures of HRV, and myocardial repolarization.

Overall, these studies provide limited evidence of joint effects of PM and NO₂ exposure, although it is not clear that the combined effect is greater than either single-pollutant effect. Further, it is not clear to what extent the multipollutant effect results can be attributable specifically to PM or NO₂ exposure or some other correlated pollutant in epidemiologic studies.

3.5. Ozone and nitrogen dioxide

There is evidence for greater than additive CVD mortality increases in relation to joint increases in long-term concentrations of O₃ and NO₂ from epidemiologic studies and conflicting evidence between epidemiologic and controlled human exposure studies for a multipollutant effect on CVD-related morbidity of short-term O₃ and NO₂ exposure. An experimental study provides evidence for a synergistic interaction of NO₂ and O₃ combined exposure on reducing cardiac output (Drechsler-Parks, 1995). In epidemiologic studies, no evidence for greater than additive multipollutant effects is indicated for the joint effects of long-term exposure to NO₂ and O₃ on CVD mortality (Jerrett et al., 2013; Crouse et al., 2015). A limited epidemiologic evidence base inconsistently shows effect measure modification (Weichenthal et al., 2014; Wong et al., 1999; Ponka et al., 1998). Many uncertainties described in preceding sections weaken inference regarding multipollutant effects of O₃ and NO₂ exposure, including differential exposure measurement error, inconsistent epidemiologic evidence for cardiovascular morbidity related to short-term O₃ exposure, and uncertainty as to whether cardiovascular effects are related to long-term O₃ exposure as well as short-term and long-term NO₂ exposure.

3.6. Other two-pollutant combinations

Multipollutant effects of other pollutant combinations were examined in one study for each pollutant combination. Epidemiologic studies reported that associations between short-term increases in ambient SO₂ concentration and mortality from stroke (Hong et al., 2002) and all CVD (Ponka, Savela, and Virtanen, 1998) increased on days with higher PM₁₀, O₃, or NO₂ concentrations (Supplemental Table S8). PM₁₀-related stroke mortality increased on days with higher SO₂ concentrations (Hong et al., 2002). In a controlled human exposure study of healthy adults, heart rate increased in response to CO exposure (relative to filtered air exposure) but not in response to exposure to peroxyacetyl nitrate (PAN) alone or in

combination with CO (Gliner, Raven, Horvath, Drinkwater, and Sutton, 1975). PAN is an oxide of nitrogen formed by atmospheric reactions involving NO₂ and organic radicals. These epidemiologic and experimental findings have uncertain implications given the lack of clear evidence linking SO₂ (U.S. EPA, 2008) or PAN exposure to cardiovascular effects.

3.7. Air pollution mixtures

Epidemiologic studies examined multipollutant effects on CVD outcomes as diverse air pollution mixtures. Various approaches were used, including whole atmosphere comparisons of locations or time periods with low and high air pollution, indices of predetermined pollutants to represent a specific source or period of higher air pollution, and clusters of days representing varied pollutant combinations. In whole atmosphere studies, cardiovascular effects were not clearly associated with air pollution mixture exposures to high and low traffic environments for adults with regard to heart rate, blood pressure, and blood glucose parameters (Kubesch et al., 2014; Larsson et al., 2007; Laumbach et al., 2010). Similarly, cardiovascular effects were not associated with air pollution mixtures examined as high and low air pollution days in Atlanta GA (Peel et al., 2010), or Tehran, Iran (Davoodi et al., 2010). Some of the inconsistency observed in whole atmosphere studies could be due to the differences in pollutant composition (mainly O₃ and CO versus mainly PM and NO₂). Mixture effects were observed in the air pollution index and cluster studies. Indices representing higher air pollution were consistently associated with cardiovascular effects from mortality and emergency department visits to subclinical effects (Baja et al., 2013, 2012; Briet et al., 2007; Chen et al., 2014; Li et al., 2015; Peters et al., 1997, 1999; Poursafa et al., 2016). In limited analysis, air pollution mixtures characterized by clusters of air mass of similar origin (Park et al., 2007) or air pollutant profiles (Grass and Cane, 2008; Mar et al., 2000) were also associated with CVD outcomes, including subclinical effects and cardiovascular mortality. However, these results do not point to a stronger effect of an air pollution mixture or any single pollutant. Many mixtures analyzed included PM_{2.5}, and results are consistent with evidence linking short-term PM_{2.5} exposure to cardiovascular effects. It is not clear how the results should be interpreted or how they might inform joint effects or effect measure modification. While both epidemiologic and experimental studies showed cardiovascular changes in relation to multipollutant exposures, the integrated evidence does not clearly indicate that multipollutant exposures have stronger effects than any single pollutant.

4. Risk of bias

Risk of bias was evaluated for the epidemiologic and experimental studies included in this review (Fig. 2; Supplemental Tables S6 and S7). Because there is limited evidence available on cardiovascular effects of multipollutant exposure, the risk of bias analysis was used to assess confidence in results rather than to eliminate studies from this review. The strongest evidence in epidemiologic studies was for effect measure modification, but several of the studies had *probably high* risk of bias related to exposure misclassification (Hong et al., 2002; Ponka et al., 1998; Samoli et al., 2007; Yu et al., 2013), selective reporting of results (Hong et al., 2002; Ponka et al., 1998; Weichenthal et al., 2014), confounding (Samoli et al., 2007), or selection of data (Weichenthal et al., 2014), adding uncertainty to findings. We had

greater confidence in effect measure modification observed between PM and O₃ in Wong et al. (1999) because risk of bias was *low* or *probably low* across categories. Several of the experimental studies (Drechsler-Parks, 1995; Farraj et al., 2015; Gliner et al., 1975; Huang et al., 2012; Kodavanti et al., 2011; Kurhanewicz et al., 2014; Tankersley et al., 2013; Wagner et al., 2014) had *probably high* risk of performance bias (mainly due to insufficient information about blinding to study group), and two of these (Farraj et al., 2015; Kodavanti et al., 2011) also had *probably high* risk of selection bias (due to insufficient information on randomization of animals and that treatment and data analyses were blinded). These studies with *probably high* risk of bias had variable results for cardiovascular effects of multipollutant exposure as did the few experimental studies with *low* or *probably low* risk of bias across categories (Brook et al., 2009; Fakhri et al., 2009; Urch et al., 2010; Sivagangabalan et al., 2011; Kusha et al., 2012; Wellenius et al., 2004). This underscores the need for additional high-quality multipollutant studies.

5. Strengths and limitations

To our knowledge, this review is the first to survey the epidemiologic and experimental literature on cardiovascular health effects related to exposure to multiple pollutants. Other reviews have identified experimental approaches (Mauderly, 1993; Mauderly and Samet, 2009) or statistical methodologies available to study health effects of multipollutant exposures (Billionnet et al., 2012; Davalos et al., 2016). The scope of this analysis was necessarily limited to one set of disease outcomes (i.e., cardiovascular disease). However, the small number of peer-reviewed studies on the cardiovascular health effects of exposure to multiple pollutants limits the ability to draw definitive conclusions in a multipollutant framework from this review.

The epidemiologic studies reviewed here form one line of evidence for evaluating cardiovascular effects due to multipollutant exposures. As observational studies, the exposures and participant selection have some biases that could influence interpretation of multipollutant effects. Differential exposure errors among pollutants may result from differences in heterogeneity of the spatial distribution of ambient air pollutants (Goldman et al., 2010) or from differences in instrument accuracy (Dunlea et al., 2007; Kleffmann et al., 2013; Steinbacher et al., 2007; U.S. EPA, 2006; Villena et al., 2012), and these biases may vary seasonally. These conditions may lead to attenuation of the health effect estimate (Dionisio et al., 2014). Higher exposure error in one copollutant has been shown to result in a lower effect estimate for that copollutant (Zeger et al., 2000); in other words, the copollutant measured with less error may produce a less biased effect estimate.

Experimental studies reviewed here form another line of evidence for evaluating CVD effects due to multipollutant exposures. A wide range of CVD effects were evaluated in a limited number of studies for any given pollutant combination. This makes it difficult to assess coherence for any duration of exposure or specific CVD effect and to reconcile evidence for early biological effects that could lead to more severe CVD health outcomes. At the same time, experimental studies may minimize uncertainty in exposures present in epidemiologic studies since concentration and duration of the pollutant exposures, composition of the air pollutant mixture, method of delivery, breeding of the animal model,

and ambient temperature and filtered air control are usually strictly managed. Several studies (Drechsler-Parks, 1995; Gliner et al., 1975; Kodavanti et al., 2011; Tankersley et al., 2013) involve highly reproducible conditions. However, the studies involving exposure to CAPs collected in different geographic locations are dependent on the composition of the ambient PM on any given day or hour and thus are subject to the same real-life variability in exposure conditions as epidemiologic studies (C. Sioutas et al., 1995; D. Sioutas et al., 1995).

6. Conclusions

In this review we examined multipollutant effects on an array of CVD outcomes in epidemiologic and experimental studies as joint effects, effect measure modification, or interactions. For completeness and to provide additional context, we also evaluate studies of air pollution mixtures. A broad summary of the results is presented in Table 1. The largest body of evidence was for PM and O₃ exposure, and when taken together, neither epidemiologic nor experimental studies consistently or coherently indicated a stronger or weaker effect of combined exposure compared with either PM or O₃ exposure alone. Similarly, heterogeneous results were observed across disciplines for other two-pollutant combinations: PM and CO, NO₂ and PM₁₀, O₃ and NO₂, CO and O₃. Epidemiologic studies of air pollution mixtures did suggest multipollutant effects examined as pollution indices and days clustered by pollutant profile or origin, but not by comparing whole atmospheres. We limited the scope of our study to multipollutant evaluations of CVD, and an important limitation is the paucity of literature on the cardiovascular effects of multipollutant exposures, which limits strong inferences. The experimental literature has shown mixed or synergistic results within a single study, and suffers from a small literature base and heterogeneity in study designs and CVD endpoints examined, which also limit confidence in inferences.

The objective of this review is not to advocate for a singular multipollutant approach that can be practically applied today. Nor are we suggesting that any of the two-pollutant combinations that we evaluate is the key to addressing air pollution policies. Instead, we acknowledge that a multipollutant approach might be valuable to policy makers, and such an approach could focus on PM sources or components, or a combination of pollutants that we have not considered in our review. Our review demonstrates that, relative to the enormous evidence base available for the health effects of individual pollutants, there remains a paucity of evidence to characterize the multipollutant effects of air pollution on health (specifically cardiovascular disease). Our review is a first step in compiling and synthesizing the existing evidence and is not intended to characterize any singular approach that will address multipollutant effects of air pollutants.

Until epidemiologic and experimental studies of multipollutant effects on CVD consistently and coherently provide evidence for a combined effect of two or more pollutants and a health outcome, it will remain implausible to take advantage of any efficiencies a multipollutant regulatory approach might afford. Additional experimental studies of commonly co-occurring pollutants at relevant exposure levels that investigate both early and more downstream biological responses in the CVD continuum of effects are likely to be

informative in disentangling multipollutant health effects and setting the course for observational studies. Furthermore, epidemiologic studies of the cardiovascular effects of multipollutant exposure that repeat existing studies at new locations would be especially informative to see if findings can be replicated, particularly for effect measure modification where some positive results have been observed. An expanded body of literature would help to shed light on reasons for seeing stronger effects of O₃ and NO₂ for low PM conditions, particularly by focusing more on the role of PM size. Greater consistency of effect modification findings would also help to counteract concerns about exposure measurement error that have the potential to add bias and uncertainty to health effect estimates. New studies could potentially provide additional evidence for establishing biological plausibility of a synergistic or antagonistic effect, or they could provide more support against those findings. Additional epidemiologic and experimental studies would also allow for better judgment of the coherence between these disciplines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We wish to thank Danelle Lobdell and Michael Stewart for comments on early versions of this manuscript and Adam Benson for assistance in formatting. This research was supported in part by an appointment to the Research Participation Program for the U.S. EPA, Office of Research and Development, administered by the Oak Ridge Institute for Science and Education through Interagency Agreement No. DW-89-92298301 between the U.S. Department of Energy and EPA. Disclaimer: The views expressed in this manuscript are those of the authors and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency.

References

- AHRQ. Grading the strength of a body of evidence when assessing health care interventions AHRQ and the effective health care program: An update: Draft report. Rockville, MD: 2012.
- Baja ES, Schwartz JD, Coull BA, Wellenius GA, Vokonas PS, Suh HH. Structural equation modeling of parasympathetic and sympathetic response to traffic air pollution in a repeated measures study. *Environ. Health.: A Glob. Access Sci. Source.* 2013; 12(1):81. <http://dx.doi.org/10.1186/1476-069x-12-81>.
- Baja ES, Schwartz JD, Coull BA, Wellenius GA, Vokonas PS, Suh HH. Structural equation modeling of the inflammatory response to traffic air pollution. *J. Expo. Sci. Environ. Epidemiol.* 2012; 23(3): 268274. <http://dx.doi.org/10.1038/jes.2012.106>.
- Billionnet C, Sherrill D, Annesi-Maesano I. Estimating the health effects of exposure to multi-pollutant mixture. *Ann. Epidemiol.* 2012; 22(2):126–141. <http://dx.doi.org/10.1016/j.annepidem.2011.11.004>. [PubMed: 22226033]
- Briet M, Collin C, Laurent S, Tan A, Azizi M, Agharazii M, Boutouyrie P. Endothelial function and chronic exposure to air pollution in normal male subjects. *Hypertension.* 2007; 50(5):970–976. <http://dx.doi.org/10.1161/hypertensionaha.107.095844>. [PubMed: 17875820]
- Brook RD, Urch B, Dvornch JT, Bard RL, Speck M, Keeler G, Brook JR. Insights into the mechanisms and mediators of the effects of air pollution exposure on blood pressure and vascular function in healthy humans. *Hypertension.* 2009; 54(3):659–667. <http://dx.doi.org/10.1161/hypertensionaha.109.130237>. [PubMed: 19620518]
- Chen L, Villeneuve PJ, Rowe BH, Liu L, Stieb DM. The Air Quality Health Index as a predictor of emergency department visits for ischemic stroke in Edmonton, Canada. *J. Expo. Sci. Environ. Epidemiol.* 2014; 24(4):358–364. <http://dx.doi.org/10.1038/jes.2013.82>. [PubMed: 24301354]

- Davalos AD, Luben TJ, Herring AH, Sacks JD. Current approaches used in epidemiologic studies to examine short-term multipollutant air pollution exposures (e141). *Ann. Epidemiol.* 2016; 27(2): 145–153. <http://dx.doi.org/10.1016/j.annepidem.2016.11.016>. [PubMed: 28040377]
- Davoodi G, Sharif AY, Kazemisaeid A, li, Sadeghian S, Farahani A, Sheikhvatan M, Pashang M. Comparison of heart rate variability and cardiac arrhythmias in polluted and clean air episodes in healthy individuals. *Environ. Health Prev. Med.* 2010; 15(4):217–221. <http://dx.doi.org/10.1007/s12199-009-0130-9>. [PubMed: 21432548]
- Dennekamp M, Straney LD, Erbas B, Abramson MJ, Keywood M, Smith K, Tonkin AM. Forest fire smoke exposures and out-of-hospital cardiac arrests in Melbourne, Australia: a case-crossover study. *Environ. Health Perspect.* 2015; 123(10):959–964. <http://dx.doi.org/10.1289/ehp.1408436>. [PubMed: 25794411]
- Dionisio KL, Baxter LK, Chang HH. An empirical assessment of exposure measurement error and effect attenuation in bipollutant epidemiologic models. *Environ. Health Perspect.* 2014; 122(11): 1216–1224. <http://dx.doi.org/10.1289/ehp.1307772>.
- Dominici F, Peng RD, Barr CD, Bell ML. Protecting human health from air pollution: shifting from a single-pollutant to a multipollutant approach. *Epidemiology.* 2010; 21(2):187–194. <http://dx.doi.org/10.1097/EDE.0b013e3181cc86e8>. [PubMed: 20160561]
- Drechsler-Parks DM. Cardiac output effects of O₃ and NO₂ exposure in healthy older adults. *Toxicol. Ind. Health.* 1995; 11(1):99–109. <http://dx.doi.org/10.1177/074823379501100109>. [PubMed: 7652755]
- Dunlea EJ, Herndon SC, Nelson DD, Volkamer RM, San Martini F, Sheehy PM, Molina MJ. Evaluation of nitrogen dioxide chemiluminescence monitors in a polluted urban environment. *Atmos. Chem. Phys.* 2007; 7(10):2691–2704.
- Fakhri AA, Ilic LM, Wellenius GA, Urch B, Silverman F, Gold DR, Mittleman MA. Autonomic effects of controlled fine particulate exposure in young healthy adults: effect modification by ozone. *Environ. Health Perspect.* 2009; 117(8):1287–1292. <http://dx.doi.org/10.1289/ehp.0900541>. [PubMed: 19672410]
- Farraj AK, Walsh L, Haykal-Coates N, Malik F, Mcgee J, Winsett D, Hazari MS. Cardiac effects of seasonal ambient particulate matter and ozone co-exposure in rats. *Part. Fibre Toxicol.* 2015; 12:12. <http://dx.doi.org/10.1186/s12989-015-0087-3>. [PubMed: 25944145]
- Gill E, Curl C, Adar S, Allen R, Auchincloss A, O'Neill M, Kaufman J. Air pollution and cardiovascular disease in the multi-ethnic study of atherosclerosis. *Prog. Cardiovasc. Dis.* 2011; 53(5):353–360. <http://dx.doi.org/10.1016/j.pcad.2011.02.001>. [PubMed: 21414470]
- Gliner JA, Raven PB, Horvath SM, Drinkwater BL, Sutton JC. Man's physiologic response to long-term work during thermal and pollutant stress. *J. Appl. Physiol.* 1975; 39(4):628–632. (1985). [PubMed: 1194154]
- Goldman GT, Mulholland JA, Russell AG, Srivastava A, Strickland MJ, Klein M, Edgerton ES. Ambient air pollutant measurement error: characterization and impacts in a time-series epidemiologic study in Atlanta. *Environ. Sci. Technol.* 2010; 44(19):7692–7698. <http://dx.doi.org/10.1021/es101386r>. [PubMed: 20831211]
- Grass D, Cane M. The effects of weather and air pollution on cardiovascular and respiratory mortality in Santiago, Chile, during the winters of 1988/1996. *Int. J. Climatol.* 2008; 28(8):1113–1126. <http://dx.doi.org/10.1002/joc.1592>.
- Greenbaum D, Shaikh R. First steps toward multipollutant science for air quality decisions. *Epidemiology.* 2010; 21(2):195–197. <http://dx.doi.org/10.1097/EDE.0b013e3181ccc52a>. [PubMed: 20160562]
- Hidy GM, Pennell WT. Multipollutant air quality management. *J. Air Waste Manag. Assoc.* 2010; 60(6):645–674. <http://dx.doi.org/10.3155/1047-3289.60.6.645>. (1990–1992). [PubMed: 20564991]
- Higgins, J., Green, S. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0. The Cochrane Collaboration; 2011.
- Hong YC, Lee JT, Kim H, Ha EH, Schwartz J, Christiani DC. Effects of air pollutants on acute stroke mortality. *Environ. Health Perspect.* 2002; 110(2):187–191. [PubMed: 11836148]
- Howe CJ, Cole SR, Mehta SH, Kirk GD. Estimating the effects of multiple time-varying exposures using joint marginal structural models: alcohol consumption, injection drug use, and HIV

acquisition. *Epidemiology*. 2012; 23(4):574–582. <http://dx.doi.org/10.1097/EDE.0b013e31824d1ccb>. [PubMed: 22495473]

- Huang YC, Rappold AG, Graff DW, Ghio AJ, Devlin RB. Synergistic effects of exposure to concentrated ambient fine pollution particles and nitrogen dioxide in humans. *Inhal. Toxicol.* 2012; 24(12):790–797. <http://dx.doi.org/10.3109/08958378.2012.718809>. [PubMed: 23033993]
- Johns DO, Stanek LW, Walker K, Benromdhane S, Hubbell B, Ross M, Greenbaum DS. Practical advancement of multipollutant scientific and risk assessment approaches for ambient air pollution. *Environ. Health Perspect.* 2012; 120(9):1238–1242. <http://dx.doi.org/10.1289/ehp.1204939>. [PubMed: 22645280]
- Kalantzi EG, Makris D, Duquenne MN, Kaklamani S, Stapountzis H, Gourgoulisanis KI. Air pollutants and morbidity of cardiopulmonary diseases in a semi-urban Greek peninsula. *Atmos. Environ.* 2011; 45(39):7121–7126. <http://dx.doi.org/10.1016/j.atmosenv.2011.09.032>.
- Kleffmann, J., Tapia, GV., Bejan, I., Kurtenbach, R., Wiesen, P. *NO₂ Measurement Techniques: Pitfalls and New Developments*. Springer; New York, NY: 2013.
- Kodavanti UP, Thomas R, Ledbetter AD, Schladweiler MC, Shannahan JH, Wallenborn JG, Parianandi NL. Vascular and cardiac impairments in rats Inhaling ozone and diesel exhaust particles. *Environ. Health Perspect.* 2011; 119(3):312–318. <http://dx.doi.org/10.1289/ehp.1002386>. [PubMed: 20980218]
- Kubesch N, De Nazelle A, Guerra S, Westerdahl D, Martinez D, Bouso L, Nieuwenhuijsen M. Arterial blood pressure responses to short-term exposure to low and high traffic-related air pollution with and without moderate physical activity. *Eur. J. Prev. Cardiol.* 2014; 22(5):548–557. <http://dx.doi.org/10.1177/2047487314555602>. [PubMed: 25326542]
- Kurhanewicz N, McIntosh-Kastrinsky R, Tong H, Walsh L, Farraj A, Hazari MS. Ozone co-exposure modifies cardiac responses to fine and ultrafine ambient particulate matter in mice: concordance of electrocardiogram and mechanical responses. *Part. Fibre Toxicol.* 2014; 11(54):54. <http://dx.doi.org/10.1186/s12989-014-0054-4>. [PubMed: 25318591]
- Larsson BM, Sehstedt M, Grunewald J, Skold CM, Lundin A, Blomberg A, Svartengren M. Road tunnel air pollution induces bronchoalveolar inflammation in healthy subjects. *Eur. Respir. J.* 2007; 29(4):699–705. <http://dx.doi.org/10.1183/09031936.00035706>. [PubMed: 17251238]
- Laumbach RJ, Rich DQ, Gandhi S, Amorosa L, Schneider S, Zhang J, Kipen HM. Acute changes in heart rate variability in subjects with diabetes following a highway traffic exposure. *J. Occup. Environ. Med.* 2010; 52(3):324–331. <http://dx.doi.org/10.1097/JOM.0b013e3181d241fa>. [PubMed: 20190650]
- Li L, Lin GZ, Liu HZ, Guo Y, Ou CQ, Chen PY. Can the Air Pollution Index be used to communicate the health risks of air pollution? *Environ. Pollut.* 2015; 205:153–160. <http://dx.doi.org/10.1016/j.envpol.2015.05.038>. [PubMed: 26057478]
- Mar TF, Norris GA, Koenig JQ, Larson TV. Associations between air pollution and mortality in Phoenix, 1995–1997. *Environ. Health Perspect.* 2000; 108(4):347–353. <http://dx.doi.org/10.2307/3454354>. [PubMed: 10753094]
- Mauderly JL. Toxicological approaches to complex mixtures. *Environ. Health Perspect.* 1993; 1014(Suppl 4):155–165.
- Mauderly JL, Burnett RT, Castillejos M, Ozkaynak H, Samet JM, Stieb DM, Wyzga RE. Is the air pollution health research community prepared to support a multipollutant air quality management framework? *Inhal. Toxicol.* 2010; 22(S1):1–19. <http://dx.doi.org/10.3109/08958371003793846>.
- Mauderly JL, Samet JM. Is there evidence for synergy among air pollutants in causing health effects? *Environ. Health Perspect.* 2009; 117(1):1–6. <http://dx.doi.org/10.1289/ehp.11654>. [PubMed: 19165380]
- NRC. *Air Quality Management in the United States*. National Academies Press; Washington, DC: 2004.
- Park SK, O'Neill MS, Stunder BJB, Vokonas PS, Sparrow D, Koutrakis P, Schwartz J. Source location of air pollution and cardiac autonomic function: trajectory cluster analysis for exposure assessment. *J. Expo. Sci. Environ. Epidemiol.* 2007; 17(5):488–497. <http://dx.doi.org/10.1038/sj.jes.7500552>. [PubMed: 17299527]

- Peel, JL., Klein, M., Flanders, WD., Mulholland, JA., Tolbert, PE., Committee, HHR. Research report. Vol. 148. Health Effects Institute; 2010. Impact of Improved Air Quality during the 1996 Summer Olympic Games in Atlanta on Multiple Cardiovascular and Respiratory Outcomes; p. 3-23.
- Peters A, Doring A, Wichmann HE, Koenig W. Increased plasma viscosity during an air pollution episode: a link to mortality? *Lancet*. 1997; 349(9065):1582–1587. [http://dx.doi.org/10.1016/S0140-6736\(97\)01211-7](http://dx.doi.org/10.1016/S0140-6736(97)01211-7). [PubMed: 9174559]
- Peters A, Perz S, Doring A, Stieber J, Koenig W, Wichmann HE. Increases in heart rate during an air pollution episode. *Am. J. Epidemiol*. 1999; 150(10):1094–1098. [PubMed: 10568625]
- Ponka A, Savela M, Virtanen M. Mortality and air pollution in Helsinki. *Arch. Environ. Occup. Health*. 1998; 53(4):281–286. <http://dx.doi.org/10.1080/00039899809605709>.
- Poursafa P, Baradaran-Mahdavi S, Moradi B, Haghjooy Javanmard S, Tajadini M, Mehrabian F, Kelishadi R. The relationship of exposure to air pollutants in pregnancy with surrogate markers of endothelial dysfunction in umbilical cord. *Environ. Res*. 2016; 146:154–160. <http://dx.doi.org/10.1016/j.envres.2015.12.018>. [PubMed: 26761592]
- Rooney AA, Boyles AL, Wolfe MS, Bucher JR, Thayer KA. Systematic review and evidence integration for literature-based environmental health science assessments. *Environ. Health Perspect*. 2014; 122(7):711–718. <http://dx.doi.org/10.1289/ehp.1307972>. [PubMed: 24755067]
- Samoli E, Touloumi G, Schwartz J, Anderson HR, Schindler C, Forsberg B, Katsouyanni K. Short-term effects of carbon monoxide on mortality: an analysis within the APHEA project. *Environ. Health Perspect*. 2007; 115(11):1578–1583. <http://dx.doi.org/10.1289/ehp.10375>.
- Sioutas C, Koutrakis P, Burton RM. A technique to expose animals to concentrated fine ambient aerosols. *Environ. Health Perspect*. 1995; 103(2):172–177. <http://dx.doi.org/10.2307/3432274>. [PubMed: 7737066]
- Sioutas D, Koutrakis P, Ferguson ST, Burton RM. Development and evaluation of a prototype ambient particle concentrator for inhalation exposure studies. *Inhal. Toxicol*. 1995; 7(5):633–644. <http://dx.doi.org/10.3109/08958379509014470>.
- Sivagangabalan G, Spears D, Masse S, Urch B, Brook RD, Silverman F, Nanthakumar K. The effect of air pollution on spatial dispersion of myocardial repolarization in healthy human volunteers. *J. Am. Coll. Cardiol*. 2011; 57(2):198–206. <http://dx.doi.org/10.1016/j.jacc.2010.08.625>. [PubMed: 21211691]
- Steinbacher M, Zellweger C, Schwarzenbach B, Bugmann S, Buchmann B, Ordóñez C, Hueglin C. Nitrogen oxides measurements at rural sites in Switzerland: bias of conventional measurement techniques. *J. Geophys. Res.: Atmos*. 2007; 112(D11):D11307. <http://dx.doi.org/10.1029/2006jd007971>.
- Tankersley CG, Georgakopoulos D, Tang WY, Sborz N. Effects of ozone and particulate matter on cardiac mechanics: role of the atrial natriuretic peptide gene. *Toxicol. Sci*. 2013; 131(1):95–107. <http://dx.doi.org/10.1093/toxsci/kfs273>. [PubMed: 22977167]
- U.S. EPA. Air QUALITY Criteria for Ozone and Related Photochemical Oxidants 1. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment-RTP Office; Research Triangle Park, NC: 2006.
- U.S. EPA. Integrated Science Assessment For Sulfur Oxides: Health criteria. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment- RTP; Research Triangle Park, NC: 2008.
- U.S. EPA. Integrated Science Assessment for Particulate Matter. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment-RTP Division; Research Triangle Park, NC: 2009.
- U.S. EPA. Integrated Science Assessment for Carbon Monoxide. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment; Research Triangle Park, NC: 2010. p. 1-593.
- U.S. EPA. Integrated Science Assessment for Ozone and Related Photochemical Oxidants. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment-RTP Division; Research Triangle Park, NC: 2013.

- U.S. EPA. Integrated science assessment for oxides of nitrogen-Health Criteria (final report). U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment; Research Triangle Park, NC: 2016a.
- U.S. EPA. U.S. EPAs Report on the Environment (ROE). 2016b. <https://cfpub.epa.gov/roe/index.cfm>
- U.S.EPA. Air Quality System (AQS). Environmental Protection Agency; 2017. (Retrieved from). <http://www.epa.gov/aqs>
- Urch B, Speck M, Corey P, Wasserstein D, Manno M, Lukic KZ, Silverman F. Concentrated ambient fine particles and not ozone induce a systemic interleukin-6 response in humans. *Inhal. Toxicol.* 2010; 22(3):210–218. <http://dx.doi.org/10.3109/08958370903173666>. [PubMed: 20088738]
- Vanderweele TJ. On the distinction between interaction and effect modification. *Epidemiology.* 2009; 20(6):863–871. <http://dx.doi.org/10.1097/EDE.0b013e3181ba333c>. [PubMed: 19806059]
- Villena G, Bejan I, Kurtenbach R, Wiesen P, Kleffmann J. Interferences of commercial NO₂ instruments in the urban atmosphere and in a smog chamber. *Atmos. Meas. Tech.* 2012; 5(1):149–159. <http://dx.doi.org/10.5194/amt-5-149-2012>.
- Wagner JG, Allen K, Yang HY, Nan B, Morishita M, Mukherjee B, Harkema JR. Cardiovascular depression in rats exposed to inhaled particulate matter and ozone: effects of diet-induced metabolic syndrome. *Environ. Health Perspect.* 2014; 122(1):27–33. <http://dx.doi.org/10.1289/ehp.1307085>. [PubMed: 24169565]
- Weichenthal S, Hatzopoulou M, Goldberg MS. Exposure to traffic-related air pollution during physical activity and acute changes in blood pressure, autonomic and micro-vascular function in women: a cross-over study. *Part. Fibre Toxicol.* 2014; 11(1):70. <http://dx.doi.org/10.1186/s12989-014-0070-4>. [PubMed: 25487431]
- Wellenius GA, Batalha JRF, Diaz EA, Lawrence J, Coull BA, Katz T, Godleski JJ. Cardiac effects of carbon monoxide and ambient particles in a rat model of myocardial infarction. *Toxicol. Sci.* 2004; 80(2):367–376. <http://dx.doi.org/10.1093/toxsci/kfh161>. [PubMed: 15141103]
- Wellenius GA, Coull BA, Batalha JRF, Diaz EA, Lawrence J, Godleski JJ. Effects of ambient particles and carbon monoxide on supraventricular arrhythmias in a rat model of myocardial infarction. *Inhal. Toxicol.* 2006; 18(14):1077–1082. <http://dx.doi.org/10.1080/08958370600945473>. [PubMed: 17050344]
- Wesson K, Fann N, Morris M, Fox T, Hubbell B. A Multi-pollutant, risk-based approach to air quality management: case study for Detroit. *Atmos. Pollut. Res.* 2010; 1(4):296–304. <http://dx.doi.org/10.5094/apr.2010.037>.
- Winqvist A, Kirrane E, Klein M, Strickland M, Darrow LA, Sarnat SE, Tolbert P. Joint effects of ambient air pollutants on pediatric asthma emergency department visits in Atlanta, 1998–2004. *Epidemiology.* 2014; 25(5):666–673. <http://dx.doi.org/10.1097/ede.0000000000000146>. [PubMed: 25045931]
- Wong TW, Lau TS, Yu TS, Neller A, Wong SL, Tam W, Pang SW. Air pollution and hospital admissions for respiratory and cardiovascular diseases in Hong Kong. *Occup. Environ. Med.* 1999; 56(10):679–683. <http://dx.doi.org/10.1136/oem.56.10.679>. [PubMed: 10658547]
- Yu IT, Qiu H, Wang X, Tian L, Tse LA. Synergy between particles and nitrogen dioxide on emergency hospital admissions for cardiac diseases in Hong Kong. *Int. J. Cardiol.* 2013; 168(3):2831–2836. <http://dx.doi.org/10.1016/j.ijcard.2013.03.082>. [PubMed: 23608392]
- Zeger SL, Thomas D, Dominici F, Samet JM, Schwartz J, Dockery D, Cohen A. Exposure measurement error in time-series studies of air pollution: concepts and consequences. *Environ. Health Perspect.* 2000; 108(5):419–426. <http://dx.doi.org/10.1289/ehp.00108419>. [PubMed: 10811568]

Fig. 1.
Schematic of the literature search and screening processes.

Fig. 2.
Risk of bias evaluation for (A) epidemiologic studies and (B) experimental studies.

Table 1

Summary and synthesis of epidemiologic and experimental evidence. (Complete study details results can be found in Supplemental Tables S8 and S9).

Combination	Epidemiologic evidence	Experimental evidence	Overall
PM and O ₃	Little evidence for joint effects	Synergistic, antagonistic, and no overall interactive effects detected across studies	Results inconsistent within disciplines
	Modest evidence for effect modification (larger effects for PM ₁₀ when O ₃ was higher) (Bobb et al. 2013; Kalantzi et al., 2011; Crouse et al. 2015; Jerrett et al. 2013; Weichenthal et al., 2014; Hong et al., 2002; Wong et al., 1999)	Limited support for ability of O ₃ to modify effect of PM (Brook et al., 2009; Urch et al., 2010; Fakhri et al., 2009; Sivagangabalan et al., 2011; Kusha et al. 2012; Farraj et al., 2015; Kurhanewicz et al. 2014a; Kurhanewicz et al. 2014b; Wagner et al., 2014; Tankersley et al., 2013; Kodavanti et al., 2011)	No coherence across scientific disciplines, CVD health effects, or time periods of exposure
PM and NO ₂	Long-term NO ₂ exposure may modify short-term PM _{2.5} exposure (larger effects for short-term exposure to PM _{2.5} when long-term concentrations of NO ₂ are higher) (Bobb et al. 2013; Weichenthal et al., 2014; Wong et al., 1999; Yu et al., 2013; Hong et al., 2002; Crouse et al. 2015; Jerrett et al. 2013)	Evidence for both synergistic and antagonistic effects depending on CVD endpoint for controlled human exposure study (Huang et al., 2012)	Results inconsistent within disciplines Modest evidence of multipollutant effects
O ₃ and NO ₂	No evidence of joint effects and inconsistent results for effect measure modification across CVD endpoints (Weichenthal et al., 2014; Wong et al., 1999; Ponka et al., 1998; Crouse et al. 2015; Jerrett et al. 2013; Kalantzi et al., 2011)	1 study provided limited evidence of synergism (Dreschler-Parks et al., 1995)	Results inconsistent within disciplines Modest evidence of multipollutant effects
PM and CO	No evidence of joint effects or effect measure modification among 3 studies (Dennekamp et al., 2015; Hong et al., 2002; Kalantzi et al., 2011)	Among 2 studies, evidence for interaction from 1 (Wellenius et al., 2004, 2006)	Limited evidence of multipollutant effects
O ₃ and CO	No evidence of joint effects or effect measure modification among 2 studies (Samoli et al., 2007; Kalantzi et al., 2011)	No studies	No evidence of multipollutant effects
Mixtures	Index studies observed consistent evidence between indices and CVD endpoints (Fink et al. 2012; Peters et al., 1997, 1999, 2001; Chen et al., 2014; Briet et al., 2007; Li et al., 2015; Poursafa et al., 2016; Johannesson et al. 2014; Baja et al., 2012, 2013)	No studies	Unclear how to use these studies to inform questions about multipollutant exposures
	Cluster studies observed consistent evidence between clusters and CVD endpoints (Park et al., 2007; Grass and Cane, 2008; Mar et al., 2000)		
	Whole atmosphere studies inconsistently associated with CVD effects (Kubesch et al., 2014; Laumbach et al., 2010; Peel et al., 2010; Davoodi et al., 2010)		