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Associations between Ambient Fine Particulate Oxidative Potential and Cardiorespiratory Emergency Department Visits

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Background: Oxidative potential (OP) has been proposed as a measure of toxicity of ambient particulate matter (PM).

Objectives: Our goal was to address an important research gap by using daily OP measurements to conduct population-level analysis of the health effects of measured ambient OP.

Methods: A semi-automated dithiothreitol (DTT) analytical system was used to measure daily average OP (OP^{DTT}) in water-soluble fine PM at a central monitor site in Atlanta, Georgia, over eight sampling periods (a total of 196 d) during June 2012–April 2013. Data on emergency department (ED) visits for selected cardiorespiratory outcomes were obtained for the five-county Atlanta metropolitan area. Poisson log-linear regression models controlling for temporal confounders were used to conduct time-series analyses of the relationship between daily counts of ED visits and either the 3-d moving average (lag 0–2) of OP^{DTT} or same-day OP^{DTT}. Bipollutant regression models were run to estimate the health associations of OP^{DTT} while controlling for other pollutants.

Results: OP^{DTT} was measured for 196 d (mean = 0.32 nmol/min/m^3, interquartile range = 0.21). Lag 0–2 OP^{DTT} was associated with ED visits for respiratory disease (RR = 1.03, 95% confidence interval (CI): 1.00, 1.05 per interquartile range increase in OP^{DTT}), asthma (RR = 1.12, 95% CI: 1.03, 1.22), and ischemic heart disease (RR = 1.19, 95% CI: 1.03, 1.38). Same-day OP^{DTT} was not associated with ED visits for any outcome. Lag 0–2 OP^{DTT} remained a significant predictor of asthma and ischemic heart disease in most bipollutant models.

Conclusions: Lag 0–2 OP^{DTT} was associated with ED visits for multiple cardiorespiratory outcomes, providing support for the utility of OP^{DTT} as a measure of fine particle toxicity. https://doi.org/10.1289/EHP1545

Introduction

Fine particulate matter (PM with aerodynamic diameter ≤2.5 μm, or $PM_{2.5}$) has been associated with hospital admissions and emergency department (ED) visits for several respiratory outcomes (e.g., asthma, chronic obstructive pulmonary disease, and bronchitis) and cardiovascular outcomes (e.g., myocardial infarction, coronary heart disease, and stroke) (Brook et al. 2010; Dockery and Pope 1994; Kim et al. 2015; Rückerl et al. 2011). Given that $PM_{2.5}$ is a heterogeneous mixture and that distinct particulate components could have different health effects (Bell et al. 2009; Zanobetti et al. 2009), measurement of mass concentration may not be the optimal way to quantify risk to human health. One commonly proposed mechanism for the toxicity of $PM_{2.5}$ is through oxidative stress-driven pathways.

$PM_{2.5}$ can contain a variety of species that contribute to its oxidative potential (OP), including transition metals (e.g., copper, iron), quinones, polycyclic aromatic hydrocarbons (PAHs), and elemental carbon (Cho et al. 2005; González-Flecha 2004; Tao et al. 2003). Several assays have been developed to attempt to measure the OP of ambient fine PM. The electron spin resistance (ESR) assay measures the capacity of PM to convert hydrogen peroxide to hydroxyl radicals (Shi et al. 2003). Assays for ascorbic acid (AA) and glutathione (GSH), two antioxidants, measure the level of depletion of these compounds when added to PM sample extract (Godri et al. 2011). The dithiothreitol (DTT) assay mimics the *in vivo* generation of superoxide radicals by particles transferring electrons from nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH) to oxygen (Kumagai et al. 2002; Verma et al. 2014). Cellular assays, such as those using rat alveolar macrophage (NR8383) cells, can directly measure the oxidation of intracellular probes (Hopke 2015). For this study, a semi-automated system was used to measure DTT activity as a measure of OP (OP^{DTT}) of water-soluble fine PM in order to generate a time-series of daily OP^{DTT} measurements for a central site in Atlanta, Georgia.

Exposure to high levels of diesel exhaust and other sources of particulate matter repeatedly has been shown to be associated with measureable amounts of oxidative stress (Møller and Loft 2010; Xiao et al. 2003). Additionally, exposure to diesel exhaust can result in acute oxidative stress and release of pro-inflammatory cytokines in airway tissues (Pourazar et al. 2005; Salvi et al. 1999). Inhalation of particulate matter is associated with the release of cytokines, activated immune cells, and other mediators of inflammation in the upper and lower airways (Ghio and Devlin 2001; Nel 2005). This respiratory inflammation can lead to exacerbation of asthma symptoms, chronic bronchitis, and decreased gas exchange. The release of pro-inflammatory mediators into the bloodstream results in elevated levels of white blood cells, platelets, and the enzyme myeloperoxidase; these changes are linked to vasoconstriction, atherosclerosis, and endothelial dysfunction, all major risk factors for future cardiac outcomes (Brook et al. 2010; Sun et al. 2010). These inflammatory

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pathways are hypothesized to be driven or mediated by oxidative stress caused by the *in vivo* generation of reactive oxygen species (Gurgueira et al. 2002; Xiao et al. 2003).

Although there is growing evidence linking OP to adverse health outcomes (González-Flecha 2004; Hopke 2015; Øvrevik et al. 2015; Qu et al. 2017; Yang and Omaye 2009), the only study to date assessing population-level impact of measured daily ambient OP did not reveal significant health effects (Atkinson et al. 2016). Additional studies are necessary to *a*) determine whether OP is a major mechanism of harm for PM; *b*) assess alternate measures of OP; *c*) determine health outcomes for people exposed to ambient levels of OP, not just experimental doses; and *d*) quantify health effects at the population level. In our study, we use time-series methodology to estimate associations between daily measured ambient OP^{DTT} and cardiorespiratory ED visits, helping to fill these critical research gaps.

Methods

Air sampling took place from June 2012 through April 2013 at a mixed industrial/residential location in Atlanta, Georgia (Jefferson Street), roughly 3.2 km (2 mi) northwest of downtown Atlanta and about 2.3 km (1.4 mi) from a major interstate highway. Daily samples were taken over eight distinct sampling periods each lasting roughly a month in order to obtain sufficient OP^{DTT} measurements over each season. During each of the sampling periods, measurements were also conducted at one of three additional locations (roadside, near-road, and rural) to characterize spatial variation in OP^{DTT}, though only the central-site observations are used in the health analysis. To measure oxidative potential, we used a semi-automated system that measures the capacity of water-soluble $PM_{2.5}$ to generate reactive oxygen species using the DTT assay. Our OP^{DTT} method and this Atlanta sampling campaign have been described extensively in previous publications (Fang et al. 2014; Verma et al. 2009, 2012, 2014). Particles were collected with a high-volume sampler (HiVol, Thermo Anderson, nondenuded, nominal flow rate 1.13 m^3/min, $PM_{2.5}$ cut size by impactor) onto prebaked 20.25 × 25.5 cm (8 × 10 in) quartz filters to collect $PM_{2.5}$ over 23-h periods (1200–1100 hours daily). After sampling, filters were immediately wrapped in prebaked aluminum foil and stored in a freezer. Analysis of filters for OP^{DTT} and other pollutant measures started in March 2013. A fraction of the high-volume filter was extracted in water, the extract was filtered and then OP^{DTT} was determined with the automated analytical system, which allowed for consistent OP^{DTT} analysis on a large number of filter samples with less effort compared with manual analysis. OP^{DTT} was measured in nanomoles per minute per cubic meter, which corresponds to the loss rate of DTT when exposed to an aerosol sample per volume of air from which the sample was collected. The coefficient of variation for standards was 12% (Fang et al. 2014). Daily measurements on additional particulate and gaseous pollutants were also taken at this location; methods for their collection have been previously described (Edgerton et al. 2005; Hansen et al. 2003, 2006). Meteorological data collected at Hartsfield-Jackson airport, about 13 km (8 mi) south of downtown Atlanta, were also acquired.

Computerized billing records on ED visits were acquired from the Georgia Hospital Association for all 38 nonfederal acute care hospitals with emergency departments in the 20-county Atlanta metropolitan area for the study period (O'Lenick et al. 2017; Sarnat et al. 2010). Patient variables included date of admission, all recorded *International Classification of Diseases, Ninth Revision* (ICD-9) diagnostic codes, date of birth, sex, race, and five-digit residential ZIP code. ED visits were included in the study if the patient residential ZIP code was located wholly or partially within the five primary urban counties of metropolitan Atlanta (Fulton, DeKalb, Gwinnett, Cobb, Clayton). Daily counts of ED visits were calculated for the following outcome categories based on primary ICD-9 codes: asthma (ICD-9 codes 493, 786.07), chronic obstructive pulmonary disease (COPD) (491, 492, 496), pneumonia (480–486), upper respiratory infection (URI) (460–465, 466.0, 477), congestive heart failure (CHF) (428), and ischemic heart disease (IHD) (410–414). In addition, daily counts were determined for combined categories of respiratory diseases (RD) (460–465, 466.0, 466.1, 466.11, 466.19, 477, 480–486, 491–493, 496, 786.07) and cardiovascular diseases (CVD) (410–414, 427, 428, 433–437, 440, 443–445, 451–453). The combined RD and CVD categories represent multiple respiratory and cardiovascular subcategories that have been shown in our previous studies to be linked to air pollution (Metzger et al. 2004; Peel et al. 2005, 2007; Winquist et al. 2012).

We estimated associations between OP^{DTT} and daily counts of ED visits for the selected cardiorespiratory outcomes using Poisson log-linear models accounting for overdispersion. We used the 3-d moving average of OP^{DTT} (the average of OP^{DTT} on the same day as the ED visit, 1 d previous, and 2 d previous, or lag 0–2) as the exposure of interest because our prior studies have shown consistent associations of multiday elevated pollutant levels (Metzger et al. 2004; Peel et al. 2005, 2007; Strickland et al. 2010). Observations without three consecutive daily OP^{DTT} measurements were excluded from this analysis. Some of our prior studies had also shown evidence of associations between ED visits and same-day (lag 0) ambient pollutant levels (Strickland et al. 2016; Winquist et al. 2016; Ye et al. 2017), so we ran separate analyses using same-day OP^{DTT} as the exposure of interest.

Information from our previous studies was used to construct time-series models with optimal confounder control. To control for seasonal trends, the models included cubic splines with monthly knots. The models also controlled for weekdays and federal holidays, as well as temperature (cubic polynomial of the lag 0–2 moving average of daily maximum temperature) and dew point (cubic polynomial of the lag 0–2 moving average of daily mean dew point). Models included indicator variables for periods of hospital data contribution (to control for hospitals opening or closing, or days for which data from individual hospitals were unavailable): Indicators for each hospital had the value 1 if the hospital contributed data on a given day and 0 if the hospital did not contribute. To determine the utility of OP^{DTT} as a measure of ambient air toxicity independent of other pollutant measures, we ran bipollutant models that included OP^{DTT} and one of several common pollutant measures for which daily values were available over this time period and were hypothesized to be potential indicators of air quality. These pollutant measures were: $PM_{2.5}$ total mass, carbon monoxide (CO), nitrogen dioxide (NO_2), ozone (O_3), and sulfur dioxide (SO_2), as well as the following $PM_{2.5}$ components: sulfate (SO_4), elemental carbon (EC), organic carbon (OC), ammonium (NH_4), nitrate (NO_3), water-soluble manganese (Mn), water-soluble iron (Fe), and water-soluble copper (Cu). Health associations were measured as risk ratio (RR) per interquartile range (IQR) of daily OP^{DTT} or other pollutants.

All analyses were performed using SAS version 9.3 (SAS Institute, Inc.).

Results

There were 196 d of daily OP^{DTT} levels recorded from 8 June 2012 through 12 April 2013 in eight separate sampling periods (Figure 1). Mean daily OP^{DTT} was 0.32 nmol/min/m^3 (range: 0.05–0.83, IQR: 0.21). OP^{DTT} tended to be highest in Sampling Period 4 (16 November 2012–30 November 2012) and Sampling

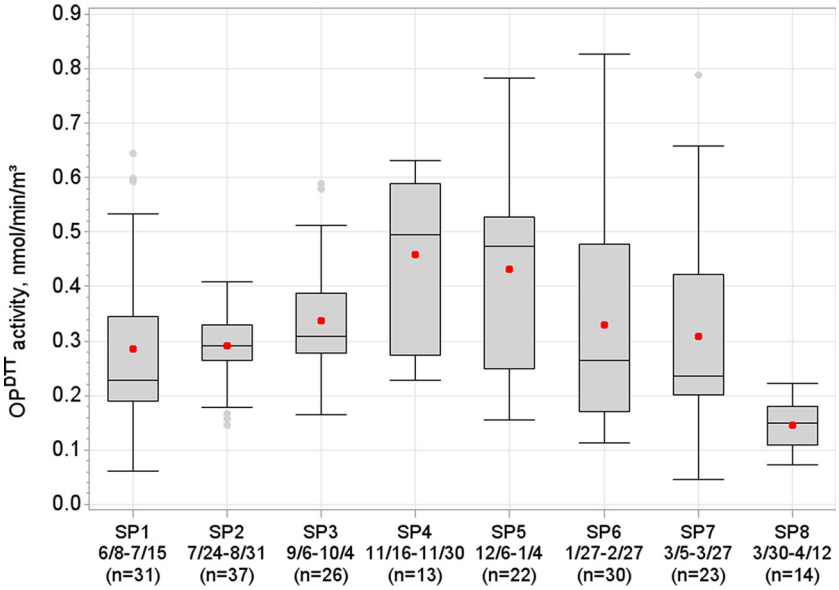

Figure 1. Distribution of the oxidative potential of water-soluble $PM_{2.5}$ as measured by the DTT assay (OP^{DTT}), for eight different sampling periods (SPs), June 2012–April 2013, Atlanta, Georgia. Boxes encompass 25th through 75th percentiles, middle horizontal line represents the median, dots within boxes represent the mean, whiskers extend to the most extreme point within 1.5 interquartile ranges (IQRs) of the box, dots outside boxes indicate outliers. Dates and number of measurements for each sampling period are displayed on the *x*-axis.

Period 5 (6 December 2012–4 January 2013). OP^{DTT} was generally higher from Friday through Sunday compared with the other days of week (see Figure S1). OP^{DTT} was most correlated with EC ($r = 0.56$), $PM_{2.5}$ ($r = 0.55$), and OC ($r = 0.51$) (Table 1). For the days with OP^{DTT} measurements, there were over 730,000 total ED visits; on average there were 391 daily ED visits per day for the combined respiratory disease group, of which an average of 85 visits were for asthma, 20 visits for COPD, 227 visits for URI, and 45 visits for pneumonia. There was an average of 99 ED visits per day for the combined cardiovascular disease group, of which an average of 25 visits were for CHF and 20 visits were for IHD. For the time-series analyses using the 3-d moving average of OP^{DTT}, excluding data for which the full 3-d moving average was unavailable left 156 d of observations. Daily values for OP^{DTT} and cardiorespiratory ED visit categories did not significantly differ between these 156 d and the remaining 40 d without a full 3-d moving average of OP^{DTT} (for all pooled *t*-tests, $p > 0.05$).

Lag 0–2 OP^{DTT} was significantly positively associated with the combined respiratory disease group (RR = 1.03, 95% CI: 1.00, 1.05) and positively associated, but not significantly, with the combined cardiovascular disease group (RR = 1.05, 95% CI: 0.98, 1.12) (Figure 2A). Within more specific outcome categories, lag 0–2 OP^{DTT} was significantly positively associated with asthma (RR = 1.12, 95% CI: 1.03, 1.22) and IHD (RR = 1.19, 95% CI: 1.03, 1.38). Point estimates for these risk ratios were all somewhat greater than associations using lag 0–2 $PM_{2.5}$ (combined respiratory disease group: RR = 1.02, 95% CI: 1.01, 1.04; combined cardiovascular disease group: RR = 1.02, 95% CI: 0.97, 1.07; asthma: RR = 1.10, 95% CI: 1.04, 1.17; and IHD: RR = 1.09, 95% CI: 0.97, 1.21). Lag 0–2 OP^{DTT} was not significantly associated with CHF, COPD, pneumonia, or URI (although the association with URI was suggestive). Lag 0 OP^{DTT} was not significantly associated with ED visits for any outcome (Figure 2B).

Given that lag 0–2 OP^{DTT} was strongly associated with asthma ED visits, we examined 13 separate bipollutant models

Table 1. Pearson correlation coefficients (upper right) between daily values for the oxidative potential of water-soluble $PM_{2.5}$ as measured by the DTT assay (OP^{DTT}) and daily mean values for other air quality variables, June 2012–April 2013, Atlanta, Georgia.

	OP^{DTT}	$PM_{2.5}$	CO	EC	NH_4	NO_2	NO_3	O_3	OC	SO_2	SO_4	Mn	Fe	Cu
OP^{DTT}	—	0.55	0.46	0.56	0.26	0.27	0.24	0.01	0.51	0.28	0.14	0.42	0.43	0.41
$PM_{2.5}$	196	—	0.44	0.65	0.63	0.36	0.14	0.41	0.86	0.24	0.66	0.38	0.62	0.48
CO	196	196	—	0.78	0.11	0.72	0.25	0.02	0.46	0.46	0.08	0.29	0.40	0.45
EC	191	191	191	—	0.23	0.59	0.22	0.07	0.70	0.45	0.21	0.40	0.51	0.50
NH_4	193	193	193	188	—	0.10	0.42	0.08	0.33	−0.03	0.83	0.07	0.31	0.22
NO_2	196	196	196	191	193	—	0.26	0.15	0.42	0.27	0.09	0.24	0.33	0.39
NO_3	194	194	194	189	191	194	—	−0.48	0.07	0.06	0.08	−0.01	−0.02	−0.05
O_3	196	196	196	191	193	196	194	—	0.43	−0.01	0.31	0.19	0.37	0.28
OC	190	190	190	185	187	190	188	190	—	0.19	0.35	0.39	0.60	0.43
SO_2	196	196	196	191	193	196	194	196	190	—	0.01	0.22	0.17	0.19
SO_4	196	196	196	191	193	196	194	196	190	196	—	0.13	0.41	0.27
Mn	158	158	158	155	157	158	156	158	152	158	158	—	0.63	0.38
Fe	157	157	157	154	156	157	155	157	151	157	157	156	—	0.70
Cu	152	152	152	149	151	152	150	152	147	152	152	151	150	—

Note: Only days with OP^{DTT} measurements were used for these correlations; the lower left section of the table shows the number of days included in each correlation. CO, carbon monoxide; Cu, copper; EC, elemental carbon; Fe, iron; Mn, manganese; NH_4, ammonium; NO_2, nitrogen dioxide; NO_3, nitrate; OC, organic carbon; O_3, ozone; $PM_{2.5}$, fine particulate matter; SO_2, sulfur dioxide; SO_4, sulfate.

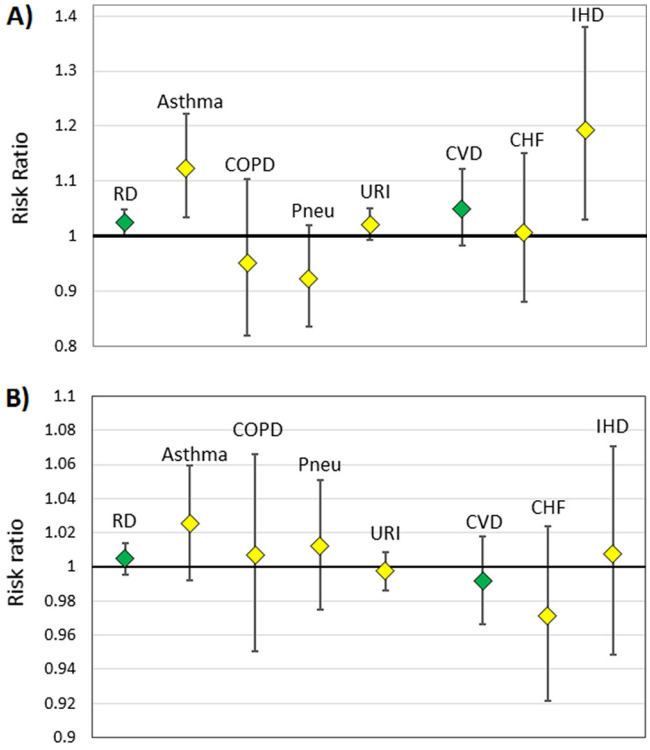

Figure 2. Risk ratio for emergency department (ED) visit outcomes per interquartile range (IQR) of the oxidative potential of water-soluble $PM_{2.5}$ as measured by the DTT assay (OP^{DTT}), for (*A*) lag 0–2 OP^{DTT} and (*B*) lag 0 OP^{DTT}, June 2012–April 2013, Atlanta, Georgia. The IQR of OP^{DTT} is 0.21 nmol/min/m^3. Note: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVD, all cardiovascular diseases (combined); IHD, ischemic heart disease; Pneu, pneumonia; RD, all respiratory diseases (combined); URI, upper respiratory infection.

that included the 3-d moving averages of both OP^{DTT} and another pollutant to assess whether the observed health associations with OP^{DTT} might be explained by a copollutant. In each bipollutant model, the risk ratio point estimate for lag 0–2 OP^{DTT} was above 1 (Figure 3A). In 11 of the 13 models, the risk ratio point estimate for lag 0–2 OP^{DTT} was greater than the risk ratio for the other lag 0–2 pollutant included; the only exceptions were models that included $PM_{2.5}$ or OC. OP^{DTT} was significantly associated with asthma ED visits in bipollutant models that included CO, NO_2, NO_3, O_3, SO_2, SO_4, Mn, Fe, and Cu. In bipollutant analyses using same-day values for OP^{DTT} and other pollutants, similar trends were observed: The risk ratio point estimate for lag 0 OP^{DTT} was greater than the risk ratio for the other lag 0 pollutant included for all models except those including $PM_{2.5}$, OC, and NH_4 (Figure 3B). Although all risk ratios for lag 0 OP^{DTT} in bipollutant models were above 1, these associations with asthma ED visits were not statistically significant except for the model that included SO_2.

In bipollutant models with IHD as the outcome, the estimated health associations for lag 0–2 OP^{DTT} were even stronger. In every bipollutant model, the risk ratio point estimate for lag 0–2 OP^{DTT} was above 1 and lag 0–2 OP^{DTT} had a higher risk ratio point estimate than the other pollutant included (Figure 4A). In all but two models, lag 0–2 OP^{DTT} was significantly and positively associated with IHD; the exceptions, which were also suggestive of positive associations, were models that included $PM_{2.5}$ (RR = 1.20, 95% CI: 0.98, 1.47) and CO (RR = 1.17, 95% CI: 0.98, 1.38). In bipollutant analyses using same-day values for OP^{DTT} and other pollutants, lag 0 OP^{DTT} was not associated with IHD in any model (Figure 4B).

Bipollutant models were also conducted for all other outcomes. For the RD and CVD categories, point estimates for lag 0–2 OP^{DTT} risk ratios remained positive in all models, and these point estimates were generally higher than point estimates for the other pollutant included; however, most lag 0–2 OP^{DTT} risk ratios confidence intervals included the null. Lag 0 OP^{DTT} was not associated with RD or CVD in bipollutant models. In bipollutant models for COPD, pneumonia, URI, and CHF, associations for lag 0 OP^{DTT} and lag 0–2 OP^{DTT} were almost entirely nonsignificant.

Discussion

This study represents an important report of population-level health associations for directly measured OP, with a focus on OP measured using the DTT assay. The study draws upon a comprehensive hospital database consisting of data from all nonfederal acute care hospitals with emergency departments serving an area with over 3.3 million residents (U.S. Census Bureau 2010). Daily measurements of collocated air quality data for OP^{DTT} and a large number of other pollutants, as well as meteorological variables, allowed for assessment of correlations and control of potential confounders. The Poisson log-linear regression models build upon our previous analyses in the Atlanta metropolitan area and use the strengths of established quantitative methodologies.

Because many methods for measuring OP are labor intensive, prior studies of the health effects of OP have typically been over relatively short time periods and have compared relatively minor clinical outcomes within small study groups. In each of two studies that exposed volunteers to PM mixtures of similar concentration but different composition, exposure to a mixture high in metals with considerable OP such as zinc, copper, and iron produced significantly higher inflammatory responses (Ghio and Devlin 2001; Schaumann et al. 2004). $PM_{2.5}$ OP measured by cellular rat macrophage was linked to decreased lung function in children with asthma and markers of inflammation in elderly subjects (Delfino et al. 2010, 2013). Markers of inflammation were associated with three separate acellular measures of particulate OP (Janssen et al. 2015). However, ascorbate-related OP (OP^{AA}) and glutathione-related OP (OP^{GSH}) have not been consistently associated with markers of respiratory or cardiovascular toxicity (Steenhof et al. 2013; Strak et al. 2012, 2013a, 2013b), and a small case-crossover study showed no association between three acellular measures of particulate OP and hospital admissions for asthma/chronic obstructive pulmonary disorder (Canova et al. 2014).

In large-scale case-crossover studies in Ontario, Canada, using city-level estimates of long-term $PM_{2.5}$ OP, OP^{GSH} was found to modify the association between $PM_{2.5}$ and respiratory disease, as well as the association between $PM_{2.5}$ and myocardial infarction, but OP^{AA} did not modify these associations (Weichenthal et al. 2016a, 2016b). OP^{DTT} had previously been found to be well correlated with OP^{GSH} but not OP^{AA} (Mudway et al. 2009). A recent study assessed population-level health impacts of directly measured OP, in which daily OP^{GSH} and OP^{AA} measurements were taken in central London and associations were estimated with daily hospital admissions and deaths (Atkinson et al. 2016). In that study, neither OP^{GSH} nor OP^{AA} were associated with daily mortality or cardiovascular hospital admissions, but there were trends toward positive associations with respiratory hospital admissions among children. Different OP measurement assays may be sensitive to dissimilar sets of particulate compounds (Fang et al. 2016; Godri et al. 2011; Janssen et al. 2014) that may be linked to different cardiorespiratory health effects (Sarnat et al. 2016), highlighting the need to assess OP^{DTT} as a potential measure of particulate toxicity.

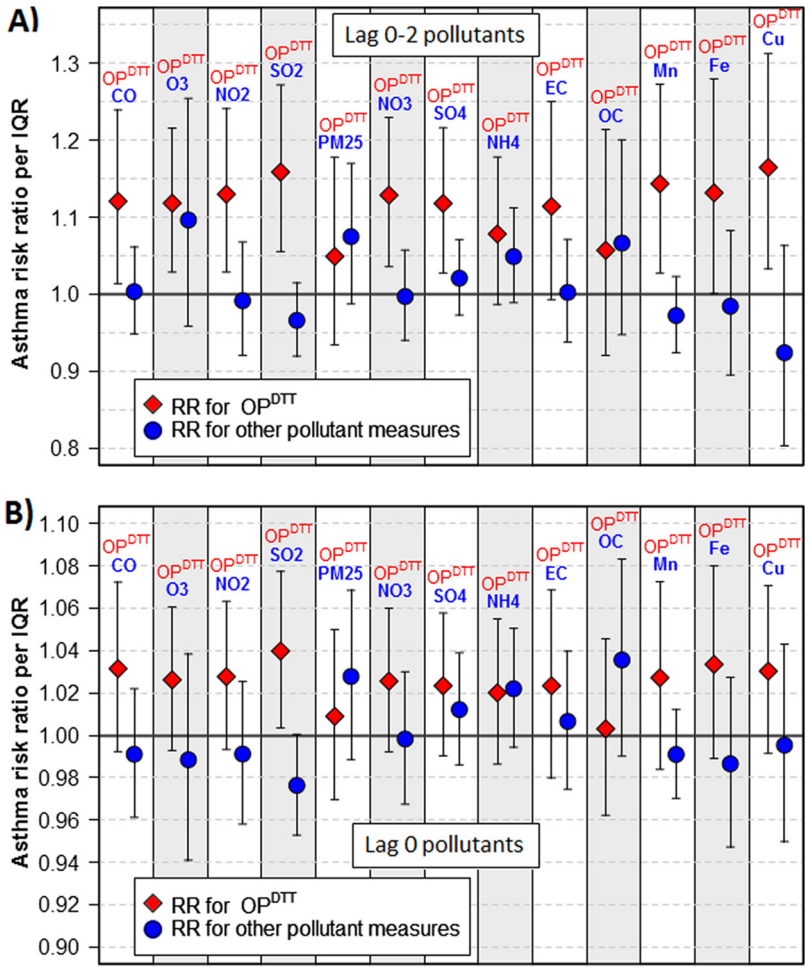

Figure 3. Asthma risk ratios for the oxidative potential of water-soluble $PM_{2.5}$ as measured by the DTT assay (OP^{DTT}) and other pollutant measures in bipollutant models, for (*A*) lag 0–2 pollutants and (*B*) lag 0 pollutants, June 2012–April 2013, Atlanta, Georgia. Risk ratio for OP^{DTT} (diamond markers) are per interquartile range (IQR) of OP^{DTT} (0.21 nmol/min/m^3); risk ratio for all other pollutant measures (circular markers) are per IQR of that particular pollutant. Note: CO, carbon monoxide; Cu, copper; EC, elemental carbon; Fe, iron; Mn, manganese; NH_4, ammonium; NO_2, nitrogen dioxide; NO_3, nitrate; OC, organic carbon; O_3, ozone; $PM_{2.5}$, fine particulate matter; SO_2, sulfur dioxide; SO_4, sulfate. EC, NH_4, NO_3, OC, SO_4, Mn, Fe, and Cu are components of $PM_{2.5}$.

A previous study by our group utilizing modeled OP estimates and the same Atlanta ED visits database found that OP^{DTT} was associated with ED visits for asthma and CHF (Bates et al. 2015), and a related study exploring additional models showed that these associations held for OP^{DTT} but not OP^{AA} (Fang et al. 2016). Another study had found that residential OP^{DTT} estimates were associated with prevalence of asthma and rhinitis and with measured lung capacity, whereas similar OP^{ESR} estimates were not (Yang et al. 2016). These studies all increased sample size by utilizing modeled OP^{DTT} values; although these results were informative, modeled ambient OP may be prone to substantial measurement errors. The results of our current study, which used directly measured OP^{DTT}, lend additional support to the usefulness of OP^{DTT} as an indicator of air pollution toxicity.

Importantly, this study only assessed health associations with modeled water-soluble $PM_{2.5}$ OP^{DTT}. Various prior analyses of these data indicate that the main sources of aerosol OP^{DTT} include biomass burning and vehicle emissions through tail pipe and tire and brake wear and that atmospheric processing following emissions plays a key role in the observed DTT activities. Water-soluble $PM_{2.5}$ OP^{DTT} measurements have been shown to capture organic components (e.g., quinones) as well as transition metal ions (e.g., soluble forms of copper and manganese) but not DTT-active species associated with solid particle surfaces of $PM_{2.5}$ such as soot or EC (Fang et al. 2017a, 2017b; Verma et al. 2012, 2014, 2015). We chose to use water-soluble $PM_{2.5}$ OP^{DTT} because the measurement of total OP^{DTT} can depend on how the solid aerosol components are brought into contact with the assay. Differences between OP^{DTT} measurements due to assay preparation are currently being investigated (Gao et al. 2017). Further epidemiological analysis of OP using different assays, measured over different time frames and geographic areas, using alternate outcomes, or focused on specific population subgroups would be useful to determine variability in adverse health effects.

In our study, a lagged 0–2 moving average of OP^{DTT} was a significant predictor of ED visits for respiratory disease, asthma, and IHD. We ran multiple bipollutant models to assess whether OP^{DTT} was a proxy for another pollutant. Lag 0–2 OP^{DTT} was more strongly associated with asthma ED visits than the other pollutant measure in 11 of 13 bipollutant models. The exceptions included $PM_{2.5}$, which had a slightly higher risk ratio for asthma than lag 0–2 OP^{DTT} in a bipollutant model (1.07 compared with 1.05 per IQR), though these risk ratios were both lower than the corresponding RRs from single-pollutant models; the same was also true for lag 0–2 OC and lag 0–2 OP^{DTT}. This finding is consistent with water-soluble OP explaining part of the respiratory toxicity of $PM_{2.5}$ and OC; these mixtures may also cause adverse effects either through oxidative stress mediated by water-insoluble particles (Fang et al. 2017b) or through pathways unrelated to OP. For IHD visits, lag 0–2 OP^{DTT} was more strongly

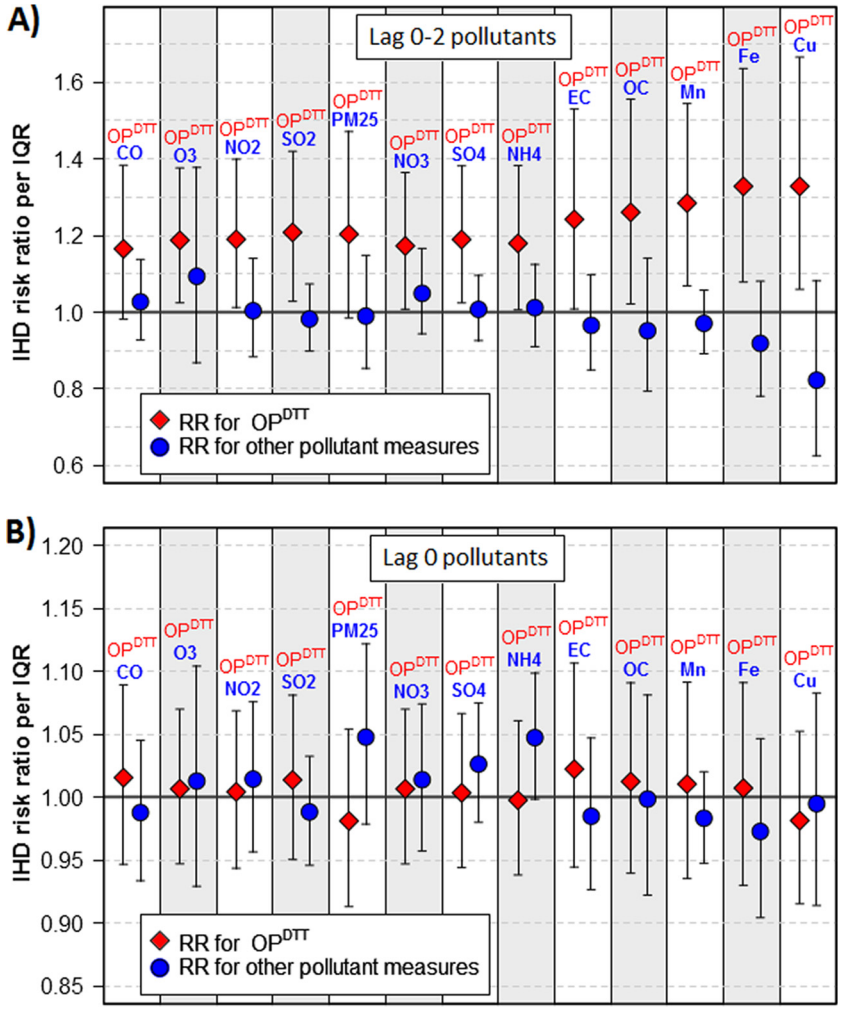

Figure 4. Ischemic heart disease (IHD) risk ratios for the oxidative potential of water-soluble $PM_{2.5}$ as measured by the DTT assay (OP^{DTT}) and other pollutant measures in bipollutant models, for (*A*) lag 0–2 pollutants and (*B*) lag 0 pollutants. Risk ratio for OP^{DTT} (diamond markers) are per interquartile range (IQR) of OP^{DTT} (0.21 nmol/min/m^3); risk ratio for all other pollutant measures (circular markers) are per IQR of that particular pollutant. Note: CO, carbon monoxide; Cu, copper; EC, elemental carbon; Fe iron; Mn, manganese; NH_4, ammonium; NO_2, nitrogen dioxide; NO_3, nitrate; OC, organic carbon; O_3, ozone; $PM_{2.5}$, fine particulate matter; SO_2, sulfur dioxide; SO_4, sulfate. EC, NH_4, NO_3, OC, SO_4, Mn, Fe, and Cu are components of $PM_{2.5}$.

predictive than the other pollutant measure in every bipollutant model. These results provide evidence that OP may offer additional information about health risks of air pollution beyond the risks captured by other pollutant measures.

In analyses of ED visits and same-day OP^{DTT}, there were no statistically significant associations, suggesting that many adverse health outcomes of oxidative stress may not be immediately fully realized. However, in bipollutant models for asthma ED visits, lag-0 OP^{DTT} point estimates were consistently positive and generally greater than the point estimate for the other pollutant in the model, which could be suggestive of some immediate toxic effect of OP on asthma exacerbation.

OP^{DTT} observations were available for 196 d from June 2012 through April 2013. Although this represents a larger sample size than available for most prior studies of OP, this group of observations comprises still relatively few observations compared with other time-series analyses of acute effects of air pollution (Atkinson et al. 2014). The time-series analyses included numerous covariates (39 additional model parameters) to control for potential temporal confounders; consequently, the risk ratio estimates had relatively large confidence intervals. Given the limited sample size, the fact that this study showed statistically significant effects of OP^{DTT} on cardiorespiratory ED visits indicates that OP^{DTT} may be a relatively strong predictor of health outcomes. Furthermore, other results were suggestive for certain outcomes (such as URI and the combined CVD ED visits), but the sample size was not sufficient to detect a significant effect. We tested more parsimonious models (e.g., without temperature and dew point control, without cubic splines and weekdays) and results were not substantially dissimilar, with estimated associations for lag 0–2 OP^{DTT} remaining strongest for respiratory disease, asthma, URI, and IHD. The results of this study should provide a strong impetus to produce longer time series of measurements of OP^{DTT} and other characterizations of OP in order to produce more stable risk estimates for multiple outcome groups and further elucidate particulate matter toxicity.

The use of pollutant measurements at a single location to predict health outcomes over a large metropolitan area is not ideal. However, other studies showed that different urban locations in Atlanta had similar daily OP^{DTT} measurements (Fang et al. 2014; Verma et al. 2014); comparison of measurements from separate locations are presented in Table S1. In addition, a previous analysis of exposure measurement error in Atlanta demonstrated that the use of measurements from urban monitors [within 32 km (20 mi) of the city center] that were located different distances from geographic subpopulations produced similar associations

between pollutants and health outcomes, particularly for secondary pollutants (Sarnat et al. 2010). Because water-soluble OP^{DTT} is strongly linked to secondary organic particles (Verma et al. 2009, 2014), this suggests the viability of using a single central monitor as a surrogate for ambient OP^{DTT} experienced by a population spread out over a sizable metropolitan area. Zeger et al. (2000) suggest that if pollutant measurements in a time-series analysis are close to the average pollutant exposure levels for the population of interest (i.e., Berkson-type error), then the associations between pollutants and health outcomes should have minimal bias. On the other hand, if the measurements differ meaningfully from population average exposures, bias can be created with the direction most likely toward the null (Zeger et al. 2000). Our group previously investigated the effects of measurement error on associations between air pollutants and health outcomes using Poisson log-linear models similar to those used in this study; the associations were all biased toward the null, though less so for Berkson-type errors (Goldman et al. 2011).

False health associations could be estimated for an air quality variable with no true causal effect if it were correlated with a toxic pollutant; this may be observed even in bipollutant models with the toxic pollutant if the variable with no effect were better measured than the variable with the true effect (Dionisio et al. 2016). If OP^{DTT} had substantially lower measurement error than the other air quality variables in this study, this potential bias would be a valid concern. However, daily values for other pollutants considered in this study were also measured at the same central location. Furthermore, instrument measurement error for OP^{DTT} is expected to be similar to all other filter-based measurements used in this study. Therefore, the significant health associations for OP^{DTT} in bipollutant models, especially in models with copollutants that were secondary pollutants or had otherwise comparable spatial variability, are not readily explained by differences in measurement error between pollutants.

Conclusions

The health effects of $PM_{2.5}$ OP have been previously explored in panel studies assessing markers of toxicity, small cohort studies assessing health outcomes in subjects with differing levels of exposure, and case-crossover studies analyzing relationships between OP and health outcomes over time; however, additional research is needed to assess population-level impacts of ambient OP. In this study, we present support for the measurement of OP^{DTT} as a predictor of acute cardiorespiratory outcomes in a time-series study of the population of a large metropolitan area. These results provide key evidence for OP as an important and useful integrated indicator of particulate matter toxicity for future air pollution studies.

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