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Short-term associations between particle oxidative potential and daily mortality and hospital admissions in London

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ABSTRACT

Background: Particulate matter (PM) from traffic and other sources has been associated with adverse health effects. One unifying theory is that PM, whatever its source, acts on the human body via its capacity to cause damaging oxidation reactions related to its content of pro-oxidants components. Few epidemiological studies have investigated particle oxidative potential (OP) and health. We conducted a time series analysis to assess associations between daily particle OP measures and numbers of deaths and hospital admissions for cardiovascular and respiratory diseases.

Methods: During 2011 and 2012 particles with an aerodynamic diameter less than 2.5 and 10 μm ($PM_{2.5}$ and PM_{10} respectively) were collected daily on Partisol filters located at an urban background monitoring station in Central London. Particulate OP was assessed based on the capacity of the particles to oxidize ascorbate (OP^{AA}) and glutathione (OP^{GSH}) from a simple chemical model reflecting the antioxidant composition of human respiratory tract lining fluid. Particulate OP, expressed as % loss of antioxidant per μg of PM, was then multiplied by the daily concentrations of PM to derive the daily OP of PM mass concentrations (% loss per m^3). Daily numbers of deaths and age- and cause-specific hospital admissions in London were obtained from national registries. Poisson regression accounting for seasonality and meteorology was used to estimate the percentage change in risk of death or admission associated with an interquartile increment in particle OP.

Results: We found little evidence for adverse associations between OP^{AA} and OP^{GSH} and mortality. Associations with cardiovascular admissions were generally positive in younger adults and negative in older adults with confidence intervals including 0%. For respiratory admissions there was a trend, from positive to negative associations, with increasing age although confidence intervals generally included 0%.

Conclusions: Our study, the first to analyse daily particle OP measures and mortality and admissions in a large population over two years, found little evidence to support the hypothesis that short-term exposure to particle OP is associated with adverse health effects. Further studies with improved exposure assessment and longer time series are required to confirm or reject the role of particle OP in triggering exacerbations of disease.

1. Introduction

Recent comprehensive reviews have concluded that there is sufficient epidemiological, toxicological and mechanistic evidence to link ambient outdoor concentrations of particulate matter (PM) with adverse effects on human health (EPA, 2009; WHO, 2013). Epidemiological time series studies have provided the evidence for associations in urban populations between daily mass concentrations of particles with a median diameter less than 2.5 μm ($PM_{2.5}$) and increased numbers of deaths and hospital admissions from a range of cardiovascular and respiratory diseases within a few days (Atkinson et al., 2014). However, better understanding of the most harmful components, and sources, of the particulate pollution is required in order to better inform policies to protect public health.

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To date, particle characteristics such as size and number, primary *vs.* secondary origin and elemental composition have all been investigated (Atkinson et al., 2015; EPA, 2011; Janssen et al., 2011; Levy et al., 2012; Ruckerl et al., 2011).

Exposure to PM from traffic or other sources is associated with a range of human responses including neutrophilic inflammation, reduced inspiratory capacity, heightened bronchial reactivity, as well as changes in blood viscosity, fibrinogen, C-reactive protein and heart rate variability (HEI, 2010). One unifying theory is that particles elicit these responses by inducing oxidative stress via a range of mechanisms: (a) related to their content of pro-oxidants, such as metals and quinones (Ayres et al., 2008); (b) via the cellular metabolism of polyaromatic hydrocarbons (Baulig et al., 2004); (c) through the induction of acute inflammation, with activation of the phagocytic NADPH oxidase (Hamad et al., 2016); and (d) by depolarisation of the mitochondrial electron transport chain (Ferecatu et al., 2010; Xu et al., 2011). The oxidative potential (OP) of PM may therefore provide a useful, unifying metric for assessing the toxicity of particles in epidemiological studies (Ayres et al., 2008; Kelly and Fussell, 2015).

Because laboratory assessment of particle OP is time and resource intensive, the use of this metric in epidemiological time series studies has been limited to a small number of experimental and panel studies (Delfino et al., 2013; Steenhof et al., 2013; Strak et al., 2012) and a single case-crossover study of COPD/asthma hospital admissions (Canova et al., 2014). The latter found no evidence of an association with particle OP, but was limited to 161 admissions to a single London hospital. In contrast, a study of emergency department visits for asthma/wheezing and congestive heart failure in Atlanta found stronger associations with particle OP than particle mass ($PM_{2.5}$) (Bates et al., 2015). Two recent studies from Canada have estimated the OP of daily $PM_{2.5}$ using regional OP estimates derived from periodic sampling of PM filters and reported stronger associations between $PM_{2.5}$ concentrations and emergency room visits for myocardial infarction and respiratory disease on days with higher particle OP (Weichenthal et al., 2016b; Weichenthal et al., 2016c). A recent cohort study found that adjustment for regional glutathione-related, but not ascorbate dependent, oxidative potential was associated with an increased risk of death and that for lung cancer the association may be stronger than for $PM_{2.5}$ mass concentrations (Weichenthal et al., 2016a). To date, daily measures of particle OP have not been evaluated in a large urban conurbation in relation to daily mortality and admissions from cardiorespiratory diseases. Using laboratory analysis of samples obtained from daily particle measurements made at a monitoring station in Central London, U.K. we derived measures of ascorbate and glutathione-dependent OP for $PM_{2.5}$ and particles with an median diameter less than 10 μm (PM_{10}) and investigated associations with daily numbers of deaths and hospital admissions for cardiovascular and respiratory diseases.

2. Methods

2.1. Health data

Daily counts of deaths from all non-accidental causes (ICD-10 Chapters A-R), cardiovascular (ICD-10 Chapter I) and respiratory causes (ICD-10 Chapter J) for people resident and dying in London, England between January 2011 and December 2012 were constructed from death registrations obtained from the UK Office of National Statistics. For the same time period and using the same ICD-10 codes, daily counts of the numbers of emergency, first episode, hospital admissions for cardiovascular disease and for respiratory diseases stratified by age (0–14, 15–64 and 65+ years) were derived from records of individual admissions obtained from the English Hospital Episode Statistics system.

2.2. Particle oxidative potential measurement

The oxidative potential of particles (PM_{10} and $PM_{2.5}$) was determined by measuring the depletion of the anti-oxidants ascorbate and glutathione from a synthetic respiratory tract lining fluid (RTLF). The synthetic RTLF contains the major low-molecular weight sacrificial antioxidants commonly found on the surface of the lung, at physiologically relevant concentrations and allows analysis of different chemical mechanisms of oxidative damage that PM may inflict on airways. The underlying principle of this assay and the derivation of the OP metrics have been described in detail previously (Godri et al., 2010; Kelly et al., 2011). This method was adapted to perform the analysis on unextracted filters to accommodate the low filter loadings associated with 24 h collections at urban background locations which impact on PM recovery from the filter, but also to avoid potential artifacts being introduced through the extraction procedure.

PM was collected onto Teflon-coated glass fibre filters (Pallfex Emfab^{TM}) using Partisol 2025 samplers (Thermo) using PM_{10} or $PM_{2.5}$ size selective inlets during 2011–12 from the North Kensington background monitoring site (51.521055_ N, 0.213432_W) in Central London. From each filter, 3 × 8 mm discs were punched (Harris Unicore, USA) and transferred into three separate microtubes for analysis. The filter punches were then incubated for 4 h at pH 7.0, 37 °C, with continual mixing throughout, in synthetic RTLF, containing equimolar concentrations (200 μmol/L) of the antioxidants ascorbate, urate and glutathione. Particle free controls to quantify auto-oxidative losses of RTLF antioxidants, and in-house positive (NIST srm 1648a) and negative (M120–an inert carbon black (Cabot Corp., USA) (Zielinski et al., 1999)) control particles were also included to control for batch-to-batch variation. At the end of the incubation period samples were centrifuged for 1-h at 13,000 rpm (4 °C) to remove the filters and any disassociated PM and the supernatant quantified for the remaining concentrations of ascorbate by reverse-phase HPLC with electrochemical detection. The concentration of glutathione remaining in the RTLF at this time point was quantified using the DTNB-enzyme recycling assay. The derivation of the ascorbate and glutathione dependent oxidative potentials was based on the percentage loss of antioxidants relative to the particle free control concentrations at the 4-h time point, normalized for the concentration of PM on the filter punch, i.e. % antioxidant loss per μg. Filter masses were based on pre- and post-weighing following exposures in the field with the masses on the filter punches calculated based on the assumption of equal particle deposition across the filter area. Finally the ascorbate (OP^{AA}) and glutathione (OP^{GSH}) depletion expressed as % loss per μg of PM were multiplied by the ambient daily $PM_{2.5}$ or PM_{10} concentrations to provide daily OP metrics (% loss) expressed per m^3. Measurements for OP^{AA} and OP^{GSH} in PM_{10} and $PM_{2.5}$ were available for 703 and 685 days in the two year study period, the difference in numbers reflecting periods when the samplers were not operating due to technical issues.

2.3. Regulated pollutants and meteorological variables

Hourly average concentrations of PM_{10}, $PM_{2.5}$, nitrogen dioxide (NO_2), sulphur dioxide (SO_2) and ozone (O_3) recorded at the urban background monitoring station at North Kensington during the study period were obtained from the Automatic Urban Rural Network and averaged to give 24-h mean concentrations in μg/m^3 for all pollutants except O_3 for which the 8 h maximum average (WHO, 2006) was computed. The Tapered Element Oscillating Microbalance—Filter Dynamics Measurement System

(TEOM-FDMS, Thermo) was used to measure PM_{10} and $PM_{2.5}$. O_3 was measured by UV absorption, NO_2 by Chemiluminescence and SO_2 by UV fluorescence as defined in the relevant EU Directives. Gas and PM_{10} and $PM_{2.5}$ instruments were independently calibrated and audited twice yearly by Ricardo-AEAT plc. Mean daily temperature (°C) and relative humidity (%) were also collected for the period 2011–12 from a meteorological station close to the North Kensington monitoring site.

2.4. Statistical analysis

To assess the relationship between the daily number of health events and OP concentrations, we used a generalised additive model assuming a Poisson distribution with adjustment for overdispersion. Penalized regression splines with natural spline basis applied to day of study were used to capture the association between omitted time-varying covariates and daily mortality. The degrees of freedom (df) for time adjustment were chosen based upon the minimization of the absolute value of the sum of the partial autocorrelation function of the residuals (lags 1–30), with a minimum of 3 df per year (Samoli et al., 2013). Average temperature on the previous day and averaged over days 1–6 prior to the date of death were modelled using spline terms and humidity modelled using the average of the same and the two previous days' measurement. Finally, dummy variables for week day and public holidays were included in the model. Based upon previously reported associations with particles (Atkinson et al., 2010), we investigated associations between total mortality and CVD outcomes using the previous days' OP values (lag1) and for respiratory outcomes, values two days prior to the event (lag2). As sensitivity analysis for the lag choice, we also investigated the cumulative effect over weekly exposure (lags0-6) using unconstrained distributed lags (DL) models (Zanobetti et al., 2002).

We also stratified our analyses by season (cool period – October-March; warm period – April–September). The model used in the seasonal analysis was similar to the annual one, except for seasonality and long-term trends control, for which we used indicator variables per month per year of the study. To explore potential confounding by other particle components and gaseous pollutants we adjusted for PM mass, and in turn, NO_2, O_3 and SO_2 using multi-pollutant models. We initially regressed the gaseous pollutant on particle mass (PM_{10} or $PM_{2.5}$) and then entered the resulting model residuals into the model estimating the effects of the oxidative potential on the health outcome (Mostofsky et al., 2012).

Relative risks (RR) and 95% confidence intervals were expressed as percentage changes (100*(RR-1)) associated with an interquartile range (IQR) increase in particle OP% loss per m^3. The R statistical package was used for all analyses (R Development Core Team, 2007).

3. Results

Descriptive statistics for the health outcomes, pollutants and meteorological variables are given in Table 1. The median daily number of deaths in London during the study period was 117. The median number of hospital admissions was greatest in the group aged 65 years and over, 104 and 91 per day for cardiovascular and respiratory diseases respectively. Ascorbate depletion was higher per m^3 than glutathione depletion in both PM_{10} and $PM_{2.5}$. Particle OP^{AA} were moderately correlated with PM mass and NO_2 ($r = 0.5–0.6$) and PM OP^{GSH} were only weakly correlated with PM mass and NO_2 ($r = 0.2–0.4$) (Table 2). Both OP metrics were negatively correlated with O_3.

We found little evidence for adverse associations between OP^{AA} and OP^{GSH} metrics and all-cause and cause-specific mortality—associations were mostly negative and all 95% confi-

Table 1
Descriptive statistics for mortality and hospital admissions counts, concentrations of oxidative potential in PM_{10} and $PM_{2.5}$ and regulated pollutants and meteorological variables in London, U.K. for 1/1/2011–31/12/2012.

	Number of days	Percentiles				
		10th	25th	50th	75th	90th
Mortality (n/day)[a]						
Total	722	99	107	117	128	139
Cardiovascular	722	27	31	35	40	45
Respiratory	722	11	13	17	21	25
Hospital Admissions (n/day)						
Cardiovascular						
15–64 years	731	39	46	57	65	71
65+ years	731	76	87	104	115	124
Respiratory						
0–14 years	731	22	33	45	56	72
15–64 years	731	48	55	63	71	81
65+ years	731	77	79	91	107	125
Particle oxidative potential metric (% loss/m^3)						
PM_{10} OP^{AA}	703	8.2	11.6	17.2	26.1	35.7
PM_{10} OP^{GSH}	703	4.0	5.7	8.9	12.7	17.4
$PM_{2.5}$ OP^{AA}	685	4.7	7.8	12.7	18.3	25.1
$PM_{2.5}$ OP^{GSH}	685	1.5	2.2	4.0	7.1	10.7
Pollutants (μg/m^3)						
PM_{10}	729	9.0	11.0	15.0	21.0	32.5
$PM_{2.5}$	730	5.0	6.0	9.0	14.0	25.0
NO_2	706	18.1	23.2	33.3	46.9	58.1
SO_2	717	0.0	0.4	1.8	2.6	3.6
O_3	716	21.7	39.5	54.7	69.8	85.9
Meteorology						
Mean Temperature (°C)	722	5.0	8.1	11.8	15.5	18.1
Relative humidity (%)	722	61.6	69.6	77.9	84.1	88.5

AA—Ascorbate depletion; GSH—Glutathione depletion.
[a] 01/01/2011 to 22/12/2012.

Table 2
Pearson correlation coefficients between particle OP metrics, daily pollutant concentrations and temperature.

Pollutants	PM_{10} OP^{AA}	PM_{10} OP^{GSH}	$PM_{2.5}$ OP^{AA}	$PM_{2.5}$ OP^{GSH}	PM_{10}	$PM_{2.5}$	NO_2	SO_2	O_3
PM_{10} OP^{GSH}	0.60								
PM_{10} OP^{AA}	0.67	0.38							
$PM_{2.5}$ OP^{GSH}	0.33	0.53	0.49						
PM_{10}	0.60	0.24	0.56	0.23					
$PM_{2.5}$	0.59	0.22	0.58	0.24	0.95				
NO_2	0.60	0.36	0.64	0.40	0.66	0.66			
SO_2	0.34	0.15	0.37	0.16	0.51	0.49	0.52		
O_3	−0.36	−0.22	−0.42	−0.14	−0.19	−0.28	−0.40	−0.17	
Temp	−0.25	−0.11	−0.22	−0.12	−0.20	−0.25	−0.39	−0.13	0.52

AA—Ascorbate depletion; GSH—Glutathione depletion.

Table 3
Percent change (and 95% confidence intervals) in all-cause (lag 1 day), cardiovascular (lag 1 day) and respiratory (lag 2 days) mortality associated with interquartile range (IQR) increases in PM_{10}, $PM_{2.5}$ and particle oxidative potential. .

Pollutant	Units	IQR	All-Cause	Cardiovascular	Respiratory
PM_{10}	μg/m³	8.0	−0.48 (−1.22, 0.25)	−0.87 (−2.13, 0.40)	−0.81 (−2.57, 0.97)
PM_{10} OP^{AA}	%/m³	14.5	−0.26 (−1.36, 0.85)	−0.96 (−2.87, 0.98)	−2.84 (−5.46, 0.16)
PM_{10} OP^{AA} + PM_{10}	%/m³	14.5	0.24 (−1.15, 1.65)	−0.25 (−2.69, 2.25)	−3.37 (−6.71, 0.09)
PM_{10} OP^{GSH}	%/m³	7.0	0.41 (−0.44, 1.27)	−0.32 (−1.83, 1.21)	−0.72 (−2.80, 1.39)
PM_{10} OP^{GSH} + PM_{10}	%/m³	7.0	0.60 (−0.29, 1.49)	−0.06 (−1.63, 1.53)	−0.49 (−2.64, 1.71)
$PM_{2.5}$	μg/m³	4.1	−0.58 (−1.24, 0.08)	−0.90 (−2.04, 0.25)	−0.47 (−2.05, 1.14)
$PM_{2.5}$ OP^{AA}	%/m³	10.5	−0.49 (−1.56, 0.58)	−1.72 (−3.57, 0.15)	−1.31 (−3.86, 1.31)
$PM_{2.5}$ OP^{AA} + $PM_{2.5}$	%/m³	10.5	0.03 (−1.28, 1.35)	−1.30 (−3.59,1.05)	−1.36 (−4.50, 1.88)
$PM_{2.5}$ OP^{GSH}	%/m³	4.8	−0.04 (−0.81, 0.73)	−0.76 (−2.13, 0.64)	0.33 (−1.49, 2.19)
$PM_{2.5}$ OP^{GSH} + $PM_{2.5}$	%/m³	4.8	0.10 (−0.69, 0.90)	−0.55 (−1.96, 0.87)	0.46 (−1.41, 2.36)

OP^{AA} – Ascorbate depletion; OP^{GSH} – Glutathione depletion.

Table 4
Percent change (and 95% confidence intervals) in cardiovascular (lag 1 day) and respiratory (lag 2 days) hospital admissions associated with interquartile range (IQR) increases in PM_{10}, $PM_{2.5}$ and particle oxidative potential.

Pollutant	Units	IQR	Cardiovascular		Respiratory		
			15–64 yrs.	65 yrs.+	0–14 yrs.	15–64 yrs.	65 yrs.+
PM_{10}	μg/m³	8.0	0.17 (−0.86, 1.21)	−0.50 (−1.27, 0.28)	0.69 (−0.85, 2.25)	−0.67 (−1.69, 0.37)	−1.14 (−2.10, −0.16)
PM_{10} OP^{AA}	%/m³	14.5	0.39 (−1.12, 1.92)	−0.14 (−1.29, 1.03)	2.30 (0.13, 4.51)	0.20 (−1.33, 1.74)	−2.45 (−3.85, −1.02)
PM_{10} OP^{AA} + PM_{10}	%/m³	14.5	0.76 (−1.17, 2.73)	0.45 (−1.03, 1.95)	2.62 (−0.06, 5.38)	1.23 (−0.71, 3.22)	−2.52 (−4.30, −0.71)
PM_{10} OP^{GSH}	%/m³	7.0	0.63 (−0.54, 1.81)	0.17 (−0.73, 1.08)	3.81 (1.89, 5.78)	0.33 (−0.86, 1.53)	−1.87 (−2.95, −0.78)
PM_{10} OP^{GSH} + PM_{10}	%/m³	7.0	0.71 (−0.51, 1.94)	0.33 (−0.60, 1.28)	0.99 (−0.63, 2.64)	0.35 (−0.87, 1.59)	−1.69 (−2.81, −0.55)
$PM_{2.5}$	μg/m³	4.1	0.19 (−0.73, 1.12)	−0.80 (−1.49, −0.10)	0.42 (−0.94, 1.81)	−0.80 (−1.72, 0.13)	−0.97 (−1.84, −0.09)
$PM_{2.5}$ OP^{AA}	%/m³	10.5	0.34 (−1.18, 1.89)	−1.16 (−2.29, −0.01)	1.69 (−0.48, 3.90)	−0.67 (−2.17, 0.85)	−1.40 (−2.79, 0.02)
$PM_{2.5}$ OP^{AA} + $PM_{2.5}$	%/m³	10.5	0.50 (−1.39, 2.44)	−0.65 (−2.07, 0.79)	1.88 (−0.73, 4.55)	0.14 (−1.72, 2.03)	−0.96 (−2.65, 0.77)
$PM_{2.5}$ OP^{GSH}	%/m³	4.8	0.07 (−1.07, 1.23)	−0.05 (−0.91, 0.82)	0.31 (−1.47, 2.12)	−0.16 (−1.23, 0.93)	−0.47 (−1.45, 0.53)
$PM_{2.5}$ OP^{GSH} + $PM_{2.5}$	%/m³	4.8	0.11 (−1.06, 1.29)	0.15 (−0.73, 1.04)	−0.56 (−2.04, 0.94)	−0.21 (−1.31, 0.89)	−0.27 (−1.28, 0.75)

OP^{AA}—Ascorbate depletion; OP^{GSH}—Glutathione depletion.

dence intervals included 0% (Table 3). Associations with cause- and age-specific hospital admissions are given in Table 4. For cardiovascular admissions, associations in younger adults (15–64 years) were positive and associations in older adults (65+ years) were generally negative with confidence intervals that included 0% other than for $PM_{2.5}$ OP^{AA} and cardiovascular admissions in 65+ age group. For respiratory admissions, positive associations were observed for children aged 0–14 years with the strongest associations observed for PM_{10} OP measures. There was little evidence for associations between particle OP and respiratory admissions in adults, except for negative associations with PM_{10} OP metrics in subjects over 65 years of age.

Adjustment for particle mass and gaseous pollutants did not materially affect the estimates nor their confidence intervals for any of the outcomes/diseases investigated (Tables 3 and 4 and Supplementary material, Table 1). When stratified by warm and cool periods of the year (Supplementary material, Table 2) seasonal differences achieved statistical significance for $PM_{2.5}$ OP^{AA} (adjusted for PM mass) and hospital admissions for both cardiovascular and respiratory causes which were increased during the warm season in subjects below the age of 65 years. Results from distributed lag models including adjustment for particle mass concentration confirmed the pattern of associations found for individual lags (data not shown).

4. Discussion

We investigated associations between daily measures of the oxidative potential of airborne particles and daily, all-cause and cause-specific mortality and cause-specific admissions in London for the period 2011–2012. Associations for OP^{AA} and OP^{GSH} were positive for all-cause mortality and generally negative for

cardiovascular and respiratory mortality. Associations with cardiovascular admissions were generally positive with confidence intervals including 0%. For respiratory admissions there was a trend, from positive to negative associations, with increasing age although all confidence intervals included 0%. We observed some evidence of an association between OP^{AA} and cardiovascular and respiratory admissions in subjects less than 65 years during the warm season (April–September).

Our study evaluated associations between daily measures of ascorbate and glutathione depletion in PM_{10} and $PM_{2.5}$ and daily counts of health events and is an example of translational research linking laboratory to epidemiology. One feature of this approach is that data assembly is labour intensive and therefore costly. The collection and analysis of particle filters to derive daily OP measures is also time consuming and therefore our study was limited by resources to approximately 700 consecutive daily measurements. In time series studies, statistical power is determined by the number of observations (days) and the mean numbers of events per day. Whilst our study was limited with regard to the number of days this was compensated for to some degree by the large study population, and hence large mean number of events, in London. However, analyses with more years of data would improve the precision of our model estimates and aid interpretation.

A further limitation of our study, one inherent in many time series studies, was the potential misclassification of exposure due to the use of measurements from a single background monitoring station in Inner London. Zeger et al. have shown that what matters is how well the exposure series matches the mean daily exposures over the city as a whole (Zeger et al., 2000). With OP measures we have no means of evaluating this but we note that in London, $PM_{2.5}$ daily measurements at monitoring stations in different geographical locations were strongly correlated (Puustinen et al., 2007), and supported by our own analysis of concentrations of PM_{10} and $PM_{2.5}$ measured at NK and at background monitoring stations across London (data not shown). We also note that a recent paper by Yang et al. has demonstrated that PM OP measured at a central monitoring site in the Netherlands was correlated with personal exposures (Yang et al., 2015).

Oxidative stress has been proposed as a unifying mechanism to explain the toxic effects of particulate matter (Kelly, 2003). In a recent review, Weichenthal et al. examined existing epidemiological evidence related to oxidative stress defence and the health effects of fine particles ($PM_{2.5}$) (Weichenthal et al., 2013). Their aim was to assess the evidence for, or against, incorporating measures of $PM_{2.5}$ oxidative burden in ambient air quality management. Their review focused on studies that explored the impact of polymorphisms in anti-oxidant related genes or anti-oxidant supplementation and concluded that "the existing evidence generally suggested that oxidant defence may modify the impact of $PM_{2.5}$ exposure on various health outcomes, particularly heart rate variability".

A small number of studies have examined the association between PM oxidative burden and cardiorespiratory morbidity. Tonne et al. assessed the association between PM_{10} oxidative burden and carotid intima-media thickness in a cohort of 2348 British civil servants (Tonne et al., 2012). The PM oxidative burden at subjects' residential addresses was estimated using a geostatistical spatio-temporal model applied to weekly OP measures. PM weighted by particle OP estimates was not more predictive of the extent of atherosclerosis than PM mass concentration. Measured PM_{10} OP, together with a range of other PM metrics, were used in an experimental study in which volunteers were exposed to PM at five different locations including an underground train station, two traffic sites, a farm, and an urban background site (Strak et al., 2012). Whilst changes in PNC, NO_2, and NO_X were associated with evidence of acute airway inflammation and impaired lung function, PM mass concentration and PM_{10} oxidative potential were not predictive of the observed acute responses. This study also investigated relationships with thrombin formation and reported ex vivo thrombin generation was associated with exposure to NO_2, nitrate and sulphate, but not PM mass, PM OP or other measured air pollutants (Strak et al., 2013). A panel of 45 schoolchildren with persistent asthma was followed over 10 days with repeated measurement of fractional exhaled nitric oxide (FE_{NO}), a biomarker of airway inflammation (Delfino et al., 2013). Ambient exposures included daily average $PM_{2.5}$, $PM_{2.5}$ elemental and organic carbon (EC, OC), NO_2, O_3, and endotoxin. $PM_{2.5}$ oxidative potential was assessed using both an abiotic and an *in vitro* bioassay on aqueous extracts of daily particle filters. FE_{NO} was associated with both OP metrics as well as traffic markers (EC, OC, and NO_2) but not $PM_{2.5}$ mass. In a bi-directional case-crossover study in patients admitted to the hospital for asthma/COPD exacerbation compared PM_{10} oxidative potential on the day of admission with that on 14 days before/after (Canova et al., 2014). OP measured by AA and GSH depletion showed no association with asthma/COPD admissions, with and without adjustment for PM_{10} mass.

Our study is the first to assess associations between daily measures of the oxidative potential of PM_{10} and $PM_{2.5}$ in a time series design including mortality and hospital admissions for cardiorespiratory diseases stratified by age groups. Our results are consistent with the generally null findings reported in the (small) literature base. There are a number of possible explanations for this lack of epidemiological evidence. First, the mechanism(s) by which particles affect human health over short durations are not driven by oxidation reactions or oxidative stress induced by particles. We note, however, that we also found no evidence for associations between PM mass and daily mortality and hospital admissions in adults over 65+ years during the same period (Atkinson et al., 2016; Samoli et al., 2016). Secondly, the exposure metrics used (measurements made at a single background site) do not represent well the exposure of the population at risk or that the day-to-day variation in OP exposure is insufficient to enable detection of associations with health. Finally, the particular assay used did not adequately reflect the true biological oxidative potential of the particles monitored (Weichenthal et al., 2013). Previous studies have demonstrated that fresh tail pipe PM has low intrinsic OP in chemical models (Barath et al., 2010), but have the capacity to elicit intra-cellular ROS via PAH activation through xenobiotic metabolism (Baulig et al., 2004). Therefore, it may be the case that the chemical models are simply not configured to be informative about this aspect of the particles downstream toxicity. As an aside a number of other assays are available to assess the intrinsic OP of PM, based on the oxidation of dithiothreitol (DTT), the oxidation of fluorescent probes, or the spin trapping of radicals and their quantification by electron paramagnetic resonance (Ayres et al., 2008). While there is no standardised assay for OP, it should be noted that some quantitative agreement between the methods has been reported with the DTT method and the OP^{GSH} metric being largely comparable, being based on thiol oxidation (Janssen et al., 2015; Künzli et al., 2006).

Our observation of positive associations between ascorbate dependent OP and cardiovascular and respiratory hospital admissions in the populations less than 65 during the warmer periods of the year is consistent with an emerging literature suggesting seasonal difference in the toxicity of ambient PM (Hamad et al., 2016), including evidence of increased oxidative activity/toxicity associated with photochemical aging (Kunzi et al., 2015; Saffari et al., 2014). Whilst this association should be interpreted with caution, as it represented a secondary analysis, we believe it warrants further investigation.

5. Conclusions

We found little evidence for short-term associations between particle OP and mortality and hospital admissions in London. To date, evidence from the small number of experimental and epidemiological studies does not support the hypothesis that particles, whatever their source, act on the human body via common mechanisms related to the capacity of the particles to cause damaging oxidation reactions or oxidative stress. However, the evidence base is very limited and further studies with improved exposure assessment and greater statistical power are required to confirm or reject the role of particle OP in triggering exacerbations of disease.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijheh.2016.06.004.

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