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REVIEW

Can 8-hydroxy-2′-deoxyguanosine be used to assess oxidative stress caused by particulate matter air pollution in the general population?

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Abstract
Objectives Assess the association between 8-hydroxy-2′-deoxyguanosine (8OHdG) levels and particulate matter air pollution in non-occupational exposure groups from peer-reviewed literature.
Methods Ovid Medline and PubMed were used to search for all peer-reviewed articles published between 1946 and May 2013. Keywords included particulate matter, air pollution, deoxyguanosine, 8-hydroxy-2′-deoxyguanosine, and known abbreviations. Seven English, non-occupational exposure, human subject studies were evaluated.
Results Of the two studies involving children one found significant positive associations between exposure to particulate matter air pollution and 8OHdG. Investigations into non-occupationally exposed adults were mixed. The lone double-blind crossover study found no relationship between diesel exhaust exposure and 8OHdG. Two out of three panel studies and one cohort study found significant associations between 8OHdG and classes of particles and for various lags.
Conclusions Analyses accounting for particle composition and lags between exposure and physiological responses had the strongest significant associations. Results are not conclusive due to the inconsistency in study designs, small sample sizes, and differences in exposure assessment techniques. Consistent methodology with representative populations including women and other non-occupationally exposed groups are recommended.

Keywords 8-hydroxy-2′-deoxyguanosine · Particulate matter · Air pollution · Exposure assessment

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Introduction

Exposure to air pollution, specifically particulate matter with an aerodynamic diameter <10 microns (PM10) and <2.5 microns (PM2.5), is associated with respiratory (Seaton et al. 1995) and cardiovascular disease morbidity and mortality (Brook et al. 2010). Inhalation of particulate matter leads to an oxidative stress response in the body (Brook et al. 2010). Oxidative stress creates reactive oxygen species and leads to a pro-oxidant and antioxidant imbalance (Ock et al. 2012) resulting in several negative biological effects including the modification of DNA base pairs.

Transverse mutation (G-T or G-A binding) can be caused by the accumulation of urinary 8-hydroxy-2′-deoxyguanosine (8OHdG) in genomic DNA. This biomarker can cross the cell membrane making it possible to measure levels in urine or blood serum (Ock et al. 2012). 8OHdG is associated with aging and disease states associated with oxidative stress (Svoboda et al. 2008). This stable byproduct can be measured in urine using high-performance liquid chromatography (HPLC) or with

enzyme-linked immunosorbent assay (ELISA), providing a non-invasive measure of oxidative stress (Barbato et al. 2010).

The specific mechanisms underlying our physiological response to air pollution exposures are not completely understood. Over 154 million US residents live in non-attainment areas. These areas are defined as having at least one criteria air pollutant (Ozone, PM_{10}, $PM_{2.5}$, SO_2, or Lead) above the Environmental Protection Agency (EPA) limits [http://www.epa.gov (2012a)]. Research shows that children (Schwarts 2004) and the elderly (Delfino et al. 2009) are most susceptible to the negative effects of air pollution. It is imperative that a non-invasive measure of air pollution exposure, for the general population, be discovered to increase our understanding of the mechanisms associated with respiratory and cardiovascular morbidity and mortality. This may lead to policies that will improve the environment and protect our health.

Several occupational studies on healthy male subjects showed associations between 8OHdG and occupational exposure to particulate matter. A study conducted with workers exposed to cobalt dust showed no relationship between exposure and 8OHdG, but when hard metal dust (primarily composed of metallic carbide particles) was evaluated, there was a positive association between exposure and 8OHdG in the same workforce (De Boeck et al. 2000). Boilermakers exposed to residual oil fly ash had significantly higher 8OHdG levels post-shift than pre-shift. Additional comparison of associations between exposures to specific components found that vanadium, manganese, nickel and lead PM2.5 were also positively associated with 8OHdG levels (Kim et al. 2004). Taiwanese long distance bus drivers had significantly higher 8OHdG levels compared to their administrative co-workers who held office positions with the same employer (Han et al. 2010). Finally, traffic control officers in India showed a similar pattern overall, but when broken down into age groups, a significant difference between traffic police and control police officers occurred for the older age groups but not the youngest group (aged 25–35 years) (Ravichandran et al. 2012).

Even though occupational studies show a relationship between exposure to air pollution and 8OHdG, it is not clear if the relationship holds for the general population or in geographical regions where exposure levels are lower. Most of the occupational studies listed above were composed primarily of healthy male subjects with particulate matter exposure levels on the order of hundreds of $\mu g/m^3$. These levels greatly exceed the US Environmental Protection Agency (EPA) particulate air pollution 24 h average limit of 35 $\mu g/m^3$ for PM2.5 and 150 $\mu g/m^3$ for PM10 [http://www.epa.gov (2012b)]. The goal of this review is to determine if 8OHdG can be used as a biomarker for particulate matter exposure levels similar to the outdoor environment experienced by the general population.

Methods

All papers published in scientific journals from 1946 through May 2013, were evaluated for inclusion in this review. The following databases were used to identify suitable peer-reviewed manuscripts: Ovid Medline and PubMed. Any relevant citations found within the queried articles were also examined. Only articles that could be accessed in English and published as complete articles were considered. For a manuscript to be included in this review, the following inclusion criteria had to be met: human subject study (any age range or gender ratio), urinary or blood serum measures of 8OHdG, sample size of at least 10, air pollution exposure to particulate matter, and subject air pollution exposure in non-occupational settings. Studies were excluded if the air pollution exposure was due to environmental tobacco smoke because 8OHdG has already been shown to be an appropriate biomarker for exposure to carcinogens (Valandis et al. 2009).

The terms used to search the databases included: deoxyguanosine, 8-hydroxy-2′-deoxyguanosine, 8-OHdG, 8-oxo-7, 8-dihydro-2-deoxiguanosine, 8oxoG and air pollution. The results of the initial search with both databases provided a combined total of 89 articles. Several research articles were removed from consideration because they did not match the inclusion criteria: 24 studies evaluated non-particulate matter exposures, 23 studies were occupational exposures, and 25 articles were on animals or used cultured cells or muscle tissue to assess oxidative stress. One article was a review of occupational exposure to vehicular exhaust and levels of 8OHdG (Barbato et al. 2010), another article considered the best method for assessing oxidative stress related genotypes and 8OHdG levels in relation to air pollution (Ren et al. 2010) and six studies focused on a different outcome variable altogether. Searching the reference lists of the remaining review articles provided one additional study (Fig. 1).

Several variables were gathered from the relevant studies. In addition to primary author and study type, exposure, assessment of 8OHdG, subjects' age range and sample size, study location and results associated with particulate matter were extracted. Characteristics of each evaluated manuscript are in Table 1. An assessment of the quality of the final manuscripts used criteria associated with exposure attainment, 8OHdG measurements, and statistical adjustments for age, gender or contact with environmental tobacco smoke.

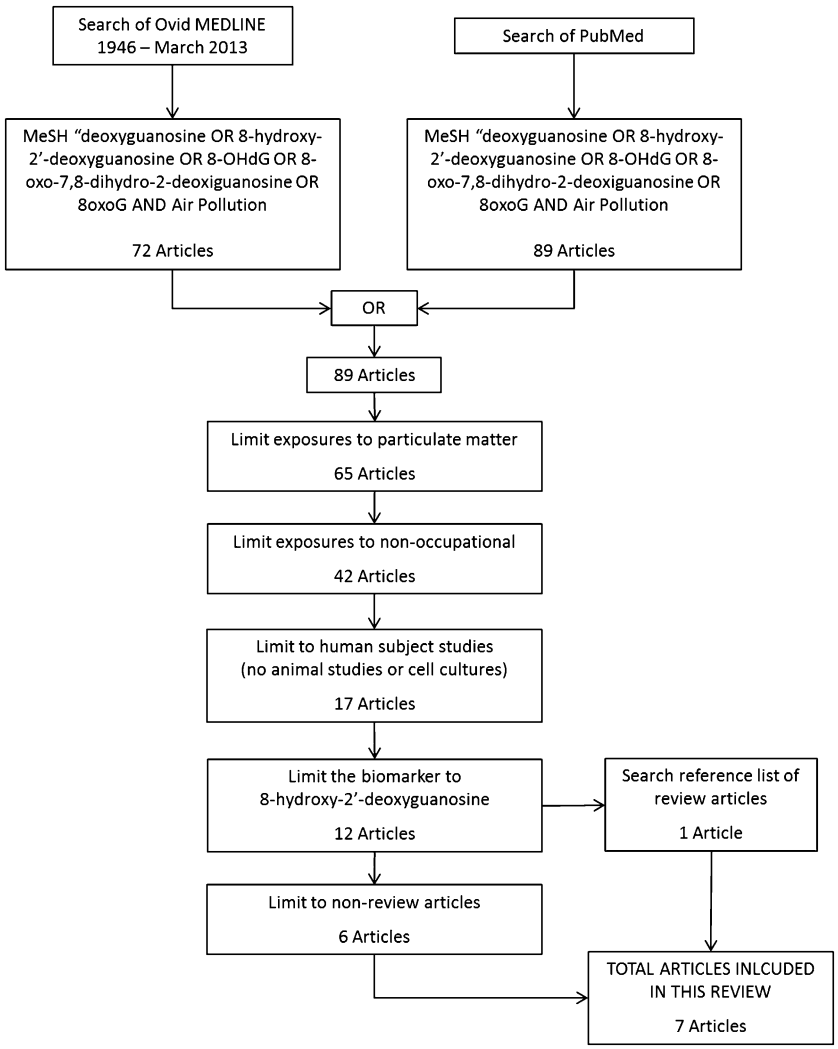

Fig. 1 Flow diagram of the peer-reviewed manuscript selection process

Results

This review included a total of 1,588 subjects. They were divided into two groups: children (1,036) and adults (552). The children evaluated in the review were located in Czech Republic (Svecova et al. 2009) and Taiwan (Wong et al. 2005). Three of the studies evaluating 8OHdG levels in adults were conducted in the US (Ren et al. 2011; Allen et al. 2009; Kim et al. 2009), one was conducted in Taipei (Chuang et al. 2007) and one was conducted in Beijing (Huang et al. 2012b). Among the studies included in our review, four reported positive, significant associations between 8OHdG and air pollution levels, two studies showed mixed results and one reported a null relationship. Exposure levels for each study are shown in Table 2.

Studies in children

The sample population distribution was similar for both studies that included children. A subset of the children was chosen from highly industrialized locations and compared to those living or going to school in suburban or agricultural communities. In the Czech Republic, 894 children who lived either in Teplice (industrial) or in Prachatice (agricultural) were assessed. The children ranged from 5.9 to 10 years of age. In addition to urinary 8OHdG, urinary cotinine levels were measured, parental demographic data on smoking, alcohol, and health status were collected, and chronic health conditions for the children were captured (allergic rhinitis, bronchial asthma, sensitization to inhalant allergens and atopic dermatitis) (Svecova et al. 2009). Likewise, in Taiwan 142 children between the ages of 10 and 12 years were sampled from three elementary schools. One was located within 1 km of the power plant and two elementary schools were in suburban locations at least 8 km from the plant (Wong et al. 2005). Both studies found significant positive associations between exposure to air pollution and urinary levels of 8OHdG.

For the prospective cohort of children in the Czech Republic exposure was measured with stationary Versatile

Table 1 Characteristics of studies conducted between 2003 and 2008 in the United States, China, Taiwan and the Czech Republic that assessed 8-hydroxy-2′-deoxyguanosine (8OHdG) levels in children and adults exposed to air pollution in non-occupational settings

Authors	Study type (year)	Exposure	Measure of 8OHdG	Age (years)	Sample	Significant findings	Results
Children							
Wong et al. (2005) Taiwan	Cross sectional (2003)	Arsenic (As) chromium (Cr) nickel (Ni)	Urinary ELISA	10–12	142 M—74 F—68	Yes	Exposure to As and Cr assoc. with ↑ 8OHdg; Exposure to high As/high Cr assoc. with higher 8OHdg than exposure to low As/low Cr (16.2 v. 11.4 ng/mg; $p < 0.01$) after adjusting for maternal education and allergic rhinitis
Svecova et al. (2009) Czech Republic Teplice Prachatice	Cohort (2004)	PM10, PM2.5, PAH	Urinary ELISA	5.9–10.5	894 M—442 F—452	Yes	Age was positively associated with 8OHdG ($p < 0.001$); Gypse ethnicity had higher 8OHdG than other groups ($p < 0.01$); multivariate regression provided positive association between 3 day averages of PM10 and PM2.5 and 8OHdG after adjusting for child's age, cotinine levels and allergic rhinitis
Adults							
Allen et al. (2009) University of Washington, USA	Double-blind crossover	Diesel exhaust	Urinary ELISA	18–49	10 with MeS M—6 F—4	NO	OHdG levels did not change 22 h post a 90 min continuous exposure of 200 μg/m^3 diesel exhaust: −0.09 (−0.13, 0.31)
Chuang et al. (2007) Taipei, Taiwan	Panel study (2004 and 2005)	PM2.5, PM10, O3, SO2, NO2, CO	Blood serum	18–25	76 M:F 3:2	Mixed	OHdG was not significantly associated with PM10 or PM2.5 but was significantly associated with 1, 2 and 3 day averages of nitrate particle and 1 day sulfate particles averages Nitrate % change in OHdG 1 day: 9.0 (4.0–14.1) 2 day: 15.1 (5.9–24.3) 3 day: 15.0 (4.9–25.0) Sulfate % change in OHdG 1 day: 1.0 (0.3–1.3) Ozone % change in OHdG 1 day: 2.2 (0.9–3.5)
Kim et al. (2009) Boston, MA, USA	Panel study (2004)	PM2.5	Urinary ELISA	21–70	12 Hyp 9 Non-hyp M—5 F—16	Mixed	No association between pollution and 8OHdG in univariate analysis. Significant negative association when adjusted for gender, age, smoking status and time of day: coefficient = −0.40 (−0.79–0.01) $p = 0.04$. When adjusted for hypertension status, no association for non-hypertensive subjects, but significant negative association for hypertensive: coefficient = −0.60 (−1.03, 0.17) $p < -0.01$.

Table 1 continued

Authors	Study type (year)	Exposure	Measure of 8OHdG	Age (years)	Sample	Significant findings	Results
Ren et al. (2011) Boston, MA, USA	Cohort (2006–2008)	PM2.5, NO2, SO4, CO, BC, EC, OC	Urinary ELISA	63–96	M—320	Yes	3 week moving average daily concentrations of PM2.5 resulted in increased urinary 8OHdG by 30.8 %: 95 % CI (9.3–52.2 %). Similar results observed for 1 and 2 weeks averages: 23.0 % (3.7–42.3) and 26.4 % (6.9–45.8)
Huang et al. (2012b) Beijing, China	Panel study Quasi-experimental (2008)	PM2.5, O3, NO2, SO2 SO4, CO, BC, EC, OC	Urinary HPLC	19–33	M—63 F—62	Yes	Significant associates were observed between PM2.5 for lags 0–4 and 8OHdG levels. Pollution and biomarker levels were captured prior to, during and after the Olympic games. The greatest increase in 8OHdG was 57.5 % per IQR increase in PM2.5

M male, *F* female, *Hyp* hypertensive, *Non-hyp* non-hypertensive, *MeS* metabolic syndrome

Air Pollution Samplers. These samplers monitor the environment and served as a proxy measure of individual exposure levels. Univariate analysis in the Czech Republic found age of the children was significantly associated with 8OHdG ($p < 0.001$) and children of Gypse ethnicity had higher levels of 8OHdG ($p < 0.01$). However, no difference was found in 8OHdG levels for children living in the two cities even though Teplice had higher environmental pollution levels. Svecova et al. (2009) performed a multivariate linear regression showing that the most important factors associated with 8OHdG levels were child's age, cotinine levels and inter-uterine growth restriction. After adjusting for child's age, cotinine levels and allergic rhinitis, a positive association was found between 3 day averages of PM10 and PM2.5 for the 4–6 days prior to urine collection as well as a 7 day average of PM10 and 8OHdG levels. Nevertheless, when similar analyses were conducted using only children who were not exposed to environmental tobacco smoke no effect was observed between PM2.5 or PM10 and 8OHdG.

Wong et al. assessed exposure to arsenic, chromium and nickel via urine analysis, but air pollution measures from the community or through personal monitoring devices were not collected. Adjustments were made for creatinine levels. Creatinine is the metabolic product of muscle tissue and is normally in urine at a concentration of 1 g/L. Adjustments are made to standardize the concentration of the analyte of interest based upon this expected value. Univariate analysis showed positive associations between environmental tobacco smoke exposure, allergic rhinitis, elementary school and maternal education with 8OHdG. Several confounders were considered for the cross sectional analysis of particulate exposure to arsenic, chromium and nickel, however, the only significant contributors to a least squares mean analysis included maternal education and allergic rhinitis. Both arsenic and chromium were associated with increased levels of 8OHdG and a combination of high arsenic/high chromium exposure led to 8OHdG levels that were significantly higher compared school students who had low arsenic/low chromium exposure (16.2 versus 11.4 ng/mg; $p < 0.01$) (Wong et al. 2005).

Wong et al. indicated that inhalation and ingestion are potential routes of exposure to metals released by vehicles and coal fired power plants. However, there was no indication that ambient environmental concentration levels were assessed. From the information provided it is impossible to determine if there was a correlation between ambient air pollution concentration levels and the children's metallic blood concentration levels. Even though metal concentrations in the blood were correlated with 8OHdG levels, there is insufficient information to associate those levels with ambient air pollution concentrations. The

Table 2 Exposure assessment and concentration levels for air pollution measured between 2003 and 2008 in the United States, China, Taiwan and the Czech Republic

Study	Exposure assessment	Pollutants	Concentration levels
Wong et al. (2005)	Urinary blood levels	Arsenic	Ambient air pollution levels for particulate matter of any kind are unknown
		Chromium	
		Nickel	
Svecova et al. (2009)	Stationary monitors		Median levels for entire sampling period
		Teplice	
		PM10	30 μg/m^3
		PM2.5	22.7 μg/m^3
		Prachatice	
		PM10	20.4 μg/m^3
		PM2.5	16.8 μg/m^3
Allen et al. (2009)	Continuous monitoring with TEOM	Filtered air	Average of continuous exposure
		PM2.5	4.8 μg/m^3
		NO2	15.5 μg/m^3
		CO	0.3 ppm
		Diesel exhaust	
		PM2.5	205.3 μg/m^3
		NO2	25.5 μg/m^3
		CO	0.7 ppm
Chuang et al. (2007)	1 stationary monitor located on the roof of a building in the center of Fu-Jen campus		1 day average levels for all subjects
		PM10	49.2 μg/m^3
		PM2.5	31.8 μg/m^3
		Nitrate	4.5 μg/m^3
		Sulfate	4.1 μg/m^3
		OC	4.5 μg/m^3
		EC	1.6 μg/m^3
		O3	28.4 ppb
		NO2	17.3 ppb
		SO2	16.3 ppb
		CO	0.8 ppm
Kim et al. (2009)	TSI incorporated model	PM2.5	12 h average
	AM510 SIDEPAK personal aerosol	All subjects	18.4 μg/m^3
	Monitor	Hypertensive	21.8 μg/m^3
		Non-hypertensive	15.8 μg/m^3
Ren et al. (2011)	1 stationary monitor located 1 mile from the examination location		Daily average
		CO	0.30 ppm
		Black carbon	0.88 μg/m^3
		EC	0.44 μg/m^3
		O3	39.2 ppb
		Sulfate	2.68 μg/m^3
		NO2	18.8 ppb
		PM2.5	13.0 μg/m^3
		OC	3.43 μg/m^3

Table 2 continued

Study	Exposure assessment	Pollutants	Concentration levels
Huang et al. (2012b)	24 h mean concentrations from one monitor located in center of campus housing for the study population		Range of the mean levels across the three phases of the study
		SO2	2.97–7.45 ppb
		NO2	14.64–41.39 ppb
		O3	15.12–39.60 ppb
		CO	0.64–1.23 ppm
		PM2.5	71.9–98.9 $\mu g/m^3$
		EC	1.4–2.2 $\mu g/m^3$
		OC	6.8–15 $\mu g/m^3$
		Sulfate	13.7–26.5 $\mu g/m^3$

exposure assessment employed by Svecova et al. was more robust with the use of stationary monitors, but the number of monitors used and their location in relation to subject's residence is unknown. Exposure misclassification is possible with stationary monitoring, but efforts were made to adjust for age, exposure to environmental tobacco smoke and allergic rhinitis.

Studies in adults

Exposure to air pollution in non-occupational settings was used as a selection criterion for studies that included adults. These studies showed mixed results. A cohort study included 320 men between the ages of 63 and 96 who were US Military veterans (Ren et al. 2011). One panel study conducted in Boston, MA looked at 21 subjects between the ages of 21 and 70. The subjects lived in close proximity to a bus terminal and were recruited from a local health clinic. Clinic medical records were used to select participants based on their health status. Twenty-seven healthy and 40 compromised people were contacted. Subjects were considered compromised if they had one of the following diagnoses: diabetes, chronic bronchitis, asthma, emphysema, and hypertension. A total of 15 subjects were compromised and 6 were healthy (Kim et al. 2009). A second panel study took place in Taipei and included 76 healthy men and women between 18 and 25 years of age from Fu-Jen Catholic University (Chuang et al. 2007). The only double-blind crossover trial included six men and four women between 18 and 49 years of age who were diagnosed with metabolic syndrome according to the ATP III criteria (Allen et al. 2009). The final panel study was a quasi-experimental design that evaluated fluctuations in air pollution levels as well as 8OHdG levels in healthy medical students between the ages of 19 and 33 years of age, who lived in Beijing prior to, during and after the 2008 summer Olympic Games (Huang et al. 2012b).

Only one study found a positive, significant association with PM2.5. Ren et al. conducted a 2 year long prospective cohort study of US military veterans and found 1, 2 and 3 week moving average levels of PM2.5 were associated with percent increases (95 % confidence interval) in urinary 8OHdG levels: 23.0 (3.7–42.3), 26.4 (6.9–45.8), and 30.8 (9.3–52.2), respectively. Pollution exposure measurements were obtained from stationary monitors located 1 mile from the examination location for the military veterans. All veterans who participated in the Normative Aging Study and came for their routine tests associated with the original cohort study between January 2006 and December 2008 were enrolled in the air pollution study. Several confounders were considered: BMI, age, smoking status, alcohol consumption, use of statin medication, season, plasma folate, and vitamins B6 and B12. However, no individual monitoring levels were obtained and there was no mention of capturing individual geographic locations (i.e., addresses) to know if the stationary monitor was a sufficient proxy of personal exposures for the study participants (2012).

Three panel studies gave mixed results. One looked at urinary 8OHdG levels in non-hypertensive and hypertensive individuals. Kim et al. captured individual exposure levels over a 36 h period with the TSI Incorporated model AM510 SIDEPAK personal aerosol monitor. The study personnel accounted for the overestimation of pollution measurements associated with such devices using correction factors for smokers and non-smokers. In multivariate analysis they also accounted for age, gender, smoking status and hypertension status. Univariate analysis found no significant relationships. Multivariate analysis adjusting for gender, age, smoking status and time of day found a significant negative relationship between PM2.5 and 8OHdG with a regression coefficient (95 % confidence interval) of -0.40 (-0.79, 0.01; $p = 0.04$). However, when hypertension status was added to the model, there was a significant decrease in urinary 8OHdG for

hypertensive individuals with no significant association for non-hypertensive individuals (2009).

The second panel used stationary monitors located near a university campus in Taipei as proxies for individual pollutant exposure levels. This study accounted for age, sex and BMI in their regression analysis, but also included day of the week, temperature and relative humidity. No significant associations between particulate matter (PM10 and/or PM2.5) and blood serum 8OHdG levels were found. Significant associations were observed for sulfate and nitrate particulates. One day average sulfate particulate levels were associated with a 1.0 (0.3–1.3) percent change (95 % confidence interval) in 8OHdG and 1 day average ozone levels corresponded to 2.2 (0.9–3.5) percent change in 8OHdG. One-, 2-, and 3-day moving averages of Nitrate particulates were associated with increased percent change in 8OHdG of 9.0 (4.0–14.1), 15.1 (5.9–24.3), and 15.0 (4.9, 25.0), respectively (Chuang et al. 2007).

Huang et al. used the 2008 summer Olympics as an opportunity to conduct an quasi-experimental panel study evaluating changes in 8OHdG levels in response to changes in air pollution levels. Air pollution levels were minimized during the Olympics due to the implementation of control mechanisms during the Olympic Games. Once the games were completed, the control mechanisms were lifted and pollution levels returned to normal. Researchers used this opportunity to assess 8OHdG levels in response to high–low–high air pollution changes. A total of 125 male and female medical residents at the Peking University First Hospital participated. Particulate air pollution was estimated from 24 h mean concentration of PM2.5 levels obtained from the roof top on a building in the center of the university campus. Several components of the air pollution were also monitored: elemental carbon, organic carbon, sulfate, sulfur dioxide, nitrogen dioxide, carbon monoxide and ozone. There were significant reductions in several components of the air pollution; however the 27 % drop in PM2.5 was not statistically significant. The reverse was observed from during the Olympics to the post-Olympic period. Levels of 8OHdG were significantly reduced from the pre-Olympic to during the Olympic period even after adjusting for temperature, relative humidity, gender and day of the week. The largest significant effect estimates were found for PM2.5, elemental carbon, organic carbon, sulfur dioxide and sulfate for lag 0. For a 1 day lag carbon monoxide and nitrogen dioxide had the largest significant effect estimates. Overall, the biggest change in 8OHdG levels due to PM2.5 was a 57.6 % increase per IQR increase in PM2.5 at lag 1. Similar changes were observed for all other constituents except ozone which showed a significant reduction in 8OHdG at lag 5 (Huang et al. 2012b).

The final study was a double-blind crossover study conducted at the University of Washington on 10 individuals with diagnosed metabolic syndrome who were otherwise healthy. Exposure levels were very carefully monitored during continuous exposure to diesel exhaust using TEOM measurements as well as Teflon filter samples collected with Harvard Impactors. Since all participants were non-smokers and BMI levels were similar, no adjustments for confounders were used in the statistical analysis (Allen et al. 2009). There was no significant difference in urinary 8OHdG levels between pre and 22 h post exposure to 90 min of 200 $\mu g/m^3$ of diesel exhaust (Allen et al. 2009).

Overall, the studies above show varying effect sizes between exposure to particulate matter air pollution and 8OHdG levels in the general population. Data collection methods and analytic techniques were not consistent. The two studies using personal monitoring were able to capture individual exposure levels thereby minimizing exposure misclassification. However, both sample sizes were below 25 limiting the power of each study. In addition, Allen et al. assessed acute exposure to high levels of PM2.5 (200 $\mu g/m^3$) which is different than exposure to lower levels of air pollution for extended periods of time. The subjects assessed as part of the Normative Aging study were given the exposure associated with levels of the clinic. This may result in exposure misclassification because veterans may have been traveling long distances and not residing in the same city as the clinic. The strongest studies methodologically were those associated with university students. The subjects lived close to the monitor measuring pollution concentrations, the air pollution was assessed as PM2.5 and PM10 as well as their constituents and exposure lags were also considered.

Discussion

Several studies have demonstrated that exposure to particulate air pollution leads to systemic oxidative stress. However, the exact mechanisms regarding local inflammation or tissue inflammation versus systemic markers are not clearly understood (Brook et al. 2010). Many biomarkers have been associated with oxidative stress. Our primary aim was to determine if 8OHdG could be used to assess exposure to environmental air pollution in the general population. Both studies involving children showed differences in 8OHdG levels between children of different exposure levels after adjusting for maternal education and allergic rhinitis. Results from the studies evaluating adult exposure to particulate matter were mixed with only two studies showing an increase in 8OHdG with increased exposure to PM2.5. One study found a significant negative association between 8OHdG and exposure in hypertensive individuals with no association found in non-hypertensive

subjects. When particulate matter was speciated into specific components, associations were found with nitrate and sulfate particulate matter and 8OHdG levels. Finally, a study on subjects with metabolic syndrome found no significant difference pre and post exposure to diesel exhaust. In general, studies included in this review evaluating specific components of particulate matter showed the strongest relationships between exposure and 8OHdG levels. Huang et al. (2012b) found significant percent increases in 8OHdG for an interquartile increase in PM2.5, sulfate, elemental carbon, organic carbon, sulfur dioxide, carbon monoxide and nitrogen dioxide. Chuang et al. (2007) investigated several components of air pollution including sulfate and nitrate particulates. These results support previous research studies investigating the breakdown of particulate matter air pollution.

For the articles reviewed several study designs were used: cohort, panel studies, and a double-blind crossover study. Even though methodology between studies varied, there were too few studies in any given study design subgroup to draw definitive conclusions. Samples sizes ranged from 10 to 894 with half of the studies using <100 subjects. The levels of 8OHdG were also assessed differently. Of the studies finding significant effects, the sample size was either large or the authors accounted for a delay between exposure and systemic 8OHdG levels during their analysis. Another factor impacting findings was type of exposure. Studies that investigated specific types of particulate matter showed stronger relationships than studies that looked at PM10 or PM2.5, collectively. The crossover study that showed no relationship between diesel exhaust exposure and 8OHdG only used a 22 h lag and never collected data on the subjects for the 2 days following their exposures or the hours directly after exposure (Allen et al. 2009) which may underestimate the effect and bias results toward the null. The authors collected blood samples continuously, but used the spot urine to estimate 8OHdG concentrations. Data from the blood samples may provide better evidence regarding how quickly the body systemically responds to exposure via the production of 8OHdG.

Kim et al. found a negative association between PM2.5 exposure and 8OHdG in hypertensive individuals. The authors argue that hypertensive individuals may have a reduced capacity to repair oxidative DNA damage. The non-hypertensive participants in the study showed non-significant trends with an increase in 8OHdG (2004). The double-blind crossover experiment of 10 adults with metabolic syndrome but no history of medical care for heart disease, hypertension, or other chronic conditions exposed to diesel exhaust then filtered air indicated no relationship between exposure and 8OHdG after 22 h (Allen et al. 2009). More studies are needed to determine if there is a threshold associated with an individual's level of chronic disease and a diminished capacity for the body to repair oxidative DNA damage.

There appear to be three key pieces to the particulate air pollution, mortality and morbidity puzzle: duration of exposure, size of the particle and particle composition. When comparing studies of acute and chronic exposure, Pope (2000) found that mortality, morbidity and respiratory symptoms were higher for individuals who were chronically exposed. Size of particulate matter is important regarding mortality and morbidity. Stronger associations were found for $PM_{2.5}$ versus PM_{10} when daily mortality was evaluated for six eastern US cities over the course of 8 years (Schwartz et al. 1996). Finally, specific components of particulate matter are associated with increases in specific health conditions. This implies that in addition to specific particulate mass limits, efforts need to be made to limit exposure to specific components of air pollution. By having a non-invasive measure (urinary 8OHdG) of exposure to air pollutants, evaluation and continued monitoring could be achieved to improve the quality of our environment and the health of our community.

Zanobetti et al. (2009) showed that emergency hospital admissions for myocardial infarction, congestive heart failure, respiratory disease and diabetes fluctuated based on which components of air pollution were highest. High levels of bromine, chromium, nickel and sodium were associated with cardiac admissions; arsenic, chromium, manganese, organic carbon nickel and sodium modified myocardial infarction admissions; and arsenic, organic carbon and sulfates modified diabetes admissions. Cardiovascular mortality has been associated with increased levels of elemental carbon, organic carbon, nitrates, iron, potassium and titanium (Ostro et al. 2007). Levels of 8OHdG may also be component specific.

Several studies show a relationship between occupational exposure to particulate matter and 8OHdG. The finest particulates come from combustion processes. Vehicular exhaust is composed of nitrates, sulfates, elemental and organic carbon and particles in both $PM_{2.5}$ and PM_{10} size ranges (http://www.osha.gov (2012). Occupations where employees are exposed to traffic pollution or other outdoor ambient exposures make for more relevant comparisons. Professional bus drivers in Taiwan had higher 8OHdG levels compared to their office working counterparts (Han et al. 2010) with similar results for Indian traffic police officers (Ravichandran et al. 2012). Neither study supplied an assessment of the average exposure difference between the drivers and their office working colleagues. Huang et al. compared traffic conductors to indoor office workers and found significantly elevated levels of 8OHdG for traffic conductors in comparison to the office workers. The median exposure levels for cases and controls were 82.87 versus 70.80 $\mu g/m^3$, respectively (Huang et al. 2012a). Fifty male

bus drivers from the Czech Republic were compared with 50 male controls that spent more than 90 % of their time indoors. The average exposure levels of PM2.5 for cases and controls were 32.1 and 20.9 μg/m^3 while the PM10 exposure levels were 38.6 and 24.1 μg/m^3 respectively. Bus drivers had significantly higher levels of 8OHdG than the controls (Rossner et al. 2007). Based on our analysis of the reviewed articles, there is a positive association between exposure to particulate air pollution and 8OHdG levels in members of the general public including children, adults and military veterans. The strongest associations were observed when specific components of particulate air pollution were assessed and when time lags were considered. The average ambient PM2.5 exposure levels for the studies evaluated in this review ranged from 13.1 to 31.8 μg/m^3. These levels are lower than those experienced by traffic conductors in Taiwan, but comparable to levels experienced by bus drivers in the Czech Republic. The results for the most robust studies reviewed mimic those found for workers exposed to vehicular exhaust. Urinary levels of 8OHdG are associated with exposure to particulate matter air pollution and provide a non-invasive measure of oxidative stress. However, results of the studies with non-occupationally exposed individuals are not consistent due to varied study designs, small sample sizes, and differences in exposure assessment techniques. Further studies with consistent methodologies, including women, individuals with chronic disease associated with oxidative stress, and other non-occupationally exposed groups are recommended.

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