Review
EPIDEMIOLOGY/GENETICS

Obesity

Obesity and the Cardiovascular Health Effects of Fine Particulate Air Pollution

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Objective: This review examines evidence related to the potential impact of obesity on the cardiovascular health effects of fine particulate air pollution ($PM_{2.5}$).
Methods: A PubMed search was conducted in December, 2013 and studies were included if they examined the relationship between $PM_{2.5}$ and cardiovascular health as well as effect modification by obesity.
Results: One hundred twenty-one citations were reviewed; three large prospective cohort studies and 14 panel studies with short-term follow-up met the above criteria. All three cohort studies reported stronger associations between $PM_{2.5}$ and cardiovascular mortality among obese subjects and one reported a significant trend of increased risk with increased body mass index. Similarly, 11 of 14 panel studies reported stronger associations between $PM_{2.5}$ and acute changes in physiological measures of cardiovascular health among obese subjects including outcomes such as blood pressure and arrhythmia. Although interactions were not always statistically significant, the consistent pattern of stronger associations among obese subjects suggests that obesity may modify the impact of $PM_{2.5}$ on cardiovascular health.
Conclusions: Epidemiological evidence suggests that obesity may increase susceptibility to the cardiovascular health effects of $PM_{2.5}$. This an important area of research as the public health impacts of air pollution could increase with increasing prevalence of obesity.

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Introduction

Worldwide obesity has nearly doubled since 1980 and high body mass index (BMI) is now recognized as one of the most important determinants of global disease burden (1,2). In North America, the 2010 Global Burden of Disease Study ranked high BMI as the second most important risk factor for disease burden behind tobacco smoking (2). In general, a BMI of 30 kg/m^2 or more is considered obese while a BMI over 25 kg/m^2 is considered overweight; however, BMI values may not correspond to the same degree of obesity in different individuals (1). Nevertheless, increased BMI is a recognized risk factor for a number of adverse health effects including cardiovascular disease, musculoskeletal disorders, and some types of cancer (1,3,4). Moreover, many of the underlying pathologies of obesity are thought to be linked to a state of chronic oxidative stress and inflammation, with obese patients having increased systemic oxidative stress and impaired oxidant defense (3,5,6). Specifically, recent toxicological evidence suggests that vascular oxidative stress may play an important role in obesity (7). This is an important point as the underlying biological mechanisms governing the adverse health effects of some environmental exposures, such as fine particulate air pollution ($PM_{2.5}$), are also thought to involve oxidative stress pathways (8-10) including increases in vascular oxidative stress (11). Therefore, since air pollution is generally thought to contribute to cardiovascular morbidity through oxidative stress, and given that obese patients have impaired oxidant defense, it seems that obese patients may be particularly susceptible to the cardiovascular health effects of air pollution. In addition, recent evidence suggests that obese subjects inhale more air per day than normal-weight individuals (12), thus potentially increasing their overall dose.

We reviewed existing epidemiological evidence related to obesity and effect modification with respect to $PM_{2.5}$ and cardiovascular health. Specifically, we examined whether the magnitudes of observed associations tended to be greater among obese subjects and whether findings were consistent across studies of similar outcomes. Both long-term and short-term exposure studies were considered as each plays an important role in developing regulatory guidelines.

Methods

Studies were identified by searching the PubMed database in December, 2013 using the key words: air pollution, fine particulate matter ($PM_{2.5}$), obesity, BMI, interaction, effect modification,

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cardiovascular health, traffic-related air pollution, and mortality. For example, a typical search included: fine particulate air pollution ($PM_{2.5}$) AND obesity AND cardiovascular health. Reference lists from the studies identified were also examined. Studies were included in this review if they were published in English and specifically examined the relationship between outdoor $PM_{2.5}$ and cardiovascular morbidity/mortality in humans as well as potential effect modification by some quantitative measure of obesity. While we explored the possibility of a formal meta-analysis, this approach was not pursued owing to the limited number of studies available for specific outcomes. In our review, we considered $P < 0.05$ as statistically significant.

Results

In total, we reviewed 121 citations and included 17 studies that met the above criteria. Three of these studies were large prospective cohort studies of long-term exposure to ambient $PM_{2.5}$ and cardiovascular mortality (13-15) (Table 1). Nearly all of the remaining studies examined the impact of short-term $PM_{2.5}$ exposures on acute changes in physiological measures including heart rate variability (HRV) (Table 2) as well as blood pressure, inflammation, ventricular arrhythmia, right ventricular diastolic pressure, and endothelial function (16-27); however, one panel study examined long-term exposures (28) (Table 3). All of the studies reviewed controlled for relevant confounding factors in their analysis or by design (covariates are listed in Tables (1–3)). Most studies used BMI as a quantitative measure of obesity but one study used waist circumference to measure obesity (22) while a second explored several measures including BMI, waist to hip ratio, and waist circumference (13). Most of the studies reviewed were conducted in the United States with the exception of one Chinese study (29) and two European studies (20,28). Most studies reported *P*-values for effect modification across strata of BMI but some simply reported effect estimate across BMI strata without formal tests for interaction. When available, *P*-values for interactions between obesity and $PM_{2.5}$ are presented in Tables (1–3). Similarly, some studies simply reported the presence/absence of a statistically significant interaction ($P < 0.05$) between obesity and $PM_{2.5}$ but did not report effect estimates across strata of BMI; when available effect estimates are presented in Tables (1 – 3). Many studies reported effect estimates per 10 $\mu g/m^3$ increase in exposure; this is common in air pollution epidemiology and reflects a reasonable change in exposure that may be experienced in daily life as one moves between more/less polluted environments.

Long-term exposure studies

Three prospective cohort studies examined the impact of obesity on the association between long-term exposure to ambient $PM_{2.5}$ and cardiovascular morbidity/mortality (Table 1). All three studies were conducted in the United States between 1992 and 2009; two cohorts were exclusively female (13,14), one included both men and women (15), and two were occupational cohorts (13,15). In all three cohorts, ambient $PM_{2.5}$ concentrations were assigned to participants' residences based either on the nearest monitoring station (13), geographic-information system (GIS)-based models (14), or remote sensing (satellite) estimates (15). Participants in all three studies were predominantly Caucasian.

Miller et al. (13) conducted a prospective cohort study among 65,893 post-menopausal women from 36 cities across the United States. Women were followed for a median time-period of 6-years and each 10 $\mu g/m^3$ increase in annual average $PM_{2.5}$ was associated with a significantly increased risk of all cardiovascular events (including the first occurrence of myocardial infarction, coronary revascularization, stroke, and death from coronary artery disease or cerebrovascular disease) after adjusting for confounding factors (hazard ratio (HR) = 1.24, 95% Confidence Interval (CI): 1.09, 1.41). When restricted to women in the highest category of BMI, the HR increased to 1.84 (95% CI: 1.33, 2.55) and a statistically significant trend of increased risk with increased BMI was reported. Similar patterns were also observed in the highest categories of waist-to-hip ratio (HR: 1.75, 95% CI: 1.29, 2.37) and waist circumference (HR: 1.73, 95% CI: 1.26, 2.36).

The second prospective cohort study followed 66,250 female nurses in the United States between 1992 and 2002 (14). This study examined the relationship between ambient $PM_{2.5}$ and three different outcomes: incident coronary heart disease (CHD), fatal CHD, and non-fatal myocardial infarctions (MI). After adjusting for confounding factors, each 10 $\mu g/m^3$ increase in annual average $PM_{2.5}$ was associated with an increased risk of fatal CHD (HR = 2.02, 95% CI: 1.07, 3.78) and the magnitude of this association was stronger among obese subjects (HR = 3.02, 95% CI: 0.97, 9.40) than in non-obese subjects (HR = 1.09, 95% CI: 0.06, 19.98). Ambient $PM_{2.5}$ was not associated with an increased risk of MI, but $PM_{2.5}$ was associated with incident CHD among obese subjects (HR = 1.97, 95% CI: 1.06, 3.63) with no association observed among participants with BMI values less than 30 kg/m^2 (HR = 0.85, 95% CI: 0.56, 1.29). Tests for statistical interactions between $PM_{2.5}$ and BMI were not statistically significant; however, the directions and magnitudes of associations were consistent with potential effect modification by obesity.

The most recent study of ambient $PM_{2.5}$, obesity, and cardiovascular mortality followed 83,378 members of the United States Agricultural Health Study cohort over a median time-period of nearly 14-years between 1993 and 2009 (15). Members of this cohort were predominantly male farmers ($n = 51{,}807$) residing in Iowa or North Carolina. In contrast to the studies above, ambient $PM_{2.5}$ was not associated with cardiovascular mortality among women in this cohort. However, increased risks were observed among men in the highest category of BMI. Specifically, after adjusting for confounding factors, men in the upper category of BMI (>26.5 kg/m^2) had a more than twofold increased risk of cardiovascular mortality for each 10 $\mu g/m^3$ increase in annual average $PM_{2.5}$ (HR = 2.35, 95% CI: 1.08, 5.10); cardiovascular mortality risk was not significantly increased among men in the lower BMI category. In addition, further adjustment for occupational exposure to pesticides or diesel exhaust did not change this estimate. As in the previous study, interactions between $PM_{2.5}$ and BMI were not statistically significant; however, cardiovascular mortality risk estimates for $PM_{2.5}$ were consistently higher among obese men in all of the models examined.

Short-term exposure studies

Thirteen panel studies examined the impact of obesity on the short-term cardiovascular health effects of $PM_{2.5}$ exposure. One additional study examined the impact of obesity on the relationship between long-term $PM_{2.5}$ exposure and markers of systemic inflammation (28). Five studies between 1998 and 2008 examined HRV as the primary outcome (Table 2); one of these studies also examined heart rate (19). The largest HRV studies included panels of nearly 500

TABLE 1 Prospective cohort studies of long-term exposure to $PM_{2.5}$, cardiovascular morbidity, and effect modification by obesity

Study	Location (Follow-up)	Population	Outcome(s)	Covariates	Obesity measure	Hazard ratio (per 10 $\mu g/m^3$) (95% CI)[a]
Miller et al. (13)	36 metropolitan areas, United States (1994-2003)	65,893 post-menopausal women Median age: 63 years	Cardiovascular events[b]	Age, race, city, education, household income, smoking status, blood pressure, diabetes, hypertension, BMI, and hypercholesterolemia		Cardiovascular events
					BMI $<$ 22.5	1.35 (0.96, 1.88)
					BMI 22.5-24.7	1.58 (1.14, 2.19)
					BMI 24.8-27.2	1.69 (1.24, 2.30)
					BMI 27.3-30.9	1.88 (1.38, 2.56)
					BMI $>$ 30.9	1.84 (1.33, 2.55)
						P-value: 0.004[d]
Puett et al. (14)	Metropolitan areas in Northeastern and Midwestern States, United States (1992-2002)	66,250 female nurses Mean age: 62 years	Coronary heart disease	Age, state of residence, year and season, smoking status, family history of myocardial infarction, BMI, diabetes, hypertension, hypercholesterolemia, median family income and house value in census tract, and physical activity		Fatal coronary heart disease
					BMI $<$ 30	1.09 (0.06, 19.98)
					BMI $>$ 30	3.02 (0.97, 9.40)
						P-value$>$0.05[d]
					BMI $<$ 30	Non-fatal coronary heart disease
					BMI $>$ 30	0.85 (0.56, 1.29)
						1.97 (1.06, 3.63)
						P-value$>$0.05[d]
Weichenthal et al. (15)	Iowa and North Carolina, United States (1993-2009)	83,378 Mean age: 46 years	Cardiovascular mortality[c]	Age, state of enrollment, birth year, smoking status, BMI marital status, education level, alcohol consumption, and vegetable intake		Cardiovascular mortality (Men)
					BMI $\leq$ 26.5	1.35 (0.62, 2.92)
					BMI $>$ 26.5	2.01 (1.01, 3.98)
						P-value$>$0.05[d]

[a]95% confidence interval.
[b]Includes the first occurrence of myocardial infarction, coronary revascularization, stroke, death from coronary heart disease, or death from cerebrovascular disease.
[c]Includes 2010 International Classification of Disease codes: I10-I70.
[d]*P*-value for the interaction between $PM_{2.5}$ and body mass index.

TABLE 2 Panel studies of short-term exposure to $PM_{2.5}$, heart rate variability, and effect modification by obesity

Study	Location	Population	Covariates	Obesity measure	Effect estimate/main findings (95% CI)[a]
Schwartz et al. (16)	Boston MA, United States	497 elderly men Mean age: 73 years	Age, smoking status, BMI, diastolic blood pressure, fasting blood glucose, alcohol consumption, heart medication, season, and temperature	BMI $\geq$ 30	Percent change in high frequency HRV per 10 $\mu g/m^3$ (48 h) • Obese, GST-M1 null: −57.3% (−88, 52) • Non-obese, GST-M1 null: −31% (−50.6, −3.6) • Obese, GST-M1 present: −34.2% (−77.9, 96.5) • Non-obese, GST-M1 present: 7.5% (−29.7, 64.3)
Chen et al. (19)	Eastern Massachusetts, United States	18 male welders Mean age: 42 years	Age, smoking, eating, and drinking habits, calendar year, exercise, blood pressure, and circadian pattern	BMI $\geq$ 30	Change in heart rate (per 1 mg/m^3) (4 h) • Obese: 8.7 bpm (6.3, 11.2) • Non-obese: 3.7 bpm (1.4, 5.9) • *P*-value = 0.001[b] Percent change in HRV (per 1 mg/m^3) (4 h) SDNN • Obese: −10.3% (−16.7, −3.9) • Non-obese: −4.0% (−9.5, 1.5) • *P* = 0.07[b] RMSSD • Obese: −3.4% (−12.6, 5.9) • Non-obese: −0.7% (−8.6, 7.3) • *P* = 0.60[b] High frequency • Obese: −11.1% (−28.4, 6.2) • Non-obese: −7.2% (−22.2, 7.8) • *P*-value = 0.70[b]
Park et al. (22)	Maryland, Illinois, North Carolina, California, New York, and Minnesota, United States	5465 elderly adults Mean age: 62 years	Age, sex, race, smoking status, BMI, fasting blood glucose, mean arterial pressure, heart medication, and temperature	Waist circumference $>$102 cm in men or $>$88 cm in women	The authors reported that statistically significant inverse relationships were observed between 2-day mean $PM_{2.5}$, and SDNN and RMSSD among obese subjects but not among non-obese subjects.
de Hartog et al. (20)	Netherlands, Germany, and Finland	122 coronary heart disease patients Mean age: 67 years	Meteorology and day of the week. Within subject factors (e.g. sex, medication use) that did not vary over time were controlled by design.	BMI $\geq$ 30	Change per 10 $\mu g/m^3$ (3-day) • SDNN: −1.99 ms (−3.69, −0.30) • High frequency: −12.6 ms^2 (−20.1, −4.24) Effect estimates were not reported for non-obese subjects; similar effects were not observed among all subjects.

TABLE 2. (continued).

Study	Location	Population	Covariates	Obesity measure	Effect estimate/main findings (95% CI)[a]
Huang et al. (29)	Beijing, China	40 cardiovascular disease patients Mean age: 66 years	Age, body mass index, gender time of day, day of week, visit, temperature, and relative humidity	BMI $\geq$ 25	Percent change in SDNN per 51.8 μg/m^3 (4 h) • Normal weight: 1.4% (−1.0, 3.9) • Overweight: −9.3% (−13.0, −5.4) • $P < 0.001$[b]

HRV, heart rate variability; SDNN, standard deviation of normal to normal intervals; RMSSD, root mean square of successive differences; GST, glutathione-S transferase; bpm, beats per minute.
[a]95% confidence interval.
[b]*P*-value for the interaction between $PM_{2.5}$ and body mass index.

elderly men (16) and more than 5,000 elderly adults (22) whereas three smaller studies included patients with CHD (20,29) and an occupational study of male welders (19). Studies of other outcomes were conducted between 1997 and 2010 and included pregnant women, elderly adults, or patients with chronic health conditions such as diabetes or heart disease (Table 3). The largest of these studies included ∼4,000 elderly adults in Germany (28); two others studies included ∼700 elderly men (18,25) and one included ∼1,700 pregnant women (27). The remaining studies were much smaller and contained between 11 and 64 subjects (17,21,23,24,26). Participants in short-term exposure studies were predominantly Caucasian, although one study did not report ethnic origin (20) and one contained Chinese adults (29). Nearly all panel studies used central monitoring sites to assign $PM_{2.5}$ exposures, although dispersion modeling was used for exposure assessment in one study (28) and personal exposures measurements were collected in two studies (19,20).

Heart rate variability. HRV is often used to assess cardiac autonomic regulation in air pollution epidemiology as altered autonomic function (i.e., decreased HRV) is thought to play an important role in determining the cardiovascular health effects of air pollution (30,31). In addition, decreased HRV is known to be associated with an increased risk of cardiovascular morbidity/mortality (32-34). Common HRV parameters include SDNN (standard deviation of all normal-to-normal (NN) intervals) which reflects overall HRV and RMSSD (root mean square of successive differences) and HF (high-frequency) which predominantly reflects parasympathetic modulation of the heart (35).

Schwartz et al. (16) examined the impact of $PM_{2.5}$ on HF in 497 elderly men. In this study, each 10 μg/m^3 increase in 48-h average $PM_{2.5}$ was associated with a 34% (95% CI: −77.9, 96.5) decrease in HF whereas a 7.5% (95% CI: −29.7, 64.3) increase was observed among men who were not obese. The strongest association between $PM_{2.5}$ and HF was among obese men who had the null genotype for the anti-oxidant enzyme glutathione-S transferase M1 (GST-M1), and thus decreased anti-oxidant capacity. While formal tests of effect modification were not presented and estimates were imprecise, findings from this study are consistent with the hypothesis that susceptibility to oxidative stress may play an important role in explaining potential interactions between air pollution and obesity.

Other studies of ambient $PM_{2.5}$, HRV, and obesity are consistent with these findings. For example, Chen et al. (19) reported stronger inverse associations between 4-h average $PM_{2.5}$ exposure and HRV among obese subjects in a small panel of occupationally exposed male welders. Interactions between $PM_{2.5}$ and obesity were not statistically significant with respect to HRV, but investigators noted a stronger positive association between $PM_{2.5}$ and heart rate among obese men and this interaction was statistically significant. Similarly, de Hartog et al. (20) reported statistically significant decreases in HRV among obese patients with CHD in Europe with increases in three-day average $PM_{2.5}$ but did not observe a similar association for the cohort as a whole. Likewise, in a panel of more than 5,000 healthy adults, Park et al. (22) reported that two-day average $PM_{2.5}$ was associated with decreased HRV among obese subjects but not among non-obese subjects. Finally, Huang et al. (29) reported a significant inverse relationship between 4-h moving average exposure to $PM_{2.5}$ and SDNN among overweight Chinese adults but not

TABLE 3 Panel studies of short-term exposure to $PM_{2.5}$, cardiovascular health, and effect modification by obesity

Study	Location	Population	Outcome(s)	Covariates	Obesity measure	Effect estimate/main findings (95% CI)[a]
Zeka et al. (18)	Boston, MA United States	710 elderly men Mean age: 73 years	Fibrinogen, CRP, Sediment rate, white blood cell count	Age, BMI, meteorology, season, heart medication, hypertension, smoking status alcohol consumption, and fasting glucose	BMI $\geq$ 30	Evidence of effect modification by obesity was not observed for $PM_{2.5}$.
Hoffmann et al. (28)	Essen, Bochum, and Mülheim, Germany	4,032 elderly adults Mean age: 60 years	Fibrinogen and CRP	Age, city, area of residence, smoking, ETS, BMI, waist circumference, physical activity, alcohol consumption, and cholesterol.	BMI $\geq$ 30	% Change per 3.91 $\mu g/m^3$ (Annual average) CRP-Men • Obese: 12.0% (−18.7, 54.3) • Non-obese: 28.7% (4.5, 58.5) CRP-Women • Obese: −15.9% (−37, 12.2) • Non-obese:7.0% (−13.2, 32) Fibrinogen-Men • Obese: 1.8% (−5.4, 9.5) • Non-obese: 4.7% (0.4, 9.1) Fibrinogen-Women • Obese: −1.6% (−7.7, 4.9) • Non-obese: 3.1% (−1.1, 7.5)
Dubowsky et al. (17)	St, Louis, MO United States	44 elderly adults Age: $\geq$ 60 years	CRP	Sex, obesity, diabetes, smoking status, temperature, trip, pollen, mould, hour, and vitamin use	BMI $\geq$ 30	Percent change per 6.1 $\mu g/m^3$ (5 days) Obese: 48% (5.3, 109) Non-obese: 12% (−25, 67) *P*-value$<$ 0.05[b]
Schneider et al. (23)	Chapel Hill, NC, United States	22 diabetic adults (Type 2) Mean age: 61 years	IL-6 and RBC count	Meteorology. Within subject factors (e.g. sex, medication use) that did not vary over time were controlled by design.	BMI $\geq$ 30	RBC count decreased with increased $PM_{2.5}$ exposure among obese subjects and a significant interaction between PM2.5 and BMI was observed ($P = 0.012$[b]). Authors also noted a stronger association between $PM_{2.5}$ and IL-6 among obese subjects.
Lee et al. (27)	Allegheny County, PA, United States	1696 pregnant women Age: 14-44 years	CRP	Gestational week, BMI, age, race, education, parity, smoking status, income, season of sample collection, year of enrollment, ETS	BMI $\geq$ 30	Evidence of effect modification by obesity was not observed for $PM_{2.5}$.

TABLE 3. (continued).

Study	Location	Population	Outcome(s)	Covariates	Obesity measure	Effect estimate/main findings (95% CI)[a]
Rich et al. (21)	New Jersey, United States	11 adults with heart failure Median age: 57 years	Right ventricular diastolic pressure	Day of the week, month, meteorology	BMI $\geq$ 30	Change per 11.62 $\mu g/m^3$ (1-day) Obese: 0.27 mmHg (0.14, 0.40) Non-obese: 0.15 mmHg (−0.02, 0.32) *P*-value = 0.22[b]
Zanobetti et al. (25)	Boston, MA, United States	701 elderly men Mean age: 73 years	Arrhythmia (ventricular ectopic beats)	Season, temperature, day of the week, medication, smoking status, diabetes, BMI, and age.	BMI $\geq$ 30	Odds ratio (OR) per 6.89 $\mu g/m^3$ (1 day) Obese: 1.80 (1.24, 2.63) Non-obese: 1.17 (0.95, 1.43) *P*-value<0.05[b]
Schneider et al. (26)	Chapel Hill, NC, United States	22 diabetic adults (Type 2) Mean age: 61 years	Endothelial Function (flow mediated dilation)	Meteorology. Within subject factors (e.g. sex, medication use) that did not vary over time were controlled by design.	BMI $\geq$ 30	The authors noted that participants with high BMI had a greater response to 24-h $PM_{2.5}$ (reduced endothelial function) but this interaction was not statistically significant (*P* = 0.1177)
Delfino et al. (24)	Los Angeles, CA, United States	64 elderly adults with coronary artery disease Mean age: 84 years	Blood pressure	Temperature, posture, activity level, hour, community, and season	BMI $\geq$ 30	Change per 16 $\mu g/m^3$ (1 h) Systolic blood pressure • Obese: 2.20 mmHg (0.42, 3.97) • Non-obese: −0.29 mmHg (−0.97, 0.38) • *P*-value = 0.009[b] Diastolic blood pressure • Obese: 1.01 mmHg (−0.0047, 2.02) • Non-obese: −0.024 mmHg (−0.40, 0.36) • *P*-value = 0.059[b] Change per 16 $\mu g/m^3$ (5-days) Systolic blood pressure • Obese: 7.73 mmHg (2.63, 12.83) • Non-obese: 2.89 mmHg (0.33, 5.44) • *P*-value = 0.097[b] Diastolic blood pressure • Obese: 3.44 mmHg (0.65, 6.24) • Non-obese: 2.05 mmHg (0.65, 3.44) • *P*-value = 0.381[b]

ETS, environmental tobacco smoke; RBC, red blood cell; CRP, C-reactive protein; IL-6, interleukin-6.
[a]95% confidence interval.
[b]*P*-value for the interaction between $PM_{2.5}$ and body mass index.

among normal weight adults. In addition, a significant interaction was observed between BMI and $PM_{2.5}$ with respect to changes in SDNN. Collectively, studies of $PM_{2.5}$, HRV, and obesity suggest that the impact of $PM_{2.5}$ on cardiac autonomic modulation may be stronger among obese subjects.

C-reactive protein. Four studies examined the impact of obesity on the relationship between ambient $PM_{2.5}$ and C-reactive protein (CRP) (17,18,27,28). CRP is a marker of systemic inflammation that is predictive of CHD (36). Dubowsky et al. (17) examined a panel of 44 elderly adults during repeated bus trips through traffic and reported a 48% increase (95% CI: 5.3, 109) in plasma CRP concentrations among obese subjects for each 6.1 $\mu g/m^3$ increase in 5-day average $PM_{2.5}$; a smaller, non-statistically significant association was reported for non-obese subjects and the interaction between $PM_{2.5}$ and obesity was statistically significant. Dubowsky et al. (17) also examined the impact of $PM_{2.5}$ on other markers of inflammation including interleukin-6 (IL-6) and white blood cell counts but did not observe evidence of effect modification by obesity.

Zeka et al. (18) examined the impact of obesity on the relationship between $PM_{2.5}$ and several measures of inflammation and thrombosis including CRP, fibrinogen, sediment rate, and white blood cell count. This study included 710 elderly men but did not report effect estimates for $PM_{2.5}$ across strata of BMI; however, the authors stated that evidence of effect modification by obesity was not observed for $PM_{2.5}$. Similarly, Lee et al. (27) examined a panel of nearly 1,700 pregnant women but did not observe evidence of effect modification by obesity in the relationship between $PM_{2.5}$ and CRP with exposures averaged over 8, 22, or 29-days; however, this study also failed to report effect estimates across strata of BMI. Likewise, a study of more than 4,000 elderly adults in Germany did not observe clear evidence of effect modification by obesity in the relationship between $PM_{2.5}$ and CRP or fibrinogen; however, effect estimates in this study tended to be strongest among non-obese subjects (28).

Blood pressure, ventricular arrhythmia, and other outcomes. The remaining studies examined the impact of obesity on the relationship between $PM_{2.5}$ and cardiovascular health measures such as right ventricular diastolic pressure (21), systemic inflammation (23), blood pressure (24), ventricular arrhythmia (25), and endothelial function (26). Specifically, Rich et al. (21) reported a statistically significant positive association between 24-h average $PM_{2.5}$ and right ventricular diastolic pressure among obese subjects in a panel of adults with heart failure. $PM_{2.5}$ was not associated with right ventricular diastolic pressure among subjects who were not obese but the interaction between obesity and $PM_{2.5}$ was not statistically significant. Conversely, Delfino et al. (24) noted a significant interaction between $PM_{2.5}$ and obesity with respect to systolic blood pressure in a study of elderly adults with CHD with stronger associations observed among obese subjects. Furthermore, Schneider et al. (23) reported a statistically significant interaction between $PM_{2.5}$ and BMI with respect to red blood cell counts in a panel of diabetic adults and also noted stronger positive associations between $PM_{2.5}$ and plasma interleukin-6 (IL-6) among obese subjects. In addition, the same authors reported decreased endothelial function (measured as flow mediated dilation) among obese participants in this panel with increased exposure to $PM_{2.5}$ over a 24-h period; however, this interaction was not statistically significant (26). Finally, Zanobetti et al. (25) reported a significant interaction between obesity and $PM_{2.5}$ with respect to ventricular arrhythmia in elderly men with a significantly increased risk observed among obese men and a smaller non-statistically significant risk observed among men who were not obese.

Supporting evidence of an interaction between obesity and outdoor air pollution

While our comprehensive review of the literature was limited to epidemiological data, it is important to note that experimental evidence from animal models also suggests that obesity may modify the cardiovascular health effects of ambient $PM_{2.5}$. For example, Sun et al. (37) reported increased vascular inflammation and atherosclerosis in response to long-term $PM_{2.5}$ exposure among mice fed a high fat diet relative to mice fed a normal diet. In addition, others have demonstrated that $PM_{2.5}$ increases insulin resistance in rats fed a high fat diet but not in rats fed a normal diet (38); a finding that is consistent with recent epidemiological data suggesting increased diabetes incidence with increased exposure to ambient $PM_{2.5}$ (39). Finally, it is important to note that evidence of an interaction between obesity and air pollution is not limited to $PM_{2.5}$ and cardiovascular health. For example, a recent study in China reported stronger associations between respiratory symptoms and annual average concentrations of nitrogen dioxide (NO_2) (a marker of traffic-related air pollution), ozone (O_3), and sulfur dioxide (SO_2) among overweight and obese children relative to those with a healthy bodyweight (40). Similarly, others have noted stronger inverse relationships between ambient O_3 and lung function among obese adults compared to non-obese subjects (41). In addition, unlike subjects with a healthy BMI, recent evidence suggests that obese patients may not experience attenuations in lung function decline with reductions in ambient air pollution concentrations (42). Collectively, these findings support a broader interaction between air pollution, obesity, and cardiorespiratory health and justify further examination of this potentially important public health issue.

Discussion

Obesity and air pollution are known to have an important impact on public health and both contribute substantially to the global burden of disease (2). However, relatively few studies have examined the complex interplay of these factors and their combined impact on cardiovascular morbidity/mortality. Indeed, because obesity is characterized by decreased oxidant defense (43) and $PM_{2.5}$ is thought to increase oxidative stress (8-10), it is plausible that obese subjects may be more susceptible to the cardiovascular health effects of ambient $PM_{2.5}$. To address this question, we reviewed existing epidemiological data related to the impact of obesity on the cardiovascular health effects of $PM_{2.5}$. To our knowledge, this is the first review to explicitly examine this question.

While the absence of a formal meta-analysis may be viewed as limitation of this investigation, too few studies were available to facilitate meaningful pooling of effect estimates across studies. For example, only three studies examined the impact of obesity on the relationship between long-term exposure to $PM_{2.5}$ and cardiovascular mortality, and each study defined the outcome differently. As a result, it is not clear how one would interpret a pooled estimate

from these studies. Similarly, while four studies examined the impact of obesity on the relationship between $PM_{2.5}$ and plasma CRP, only two reported effect estimates while the others simply stated that evidence of effect modification was not observed. Likewise, three or fewer studies were available for specific measures of HRV and one of these was an occupational study of welders who were likely exposed to $PM_{2.5}$ of different composition than typically monitored in the ambient environment. Therefore, while a formal meta-analysis may help to clarify the impact of obesity on the relationship between $PM_{2.5}$ and cardiovascular morbidity, sufficient evidence is not yet available to support such an assessment.

In general, current epidemiological evidence suggests that obese people may be more susceptible to the cardiovascular health effects of ambient $PM_{2.5}$ as associations tended to be strongest among these subjects. This was true for long-term prospective cohort studies of $PM_{2.5}$ and cardiovascular morbidity/mortality as well as short-term studies of outcomes such as HRV, blood pressure, and ventricular arrhythmias. However, interactions between obesity and $PM_{2.5}$ were not always statistically significant and risk estimate were sometimes imprecise owing to small numbers of subjects within strata for BMI. In addition, existing evidence is largely limited to Caucasians in the United States and only one large cohort study examined the impact of obesity on the relationship between $PM_{2.5}$ and cardiovascular mortality among men. Studies of children are also absent and may be helpful in understanding the early impacts of obesity on the relationship between $PM_{2.5}$ and physiological measures of cardiovascular health. Nevertheless, the consistent pattern of stronger associations among obese subjects across multiple outcomes supports the hypothesis that obesity may modify the impact of $PM_{2.5}$ on cardiovascular health. In particular, all three prospective cohort studies of $PM_{2.5}$ exposure reported a higher risk of cardiovascular mortality among obese subjects after adjusting for a number of potentially important confounding factors (13-15) and one reported a significant trend across strata of BMI (13). Similarly, all four panel studies of $PM_{2.5}$ and HRV reported stronger inverse associations among obese subjects suggesting that obesity may modify the impact of $PM_{2.5}$ on cardiac autonomic modulation (16,19,20,22). Four studies examined the impact of obesity on the relationship between $PM_{2.5}$ and serum concentrations of CRP (17,18,27,28) but only one reported a significant interaction (17). However, two of these studies (18,27) did not report effect estimates across strata of BMI so it is not clear how the magnitudes of associations compared between obese and non-obese subjects. Gauging consistency across studies of other outcomes such as blood pressure, right ventricular diastolic pressure, ventricular arrhythmia, and endothelial function is more difficult as findings for these measures were limited to single studies. However, each of these studies employed appropriate statistical methods to address potential confounding and future studies should aim to replicate these findings to clarify the role of obesity in modifying the impact of $PM_{2.5}$ on acute changes in cardiovascular physiology.

While a number of epidemiological studies were identified that examined the impact of obesity on the relationship between $PM_{2.5}$ and cardiovascular health, few were specifically designed to evaluate potential effect modification by obesity. As a result, analysis of effect modification by obesity was typically conducted as a secondary analysis and power to detect interactions between obesity and $PM_{2.5}$ was likely limited in many studies. Future efforts should consider the detection of effect modification by obesity at the design stage to ensure sufficient statistical power; this may be most feasible in panel studies designed to evaluated specific biological mechanisms. In addition, analysis of effect modification at a finer scale of BMI is also warranted as this would allow clinicians and policy makers to more accurately identify potentially sensitive populations beyond the broad cut-offs currently employed (e.g., above or below BMI = 30 kg/m^2). Furthermore, future studies should explore other quantitative measures of obesity since BMI is known to be an imperfect measure. For example, a recent longitudinal study of obesity reported that BMI was not sensitive to changes in central adiposity over time whereas waist circumference was able to capture this measure (44). Conversely, others have reported that waist-to-hip ratio is associated with circulatory mortality in the elderly whereas similar associations were not observed for BMI or waist circumference (45). In general, potential misclassification of obesity status is an important issue to consider as this may impede the detection of important interactions between air pollution, obesity, and cardiovascular health.

It is important to understand how obesity may influence population susceptibilities to common environmental exposures given the rising prevalence of this condition. In particular, air pollution is of interest owing to the fact that oxidative stress is known to play an important role in air pollution health effects as well as in the underlying pathology of obesity. Indeed, this is an important area of future research as the population health impacts of air pollution could increase with increasing prevalence of obesity even if ambient concentrations remain stable. If confirmed, a robust interaction between obesity and $PM_{2.5}$ may provide clinicians and public health officials with additional justification in promoting the maintenance of a healthy body weight. Moreover, recognition of this susceptibility may provide further impetus to continue efforts to improve air quality. Finally, while further evidence is required, it may be time to consider adding obese citizens to the list of potentially sensitive sub-populations targeted by public health messaging during poor air quality events. O

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References

1. WHO. World Health Organization fact sheet (Number 311) for worldwide prevalence of obesity. 2013. Available online: http://www.who.int/mediacentre/factsheets/fs311/en/ (accessed October 1, 2013).
2. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2224-2260.
3. De Pergola G, Silvestris F. Obesity as a major risk factor for cancer. *J Obes* 2013; 2013:291546.
4. The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effects). Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: A pooled analysis of 97 prospective cohorts with 1.8 million participants. *Lancet* 2014;15:970-983.
5. Matsuda M, Shimomura I. Roles of adiponectin and oxidative stress in obesity-assocaited metabolic and cardiovascular diseases. *Rev Endocr Metab Disord* 2014;15:1-10.
6. Keaney JF, Larson MG, Vasan RS, et al. Obesity and systemic oxidative stress: clinical correlates of oxidative stress in the Framingham Study. *Arterioscler Thromb Vasc Biol* 2003;23:434-439.
7. Youn JY, Siu KL, Lob H, Itani H, Harrison DG, Cai H. Role of vascular oxidative stress in obesity and metabolic syndrome. *Diabetes* 2014; Feb 18 doi: 10.2337/db13-0719. [Epub ahead of print].

8. Araujo JA, Nel AE. Particulate matter and atherosclerosis: Role of particle size, composition and oxidative stress. *Part Fibre Toxicol* 2009;6:24.
9. Li N, Hao M, Phalen RF, Hinds WC, Nel AE. Particulate air pollutants and asthma: A paradigm for the role of oxidative stress in PM-induced adverse health effects. *Clin Immunol* 2003;109:250-265.
10. Weichenthal S, Godri-Pollitt K, Villeneuve PJ. $PM_{2.5}$, oxidant defence and cardiorespiratory health: A review. *Environ Health* 2013;12:40.
11. Wauters A, Dreyfuss C, Pochet S, et al. Acute exposure to diesel exhaust impairs nitric oxide-mediated vasomotor function by increasing endothelial oxidative stress. *Hypertension* 2013;62:352-358.
12. Brochu P, Bouchard M, Haddad S. Physiological daily inhalation rates for health risk assessment in overweight/obese children, adults, and elderly. *Risk Anal* 2013; Oct 22. doi: 10.1111/risa.12125 [Epub ahead of print].
13. Miller KA, Siscovick DS, Sheppard L, et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med* 2007;356:447-458.
14. Puett RC, Hart JE, Yanosky JD, et al. Chronic fine and coarse particulate exposure, mortality, and coronary heart disease in the Nurses' Health Study. *Environ Health Perspect* 2009;117:1697-1701.
15. Weichenthal S, Villeneuve PJ, Burnett RT, et al. Long-term exposure to fine particulate matter: Association with non-accidental and cardiovascular mortality in the agricultural health study cohort. *Environ Health Perspect* 2014; Mar 14. doi:10.1289/ehp.1307277.
16. Schwartz J, Park SK, O'Neill MS, et al. Glutathione-s-transferase M1, obesity, statins, and autonomic effects of particles. *Am J Respir Crit Care Med* 2005;172: 1529-1533.
17. Dubowsky SD, Suh H, Schwartz J, Coull BA, Gold DR. Diabetes, obesity, and hypertension may enhance associations between air pollution and markers of systemic inflammation. *Environ Health Perspect* 2006;114:992-998.
18. Zeka A, Sullivan JR, Vokonas PS, Sparrow D, Schwartz J. Inflammatory markers and particulate air pollution: Characterizing the pathway to disease. *Int J Epidemiol* 2006;35:1347-1354.
19. Chen JC, Cavallari JM, Stone PH, Christiani DC. Obesity is a modifier of autonomic cardiac responses to fine metal particulates. *Environ Health Perspect* 2007;115:1002-1006.
20. de Hartog JJ, Lanki T, Timonen KL, et al. Associations between $PM_{2.5}$ and heart rate variability are modified by particle composition and beta-blocker use in patients with coronary heart disease. *Environ Health Perspect* 2009;117:105-111.
21. Rich DQ, Freudenberger RS, Ohman-Strickland P, Cho Y, Kipen HM. Right heart pressure increases after acute increases in ambient particulate concentration. *Environ Health Perspect* 2008;116:1167-1171.
22. Park SK, Auchincloss AH, O'Neill MS, et al. Particulate air pollution, metabolic syndrome, and heart rate variability: The multi-ethnic study of atherosclerosis (MESA). *Environ Health Perspect* 2010;118:1406-1411.
23. Schneider A, Neas LM, Graff DW, et al. Association of cardiac and vascular changes with ambient PM2.5 in diabetic individuals. *Part Fibre Toxicol* 2010;7:14.
24. Delfino RJ, Tjoa T, Gillen DL, et al. Traffic-related air pollution and blood pressure in elderly subjects with coronary artery disease. *Epidemiology* 2010;21: 396-404.
25. Zanobetti A, Coull BA, Gryparis A, et al. Associations between arrhythmia episodes and temporally and spatially resolved black carbon and particulate matter in elderly patients. *Occup Environ Med* 2014;71:201-207.
26. Schneider A, Neas L, Herbst MC, et al. Endothelial dysfunction: Associations with exposure and ambient fine particles in diabetic individuals. *Environ Health Perspect* 2008;116:1666-1674.
27. Lee PC, Talbott EO, Roberts JM, Catov JM, Sharma RK, Ritz B. Particulate air pollution exposure and C-reactive protein during early pregnancy. *Epidemiol* 2011; 22:524-531.
28. Hoffmann B, Moebus S, Dragano N, et al. Chronic residential exposure to particulate matter air pollution and systemic inflammatory markers. *Environ Health Perspect* 2009;117:1302-1308.
29. Huang W, Zhu T, Pan X, et al. Air pollution and autonomic and vascular dysfunction in patients with cardiovascular disease: interactions of systemic inflammation, overweight, and gender. *Am J Epidemiol* 2012;176:117-126.
30. Zareba W, Nomura A, Couderc JP. Cardiovascular effects of air pollution: What to measure in ECG? *Environ Health Perspect* 2001;109 (Suppl 4):533-538.
31. Simkhovich BZ, Kleinman MT, Kloner RA. Air pollution and cardiovascular injury: Epidemiology, toxicology, and mechanisms. *J Am Coll Cardiol* 2008;52:719-726.
32. Tsuji H, Larson MG, Venditti FJ, et al. Impact of reduced heart rate variability on risk for cardiac events. *Circulation* 1996;94:2850-2855.
33. Liao D, Cai J, Rosamond WD, et al. Cardiac autonomic function and incident coronary heart disease: A population-based case-cohort study. *Am J Epidemiol* 1997;145:696-706.
34. Bigger JT, Fleiss JL, Steinman RC, et al. Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation* 1992;85: 164-171.
35. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. *Circulation* 1996;93:1043-1065.
36. Danesh J, Wheeler JG, Hirschfield GM, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med* 2004;350:1387-1397.
37. Sun Q, Wang A, Jin X, et al. Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model. *JAMA* 2005;294: 3003-3010.
38. Yan YH, Chou CC, Lee CT, Liu JY, Cheng TJ. Enhanced insulin resistance in diet-induced obsess rates exposed to fine particles by instillation. *Inhal Toxicol* 2011;23: 507-519.
39. Chen H, Burnett RT, Kwong JC, et al. Risk of incident diabetes in relation to long-term exposure to fine particulate matter in Ontario, Canada. *Environ Health Perspect* 2013;121:804-810.
40. Dong GH, Qian Z, Liu MM, et al. Obesity enhanced respiratory health effects of ambient air pollution in Chinese children: The Seven Northeaster Cities study. *Int J Obes* 2013;37:94-100.
41. Alexeeff SE, Litonjua AA, Suh H, Sparrow D, Vokonas PS, Schwartz J. Ozone exposure and lung function: Effect modified by obesity and airways hyper-responsiveness in the VA Normative Aging Study. *Chest* 2007;132:1890-1897.
42. Schikowski T, Schaffner E, Meier F, et al. Improved air quality and attenuated lung function decline: Modification by obesity in the SAPALDIA cohort. *Environ Health Perspect* 2013;121:1034-1039.
43. Savini I, Catani MV, Evangelista D, Gasperi V, Avigliano L. Obesity-associated oxidative stress: Strategies finalized to improve redox state. *Int J Mol Sci* 2013;14: 10497-10538.
44. Griffiths C, Gately P, Marchant PR, Cooke CB. A five year longitudinal study investigating the prevalence of childhood obesity: Comparison of BMI and waist circumference. *Public Health* 2013;127:1090-1096.
45. Price GM, Uauy R, Breeze E, Bulpitt CJ, Fletcher AE. Weight, shape, and mortality risk in older persons: Elevated waist hip ratio, not high body mass index, is associated with a greater risk of death. *Am J Clin Nutr* 2006;84:449-460.