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 (PM2.5).

Methods: A PubMed search was conducted in December, 2013 and studies were included if they examined the relationship between PM2.5 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 PM2.5 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 PM2.5 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 PM2.5 on cardiovascular health.

Conclusions: Epidemiological evidence suggests that obesity may increase susceptibility to the cardiovascular health effects of PM2.5. This an important area of research as the public health impacts of air pollution could increase with increasing prevalence of obesity.

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/m2 or more is considered obese while a BMI over 25 kg/m2 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 (PM2.5), 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 PM2.5 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 (PM2.5), obesity, BMI, interaction, effect modification,
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
| 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) |
| 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: 0.85 (0.56, 1.29)  
BMI > 30: 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 ≤ 26.5: 1.35 (0.62, 2.92)  
BMI > 26.5: 2.01 (1.01, 3.98) |
| P-value > 0.05\(^d\)  
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) |

\(^a\)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 PM2.5 and body mass index.
| Study                | Location                                      | Population         | Covariates                                                                                                                                                                                                 | Obesity measure | Effect estimate/main findings (95% CI) |
|----------------------|-----------------------------------------------|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|-------------------------------------|
| Schwartz et al. (16) | Boston MA, United States                      | 497 elderly men   | Age, smoking status, BMI, diastolic blood pressure, fasting blood glucose, alcohol consumption, heart medication, season, and temperature                                                                       | BMI ≥ 30         | Percent change in high frequency    |
| Chen et al. (19)     | Eastern Massachusetts, United States          | 18 male welders   | Age, smoking, eating, and drinking habits, calendar year, exercise, blood pressure, and circadian pattern                                                                                        | BMI ≥ 30         | Change in heart rate (per 1 mg/m³)(4 h) |
| Park et al. (22)     | Maryland, Illinois, North Carolina, New York, and Minnesota, United States | 5465 elderly adults | 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 | 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 ≥ 30         | Change per 10 μg/m³ (3-day)         |

- Percent change in high frequency HRV per 10 μg/m³ (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)

- Change in heart rate per 1 mg/m³ (4 h)
  - Obese: 8.7 bpm (6.3, 11.2)
  - Non-obese: 3.7 bpm (1.4, 5.9)
  - P-value = 0.001

- Percent change in HRV (per 1 mg/m³)(4 h)
  - Obese: 10.3% (−16.7, −3.9)
  - Non-obese: −4.0% (−9.5, 1.5)
  - P = 0.07

- RMSSD
  - Obese: −3.4% (−12.6, 5.9)
  - Non-obese: −0.7% (−8.6, 7.3)
  - P = 0.60

- High frequency
  - Obese: −11.1% (−22.4, 6.2)
  - Non-obese: −7.2% (−22.2, 7.8)
  - P-value = 0.70
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 $\mu$g/m$^3$ increase in 48-h average PM$_{2.5}$ was associated with a 34% (95% CI: 27.7, 96.5) decrease in HF whereas a 7.5% (95% CI: -9.3, -9.3) 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

| Study                  | Location  | Population |
|------------------------|-----------|------------|
| Huang et al. (29)      | Beijing, China | 40 cardiovascular disease patients |
| Age, body mass index, gender, time of day, day of week, visit, temperature, and relative humidity |
| Mean age: 66 years | BMI ≥ 25 | 48-h average PM$_{2.5}$ |
| Covariates            |           |            |
| Obesity measure       |           |            |
| Effect estimate/main findings (95% CI)$^a$ |           |            |
| Percent change in SDNN per 51.8 $\mu$g/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.
| Study          | Location                  | Population | Outcome(s)                                      | Covariates                                                                 | Obesity measure | Effect estimate/main findings (95% CI) |
|---------------|---------------------------|------------|------------------------------------------------|-----------------------------------------------------------------------------|-----------------|----------------------------------------|
| Zeka et al.   | Boston, MA United States  | 710 elderly men | Fibrinogen, CRP, Sediment rate, white blood cell count | Age, BMI, meteorology, season, heart medication, hypertension, smoking status alcohol consumption, and fasting glucose | BMI ≥ 30        | Evidence of effect modification by obesity was not observed for PM$_{2.5}$. |
| Hoffmann et al. | Essen, Bochum, and Mülheim, Germany | 4,032 elderly adults | Fibrinogen and CRP | Age, city, area of residence, smoking, ETS, BMI, waist circumference, physical activity, alcohol consumption, and cholesterol. | BMI ≥ 30        | % Change per 3.91 µg/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% (4.1, 9.1) Fibrinogen-Women • Obese: -1.6% (-7.7, 4.9) • Non-obese: 3.1% (-1.1, 7.5) P-value < 0.05 |
| Dubowsky et al. | St, Louis, MO United States | 44 elderly adults | CRP | Sex, obesity, diabetes, smoking status, temperature, trip, pollen, mould, hour, and vitamin use | BMI ≥ 30        | Percent change per 6.1 µg/m$^3$ (5 days) Obese: 48% (5.3, 109) Non-obese: 12% (-25, 67) P-value < 0.05 |
| Schneider et al. | Chapel Hill, NC, United States | 22 diabetic adults (Type 2) | 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 ≥ 30        | RBC count decreased with increased PM$_{2.5}$ exposure among obese subjects and a significant interaction between PM$_{2.5}$ 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.     | Allegheny County, PA, United States | 1696 pregnant women | CRP | Gestational week, BMI, age, race, education, parity, smoking status, income, season of sample collection, year of enrollment, ETS | BMI ≥ 30        | Evidence of effect modification by obesity was not observed for PM$_{2.5}$, |
| 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          | Right ventricular diastolic pressure | Day of the week, month, meteorology                                        | BMI ≥ 30        | Change per 11.62 µg/m³ (1-day)                                                                                                    |
|                |                         | Median age: 57 years                 |                                     |                                                                             |                 | Obese: 0.27 mmHg (0.14, 0.40) Non-obese: 0.15 mmHg (−0.02, 0.32) P-value = 0.22b |
| Zanobetti et al. (25) | Boston, MA, United States | 701 elderly men                      | Arrhythmia (ventricular ectopic beats) | Season, temperature, day of the week, medication, smoking status, diabetes, BMI, and age. | BMI ≥ 30        | Odds ratio (OR) per 6.89 µg/m³ (1 day)                                                                                           |
|                |                         | Mean age: 73 years                   |                                     |                                                                             |                 | Obese: 1.80 (1.24, 2.63) Non-obese: 1.17 (0.95, 1.43) P-value < 0.05b                                                        |
| Schneider et al. (26) | Chapel Hill, NC, United States | 22 diabetic adults (Type 2)          | 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 ≥ 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 | Blood pressure                      | Temperature, posture, activity level, hour, community, and season           | BMI ≥ 30        | Change per 16 µg/m³ (1 h)                                                                                                        |
|                |                         | Mean age: 84 years                   |                                     |                                                                             |                 | Systolic blood pressure                                                                                                          |
|                |                         |                                     |                                     |                                                                             |                 | • Obese: 2.20 mmHg (0.42, 3.97)                                                                                                  |
|                |                         |                                     |                                     |                                                                             |                 | • Non-obese: −0.29 mmHg (−0.97, 0.38)                                                                                           |
|                |                         |                                     |                                     |                                                                             |                 | • P-value = 0.009b                                                                                                                |
|                |                         |                                     |                                     |                                                                             |                 | Diastolic blood pressure                                                                                                         |
|                |                         |                                     |                                     |                                                                             |                 | • Obese: 1.01 mmHg (−0.0047, 2.02)                                                                                               |
|                |                         |                                     |                                     |                                                                             |                 | • Non-obese: −0.024 mmHg (−0.40, 0.36)                                                                                           |
|                |                         |                                     |                                     |                                                                             |                 | • P-value = 0.059b                                                                                                                |
|                |                         |                                     |                                     |                                                                             |                 | Change per 16 µg/m³ (5-days)                                                                                                    |
|                |                         |                                     |                                     |                                                                             |                 | Systolic blood pressure                                                                                                         |
|                |                         |                                     |                                     |                                                                             |                 | • Obese: 7.73 mmHg (2.63, 12.83)                                                                                                 |
|                |                         |                                     |                                     |                                                                             |                 | • Non-obese: 2.89 mmHg (0.33, 5.44)                                                                                              |
|                |                         |                                     |                                     |                                                                             |                 | • P-value = 0.097b                                                                                                                |
|                |                         |                                     |                                     |                                                                             |                 | Diastolic blood pressure                                                                                                         |
|                |                         |                                     |                                     |                                                                             |                 | • Obese: 3.44 mmHg (0.65, 6.24)                                                                                                  |
|                |                         |                                     |                                     |                                                                             |                 | • Non-obese: 2.05 mmHg (0.65, 3.44)                                                                                              |
|                |                         |                                     |                                     |                                                                             |                 | • P-value = 0.381b                                                                                                                |

ETS, environmental tobacco smoke; RBC, red blood cell; CRP, C-reactive protein; IL-6, interleukin-6.
a95% confidence interval.
bP-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 µg/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 cardiorespiratory 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 body weight (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$_{2.5}$ 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.

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