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Perspective

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Ozone Exposure, Cardiopulmonary Health, and Obesity: A Substantive Review

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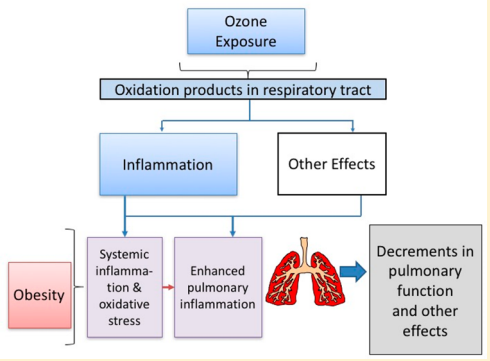
Supporting Information

ABSTRACT: From 1999−2014, obesity prevalence increased among adults and youth. Obese individuals may be uniquely susceptible to the proinflammatory effects of ozone because obese humans and animals have been shown to experience a greater decline in lung function than normal-weight subjects. Obesity is independently associated with limitations in lung mechanics with increased ozone dose. However, few epidemiologic studies have examined the interaction between excess weight and ozone exposure among adults. Using PubMed keyword searches and reference lists, we reviewed epidemiologic evidence to identify potential response-modifying factors and determine if obese or overweight adults are at increased risk of ozone-related health effects. We initially identified 170 studies, of which seven studies met the criteria of examining the interaction of excess weight and ozone exposure on cardiopulmonary outcomes in adults, including four short-term ozone exposure studies in controlled laboratory settings and three community epidemiologic studies. In the studies identified, obesity was associated with decreased lung function and increased inflammatory mediators. Results were inconclusive about the effect modification when data were stratified by sex. Obese and overweight populations should be considered as candidate at-risk groups for epidemiologic studies of cardiopulmonary health related to air pollution exposures. Air pollution is a modifiable risk factor that may decrease lung function among obese individuals with implications for environmental and occupational health policy.



INTRODUCTION

Obesity prevalence has been on the rise among adults in the U.S. (Figure 1). Approximately two-thirds of the U.S. adult population were overweight or obese in 2010.[1] The study of community air pollution and ozone exposures has not accounted for the rise in obesity prevalence. Scientific investigations of the respiratory effects of obesity spanning the past 40 years have reported that obesity and overweight conditions have a direct negative effect on respiratory well-being in addition to cardiovascular health, and these changes could have a direct effect on received dose and response to ozone (Figure 2).[2−7] Understanding the effect of ozone exposures among adults with excess weight is important because the obesity problem is spreading around the globe with high calorie diets, sedentary lifestyles, and aging populations at a time when air pollution is increasingly adding to the global burden of disease.[8]

Most ozone exposure studies, however, do not account for how the increased prevalence of obesity or overweight status modifies the relationship between air pollution and cardiopulmonary health in the general population. Time series epidemiologic methods that examine death certificates or hospital admissions data do not provide direct information on patients' weight and other anthropometric measures. Previous controlled ozone exposure laboratory, panel, and cohort studies do not reflect today's increased prevalence of obesity. The National Institute of Health (NIH) defines obese a body mass index (BMI) of 30 kg/m^2 or greater and overweight as adults with a BMI of 25−29.9 kg/m^2.[9] According to NHANES data, in 2013−2014, the age-adjusted prevalence of obesity in the U.S. was 37.7% (95% CI, 35.8%, 39.7%); among men, obesity prevalence was 35.0% (95% CI, 32.8%, 37.3%); and among women, it was 40.4% (95% CI, 37.6%, 43.3%).[10]

Ozone exposure has long been shown to reduce air flow and volume on a short-term basis (e.g., as measured by forced expiratory volume in one second (FEV_1)) in mainly normal weight healthy adults.[11,12] Epidemiologic studies have shown that chronic reduction in FEV_1 is a powerful marker of future morbidity and cardiovascular mortality in the general population.[13,14] Ozone exposures are associated with increased respiratory hospitalizations and mortality.[15−19] Accordingly, the U.S. Environmental Protection Agency (EPA) has judged the relationships between short-term (e.g., hours, days, weeks) exposure to ozone and respiratory morbidity to be causal.[11] Moreover, EPA has judged the relationship between long-term (e.g., months to years) ozone exposures and respiratory effects, cardiovascular disease, central nervous system effects, and total

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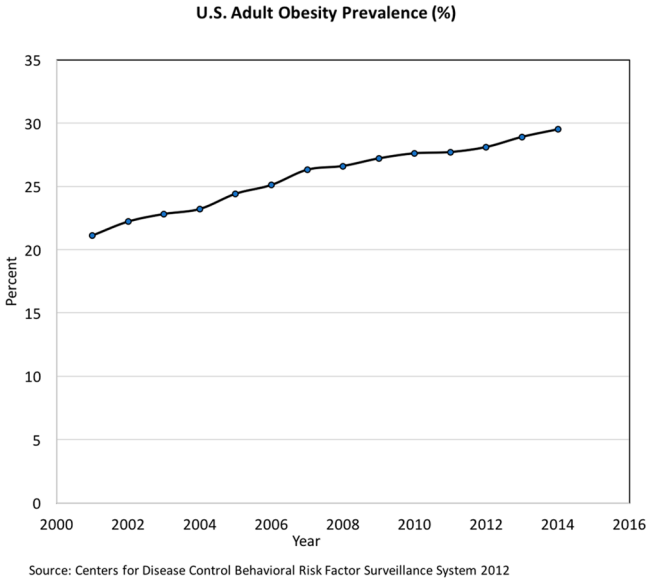

Figure 1. Obesity prevalence among adults has increased since the early 2000s in the U.S. based on Behavioral Risk Factor Surveillance System data.[72]

mortality as "likely causal."[11] In the EPA's 2015 review of the science related to the national ambient air quality standards for ozone, EPA designated at-risk populations for these effects as shown in Table 1 (80 *Federal Register* 65291, October 26, 2015).

EPA's 2015 review of at-risk populations considered ozone exposure studies from 2006 to July 2012 from the perspective of the Clean Air Act.[20] Although EPA's approach to at-risk populations characterized the available air pollution studies, the review did not consider other relevant biomedical evidence about the effects of obesity or overweight status from a population health perspective or the pulmonary health of overweight and obese groups, as summarized in Table 2. Moreover, evidence from animal models suggests that obese individuals may be susceptible to proinflammatory and oxidative stress injury of air pollution.[21,22]

Independently from air pollution exposure effects, pulmonary function is known to decline with increased abdominal adiposity or BMI, which may increase susceptibility to ozone-related effects.[5,23−25] In the U.S., adults generally gain weight as they age, which may predispose them for worse outcomes from air pollution exposures than seen in previous epidemiologic studies.[5] The increased mass of the chest wall in obese individuals reduces compliance and respiratory muscle endurance, which increases the work of breathing.[26,27] Obese and overweight adults with increased abdominal fat mass may have less functional residual capacity than healthy-weight adults.[5] Reduced lung volume contributes to closure of gas exchange units and ventilation-perfusion mismatching resulting in arterial hypoxemia and trapping of CO_2.[3,28,29] These abnormalities contribute to inflammation, the pathogenesis of asthma, obstructive sleep apnea, and other respiratory diseases.[6,30−32] Although there are obese individuals with healthy lung function, the literature documenting the respiratory status of obese and overweight populations suggests they are compromised compared to normal-weight adults, and as a result, obese people may experience a chronic inflammatory state.

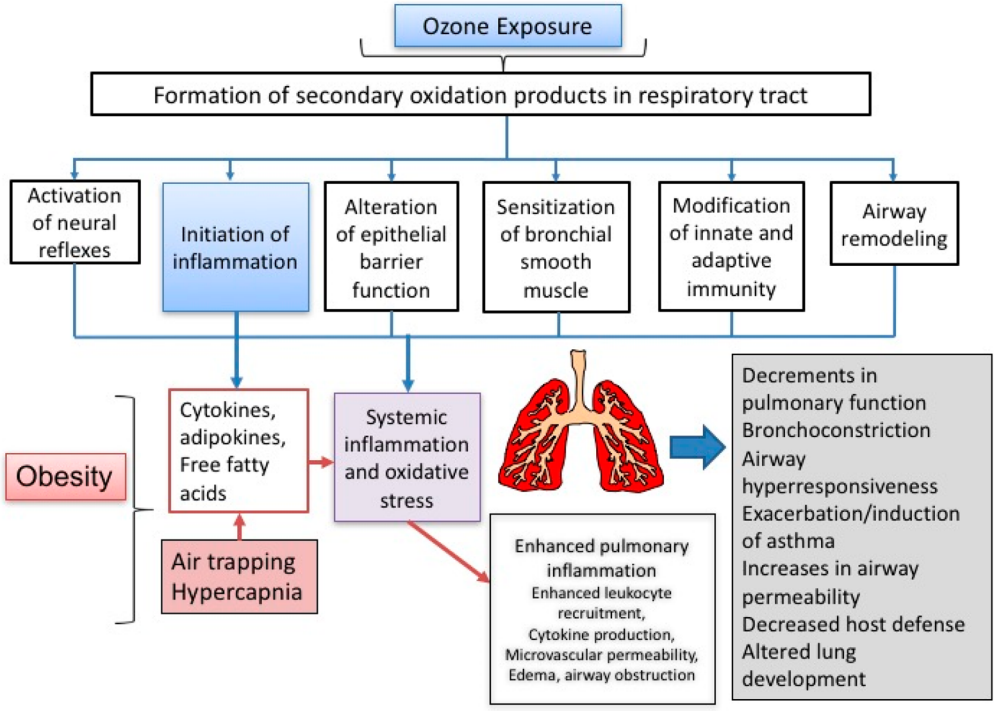

Figure 2. Overview of ozone exposure and obesity on inflammation and oxidative stress in the lung. When the respiratory system is challenged by ozone (O_3), particulate matter (PM), allergens, or bacteria, cytokines generated in the lungs (TNF-α, IL-1β, and IL-6), and LPS from disseminated bacteria can enhance the production of proinflammatory mediators released systemically by adipose tissue. The augmentation of systemic inflammation in the obese can enhance pulmonary inflammatory responses by enhancing leukocyte recruitment, cytokine production, microvascular permeability, and edema, which could potentially increase airway obstruction in preexisting lung disease.[44]

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Table 1. U.S. Environmental Protection Agency's Designated At-Risk Populations for Ozone Air Pollution (2015)[a]

category of evidence	population
adequate evidence	asthmatics
	children under 18 years
	older adults at and above 65 years
	populations with poor diets with nutritional (antioxidant or vitamin) deficiencies
	outdoor workers
suggestive evidence	obese populations[b]
	populations with genetic markers
	women
	populations of low socioeconomic status
inadequate evidence	patients with the following:
	chronic obstructive pulmonary disease
	cardiovascular disease
	diabetes
	hyperthyroidism
	influenza and other respiratory infections
	racial groups
	smokers
evidence of no effect	
not assessed	overweight populations[b]
	pregnant women
	outdoor athletes

[a]Note: Data are adapted from U.S. Environmental Protection Agency Integrated Science Assessment for Ozone (2012), Section 8.5, Tables 8–4.[11] [b]NIH defines obese a BMI of 30 kg/m^2 or greater and overweight as adults with a BMI of 25–29.9 kg/m^2.[9]

Furthermore, experiments in animal models have shown that the pulmonary inflammatory response elicited by ozone exposure is enhanced in obese animals, which suggests that obese humans compared to nonobese individuals may be at risk of more adverse effects of air pollution.[21,33−37] Enhanced pulmonary inflammation and injury have been shown with short-term ozone exposure in genetic and diet-induced obese mice.[21,33−35,37−41] Higher levels of proinflammatory cytokines and chemokines (IL-6, CXCL1, MIP-2, MCP-1) have also been observed in obese animals following ozone exposure.[21] Additional studies have investigated the role of diet and sedentary behavior on ozone exposure responses.[42,43]

A similar enhanced inflammatory response has been observed in obese human populations following ozone exposure. This response may augment bronchoconstriction, airway hyperreactivity, and mucus secretion, reducing the patency of conducting airways.[44] Additionally, obese people may possess a greater number of peripheral blood leukocytes, which are known to contribute to pulmonary inflammation following exposure to ozone.[45] Proinflammatory mediators may be produced locally in the lung or may accumulate in the lung with the leakage of plasma fluid following disruption of the alveolar epithelium.[44] Higher levels of proinflammatory cytokines and adipokines have also been reported in the serum of obese subjects, which might contribute to greater airway inflammation.[46,47]

One of the underlying pathologies of obesity has been hypothesized to be linked to a chronic state of oxidative stress and impaired oxidant defense.[48] Ozone mediates some of its adverse effects through oxidative stress; thus, antioxidant nutritional status may affect the risk of ozone-related health effects.[49] In addition, individuals with reduced dietary intake of vitamins E and C are at increased risk for ozone-related health effects.[20] Thus, poor diets associated with obesity might also be a factor.

Other air pollution literature about particulate matter exposures have highlighted enhanced responsiveness to cardiac end points with excess weight.[50] Finally, emerging evidence suggests that improvements in particulate matter air pollution do not offer corresponding improvements for obese adults' lung function.[51]

For all these reasons, we hypothesized that people with excess weight would be more reactive to the same ambient concentration of ozone. To test our hypothesis, we reviewed the epidemiological literature to identify potential response-modifying factors to determine if obese adults are at increased or decreased risk of health effects from ozone exposures. We also examined differences by sex in these associations.

MATERIALS AND METHODS

To identify epidemiology studies addressing the interaction between air pollution and obesity/overweight status on respiratory system effects, keyword and reference lists searches using PubMed were conducted using keywords, medical headings, and medical subject headings from three groups connected with "AND":

(1) air pollution or air pollutants, adverse effects and
(2) obesity, body mass index, adiposity and
(3) lung function tests; lung, drug effects; lung, growth, and development.

Conducted on December 1, 2015 and updated on August 29, 2016 and March 14, 2017, the search was restricted to studies published in English in the past 10 years and where the study subjects were adults. We searched for studies published since 2006 to be consistent with the 2015 EPA national ambient air quality standards review and integrated science assessment.

This search initially identified 170 studies; abstracts were reviewed for ozone exposure among adults and a cardiopulmonary outcome. Studies within the past 10 years were then examined for information about the effect of both weight and ozone exposure among adults regarding a cardiopulmonary function. We excluded studies which controlled for BMI or other measures of obesity as an independent predictor of lung function but did not evaluate an interaction between excess weight and ozone. Physiological and biomedical studies of obese adults and ozone exposure studies in humans and animal models were reviewed for factors related to obese and overweight status that may modify the relationship between both short-term and long-term ozone exposure and health effects.

RESULTS

Of the 170 studies identified, four studies were excluded because the subjects were children,[52−56] and 159 were excluded because they did not examine the interaction of obesity and air pollution. Many excluded studies examined BMI as a covariate but did not analyze the interaction of BMI and ozone exposure. As shown in Table 3, seven studies met the criteria of examining the interaction of excess weight and ozone exposure on health outcomes in adults.[57−63] They can be divided into controlled ozone exposure human studies in laboratories and community studies. Two of the community cross-sectional studies examined cardiovascular end points in the same Chinese study population.[61,63]

All studies used BMI as a quantitative measure of obesity, and one included waist circumference as a secondary selection criterion, and measured percent body fat by bioelectric impedance analysis although these measures were not analyzed

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Table 2. Summary of Evidence that Obese Populations are At-Risk for Ozone Exposure[a]

at-risk population criterion	summary of evidence
(1) higher exposures	not likely a factor
(2) higher dose for given ambient concentration	BMI associated with graded increases in the estimated total lung dose of fine particulates in children[73b]
	increased minute ventilation[3,6,73]
	more work to maintain appropriate levels of circulating oxygen in their bloodstreams[28,74]
	increased oxygen consumption[3]
	stiffening of the chest wall and increasing the mechanical work of breathing[3,4,6,28]
	airway closure and gas exchange deficiencies in obese populations[3,29]
	dyspnea at rest in obese men[75]
	obese individuals are less efficient and need to exert more due to the increased work of breathing and reduced cardiovascular fitness compared to normal weight people; the increased respiratory rate would increase the dose[76]
(3) more responsive to same dose	among healthy nonsmoking women, enhanced FEV_1 decrements following ozone exposure in the overweight/obese category (BMI $\geq$ 25) compared with the normal weight women although not in men[59,65b]
	enhanced pulmonary inflammation and injury with short-term ozone exposure in genetically and dietarily obese mice[21,33,34,77b]
	in healthy normal-weight adults, increased BMI associated with enhanced FEV_1 responses to ozone[60b]
	greater decline in FEV_1 and FVC in the obese than in the nonobese white elderly men associated with short-term ozone exposure. Three-way interaction trend test demonstrated a multiplicative effect of airway hyper-responsiveness (AHR) and obesity factors[57b]
	obese individuals may be uniquely susceptible to the proinflammatory effects of ozone since obese humans and animals have been shown to experience a greater decline in lung function than normal weight subjects[21,35,39,57b]
	higher levels of proinflammatory cytokines and chemokines (IL-6, CXCL1 (KC), MIP-2, MCP-1) have been observed in obese animals following ozone exposure[21b]
	increased responses to short-term ozone in obese db/db mice compared to wild-type controls[37−39]
	evidence of effect modification for ozone exposures and cough and phlegm but not wheeze or asthma for annual ozone[52]
	additional evidence of obese individuals' susceptibility to proinflammatory effects of ozone since obese humans and animals have been shown to experience a greater decline in lung function than normal weight subjects[35,39,44]
	obese may possess a greater number of peripheral blood leukocytes known to contribute to pulmonary inflammation following exposure to ozone[43]
	proinflammatory mediators may be produced locally in the lung or may accumulate in the lung with the leakage of plasma fluid following disruption of the alveolar epithelium[44]
	higher levels of proinflammatory cytokines and adipokines reported in the serum of obese subjects, which might contribute to greater airway inflammation[35,78]
	elevations in systemic acute phase proteins such as C-reactive protein, known to be elevated in the obese following PM exposure, may also contribute to greater pulmonary inflammation[78,79]
	suggestive evidence of lack of recovery of obese groups compared with normal weight groups from improvements in air pollution from PM exposures[80]
(4) population-based perspective: diminished pulmonary function	obesity and overweight conditions have direct negative effect on respiratory well-being in addition to cardiac health[2−7,63]
	increased fat mass and increasing BMI reduces lung volumes and FEV_1[81]
	weight gain reduces lung function in healthy overweight and obese adults[5,28]
	subjects who gained the most weight over 10 years lost the most lung function[5]
	in 8-year study of adults in which lung function changes (FVC, FEV_1, and vital capacity) decreased with increasing BMI quartiles[24]
	abdominal obesity was strongly associated with lung function impairment in study of more than 150 000 adults examining metabolic syndrome (a cluster of cardiovascular risk factors)[82,83]
	inverse relationship between multiple measures of fatness with both spirometry and static lung volumes[84]

[a]Abbreviations: body mass index (BMI); forced expiratory volume in one second (FEV_1); forced vital capacity (FVC); forced expiratory flow at 25−75% of FVC ($FEF_{25-75\%}$); interleukin (IL); chemokine (C-X-C motif) ligand 1 (KC); polymorphonuclear (PMN); eosinophils (Eos); tumor necrosis factor alpha (TNF-α); U.S. Environmental Protection Agency (EPA). [b]Evidence considered by U.S. EPA Integrated Scientific Assessment for Ozone.[11]

further.[58] The controlled human studies generally reported a positive interaction between obesity and ozone exposure with increasing FEV_1 responsiveness, with the exception of one retrospective analysis of 40 adults reporting no interaction.[64] The one longitudinal cohort study among older men reported a greater decline in lung function among the obese group.[57]

Most studies reported *p*-values for effect modification across strata, with one study reporting a three-way interaction trend test among ozone, obesity, and airway hyper-responsiveness.[57] The community epidemiologic studies used a variety of ozone exposure metrics including short-term and long-term exposure metrics. In the Boston study, a mean of ozone measurements 48 h prior to the exam, averaged across four local monitors using EPA protocols was selected after an assessment of averages of measurements on 1−5 days prior to exam.[57] In the long-term exposure studies in China, researchers used the 3-year annual average ozone (removing outliers) from a central monitor within 1 km of participants' homes in 33 northeastern Chinese cities. Compared to U.S. ambient levels, the Chinese study assessed significantly higher ozone concentrations: the Chinese 3-year mean was 1.2589 ppm (SD 0.35856) compared to Boston's 48 h average of 0.0244 ppm (SD 0.011). As a point of reference, the U.S. EPA set the 2015 national ambient air quality standards for ozone at 0.070 ppm maximum 8 h average (80 Federal Register 65291, October 26, 2015).

DISCUSSION

Weight gain has been shown to reduce lung function in healthy overweight and obese adults.[28] In a cohort study of healthy subjects, the quartile who gained the most weight over 10 years compared to the lowest quartile had the largest decrease in forced vital capacity (FVC) and FEV_1.[5] Thus, increased obesity

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Table 3. Effect Modification by Obesity and Overweight of Ozone Exposure Studies[a]

study and location	study design and population	covariates	obesity measure	ozone measure	outcomes	main findings effect estimates (95% CI)
Controlled Human Exposure Studies						
Bennett et al. 2007[59]	controlled human exposure study	age, sex	BMI, men (range 19.1−32.9 kg/m^2), women (range 15.7−33.4 kg/m^2)	short-term: exposed to 0.42 ppm ozone for 1.5 h with intermittent exercise designed to produce a minute ventilation of 20 l/min/m^2 body surface area (BSA)	lung function	BMI was positively related to greater acute spirometric response to controlled ozone exposure. In women, ozone-induced decrements in pulmonary function increased with increased weight across three categories (p-value trend ≤ 0.22 for four outcomes). A weaker, nonsignificant relationship was observed among men.
North Carolina (1992−1998)	197 nonasthmatic young adults (aged 18−35 years, 122 males, 75 females)	Independent of the modeling, checks of confounding by lung volume, tidal volumes, and breathing frequency were also performed.			%ΔFEV$_1$	A one unit increase in BMI was associated with a greater response to ozone exposure of 0.580% ΔFEV$_1$ (p = 0.014). Among women, one unit increase in BMI was associated with a 0.716 unit decrease in %ΔFEV$_1$ following ozone dose (p = 0.044). Among men, a one unit increase in BMI was associated with a 0.533 decrease in %ΔFEV$_1$ (p = 0.11).
					%ΔFVC	A one unit increase in BMI was associated with a 0.288 decrease %ΔFVC following ozone dose (p = 0.038).
					%ΔFEF$_{25-75}$	A one unit increase in BMI is associated with a decrease of 0.952% ΔFEF$_{25-75}$ (p = 0.008). Among women, a one unit increase in BMI was associated with a decrease of 1.336% ΔFEF$_{25-75}$ (p = 0.012).
					FEV$_1$/FVC	A one unit increase in BMI was associated with a decrease of 0.259 ratio FEV$_1$/FVC (p = 0.050).
					FEF$_{25-75}$/FVC	A one unit increase in BMI was associated with a decrease of 0.732 FEF$_{25-75}$/FVC (p = 0.023).
Bennett et al. 2016[58]	double blinded random crossover controlled human exposure study with attempt to match group composition by race	age, race	BMI and waist circumference (WC)	short-term: exposed to 0.4 ppm ozone for 2 h with intermittent exercise and rest designed to produce a minute ventilation of 20−30 l/min using Lifeshirt vest	%ΔFEV$_1$	Ozone-induced decrements in obese versus normal-weight participants not significant (p = 0.11). Mean %ΔFEV$_1$ (SD) among obese 15.9 (8.6) and among normal-weight group 11.7 (7.1).
North Carolina (date not specified)	38 nonasthmatic nonsmoking young women (aged 18−35 years)		Normal (n = 19) defined as BMI ≤ 25 kg/m^2 and WC ≤ 29.5 in. Obese (n = 19) defined as BMI range 30−40 kg/m^2 and WC ≥ 35 in.		%ΔFVC	mean (SD) among obese 12.5 (7.5) and among normal-weight group 8.0 (5.8) (p < 0.05)
					cough frequency and severity	Ozone-induced cough frequency increased among normal weight (p < 0.01) but not among obese participants. Mean (SD) cough frequency was low and did not differ between groups: obese 2.6 (5.4) (p > 0.05) and among normal-weight group 4.9 (6.5).
					methacholine reactivity, inspiratory capacity (IC), and sGAW (specific airway conductance)	Ozone-induced differences in obese versus normal-weight participants not significant. Mean IC among obese 16.7 (14.2) and among normal-weight group 10.2 (13.2) (p = 0.12). Mean sGAW among obese 12.6 (26.2) and among normal weight group 12.4 (21.0), not significant.
					plasma IL-6	Ozone-induced plasma IL-6 was increased in both groups (p < 0.005) and more pronouncedly among obese versus normal-weight participants at 4 h (p interaction < 0.006) and returned to normal at 20 h.

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Table 3. continued

study and location	study design and population	covariates	obesity measure	ozone measure	outcomes	main findings effect estimates (95% CI)
Controlled Human Exposure Studies						
					plasma CRP, leptin, IL-1β, IL-8, TNF-α	Ozone-induced changes were not observed in obese or normal-weight participants.
					sputum PMN	Ozone-induced increases were not observed in obese or normal-weight participants. Some evidence of trend among obese for ozone versus air treatment using Wilcoxon matched pairs sign rank test (p = 0.11).
					sputum IL-6	Ozone-induced increases among normal weight but not among obese participants.
					sputumIL-1β, IL-8, TNF-α	Ozone-induced increases were not observed in obese or normal-weight participants.
McDonnell et al. 2009[60]	meta analysis of 15 controlled human exposure studies	age, stratified by ozone exposure pattern	BMI (mean 23.41 kg/m^2)	short-term: exposures ranged from 0.04−0.12 ppm for 6.6 h with intermittent exercise	%ΔFEV$_1$	Increasing BMI was associated with increasing FEV$_1$ responsiveness (beta 0.4855 (95% CI 0.1018, 0.8693, p-value 0.013). Inclusion of BMI in the model resulted in individual predicted values within 0.3% of FEV$_1$ decrement.
North Carolina and Davis, CA (1981−1992)	541 healthy normal weight young adults (aged 18−35 years, 90 females)	Sex was available but not included in final model.				
Todoric et al. 2014[62]	retrospective analysis of existing controlled human trial; Spearman correlations; regression analysis	age, ethnicity, sex, asthma status	BMI (14 of 40 subjects were overweight, BMI $\geq$ 25 kg/m^2, (mean 24.1, range 21.8−27.5 kg/m^2)	short-term: 0.4 ppm, averaging time not listed	% predicted FEV$_1$, FVC	no significant correlation between BMI and change in % predicted FVC or FEV$_1$ with ozone exposure
North Carolina	40 adults (31 healthy, 9 with allergic asthma)			measurements compared baseline either 2 days or 2 weeks before controlled ozone exposure and then 4 h (spirometry, sputnum and blood) and 24 h (for sputnum and blood)	delta IL-1β, delta IL-6, and delta IL-8	BMI was positively associated with sputum IL-1β 24 h after controlled ozone exposure (r = 0.5, p = 0.004) but not either IL-6 or IL-8.
					delta IL-1β	BMI was weakly correlated with change in sputum IL-1β (Spearman correlation R = 0.4, p = 0.03) and in blood (Spearman correlation R = 0.7, p = 0.003) after 24 h. A one unit increase in BMI was associated with 20 pg/mL increase in sputum IL-1β with ozone exposure.
					sputnum %ΔPMN	No correlation between BMI and change in sputum % ΔPMN (p = 0.30) or %Eos (p = 0.09) with ozone exposure.
					serum %ΔPMN	Serum %PMNs significantly increased (p < 0.01), and % Eos decreased (p = 0.01) with ozone exposure.
Community Studies						
Alexeeff et al. 2007[57]	longitudinal cohort study	age, race, smoking status, lifetime smoking pack years, chronic diseases, airway hyperresponsiveness (AHR)	BMI (mean 27.8, SD 3.7 kg/m^2)	short-term: 2-day mean (mean 24.4, SD 11.0)	lung function	Greater declines in %ΔFEV$_1$ and %ΔFVC are observed in the obese than in the nonobese white elderly men associated with short-term ozone exposure. Three-way interaction trend test demonstrated a multiplicative effect of AHR and obesity factors.
Greater Boston area (1995−2005), Veterans Administration Normative Aging Study cohort	904 elderly mainly white men				%ΔFEV$_1$	For each 15 ppb increase in ozone, obese participants had a greater decrease in %ΔFEV$_1$ than nonobese (−2.63% (−3.85, −1.39) vs −1.15% (−1.91,- 0.39), interaction p < 0.05).
					%ΔFVC	For each 15 ppb increase in ozone, obese participants had a greater decrease in %ΔFVC than nonobese (−2.05% (−3.17, −0.919) vs. −1.18% (−1.88, −0.48), interaction not significant).

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Table 3. continued

study and location	study design and population	covariates	obesity measure	ozone measure	outcomes	main findings effect estimates (95% CI)
Community Studies						
Zhao et al. 2013[63]	cross-sectional epidemiologic study	age, race, gender, education, income, smoking, drinking, exercise, diet, sugar, family history of hypertension, and district	BMI (normal weight n = 14, 646; overweight n = 8, 764; obese n = 1, 435)	long-term: annual arithmetic mean ozone from central monitor within 1 km of participants' homes in 11 NE Chinese cities mean 49.4 $\mu g/m^3$ (SD 14.07, range 27−71 $\mu g/m^3$)	prevalence of hypertension	Interaction between weight status and ozone exposure was observed among males (p = 0.041) and all participants (p < 0.001), but not among females (p = 0.177).
33 communities in three northeastern Chinese cities (2006−2008)	24 845 adults (aged 18−74, 50.1% male)					Odds ratio (OR) increased with increasing weight category. For a 22 $\mu g/m^3$ increase in ozone, a lower OR of hypertension among normal weight 1.05 (0.99, 1.13) was reported, compared to among overweight 1.19 (1.10, 1.28), and among obese 1.24 (1.03, 1.49).
						Males: OR increased with increasing weight category. For a 22 $\mu g/m^3$ increase in ozone, the OR of hypertension among normal weight males was 1.10 (1.01−1.21), among overweight 1.24 (1.13−1.37), and among obese 1.49 (1.15−1.93).
						Females: For a 22 $\mu g/m^3$ increase in ozone, the OR for hypertension among normal weight females was not significant: 0.94 (0.85−1.04), among overweight 1.07 (0.95−1.21), or among obese 0.89 (0.67−1.18).
					systolic blood pressure (SBP)	Ozone exposure was positively associated with higher systolic and diastolic BP and increasing BMI. The relationship was stronger for systolic BP than diastolic BP, and among all participants and males, but not among females.
					systolic blood pressure (SBP)	Change increased with increasing weight category. For a 22 $\mu g/m^3$ increase in ozone, among normal weight, SBP increased 0.34 (−0.11, 0.79), among overweight 1.72 (1.08, 2.33), and among obese subjects 3.46 (1.77, 5.14)
						Males: Change increased with increasing weight category. For a 22 $\mu g/m^3$ increase in ozone, among normal weight males, SBP increased 0.34 (−0.11, 0.79), among overweight 1.72 (1.08, 2.33), and among obese subjects 3.46 (1.77, 5.14)
						Females: Among all three weight categories, SBP changes were not significant.
					diastolic blood pressure (DBP)	For a 22 $\mu g/m^3$ increase in ozone, among normal weight participants, DBP increased 0.29 (0.02, 0.56), among overweight 0.35 (−0.02, 0.72), and among obese subjects 1.31 (0.36, 2.27)
						Males: For a 22 $\mu g/m^3$ increase in ozone, among normal weight males, DBP increased 0.67 (0.27, 1.07), among overweight 0.65 (0.15, 1.14), and among obese subjects 1.94 (0.64, 3.22)
						Females: Among all three weight categories, DBP changes were not significant.
Qin et al. 2015[61]	cross-sectional epidemiologic study	age, race, gender, education, income, smoking, drinking, exercise, diet, sugar, family history of hypertension and district	BMI (normal weight n = 14, 646, overweight n = 8, 764, obese n = 1, 435)	long-term: annual arithmetic mean ozone from central monitor within 1 km of participants' homes in 11 NE Chinese cities mean 49.4 $\mu g/m^3$ (SD 14.07, range 27−71 $\mu g/m^3$)	self-reported stroke	Being overweight or obese modified the effects of ozone on self-reported stroke. Effect estimates were stronger among obese compared to normal and overweight categories (interaction p = 0.002). When stratified by gender, interaction between ozone and BMI category was statistically significant among women (p = 0.046) but not among men (p = 0.501).

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Table 3. continued

study and location	study design and population	covariates	obesity measure	ozone measure	outcomes	main findings effect estimates (95% CI)
Community Studies						
33 communities in three northeastern Chinese cities (2006–2008)	24 845 adults (aged 18–74, 50.1% male)					For a 22 $\mu g/m^3$ increase in ozone, a higher OR of stroke among normal weight 0.98 (0.82, 1.18), compared to among overweight 1.29 (1.05, 1.59), and among obese 1.47 (0.83, 2.59).
						Males: OR were not different by binary weight category. For a 22 $\mu g/m^3$ increase in ozone, the OR of stroke among normal weight males was 1.15 (0.93–1.44), among overweight/obese 1.30 (0.99–1.77).
						Females: For a 22 $\mu g/m^3$ increase in ozone, the OR for stroke among normal weight females was not significant: 0.88 (0.63–1.21) but was significant among overweight/obese 1.36 (1.02–1.80).
					self-reported cardiovascular disease	Being overweight or obese modified the effects of ozone on self-reported CVD. Effect estimates were stronger among obese compared to normal and overweight categories but did not reach statistical significance at 95% confidence level (interaction $p = 0.121$).
						For a 22 $\mu g/m^3$ increase in ozone, a lower OR of hypertension among normal weight 1.08 (0.8, 1.135) and among overweight 1.08 (0.86, 1.35), compared to among obese 1.56 (1.02, 2.39).
						When stratified by gender, a two-category weight effect modification was not significant.

[a]Abbreviations: airway hyperresponsiveness (AHR), body mass index (BMI); cardiovascular disease (CVD); diastolic blood pressure (DBP); eosinophils (Eos); forced expiratory volume in one second (FEV_1); forced vital capacity (FVC); forced expiratory flow at 25–75% of FVC ($FEF_{25-75\%}$); interleukin (IL); polymorphonuclear (PMN); odds ratio (OR); systolic blood pressure (SBP); tumor necrosis factor alpha (TNF-α); U.S. Environmental Protection Agency (EPA); $\mu g/m^3$ micrograms per cubic meter.

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prevalence contributes to the poor respiratory health of the general adult population. The altered physiological and proinflammatory states typical of obese populations may place an additional burden on their cardiac and respiratory systems from air pollution exposure. Experimental evidence from animal models also supports that obesity modifies the association between ozone exposure and cardiorespiratory health via inflammation[34] and oxidative stress.[22]

Evaluating pulmonary susceptibility is complicated, however, because obesity is a complex metabolic condition that influences many systems and results in a variety of comorbidities (e.g., hypertension, asthma) that may also affect respiratory health. In the seven human subject studies identified, increased BMI was associated with ozone-related decreased lung function and increased inflammatory mediators. Controlled ozone exposure studies in human subjects provided the strongest evidence that the ozone-induced decrement in lung function is greater in the obese group compared to normal weight participants.[58,60] Results from a longitudinal cohort study supported this finding; however, the subjects were mainly older white males.[57] In the larger Chinese cross-sectional studies, greater positive associations with cardiovascular outcomes were reported for obese than normal-weight participants for long-term relatively higher ozone concentrations (mean 3-year average ozone level of 1.26 ppm).

There is evidence that obese populations receive an increased dose of ozone for the same ambient concentration (Table 2). In controlled air pollution exposure studies among human subjects, researchers can control the dose. In the four studies identified in this review, researchers assigned exposures to known doses of ozone in laboratory-controlled settings among generally healthy nonsmoking adult volunteers. Researchers administered known concentrations of ozone via chamber or facemask exposures and used exercise and body surface area to calculate and control target ventilation. This controlled exposure study design allowed for direct causal inference, control over confounding by copollutants, and assignment of the received dose of ozone to construct dose−response curves. The investigators collected detailed anthropomorphic information, such as body weight and percent body fat measurements, controlled for age, asthma status, smoking, and sex, and used a relatively large sample size. In general, for the ozone-induced effect, subjects served as their own control; investigators compared outcomes with the ozone dose to outcomes with a filtered air exposure. A further advantage was that the lung function measurements were well documented using standardized, reproducible techniques.

While significant insights were gained from controlled human exposure studies, three of the studies were not originally designed to evaluate the potential effect modification by obesity. Thus, few obese subjects were included, and the analysis of effect modification by BMI was typically conducted as a secondary analysis. As a result, BMI may more appropriately be interpreted as differences in body size among normal individuals rather than the effect of obesity on the relationship between ozone dose and lung function. A notable exception was the Bennett et al. 2016 study, which was designed to examine the effect of obesity on ozone exposure effects among healthy nonsmoking women with 0.4 ppm short-term ozone exposures. Future research should consider the detection of effect modification by obesity and overweight status of the ozone dose−response relationship over a wider range of concentrations, averaging times, and types of subjects.

While there are significant advantages to controlling ozone exposure in a laboratory setting, the pattern may deviate significantly from ambient exposure patterns. Another limitation is that chamber study subjects differ from the general population and are generally healthier, younger, and nonsmoking. Thus, insights from community epidemiologic studies augment these inherent limitations. In community studies, fuller ozone exposure patterns are evaluated among larger populations including a broader spectrum of health, lung function, and disease status. Community studies are especially important in studying ozone exposures because of the heterogeneous responses to ozone including presence of weak responders and smaller response among those older than 35 years.[65] Strengths of the Normative Aging Study included its study design, long follow-up period, well-characterized spirometry outcomes, control of known confounders, and the quality of the short-term ozone measurements.[57] Strengths of the Chinese studies included the large sample size with significant numbers of overweight (n = 8 764) and obese (n = 1 435) participants with a broad age and air pollution range.[54,63] Limitations of the Chinese studies included lack of temporality between the exposure and outcome; ozone exposure misclassification; selection bias (e.g., healthy subjects were more likely to participate); and information bias (e.g., recall bias and self-reported end point, the use of prevalence rather than incidence of hypertension). Because of a moderate correlation between ambient ozone and particulate matter concentrations in the study districts, there may also be confounding by particulate matter, which is more strongly associated with cardiovascular outcomes.[50]

In general, few studies examined the interaction of excess weight and ozone exposure. The studies generally reported greater lung function decrements associated with ozone at increased weight categories. However, the results were inconclusive about effect modification when data were stratified by sex; these results are consistent with primary evidence (not examining the interaction with excess weight) about potential differences by sex in ozone exposure epidemiologic studies of respiratory hospital admissions.[66,67] In general, after multiple exposures over a period of days, individuals have lower responses to ozone.[68−70] However, young women lose ozone-responsiveness with multiple exposures to ozone three-times faster than young men, although in middle age, men and women lose responsiveness at the same rates.[65] In addition, Vancza et al. reported small strain-dependent differences in effects by sex in adult mice with respect to pulmonary inflammation and injury after ozone exposure, with adult females generally more at risk. Lactating female mice incurred the greatest lung injury and inflammation among several strains of mice.[71] However, some toxicological studies found some strains exhibiting greater risk in males. Thus, although experimental studies have provided potential biological plausibility for potential sex differences for the effect of ozone exposure on lung function, the results of these limited number of studies are inconclusive.

While the absence of a formal meta-analysis of the epidemiologic studies may be viewed as a limitation of this review, too many differing study designs and too few studies were identified to facilitate meaningful pooling of effect. However, the McDonnell et al. study provides a set of equations for researchers to test new controlled human subject data as they become available.[60]

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CONCLUSION

The pulmonary inflammatory response elicited by ozone is enhanced in obese animals, which suggests that obese humans may be at increased risk of adverse effects of air pollution. Because obese and overweight populations exhibit limitations in pulmonary function and receive a greater dose of ambient pollution, the extent to which exposure to ozone induces adverse effects should be directly evaluated in additional studies. However, the current evidence generally supports a positive effect of excess weight on the relationship between ozone and lung function. There is a suggestion of a positive interaction for cardiac end points; however, the results by sex are inconclusive in cross-sectional studies. If confirmed, an interaction between excess weight and enhanced ozone response may provide public health advocates and clinicians with additional reason to promote the maintenance of a healthy body weight and diet.

The World Health Organization estimated that approximately 2.3 billion adults worldwide in 2015 were overweight.[32] As obesity prevalence increases, there is increasing uncertainty as to how well the principal studies used to calculate end points in risk assessment, economic benefit assessment, or burden of disease calculations represent the impacts with respect to obese or overweight adult and elderly populations. In addition, while further evidence is required, recognition of this susceptibility could help regulators to designate obese populations as at-risk populations under the Clean Air Act for consideration in standard setting and public health warnings for air pollution.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.chemrestox.7b00077.

Brief description of each ozone and obesity study in the review (PDF)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. P.D.K. wrote most of the first draft of the manuscript with portions written by P.M. Both of the authors contributed to the analysis and interpretation of data and editing of the final draft.

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Notes

The authors declare no competing financial interest.

ABBREVIATIONS

BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; $FEF_{25-75\%}$, forced expiratory flow at 25−75% of FVC; IL, interleukin; PMN, polymorphonuclear; Eos, eosinophils; SBP, systolic blood pressure; TNF-α, tumor necrosis factor alpha; EPA, U.S. Environmental Protection Agency; $\mu g/m^3$, micrograms per cubic meter

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