**Associations of Long-term Particulate Matter and Ozone Air Pollution Exposures
with Pulmonary Function:
Does Excess Weight Increase Risk of Enhanced Decrements?**

by

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DEDICATION

With all my heart to my husband, Dr. Richard Norton, and to our sons, Will and Jake

Norton.

I am sincerely grateful to my husband, for holding my hand every day. We passed that milestone during this period where we have been together longer than I've been alive by myself, and I am absolutely a better person with you. I would never have made it through without you by my side. I am also so thankful to and proud of our sons. I do regret, however, that you often had to come home to a dark house. Thank you for picking up the slack in every way big and small: for shopping for groceries, cooking meals, taking yourself to dentist appointments, for doing homework without help or asking someone else, for staying out of trouble, and for finding friendship in each other. I missed your first steps working to reduce air pollution, and now I missed your last steps in our home working on this degree. I know your steps have always been your own, and thank you for letting me share a part of your path. Thank you for putting up with this and reassuring me that you understood.

Through this process, l reminded myself how to fail gloriously and get back up, and I learned that I am never too old to become anew. As my centenarian Aunti Jo said, "Honey, you're just getting started." I hope that is true.

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ABSTRACT

Background: Few studies evaluate how long-term air pollution exposures affect lung function among young adults. Data from existing epidemiologic and toxicologic studies support the hypothesis that obese adults' lung function responds more negatively to long-term air pollution exposure compared to non-obese adults.

Methods: 5,026 Black and White participants in the Coronary Artery Risk Development In Young Adults Study (CARDIA), aged 18 to 30 years in 1985-86, provided lung function measurements, demographic and clinical data, and were followed 2, 5, 10 and 20 years later. Using air quality monitoring data and residential history, for each participant we estimated one long-term average exposure over the period of study attendance for particulate matter (PM_{10}) and ozone. We fit linear mixed effects models to estimate associations between long-term air pollution and level and rate of change per year in forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and FEV_1/FVC, adjusting for confounders. We examined effect modification by obesity status using body mass index (BMI) $\geq$ 30.0 kg/m^2.

Results: An increase of 10 $\mu g/m^3$ in long-term (1984-2006) PM_{10} exposure was associated with a decreased rate of change in FEV_1 of 1.7 ml per year of followup (p-value 0.04) and a decrease in level of FVC of 56.0 ml (p-value 0.04). Associations with rate of change were stronger among women than men. No associations were observed

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between long-term PM_{10} exposure and FEV_1/FVC, nor between long-term ozone exposures and any lung function measure, for all participants. For the most part, obesity status did not modify the association between long-term PM_{10} and ozone exposures and FEV_1, FVC, or FEV_1/FVC. Only ozone associations with FEV_1 and FVC differed by obesity status as participants aged.

Conclusions: In CARDIA, long-term PM_{10} exposures were associated with decreases in lung function but ozone exposures were not. We did not observe effect modification in level by obesity status; however, BMI and obesity status are imprecise measures. Research with more precise obesity and exposure estimation and different designs in CARDIA and other cohorts is needed to understand how air pollution exposure may affect pulmonary health in young adults as they age and gain weight.

CHAPTER I

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

Summary

Background: Exposures to ozone are associated with adverse respiratory effects including changes in lung function as measured by forced expiratory volume in one second (FEV_1) in healthy adults, respiratory symptoms, new-onset asthma, respiratory and total mortality, cardiovascular disease, and central nervous system effects. Obese individuals may be uniquely susceptible to the pro-inflammatory 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 and increased ozone dose. With over 78 million adults in the U.S. classified as obese, there is widespread potential for exposure to ozone air pollution among obese population. However, few epidemiologic studies examine the interaction between excess weight and ozone exposure among adults.

Objectives: To identify potential response-modifying factors to determine if obese adults are at increased risk of ozone exposure-related health effects.

Methods: We reviewed epidemiologic evidence to identify potential response-modifying factors and to determine if obese or overweight adults are at increased or decreased risk of ozone-related respiratory health effects.

Results: Using PubMed and reference lists, keyword searches initially identified 169 studies, which were then examined for information about the effect of both weight and ozone exposure among adults regarding a respiratory function within the past 10 years. Six studies met the criteria of examining the interaction of excess weight and ozone exposure on health outcomes in adults, including three short-term ozone exposures in controlled laboratory settings. Two of the community cross-sectional studies examined cardiovascular endpoints. Two additional studies examining the obesity and long-term ozone exposure interaction among children were excluded.

Discussion: The pulmonary inflammatory response elicited by ozone exposure is enhanced in obese animals and suggests that obese humans may be at risk of a more adverse effect of air pollution. Previous analyses did not examine physiological data from a population perspective. In the epidemiologic studies identified, increased Body Mass Index (BMI) was associated with decreased lung function and increased inflammatory mediators. Results were mixed about the effect modification when data were stratified by sex.

Conclusions: The data evaluated in this review suggest that obese and overweight populations should be considered as candidate at-risk groups for protection from air pollution both in risk communication and standard settings with implications for environmental and occupational health policy.

Background and Motivation for Research

The impact of air quality exposure on human health is an important public health issue, and the obesity epidemic may be complicating our understanding. Under the Clean Air Act, the U.S. Environmental Protection Agency (EPA) is tasked with setting standards to protect sensitive populations with an adequate margin of safety. EPA finalized the particulate matter national ambient air quality standards (PM NAAQS) in December 2012 and the ozone NAAQS in December 2015 (78 *FR* 3086, 80 *FR* 65291, 79 *FR* 75233).

As part of the standards setting process, EPA's Administrator identifies and takes into account which populations are at risk (Sacks et al. 2011; U.S. EPA 2009, 2012a; Vinikoor-Imler et al. 2014). Designating sensitive populations is one of the key actions in EPA's reviews of NAAQS. It conveys whom the standards will protect with an adequate margin of safety. The law directs the EPA Administrator to address the margin of safety by considering the nature and severity of the health effects, the size of sensitive population at risk, and the uncertainties about the data (42 U.S.C. Section 7401, 77 *FR* 126, Friday, June 29, 2012, p. 38895). Thus, appropriately identifying sensitive populations goes to the very heart of the public health protection afforded by the air quality standards.

One of the candidate sensitive populations considered in EPA's recent reviews is obese people. According to the National Center for Health Statistics, many Americans are obese and overweight, comprising about two-thirds of the U.S. adult population in 2008 (Flegal and Carroll 2002; Institute of Medicine 2012) and their numbers are projected to grow (Finkelstein et al. 2012). The National Institute of Health (NIH) defines obese as

having a body mass index (BMI) of 30 kg/m^2 or greater. Similarly, NIH defines "overweight" as adults with a BMI of 25 – 29.9 kg/m^2. Both the increased prevalence of obesity and the tendency of Americans to gain weight as they age have important implications for the standard setting, implementation and planning including health advisories, and future research.

However, the information to date is incomplete about whether obese adults satisfy the criteria as a sensitive at-risk population. In its reviews, EPA listed candidate susceptible populations and evaluated the evidence, examining short-term and long-term exposure effects, and cardiac and pulmonary effects among others. In sum, based on the criteria, EPA presents four ways to consider a sensitive population for consideration in the margin of safety:

- A group experiences higher exposures of pollution;
- A group receives a higher dose for a given ambient concentration due to greater inhalation rates, deposition in the lung, or other factors;
- A group responds more to the same dose as compared to the general population; or
- A group as a population has a diminished reserve pulmonary function and, therefore, would be at increased risk to further insult from pollution or other factors.

Research Objectives and Document Organization

The purpose of this research was to provide evidence that can be used to better understand and describe candidate groups of at-risk populations: namely non-elderly adults and adults with excess weight. We also examined differences by sex in these associations.

This research is divided into three sections. In the first chapter, using the at-risk population framework, I described the hypotheses in more detail and conducted a literature review of the effect modification by obesity and overweight status on the

association of ozone exposure on cardiopulmonary health in adults in community studies and in controlled laboratory experiments.

In Chapter 2, I estimated air quality exposure data which was added to an existing cohort to test hypotheses. Specifically, I estimated PM_{10} and ozone long-term (1984-2006) air pollution exposures based on residential history for participants in the Coronary Artery Risk Development in Young Adults (CARDIA) study. I assigned air pollution exposure using the inverse distance weighted average of the 12 nearest air pollution community monitors within a 200-mile radius. I examined longitudinally the relationship among PM_{10} and ozone exposures with lung function (forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and the ratio FEV_1/FVC) in non-elderly adults. FVC reflects total lung compliance, which encompasses both the lung and the chest wall. The FEV_1 incorporates these factors plus airway resistance. In a healthy population, the decrease in elasticity with age affects FEV_1 more than FVC, resulting in a decrease in the FEV_1/FVC ratio over time (Lin and Lin 2012).

The Chapter 2 hypotheses were that long-term PM and ozone exposures are negatively associated with FEV_1 and FVC and positively associated with FEV_1/FVC among non-elderly adults. I also hypothesized that with increased age, long-term PM and ozone exposures are more negatively associated with FEV_1 and FVC and more positively associated with FEV_1/FVC among non-elderly adults. I hypothesized that these associations would be stronger among women (Thyagarajan et al. 2008). Our hypotheses are supported by data from controlled ozone exposures on human subjects (Brown et al. 2008; McDonnell 2010), toxicologic data for ozone and particulate matter, and epidemiologic data for ozone and particulate matter (Adam et al. 2015; Alexeeff et al.

2007; Downs et al. 2007; Gauderman et al. 2015; U.S. EPA 2009, 2012a). Our Chapter 2 study focused on the long-term study mean (1984- 2006) association of air pollution with average lung function during the study among all participants.

In Chapter 3, I tested additional hypotheses in the CARDIA cohort regarding the effect of obesity status. The primary goal was to characterize the extent to which obesity among non-elderly adults modified the association between air pollution and pulmonary function metrics. The dissertation is organized following the three-manuscript model. Each aim is structured to answer a unique set of research questions and assess strengths and limitations.

Ozone Exposures, Obesity and Cardiopulmonary Health

Short-term and long-term exposures to ozone pollution are associated with adverse respiratory effects. Ozone exposure has long been shown to reduce air flow and volume of lung function on a short-term basis (e.g., as measured by forced expiratory volume in one second (FEV_1)) in mainly normal weight healthy adults (Götschi et al. 2008; U.S. EPA 2012a). Epidemiologic studies have shown that chronic reduction in FEV_1 is a powerful marker of future morbidity and cardiovascular mortality in the general population (Sin et al. 2005; Young et al. 2007a). Ozone exposures are associated with increased respiratory hospitalizations and mortality (Katsouyanni et al. 2009; Medina-Ramón and Schwartz 2008; Silverman and Ito 2010; Tolbert et al. 2007; Zanobetti et al. 2008). Accordingly, the U.S. Environmental Protection Agency (EPA) judges the relationships between short-term (e.g., hours, days, weeks) exposure to ozone and respiratory morbidity to be causal (U.S. EPA 2012a). EPA has judged the relationship between long-term (e.g., months to years) ozone exposures and respiratory

effects (including respiratory symptoms, new-onset asthma, and respiratory mortality), cardiovascular disease, central nervous system effects and total mortality as "likely causal" (U.S. EPA 2012a). EPA designated at-risk populations for these effects as shown in Table 1.1.

Existing ozone exposure studies, however, generally 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. According to NHANES data, obesity prevalence in 2007-2008 was 33.8 percent (95% CI 31.6 – 36.0 percent) (Flegal & Carroll, 2002), representing a greater than 100 percent increase from 1976-1980 and a 50 percent increase from 1988-1994 (Finkelstein et al., 2012). Approximately two-thirds of the U.S. adult population were overweight or obese in 2010 (Ogden et al. 2013).

Thus, 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 (Mathers and Loncar 2006). 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 (Chen et al. 1993; Lin and Lin

2012; Naimark and Cherniack 1960; Salome et al. 2010a; Thyagarajan et al. 2008; Wang and McCabe 1997).

A previous comprehensive review of at-risk populations considered ozone exposure studies from 2006 to July 2012 but did not consider other relevant biomedical evidence about the effects of obesity from a population health perspective (Vinikoor-Imler et al. 2014). Overweight status was not evaluated. Despite the limitations of direct studies of ozone exposure and excess weight on respiratory health, the pulmonary status of overweight and obese groups is well characterized and this contributes to the reasons to hypothesize that excess weight would amplify the response to air pollution, including evidence of enhanced dose with excess weight and decreases in lung function with excess weight independent of air pollution exposures, as summarized in Table 1.2. Moreover, evidence from animal models suggests that obese individuals may be susceptible to pro-inflammatory and oxidative stress injury of air pollution.

Obese populations receive a greater dose of ozone for the same ambient concentrations compared to other populations (Gidding et al. 2004; Hurewitz 1985; Lin and Lin 2012; Naimark and Cherniack 1960; Parameswaran et al. 2006; Sahebjami 1998; Salome et al. 2010a). Compared to normal weight individuals, obese individuals have increased tidal volumes, increased energy cost of breathing, a stiffening of the chest wall, and increased mechanical work of breathing (Lin and Lin 2012; Naimark and Cherniack 1960; Parameswaran et al. 2006; Salome et al. 2010a). Obese individuals are less efficient and exert more effort due to the increased work of breathing and reduced cardiovascular fitness. Dyspnea has been observed among obese men at rest (Sahebjami 1998). Increased BMI is also associated with increased minute ventilation (Bennett and

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Zeman 2004; Lin and Lin 2012; Salome et al. 2010a). Among adults, Brochu and colleagues have reported inhalation values between 75th and 99th percentiles of body mass index (BMI) in males aged 16.5 to <35 years, 35 to <45years, 45 to <65 years old varying from 26.92 to 50.55 m^3/day, 30.33 to 47.52 m^3/day, and 24.63 to 32.24 m^3/day, respectively (Brochu et al. 2014). As a consequence, the increased respiratory rate would increase the dose of polluted air (Brochu et al. 2014; Gidding et al. 2004). This has been observed in children in which graded increases in the estimated total lung dose of fine particulates has been positively associated with BMI (Bennett and Zeman 2004).

In addition to receiving a higher dose and independently from air pollution exposure effects, pulmonary function declines with increased abdominal adiposity or BMI (Bottai et al. 2002b; Collins et al. 1995; De Leon et al. 2003; Thyagarajan et al. 2008). 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 among elderly populations (Thyagarajan et al. 2008). For example, the increased mass of the chest wall in obese individuals reduces compliance and respiratory muscle endurance, which increases the work of breathing (Babb et al. 2008; Ochs-Balcom et al. 2006). As a population, obese and overweight adults with increased abdominal fat mass may have less functional residual capacity than healthy weight adults (Thyagarajan et al. 2008). Reduced lung volume contributes to closure of gas exchange units and ventilation-perfusion mismatching resulting in arterial hypoxemia and trapping of CO_2 (Lin and Lin 2012; Parameswaran et al. 2006; Sood 2010). These abnormalities contribute to inflammation, the pathogenesis of asthma, obstructive sleep apnea, and other respiratory diseases (Canoy et al. 2004; Chen et al. 2007; McClean et al. 2008; Salome et al. 2010b).

Although there are obese 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.

The pulmonary inflammatory response elicited by ozone exposure is enhanced in obese animals and suggests that obese humans may be at risk of a more adverse effect of air pollution (Johnston et al. 2006a; Rivera-Sanchez et al. 2004; Shore et al. 2003, 2009; Shore 2008; Williams et al. 2013). Enhanced pulmonary inflammation and injury has been shown with short-term ozone exposure in genetic and diet induced obese mice (Johnston et al. 2008; Shore et al. 2003, 2009; Shore 2008) (Johnston et al. 2010; Lu et al. 2006; Rivera-Sanchez et al. 2004) . Higher levels of proinflammatory cytokines and chemokines (IL-6, KC, MIP-2, MCP-1) have also been observed in obese animals following ozone exposure (Shore et al. 2003).

Enhanced inflammatory responses are observed in obese human populations following ozone exposure. This response may augment bronchoconstriction, airway hyperreactivity and mucus secretion, reducing the patency of conducting airways (Mancuso 2010). Obese people may possess a greater number of peripheral blood leukocytes known to contribute to pulmonary inflammation following exposure to ozone (Kim and Park 2008). 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 (Mancuso 2010). Higher levels of proinflammatory cytokines and adipokines are reported in the serum of obese subjects, which might contribute to greater airway inflammation (Johnston et al. 2006b; Visser et al. 1999a). 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

(Dubowsky et al. 2006; Dye et al. 2015a; Visser et al. 1999a).

One of the underlying pathologies of obesity is hypothesized to be linked to a chronic

state of oxidative stress and impaired oxidant defense(Dye et al. 2015b). Ozone mediates

some of its adverse effects through oxidative stress; thus, antioxidant nutritional status

may affect the risk of ozone-related health effects (Romieu et al. 2009). People with

reduced dietary intake of vitamins E and C are at increased risk for ozone-related health

effects (Vinikoor-Imler et al. 2014). Thus, poor diets associated with obesity might also

be a factor.

Other air pollution literature with particulate matter exposures highlights enhanced

responsiveness to cardiac endpoints with excess weight (Weichenthal et al. 2014). In

addition, emerging evidence suggests that improvements in particulate matter air

pollution does not offer corresponding improvements for obese adults' lung function

(Schikowski et al. 2013a).

For these reasons, we hypothesize that people with excess weight would be more

reactive to the same ambient concentration of ozone. We reviewed epidemiological

evidence to identify potential response-modifying factors to determine if obese adults are

at increased or decreased risk of health effects from ozone exposures.

Methods

To identify epidemiology studies addressing the interaction between air pollution

and obesity/overweight status on respiratory system effects, keyword and reference lists

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searches using PubMed were conducted using the key words, 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, the search was restricted to studies published in

English in the past 10 years and where the study subjects were adults.

This search initially identified 169 studies, which were then examined for ozone

exposure among adults and a respiratory system outcome. 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

Using PubMed and reference lists, keyword searches initially identified 169

studies, which were then examined for information about the effect of both weight and

ozone exposure among adults regarding a respiratory function within the past 10 years.

Four studies were excluded because the subjects were children, and 159 were excluded

because they did not examine the interaction of obesity and air pollution. Some studies

included BMI as a covariate but did not analyze the interaction of BMI and ozone

exposure. As shown in Table 1.3, six studies met the criteria of examining the interaction

of excess weight and ozone exposure on health outcomes in adults (Alexeeff et al. 2007;

Bennett et al. 2007; McDonnell 2010; Qin et al. 2015; Todoric et al. 2015; Zhao et al.

2013), including three short-term ozone exposures in controlled laboratory settings. Two of the community cross-sectional studies examined cardiovascular endpoints in the same Chinese study population (Qin et al. 2015; Zhao et al. 2013). Four additional studies examining the obesity and long-term ozone exposure interaction among children were excluded and are not discussed here due to differences about studying effect modification of excess weight among growing children versus adults (Calderón-Garcidueñas et al. 2015; Dong et al. 2013, 2015; Le et al. 2012; Lu et al. 2013b). We excluded studies which controlled for BMI as an independent predictor of lung function but did not evaluate an interaction between excess weight and ozone.

The studies summarized in Table 1.3 were conducted in the U.S. and China. All studies used BMI as a quantitative measure of obesity. In other studies of particulate matter, alternative adiposity variables such as waist circumference and waist-to-hip ratio have been used to measure obesity (Park et al. 2010; Weichenthal et al. 2014).

Most studies in this review reported p-values for effect modification across strata, with one study reporting a three-way interaction trend test among ozone, obesity and airway hyperresponsiveness (AHR)(Alexeeff et al. 2007). The community epidemiologic studies used a variety of ozone exposure metrics, including a short-term and long term-exposure metrics. In the Boston study, a mean of ozone measurements 48-hour prior to the exam, averaged across 4 local monitors using EPA protocols was selected after an assessment of 1 to 5 days prior to exam (Alexeeff et al. 2007). 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. The Chinese study assessed significantly higher ozone concentrations. The

Chinese 3-year mean was 1.2589 ppm (SD 0.35856) compared to Boston 48-hour

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 of 0.070 ppm maximum 8-hour average,

acknowledging suggestive evidence of the obese constituting an at-risk population.

The studies identified in this review can be divided into controlled ozone exposure

human studies in laboratories and community studies.

Controlled Ozone Exposure Studies in Human Subjects

In Bennett et al. (2007), 197 non-asthmatic non-smoking young adults from North

Carolina aged 18 to 35 were exposed to standardized dose with exertion. Of these, 57

subjects (42 men and 15 women) were categorized as overweight or obese (BMI ≥ 25

kg/m^2). BMI was positively related to greater response to 0.42 ppm ozone for 90 minutes

with intermittent exercise. Previous publications about this study population indicated no

gender differences in response to ozone, controlling for age, and a repeatable unexplained

stratification of strength of response (Hazucha et al. 2003). In the more recent Bennett et

al. publication, obesity and overweight status explains some of the difference in

responsiveness to ozone dose by change in standard BMI categories among all

participants, and the effect modification of BMI was stronger and more significant

among young women than young men. Controlling for age, BMI was negatively

associated with a larger decrement of $\%\Delta FEV_1$ (beta -0.580 (p-value = 0.014)), $\%\Delta FVC$

(beta -0.288 (p-value = 0.038)), $\%\Delta FEF_{25-75}$(beta -0.952 (p-value =

0.008)), $\%\Delta FEV_1/\%\Delta FVC$ (beta -0.259 (p-value = 0.050)), $\%\Delta FEF_{25-75}/\%\Delta FVC$ (beta -

0.732 (p-value = 0.023)). The effect of BMI on ozone responsiveness among women was

most pronounced for ΔFEF_{25-75} (p<0.05).

A reanalysis of 22 combined controlled exposure human subject datasets (n=541) was consistent with Bennett et al. (2007), reporting that BMI was positively associated with enhanced ozone-induced FEV_1 decrement (McDonnell 2010). Sixteen controlled human ozone exposure studies were conducted in the U.S. EPA exposure facility in Chapel Hill, NC mainly during 1981-1992, and six controlled human ozone exposure studies conducted at the laboratory at the University of California at Davis, with roughly equal numbers of men and women. The mean BMI in the combined dataset was 23.41 kg/m^2. A nonlinear random effects model was fit with and without BMI as a covariate. In the study, increasing BMI was associated with increasing FEV_1 response to ozone among 18-35 year old healthy males. Specifically, a one unit increase in BMI was associated with a 0.4855 (95% CI 0.1018, 0.8693) larger decrease $\%\Delta FEV_1$ at a given ozone dose (p=0.13). The addition of BMI to the model resulted in modest changes in individual predicted FEV_1, with most being within +/- 0.3 of a percentage point of FEV_1 decrement. Among young volunteers, there was no evidence of an interaction between age and BMI or confounding by other factors.

In contrast, the Todoric et al. (2015) retrospective study reported no significant correlation between BMI and ozone-induced decrements in FEV_1 or FVC. The retrospective analysis included subjects who underwent a baseline exam followed by a 0.4-ppm ozone exposure, and a 24-hour follow up of additional spirometry, sputum induction and blood collection. Eighteen of the 40 healthy subjects (aged 20 – 28.7 years) were overweight (BMI $\geq$ 25 kg/m^2) and none were obese, with an average BMI of 24.1 kg/m^2 (21.8 – 27.5 kg/m^2). Baseline and post-exposure sputum and blood samples were evaluated for changes in percentage of polymorphonuclear leukocytes (%PMN),

percentage of eosinophils (%Eos), IL-1β, IL-6 and IL-8. IL-1β is an important mediator of the inflammatory response. Cytokines were measured using multiplex technology. The study suggests that airway and systemic inflammation after ozone exposure, measured by IL-1β, is positively correlated with BMI in human subjects. For all subjects, controlling for sex, age, ethnicity and asthma status, a one unit increase in BMI was associated with a 20 pg/mL increase in sputum (p=0.02). BMI was significantly associated with IL-1β but not with other measures of inflammation such as %PMN, %Eos, IL-6 or IL-8 in humans after ozone exposure. This study suggests that NLRP3 inflammasome activation or priming with IL-1β is uniquely involved in ozone-induced BMI-related inflammation in human subjects.

Community Ozone Studies

The Normative Aging Study

As part of the Veterans Administration Normative Aging Study, started in 1963, enrolling 2,280 men in the Greater Boston area (Alexeeff et al. 2007). This longitudinal study included a subset of 904 mainly white elderly men whose pulmonary function and body measurements were taken every three years between 1995 and 2005. A subject was considered to have airway hyper-responsiveness (AHR) with a positive response to methacholine challenge of more than a 20% decline in FEV_1 in the most recent testing available from testing conducted from 1984 and 2000. About 23 percent of the subjects were classified as obese (BMI ≥ 30kg/m^2). The mean BMI was 27.8 (SD 3.7) kg/m^2. Atopy (allergy) as measured by blood eosinophil count, was associated with responsiveness to methacholine in this cohort.

Ozone concentrations were obtained from four monitoring sites in the Greater Boston area that conformed to EPA protocols. Because of observed low correlations with other pollutants such as $PM_{2.5}$, CO and NO_2, a single pollutant ozone linear mixed model was constructed, using a 48-hour average prior to the exam dateas the exposure ; the 48-hour mean ozone concentration was 24.4 ppb (SD 11.0).

The linear mixed model allows each subject to act as his own control; it accounts for intra-subject variability and allows controlling for unmeasured within-subject variation via a random subject-specific intercept. For a 15 ppb increase in ozone, the obese exhibited an enhanced FEV_1 and FVC decrement compared to non-obese subjects. The interaction term was significant for FEV_1 (p=0.022) but not for FVC (p>0.05). A three-way interaction between obesity, ozone and AHR was investigated. For a 15 ppb increase of ozone, for both FEV_1 (p=0.048) and FVC (p<0.001), the estimated decrease in lung function associated with a 15 ppb increase in ozone was greatest among obese with AHR. Because increased inflammation is independently associated with each AHR and obesity, patients with either condition may be more likely to be susceptible to the inflammatory effects of ozone, leading to lower lung function. The combination of the two conditions was associated with a larger ozone-response decrement. This study suggests that AHR and obesity may interact in modifying a person's response to short-term ozone exposure and that the size of the effect was more than additive among elderly white men. Strengths of the study include its well-characterized spirometry outcomes and the quality of the short-term air pollution measurements. Limitations of this study are that women are excluded, other racial groups are not well represented, and because the

subjects live in one metropolitan area, differences in long-term ozone exposures were not studied.

Thirty-three Communities of North China Study

Two Chinese studies examined the effect of BMI in the same population of men and women on the association of long-term annual ozone levels with cardiovascular endpoints in 11 districts in three northeastern cities with a gradient of ozone concentrations (Qin et al. 2015; Zhao et al. 2013).

The two studies used a cross-sectional design to study 24,845 randomly selected adults, aged 18 to 74 years, from three northeastern Chinese cities: Shenyang, Anshan and Jinzhou (Dong et al. 2013). Air pollution was measured at municipal monitoring stations from 2006 to 2008 adhering to the State Environmental Protection Administration of China using ultraviolet photometry. Although there are several advantages to this ozone monitoring technique, the performance of the ozone zero air scrubber can be affected by changes in humidity as well as interferences by other compounds such as CO_2, H_2S, Hg, and aromatic hydrocarbons, which can lead to bias in measurements. Because of the shortcomings, this technique is not recommended in U.S. compliance networks. The Chinese studies used daily 8-hour averages (10 am – 6pm) for days with at least 75% data completeness and excluded outliers in the hourly measurements (Qin et al. 2015). The mean ozone level was 49.4 mg/m^3 (SD 14.07) (range among districts of 27 – 71 mg/m^3, IQR 22 mg/m^3). For comparison to other studies, at standard temperature and pressure, these concentrations correspond to a mean of 1.259 ppm (SD 0.3586 ppm) (district range 0.688 – 1.809 ppm).

Qin et al. (2015) used questionnaires to assess self-reported doctor determination of cardiovascular and cerebrovascular status. Two-level logistic regression models were used to predict the probability of CVD and stroke, controlling for age, sex, race, education, income, smoking, alcohol drinking, exercise, diet, sugar intake, family history of CVD, family history of stroke and study district. The effects of ozone on stroke were strongest in obese subjects (OR 1.47 (0.83, 2.59)), and less strong among overweight (OR 1.29 (1.05, 1.59)) and normal weight individuals (OR 0.98 (0.82, 1.18)) with a significant interaction (p=0.002). For cardiovascular disease, the OR among the obese was greater (OR 1.56 (1.02, 2.39)) than overweight (OR 1.08 (0.86, 1.35)) and normal weight (OR 1.08 (0.87, 1.35)) with a non-significant interaction (0.121). However, a cross-level interaction between BMI categorized above and below the overweight mark (< 25 kg/m^2 compared to ≥ 25kg/m^2) was not significant at the 95% confidence level among all subjects with stroke, (p=0.062) or with CVD (p=0.635). However, when stratified by sex, the interaction was significant among women for stroke (stroke p=0.046, CVD p=0.110), but not among men. An analysis using the obesity cut point (BMI ≥ 30 kg/m^2) might be a better way to examine the CVD data.

A second study using the same cohort examined the effect of air pollution and BMI on the prevalence of hypertension and blood pressure (Zhao et al. 2013). The associations between long-term ozone exposure and prevalence of hypertension were consistently stronger among overweight and obese adults compared with normal weight individuals, controlling for the same covariates as above. Interaction terms between ozone and BMI category were significant for hypertension ($p \leq 0.001$). However, when

stratified by sex, the associations were observed only among men (p = 0.041). Among women, ozone was not associated with hypertension among any of the BMI subgroups.

For all participants, ozone exposure was significantly associated with higher systolic and diastolic blood pressure. When stratified by sex, the associations were observed only among men, with a larger negative effect on systolic blood pressure (SBP) per interquartile range (IQR) of ozone.

Strengths of the study include its 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. The study controlled for known confounders. Limitations of the studies include the inability to draw causal interpretations due to the cross-sectional nature of the study and lack of temporality between the exposure and outcome; ozone exposure misclassification may bias the study toward the null; selection bias (e.g., healthy subjects are more likely to participate) and information bias (e.g., recall bias and self-reported endpoint, the use of prevalence rather than incidence of hypertension). There may also be confounding with particulate matter, which is more strongly associated with cardiovascular outcomes, due to a moderate correlation between ambient ozone and PM concentrations in the study districts.

Discussion

Weight gain has been shown to reduce lung function in healthy overweight and obese adults (Parameswaran et al. 2006). For example, in a cohort of subjects the top quartile of subject 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 (Thyagarajan et

al. 2008). Thus, the obesity epidemic 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. While our review of the literature was limited to human subjects, experimental evidence from animal models also support that obesity modifies the association between ozone exposure and cardiorespiratory health via inflammation (Shore 2008) and oxidative stress (Dye et al. 2015b). Comorbidities of obesity such as hypertension may also contribute to pulmonary inflammation observed in obese asthmatic people. Evaluating pulmonary susceptibility is complicated because obesity is a complex metabolic condition that influences many systems and results in a variety of co-morbidities that may also impact respiratory health. The pulmonary inflammatory response elicited by ozone exposure is enhanced in obese animals and suggests that obese humans may be at risk of a more adverse effect of air pollution. In the epidemiologic studies identified, increased BMI was associated with decreased lung function and increased inflammatory mediators. This review identified six studies that evaluated this hypothesis, and the results were generally mixed among the community studies.

A population perspective aids in the evaluation of literature about obese and overweight populations' risk from ozone exposures. There is evidence that obese populations receive an increased dose of ozone for the same ambient concentration. In controlled air pollution exposure studies among human subjects, researchers can control the dose. In the studies identified in this review, researchers assigned exposures to known doses of ozone in laboratory-controlled settings among generally healthy non-

smoking adult volunteers. Researchers administer known concentrations of ozone via chamber or facemask exposures and use exercise and body surface area to calculate and control target ventilation. This controlled exposure study design allows for direct causal inference, control over confounding by co-pollutants, assignment of the received dose of ozone to construct dose-response curves, and the collection of detailed anthropomorphic information like body weight measurements. The three recent studies identified in this review also controlled for age, asthma status, smoking, and sex. In general, subjects serve as their own control, by comparing effects with the ozone dose with those related to a filtered air exposure. A further advantage is that the lung function measurements are well documented using standardized, reproducible techniques. The three studies evaluated here have a relatively large sample size.

Among the controlled human exposure studies, the studies were not originally designed to evaluate the potential effect modification by obesity. Thus, few obese subjects are included and the analysis of effect modification by BMI is typically conducted as a secondary analysis and BMI may more appropriately be interpreted as differences in body size among normal individuals rather than a comparison of obesity. Future research should consider the detection of effect modification of the ozone-lung function response relationship by obesity and overweight status to ensure the appropriate selection of subjects and to ensure sufficient statistical power.

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 non-smoking. Insights from community epidemiologic studies can augment laboratory investigations.

The advantage of epidemiologic studies is that ozone exposures with realistic exposure patterns can be evaluated among larger populations, including a broader spectrum of health, lung function, and disease status. Community studies are especially important in ozone exposures because of the heterogeneous responses to ozone, including presence of weak responders and smaller response among those older than 35 years (Hazucha et al. 2003).

Limitations include presence of confounders; measurement errors in ozone exposure using community monitors; exposure misclassification due to activity patterns in micro-environments such as workplaces with other exposures or time spent in air conditioned spaces; lack of ability to demonstrate cause and effect in a cross-sectional studies where exposure may not precede the outcome; subject selection bias; and information bias in outcomes. Careful study design and use of statistical techniques can reduce these sources of bias.

In general, few studies examined the interaction of excess weight and ozone exposure and results were mixed about the effect modification when data were stratified by sex. This is consistent with overall evidence about potential differences by sex in ozone exposure epidemiologic studies of respiratory hospital admissions (Cakmak et al. 2009; Middleton et al. 2008). Individuals have lower responses to ozone after multiple exposures over a period of days (Devlin et al. 1997; Folinsbee et al. 1994; Gong et al.). 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 (Hazucha et al. 2003). Vancza et al. (2009) 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 of the strains of mice (Vancza et al. 2009). However, not all toxicological studies have found differences in the response to ozone exposure, with some strains exhibiting greater risk in males. Although experimental studies provide potential biological plausibility for potential differences for ozone exposure effects on lung function between sexes generally, the results are inconclusive.

Sex has been studied as an effect modifier in the primary effect of ozone on lung function in adults and children. Sex may also play a significant role with respect to the interaction of excess weight and ozone exposures. Among healthy nonsmoking women, Bennett et al. reported enhanced FEV_1 decrements following ozone exposure in the overweight/obese category (BMI ≥ 25 kg/m^2) compared with the normal weight women although not in men (Bennett et al. 2007; Hazucha et al. 2003). The Normative Aging Study only included men in the study design, and the researchers reported a greater short-term ozone-related decline in FEV_1 and FVC among obese than nonobese elderly men compared to normal weight men (Alexeeff et al. 2007). A three-way interaction trend test demonstrated a multiplicative effect of airway hyperresponsiveness (AHR) and obesity factors (Alexeeff et al. 2007).

The long-term ozone exposure cross-sectional studies of a Chinese population reported opposite results by sex for different cardiac endpoints. Zhao et al. reported increased odds ratio for prevalence of hypertension among obese compared to overweight

and normal weight men, but no association among women (Zhao et al. 2013). For both self-reported stroke and cardiovascular disease, the effect modification was significant for women, but not among men (Dong et al. 2015). The authors hypothesize that these sex differences may relate to the differential prevalence of the disease endpoints by sex.

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. The McDonnell et al. study provides a set of equations with which researchers can test new controlled human subject data as they become available (McDonnell 2010).

The World Health Organization estimates that approximately 2.3 billion adults worldwide in 2015 are overweight, with widespread potential for air pollution exposures (K. M. McClean et al., 2008b). The changing prevalence of obesity has implications for applying concentration-response functions derived from studies of ozone exposures. As obesity prevalence increases, there is increasing uncertainty as to how well the principal studies used to calculate endpoints in risk assessment, economic benefit assessment, or burden of disease calculations represent the impacts with respect to obese or overweight adult and elderly populations.

For example, an important new endpoint for study of the effect of air pollution among the obese was reported in the SAPALDIA cohort in Europe, showing that improvements in air quality are not reflected in corresponding improvements in the lung function measurements of obese and overweight adults for particulate matter (Schikowski et al. 2013a). Reducing community air pollution should ameliorate the detrimental effect of air pollution on lung function. However, for overweight and obese individuals in the

Swiss study of 4,664 randomly sampled adults, little or no evidence of a beneficial effect of improved air quality on their lung function profiles over an 11-year period was observed. The evidence that obese and overweight adult populations may be responding differently to the presence and absence of particulate matter air pollution deserves further study with ozone and enhanced obesity metrics such as abdominal adiposity. For future policy, this will be an important area of further research.

New studies are also needed to determine which adiposity measurements are the most relevant for the study of cardiac and pulmonary effects of ozone exposures for obese and overweight groups. Other metrics of central adiposity besides BMI, such as waist circumference, should be directly evaluated. Some research has been done considering BMI and waist circumference in an air pollution context (Collins et al., 1995; Finucane et al., 2011; Kannan et al., 2010). 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) (De Leon et al. 2003; Leone et al. 2009). An essential aspect of future research is to understand what characteristic various adiposity metrics might be representing. It would be helpful to consider other markers for respiratory fitness, sedentary lifestyles or other factors. Currently, BMI is one possible metric to consider the correspondence between the study cohorts and current and future U.S. populations. A hypothesis for what adiposity measurement is indicating is important because, for example, lower BMI can also be an indication of wasting in COPD or chronically ill patients.

Conclusions

This review suggests that obese and overweight populations should be considered as candidate at-risk groups for additional research and protection from air pollution both in risk communication and standard setting. The pulmonary inflammatory response elicited by ozone is enhanced in obese animals and suggests that obese humans may be at risk of a more adverse effect 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 is mixed and possibly confounded by sex and age in community-based 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. 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.

Tables

Table 1.1 U.S. Environmental Protection Agency's Designated At-Risk Populations for Ozone Air Pollution (2012)

Category of Evidence	Population
Adequate evidence	Asthmatics
	Children under 18 years
	Older adults at and above 65 years
	Populations with poor diets with nutritional (anti-oxidant or vitamin) deficiencies
	Outdoor workers
Suggestive evidence	Obese populations[*]
	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[*]
	Pregnant women
	Outdoor athletes

Note: Adapted Section 8.5, Table 8-4 (U.S. EPA 2012a).The National Institute of Health (NIH) defines obese a body mass index (BMI) of 30 kg/m^2 or greater. NIH defines "overweight" as adults with a BMI of 25 – 29.9 kg/m^2 (Wang and Beydoun 1998).

Table 1.2 Summary of Evidence that Obese Populations are At-Risk for Ozone Exposure

At-Risk Population Critierion	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 (Bennett and Zeman 2004)* • Increased minute ventilation (Bennett and Zeman 2004; Lin and Lin 2012; Salome et al. 2010a) • More work to maintain appropriate levels of circulating oxygen in their bloodstreams (Hurewitz 1985; Parameswaran et al. 2006) • Increased oxygen consumption (Lin and Lin 2012) • Stiffening of the chest wall and increasing the mechanical work of breathing (Lin and Lin 2012; Naimark and Cherniack 1960; Parameswaran et al. 2006; Salome et al. 2010a) • Airway closure and gas exchange deficiencies in obese populations (Lin and Lin 2012; Sood 2010) • Dyspnea at rest in obese men (Sahebjami 1998) • 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 (Gidding et al. 2004)
3. More responsive to same dose	• Among healthy nonsmoking women, enhanced FEV_1 decrements following ozone exposure in the overweight/obese category (BMI ≥25) compared with the normal weight women although not in men (Bennett et al. 2007; Hazucha et al. 2003) * • Enhanced pulmonary inflammation and injury with short-term ozone exposure in genetically and dietarily obese mice (Johnston et al. 2008; Shore et al. 2003, 2009; Shore 2008) * • In healthy normal-weight adults, increased BMI associated with enhanced FEV_1 responses to ozone (McDonnell 2010) * • 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 hyperresponsiveness (AHR) and obesity factors (Alexeeff et al. 2007) * • Obese individuals may be uniquely susceptible to the pro-inflammatory effects of ozone since obese humans and animals have been shown to experience a greater decline in lung function than normal weight subjects (Alexeeff et al. 2007; Johnston et al. 2006a, 2010; Shore et al. 2003) * • Higher levels of proinflammatory cytokines and chemokines (IL-6, KC, MIP-2, MCP-1) have been observed in obese animals following ozone exposure (Shore et al. 2003) * • Increased responses to short-term ozone in obese db/db mice compared to wild-type controls (Johnston et al. 2010; Lu et al. 2006; Rivera-Sanchez et al. 2004) • Evidence of effect modification for ozone exposures and cough and phlegm but not wheeze or asthma for annual ozone (Dong et al. 2013)

	• Additional evidence of obese individuals' susceptibility to pro-inflammatory effects of ozone since obese humans and animals have been shown to experience a greater decline in lung function than normal weight subjects (Johnston et al. 2006a, 2010; Mancuso 2010) • Obese may possess a greater number of peripheral blood leukocytes known to contribute to pulmonary inflammation following exposure to ozone (Kim and Park 2008) • 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 (Mancuso 2010) • Higher levels of proinflammatory cytokines and adipokines reported in the serum of obese subjects which might contribute to greater airway inflammation (Johnston et al. 2006b; Visser et al. 1999) • 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 (Dubowsky et al. 2006; Visser et al. 1999) • Suggestive evidence of lack of recovery of obese groups compared with normal weight groups from improvements in air pollution from SAPALDIA Cohort and PM exposures (Schikowski et al. 2013b)
4. Population-based perspective: diminished pulmonary function	• Obesity and overweight conditions have direct negative effect on respiratory well-being in addition to cardiac health (Chen et al. 1993; Lin and Lin 2012; Naimark and Cherniack 1960; Salome et al. 2010a; Thyagarajan et al. 2008; Wang and McCabe 1997; Zhao et al. 2013) • Increased fat mass and increasing BMI reduces lung volumes and FEV1 (Zammit et al. 2010b) • Weight gain reduces lung function in healthy overweight and obese adults (Parameswaran et al. 2006; Thyagarajan et al. 2008) • Subjects who gained the most weight over 10 years lost the most lung function (Thyagarajan et al. 2008) • In 8-year study of adults in which lung function changes (FVC, FEV_1 and vital capacity) decreased with increasing BMI quartiles (Bottai et al. 2002) • 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) (De Leon et al. 2003; Leone et al. 2009) • Inverse relationship between multiple measures of fatness with both spirometry and static lung volumes (Collins et al. 1995b)
	* Evidence considered by EPA Integrated Scientific Assessment for Ozone (2013)

Table 1.3. Effect Modification by Obesity and Overweight of Ozone Exposure Studies

Study and Location	Population and Study Design	Covariates	Obesity measure	Ozone measure	Outcomes	Main Findings Effect Estimates (95% CI)
Bennett et al. 2007 North Carolina (1992 - 1998)	Controlled human exposure study 197 non-asthmatic young adults (aged 18-35 years, 122 males, 75 females)	Age, Sex Independent of the modeling, checks of confounding by lung volume, tidal volumes, breathing frequency were also performed.	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 hour 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 3 categories (p-value trend ≤ 0.22 for 4 outcomes). A weaker, non-significant relationship was observed among men.
					%ΔFEV$_1$	All: A one unit increase in BMI was associated with a greater response to ozone exposure of 0.580 %ΔFEV$_1$ (p-value 0.014). Among women, a one unit increase is BMI was associated with a 0.716 unit decrease in %ΔFEV$_1$ following ozone dose (p-value 0.044). Among men, a one unit increase in BMI was associated with a 0.533 decrease in %ΔFEV$_1$ (p-value 0.11).
					%ΔFVC	All: A one unit increase in BMI was associated with a 0.288 %ΔFVC following ozone dose (p-value 0.038).
					%ΔFEF$_{25-75}$	All: A one unit increase in BMI is associated with a decrease of 0.952 %ΔFEF$_{25-75}$ (p-value 0.008). Among women a one unit increase in BMI was associated with a decrease of 1.336 %ΔFEF$_{25-75}$ (p-value 0.012).
					FEV$_1$/FVC	All: A one unit increase in BMI was associated with a decrease of 0.259 ratio FEV1/FVC (p-value 0.050).
					FEF$_{25-75}$/FVC	All: A one unit increase in BMI was associated with a decrease of 0.732FEF25-75/FV (p-value 0.023).
McDonnell et al. 2009 North Carolina and Davis, CA (1981-1992)	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 ppm to 0.12 ppm for 6.6	%ΔFEV$_1$	Increasing BMI was significantly 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.

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	541 healthy normal weight young adults (aged 18-35 years, 90 females)	Sex was available but not included in final model		hour with intermittent exercise		
Todoric et al. 2014 North Carolina	Retrospective analysis of existing controlled human trial; Spearman correlations; regression analysis 40 adults (31 healthy, 9 with allergic asthma)	Age, Ethnicity, Sex, Asthma status	BMI (14 of 40 subjects were overweight BMI >= 25 kg/m^2, (mean 24.1, range 21.8 - 27.5 kg/m^2)	Short-term: 0.4 ppm, averaging time not listed Measurements compared baseline either 2 days or 2 weeks before controlled ozone exposure and then 4 hours (spirometry, sputum and blood) and 24 hours (for sputum and blood)	% Predicted FEV$_1$, FVC	No significant correlation between BMI and change in % predicted FVC or FEV$_1$
					Delta IL-1Beta, Delta IL-6 and Delta IL-8	BMI was positively associated with sputum IL-1Beta 24 hours after controlled ozone exposure (r=0.5, p-value =0.004) but not either IL-6 or IL-8.
					Delta IL-1Beta	BMI was weakly correlated with change in sputum IL-1Beta (Spearman correlation R = 0.4, p-value =0.03) and in blood (Spearman correlation R= 0.7, p-value 0.003) after 24 hours. For each 1 unit increase in BMI, there was a 20-pg/mL increase in sputum IL-1Beta.
					Sputum %Δ PMN	No correlation between BMI and change in sputum %ΔPMN (p-value =0.30) or %Eos (p-value=0.09)
					Serum %ΔPMN	Serum %PMNs significantly increased (p-value <0.01), and %Eos decreased (p-value=0.01)
Alexeeff et al. 2007 Greater Boston area (1995-2005), Veterans Administration Normative Aging Study cohort	Longitudinal cohort study 904 elderly mainly white men	Age, Race, Smoking status, Lifetime smoking pack years, Chronic diseases, Airway Hyperrespon-siveness (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 decline 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
					%ΔFEV$_1$	For each 15 ppb increase in ozone, obese participants had a greater decrease in %ΔFEV$_1$ than non-obese (-2.63 % (95% CI -3.85,-1.39) v.-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 non-obese (-2.05 % (95% CI -3.17,-0.919) v.-1.18 %(-1.88,- 0.48), interaction not significant)
Zhao et al. 2013 33 com-munities in 3 north-eastern Chinese cities (2006-2008)	Cross-sectional epidemiologic study 24,845 adults (aged 18 - 74, 50.1% male)	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 μg/m^3 (SD	Prevalence of hypertension	Interaction between weight status and ozone exposure was observed among males (p-value 0.041) and all participants (<0.001), but not among females (p-value 0.177).
						All: OR increased with increasing weight category. For a 22 μg/m^3 increase in ozone, a lower odds ratio (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).

				14.07, range 27 - 71 μg/m³)		Males: OR increased with increasing weight category. For a 22 μg/m³ 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 μg/m³ 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).
					Blood pressure (BP)	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)	All: Change increased with increasing weight category. For a 22 μg/m³ 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 μg/m³ 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)	All: For a 22 μg/m³ 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 μg/m³ 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 33 com-munities in 3 north-eastern Chinese cities (2006-2008)	Cross-sectional epidemiologic study 24,845 adults (aged 18 - 74, 50.1% male)	Age, Race, Gender, Education, Income, Smoking, Drinking, Exercise, Diet, Sugar, Family history of	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	Self-reported stroke	All: 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).

		hypertension and district		49.4 μg/m³ (SD 14.07, range 27 - 71 μg/m³)		All: For a 22 μg/m³ 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 μg/m³ 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 μg/m³ 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	All: 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)
						All: For a 22 μg/m³ 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.

CHAPTER II

Associations of Long-term Particulate Matter and Ozone Air Pollution Exposures with Pulmonary Function in the CARDIA Study

Introduction

Air pollution exposure is a modifiable risk factor that contributes to cardiopulmonary disease and the global burden of disease (Lim et al. 2012; Mathers and Loncar 2006), but knowledge about characteristics of populations at risk is incomplete (Sacks et al. 2011; U.S. EPA 2009, 2012a; Vinikoor-Imler et al. 2014). Short-term and long-term exposures to particulate matter (PM) less than ten microns in aerodynamic diameter (PM_{10}) and ozone have contributed independently to adverse pulmonary health effects in at-risk populations (Götschi et al. 2008). Long-term exposures can lead to changes in pulmonary function over the life course. The evidence suggests that the differences in lung function with increases in pollution among adults are due to both growth deficits from childhood exposures and an acceleration of lung aging by air pollution (Ackermann-Liebrich et al. 1997; Gauderman et al. 2015; Gauderman and Avol 2004).

Several PM exposure studies in children report associations between air pollution and increases in respiratory symptoms (Bayer-Oglesby et al. 2005; Ghio et al. 2000; Lu et

al. 2013a; McConnell and Berhane 2003), decreases in lung function and peak flow (Oftedal et al. 2008; Dockery et al. 1996; Raizenne et al. 1996), and deficits in lung function growth (Rojas-Martinez et al. 2007; Gauderman et al. 2004; Alvos et al.) However, fewer studies have been conducted among healthy non-elderly adults in the U.S. (Adam et al. 2015; Goss and Newsom 2004).

A natural experiment in Switzerland, where PM levels had decreased, reported that improvement in air quality may slow the annual rate of decline in lung function in adulthood, indicating positive consequences for public health (Downs et al. 2007). Downs et al. prospectively examined 9,651 randomly selected adults (age 18-60 years) in eight cities in Switzerland (Ackermann-Liebrich et al. 1997; Downs et al. 2007). Decreasing PM_{10} concentrations were associated with attenuated age-related decline in lung function (forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and forced expiratory flow at 25–75% of forced vital capacity (FEF_{25-50})), and effects were greater in measurements reflecting small airway function.

A pollution-related accelerated decline in lung function may represent a step toward increased mortality risk. FEV_1 is an early indicator of respiratory and systemic inflammation, and associated with cardiorespiratory morbidity and mortality (Engström et al. 2002; Young et al. 2007b). Two large U.S. cohort studies examined the effect of long-term exposure to $PM_{2.5}$ on respiratory mortality with mixed results. In the American Cancer Society (ACS) study, Pope et al. (2004) reported positive associations with deaths from specific cardiovascular diseases, but no $PM_{2.5}$ associations were reported with respiratory mortality (Pope et al. 2002). In a follow-up analysis examining ozone exposure in the ACS cohort (Krewski et al. 2009), cardiopulmonary deaths were

subdivided into respiratory and cardiovascular, separately. A 10-ppb increment in ozone exposure was associated with higher risk of death from respiratory causes and this effect was robust to the inclusion of $PM_{2.5}$. An extension of the Harvard Six Cities study reported reduction in cardiovascular and respiratory, but not lung cancer, mortality with reduced long-term fine particle concentrations (Laden and Schwartz 2006). An association between long-term ozone exposure and elevated risk of mortality was observed among Medicare enrollees who had previously experienced an emergency hospital admission due to chronic obstructive pulmonary disease (COPD) (Zanobetti et al. 2008).

The results from epidemiologic associations are supported by subchronic and chronic toxicologic studies of inhalation exposure to concentrated particles, diesel exhaust, gasoline exhaust, and wood smoke studies (Gottipolu et al. 2009; Ishihara and Kagawa 2003; Mauad et al. 2008; Reed et al. 2008; Seagrave et al. 2005). The studies provide evidence of altered pulmonary function, inflammation, histopathological changes and oxidative and allergic responses following PM exposures.

The dose-response curve for ozone is well characterized from controlled laboratory studies in humans and animal models; however, in community studies, ozone exposure is less consistently associated with lung function decrements in populations of adults not restricted to those with asthma. In a study that included only healthy adults, increases in ambient ozone concentration were associated with decreases and increases in lung function across the various lags of exposure examined (Alexeeff et al. 2007; Steinvil et al. 2009).

In this study, we estimate PM and ozone air pollution exposures based on residential history for participants in the CARDIA cohort in order to examine longitudinally the relationship among PM_{10} and ozone exposures on lung function (FEV_1, FVC and/or FEV_1/FVC) in non-elderly adults. We assigned air pollution exposure using the inverse distance weighted average of the 12 nearest air pollution community monitors within a 200-mile radius. Our hypotheses are that long-term PM and ozone exposures are negatively associated with FEV_1 and FVC and positively associated with FEV_1/FVC among non-elderly adults. We also hypothesize that with increased age, long-term PM and ozone exposures are more negatively associated with FEV_1 and FVC and more positively associated with FEV_1/FVC among non-elderly adults. We hypothesize that these associations are stronger among women than men.

Methods

Study Participants. Starting in 1985-86, 5,115 Black and White men and women aged 18 to 30 years participated in the Coronary Artery Risk Development In Young Adults Study (CARDIA) study, a multi-center cohort study of generally healthy U.S. adults. Equal numbers by sex/race groups were recruited from the general population, mostly by telephone in Oakland, CA, Birmingham, AL, Chicago, IL, and Minneapolis, MN, with a response rate of about 50% (Friedman et al. 1988; Hughes et al. 1987). Participants were originally drawn primarily from four counties in four states and over the course of the 25 years of follow up resided in 753 counties. Institutional Review Board (IRB) approval was granted at each study site and written informed consent was

obtained from all participants. The current secondary data analysis was reviewed and approved by the University of Michigan IRB.

Loss to follow up occurred in two ways: attendance at exams and assignment of air pollution exposure, described below. The retention rate in Year 7 was 81% and in Year 20 was 72%. Participants lost to follow up after years 2 or 5 did not differ significantly in most of their baseline characteristics including mean FEV_1 and FVC (Thyagarajan et al. 2008). Participants lost to follow up in the early periods were generally younger and more likely to be Black (Kalhan et al. 2010). For Blacks and Whites combined, more females than males were lost to follow up.

Lung Function. Lung function measurements are the primary outcome in the analysis. Measurements of pulmonary function of CARDIA participants have been used in previous studies and followed American Thoracic Society standard protocols (Thyagarajan et al. 2008). Additionally, instruments were calibrated to create continuity in these measures over time due to minor changes in spirometric procedures and the use of different technicians (Jacobs et al. 1999). The present analysis used the values from all available exams during the 25 years of follow up. Specifically, lung function tests were performed at years 0, 2, 5, 10 and 20. The maximum volume out of five satisfactory maneuvers was selected as the representative value during a single exam. As described elsewhere in detail, lung function was measured at the four field centers using a Collins Survey 8-liter water sealed Spirometer and an Eagle II microprocessor (Warren E. Collins, Inc., Braintree, MA) (Burke et al. 1992). To minimize artifacts between exams, daily checks for leaks, volume calibration with a 3-liter syringe and weekly calibration in the 4 to 7 liter range were performed. Previous assessments of the agreement of

maximum and second highest maneuvers found that in almost all cases they agreed to within 150 ml, per protocol (Thyagarajan et al. 2008). The CARDIA participants were examined over a 16-month period at year 0 and 13-month periods at follow up exams with spirometry tests generally in the morning, during weekdays and Saturdays, with roughly equal numbers of participants assessed during each season. There were strong attempts to examine participants within a 6 week window of their year 0 anniversary date; however, this was relaxed in many cases, for practical reasons.

Environmental exposures. The primary environmental exposure variables are long-term ozone and PM_{10} air pollution during the study period. Individual-level air pollution exposures were estimated using air pollution measurements (1984-2006) from the U.S. Environmental Protection Agency (EPA) Aerometric Information Retrieval System (AIRS) monitoring system. Quality assurance and quality control for the ozone monitoring includes data completeness and biweekly precision checks mandated by regulations. Similar quality assurance/quality control procedures are in place for PM_{10}. As the PM monitoring network expanded and methods improved, the precision of the measurements has also improved. For manual methods, EPA requires by regulation collocation of PM monitors, flow rate checks and comparisons, and data completeness (EPA 2007).

In this study, we calculated inverse distance weighted (IDW) averages of the closest monitors to geographic coordinates of the participant's residence(s), limiting the distance to those operating monitors within 200 miles and selecting the closest 12 monitors. This technique is deemed appropriate because PM and ozone are relatively

spatially homogeneous pollutants and exhibit high correlations among monitors compared to other pollutants (U.S. EPA 2012; U.S. EPA 2009).

Geocoordinates for Air Pollution Exposure Assignment. The anonymized (not linked to participant identifiers) street addresses for each respondent's residence at each CARDIA exam was submitted for batch geocoding by Tele Atlas, Inc. in 2004 and 2008 (Gordon-Larsen 2015). Only geocodes created through this procedure were available for matching with environmental variables in this study; respondents who had no current address on file or whose address could not be resolved by the geocoding software were not included in this study. In particular, geocoding was attempted as a street segment address match, then as a 9-digit zipcode centroid match, which is roughly equivalent to a street segment match. If this failed, a less precise 7- and 5- digit zipcode centroid match was attempted. To protect confidentiality, a random shift of 0 to 50 meters was added, creating a fuzzed geocoded location (within a maximum of 100 meters from the respondents' residential locations). Geocodes were not available for Year 2 or Year 5. For this study, missing exam Year 2 and Year 5 geocodes were imputed from Year 0 and Year 7 addresses and county codes. If a participant moved between exams but remained in the same county, we randomly assigned their imputed exposure to either the initial or final year location. If the participant moved out of the county or did not have an exam date, we did not impute a value for Years 2 and 5.

To protect confidentiality, a separate analyst performed the imputation and assigned maximum 8-hour ozone and 24-hour PM_{10} values from a set of air quality monitors closest to the fuzzed participant residential coordinate. The IDW values (using the inverse of the squared distance) were calculated from measured pollutant

concentrations from the nearest 1 to 12 monitors with a 200-mile radius of the participant's residential address, using standard practices widely used in air pollution epidemiologic studies (Jerrett et al. 2005; Rivera-González et al. 2015). The residential geocodes were deleted and the environmental variables were matched via an interim participant identification number with the other CARDIA variables for analysis.

With respect to pollution indicator, $PM_{2.5}$ was not routinely monitored until after the 1997 standards were set; thus, for this study, PM_{10} was selected to represent particulate exposures. For pre-1990 values, Total Suspended Particles (TSP) values were multiplied by 0.55 to represent the PM_{10} fraction (Ostro 2004; U.S. EPA 1982). For winter periods when ozone monitors are not operated, we used a random draw from a distribution of background concentration of wintertime ozone values that was generated using observations collected during a cold season that spanned October April 2007 – 09 (n= 340,852, mean=36ppb, SD=12ppb) (U.S. EPA 2012a). Most PM monitors are operated year round on a 1-in-3 or 1-in-6 day schedule. With respect to exposure period, we selected *a priori* the annual averaging time for the days prior to the exam and the creation of a long-term exposure variable. The exposure assessment thus effectively assumed that the CARDIA participants lived at the address for one year prior to the exam. That is, for each participant, we computed annual averages (AP_{ij}) of either PM_{10} or ozone exposure. These exposures were in turn then averaged over all the exams that participant attended during the study period to create the long-term exposure variable ($APStudyMean_i$) that we used in our models. We defined $APStudyMean_i$ as follows:

$$APStudyMean_i = \Sigma (AP_{ij}) \div (NumberExams_i)$$

where AP_{ij} is the annual average air pollution exposure for participant i prior to exam j and $NumberExams_i$ represents the number of exams attended by participant i during the study. Thus, $APStudyMean_i$ is the participant's mean of either PM_{10} or ozone exposure, averaged over all available estimates.

Covariates. Because PM and ozone exposures may act independently on the body through different mechanisms, we examined the covariates used in the literature for both pollutants and exposure periods. We selected other covariates *a priori* based on covariates used in studies of long-term PM exposures (Eckel et al. 2012a) (Downs et al. 2007; Rice et al. 2015b; Schwartz 1993b) for ozone exposures (Alexeeff et al. 2007; Forbes et al. 2009; Gauderman et al. 2015; Rice et al. 2015a). We included both time-invariant and time-varying variables and interactions with time. Time-invariant covariates included an indicator variable of CARDIA field center for initial exam, sex verified at second exam, race/ethnicity (Black or White), education (attainment by age 30), and height. In addition, we included time-varying variables including age and age-squared, and the cumulative markers lifetime smoking pack-years, and lifetime asthma.

In the CARDIA cohort, demographic, lifestyle characteristics and medical history were self-reported using a questionnaire. Disease status was obtained through self-report of doctor diagnosis, and medication use. The definition of current and lifetime asthma evolved over the period of the study. In Years 0 and 2 current asthma indicated if a doctor had ever confirmed asthma or participant was still having asthma or on asthma medications. In Year 5, current asthma was defined as a participant who responded that he or she was taking asthma medications, and in other years, current asthma indicated

self-report of ever having asthma or having asthma within the last year or on asthma medications. Lifetime asthma is defined as ever having current asthma.

Lifetime smoking pack-years is a continuous variable and represents the accumulated pack years assuming continuous smoking among exam years. In annual contacts between exams, participants were asked about current number of cigarettes smoked, which were then included in the lifetime smoking pack-years variable. Current smoking status has three categories: never smokers, former smokers, and current smokers. Additional information about the definitions of variables and the forms used to collect the data are available on the CARDIA webpage (http://www.cardia.dopm.uab.edu/study-information/derived-variables-from-cardia-data).

Analytic Dataset. We excluded two transgender participants and one participant who withdrew consent. Of the 5,115 participants initially enrolled in CARDIA, after exclusions, 5,029 had complete data on the lung function outcome and clinical covariates used for the analyses. For annual average PM_{10}, 4,360 participants (18,600 observations) had information about residential history and exam date during 1985–2006 and an operating nearby community air quality monitor that allowed us to assign air pollution concentrations. We also imputed baseline center by closest state of residence at Year 0 or Year 2 for 175 participants with missing baseline center using baseline state of residence. As shown in Figure 2.1, we restricted our primary analyses to participants with complete outcome and covariate information at a given exam, for a final analysis dataset of 5,029 participants (18,747 observations). Because we were unable to match air quality values to all participants, we also examined characteristics in our analytic dataset (i.e., participants

with air quality values at an exam) compared to participants without air quality assignment.

Descriptive Statistics. We calculated descriptive statistics on the characteristics of the study population at baseline by quartiles of annual average PM_{10} prior to the year 0 visit. We also calculated descriptive statistics for the annual air pollution exposures and lung function outcome variables by sex. We performed correlation analyses and constructed graphics such as box plots and scatter plots to visualize relationships in the data and to check distributional assumptions.

Statistical techniques. Several temporal trends in both outcome and response variables, in addition to temporal correlations among them, need to be accounted for in our methods. Air pollution was significantly reduced (U.S. EPA 2012b) over the time period of the CARDIA follow up; however, average CARDIA participant exposure to ozone increased during the study. Because the percent change in FEV_1 depends on the short-term dose of ozone (Brown et al. 2008), and doses may cumulate over time, one would expect the FEV_1 decrement to increase as ozone exposures increase over time, and by geography. Age of participant further complicates the relationship because factors related to age simultaneously increase and decrease the expected response to air pollutants. Lung function trajectory over time varies by sex. During an adult's lifetime, lungs develop, plateau, and decline.

Considering these complexities and the study's repeated measure structure, we selected mixed effects longitudinal regression models because lung function measures over time in the same individual are not independent. We fitted the models in SAS v 9.4 (Cary, NC). First, we determined the best fitting model for the main effect of air pollution

exposure on lung function using lower Akaike's Information Criterion (AIC), which is an indicator of goodness of fit penalized by the number of parameters in the model, to select the best fitting model (Singer, Judith D; Willett 2003). Our final model followed Jacobs et al. (Jacobs et al. 1999) and is presented below.

The linear mixed model we fit for Y_{ij} (i.e., FEV_1, FVC, FEV_1/FVC) for participant i at exam observation j the linear mixed model we fit is given by:

$$Y_{ij} = \beta_0 + b_i + \beta_1 Age_{ij} + \beta_2 Age_{ij}^2 + \beta_3 Time_{ij} + \beta_4 APStudyMean_i$$

$$+ \beta_5 APStudyMean_i * Time_{ij} + \alpha X_{ij} + \gamma X_i + \delta X_i * Time_{ij} + \varepsilon_{ij}$$

where b_i represents participant i's random intercept. Age_{ij} represents age as a continuous centered variable measured in years minus 25 years for each individual from birth, and $Time_{ij}$ is the continuous time since a participant's first exam in years. Variables rescaled in an effort to increase interpretability, and the rescaling was performed to retain the property that change in age equals change in time within each participant. As defined above, $APStudyMean_i$ is the participant's mean of either PM_{10} or ozone, averaged over all available estimates for the year before the exam. X_{ij} represents repeated measure adjustment covariates, X_i represents time-invariant covariates, and $\delta X_i * Time_{ij}$ represents the change over time in adjustment covariates. We tested for a three-way interaction $Race_i Sex_i Time_{ij}$. Although the term was not significant at the 95% confidence level, we retained it because it improved AIC. For each of the three lung function outcomes, we fit separately PM_{10} and ozone exposure models each with one set of participant-specific random effect variables, adjusting for fixed effects. Longitudinal models were estimated by means of restricted maximum likelihood.

The main variables of interest to test our hypotheses are the two air pollution exposure variables. To test our hypotheses, we conducted a Wald test of significance on the beta coefficients of these two variables using 0.05 as significance level. We reported the associations over the 21 years of study (1985-2006), adjusting for covariates. Accordingly, the air pollution exposure variable $APStudyMean_i$ represents individual–level air pollution exposure averaged over the entire study attendance for each participant, and β_4 represents the amount of average lung function (over all measures during the study within a person) difference per unit of average annual exposure, over the entire study period attendance. In the modeling, some of the long-term air pollution exposure is ecologic, and the variability may also be captured in the baseline field center variable.

The coefficient β_5 for the interaction with time ($APStudyMean_i * Time_{ij}$) can be interpreted as per year change in lung function per unit of the average annual air pollution exposure (Jacobs et al. 1999). Our interpretation assumes a negligible birth cohort effect. We were able to partially test for the birth cohort effect at baseline with a baseline-age*time interaction which was significant (P-value <0.001); this interaction term captures the differential variation in lung function-air pollution exposure relationship for people born in different years. However, adding a categorical variable for 3 age groups was not significant and did not improve model fit. Thus, we did not include these terms in the final model.

In our model, we captured the independent long-term associations between a single air pollutant and lung function. We did not construct models with co-pollutants due to the correlation between PM_{10} and ozone exposure (correlation of PM_{10} and ozone

long-term study means is 0.654). Our reference category was white male, average height (1.7 meters), age 25 years, average long-term air pollution, high school education, non-smoker, and attending the Oakland field center. The annual average PM_{10} and ozone long-term exposures were 30.5 µg/m^3 (SD 5.2) and 35.3 ppb (SD 5.8), respectively. We evaluated separately the effect of a 10 µg/m^3 increase in PM_{10} and 10 ppb increase in ozone participant-specific air pollution study mean exposure on lung function, examining both association with level and rate of change. Standard model diagnostics were explored including graphics of residuals for evidence of non-normality, influential outliers, and omitted covariates. As sensitivity analyses, we examined a series of cross-sectional models by age categories. We also stratified by sex.

Results

Participant Characteristics. In Table 2.1 we presented the exam observations among participants, divided into baseline PM_{10} annual mean quartiles. The original study design sought approximately equal numbers of men and women, Blacks and Whites, and 18-24 year-olds and 25-30 year-olds.

In our analytic dataset, participant characteristics differed by baseline PM or ozone annual mean quartile. As shown in Table 2.1, baseline characteristics were similar across most categories. However, fewer people with asthma appeared in the top two baseline PM_{10} annual mean quartiles. In addition, participants attending the Oakland and Minneapolis field centers at baseline experienced baseline PM_{10} annual average exposures in the lower half. One percent or fewer of participants attending the Oakland

and Minneapolis field centers at baseline were in the top quartile for PM_{10} annual exposures. Conversely, for participants attending Birmingham and Chicago field centers at baseline, fewer than 1 percent were in the lowest two baseline PM_{10} annual average quartiles.

A total of 6,008 observations with lung function were missing air quality values. The characteristics of the CARDIA participants used in the model fitting compared to those excluded did not differ except in the following ways. In our analytic dataset, differences in baseline FEV_1 and FVC were evident across the 20 years of observation; specifically, participants with higher average baseline lung function measurements were missing air quality values in our analytic dataset in Year 0. Although in the overall study more Blacks were lost to follow up than Whites, among those participants with lung function measurements, we were unable to assign air quality exposures to more White (71%, 346 participants) than Black participants (29%, 142 participants) in the baseline year. Approximately 73% of the participants (356) without air quality assignment attended the Minneapolis field center in the baseline year, but in subsequent years, a more even distribution across initial field centers was noted.

Air pollution exposure and covariate analysis

Table 2.1 shows the descriptive statistics for the long-term air pollution exposures. In Table 2.1, we presented the cross-sectional air pollution annual average exposures by sex and exam year. The distribution of air pollution exposures differed over time and by baseline center. In general, PM_{10} levels were declining after Year 5 (1990). Moreover, the highest PM_{10} exposures for the 21 years were observed more frequently during the baseline year (1985-86) and more often in Birmingham and Chicago compared

with Minneapolis and Oakland in 1985-86. In our sample, mean ozone annual average exposures were rising over the study period.

The annual average PM_{10} and ozone long-term exposures across all years and sites were 30.5 µg/m^3 (SD 5.2) and 35.3 (SD 5.8), respectively. The long-term participant-specific PM_{10} exposure varied by baseline field center: Birmingham 36.7 µg/m^3 (SD 2.8), Chicago 34.0 µg/m^3 (SD 2.8), Minneapolis 26.8 µg/m^3 (SD 2.1) and Oakland 26.2 µg/m^3 (SD 2.3). Likewise, the long-term participant-specific ozone exposure varied by baseline field center: Birmingham 42.5 ppb (SD 1.4), Chicago 35.4 ppb (SD 2.3), Minneapolis 36.2 ppb (SD 1.8) and Oakland 28.8 ppb (SD 4.7).

At initial recruitment, CARDIA participants lived in 4 counties in 4 states. About 4 percent (n=216) of individuals reported residence in 45 additional unique counties; we assume that these were parental or permanent addresses given by the young adults under study. Over the 20 years of follow up, CARDIA participants resided in 753 unique counties across all participants and exams. About 80% of the participants still lived in the baseline county at year 7 (Birmingham 83%, Chicago 99%, Minneapolis 74%, Oakland 73%), 72% in year 20, and 56% in year 25.

Air pollution levels vary by geographic region. Because of the way ozone is formed photochemically from precursors, ozone is especially highly correlated regionally across urban and suburban areas (U.S. EPA 2012a). In our analytic dataset, air pollution exposures as well as other covariates (e.g., educational attainment, socioeconomic class) and unmeasured potential confounders (access to health care or anti-oxidant diets) may be spatially related (Richardson et al. 2014; Zamora et al. 2010). Overall, neighborhoods improved in terms of economic and social indicators for the CARDIA participants over

20 years (Richardson et al. 2014). One of the strongest period relationships in the study was that air pollution varied by age category in our sample, with opposite directions for PM_{10} and ozone (Table 2.2).

PM$_{10}$ Exposure and Lung Function

As shown in Table 2.3, we examined two aspects of the relationship of long-term PM_{10} study mean exposure to average lung function during the study follow up: the relationship during the study and if this relationship changed with time.

We first examined the association of PM_{10} long-term exposure with level and rate of change of FEV_1 and only change was related to PM_{10}. No associations were observed between FEV_1 and PM_{10} long-term study mean. We detected a negative effect modification by time – as time increases the association between FEV_1 and PM_{10} long-term exposure becomes more negative. For a 10 µg/m^3 higher PM_{10} long-term exposure, FEV_1 decreased 1.7 ml per year (p-value 0.04). When stratified by sex, there was no difference in the effect modification by time with FEV_1 for level or rate of change.

We examined the association of PM_{10} long-term exposure with level and rate of change of FVC, and only level was related to PM_{10}. Thus, for FVC, our model's result implies a time-invariant decrease; specifically, for a 10 µg/m^3 increase in PM_{10} long-term exposure, long-term mean FVC decreased 56.0 ml (p-value 0.04), and this relationship does not change with time for all participants. When stratified by sex, the effect modification by time is stronger among women than men for FVC (sex interaction p-value 0.05). When stratified by sex, considering the rate of change for a 10 µg/m^3 higher

PM_{10} long-term exposure, FVC decreased 2.76 ml per year (p-value 0.02) among women. No change in the relationship over time was observed among men.

Consistent with our hypothesis, we observed a small positive association between FEV_1/FVC and PM_{10} long-term exposure, but the relationship was not statistically significant at the 95% confidence level. We observed some evidence for a positive association among men but not among women; however, we did not observe a difference between men and women (interaction p-value 0.25). Regarding rate of change when stratified by sex, the effect modification by time is stronger among men than women for FEV_1/FVC (p-value interaction 0.008). Specifically, examining the rate of change for a 10 $\mu g/m^3$ increase in PM_{10} long-term exposure among men, FEV_1/FVC decreased 0.059 per year (p-value 0.004); for a 10 $\mu g/m^3$ higher PM_{10} long-term exposure among women, no association with FEV_1/FVC was observed (p-value 0.40).

Ozone Exposure and Lung Function

Likewise, we examined two aspects of the relationship of long-term ozone long-term exposure to average lung function during the study follow up: the relationship during the study and if this relationship changes with age (Table 2.3).

No associations were observed between FEV_1 and long-term ozone exposure or its time-interaction. When stratified by sex, we observed a positive association among women, but not among men. When stratified by sex, a 10 ppb increase in long-term ozone exposure was associated with an increase of 42.4 ml in FEV_1 (p-value 0.04) among women, but we did not observe a difference between men and women (interaction p-value 0.36).

Similarly, for FVC, some evidence was seen of a positive association between FVC and long-term ozone exposure. A 10 ppb increase in long-term ozone exposure was associated with 37.3 ml higher study average FEV_1 (p-value 0.1). When stratified by sex, among women a 10 ppb increase in long-term ozone exposure was associated with an increase of 59.5 ml in FEV_1 (p-value 0.02), but we did not observe a difference between men and women (p-value 0.44). We did not observe associations with the time-interaction, but there was some evidence of a difference by sex with the diminishment of the positive association between ozone exposure and FVC (interaction p-value 0.09).

No associations were observed between FEV_1/FVC and long-term ozone exposure or its time-interaction. When stratified by sex, we observed a small positive association between long-term ozone exposure and the rate of change of FEV_1/FVC, consistent with our hypothesis (interaction p-value 0.03). Among women we observed a positive interaction with time; specifically, a 10 ppb higher long-term ozone exposure is associated with an increase of 0.033 per year FEV_1/FVC (p-value 0.05) among women. Among men, no association was observed (p-value 0.22).

Discussion

The primary goal of the present study was to characterize the association between long-term air pollution exposure and lung function metrics. We hypothesized that increased PM and ozone exposures are more strongly and negatively associated with FEV_1 and FVC and more strongly and positively associated with FEV_1/FVC. The long-term participant-specific air pollution exposures were significantly associated with some but not all measures of lung function. Despite national trends to the contrary, ozone

exposures for CARDIA participants were rising and consistent with national trends, PM exposures were declining. Because PM_{10} and ozone had different exposure patterns and may act on lungs through different mechanisms, different patterns emerged for the association of lung function with exposure to PM_{10} and ozone, especially for FVC. FVC reflects total lung compliance, which encompasses both the lung and the chest wall. FEV_1 reflects these factors plus airway resistance. In a healthy population, the decrease in elasticity with age affects FEV_1 more than FVC, resulting in a decrease in the FEV_1/FVC ratio over time (Lin and Lin 2012).

First, associations were observed between FEV_1 and the PM_{10} participant-specific study mean. For a 10 $\mu g/m^3$ higher PM_{10} exposure, FEV_1 decreased by 1.7 ml per year (p-value 0.04). This implied that during 21 years with a 10 $\mu g/m^3$ higher PM_{10}, on average a participant's FEV_1 would have decreased 36 ml (or a loss of 0.9 % of baseline FEV_1 of 4,095.6 ml for a man or 36 ml to 44 ml decrease for or (1.2%- 1.4%) for a women of baseline FEV_1 of 3,046.8 ml). This finding is consistent with a long-term effect of PM_{10} on lung function.

Long-term PM_{10} exposure was also associated with FVC. Our results implied a time-invariant a loss of 56 ml for a 10 $\mu g/m^3$ increase in PM_{10} exposure (p= 0.04). Stated another way, on average, a participant living for 21 years with PM_{10} exposures like in Birmingham (study mean 36 $\mu g/m^3$) compared to Oakland or Minneapolis (study mean 26 $\mu g/m^3$) would have experienced a reduction of 56 ml in FVC (or about 1.3% of FVC for the average CARDIA man at baseline or 1.8% for the average CARDIA woman at baseline). No significant association of PM_{10} with FEV_1/FVC was seen at the 95% confidence level. When stratified by sex, we observed a stronger time effect modification

of the relationship between FEV_1 and FVC with long-term PM_{10} exposure among women compared to men.

In earlier community studies of long-term PM exposure and respiratory conditions, a non-linear shape was observed, indicating higher levels may have a different slope compared to lower levels in the PM exposure-response relationship (Abbey et al. 1998; Chestnut et al.; Schwartz 1993a). More recently, in the largest of the predominantly cross-sectional studies, Forbes et al. reported decreases of about 3% in FEV_1 associated with an increase of 10 $\mu g/m^3$ PM_{10} (Forbes et al. 2009). At first spirometry the SAPALDIA researchers reported 3.4% lower FVC and 1.6% lower FEV_1 associated with a 10 $\mu g/m^3$ increase in annual average PM_{10} exposure (Ackermann-Liebrich et al. 1997). Eckles et al. calculated a cumulative long-term exposure to ambient PM_{10} and ozone quantified using an exposure metric similar to pack-years in smoking. They observed associations of increases in this metric with declines in both FEV_1 and FVC decline in an elderly population. This result suggested an increased susceptibility among frail persons (Eckel et al. 2012a). Downs et al. reported associations of decreases in long-term pollution on lung function decline in adults from a longitudinal study demonstrating that improvements in PM_{10} exposure over a period of 11 years were linked with attenuated age-related decrease in respiratory function (Downs et al. 2007). Specifically, an increase of 10 $\mu g/m^3$ in PM_{10} was associated with a 44.6 ml decrease in FEV_1 (95% CI −85.4, −3.8) and a 59.0 ml decrease in FVC (95% CI −112.3, −5.7). Our results are consistent with these findings of a long-term of PM_{10} exposure association.

For ozone, no associations were observed between FEV_1 or FVC and long-term ozone exposure or its time-interaction in our CARDIA sample. When stratified by sex,

we observed a positive association between long-term ozone exposure and FEV_1 and FVC among women, but not among men. When stratified by sex, among women we also observed a small positive effect modification by time of the association between FEV_1/FVC and long-term ozone exposure by time in women, consistent with our hypothesis.

The stronger positive long-term ozone exposure association we observed among women is opposite to what has been observed in controlled ozone exposure experiments. The short-term ozone dose-response curve for pulmonary function among young adults is better characterized than that for PM because of data from laboratory human studies conducted at a variety of short-term controlled intake doses and exercise levels. Short-term ozone exposures exhibit a smooth non-threshold intake dose-response curve (Brown et al. 2008; McDonnell 2010). Considerable inter-subject variability is reported in studies at higher exposure concentrations ($\geq$ 70 ppb), with greater response and variability in young adults (<35 years) compared to older adults (Hazucha et al. 2003). A 2-day average ozone exposure was found to be negatively associated with FEV_1 in the Normative Aging Study among elderly men (Alexeeff et al. 2007). In addition to the effects of ozone exposure on the large airways measured by spirometric responses, ozone exposure also affects the function of the small airways and parenchymal lung (Foster et al. 1997, Foster et al. 1993). These studies suggest a prolonged ozone effect on the small airways and ventilation distribution in healthy young individuals.

We would expect stronger and more varied FEV_1 responses in younger (age <35 years) participants with identical ozone doses compared to the FEV_1 responses of those over 35 years (Hazucha et al. 2003). In the CARDIA study, participants experienced

higher ozone exposures later in the study as they aged, which may explain our null finding. Participants aged 35 and older experienced on average 3.6 ppb higher 2-day averages than on average for participants earlier in the study. Higher ozone levels are related to higher FEV_1 responses, which complicates the comparison (Brown et al. 2008).

In light of significant national downward trends in air pollution concentrations, we would have expected a period effect in which exposures prior to visits where participants were 35 years and older to have consistently lower levels of both PM and ozone. However, we observed this only in the PM_{10} data and not with ozone exposures. The exam visits (ranging in start-dates from 1990 to 2006) would have occurred after significant national air pollution control compared with 1985. Different regions would have implemented controls at different times. California instituted controls before the national controls; however, some areas of California had especially high air pollution concentrations. CARDIA participants may have moved from their initial locations during the study or sources of pollution in the vicinity of their residence may have changed in a way that affects their exposures. In the CARDIA data, air pollution exposures as well as other covariates (e.g., educational attainment, socioeconomic class) and unmeasured potential confounders (access to health care or anti-oxidant diets, neighborhood characteristics) may be spatially related and associated with overall improvements in neighborhood traits (Richardson et al. 2014; Zamora et al. 2010).

Strengths. This study benefits from a young cohort followed for 25 years with large number of observations and standard outcome definition and data collection. This analysis tested community air pollution-related hypotheses in the CARDIA cohort, expanding our knowledge of air pollution-related lung function effects in Black and

White young adults. The air pollution monitoring data are well documented, quality

assured, and represent large portions of the U.S. population over a significant period of

time and geography during the study. For example, for ozone in 2009 56% of the

Birmingham population was within 10 kilometers of a community monitor, 73% within

20 km (U.S. EPA 2012a). For Chicago, 63% of population was within 10 km and 89%

within 20 km of a community monitor. For Minneapolis, 16% of the population was

within 10 km and 57% within 20 km and for the San Francisco-Oakland area 81% of the

population was within 10km and 98% within 20 km of a community ozone monitor. The

earlier monitoring system was less dense. However, monitoring data are moderately well

correlated with personal exposures (U.S. EPA 2012a). The air pollution exposures were

calculated at the individual level, strengthening our inferences over simple area-wide

annual averages. The study contained a substantial number of observations with

individual, detailed participant data. The four original study areas comprised of mainly

four counties in four states were expanded as participants moved, covering a range of

different types of environments and climates. However, this study has also several

limitations.

Limitations. Exposure misclassification is a main limitation in the study. For air

pollution, misclassification may be greater for those participants who reside or spend

their day in climate controlled settings, have occupational exposures not reflected in

community monitors, further away from monitors, near heavy traffic, or who have

lengthy commutes in traffic (higher PM_{10} if within 300 meters and lower ozone due to

nitrogen dioxide scavenging). We have less confidence in the longer averaging times due

to lack of information about place of residence before the exam. Time of day of exam

may be an additional factor contributing to exposure misclassification due to the diurnal patterns of photochemical air pollutants.

Air pollution indicator and measurement method can affect the quality of the data. The indicator of PM_{10} and TSP may add measurement error and more variability from the coarse fraction than a fine particle indicator for the hypothesized causal agents. $PM_{2.5}$ would be a better indicator than PM_{10} but was not monitored routinely until the late 1990s. A potential improvement would be to consider $PM_{2.5}$ measures or air quality modeling to improve more recent exposure estimates (Sampson et al. 2013). The addition of random low-level winter ozone values may have limited the ability to detect ozone effects. Another source of measurement error stems from our use of unadjusted spirometric measurements. In general, our community-monitor based air pollution measures may not have been sufficiently precise at the personal level to detect stronger and real associations with lung function.

Differential loss to follow up for the exams could also be a limitation. Other CARDIA studies report no major differences in terms of education, and other covariates with the exception of more Blacks were lost to follow up in the early years. In this study, we also may have had differential ability to assign air pollution exposures due to different patterns of residential moving. Moving may be related to SES and educational attainment, and educational attainment is related to air pollution exposure in our data, with both the lowest (less than high school) and highest educated participants experiencing higher exposures than high school graduates or some college.

There are several time-related trends during the study period. For ozone, two opposite trends in the data may contribute to a null association. Upper percentile

distributions of air pollution exposure can be important to changes in lung function because, for example, FEV_1 response to ozone depends on the ozone concentration, with larger response related to higher levels (Brown et al. 2008). In these data, higher ozone levels were observed later in the study when participants were older and possibly less responsive. As people age, gain excessive weight, or develop chronic diseases, they may also take more medication or change behavior, which may in turn affect their exposures or their responsiveness to air pollution.

Another limitation for both pollutants is that our modeling does not control for lifetime air pollution exposure. We note that most participants would likely have experienced significantly higher childhood exposures due to widespread lack of air pollution control, especially if the participant was older upon enrollment, lived near an uncontrolled source (Sloyan 1972), or lived in a high pollution location. Variables for historical exposures were not constructed for the analysis.

Conclusions

In the CARDIA sample, long-term PM_{10} exposure was associated with small reductions in levels and rates of change in lung function in healthy young adults followed over the 21 years of study. Specifically, increases in PM_{10} long-term exposures were associated with decreases in FVC levels and larger decreases in rate of change in FEV_1. The findings imply that on average a participant living for 21 years with PM_{10} exposures like Birmingham compared to Oakland or Minneapolis would experience a reduction of 56 ml in FVC (or about 1.3% for the average CARDIA man at baseline and 1.8% for the average CARDIA woman at baseline). For long-term PM_{10} exposures, the rate of change in FVC decreased more among women than men. No consistent associations between long-term ozone exposures and lung function were observed, although when stratified by sex, we observed an unexpectedly positive association between increases in study mean ozone and average FEV_1 and FVC levels among women. Given nonlinear temporal trends in exposure, outcome and covariates, and different modeling strategies across studies, further work is warranted to allow comparison of conflicting results in healthy young adults and with special attention to the effect of weight as participants age.

Figures

Figure 2.1. Summary of Inclusion Criteria
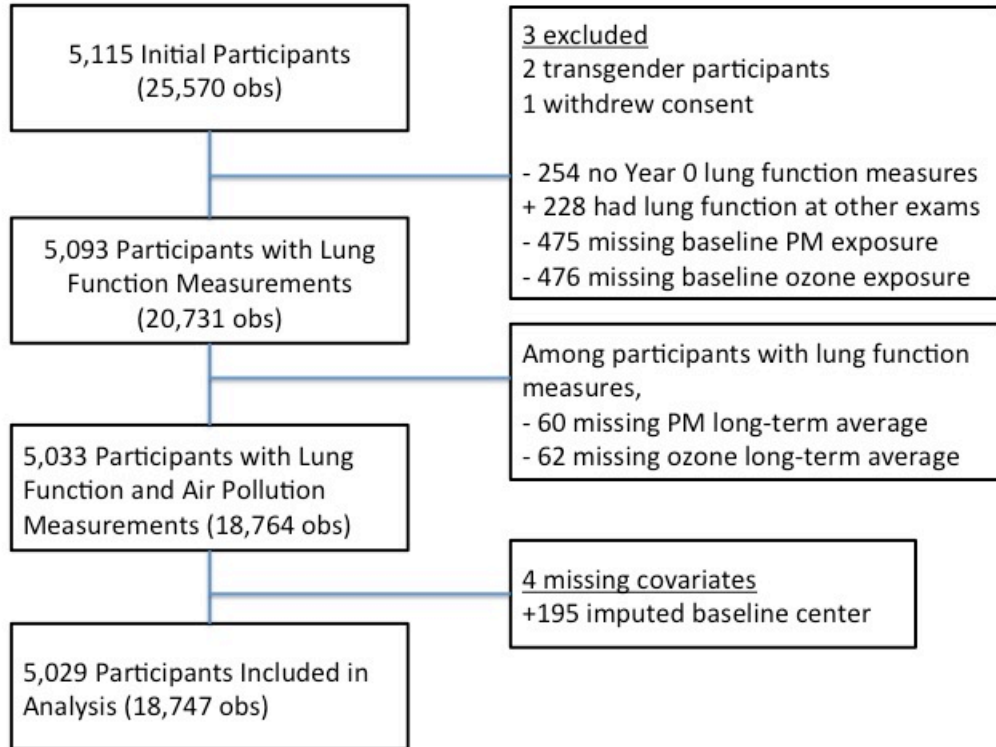
Tables

Table 2.1. Demographic, Clinical, and Air Pollution Baseline Characteristics by Annual PM_{10} Baseline Quartile for Participants Included in the Analyses (n=4,360); CARDIA 1985-2006.

	Q1	Q2	Q3	Q4
	$PM_{10} < 27.5$ µg/m³ n=1092	27.5 to < 29.2 µg/m³ n=1086	29.2 to < 36.3 µg/m³ n=1091	> 36.3 µg/m³ n=1091
Demographic Characteristics				
Age, years (mean±SD)	25.0 ± 3.7	24.8 ± 3.7	24.9 ± 3.6	24.6 ± 3.6
% Female	56%	54%	54%	50%
% Black	52%	59%	50%	53%
Education attained by age 30 years (mean)	15.0	14.4	15.2	14.7
< High school	5%	6%	4%	5%
High school graduate	18%	25%	18%	20%
Some college	31%	34%	30%	34%
College graduate or more	46%	35%	49%	40%
Baseline Exam Center (% distribution)				
Birmingham, AL	0.0%	0.2%	33%	63%
Chicago, IL	0.1%	0.1%	58%	36%
Minneapolis, MN	38%	51%	2%	0.0%
Oakland, CA	62%	48%	7%	1%
Baseline Body Mass Index				
Baseline BMI, kg/m² (mean±SD)	24.6 ± 5.0	24.8 ± 5.2	24.4 ± 4.8	24.9 ± 5.3
Height, m, (mean±SD)	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1
Weight, lbs, (mean±SD)	156.9 ± 35.3	158.9 ± 36.3	156.7 ± 35.5	160.4 ± 37.4
Waist circumference, cm (mean±SD)	77.6 ± 11.2	78.1 ± 11.9	77.9 ± 11.1	79.1 ± 11.9
Baseline Smoking and Disease Status				
Pack-year of cigarettes (mean±SD)	2.2 ± 4.5	2.3 ± 4.5	2.0 ± 4.2	2.3 ± 4.6
Smoking status (% distribution)				
Never	56%	53%	59%	59%
Former	14%	13%	13%	11%
Current	30%	33%	28%	31%
Alcohol consumption, ml	11.5 ± 22.0	12.1 ± 22.3	12.4 ± 19.1	12.4 ± 22.4
Lifetime asthma[a] (% distribution)	11.2%	12.1%	7.8%	8.7%
Elevated blood pressure[b] (% distribution)	8.8%	9.7%	8.1%	6.9%
Diabetes[c] (% distribution)	0.7%	0.6%	0.4%	0.6%
Baseline Air Pollution Exposure				
PM_{10} annual average, µg/m³ (mean±SD)	27.0 ± 0.5	28.2 ± 0.4	34.1 ± 1.8	38.8 ± 2.1
Ozone annual average 8-hour max, ppb (mean±SD)	26.4 ± 3.0	27.0 ± 2.7	34.1 ± 5.8	39.3 ± 3.8
Participant-Specific Study Mean Pollution Exposure				
PM_{10} annual study mean, µg/m³ (mean±SD)	26.4 ± 2.0	26.7 ± 2.1	33.5 ± 3.6	36.2 ± 3.3
Ozone annual study mean, ppb (mean±SD)	31.0 ± 4.9	31.8 ± 4.9	37.2 ± 4.5	40.2 ± 3.7
Baseline Lung Function				
FEV_1, ml (mean±SD)	3,546.3 ± 770.9	3,505.6 ± 804.6	3,526.9 ± 773.3	3,544.3 ± 788.3
FVC, ml (mean±SD)	4,312.2 ± 1,002.8	4,260.0 ± 1,002.1	4,258.3 ± 1,009.5	4,278.5 ± 1,024.2
FEV_1/FVC (mean±SD)	0.83 ± 0.068	0.83 ± 0.064	0.83 ± 0.064	0.83 ± 0.065

[a] Lifetime Asthma is defined as current asthma at any exam. Years 0 & 2, doctor confirmed or on asthma medications. Year 5, taking asthma medications, and other years, self-report of ever having asthma within last year or on asthma medications.
[b] Systolic BP ≥ 130 mm Hg or diastolic BP ≥ 85 mm Hg or on hypertensive medications.
[c] Fasting glucose level ≥ 126 mg/DL or on diabetic medications but not pregnant.

Abbreviations: PM_{10} particulate matter with aerodynamic diameter <10 microns; SD, standard deviation; CI, confidence interval; FEV_1 forced expiratory volume in 1 second; FVC, forced vital capacity; ppb, parts per billion; ug/m³ micrograms per cubic meter; ml, milliliter.

Table 2.2. Particulate matter (PM_{10}) and ozone exposures and lung function outcomes (annual mean and standard deviation) averaged across all sites and by sex and exam period for participants included in the analyses (n=4,360); CARDIA 1984-2006.

	Men (nobs=8,417)				
	Year 0	Year 2	Year 5	Year 10	Year 20
Lung Function	n=2,028	n=1,669	n=1,598	n=1,668	n=1,454
FEV_1, ml	4095.6 (673.5)	4042.3 (686.0)	4031.8 (707.0)	3946.7 (706.9)	3610.9 (706.9)
FVC, ml	5039.7 (843.6)	5013.0 (861.2)	5033.5 (873.8)	5024.7 (885.3)	4655.3 (891.8)
Ratio FEV_1/FVC, %	81.6 (6.7)	80.9 (6.8)	80.3 (6.7)	78.8 (6.6)	77.8 (7.0)
Air Pollution					
PM_{10} annual average exposures, $\mu g/m^{3\,a}$	32.29 (5.07)	34.54 (5.31)	34.21 (5.68)	27.65 (5.35)	25.41 (6.94)
Ozone annual average exposures, ppb[b]	32.13 (6.66)	36.39 (5.52)	35.46 (6.86)	36.67 (6.63)	38.39 (4.91)

	Women (nobs=10,183)				
	Year 0	Year 2	Year 5	Year 10	Year 20
Lung Function	n=2,332	n=1,965	n=1,918	n=2028	n=1,940
FEV_1, ml	3046.8 (487.9)	2997.1 (487.4)	3021.8 (507.4)	2947.3 (499.1)	2603.4 (523.1)
FVC, ml	3622.4 (597.5)	3596.4 (600.0)	3643.9 (628.5)	3646.3 (629.6)	3293.8 (680.9)
Ratio FEV_1/FVC, %	84.4 (6.1)	83.6 (6.3)	83.3 (6.9)	81.1 (5.9)	79.3 (6.4)
Air Pollution					
PM_{10} annual average exposures, $\mu g/m^{3\,a}$	31.87 (4.85)	34.36 (5.38)	33.74 (5.62)	27.52 (5.32)	25.41 (6.81)
Ozone annual average exposures, ppb[b]	31.39 (6.70)	36.22 (5.61)	34.62 (7.14)	36.22 (6.91)	38.17 (5.12)

[a] Inverse distance-weighted average 24-hour value from nearest 1 to 12 monitors within 200 miles during period prior to the exam. Includes converted Total Suspended Particles (TSP*0.55) prior to 1990.
[b] Parts per billion (ppb). Inverse distance-weighted average 8-hour max from nearest 1 to 12 monitors within 200 miles during period prior to the exam. Includes imputed winter values when ozone not measured.

Table 2.3. Adjusted Difference in Lung Function per 10 unit Increase in Long-term (1984-2006) Air Pollution Exposure At Baseline and Rate of Change per Year for All Participants and Stratified by Sex, CARDIA (1985-2006).

Pollutant, category	Long-term Air Pollution Exposure$_i$				(Long-term Air Pollution Exposure$_i$)*Time$_{ij}$			
	Beta Coefficient	SE	p-value	Sex Difference p-value	Beta Coefficient	SE	p-value	Sex Difference p-value
FEV$_1$, ml								
PM$_{10}$								
All Participants	-22.1	22.8	0.33		-1.72	0.85	0.04	
Male	-35.6	38.9	0.36	0.44	-1.49	1.37	0.27	0.73
Female	-0.6	25.8	0.98		-2.11	1.05	0.04	
Ozone								
All Participants	21.8	19.4	0.26		0.63	0.71	0.37	
Male	5.9	35.4	0.87	0.36	0.98	1.24	0.43	0.64
Female	42.4	20.8	0.04		0.30	0.83	0.72	
FVC, ml								
PM$_{10}$								
All Participants	-56.0	27.2	0.04		-0.84	0.98	0.39	
Male	-82.3	45.6	0.07	0.22	1.06	1.57	0.50	0.05
Female	-15.9	31.0	0.61		-2.82	1.21	0.02	
Ozone								
All Participants	37.3	23.2	0.11		0.51	0.82	0.53	
Male	23.0	41.5	0.58	0.44	2.23	1.42	0.12	0.09
Female	59.5	25.1	0.02		-0.62	0.96	0.52	
Ratio %								
PM$_{10}$								
All Participants	0.50	0.31	0.11		-0.018	0.015	0.22	
Male	0.87	0.47	0.07	0.25	-0.059	0.021	0.004	0.008
Female	0.14	0.41	0.72		0.018	0.021	0.39	
Ozone								
All Participants	-0.23	0.26	0.38		0.012	0.012	0.33	
Male	-0.09	0.43	0.83	0.63	-0.023	0.019	0.22	0.03
Female	-0.34	0.33	0.30		0.033	0.016	0.05	

[a]Adjusted for age, age-squared, time since initial exam, education attained by age 30 years, sex, race/ethnicity, interaction of sex*race/ethnicity, baseline center, height, lifetime pack years smoking, lifetime asthma, and time-interactions with time-invariant variables.

Abbreviations: PM$_{10}$ particulate matter with aerodynamic diameter <10 microns; CI, confidence interval; FEV$_1$ forced expiratory volume in 1 second; FVC, forced vital capacity; ppb, parts per billion; ug/m^3 micrograms per cubic meter.

CHAPTER III

Associations of Long-term Particulate Matter and Ozone Air Pollution Exposures

with Pulmonary Function:

Does Obesity Status Increase Risk of Enhanced Decrements?

Introduction

Understanding the relationship between air pollution exposures and lung function decrements among those with excessive weight compared to lower weight adults is important because of the widespread prevalence of obesity and typical increases in body weight with age. Two-thirds of U.S. adults are currently overweight or obese (Institute of Medicine 2012; Ogden et al. 2012). Overweight and obese individuals receive a larger dose for the same concentration and the altered physiological states related to obesity place an additional burden on the cardiac and respiratory systems, which in turn could affect response to air pollution exposures (Bennett and Zeman 2004; Bottai et al. 2002a; Gidding et al. 2004; Lin and Lin 2012).

Despite the growing numbers of obese and overweight people worldwide, regulatory agencies have concluded that evidence is lacking about the extent to which obesity or overweight status increases risk from PM and ozone air pollution exposures (U.S. EPA 2012; U.S. EPA 2009). One reason for the insufficient evidence is the limitation in the published literature and available data. Current methods that examine

death certificates or hospital admissions data do not provide direct information on patients' weight and other anthropometric measures. Previous air pollution exposure cohort studies did not capture today's increased prevalence of obesity, did not involve significant numbers of overweight/obese subjects, or did not distinguish between wasting diseases (e.g., lung cancer) in which additional weight might be protective and other pathways in which excess weight might be detrimental (Dockery and Pope 1993; Pope et al. 2002).

Long-term and short-term exposures to particulate matter less than ten microns in aerodynamic diameter (PM_{10}) and ozone have contributed independently to adverse health effects in at-risk populations (Götschi et al. 2008; U.S. EPA 2009, 2012a). Long-term exposures can lead to changes in pulmonary function over the life course. Differences in lung function with increases in pollution among adults are due to both growth deficits from childhood exposures and an acceleration of lung aging by air pollution (Ackermann-Liebrich et al. 1997; Gauderman et al. 2015; Gauderman and Avol 2004).

Lung function may be decreased by the pro-inflammatory effects of ozone since obese humans and animals experience a greater decline in lung function than normal weight subjects, with suggestive evidence that this occurs via mechanisms other than the inflammatory pathway (Alexeeff et al. 2007; Lu et al. 2013a; Mancuso 2010; Shore et al. 2003, 2009; Visser et al. 1999b; Williams et al. 2013). In addition, one underlying pathology of obesity is hypothesized to be linked to a chronic state of oxidative stress and impaired oxidant defense (Dye et al. 2015b). Ozone mediates some of its adverse effects through oxidative stress; thus, antioxidant nutritional status may affect the risk of ozone-

related health effects (Romieu et al. 2009). People with reduced dietary intake of vitamins E and C are at increased risk for ozone-related health effects (Vinikoor-Imler et al. 2014), so antioxidant-poor diets associated with obesity might also be a factor. PM may act via similar inflammatory mechanisms or via the central nervous system to reduce lung function more pronouncedly among overweight and obese people. However, the mechanisms for particles' influence on lung function are more poorly understood than for ozone.

Three recent cohort studies of long-term PM exposure and cardiovascular mortality among adults suggest that participants with overweight and/or obesity may be more vulnerable (Miller et al. 2007; Puett et al. 2008; Weichenthal et al. 2014). With respect to pulmonary function and long-term PM exposures, recent studies support the hypothesis that long-term air pollution-related lung function (forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC)) decline is more pronounced among people with excess weight than their normal weight peers (Adam et al. 2015; Schikowski et al. 2013a). The SAPALDIA study points to a novel endpoint of permanent lung function loss among the obese; specifically, among 4,664 adults studied in a low pollution area, the authors reported no evidence of a beneficial effect of decreasing PM concentrations on obese subjects' lung function profiles over an 11-year period, compared to normal weight adults, (Schikowski et al. 2013a). In China, a cross-sectional study reported suggestive evidence that obese and overweight children may have higher associations between PM and ozone and some respiratory symptoms (Dong et al. 2013). A previous study of the Coronary Artery Risk Development In Young Adults (CARDIA) cohort observed that lung function losses were larger by an estimated 65 ml in FEV_1

(95% CI -161, +34 ml) and 185 ml in FVC (95% CI -298, -71ml) over 10 years among the heaviest subjects compared to the lightest quartile participants at baseline, with the heaviest class defined as having a body mass index (BMI) ≥ 26.4 kg/m^2 (Thyagarajan et al. 2008). Lung function decline began as participants gained weight (overweight status), and those participants who gained the most weight (≥ 6 kg/m^2 BMI) lost the most lung function (-216 ml (95% CI -236, -195 ml) in adjusted FEV$_1$ and -264 ml (95% CI -286, -243 ml) in adjusted FVC over 10 years. However, the extent of this reduction in lung function that was attributable to long-term air pollution exposures was unknown.

Consequently, given age-related increases in weight and overall population increases in weight and obesity prevalence, the primary goal of this study is to characterize the extent to which obesity and overweight status among non-elderly adults modifies the association between air pollution and pulmonary function metrics. We quantify PM$_{10}$ and ozone air pollution exposures using the inverse distance weighted average of the 12 nearest air pollution community monitors within a 200-mile radius for participants in the CARDIA study in order to test our hypotheses:

(1) Among obese adults (BMI ≥ 30 kg/m^2), PM$_{10}$ and ozone long-term exposures are more strongly and negatively associated with FEV$_1$ and FVC than among adults with BMI < 30 kg/m^2.

(2) Among obese adults, PM$_{10}$ and ozone long-term exposures are more strongly and positively associated with the ratio FEV$_1$/FVC than among adults with BMI < 30 kg/m^2.

(3) Among obese adults, the association between PM_{10} and ozone long-term exposures and FEV_1 and FVC become more negative with age than among adults with BMI < 30 kg/m^2.

(4) Among obese adults, the association between PM_{10} and ozone long-term exposures and FEV_1/ FVC become more positive with age than among adults with BMI < 30 kg/m^2.

Methods

Study Participants. As described in Chapter 2, starting in 1985-86, 5,115 Black and White men and women aged 18 to 30 years participated in the CARDIA study, a multi-center cohort study of generally healthy U.S. adults. Equal numbers by sex/race groups were recruited from the general population, mostly by telephone in Oakland, CA, Birmingham, AL, Chicago, IL, and Minneapolis, MN, with a response rate of about 50% (Friedman et al. 1988; Hughes et al. 1987). Participants were originally drawn primarily from four counties in four states and over the course of the 25 years of follow up resided in 753 counties. Institutional Review Board (IRB) approval was granted at each study site and written informed consent was obtained from all participants. The current secondary data analysis was reviewed and approved by the University of Michigan IRB.

We considered the loss to follow up in two ways: attendance at exams and assignment of air pollution exposure, described below. We considered the loss to follow up in the overall study. The retention rate in Year 20 was 72%. Participants lost to follow up after years 2 or 5 did not differ significantly in most of their baseline characteristics

including mean FEV_1 and FVC (Thyagarajan et al. 2008). Participants lost to follow up in the early periods were generally younger and more likely to be Black (Kalhan et al. 2010). For Blacks and Whites combined, more females than males were lost to follow up.

Lung Function. Lung function measurements are the primary outcomes in the analysis. Measurements of pulmonary function of CARDIA participants have been used in previous studies and followed American Thoracic Society standard protocols (Thyagarajan et al. 2008). Additionally, instruments were calibrated to create continuity in these measures over time due to minor changes in spirometric procedures and the use of different technicians (Jacobs et al. 1999). The present analysis used the unadjusted values from all available exams during the 25 years of follow up. Specifically, lung function tests were performed at years 0, 2, 5, 10 and 20. The maximum volume out of five satisfactory maneuvers was selected as the representative value during a single exam. As described elsewhere in detail, lung function was measured at the four field centers using a Collins Survey 8-liter water sealed Spirometer and an Eagle II microprocessor (Warren E. Collins, Inc., Braintree, MA) (Burke et al. 1992). To minimize artifacts between exams, daily checks for leaks, volume calibration with a 3-liter syringe and weekly calibration in the 4 to 7 liter range were performed. Previous assessments of the agreement of maximum and second highest maneuvers agreed to within 150 ml (Thyagarajan et al. 2008). The CARDIA participants were examined over a 16-month period at year 0 and 13-month periods at follow up exams with spirometry tests generally in morning, during weekdays and Saturdays, with roughly equal numbers of participants assessed during each season. There were strong attempts to examine participants within a

6 week window of their year 0 anniversary date; however, this was relaxed in many cases, for practical reasons.

Environmental exposures. The primary environmental exposure variables are long-term ozone and PM_{10} air pollution during the study period. Individual-level air pollution exposures were estimated using air pollution measurements from the U.S. Environmental Protection Agency (EPA). EPA Aerometric Information Retrieval System (AIRS) monitoring system. We used inverse distance weighted (IDW) averages of the closest monitors to geographic coordinates of the participant's residence(s), limiting the distance to those operating monitors within 200 miles and selecting up to the closest 12 monitors. This technique is appropriate because PM and ozone are relatively spatially homogeneous pollutants and exhibit high correlations among monitors (U.S. EPA 2012; U.S. EPA 2009). Ozone is more spatially homogeneous than PM; however, PM is more representative of personal exposures that include indoor and outdoor exposure to ambient source pollution compared to ozone.

Geocoordinates for Air Pollution Exposure Assignment. The anonymized (not linked to participant identifiers) street addresses for each respondent's residence at each CARDIA exam were submitted for batch geocoding by Tele Atlas, Inc. in 2004 and 2008 (Gordon-Larsen 2015). Only geocodes created through this procedure were available for matching with environmental variables in this study; respondents who had no current address on file or whose address could not be resolved by the geocoding software were not included in this study. In particular, geocoding was attempted as a street segment address match, then as a 9-digit zipcode centroid match, which is roughly equivalent to a street segment match. If this failed, a less precise 7- and 5- digit zipcode centroid match

was attempted. To protect confidentiality, a random shift of 0 to 50 meters was added, creating a fuzzed geocoded location (within a maximum of 100 meters from the respondents' residential locations). Geocodes were not available for Year 2 or Year 5. For this study, missing exam Year 2 and Year 5 geocodes were imputed from Year 0 and Year 7 addresses and county codes. If a participant moved between exams but remained in the same county, we randomly assigned their imputed exposure to either the initial or final year location. If the participant moved out of the county or did not have an exam date, we did not impute a value for Years 2 and 5.

To protect confidentiality, a separate analyst performed the imputation and assigned maximum 8-hour ozone and 24-hour PM_{10} values from a set of air quality monitors closest to the fuzzed participant residential coordinate. The IDW values (using the inverse of the squared distance) were calculated from measured pollutant concentrations from the nearest 1 to 12 monitors with a 200-mile radius of the participant's residential address, using standard practices widely used in air pollution epidemiologic studies (Jerrett et al. 2005; Rivera-González et al. 2015). The residential geocodes were deleted and the environmental variables were matched via an interim participant identification number with the other CARDIA variables for analysis. With respect to pollution indicator, $PM_{2.5}$ was not routinely monitored until after the 1997 standards were set; thus, for this study, PM_{10} was selected to represent particulate exposures. For pre-1990 values, Total Suspended Particles (TSP) values were multiplied by 0.55 to represent the PM_{10} fraction (Ostro 2004; U.S. EPA 1982). For winter periods when some ozone monitors are not operated, we used a random draw from a distribution of background concentrations of measured wintertime ozone values estimated using

observations (n= 340,852) collected during the cold season October – April 2007 - 09 (mean of 36 ppb, SD 12 ppb) (U.S. EPA 2012a). Most PM monitors are operated year-round on a 1-in-3 or 1-in-6 day schedule. With respect to exposure period prior to the exams, we selected *a priori* the annual averaging time and the creation of a long-term exposure variable. The exposure assessment thus effectively assumed that the CARDIA participants lived at the address for one year prior to the exam. Under this assumption, we computed annual averages (AP_{ij}) of either PM_{10} or ozone exposure. These annual mean exposures were in turn averaged over all the exams that participant attended during the study period to create the long-term exposure variable ($APStudyMean_i$) that we used in our models. We defined $APStudyMean_i$ as follows:

$$APStudyMean_i = \Sigma (AP_{ij}) \div (NumberExams_i)$$

where AP_{ij} is the annual average air pollution exposure for participant *i* prior to exam *j* and $NumberExams_i$ represents the number of exams attended by participant *i* during the study. Thus, $APStudyMean_i$ is the participant's mean of either PM_{10} or ozone exposure, averaged over all available estimates.

Obesity Status. Participant body weight was measured at each exam in light clothing to the nearest 0.1 kg using a calibrated balance beam scale. Height was recorded without shoes to the nearest 0.5 cm using a vertical ruler. Body Mass Index (BMI) was computed in kg/m^2. Waist and hip measurements were recorded to the nearest 0.5 cm. Comparison across technicians was performed for body size measurements and overseen by a study certification review committee. We considered alternatives to BMI but many of these measurements were not available during the exam in which lung function measurements were taken. In preliminary modeling analysis, we used continuous BMI as

well as standard classifications of obesity and overweight based on BMI at each exam (Baseline and years 2, 5, 10 and 20). In the final model for clarity of interpretation, we used a two-part definition excluding pregnant participants and using standard cutpoint for obesity of BMI $\geq$ 30.0 kg/m^2.

Covariates. Because PM and ozone exposures may act independently on the body through different mechanisms, we examined the covariates used in the literature for both pollutants and exposure periods. We selected other covariates *a priori* based on covariates used in studies of long-term PM exposures (Downs et al. 2007; Eckel et al. 2012b; Rice et al. 2015b; Schwartz 1993b) and for ozone exposures (Alexeeff et al. 2007; Forbes et al. 2009; Gauderman et al. 2015; Rice et al. 2015a). We included both (1) time-invariant covariates and their interaction with time and (2) repeated measure time-varying variables. Time-invariant covariates included an indicator variable of CARDIA field center for initial exam, sex verified at second exam, race/ethnicity (Black or White), education (attainment by age 30), and height. In addition, we included time-varying variables including age, age-squared, lifetime smoking pack-years, obesity status, and lifetime asthma.

In the CARDIA cohort, demographic, lifestyle characteristics and medical history were self-reported using a questionnaire. Disease status was obtained through self-report of doctor diagnosis, and medication use. The definition of current and lifetime asthma evolved over the period of the study. In Years 0 and 2 current asthma indicated if a doctor had ever confirmed asthma or the participant was still having asthma or on asthma medications. In Year 5, current asthma was defined as a participant who responded that he or she was taking asthma medications, while in other years, current asthma indicated

self-report of ever having asthma or having asthma within the last year or on asthma medications. Lifetime asthma is defined as ever having current asthma.

Lifetime smoking pack-years is a continuous variable and represents the accumulated pack years assuming continuous smoking among exam years. In annual contacts between exams, participants were asked about current number of cigarettes smoked, which were then included in the lifetime smoking pack-years variable. Current smoking status has three categories: never smokers, former smokers, and current smokers. Additional information about the definitions of variables and the forms used to collect the data are available on the CARDIA webpage (http://www.cardia.dopm.uab.edu/study-information/derived-variables-from-cardia-data).

Analytic Dataset. As shown in Figure 2.1, we excluded transgender participants (n=2) and one participant who withdrew consent. Of the 5,115 participants initially enrolled in CARDIA, after exclusions, 5,026 had complete data on the lung function outcome and clinical covariates used for the analyses. The obesity variable does not include women pregnant at the time of exam, and they are excluded for those exams. After these exclusions, for annual average PM_{10} 5,033 participants (18,404 observations) had information about residential history and exam date during 1985–2006 and an operating nearby community air quality monitor that allowed us to assign air pollution concentrations. We also imputed baseline center by closest state of residence at Year 0 or Year 2 for 175 participants with missing baseline center using baseline state of residence. We restricted our primary analyses to participants with complete outcome and covariate information at a given exam, for a final analysis dataset of 5,026 participants (18,600 observations).

Descriptive Statistics. We calculated descriptive statistics on the characteristics of the study population at baseline by obesity status. We also analyzed the long-term air pollution concentrations and lung function outcome variables by sex. We computed correlation and constructed graphs such as box plots and scatter plots to visualize relationships in the data and to check distributional assumptions.

Statistical Techniques. Several temporal trends in both outcome and response variables, in addition to temporal correlations among them were accounted for in our methods. Considering the study's repeated measure structure, we selected mixed effects longitudinal regression models because lung function measures over time in the same individual are not independent. We fitted the models in SAS v 9.4 (Cary, NC). First, we selected the best fitting model for the main effect of long-term air pollution exposure on lung function using Akaike's Information Criterion (AIC), which is an indicator of the goodness of fit of a model penalized by the number of parameters in the model (Singer, Judith D; Willett 2003). Our final model followed Jacobs et al. (Jacobs et al. 1999).

For Y_{ij} (i.e., FEV_1, FVC, FEV_1/FVC) from participant i at exam observation j we assume:

$$Y_{ij} = b_i + \beta_0 + \beta_1 Age_{ij} + \beta_2 Age_{ij}^2 + \beta_3 Time_{ij} + \beta_4 APStudyMean_i$$
$$+ \beta_5 APStudyMean_i * Time_{ij} + \beta_6 Obesity_{ij} + \beta_7 Obesity_{ij} * Time_{ij}$$
$$+ \beta_8 Obesity_{ij} * APStudyMean_i$$
$$+ \beta_9 Obesity_{ij} * APStudyMean_i * Time_{ij}$$
$$+ \alpha X_{ij} + \gamma X_i + \delta X_i * Time_{ij} + \varepsilon_{ij}$$

where b_i represents participant i's random intercept. Age_{ij} represents age as a continuous centered variable measured in years minus 25 years for each individual from birth, and $Time_{ij}$ is the continuous time in years since a participant's first exam. Variables were

centered and rescaled to retain the property that change in age equals change in time within each participant. As defined above, $APStudyMean_i$ represents individual–level long-term air pollution exposure. $Obesity_{ij}$ represents the time-varying binary variable for obesity status ($BMI \geq 30$ kg/m^2). X_{ij} indicates time-varying adjustment covariates, while X_i denotes time-invariant covariates. Finally, X_i*Time_{ij} represents the change over time in adjustment covariates. We tested the significance of the association of a three-way interaction $Race_iSex_iTime_{ij}$ with lung function. Although the term was not significant at the 95% confidence level, we retained it because it improved AIC. For each of the three lung function outcomes, we fit PM_{10} and ozone exposure models each containing a subject specific random intercept and each adjusting for fixed effects. We estimated the parameters in these models via restricted maximum likelihood.

To test our hypotheses, we conducted a Wald test of significance (at the 0.05 level) for the beta coefficients of the two terms related to the obesity effect modification on level and rate of change: $Obesity_{ij}*APStudyMean_i$ and $Obesity_{ij}*APStudyMean_i*Time_{ij}$. β_4 represents the amount of average lung function (over all measures during the study within a person) difference per unit of long-term exposure for those with $BMI < 30.0$ kg/m^2. When added to β_4, the coefficient β_8 of $Obesity_{ij}*APStudyMean_i$, represents the average effect that the individual–level long-term air pollution exposure has on lung function among participants who were obese at any exam compared to participants with $BMI < 30.0$ kg/m^2. Accordingly, β_8 represents the difference in lung function level at the initial exam per one unit increase in the long-term air pollution exposure among the participants who were or became obese compared to the non-obese participants. Similarly for rate of change, the β_9 for the three-way interaction $Obesity_{ij}*APStudyMean_i*Time_{ij}$, added to

β_5, can be interpreted as the per year change in lung function per unit of the long-term air pollution exposure among the participants who were or became obese compared to the non-obese participants.

We examined only additive scale effect models for the interaction. Our reference category was white male, average height (1.7 meters), age 25 years, with average long-term air pollution exposure, high school education, non-smoker, no asthma, BMI <30 kg/m^2, and attending the Oakland field center at baseline. We evaluated separately a 10 µg/m^3 increase in long-term PM$_{10}$ exposure and a 10 ppb increase in long-term ozone exposure Note that long-term here means approximately 21 years, depending on followup period per participant. Standard model diagnostics were explored including graphics of residuals for evidence of non-normality, influential outliers, and omitted covariates. As sensitivity analyses, we examined a series of cross-sectional models by age categories, and we stratified by sex.

Results

Participant Characteristics. In Table 3.1 we present the exam observations among participants, divided into three baseline BMI categories. The original study design sought approximately equal numbers of men and women, Blacks and Whites, and 18-24 year-olds and 25-30 year-olds. In our analytic dataset, participant characteristics differed by BMI category. Transitions in obesity status were common, with those who were heaviest at baseline gaining the most weight during the study period. As shown in Table 3.1, about 63% of the baseline participants had a baseline BMI < 25 kg/m^2. About 24% of the baseline participants were overweight (BMI $\geq$ 25 kg/m^2 and less than 30.0 kg/m^2)

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at the baseline exam and 12% were obese (BMI $\geq$ 30.0 kg/m^2). Although weight and BMI differ among these categories, average height was similar across the three groups, indicating that BMI may be representing weight and not simply frame size. Of the observations among the obese compared to among the leanest group, the average age was higher, more Blacks (73%), female (67%), less educated (14.3 years education by age 30 years), and higher prevalence of illness at baseline. CARDIA participants tend to have higher weight than contemporary national samples (Thyagarajan et al. 2008).

With respect to PM$_{10}$ exposures, the lean group had slightly lower baseline annual average and long-term exposure mean than overweight or obese participants. For ozone exposures, the lean group had slightly lower baseline annual mean and similar long-term exposures compared to overweight or obese participants.

Because we were unable to match air quality values to all participants, we examined characteristics in our analytic dataset (i.e., participants with air quality values at an exam) compared to participants without air quality assignment. A total 475 participants (6,008 observations) with lung function measurements were missing air quality values. The characteristics of the CARDIA participants used to fit the model compared with those excluded did not differ except in the following ways. Participants with higher average baseline lung function measurements were missing air quality values in Year 0. Although in the overall study more Blacks were lost to follow up than Whites, among those participants with lung function measurements, we were unable to assign air quality exposures to more White (73%, 346 participants) than Black participants (30%, 142 participants) in the baseline year. Approximately 75% of the participants (356)

without air quality assignment attended the Minneapolis Field Center in the baseline year, but in subsequent years, a more even distribution across initial field centers was noted.

Annual Average Air Pollution Exposure and Lung Function by Exam. Table 3.2 shows the cross-sectional air pollution annual average exposures that constitute the study mean by sex and exam year. The distribution of air pollution exposures differed over time and by baseline center. In general, PM_{10} levels were declining after Year 5 (1990). Moreover, the highest PM_{10} exposures for the 21 years were observed more frequently during the baseline year (1984-86) and in Birmingham and Chicago compared with Minneapolis and Oakland in 1984-86. In our sample, mean ozone annual average exposures were rising over the study period.

The annual average PM_{10} and ozone long-term exposures were 30.5 µg/m^3 (SD 5.2) and 35.3 (SD 5.8), respectively. The long-term PM_{10} exposure varied by baseline field center: Birmingham 36.7 µg/m^3 (SD 2.8), Chicago 34.0 µg/m^3 (SD 2.8), Minneapolis 26.8 µg/m^3 (SD 2.1) and Oakland 26.2 µg/m^3 (SD 2.3). Likewise, the long-term ozone exposure varied by baseline field center: Birmingham 42.5 ppb (SD 1.4), Chicago 35.4 ppb (SD 2.3), Minneapolis 36.2 ppb (SD 1.8) and Oakland 28.8 ppb (SD 4.7).

At initial recruitment, CARDIA participants lived in 4 counties in 4 states. Approximately 4 percent (n=216) reported residence in 45 additional unique counties; we assume that these were parental or permanent addresses given by the young adults under study. Over the 20 years of follow up, CARDIA participants resided in 753 unique counties across all participants and exams. About 80% of the participants still lived in the baseline county at year 7 (Birmingham 83%, Chicago 99%, Minneapolis 74%, Oakland

73%), 72.4% in Year 20. Air pollution levels vary by geographic region. Because of the way ozone is formed photochemically from precursors, ozone is especially highly correlated regionally across urban and suburban areas (U.S. EPA 2012a). In our analytic dataset, air pollution exposures as well as other covariates (e.g., educational attainment, socioeconomic class) and unmeasured potential confounders (access to health care or dietary intake of anti-oxidants) may be spatially related (Richardson et al. 2014; Zamora et al. 2010). Overall, neighborhoods improved in terms of economic and social indicators for the CARDIA participants over 20 years (Richardson et al. 2014). One of the strongest period relationships in the study was that air pollution varied by age category in our sample, with opposite directions for PM_{10} and ozone (Table 3.2).

Models with Lung Function, Air Pollution and Obesity Status

Particulate Matter Exposure, Lung Function, and Obesity Status. As shown in Table 3.3, we examined two aspects of the effect modification relationship between long-term PM_{10} exposure and average lung function during the study follow up: the effect modification by obesity in the level and the rate of change; in other words we studied if the effect modification by obesity changed with time. As shown in Table 3.3, no effect modification by obesity was observed for the associations between long-term PM_{10} exposure and FEV_1, FVC or the ratio FEV_1/FVC. This lack of effect modification did not vary with time, nor when we stratified by sex.

Ozone Exposure, Lung Function, and Obesity Status. Likewise, we examined two aspects of the effect modification of the relationship of long-term ozone study mean

exposure with average lung function during the study follow up: we assessed the effect modification by obesity and we examined if this effect modification changed with time (Table 3.3).

No effect modification by obesity was observed for the associations between FEV_1 or FVC and long-term ozone exposure level. With respect to the rate of change, the effect modification by obesity status was different for FEV_1 and FVC. A 10 ppb higher ozone long-term exposure was associated with a 2.3 ml per year higher FEV_1 (SE 1.0, p-value 0.04) among participants who were obese at any exam compared to non-obese participants. When stratified by sex, there was no evidence of a stronger obesity effect-modification in either the level or rate of change in FEV_1 among women compared to among men.

For FVC level, after accounting for the temporal and correlation in the data and controlling for confounders, we found that a 10 ppb higher ozone long-term exposure was associated with a 27 ml greater decrease in FVC (SE 16.5, p-value 0.1) among participants who were obese at any given time compared to non-obese participants, accounting for the repeated measures in the same subjects and controlling for confounders. This relationship becomes less negative with the passage of time; specifically, a 10 ppb increase in ozone long-term exposure is associated with a 2.1 ml per year increase in FVC (SE 1.05, p-value 0.04) among participants who were obese at any exam compared to non-obese participants. When stratified by sex, no difference in the effect modification by time with FVC was seen.

No effect modification by obesity was observed for the relationship of long-term ozone exposure with the ratio FEV_1/FVC. The data do not provide significant evidence

that the relationship between long-term ozone exposure and lung function in the obese changed with time or by sex.

Discussion

Given age-related increases in weight and overall population increases in weight and obesity prevalence, the primary goal of this study was to characterize the extent to which obesity status among non-elderly adults modifies the association between air pollution exposure and lung function metrics. We hypothesized that among obese non-elderly adults compared to non-obese adults, long-term PM and ozone long-term exposure are (1) more strongly and negatively associated with FEV_1 and FVC, and (2) more strongly and positively associated with FEV_1/FVC than among non-obese adults, (3) the association between PM_{10} and ozone long-term exposures and FEV_1 and FVC become more negative with time, and (4) the association between PM_{10} and ozone long-term exposures and FEV_1/FVC become more positive with time.

Our hypotheses are supported by data from controlled ozone exposures and deposition studies in human subjects (Bennett and Zeman 2004; Brown et al. 2008; McDonnell 2010), toxicologic data for ozone and particulate matter (Dye et al. 2015b; Shore et al. 2003, 2009), and epidemiologic data for ozone and particulate matter (Adam et al. 2015; Alexeeff et al. 2007; Dong et al. 2013; Downs et al. 2007; Gauderman et al. 2015; Miller et al. 2007; Schikowski et al. 2013a; U.S. EPA 2009, 2012a). The results do not support our first hypotheses. Instead we observed no effect modification by binary obesity status ($BMI \geq 30$ kg/m^2) for long-term ozone or PM exposures. Our results did not support our second hypothesis that obesity status modifies the positive association

between long-term PM and ozone exposures and FEV_1/FVC. In contrast to our third hypothesis, our results provided evidence of a positive effect modification by time of the obesity/ozone air pollution association with FEV_1 and FVC. We observed no effect modification by sex of this relationship. Finally, we observed no evidence of a change in therate of the effect modification by obesity status of the long-term pollution exposure association with FEV_1/FVC association. FVC reflects total lung compliance, which encompasses both the lung and the chest wall. FEV_1 reflects these factors plus airway resistance. In a healthy population, the decrease in elasticity with age affects FEV_1 more than FVC, resulting in a decrease in the FEV_1/FVC ratio over time (Lin and Lin 2012). However, among the obese, the FEV_1/FVC ratio is larger and the loss of elasticity has a greater effect on FVC, resulting in an expected increase in the ratio among this subgroup.

Our PM exposure results are in contrast to the Schikowski et al. study in which they reported that long-term PM exposure related decline is more pronounced among people with excess weight than normal weight participants (Schikowski et al. 2013a). Few studies examine the effect of excess weight and obesity on the association of long-term PM exposure and lung function. Some of the observed long-term ozone associations with FEV_1 and FVC are opposite of what we hypothesized.

Similarly, few long-term ozone studies have examined the joint question of the effect of obesity and long-term ozone exposures on lung function. In the model with long-term ozone exposure, when we considered rate of change and obesity, the aging effect modification of the relationship between ozone long-term exposure and FEV_1 and FVC was positive for obese participants and for obese men, indicating an improvement or lessening of lung function decline related to long-term ozone with the passage of time.

We observed no evidence of a sex difference with respect to the effect modification by time-varying obesity of the association of lung function and long-term PM_{10} or ozone exposure.

Few studies have explicitly addressed the question of whether associations between long-term pollution exposures and lung function are modified by excess weight, thus making comparison challenging. Effect modification by obesity of a short-term 2-day ozone exposure on lung function in 904 mainly White elderly men from the Veterans Administration Normative Aging Study (NAS) was evaluated (Alexeeff et al. 2007). An increase of 15 ppb 2-day mean ozone was associated with a greater percent decline in FEV_1 among obese (-2.07% (95% CI -3.25, -0.89%)) compared to nonobese (-0.96% (95% CI -1.70, -0.20%)) participants and similar associations were reported with FVC (Alexeeff et al. 2007). Although our model is examining the long-term (~21-year) exposures and not period cross-sectional associations, the implication is that as time passes, participants who were obese at any given exam, would have an increasingly positive relationship between the long-term ozone exposure and the average lung function (FEV_1 and FVC) over the duration of the study. Our model also assessed our hypotheses in a population that included a larger number of Black participants than the NAS, and the CARDIA sample included women.

Other ozone short-term exposure studies have examined spirometry in women and men with mixed results by sex. Among healthy nonsmokers, enhanced FEV_1 decrements were reported following short-term ozone exposure in the overweight and obese category compared with normal weight women, although not in men (Bennett et al. 2007; Hazucha et al. 2003). In controlled human short-term ozone exposure studies of healthy adults,

increased BMI was associated with greater FEV_1 responses (McDonnell 2010). In contrast, a retrospective study reported no significant correlation between BMI and ozone-induced decrements in FEV_1 or FVC but did report associations between short-term ozone exposure and IL-1β in sputum and blood among overweight participants (Todoric et al. 2015).

Strengths. This study contributes to the limited literature in this field by analyzing a young cohort followed for over 20 years with a large number of observations, individual, detailed participant data, and standard outcome definition and data collection. The study contained a substantial number of observations with obese and overweight participants. Limited evidence is available on air pollution-related pulmonary effects among obese and overweight groups. This analysis tested community air pollution-related hypotheses in the CARDIA cohort, expanding our knowledge of air pollution-related lung function effects in Black and White young adults, especially with respect to the effect modification by obesity status. The air pollution exposure was assigned to participants based on individual residential history using techniques established in the literature. The air pollution monitoring data are well-documented, quality assured and represent large portions of the U.S. population over a significant period of time and geography during the study. Monitoring data are moderately well correlated with personal exposures (U.S. EPA 2012a). The air pollution exposures were calculated at the individual level, strengthening our inferences over simple area-wide annual averages. The four original study areas comprised of mainly four counties in four states were expanded as participants moved, covering a range of different types of environments and climates.

Limitations. The use of a binary obesity status covariate is a principal limitation in this analysis. Furthermore, BMI on which this variable is based has limitations as a measure of obesity. For example, at the same BMI, women tend to have more body fat than men and Whites have more body fat than Blacks (Wagner 2000). Waist circumference may better reflect abdominal adiposity. Although the correlation between BMI and fatness is fairly strong, BMI does not account for body composition. Other direct measures of body fat may be preferable, such as skinfold thickness measurements, bioelectrical impedance, densitometry (underwater weighing), or dual energy x-ray absorptiometry.

Potential exposure and outcome misclassification is another limitation in the study. For air pollution exposure, community monitoring of ambient levels may misclassify individual exposure. For instance, misclassification may be greater for those participants who reside or spend their day in climate controlled settings, have occupational exposures not reflected in community monitors, further away from monitors, near heavy traffic, or who have lengthy commutes in traffic (higher PM_{10} if within 300 meters and lower ozone due to nitrogen dioxide scavenging). Time of day of exam may be an additional factor contributing to exposure misclassification due to the diurnal patterns of photochemical air pollutants. Because of its spatial homogeneity and superiority as an indicator for causal agents, $PM_{2.5}$ would be a better indicator than PM_{10} but was not monitored routinely until the late 1990s. A potential improvement would be to consider $PM_{2.5}$ measures or air quality modeling to improve more recent exposure estimates (Sampson et al. 2013). The addition of random low-level winter ozone values may have limited the ability to detect ozone effects. Another source of measurement error

stems from the precision of measurement for individual pollutants, although this is likely a small source based on EPA's Quality Assurance audit program analysis (Cox 2007; Musick 1995). As the monitoring network expanded and methods improved, the precision of the measurements has also improved. EPA requires by regulation collocation of PM monitors, flow rate checks and comparisons, and data completeness (Cox 2007).

Another potential limitation is the possibility that participants who lived in more polluted areas were differentially lost to follow up. We were unable to assign estimated exposures to more participants who attended the Minnesota center, which was a relatively lower ambient concentration area in the year 2 and 5 exams, which might introduce a negative bias in the results. Other studies in the CARDIA cohort- report no major systematic differences in terms of education and other covariates among participants lost to follow up, with the exception of more Blacks were lost to follow up in the early years. In the present study, different patterns of residential moving may be a limitation since moving may be related to SES and educational attainment, and educational attainment is related to air pollution exposure in our data, with both the lowest (less than high school) and highest educated participants experiencing higher exposures than high school graduates or those with some college.

Several time-related trends during the study period may have affected the observed associations. For ozone, opposite trends in the data may contribute to a null association. Participants are aging, and controlling for other covariates, people over age 35 are less responsive to the same ozone concentration than those under 35 years. Air pollution levels change over time. Upper percentile distributions of air pollution exposure

can be important to changes in lung function because, for example, FEV_1 response to ozone depends on the ozone concentration, with larger response related to higher concentrations (Brown et al. 2008). Moreover, between-participant variability complicates the identification of the seasonal and meteorological trends in the health data (Szpiro et al. 2013).

As people age, gain excessive weight, or develop chronic diseases, they may also take more medication or change behavior, which may in turn affect their exposures or their responsiveness to air pollution. In addition, an obesity paradox has been observed among COPD, chronic heart and kidney disease patients in which, without control for musculature or early medical intervention, obese patients appear to survive longer than non-obese (Galesanu et al. 2014). Our modeling did not control for medication use, change in behaviors, or muscle mass. Our study suggests the need for more investigations, perhaps using alternate metrics of obesity, to confirm the observation of a protective effect of age and obesity on the long-term ozone exposure-lung function relationship.

Conclusions

Excess weight was not an effect modifier of the relationship between either PM_{10} or ozone exposures and lung function levels in this study. We observed a small positive effect modification by obesity of the rate of change in the relationship between long-term ozone exposure and FEV_1 and FVC. However, although the relationship between ozone short-term exposure and lung function decrements has been shown to be causal in humans in controlled laboratory experiments, in our community sample, we generally did

not observe a primary association or interaction among lung function, obesity status and ozone long-term exposure for FEV_1 and FVC. We did not observe sex differences.

In light of the few published studies on the effect modification by obesity of the air pollution/lung function association, and the importance of this potentially vulnerable population, this study adds new evidence to the discussion about at-risk populations and the associations between long-term air pollution exposure and lung function. Our unexpected results deserve further exploration both in the CARDIA population, using more precise exposure and adiposity estimation and models, and in other cohorts.

Figures

Figure 3.1. Summary of Inclusion Criteria
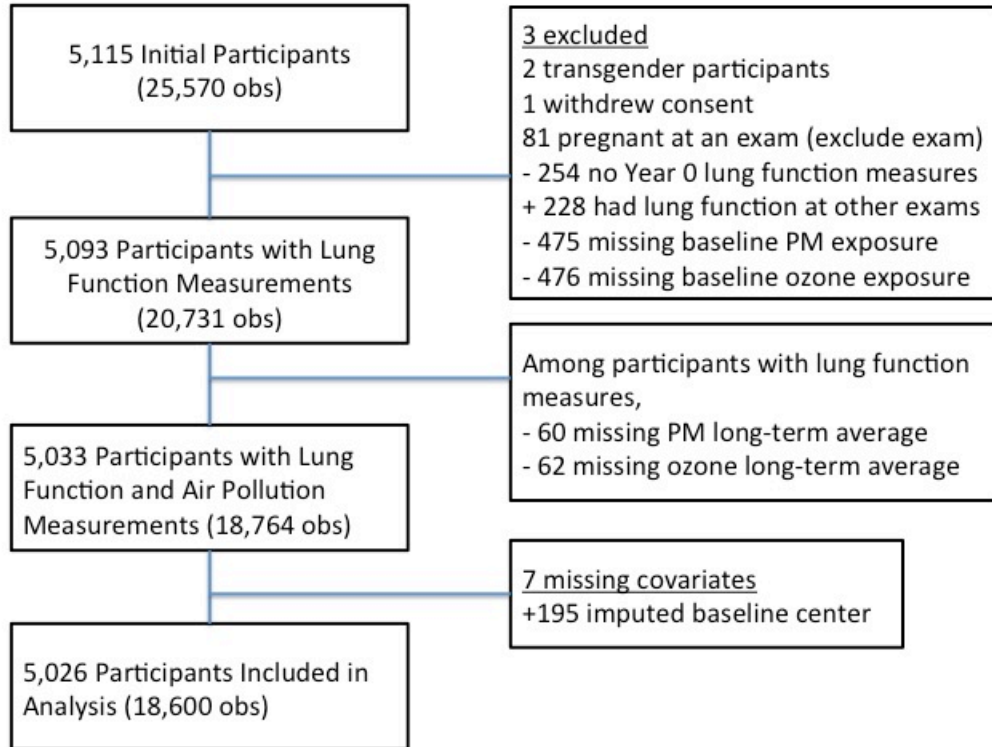
Abbreviations: PM, particulate matter; BMI, body mass index; obs, observations

Tables

Table 3.1. Demographic, Clinical, and Air Pollution Baseline Characteristics by Baseline BMI Category for Participants Included in the Analyses (n=4,360); CARDIA 1985-2006.

	Lean	Overweight	Obese
	BMI < 25.0 kg/m^2 n=2,781	25.0 to < 30.0 kg/m^2 n=1,034	≥ 30.0 kg/m^2 n=545
Demographic Characteristics			
Age, years (mean±SD)	24.6 ± 3.7	25.2 ± 3.6	25.5 ± 3.6
% Female	54%	45%	67%
% Black	48%	58%	73%
Education attained by age 30 years (mean)	15.0	14.7	14.3
< High school	5%	5%	6%
High school graduate	19%	22%	24%
Some college	30%	35%	41%
College graduate or more	47%	38%	30%
Baseline Exam Center (% distribution)			
Birmingham, AL	23%	25%	28%
Chicago, IL	23%	24%	22%
Minneapolis, MN	23%	24%	21%
Oakland, CA	31%	27%	30%
Baseline Body Mass Index			
Baseline BMI, kg/m^2 (mean±SD)	21.8 ± 2.0	27.0 ± 1.4	35.0 ± 4.9
Height, m, (mean±SD)	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1
Weight, lbs, (mean±SD)	140.0 ± 21.1	175.3 ± 20.9	218.9 ± 37.9
Waist circumference, cm (mean±SD)	72.4 ± 6.7	83.8 ± 6.9	97.4 ± 11.9
Baseline Smoking and Disease Status			
Pack-year of cigarettes (mean±SD)	2.2 ± 4.4	2.3 ± 4.5	2.3 ± 4.7
Smoking status (% distribution)			
Never	56%	59%	58%
Former	13%	13%	10%
Current	31%	29%	32%
Alcohol consumption, ml	12.3 ± 21.1	13.0 ± 22.3	9.6 ± 21.7
Lifetime asthma[a] (% distribution)	9.6%	9.4%	12.1%
Elevated blood pressure[b] (% distribution)	5.6%	11.1%	17.1%
Diabetes[c] (% distribution)	0.4%	0.4%	1.7%
Baseline Air Pollution Exposure			
PM$_{10}$ annual average, µg/m^3 (mean±SD)	31.9 ± 5.0	32.2 ± 5.0	32.3 ± 5.1
Ozone annual average 8-hour max, ppb (mean±SD)	31.5 ± 6.7	32.0 ± 6.5	32.3 ± 6.8
Participant-Specific Long-term Air Pollution Exposure			
PM$_{10}$ annual study mean, µg/m^3 (mean±SD)	30.5 ± 5.0	31.0 ± 5.2	31.2 ± 5.2
Ozone annual study mean, ppb (mean±SD)	35.0 ± 5.9	35.0 ± 8.8	35.1 ± 6.3
Baseline Lung Function			
FEV$_1$, ml (mean±SD)	3,552.3 ± 760.1	3,631.3 ± 827.9	3,240.9 ± 755.6
FVC, ml (mean±SD)	4,286.0 ± 986.2	4,444.6 ± 1,061.3	3,929.2 ± 981.9
FEV$_1$/FVC (mean±SD)	0.83 ± 0.07	0.82 ± 0.06	0.83 ± 0.06

[a] Lifetime Asthma is defined as current asthma at any exam. Years 0 & 2, doctor confirmed or on asthma medications. Year 5, taking asthma medications, and other years, self-report of ever having asthma within last year or on asthma
[b] Systolic BP ≥ 130 mm Hg or diastolic BP ≥ 85 mm Hg or on hypertensive medications.
[c] Fasting glucose level ≥ 126 mg/DL or on diabetic medications but not pregnant.

Abbreviations: PM$_{10}$ particulate matter with aerodynamic diameter <10 microns; CI, confidence interval; FEV$_1$ forced expiratory volume in 1 second; FVC, forced vital capacity; ppb, parts per billion; ug/m^3 micrograms per cubic meter, kg/m^2, kilograms per meter squared; Lean Body Mass Index (BMI) <25 kg/m^2; Overweight, BMI greater than or equal to 25 kg/m^2 and less than 30 kg/m^2; Obese, BMI equal to or greater than 30 kg/m^2; ml, milliliters.

Table 3.2. Particulate matter (PM$_{10}$) and ozone exposures and lung function outcomes (annual mean and standard deviation) averaged across all sites and by sex and exam period for participants with complete data (n=4,360); CARDIA 1985-2006.

	Men (nobs=8,417)				
	Year 0	Year 2	Year 5	Year 10	Year 20
Lung Function	n=2,028	n=1,669	n=1,598	n=1,668	n=1,454
FEV$_1$, ml	4095.6 (673.5)	4042.3 (686.0)	4031.8 (707.0)	3946.7 (706.9)	3610.9 (706.9)
FVC, ml	5039.7 (843.6)	5013.0 (861.2)	5033.5 (873.8)	5024.7 (885.3)	4655.3 (891.8)
Ratio FEV$_1$/FVC, %	81.6 (6.7)	80.9 (6.8)	80.3 (6.7)	78.8 (6.6)	77.8 (7.0)
Air Pollution					
PM$_{10}$ annual average exposures, µg/m^{3} [a]	32.29 (5.07)	34.54 (5.31)	34.21 (5.68)	27.65 (5.35)	25.41 (6.94)
Ozone annual average exposures, ppb [b]	32.13 (6.66)	36.39 (5.52)	35.46 (6.86)	36.67 (6.63)	38.39 (4.91)

	Women (nobs=10,183)				
	Year 0	Year 2	Year 5	Year 10	Year 20
Lung Function	n=2,332	n=1,965	n=1,918	n=2028	n=1,940
FEV$_1$, ml	3046.8 (487.9)	2997.1 (487.4)	3021.8 (507.4)	2947.3 (499.1)	2603.4 (523.1)
FVC, ml	3622.4 (597.5)	3596.4 (600.0)	3643.9 (628.5)	3646.3 (629.6)	3293.8 (680.9)
Ratio FEV$_1$/FVC, %	84.4 (6.1)	83.6 (6.3)	83.3 (6.9)	81.1 (5.9)	79.3 (6.4)
Air Pollution					
PM$_{10}$ annual average exposures, µg/m^{3} [a]	31.87 (4.85)	34.36 (5.38)	33.74 (5.62)	27.52 (5.32)	25.41 (6.81)
Ozone annual average exposures, ppb [b]	31.39 (6.70)	36.22 (5.61)	34.62 (7.14)	36.22 (6.91)	38.17 (5.12)

[a] Inverse distance-weighted average 24-hour value from nearest 1 to 12 monitors within 200 miles during period prior to the exam. Includes converted Total Suspended Particles (TSP*0.55) prior to 1990.

[b] Parts per billion (ppb). Inverse distance-weighted average 8-hour max from nearest 1 to 12 monitors within 200 miles during period prior to the exam. Includes imputed winter values when ozone not measured.

Abbreviations: PM$_{10}$ particulate matter with aerodynamic diameter <10 microns; CI, confidence interval; FEV$_1$ forced expiratory volume in 1 second; FVC, forced vital capacity; ppb, parts per billion; ug/m^3 micrograms per cubic meter; nobs, number of observations; n, number of participants

Table 3.3. Effect Modification by Obesity Status: Adjusted[a] Difference in Lung Function per 10 unit Increase in Long-term (1984-2006) Air Pollution Exposure Level and Rate of Change per Year for All Participants and Stratified by Sex, (n=5,026) CARDIA 1985-2006.

Pollutant, category	Air Pollution Exposure$_i$		(Air Pollution Exposure$_i$)*Time$_{ij}$		Obesity$_{ij}$*(Air Pollution Exposure$_i$)			Obesity$_{ij}$*(Air Pollution Exposure$_i$)*Time$_{ij}$		
	Estimate	SE	Estimate	SE	Estimate	SE	Sex Diff p-value	Estimate	SE	Sex Diff p-value
FEV$_1$, ml										
PM$_{10}$										
All Participants	-20.4	22.9	-1.61	0.89 #	-10.8	15.8		0.60	1.02	
Male	-34.1	38.9	-1.89	1.43	-6.2	28.1	0.74	0.96	1.79	0.91
Female	1.9	25.9	-1.78	1.10 #	-14.0	18.2		0.59	1.20	
Ozone										
All Participants	24.7	19.5	0.072	0.74	-13.5	14.6		2.25	0.93 *	
Male	7.0	35.4	0.03	1.27	-4.8	27.5	0.61	3.57	1.72 *	0.36
Female	47.3	21.0 *	-0.10	0.88	-18.3	16.1		1.73	1.06 #	
FVC, ml										
PM$_{10}$										
All Participants	-53.6	27.3 *	-0.48	1.00	-17.3	17.9		0.84	1.15	
Male	-79.2	45.8 #	0.46	1.59	-7.7	31.5	0.63	0.87	2.00	0.88
Female	-13.9	31.1	-1.98	1.25 ††	-22.2	20.8		1.10	1.36	
Ozone										
All Participants	40.9	23.3 #	0.24	0.84	-27.0	16.5 *		2.10	1.05 *	
Male	25.8	41.6	1.57	1.42	-30.0	30.9	0.92	3.76	1.93 *	0.32
Female	63.8	25.2 *	-0.79	1.00	-24.9	18.4		1.55	1.20	
FEV$_1$/FVC Ratio %										
PM$_{10}$										
All Participants	0.49	0.31	-0.021	0.015	0.11	0.27		-0.006	0.018	
Male	0.84	0.47 #	-0.057	0.022 †	0.05	0.41	0.87	0.003	0.027	0.68
Female	0.17	0.41	0.010	0.022 ††	0.12	0.35		-0.012	0.024	
Ozone										
All Participants	-0.24	0.27	0.006	0.013	0.19	0.24		0.007	0.016	
Male	-0.13	0.43	-0.028	0.019	0.51	0.40	0.32	-0.004	0.026	0.62
Female	-0.31	0.33	0.026	0.017 ††	0.01	0.30		0.011	0.021	

[a] Adjusted for age, age-squared, time since initial exam, education attained by age 30 years, sex, race/ethnicity, interaction of sex*race/ethnicity, baseline center, obesity, height, lifetime pack years smoking, lifetime asthma, and time-interactions with time-invariant variables.

p-value ≤ 0.10   * p-value ≤ 0.05   † p-value ≤ 0.01
†† Sex Difference interaction p < 0.05

Abbreviations: PM$_{10}$ particulate matter with aerodynamic diameter <10 microns; CI, confidence interval; FEV$_1$ forced expiratory volume in 1 second; FVC, forced vital capacity; ppb, parts per billion; ug/m^3 micrograms per cubic meter, kg/m^2, kilograms per meter squared; Obese, BMI equal to or greater than 30 kg/m^2; ml, milliliters

CHAPTER IV
Conclusions and Future Research

The overall goal of this dissertation was to understand factors that contribute to vulnerability and susceptibility of populations to respiratory effects from air pollution. Exposures to ozone and PM_{10} are independently associated with adverse respiratory effects including changes in lung function as measured by forced expiratory volume in one second (FEV_1) in healthy adults, respiratory symptoms, new-onset asthma, respiratory and total mortality, cardiovascular disease, and central nervous system effects.

Obese individuals may be uniquely susceptible to the pro-inflammatory effects of ozone and PM_{10} because obese humans and animals have been shown to experience a greater decline in lung function than normal weight subjects with ozone exposure. Obesity is independently associated with limitations in lung mechanics and increased ozone and PM_{10} dose. With over 78 million adults in the U.S. classified as obese, there is widespread potential for exposure to ozone air pollution among obese populations. However, few epidemiologic studies examine the interaction between excess weight and ozone exposure among non-elderly adults. This study was a first step toward addressing that gap in knowledge.

Chapter I Conclusions

We reviewed evidence in human adult subjects to identify potential response-modifying factors and to determine if obese or overweight adults are at increased risk of ozone-related lung function changes. Using PubMed and reference lists, keyword searches initially identified 169 studies, which were then examined for information about the effect of both weight (or BMI) and ozone exposure among adults regarding a respiratory function within the past 10 years. In the six studies that met the criteria, increased Body Mass Index (BMI) was associated with decreased lung function and increased inflammatory mediators. Results were mixed about the effect modification when data were stratified by sex.

The evidence suggests that obese and overweight populations should be considered as candidate at-risk groups for additional research and protection from air pollution both in risk communication and standard setting.

Chapter II Conclusions

Few studies evaluate how longer term air pollution exposures might impact lung function among young adults. We first examined the association of long-term (1984-2006) air pollution exposures with lung function level and rate of change in the CARDIA cohort. We added for the first time an air pollution exposure metric to this study.

In the CARDIA sample, long-term PM_{10} exposure was associated with small reductions in levels and rates of change of lung function in healthy young adults followed over the 21 years of study (1985- 2006). Specifically, increases in mean study-period

PM$_{10}$ exposures were associated with decreases in FVC levels and steeper decreases in aging-related rate of change in FEV$_1$. The findings imply that on average a participant living for 21 years with PM$_{10}$ exposures like in Birmingham compared to Oakland or Minneapolis would experience a reduction of 56 ml in FVC (or about 1.3% for the average CARDIA man at baseline or 1.8% for the average CARDIA woman at baseline). For long-term PM$_{10}$ exposures, rate of change in FVC decreased more among women than men. No consistent associations between long-term ozone exposures and lung function were observed among all participants, although when stratified by sex, among women we observed unexpectedly positive associations between increases in long-term ozone exposure and average FEV$_1$ and FVC level. However, the sex difference interaction was not significant at the 0.05 level. Given nonlinear temporal trends in exposure, outcome and covariates, and different modeling strategies across studies, further work is warranted to allow comparison of conflicting results in healthy young adults. Improvements in exposure assessment and other averaging times could be explored.

Chapter III Conclusions

This chapter directly tested the hypotheses that obese status populations respond more to long-term air pollution exposure than people with BMI < 30.0 kg/m^2. Higher BMI was not an effect modifier of the relationship between either long-term (1984-2006) PM$_{10}$ or ozone exposures and lung function levels in this study. We observed a small positive effect modification by obesity status of the rate of change in the relationship between long-term ozone exposure and FEV$_1$ and FVC. However, although the

relationship between short-term ozone exposure and lung function decrements has been shown to be causal in humans in controlled laboratory experiments, in our community sample, we generally did not observe a primary association or interaction among lung function, obesity status and ozone long-term exposure for FEV_1 and FVC. We did not observe sex differences.

In light of the few published studies on the effect modification by obesity of the air pollution/lung function association, and the importance of this potentially vulnerable population, this study adds new evidence to the discussion about at-risk populations and the associations between long-term air pollution exposure and lung function. Improvements could be made to overcome the limitations in this approach from the air pollution exposure estimation (in terms of averaging time and use of community monitors near residences as proxy for exposure) and the adiposity metric (binary obesity status at exam). Our unexpected results deserve further exploration both in the CARDIA population, using more precise exposure and adiposity estimation and models, and in other cohorts.

Future Directions

A practical contribution of this work was to assign air pollution exposure to CARDIA participants and to develop a SAS coding technique to assign air quality exposures to any geocoded address in the U.S. The availability of the air quality exposures in this cohort creates an opportunity to test additional air pollution exposure hypotheses in the CARDIA study.

Future directions could include improving abdominal adiposity measures and air pollution exposure metrics. More precise identification of the appropriate exposure averaging period or specific window of exposure could expand our knowledge. The use of air pollution modeling could better account for spatial variability. Regarding the hypotheses for excess weight modifying the associations with lung function, better metrics could be employed such as continuous BMI, waist circumference, or physical activity. Finally, placing the study into a cumulative environmental risk framework could improve the applicability and enhance the ability to examine hypotheses related to neighborhood or social determinants of health. This research is vitally important because both air pollution exposures and excess weight are modifiable risk factors affecting millions of people worldwide.

Additional Tables

Table A1. Adjusted[a] Difference In Lung Function Per 10 Unit Increase In Long-Term (1984-2006) Air Pollution Exposure For All Participants By Obesity Status; CARDIA (1985-2006) (n=5,026)

Pollutant, category	Pollution Year	R^2	Baseline Annual Mean$_i$			
			Beta Coefficient	SE	p-value	N
FEV$_1$, ml						
PM$_{10}$ annual average	**Y0**					
Y2-Y0 Lung Fxn		1.4	-32.2	12.2	0.01	3,713
Y5-Y0 Lung Fxn		3.3	-15.9	16.1	0.32	3,556
Y10-Y0 Lung Fxn		7.3	-19.4	14.8	0.19	3,695
Y20-Y0 Lung Fxn		17.5	-11.2	18.9	0.55	3,394
Ozone annual average	**Y0**					
Y2-Y0 Lung Fxn		1.2	-11.9	9.5	0.21	3,714
Y5-Y0 Lung Fxn		3.3	-8.3	12.3	0.50	3,556
Y10-Y0 Lung Fxn		7.3	-15.0	10.9	0.17	3,693
Y20-Y0 Lung Fxn		17.4	-11.3	13.9	0.41	3,392
FVC, ml						
PM$_{10}$ annual average	**Y0**					
Y2-Y0 Lung Fxn		4.8	-27.9	12.5	0.03	3,713
Y5-Y0 Lung Fxn		6.5	-11.5	16.9	0.49	3,556
Y10-Y0 Lung Fxn		12.2	-12.8	16.9	0.45	3,695
Y20-Y0 Lung Fxn		22.9	-1.1	23.4	0.96	3,394
Ozone annual average	**Y0**					
Y2-Y0 Lung Fxn		4.8	-15.9	9.7	0.10	3,714
Y5-Y0 Lung Fxn		6.7	-24.2	13.0	0.06	3,556
Y10-Y0 Lung Fxn		12.2	-12.0	12.4	0.33	3,693
Y20-Y0 Lung Fxn		22.7	-7.8	17.2	0.65	3,392

[a]Adjusted for age, age-squared, time since initial exam, education attained by age 30 years, sex, race/ethnicity, interaction of sex*race/ethnicity, baseline center, height, lifetime pack years smoking, lifetime asthma, and time-interactions with time-invariant variables.

Table A2. Cross sectional by Age Adjusted[a] Difference in Forced Vital Capacity (FVC) per 10 unit Increase in Participant-Specific Long-term Study Mean and Annual Mean Deviation in Air Pollution Exposure; CARDIA (1985-2006)

Pollutant	(PM Annual Avg StudyPeriodi)*Time		(PM Deviation from StudyPeriodi)*Time	
	Beta	p-value	Beta	p-value
FVC, ml				
PM_{10} annual average				
Age <30	-0.00028	0.53	0.00043	0.16
Age 30 to <40	0.000282	0.53	0.000883	0.0006
Age 40 and up	0.001487	0.19	-0.00167	0.29
Ozone annual average				
Age <30	0.000019	0.12	0.000046	0.0003
Age 30 to <40	0.000163	0.66	-0.00047	0.20
Age 40 and up	-0.00053	0.70	-0.00129	0.56

Table A3. Adjusted[a] Difference And Confidence Intervals In Lung Function Per 10 Unit Increase In Long-Term (1984-2006) Air Pollution Exposure For All Participants By Obesity Status; CARDIA (1985-2006) (n=5,026)

Pollutant BMI category	Year 0		Year 10	
	Difference (95% CI)	p-value	Difference (95% CI)	p-value
FEV_1, ml				
PM_{10}				
BMI < 30.0 kg/m^2	-20.9 (-65.7, 23.8)	0.36	-36.7 (-80.4, 7.1)	0.10
Obese	-31.9 (-83.9, 20.2)	0.23	-104.0 (-166.1, -41.9)*	0.001
Ozone				
BMI < 30.0 kg/m^2	24.4 (-13.8, 62.6)	0.21	24.6 (-13.0, 62.2)	0.20
Obese[d]	11.3 (-34.1, 56.6)	0.63	-87.5 (-149.5, -25.6)*	0.006
FVC, ml				
PM_{10}				
BMI < 30.0 kg/m^2	-54.5 (-107.8, -1.1)*	0.05	-58.4 (-110.8, -6.1)*	0.03
Obese	-71.2 (-132.4, -10.0)*	0.02	-220.2 (-292.3, -148.1)[†]	<0.0001
Ozone				
BMI < 30.0 kg/m^2	40.5 (-5.1, 86.1)[#]	0.08	42.5 (-2.4, 87.5)[#]	0.06
Obese	14.3 (-39.0, 67.6)	0.60	-154.5 (-225.9, -83.2)[†]	<0.0001
Ratio FEV_1/FVC				
PM_{10}				
BMI < 30.0 kg/m^2	0.49 (-0.12, 1.10)	0.12	0.28 (-0.31, 0.87)	0.36
Obese	0.60 (-0.16, 1.36)	0.12	1.96 (1.00, 2.93)[†]	0.0001
Ozone				
BMI < 30.0 kg/m^2	-0.25 (-0.77, 0.27)	0.35	-0.19 (-0.69, 0.32)	0.47
Obese	-0.05 (-0.71, 0.61)	0.88	1.20 (0.21, 2.19)*	0.02

[a]Adjusted for age, age-squared, time since initial exam, education attained by age 30 years, sex, race/ethnicity, interaction of sex*race/ethnicity, baseline center, obesity, height, lifetime pack years smoking, lifetime asthma, and time-interactions.

[#] p-value ≤ 0.10   * p-value ≤ 0.05   [†] p-value ≤ 0.01

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