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Application of Causal Inference Methods to Estimate Single Pollutant and Multi-Pollutant Health Effects in Asthmatic Children in Fresno, California

By

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Professor Ira B. Tager, Chair
Professor Kathleen M. Mortimer
Professor Alan Hubbard
Professor S. Katharine Hammond

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Jonathan Maclean Snowden

Abstract

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The methodological challenges associated with conducting research on air pollution mixtures are well-known: correlated co-pollutants result in unstable effect estimates and large standard errors, hindering the assignment of causality to any one exposure. There is still relatively little research in the growing multi-pollutant literature that is focused on the mixture itself as the unit of analysis. In this dissertation, I implement a statistical method from the causal inference literature to estimate the effects of ambient air pollution, as single pollutants and in a two-pollutant mixture.

I analyze the effects of single-pollutant and multi-pollutant summertime ambient air pollution exposures on pulmonary function in a cohort of children with asthma living in Fresno, California. I employ a technique from the causal inference literature, the Population Intervention Model (PIM), to describe the health effects that would result from several hypothetical interventions that involve lowering concentrations of ambient air pollution. By describing the health effects of the ambient air pollutants in these terms, this approach estimates results that are relevant to real-world policy questions. Furthermore, this analytical approach permits the calculation of air pollution health effects that correspond to multiple pollutants dynamically changing within a mixture, as ambient air pollution is actually experienced by people. I interpret each of these health effects according to whether it reflects a realistic, or even a possible, exposure scenario during the study period and in the region where data were collected. I achieve this through an examination of the individual and joint distributions of the pollutants under study.

This dissertation contains several analyses, corresponding to single- and multi-pollutant exposure regimens. In the first analysis, I analyze the effects of ambient summertime NO_2 on FEF_{25-75} in a single-pollutant approach that demonstrates the methodological approach. All analyses use central-site exposure data, assigning all subjects on a given study day the same air pollution exposure values. Ambient $PM_{10-2.5}$ is analyzed throughout as a summertime pollutant of secondary interest, both in a single-pollutant $PM_{10-2.5}$ analysis, and in a mixture analysis. For the multi-pollutant mixture analysis, I extend the Population Intervention Model framework demonstrated in the single-pollutant analyses to a two-pollutant summer analysis of ambient NO_2 and $PM_{10-2.5}$, estimating health effects associated with an intervention that dynamically alters levels of one or both pollutants. In this two-pollutant analysis, I estimate the effects of lowering

levels of one co-pollutant while "controlling for" the other (i.e., holding it at observed levels), as well as the effects of a joint intervention that decreases levels of both pollutants.

The Background chapter presents a brief history of air pollution epidemiology and policy, and reviews the epidemiologic and statistical research upon which this dissertation builds. The Methods chapter describes the data collection protocol of the Fresno Asthmatic Children's Environment Study (FACES), the theoretical basis for the chosen methodological approach, and the details of the statistical methods employed in these analyses. In the Results section, I describe the characteristics of the FACES study sample, provide tabular and graphical descriptions of the distribution of ambient air pollution in the study, and present the results of the single- and multi-pollutant PIM analyses. In the Discussion section, I provide interpretation of the effects estimated in these various analyses, and refer back to the single- and multi-pollutant exposure distributions to situate the various health effects in appropriate context, and to speculate on potential sources of bias.

All health effects calculated in these analyses were estimated relatively imprecisely; however, comparison of the magnitude and direction of the risk differences across analyses demonstrates patterns and provides information about the respiratory effects of the pollutants analyzed in this study. Furthermore, consideration of the individual and joint distributions of the two exposures yields key insight that guides the interpretation of these findings, especially as relates to parameter identifiability. In this analysis, there is ample evidence that the types of air pollution profiles described by two interventions are not realistic given the observed data, and furthermore that there is not support in the data to estimate health effects for these interventions. These parameters were defined to be comparable to standard practice in the multi-pollutant literature. The finding that they were not identifiable in the FACES data argues against giving weight to these specific findings, and also raises broader questions about parameters of this type: large, isolated single-pollutant concentration changes in a multi-pollutant exposure regimen. The work presented here emphasizes that such parameters should be scrutinized for positivity and data support before commencing analysis, regardless of the analytical approach chosen.

This dissertation is dedicated to my wonderful, loving family:

Lonnie Snowden, Alice Hines,
Frances Johnston, and to the memory of Tim M. O'Shea

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I. Background

Introduction

In this dissertation, I analyze the health effects of single-pollutant and multi-pollutant summertime ambient air pollution exposures on pulmonary function in a cohort of children with asthma living in Fresno, California. I employ a technique from the causal inference literature, the Population Intervention Model (PIM), to describe the health effects that would result from several hypothetical interventions that involve lowering concentrations of ambient air pollution. By describing the health effects of ambient air pollution in these terms, I aim to make the results of this study relevant to real-world policy questions. Toward the same end, I estimate the health effects associated with a multi-pollutant exposure regimen. This analytical approach permits the calculation of air pollution health effects that correspond to multiple pollutants dynamically changing within a mixture—as ambient air pollution is actually experienced by people—rather than a single pollutant. I subsequently interpret each of these health effects according to whether it reflects a realistic, or even a possible, exposure scenario during the study period and in the region where data were collected. I achieve this through an examination of the individual and joint distributions of the pollutants under study.

This Background chapter presents a brief history of air pollution epidemiology and policy, and reviews the epidemiologic and statistical research upon which this dissertation builds. I discuss asthma epidemiology, research on air pollution mixtures, and causal inference. I conclude by posing the specific aims set up by this background material. The Methods chapter describes the data collection protocol of the Fresno Asthmatic Children's Environment Study (FACES), the theoretical basis for the chosen methodological approach, and the details of the statistical methods employed in these analyses. In the Results section, I describe the characteristics of the FACES sample, both the overall sample and the sub-sample whose summertime data are analyzed in this dissertation. I provide tabular and graphical descriptions of the distribution of ambient air pollution in the study, both the observed air pollution concentrations and the air pollution concentrations under the hypothetical interventions whose effects I am estimating. I also present the results of the single- and multi-pollutant PIM analyses. In the Discussion section, I provide interpretation of the effects estimated in these various analyses, and refer back to the single- and multi-pollutant exposure distributions to situate the various health effects in appropriate context, and to speculate on potential sources of bias. I conclude by discussing the contributions and limitations of the present work, and then pose research questions for future analyses to build on the present study.

Historical perspective on ambient air pollution science

Ambient air pollution was recognized to be a problem in antiquity and became a more grave threat to human health with the rise of populous cities and the advent of industrialization[1]. The rise of fossil fuel-based economies and increasing urbanization exacerbated the problem. By the turn of the twentieth century, there was a broad awareness of air pollution's ill effects, but there was little scientific evidence of causal mechanisms to explain the phenomenon. In the mid-twentieth century, a series of concentrated urban air pollution episodes (including ones in Belgium in 1930, Pennsylvania in 1948, and London in 1952) resulted in increased morbidity and mortality, dramatically demonstrating the acute effects of outdoor air pollution[2]. These episodes spurred scientific interest in ambient air pollution, resulting in studies that laid the groundwork for modern air pollution science[2-7]. The second half of the

twentieth century saw the rapid growth in laboratory, clinical, and epidemiologic research on ambient air pollution.

In the 1970s, the first large-scale studies of ambient air pollution health effects were initiated in the United States. The landmark CHESS (Community Health and Surveillance System) study was initiated by the United States Environmental Protection Agency[8], and the Six Cities Study was initiated by researchers at the Harvard School of Public Health[9]. With the continuing growth of air pollution epidemiology, researchers implemented an array of study designs and analyzed multiple health outcomes. Ecologic studies comparing group-level outcome measures across various geographic regions, or over time in a single region, were conducted, sometimes using routinely collected exposure and health data[10, 11]. A time-series re-analysis of the 1952 London Smog by Schwartz *et al*. demonstrated another analytical technique to estimate air pollution health effects from ecological data[12]; time-series analyses subsequently appeared in the literature with increasing frequency[13-15].

Additional individual-level studies investigating a variety of health outcomes followed the landmark Harvard Six Cities study. The same researchers analyzed respiratory outcomes in the 24 Cities Study[16]; epidemiologists examined air pollution health effects in the large American Cancer Society cohort[17]; and cardiovascular outcomes were the focus of the Multi-Ethnic Study of Atherosclerosis (MESA-Air)[18, 19]. Research has focused on a variety of exposure time-frames, both acute and long-term[20, 21]. Beginning in the 1960's, a study design that was prominently used to analyze acute effects was the panel design, wherein a group of individuals (often susceptible people) were followed intensively, usually for a short time[22, 23]. In this dissertation I analyze data from the Fresno Asthmatic Children's Environment Study (FACES), a prospective cohort study initiated in 2000 that incorporates the panel design to collect detailed data on individual participants. The studies mentioned above, including FACES, seek to advance our scientific knowledge of air pollutions health effects, to guide clinical practice, and to inform policy.

Air pollution epidemiology and policy

The environmental contamination that resulted from urbanization and industrialization also ushered in the contemporary era of air pollution regulation[1]. The concentrated air pollution episodes of the mid-twentieth century helped motivate a coordinated, government-led drive to abate air pollution in the United States. These events, and the overall high background levels of air pollution in US cities in the first half of the twentieth century[24], motivated the passage of the Clean Air Act (CAA) in 1963, and the subsequent creation of the Environmental Protection Agency (EPA) in 1970. The1970 amendments to the CAA designated several "criteria pollutants" that had been demonstrated to be harmful to human health, and which were to be monitored and regulated by the states. The CAA further mandated the formulation of National Ambient Air Quality Standards (NAAQS) to set the levels of these criteria pollutants allowable to protect the public health within an adequate margin of safety. This iteration of the CAA created the framework that has evolved into the regulatory structure that exists in the present day[24]. Throughout this dissertation I make reference to these standards; Results Table 6 presents the current NAAQS levels for pollutants of interest in FACES.

Air pollution research gained additional significance with the amendments to the CAA: the NAAQS were to be created and periodically revised to protect public health based on the latest scientific data. Consequently, in addition to the scientific and public health motivations for conducting air pollution health research, there is an audience of policy-makers that use the

findings of research to inform regulation. The methodological approach employed in this dissertation focuses on health effects associated with hypothetical environmental interventions that would lower air pollution levels, facilitating the translation of epidemiologic findings into policy. In considering what constitutes an adequate margin of safety, the CAA required that policy-makers to consider sensitive groups defined to include children, the elderly, and people suffering from chronic respiratory diseases, all of whom are especially susceptible to air pollution health effects. Thus, the regulatory mandate for science-based air quality criteria motivates air pollution epidemiology that focuses on both the general population and sensitive populations[25]. Children with asthma are one such sensitive population and make up the study sample for FACES. Subsequent sections will discuss clinical and epidemiologic features of childhood asthma.

As environmental science and policy have advanced in the decades since the passage of the CAA, focus has turned to defining the exposure and characterizing its effects with increasing sophistication. One manner in which both scientists and policymakers are moving forward with characterizing the environment with more complexity is the consideration of air pollution mixtures. While the science and the regulation of ambient air pollution have historically focused on single pollutants in isolation[26], in the last decade, scientists and policy-makers have been moving toward a more multi-pollutant framework. Amid calls for novel analytical approaches to the study of air pollution mixtures[26], the EPA has made multi-pollutant research a major component of its agenda[27, 28]. In this dissertation, I implement a technique that has heretofore not been applied to study air pollution mixtures, and address some of the methodological challenges associated with multi-pollutant analysis.

Studies of mixtures in air pollution epidemiology

The methodological challenges associated with conducting research on air pollution mixtures are well-known: correlated co-pollutants result in unstable effect estimates and large standard errors, hindering the assignment of causality to any one exposure[29]. Differential measurement errors between co-pollutants also introduce complexity; research has shown that a better-measured benign pollutant can absorb some the effects of a correlated deleterious co-pollutant that is poorly measured[30]. In light of these challenges, it is not surprising that most air pollution epidemiology and policy has historically dealt with single pollutants. In the last decade, researchers have increasingly attempted to overcome these challenges to estimate health effects for single pollutants adjusted for co-pollutants, or for multiple pollutants simultaneously in a mixture. Here I summarize the work to date on these topics, which I refer to broadly as "mixtures," despite the differences in target parameters.

Up to this point, researchers have employed one of several techniques to analyze air pollution mixtures. The most common approach has been multi-pollutant modeling in a generalized linear model framework, in which investigators include multiple pollutants in a single statistical model as independent variables[31]. Under this approach, co-pollutants are frequently considered potential confounders of the single main pollutant's effect, rather than separate exposures of interest[32, 33]. The aim of this approach is often to determine the causal agent by estimating the effects of one pollutant, controlling for another. The level of inference for research questions of this type is the individual pollutant (e.g., ozone[33] or particulate matter[32]) rather than the mixture itself. Researchers have employed various techniques to estimate health effects of an index pollutant conditional on levels of one or more co-pollutants, including hierarchical models[32] and matching in a case-crossover design[34]. This analytical

approach—estimating health effects for a change in one pollutant while controlling for a correlated co-pollutant—is a reference that I return to throughout the Results and Discussion sections, for the purpose of comparison to standard practice.

Another established method to the study of mixtures is source apportionment. In this approach, investigators use factor analysis or similar techniques to generate composite variables that combine observed environmental variables[35, 36]. These factors are then assigned sources based on factor loadings (e.g., crustal materials factor, coal combustion factor), and health effects are regressed on the factors as exposures, in order to estimate health effects corresponding to the putative underlying source. This source-based framework is concerned with identifying pollution from various emissions categories and estimating health effects that correspond to the various categories. Thus, in contrast with the multi-pollutant modeling approach, the level of inference in this approach is the source rather than the single pollutant.

These disparate approaches reflect not only different methodologies, but also different research questions and levels of inquiry. Some research, including most multi-pollutant modeling, focuses on the effects of individual pollutants in the context of co-pollutants, while source apportionment characterizes the health effects of emissions sources. There is still relatively little research in this emerging literature that is focused on the mixture itself as the unit of analysis. In this dissertation, I implement a statistical method from the causal inference literature to estimate the effects of ambient air pollution, as single pollutants and in a two-pollutant mixture. This approach enables the estimation of effects that correspond to the mixture itself, allowing multiple pollutants to vary in the mixture, rather than holding one constant. I also analyze the joint distribution of the co-pollutants in order to evaluate the validity of the health effects estimated in each model, and the extent to which they correspond to real-world effects of interest.

Epidemiology and clinical features of childhood asthma

As a sensitive subgroup, children with asthma are of particular interest to researchers and regulators when studying the health effects of air pollution. Health effects among this subgroup have become increasingly important at the population level as childhood asthma has reached an unprecedented prevalence in developed societies in recent decades. The prevalence increased dramatically in the United States in the 1980s, reaching a plateau in the late 1990s[37, 38], with similar trends in much of the developed world[39]**.** Asthma is now the most common chronic health problem affecting American children, with an estimated prevalence of 9.1%[40, 41]. Symptoms and management of asthma impede a child's performance in school, engagement in physical activity, and ability to sleep. Asthma is also the most prevalent cause of childhood disability in the US, and exacts a high social and economic toll in terms of restricted activity, school days missed, physician visits, and hospitalizations[42].

The contemporary clinical definition of asthma is characterized by reversible airflow obstruction, airway inflammation, and increased bronchial reactivity[43]. The classical presentation of asthma involves recurrent exacerbations characterized by chest tightness, wheezing, and coughing in response to a variety of stimuli[43]. Although these symptoms make up the basis of the diagnostic description of asthma, the phenotypes of the disease vary considerably with regard to age at onset, symptoms, triggers of exacerbation, and severity [44, 45]. The clinical characteristics of asthma are further complicated by the fact that asthma may develop at various stages of childhood or adulthood, and may worsen or attenuate over the lifetime of the patient[46, 47].

Asthma's large toll on population health has motivated an increased focus on the disease's etiology. Epidemiologic research on asthma etiology focuses on both 1) identifying factors that cause the onset of asthma among healthy people, and 2) identifying factors that affect prognosis (e.g., precipitate exacerbations or worsen symptoms) among subjects that already have asthma[39]. FACES focuses on research questions in the latter category, investigating the factors that affect respiratory health among children with asthma. Studies of disease progression and prognosis among asthmatics can analyze various outcomes: asthma-related healthcare utilization, symptoms (e.g., wheeze, cough) and pulmonary function as measured by spirometry.

Exacerbations and symptoms are often elicited by triggers, and an asthmatic child's response to triggers depends on factors such as age, use of controller and rescue medications, and atopy (the tendency to mount IgE-type responses to environmental allergens, commonly assayed through skin-prick testing[48]). Known triggers for asthma exacerbation include allergens, viral infections, exercise, tobacco smoke, and air pollution[49]. As a ubiquitous and involuntary exposure with great potential population health impact[50], ambient air pollution receives much scientific attention in asthma epidemiology. In this dissertation I examine this topic, analyzing the effects of ambient air pollution in children with asthma using an approach that estimates policy-relevant effects.

Air pollution health effects among children with asthma: Study designs and methodological issues

There is broad evidence that ambient air pollution aggravates symptoms and worsens pulmonary function in people with asthma[51]. One study design that has provided evidence of this effect is the ecological study, frequently coupled with time-series analysis. Investigators using this approach have analyzed how ambient levels of air pollution affect an ecologic outcome (e.g., asthma-related emergency room visits) over time. Several of the early time-series studies on children with asthma focused on the criteria pollutant ozone, a secondary pollutant generated by photochemical reactions. These studies analyzed hospitalization data from the U.S. and Mexico in the 1980s and 1990s and found that increased ozone concentration predicted higher respiratory hospitalization rates[52-54]. In addition to ozone, time series research among children with asthma has found evidence for ill health effects of PM_{10} (particulate matter with diameter less than 10 μm)[54] and SO_2[53]. The coefficient for a single unit change in air pollution concentration (e.g., 1 part per billion [ppb] or 1 $\mu g/m^3$) does not generally have an intuitive interpretation, and it varies according to the scale and distribution of each pollutant. Accordingly, the authors in these and other studies present effect estimates associated with some meaningful change in pollution concentration, for example 20 ppb [54] and 50 ppb of ozone[53].

Panel studies are another design to analyze health effects among children with asthma, that while more expensive than many ecologic analyses, permit more nuanced analysis of a variety of respiratory outcomes. In this design, subjects with asthma are monitored intensively, often answering symptom questions and performing spirometric forced expiratory maneuvers on a daily basis. The demanding data collection protocol required of participants and study staff cause panel studies to be shorter in duration, but the fine-grained health data generated by these studies enable analysis of pulmonary function and symptom outcomes that do not rise to the level of healthcare utilization[23]. FACES, which provides the data that I analyze in this dissertation, incorporates elements of panel studies into its longitudinal design.

The earliest panel studies of subjects with asthma from the 1960s yielded mixed results; these studies largely relied on simple correlation analyses that did not control for potential

confounders[22, 55]. The 1970s brought additional panel studies with more advanced methods, including multivariable regression, and found more consistent effects of ambient air pollution. Many of these studies focused on particulate matter (PM) and sulfur oxides (SO_x), which are regulated by the NAAQS. Cohen *et al*. studied a panel of asthmatics residing in close proximity to a coal-fired power plant and found an increased asthma attack rate associated with PM and SO_X, even after controlling for various weather variables[56]. Data from the same time period in Los Angeles indicated that days of high particulate and oxidant air pollution predicted asthma attacks; the authors of this study used Poisson regression to control for day of the week, previous asthma attack, and several meteorological variables[21]. These early studies analyzed respiratory outcomes collected on individuals and ambient exposure data collected from central monitors, assigning the same air pollution exposure to all subjects on a given day. This mixed-level analysis, called a semi-individual study[57], exploits temporal but not spatial variability in exposure and is still in use today. The present study uses this approach.

In subsequent decades, panel studies have examined pulmonary function and symptom outcomes other than asthma attacks. Ostro *et al*. enrolled a panel in Los Angeles made up of African-American children (a group with an increased prevalence of asthma), and analyzed respiratory symptom outcomes such as wheeze, cough, and shortness of breath during the summer[58]. Using multiple analytical approaches, the authors consistently found that PM_{10} and ozone, separately analyzed, predicted shortness of breath. Peters *et al*. analyzed the effects of wintertime PM and SO_2 on peak expiratory flow in a panel of asthmatic children in Eastern Europe, finding significant effects for both pollutants[59]. In a panel study following children with asthma in Mexico City, Romieu and colleagues found associations between ambient ozone and outcomes including cough, phlegm, and peak flow[60]. Numerous panel studies on the acute health effects of ambient air pollution in children with asthma have been conducted since this time; they have been reviewed in meta-analyses by Ward and Ayres[23] and Weinmayr and colleagues[61]. Subsequent sections will describe more studies in detail, focusing on those that studied the pollutants analyzed in this dissertation.

Most ambient air pollution studies are characterized by complex periodicity and trends in the exposure variables, and in the case of multiple pollutant exposures, correlation between co-pollutants. Ambient air pollution variables are often collinear, which complicates assignment of air pollution health effects to a single pollutant[62, 63]. The periodicity in exposures may operate at multiple levels, including the season and day of the week. Investigators often deal with these time-related issues by using time-series methods[64, 65], by including time-related variables in statistical models[53, 66, 67], through restriction (e.g., season-restricted analyses[58, 59, 68]), or some combination of these approaches. In addition to these exposure-related issues that affect analysis of most ambient air pollution data, the use of the panel design introduces additional methodological complexity through the collection of repeated measures on study participants. This data structure requires that the investigator account for autocorrelation in the outcome data during the analysis phase, which is often accomplished through the use of generalized estimated equations[67, 69, 70] or mixed models[66, 71, 72]. The analytical approach employed in this dissertation incorporates various elements of these approaches, including season-restriction and consideration of temporal candidates, to account for the methodological challenges posed by temporal issues and repeated measurements.

Review of acute effects of ambient NO_2 on childhood asthma outcomes

Nitrogen dioxide (NO_2) is another of the criteria pollutants that has been studied as a health threat to children with asthma. Ambient NO_2 is largely a secondary pollutant arising from oxidation of NO, which is emitted during combustion. Outdoor NO_2 in urban areas arises mainly from automobile tailpipe emissions, and is considered a good marker for traffic[61, 73]. Much epidemiologic research has been conducted on the acute effects of this pollutant among asthmatic children in Europe, North America, and Australia. The analyses in this dissertation will estimate NO_2 effects in the FACES data, analyzing the pollutant's health effects both independently and in a mixture.

The research on NO_2 effects in children with asthma has analyzed general respiratory symptoms[72, 74], as well as specific symptoms such as wheeze[65] and cough[75]. The pulmonary function parameters analyzed as outcomes for NO_2 include peak expiratory flow (PEF or peak flow) [67, 72], forced expiratory volume in 1 second (FEV_1)[71], and most recently forced expiratory flow between 25% and 75% of forced vital capacity (FEF_{25-75})[76]. These studies have yielded mixed results, finding that NO_2 significantly increases symptoms among children with asthma, but has no significant effect on pulmonary function as measured by peak flow, in contrast to ozone and PM[67, 72, 74, 75]. Weinmayr *et al*. conducted a meta-analysis summarizing short-term NO_2 effects on symptoms and PEF among children with asthma, standardizing the NO_2 effects across all studies as a 10 $\mu g/m^3$ change[61]. They calculated a significant effect for asthma symptoms overall, but not for cough or peak flow. Interpretation of these findings were complicated by a large number of null results from a single European multi-center study[77], and in a sensitivity analysis the authors found that significant pooled effects for cough but not PEF when these studies were excluded.

Few studies to date have examined the acute effects of ambient NO_2 on pulmonary function outcomes other than PEF. Delfino *et al*. found a borderline significant association between an interquartile increase in outdoor NO_2 and FEV_1, an association which became null when an individual measurement of PM was included in the model[71]. More recently, Liu and colleagues analyzed the outcome FEF_{25-75} in addition to FEV_1 and found a significant association between NO_2 and FEF_{25-75}, but not FEV_1.

Review of acute effects of ambient $PM_{10-2.5}$ and PM_{10} on childhood asthma outcomes

Air pollution science delineates particulate matter by the aerodynamic diameter of the particle, in categories corresponding to different health effects and combustion categories[78]. PM_{10}– a physiologically based category approximating thoracic particles, those that penetrate to the thorax—is defined as the fraction of particulate air pollution that has aerodynamic diameter less than 10 µm, and for which particles with aerodynamic diameter equal to 10 µm are collected with 50% efficiency. $PM_{2.5}$ has an analogous definition, and corresponds to particles from combustion sources (and is similar to the respirable fraction). $PM_{10-2.5}$, commonly referred to as the "coarse fraction," is made up of the large-diameter particles of PM_{10} minus the mass from $PM_{2.5}$, or fine fraction.

The health effects of ambient PM_{10} on children with asthma have been well documented[79]. In a meta-analysis of PM health effects among children with asthma, Ward and Ayres found small but significant pooled effect estimates for ambient PM_{10} on peak flow, respiratory symptoms, and cough, though there was evidence of publication bias[23]. The results of a meta-analysis by Weinmayr *et al*. found similar results for PM_{10}: a 10 $\mu g/m^3$ increase in PM_{10} significantly increased respiratory symptoms, and was associated with PEF and cough at

borderline significance[61]. The authors noted that PM_{10} effects were greater in areas with higher NO_2 concentrations.

In contrast to the well-documented health effects of PM_{10} and $PM_{2.5}$, health effects of ambient $PM_{10-2.5}$ have received less attention in epidemiologic research until recently. $PM_{10-2.5}$, which is dominated by crustal materials, particles generated from mechanical processes, and metals[80], has been demonstrated to have a significant association with respiratory hospitalizations in a number of studies. In some cases the association with was stronger for ambient $PM_{10-2.5}$ than for $PM_{2.5}$[81, 82], and in some cases the two were of similar magnitude[83, 84]. To date, ambient $PM_{10-2.5}$ has not been the focus of panel studies studying symptoms and pulmonary function among asthmatic children. This probably owes to the increasing appreciation of the distinction between PM_{10} and $PM_{10-2.5}$, and the relatively recent scientific focus on measuring and analyzing the coarse fraction separate from fine particles[85].

Causal inference methods in epidemiology

Epidemiologists and other non-laboratory scientists have long strived to implement analytical techniques that estimate causal effects from observational data, rather than associations that are of less scientific interest. In the 1970s, Rubin *et al*. introduced a causal framework for analysis of observational data, wherein such observational study designs are considered randomized controlled trials with "broken randomization."[86] Building upon this concept, a body of statistical techniques that focus on causal effect estimation has been introduced into the epidemiology literature in the last decade. This literature often makes reference to the "ideal experiment," a hypothetical study design that would enable unbiased causal inference[87]. The requirements of this ideal experiment are more stringent than any randomized controlled trial that a scientist could empirically conduct, requiring each participant to be observed under the same conditions, at the same time, under the various experimental conditions that are of interest.

These statistical approaches for causal effect estimation, henceforth called "causal inference methods," build on the concept of the ideal experiment by encouraging the investigator to define the specific ideal experiment underlying any given research question. The causal inference literature provides several approaches to estimate effects that are more causal in nature from observational data. The causal interpretation of parameter estimates relies on several assumptions relating to causality, which will be discussed in detail the Methods section. One assumption in particular—the positivity assumption—is a crucial concept that will inform the present analyses and therefore is elaborated on in a subsequent section.

The framework for causal inference methods in epidemiology is laid out in Robins' 2000 paper on Marginal Structural Models (MSMs), which focuses on the Inverse Probability of Treatment Weighting (IPTW) estimator[88]. Subsequent work has introduced additional causal inference estimators to the epidemiology literature, including g-computation (first described by Robins[89], and subsequently elaborated on in the epidemiology literature[90, 91]). This paper will employ g-computation to estimate the parameters of a Population Intervention Model in a way that is intervention-relevant, as demonstrated by Ahern and colleagues[91].

The last decade has seen epidemiologists implement causal inference methods with increasing frequency across a variety of subject matter domains. Causal inference methods are characterized by a focus on marginal effect estimation, wherein the effects of exposures are measured across an entire sample, not conditional on covariates. By using methods from the causal inference literature, a researcher is able to estimate population-level effect parameters that

correspond to hypothetical interventions[91], which is particularly relevant to policy-related fields such as air pollution. The use of causal inference methods, along with Directed Acyclic Graphs[92, 93], has brought to epidemiology new tools to explicitly define research questions, to focus on estimating parameters of *a priori* interest, and to justify analytical decisions by referring to long-standing epidemiologic concepts such as confounding and selection bias. Another convention in the causal inference literature is to explicitly state assumptions and evaluate the extent to which they are met or violated in a given analysis (though not all of the causal assumptions are distinct from the assumptions of standard epidemiologic analysis).

The positivity assumption and parameter identifiability

One assumption for causal inference is the positivity assumption[94], also referred to as the Experimental Treatment Assignment assumption[95]. In a simple binary exposure setting, this assumption requires that there be both exposed and unexposed subjects in every stratum of the data, with strata defined conditional on the confounders. Intuitively, the estimation of exposure effects requires the comparison of exposed and exposed subjects; the positivity assumption formalizes this precept across the data space. Violations of the positivity assumption (referred to as nonpositivity) can be categorized as deterministic or random[96]. Nonpositivity is deterministic if some subgroup of the data is structurally prevented from ever receiving one level of the exposure; for example women will never be exposed to prostate cancer screening so this exposure's effect can never be estimated in this stratum even at an infinitely large sample size. Random nonpositivity occurs when some level of exposure is unobserved in a stratum of the data by chance rather than by design, and often results from sparse data due to small sample size, a large set of confounders, or the continuous coding of confounders. Random nonpositivity may pose less of a challenge to valid estimation if this nonpositivity is "surrounded" by regions of positivity and requires interpolation rather than extrapolation beyond the observed data[96].

The discussion of the positivity assumption in epidemiology has become widespread only recently, in comparison with assumptions of model specification and confounder control, and investigators have proposed multiple approaches to diagnosing and addressing nonpositivity[95-97]. The unifying message that emerges is the importance of examining exposure distribution across levels of confounders in the data. Violations in the positivity assumption compromise the identifiability of parameters and can bias estimation[97]. Identifiability, a concept defined decades ago in the social sciences[98, 99] and epidemiology[100], describes the extent to which parameters can be estimated given a particular dataset. In addition to nonpositivity, effects may be non-identified or poorly identified due to insufficient confounder control[97], or extrapolation beyond the observed data[99]. The latter problem, wherein statistical estimation is based upon cells with no data, is another example of data sparsity that hinders valid estimation of effects due to non-identifiable parameters. Another term to describe this sparsity is a lack of "support" in the data, or the parameter being "off-support" in the dataset[101, 102]. The analyses in this dissertation will focus on the positivity of single pollutants across levels of the confounders and co-pollutants (in the case of the multi-pollutant model), in order to evaluate the extent to which various parameters are identified in the observed data.

Specific aims and rationale

In this dissertation, I apply causal inference techniques to estimate marginal effects associated with hypothetical population interventions that involve lowering levels of ambient air pollution. In the first analysis, I analyze the effects of ambient summertime NO_2 on FEF_{25-75} in a

single-pollutant approach that demonstrates the methodological approach (the Population Intervention Model), and also enables comparison to standard practice. NO_2 is the focus because though there is evidence for its health effects among children with asthma, the evidence is mixed and is relatively scant for pulmonary function outcomes other than FEV_1. I selected FEF_{25-75} as the outcome because it has not been as widely studied as FEV_1, and there is evidence that it is a better proxy for function in small airways, which are affected in asthma[103]. Throughout these analyses I use central-site exposure data, assigning all subjects on a given study day the same values of NO_2 and co-pollutant.

Ambient $PM_{10-2.5}$ is analyzed throughout as a summertime pollutant of secondary interest, both in a single-pollutant $PM_{10-2.5}$ analysis, and in a mixture analysis. The health effects of $PM_{10-2.5}$ among children with asthma are still not well characterized. For the multi-pollutant mixture analysis, I extend the Population Intervention Model framework demonstrated in the single-pollutant analyses to a two-pollutant summer analysis of ambient NO_2 and $PM_{10-2.5}$, estimating health effects associated with an intervention that dynamically alters levels of one or both pollutants. In this two-pollutant analysis, I estimate the effects of lowering levels of one co-pollutant while "controlling for" the other (i.e., holding it at observed levels), as well as the effects of a joint intervention that decreases levels of both pollutants. Both ambient NO_2 and $PM_{10-2.5}$ are analyzed as 24-hour average concentrations with lag 0 (i.e., the exposure period the day before outcome measurement), in order to examine individual and joint acute affects over the same time period. This dissertation contributes to both subject matter knowledge and applied methodology, but the goal is not to perform an exhaustive examination of the lag structure and exposure timing.

The analysis is restricted to the summer months to allow for the likely scenario that the nature of the correlation between the pollutants, and possibly their effects, varies by season. In addition to estimating health effects for these single- and multi-pollutant exposure regimens, a major focus of this dissertation is the evaluation of all treatment regimens with regard to concerns of parameter identifiability and positivity.

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II. Methods

I begin by reviewing the methodological foundation of the causal inference approach to effect estimation, then focus specifically on the g-computation estimator and the Population Intervention Model. After an explanation of the study population and data collection methods, I introduce the mechanics of this methodological approach with the single-pollutant NO_2 analysis. I subsequently extend this description to the single-pollutant $PM_{10-2.5}$ analysis, and into the multi-pollutant setting for the estimation of NO_2/$PM_{10-2.5}$ mixture effects. I describe the details of confounder selection, model fitting, parameter estimation, and statistical inference for each exposure regimen analyzed.

The counterfactual framework and statistical techniques for causal inference from observational data

Causal inference methods can be understood and implemented through the use of the counterfactual framework. Introduced in the mid-twentieth century[1, 2], the counterfactual framework posits the existence of unobserved outcomes corresponding to theoretical unobserved exposures, in addition to the observed data that are collected in any given dataset. These unobserved outcomes are called "counterfactual" because they describe the outcome that would have occurred if, contrary to fact, a person had experienced some exposure that she did not. Because it is impossible to observe each study participant under all possible treatment or exposure regimens (words that I use interchangeably), the data that would have occurred under alternate exposure scenarios can be considered missing data, whose absence prevents the straightforward estimation of unbiased causal effects. The data that an investigator collects and analyzes are thus considered the "observed data," while the entire set of counterfactual exposures and outcomes (some observed and some unobserved) that would enable causal effect estimation is called the "full data." Methods for causal inference can use the existence of counterfactuals (i.e., the entire set of possible outcomes) to enable unbiased estimation of marginal causal effects.

The notation commonly used in the causal inference literature describes the different variables of the dataset and delineates observed exposures and outcomes from counterfactual exposures and outcomes, both observed and unobserved. In this discussion, Y denotes the random variable for outcome and A denotes the random variable for exposure (multiple exposure variables can be indexed as A_1, A_2, etc.). W denotes the vector of confounding variables for estimating the effect of A on Y; individual confounders may also be indexed as W_1, W_2, etc. In contrast to the actual outcome Y which is in the observed data, Y_a denotes the counterfactual outcome when exposure is set to the level a (or $A = a$). Thus, in the instance of a binary treatment variable ($A = \{0, 1\}$), the set of potential counterfactual outcomes is described as $Y_a = \{Y_0, Y_1\}$, corresponding to untreated and treated, respectively. Throughout this discussion, I use a simplified subject matter example from the present analysis to anchor the notation and concepts in a real-world data setting. For this heuristic, I use NO_2 as the example of exposure (A; binary, dichotomized at the median level) and FEF_{25-75} as the example of outcome (Y; continuous, units of liters/second). Not all of the parameters that I describe in this theoretical discussion will actually be estimated in the analysis; most are presented for didactic purposes only. There is one example confounder, age at asthma diagnosis (W; coded as binary, >2 years old or ≤2 years old). In order to simplify the demonstration, I will assume that a very simple model specification is a

good fit to this hypothetical research question and dataset, leaving aside all of the model-fitting concerns that should be considered with actual data:

$$E(Y \mid A,W) = \alpha_0 + \alpha_1 * A + \alpha_2 * W \quad (1)$$

The counterfactual framework defines causal effects for both individual- and population-level parameters[3]. The individual causal effect on the absolute scale is defined as:

$$Y_1 - Y_0 \quad (2)$$

This parameter corresponds to the individual-level ideal experiment discussed in the Background chapter, and cannot be estimated from observed data due to missing data: one of the counterfactual outcomes will be necessarily be unobserved. More concretely, each individual can be exposed only to either NO_2 above the median (corresponding to the outcome Y_1) or NO_2 below the median (corresponding to the outcome Y_0) in a given time period; therefore the individual causal effect ($Y_1 - Y_0$) cannot be estimated.

In contrast, the population-level causal effect on the absolute scale is defined as:

$$E[Y_1] - E[Y_0] \quad (3)$$

This parameter corresponds to the difference between the mean counterfactual outcome when the entire population is exposed versus unexposed. Using the simple subject matter example, this is defined as the difference between the mean FEF_{25-75} level when the entire sample is exposed to NO_2 above and below the median. Most conventional statistical techniques estimate the association between exposure and outcome by calculating:

$$E[Y \mid A=1] - E[Y \mid A=0] \quad (4)$$

This approach estimates a conditional association, comparing the mean outcome among the exposed to the mean outcome among the unexposed. Such an approach assumes that the two groups are exchangeable. This contrasts with the marginal effect estimate $E[Y_1] - E[Y_0]$, which does not compare outcome levels among subgroups of the observed data, but rather uses the hypothetical full data to estimate an effect across the entire sample.

The discussion of causal effects in the previous paragraph assumed that the effect of A on Y was not confounded; such a situation is uncommon in observational data. When considering the role of confounding variables in effect estimation, the contrast between marginal and conditional effects becomes more pronounced. A traditional statistical approach conditions on the confounding variables W, often by including them as independent variables in a multivariable regression model that estimates the exposure/outcome association. The associations estimated through this approach are conditional on W in addition to A:

$$E[Y \mid A=1, W=w] - E[Y \mid A=0, W=w] \quad (5)$$

In the simple subject matter example, this parameter compares the mean FEF_{25-75} level among subjects exposed to NO_2 above and below the median, within strata of the confounder age at

asthma diagnosis. Thus, the NO_2/FEF_{25-75} association is conditional on levels of the exposure and the confounder.

In addition to estimating the treatment/outcome association within strata of the confounders, under this approach the regression model estimates the effect of confounding variables whose effects are not of interest. In the subject matter example, the investigator's model will have estimated the effects of age at asthma diagnosis (represented by the coefficient α_2 in model 1 above) in addition to the effects of NO_2 (α_1 in model 1 above). In reality, only the NO_2 effect is a parameter of interest; the effect of age at asthma diagnosis can be referred to as a nuisance parameter. In the causal inference framework, confounders are considered to be nuisance variables, and their confounding effects are controlled at different stages in the analysis. These nuisance variables are modeled in nuisance models that precede the final model that estimates the effect of treatment A. The specific nuisance models employed in this study will be discussed in a subsequent section. This approach to confounder control and marginal effect estimation estimates the following observed-data parameter, averaged across strata of the confounders W:

$$E_W[E(Y \mid A=1, W=w) - E(Y \mid A=0, W=w)] \quad (6)$$

By making explicit references to causal assumptions, this parameter of the observed data estimates the total effect parameter of the full data, defined in equation 2: $E[Y_1] - E[Y_0]$.[4] When the researcher is concerned with effect modification, conditional effects may also be estimated within sub-groups of interest[5].

The causal inference framework relies on assumptions regarding the data structure and the nature of associations between variables. These causal assumptions are formally encoded in the causal inference framework, but most of them correspond to assumptions and considerations from traditional statistical and epidemiological analysis. Causal inference relies on the positivity of experimental treatment assignment assumption, discussed at length in the Background chapter. Briefly, the positivity assumption requires that there be a non-zero probability of each treatment regimen within all subgroups for which the effect of treatment is being assessed[6, 7]. This is analogous to the caution against extrapolating beyond the observed data in a traditional regression framework, and is related to the concepts of data support and parameter identifiability[8-10]. Positivity is of particular concern when the set of confounders or co-exposures is high-dimensional (for example, containing a large number of variables or continuous variables)[7, 11], as is often the case with air pollution mixtures.

The causal inference framework assumes no unmeasured confounding for unbiased estimation, which is also a tenet of standard epidemiological analysis[12].Time-ordering of certain variables (e.g., A occurs before Y) is also required, as is correct model specification. In causal inference approaches, the investigator assumes that the nuisance model(s) are correctly specified, in addition to the effect model if a parametric approach is used to estimate the treatment effect (in contrast with approaches that calculate effects from the full data without an additional model, e.g., a simple risk difference). The causal inference framework further assumes the existence of counterfactuals and the consistency of counterfactuals[13]. The consistency assumption, which has traditionally received less attention in epidemiology, states that the observed outcome is equal to the counterfactual outcome that would have occurred given the observed treatment, regardless of the route of treatment administration[14]. In this air pollution

subject matter, one practical assumption implied by the consistency assumption is that the effect of lowering a pollutant concentration is the same regardless of the mechanism used to lower it.

The g-computation estimator

Among the estimators for causal inference, the Inverse Probability of Treatment Weighting (IPTW) estimator is the most common in published analyses in the epidemiology literature[15-17], and its properties have been more widely discussed in epidemiology[6, 18, 19]. IPTW is an inverse-weighted regression approach that estimates marginal effects from the full data through knowledge of subject's probability of being exposed ($\Pr(A=1 \mid W)$). While this technique has appealing properties in dealing with time-dependent confounding for longitudinal treatment regimens (see [17, 20, 21]), the g-computation estimator has been proposed as a technique for estimating population-level effects corresponding to hypothetical interventions[22], and is being implemented with increasing frequency in epidemiology[23-25]. The use of g-computation here enabled the analysis of pollutants as continuous variables, and also enabled parameter estimation for a dynamic treatment regimen (explained in a subsequent section).

The first step of g-computation is to fit a regression of the outcome on the exposure and relevant covariates, using the observed dataset. This regression model is called the "Q-model" in the context of g-computation. The Q-model is not conceptually different from a traditional regression of Y on A and W. In a traditional regression approach such as maximum likelihood estimation, this model would be the final step of the estimation process, and the coefficient for A would be presented as the exposure/outcome association. The Q-model differs from a traditional regression model in that the Q-model is a nuisance model that estimates nuisance parameters in addition to parameters of interest. In contrast with a traditional regression framework, fitting this model is not the last step of effect estimation; the Q-model is applied to estimate effects in a later stage of analysis.

For g-computation to estimate an unbiased exposure effect, the Q-model must be correctly specified. Once the investigator fits the model, the Q-model is used to predict counterfactual outcomes for each observation under each exposure regimen that corresponds to the research question. For example, in order to calculate the marginal total effects parameter $E[Y_1] - E[Y_0]$, the investigator plugs in both $a=1$ and $a=0$ into the Q-model to obtain a predicted outcome under these two settings. The investigator computes Y_1 and Y_0 for all subjects in the observed dataset, generating the hypothetical full dataset that is free of confounding. Thus, the investigator has resolved the missing data problem and, assuming that the causal assumptions hold, can estimate marginal causal effects. To illustrate this process using the simple subject matter example, the investigator plugs in both exposures—NO_2 exposure below the median level and NO_2 exposure above the median level (a=0 and a=1, respectively)— into the Q-model described in equation 1 ($E(Y \mid A,W) = \alpha_0 + \alpha_1 * A + \alpha_2 * W$). This generates two counterfactual FEF_{25-75} values for each subject, corresponding to high and low NO_2 exposures (Y_1 and Y_0, respectively), regardless of the actual exposure he received. Though the exposure is toggled between both exposures for each subject, the level of the confounder remains at its observed level ($W=w$).

Having generated the full data with g-computation, the investigator may estimate the marginal effect of treatment using a number of approaches including the non-parametric calculation of a risk difference, or alternatively the implementation of an MSM. The MSM is a common approach to causal effect estimation in epidemiology[15, 16, 26], yielding marginal

effect estimates. These analyses are most readily implemented with binary exposure variables, and the effect estimate is interpreted as the marginal effect comparing the outcome when the entire population is exposed versus unexposed.

Population intervention parameters and policy implications

In addition to the total effects parameter discussed above, another type of parameter from the causal inference literature is the Population Intervention Parameter (PIP), which is estimated by the Population Intervention Model (PIM)[27]. The Population Intervention Parameter is analogous to a causal population attributable risk[4], describing the population-level effect of a hypothetical intervention that the investigator specifies in the research question. By focusing on relevant exposures and interventions, this approach can yield insight into the relative impact associated with modifiable exposures in a population. In contrast with a traditional population attributable risk, the PIP incorporates the causal assumptions described above and reflects a marginal effect estimate, averaged across strata of the population.

In contrast with the total effects parameter that compares the mean outcome when the population is exposed versus unexposed ($E[Y_1] - E[Y_0]$), a PIP compares the mean outcome under some hypothetical "intervention" exposure scenario to the mean outcome under the observed exposure scenario. The investigator selects an intervention exposure regimen, for example one that corresponds to a minimum realistic exposure level, or some other health-optimizing exposure setting; the PIP is interpreted as the population-level health impact of this hypothetical intervention. Letting Y_a denote the counterfactual outcome under this intervention exposure scenario, this parameter can be represented as:

$$E[Y] - E[Y_a] \tag{7}$$

The lowercase notation indicates that the random variable for exposure (A) is intervened upon and set to a level specified by the investigator's choice of intervention (a). G-computation, IPTW, or other causal estimators can be used to estimate PIPs[4].

Making reference to the simple subject matter example, the total effects parameter $E[Y_1] - E[Y_0]$ compares the mean outcome when everyone in the sample is exposed to NO_2 above the median level, versus when everyone in the sample is exposed to NO_2 below the median. This corresponds to the ideal experiment (each person exposed and then unexposed), but in some circumstances an investigator may decide that a population attributable risk is of more interest. For example, in a regulatory setting, the Population Intervention Parameter ($E[Y] - E[Y_a]$) likely describes an effect of greater interest. One appealing characteristic of a PIP in this setting is that the investigator uses the observed outcome distribution in the sample as the baseline against which to describe a potential effect. This is an especially logical approach for estimating effects corresponding to a hypothetical policy, because the effects of a real-world intervention would depend on the baseline level of exposure in the population. I demonstrate this point making reference to the simple subject matter example and the National Ambient Air Quality Standards (NAAQS).

An example of a parameter of regulatory interest that can be defined using a PIP is the effect of bringing all days with NO_2 concentrations above the NAAQS level of 100 parts per billion (ppb; 1-hour average) into compliance with the regulation. In such a situation, the intervention would be defined as 100 ppb, with $E[Y]$ defined as the observed FEF_{25-75}

distribution in the dataset, and $E[Y_a]$ defined as the counterfactual FEF_{25-75} distribution if all days were brought into regulatory compliance. In a manner comparable to the Population Attributable Risk, the magnitude of the PIP will vary according to the prevalence of exposure. Specifically, if few days are above the standard level (i.e., few are observed $A = 1$), then the effect of a population intervention would be attenuated, as compared to a study period with many days out of compliance (i.e., observed $A = 1$ is more common), or as compared with the total effects parameter. Other example interventions include lowering NO_2 levels to the 25^{th} percentile or the 10^{th} percentile of observed concentrations; the investigator determines what hypothetical intervention is of greatest interest (and also indentifiable in the data), and defines the Population Intervention Parameter accordingly.

Fresno Asthmatic Children's Environment Study

This project analyzes data collected in the Fresno Asthmatic Children's Environment Study (FACES), a prospective longitudinal cohort study[28, 29]. FACES was designed to examine the acute and long-term effects of ambient air pollution on respiratory health in children with asthma. Fresno and neighboring city Clovis are located in California's San Joaquin Valley, surrounded by major agricultural production and transportation corridors. Being a largely flat air basin surrounded by mountains, the topography of the region causes air pollution to be trapped in the San Joaquin Valley. The region is one of the most polluted air basins in the United States, and is characterized by high levels of ambient air pollution and regular non-attainment of regulatory standards[30-32].

Between 2000 and 2005, 315 children with asthma were recruited in Fresno and Clovis through school nurses, doctor's offices, radio and print advertisements. Some asthmatic siblings of study participants were recruited into the study after the first year (n = 27). Eligibility requirements for the study were as follows: children needed to 1) be between 6 and 11 years of age upon recruitment, 2) have physician-diagnosed asthma that was characterized as "active" through the current use of medications or recent asthma symptoms or healthcare utilization, 3) speak English, 4) reside within 20 kilometers of the California Air Resources Board (CARB) monitor in Downtown Fresno for at least three months, 5) spend at least four nights a week in the same residence. For their children to be eligible, parents needed to 1) speak either English or Spanish and 2) plan to reside within the study area for at least one year. Study participants were followed through 2008.The Committee for the Protection of Human Subjects at the University of California, Berkeley approved the study protocol; written informed consent was obtained from parents/legal guardians for all procedures.

At baseline, each child and parent/legal guardian completed a field office visit and interview, where extensive background data were collected on medical history, residence, and socio-demographic factors. During this visit study personnel administered skin-prick tests on the children, testing them for sensitivity to several local antigens (test: MultiTest, donated by Lincoln Labs, Decatur, IL; antigens: Hollister-Stier, Spokane, WA). Experienced field study staff also trained children and parents in the use of the EasyOne portable spirometer (ndd Medical Technologies Inc., Zurich, Switzerland), including how to perform the forced expiratory maneuver and how to answer questions on symptoms and medication use that were programmed into the device's interface. The EasyOne portable spirometer has been demonstrated to have good agreement with the gold standard for lung-function assessment, laboratory-based spirometry[33]. Study staff who conducted this baseline visit and instructed participants in the use of spirometers had been trained by pediatric pulmonologists on the proper operation of the

equipment. As part of the study's compensation system, participating families were given gift packages upon completion of the baselines visit. These packages contained coupons worth $50 that could be redeemed at local vendors and food establishments.

After the initial baseline visit, participating families were followed up through periodic clinic visits (annual or semiannual) and semiannual phone calls. The in-person clinic visits allowed collection of up-to-date socio-demographic, medical, and anthropometric data on the children and families throughout the study period. During the clinic visits, trained study stuff measured standing height (in stocking feet) using a wall-mounted stadiometer. During the follow-up telephone calls, study personnel queried parents about potential changes in household or medical characteristics (e.g., changes in medication or pet ownership since the previous contact).

The pulmonary function outcome data used in this analysis come from periodic panel sessions during which participants performed home-based spirometry. Participating children completed two or three panel sessions per year, across different seasons. We based our season definitions upon local meteorological and air quality profile; the seasons were spring (February - May), summer (June - September), and winter (October - January). After study personnel installed new batteries and checked calibration on each portable spirometer, they dropped the device off at the participant's home, along with photographic instructions on the device's use. In each of these 14-day panel sessions, children performed spirometry maneuvers and answered questions programmed into the EasyOne spirometers about recent symptoms and medication use. Participants provided data twice daily during their panel sessions, the first time at 7:00 – 9:00AM after waking up, and again at 7:00 – 10:00PM, before going to bed. The study compensation program included an incentive system by which children accumulated points for performing these daily measurements; points could subsequently be redeemed for prizes at in-person clinic visits. At the beginning of the study, children were assigned to eight separate groups that completed panels during the same time period; therefore the periods of intensive data collection do not overlap between all children. These panel sessions give rise to the repeated panel structure of the data.

Pulmonary function and symptom data collected by the portable spirometers during the panel sessions were date- and time-stamped. After completion of panel sessions, study personnel picked up the devices from participants' homes and downloaded the data stored in the devices into a database. In addition to a Quality Assurance (QA) algorithm programmed into the EasyOne spirometers, panel data were subject to rigorous QA protocols by FACES study personnel. Each time- and flow-volume curve was individually reviewed for acceptability, for all test sessions on every participant during the 14-day data-collection periods. The staff member reviewing the curves was trained and overseen by a pulmonologist.

Hourly ambient exposure and meteorological data were collected at the Fresno Supersite monitor in downtown Fresno. Quality-assured exposure data from the study time period were obtained from CARB, and daily ambient exposure levels were assigned to individual children from these central-site measurements. For all ambient pollution and meteorological variables, the same value (as measured at the central site) was assigned to all children on a given day. Once obtained from CARB, the ambient air pollution data underwent additional quality assurance checks, including comparison with nearby monitoring sites, range checks, and checks for consistency with historical diurnal and temporal patterns.

NO_2 concentration in parts per billion (ppb) was calculated as a 24-hour average, as was $PM_{10-2.5}$ concentration in $\mu g/m^3$. $PM_{10-2.5}$ mass was calculated as the difference between PM_{10}

mass and $PM_{2.5}$ mass measurements (Beta–Attenuation Mass Monitors; Met One Instruments, Grants Pass, OR). Among the other pollutants examined in these analyses, concentrations of fine particles ($PM_{2.5}$), elemental carbon, and aerosol nitrate (NO_3) were calculated as 24-hour averages, while ozone was calculated as an 8-hour daily maximum concentration. Elemental carbon concentrations were estimated from Black Carbon[34], which was determined by aethalometer measurements (model AE42; Magee Scientific, Berkeley, CA) of the optical absorption of $PM_{2.5}$ ambient aerosol at 880 nm. The NO_3 content in $PM_{2.5}$ was measured by the Rupprecht and Patashnick 8400 Continuous Nitrate Analyzer (Rupprecht and Patashnick, Albany, NY); measurements were adjusted for equivalency with collocated filter-based measurements of $PM_{2.5}$ NO_3 from Harvard impactors and backup filters.

Single-pollutant PIM analysis of acute effects of ambient summer NO_2 on pulmonary function

Framing the research question

I explain the analytical approach employed in this dissertation using the single-pollutant NO_2 analysis as an example, because the method is more clearly demonstrated with a single-pollutant exposure regimen, and because ambient NO_2 is the exposure of principal interest. This single-pollutant NO_2 analysis focused on the acute effects of ambient NO_2 on pulmonary function in this cohort of children with asthma during the summer months (June – September). I chose to focus on the spirometric parameter forced expiratory flow between 25% and 75% of forced vital capacity (FEF_{25-75}). FEF_{25-75}, measured in liters/second, has been demonstrated to be a more sensitive measure of obstruction in the small airways, relative to other commonly analyzed outcomes like FEV_1, and is considered a more sensitive measure of impaired pulmonary function in people with asthma[35, 36]. Morning FEF_{25-75} was chosen over the evening FEF_{25-75} as the outcome variable to minimize the heterogeneity in activities and exposure that children experienced in the period immediately preceding the forced expiratory maneuver. Children would be expected to be sleeping prior to the morning measurement, while the range of activities preceding the evening measurement is more variable, including various activities that could increase or decrease exposure or pulmonary function. Furthermore, the morning measure would be more sensitive to detecting impaired pulmonary function given that spirometric measures are at their lowest upon awakening[37, 38].

Acute NO_2 effects were estimated using the lag 0 exposure window: the 24 hours preceding the morning outcome measurement (8:00AM the previous day – 8:00AM on the index day). Studies of acute NO_2 effects often examine multiple lags and moving averages, and prior studies have found significant results using various exposure time-frames[39, 40]. The studies examining associations between ambient NO_2 and respiratory symptoms have most consistently found associations at medium-length moving averages (two- to three-day windows), though in the study that specifically examine FEF_{25-75}, Liu *et al*. found significant associations between NO_2 and the outcome at shorter time-frames[41].

The analysis was restricted to summer months, as some studies of acute health effects have done in the past[42-44], in light of the variations in air pollution profile, meteorology, and underlying respiratory health by season. This cross-season heterogeneity might pose a challenge the valid estimation of single-pollutant health effects, and the challenge is compounded by the analysis of a more complex multi-pollutant exposure regimen.

Confounder selection and model-fitting

To identify and control for confounding bias present in the data, I considered several categories of variables that might be expected to be associated with both exposure and outcome. Information on the measurement and variability of the exposure and outcome variables analyzed in this dissertation (i.e., ambient air pollution as measured at a central monitor and individual pulmonary function) informs the discussion of the potential sources of confounding that follows.

There were three levels of confounding that were possibly present in this analysis; each is represented by a separate causal diagram. First, individual-level covariates were considered as potential confounders (Figure 1). Factors such as race/ethnicity and age at asthma diagnosis are likely to be associated with pulmonary function, but their possible association with exposure in this study is less obvious. In these analyses, I used central-site measurements of ambient pollutants as the exposure metric, variables that are characterized by temporal but not between-person variability. Although such population-level exposure measurements would not typically be associated with individual characteristics, the repeated panel data structure of the FACES data resulted in different groups of children being observed on different study days. This data structure created the possibility that the central-site air pollution measurements could be associated with individual traits, therefore warranting their consideration as potential confounders (see Mann *et al.* for a discussion of this topic[28]).

The second class of potential confounders were the environmental factors frequently considered in epidemiologic studies on the effects of ambient air pollution (Figure 2)[40, 45, 46]. Ecologic-level variables such as temperature and day of week (a surrogate for commuting patterns) may be associated with both ambient NO_2 and FEF_{25-75}, warranting their consideration as potential confounders.

Calendar time, age, and other factors associated with long-term time trends were the third class of potential confounders considered (Figure 3). The study was conducted over the course of many years during which physiologic parameters of children are certain to change with age, including height, which a strong predictor of pulmonary function. During the nine-year study period air pollution levels could also reasonably be expected to change. Preliminary review of the data confirmed these hypothesized associations, demonstrating both a decrease in pollutants (our exposure of interest; arrow A in Figure 3) over the course of the study, and in an unrelated way, an increase in the children's height due to the many years of follow-up (arrows B and C, Figure 3). Since height strongly predicts pulmonary function (our outcome of interest; arrow D in Figure 3), this imposed a confounding structure on the data that was difficult to model. Therefore, early in the analysis, I decided to do age-stratified analyses to diminish or remove the link between the natural growth of the children (and their pulmonary function) and any possible effect of changing air pollutant levels. By conditioning on child's age, I aimed to block the backdoor path in the causal diagram (Figure 3, blocking the path between arrows B and C).

Another factor motivating the age-stratified analyses was the desire to study the effects of air pollution on pulmonary function in sub-samples of children that were more homogeneous with regard to age, stage of development, and height. Based on this subject-matter consideration and the age/height-related confounding, children were divided between 6 to 9 year olds, 10 – 12 year olds, and 13 – 17 year olds for these acute effects analyses. Each stratum contained observations from children within a narrower age range than the entire study, which included children observed at ages between 6 and 17. Childhood asthma has a complicated natural history with age-based differences in presentation and symptoms[47-49], and this stratified analysis enabled estimation of more age-specific effects. The specific cut-points were chosen based on the distribution of the data (i.e., to ensure a large number of observations in each age group) and

based on subject matter considerations (i.e., splitting the pre-pubertal years from the pubertal years, and sub-dividing the pubertal years, which are characterized by hormonal changes that affect asthma prognosis[50, 51]).

Within each of the three age strata, I conducted parallel processes of confounder selection and model-fitting. All analyses were conducted using R (version 2.10.0; R Foundation for Statistical Computing, Vienna Austria). Based on knowledge of the subject matter and prior studies, the covariates considered as potential individual-level confounders were: race/ethnicity (African-American, white, Hispanic), asthma diagnosis at less than two years old, skin-prick test sensitization (positive to at least one allergen on the skin-test panel or reported history of severe reaction to prior allergy skin test), GINA classification of asthma severity[52] (mild-intermittent, mild-persistent, moderate, severe), and income (categorized in 4 groups). The potential environmental confounders were apparent temperature and day of week. Apparent temperature is a composite meteorological variable describing the perceived temperature accounting for relative humidity; see Basu *et al*. for details[53]. Use of this composite variable enabled adjustment for potential confounding by temperature and relative humidity collectively. I selected height-cubed as the proxy variable to control for potential residual confounding by calendar time that remained within age strata. Height-cubed was considered because any residual confounding by calendar time would be expected to be associated with the outcome through height (Figure 3, arrows B, C and D), and because height is strongly predictive of lung-function parameters[54] and also increases monotonically with time among this age group. I analyzed the cube of height because prior research has demonstrated this power of height to be most strongly predictive of spirometric outcomes, due to the volumetric shape of the lung[54-56].

The first step of model-fitting was to reduce this list of candidate covariates to a list of potential confounders for each age group-specific analysis. For each age group, FEF_{25-75} and NO_2 were separately regressed on each of the individual candidate covariates to assess bivariate associations. I used the Candidate Reduction routine in the Deletion/Substitution/Addition package in R (version 3.1.3[57]) to fit Generalized Estimating Equations for each exposure-covariate pair and each outcome-covariate pair, assuming independent working correlation structure[58]. Using the robust standard errors as a guide, those covariates that were associated with both exposure and outcome at the $P<0.2$ level were selected as confounders of the effect of NO_2 and FEF_{25-75} in each age group. These confounders were considered in the fitting of the Q-model.

After selecting the confounding variables from the list of candidate covariates, I fit Q-models for the effects of NO_2 on FEF_{25-75} in each of the three age groups. While subject matter knowledge and empirical associations informed the selection of candidate covariates and confounders, there was no guidance on which model specification would be optimal for this research question and specific dataset[4]. In light of this, I used a flexible model-fitting algorithm, Deletion/Substitution/Addition, to select the optimal Q-model for each age group. The DSA algorithm searches the model space, considering various parameterizations including interaction terms and higher-order polynomials, according to the user's specifications. The algorithm employs cross-validation to select the most predictive model, using the criterion of minimized loss function[57]. Each DSA run forced in the exposure variable and considered the confounders selected by dimension reduction, considering models with up to 2-way interactions and quadratic terms. The cross-validation was specified to run with 10 5-fold splits of the data. In order to ensure that the DSA algorithm was consistently selecting the same model for each age group, the DSA model-fitting procedure was run in 10 repetitions for each of the three age

groups. If the algorithm converged on the same model in at least 8 of 10 runs, then that model was selected as the Q-model. If the DSA algorithm did not select the same model in at least 8 of 10 runs, then I increased the number of data splits used in cross validation by 10 until convergence. The model specification selected during this step served as the Q-model for the g-computation procedure.

Parameter estimation

For each age group, I fitted a Q-model, using linear regression to model the outcome as a function of the exposure and confounders ($E(Y \mid A, W)$), with the confounders and specification selected by the DSA algorithm. In order to ensure that each child contributed equally to the regression in the presence of repeated measures (with unequal number of measurements per child), I ran a weighted regression. Every observation from a given child was weighted by the inverse number of observations contributed by the child, so that the children were weighted equally in the model.

This Q-model was then used to predict the unobserved outcomes that provided the full data for this analysis: the counterfactual outcome under the intervention pollution profile. I mechanically implemented the prediction of unobserved counterfactual outcomes by generating a dataset in which no NO_2 level exceeded the intervention level. The "intervention level" here refers to a hypothetical maximum NO_2 cutoff that I selected in order to determine the population effects of reduced air pollution on pulmonary function. The selection of the NO_2 intervention level was informed by the observed distribution of NO_2 in the study sample and considerations of parameter identifiability. I chose the 25^{th} percentile of NO_2 across study days within each age group, which corresponded to 9.9 ppb for the younger age group, 9.7 ppb for the middle age group, and 9.1 ppb for the older age group. This intervention level was selected as one that was reasonable (as opposed to lowering NO_2 concentration to its minimum level), and also to ensure that there would be support in the data to estimate health effects at the chosen level. Details of the single-pollutant NO_2 intervention and the distribution of NO_2 concentrations are provided in the Results section.

In the intervention dataset, which was used to generate the Y_a counterfactual outcomes, NO_2 levels above the intervention cutoff level were reduced to the intervention level, while NO_2 levels at or below the intervention level were unchanged. For a hypothetical intervention designed to examine the effects of decreasing air pollution exposure, the possibility of raising NO_2 levels for some people did not serve the question of interest, hence the NO_2 measurements below the intervention level were unaffected. In the causal inference literature, this type of hypothetical treatment regimen, in which the assignment of the hypothetical exposure depends on the observed exposure characteristics, can be considered a dynamic treatment regimen[59]. The Y_a intervention outcomes were predicted for each age group, using the Q-model with the intervention dataset, which held all covariates constant but lowered exposure levels for some observations. The outcome under the observed exposure distribution ($E[Y]$) was calculated from the empirically observed FEF_{25-75} values.

After generating the full data set, composed of the Y and Y_a outcomes for each observation, I calculated a risk difference comparing the mean outcome under observed exposure and the mean outcome when NO_2 levels were reduced to the 25^{th} percentile: the Population Intervention Parameter $E[Y] - E[Y_a]$ (expression 7). Weighting was also used at this stage of the estimation to ensure that each child was weighted equally in the calculation of the risk difference. Again, observations within a child were inverse-weighted by the number of

observations contributed per child to calculate weighted averages (both observed and unobserved), and a weighted risk difference.

To generate standard errors for the effect estimates, I conducted a bootstrap of the weighted Q-model regression, the g-computation procedure, and the weighted risk difference calculation. The bootstrap procedure was conducted using resampling with replacement by child rather than by observation. In each bootstrap repetition, the same absolute NO_2 levels (9.9 ppb, 9.7 ppb, and 9.1 ppb) were implemented as the population intervention, rather than the 25th percentile of NO_2 in the bootstrap-resampled population. The bootstrap was conducted with 1,000 repetitions, and the standard errors were calculated from these repeated point estimates.

Single-pollutant $PM_{10-2.5}$ PIM analysis

I applied the same approach described above to calculate a single-pollutant Population Intervention Parameter for the effects of ambient summer $PM_{10-2.5}$ on FEF_{25-75}. This analysis mirrored the single-pollutant NO_2 analysis, employing the same season restriction, lag structure, age stratification, candidate covariates, confounder selection, Q-model fitting, weighted parameter estimation, and bootstrapping. The PIP can be represented in the same manner as the NO_2 single-pollutant parameter ($E[Y] - E[Y_a]$), but the A in this case is coarse fraction. For reasons that I elaborate on in the next section, the hypothetical intervention that is estimated by the PIP represents lowering $PM_{10-2.5}$ concentrations to approximately the 20th percentile of the observed distribution of coarse fraction concentrations (specifically, 16.5, 16.3 and 15.9 $\mu g/m^3$ for the younger, middle, and older age groups, respectively). Again, this corresponds to a parameter that is realistic and identifiable given the single-pollutant distribution of ambient coarse fraction. Further details of the distribution of $PM_{10-2.5}$ concentrations, and the single-pollutant $PM_{10-2.5}$ intervention, are provided in the Results section. This hypothetical exposure scenario was plugged into the age group-specific Q-models to predict Y_a for each observation given the single-pollutant $PM_{10-2.5}$ intervention. The counterfactual outcomes and the observed FEF_{25-75} were used to calculate weighted averages ($E[Y_a]$ and $E[Y]$, respectively), weighting each child equally. These averages were subsequently used to calculate the Population Intervention Parameter for the single-pollutant $PM_{10-2.5}$ effect in each age group.

PIM analysis of NO_2 and $PM_{10-2.5}$ mixture effects

In order to estimate the effects of a summertime mixture of ambient NO_2 and ambient $PM_{10-2.5}$ on pulmonary function, I extended this dynamic treatment PIM procedure described above to a two-pollutant framework. The outcome was the same, morning FEF_{25-75}, and I used the same lag structure as for the single-pollutant analyses, lag 0. The data were age-stratified into the same categories to estimate age-specific mixture effects, and to control for confounding by height/calendar time.

The approach to confounder control and model-fitting paralleled the process in the single-pollutant analyses. Using the same candidate covariate list as described above, bivariate $PM_{10-2.5}$/covariate associations, NO_2/covariate associations, and FEF_{25-75}/covariate associations were calculated using the Candidate Reduction routine in the DSA package. Any covariate that was associated with the outcome and with either exposure at the $P<0.2$ level was considered a potential confounder, and was submitted as a potential predictor to the DSA algorithm. I implemented the DSA algorithm to determine the model specification for the two-pollutant mixture, forcing in both exposures as linear terms. The details of the implementation of DSA

were the same: 10 5-fold splits of the data, permitting up to two-way interactions and quadratic polynomial terms, run in sequence 10 times until at least 8 runs converged on the same model.

Once the confounders and model specification were selected for each age group, I fitted the age-specific 2-pollutant Q-models using inverse-weighted linear regression, using the same approach as for the single-pollutant analyses. For each age group, I then used the same Q-model to estimate the population-level effects of three distinct interventions on a 2-pollutant exposure regimen composed of NO_2 and $PM_{10\text{-}2.5}$. I begin by describing these three population interventions conceptually, and then explain the details of each. One population intervention, which I designate intervention A, involved lowering NO_2 while holding the co-pollutant at observed levels. This enabled comparison to the single-pollutant NO_2 PIP, in which NO_2 was the only pollutant modeled in the exposure regimen. Conversely, intervention B lowered $PM_{10\text{-}2.5}$ concentrations while holding NO_2 concentrations at their observed levels, enabling comparison to the single-pollutant $PM_{10\text{-}2.5}$ PIP. Both of these population interventions are analogous to the multi-pollutant modeling approaches common in the literature, in which multiple pollutants are modeled as independent variables and one pollutant coefficient is multiplied by a large exposure interval, while holding the co-pollutants in the model constant[40, 41, 60-62].

In contrast with this approach of intervening on only one pollutant in the 2-pollutant exposure regimen, intervention C was to lower concentrations of both NO_2 and $PM_{10\text{-}2.5}$ simultaneously. Table 1 summarizes the three 2-pollutant population interventions, and both single-pollutant interventions alongside each other, highlighting which pollutant(s) were included in the exposure regimen for each intervention, and which pollutant(s) were lowered in each. The specific levels that NO_2 and $PM_{10\text{-}2.5}$ concentrations were lowered to in the 2-pollutant population interventions were the same as the cutoff concentrations employed in the respective single-pollutant interventions. Specifically, in 2-pollutant interventions A and C, NO_2 was lowered to 9.9 ppb, 9.7 ppb, and 9.1 ppb for the younger, middle, and older age groups (respectively). These are the age-group specific 25^{th} percentile of NO_2 concentrations. As in the single-pollutant $PM_{10\text{-}2.5}$ intervention, the 2-pollutant interventions B and C involved lowering $PM_{10\text{-}2.5}$ to 16.5, 16.3 and 15.9 $\mu g/m^3$ for the younger, middle, and older age groups, respectively. These values correspond to approximately the 20^{th} percentile, and were chosen for reasons of parameter identifiability. Toward the end of estimating two-pollutant mixture effects for which there was support in the data, I considered the joint exposure distribution of the two co-pollutants to inform the selection of $PM_{10\text{-}2.5}$ intervention levels. Specifically, these $PM_{10\text{-}2.5}$ intervention concentration cutoffs represent the median $PM_{10\text{-}2.5}$ concentration on the observed 25% of study days that had NO_2 concentrations at or below the NO_2 intervention cutoff level. These same $PM_{10\text{-}2.5}$ intervention cutoffs were used in all analyses that involved decreasing the concentration of coarse fraction, namely the single-pollutant $PM_{10\text{-}2.5}$ intervention and 2-pollutant interventions B and C. In the Results section I return to these 2-pollutant parameters, explaining them in detail and elaborating on the issues of positivity and parameter identifiability.

Defining NO_2 as exposure A_1 and $PM_{10\text{-}2.5}$ as exposure A_2, the Population Intervention Parameter estimated by 2-pollutant intervention A can be represented as:

$$E[Y] - E[Y_{a_1, A_2}] \tag{8}$$

The baseline outcome against which the intervention's effects are being compared is still the weighted mean of the observed $FEF_{25\text{-}75}$ outcome ($E[Y]$). The counterfactual outcome predicted by intervention A is $E[Y_{a_1, A_2}]$, which describes the mean counterfactual outcome when exposure

A_1 is intervened upon and lowered to intervention levels (as indicated by the lowercase a_1), while co-pollutant A_2 is held at its empirically observed levels (as indicated by the uppercase notation).

Conversely, the PIP estimated by 2-pollutant intervention B is:

$$E[Y] - E[Y_{A_1, a_2}] \tag{9}$$

Exposure A_1 is held at empirically observed levels while exposure A_2 is intervened on and (represented by the lowercase a_2). When both exposures are simultaneously intervened on and lowered to intervention levels under intervention C, the PIP is defined as:

$$E[Y] - E[Y_{a_1, a_2}] \tag{10}$$

While the PIPs estimated by interventions A and B enabled comparison to the single-pollutant population interventions (and to standard practice in multi-pollutant modeling), 2-pollutant intervention C presents an approach to estimating cumulative effects for multiple pollutants changing simultaneously in a mixture. Interventions A and B are in the spirit of "controlling for" co-pollutants as confounders, i.e. estimating the effects of a single exposure while adjusting for a potential confounder. This is often the stated goal of multi-pollutant modeling in the literature[60-62]. In contrast, Intervention C treats the co-pollutants as a joint exposure regimen composed of two co-exposures that vary simultaneously. The exposure characteristics and data support will for each of these three 2-polltant interventions will be examined in detail in the Results section.

Heuristic demonstration of exposure manipulation under the 2-pollutant intervention C

In order to give concrete examples of how exposure is manipulated under a mixture intervention, Figure 4 presents a heuristic diagram explaining how intervention C would change NO_2 and $PM_{10-2.5}$ concentrations on several days depending on the observed pollution profile. There is a representative day to demonstrate each possibility. To simplify the demonstration, the figure uses NO_2 and $PM_{10-2.5}$ intervention cutoff levels corresponding to the entire sample of study days, rather than any one of the age-stratified analyses (which have similar but slightly varying intervention cutoff concentrations).

Day α represents August 2, 2003, a day with a high ambient NO_2 concentration above the intervention cutoff level and a $PM_{10-2.5}$ concentration below the cutoff level. Therefore, as Table 2 demonstrates, intervention C decreases the NO_2 concentration on day α to the cutoff level while leaving the $PM_{10-2.5}$ concentration unaffected. Conversely, day β (June 10, 2002) is characterized by an ambient $PM_{10-2.5}$ concentration above the intervention cutoff and a NO_2 concentration below the cutoff. Thus, intervention C decreases the $PM_{10-2.5}$ concentration on day β while leaving the NO_2 concentration unaffected. Day γ (June 14, 2001) is characterized by high ambient concentrations of both pollutants. Both NO_2 and $PM_{10-2.5}$ concentrations are above their respective intervention cutoff levels, so both are decreased under intervention C. The levels of ambient NO_2 and $PM_{10-2.5}$ observed on day δ (June 9, 2004) are both below their respective intervention cutoff levels, therefore neither concentration is altered by intervention C.

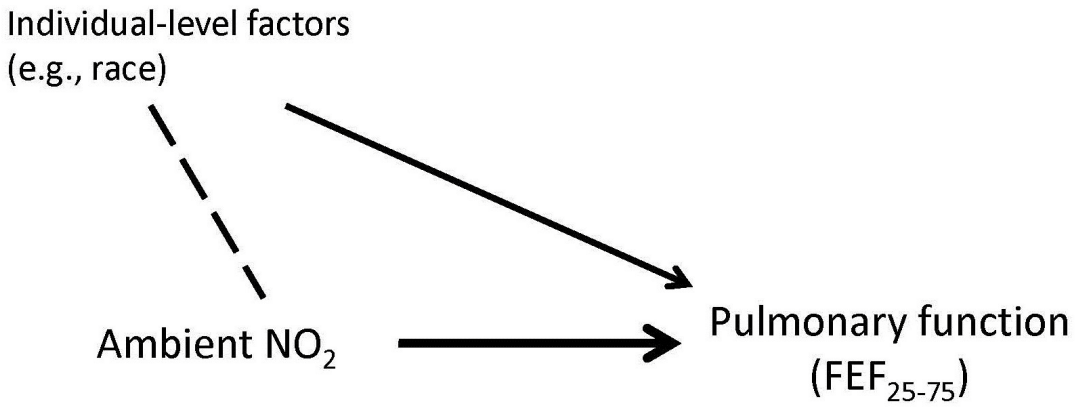
TABLES AND FIGURES.

Table 1. Description of all analyses and exposure regimens conducted in this project.

Name of analysis	Exposure regimen		Description of Intervention*	
	NO_2 exposure?	**$PM_{10-2.5}$ exposure?**	**NO_2 lowered?**	**$PM_{10-2.5}$ lowered?**
Single-pollutant NO_2	✓		✓	
Single-pollutant $PM_{10-2.5}$		✓		✓
2-pollutant intervention A	✓	✓	✓	–
2-pollutant intervention B	✓	✓	–	✓
2-pollutant intervention C	✓	✓	✓	✓

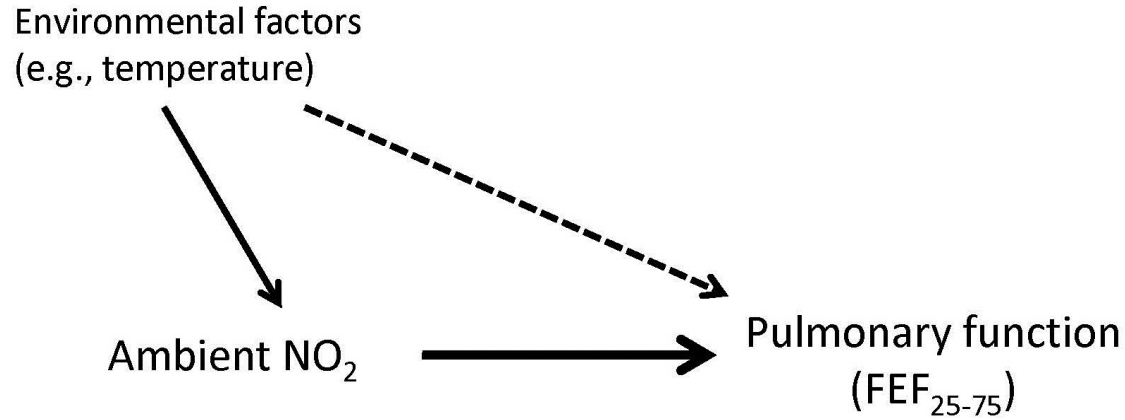
*Shading indicates that the pollutant was not included in the exposure regimen; a dash indicates that the pollutant was included in the exposure regimen and was held at its observed levels in the population intervention.

Figure 1. Causal diagram demonstrating potential confounding by individual-level factors.



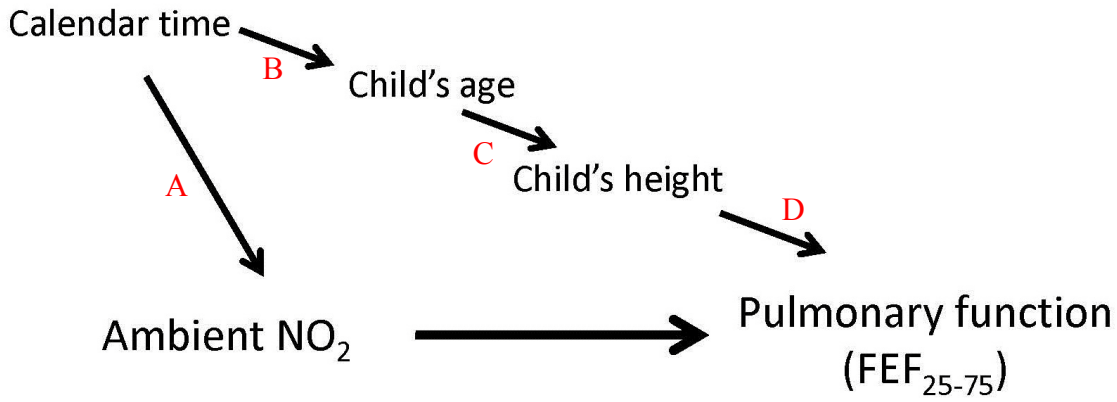
The casual effect of interest is the heavy arrow between ambient NO_2 and pulmonary function. This causal diagram shows that individual level factors such as race are likely to be associated with the outcome (solid arrow), and may be associated with ambient NO_2 due to the repeated panel structure of the data (dashed line). The presence of this association would bias the effect estimate by introducing empirical confounding.

Figure 2. Causal diagram demonstrating potential confounding by environmental factors.



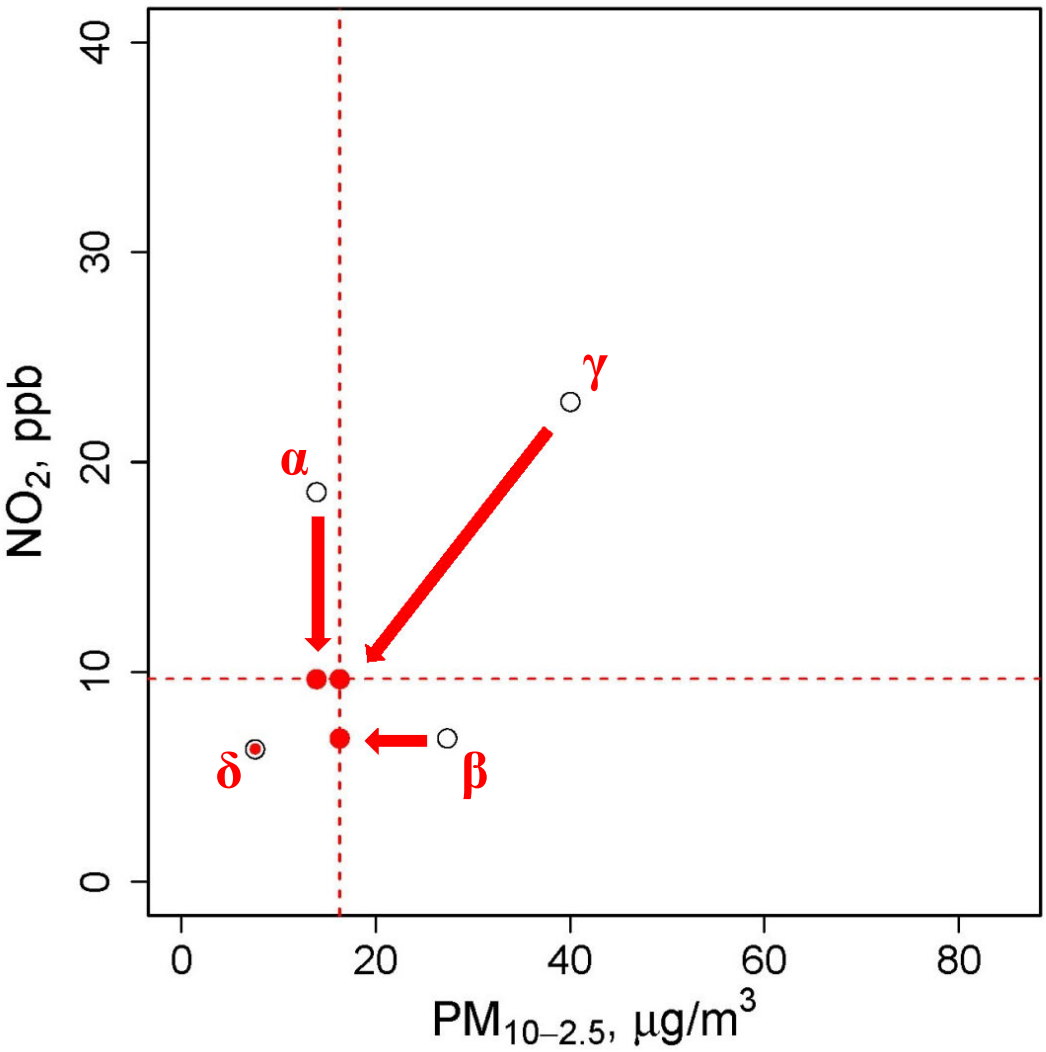
The casual effect of interest is again the heavy arrow between ambient NO_2 and pulmonary function. Environmental factors such as temperature are likely to be associated with ambient NO_2 (solid arrow), and if they also predict pulmonary function (dashed arrow), then the exposure-outcome association will be biased due to confounding.

Figure 3. Causal diagram demonstrating potential confounding by calendar time.



The casual effect of interest is again the heavy arrow between ambient NO_2 and pulmonary function. Calendar time may introduce confounding bias into that association because pollutant levels changed over time, and pulmonary function also increased with time, as children aged and grew taller.

Figure 4. Heuristic demonstration of how pollutant concentrations change for four unique days given 2-pollutant population intervention C (lowering levels of both NO_2 and $PM_{10-2.5}$).



Guide to interpreting this figure:

- Each red dot/black circle pair represents a unique study day.
- Open black circles represent empirically observed NO_2 and $PM_{10-2.5}$ concentrations on the study day.
- Red dots represent the pollutant concentrations for each day under the 2-pollutant intervention C; the red arrows represent the change between observed and intervention concentrations (when applicable).
- Hashed red lines represent the cutoff concentrations of NO_2 and $PM_{10-2.5}$ under intervention C.

- The following table explains which pollutant concentrations change on each of the four example study days, given intervention C.

Table 2. Explanation of which pollutant concentrations were changed* on the four example study days, given 2-pollutant intervention C (Figure 4).

		Day α	**Day β**	**Day γ**	**Day δ**
Intervention C	NO_2	✓	Observed	✓	Observed
	$PM_{10-2.5}$	Observed	✓	✓	Observed

* A check indicates that the value of the pollutant concentration was re-assigned under intervention C; "observed" indicates that the pollutant concentrations remained at their observed levels under intervention C.

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III. Results

Characteristics of the entire sample

Of the 315 children recruited into the FACES study, 16 participated in baseline clinic visits but did not provide any panel data. As the present study examined pulmonary function data gathered during these panel observations, these children were not considered for analysis. Of the 299 children who contributed any panel data, an additional 42 children did not contribute any panel data during the summer months (June – September) which were the focus of these analyses, so their pulmonary function data were not analyzed. Table 1 provides descriptive statistics of demographic and health characteristics at baseline for both the entire sample of 299 children who contributed any panel data and the subset of 257 children that contributed panel data during summer months, whose pulmonary function data were analyzed in this study. The subset of 257 children analyzed in this study did not significantly differ from the entire sample of 299 children by any of these factors ($P>0.2$ for all chi-square/Fisher's Exact tests).

Like the overall sample, the subset of 257 children was over half male, predominately Hispanic and white with a sizable minority of African-American children, and had a median age of 8 years old at enrollment. Almost a fifth of the children came from households with an annual income of less than $15,000, with approximately half having incomes between $15,000 - $50,000. Using the Global Initiative of Asthma to classify asthma severity[1], approximately three quarters of the children had mild-intermittent or mild-persistent cases of asthma, with the latter being the more common designation. The proportion of children with moderate or severe asthma was nearly one fourth. Just over half of the children tested positive to at least one allergen on the skin-test panel or had a reported history of severe reaction to prior skin tests. Over a third of children had been diagnosed with asthma before the age of two years old; age at asthma diagnosis acts as a surrogate for severity and decreased pulmonary function because most cases of chronic, persistent asthma begin in the first years of life[2].

Characteristics of the age-stratified sub-samples

I stratified the sample of 257 children by age in order to allow for the possibility of effect heterogeneity by age and to control for the confounding related to calendar time and height, as described in the Methods section. The data were divided into observations from children aged 6 – 9 years old, children aged 10 – 12 years old, and children aged 13 – 17 years old. Stratification was conducted on the basis of child-days rather than children, so the same child could and did contribute data to multiple age categories. Table 2 enumerates the number of age categories that each child was observed in, and the frequency of each specific age group combination. 99 children contributed to only one age group, with almost all of these children being observed in only the 6 – 9 or 10 – 12 years-old age categories. 125 children contributed to a total of two age categories; unsurprisingly all but two of these children were observed in two consecutive age categories (i.e., 6 – 9 and 10 – 12 year old, and 10 – 12 and 13 – 17 years old). 33 children were observed in all three age groups.

Table 3 presents descriptive statistics of the sub-sample of children that were observed in each age category. There were a total of 151 children observed as 6 – 9 year olds, 196 children as 10 – 12 year olds, and 101 children between the ages of 13 and 17. The total number of observation-days contributed by children in each age group mirrored the pattern of the number of unique children, with the middle age group (10 – 12 years old) having the most panel-days, and the older age group (13 – 17) having the least. Most demographic and health characteristics did

not differ significantly between the three age groups (P>0.2 on chi square tests), except for skin-test positivity and asthma diagnosis at age 2 or younger. For both of these variables, the chi square test statistic indicated that there were significant differences between the three groups (P=0.06 and P=0.05, respectively). Children observed in the older age category tended to be more atopic, as indicated by a higher proportion testing positive on the skin-test panel, and had a lower proportion diagnosed with asthma at or before age 2. The younger age group was characterized by younger age at asthma diagnosis and less atopy.

Anthropometric and pulmonary parameters of each age group are summarized in Table 4. Because FEF_{25-75} and standing height both varied within children over time and the participants contributed different numbers of panels and observations, Table 4 summarizes child-specific mean values of each variable. The mean and median values of the average height increase across the age groups. The same pattern is observed in mean and median values of FEF_{25-75}, which is strongly predicted by height. Because age is determined by calendar year, a similar trend of increasing height and FEF_{25-75} is observed across calendar time (data not shown). Taken together, these data demonstrate that the outcome, FEF_{25-75}, is associated with calendar time transitively through height (see also the causal diagram in the Methods section, Figure 3).

Distribution of ambient air pollution concentrations during summer months

Table 5 presents the distribution of ambient air pollution and meteorological variables during summer months (June – September), as measured at the U.S. EPA Supersite monitor in Fresno, California. In addition to the pollutants whose health effects are being studied in these analyses, pollutant distributions are presented for other pollutants in order to more fully describe the summertime ambient air pollution mixture in Fresno during the FACES study period. Although the FACES study was conducted from 2000 – 2008, the first panel data were collected after the end of summer in 2000; therefore all descriptions of summer-specific data, including Table 5, apply to the years 2001 – 2008. The exposure data tables present distributions of environmental variables on unique study days rather than child-days (which have repeat exposure measurements from children observed on the same day). There were 648 unique summer study days on which FACES participants contributed panel data. For the purposes of comparison to observed pollution concentrations, Table 6 presents the regulatory standard levels for the relevant pollutants, as codified by the U.S. EPA's National Ambient Air Quality Standards (NAAQS; primary standards are presented and discussed)[3].

The median 24-hour average concentration of ambient NO_2 was 12.9 ppb, with an interquartile range (IQR) of 7.9 ppb. Because I employed an averaging time of 24 hours and NAAQS regulate NO_2 levels with annual and 1-hour averaging times, it is not possible to compare these observed concentration to regulatory standards. The ambient summer $PM_{10-2.5}$ concentration, also measured with a 24-hour averaging time, had a median of 22.0 $\mu g/m^3$, with an IQR of 12.1 $\mu g/m^3$. There is no NAAQS standard that regulates $PM_{10-2.5}$.

Ozone and $PM_{2.5}$ are also part of the summertime air pollution mixture in Fresno to varying degrees. The median ambient ozone concentrations (maximum 8-hour average) was 72.4 ppb, with an IQR of 21.0 ppb. Given that the 2008 NAAQS ozone standard is 75 ppb, a large number of summer days in Fresno exceeded the regulatory standard during the FACES study period. Ambient fine particulate matter with an aerodynamic diameter equal to or less than 2.5 μm ($PM_{2.5}$) had a median concentration of 10.5 $\mu g/m^3$ (24-hour averaging period). While the maximum ambient summer $PM_{2.5}$ concentration observed did exceed the NAAQS 24-hour standard of 35 $\mu g/m^3$, the majority of days were well below the regulatory standard (75^{th}

percentile concentration of $PM_{2.5}$ = 13.8 μg/m^3). Table 5 also presents the distributions of Elemental Carbon (EC) and NO_3, along with apparent temperature (calculated as described by Basu *et al.*[4]).

Trends and patterns in ambient air pollution concentrations

Tables 7 and 8 and Figures 1 – 3 present temporal trends in ambient air pollution and meteorological variables in Fresno during the FACES study period. Despite fluctuations from year to year, Table 7 demonstrates a downward trend in ambient summer concentrations of both NO_2 and $PM_{10-2.5}$ between 2001 and 2008. The correlation between ambient summer NO_2 concentration and study year was -0.21; for $PM_{10-2.5}$ the correlation was -0.20. The number of unique study days in the same table demonstrates that FACES participants were observed on a greater number of summer days in the early years of the study (2002 – 2004). When comparing summer concentrations of ambient pollution variables across age groups (Table 8), the concentrations of both NO_2 and $PM_{10-2.5}$ are slightly lower on the study days in which the older group was observed (13 – 17 year-olds). These concentrations also correspond to the smallest number of unique summer days of any age group (329, versus 563 for the younger age group and 607 for the middle age group), and do not include many of the high-pollution days that occurred early in the study period when the sample of children was younger. In contrast with the air pollution variables, the apparent temperature distribution did not vary between the age groups.

Correlations between pairs of ambient summertime pollutants are presented in Table 9. The exposure variables of NO_2 and $PM_{10-2.5}$ are moderately positively correlated during summer months, with a Pearson's correlation coefficient of 0.67. Both NO_2 and $PM_{10-2.5}$ are only slightly positively correlated with ozone and $PM_{2.5}$ (correlation coefficients between 0.29 and 0.36).

The temporal and seasonal trends in ambient NO_2 and $PM_{10-2.5}$ concentrations are graphically presented in Figures 1 – 3. These figures are Kernel smoothes of each pollutant throughout the FACES study period, separately and with the two overlaid, with summer months demarcated by shading. I implemented the Nadaraya-Watson Kernel smoother[5, 6] with bandwidth of 20 days. The decrease in summertime pollution over the study period is visually evident in the case of ambient NO_2 (Figure 1). These figures also demonstrate that the seasonality of NO_2 differs from that of $PM_{10-2.5}$. The early summer season captures the low point of the NO_2 cycle in Fresno, after which concentrations begin to approach their winter peak late in the summer months. In contrast, $PM_{10-2.5}$ is lowest between winter and spring with the concentration approaching its peak in later summer, as demonstrated in Figure 2. Figure 3 visually demonstrates the positive correlation between the two pollutants during summer months. The magnitude and direction of their correlation is different outside the summer months, further making the case for conducting a season-specific multi-pollutant analysis.

Description of population interventions

In the Methods section I conceptually described the population interventions whose health effects I am estimating; Tables 10a – 10c and Figures 4 – 10 elaborate on the details and mechanics of the interventions. Figure 4 is a scatter plot of the ambient NO_2 concentrations against ambient $PM_{10-2.5}$ concentrations in Fresno during all summer study days, graphically demonstrating the positive correlation between the two pollutants. This figure and the ones that follow (Figures 5 – 10) heuristically demonstrate the research approach on the full set of unique summer days, across all ages. Tables 10a – 10c contain the distributional details of the

population interventions as they are applied within each of the three age groups, including the specific concentration cutoff for each pollutant in each age group.

For the population interventions that involved decreasing NO_2 concentrations, I selected the 25th percentile of NO_2 concentrations in each age group as the cutoff level that no day would exceed under intervention. The specific cutoff values were 9.9 ppb, 9.7 ppb, and 9.1 ppb for the analyses on the younger, middle, and older age groups, respectively. Days at or below the intervention cutoff concentrations were not affected by the population intervention; that is, the observed values were retained. These population interventions were applied when NO_2 was the only pollutant in the model (Table 10a), as well as when NO_2 was modeled in a mixture with $PM_{10-2.5}$ (Table 10c, Interventions A and C). The NO_2 threshold concentration was defined in relation to the age-specific ambient NO_2 distribution in the same manner for each age group: the 25th percentile. Therefore, the percentile of the observed NO_2 distribution that the population intervention corresponds to is by definition equal for NO_2 interventions (namely, the single-pollutant NO_2 intervention and 2-pollutant interventions A and C; right column in Tables 10a and second column in 10c). This contrasts with the $PM_{10-2.5}$ population intervention.

Because $PM_{10-2.5}$ was analyzed secondarily to NO_2 (the primary exposure of interest), the $PM_{10-2.5}$ intervention was determined with respect to the distribution of NO_2. To define an identifiable parameter of interest for a 2-pollutant exposure regimen, I considered the joint distribution of the two co-pollutants to inform the $PM_{10-2.5}$ intervention. Table 11 presents the age-group-specific distribution of ambient NO_2 and $PM_{10-2.5}$ on the 25% of observed study days that had NO_2 concentrations below the age-group-specific NO_2 intervention level. As would be expected based on the correlation between the two pollutants, the $PM_{10-2.5}$ concentration on these days of low NO_2 concentration is also low, relative to the overall $PM_{10-2.5}$ concentration (lower half of Table 11). For each age group, the median concentration of $PM_{10-2.5}$ across all study days is greater than the 75th percentile of $PM_{10-2.5}$ on observed low-NO_2 days. I selected the median $PM_{10-2.5}$ concentration on observed study days with NO_2 concentrations at or below the 25th NO_2 percentile as the $PM_{10-2.5}$ intervention levels: 16.5, 16.3, and 15.9 $\mu g/m^3$ for the younger, middle, and older age groups, respectively. Tables 10b and 10c present the percentile of age-group-specific $PM_{10-2.5}$ distributions to which these cutoff levels correspond, between the 19th and 22nd percentile of $PM_{10-2.5}$. The $PM_{10-2.5}$ intervention cutoff concentrations differ by age group because of how the $PM_{10-2.5}$ population intervention was defined (i.e., in relation to the observed age-specific NO_2 distributions rather than as a fixed percentile). This contrasts with the NO_2 intervention cutoff levels, which were by definition all equal to the 25th percentile of observed NO_2 concentrations. This $PM_{10-2.5}$ population intervention was applied when $PM_{10-2.5}$ was the only pollutant in the model (Table 10b) and in some cases, when $PM_{10-2.5}$ was modeled as a part of a 2-pollutant exposure regimen (Table 10c, Interventions B and C). Days with observed ambient $PM_{10-2.5}$ concentration at or below these concentrations were unaffected by the intervention.

In order to consider how realistic and identifiable each 2-pollutant health effect is, Tables 11 – 13 present the distributions of NO_2 and $PM_{10-2.5}$ concentrations on observed study days that meet the requirements of each intervention, in comparison with the counterfactual distribution of the pollutant when the population intervention is applied. Table 11 applies to the 2-pollutant population intervention A, wherein NO_2 levels are lowered and $PM_{10-2.5}$ levels are held at their observed values. Because the NO_2 intervention level was defined as the 25th percentile of the observed NO_2 distribution, the number of observed study days with NO_2 below the intervention level is approximately equal to one quarter the total number of unique days for each age group.

The same ratio applies to the number of days described by the $PM_{10-2.5}$ concentrations given intervention A (bottom half of Table 11). For conciseness in discussing Tables 11 - 13, the pollutant distribution on observed study days that conform to the population intervention will hereafter be called "the observed pollutant distribution," and the counterfactual pollutant distribution when the population intervention is applied will be termed "the intervention pollutant distribution." It is important to note that the "intervention pollutant distribution" will in some cases be the same as the observed pollutant distribution on all study days, when the intervention does not change levels of the pollutant in question (as with the "intervention" $PM_{10-2.5}$ distribution under intervention A).

In Table 11, the age-group-specific maximum NO_2 concentrations are equal between the observed distributions and the intervention distributions given intervention A; this is an artifact of how the intervention was defined. Because the intervention was defined as lowering all concentrations above a certain threshold down to the threshold value, both the observed and the intervention concentration distributions are explicitly defined as having the same maximum (threshold) concentration. While the intervention NO_2 distributions are skewed more toward these maximum values (by virtue of 75% of study days being equal to the distribution maximum), the two distributions overlap entirely. In contrast, the observed $PM_{10-2.5}$ distribution and the intervention $PM_{10-2.5}$ intervention (here, equal to the observed distribution of $PM_{10-2.5}$ on all study days) have strikingly different distributions in intervention A, with the observed $PM_{10-2.5}$ being much lower than the intervention distribution. The maximum concentration in the intervention $PM_{10-2.5}$ distribution is more than 75% greater than the maximum concentration in the observed $PM_{10-2.5}$ distribution for all age groups. Put differently, the median concentration in the intervention $PM_{10-2.5}$ distribution is above the 75^{th} percentile of the observed $PM_{10-2.5}$ distribution for all age groups. Figures 5 and 6 graphically demonstrate the health effect being calculated by the PIM with intervention A. Figure 5 presents the joint distribution of the ambient NO_2 and $PM_{10-2.5}$ exposure regimen given intervention A, while Figure 6 shows this hypothetical distribution laid over the empirically observed joint distribution of the two pollutants. Lowering only NO_2 levels in this dataset results in a large density of red dots (representing concentrations on intervention days) being moved to a part of the graph where the black dots (observed days) are sparsely distributed. (For simplicity in graphical presentation, Figures 5 – 6 as well as Figures 7 – 10 depict all summertime study days, rather than age-group-specific subsets of summer study days. The intervention cutoff levels in each graphic were also calculated based on the entire sample of study days, in the same manner as the age-group-specific values.)

Table 12 and Figures 7 and 8 demonstrate the converse situation as applies to intervention B. In Table 12, the observed $PM_{10-2.5}$ distribution and the intervention $PM_{10-2.5}$ overlap entirely. In contrast, the range of the intervention NO_2 distribution far exceeds the range of the observed NO_2 distribution, with the distribution of intervention NO_2 concentrations greater than the concentrations observed on low $PM_{10-2.5}$ days. Within each age group, more than half of intervention days have NO_2 concentrations exceeding the 75^{th} percentile of the observed NO_2 distribution on low $PM_{10-2.5}$ days; almost a quarter of intervention days have NO_2 concentrations that exceed the maximum NO_2 concentration on low $PM_{10-2.5}$ days. As with intervention A, the concentrations of the index pollutant (here, $PM_{10-2.5}$) exhibit complete overlap between intervention and observed distributions. However, the concentration distribution of the pollutant that it not intervened upon (here, NO_2) differs between the intervention and observed distributions, with the intervention distribution exceeding the observed distribution in terms of range and concentration values. Figure 7 presents a scatter plot of the hypothetical air pollution

profile when intervention B is applied and Figure 8 shows the intervention B air pollution profile laid over a scatter plot of the empirically observed distribution of NO_2 and $PM_{10-2.5}$. As with intervention A, there is a clustering of red dots (intervention days) in a part of the graph where there are no black dots (observed days). This region of the graph corresponds to days with high NO_2 and low $PM_{10-2.5}$—a type of day that exists in intervention B, but which was not empirically observed in Fresno during the study period.

Intervention C is likewise demonstrated in Table 13 and Figures 9 and 10. On the small number of observed days that conform to the air pollution profile described by intervention C, the empirically observed distribution of ambient NO_2 and $PM_{10-2.5}$ is not dissimilar from the distribution of NO_2 and $PM_{10-2.5}$ given the intervention. In contrast with interventions A and B, the observed distributions and the intervention distributions overlap for both NO_2 and $PM_{10-2.5}$ (Table 13). A similar point is made in Figures 9 and 10, in which the red dots representing the pollution profile when intervention C is applied (Figure 9) lie entirely within the joint co-pollutant distribution of the observed days, represented by empty black dots (Figure 10). Unlike interventions A and B, estimation of health effects corresponding to intervention C does not require shifting the joint air pollution distribution in a way that moves days beyond the extent of the observed data.

Tables 14 and 15 present the distribution of changes in NO_2 and $PM_{10-2.5}$ concentrations in their respective interventions. The age-group-specific median change in NO_2 under interventions A and C is between -3.3 and -2.4 ppb, with maximum changes between -28.5 and -27.7 ppb. For $PM_{10-2.5}$ concentration changes under interventions B and C, the median change is between -6.3 and -4.8 $\mu g/m^3$, with a maximum change ranging from -65.1 to -64.5 $\mu g/m^3$. These distributions indicate that for both pollutant concentrations, the majority of days are lowered by relatively small amounts (relative to the observed distribution of concentrations) under the population interventions. At the tail end of the distribution, a small number of days see greatly reduced concentrations.

Results of confounder selection and model-fitting

The covariates that were considered as potential confounders are presented in Table 16. Each covariate is described in terms of the source of potential confounding: environmental, calendar time-related, or individual (as explained in the causal diagrams in the Methods section). The table also enumerates the types of variation that each covariate exhibits, the variable's coding, and information on how it was collected. Ambient apparent temperature and weekend were the environmental covariates considered; these variables are characterized by temporal but not spatial variability. Height[3] was the variable considered as the marker of calendar time, and varied both over time and between children. The individual-level covariates that were considered as potential confounders, exhibiting inter-person but not temporal variability, included gender, race/ethnicity, baseline income, and baseline asthma severity. The latter two covariates are examples of variables that could possibly vary over time, but were collected only once in this study (at baseline).

Table 17 lists the covariates that were selected by candidate reduction for inclusion in the Deletion/Substitution/Addition (DSA) model-fitting routine for each age group and exposure regimen (NO_2, $PM_{10-2.5}$, and $NO_2/PM_{10-2.5}$ mixture). Details of DSA procedure are presented in the Methods section. The basis for submission to the DSA as an independent variable was a bivariate association with the outcome and exposure at the $P<0.2$ level; for the $NO_2/PM_{10-2.5}$ mixture analysis, variables that were associated with the outcome and either exposure were

submitted to the DSA algorithm. For the younger age group analysis, asthma diagnosis at less than 2 years old and an income indicator were included in the NO_2 model-fitting routine, and African-American and Hispanic race/ethnicity were included in the $PM_{10-2.5}$ model-fitting. All four variables were included in the 2-pollutant mixture model-fitting. Height^3 was submitted to the DSA algorithm for all of the middle age group analyses, and male gender was submitted for the middle age group analysis for $PM_{10-2.5}$ and the 2-pollutant exposure regimens. Hispanic ethnicity and weekend were submitted for the older age group analysis in each exposure regimen.

Table 18 presents the models that were fitted as Q-models for each analysis. For each exposure regimen and age group, I fit a crude model (containing only the exposure variable(s) as predictor variables), and the adjusted models as selected by DSA. For the analysis of 6 – 9 year-olds, the adjusted Q-model included asthma diagnosis at less than 2 years old as a confounder for the single-pollutant NO_2 analysis and the 2-pollutant mixture analysis. For the single-pollutant $PM_{10-2.5}$ analysis on 6 – 9 year-olds, the crude model was selected by the DSA algorithm, so only one Q-model was fit. For all three exposure regimens, the middle age group's adjusted Q-model included a squared term for height^3. Pulmonary research indicates that a cubed term is the optimal polynomial to describe height's prediction of pulmonary function[7, 8], but in this case height was a marker for the confounding effects of calendar time, a relation whose functional form is unknown. For the analysis of the older age group, the DSA algorithm selected a model with no confounders for all three exposure regimens; therefore the crude Q-model was the only one fit in each case.

To diagnose the extent to which the adjusted analyses met the positivity assumption with respect to confounders, I examined the distribution of air pollution within levels of the confounding variables. Diagnosing positivity is difficult with continuous exposures[9], a challenge that is compounded by the presence of a multi-variable exposure regimen and a very large number of actual exposure "categories." The continuous confounder height^3 was categorized in quartiles for this exploration, an approach that has been employed in previous studies with continuous covariates[10, 11]. Figures 11 and 12 present box plots of the single-pollutant exposure distribution in different strata of the confounders for each exposure regimen. Figures 11a and 11b focus on confounders of NO_2 effects, demonstrating that while not identical, the NO_2 distributions substantially overlap across strata of both age at asthma diagnosis and height^3. Figures 12a and 12b make the same point about distribution of $PM_{10-2.5}$: exposure overlaps across strata of the confounders, indicating that the confounding variables do not deterministically assign exposure in regions of the $PM_{10-2.5}$ distribution (which would indicate nonpositivity). While these figures apply to all study days rather than age-specific analyses, they provide evidence that the positivity assumption is not violated in this dataset.

Effects of Population Interventions

The results of the Population Intervention Model analyses are presented in Tables 19 – 21 and Figures 13 – 14. Results are presented for crude and adjusted models, as absolute point estimates and 95% confidence intervals (in liters/second [L/sec], the unit of FEF_{25-75}), and in relative terms as a percentage of the age-specific mean outcome (weighted mean FEF_{25-75}). The effect estimates correspond to parameters of the form $E[Y] - E[Y_a]$ (single-pollutant analyses) and $E[Y] - E[Y_{a_1, a_2}]$ (2-pollutant analysis, intervention C). Thus, a positive risk difference indicates that the intervention decreased pulmonary function, and a negative point estimate indicates increased FEF_{25-75} under the intervention. The standard errors and 95% Confidence

Intervals (CIs) were calculated using the bootstrap procedure with replacement by child rather than observation, using 1,000 repetitions. These findings were generated by fitting and applying the Q-models presented in Table 18. Coefficients for crude and adjusted Q-models, for all age groups and exposure regimens, are presented in Supplementary Tables S1 – S3. Because the pollution coefficients on their own are difficult to interpret (corresponding as they do to a 1-ppb or a 1-$\mu g/m^3$ change in exposure), and because the confounder coefficients were estimated only as nuisance parameters, results and discussion will focus on the PIM parameters (Tables 19 – 21) rather than these supplementary tables.

The single-pollutant NO_2 intervention effects shown in Table 19 demonstrate a consistent, small, negative association between NO_2 and FEF_{25-75}, though none of the estimates are significant at the $P<0.05$ level. The absolute magnitude of the crude risk difference ranged from -0.048 L/sec (middle age group, 95% CI: -0.119, 0.023 L/sec) to -0.015 L/sec (younger age group, 95% CI: -0.061, 0.031), with the older age group's crude risk difference being -0.021 L/sec (95% CI: -0.087, 0.045). The adjusted risk difference changed the point estimates slightly for the younger age group (adjusted risk difference = -0.023 L/sec, 95% CI: -0.068, 0.023) and the middle age group (-0.045 L/sec, 95% CI: -0.113, 0.023). Expressed in relative terms, the older age group's parameter estimate had the smallest magnitude, -0.8% (95% CI: -3.4, 1.7). The adjusted relative effect estimates for the younger and middle age groups were -1.7% (95% CI: -5.1, 1.7) and -2.5% (95% CI: -6.4, 1.3), respectively. The relative effect estimates have different denominators, as the three age group have different weighted mean FEF_{25-75} values (Table 4). The average FEF_{25-75} increases with age, so similar absolute risk difference can translate to relative risk differences of different magnitudes (as between the younger and older age groups here).

Table 20 presents the PIM effects for the single-pollutant $PM_{10-2.5}$ analysis. As with NO_2, no associations were significant at the $P<0.05$ level. The effects of the $PM_{10-2.5}$ single pollutant intervention were small and positive in the younger age group, with an absolute magnitude of 0.015 L/sec (95% CI: -0.031, 0.060) and a relative magnitude of 1.1% (95% CI: -2.3, 4.5). No confounders were selected for the corresponding Q-model, so these crude effect estimates are the final estimate for this age group. For the middle and older age groups, the $PM_{10-2.5}$ parameter estimates were small and negative. The middle age group had an adjusted absolute effect size of -0.025 L/sec (95% CI: -0.085, 0.035), which translates to a relative effect size of -1.4% (95% CI: -4.9, 2.0). For the older age group, the relative effect size was the same (-1.4%, 95% CI: -5.5, 2.7), while the absolute effect size was of a larger magnitude (-0.037, 95% CI: -0.143, 0.069).

The results of the two-pollutant $NO_2/PM_{10-2.5}$ mixture analysis are presented in Table 21. The intervention A results describe the effects of lowing NO_2 while holding $PM_{10-2.5}$ at observed levels. As with the single-pollutant NO_2 analysis, all associations are small, negative, and non-significant. The older age group exhibited the smallest absolute and relative effect for intervention A: -0.011 L/sec (95% CI: -0.088, 0.065) and -0.4% (95% CI: -3.4, 2.5), respectively. The adjusted absolute risk difference for the younger and middle age groups were of a similar magnitude: -0.046 L sec (95% CI: -0.099, 0.007) for the younger age group and -0.056 (95% CI: -0.141, 0.028) for the middle age group. Relative parameter estimates were also of a similar magnitude for the younger and middle age groups. This contrasted with the single-pollutant NO_2 analysis, in which the absolute effect was twice as large for the middle group, and the relative effect estimate was 50% greater.

For intervention B in the 2-pollutant analysis, associations were small and non-significant, but the magnitude of the parameter estimates was positive for the younger and

middle age groups. The adjusted absolute risk difference for the younger age group was 0.039 (95% CI: -0.013, 0.090), for a relative effect of 2.9% (95% CI: -1.0, 6.7). For the middle age group, the adjusted effects were positive but smaller, on both an absolute scale (0.014 L/sec, 95% CI: -0.056, 0.085) and a relative scale (0.8%, 95% CI: -3.2, 4.8). The effect of intervention B in the older group was negative and non-significant.

Intervention C, in which both pollutants were lowered, resulted in adjusted effect estimates that were consistently small in magnitude, negative in direction, and non-significant. The magnitude of the association was smallest in the younger age group, with an adjusted absolute effect of -0.007 L/sec (95% CI: -0.061, 0.046) and a relative effect of -0.6 (95% CI, -4.5, 3.4). The absolute magnitude of intervention C effect was similar between the middle age group (-0.042 L/sec, 95% CI: -0.114, 0.029) and the older age group (-0.044 L/sec, 95% CI: -0.142, 0.054), but the magnitude of the relative effect was greater in the middle group (-2.4%, 95% CI: -6.4, 1.7) as compared to the older age group (-1.7%, 95% CI: -5.5, 2.1).

Figures 13 and 14 graphically demonstrate the results (point estimates and 95% confidence intervals) for all exposure regimens and interventions, across all age groups. Figure 13 presents absolute results in units of L/sec, and Figure 14 presents relative results, expressed as a percentage of the weighted age-specific mean FEF_{25-75}. The figures demonstrate that the 95% confidence intervals cross the null values of zero for all estimates. The figures also visually confirm that there was a trend of small negative estimates for most analyses, except for the $PM_{10-2.5}$-related analyses, namely the single-pollutant $PM_{10-2.5}$ intervention and the 2-pollutant intervention B.

TABLES

Table 1. Descriptive statistics of the sample at baseline, for children included in the summertime analysis and for all children who contributed panel data (overall sample).

	Summertime analysis (n=257)		**Overall sample (n=299)**	
Continuous variable	**Median**	**IQR**	**Median**	**IQR**
Age	8	6 - 9	8	7 - 9
Categorical/binary variables	**Number**	**%**	**Number**	**%**
Male	146	56.8	170	56.9
Race/ethnicity				
African-American	33	12.8	48	16.0
Asian-American	1	0.4	2	0.7
Hispanic	103	40.1	118	39.5
White (non-Hispanic)	113	44.0	124	41.5
Missing	7	2.7	7	2.3
Income				
< $15,000	46	17.9	58	19.4
$15,000 - $30,000	63	24.5	73	24.4
$30,000- $50,000	60	23.3	72	24.1
> $50,000	80	31.1	86	28.8
Missing	8	3.1	10	3.3
Asthma severity*				
Mild intermittent	73	28.4	87	29.1
Mild persistent	125	48.6	139	46.5
Moderate or severe	59	23.0	73	24.4
Skin-test positive**	142	55.3	165	55.2
Asthma diagnosis ≤ 2 y.o.	92	35.8	118	39.5

* Based on the Global Initiative for Asthma severity guidelines[1].

** Positive to at least one allergen on skin-test panel or reported history of severe reaction to prior allergy skin test.

Table 2. Number of distinct age groups to which each child contributed data, and the frequency of each age group pattern.

	6 – 9 years old	10 – 12 years old	13 – 17 years old	Number of children
1 age group	✓			55
		✓		40
			✓	4
Sum of children in 1 age group:				**99**
2 age groups	✓	✓		61
	✓		✓	2
		✓	✓	62
Sum of children in 2 age groups:				**125**
3 age groups	✓	✓	✓	33
Sum of children in 3 age groups:				**33**
Sum of children in each age group:	**151**	**196**	**101**	

Table 3. Descriptive statistics for children in each age group.

	6 – 9 year-olds (n=151; 2304 panel-days)		10 – 12 year-olds (n=196; 2779 panel-days)		13 – 17 year-olds (n=101; 1313 panel-days)	
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Summer panel-days per child	13	7 – 20	12	6 – 21	10	5 – 19
Summer panels per child	2	1 – 2	2	1 – 2	2	1 – 2
	Number	**%**	**Number**	**%**	**Number**	**%**
Male	87	57.6	111	56.6	57	56.4
Race/ethnicity						
African-American	20	13.2	24	12.2	14	13.9
Asian-American	1	0.7	0	0	0	0
Hispanic	66	43.7	81	41.3	39	38.6
White (non-Hispanic)	60	39.7	85	43.4	44	43.6
Missing	4	2.7	6	3.1	4	4.0
Income						
< $15,000	33	21.9	31	15.8	12	11.9
$15,000 - $30,000	35	23.2	45	23.0	25	24.8
$30,000- $50,000	38	25.2	47	24.0	28	27.7
> $50,000	40	26.5	68	34.7	35	34.7
Missing	5	3.3	5	2.6	1	1.0
Asthma severity*						
Mild intermittent	41	27.2	52	26.5	30	29.7
Mild persistent	73	48.3	99	50.5	50	49.5
Moderate or severe	37	24.5	45	23.0	21	20.8
Skin-test positive**	70	46.4	112	57.1	67	66.3†
Asthma diagnosis ≤2 y.o.	66	43.7	66	33.7	30	29.7†

* Based on the Global Initiative for Asthma severity guidelines[1].

** Positive to at least one allergen on skin-test panel or reported history of severe reaction to prior allergy skin test.

† Chi-square test $P<0.1$

Table 4. Distribution of child-specific mean height and FEF_{25-75} measurements within each age group.

	Mean	Median	IQR
Mean FEF_{25-75} (L/sec)			
6 – 9 year-olds	1.35	1.31	0.94 - 1.66
10 – 12 year-olds	1.77	1.71	1.22 - 2.27
13 – 17 year-olds	2.59	2.60	1.8 - 3.32
Mean Standing Height (cm)			
6 – 9 year-olds	131.1	131.3	124.1 - 137.9
10 – 12 year-olds	147.8	147.6	141.2 - 153.9
13 – 17 year-olds	163.3	164.1	157.1 - 168.7

Table 5. Distribution of ambient environmental and meteorological variables measured at the central site during summer months (June – September), from 2001 to 2008 in Fresno, California (648 unique study days).

Variable*	Minimum	25th percentile	Median	Mean	75th percentile	Maximum	IQR	# Days missing
NO_2 (ppb)	4.2	9.7	12.9	14.3	17.6	37.6	7.9	9
$PM_{10-2.5}$($\mu g/m^3$)	3.7	17.8	22.0	24.4	29.9	80.9	12.1	30
Ozone (ppb)	26.3	63.0	72.4	73.7	84.0	132.2	21.0	6
$PM_{2.5}$($\mu g/m^3$)	1.9	7.2	10.5	11.4	13.8	63.3	6.6	1
Elemental carbon ($\mu g/m^3$)	0	0.6	0.9	1.1	1.4	5.3	0.9	50
NO_3 ($\mu g/m^3$)	0.2	0.8	1.3	1.5	2.0	5.9	1.2	16
Apparent temperature (°C)†	13.0	23.4	26.2	25.9	28.5	36.7	5.1	2

* All variables are lag 0.

NO_2, $PM_{10-2.5}$, $PM_{2.5}$, EC, and NO_3 concentrations are 24-hour averages. Ozone concentration is the maximum 8-hour average.

†Apparent temperature as described by Basu et al[4].

Table 6. The Primary Standards (level and averaging time) for the criteria pollutants measured in the FACES study, as codified by the National Ambient Air Quality Standards.

	Primary Standards	
Pollutant	**Level**	**Averaging Time**
NO_2	53 ppb	Annual (arithmetic average)
	100 ppb	1-hour
PM_{10}	150 $\mu g/m^3$	24-hour
$PM_{2.5}$	15 $\mu g/m^3$	Annual (arithmetic average)
	35 $\mu g/m^3$	24-hour
Ozone	75 ppb	8-hour (2008 standard)
	80 ppb	8-hour (1997 standard)
	120 ppb	1-hour

Table adapted from the NAAQS[3], http://epa.gov/air/criteria.html, accessed March 23, 2011.

Table 7. Annual distribution of ambient environmental variables* measured at the central site during summer months (June – September), in Fresno, California.

	25th percentile	**Median**	**75th percentile**	**Unique study days**
NO_2 (ppb)				
2001	10.6	14.2	18.2	66
2002	11.1	14.7	20.1	122
2003	10.5	14.8	18.2	122
2004	9.8	12.6	16.2	122
2005	7.6	10.8	14.5	72
2006	9.8	12.8	18.0	51
2007	8.1	9.2	12.0	44
2008	9.3	11.5	16.0	40
$PM_{10-2.5}$ ($\mu g/m^3$)				
2001	17.9	23.1	31.4	58
2002	21.2	26.1	35.1	122
2003	18.3	24.4	30.9	113
2004	18.0	21.5	29.5	114
2005	14.5	18.5	21.6	74
2006	16.8	20.2	26.5	50
2007	15.8	19.1	22.1	44
2008	17.0	21.3	32.3	43

*Both variables are lag 0.

NO_2 and $PM_{10-2.5}$ concentrations are 24-hour averages.

Table 8. Age-group-specific distributions of ambient environmental and meteorological variables* measured at the central site during summer months (June – September), from 2001 to 2008 in Fresno, California.

	25th percentile	Median	75th percentile	IQR	Unique days	Days missing
NO_2 (ppb)						
6 – 9 year-olds	9.9	13.0	17.7	7.8	563	6
10 – 12 year-olds	9.7	12.9	17.6	7.9	607	9
13 – 17 year-olds	9.1	11.5	15.9	6.8	329	8
$PM_{10-2.5}(\mu g/m^3)$						
6 – 9 year-olds	18.0	22.7	30.1	12.1	563	29
10 – 12 year-olds	17.8	22.1	30.0	12.2	607	22
13 – 17 year-olds	16.4	20.6	27.1	10.7	329	12
Apparent Temperature (°C)†						
6 – 9 year-olds	23.4	26.1	28.5	5.1	563	2
10 – 12 year-olds	23.3	26.0	28.5	5.2	607	2
13 – 17 year-olds	23.2	25.9	28.3	5.1	329	2

*Both variables are lag 0.

NO_2 and $PM_{10-2.5}$ concentrations are 24-hour averages.

† Apparent temperature as described by Basu *et al*.[4]

Table 9. Correlation coefficients* for each pair of pollutants** during summer months (June – September) in Fresno, California (648 unique study days).

	NO_2	**$PM_{10-2.5}$**	**Ozone**	**$PM_{2.5}$**	**EC**	**NO_3**
NO_2	1	0.67	0.36	0.36	0.68	0.56
$PM_{10-2.5}$		1	0.32	0.29	0.55	0.41
Ozone			1	0.57	0.57	0.35
$PM_{2.5}$				1	0.69	0.63
EC					1	0.58
NO_3						1

* All coefficients are Pearson's correlation.

** All variables are lag 0.

NO_2, $PM_{10-2.5}$, $PM_{2.5}$, EC, andNO_3 concentrations are 24-hour averages.

Ozone concentration is the maximum 8-hour average.

Tables 10a-c. Summary of the population interventions.

Table 10a. Summary of the NO_2 single-pollutant population intervention.

Age group	NO_2 concentration (ppb) assigned to values above intervention cutoff level	Percentile of observed NO_2 distribution
6 – 9 year-olds	9.94	25
10 – 12 year-olds	9.68	25
13 – 17 year-olds	9.12	25

Table 10b. Summary of the $PM_{10-2.5}$ single-pollutant population intervention.

Age group	$PM_{10-2.5}$ concentration ($\mu g/m^3$) assigned to values above intervention cutoff level	Percentile of observed $PM_{10-2.5}$ distribution
6 – 9 year-olds	16.47	19
10 – 12 year-olds	16.33	20
13 – 17 year-olds	15.85	22

Table 10c. Summary of the mixture population interventions.

	NO_2		$PM_{10-2.5}$	
	Concentration (ppb) assigned to values above intervention cutoff level	**Percentile of observed NO_2 distribution**	**Concentration ($\mu g/m^3$) assigned to values above intervention cutoff level**	**Percentile of observed $PM_{10-2.5}$ distribution**
Intervention A				
6 – 9 year-olds	9.94	25	Observed	NA
10 – 12 year-olds	9.68	25	Observed	NA
13 – 17 year-olds	9.12	25	Observed	NA
Intervention B				
6 – 9 year-olds	Observed	NA	16.47	19
10 – 12 year-olds	Observed	NA	16.33	20
13 – 17 year-olds	Observed	NA	15.85	22
Intervention C				
6 – 9 year-olds	9.94	25	16.47	19
10 – 12 year-olds	9.68	25	16.33	20
13 – 17 year-olds	9.12	25	15.85	22

Table 11. Two-pollutant intervention A: Air pollution profile on observed days that met the requirements of Intervention A (i.e., days that were below the age-specific 25th percentile of NO_2), and on all days in counterfactual exposure distribution when Intervention A is applied.

	Minimum	25th Percentile	Median	Mean	75th percentile	Maximum	Number of unique days
NO_2 distribution (ppb)							
Observed NO_2 data on days when NO_2 is below intervention level A							
6 – 9 year-olds	4.7	7.29	8.45	8.18	9.18	9.94	140
10 – 12 year-olds	4.17	7.18	8.3	7.99	9.04	9.68	150
13 – 17 year-olds	4.17	6.83	7.48	7.45	8.41	9.12	81
Counterfactual NO_2 data given intervention A							
6 – 9 year-olds	4.7	9.88	9.94	9.49	9.94	9.94	529
10 – 12 year-olds	4.17	9.62	9.68	9.25	9.68	9.68	577
13 – 17 year-olds	4.17	9.12	9.12	8.69	9.12	9.12	310
$PM_{10-2.5}$ distribution (µg/m³)							
Observed $PM_{10-2.5}$ data on days when NO_2 is below intervention level A							
6 – 9 year-olds	3.74	13.00	16.46	17.15	20.33	48.47	134
10 – 12 year-olds	3.74	13.36	16.33	17.12	20.12	48.47	147
13 – 17 year-olds	3.74	12.39	15.85	16.23	19.2	43.16	79
$PM_{10-2.5}$ data given intervention A (equivalent to the observed $PM_{10-2.5}$ distribution)							
6 – 9 year-olds	3.74	18.05	22.75	24.68	30.11	80.92	529
10 – 12 year-olds	3.74	17.8	22.14	24.51	29.98	80.92	577
13 – 17 year-olds	3.74	16.42	20.68	22.77	27.1	80.92	310

Table 12. Two-pollutant intervention B: Air pollution profile on observed days that met the requirements of Intervention B (i.e., days that were below the age-specific $PM_{10-2.5}$ cutoffs), and on all days in counterfactual exposure distribution when Intervention B is applied.

	Minimum	25th Percentile	Median	Mean	75th percentile	Maximum	Number of unique days
$PM_{10-2.5}$ distribution ($\mu g/m^3$)							
Observed $PM_{10-2.5}$ data on days when $PM_{10-2.5}$ is below intervention level B							
6 – 9 year-olds	3.74	11.16	13.4	12.73	15.06	16.41	104
10 – 12 year-olds	3.74	11.2	13.47	12.78	15.01	16.33	118
13 – 17 year-olds	3.74	10.11	13.2	12.24	14.64	15.85	69
Counterfactual $PM_{10-2.5}$ data given intervention B							
6 – 9 year-olds	3.74	16.46	16.46	15.73	16.46	16.46	529
10 – 12 year-olds	3.74	16.33	16.33	15.61	16.33	16.33	577
13 – 17 year-olds	3.74	15.85	15.85	15.05	15.85	15.85	310
NO_2 distribution (ppb)							
Observed NO_2 data on days when $PM_{10-2.5}$ is below intervention level B							
6 – 9 year-olds	4.7	7.29	8.79	9.51	10.78	18.58	103
10 – 12 year-olds	4.17	7.27	8.79	9.37	10.7	18.58	117
13 – 17 year-olds	4.17	7.02	8.32	8.79	9.61	21.3	68
NO_2 data given intervention B (equivalent to the observed distribution of NO_2)							
6 – 9 year-olds	4.7	9.88	13.05	14.55	17.74	37.6	529
10 – 12 year-olds	4.17	9.62	12.96	14.34	17.63	37.6	577
13 – 17 year-olds	4.17	9.12	11.53	13.28	15.89	37.6	310

Table 13. Two-pollutant intervention C: Air pollution profile on observed days that met the requirements of Intervention C (i.e., days that were below the age-specific cutoffs for both NO_2 and $PM_{10-2.5}$), and on all days in counterfactual exposure distribution when Intervention C is applied

	Minimum	25th Percentile	Median	Mean	75th percentile	Maximum	Number of unique days
$PM_{10-2.5}$ distribution ($\mu g/m^3$)							
Observed $PM_{10-2.5}$ data on days when NO_2 & $PM_{10-2.5}$ are below intervention levels							
6 – 9 year-olds	3.74	10.74	12.99	12.45	14.74	16.41	67
10 – 12 year-olds	3.74	11.07	13.36	12.55	14.68	16.33	74
13 – 17 year-olds	3.74	10.73	12.39	11.99	14.5	15.85	40
Counterfactual $PM_{10-2.5}$ data given intervention C							
6 – 9 year-olds	3.74	16.46	16.46	15.73	16.46	16.46	529
10 – 12 year-olds	3.74	16.33	16.33	15.61	16.33	16.33	577
13 – 17 year-olds	3.74	15.85	15.85	15.05	15.85	15.85	310
NO_2 distribution (ppb)							
Observed NO_2 data on days when NO_2 & $PM_{10-2.5}$ are below intervention levels							
6 – 9 year-olds	4.7	6.92	7.87	7.783	8.78	9.94	67
10 – 12 year-olds	4.17	6.848	7.72	7.659	8.765	9.68	74
13 – 17 year-olds	4.17	6.632	7.11	7.044	7.665	9.09	40
Counterfactual NO_2 data given intervention C							
6 – 9 year-olds	4.7	9.88	9.94	9.49	9.94	9.94	529
10 – 12 year-olds	4.17	9.62	9.68	9.25	9.68	9.68	577
13 – 17 year-olds	4.17	9.12	9.12	8.69	9.12	9.12	310

Table 14. Distribution of NO_2 concentration changes under population interventions A and C (ppb).

Age group	Minimum	25th Percentile	Median	Mean	75th percentile	Maximum	Number of unique days
6 – 9 year-olds	0	0	-3.11	-5.06	-7.8	-27.66	529
10 – 12 year-olds	0	0	-3.28	-5.09	-7.95	-27.92	577
13 – 17 year-olds	0	0	-2.41	-4.59	-6.77	-28.48	310

Table 15. Distribution of $PM_{10-2.5}$ concentration changes under population interventions A and C ($\mu g/m^3$).

Age group	Minimum	25th Percentile	Median	Mean	75th percentile	Maximum	Number of unique days
6 – 9 year-olds	0	-1.59	-6.29	-8.94	-13.64	-64.46	529
10 – 12 year-olds	0	-1.47	-5.81	-8.9	-13.65	-64.59	577
13 – 17 year-olds	0	-0.57	-4.83	-7.72	-11.25	-65.07	310

Table 16. Candidate covariates considered as potential confounders in all analyses and for all age groups.

Covariate	Level of potential confounding	Type of variation	Coding	Collection information
Apparent temperature*	Environmental	Temporal	Continuous, °C	Measured at the central site monitor in Fresno
Weekend	Environmental	Temporal	Binary	
Height[3]	Calendar time	Temporal, between children	Continuous, cm^3	Measured at semi-annual clinic visit; nearest absolute measurement assigned
Male	Individual	Between children	Binary	Baseline
Race/ethnicity	Individual	Between children	Categorical: African-American, Asian-American, Hispanic, White	Baseline
Income	Individual	Between children	Ordinal (dummy variables): < $15,000; $15,000 - $30,000; $30,000 - $50,000; > $50,000	Baseline
Asthma severity**	Individual	Between children	Categorical: mild-intermittent, mild-persistent, intermediate/severe	Baseline
Skin-test positive†	Individual	Between children	Binary	Baseline
Asthma diagnosis less than 2 years old	Individual	Between children	Binary	Baseline

* As described by Basu et al., *Epidemiology* 2008[4].

** Based on the Global Initiative for Asthma severity guidelines[1].

† Positive to at least one allergen on skin-test panel or reported history of severe reaction to prior allergy skin test.

Table 17. Potential confounders considered for age- and pollutant-specific model-fitting using the DSA algorithm, based upon bivariate associations with both exposure and outcome at the P<0.2 level.

Analysis	**Potential confounders**
NO_2	
6 – 9 year-olds	Asthma diagnosis less than 2 years-old Income category: $15,000 - $30,000
10 – 12 year-olds	Height[3]
13 – 17 year-olds	Hispanic Weekend
$PM_{10-2.5}$	
6 – 9 year-olds	African-American Hispanic
10 – 12 year-olds	Height[3] Male
13 – 17 year-olds	Hispanic Weekend
2-pollutant mixture ($NO_2$and $PM_{10-2.5}$)	
6 – 9 year-olds	African-American Asthma diagnosis less than 2 years-old Hispanic Income category: $15,000 - $30,000
10 – 12 year-olds	Height[3] Male
13 – 17 year-olds	Hispanic Weekend

Table 18. Q-models for each of the three analyses; crude models and adjusted models selected by DSA.

Analysis	Crude model	Adjusted model, selected by DSA†
NO_2		
6 – 9 year-olds	$E(\mathrm{FEF}_{25\text{-}75} \mid \mathrm{NO}_2) = \alpha_0 + \alpha_1 * \mathrm{NO}_2$	$E(\mathrm{FEF}_{25\text{-}75} \mid \mathrm{NO}_2, W) = \alpha_0 + \alpha_1 * \mathrm{NO}_2 + \alpha_2 * \mathrm{AsthLe2}$ ‡
10 – 12 year-olds	$E(\mathrm{FEF}_{25\text{-}75} \mid \mathrm{NO}_2) = \alpha_0 + \alpha_1 * \mathrm{NO}_2$	$E(\mathrm{FEF}_{25\text{-}75} \mid \mathrm{NO}_2, W) = \alpha_0 + \alpha_1 * \mathrm{NO}_2 + \alpha_2 * (\mathrm{Height}^{3})^{2}$
13 – 17 year-olds	$E(\mathrm{FEF}_{25\text{-}75} \mid \mathrm{NO}_2) = \alpha_0 + \alpha_1 * \mathrm{NO}_2$	–
$PM_{10\text{-}2.5}$		
6 – 9 year-olds	$E(\mathrm{FEF}_{25\text{-}75} \mid \mathrm{PM}_{10\text{–}2.5}) = \alpha_0 + \alpha_1 * \mathrm{PM}_{10\text{–}2.5}$	–
10 – 12 year-olds	$E(\mathrm{FEF}_{25\text{-}75} \mid \mathrm{PM}_{10\text{–}2.5}) = \alpha_0 + \alpha_1 * \mathrm{PM}_{10\text{–}2.5}$	$E(\mathrm{FEF}_{25\text{-}75} \mid \mathrm{PM}_{10\text{–}2.5}, W) = \alpha_0 + \alpha_1 * \mathrm{PM}_{10\text{–}2.5} + \alpha_2 * (\mathrm{Height}^{3})^{2}$
13 – 17 year-olds	$E(\mathrm{FEF}_{25\text{-}75} \mid \mathrm{PM}_{10\text{–}2.5}) = \alpha_0 + \alpha_1 * \mathrm{PM}_{10\text{–}2.5}$	–
2-pollutant mixture (NO_2 and $PM_{10\text{-}2.5}$)		
6 – 9 year-olds	$E(\mathrm{FEF}_{25\text{-}75} \mid \mathrm{NO}_2, \mathrm{PM}_{10\text{–}2.5}) = \alpha_0 + \alpha_1 * \mathrm{NO}_2 + \alpha_2 * \mathrm{PM}_{10\text{–}2.5}$	$E(\mathrm{FEF}_{25\text{-}75} \mid \mathrm{NO}_2, \mathrm{PM}_{10\text{–}2.5}, W) = \alpha_0 + \alpha_1 * \mathrm{NO}_2 + \alpha_2 * \mathrm{PM}_{10\text{–}2.5} + \alpha_3 * \mathrm{AsthLe2}$ ‡
10 – 12 year-olds	$E(\mathrm{FEF}_{25\text{-}75} \mid \mathrm{NO}_2, \mathrm{PM}_{10\text{–}2.5}) = \alpha_0 + \alpha_1 * \mathrm{NO}_2 + \alpha_2 * \mathrm{PM}_{10\text{–}2.5}$	$E(\mathrm{FEF}_{25\text{-}75} \mid \mathrm{NO}_2, \mathrm{PM}_{10\text{–}2.5}, W) = \alpha_0 + \alpha_1 * \mathrm{NO}_2 + \alpha_2 * \mathrm{PM}_{10\text{–}2.5} + \alpha_3 * (\mathrm{Height}^{3})^{2}$
13 – 17 year-olds	$E(\mathrm{FEF}_{25\text{-}75} \mid \mathrm{NO}_2, \mathrm{PM}_{10\text{–}2.5}) = \alpha_0 + \alpha_1 * \mathrm{NO}_2 + \alpha_2 * \mathrm{PM}_{10\text{–}2.5}$	–

† Dashes indicate that the DSA algorithm did not select any confounders, and therefore the adjusted model is identical to the crude model.

‡ AsthLe2: Asthma diagnosis less than 2 years-old

Table 19. Effect estimates for NO_2 single-pollutant PIM.

	Crude Model				Adjusted Model†			
	Absolute (L/sec)		Relative (expressed as % of mean FEF_{25-75})		Absolute (L/sec)		Relative (expressed as % of mean FEF_{25-75})	
	Point estimate (SE)	95% Confidence Interval	Point estimate	95% Confidence Interval	Point estimate (SE)	95% Confidence Interval	Point estimate	95% Confidence Interval
6 – 9 year-olds	-0.015 (0.023)	-0.061 , 0.031	-1.1	-4.5 , 2.3	-0.023 (0.023)	-0.068 , 0.023	-1.7	-5.1 , 1.7
10 – 12 year-olds	-0.048 (0.036)	-0.119 , 0.023	-2.7	-6.8 , 1.3	-0.045 (0.035)	-0.113 , 0.023	-2.5	-6.4 , 1.3
13 – 17 year-olds	-0.021 (0.034)	-0.087 , 0.045	-0.8	-3.4 , 1.7	-	-	-	-

† Dashes indicate that the DSA algorithm did not select any confounders, and therefore the adjusted model is identical to the crude model.

Table 20. Effect estimates for $PM_{10-2.5}$ single-pollutant PIM.

	Crude Model				Adjusted Model†			
	Absolute (L/sec)		Relative (expressed as % of mean FEF_{25-75})		Absolute (L/sec)		Relative (expressed as % of mean FEF_{25-75})	
	Point estimate (SE)	95% Confidence Interval	Point estimate	95% Confidence Interval	Point estimate (SE)	95% Confidence Interval	Point estimate	95% Confidence Interval
6 – 9 year-olds	0.015 (0.023)	-0.031 , 0.06	1.1	-2.3 , 4.5	-	-	-	-
10 – 12 year-olds	-0.035 (0.032)	-0.097 , 0.028	-2.0	-5.5 , 1.6	-0.025 (0.031)	-0.085 , 0.035	-1.4	-4.8 , 2.0
13 – 17 year-olds	-0.037 (0.054)	-0.143 , 0.069	-1.4	-5.5 , 2.7	-	-	-	-

† Dashes indicate that the DSA algorithm did not select any confounders, and therefore the adjusted model is identical to the crude model.

Table 21. Effect estimates for the two-pollutant PIM.

	Crude Model				Adjusted Model†			
	Absolute (L/sec)		Relative (expressed as % of mean FEF_{25-75})		Absolute (L/sec)		Relative (expressed as % of mean FEF_{25-75})	
	Point estimate (SE)	95% Confidence Interval	Point estimate	95% Confidence Interval	Point estimate (SE)	95% Confidence Interval	Point estimate	95% Confidence Interval
Intervention A								
6 – 9 year-olds	-0.041 (0.028)	-0.096 , 0.014	-3.0	-7.1 , 1.1	-0.046 (0.027)	-0.099 , 0.007	-3.4	-7.3 , 0.5
10 – 12 year-olds	-0.052 (0.045)	-0.141 , 0.036	-3.0	-8.0 , 2.1	-0.056 (0.043)	-0.141 , 0.028	-3.2	-8 , 1.6
13 – 17 year-olds	-0.011 (0.039)	-0.088 , 0.065	-0.4	-3.4 , 2.5	-	-	-	-
Intervention B								
6 – 9 year-olds	0.042 (0.027)	-0.011 , 0.095	3.1	-0.8 , 7.0	0.039 (0.026)	-0.013 , 0.09	2.9	-1.0 , 6.7
10 – 12 year-olds	-0.001 (0.037)	-0.074 , 0.071	-0.1	-4.2 , 4.0	0.014 (0.036)	-0.056 , 0.085	0.8	-3.2 , 4.8
13 – 17 year-olds	-0.033 (0.064)	-0.158 , 0.093	-1.3	-6.1 , 3.6	-	-	-	-
Intervention C								
6 – 9 year-olds	0.002 (0.027)	-0.051 , 0.054	0.1	-3.8 , 4.0	-0.007 (0.027)	-0.061 , 0.046	-0.6	-4.5 , 3.4
10 – 12 year-olds	-0.054 (0.038)	-0.128 , 0.021	-3.0	-7.2 , 1.2	-0.042 (0.036)	-0.114 , 0.029	-2.4	-6.4 , 1.7
13 – 17 year-olds	-0.044 (0.05)	-0.142 , 0.054	-1.7	-5.5 , 2.1	-	-	-	-

† Dashes indicate that the DSA algorithm did not select any confounders, and therefore the adjusted model is identical to the crude model.

FIGURES

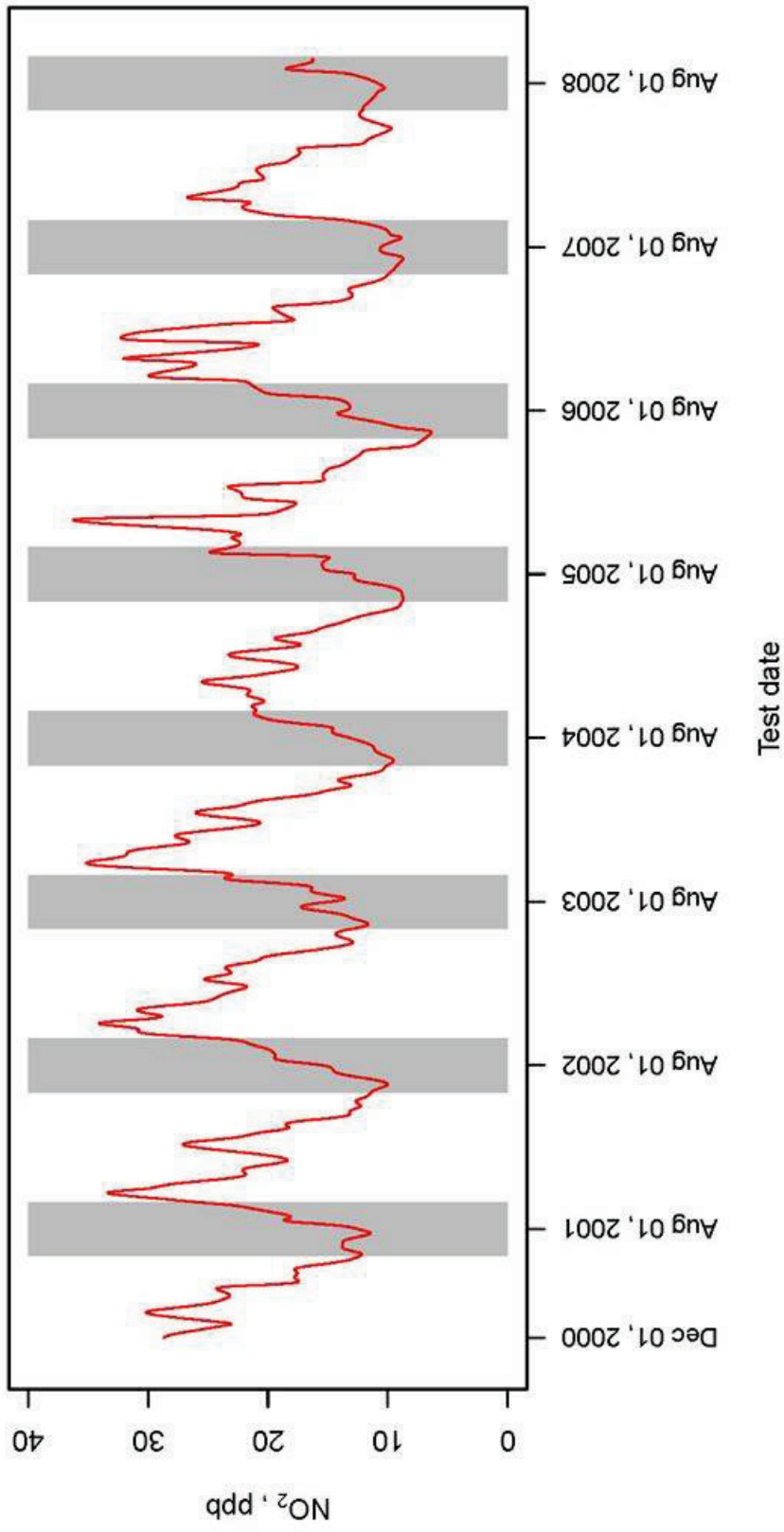
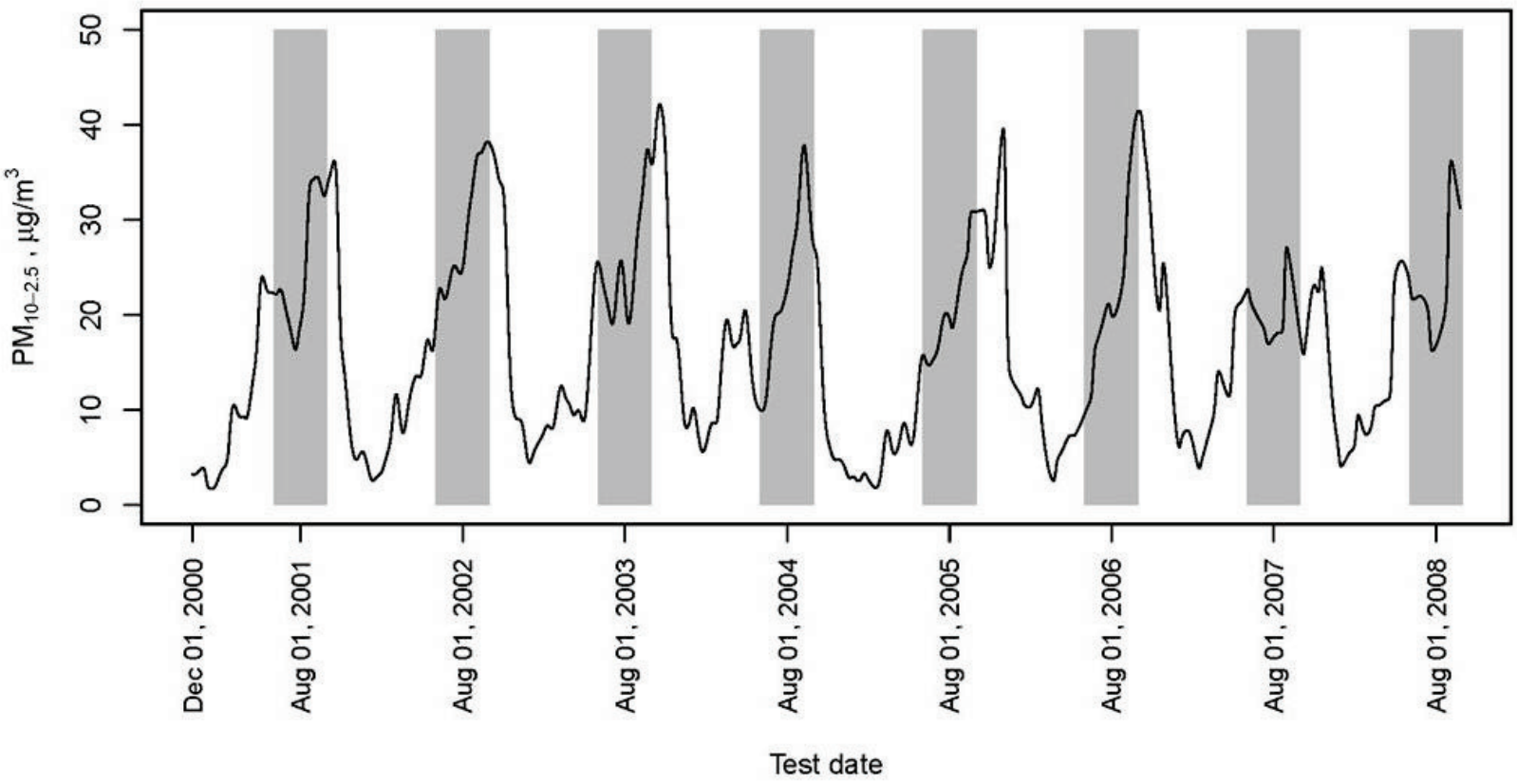


Figure 1. Kernel density smooth* of ambient NO_2 concentrations† in Fresno, California throughout the year‡ during the FACES study period (2000 – 2008).

* Nadaraya-Watson Kernel density estimation[5, 6] was implemented with a bandwidth of 20 days.
† Concentrations are 24-hour average, as measured at the central site monitor.
‡ Shaded regions indicate the summer months (June – September).

Figure 2. Kernel density smooth* of ambient $PM_{10-2.5}$ concentrations† in Fresno, California throughout the year‡ during the FACES study period (2000 – 2008).

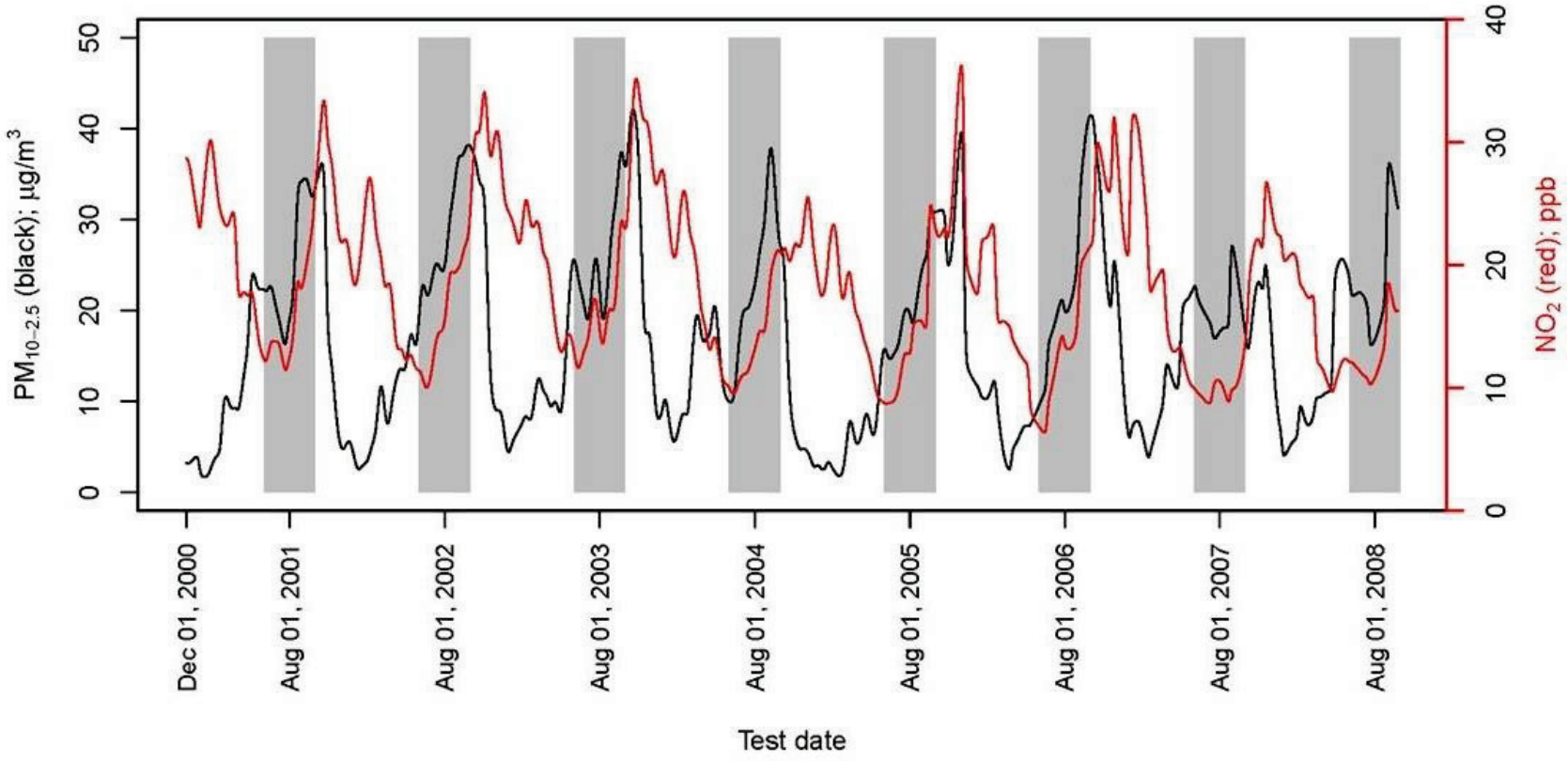


* Nadaraya-Watson Kernel density estimation[5, 6] was implemented with a bandwidth of 20 days.

† Concentrations are 24-hour average, as measured at the central site monitor.

‡ Shaded regions indicate the summer months (June – September).

Figure 3. Kernel density smooth* of ambient NO_2 concentration overlaid with $PM_{10-2.5}$ concentration† in Fresno, California throughout the year‡ during the FACES study period (2000 – 2008).

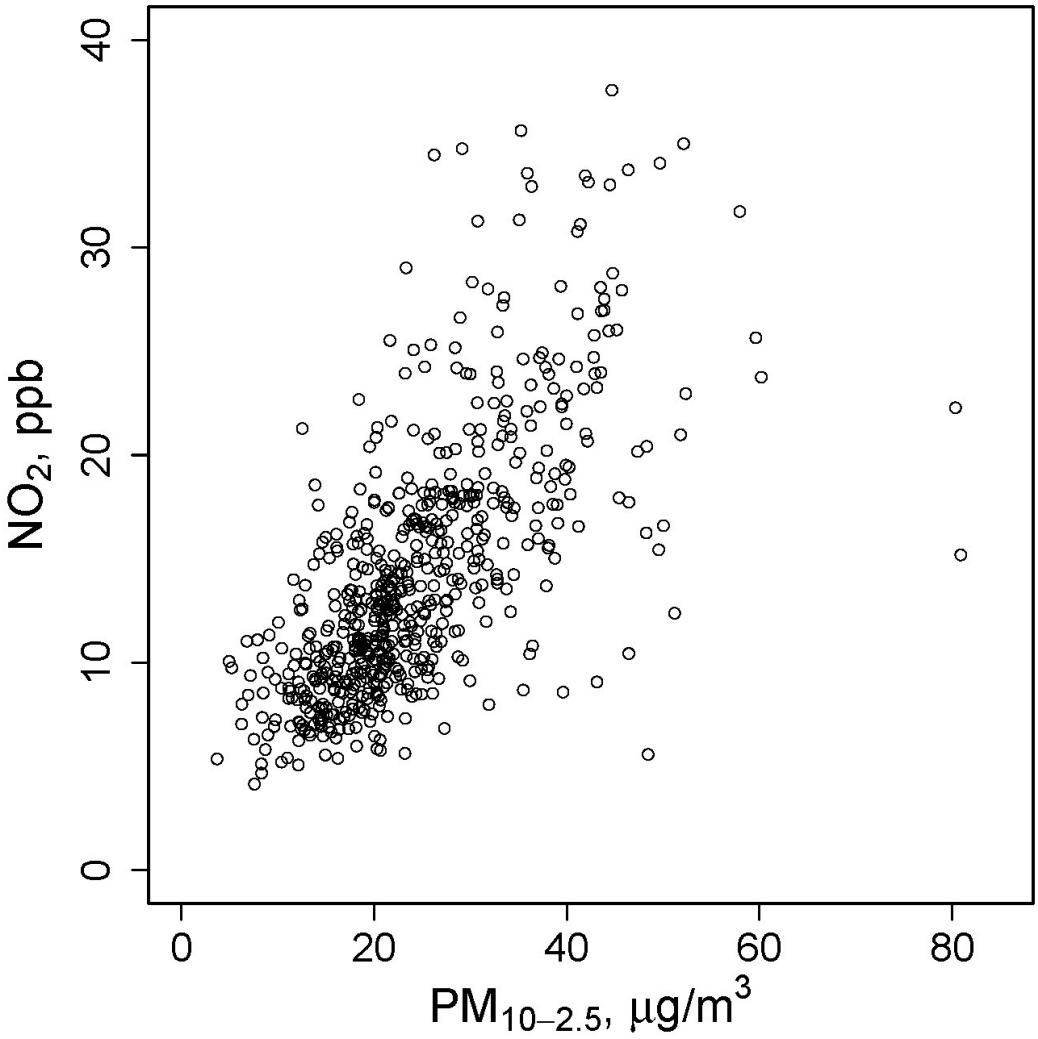


* Nadaraya-Watson Kernel density estimation[5, 6] was implemented with a bandwidth of 20 days.

† Concentrations are 24-hour average, as measured at the central site monitor.

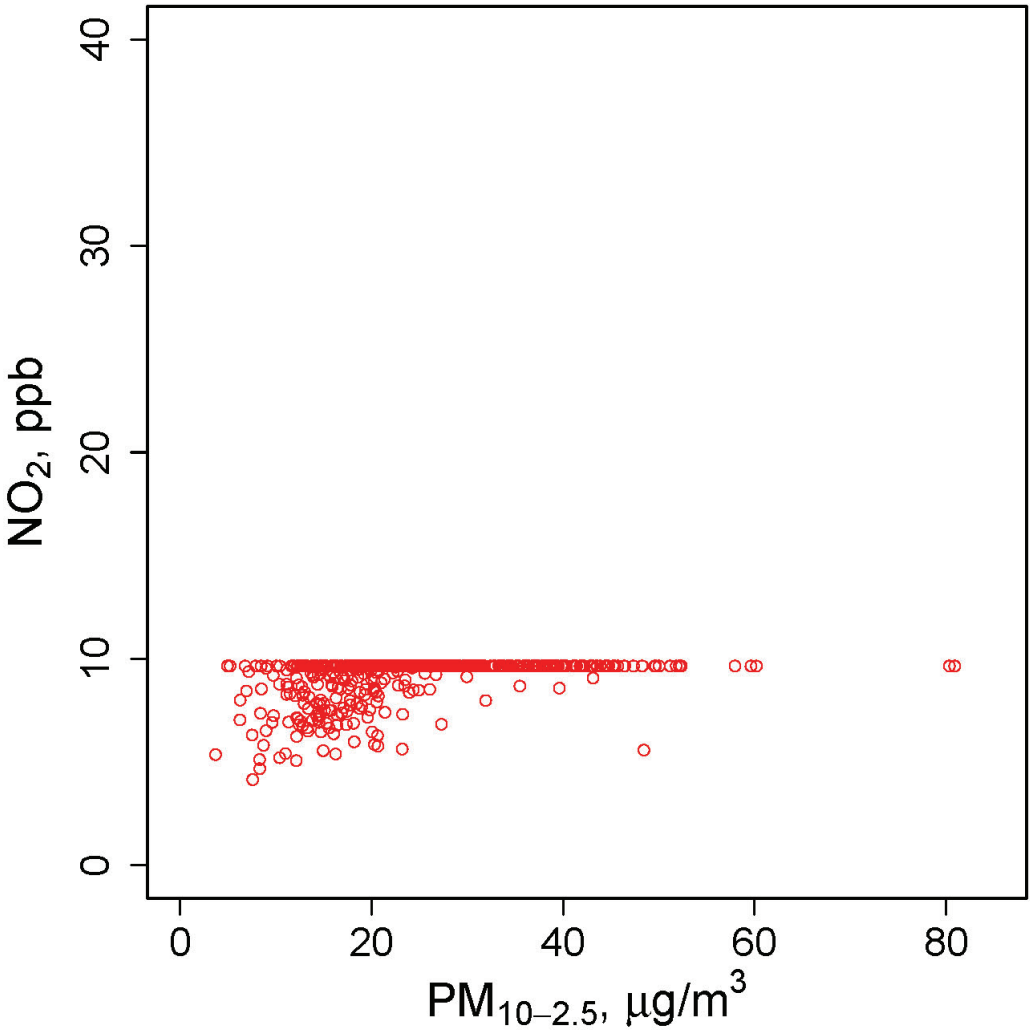
‡ Shaded regions indicate the summer months (June – September).

Figure 4. Scatter plot of observed NO_2 and $PM_{10-2.5}$ concentrations* during summer months (June – September) between 2001 and 2008 in Fresno, California (ambient measurements taken at central site monitor; n = 648 unique study days).



* Based on lag 0 and 24-hour average for both pollutants

Figure 5. Intervention A: Scatter plot of summertime NO_2 and $PM_{10-2.5}$ concentrations* under a hypothetical 2-pollutant intervention keeping $PM_{10-2.5}$ at observed concentration and lowering NO_2 to the 25th percentile of the observed concentration distribution (9.7 ppb).



* N = 648 unique study days, based on lag 0 and 24-hour average for both pollutants

Figure 6. Intervention A overlay: Distribution of summertime NO_2 and $PM_{10-2.5}$ under hypothetical 2-pollutant intervention A (lowering only NO_2), laid over the observed summertime distribution of ambient NO_2 and $PM_{10-2.5}$ between 2001 and 2008 in Fresno, California.

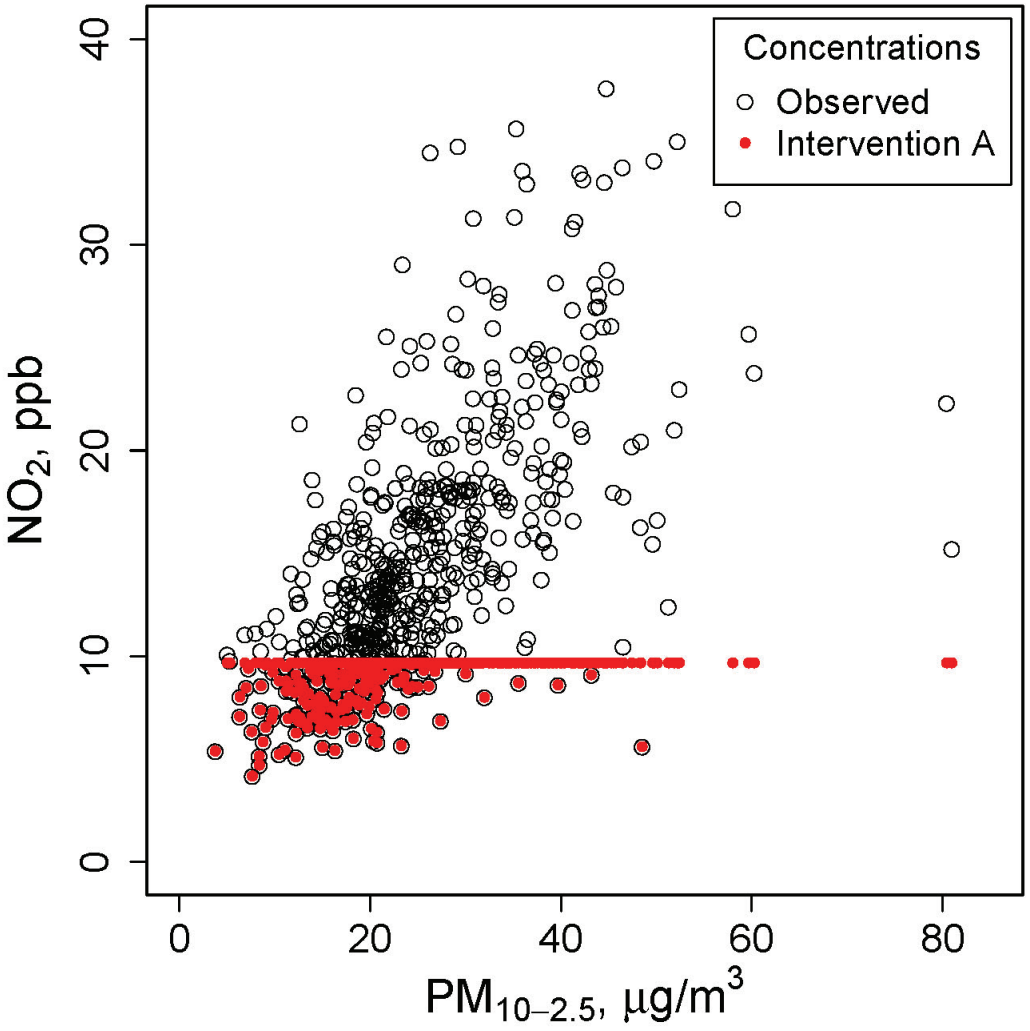
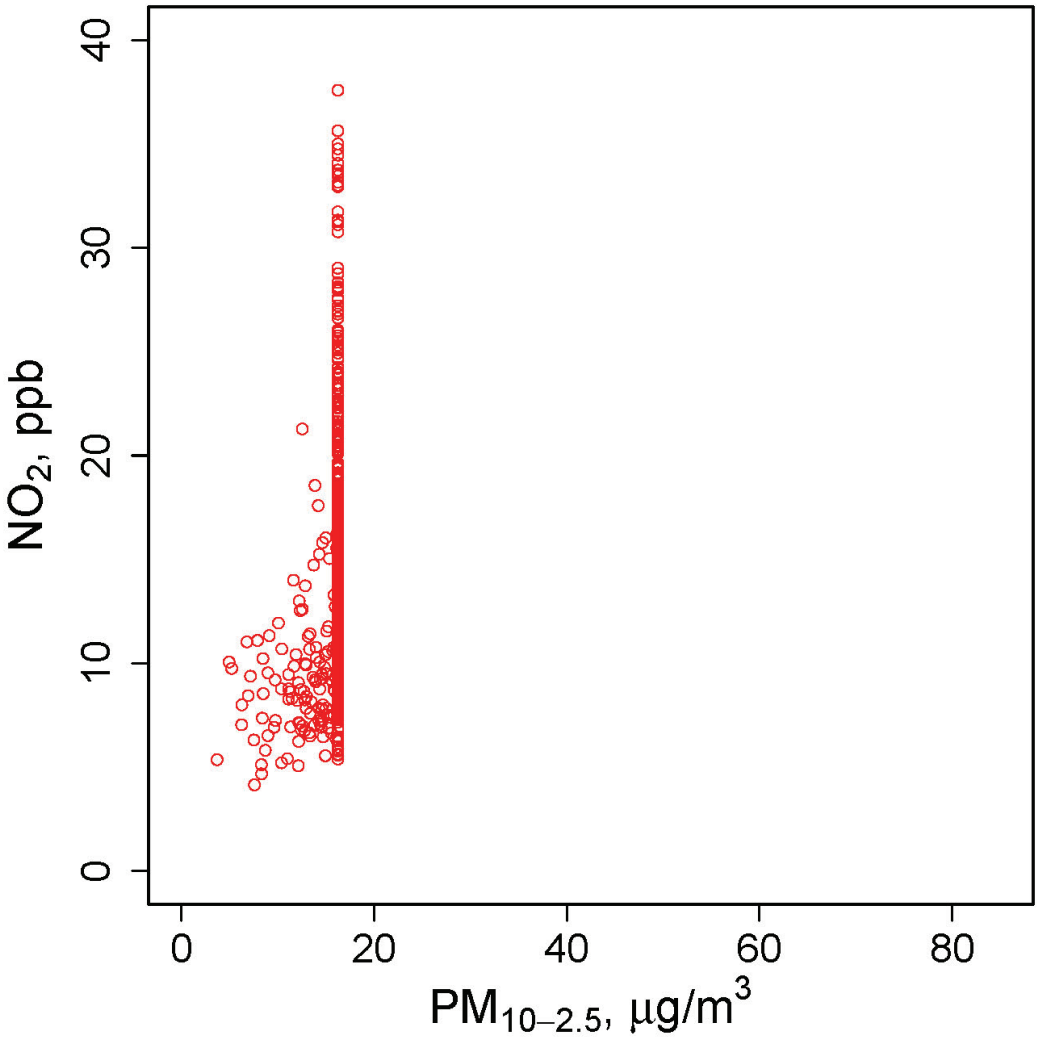


Figure 7. Intervention B: Scatter plot of summertime NO_2 and $PM_{10-2.5}$ concentrations* under a hypothetical 2-pollutant intervention keeping NO_2 at observed concentration and lowering $PM_{10-2.5}$ to the 20th percentile of the observed concentration distribution (16.3 µg/m^3).



* N = 648 unique study days, based on lag 0 and 24-hour average for both pollutants

Figure 8. Intervention B overlay: Distribution of summertime NO_2 and $PM_{10-2.5}$ under hypothetical 2-pollutant intervention B (lowering only $PM_{10-2.5}$), laid over the observed summertime distribution of ambient NO_2 and $PM_{10-2.5}$ between 2001 and 2008 in Fresno, California.

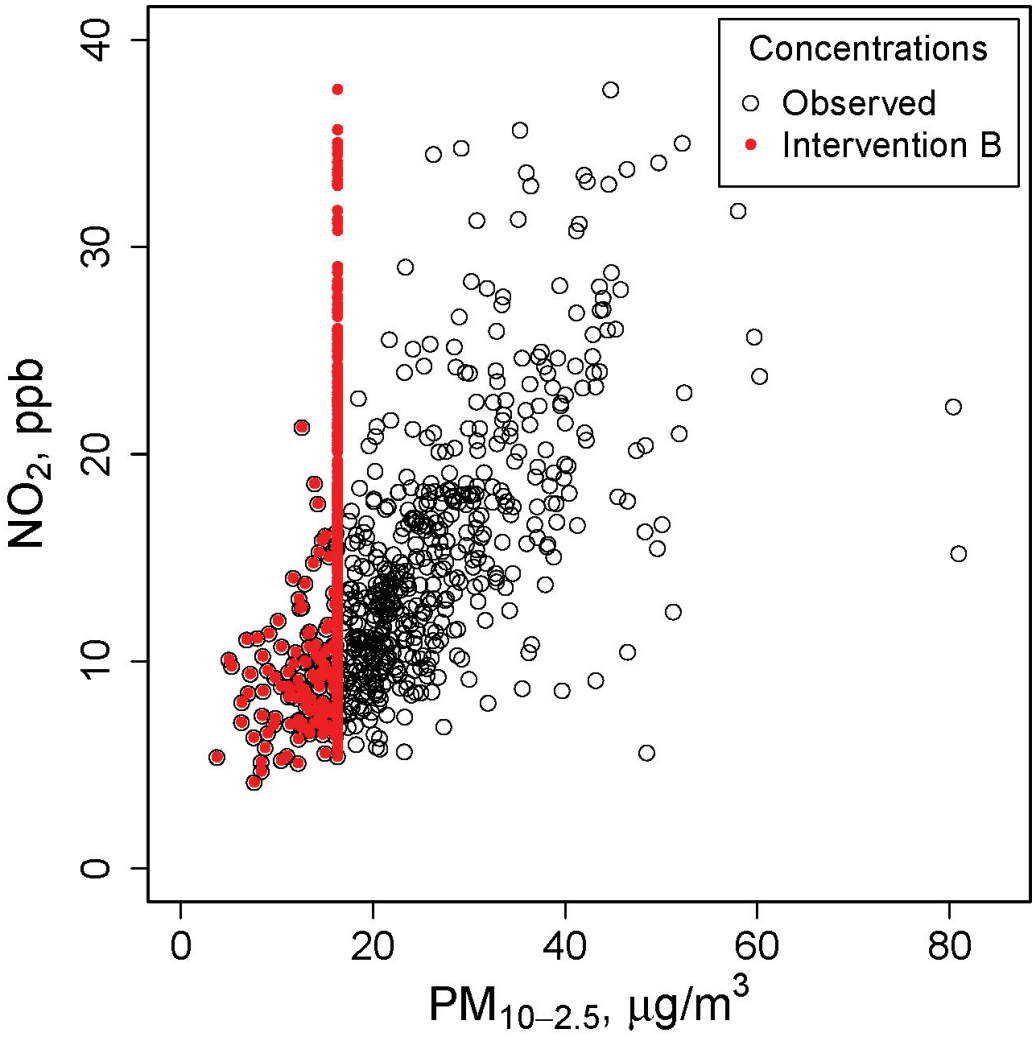
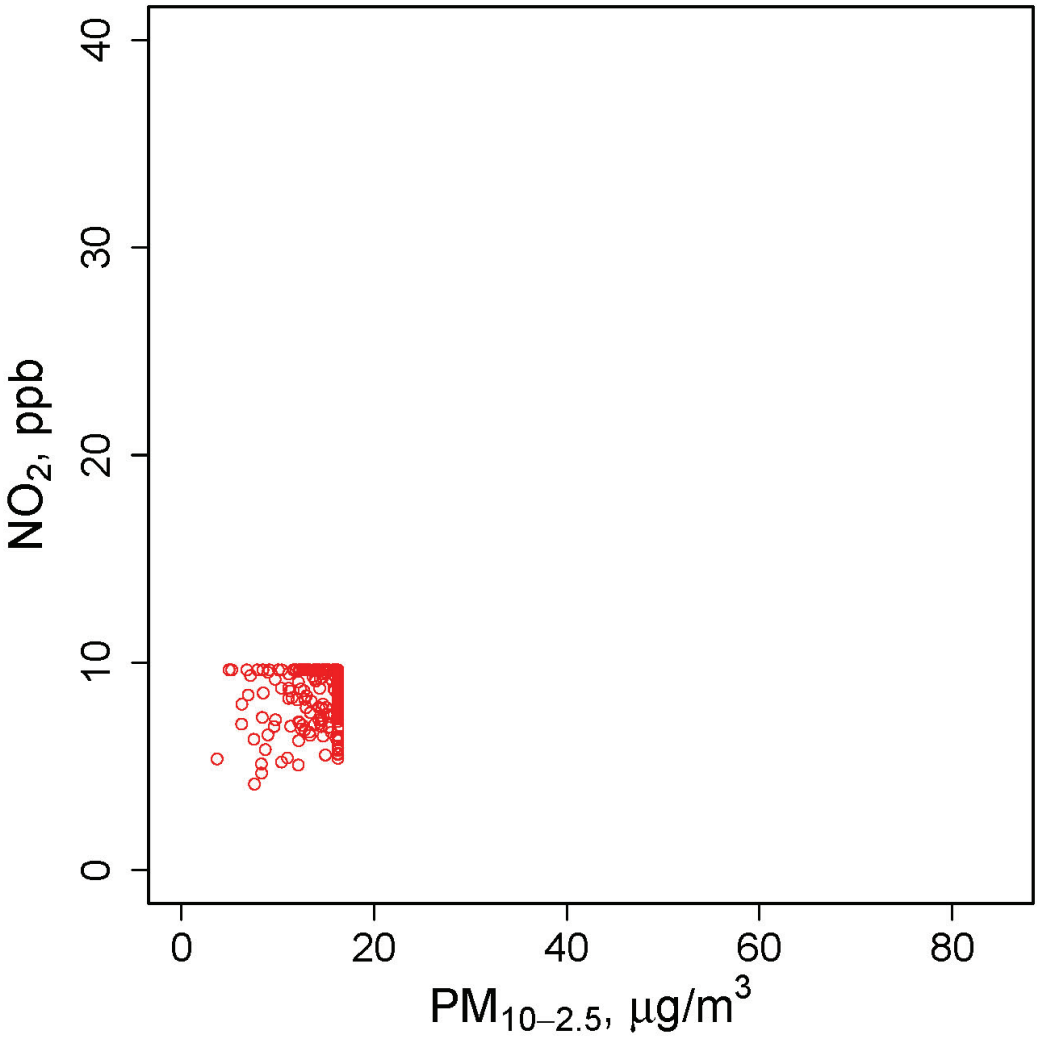
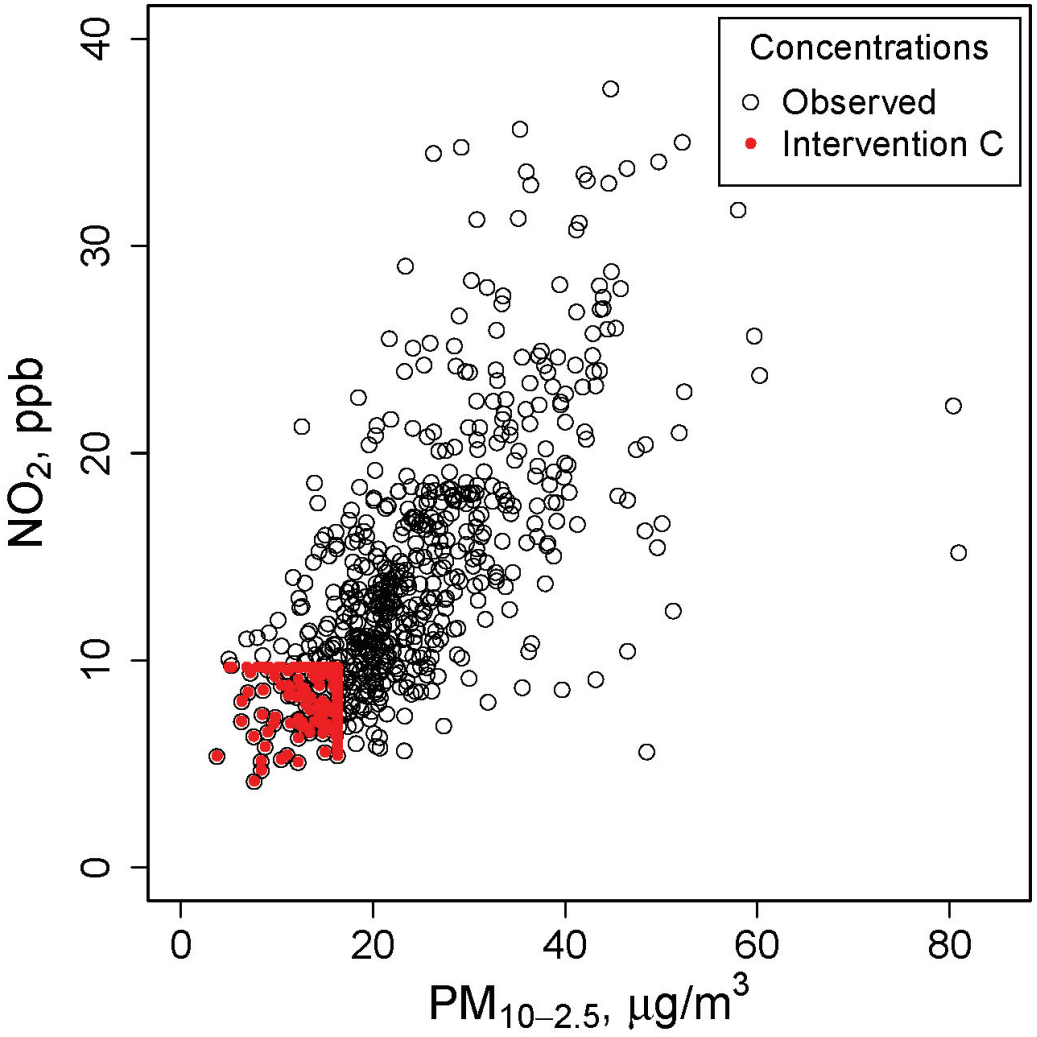


Figure 9. Intervention C: Scatter plot of summertime NO_2 and $PM_{10-2.5}$ concentrations* under a hypothetical 2-pollutant intervention lowering NO_2 to the 25th percentile of the observed concentration distribution and lowering $PM_{10-2.5}$ to the 20th percentile of the observed concentration distribution (9.7 ppb and 16.3 µg/m^3, respectively).



* N = 648 unique study days, based on lag 0 and 24-hour average for both pollutants

Figure 10. Intervention C overlay: Distribution of summertime NO_2 and $PM_{10-2.5}$ under hypothetical 2-pollutant intervention C (lowering both pollutants), laid over the observed summertime distribution of NO_2 and $PM_{10-2.5}$ between 2001 and 2008 in Fresno, California.



Figures 11a & 11b. NO_2 confounder positivity diagnostics: box plots of the distribution of ambient NO_2 across levels of the age-specific confounders of NO_2 effects.
Figure 11a. Distribution of ambient NO_2 across asthma diagnosis at less than 2 years old, a confounder in the younger age group analysis.

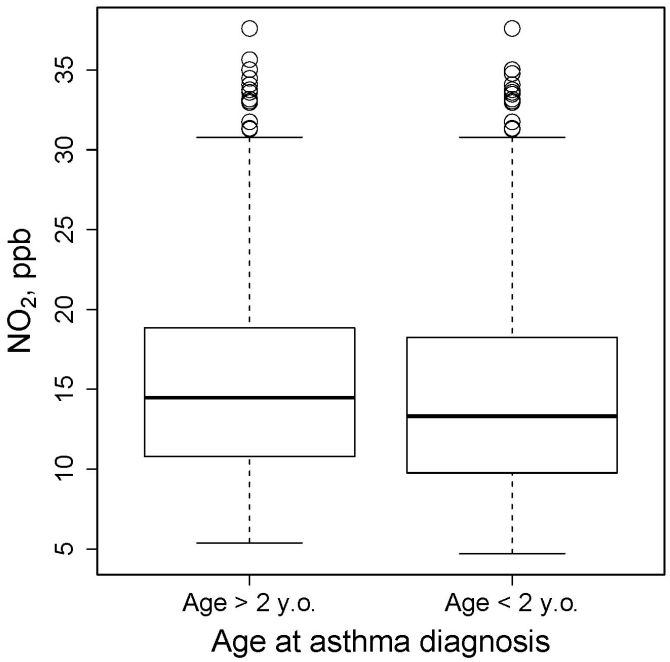
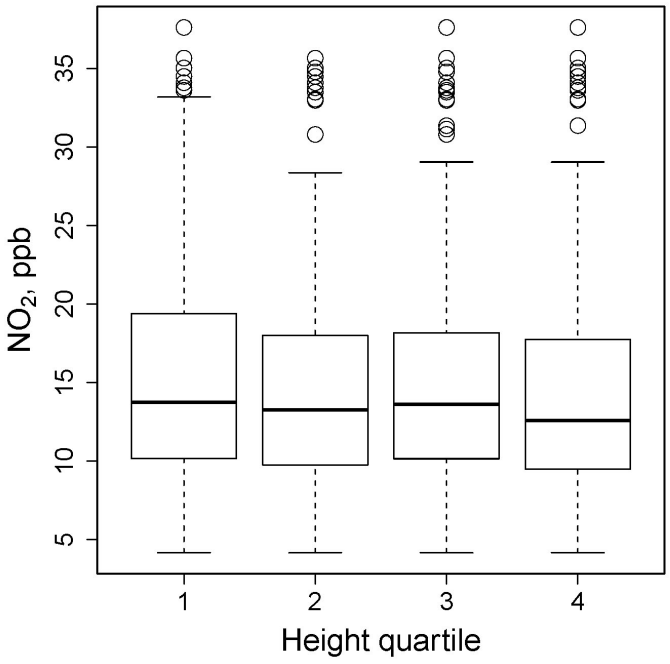


Figure 11b. Distribution of ambient NO_2 across quartiles of height[3], a confounder in the middle age group analysis.



Figures 12a & 12b. $PM_{10-2.5}$ confounder positivity diagnostics: box plots of the distribution of ambient $PM_{10-2.5}$ across levels of the age-specific confounders of $PM_{10-2.5}$ effects.
Figure 12a. Distribution of ambient $PM_{10-2.5}$ across asthma diagnosis at less than 2 years old, a confounder in the 2-pollutant analysis among the younger group.

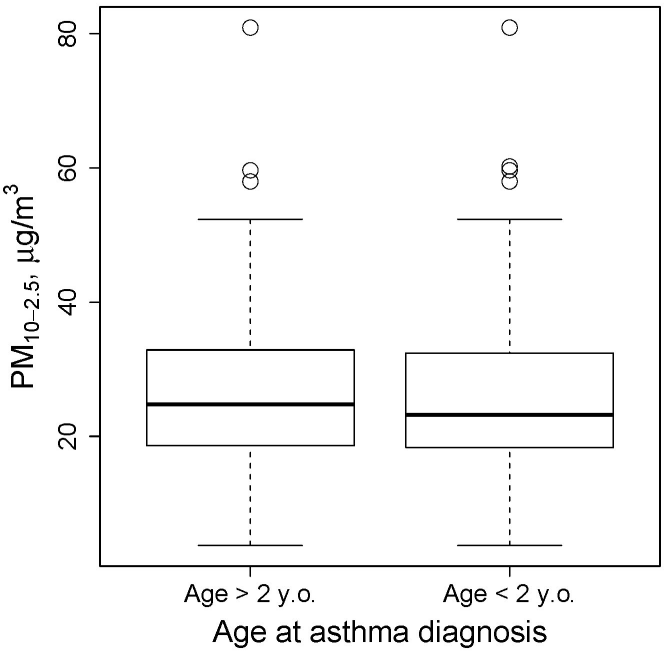


Figure 12b. Distribution of ambient $PM_{10-2.5}$ across quartiles of height[3], a confounder in the middle age group analysis.

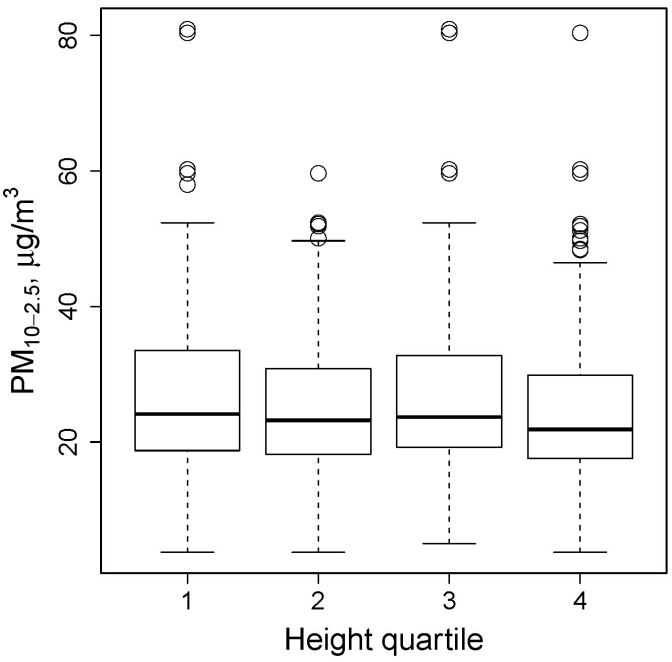


Figure 13. Summary graph of the absolute PIM effect estimates and 95% confidence intervals, across analyses and interventions.

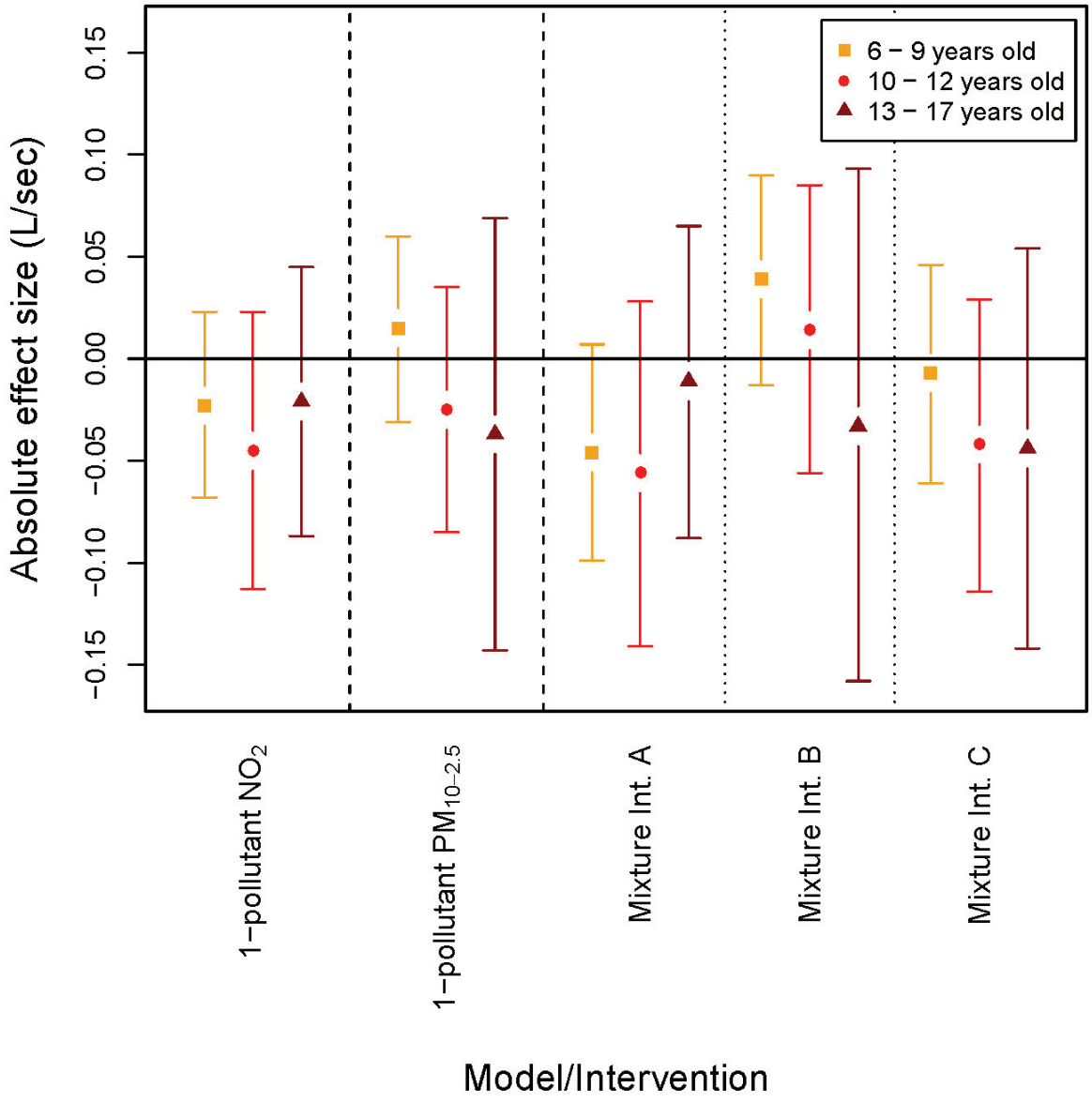
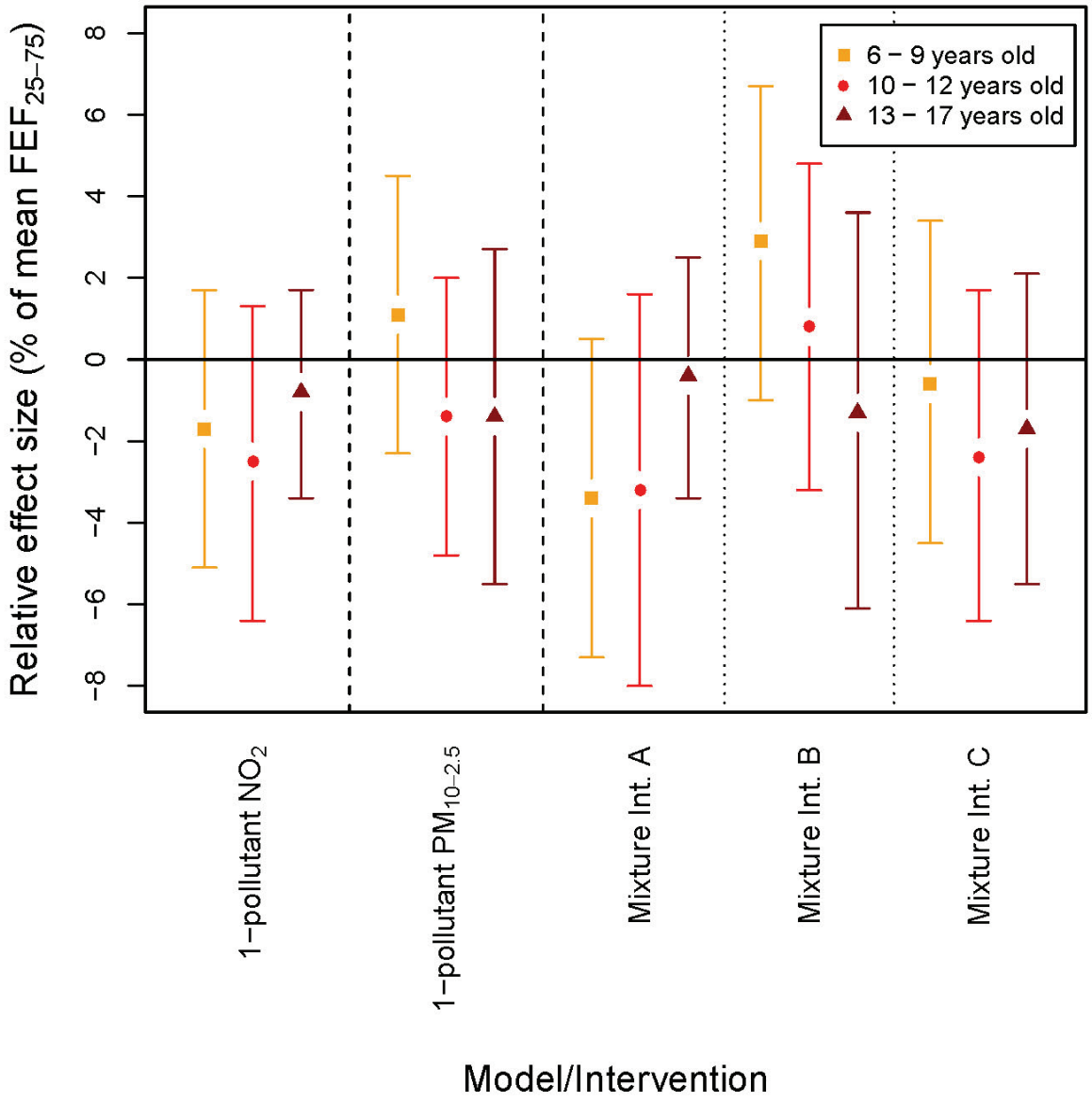


Figure 14. Summary graph of the relative PIM effect estimates and 95% confidence intervals, across analyses and interventions.



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SUPPLEMENTARY MATERIALS

Table S1. Coefficient values for the Q-models for the NO_2 single-pollutant analysis, crude and adjusted models.

NO_2 analysis	**Crude model**		**Adjusted model, selected by DSA†**	
	Model term	**Coefficient value (L/sec)**	**Model term**	**Coefficient value (L/sec)**
6 – 9 year-olds	Intercept	1.39	Intercept	1.51
	NO_2	-2.67 E-03	NO_2	-3.91 E-03
			AsthLe2‡	-0.23
10 – 12 year-olds	Intercept	1.89	Intercept	1.12
	NO_2	-9.29 E-03	NO_2	-8.61 E-03
			$(Height^3)^2$	7.03 E-14
13 – 17 year-olds	Intercept	2.63	–	–
	NO_2	-4.61 E-03	–	–

† Dashes indicate that the DSA algorithm did not select any confounders, and therefore the adjusted model is identical to the crude model.
‡ AsthLe2: Asthma diagnosis less than 2 years old

Table S2. Coefficient values for the Q-models for the $PM_{10-2.5}$ single-pollutant analysis, crude and adjusted models.

$PM_{10-2.5}$ analysis	**Crude model**		**Adjusted model, selected by DSA†**	
	Model term	**Coefficient value (L/sec)**	**Model term**	**Coefficient value (L/sec)**
6 – 9 year-olds	Intercept	1.31	–	–
	$PM_{10-2.5}$	1.42 E-03	–	–
10 – 12 year-olds	Intercept	1.86	Intercept	1.06
	$PM_{10-2.5}$	-4.06 E-03	$PM_{10-2.5}$	-2.89 E-03
			$(Height^3)^2$	7.03 E-14
13 – 17 year-olds	Intercept	2.69	–	–
	$PM_{10-2.5}$	-4.28 E-03	–	–

† Dashes indicate that the DSA algorithm did not select any confounders, and therefore the adjusted model is identical to the crude model.

Table S3. Coefficient values for the Q-models for the 2-pollutant NO_2 and $PM_{10-2.5}$ analysis, crude and adjusted models.

2-pollutant mixture ($NO_2$and $PM_{10-2.5}$)	**Crude model**		**Adjusted model, selected by DSA†**	
	Model term	**Coefficient value (L/sec)**	**Model term**	**Coefficient value (L/sec)**
6 – 9 year-olds	Intercept	1.35	Intercept	1.48
	NO_2	-6.97 E-03	NO_2	-7.89 E-03
	$PM_{10-2.5}$	4.11 E-03	$PM_{10-2.5}$	3.76 E-03
			AsthLe2‡	-0.23
10 – 12 year-olds	Intercept	1.91	Intercept	1.11
	NO_2	-9.90 E-03	NO_2	-1.06 E-02
	$PM_{10-2.5}$	-1.27 E-04	$PM_{10-2.5}$	1.65 E-03
			$(Height^3)^2$	7.05 E-14
13 – 17 year-olds	Intercept	2.71	–	–
	NO_2	-2.41 E-03	–	–
	$PM_{10-2.5}$	-3.82 E-03	–	–

† Dashes indicate that the DSA algorithm did not select any confounders, and therefore the adjusted model is identical to the crude model.

‡ AsthLe2: Asthma diagnosis less than 2 years old

IV. Discussion

Interpretation of findings from PIM analyses

Statistical inference, exposure distributions, and scientific inference

Despite the relative imprecision of the statistical inference around the effect estimates, comparison of the magnitude and direction of the risk differences (RDs) across analyses demonstrates patterns and provides information about the respiratory effects of the pollutants analyzed in this study. Furthermore, consideration of the individual and joint distributions of the two exposures yields key insight that guides the interpretation of these findings, especially as relates to parameter identifiability. Taken together, the analysis of exposure distributions and the results from the Population Intervention Models have implications for evaluating the various analytical approaches implemented in this project. These implications also apply more broadly to estimation of multi-pollutant health effects.

Comparing overall NO_2 findings to overall $PM_{10-2.5}$ findings

In both of the single-pollutant analyses and the 2-pollutant analysis, the risk differences tended to be small in magnitude. To interpret the meaning of each intervention, recall that the parameter of interest was defined as the effect on FEF_{25-75} resulting from an intervention that decreased pollution concentrations: $E[Y] - E[Y_a]$ (single pollutant analysis). Therefore, if a decrease in ambient pollution improves pulmonary function as measured by FEF_{25-75}, the higher value of $E[Y_a]$ relative to $E[Y]$ would result in a risk difference with a negative sign.

When NO_2 was decreased as part of the intervention (single-pollutant NO_2 intervention and 2-pollutant interventions A and C), the direction of the association was the same across all age groups: decreasing the NO_2 concentration resulted in an increased in FEF_{25-75}, indicating improved respiratory function (as evidenced by a negative sign on the risk difference). In these NO_2 analyses, the magnitude of the risk difference was greatest is the middle age group, observations from 10 – 12 year-olds.

In the single-pollutant $PM_{10-2.5}$ analysis and the 2-pollutant intervention B (lowering $PM_{10-2.5}$ while holding NO_2 at observed levels), there were some risk differences with a positive sign, indicating that increased $PM_{10-2.5}$ concentrations actually increased pulmonary function. In the single-pollutant $PM_{10-2.5}$ analysis, this unexpected finding was only seen in the younger age group (6 – 9 year-olds). In the 2-pollutant intervention B, the sign of the risk differences was counterintuitive in both the younger and the middle age groups. In the case of intervention B, the joint exposure distribution of the two co-pollutants indicates that the parameter was not identifiable in the observed data, discrediting these findings. I expanded upon this point below.

The nature of the exposure-outcome association was more consistent across analyses for NO_2 exposure, as compared to the analyses in which $PM_{10-2.5}$ concentration was decreased. The NO_2/FEF_{25-75} association estimated was a small, inverse association across all analyses (indicating increased FEF_{25-75} with decreased NO_2), as compared to the mixed directions of the $PM_{10-2.5}$ analyses, in which some age groups and exposure regimens saw decreased pulmonary function with decreased pollution. These findings collectively provide stronger evidence for a deleterious effect of NO_2 on FEF_{25-75} than for an effect of any direction for $PM_{10-2.5}$.

Single-pollutant NO_2 findings as compared to multi-pollutant NO_2 findings across age groups

Three analyses involved lowering NO_2 concentrations: the single-pollutant NO_2 analysis and 2-pollutant interventions A and C. It is informative to compare Intervention A to single-

pollutant NO_2 intervention, because both involve decreasing the concentration of only ambient NO_2. The key difference between these two parameter estimates is that the Population Intervention Parameter for intervention A is conditioned on the co-pollutant $PM_{10-2.5}$ (which is held at the observed values in intervention A). The pattern of parameter estimates is approximately the same between the two interventions. In both analyses, all risk differences have a negative sign, indicating improved FEF_{25-75} resulting from decreased NO_2. Both approaches estimate the largest absolute effect in the middle age group; the magnitude is larger for intervention A. In these approaches, as in the others, the relative magnitude attenuates moving up the age groups, due to the increase in the denominator (average FEF_{25-75}, which increases with age).

Single-pollutant $PM_{10-2.5}$ findings as compared to multi-pollutant $PM_{10-2.5}$ findings across age groups

Analogous to the comparison of the single-pollutant NO_2 PIP and the intervention A PIP, it is instructive to compare the single-pollutant $PM_{10-2.5}$ results to the results from 2-pollutant intervention B. Both approaches model the effects of lowering only $PM_{10-2.5}$, although the intervention B effect is different in that it is conditioned on holding ambient NO_2 concentration at observed levels. These two analyses are the ones that estimated risk differences of both signs, indicating that in some age groups, decreasing ambient air pollution decreased lung function (the RDs with the positive sign). In the single-pollutant $PM_{10-2.5}$ analysis, this unexpected finding (a RD with positive sign) only found in the younger age group (6 – 9 year-olds), and like all risk differences in this analysis, was of a small magnitude (<1.5% in absolute value). However, in the case of intervention B, the risk difference in the younger group that indicated decreased FEF_{25-75} resulting from decreased $PM_{10-2.5}$ was among the larger relative effects estimated in any analysis: 2.9%. While not estimated with a high level of precision, this PIP estimate stands out as unique among the other findings, which are uniformly in the other (expected) direction, except for one risk difference of small magnitude. This finding that under 2-pollutant intervention B, lowering ambient $PM_{10-2.5}$ decreased pulmonary function in one age group (at an equal relative magnitude to the findings in the other direction), is based on a parameter that is not identifiable, i.e., is not supported by actual data. This finding, and the underlying approach used to calculate it, will be discussed in further detail in order to shed light on this finding.

Results compared across the various 2-pollutant interventions

Of the three 2-pollutant interventions for which health effects were estimated, interventions A and B differ most greatly. The risk differences calculated for intervention A present a trend of small, imprecisely estimated increases in FEF_{25-75} resulting from decreasing only NO_2 in a 2-pollutant exposure regimen. The picture for intervention B is more mixed, with at least one age group exhibiting diminished FEF_{25-75} resulting from decreased $PM_{10-2.5}$. This finding, in the unexpected direction, was equal in magnitude to the largest risk differences calculated in any analysis here. Strikingly, the adjusted risk differences of intervention A and intervention B in the younger age group were among the largest relative associations estimated in any analysis, and were in opposite directions. As with intervention B, the parameter that intervention A defines was not identifiable in the observed data; both interventions A and B were based on areas of no data support. Thus, the results corresponding to intervention A should also not be considered credible, given that they were based on extrapolations beyond the observed

data and are likely biased. Given the validity concerns with the health effects estimated by interventions A and B, the conflicting results described above do not merit logical interpretation.

In contrast, the results for intervention C are comparable to the patterns from the single-pollutant analyses: small, imprecisely estimated associations with the same sign (indicating improved FEF_{25-75} with decreased air pollution), with the largest relative magnitude in the middle age group. In contrast with interventions A and B, the results from intervention C are not compromised by nonpositivity across levels of the co-pollutants. Therefore, these results, along with the single-pollutant results, should be given the most scientific weight. For each age group, the intervention C risk difference is equal to the sum of the risk differences for interventions A and B. This results from the fact that intervention C incorporates the changes in exposure concentration from both interventions A and B, and the fact that the Q-model was specified without an interaction term.

Comparing these findings to results from the literature

A comparison between these results and findings from the literature is hampered by the difference in estimation approaches. Studies on ambient NO_2 health effects on pulmonary function in children with asthma have presented results corresponding to IQR changes in concentration[1, 2]. Still, the studies that have examined this association have found inverse associations between NO_2 and pulmonary function parameters (including FEV_1[1] and FEF_{25-75}[2]) on magnitude of 1 – 3% per IQR. Another difference to bear in mind while considering these prior studies in that the NO_2 concentrations in these settings was higher than in the present study. For example, in the studies by Liu *et al.* and Delfino *et al*., median/mean ambient NO_2 concentrations were 50% higher than in the present study[1, 2]. If the exposure-response curve is not linear across a broad range of pollutant concentrations, then the findings from this study would be further incomparable with these prior studies.

Issues of positivity and parameter identifiability

Interpretation of these risk differences must be informed by the nature of the interventions whose health effects are being estimated. The health effects estimated by single-pollutant models in this study were "on-support"; that is, the interventions were within the range of observed air pollution concentrations for the respective exposure. The single-pollutant interventions were explicitly defined to be within the observed distribution; this is demonstrated in the Results, Tables 10a and 10b. In other words, estimating the effects of each hypothetical single-pollutant intervention did not require extrapolation beyond the observed exposure data. This ensured that the parameters were identifiable in the observed data. Parameter identifiability also requires positivity, or variation of exposure within confounder strata. This issue of positivity within strata of the confounders was also addressed in Figures 11 and 12, demonstrating evidence for experimentation (i.e., a range of exposure values) within each stratum of age-specific confounders.

Consideration of parameter identifiability is more complex with multi-pollutant exposure regimens. It is still important to consider the single-pollutant exposure distribution of each individual exposure in the regimen, which is simplified here because the intervention cutoff concentrations applied to NO_2 and to $PM_{10-2.5}$ in the 2-pollutant analyses were the same as the intervention cutoffs employed in the single-pollutant analyses. Therefore, both intervention cutoffs were known to be within the observed single-pollutant distribution of the respective

exposure. Table 10c demonstrates that both intervention cutoff concentrations lie within the respective observed single-pollutant distribution.

When estimating the effects of a multi-pollutant exposure regimen, examining single-pollutant distributions for issues of identifiability and positivity is necessary but insufficient. The investigator must also consider the joint distribution of the co-pollutants. When an outcome is modeled as a function of multiple pollutants, the independent effect of each pollutant is conditioned on the co-pollutant in the model, along with confounding variables included in the model as independent variables. In other words, the effect of each pollutant is estimated within strata of the co-pollutants; indeed, co-pollutants are sometimes termed confounders rather than exposures[3-5]. Therefore, when using a multi-pollutant model to infer about health effects of a single pollutant, one must consider positivity not just with regard to the confounders, but also as relates to the co-pollutants. Failure to do so may result in estimation of effects that are not identifiable, or effects that are "off support" (i.e., not based on any real data that were collected)[6, 7]. These considerations greatly affect the interpretation of the parameter estimate.

Simply using the model coefficients to infer about the effect of a one-unit change in pollution (here, ppb or $\mu g/m^3$) while holding the co-pollutant constant may generally correspond to an identifiable parameter, if there is variability in the index pollutant across the range of the co-pollutant. However, epidemiologists and policymakers are seldom interested in the effects of one-unit pollutant changes, and frequently estimate the effects of larger pollution changes by multiplying the coefficient by an IQR or some other interval, such as 10 ppb[1, 8-10]. The appropriateness of this practice should be examined in all analyses, including single-pollutant analyses. Effects of this sort may not be appropriate, as when the concentration interval extends beyond the range of pollution concentrations observed in the sample (for example, [11]), or when the interval is larger than the daily concentration difference that the sample experiences. (See Mann *et al*. for a discussion of this phenomenon[12].) In the former case, the parameter can be described as off-support in the sample, because the range of the data collected do not permit inference across the range of values that the investigator is studying[6]. In the latter case, there may be support in the data, but the effect size is not realistic to examine daily variation in the pollutant.

These issues of support and identifiability are compounded when the effects of multiple pollutants are modeled simultaneously in the same model. It is also standard practice to estimate a single-pollutant effect "adjusted for" a co-pollutant by multiplying the coefficient of one pollutant in a multi-pollutant model by an IQR or an increment of 10 units, holding the co-pollutant(s) constant[1-4]. This approach may fail to take into account the correlation between co-pollutants that is common in practice[13, 14]; Dominici *et al*. and others have remarked on the potential consequences of modeling correlated co-pollutants in a multivariable regression[4, 14]. In addition to the issue of unstable estimates, this practice may also introduce additional, fundamental issues of parameter non-identifiability.

In some circumstances, it may be unrealistic to significantly alter the concentration of one pollutant while holding constant the co-pollutants. The distribution of co-pollutant concentrations might also be affected by a large change in the index pollutant. This correlation may also pose a challenge to the assignment of specific health effects to one pollutant in a single-pollutant analysis (such as the ones conducted in this study). This type of problem relates to the logical interpretation of the results. It raises questions of the sort, "is this estimated health effect a result of the pollutant under study, or might the pollutant be acting as a surrogate for the true causal factor?". Investigators commonly raise questions of this type in air pollution

epidemiology[4, 15], but rarely provide answers. Tolbert *et al*. provide a useful framework for assessing questions of this type, and conclude that in many cases using a multi-pollutant model to answer the question may introduce bias (as when there is differential measurement error).

Multi-pollutant analyses present other fundamental methodological challenges in addition to this problem of assigning health effects to specific pollutants. When statistically modeling the health effects of multiple pollutants, one must consider what parameters, and therefore what study questions, the joint exposure distribution provides support for. If it is possible to raise one pollutant by a large amount without substantially changing the distribution of the co-pollutant—i.e., if the observed data contain days when the index pollutant has high concentration and the co-pollutant(s) have average concentration—then there may be support in the data to ask such a question. In practice, the correlation observed between co-pollutants should caution investigators against estimating these types of parameters (large changes in one pollutant while holding co-pollutants constant), without first examining the joint distribution of the co-pollutants for positivity concerns.

In this analysis, there is ample evidence that the types of air pollution changes described by interventions A and B are not realistic given the observed data, and furthermore that there is not support in the data to estimate health effects for these interventions. Evidence for this conclusion is provided by Tables 11 – 12 and Figures 5 – 8 in the Results section. Table 11 demonstrates that in Fresno during the study period, days with low NO_2 concentrations had a limited range of $PM_{10-2.5}$ concentrations relative to the overall distribution of $PM_{10-2.5}$ concentrations. Specifically, the concentrations of $PM_{10-2.5}$ were lower on days of low NO_2. At the higher end of the $PM_{10-2.5}$ distribution, intervention A defines some hypothetical days the likes of which were never observed. Therefore, calculation of health effects corresponding to these days relies on extrapolation where there are no data. To relate this situation to the issue of positivity, across the strata of the co-pollutant (e.g., high $PM_{10-2.5}$ concentrations), there is not a positive probability of receiving the treatment of interest (i.e., low NO_2 concentrations). Figure 6 demonstrates this, with the scarcity of observed data in the lower right quadrant of the graph, where there is a large density of intervention days. The single-pollutant NO_2 distribution defined by intervention A is realistic given the observed data, as is the single-pollutant $PM_{10-2.5}$ distribution. What is unrealistic, and indeed unobserved in the FACES data, is the joint distribution of the two pollutants. The 2-dimensional Cartesian space defined by the black dots in Figure 6 represents the extent of the joint two-pollutant distribution observed in Fresno between summers of 2001 and 2008. Referring again to Figure 6, lowering NO_2 levels as described by intervention A without a corresponding change in $PM_{10-2.5}$ concentrations moves many of the red dots (hypothetical intervention A days) into regions of the graph where there is very sparse to no observations. These observations raise critical questions about the identifiability of this parameter, and parameters of this type in multi-pollutant analyses with correlated exposures.

Table 12 and Figures 7 – 8 raise conversely analogous issues for intervention B. By lowering $PM_{10-2.5}$ concentrations without changing NO_2 concentrations, a large density of study days are intervened on in ways that extrapolate beyond the observed data. Intervention C, described in Table 12 and Figures 9 – 10, stands in contrast to interventions A and B in this regard. Because both NO_2 and $PM_{10-2.5}$ concentrations are lowered through intervention, and $PM_{10-2.5}$ is lowered in a manner that is based upon the observed distribution of $PM_{10-2.5}$ on low-NO_2 days, the resulting parameter is identifiable from the data observed in the present study. This is demonstrated by the overlap between the observed and intervention distributions of each pollutant in Table 12, and the fact that the pollution profile of the hypothetical intervention days

(represented by red dots in Figure 10) falls entirely within the range of the joint 2-pollutant exposure distribution of observed days (black circles).

As there is support in the data to estimate a parameter corresponding to both single-pollutant analyses and intervention C, these results should be given more weight than the results for 2-pollutant interventions A and B. Non-positivity results in biased parameter estimation[16, 17], so the conflicting results from interventions A and B can be dismissed. More importantly, research questions of the form of interventions A and B—large, isolated single-pollutant concentration changes in a multi-pollutant exposure regimen—should be scrutinized for positivity and data support before commencing analysis.

Relating this approach to non-PIM approaches

The g-computation-PIM approach has not been applied to air pollution research as of yet, but it is related to the existing approaches. Moreover, the positivity issues raised in this study are not unique to the PIM approach. In fact, using a g-computation estimator in a dataset without repeated measures, in a model without interaction terms and with a continuous outcome, the single-pollutant PIM effect estimate is equal to model-derived the pollutant coefficient multiplied by the mean pollutant concentration change under intervention (as presented in the Results section, Tables 13 and 14). Under these same circumstances, the 2-pollutant effect estimates could be calculated by multiplying each pollutant coefficients by the mean pollutant concentration change, and summing the resulting risk differences.

As I stated in the Methods section, the Q-model is not mechanically different from a traditional regression model used to estimate air pollution health effects; it differs in its implementation for parameter estimation. Whether an investigator uses a model in a traditional regression approach or a Q-model for g-computation, the issues of positivity and parameter identifiability remain important. The causal inference literature has brought increased attention to the issue of positivity to epidemiologic analysis[18-20], but the concern is not unique to analyses employing these methods. Other fields of epidemiology are focusing more attention of the issues of positivity and parameter identifiability (e.g., social epidemiology[21-23]), and bringing this focus to environmental epidemiology can improve the inference that we draw from our data, and the relevance and validity of our work to inform policy. Especially as calls for renewed focus on air pollution mixtures motivate investigators to analyze increasingly complex exposure regimens, the need to consider issues of positivity and parameter identifiability is compounded.

Contributions of this study

This study contributes to air pollution epidemiology by studying two pollutants whose effects on FEF_{25-75} in children with asthma are still not fully understood, and for which prior results has proven inconclusive, at best. Additionally, by analyzing FEF_{25-75}, the present study contributes to the small body of air pollution epidemiology examining this outcome that may be a better marker for health effects in people with asthma[24, 25] but is not yet widely studied. Though statistical inference does not support a strong conclusion that ambient NO_2 and $PM_{10-2.5}$ are inversely associated with FEF_{25-75}, either independently or jointly, the analyses that estimated identifiable parameters did find internally consistent findings: small, imprecisely estimated increases in FEF_{25-75} associated with decreasing pollution levels.

This study also contributes to the literature by implementing a methodological approach that is not widely used in environmental epidemiology, but which is relevant for air pollution epidemiology. The causal inference framework generally, and the Population Intervention Model

specifically, are well equipped to estimate parameters associated with potential interventions[26, 27] which are often of interest in air pollution policy and therefore air pollution science. The health effects associated with an intervention explicitly defined with reference to the observed pollutant concentrations offers an alternative method to quantify air pollution health effects, in addition to the existing methods based on an IQR or 10-unit increase in pollution concentration (methods which do not always correspond to realistic[12] or identifiable[11] parameters). By demonstrating the implementation of this method on air pollution data, I have attempted to answer a question of scientific and policy relevance, but also to demonstrate the applicability of these methods to the subject matter of air pollution.

The methodological approach employed here is most relevant for its implications for multi-pollutant air pollution research. There is a well-known need for new approaches to estimate health effects of mixtures[14, 28], and the method employed here is a promising candidate approach. By estimating the overall health effects of multiple, simultaneously changing pollutants, the Population Intervention Model enabled analysis of multi-pollutant health effects at the mixture level, rather than the level of the independent co-pollutant. This approach may represent a more realistic framework for considering health effects of mixtures, especially in the presence of correlated co-pollutants.

This study also provided in-depth analysis of co-pollutants in a multi-pollutant model, focusing on concepts of positivity and parameter identifiability as they related to the data collected for the FACES study. This examination yielded important conclusions about the nature of multi-pollutant research questions that can be validly estimated in the FACES data. Although they could be and were calculated, the examination of the joint exposure distribution suggested that some of the health parameters estimated here (namely, interventions A and B) were based on extrapolation in regions of the joint exposure space where there were no observed data. On this basis, these parameters were deemed off-support for this dataset, and the corresponding results were given less weight than those which were supported by actual data.

This finding does not imply that questions encoded in interventions A and B are not identifiable for all datasets collected in all geographical regions. In areas where the two pollutants are less correlated, and where there are observed days of high NO_2 and low $PM_{10\text{-}2.5}$ (and vice versa)—in other words, where there is a positive probability of one pollutant having a high concentration in the presence of a low-concentration of the co-pollutant—such questions may be asked. However, in Fresno during the summers of 2001 – 2008, the research questions that interventions A and B encode are not answerable, because they require the estimation of non-identifiable parameters. This examination applies to other multi-pollutant analyses, and points to the broad importance of considering the identifiability of multi-pollutant health effects.

Limitations of this study

One byproduct of the use of an uncommon method is that the results of this study are not readily compared to the results from prior research. This prevents assessing the extent to which the results are coherent and consistent with the existing literature on this topic.

The lack of statistical precision with which these results were estimated prevents rejection of the null hypothesis for any of the research questions posed. With all 95% confidence intervals crossing this null value here, it is difficult to decisively conclude whether the patterns observed in the findings indicate genuine health effects or are a result of chance.

The analysis of repeated measures data, with unequal number of repeat observations per participant, complicated the analyses conducted in this study. Data from each child were equally

weighted in the calculation of health effects, both in the regression model and in the calculation of the risk difference. Still, there may be auto-correlation between the repeated measurements from with a child that introduce bias into the results (point estimates and/or standard errors). The correlation structure for this dataset was sufficiently complicated (with repeated measures within a panel and repeated panels within a child, sometimes years apart) to call into question the appropriateness of many of the common auto-correlation structures used in approaches that explicitly account for auto-correlation, such as Generalized Estimating Equations. Still, future work should examine the effects of using various approaches to account for the repeated measures in the FACES data.

Missingness of observations within panels is another important issue that this study did not address. Basic statistical tests indicated that the overall sample of children contributing panel data did not differ from the subset of children who contributed summer panel data on the basis of individual variables. Still, the missingness of FEF_{25-75} measurements from single days within observed panels may be an important source of censoring. If this censoring is informative (i.e., associated with the exposure or other important covariates), then it could introduce bias into these findings. Future research should explore the issue of missingness.

Relatively simple models were fitted to estimate the health effects of the pollutants studied here. In fact, four of the nine final age- and regimen-specific models were the crude model and contained no confounders. These unadjusted models were selected by the DSA algorithm, even though potential confounders were submitted to the algorithm in all cases, having been chosen by candidate reduction. From one perspective, the models' relative simplicity is unsurprising, given that ambient pollutant concentrations were analyzed as the exposure, and these are unlikely to be associated with many individual-level covariates. Still, as in any analysis there is the possibility that uncontrolled confounding introduced bias into the effect estimates shown here. A concrete example is potential residual confounding by calendar time even after age stratification. The testing of all candidate covariates for bivariate associations with both exposure and outcome diminished the probability of this scenario, as regards measured confounders.

A final limitation is the use of central-site data for exposure assignment. While the research question of the present study does focus on ambient pollution, the concentration of pollutants at a central monitor does not measure an individual's personal exposure to ambient pollution. In the case of particulate matter, various methods have been proposed to model personal exposure to ambient pollution[29-31], though implementation of these techniques in applied epidemiology remains rare[32]. The use of ambient exposure assignment in the present study doubtless introduces measurement error, which poses a more serious threat to validity if it is differential with regard to outcome.

Directions for future research

Future research should explore the methodological issues highlighted in the limitations section, including auto-correlation of outcome, missingness of panel days, and exposure measurement. There are also a number of next steps that this methodological approach can be applied to.

In the area of summertime air pollution mixtures, future research should estimate the health effects of different pollutant combinations. Ozone is an important component of the summertime air pollution profile in Fresno, and is also related to NO_2 through chemical pathways that cause their correlation to be different from that observed between NO_2 and PM_{10-}

$_{2.5}$ in this analysis[33]. Future analyses using ozone, or any other summertime pollutant, should consider the joint exposure distribution of the co-pollutants and proceed with the estimation of identifiable parameters.

Another area of interest is the health effects of season-specific mixtures in different geographic locations, or in Fresno during seasons other than summer. The exposure plots in the Results section demonstrated that NO_2 is at its peak early in the winter season, making winter another season of interest in this dataset. Different seasonal combustion sources and meteorological factors ensure that the air pollution mixture is different across seasons, and each represents an interesting future application of this methodological approach. Another way of extending analyses from this study would be to apply the approach to estimate mixture health effects in other regions that have different air pollution profiles: sources, pollutants, seasonal patterns, and correlation structures. Conducting analyses in different geographical regions may provide data that support the estimation of parameters that are non-identifiable in the current dataset, enabling investigators to ask and validly answer different types of questions.

On the topic of identifiability, future research should examine how the estimation of health effects that are off-support for a given dataset affects parameter estimation and scientific inference. The work on the statistical effects of positivity violations[16] could be extended into air pollution subject matter, so that we can more fully appreciate the effects of random and deterministic violations of this crucial assumption.

Future research should also examine the analytical issues involved in multi-pollutant modeling with more than two exposure variables. Several of the analytical steps and methodological considerations discussed in the present study would be greatly complicated in the presence of three or more co-pollutants. Even examining the joint distribution between the co-pollutants, while certainly achievable with current statistical tools, would nonetheless be more complicated than the two-pollutant example discussed here. Examining the issues of positivity and parameter as they relate to a three- or more-pollutant exposure regimen would be the first stop enabling the estimation of effects corresponding to increasingly complex air pollution mixtures.

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