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The effect of air pollution and time spent outdoors on pulmonary function in a diverse New England population

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THE EFFECT OF AIR POLLUTION AND TIME SPENT OUTDOORS ON PULMONARY FUNCTION IN A DIVERSE NEW ENGLAND POPULATION

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DEDICATION

I would like to dedicate my thesis to my mother, father, sister, and friends.

They have always been there for me.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

THE EFFECT OF AIR POLLUTION AND TIME SPENT OUTDOORS IN A DIVERSE NEW ENGLAND POPULATION

by

Thomas Daniel Lambert

University of New Hampshire, December, 2006

Outdoor air pollution has been associated with declines in pulmonary function. We collected daily pulmonary function measures from 165 participants in New England during July and August, 2004 and compared these measures to outdoor air pollution using single and multiple pollutant models. Increases of 10μg/m^3 $PM_{2.5}$, 10 ppb O_3, and 1 ppb NO_2 were associated with -1.29%, -0.54%, and -0.151% changes in FEV_1 of asthmatic participants spending more than 5 hours outdoors, respectively. Effects for non-asthmatic and all participants spending less than 5 hours outdoors were near zero and not significant. There was also evidence indicating that the largest effects were observed 3 days after the pollution event. Results suggest that asthmatic participants should avoid prolonged exposure to even moderately elevated levels of O_3, $PM_{2.5}$, NO_2. We found that measuring the amount of time spent outdoors was important in determining effect estimates.

INTRODUCTION

While there are still hotspots of severe air pollution around the globe, much of the developed world has eliminated events such as those that occurred in London, England (1952) and in Donora, Pennsylvania the (1948) which darkened noontime skies and resulted in a significant number of deaths during and shortly after the events. Since the passage of the Clean Air Act of 1970, The US now deals with the harder to quantify low-level chronic exposures and relatively moderate air pollution event exposures that result in adverse health effects such as premature death, respiratory disease, respiratory symptoms, asthma attacks, and lost productivity.

Increased mortality, respiratory disease morbidity, hospitalizations, respiratory symptoms, lost productivity days, and declines in pulmonary function are all associated with air pollution. These effects are being observed at pollution concentrations below the current US national ambient air quality standards. Controlled exposure studies have identified potential concentration thresholds, below which health effects were not observed. However, when real world pollution exposures were investigated, health effects were observed below the threshold values proposed by the controlled experiments (Spektor et al., 1988). In addition, it has been observed that many different sensitive subpopulations exist and that an individual's behavior can control exposures and have large impacts to the individual's health. Identifying and quantifying the most

important sensitive subgroups, behaviors, and exposures appears to be the direction of current research. The research presented here examines the relationships between air pollution and pulmonary function, which is a measure of a person's basic lung function. We chose to measure pulmonary function, respiratory symptoms, and behavior in a large and broad study population over two summer months in New England and explore the associations between these effects and chemical and physical air quality. This thesis examines the effect of air quality on pulmonary function. It is organized into four chapters as outlined below.

Chapter I: Literature Review. A discussion of a representative sampling of literature on the effects of air pollution on pulmonary function from the past 20 years which will be submitted for publication in the journal *Environmental Research.*

Chapter II: Methods. A detailed account of the data collection procedures.

Chapter III: The effect of air pollution and time spent outdoors on pulmonary function in a diverse New England population. This chapter represents a standalone manuscript of a paper to be submitted to the journal *Environmental Health Perspectives*, and contains its own introduction, methods, results, and discussion.

Chapter IV: Conclusion and future recommendations.

CHAPTER I

LITERATURE REVIEW

Introduction

Multiple studies have shown that air pollution is significantly associated with increased mortality, respiratory disease morbidity, respiratory and cardiac hospital admissions, respiratory symptoms, and decreases in pulmonary function (PF). These effects have been occurring at concentrations that are currently observed throughout the United States and at levels below the established National Ambient Air Quality Standards (NAAQS). Two thorough reviews of recent literature on the health effects associated with ozone (O_3) and particulate matter (PM) found enough evidence to call for a reduction of the NAAQS pollutant levels and provide a detailed discussion of the findings and limitations of the available body of literature (U.S. EPA 2004; U.S. EPA 2006).

Seminal air pollution and health studies such as the Harvard Six Cities study (Dockery et al. 1993), National Morbidity, Mortality, and Air Pollution Study (NMMAPS - Samet et al. 2000a,b), American Cancer Society Study (Pope et al. 1995), and 95 cities study (Bell et al. 2004) have shown that air pollution in the form of O_3, PM, sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and aerosol acidity is associated with premature death. The Six Cities Study and the American Cancer Society Study have withstood detailed reanalysis which concluded that

both studies used high quality data and that the findings were actually more robust than originally reported (Health Effects Institute 2000).

The Harvard Six Cities study (Dockery et al., 1993) used a survival analysis modeling approach to determine that mortality in six different cities across the United States (U.S.) was related to the levels of coarse particulates (PM_{10}), fine particulates ($PM_{2.5}$), SO_2, NO_2, and aerosol acidity. Ozone was the only criteria pollutant not associated with mortality, but probably because there was little difference in O_3 concentrations between the six cities and the Cox-Proportional Hazard model includes background pollutant levels for each city as an indicator variable only. The six cities study has withstood criticism and subsequent reanalysis with only slight modification of the results (Health Effects Institute, 2000; Krewski et al., 2003).

The American Cancer Society study (Pope et al. 1995) tracked over 500,000 participants in a prospective study of mortality associated with sulfate ($SO_4^=$) and $PM_{2.5}$ in 151 different urban centers. Sulfate and $PM_{2.5}$ were significantly (α=0.05) associated with increases in risk of mortality although the effects were small as compared to risk from cigarette-smoking. This study is important and unique as it was a large scale prospective mortality study with the ability to control and assess individual risk factors and robust to other potentially correlated pollutants because it was conducted across many locations.

Using mortality and air quality data from 90 cities across the U.S. the National Morbidity, Mortality, and Air Pollution Study (NMMAPS; Samet et al., 2000a,b) found that a 10 $\mu g/m^3$ increase in PM_{10} resulted in a roughly 0.5%

increase in deaths the following day. Using similar methods, but with an updated data set comprising 95 cities across the U.S., Bell et al. (2004) found that a 10 ppb increase in the previous week's O_3 led to a 0.52% increase in total daily mortality, and a 0.64% increase in cardiovascular and respiratory mortality. The Samet (2000a,b) and Bell (2004) results were robust to climate and other pollution because the study area encompassed such a wide variety of climate types and the multiple pollutant models showed little confounding from other pollutants.

Criteria air pollutants and acid aerosols have also been associated with increases in hospital utilization for asthma, chronic obstructive pulmonary disease (COPD), and for cardiopulmonary diagnoses in many regions of the world (e.g. Lipfert 1993; Wilson et al., 2004 and references therein). These mortality, morbidity, and hospitalization studies focus on the most severe health effects associated with air pollution and have been instrumental in determining the NAAQS. While mortality and hospitalization are the most severe health outcomes, they represent less than 0.2% of the adverse impact cases associated with air pollution (Thurston et al. 1997a). The remaining 99.8% of adverse impacts are made up by less severe outcomes such as lost productivity, asthma attacks, school absences, and respiratory symptom days.

Understanding these less severe outcomes has proven difficult because the data is not collected on a routine basis. As a result, studies that focus on these adverse health effects must collect data on a group of individuals, which is resource intensive and requires the use of many statistical controls. This

approach has manifested itself in a variety of applied research methods that makes comparing results and finding common themes between studies complicated. The necessity of choosing a study population to track, the health outcomes to measure, the air pollutants of concern, and the type of statistical analysis has created several different study designs. Furthermore, the individual's behavior, such as exercising and the amount of time spent outdoors, affects personal exposures and can substantially alter the interpretation off the data. Because of these intricacies, even studies with the broadest scope provide relatively narrow insights, making it difficult to generalize effects to the population level.

Such studies typically analyze for the effects of a single pollutant on one specific health effect within a specific demographic. They often use either a short-term or a long-term study design in a single population center. While these methods allow researchers to focus their results, adverse effects are likely to stem from a combination of short- and long-term exposures and have additive or multiplicative effects resulting from more than one pollutant.

Within these study designs, many factors must be corrected for before calculating accurate effect estimates. Adverse health effects are often correlated with the day of the study, especially in studies of growing children. Because collecting point specific exposure measurements is cost prohibitive, most studies of the effects of outdoor air pollution ignore a subject's personal exposure to indoor air or to specific outdoor exposures such as being adjacent to a roadway (Kim et al., 2004).

As less severe respiratory health effects are investigated the results become sensitive to the study design, the cohort, and statistical methods. Disagreement in the literature is common with respect to the details within methods, results, and conclusions. Although there may be disagreement in the details, there is a consensus that even low levels of air pollution are harmful to human health.

The wide range of study designs, cohorts, and statistical analyses in the literature makes results difficult to compare across studies. The study design and context are critical in determining the comparability of studies. This literature review has been structured to first discuss the basic design and major findings of each study and then, where appropriate, to make comparisons among studies. The findings are then discussed together within subjects of relevance for future research. The studies reviewed here are representative of the literature focused on air pollution effects on pulmonary function and have been chosen either for the importance or uniqueness of their results and study design, or because they significantly influenced the design and interpretation of subsequent research.

Basic Study Design and Major Findings

Ward and Ayres (2004) systematically reviewed 22 PM, pulmonary function (PF), and respiratory symptom time-series studies from around the world. They found that PM is associated with small (probably clinically insignificant) decreases in PF, and increases in symptom prevalence (cough and lower respiratory symptoms) with fine particles with diameter < 2.5 μm ($PM_{2.5}$) having

more of an effect than coarse particles with diameter < 10 μm (PM_{10}). More than 50% of reported results for cough and lower respiratory symptoms were found to be statistically insignificant. The effects of PM were found to be more prominent in studies with higher average levels of O_3 and studies that incorporated random effects within the model typically had larger parameter estimates. Signs of publication bias were also found among the studies where only the most significant adverse health effect estimates were reported.

Using a cross-sectional study design Peters et al. (1999) found relatively clear differences between males and females for changes in PF associated with long-term exposures to both PM and O_3. They observed negative effects in female PF from all pollutants considered in the model, but only some were significant. Negative parameter estimates were observed for all pollutants on Forced Vital Capacity (FVC) and Forced Expiratory Volume in the First Second (FEV_1), but only O_3 and acid vapor had negative parameter estimates for PEFR and Mid Maximal Expiratory Flow (MMEF). Conversely, most of the parameter estimates for male PF were positive, only some of which were significant. The only factor that altered the effects in males was time spent outdoors, where males spending less time outdoors only had negative parameter estimates for the FVC-NO_2 relationship, and the MMEF-PM_{10} relationship. An IQR increase in O_3 of 40 ppb in 1986-1990 resulted in a 94.2 l/min decline in PEFR measurements taken in 1993 in the whole population, and 187.2 l/min decline in just females (although the parameter estimate was positive for males). In general, these findings contradict Mortimer et al. (2000), where boys were found

to be more sensitive to O_3 than girls, although the differences were not consistent across different health measures.

Neas et al. (1995) measured the PEFR of 83 non-medicated child asthmatics twice daily to determine the effects of acid particles, PM_{10}, $PM_{2.5}$, and O_3 on PEFR and symptoms over the course of the summer in Pennsylvania. Full spirometry tests were performed occasionally, and participants measured PEFR on their own with a Mini-Wright mechanical peak flow meter. They found that an interquartile (IQR) increase of 125-nmol/m^3 (12-hour exposure) in same day particle strong acidity resulted in a 2.5 l/min decrease in group mean PEFR whereas an IQR increase of 30 ppb O_3 (previous 12 hours) caused a 2.8 l/min PEFR decrease. The FEV_1 and FVC measurements were taken only during the full spirometry tests and correlations between them and air quality were not reported. Effects were more severe in children with a history of wheezing or coughing compared to those without.

Pope and Dockery (1992) investigated the effect of coarse particles on the PEFR and respiratory symptoms of 79 symptomatic and asymptomatic asthmatic children using a distributed lag time-series model. They found symptoms to be more strongly correlated with coarse particles than was PEFR, and that the symptomatic children were consistently more sensitive. Some individual participants had more than twice the variability of the group mean PEFR on given days, suggesting strong inter-subject variability in sensitivity.

Romieu et al. (1997) investigated the relationship between PEFR, respiratory symptoms, and O_3 in asthmatic children in heavily polluted Mexico

City by using a combined time-series and cross-sectional study design. Maximum 1 hour O_3 was 390 ppb and on 88.5% of the study days it exceeded 110 ppb. The air pollution levels in Mexico City during this study were extremely high and not representative of most North American cities. They found that an increase of 50 ppb in daily 1h max O_3 resulted in a 1.81 l/minute decrease in PEFR. Children in Mexico City did not respond as strongly to O_3 as compared to children from studies on the east coast of the U.S. (Neas et al. 1995). The authors hypothesize that this is due to enhancement from exposure to acid aerosols in the eastern U.S., or to increased tolerance to high O_3 in Mexico City, or both. In order to normalize the PEFR distributions, the daily scores were standardized to z-scores. This method does not allow for inter-subject variability because it converts means for all subjects to 0 and standard deviations to 1. This approach is counter intuitive as individuals can have different PF variability from each other brought on by differences in sensitivity, different personal exposures, or different measurement techniques (Kinney and Lippmann, 2000; Pope and Dockery,1992), although the effect estimate trends should be the same, the effect estimate sizes are probably less accurate.

Vedal et al. (1998) investigated whether or not children with asthma are more susceptible to PM_{10} compared to non-asthmatic children by using a time series analysis of daily PF and symptom data. A unique aspect of this study is that they tracked all of the children with physician diagnosed asthma, and all of the children with an exercise induced decrease in FEV_1 in the community, as well as an additional control group. They had a large sample of about 70

measurements per day for a span of roughly 600 days with a few large breaks in the data. The final analysis shows that an increase in 1-4 day lagged PM_{10} of 10 $\mu g/m^3$ over the mean (27.3 $\mu g/m^3$) results in a 0.55 l/min decline in PEFR in diagnosed asthmatics, but there were no significant effects in the other subgroups. No significant differences in effects were found when stratifying by respiratory medication use. They also found that increasing model complexity from basic ordinary least squares regression with group averages calculated for each day to a generalized estimating equation (GEE) based model that uses individual level data and accounts for random effects and autocorrelation improves the standard error of the estimates, but reduced the effect estimates themselves.

Delfino et al. (2004) investigated FEV_1 and exposure estimates as measured at a central site, just outside the home, and at the personal level. Because the resources necessary to collect such detailed data were extremely high, the cohort consisted of 19 participants (tracked 3 at a time) who measured their own FEV_1 each morning, noon, and night over two weeks. The central site $PM_{2.5}$ was significantly associated with declines in FEV_1. However, the estimates were not as significant as when the personal PM monitoring estimates were used. An IQR increase in personal exposure of 40$\mu g/m^3$ resulted in a maximum effect of 11% to 33% decline in FEV_1.

Kinney and Lippmann (2000) measured the PF and symptoms of cadets before and after a summer of training at 4 different locations with varying levels of O_3. Participant's PF declined over the course of the summer for 3 of the 4

study sites, with the sites showing the highest average summer time O_3 also having the largest decrease in PF. Overall group mean FEV_1 decreased 1% over the course of the summer, but 10% of the individuals had variation at least 6 times greater than this. Ozone was the only pollutant used in the analyses, and the authors suggest that the decreases were likely caused by O_3 after accounting for second hand cigarette smoke and dust exposures marked in recall questionnaires filled out at the end of the study. Possible other drivers of the decline could be unspecified allergies, indoor environmental condition changes, or temperature. Since there are only two data points it was not possible to distinguish if the decline was caused by constant reduction over the course of the summer, or from an acute PF reduction (increase) event at the end (start) of the summer.

Korrick et al. (1998) measured the FEV_1, FVC, MMEF, and PEFR of adult hikers on Mt. Washington, NH during summer 1991 and 1992 before and after hiking. For a 50 ppb increase in O_3, declines of 2.6% and 2.2% were observed in FEV_1 and FVC respectively. Forced vital capacity and PEFR were also correlated with increases in $PM_{2.5}$ and aerosol strong acidity. Hikers with asthma suffered up to four times more reduction in FEV_1, and roughly twice more reduction in FVC than otherwise healthy participants. These estimates are consistent with other studies which examine exercising subjects (Brunekreef et al., 1994; Spektor et al., 1998), but somewhat higher than studies not focusing on exercise. The number of hours hiked was correlated with PF declines suggesting

that exercising for a sustained period even during relatively low O_3 exposures (~40 ppb) is harmful.

Ostro et al. (2001) used generalized estimating equations to determine the effects of O_3, NO_2, PM_{10}, $PM_{2.5}$, and the fungi *Alternaria*, and *Cladosporium* on African-American asthmatic children in Los Angeles and Pasadena, CA. The authors mention collecting PEFR data, but there are no results presented in the paper. Symptom prevalence and onset were related to PM_{10}, $PM_{2.5}$, NO_2, and the fungi species but no significant associations were found with O_3.

Delfino et al. (1998) tracked the respiratory symptoms of 25 asthmatics in southern California over the course of August to October for a total of 1759 observation days in order to identify sensitive subgroups and also to find the most appropriate particulate averaging times. Generalized estimating equations were used to account for intra-subject variability with a first order autoregressive structure included. They measured hourly temperature, relative humidity (RH), wind speed, pollen, fungal spores, PM_{10}, and O_3. Current day O_3 affected the less symptomatic subjects. More symptomatic subjects were less affected by 5-day PM_{10} although the effects were about half that for the less symptomatic subjects. Less symptomatic subjects not on maintenance medications were more susceptible to PM and O_3, suggesting that daily medications are protective. No large effects were seen in the medicated group. They found that the dose response relationship for O_3 was linear for some subjects, but there were thresholds in other subjects. They suggest that more symptomatic subjects had

little response to O_3 because they were avoiding the outdoors more than less symptomatic subjects.

Mortimer et al. (2000) investigated the sensitivity of asthmatic subpopulations to O_3 by combining a cross-sectional and time-series analysis of 846 inner city asthmatic children from multiple cities in the eastern U.S. By having parents record the daily symptoms and PEFR of their children for 2 weeks during the summer they found that asthmatic children born premature, or with low birth weight, were significantly more susceptible to reductions in PEFR when exposed to O_3 (-1.8% vs. 0.3% per 15 ppb increase in O_3, both significant at α=0.5) than those asthmatics born on time with normal birth weight. They also report confounding of this result by medication use as normal birth weight participants taking medication were more susceptible to O_3. However, in the low birth weight group the results were opposite, suggesting that medication use is protective of PEFR. Atopic children showed their PEFR reductions to be triggered by their respective allergy, while non-atopic children were triggered by other factors including air pollution, suggesting that allergic response plays a role in determining sensitivity to O_3.

Gielen et al. (1997) collected PEFR and symptom measures from 61 asthmatic children for about 12 weeks in Europe along with atmospheric measures of PM_{10}, O_3, black smoke (BS), temperature, and pollen. Group averages were used in the analysis and they grouped nose and throat symptoms as Upper Respiratory Symptoms (URS), and Shortness of Breath (SOB) and wheeze as Lower Respiratory Symptoms (LRS). The strongest associations for

PEFR were with 2 day lagged O_3, 2-day lag and 5-day mean BS, but there were no significant associations with PM_{10}. The URS were associated with current day O_3 and 5-day mean BS while LRS were associated with 5 day mean PM_{10} and 5-day mean BS. Five day black smoke was also associated with itchy watery eyes, nighttime wakening, and bronchodilator use. Compared to results from other studies, these subjects (severe asthmatics) were found to be more affected by PM and black smoke suggesting that severe asthmatics and asthmatics taking respiratory medications are more sensitive than otherwise healthy people or less symptomatic asthmatics.

Thurston et al. (1997b) tracked PEFR and symptoms in 166 moderate to severely asthmatic children in groups of ~55 for one week each year during 1991-1993 while tracking O_3, $SO_4^=$ particles, and H^+ content of aerosols (aerosol strong acidity), temperature, pollen, and RH. An increase in O_3 from 84 ppb (mean) to the maximum 160 ppb was associated with a large increase in relative risk of chest symptoms (40%). Ozone was found to be most consistently and most strongly associated with daytime change in PEFR (PM – AM PEFR), although $SO_4^=$ and H^+ were both correlated as well. A comparison of group-day-mean and individual-day versus health effects show little difference in parameter estimates and significance levels in the analysis. This suggests that a simpler group-day-mean analysis may be appropriate in studies of this type where all measurements are conducted at a single site. Participants in this study were moderate to severe asthmatics and did not exercise during the study period and the observed health effects were roughly half of those found in studies of

exercising asthmatic children. The results suggest that exercise has an important role in amplifying the adverse health effects of air pollution and is likely related to the increase in exposure associated with increased activity.

Jalaludin et al. (2000) measured twice daily PEFR and daily respiratory symptoms of 148 children with a history of wheeze for 11 months while tracking O_3, PM_{10}, NO_2, temperature, RH, and pollen in Australia. This is the largest pulmonary function tracking study to date with 31,209 child-days. They used over-fit models that corrected for time trend, temperature, humidity, pollen count, number of hours spent outdoors, season, PM_{10} and NO_2. Although there was no discussion of confounding or effect estimate stability, they mention that O_3 and PM measures were uncorrelated in the area. There was no mention of how time spent outdoors altered the pollution effect estimates. They found that GEE models were more likely to give negative parameter estimates as compared to group-average regression models. This suggests that using the individual-day rather than the group average-day unit of observation can change model results. There was a linear relationship between a quasi-measure of asthma severity (three stratifications of the group were made based on history of wheeze and asthma diagnosis) and O_3. The least severe asthmatics actually had a positive relationship with O_3 which is surprising considering that they are still in fact asthmatics with a history of wheezing. A 40 ppb increase in mean daily O_3 resulted in PEFR declines of ~1% for all children in the study and a ~4% decline for the most severe asthmatics in PEFR. The elevated O_3 also resulted in a 20% increase in the number of individuals at least 20% below the median PEFR. This

suggests that small shifts in the mean PF can lead to large changes in individual PF.

Linear Trend for Time, Meteorology, and Multi-collinearity

Linear trends for time, temperature, RH, and covariance among the various atmospheric variables are all factors that have been considered in the analysis of the acute health effects of air quality. The extent to which studies have included these factors depends on their cohort, length of study, and the variables available for analysis. Delfino et al. (2004) found no confounding of personal PM (measure roughly equal to $PM_{2.5}$) parameter estimates from personal air temperature or personal RH measurements. Delfino et al. (1998) designated a climate variable to be confounding of the relationship between the pollutant and health effect when it is related to at least a 15% change in the parameter estimate. They found no confounding from temperature, RH, or wind speed with parameter effect estimates under these criteria. Ostro et al. (2001) included 1-day lags of temperature and RH in their models (fit before pollutants are added) but they do not explain if these covariates actually add strength to the final model (pollutants were later included as various lags and averages). Delfino et al. (1997) found that higher temperatures reduced the effects of pollutants on asthma symptoms, PEFR, and β-agonist inhaler use, but probably because participants remained indoors with increased air conditioning use. Romieu et al. (1997) adjusted for minimum temperature because it was significantly associated with PEFR.

Vedal et al. (1998) found that adding a linear term for day of study as a covariate halved the parameter estimate for the effect of PM_{10} on PEFR, and then reduced it by one-third again when meteorology was added to the model. Vedal's study of the growing children spanned up to 600 days and a linear trend for time was needed to correct for the significant growth in the children's lung volume and function. The respiratory symptoms were less affected than PEFR by adding a linear trend for time which is logical considering that symptoms are not generally a function of lung size or function. Adding a linear trend for time increased the parameter estimates for nose symptoms but not to the extent that it did for PEFR. Adding meteorology and time trend reduced the parameter estimates for some symptoms but increased the estimates for others. First, this suggests that symptom prevalence may be a more suitable and ultimately simpler measure to use for assessing the effect of air pollution on growing children. Second, it seems reasonable that a linear trend for time should always be included in lengthy studies when examining PF in growing children; if a growth trend is not apparent over time it should at least be explained.

Thurston et al. (1997b) found that change in PEFR during the day was significantly negatively correlated with maximum daily temperature (although not as strongly as with O_3). Given that the correlation between temperature and O_3 was high (r=0.7), and that the temperature and PEFR relationship was the opposite sign of what was expected, it is more likely that O_3 was dominating the relationship. Adding temperature to the model typically reduced the parameter estimates and significance of all of the pollutants considerably. First order

autocorrelation was not strong, although the study only lasted for one week during each of the study years.

Jalaludin et al. (2000) included linear trend for time, time spent outdoors, pollution, meteorology, pollen, and *Alternaria* (mold) in all model analyses. Rather than adjust the covariates included in the model by refining model fit statistics, the authors opted to include all covariates that seemed logical to include. A linear trend for time was included in the model to account for PF growth in the children as the study ran for 11 months and data were collected from growing children. Temperature and season were included in models to adjust for long-term cyclical variations although their significance in the model is not discussed. Ozone was significantly correlated with other atmospheric variables in the model which increases the likelihood of unstable parameter estimates.

Copollutant models

The literature is mixed on whether or not copollutant models strengthen or detract from parameter estimates and their significance. The U.S. EPA's Air Quality Criteria for Ozone and Related Photochemical Oxidants (U.S. EPA 2004; U.S. EPA 2006) provides a literature review of copollutant models and their limitations, definitions of confounders vs. effect modifiers, and common techniques used to assess error and uncertainty caused by multicollinearity.

Multicollinearity between pollutants in models makes it difficult to determine how effects are distributed between the pollutants. One approach to

resolve the issue is to ensure that it is biologically plausible for the pollutant to cause such an observed response. This can be done by reviewing toxicology literature. If the response observed is not biologically plausible then it is not likely that the response is from that measure, even though it may be significant. When multicollinearity is present and the response is biologically plausible for both pollutants, such as between O_3 and $PM_{2.5}$, it becomes more difficult to assess the effect distribution.

The EPA's O_3 and PM criteria review documents also provide suggestions for addressing multicollinearity and confounding issues between pollutants in multivariate statistical models. They suggest to first run single pollutant models and then include the confounding pollutants and examine the extent to which the effect changes. If large changes in the effects are seen it is possible that multicollinearity is a serious issue. When data are available from multiple locations, the relationships between the effect size of the pollutant as compared to the effect size of the copollutant should be explored. If a relationship is observed then confounding is probably occurring.

Delfino et al. (2004) found that the relationship between personal PM and reductions in FEV_1 were not confounded by central site O_3 exposure estimates. In earlier research Delfino et al. (1998) found significant effects from both O_3 and PM_{10}, but there was no noticeable change in effects when O_3 was added to the PM_{10} model or vice-versa. Ozone had significant effects on asthma symptom severity and was also robust of PM_{10}. However, Korrick et al. (1998) found that $PM_{2.5}$ and aerosol strong acidity parameter estimates became insignificant to

PEFR, FEV_1, and FVC after O_3 was added to the model; this is in agreement with Neas et al. (1995), but contrary to Delfino et al. (2004). Gent et al. (2003) finds that only O_3 is associated with increased symptom prevalence in medicated asthmatic children and when $PM_{2.5}$ is included in the model the parameter estimate for O_3 becomes stronger and more significant. Both Pope and Dockery (1992) and Ostro et al. (2001) collected health data over winter months when O_3 is generally at lower levels and therefore they did not include it O_3 in their models. It is unknown if O_3 was correlated with the health measures, PM measures, or even if there were any winter O_3 events.

It is likely that enhancing model fit by using multi-pollutant models is dependant on the level of exposures for each pollutant, the composition of the PM, and the composition of the cohort. For example, PM may be more damaging if O_3 is at high but not low concentrations, whereas O_3 may be more damaging if there is also a simultaneous particulate event that has high levels of a certain heavy metal or other toxins. It is also possible that these effects vary over different types of populations such as between asthmatics and nonasthmatics.

Jalaludin et al. (2000) included PM_{10} and NO_2 in their models focusing on the effects of O_3 on PEFR and found that they did not contribute significantly to the model as the effects of O_3 remained largely unchanged when they were included. There were significant correlations between O_3, PM_{10}, and NO_2 which may have confounded the analysis.

It is difficult or sometimes impossible to calculate the partial health effect from a specific pollutant in multiple pollutant models when the pollutants are often correlated and the exposures simultaneous. Air pollution events typically contain multiple types of pollutants and multicollinearity of pollutants will always be an issue. The U.S. EPA report of Air Quality Criteria for Particulate Matter (2004) report (and references therein) suggests using biological plausibility from toxicology research to support the results from multiple pollutant models.

Exposure times in models

Delfino et al. (2004), Delfino et al. (1998), and Pope and Dockery (1997) found that the strongest health effects from PM were observed using a 5 day moving average. Delfino et al. (2004) found no short-term effects from PM exposures in the 2-hours preceding the measurement and Pope and Dockery (1992) found lower level and less significant effects coming from same day exposures. Vedal et al. (1998) found that a 4 day cumulative measure was the most significant exposure time variable found in the models, although effects were seen out to 1 week prior for group estimates, and out to 2 weeks for some individuals. Ostro et al. (2001) found that 2-3 day lags, plus up to 4 day moving averages of both $PM_{2.5}$ and PM_{10} daily maximums were associated with respiratory symptoms (shortness of breath, cough, and wheeze) while shorter lags were not associated. Neas et al. (1995) found that particle-strong acidity was not associated with PEFR over 1-4 day lags, but was for 3 and 5 day averages and same day measurements. Mortimer et al. (2000) found that the 3-

5 day prior average O_3 exposure was found to be the most important air quality parameter in determining PEFR. Delfino et al. (1998) found that 24 hour average PM_{10} was less significant than 1hr and 8hr averaging times for all cumulative, lagged, and multi-day averaging times. Also, 5 day moving average effects were larger than for current day effects for 24hr and 8hr averages, but not for 1hr and the results were robust to changing O_3. These results suggest that PM has an inflammatory effect on PF and symptoms, that cumulative exposures are more important, or that response timing in individuals is variable (Ostro et al., 2004; Pope and Dockery, 1992).

Jalaludin et al. (2000) found that same day mean O_3 was most significant in multi-pollutant models of the effects of O_3 on PEFR; however, maximum daily O_3 was also significant but with a smaller effect. No significant negative parameter estimates were found for lags of up to 4-days and means up to 5-days.

Indoor air quality

Delfino et al. (2004) found that an IQR increase in personal PM of 53.7 $\mu g/m^3$ had effects ranging from 4% to 22% declines in FEV_1 in individuals. The parameter estimates for central site PM_{10} measurements were much smaller. The personal PM monitors showed roughly twice the exposure during daytime hours compared to night-time whereas the central site PM_{10} showed 1.5 times more during the daytime, indicating that personal exposure concentrations show stronger diurnal. This is logical considering the strong daytime sources of

particles indoors from cooking, smoking, vacuuming etc (Wallace et al., 2003). Delfino et al. (2004) found that the correlation between central-site and personal PM had a Spearman's rank coefficient of 0.39 which is relatively low and indicates that central-site PM monitors do not provide an accurate measure of personal exposures in PF studies. Correlations between PM_{10} monitors inside, and just outside the home had coefficients of 0.74, suggesting that focused outdoor PM_{10} monitoring is better suited than a central-site monitor for estimating indoor PM_{10} exposures in specific settings. Indoor PM_{10} was found to be greater than PM_{10} measured just outside the home, which was in turn greater than central site PM_{10} measurements. This suggests that there is considerable spatial variability in PM_{10} as well as a significant local and indoor source of particles that elevate PM_{10} concentrations above what central site monitors measure.

Delfino et al. (1997) found that participants spending more time indoors reduced O_3 exposure and subjects preferentially remain indoors during hot weather. Presumably, aeroallergen exposures were reduced as well via filtration from air conditioner use. Personal exposure to O_3 is generally lower than O_3 exposure estimates derived from outdoor measurements as O_3 is commonly attenuated as it passes to indoor environments via reaction on filter surfaces and reduced photochemical production. If health effects can be related with outdoor central site measures of O_3, then it is reasonable to assume that actual personal exposure to O_3 was somewhat less, and therefore the parameter estimates of the central site O_3 and health effect relationship is artificially deflated. This may be important as personal exposures have been observed at less than 1/3 of what

central-site measures suggest (Delfino et al., 1996; Delfino et al., 2004). This scenario is reversed for the central site vs. personal PM and health effect relationship as personal PM exposure estimates tend to be higher than central site PM exposure estimates. Strategies to reduce personal exposure to both PM and O_3 should take into account that personal exposures for PM are higher than central site exposure estimates while personal O_3 exposures are typically less than central site measures.

The by-products of outdoor air pollution reacting with indoor air and surfaces creates an endless possibility for acute personal exposures. Weschler (2004a,b) provides a review of recent literature regarding indoor air quality, the difficulties in measuring it, and the indoor products of reactions involving pollution from outdoor sources, much of which is unknown. They even suggest since the amount of time spent indoors is considerable, the indoor products of ozone initiated reactions may be more important than O_3 itself. Weschler (2000) reviewed studies that examined indoor to outdoor ratios of O_3 in various locations, urban settings, and building types and found that indoor O_3 was typically between 30% and 70% of outdoor values, overall range of 10% to 80% and the factor that determined indoor O_3 most was room ventilation rate.

Indoor exposures to chemical and particulate pollution are important considering the amount of time many individuals spend indoors. However, it is often resource prohibitive to conduct large scale panel studies of direct measures of personal exposures and human health. It was only possible for Delfino et al.

(2004) to conduct measurements on 3 subjects simultaneously for 2 weeks at a time.

Aeroallergens

Yet another family of variables which has been studied in relation to pulmonary function are airborne allergens which are both particulates and biologically active. In a study of 22 asthmatic subjects followed for 8 weeks, Delfino et al. (1997) found that higher temperatures reduced the negative effects of aeroallergens. This was attributed to air conditioning which reduced allergen levels. Fungus was associated with reductions in PEFR and increases in asthma symptom severity and rescue medication use. Specifically, *Alternaria*, basidiospores, and hyphal fragments had even greater effects, especially in the 16 subjects that presented as allergic to deuteromycete fungi. Neither total pollen or speciated pollen was associated with symptoms or PEFR. No associations were found between O_3 and health outcomes; however, PM_{10} was associated with inhaler use. Moderate correlations were found between PM_{10}, O_3, and total pollen. Delfino et al. (1997) results are similar to the Delfino et al. (1996) results, except in 1996 O_3 was found to be associated with all three health outcomes. The differences were attributed to sample size, cohort, geographical, and seasonal factors. The authors call for more similar studies in different areas for generalizations to be made. Jalaludin et al. (2000) found no significant associations between PEFR and total pollen or *Alternaria*, but they left the parameters in the model of O_3 and PEFR anyways.

Gielen et al. (1997) collected pollen measurements for their analysis, but only grass pollen was used because other pollen species were not active during the study time and 52% of the children reported grass atopy. They found pollen and temperature to be highly correlated (r=0.71) so they adjusted only for grass pollen in the analysis but the effects of adding it into the model were not provided, and no specific models were run to assess the effects of grass pollen alone.

Knox et al. (1997) found that diesel particles can adhere to pollen grains, and in turn allergic starches derived from grass pollens can adhere to $PM_{2.5}$ diesel particulates. This provides a pathway for allergens to be concentrated and combined with particulates during pollution events and thus potentially raise the adverse effect on human health. Parnia et al. (2002) provides a review of the pathways by which different types of pollution could cause allergic sensitization and development of asthma, including direct absorbance of allergic starches on PM, or attachment of PM to larger pollen grains (Knox et al., 1997; Ormstad et al., 1998). This provides a mechanism for allergens to become concentrated during pollution events.

Ziska et al. (2003) show that ragweed grew significantly more biomass, bloomed earlier in the season, and produced more pollen when growing in an urban environment with more CO_2 and higher temperatures than a rural climate. This suggests that the well documented global increases in atmospheric CO_2 and temperature associated with climate change will increase the amount of ragweed and change its seasonality. Wayne et al. (2002) shows that ragweed pollen

production is increased in CO_2 rich environments and Freye et al. (2001) found that the pollen and mold season was markedly different in the Northeast U.S. during 1998, a strong El Nino year. This may suggest increases in CO_2 and shifts in the El Nino – La Nina Pacific cycles caused by climate change could affect the nature of allergens in the Northeast U.S. on a seasonal basis.

Discussion

Long-term exposures to pollutants have been associated with increased risk of asthma diagnosis, reduced lung function, reduced lung function growth, and increases in the frequency of respiratory symptoms (McConnell et al., 2002; Gauderman et al., 2004; Frischer et al., 1999; Galizia et al., 1999; Kopp et al., 2000). Reduced PF has also been associated with elevated O_3 and PM exposures over the course of one summer (Frischer et al., 1999; Kinney et al., 2000; Ihorst et al., 2004), although Ihorst et al. (2004) also found that lung function growth recovered over the course of 3.5 years.

The extremely high ambient concentrations of O_3 and coarse particulates (PM_{10}) observed in a Mexico City panel study were strongly associated with significant reductions in PF and increases respiratory symptoms (Romieu et al., 1996, and 1997). However these effect estimates were comparatively smaller than effects observed in less chronically polluted areas. This may suggest that these children were developing tolerances to high exposures, or that acid aerosols (which aren't generally present in Mexico City PM) may be an important aspect of the effect level of PM. Acidic aerosols were associated with declines in

PF and increases in symptoms in a variety of studies (e.g., Ostro et al., 1991; Neas et al., 1995; Korrick et al., 1998; Jedrychowski and Krzyzanowski 1989; Raizenne et al., 1989). Although health effects have been observed from coarse particulates (2.5-10 μm in diameter), fine particulates (less than 2.5 μm in diameter) are being investigated more frequently and thought to be even more important with regard to health effects (e.g., Schwartz and Neas 2000).

Health effects have also been observed at relatively low outdoor ambient air pollution levels. Vedal et al. (1998) found effects associated with PM_{10} remained even after excluding all observations when PM_{10} was >40 $\mu g/m^3$. Gent et al. (2003) found significant increases in respiratory symptoms associated with relatively low concentrations of O_3, but only in asthmatic participants who used maintenance medication. Geilen et al. (1997) also found increases in respiratory symptoms and medication use from O_3, black smoke, and PM_{10} at relatively low levels.

Longitudinal panel study designs, where each subject becomes their own control, have been used to control for inter-subject variability that is time invariant (e.g. Gent et al., 2004; Vedal et al., 1998; Jalaludin et al., 2000). This method allows the analysis to focus on factors that vary over time such as air quality, but some time-invariant factors such as an individual's sensitivity to air pollution or respiratory medication use can still limit the inference of the results. For example, Korrick et al. (1998) observed O_3 to affect asthmatic hikers nearly four times more than non-asthmatic hikers and Vedal et al. (1998) observed significant effects from PM_{10} only in the study's asthmatic population. Also, the

effects of air pollution have been found to become greater as the severity of asthma in the individual worsens (Jalaludin et al. 2000; Gielen et al. 1997; Pope and Dockery 1992). Among asthmatics, it is still not clear if maintenance medication is effective at desensitizing an individual to air pollution. Gielen et al. (1997) and Gent et al. (2003) found that asthmatics using maintenance medication (used as one measure of asthma severity) were more sensitized than asthmatics not on medication, while Delfino et al. (1998) found that medication users showed less sensitivity. These time-invariant factors need to be addressed either in the study design or in the statistical analysis before generalizing the results to a population.

It is difficult to accurately measure an individual's exposure given that individuals often move into different indoor and outdoor environments (e.g. home, office, outdoors, motor vehicles). Each of these environments can have very different levels of air pollution, such a bedroom versus kitchen, or a rural area versus urban center. To accurately measure an individual's exposure, high resolution (i.e. minute) air pollution measurements of the air they are breathing and their ventilation rate are required. Unfortunately, this requires significant resources. To work around this issue researchers often choose subjects that spend much of their time outdoors, such as those at summer camps. Selectively choosing subjects helps minimize confounding from indoor air and homogenizes the group's exposure, but again decreases the ability to generalize results to a broader population.

Including indoor air quality conditions significantly modifies the effect estimate from outdoor air pollution. Delfino et al. (2004) observed greater and more significant effects when using personal air quality measures from a monitor carried at all times by the subject as opposed to when using measures from central-site outdoor monitors. Ostro et al. (1991) used a rough estimate of the correlation between indoor and outdoor concentrations taken from the literature to weight exposures based on the time the participant was indoors and outdoors. This was only part of a more sophisticated exposure assessment technique and represents an improved method but assumes the relationship between indoor and outdoor air quality is linear, and the only pollution source is outdoors. Even though outdoor air pollution can infiltrate the indoors, concentrations can be quite different and correlations can be quite low. Given the low correlations (R^2~0.3) between central site monitors and personal measures reported by studies such as Delfino et al. (2004) and that strong indoor sources of particulates exist (e.g. Wallace et al. 2003), it is likely that measures of outdoor air pollution can not be used to accurately predict the exposure of individuals spending most of their time indoors.

Outdoor air pollution has repeatedly been found to cause decreases in group mean pulmonary function and increases in respiratory symptoms. The declines in group mean PF are typically small enough that they are of little clinical importance; however, it is often the case that small shifts in group mean PF translates to large shifts for individuals at the distribution extremes. It is still not clear if the lung function of individuals with asthma or COPD are more sensitive

to air pollution than those individuals without asthma or COPD. Although the results from the literature are mixed, the general trend is in the direction of increased sensitivity to air pollution among asthmatics. It is still unclear if sensitized individuals taking respiratory maintenance medication to reduce their sensitivity are still more sensitive to air pollution than non-sensitized individuals, or if the medication has reduced their sensitivity to levels below those of non-sensitized individuals.

Methods for choosing final statistical models to test hypotheses of the effects of air pollution on pulmonary function vary substantially. Final models are often multivariate with autoregressive structures and explain only a small amount of variance in the outcome variable. The effect of many different covariates are tested in the model in a stepwise fashion in order to determine if that variable increases the total explained variance (e.g. Vedal et al., 1998). Occasionally, covariates are included merely if it seems logical (e.g. Jalaludin et al., 2000).

With so many covariates (including calculated variations of the same covariate i.e. maximum *or* minimum daily temperature) to choose from, the probability of increased and incorrect explained variance is raised. More recent studies use model fit statistics that penalize for model complexity. However, these penalties only apply to the final model, and do not take into account the total number of model attempts or cumulative number of variables tested before the final model was selected. Both of these issues increase the chance of significant results occurring purely by chance.

Several studies have focused on the positive health effects observed after the air has been cleaned and give us a sense of what it could be like with a cleaner atmosphere. Pope et al. (1989) found that PM_{10} pollution was two times higher, and that respiratory hospital admissions for children were two to three times higher during a winter when the local steel mill in Utah was open rather than closed. During the summer Olympics in Atlanta Friedman et al. (2001) found O_3 and PM_{10} were reduced by 30% and 16% respectively and inner city traffic counts were reduced by 23% and public transportation was increased 216%,.that Medicaid and Kaiser HMO claims, pediatric emergency room visits, and hospital admissions were all reduced for asthma related visits but not for non-asthma related visits.

The literature reviewed here demonstrates that air pollution adversely affects human health on multiple levels across almost all demographics. From large scale studies on mortality to small scale studies on symptoms, adverse health effects associated with air pollution are consistently observed. The largest remaining question is at what concentration does mixed outdoor air pollution start affecting human health. Other remaining questions revolve around how to measure single pollutant and mixed pollutant exposures accurately on the personal level, including how to separate effects associated with personal exposures from effects associated with outdoor exposures, how to classify personal characteristics, and how to measure the behavior of the individual.

CHAPTER II

METHODS

Study Overview

As part of the International Consortium for Atmospheric Research on Transport and Transformation (Fehnsenfeld et al., 2006) project during summer 2004, the University of New Hampshire (UNH) Integrated Human Health and Air Quality (INHALE) project (http://inhale.unh.edu) collected daily health effects data from participants across New England. The research was focused on better understanding the link between air quality and human health by forming a high spatial and temporal resolution health effects database to complement the measurements made during ICARTT.

The participants were recruited, asked to complete a release form and a vital-statistic survey, given a handheld electronic spirometer and a symptom questionnaire booklet, and then trained how to use the equipment. Follow up visits were conducted throughout the summer to download data from the spirometers and to collect and distribute additional symptom questionnaire booklets.

The participant's exposure to air quality and meteorological variables were calculated using the monitoring sites closest to their home. Analyses were performed using mixed linear models and took into consideration linear trends for time in the PF data and autoregressive error structures.

Data collection

Cohort Identification. Participants were identified from the INHALE project range of stakeholders comprising businesses, state agencies, and other groups that had expressed an interest in air quality and health. The 13 sites (Figure 2-1; Table 2-1) were chosen based upon their population demographics, proximity to criteria air pollutant monitoring stations, and local interest in the project.

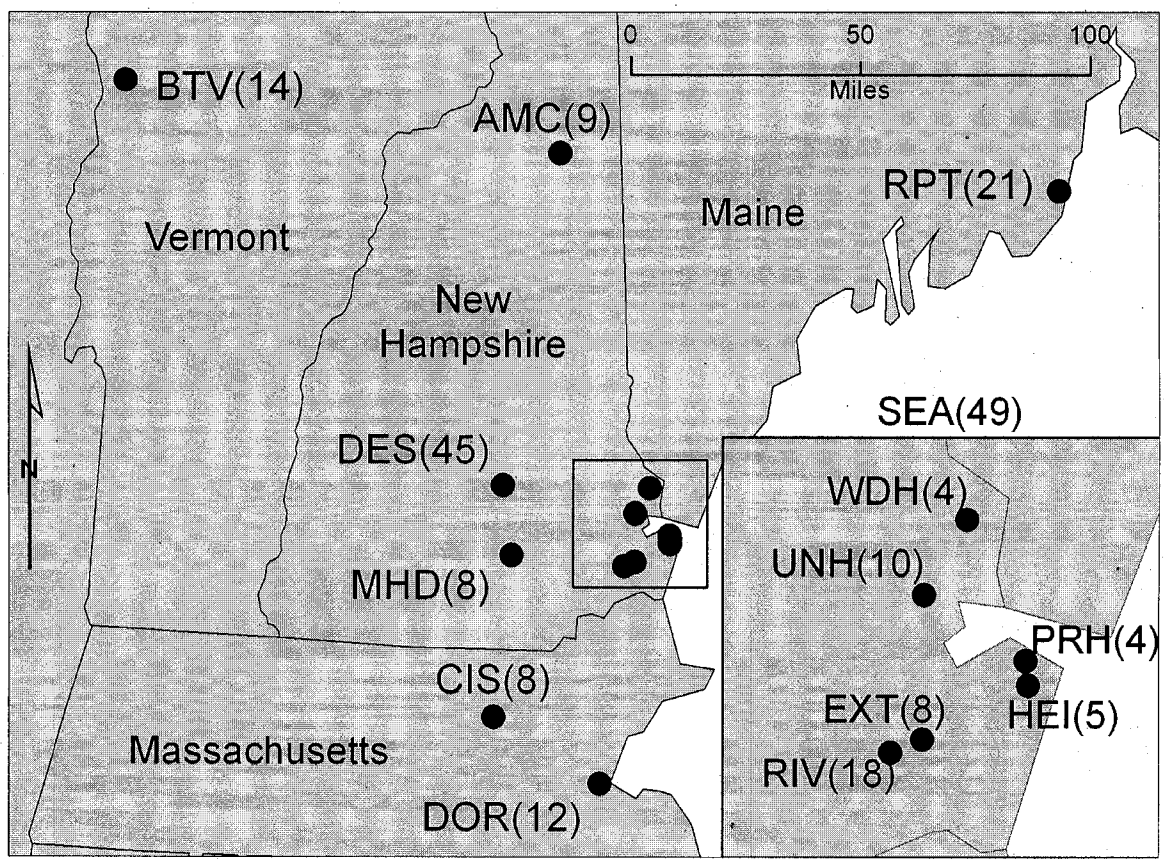

Figure 2-1. Health tracking locations in New England for our study and the number of participants at each location.

Table 2-1. Study population description for each study location.

Site	Location	Description
DES	Concord, NH	NH Department of Environmental Services employees
SEA	Seacoast, NH	
	Durham, NH	University of New Hampshire employees and students (UNH)
	Exeter, NH	Riverwoods retirement community (RIV)
	Portsmouth, NH	New Heights day camp (HEI)
	Dover, NH	Wentworth Douglas Hospital (WDH)
	Portsmouth, NH	Portsmouth Regional Hospital (PRH)
	Exeter, NH	Exeter Hospital employees (EXT)
RPT	Rockport, ME	Penobscot Bay Medical Center Asthma and COPD
AMC	Gorham, NH	Appalachian Mountain Club trail workers
BTV	Burlington, VT	University of Vermont students
CIS	Boxboro, MA	CISCO Systems employees
DOR	Dorchester, MA	John Snow Institute, Dorchester House teens
MHD	Manchester, NH	Manchester Health Department employees

We focused on similar demographic participants within locations. Sites with mostly working age Caucasian participants characterized the Department of Environmental Services (DES), CISCO (CIS) Systems, Burlington, VT (BTV), Wentworth Douglas Hospital (WDH), Portsmouth Regional Hospital (PRH), Exeter Hospital (EXT), University of New Hampshire (UNH), and the Manchester Health Department (MHD) sites. Rockport, ME participants (RPT) were mostly elderly with a history of severe asthma or COPD. The Appalachian Mount Club (AMC) site consisted of trail maintenance crews who were continually hiking the trails in and around the White Mountain National Forest in New Hampshire. The participants at Riverwoods Retirement Community (RIV) in Exeter, NH were mostly elderly. The New Heights (HEI) participants were mostly teenage Caucasians while the Dorchester, MA (DOR) participants were mostly African American and Hispanic teenagers.

We recruited as many participants as were interested in and capable of performing the measurements regardless of health status because we wanted to collect data from a diverse cross section of the public, including participants with asthma and COPD.

The only study entry restriction was that the participant be older than 10 years of age as we felt that young children would not provide accurate PF data under limited supervision. Children 10 to 17 years old required parental permission to participate and were asked to perform their measurements with parental supervision. Encouraging a broad population to participate allowed us to investigate the effects of poor air quality on individuals with compromised pulmonary function and on otherwise healthy individuals. We often had adult participants interested in the study because they had an asthmatic child, and in these instances we provided an extra meter to the parent so they could track the health of their asthmatic child. We only collected and analyzed the child's data if they were older than 10 years. The study population includes asthmatics, COPD sufferers, the elderly, respiratory medication users, minority children, and the handicapped. Because this was a study of population response to air pollution the construction of a diverse sample was viewed as a strength.

Sixty-five percent of the participants were female, and 27% self reported as having asthma or COPD. Females were not targeted in particular, and asthmatics had a higher compliance rate for the study period than otherwise healthy participants. The population was not completely random, as most participants expressed some kind of interest in air quality and their own health,

which interested them to volunteer for the study. During recruiting, some participants told us that they paid attention to available air quality forecasts in an effort to protect their own health. We did not make any attempt to correct for the possibility that some people may have avoided pollution exposure as a result of added awareness from participating in the study.

We excluded smokers from the analysis if they checked off the "current smoker" box on the baseline survey. We stopped collecting data from several participants because of events that compromised their pulmonary function. One participant fell and fractured several ribs, and several underwent routine surgery. Adult participants were not compensated for their effort (except a token compensation at the Camden site), and children were given theme park tickets as a reward for participation.

Study Set Up and Confidentiality. When a participant was recruited, they were given a signature release form (Appendix I) or a parental consent form if under 18 years old (Appendix II). These forms also contained the vital statistics survey. We used responses from the vital statistic surveys to stratify the sample and for programming the spirometers for the participant's characteristics. The vital statistics survey requested information on name, gender, ethnicity, date of birth, height, weight, home zip code, work zip code, contact information, medication use, if they had asthma, COPD, and their smoking history (current, years since quit, amount smoked). The signature release form, parental consent form, and vital statistics survey were approved by the University of New Hampshire Institutional Review Board (Appendix III, IV).

Height, weight, age, gender, and ethnicity were used to calculate predicted PEFR as the spirometer displays the percent of predicted PEFR (%PEFR) for each maneuver based on Hankinson (1999) standards.

To maintain confidentiality, the release forms with the participants' name and vital statistics were transported to the central site (UNH) for data entry. The physical release form was the only material which had both ID and name together in one place. Two separate databases were created by one person. The contact database held only the name and contact information of the participant (no ID). We used the contact database for contacting the participants throughout the study. The vital statistics database held the participant ID and vital statistics which were used in the analyses (no participant name). The release forms were locked in a storage cabinet at UNH once the contact and vital statistics databases were created.

The contact information database was given to the site coordinators for follow up visits, and only when downloading data from a participant's spirometer could the participant be connected to his/her ID. The procedure we used maintained participant confidentiality and adhered to the procedures approved by the University of New Hampshire Institutional Review Board. Details of our procedures are provided in Appendix V.

Meter Selection and Symptom Questionnaire Booklet Design. We asked the study participants to measure PEFR, FEV_1, FEV_6 twice daily using a KoKo Peak Pro 6 asthma management tool (hereinafter referred to as the spirometer; Ferraris Medical, USA; Figure 2-2). We chose this meter based on its ability to

record up to 64 measurements electronically (with the date and time recorded for each measurement), software interface, and relatively low price. The spirometers are certified by the American Thoracic Society (ATS), are capable of measuring flows between 60 l/min and 840 l/min, and have an accuracy for PEF: ± 10% or ± 24 l/min, FEV_1: ± 5% or ± 0.10 l, FEV_6: ± 5% or ± 0.10 l. The spirometers only record the measurement with the highest PEFR value in a 3-minute window. This feature assumes that the maneuver with highest PEFR also provides acceptable measures for FEV_1 and FEV_6. We used the KAMP© Professional software to program the spirometer for the participant and to download data from the spirometers.

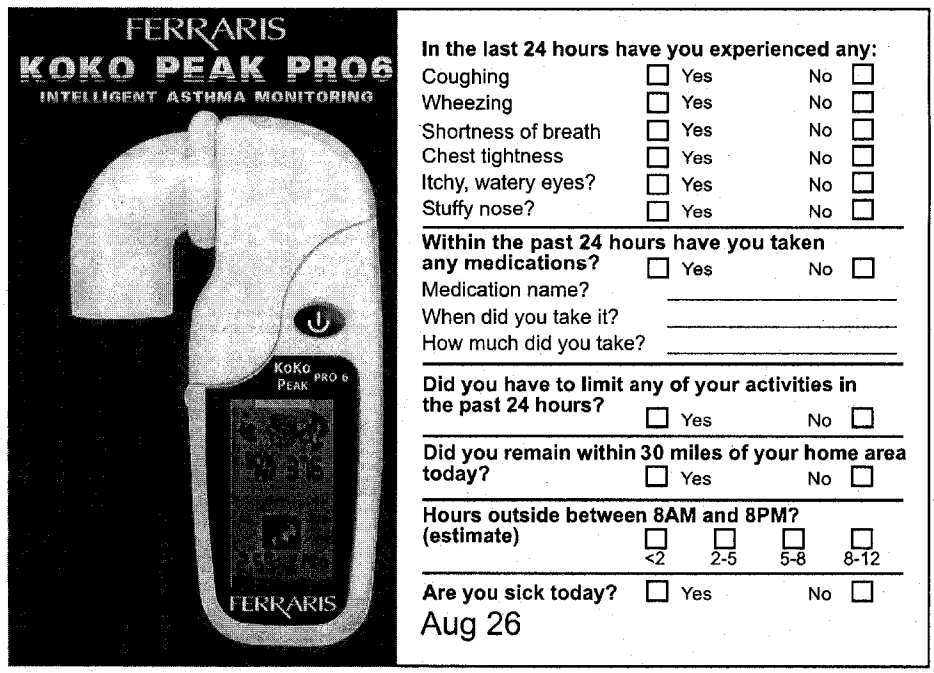

Figure 2-2. The KoKo Peak Pro6 asthma management tool used to measure pulmonary function and the daily symptom questionnaire.

The spirometers were programmed with a confidential identification number (ID), synchronized with the date, time, and the predicted PEFR value as calculated automatically by the software using Hankinson (1997) standards (calculated using age, height, weight, ethnicity, and gender). The ID, date, time, and predicted PEFR were uploaded to the meter before it was given to the participant using information provided from the survey form filled out by the participant. When downloading data from the spirometers the software recognized the ID programmed in the spirometer and directed the data to the appropriate file on the personal computer. If a meter ran out of memory it displayed an "M" and began replacing the earliest measurements in memory with the most recent measurement. With this system there was little to no error generated from manual data entry, and no subjective rounding error.

The relatively inexpensive KoKo Peak Pro 6 allowed us to carry out the study design. The automatic electronic memory was both help and hindrance. It eliminated data entry issues but some data was lost because of meter failure. Additionally, we feel that having electronic memory may have increased the amount of measurements made with improper technique as the participant did not need to view the actual measurement. Although we did have significant findings, the measurement error of the meter compounded with unsupervised measurements probably increased the standard error of our effect estimates. Between the time we collected the data and this publication Ferraris Medical USA replaced the KoKo Peak pro 6 asthma management tool and KAMP© software with updated version. We would recommend a similar electronic

spirometer for future research if several key requirements were met. First, the electronic memory should not lose stored data if the battery is removed. Second, the spirometer should record each measure from each session and not automatically choose the highest measure based on PEFR. Third, the software interface should be more streamlined and easier to use.

Although the spirometer contained a symptom recording function we did not use it because it was cumbersome and did not have the range of questions we required. Instead daily symptoms were recorded in pocket-size booklets (Figure 2-2) which contained individual questionnaire pages for each day of the study. Each booklet was used to record one month of symptom information at a time. Also, the booklets had our contact information, measurement instructions, and advice for troubleshooting the spirometer. The date was displayed on each page, a month calendar was printed on the cover for the participant to check off measurements, and there was a place on the back cover for the participant ID. The back of each questionnaire page was blank and provided a place for the participant to provide additional information including specific or unusual exposures.

In addition to the standard questionnaire described above, at the Rockport, ME site where the participants were severely asthmatic or had COPD, we asked if they experienced any night-time wakening and if they had visited the hospital. At the Gorham, NH (Appalachian Mountain Club) site where the population consisted of trail workers that were hiking up and down mountains, we

requested the elevation at which each measurement was taken in addition to the questions described above.

Participant Training. We trained each participant on how to use the spirometer and how to complete the questionnaire booklet and gave them a detailed handout on how to perform an acceptable peak flow maneuver (Appendix VI). The training session ranged from between 5 and 10 minutes per person and the session included an overview of proper technique, a demonstration of an acceptable maneuver by the site coordinator, at least one maneuver by the participant, with the coordinator providing comments on the participant's technique.

The form of the instructional overview was to: 1) Inhale as deeply as possible and at the same time 2) push the initiation button on the meter, then 3) wait for the second beep (~1 second) and 4) exhale as forcefully and completely as possible until you have no air left in your lungs. We emphasized that we wanted them to make each maneuver their best maneuver. We informed the participants what "normal" values should be and the meaning of the measurements on LED screen on the spirometer. Nose clips were not used during the maneuvers and we requested participants to perform maneuvers in the standing position; however, several participants performed the maneuvers in a sitting position. We instructed the participant to use the same position for all of their measurements and to fill out the questionnaire during their evening measurement session. We also noted that the medication use field was only for any medications that they felt affected their respiratory system.

We instructed the participant to perform three maneuvers with at least 30 seconds between the maneuvers, although several participants required more time between maneuvers to recover. After the initial training session we had no knowledge of how many maneuvers the participant actually performed during each measurement session. Without doubt, some participants performed less than three.

During follow up sessions the participant and site coordinator sat down together and discussed the participant's progress while the data was being downloaded to the computer (~ 2-5 minutes). Sessions involved discussion about how the meter was performing, if they had noticed problems with the meter, if they were having problems complying with the protocol, and any questions about air quality. If the participant was concerned that their measurements were not as good as they thought they should be, or if they expressed health concerns to us, we immediately referred them to talk to their physician or a pulmonologist.

The KAMP© Professional software immediately displays the pulmonary function data downloaded from the participant's meter in a graphical format on the computer. The participant and coordinator reviewed the graph together. The most common comment made by a coordinator to a participant was that FEV_6 was approximately equal to FEV_1, which means that the participant was not finishing their exhalation. Participants were reinstructed concerning proper technique.

In some circumstances, mostly with elderly participants, it was physically impossible for the participant to finish the maneuver within 6-seconds. We attempted to separate these participants as their FEV_6 value does not have the same inference as someone who can finish exhalation within the allotted 6 seconds. Completing the maneuver within 6 seconds allows the FEV_6 measure to be used in place of Forced Vital Capacity (FVC) more appropriately than if it is not completed.

We gave spirometers to several adult participants who were not able to attend the training session. These participants were given the detailed instruction sheet followed up by instruction over the phone. We discussed proper technique with the participants during their follow up session.

CHAPTER III

THE EFFECT OF AIR POLLUTION AND TIME SPENT OUTDOORS ON PULMONARY FUNCTION IN A DIVERSE NEW ENGLAND POPULATION

Introduction

Multiple studies have shown that air pollution is significantly associated with increased mortality, respiratory disease morbidity, respiratory and cardiac hospital admissions, respiratory symptoms, and reductions in pulmonary function (PF). These effects have been occurring at concentrations that are currently observed throughout the United States and at levels below the established National Ambient Air Quality Standards (NAAQS). Two thorough reviews of recent literature on the health effects associated with ozone (O_3) and particulate matter (PM) found enough evidence to call for a reduction of the NAAQS pollutant levels and provides a detailed discussion of the findings and limitations of the available body of literature (U.S. EPA 2004; U.S. EPA 2006).

Seminal air pollution and health studies such as the Harvard Six Cities study (Dockery et al. 1993), National Morbidity, Mortality, and Air Pollution Study (NMMAPS - Samet et al. 2000a,b), American Cancer Society Study (Pope et al. 1995), and 95 cities study (Bell et al. 2004) have shown that air pollution in the form of O_3, PM, sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and aerosol acidity all to be associated with premature death. The Six Cities Study and the American Cancer Society Study both withstood a detailed reanalysis which found

that both studies used high quality data and the findings were actually more robust than originally reported (Health Effects Institute 2000).

Criteria air pollutants and acid aerosols have also been associated with increases in the demand for hospital services for asthma, chronic obstructive pulmonary disease (COPD), and for cardiopulmonary diagnoses in many regions of the world (e.g. Lipfert 1993; Wilson et al., 2004 and references therein). These seminal mortality, morbidity, and hospitalization studies focus on the most severe health effects associated with air pollution and provide the foundation for establishing the NAAQS. However important, mortality and hospital admissions represent less than approximately 0.2% of the adverse impact cases associated with severe air pollution (Thurston et al. 1997a). The remaining 99.8% of adverse impacts consist of less severe outcomes such as lost productivity, asthma attacks, school absences, and respiratory symptom days.

Understanding these less severe outcomes has proven difficult because data on these outcomes is not routinely collected. As a result, studies focusing on these adverse health effects must collect data on a group of individuals. These studies are typically limited in size because they are resource intensive. The necessity of choosing a study population to track, the health outcomes to measure, the air pollutants of concern, and the type of statistical analysis employed has resulted in many possible study designs. This has resulted in a variety of applied research methods which makes comparisons between studies difficult.

Results from studies with even the broadest scope provide only narrow insights which makes generalizing effects to the population level difficult. Within all cohort study designs certain factors must be addressed. One of the most important is an individual's exposure which is determined by behavior such as exercising or the amount of time spent outdoors. Determining if effects are due to short- or long-term exposures is often presented as an either-or scenario. However, the overall health effect is likely to be determined by a combination of long- and short-term exposures which adds another dimension to the analysis. Long-term exposures can alter the susceptibility of an individual to short-term exposures while short-term exposures can also affect the observed health measure used in a long-term analysis.

Long-term exposures to pollutants have been associated with increased risk of asthma diagnosis, reduced lung function, reduced lung function growth, and increases in the frequency of respiratory symptoms (McConnell et al., 2002; Gauderman et al., 2004; Frischer et al., 1999; Galizia et al., 1999; Kopp et al., 2000). Reduced PF has also been associated with elevated O_3 and PM exposures over the course of one summer (Frischer et al., 1999; Kinney et al., 2000; Ihorst et al., 2004), although Ihorst et al. also found that lung function growth recovered over the course of 3.5 years.

In a study of the acute effects of air pollution in a panel of children in highly polluted Mexico City, the elevated long-term exposures may have caused the children to develop a tolerance to short-term exposures. Extremely high concentrations of O_3 and coarse particulates (PM_{10}) were strongly associated

with significant reductions in PF and increases respiratory symptoms (Romieu et al., 1996, and 1997). However strong, the estimates of these associations were smaller compared to the effects observed in less chronically polluted areas. An alternate hypothesis presented for the smaller effect sizes was that the acid component of the aerosols (which is typically lower in Mexico City PM than other regions) may be an important aspect in determining the effect of the PM.

Acidic aerosols have been associated with declines in PF and increases in symptoms (e.g., Ostro et al., 1991; Neas et al., 1995; Korrick et al., 1998; Jedrychowski and Krzyzanowski 1989; Raizenne et al., 1989). Regardless of acidity, the size of the aerosol appears to be a significant PM effect modifier. Although health effects have been observed from the coarse fraction of particulates (2.5-10 μm in diameter), $PM_{2.5}$ are being investigated more frequently and thought to be even more important with regard to health effects (e.g., Schwartz and Neas 2000; EPA, 2004).

The longitudinal panel study is the most common design for investigating associations between acute air pollution exposures and PF as each subject becomes their own control and serves to control for inter-subject variability that is time invariant (e.g. Gent et al., 2004; Vedal et al., 1998; Jalaludin et al., 2000). This method allows the analysis to focus on factors that vary over time such as air quality, but some time-invariant factors can still limit the inference of the results. For example, Korrick et al. (1998) observed O_3 to affect asthmatic hikers nearly four times more compared to non-asthmatic hikers and Vedal et al. (1998) observed significant effects from PM_{10} only in the study's asthmatic population.

Also, the effects of air pollution have been found to become greater as the severity of asthma in the individual worsens (Jalaludin et al. 2000; Gielen et al. 1997; Pope and Dockery 1992). Among asthmatics, it is still not clear if maintenance medication is effective at desensitizing an individual to air pollution. Gielen et al. (1997) and Gent et al. (2003) found that asthmatics using maintenance medication (used as one measure of asthma severity) were more sensitized than asthmatics not on medication, while Delfino et al. (1998) found that medication users showed less sensitivity. These time-invariant factors need to be addressed either in the study design or in the statistical analysis before generalizing the results to a population.

In longitudinal panel studies it remains difficult to accurately measure an individual's exposure given that individuals often move into different indoor and outdoor environments (e.g. home, office, outdoors, retail stores, vehicles). Each of these environments can have large differences in the concentration of atmospheric pollutants, such a bedroom versus kitchen, or a rural area versus urban center. To accurately measure an individual's exposure, high resolution or cumulative air pollution measurements of the air they are breathing and their ventilation rate are required. Unfortunately, this requires a significant amount of resources (e.g. Delfino et al., 2004 tracked only 3 participants at a time for two weeks). To work around this issue researchers often choose subjects that spend much of their time outdoors, such as those at summer camps. Selectively choosing subjects helps minimize confounding from indoor air and homogenizes

the group's exposure, but again decreases the ability to generalize results to a broader population.

Even though outdoor air pollution can infiltrate indoors, concentrations can be quite different and correlations can be quite low between indoor and outdoor monitors. Low correlations (R^2~0.3) between central site monitors and personal measures have been observed (Delfino et al., 2004). Further, strong indoor sources of particulates also exist (Wallace et al., 2003). Given these observations it is likely that measures of outdoor air pollution cannot be used to accurately predict the exposure of individuals spending most of their time indoors.

Including indoor air quality measures significantly modifies the effect estimate from outdoor air pollution. Delfino et al. (2004) observed larger and more significant effects when using personal air quality measures from a monitor carried at all times by the subject as opposed to when using measures from central-site outdoor monitors. Ostro et al. (1991) used a rough estimate of the correlation between indoor and outdoor concentrations taken from the literature to weight exposures based on the time the participant was indoors and outdoors. This was only part of a more sophisticated exposure assessment technique and represents an improved method but assumes the relationship between indoor and outdoor air quality is linear, and the only pollution source is outdoors.

Aside from the methodological details presented above, acute health effects have been observed at relatively low outdoor ambient air pollution levels. Vedal et al. (1998) found effects associated with PM_{10} remained even after

excluding all observations when PM_{10} was >40 $\mu g/m^3$. Gent et al. (2003) found significant increases in respiratory symptoms associated with relatively low concentrations of O_3, but only in asthmatic participants who used maintenance medication. Geilen et al. (1997) found increases in respiratory symptoms and medication use from O_3, black smoke, and PM_{10} at relatively low levels. Many of these effects are being observed at pollutant concentrations which are below the NAAQS.

Using a longitudinal panel study design we investigate the effects of relatively low levels of outdoor air pollution during the summer of 2004 in New England on the PF of a mixed population. We report on how the effects are modified by the amount of time spent outdoors, asthmatic status, and the use of asthma medication. These observations were collected as part of the large-scale summer 2004 International Consortium for Atmospheric Research on Transport and Transformation research campaign (Fehnsenfeld et al., 2006).

Methods

Overview. We recruited 418 participants from across New England and had them measure their daily pulmonary function and record respiratory symptoms from July 1st to August 31st, 2004. These health effect measures were paired with chemical and physical air quality measures from the nearest monitoring location to the participant's home zip code. We used ordinary least squares (OLS), multivariate regression, mixed linear models, and logistic

regression to estimate the effects of air pollution on respiratory health. We used SAS Institute software (Cary, NC) to organize and analyze the data.

Participant Recruitment. In total, 418 participants were recruited at 14 different sites across New England (Table 2-1; Figure 2-1). Of the 418 participants recruited, 165 (40%) were retained for the analysis because they reported 21 or more PF observation days. We grouped the sites within coastal New Hampshire together to form the Seacoast, NH site (SEA) because of their close proximity. The study locations typically contained a cluster of a certain population demographic. For example, participants from the Department of Environmental Services (DES) were mostly working age Caucasians while participants from the Dorchester, MA (DOR) site were mostly Black or Hispanic teenagers. The only requirement for recruitment was that the participant be older than 10 years of ages. Current smokers were excluded from the analysis.

Participants filled out an initial survey and signed a release form. The survey requested information on the age, gender, and physical characteristics of the participant, whether or not the participant had asthma or COPD, if and what medications the participant took for these conditions, smoking history, and the participants location. All study procedures were approved by the University of New Hampshire Institutional Review Board for research on human subjects.

Pulmonary Function and Respiratory Symptoms. The participant measured PF twice daily (morning and night) using the KoKo Peak Pro 6 asthma management tool (Ferraris Medical, Louisville, CO). The handheld electronic spirometer measures peak flow rate (PEFR), forced expiratory volume in the first

second (FEV_1), and in 6 seconds (FEV_6). The spirometer stores each measurement in electronic memory. The measurements in memory were downloaded approximately every two weeks (during follow up visits) using Koko Asthma Management Program (KAMP©) Professional software. Each observation stored in the meter is the measurement with the highest PEFR taken within a 3 minute window. For the analysis, we chose to use the FEV_1 measure because it had a measurement error of half that of PEFR (±5% as compared to the ±10%), because some elderly participants could not complete the FEV_6 measurement with 6 seconds, and because we felt the FEV_6 measure was unreliable when not performed under trained supervision.

We trained each participant on how to use the spirometer and gave them a detailed handout on how to perform an acceptable peak flow maneuver. Participants were instructed to perform their measurements at least 1 hour after waking up, at least one half hour after eating, and at least 1 hour after exercising. We had the participant fill out a daily questionnaire which requested information concerning the past 24 hours of the participant's health and activity including presence of coughing, wheezing, shortness of breath, chest tightness, itchy-watery eyes, stuffy nose, and sickness. We also had the participant mark down medication use (type, quantity, time), any activity limitations, travel out of area, and time spent outdoors from 8:00 AM to 8:00 PM, (<2 hours, 2 to 5 hours, 5-8 hours, and >8+ hours). We deleted observations where the participant indicated that they were more than 30 miles from their home area.

Pulmonary Function Data Validation and Calculations. We removed the first two FEV_1 observations from the start of each individual's record. We then removed extremely high values that occasionally occurred from a malfunction of the spirometer by removing points that were more than 3 standard deviations away from the individual's mean during the study. We also tested for influential observations and influential participants in the analysis and removed them if necessary (see analysis methods section below).

Air Quality and Meteorological Data. To form daily exposure estimates for each study participant we assembled atmospheric observations made by the U.S. EPA, the National Oceanic and Atmospheric Administration (NOAA), and University of New Hampshire AIRMAP atmospheric observing stations.

Table 3-1. Air quality quartiles for the New England region, the default units used in the analysis for each parameter, and the unit equivalent of a 1% change in the parameter.

Parameter	Minimum	Q1	Median	Q3	Maximum	1%	Unit
O_3 max8[a]	9	32	39	50	94	0.85	ppb
$PM_{2.5}$ mean24	0.5	8	12	18	52	0.51	$\mu g/m^3$
CO mean24	0	0.15	0.18	0.33	0.71	0.007	ppm
NO_2 mean24	0.03	4.3	7.4	10.7	27.9	0.086	ppb
SO_2 mean24	0	0.40	0.85	1.67	10.04	0.087	ppb
Acid Aerosol	-609[b]	20	268	644	2816	34.3	pptv
Temp max24	4	21	24	27	32	0.28	°C
Temp min24	0	12	14	17	25	0.25	°C
RH mean24	50	74	79	87	98	0.48	%RH
RH min24	23	47	56	68	94	0.71	%RH
Dewpoint min24	1	14	17	19	24	0.45	°C
Dewpoint max24	-23	9	12	15	22	0.23	°C

[a]Max24 = Maximum 1 hour value each day, Max8 = Maximum 8 consecutive hour average value each day, Min24 = Minimum 1 hr value each day, Mean24 = Mean of all 1 hour measurements each day.
[b]A negative charge balance indicates a basic aerosol measure.

Criteria air pollutant data were obtained from the U.S. EPA's Air Quality System (EPA – AQS 2005, www.epa.gov/ttn/airs/airsaqs) database and from the AIRMAP monitoring stations (http://airmap.unh.edu). We calculated the 1-hour maximum daily value and 24-hour mean daily value for all parameters except O_3 where we calculated the daily maximum 8 consecutive hour mean value in place of the 24-hour mean. We used only validated observations from the EPA and NOAA databases; AIRMAP provided already validated observations. All observational units were converted so that only one common unit was used for each variable (Table 3-1).

Sulfate ion ($SO_4^{=}$), nitrate ion (NO_3^{-}), and ammonium ion (NH_4^{+}) measures were extracted from bulk aerosol filters which were collected at the AIRMAP monitoring stations (Ziemba et al., 2006). The aerosol acidity was calculated as the charge balance of the acid/base components using the formula:

$$[\text{Acid aerosol}]_{pptv} = 2*[SO_4^{=}]_{pptv} + [NO_3^{-}]_{pptv} - [NH_4^{+}]_{pptv}$$

Temperature, relative humidity (RH), and dewpoint were collected from NOAA weather stations, EPA air quality monitoring sites where available, and AIRMAP monitoring sites.

To compare the relative size of effects across parameters we rescaled each parameter in the analysis to have a range of 0 to 100 with 0 and 100 corresponding to the lowest and highest values for that parameter. The scaled effect estimates have the units percent change in FEV_1 per 1% increase in pollutant concentration and can not be compared to estimates from other studies.

However, the per unit estimates which can be compared to other studies are provided in the results tables.

Estimating Exposures. We identified the closest air quality monitor to each health tracking site for each air quality parameter and used that data in the analyses. A graphical inspection of the data from the closest monitor for each parameter at each location revealed that most air pollution data was complete with no systematically missing data. This exposure estimation approach means that the health outcomes of every individual at a given location are compared to the ambient air quality collected close to the individual's location regardless of how distant the individual's residence or work was from the pollution monitor.

Air Quality and Population Descriptions

Air Quality Description. July and August 2004 in New England had relatively clean air and there were no excessive heat events. The quartiles for the chemical, physical, and biological air quality parameters used in the analysis are displayed in Table 3-1. Median daily 8-hr O_3 was 39 ppb during July and August and the NAAQS of 80 ppb O_3 was only violated on two days at SEA and DES, one day at Manchester, NH (MHT; Figure 3-1). There were 5 events when 8-hr O_3 exceeded 60 ppb during the study. No $PM_{2.5}$ violations were occurred in the study region with a peak mean 24-hr concentration of 51 $\mu g/m^3$ recorded at DOR. There were four periods where regional $PM_{2.5}$ was distinctly elevated above background levels during the study. Sulfur dioxide never exceeded 10% of the 24 hour mean NAAQS standard value of 140 ppb at any site.

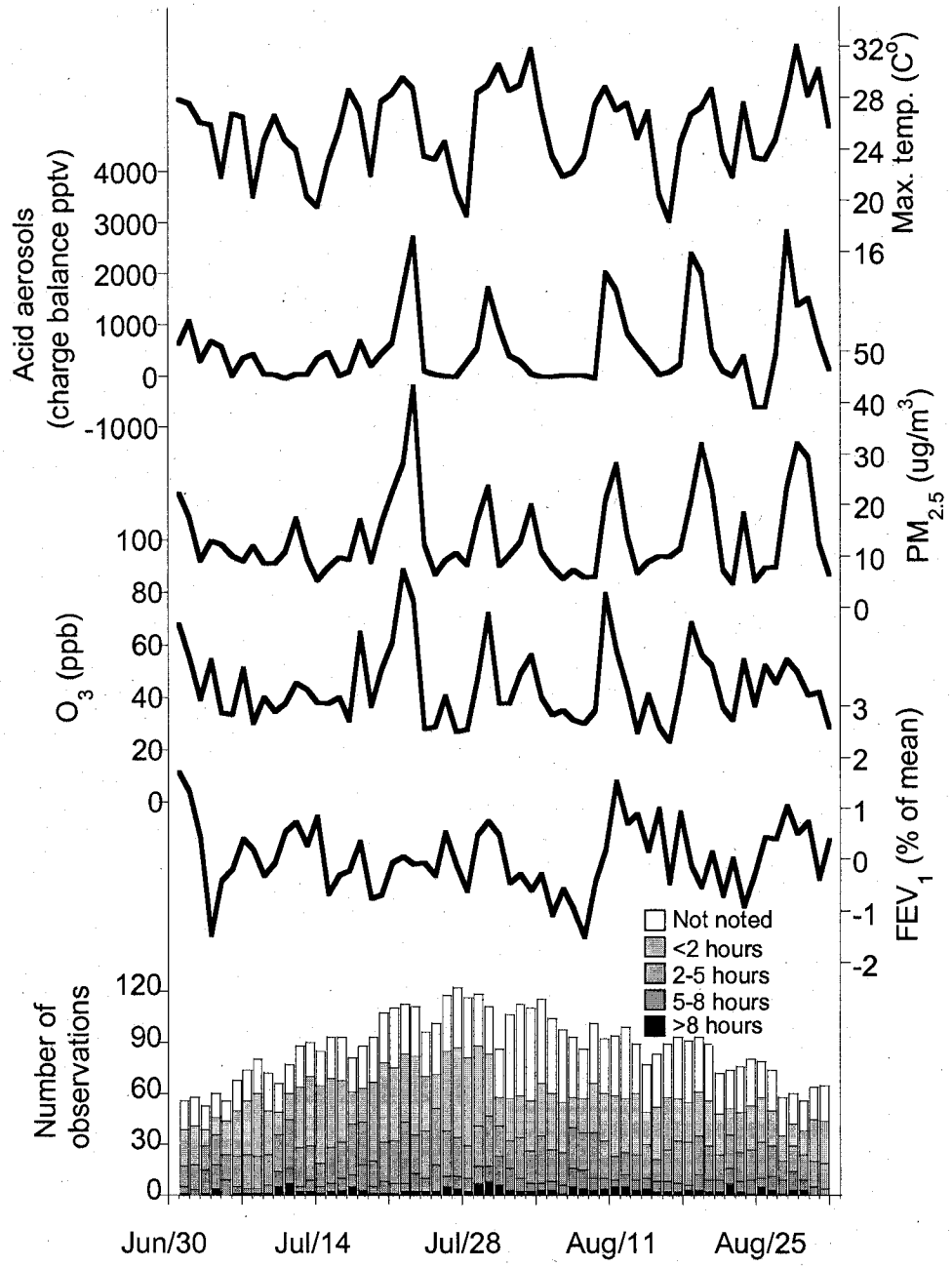

Figure 3-1. Time series plots of study parameters. From bottom to top: Number of FEV_1 observations each day stratified by the amount of time spent outdoors, mean daily percent deviation in FEV_1 of all participants, mean pollutant concentration at the two largest study sites (DES and SEA) of daily 8hr maximum O_3 (ppb), $PM_{2.5}$ ($\mu g/m^3$), acid aerosol (charge balance pptv), and maximum temperature.

Table 3-2. The Pearson product moment correlation between pollutant and copollutant at each study site. Missing values mean there was no data available for one of the parameters at the site.

	Study area								
	AMC	**BTV**	**CIS**	**DES**	**DOR**	**MHD**	**RPT**	**SEA**	**Mean**
Correlation with O_3									
$PM_{2.5}$		0.75*	0.73*	0.70*	0.73*	0.67*	0.56*	0.75*	0.70
Acid aerosols				0.65*				0.69*	0.67
CO mean24[a]	0.45*	0.21	0.40*	0.50*	0.32*	0.46*	0.30*	0.76*	0.43
NO_2 mean24		0.13	0.59*	0.51*	0.39*	0.44*	0.35*	0.28*	0.38
SO_2 mean24	0.46*	0.45*	0.56*	0.15	-0.10	0.30*	0.53*	0.10	0.31
Temp max24	0.31*	0.65*	0.63*	0.59*	0.60*	0.60*	0.18	0.59*	0.52
Temp min24	0.25	0.34*	0.01	-0.07	0.24	-0.04	-0.16	0.02	0.07
Dew max24	0.29*	0.44*	0.14	0.11	0.23	0.12	0.14		0.21
Dew min24	0.11	0.26*	0.02	0.08	0.24	0.09	-0.02		0.11
RH mean24	0.06	0.10	-0.33*	-0.29*	-0.23	-0.28*	-0.29*		-0.18
RH min24	0.02	0.02	-0.42*	-0.36*	-0.30*	-0.35*	-0.36*		-0.25
Correlation with $PM_{2.5}$									
O_3		0.75*	0.73*	0.70*	0.73*	0.67*	0.56*	0.75*	0.70
Acid aerosols				0.82*				0.75*	0.78
CO mean24		0.52*	0.51*	0.63*	0.42*	0.63*	0.36*	0.75*	0.55
NO_2 mean24		0.21	0.56*	0.54*	0.37*	0.54*	0.36*	0.27*	0.41
SO_2 mean24		0.54*	0.47*	0.02	-0.17	0.08	0.43*	0.12	0.21
Temp max24		0.55*	0.52*	0.47*	0.52*	0.47*	0.13	0.62*	0.47
Temp min24		0.44*	0.26*	0.22	0.43*	0.22	0.27*	0.28*	0.30
Dew max24		0.45*	0.36*	0.39*	0.48*	0.39*	0.31*		0.40
Dew min24		0.48*	0.31*	0.39*	0.52*	0.39*	0.35*		0.41
RH mean24		0.21	-0.03	-0.09	0.07	-0.09	-0.10		-0.01
RH min24		0.14	-0.04	-0.07	0.05	-0.07	-0.13		-0.02

[a]See Table 3-1 for abbreviations.
*Significant at α=0.05.

We found that O_3 and $PM_{2.5}$ were moderately correlated with other pollutants at some study locations (Table 3-2). Ozone was moderately correlated with maximum temperature at the more urban study sites (DES, DOR, SEA, BTV) than at more rural locations (RPT, AMC). Sulfate and NH_4^+ were highly correlated (R=0.98), and the acid aerosol charge balance was highly correlated with $SO_4^=$ (R=0.94) and NH_4^+ (0.89). Nitrate was not correlated with $SO_4^=$ or NH_4^+. We chose to use only the acid aerosol charge balance in analyses

because NO_3^- has not been known to be significantly associated with health effects and the high correlations between the acid aerosol measures, $SO_4^=$, and NH_4^+ make the parameters nearly identical.

Population Description. A total of 13,146 observations were collected in 7,615 observation days (Table 3-3). Of the 165 participants, 40 self reported as having asthma, 11 self reported as having COPD, and 45 self reported as having either asthma or COPD. The two largest study locations were DES and SEA and together they contained more than half of the observations. The majority of participants were female and did not have asthma or COPD.

Table 3-3. Description of study population and mean (stdev) PF measures.

	Participants	PF days	age	PEFR[a]	FEV_1[a]	FEV_6[a]
All	165	6456	45	424(136)	2.9(1.0)	3.6(1.2)
Respiratory condition						
Asthma	40	1676	44	374(135)	2.6(1.0)	3.4(1.2)
COPD	11	551	64	242(112)	1.6(0.9)	2.3(0.9)
Asthma or COPD	44	1872	47	358(142)	2.5(1.1)	3.3(1.2)
Otherwise healthy	121	4584	45	448(126)	3.0(0.9)	3.8(1.1)
Medication Use (asthmatics)						
Maintenance	24	1035	43	346(125)	2.4(1.0)	3.2(1.2)
No maintenance	16	641	47	417(142)	2.8(1.1)	3.7(1.3)
Gender						
Male	59	2312	46	503(155)	3.4(1.2)	4.3(1.3)
Female	106	4144	45	380(101)	2.6(0.8)	3.3(0.9)
Age						
10-18	24	855	14	405(119)	2.9(0.8)	3.4(1.0)
18 To 65	114	4381	44	461(115)	3.2(0.9)	4.0(1.1)
>65	27	1220	78	282(139)	1.7(0.8)	2.4(0.9)
Ethnicity						
Caucasian	147	5783	48	427(134)	2.9(1.0)	3.7(1.2)
Black	7	227	16	490(124)	3.3(0.9)	3.8(1.1)
Asian	8	312	21	395(121)	2.6(0.7)	3.0(0.7)
Other ethnicity	3	134	48	193(73)	1.7(0.6)	2.3(0.4)

[a]PEFR is in units of liters/minute, FEV_1 and FEV_6 are in units of liters.

Mean PF was significantly lower (t test, α=0.05) in the asthmatic group than the otherwise healthy group and their standard deviation was higher (Table 3-3). There was no significant difference in age between the asthmatic population and otherwise healthy population but the mean PEFR, FEV_1, and FEV_6 values were significantly lower for the asthmatic group (α=0.05). The group self reported as having COPD had lower PF values than both the asthma and otherwise healthy groups and the group was also significantly older (α=0.05).

The majority of PF observations were made when participants spent less than 2 hours outdoors, and relatively few observations were made when participants spent more than 8 hours outdoors (Figure 3-1). Nearly twice as many participants spent more than 8 hours outdoors on weekends versus weekdays (significant at the α=0.5 level) although there was no significant difference in FEV_1 between weekends and weekdays. Compliance varied from day to day during the study. A rough calculation (because of varying start and end dates for each individual) showed the lowest daily compliance was approximately 50% and the highest approximately 74%. The 2nd day, 5th day, and last two days of the study had no observations taken when the participant spent more than 8 hours outdoors. We attribute this to slightly lower enrollment numbers early and late in the study and because these were weekdays and not weekends.

Checking for constant variance. In the analytic dataset we found that there was a significant increase in mean daily FEV_1 (liters) associated both with increases in the number of daily observations and decreases with mean daily

participant age. We also found that the number of observations taken each day was significantly negatively associated with mean daily participant age (α=0.05). This suggests that we had a younger population when participation increased in the middle of the study period and was older on either end.

Additionally, there was a significant decrease in mean daily FEV_1 deviance (%) associated with the number of daily observations (but not with mean daily age). However, this effect was extremely small with a 0.01% increase in daily $\%FEV_1$ occurring over the whole range of number of daily observations. Because it was so small, we do not believe this affected study results. Neither total daily observations or the number of observations taken when the participant spent >5 hours outdoors were significantly associated with O_3, $PM_{2.5}$, or acid aerosols. However, the number of observations taken when the participant spent >5 hours outdoors significantly (α=0.05) increased with maximum daily temperature. These results suggest that there was a tendency for participants to spend more time outside when the air was hotter but not polluted.

Linear Trend with Time. We observed a significant time trend in the FEV_1 of many individuals. Sixty-seven of the 165 participants had significant correlation with study day (a counter starting on July 1st) at the α=0.05 level. There were 45 participants with a significant negative trend and 22 with a significant positive trend. Out of these 67 participants, 60 of them were more significantly correlated with study day than any of the measures for $PM_{2.5}$, O_3, or temperature. The mean explained variance (R^2) that study day explained per individual was 14% with a minimum of ~0 and a maximum of 72%. The mean

explained variance per person for any of the atmospheric variables ranged from 3.9% for maximum temperature to 5.0% for minimum temperature. These results suggest that the long-term trends were better explained by a linear trend for time and less by air pollution.

We could find no common demographic link between the participants with significant negative or positive trends. There was no difference in the rate or proportion of asthma, COPD, gender, ethnicity, age, time spent outdoors, or obesity index (height/weight) between participants with significant trends and those without, as well as no observed clustering within study locations. We conclude that the long-term trend in FEV_1 was specific to the individual and could not be explained with the available variables.

The negative trends could have been caused by cumulative exposures to pollutants, a buildup of phlegm on the spirometer valve, or a decrease in the level of effort by the participant. Cumulative exposures were not likely to have caused the negative trends because it was not clustered by study location where locations with worse air quality should have been associated with more negative trends. Phlegm buildup on the spirometer valves was not likely as we examined the eight spirometers with the most visible buildup of phlegm and found that the individuals using these spirometers showed both negative trends (n=3) and positive trends (n=5). We cannot rule out that there was a decrease in effort by the individual over the course of the study.

Positive trends could have been caused by a change in lifestyle (removal of exposure or change in exercise), an increase in the level of effort by the

participant, or in the case of growing children it could have represented lung function growth. An increase in the level of effort was not likely as we reviewed technique during follow up visits and the positive trends were not specific to children. Because the positive trends were not clustered by site we think the trends were not due to a removal of a particular outdoor air pollution exposure but could have been from the removal of personal level exposures.

Single pollutant models

Model Specification. We fit mixed linear models to the data using SAS's PROC MIXED procedure in SAS Version 9 (Littell et al., 1996). We include asthmatic status (0=no asthma, 1=asthma) and the amount of time spent outdoors (0=<5 hours, 1=>5 hours, 2=missing) as classification variables and the scaled pollutant as a continuous variable. We calculated the effect of the pollutant for each level of class variable. Observations with missing information for the amount of time spent outdoors were included to increase the accuracy of the covariance parameter structure and time trend adjustment for each participant. Separate effects were calculated for the observations with missing information for the amount of time spent outdoors.

A random variable was added to the model which adjusted for the time trend of each participant (discussed above). We calculated the actual covariance structure of the FEV_1 observations by calculating the correlation between observations 1 day apart, 2 days apart, and so on up to 10 days apart, averaged the correlation across participants, and found the covariance structure followed

exponential decay. The AR(1) (exponential decay) modeled covariance structure was a good fit for the actual covariance structure for observations up to 4 days apart. The AR(1) structure provided improved model fit (evaluated using Akaike's Information Criterion) over allowing each participant to have their own variance component or over no specification.

We also ran models for lagged values of air pollution up to 4 days prior and also on a 5 day cumulative value which was the sum of the same day and previous 4 days pollutant values. We did this for all observations by asthma status, but not for but not for amount of time spent outdoors because of the complexity of interpreting results and a reduced number of observations caused by the increase in chance needed to have a participant perform a measurement a certain number of days after spending a certain amount of time outdoors.

We reduced the number of class variables for time spent outdoors from four to two for two reasons. First, the initial analyses showed that observations taken when the participant spent <2 hours outdoors, and 2-5 hours outdoors had no measurable association with outdoor air pollution as monitored at central sites, while the 5-8 hours, and >8 hours outdoors groups had stronger effect estimates. The second reason was that the number of >8 hours outdoors was too low to have significance (although initial analysis showed this group to be more strongly affected than the 5-8 hours outdoors group).

Results. We found that O_3, $PM_{2.5}$, and NO_2 were significantly associated with declines in the FEV_1 (α=0.05) of asthmatic participants spending >5 hours outdoors (Figure 3-2). Effects from atmospheric parameters were near zero and

not significant when the participant spent <5 hours outdoors on the day of the measurement (Figure 3-2) and the only significant effects (α=0.05) were for asthmatic participants and asthmatic participants taking asthma maintenance medication spending >5 hours outdoors. In single pollutant models increases in O_3, $PM_{2.5}$, and NO_2 were significantly (α=0.05) associated with declines in FEV_1 in asthmatic participants (Figure 3-3). There were roughly 200 observations where asthmatic participants spent >5 hours outdoors. Out of the 9 study areas these observations were spread across participants from 5 areas for $PM_{2.5}$ and 6 sites for O_3 with most participants and observations being from DES and RPT (No $PM_{2.5}$ data were available at AMC).

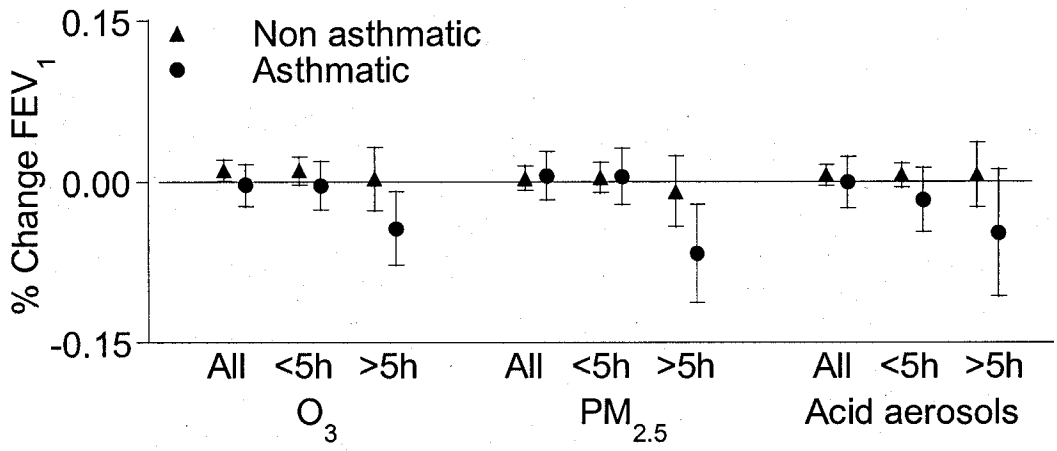

Figure 3-2. Effect estimates for a 1% increase in same day O_3, $PM_{2.5}$, or acid aerosols on FEV_1 for all, <5 hours outdoors, and >5 hours outdoors observations. Error bars indicate the 95% confidence interval of the estimate. Scaled effect estimates are comparable between parameters and have units of % change in FEV_1 per 1% change in pollutant.

Thirty-eight of the 40 asthmatic participants were using an inhaler, and 24 took an asthma maintenance medication. The effects became stronger for $PM_{2.5}$ in the group of asthmatics taking asthma maintenance medication but not for O_3 or NO_2 which were the only other parameters with significant effects (Table 3-4).

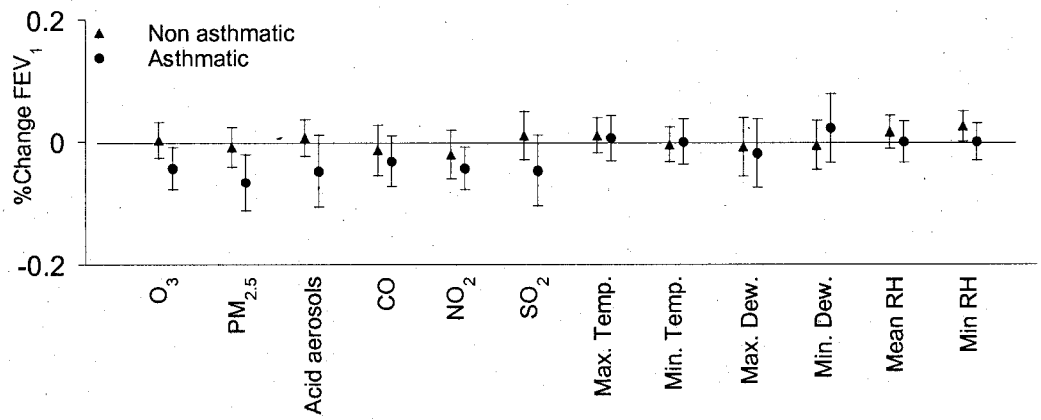

Figure 3-3. The effect of each atmospheric parameter considered in the analysis when the participant spent >5 hours outdoors. Results are expressed as the percent change in FEV_1 per 1% change in pollutant.

The 3-day lag values for O_3, $PM_{2.5}$, and acid aerosols had the largest effect on the FEV_1 regardless of time spent outdoors (Figure 3-4). The 5-day cumulative measure was significantly negative for O_3 and acid aerosols but not for $PM_{2.5}$ and the effect was less negative than the 3-day lag. We did not include any information from the amount of time spent outdoors in a formal analysis.

We tested the influence of single observations and participants with the influence diagnostic tools within PROC MIXED which calculates several different statistics for influence on both model fit and fixed effects. One out of the 165 participants had restricted likelihood distance estimates which were outside of the 75^{th} percentile of the Chi-square distribution, indicating that the model was

not a good fit for this participant. We removed this participant from the analysis and ran the models again finding that the parameter estimates and significance did not change, we then removed the next most influential participant and again, found that the results did not change. No single observation was outside of the 75th quartile of the Chi-square distribution in the outlier analysis.

Table 3-4. The percent change in FEV_1 associated with increases in the concentration of different atmospheric parameters for asthmatic participants and participants using respiratory maintenance medication when they spent >5hrs outdoors. Effects are expressed as percent change in FEV_1 per 1% change in parameter, percent change in FEV_1 per unit change in parameter.

		Asthmatic participants			Medication users		
Parameter	**Unit change**	**per 1%[a]**	**unit change**	**prob>t[b]**	**per 1%**	**unit change**	**prob>t**
O_3 8hr[c]	10 ppb	-0.043	-0.504	0.013	-0.043	-0.503	0.017
$PM_{2.5}$ mean24	10 µg/m^3	-0.066	-1.293	0.005	-0.079	-1.537	0.002
Acid aerosol	100 pptv	-0.047	-0.138	0.115	-0.030	-0.087	0.291
CO mean24	10 ppb	-0.031	-0.031	0.137	-0.040	-0.040	0.081
NO_2 mean24	1 ppb	-0.043	-0.151	0.153	-0.041	-0.144	0.023
SO_2 mean24	1 ppb	-0.046	-0.458	0.119	-0.061	-0.606	0.066
Temp. 1hr max.	10 °C	0.006	0.213	0.734	-0.012	-0.384	0.579
Temp. 1hr min.	10 °C	0.000	0.013	0.986	-0.016	-0.655	0.436
RH mean24	10%	0.000	0.005	0.986	0.001	0.023	0.951
RH 1hr min	10%	0.000	0.002	0.993	0.004	0.060	0.806
Dewpoint 1hr max.	10 °C	-0.019	-0.580	0.517	-0.039	-1.208	0.233
Dewpoint 1hr min.	10 °C	0.023	0.501	0.427	0.010	0.220	0.768

[a]See Table 3-1 for 1% pollutant changes.
[b]The probability that the estimate is not statistically different from zero.
[c]See Table 3-1 for abbreviations.

We compared the mixed model results to those of ordinary least squares (OLS) regression models of detrended FEV_1 observations which were collapsed to each level of asthma status and time spent outdoors. We found that the mixed model pollutant effect estimates were comparable in size to the OLS estimates with slightly tighter standard errors. The pollutant effect estimates changed only

slightly, and the confidence intervals tended to tighten. Although there was little change in the model results the mixed models incorporated all of the FEV_1 observations to adjust for the time trends of each participant and estimate the covariance structure which provides more accurate effect estimates.

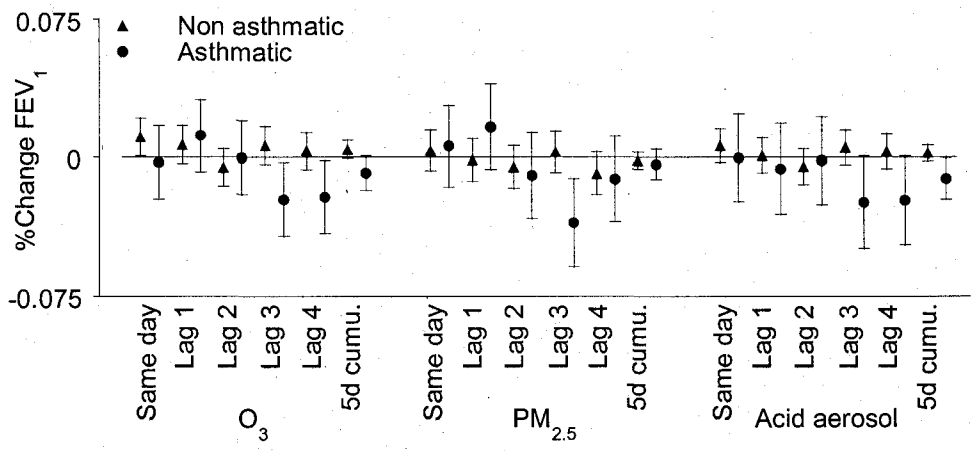

Figure 3-4. Lagged effects of O_3, $PM_{2.5}$ and acid aerosols. The 5 day cumulative measure was the sum of the same day and previous 4 day measurements. Results are expressed as the % change in FEV_1 per 1% change in pollutant.

Two pollutant models

Model specifications. In the two pollutant models we focused on the effects of O_3, $PM_{2.5}$, and acid aerosols while adjusting for other pollutants and meteorological parameters. Models were specified similar to the single pollutant models with the addition of a second continuous atmospheric variable as a fixed effect with effect estimates being calculated for each level of asthma and time spent outdoors. We did not specify an interaction term between pollutants in the

final model because initial results indicated interaction effects to be near zero and not significant.

Results. Effect estimates for O_3, $PM_{2.5}$, acid aerosols, and NO_2 were still near zero and not significant regardless of asthma status or medication use when participants spent <5 hours outdoors and a second atmospheric parameter was added to the models. The following results of the two parameter models describe those observations which were taken when the participant spent >5 hours outdoors (Table 3-5; Figure 3-5).

Table 3-5. The percent change in FEV_1 associated with increases in NO_2, O_3, $PM_{2.5}$, and acid aerosols after controlling for other atmospheric parameters. Effects are for observations from asthmatic participants spending >5 hours outdoors. Effects are expressed as percent change in FEV_1 per 1% change in parameter and percent change in FEV_1 per unit change in parameter.

Second model	**O_3 8hr**			**$PM_{2.5}$ mean24**			**Acid aerosols**		
parameter	**1%[a]**	**10 ppb**	**p>t[b]**	**1%**	**10µg/m^3**	**p>t**	**1%**	**100pptv**	**p>t**
Alone	-0.043	-0.504	0.013	-0.066	-1.293	0.005	-0.047	-0.138	0.115
Acid aerosol	-0.053	-0.614	0.350	-0.072	-1.395	0.417			
$PM_{2.5}$ mean24[c]	-0.021	-0.245	0.386				0.003	0.008	0.964
O_3 8h				-0.045	-0.877	0.182	-0.014	-0.041	0.837
NO_2 mean24	-0.053	-0.623	0.022	-0.072	-1.399	0.014	-0.047	-0.136	0.300
CO mean24	-0.040	-0.465	0.101	-0.063	-1.217	0.031	-0.034	-0.098	0.593
SO_2 mean24	-0.042	-0.494	0.020	-0.070	-1.359	0.008	-0.046	-0.134	0.177
Temp. 1h max	-0.071	-0.835	0.004	-0.095	-1.855	0.001	-0.083	-0.243	0.117
Temp. 1h min	-0.043	-0.499	0.057	-0.086	-1.666	0.005	-0.070	-0.204	0.160
Dew. 1h max	-0.043	-0.505	0.081	-0.074	-1.443	0.015	-0.088	-0.256	0.043
Dew. 1h min	-0.052	-0.603	0.033	-0.094	-1.831	0.002	-0.087	-0.255	0.044
RH mean24	-0.055	-0.647	0.054	-0.076	-1.471	0.028	-0.067	-0.196	0.133
RH 1h min	-0.050	-0.586	0.056	-0.073	-1.429	0.020	-0.053	-0.155	0.166

[a]See Table 3-1 for 1% pollutant changes.
[b]The probability that the estimate is not statistically different from zero.
[c]See Table 3-1 for abbreviations.

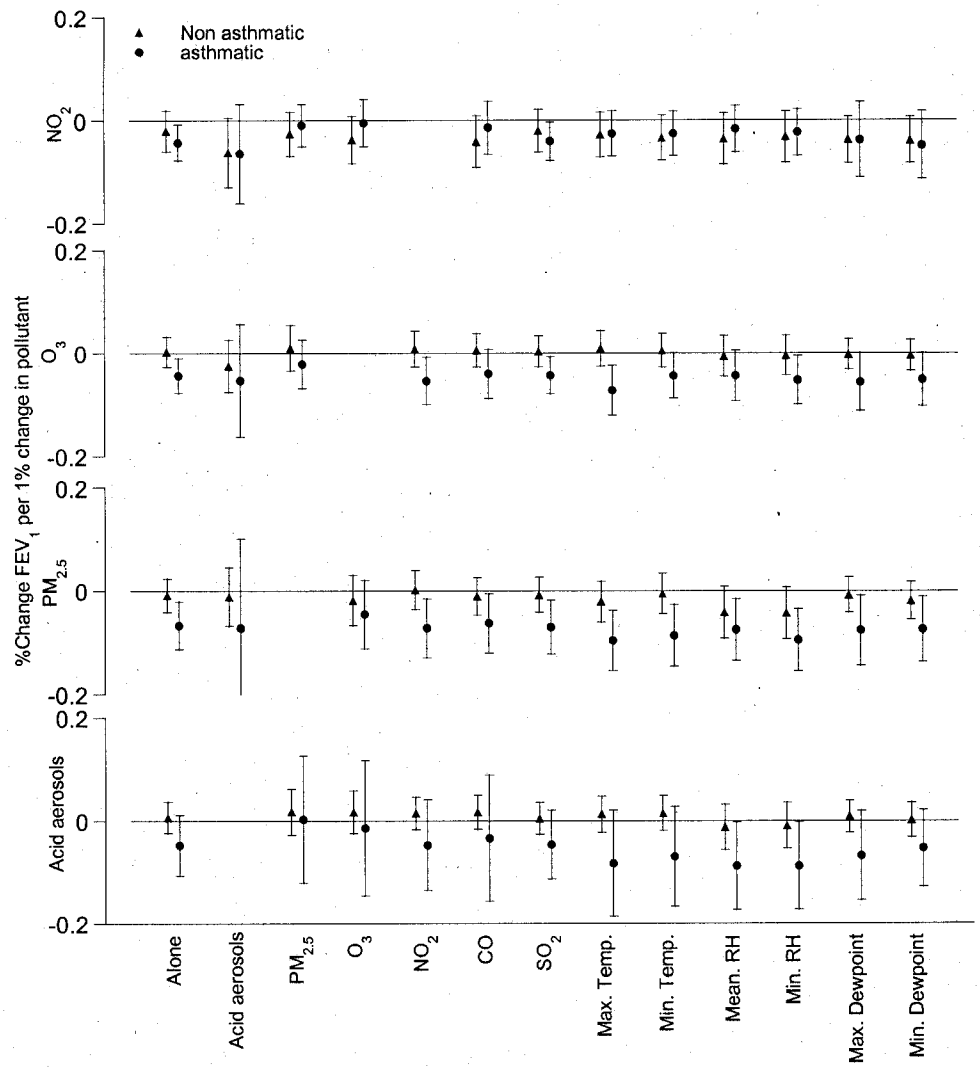

Figure 3-5. Multiple pollutant models. Percent change in FEV_1 associated with a 1% change in (top to bottom) NO_2, O_3, $PM_{2.5}$, and acid aerosols for asthmatic and non-asthmatic participants after controlling for the variable on the x-axis. Effect estimate units are % change in FEV_1 per % change in pollutant and are comparable across all copollutants. Whiskers indicate the 95% confidence interval of the estimate.

Effect estimates for $PM_{2.5}$ on observations from asthmatic participants was slightly diminished and no longer significant after including O_3 in the mixed models. Also, the confidence interval for the $PM_{2.5}$ estimates widened greatly

after adjusting for acid aerosols. This is probably due to a reduced number of observations (only two sites had acid aerosol measures) with both $PM_{2.5}$ and acid aerosols present, and because of the higher degree of correlation between the parameters at the two study sites. The $PM_{2.5}$ effect estimates became stronger when meteorological variables were included in the model, and more significant after adjusting for maximum or minimum temperature. The effect estimates for $PM_{2.5}$ on non-asthmatic participants became stronger and close to significant after controlling for RH.

Effect estimates for O_3 on observations from asthmatic participants was slightly diminished and no longer significant after including $PM_{2.5}$ in the mixed models. Also, the standard error was widened after controlling for acid aerosols, probably for the same reason as for $PM_{2.5}$. The O_3 effect estimates became stronger and significant after controlling for maximum temperature, but the other meteorological variables did little to change them.

Acid aerosol effect estimates became more negative for asthmatic participants after controlling for meteorological variables, and became significant after controlling for RH. The acid aerosol estimates were reduced to near zero after controlling for O_3 or $PM_{2.5}$. The effect of NO_2 became stronger with acid aerosols in the model, and significant with minimum SO_2 in the model, although it lost significance after including any of the other parameters.

PROC MIXED has no output showing the stability of estimates in the presence of multi-collinearity amongst the atmospheric parameters in the model but it accounts for the downward bias by using the approximate t and F statistics.

Also, in the OLS comparison models we used the VIF and COLLINOINT diagnostic options in PROC REG to assess the stability of the parameter estimates. A variance inflation factor (VIF) or Eigenvalue index of 10 or more indicates that the estimates are starting to become unstable, and indexes of 100 or more indicate serious collinearity issues (Belsley et al., 1980). The VIF for the estimates in the two variable OLS models which used observations only from asthmatics spending >5 hours outdoors were between 1 and 1.5. Most condition indexes for the lowest eigenvalue in models with significant effects were less than 2. Although the level of correlation between pollutants and copollutants of models presented here were not high enough to cause statistical instability in the parameter estimates, caution should still be used when interpreting the results.

The second method (suggested in U.S. EPA, 2004) we used to assess the effect of collinearity on pollutant effect estimates was to examine for trends occurring in the relationships between the site-specific pollutant effect estimates and the respective coefficient of the linear regression between the pollutant and copollutant. To do this, at each site we calculated the pollutant effect estimates for O_3 and $PM_{2.5}$ after controlling for a second parameter in the model, and also the coefficient of the linear regression between O_3 or $PM_{2.5}$ and the second parameter. We then performed second-stage linear regressions on the effect estimates and linear regression coefficients across sites. A pattern in the second-stage regression could indicate the dependence of the pollutant effect on the presence of the second parameter in the model. We found no significant relationships (at α=0.05) in the second-stage regressions for all participant and or

asthmatic participant only models for observations made when the participant spent >5 hours outdoors. A suggestive positive increase in the effect estimate for O_3 for all participants was apparent when its regression coefficient with NO_2 was larger at a site (p=0.06 for the second-stage regression). This was not true for asthmatic participants.

Discussion

In this study we found O_3 and $PM_{2.5}$ to be significantly associated with declines in FEV1 of asthmatic participants spending >5 hours outdoors. Same day O_3 and $PM_{2.5}$ were more negatively associated with FEV_1 than any other pollutant or meteorological variables considered. The acid aerosol component of the PM also demonstrated negative associations but fell short of significance (at α=0.05) as the number of observations were limited as it was measured at fewer study locations. These findings are consistent with the recent body of literature suggesting that O_3, $PM_{2.5}$, and acid aerosols are the outdoor pollutants of primary concern for pulmonary health. The size of the effect estimates presented here are slightly smaller but in the same order of magnitude of those from recent research. Our effect estimates from the multiple pollutant models presented here were mathematically stable. However, assigning causality to observed effects to any specific pollutant or combination of pollutants could not be performed because of multicollinearity among the pollutants.

Many studies have focused on the effects of air pollution on participants who were primarily outdoors during the day (e.g. summer camp studies) and also

participants with relatively normal exposures. There were few studies that examined or reported specifically how the effect of air pollution is modified by the amount of time spent outdoors. Here, we found that same day O_3, $PM_{2.5}$, and acid aerosols significantly affected the FEV_1 of asthmatic participants spending >5 hours outdoors, but the same day estimated effects of pollutants were near zero for participants spending <5 hours outdoors. The lack of relationship between the <5 hours outdoors observations and outdoor air pollution as measured at a central-site was not surprising given that indoor air quality can be very different from outdoor air quality (Delfino et al., 2004; Wallace et al., 2003).

We found larger effect estimates for asthmatic participants than we did for non-asthmatics. This concurs with the majority of previous findings. We found no clear differences in effect estimates between asthmatic participants taking asthma maintenance medication and those not. Of the parameters with significant effects, only $PM_{2.5}$ had more negative effect estimates for maintenance medication users. Our findings did not demonstrate clear differences between medication users and non-users because only two asthmatic participants were not using an inhaler.

Our effect estimates were not significant for same day air pollution on asthmatic participants spending <5 hours indoors or for non-asthmatic participants regardless of time spent outdoors. However, for asthmatics, lagged values of air pollution including O_3, $PM_{2.5}$, and acid aerosols became more negative with each successive lagged day, reaching maximum effect at a 3-day lag. Lagged effects have been observed in previous research. Vedal et al.

(1998) found that the strongest lags for PM10 were for 2, 3, and 4 days, but found effects up to a 7 day lag. Delfino et al. (1998), Pope et al., (1992), and Delfino et al. (2004) found that the strongest effects from PM were associated with a 5 day moving average of PM. Our 5-day cumulative exposure estimates (divide by 5 for average) were not as strongly associated with declines in FEV_1 in asthmatics as was the 3-day lag.

Our $PM_{2.5}$ effect estimates for asthmatics spending >5 hours outdoors were similar in size to those of Delfino et al. (2004) for when they associated FEV_1 with central site 24 hour mean $PM_{2.5}$ measures. However, our effect estimates for asthmatics that do not account for the amount of time spent outdoors are an order of magnitude smaller. Our effect estimates for O_3 were slightly smaller than those of Korrick et al. (1998; -1.9% vs. -2.2%) but their participants were actively hiking during the time of exposure whereas we are uncertain of the level of physical activity of our participants. Our effect estimates for O_3 on asthmatic participants were slightly less than half of what Jalaludin et al. (1999) found in their cohort of children with a history of wheeze (-0.38% vs. -0.9%), but their estimates were for PEFR. Comparison with other studies is difficult because volumetric effects are calculated for each individual and then the estimates are polled together, where we have calculated percent deviation after correcting for individual characteristics. We chose not to calculate volumetric estimates because our choice of mixed linear models was better facilitated by our analysis and this method produces results as percent deviation. Our technique let us take advantage of all of the participants data when calculating the effect

estimates for the relatively few observations taken when the participant spent a significant amount of time spent outdoors.

The effect estimates observed here are relatively small, and we agree with Korrick et al. (1998) in that a <1% change in FEV_1 is probably clinically insignificant. However, our effects represent group averages, and small changes in group effect estimates can translate to large effects in individuals at the distribution extremes. Kinney et al. (2000) found that group effects averaged to a -1% change from O_3 over the course of the summer, but up to -6% changes were seen in 10% of the individuals. Jalaludin et al. (2000) found that some participants had much larger effect estimates than what the group mean estimate suggested. They found that a 40 ppb increase in O_3 led to a 1-4% decline in PEFR but also to a 20% increase in the number of individuals with PEFR more than 20% below the group mean.

Given that $PM_{2.5}$ and O_3 are often correlated with meteorology, and specifically temperature, there has been some concern that studies similar to this one are inaccurate because they do not adequately control for meteorological confounding and are not able to associate effects with the actual causative parameter accurately. Here, we observed a low to moderate level of correlation between atmospheric parameters depending on parameter and study site. The effects of O_3, $PM_{2.5}$, and acid aerosols lost significance when any of them were in the same model together which is similar to what Korrick et al. (1998) observed (although they still simultaneously adjusted for $PM_{2.5}$ and acid aerosols in the O_3 effect estimates). This suggests that the variance explained by $PM_{2.5}$, O_3, and

acid aerosols was shared or that one or two of them had effects because of their correlation with the third. The effect of $PM_{2.5}$ was robust to the addition of any meteorological parameters and the relationships generally displayed increased significance. The effect of O_3 did not change in magnitude but after including different meteorological parameters had p values closer to 0.05 with some causing O_3 to lose significance. Our two pollutant model results suggest that the pollutants more likely to be associated with the declines in FEV_1 were O_3, $PM_{2.5}$, and if more observations were available, probably acid aerosols as well.

Overall, model fits explained less than 5% of the variance in FEV_1 in asthmatics spending >5 hours outdoors. This estimate was calculated from the adjusted R^2 from OLS models on a dataset collapsed to observations taken when the participant was asthmatic and spent >5 hours outdoors. In the mixed models, the null model likelihood ratio test gave unrepresentative estimates of explained variance (which were approximately less than 2%) because the majority of observations in the model were taken when the participant spent <5 hours outdoors. Therefore, the bulk of observations in the model couldn't be explained with outdoor air quality as measured at a central location. These observations were included to help builder stronger covariance structures and allow the model to more accurately adjust for time trends in the participants measures. It was not possible to calculate the explained variance in the mixed models only for observations made by asthmatics when they spent >5 hours outdoors. Given that the R^2 of the collapsed dataset OLS models was 5%, we assume that the explained variance for those observations in the mixed models were at least 5%.

Our models suggest that upwards of 95% of the variance in FEV_1 can be attributed to factors other than outdoor air pollution as measured at a central site. We hypothesize that a larger portion of the explained variance could be explained if higher quality pulmonary function measures (i.e. clinical spirometry) and ventilation rate and personal air pollution measures could be made on each individual.

This study is one of the larger of its kind and we found the number of observations >5 hours outdoors to be limiting with respect to statistical strength. We feel that the estimated effects are robust to statistical outliers of both individual participants and observations, and additional observations would probably serve to reduce the standard error of the estimate but not significantly change its size.

Conclusions

In this longitudinal panel study we collected twice daily FEV_1 measurements from 165 participants over the course of two summer months with relatively low air pollution in New England. The resulting dataset contained over 7,000 observation days, making it a comparably large study. Pulmonary function observations were paired with criteria air pollutants, acid aerosols, and meteorological measures. We found significant results when we examined a sensitive subpopulation (asthmatics) spending >5 hours outdoors who were exposed to higher outdoor air pollutant levels.

The key findings of our research were as follows: *a*) in single pollutant models we found O_3 and $PM_{2.5}$ to have significant (α=0.05) effects on the FEV_1 of

asthmatic participants spending more than 5 hours outdoors; *b*) we found no significant effects from same day air pollution when the participant, asthmatic or not, spent less than 5 hours outdoors; and *c*) because of the correlation between pollutants and the results of our models, we could not isolate with certainty which of O_3, $PM_{2.5}$, acid aerosols, or a combination of these pollutants was associated with the FEV_1 declines. Our results suggest that outdoor air pollution as measured at a central monitoring site is associated with small but significant declines in FEV_1 within sensitive subpopulations in New England. Up to 95% of the variance in a participants ability to breathe was explained by factors other than outdoor air pollution as measured at a central site.

We found FEV_1 to be significantly affected by $PM_{2.5}$, O_3, and acid aerosols when participants spent >5 hours outdoors after controlling for meteorological conditions. The amount of time spent outdoors was an important air pollution effect modifier and we recommend it be included in future research. The effects observed in this study occurred at relatively low levels of air pollution with no NAAQS violations for $PM_{2.5}$ and only 2 violation days for maximum 8-hour O_3 in the region. Ideally, we would have measured the level of air pollution that each individual was breathing at a high resolution and also their ventilation rate. This would increase the accuracy and precision of the outdoor air pollution effect estimates as this component could be better isolated from complete personal exposure profiles.

CHAPTER IV

DISCUSSION AND RECOMMENDATIONS FOR FUTURE RESEARCH

Our goal for the analyses were to obtain pollutant specific health effect estimates that would help us in forming regionally accurate decision relevant mitigation strategies that could be implemented by individuals and institutions. Our data collection goal was to obtain a high spatial and temporal resolution database to be used to assess the effects of moderate air pollution on an individual's pulmonary function and daily respiratory symptoms. To do this we collected as many health measures from as many participants as possible in a diverse population.

In our analysis of the ensuing data we found associations between asthmatic participants spending >5 hours outdoors and outdoor air pollution as measured at a central site. However, we did not observe significant effects from same day pollution or meteorological parameters in the non-asthmatic population or in observations from asthmatics spending <5 hours outdoors. These observations greatly outnumbered the number of observations >5 hours outdoors. Our analyses suggests that when air pollution in New England is relatively mild, as it was in summer 2004, that the effects of same day outdoor air pollution as measured at a central location are limited to those persons who are sensitive (asthmatics and probably those with COPD) and spending a significant portion of their day outdoors. We did find evidence that asthmatic participants

were affected by air pollution up to 3 days after the air pollution event regardless of how much time they spent outdoors on the day of the air pollution event or day of the FEV_1 measure.

Most studies acknowledge their limitation regarding the lack of personal exposure measurements. They apply the assumption that if enough observations are collected the health effects associated with outdoor air pollution as measured at a central location will emerge through the cloud of health effects associated with the true behavior modified personal atmospheric exposures. However, as our results suggest, that the effects (at least to FEV_1) associated with outdoor air pollution as measured at a central site make up roughly only 2% of a person's total variation in FEV_1. Further, if the measurement error between and within individuals could be accounted for there would be even less total variance for the pollution measures to explain.

In previous research, little attention has been paid to the amount of time spent outdoors. At the time we were designing this study we were not focusing on assessing the influence of the amount of time spent outdoors on pollution effect estimates. We now understand that our classification variable for time spent outdoors used somewhat arbitrary classification levels and that better measures of time spent outdoors could have been implemented. Capturing a more appropriate exposure measure without significantly increasing study cost could be accomplished by collecting a binary classification variable for each hour of the day indicating whether the participant was indoors or outdoors and another binary variable for physical exertion during those hours. These variables could

be used to re-weight daily exposure estimates or to form cumulative daily outdoor air pollution exposures for each level of exertion. For our study design (which was almost completely volunteer participants) this might have been an unreasonable request. However, the results could be used directly in a system which could provide decision relevant air pollution information to the public.

It is clear that there is a large amount of variation in exposure between individuals which depends on lifestyle and behavior. The combinations of personal exposure are many and difficult to group if the home, workplace, transportation, and regional environments are considered along with activity level and sensitivity of the individual. We have only started to scratch the surface of which of these environments and behaviors are most important in determining exposures and affecting health (Delfino et al., 2004; Wallace et al., 2003).

The research performed by Delfino et al. (2004) demonstrates that measuring personal exposures is an arduous and resource intensive process. Although their methodology is almost exactly what is needed to accurately assess the effects of air pollution on pulmonary function, the scale of their study is nowhere near what will be needed to accurately assess the effects on a diverse population. Their work determined that personal exposures were as or more important in explaining pulmonary function variance than outdoor air pollution as measured outside the home or at a central site. This also is reinforced by our ability to explain only about 2% of the variance in FEV_1 of our participants with outdoor air pollution as measured at a central site.

These findings suggest that there is certainly a place for research that focuses on the effects of outdoor air pollution as mitigation and intervention strategies can potentially protect 5% of an individual's pulmonary function, even when air pollution is only moderate. However, if we take personal exposures into account as well, we can develop mitigation and intervention strategies which have a larger impact. Because societal and economic limitations on the individual don't always allow for the individual to protect themselves from outdoor air pollution (e.g. a low-income worker who will not be paid if they refuse to work outdoors in polluted conditions or a student athlete on a sports scholarship), combined strategies would be further reaching as they could allow for the individual to at least protect themselves and family from personal and personally created exposures.

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APPENDICES

APPENDIX A

PARTICIPANT CONSENT FORM

HEALTH
AIR INHALE
INTEGRATED HUMAN HEALTH AND AIR QUALITY ASSESSMENT

Climate Change Research Center • Institute for the Study of Earth, Oceans, and Space
University of New Hampshire, Durham, NH 03824 • 603-862-2329 • http://inhale.unh.edu

Summer 2004 New England Health Tracking

Permission to Participate

I, _____, agree to allow UNH to use my daily pulmonary function measurements, daily health symptom and medication questionnaire responses to examine the effect of outdoor air quality on human health during the summer of 2004

I realize that participation in this study involves:

- Twice daily spirometry measurements. Spirometry is a non-invasive procedure which requires the participant to breathe into an apparatus to record lung capacity. The spirometry procedure presents no risk to the participant.
- Filling out a daily respiratory symptom questionnaire.

I also realize that I can stop my participation in this study at any time.

I also give the researchers from UNH access to study questionnaire responses to assist them in identifying any health-related factors that may be important in the analysis of the data.

If you have any questions about your rights as a research subject, you may contact Julie Simpson in the UNH Office of Sponsored Research at 603-862-2003 to discuss them

_____
(Signature)

_____
(Print name)

Over

Summer 2004 - New England Health Tracking

Participant Questionnaire

Name _____ Date:_____
Last *First*

Gender (circle) Male Female

Ethnicity (circle) Asian Black Caucasian Hispanic Other_____

Date of Birth MM_____ DD_____ YYYY_____

Height (inches) _____ Weight (pounds) _____

Home address City_____ State_____ Zip_____

Work address City_____ State_____ Zip_____

Phone: Work_____ Home_____ Mobile_____

Email _____

Has/Does the participant	Yes	No	List all medications taken routinely: Medication type	Frequency taken
Have asthma?	☐	☐	_____	_____
(Circle one) If yes, do you use an inhaler?	Yes	No	If Yes, how often? _____	
Have allergies?	☐	☐	_____	_____
Have COPD* *(Chronic Obstructive Pulmonary Disorder)*	☐	☐	_____	_____
Smoke	☐	☐	Years smoked	_____
			Date stopped	_____
			Amount smoked	_____
Take other medication	☐	☐	_____	_____

Detail any "Yes" answers below, include allergy types:

_____

_____

_____

_____

Over

APPENDIX B

PARENTAL CONSENT FORM

HEALTH
AIR INHALE
INTEGRATED HUMAN HEALTH AND AIR QUALITY ASSESSMENT

Climate Change Research Center • Institute for the Study of Earth, Oceans, and Space
University of New Hampshire, Durham, NH 03824 • 603-862-2329 • http://inhale.unh.edu

Summer 2004 New England Health Tracking

Permission to Participate

My child, _____, has my permission to participate in the UNH study to examine the effect of outdoor air quality on human health during the summer of 2004

I realize that participation in this study involves:

- Twice daily spirometry measurement of my child. Spirometry is a non-invasive procedure which requires the child to breath into an apparatus to record lung capacity. The spirometry procedure presents no risk to the child.
- Filling out a daily respiratory symptom questionnaire.

I also realize that either I or my child can stop my child's participation in this study at any time.

I also give the researchers from UNH access to study questionnaire to assist them in identifying any health-related factors that may be important in the analysis of the data. Any information from your child's camp health form will be kept strictly confidential.

If you have any questions about your child's rights as a research subject, you may contact Julie Simpson in the UNH Office of Sponsored Research at 603-862-2003 to discuss them

_____
(Parent or legal guardian signature)

_____
(Print name)

Over

Summer 2004 - New England Health Tracking

Participant Questionnaire

Name _____ Date: _____
Last *First*

Gender (circle) Male Female

Ethnicity (circle) Asian Black Caucasian Hispanic Other_____

Date of Birth MM_____ DD_____ YYYY_____

Height (inches) _____ Weight (pounds) _____

Home address City_____ State_____ Zip_____

Work address City_____ State_____ Zip_____

Phone: Work_____ Home_____ Mobile_____

Email _____

Has/Does the participant	Yes	No	List all medications taken routinely: Medication type	Frequency taken
Have asthma?	☐	☐	_____	_____
(Circle one)				
If yes, do you use an inhaler?	Yes	No	If Yes, how often? _____	
Have allergies?	☐	☐	_____	_____
Have COPD* *(Chronic Obstructive Pulmonary Disorder)*	☐	☐	_____	_____
Smoke	☐	☐	Years smoked	_____
			Date stopped	_____
			Amount smoked	_____
Take other medication	☐	☐	_____	_____

Detail any "Yes" answers below, include allergy types:

_____

_____

_____

_____

Over

APPENDIX C

INSTITUTIONAL REVIEW BOARD APPLICATION

B. Description of Project

1. Introduction

Overall Goal: The proposed project, "Summer 2004 - New England Health Tracking" partners with several health related organizations throughout New England to assess the impact of air quality on the respiratory health of children and adults at 24 sites in New England and one site in New Brunswick during the summer of 2004. This health tracking effort is closely linked with a large air quality study in New England that will occur during July and August 2004 (see attachment on ICARTT).

2. Specific Aims

(i). Use trained staff to collect health outcomes data from study participant using daily symptom questionnaires and twice daily spirometry data to determine levels of respiratory distress at thirty location in New England.
(ii). Compare daily spirometry data, symptom data and clinic visits data for respiratory with and quality indicators (ozone, fine particles, sulfur dioxide, pollen, etc.) to determine the effect of air quality on health outcomes.

3. Research Protocol

A. Setting

The subject sample used for health outcomes data will be children (older than 12) and adults at 24 sites in new England and one site in New Brunswick (Table 1). The study sites identified as Sentinel Physician Sites, Hospitals and Companies, Summer Camps, and Scientists. For the Sentinel Physician Sites and Summer Camps we will be working with local health care providers to identify participants and collect data. At the other sites, we will work directly with hospital employees and scientists to collect health effects data. Data collection will occur from June 21 to August 28, 2004.

B. Investigator Experience

Cameron Wake is Research Associate Professor, Climate Change Research Center, Institute for Earth, Oceans, and Space and the Department of Earth Science. He is a geochemist and climatologist, as well as PI and co-PI on grants investigating air quality and human health in New England. For the past three years, Dr. Wake has been PI on the INHALE (integrated Human Health and Air Quality Research) integrated assessment funded by NOAA.

J.C. Salloway is Professor of Health Management and Policy. He has been the PI on many projects and has published four books and many articles.

Tom Lambert is a masters student in earth Sciences working with Dr. Cameron Wake

Table 1. Planned Sites for New England Health Tracking - Summer 2004

	City, State	Participating Institution	n
II	**Sentinel Physician Sites**		
1	Burlington, VT (NECF)	Community Health Center of Burlington	30
2	Dartmouth, NH	Dartmouth Hitchcock Medical System	50
3	Camden, ME	Penobscot Bay Medical center	50
4	Manchester, NH		30
5	Laconia, NH	Lakes Region Pediatrics	30
6	Roxbury, MA	John Snow Institute	30
7	Pawtucket, RI (NECF)	Blackstone valley Community Health Center	30
8	New Haven, CT (NECF)	Hill Health Center	30
II	**Hospitals/Companies**		
9	Exeter	Exeter Hospital	100
10	Portsmouth	Portsmouth Regional Hospital	100
11	Dover	Wentworth Douglas Hospital	100
12	Marlboro	CISCO Systems	100
13	Exeter	Riverwoods	30
III	**Summer Camps**		
14	Burlington VT	University of Vermont	30
15	Bar Harbor	College of the Atlantic	30
16	Portsmouth,NH	New Heights	30
17	Bridgeport, CT	Harding Horticultural Society	30
IV	**Scientists at Research Facilities**		
18	Bar Harbor	Jackson Lab	30
19	Boothbay Harbor	Bigelow Laboratory	30
20	Appledore Island	Isles of Shoals Marine Laboratory	30
21	Portsmouth NH	NEAQS 2004 staff scientists	50
22	Petersham MA	Harvard Forest Research Site	30
23	Gulf of Maine	NOAA Vessel Ron Brown	20
24	White Mountains	App Mountain Club	20
VI	**New Brunswick**		
25	New Brunswick	New Brunswick Lung Association	30
		Total number of subjects	**1070**

C. Protocols

Summer 2004 - New England Health Tracking will study the effect of ambient air quality on participants, with special attention to spirometry data and behavioral data as outcome measures. The total N for the entire project will be approximately 1070 individuals.

All participants will fill out a questionnaire (Attached document 1) prior to the study. We expect to identify three study groups: diagnosed asthmatics who have been identified on their questionnaires, undiagnosed asthmatics, and normal controls

Participants will be blow into a spirometer (Figure 1) twice daily and will fill out a daily form (Figure 2) detailing any respiratory symptoms they experience and medication they may have taken. Each participant will be provided their own individual spirometer. The spirometer will provide a measure of twice-daily peak expiratory flow rate (PEFR) and forced expiratory volume in one second (FEV_1) and six seconds (FEV_6). These data are stored electronically for up to one month. The data are easily downloaded via an infrared communication port by placing the unit on a cradle connected to a computer. Each study site will have a dedicated cradle and computer.

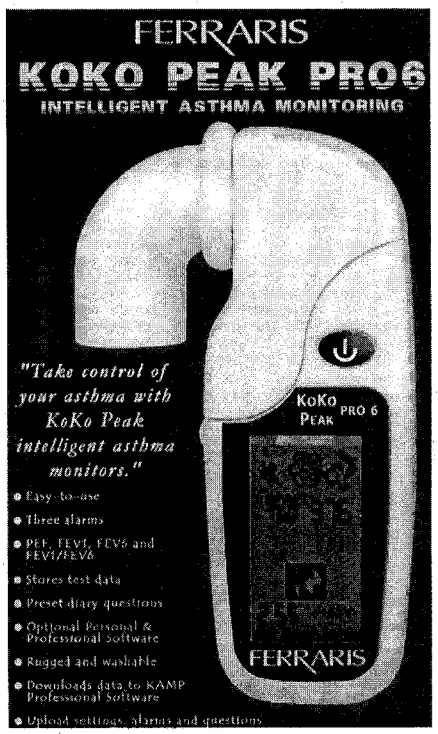

Figure 1. Spirometer

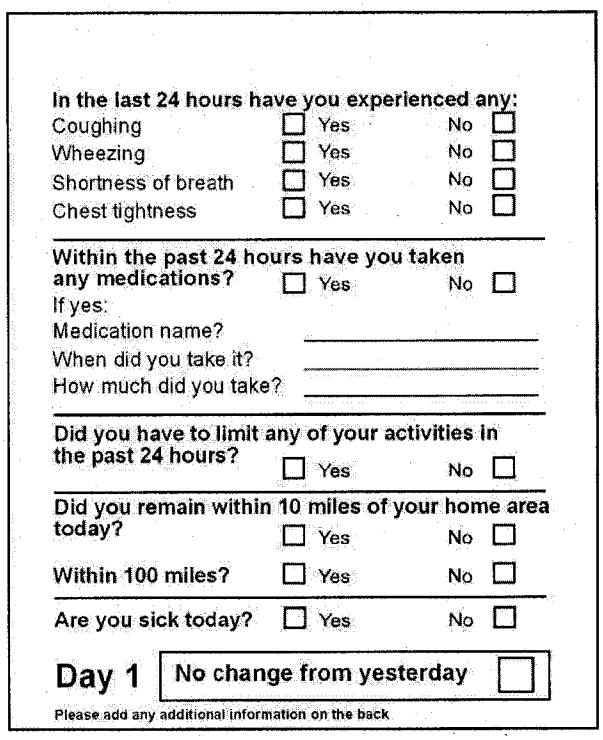

Figure 2. Daily symptom questionnaire.

In addition, by entering the participants height, sex, ethnicity and age data into the spirometer, it is possible to calculate their total potential expiratory volume and their actual expiratory volume and thus to derive a measure of respiratory distress which is displayed on the spirometer readout every time lung function is tested

Data confidentiality is a primary concern. All data will be gathered in a three-part system. In part one, participants will fill out a questionnaire (Attached document 1). Second, each participant name will be assigned an ID number that will also be used to

identify the spirometer. The data will be entered into a computer spread sheet by name. There will be no other data on this list. Third, all pulmonary function data and daily symptom data will be collected based on participant/spirometer ID number, not by name. The two lists, both of which are necessary to identify an individual camper will, then be separated and stored in locked file cabinets at UNH. Thus, it will be possible under emergency need to re-create the links from name to data, but only if the keepers of both lists agree that this is necessary. This process will be used for all data as it is collected. The overall results of the study will be made available to participants.

D. Procedures for Obtaining Consent

Consent for children will be obtained via a 'permission to participate' form (Attached document 2). We will send this form home to the parents with a letter (Attached document 3). In addition, assent will be obtained from all children participating in the study via an initial interview with each child before any measurements are taken. This will be accomplished in the presence of the two trained research assistants (one will ask the question and the second will be the witness).

4. Data

Hourly ozone and fine particles will be measured by AIRMAP and at EPA sites around New England. Air quality measures will be analyzed using a series of Poisson (log-linear) regressions to model the health outcomes variables as functions of air pollution. The ultimate goal is to understand the association of certain pollutants (especially ozone, fine particles, and allergens) with respiratory function, and respiratory symptoms. One important outcome of this analysis will be to quantify any increase above baseline measures of pulmonary function and respiratory complaints which occur in response to increases in ambient air pollution.

The Poisson regression will be used to find pollutant coefficients which will estimate the number of negative health outcomes due to a specific level of increase in the concentration of specific pollutants. By stratifying the samples into diagnosed asthmatics, non-diagnosed but symptomatic, and non-symptomatic samples, we will be able to determine if air pollution has differential effects on sub-samples of the population.

Atmospheric Episode Studies

The most obvious analyses will be studies of pulmonary function as a result of discrete atmospheric episodes. This study will assess the respiratory function of participants on days as these relate to episodes of high levels of ozone, fine particles and allergens, etc. The hypothesis here is that during air pollution events pulmonary function in participants will show declines and lead to decreased activity and/or use of medications.

Time Trend Studies

Further, it will be possible to assess pulmonary function with regard to time. Time studies will include two dimensions—time accumulation and incubation period. In the first, we can examine the relationship between pulmonary function and total time exposed to atmospheric agents. This will prove a dose-response study. We will hypothesize that the higher the dose of pollutants, the more compromised the pulmonary function and the higher the number of decreased activity days and use of medications. In

the second set of time-trend studies we will assess incubation period and ask how long it takes from exposure to atmospheric agents and compromised pulmonary function as evidenced by peak flow declines and complaints. We will ask if the compromise is fast appearing or if there is a latency period before loss of function appears.

Additional Research Design

There are a number of research designs which will be employed in the studies which will enable us to reach defensible conclusions. Such will include time trend studies, ecological studies, and dose-response studies.

The first of these, time trend studies, will track atmospheric events on a time line and will track respiratory events as well. Thus, it will be possible to graph peaks in atmospheric particulates and ozone, for example, and to graph reports of breathing difficulty and compromised (though possibly unreported) respiratory compromise.

Dose-response studies are another tactic which helps to isolate causality. Efforts will be made to assess exposures to outdoor atmospheric events and to determine if there is relationship between the degree of exposure and health outcomes. If there is, this is a powerful argument for the centrality of the exposure to the outcome. If there is not a dose-response relationship, the data is more questionable.

5. Risks

There are no risks to participants in the study. Spirometers are often used in such studies of children and there are no reported adverse effects (e.g., Kopp et al., 2000, Mortimer et al., 2002, Spektor et al. 1988, Thurston et al., 1997). Furthermore, spirometers are often used by asthmatics as a personal asthma management tool.

6. Benefits

Campers will experience an environment in which the local air will be monitored for and efforts will be made to alert camp officials to the presence of hazardous air pollution. Further, campers who show declines in respiratory function will be identified to the camp nurse for a program of intervention.

C. References

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Attached documents

1. Questionnaire

2. Consent Form

3. Letters to Parents

Summer 2004 - New England Health Tracking

Participant Questionnaire

Name _____
Last *First*

Gender (circle) Male Female

Ethnicity (circle) Asian Black Caucasian Hispanic Other

Date of Birth MM_____ DD_____ YYYY_____

Height (inches) _____ Weight (pounds) _____

Home address City_____ State_____ Zip_____

Work address City_____ State_____ Zip_____

Phone Work_____ Home_____

Email _____

Has/Does the participant taken	Yes	No	If yes: list all medications taken routinely medication type	frequency
Have asthma?	☐	☐	_____	_____
Have allergies?	☐	☐	_____	_____
Have COPD*	☐	☐	_____	_____

(*Chronic Obstructive Pulmonary Disorder)

Smoke ☐ ☐ Years smoked _____

Date stopped _____

Amount smoked _____

Take other medication ☐ ☐ _____ _____

Detail any "Yes" answers below:

_____

_____

_____

_____

Permission to Participate

My child, _____, has my permission to participate in the UNH study to examine the effect of outdoor air quality on human health during the summer of 2003

I realize that participation in this study involves :

- Twice daily spirometry measurement of my child. Spirometry is a non-invasive procedure which requires the child to breath into an apparatus to record lung capacity. The spirometry procedure presents no risk to the child.
- Filling out a daily respiratory sympton questionnaire.

I also realize that either I or my child can stop my child's participation in this study at any time.

I also give the researchers from UNH access to study questionnaire to assist them in identifying any health-related factors that may be important in the analysis of the data. Any information from your child's camp health form will be kept strictly confidential.

If you have any questions about your child's rights as a research subject, you may contact Julie Simpson in the UNH Office of Sponsored Research at 603-862-2003 to discuss them

_____

(Parent or legal guardian)

INHALE/UNH Letterhead

June , 2004

[Click **here** and type recipient's address]

Dear Parent:

This summer <our clinic> will be joining the University of New Hampshire's Climate Change Research Center in a project to study the effect of outdoor air quality on human health. We are asking that you consider having your son or daughter participate in this project.

The study involves monitoring the air quality while concurrently monitoring the children's respiratory health. Twice day participants will be asked to breathe into a small hand held spirometer that measures lung capacity. These measurements will then be analyzed against the air quality measurements. The procedure of blowing into the spirometer is non-invasive and takes but a few moments. The participants will also be asked to fill out a daily respiratory symptom questionnaire

Participation in the study will not affect the child's participation in any activities. We anticipate that the spirometric measurements will be collected before or after breakfast and before the dinner hour.

<our clinic> is very excited about our role in this very important and timely study. Participation in the study is voluntary. If you wish your child to participate, please sign and return the enclosed permission slip. We are also asking that you grant the researchers access to the camp health form. This will enable them to identify any additional health-related factors that may be important in the analysis of the data. The researchers agree to keep all information confidential.

If you have, any questions regarding this research project please do not hesitate to call me at _____

Sincerely,

<clinic representative>

APPENDIX D

INSTITUTIONAL REVIEW BOARD APPROVAL LETTER

UNIVERSITY of NEW HAMPSHIRE

June 16, 2004

Wake, Cameron
Climate Change Research Center
Morse Hall
Durham, NH 03824

IRB #: 2967
Study: Integrated Human Health and Air Quality Research (INHALE)
Approval Expiration Date: 06/06/2005 **Modification Approval Date:** 06/16/2004
Modification: Addition of sites and expanded sample

The Institutional Review Board for the Protection of Human Subjects in Research (IRB) has reviewed and approved your modification to this study as indicated above with the following coment(s):

- Before recruiting or involving any participants from the Sentinel Physician (group I) and the summer camps (group III) sites, the investigator needs to forward a letter of support for the study from the director/person in charge of each site. If patients are being recruited from hospitals/companies (group III) sites or New Brunswick Lung Association (group V), then the investigator needs to forward to the IRB for each site a copy of the IRB approval letter (if the site has an IRB) or a letter in support of the study from the director prior to any recruitment activities.

Further changes in your study must be submitted to the IRB for review and approval prior to implementation.

Approval for this protocol expires on the date indicated above. At the end of the approval period you will be asked to submit a report with regard to the involvement of human subjects in this study. If your study is still active, you may request an extension of IRB approval.

Researchers who conduct studies involving human subjects have responsibilities as outlined in the document, *Responsibilities of Directors of Research Studies Involving Human Subjects.* This document is available at http://www.unh.edu/osr/compliance/IRB.html or from me.

If you have questions or concerns about your study or this approval, please feel free to contact me at 603-862-2003 or Julie.simpson@unh.edu. Please refer to the IRB # above in all correspondence related to this study. The IRB wishes you success with your research.

For the IRB,

Julie F. Simpson
Manager

cc: File
Jeffrey Salloway
Tom Lambert

Research Conduct and Compliance Services, Office of Sponsored Research, Service Building, 51 College Road, Durham, NH 03824-3585 * Fax: 603-862-3564

APPENDIX E

CONFIDENTIALITY PROCEDURES

AIR HEALTH INHALE

INTEGRATED HUMAN HEALTH AND AIR QUALITY ASSESSMENT

Climate Change Research Center • Institute for the Study of Earth, Oceans, and Space
University of New Hampshire, Durham, NH 03824 • 603-862-2329 • http://inhale.unh.edu

PULMONARY FUNCTION MEASUREMENT GUIDELINES

http://inhale.unh.edu

Contact Tom Lambert at 603-862-4046 or at
Lambert@ccrc.sr.unh.edu for questions or more information

This document provides detailed information for using the KoKo Peak Pro 6 electronic peak flow meter and the KAMP Professional software package.

The spirometer, questionnaire, and study design

We are using KoKo Peak Pro 6 electronic peak flow meters (we refer to it as a spirometer) to measure the daily pulmonary function of individuals throughout New England. The spirometers make three specific measurements:

Peak expiratory flow rate (PEFR)
The PEFR is the maximum rate of flow that is exhaled, measured in liters per minute.

Forced expiratory volume in the first second of exhalation (FEV_1)
FEV_1 measures the volume of air that is exhaled during the first second, measured in liters.

Forced expiratory volume in the first 6-seconds of exhalation (FEV_6)
FEV_6 measures the volume of air exhaled over 6 seconds, also measured in liters. This measurement approximates forced vital capacity, which is the tidal volume of your lungs. The idea here is that if you are exhaling with a maximum effort, you will run out of breath before the 6 seconds ends, and the meter will have recorded the volume of air that has passed through.

For the analysis we will use these measurements, as well as several measurement combinations, such as the FEV_1/FEV_6 ratio, which represents the percent of volume that is exhaled in the first second (higher is better). The spirometer calculates this measurement automatically.

We are providing each participant with their own spirometer. The spirometer can hold 64 measurements in memory, as well as store a unique identification number. This allows each spirometer to be personalized to the subject. The spirometer has several capabilities that we will not use, for example, the questionnaire function will not be used because it is rather cumbersome and time consuming compared to the paper questionnaire we are using.

The spirometer has a feature that allows us to set pulmonary function "zones" for the participant. Each measurement will fall into a specific zone: green, yellow, and red. This allows the participant to see how they are performing compared to average people with their age, height, gender, ethnicity, and weight. Green indicates that the participant is above 80% of their predicted normal. Yellow indicates between 50 and 80% of the predicted normal peak expiratory flow rate (PEFR), orange is not active, and red indicates below 50%. The participant should be informed of what these zones mean, and if they are concerned with their pulmonary function values or performance they should consult a physician. We can and should not attempt to make any type of medical diagnosis.

The spirometer will automatically select the highest value in a 3-minute window, save it, and then discard the lower values. This means that you can blow into the meter as many

times as you want in 3-minutes, but only the highest value is kept. This feature is in place to save memory.

We will supply you with an infrared cradle and KoKo Asthma Management Program (KAMP) Professional software, which you will use to transfer data to and from the spirometers. We will provide you with the software and instruction on how to use it in addition to having this document.

Each participant will also receive a health symptom questionnaire that is to be completed daily. The questionnaire is a pocket-size booklet that holds one month worth of data (one page per day), has measurement protocol information, quick reference guide to meter problems, and instructions for filling out the questionnaire. The back of each page is blank so the participants may take note of any abnormal events.

You will need to ensure the participant knows the proper technique for blowing into the spirometer (Section 6), how to operate the spirometer, when to blow into the spirometer, and when to fill out each questionnaire. You should also provide the protocol page (section 6) to the participant, and tell them what the measurements mean. It is all about redundancy.

The Confidentiality Procedure:

No person should EVER be able to see both the participant's Identification Number (ID#) and name together in the same place. No person should EVER be able to see the participant's name and their data together. This data will be held in a locked and secure location at UNH by Tom Lambert. You should never need identifying information. Do not ever create a list of ID# and participant name for your own use. Even though spirometry information is an easy, non invasive, and socially benign procedure, confidentiality can not be broken. If you follow the procedures outlined below carefully, you will not violate participant confidentiality.

Project Overview:

1) Install the software on your computer and attach the cradle
2) Have the participant fill out the Participant Questionnaire
3) Enter a participants information into the program
4) Program the participants spirometer
5) Instruct the participant on the protocol
6) Contact the participant each week
7) Download data from the participant every-other week
8) Report the data to UNH

Setting Up the Software:

1) Installing the Software

- Close all programs (the computer will need to be restarted when finished installing)
- Follow the setup instructions on the CD Jacket
- Restart your computer
- Attach the cradle to the computer
- If you do not have the appropriate connection port on the back of your computer you will need an adapter. Contact Tom and he will get you one.
- You will need to update the Kamptool.dll file with the new one. Contact Tom for the new file (accounts for it being a leap-year).
- Open the software and click on the "settings" pull down menu, then on the "default settings" button.
- On the "general settings" tab check the "enable change subject ID" checkbox and change the predicted normals to "Hankinson"; click "apply".
- On the "communications tab" check the "create background text export file automatically" check box and highlight the "test data only" radio button at the bottom. Ensure that the "all tests to date" radio button is highlighted and then click "OK".

2) Have the Participant Fill out the Initial Questionnaire

- This is a one-time questionnaire. All information on the questionnaire is strictly confidential.
- We only NEED to know about respiratory medications. The "other medication" question is not absolutely necessary unless it is related to the respiratory system.
- Make a list that includes subject name, phone number, and email address so you can get in contact with the participant. DO NOT INCLUDE THE ID# in this list, if you do you will be in violation of confidentiality. The list can be computerized or on paper.
- Write the subjects ID# on the corner of the participant questionnaire

3) Entering a participants information

- Open the KAMP Software
- Click on the "subject entry/edit" button (looks like a head)
- Click the eraser button to clear all of the fields (this will not erase existing data)
- Use the initial questionnaire form to enter participant information
  - Enter the ID# into the first, last, and ID# fields
  - Enter an "X" into the middle initial field
  - Fill out the height, weight, birth-date, sex, and ethnicity, and click the "calendar" button next to the "Intake Date" field to enter in the current date.

    Do not enter the subject's name into the KAMP Pro software. For first and last name please use the subject's ID# instead, and use an "X" for the middle initial. The name and ID# should never be seen together, and the subject's name and data should never be seen together. The name and ID# list will be locked away at UNH. Do not ever create a list for yourself that contains ID# and name.

- Click the "insert/update record" button (looks like a folder with a plus sign through it)
- Click the "More Subject Info" button (looks like a piece of paper with the corner folded), then click the "Subject Zones" tab. Click "OK". (This step corrects a glitch in the software and will ensure the subject's predicted normal PEFR will be uploaded to the spirometer).
- Exit to the main Kamp Pro screen by clicking the "exit" button (looks like an arrow and a door).

4) Programming a spirometer for a participant

This step has two major components. They are:

1) Uploading the participant's information to the spirometer which sets the predicted normal, the ID#, and the correct time on the spirometer.
2) You then need to have the subject blow a test and then you download it, and then blow another test and download it again. This double blow/download is necessary; it is what synchronizes the date on the spirometer.

Uploading information to the spirometer (1)

- Take the top portion off the spirometer by pushing the white button on the side of the device
- Go into the subject list and select the participant that you want to work with, click the green "go" button. Ensure the appropriate identification number is showing on the window title bar.
- Use a pen, or a paperclip to push the smaller of the two black buttons on the top of the spirometer (small arrows should start moving across the bottom of the LCD display)
- Click the "communications" pull down menu and click "upload data"
- Click the "upload data" button
- Wait for it to finish and keep clicking "OK"

Double blow/download (2)

- Have the participant blow a test on the spirometer
- Download the test by taking off the top of the spirometer and pushing the smaller of the two black buttons (similar to above).
- Click the "download data" button on the KAMP Pro main screen (looks like a head)
- Click the "download data" button again

  Two error messages may appear, one says that the "test dates could not be properly determined", the other says "could not upload new cal date". These messages are OK during the first download.
- Have the participant blow one more test, and download it again. This should sync the date and time on the spirometer. Check the date/time by viewing the graph, or data table. You should receive no error messages during the second download
- Check the date and time of the second measurement by clicking the graphical trends button on the main screen (looks like a graph) and looking at the measurement date and time on the x-axis. The right most measurement should have the correct date and time. If it does not, perform a third measurement/download and check again. If the date is still incorrect contact Tom.

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Measurement Procedure

WHEN:

Each morning

Blow through the meter 3-times each morning, one hour after waking up.

Each evening

Blow through the meter 3-times each evening before dinner.
Fill out the daily questionnaire

ALWAYS:

Wait 1-hour after heavy exercise.
Wait ½ hour after a large meal.

How to Do It

Peak Expiratory Flow Rate (PEFR), Forced expiratory volume in one second (FEV_1), and in six seconds (FEV_6) require a maximal exhalation effort. This means you must inhale as deep as you possibly can, and blow out as fast and as hard as you possibly can until there is no air left in your lungs.

This maximal effort is what makes the measurements reproducible. If it is not done maximally, the tests are of no use. FEV_6 requires that you blow out until you have absolutely no air left, as it is a measure of your effective lung volume. If you still have air left, the test is no good. All of these measurements require that you inhale as deeply as possible, until you cannot take in any more air.

Do the test in a standing, upright position. Try to keep from slouching over or leaning forward at the end of your exhalation.

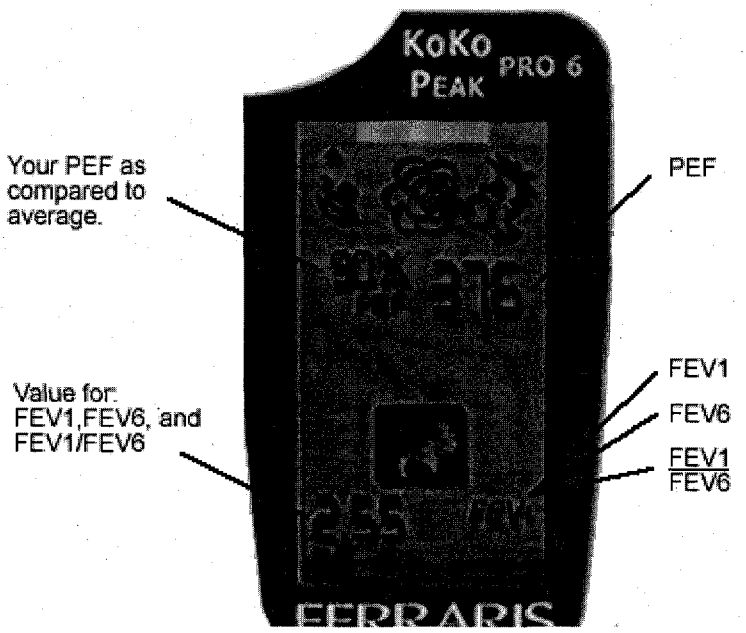
Procedure with the KOKO Peak Pro 6.

- hold the meter away from the mouth (making sure the vents are not covered) and breathe in as **DEEPLY** as possible
- press the blue button on the device, and wait for the second beep
- **seal** your lips around the mouthpiece
- **blast** air out as fast and as far as you can, until the lungs are absolutely empty
- in a few seconds the PEF, FEV1, and FEV6 readings will be displayed
- wait for at least 30-seconds before performing the next maneuver
- repeat the measurement 3-times

Essentials for getting quality measurements

- You MUST breathe in as deeply as possible; this is critical for a reproducible measurement.
- Put the mouth piece in your mouth and seal your lips, do not just press the mouthpiece up against you lips.
- Give a MAXIMUM effort right from the start, and continue until there is absolutely no more air.
- Wait for at least 30 seconds between tests.

The Display



PEF – Peak Expiratory Flow rate
PEF is the highest rate of flow that you can exhale. It can occur at any time during your exhalation. PEF is a measure of the respiratory system's ability to clear air from the lungs. PEF depends on your body size, sex, race, gender and age. PEF is measured in liters per minute.

FEV_1 – Forced Expiratory Volume in the first second
FEV_1 is the volume of air that you exhaled during the first second. Measured in liters.

FEV_6 – Forced Expiratory Volume in 6-seconds
FEV6 is the volume of air you blew out in 6-seconds. If you run out before 6-seconds then the meter measures the usable volume of your lungs. Measured in liters.

FEV1/FEV6 ratio
FEV1/FEV6 is the percentage (displayed as a decimal) of your total volume that you exhaled in the first second. The ratio is a unitless percentage.

6) Contact the participant each week

Try to contact the participant each week by phone, or visit them, please try to do more than email the participant. Try to give them a quick reminder and ask about their progress. Suggest tips to the subject (i.e. Keep the spirometer by the front door, or kitchen) if they are forgetting to do their measurements.

Be friendly and courteous of the participants time. Do not get aggravated. If they decide to leave the study thank them for their time and for trying and see if they will return the spirometer.

7) Download the data every other week

- Take the top off of the spirometer
- Press the smaller of the two buttons quickly
- Put the spirometer on the cradle
- Click the "download data" button on the KAMP Pro main screen
- Ensure the data is going to the correct participant
- Quickly view the data to make sure the date and time are correct
- Make sure the number of measurements is adequate
- Look for zero data in the graphs and make sure there are little to no error codes
- Compare his/her measurements with their controlled measurements

If you see that a participant is in the "Red" zone sporadically or consistently when you download their data and check it, please try to determine if it is a result of measurement error, or if it is a real problem with the individual's lung function. If you feel that the person is at risk and is unaware of the situation you should recommend that they contact a physician immediately. Please contact Tom at 603-862-4046, or Cameron at 603-862-2329 if you have any issue or questions. Do not violate participant confidentiality on your own in any way.

8) Reporting and backing up data

We will be backing up and reporting data regularly to a server at UNH. This will be individualized for each coordinator, but the general procedure is to:

- Create a new network place connection to ftp://lambert@gust.sr.unh.edu on your computer. You can do this through the "my network places" feature on your computer.
- Once on the ftp site, you will place the C:\program_files\kamp_professional\database folder into your personal folder on the server. Depending on your connection speed and database file this may take some time to upload.
- Backup the database folder each time you download the data for all of your participants

APPENDIX F

PEAK FLOW MEASUREMENT PROCEDURE HANDOUT

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Measurement Procedure

WHEN:

Each morning

Blow through the meter 3-times each morning, one hour after waking up.

Each evening

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Wait ½ hour after a large meal.

How to Do It

Peak Expiratory Flow Rate (PEFR), Forced expiratory volume in one second (FEV_1), and in six seconds (FEV_6) require a maximal exhalation effort. This means you must inhale as deep as you possibly can, and blow out as fast and as hard as you possibly can until there is no air left in your lungs.

This maximal effort is what makes the measurements reproducible. If it is not done maximally, the tests are of no use. FEV_6 requires that you blow out until you have absolutely no air left, as it is a measure of your effective lung volume. If you still have air left, the test is no good. All of these measurements require that you inhale as deeply as possible, until you cannot take in any more air.

Do the test in a standing, upright position. Try to keep from slouching over or leaning forward at the end of your exhalation.

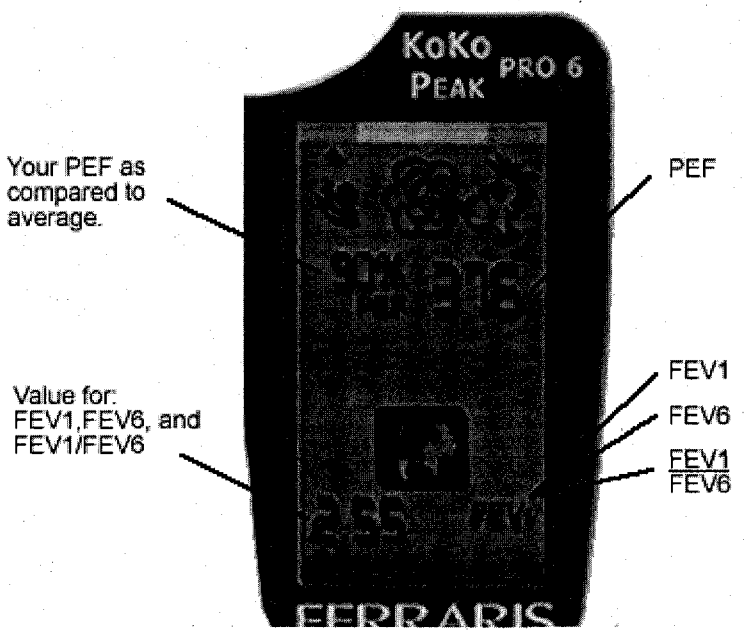
Procedure with the KOKO Peak Pro 6.

- hold the meter away from the mouth (making sure the vents are not covered) and breathe in as **DEEPLY** as possible
- press the blue button on the device, and wait for the second beep
- **seal** your lips around the mouthpiece
- **blast** air out as fast and as far as you can, until the lungs are absolutely empty
- in a few seconds the PEF, FEV1, and FEV6 readings will be displayed
- wait for at least 30-seconds before performing the next maneuver
- repeat the measurement 3-times

Essentials for getting quality measurements

- You MUST breathe in as deeply as possible; this is critical for a reproducible measurement.
- Put the mouth piece in your mouth and seal your lips, do not just press the mouthpiece up against you lips.
- Give a MAXIMUM effort right from the start, and continue until there is absolutely no more air.
- Wait for at least 30 seconds between tests.

The Display



PEF – Peak Expiratory Flow rate

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FEV_1 – Forced Expiratory Volume in the first second

FEV_1 is the volume of air that you exhaled during the first second. Measured in liters.

FEV_6 – Forced Expiratory Volume in 6-seconds

FEV_6 is the volume of air you blew out in 6-seconds. If you run out before 6-seconds then the meter measures the usable volume of your lungs. Measured in liters.

FEV_1/FEV_6 ratio

FEV_1/FEV_6 is the percentage (displayed as a decimal) of your total volume that you exhaled in the first second. The ratio is a unitless percentage.