Contribution of the in-vehicle microenvironment to individual ambient source-derived NO_2 exposure concentration

Tyler Nicholas

A thesis
submitted in partial fulfillment of the
requirements for the degree of

Master of Science

University of Washington
2014

Supervisory Committee:
Joel Kaufman, Chair
Lianne Sheppard
Scott Meschke

Program Authorized to Offer Degree:
Department of Environmental and Occupational Health Sciences

University of Washington

ABSTRACT

Contribution of the in-vehicle microenvironment to individual ambient source-derived NO_2 exposure concentration

Tyler Nicholas

Chair of the Supervisory Committee:
Professor Joel Kaufman
Department of Environmental and Occupational Health Sciences
Department of Epidemiology
Department of Medicine

In-vehicle exposures to traffic-related air pollution (TRAP) may be an important part of an individual's overall exposure to pollutants. Prior epidemiological and exposure assessment studies used outdoor NO_2 concentrations as a surrogate for individual TRAP exposures and generally did not explicitly account for in-vehicle exposures. In this study, we assessed the contribution of the in-vehicle microenvironment to an individual's ambient source-derived NO_2 exposure concentration in a subset of MESA Air participants residing in Winston-Salem, NC (n=46). We measured time-integrated microenvironmental (residential indoor, residential outdoor, and in-vehicle) and personal NO_2 concentrations as surrogates of TRAP during a winter sampling campaign; time-location data was collected through a time-location diary. For our primary aim, we calculated microenvironmental contributions to each individual's ambient source-derived NO_2 exposure concentration using a time-weighted model. Secondarily, we evaluated the correlations between microenvironmental NO_2 concentrations and the ambient source-derived individual NO_2 exposure concentration using Pearson correlation coefficients. Finally, we attempted to predict in-vehicle NO_2 masses using the time spent in different travel conditions using multiple linear regression in a person-level analysis, whose model was evaluated using leave-one-out cross-validation. Data for analysis was available on 38 participants, who spent an average of one hour per day in-vehicle. The in-vehicle microenvironment was a major contributor to each individual's ambient source-derived NO_2 exposure concentration, accounting for an estimated 48.9±10.4%. Indoor ambient source-derived and outdoor NO_2 concentrations showed stronger correlations (r=0.73) with each individual's ambient source-derived NO_2 exposure concentration than in-vehicle NO_2 concentrations (r=0.44). The time spent in different travel conditions explained 44% of the in-sample variation within in-vehicle NO_2 masses with a RMSE of 0.25 ppb, and demonstrated good predictive value when tested out of sample (CV R^2=0.42; CV RMSE=0.15 ppb); the number of trips driven during the two-week sampling period was the most important predictor of in-vehicle NO_2 masses (partial R^2=0.33). These results indicate a high contribution of the in-vehicle microenvironment to individual ambient source-derived NO_2 exposure concentration, suggesting the need to account for in-vehicle exposures in studies of traffic-related air pollution.

TABLE OF CONTENTS

LIST OF EQUATIONS ii
LIST OF FIGURES iii
LIST OF TABLES iv
LIST OF ABBREVIATIONS v
ACKNOWLEDGEMENTS vi
DEDICATION viii
Introduction 1
Methods 8
I. Participant recruitment 10
II. Sampling methods and equipment 10
II.1. Indoor sampling *10*
II.2. Outdoor sampling *11*
II.3. In-vehicle sampling *11*
II.4. Personal sampling *11*
II.5. GPS monitoring *12*
II.6. Proximity monitoring *12*
II.7. Time-location diary *12*
II.8. Meteorological data *13*
II.9. Passive samplers *13*
III. Sample collection, storage, and shipment 13
IV. Sample analysis 14
VI. Sample QA/QC 16
Data analysis 16
I. Time-weighted model 16
I.1. Determination of most accurate time source *17*
I.2. Determination of indoor ambient source-derived NO_2 concentrations *17*
I.3. Determination of most accurate I/O *19*
Statistical analysis 20
Results 20
Discussion 36
I. Previous studies 36
II. Strengths and limitations 38
III. Implications 40
IV. Future studies 40
Conclusions 41
Appendix 42
REFERENCES 50

LIST OF EQUATIONS

Equation I. Calculation of NO_2 concentration conversion coefficient (dimensionless) 15
Equation II. Calculation of NO_2 concentration (ppb) 15
Equation III. Time-weighted model of individual ambient source-derived NO_2 exposure concentration (ppb) 20

LIST OF FIGURES

Figure I. Comparison of measured indoor NO_2 concentrations with indoor ambient source-derived NO_2 concentrations 25
Figure II. Bland-Altman plot: comparison of average with difference in measured indoor NO_2 concentrations and indoor ambient source-derived NO_2 concentrations 26
Figure III. Distribution of individual ambient source-derived NO_2 exposure concentration 29
Figure IV. Distribution of microenvironmental contributions to individual ambient source-derived NO_2 exposure concentration 29
Figure V. Comparison of indoor ambient source-derived and outdoor NO_2 concentrations with individual ambient source-derived NO_2 exposure concentration 31
Figure VI. Comparison of in-vehicle NO_2 concentrations with individual ambient source-derived NO_2 exposure concentration 32
Figure VII. Comparison of measured in-vehicle NO_2 masses and predicted in-vehicle NO_2 masses using leave-one-out cross-validation 36
Figure VIII. Time-location diary 48

LIST OF TABLES

Table I. Demographics of MESA Air, Winston-Salem, NC, and participants 21
Table II. [a]Meteorological data (January 30, 2013 to February 20, 2013) 22
Table III. [a]QA/QC of microenvironmental and personal NO_2 samples 23
Table IV. [a]QA/QC of microenvironmental NO_2 samples 23
Table V. [a]Proximity monitor and time-location diary data (h) 24
Table VI. [a]Predicted indoor NO_2 concentrations (ppb), adjusted for indoor gas sources 26
Table VII. Results of Bland-Altman plot 26
Table VIII. [a]Microenvironmental and individual ambient source-derived NO2 exposure concentrations (ppb) 27
Table IX. [a]Microenvironmental contributions to individual ambient source-derived NO_2 exposure concentration (%) 28
Table X. [a]Correlations between microenvironmental NO_2 concentrations with individual ambient source-derived NO_2 exposure concentration (ppb) 31
Table XI. [a]Travel conditions derived from self-reported time-location diary data 33
Table XII. [a]Correlations between percent of time spent during rush hour, on major roads, and in heavy traffic with the time spent for the average trip 34
Table XIII. [a]Predicted and cross-validated estimates of in-vehicle NO_2 masses (µg), adjusted for travel conditions derived from self-reported time-location diary data 35
Table XIV. [a]In-vehicle NO_2 concentrations as reported in previous studies (ppb) 37
Table XV. Results of pilot studies for NO_2 43
Table XVI. Modeled I/O, recalculated using permutations of the lower, central, and higher values of ACH and K 44
Table XVII. [a]Microenvironmental contributions to individual ambient source-derived NO_2 exposure concentration (%), recalculated using minima and maxima modeled I/O 45
Table XVIII. [a]Microenvironmental contributions to individual ambient source-derived NO_2 exposure concentration (%), recalculated excluding participants who drove <7 hours 45
Table XIX. [a]Microenvironmental contributions to individual ambient source-derived NO_2 exposure concentration (%), difference between participants with primary and duplicate in-vehicle samples 46
Table XX. [a]Predicted and bootstrapped estimates of in-vehicle NO_2 masses (µg), adjusted for travel conditions derived from self-reported time-location diary data 47

LIST OF ABBREVIATIONS

95% CI, 95% confidence interval
ACH, Air exchange rate
CO, Carbon monoxide
CPD, Cardiopulmonary disease
CV, Leave-one-out cross-validation
CVD, Cardiovascular disease
DQO, Data quality objective
f, Penetration factor
GIS, Geographic information systems
GPS, Global positioning system
HNO_3, Nitric acid
I/O, Indoor/outdoor ratio
ICS, Ion Chromatography System
IHD, Ischemic heart disease
K, Decay rate of NO_2
LOD, Limit of detection
MESA Air, Multi-Ethnic Study of Atherosclerosis and Air Pollution
MI, Myocardial infarction
MR, Mortality ratio
NAAQS, National Ambient Air Quality Standards
NO, Nitrogen oxide
NO_2, Nitrogen dioxide
NO_3^-, Nitrate
NOAA, National Oceanic and Atmospheric Association
NO_x, Oxides of nitrogen
O_3, Ozone
OR, Odds ratio
p, p-value
Partial/Model R^2, Partial/model coefficient of determination
PITO, 2-phenyl-4,4,5,5-tetramethylimidazoline-3-oxide-1-oxyl
$PM_{2.5}$, Particulate matter of 2.5 µm or less in diameter
QA/QC, Quality Assurance/Quality Control
r, Pearson correlation coefficient
R^2, Coefficient of determination
RMSE, Root mean square error
RPD/√2, Relative percent difference divided by √2
RR, Relative risk
SO_2, Sulfur dioxide
SO_4, Sulfate
TEA, triethanolamine
TRAP, Traffic-related air pollution
USEPA, United States Environmental Protection Agency
VOCs, Volatile organic compounds
β, Beta coefficient

ACKNOWLEDGEMENTS

I am so grateful for the support of the incredible people who have helped me throughout this process. First and foremost, I would like to express my sincere appreciation to Dr. Joel Kaufman, for his insightful guidance throughout this study. Dr. Kaufman's eye for detail and encouraging mentorship has transformed this work into something I am very proud of. I would also like to acknowledge the other members of the Supervisory Committee, Drs. Lianne Sheppard and Scott Meschke. I would like to thank Dr. Sheppard for helping me to develop competence in statistical analysis, for teaching me the importance of conducting ethical research, and to not lose sight of the people behind the numbers. I would also like to thank Dr. Meschke for his valuable insight throughout this process. I want to thank the MESA Air and University of Washington Center for Clean Air Research staff, whose laughter made our lab such an enjoyable place to work. In particular, I would like to thank Cynnie Curl, who graciously helped me formulate the proposal for this work while in the midst of writing her own dissertation. I would like to thank Elizabeth Spalt, who has been an incredible mentor through patiently helping me navigate the bumps along the road towards refining this work. I would like to thank Amanda Gassett, whose sense of humor and statistical expertise made programming in SAS (almost) painless. I would like to thank my fellow field technicians, Marnie Hazlehurst, Kris Hartin, Mark Hensley, Mark Davey, and Griffith Bell, who demonstrated tireless dedication while collecting the data analyzed in this work. I would like to thank our participants for allowing me to come full-circle by giving me the opportunity to actually meet the people behind the numbers…and for bringing me to the land of chicken and waffles. My family and friends are tremendous, and I cannot thank them enough for the love and patience they have demonstrated through their willingness to listen to the minutiae of my daily grind. Get ready for round two. Finally, I would like to thank the University of

Washington Graduate Opportunities for Minority Achievement Program, the Department of Environmental and Occupational Health Sciences, and the Center for Clean Air Research (supported by USEPA grant *RD-83479601-0*) who all generously funded this work.

DEDICATION

This is for my family, who promised to read this thing one day. You guys are my greatest champions in life, and I never could have done this without your love and encouragement.

Introduction

Traffic-related air pollution (TRAP) consists of particles, vapors, and gases; it changes with respect to emission source, road surface, physical aging, atmospheric processing, and photochemical reactions, and is a global contributor to air pollution exposures (Cho et al. 2009). Künzli et al. estimated that TRAP exposures were responsible for 15,000 CVD-related hospital admissions in Austria, France, and Switzerland, and were attributed to about 50% (22,000) of their adult mortality due to air pollution exposures (Künzli et al. 2000). While the mechanisms leading to CVD have yet to be fully elucidated, they are thought to include: systemic inflammation, autonomic nervous system imbalance, changes in vascular compliance, altered cardiac structure, and the development of atherosclerosis (Van Hee et al. 2009). Previous studies contribute to current uncertainty underlying these mechanisms, as their cross-sectional design failed to account for temporality due to the simultaneous assessment of TRAP exposures and CVD (Gill et al. 2011). According to Vedal, associating TRAP exposures with CVD is a challenging prospect since no single constituent serves as an ideal surrogate for this diverse pollutant mixture. Previous studies have utilized CO and NO_2 as surrogates of TRAP, but were imperfect due to the potential of exposure from other sources (Vedal 2009). In a series of toxicological studies, Frampton et al. demonstrated that NO_2 reacts with ammonia and moisture to form HNO_3-related particles and vapors, is capable of penetrating into the alveolar region of the lungs, and can aggravate existing emphysema, bronchitis, or CVD (Frampton et al. 2002). In concert with previous studies, they showed that associations between TRAP/NO_2 exposures and CVD have the potential to be serious, which has been the focus of numerous epidemiological and exposure assessment studies.

Epidemiological studies have associated TRAP/NO_2 exposures with CVD. The first of several North American studies is the Harvard Six Cities Study conducted by Dockery et al., who assessed air pollution exposures and mortality in a cohort of white adults aged 25 to 74 (n=8,111) in six US cities, including: Harriman, TN; Portage, WI; St. Louis, MO; Steubenville, OH; Topeka, KS; and Watertown, MA (1976-1988). They found that mortality showed stronger associations with the ambient concentrations of inhalable, fine, and SO_4 particles than with NO_2, $PM_{2.5}$, SO_2, or the actual acidity of the aerosol. Cardiopulmonary mortality contributed to 53.1% of all-cause mortality and demonstrated a positive association with the concentrations in the most (Steubenville, OH) vs. least (Portage, WI) polluted cities (MR 1.37, 95% CI: 1.11-1.68). This study considered each individual in a metropolitan area to have the same air pollution exposures, hence studying primarily regional-scale pollution and not the traffic-related component (Dockery et al. 1993). Jerrett et al. studied the association between TRAP exposures and circulatory mortality in Toronto, ON, CA, where they assigned predicted TRAP exposures in a cohort of adults aged 49 to 69 (n=2,360) from a respiratory clinic and retrospectively assessed their mortality rate (1992-2002). Using NO_2 as a surrogate for TRAP, they reported a positive association between this exposure and circulatory mortality (RR 1.39, 95% CI: 1.05-1.85), but warned that a high prevalence of CPD in this cohort could reduce the generalizability of their findings to other susceptible populations (Jerrett et al. 2009). They conducted a follow-up study to ensure that VOC exposures did not confound this association, and found that these exposures demonstrated a stronger association with cancer-related mortality (Villeneuve et al. 2013). Chen et al. studied the association between NO_2 exposures and CVD-related mortality in a cohort of adults aged 35 to 85 (n=205,440) from the federal family income tax database, who lived in Toronto, Hamilton, or Windsor, ON, CA between 1982 and 1986, and retrospectively assessed their mortality rate (2004). They found a positive association between a 5 ppb increase for all CVD-related mortality (RR 1.12, 95% CI: 1.07-1.17) and IHD mortality (RR 1.15, 95% CI: 1.08-1.21), and concluded that low-level NO_2 exposures were associated with CVD-related mortality (Chen et al. 2013). They also warned that short-term exposures are capable of increasing the risk of CVD-related mortality, indicating that that the time spent in high exposure microenvironments could contribute to this risk.

Historically, indoor and outdoor NO_2 concentrations have been used as surrogates of personal NO_2 exposures (Spengler et al. 1994; Liard et al. 1999; Adgate et al. 2002; Kousa et al. 2001). Spengler et al. conducted the “Nitrogen Dioxide Exposure Studies”, a microenvironmental exposure assessment of NO_2 for participants residing in Los Angeles (Spengler et al. 1994). They sampled a representative population of 482 homes and 682 participants, and measured personal NO_2 exposures, as well as residential indoor and residential outdoor NO_2 concentrations using passive time-integrated filter badges. They also collected time-location data, and information pertaining to personal and home characteristics. Each participant (n=48) provided two consecutive days of data up to eight times per year (May 1987-1988). They wore a personal badge while at home and wore a different one while they were away from home. The personal badges measured the highest NO_2 exposures (37.6 ppb), followed by the outdoor (38.3 ppb), and indoor badges (27.2 ppb). Indoor NO_2 concentrations originating from the kitchen were not collected; however, participants who used a gas stove demonstrated higher personal NO_2 exposures than those who used electric stoves. They found that 40% of the variation within indoor NO_2 concentrations was explained by those of outdoors; 59% of the variation within personal NO_2 exposures was explained by indoor NO_2 concentrations, and that 48% was explained by outdoor NO_2 concentrations.

Spengler et al. showed that indoor NO_2 concentrations explained 59% of the variation within personal NO_2 exposures. Through the "Boston Residential Nitrogen Dioxide Characterization Study", Lee et al. studied the covariates that might predict these concentrations, and found that lower air exchange rates and lower home volumes, as well as higher outdoor NO_2 concentrations were associated with higher indoor NO_2 concentrations in both apartments and condominiums (Lee et al. 1998). They sampled 417 homes, and measured residential indoor and residential outdoor NO_2 concentrations using time-integrated Palmes tubes. Each home provided consecutive two weeks of data up to three times per year (fall, winter, and summer of 1996). They stratified indoor NO_2 concentrations by homes with electric, gas (with and without pilot light) stoves and found them to be two to three times higher in homes with gas stoves, across all seasons. Their measurements were lower than those reported by Spengler et al., demonstrating the variability of indoor NO_2 concentrations across study locations.

Indoor NO_2 concentrations are important since people spend the majority of their time indoors; according to Allen et al., previous studies have not accounted for the ratio of indoor to outdoor NO_2 concentrations (I/O), and have thus incorrectly assumed a constant relationship outdoor NO_2 concentrations and personal NO_2 exposures (Allen et al. 2012). Like indoor NO_2 concentrations, I/O also varies based upon study location, the use of a gas stove or air conditioner, and personal habits (Schwarzenegger 2006). In the previous study, Lee et al. measured I/O for 517 Boston homes, which ranged from 0.97 to 1.54 (Lee et al. 1998). In a more recent study, Lee et al. measured I/O for two mountain and valley sites in southern California, with low and high ambient NO_2 concentrations, respectively; they found that the measured I/O was higher at the mountain site (3.24) compared to the valley site (1.07). In homes with and without gas stoves, the measured I/O was 2.27 and 1.22, respectively; in homes with and without air conditioners, the measured I/O was 1.07 and 3.03, respectively. The authors noted that 93% of the homes at the valley site were air conditioned compared to only one home at the mountain site, demonstrating the importance of considering air exchange rates in addition to indoor gas sources when measuring I/O (Lee et al. 2002). Several international studies have also measured I/O; Heal et al. measured I/O of 0.91 in British homes without indoor gas sources (Heal et al. 1999). Yang et al. measured I/O of 0.82 and 0.88 in Australian and Korean homes, respectively (Yang et al. 2004). Monn et al. measured I/O ranging from 0.4-0.8 in Swiss homes without indoor gas sources, and measured I/O about three times higher in those with indoor gas sources (Monn 2001). Chao et al. measured I/O of 0.80 and 0.79 in Hong Kong homes and non-smoking offices, respectively (Chao et al. 2000, 2001). Levy et al. found that the use of a gas stove was the strongest predictor of indoor NO_2 concentrations through an international study, and measured I/O ranging from 0.7-1.2 in homes using a gas stove (Levy et al. 1998). Dimitroupoulou et al. modeled I/O (ranging from 0.44-1.24) for British homes with and without indoor gas sources, offices with and with out mechanical ventilation, and classrooms (winter and summer of 2000); they found the modeled I/O was usually higher during the winter (Dimitroupoulou et al. 2001). Several studies measured higher indoor NO_2 concentrations during the winter, and hypothesized that seasonal differences are related to changes in personal habits, such as increased use of gas heaters, longer time spent cooking, as well as higher ambient NO_2 concentrations, and lower air exchange rates (Spengler et al. 1983; Ryan et al. 1988).

Other types of exposure assessments have reviewed TRAP exposures through ambient surrogate (Dubowsky et al. 1999), source apportionment (Laden et al. 2000), GIS (Hoek et al. 2002; Hoffman et al. 2006; Tonne et al. 2007, 2009; Zhang et al. 2013), and in-vehicle studies (Lee et al. 2000; Farrar et al. 2001; Zagury et al. 2000; Son et al. 2004; Chan et al. 1999; Riediker et al. 2003; Peters et al. 2004). Small spatial scale studies predicted TRAP exposures by proximity to major roads, length of major roads or their traffic density within a defined distance, or emissions based on small spatial scale dispersion models (Zhou and Levy 2007; Tonne et al. 2007; Van Hee et al. 2009). Large spatial scale studies predicted TRAP exposures with latent variable regression utilizing ambient concentrations to isolate specific surrogates of TRAP (Tonne et al. 2009). These study designs did not explicitly account for in-vehicle exposures, and may have underestimated their predicted TRAP exposures. In-vehicle studies have been conducted worldwide, and suggest that this microenvironment could be an important contributor to personal NO_2 exposures. In the first of two Australian studies, Lee et al. found that their predicted personal NO_2 exposures were much lower than those measured for Brisbane office workers (n=57). Their regression analyses with non-measured microenvironments suggested that in-vehicle exposures were a major contributor to the observed difference, and that they should be evaluated to improve personal NO_2 exposure models (Lee et al. 2000). Farrar et al. measured in-vehicle NO_2 concentrations in Perth for various types of transit and found lower measurements in taxis compared to buses, which could have been caused by different engine types, operation patterns, or locations (Farrar et al. 2001). However, in a French study, Zagury et al. measured in-vehicle NO_2 concentrations in Paris for non-smoking taxi drivers (n=29) and found that they were highly exposed, recommending a medical follow-up for this occupational cohort (Zagury et al. 2000). These results were supported by a Korean study, where Son et al. measured in-vehicle

NO_2 concentrations and personal NO_2 exposures in Asan and Chunan for both smoking and non-smoking taxi drivers (n=14, Asan; n=17, Chunan) in multiple microenvironments, and found that their personal NO_2 exposures showed stronger correlations with in-vehicle rather than residential indoor or residential outdoor NO_2 concentrations (Son et al. 2004). In a Chinese study, Chan et al. measured in-vehicle NO_2 concentrations in Hong Kong for various types of transit and found that in-vehicle NO_2 concentrations were higher than those found in ferries, buses, trams, and trains (Chan et al. 1999). In a US study, Riediker et al. measured in-vehicle NO_2 concentrations in Wake County, NC for non-smoking North Carolina State Highway Patrol troopers (n=10), and found low measurements compared to the NAAQS, but noted that high measurements were related to driving on major roads with high traffic densities, suggesting that combustion engine emissions from other vehicles was an important source of in-vehicle NO_2 concentrations (Riediker et al. 2003). In-vehicle studies are effective when the temporality between TRAP exposures and CVD is short (Adar and Kaufman 2007), as shown in a case-crossover study conducted by Peters et al., who associated TRAP exposures with the onset of MI. Their cases (n=691) were identified through the Cooperative Health Research in the Region of Augsburg Myocardial Infarction Registry in Augsburg, Germany. They found: an association between the onset of an MI within one hour post-exposure (OR 2.92, 95% CI: 2.22-3.83), that the time spent in various transit was significantly related to an increase in the risk of MI, and that vehicles were the most common mode of TRAP exposures, demonstrating an association between the onset of an MI within one hour post-exposure (OR 2.60, 95% CI: 1.89-3.57) (Peters et al. 2004). Associating in-vehicle exposures to slower progressing CVD, such as subclinical atherosclerosis; however, is challenging, but studying shorter-term changes and allowing for within-participant comparisons could reduce residual confounding by personal factors. In-vehicle studies enhance statistical power to detect such associations due to increased variability of TRAP exposures, but are expensive to conduct and are less generalizable due to fewer participants than epidemiological studies (Adar and Kaufman 2007).

Prior epidemiological and exposure assessment studies did not explicitly account for the fraction of ambient source-derived NO_2 exposures originating from the time spent in-vehicle. In this study, we assessed the contribution of the in-vehicle microenvironment to individual ambient source-derived NO_2 exposure concentration in a subset of MESA Air participants residing in Winston-Salem, NC (n=46). We hypothesize a high contribution, despite the little time spent in-vehicle relative to other microenvironments. We measured time-integrated microenvironmental (residential indoor, residential outdoor, and in-vehicle) and personal NO_2 concentrations as a surrogate of TRAP, and estimated the ambient contribution to indoor NO_2 concentrations; time-location data were collected through a time-location diary. For our primary aim, we calculated microenvironmental contributions to each individual's ambient-source derived NO_2 exposure concentration using a time-weighted model. Secondarily, we evaluated the correlations between microenvironmental NO_2 concentrations and each individual's ambient-source derived NO_2 exposure concentration. Finally, we aimed to predict in-vehicle NO_2 concentrations based on the time spent in different travel conditions in a person-level analysis.

Methods

MESA Air is a prospective cohort study of air pollution exposures and the progression of subclinical measures of CVD; it is following men and women aged 45 to 84 years at recruitment (n=7,562; 11% Asian-American, 29% Black/African-American, 24% Hispanic/Latino-American, and 37% White/Caucasian) in six US cities (Baltimore, MD;

Chicago, IL; Los Angeles, CA; New York, NY; St. Paul, MN; and Winston-Salem, NC) (Kaufman et al. 2012). It represents advancement through a prospective design and exposure assessment that integrates data from questionnaires, community, home, and personal sampling campaigns. It was not feasible to assess each individual's pollutant exposures for the entire cohort, so the MESA Air individual-level exposure model has been used to estimate their exposures. While $PM_{2.5}$ is the primary pollutant of interest, TRAP is now being measured due to its potential effect on within-city associations between $PM_{2.5}$ and CVD (Cohen et al. 2009). The objective of this study is to understand the importance of the in-vehicle microenvironment, which has not routinely been incorporated into the MESA Air individual-level exposure model. Further understanding of this microenvironment may help us better understand the association between TRAP and subclinical measures of CVD.

Participants residing in Los Angeles, CA and Winston-Salem, NC (n=144) were recruited for two-week sampling periods in each of two seasons (winter and summer, 2013 to 2014). Field technicians measured time-integrated microenvironmental (residential indoor, residential outdoor, and in-vehicle) and personal concentrations of NO_2/NO_x, O_3, SO_2, and a suite of 10 VOCs as surrogates of TRAP; time-location data was collected through GPS monitoring, proximity monitoring, and time-location diaries for each participant. Collectively, these methods will characterize the variability in microenvironmental and personal NO_2 concentrations due to the time spent within the indoor, outdoor, and in-vehicle microenvironments. This analysis is limited to NO_2 and one of two two-week sampling periods in Winston-Salem, NC (winter 2013).

I. *Participant recruitment*

Wake Forest University School of Medicine staff managed participant recruitment and consent, whose residences were not visited without a signed consent form. Participants (n=46) were selected based upon: having (at least partially) filled out at least one MESA Air questionnaire; having previously consented to participation in a personal monitoring study; owning and using a vehicle as their primary mode of transportation; living at their indicated primary residence during the two-week sampling period; being a non-smoker and not living with a smoker; reporting that they drive their vehicle for at least 30 minutes per day (in order to achieve detection limits); having a yard, porch, or other area where the outdoor sampler could be deployed, and identifying as Black/African-American or White/Caucasian in order to be representative of the cohort residing in Winston-Salem, NC.

II. *Sampling methods and equipment*

II.1. Indoor sampling

An indoor sampler was installed inside participants' homes, and included: O_3 and $NO_2/NO_x/SO_2$ Ogawa passive samplers (Ogawa & Co., Pompano Beach, FL), a 3M 3500 Organic Vapor Monitor (3M Co., Maplewood, MN) proximity monitor (developed for our study), and an Onset HOBO U10 data logger (Onset Computer Corp., Bourne, MA). The location was chosen based upon: a flat surface in the main activity room of the home that was at least one meter off the floor and away from the corners of the room, walls, windows, air conditioners, other ventilation outlets or inlets, and was not behind furniture, near gas stoves, the door to the garage, or sources of water.

II.2. Outdoor sampling

An outdoor sampler was installed outside participants' homes, and included: O_3 and $NO_2/NO_x/SO_2$ Ogawa passive samplers and a 3M 3500 Organic Vapor Monitor (all covered by metal tins for water-resistance). Participants were instructed to mow, fertilize, or water at least 10 feet away from the outdoor sampler if needed. The location was based upon: at least 30 feet from the road or driveway; at least 15 feet from any walls, trees (and not under tree canopies), and at least 10 feet from areas with dirt-blowing potential.

II.3. In-vehicle sampling

An in-vehicle sampler was installed on the passenger seat of participants' primary vehicles, and included: O_3 and $NO_2/NO_x/SO_2$ Ogawa passive samplers, a 3M 3500 Organic Vapor Monitor (all covered by an airtight metal container), proximity monitor, and an Onset HOBO U10 data logger. Participants were instructed to: open and close the container when entering and exiting the vehicle, so sampling took place only while they were driving; transfer the in-vehicle sampler to the back side of the front passenger seat if someone sits there, or take the in-vehicle sampler when driving in a secondary vehicle.

II.4. Personal sampling

The participants wore a personal sampler for the duration of the two-week sampling period, which included: O_3 and $NO_2/NO_x/SO_2$ Ogawa passive samplers and a 3M 3500 Organic Vapor Monitor, except while engaging in activities that could damage the sampler, such as: sleeping, showering, cooking, washing dishes, or walking outside during inclement weather. When engaging in such activities, the participant was instructed to keep the personal sampler in a dry, nearby location.

II.5. GPS monitoring

The participants were instructed to carry 747ProS GPS data loggers (TranSystem Inc., Fremont, CA) whenever they left their home during the two-week sampling period. The acquisition rate was set to: every 30 seconds for speeds at least 3 km/h, every 15 seconds for 3-20 km/h, and every five seconds for speeds greater than 20 km/h, and recorded in the "Smart Log" position. An external battery allowed the GPS unit to run for the duration of the two-week sampling period. While the GPS unit was able to capture in-vehicle travel patterns, current technology cannot capture high-resolution travel patterns, such those occurring within residential indoors and residential outdoors.

II.6. Proximity monitoring

In order to verify the GPS unit and the time spent residential indoors vs. residential outdoors, the first of two proximity monitors was placed on the indoor sampler; the second was placed on the in-vehicle sampler. Participants were instructed to activate or deactivate the proximity monitors by tapping them with the GPS unit (containing a magnet that activated a sensor) each time they entered or exited their home or vehicle, and to move the in-vehicle sampler when driving in a secondary vehicle. Like stopwatches, the proximity monitors accumulated the time spent indoors and in-vehicle during the two-week sampling period.

II.7. Time-location diary

In order to verify the GPS units and proximity monitors, participants were instructed to self-report their time spent indoors, outdoors, and in-vehicle in time-location diaries (developed for our study; Appendix, Figure VI). Each page represented one day and each row represented one location, specified by five columns as "indoors at home", "indoors away from home", "outdoors at home", "outdoors away from home", and "in-vehicle". The participants were instructed to record the start and end times of their location in each row. Whenever "in-vehicle" was selected, they were instructed to specify: the vehicle type, road types, traffic conditions, and if the windows were open at any time.

II.8. Meteorological data

HOBO U10 data loggers were placed on participants' indoor and in-vehicle samplers to record temperature and relative humidity every five minutes, starting at 7:00 AM on the day of deployment. For the outdoor microenvironment, these data were downloaded from the NOAA station at the Piedmont Triad International Airport of Greensboro, NC.

II.9. Passive samplers

O_3 and $NO_2/NO_x/SO_2$ were measured using Ogawa passive samplers, one-sided for O_3 and two-sided for $NO_2/NO_x/SO_2$. The samplers feature a badge clip and a barrel shaped body with cellulose filters (one for O_3, two for $NO_2/NO_x/SO_2$) supported by two metal screens and capped with a fixed diffusion barrier. For O_3 and $NO_2/NO_x/SO_2$, the filters were coated with NO_3^-, PTIO, and TEA, respectively.

III. Sample collection, storage, and shipment

All samples were collected, stored, and shipped by the field technicians, who noted problems, transfers, and deviations from handling protocols for each sample on the logs and observation forms. After collection, the samples were refrigerated at the field center laboratory until they were shipped within less than 30 days from Wake Forest University (Winston-Salem, NC) to the University of Washington (Seattle, WA). The field technician logs and observation forms were entered into a Microsoft Access (Microsoft Corp., Redmond, WA) database and the samples were analyzed for time-integrated concentrations.

IV. Sample analysis

NO_2/SO_2 and O_3 and samples were analyzed using the ICS, made by Dionex. The main module is the “ICS-1000”, to which the AS-40 model autosampler and a Dell GX280 PC are connected. The ICS-1000 contains a pump, six-port sampler valve, analytical and guard columns, suppressor, conductivity cell, and associated tubing. The system is plumbed as a “4 mm” system; that is, the diameters of the columns are 4 mm and the associated tubing and suppressor were designed for these columns. The samples were prepared according to Ogawa’s “Analytical method for NO, NO_2, NO_x, and SO_2”. The Ogawa passive samplers were disassembled and their filters were stored in plastic vials for extraction with 8 mL of deionized water. Sample extracts were swirled or sonicated for approximately 30 minutes prior to loading into IC vials for analysis. After the filters and screens were extracted with the appropriate liquid, aliquots were transferred to IC sample vials; the vials were loaded onto an eight-vial cassette, and the cassettes were then loaded onto the autosampler. IC methods for each kind of anion or anion mixtures were created and selected for the appropriate sample set. These methods controlled the various physical parameters of the analysis, such as detector sensitivity, eluent strengths, time of runs, amount of sample injected, etc. Analytical IC schedules were controlled on the PC. The sample schedules are spreadsheets in which each row is a sample injection event; columns are parameters such as “sample ID” or “IC method”. Data for each injection were saved in a file on the PC, as specified in the sample schedule. All sample schedules included control standards and lab blanks. A standard curve, calculated by least squares regression, was used to convert the peak height data to concentration data. A control standard was run for each sample schedule, depending on their frequency. For frequent sample schedules, the control standards provided information about daily changes in detector response. Analyses were not scheduled until a valid calibration curve was obtained.

V. Sample concentration

The sample concentrations were calculated according to Ogawa's "Analytical method for NO, NO_2, NO_x, and SO_2". As shown in Equations I and II below, the sample concentration (ppb) is calculated by multiplying the concentration conversion coefficient (α_{NO2}) by the collected mass of NO_2 (µg) and dividing by the exposure time (h), which was estimated using participants' self-reported time-location diary data of the time spent within each microenvironment, for their respective sample concentrations.

Equation I. Calculation of NO_2 concentration conversion coefficient (dimensionless)

$$\alpha_{NO_2}{}^{a} = \frac{10{,}000}{0.677 \cdot [P]^{b} \cdot RH^{c} + 2.009 \cdot T^{d} + 89.8}$$

[a]NO_2 concentration conversion coefficient (dimensionless), [b]Vapor pressure coefficient (dimensionless)
[c]Microenvironmental relative humidity (%); [d]Microenvironmental temperature (°C)

Equation II. Calculation of NO_2 concentration (ppb)

$$[NO_2] = \frac{1000 \cdot M^{e} \cdot \alpha_{NO_2}}{t_i{}^{f} \cdot 60}$$

[a]Microenvironmental NO_2 mass (µg), [b]Time spent within each microenvironment, proportionally adjusted for the time of participation (h)

VI. Sample QA/QC

Indoor and outdoor samples were considered to be invalid if: they were deployed for less than nine or more than 20 days, they were damaged or missing, or if notes in the field technician logs indicated that the sample was not representative of exposure during the two-week sampling period. In-vehicle samples were considered invalid if the in-vehicle sampler was open upon retrieval, the participant never opened the in-vehicle sampler, their time-location diary was missing, or they did not participate in the study. Field blank samples were deployed to assess contamination (indoor), and duplicate samples to assess precision (indoor, outdoor, and in-vehicle). Neither field bank nor duplicate samples were deployed for personal samples. Field blank samples were handled identically to the primary and duplicate samples, except they were exposed for five seconds before being re-sealed. The DQO for field blank samples is to have the count equal to 10% of all primary samples, and the DQO for duplicate samples is for the estimated precision (RPD/$\sqrt{2}$) to equal less than 10%.

Data analysis

I. Time-weighted model

We used a time-weighted model to calculate microenvironmental contributions to individual ambient source-derived NO_2 exposure concentration (Equation III). NO_2 exposure concentration for each participant was calculated using their measured values of the time spent within each microenvironment (h) multiplied by their respective NO_2 concentrations (ppb), all divided by their time of participation (h). The time spent within each microenvironment was selected based upon a comparison of two of our three time sources.

I.1. Determination of most accurate time source

We compared the proximity monitor and time-location diary data using paired t-tests, five-number summaries, correlation plots, and box plots in order to use the most accurate source of time spent indoors and in-vehicle. The GPS data were not considered in this analysis since they have not yet been processed for all participants.

I.2. Determination of indoor ambient source-derived NO_2 concentrations

Indoor NO_2 concentrations include indoor gas sources, and our interest is primarily in those of ambient origin, which were not directly measured. The two potential approaches to estimating the fraction of indoor NO_2 concentrations of ambient origin include: understanding the contribution of indoor gas sources to indoor NO_2 concentrations or the fraction of outdoor NO_2 concentrations that infiltrate the indoor microenvironment. We determined that the literature formed an adequate basis for estimating the fraction of outdoor NO_2 concentrations that infiltrate the indoor microenvironment. We multiplied the indoor NO_2 exposure concentration by a modeled I/O derived from the literature, which accounted for the fraction of outdoor NO_2 concentrations that infiltrate the indoor microenvironment.

I.2.i. Modeled I/O

Past studies have used outdoor NO_2 concentrations a surrogate of personal NO_2 exposures, but people spend most of their time indoors. We accounted for the fraction of outdoor NO_2 concentrations that infiltrate the indoor microenvironment in order to better understand indoor exposure to NO_2 concentrations of ambient origin. Such a parameter for use in epidemiological studies has yet to be developed for NO_2, and the modeled I/O served as a temporary solution for this analysis.

Dimitroupoulou provided the modeled I/O, which is a simplified approach for gases that serves the same purpose as the $PM_{2.5}$ infiltration factor derived by Allen et al., and assumes a box model in which a constant concentration is maintained inside each microenvironment under steady-state conditions without indoor gas sources (Dimitroupoulou et al. 2001; Allen et al. 2012). Indoor NO_2 concentrations were measured during the two-week sampling period, but were not used in this analysis since our model also assumes NO_2 exposures from ambient sources, and not indoor gas sources. During each site visit, the field technicians interviewed participants about indoor gas sources in their homes, such as: stoves, ovens, clothes dryers, water heaters, furnaces, floor/wall heaters, or fireplaces, which addressed our concern of NO_2 being an imperfect surrogate of TRAP due to exposure from other sources. The constants for air exchange rate (ACH), penetration factor (*f*), and decay rate (K) were adjusted by using average values reported in the literature as a measure of central tendency, which were specifically selected to representative of the conditions measured in our study.

I.2.i.i. ACH

Sherman provided county-level estimates of ACH using US Census (2000) and RECS (2001) data. Assuming infiltration only, their estimates of ACH for Forsyth County, NC ranged from 0.37-0.63 h^{-1}, with an average of 0.50 h^{-1} (Sherman 2007), which was used for the modeled I/O.

I.2.i.ii.f

Thatcher and Layton found that the *f* of naturally ventilated buildings provides no barrier to particulate pollutants when no resuspension or generation activities were present, indicating that the building envelope was not effective at removal (Thatcher and Layton 1995). Stephens et al. demonstrated the variability of *f* for O_3 due to differences in building age, leakage paths, and envelope material reaction probabilities, but acknowledged that without experimental data, it is assumed that O_3 penetrates with 100% efficiency (Stephens et al. 2011). While Stephens et al. measured values of *f* for O_3, they were not used for the modeled I/O since O_3 is a more reactive gas than NO_2. Dimitroupoulou et al. assumed that NO_2 could not penetrate less efficiently than particulate pollutants, and an *f* of 1.00 was used for the modeled I/O.

I.2.i.iii. K

Yamanaka found that NO_x (NO and NO_2) are still reactive and can be removed from the indoor microenvironment through processes other than ventilation. K (ppb lost per hour) was found to follow first-order kinetics in a typical Japanese living room, and was influenced by air exchange rate, relative humidity, and surface properties. At low relative humidity (43.5-50%), surface effects were not detected and K was found to be $0.99 \pm 0.19\ h^{-1}$; however, it increased in proportion to relative humidity above 50% (72.5%). The mean indoor relative humidity measured in our study was 36.4±7.3%, and since K is not influenced by surface properties at low relative humidity, a K of $0.99\ h^{-1}$ was used for the modeled I/O.

I.3. Determination of most accurate I/O

We compared the modeled and measured I/O of participants who self-reported no indoor gas sources in their homes using a paired t-test and the field technician observation forms.

Equation III. Time-weighted model of individual ambient source-derived NO_2 exposure concentration (ppb)

$$E^{a}_{(A)i} = \frac{\frac{I}{O}^{b} \cdot t^{c}_{(I)i} \cdot [NO_2]^{d}_{(O)i} + t_{(O)i} \cdot [NO_2]_{(O)i} + t_{(IV)i} \cdot [NO_2]_{(IV)i}}{t^{e}_{(P)i}} = E^{f}_{(I)i} + E_{(O)i} + E_{(IV)i},\ where\ \frac{I}{O} = \frac{ACH \cdot f}{K + ACH}$$

[a]Individual ambient source-derived NO_2 exposure concentration (ppb), [b]Ratio of indoor to outdoor NO_2 concentrations (I/O = 0.34; ACH = 0.50 h^{-1}, f = 1.00, K = 0.99 h^{-1}), [c]Time spent within each microenvironment, proportionally adjusted for the time of participation (h; I = Indoor (ambient), O = Outdoor, IV = In-vehicle), [d]Microenvironmental NO_2 concentration (ppb), [e]Time of participation (h), [f]Microenvironmental NO_2 exposure concentration (ppb)

Statistical analysis

Three specific aims were met using SAS, version 9.3 (SAS Institute Inc., Cary, NC) for statistical analysis, and Stata, version 12.1 (StataCorp, College Station, TX) for graphical output:

I. Calculate microenvironmental contributions to individual ambient source-derived NO_2 exposure concentration using a time-weighted model.

II. Correlate microenvironmental NO_2 concentrations and individual ambient source-derived NO_2 exposure concentration using Pearson correlation coefficients.

III. Predict in-vehicle NO_2 concentrations using the time spent in different travel conditions using multiple linear regression in a person-level analysis, and evaluate this model out of sample using the CV R^2 and CV RMSE from a leave-one-out cross-validation.

Results

MESA Air represents a balanced gender ratio from four racial/ethnic groups, and Table I shows that the participants (n=46) were selected to be representative of the cohort residing in Winston-Salem, NC (n=912). Nine participants were excluded from different analyses, and the first eight were excluded from Aims 1-3. Two left their in-vehicle samplers open, another two spent about 12 hours on buses, the fifth never opened their in-vehicle sampler, the sixth did not participate in the study, the seventh self-reported less than 80% of their time-location diary data, and the eighth was conditionally excluded because they did not self-report time-location diary data, but will be included in future analyses if their time spent in-vehicle can be estimated utilizing GPS data. The final participant was excluded from Aims 1 and 2; they spent about half of the two-week sampling period away from home, and their measured personal NO_2 concentration was anticipated to not represent if they had been home during the whole two-week sampling period.

Table I. Demographics of MESA Air, Winston-Salem, NC, and participants

	[a]MESA Air (n=6,264)		Winston-Salem, NC (n=912)		Participants (n=46)	
Demographics	**N**	**%**	**N**	**%**	**N**	**%**
Race/Ethnicity						
Asian-American	674	10.8	-	-	-	-
Black/African-American	1,757	28.1	440	48.3	26	56.5
Hispanic/Latino-American	1,470	23.5	4	0.4	-	-
White/Caucasian	2,363	37.7	468	51.3	20	43.5
Gender						
Female	3,324	53.1	489	53.6	25	54.4
Male	2,940	46.9	423	46.4	21	45.7
Age						
45-54	1,031	16.5	104	11.4	5	10.9
55-64	2,035	32.6	321	35.2	14	30.4
65-74	1,888	30.3	290	31.8	19	41.3
75-84	1,121	18.0	178	19.5	6	13.0
85+	142	2.3	17	1.9	2	4.4
Health status						
[b]BMI (kg/m^2)						
Normal	1352	28.9	165	23.1	6	13.6
Grade 1 overweight	1742	37.2	279	39.1	23	52.3
Grade 2 overweight	1405	30.0	236	33.1	15	34.1
Grade 3 overweight	186	4.0	33	4.6	0	0.0
[c]Breathlessness						
No	4084	87.1	636	85.0	41	89.1
Yes	582	12.4	105	14.0	5	10.9
Unknown	22	0.5	7	0.9	0	0.0
[d]Diabetes						
Normal	2785	60.0	464	64.7	28	62.2
Impaired fasting glucose	944	20.3	109	15.2	6	13.3
Untreated diabetes	82	1.8	11	1.5	1	2.2
Treated diabetes	832	17.9	133	18.6	10	22.2
Hypertension stage						
Optimal	2224	47.6	306	42.7	26	57.8
Normal	796	17.1	132	18.4	7	15.6
High-normal	658	14.1	111	15.5	7	15.6
Stage 1 hypertension	727	15.6	123	17.2	4	8.9
Stage 2 hypertension	198	4.2	34	4.7	1	2.2

Stage 3 hypertension	66	1.4	11	1.5	0	0.0
[e]Perceived health status						
Better	2805	59.9	469	62.8	31	67.4
Same	1624	34.7	232	31.1	14	30.4
Worse	258	5.5	46	6.2	1	2.2
[f]Total cholesterol (mg/dl)						
<200	3138	67.8	512	71.6	33	73.3
200-239	1160	25.0	163	22.8	10	22.2
240+	334	7.2	40	5.6	2	4.4
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Systolic blood pressure (mmHg)	124.0	20.9	126.3	21.3	120.1	16.4

[a]Includes participants that (at least partially) filled out at least one MESA Air Questionnaire, [b]Body mass index, [c]Ever had to stop walking from breathlessness, [d]2003 ADA fasting criteria, WHO categories; [e]Perceived health status compared to others of the same age, [f]NCEP categories

Table II shows the measured temperature and relative humidity in each of three microenvironments for the duration of the two-week sampling period. The indoor microenvironment demonstrated the highest mean temperature (21.3±1.9°C), while the outdoor microenvironment demonstrated the lowest (5.3±0.2°C). However, the outdoor microenvironment demonstrated the highest relative humidity (60.8±0.7%), while the indoor and in-vehicle microenvironments were nearly equivalent (36.4±7.3% and 37.2±6.0%, respectively). The meteorological conditions in the three microenvironments for all partiicpants demonstrated little overall variability through low standard deviations.

Table II. [a]Meteorological data (January 30, 2013 to February 20, 2013)

	Temperature (°C)		**Relative Humidity (%)**	
Microenvironment	**Mean**	**SD**	**Mean**	**SD**
Indoor	21.3	1.9	36.4	7.3
Outdoor	5.3	0.2	60.8	0.7
In-vehicle	12.5	2.8	37.2	6.0

[a]MESA Air participants (n=46)

We found that 95.6% of primary microenvironmental and personal samples met our criteria for validity for all participants (n=46); however, only primary microenvironmental samples were used in this analysis (n=114), as shown in Table III. The DQOs were met for both field blank samples (count equal to 10% of all primary samples) and duplicate samples (precision equal to less than 10%) for included participants (n=38), as shown in Table IV.

Table III. [a]QA/QC of microenvironmental and personal NO_2 samples

Sample	Deployed (N)	Valid (N)	Valid (%)
Indoor	46	45	97.8
Outdoor	46	46	100.0
In-vehicle	46	41	89.1
Personal	46	42	91.3
Total	184	174	95.6

[a]MESA Air participants (n=46)

Table IV. [a]QA/QC of microenvironmental NO_2 samples

Metric	N	Minimum	25^{th}	Median	75^{th}	Maximum	IQR	Mean	SD	Count (%)	[b]Precision (%)
Blanks											
Indoor (µg)	14	0.4	0.4	0.4	0.5	0.7	0.2	0.4	0.1	10.1	-
Indoor (ppb)	14	1.2	1.2	1.2	1.7	2.3	0.5	1.4	0.4	10.1	-
[c]Duplicates (µg)											
Indoor	2	8.9	8.9	9.4	9.9	9.9	0.9	-	-		9.4
Outdoor	4	2.2	2.6	5.2	9.2	10.8	6.6	-	-		5.9
In-vehicle	4	2.1	3.3	9.2	14.4	14.9	11.1	-	-		8.8
Total	10	2.1	2.9	8.3	10.8	14.9	7.9	-	-		7.8

[a]MESA Air participants (n=38), $\frac{^{b}100 \cdot \left(\frac{|\text{primary}-\text{duplicate}|}{\text{average(primary, duplicate)}}\right)}{\sqrt{2}}$, [c]Difference in mass between primary and duplicate samples (µg)

We compared the proximity monitor and time-location diary data using paired t-tests, five-number summaries, correlation plots, and box plots in order to use the most accurate source of time spent indoors and in-vehicle. Downward adjustments were made for participants whose proximity monitors did not start on 0:00. Upward adjustments were made for those who self-reported less than 100% time-location dairy data (336 h) and/or no data for at least 20% of the two-week sampling period. Paired t-tests indicated that the time spent indoors and in-vehicle was statistically different across time sources (indoor: $p<0.0001$; in-vehicle: $p<0.0003$). Outliers were then diagnosed via five-number summaries, as well as correlation plots and box plots (indoor: <200 or >336 h; in-vehicle: >60 h). The time-location diary was chosen as the most accurate source, which demonstrated less variability through lower interquartile ranges and standard deviations. The time spent within each microenvironment was then proportionally adjusted for the time of participation to account for differences between participants, as shown in Table V.

Table V. [a]Proximity monitor and time-location diary data (h)

Source	Minimum	25th	Median	75th	Maximum	IQR	Mean	SD
Proximity monitor (h)								
Indoor	206.8	262.1	279.4	298.9	360.3	36.8	278.9	33.1
In-vehicle	4.6	11.2	22.9	60.1	183.9	48.9	40.7	41.0
Time-location diary (h)								
Indoor	278.8	302.5	315.3	320.9	361.2	18.5	312.6	15.2
Outdoor	0.0	1.3	4.1	5.9	40.6	4.6	7.4	10.1
In-vehicle	5.3	8.8	13.1	17.7	36.2	9.0	14.8	7.4

[a]MESA Air participants (n=37)

We also compared the modeled I/O (0.34) and the measured I/O of participants who self-reported no indoor gas sources in their homes (0.47±0.11; n=18). A one-sample t-test showed a statistically significant difference ($p<0.0001$), providing an initial indication that the modeled I/O was not a reasonable approximation. We then reviewed the field technician observation forms for possible indoor gas sources, and found that six participants with a higher measured I/O (>0.40) also had attached garages. We excluded those participants, and found that the measured I/O decreased to 0.45±0.13, which included the modeled I/O within one standard deviation of the mean. Figure I shows indoor ambient source-derived NO_2 concentrations and measured indoor NO_2 concentrations, by participants with and without indoor gas sources. We predicted person-level measured indoor NO_2 concentrations using the presence of indoor gas sources using simple linear regression, as shown in Table VI. The presence of indoor gas sources predicted 19% of the variation within indoor NO_2 concentrations. On average, participants who lived in homes with indoor gas sources were exposed to 17.1 (95% CI: 5.1, 29.0) ppb higher indoor NO_2 concentrations, compared to those who lived in homes without indoor gas sources ($p<0.006$; $R^2=0.19$). Figure II shows a Bland-Altman plot for participants without indoor gas sources, which demonstrates a low mean difference, some bias, and good agreement between the average and the difference in their measured indoor NO_2 concentrations and indoor ambient source-derived NO_2 concentrations; the quantitative results of the Bland Altman plot are shown in Table VII. These analyses show that the modeled I/O reasonably approximated the measured I/O of participants without indoor gas sources.

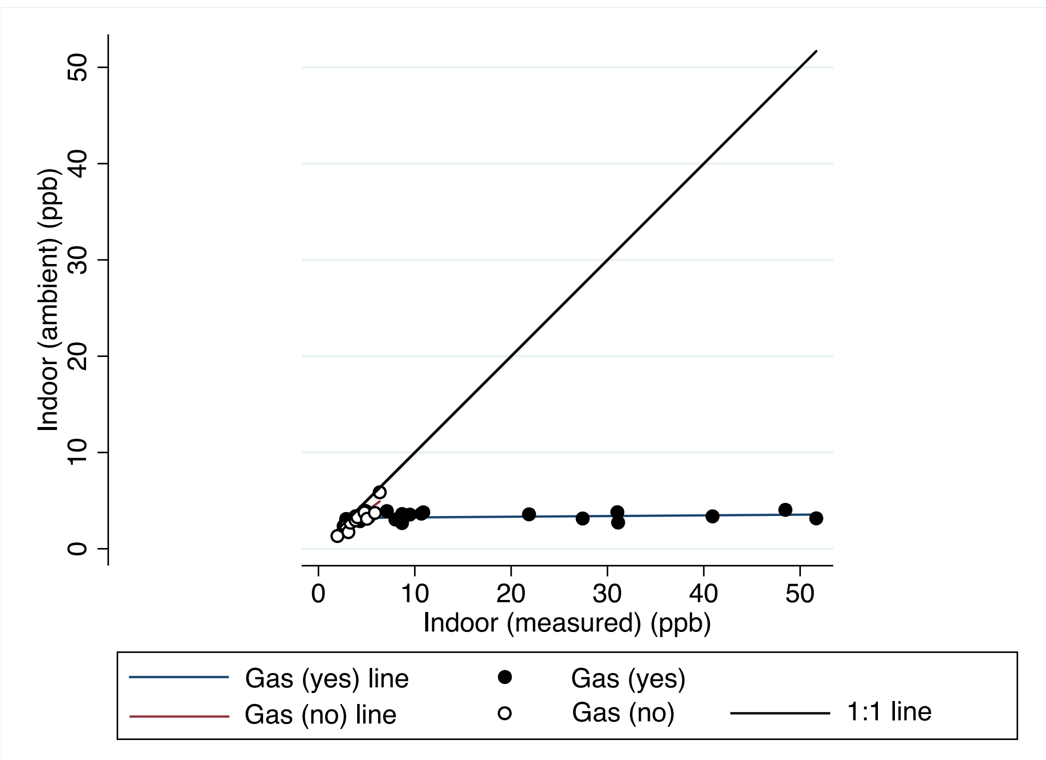

Figure I. Comparison of measured indoor NO_2 concentrations with indoor ambient source-derived NO_2 concentrations

Table VI. [a]Predicted indoor NO_2 concentrations (ppb), adjusted for indoor gas sources

	[b]**Model**			
	β	**95% CI**	**R^2**	**RMSE**
Indoor [NO_2] (ppb)			0.19	17.7
β_0	3.8	(-5.2, 12.8)		
Indoor gas sources (yes)	17.1§	(5.1, 29.0)		
Indoor gas sources (no)	-	-		

Results of ANOVA: § = for these values, $p<0.01$; ¶ = for these values, $p<0.05$ [a]MESA Air participants (n=37), [b]Model (β, 95% CI, R^2, and RMSE) = change and 95% confidence interval (ppb), total variation (%), and root mean square error (ppb) of model, adjusted for the presence of indoor gas sources

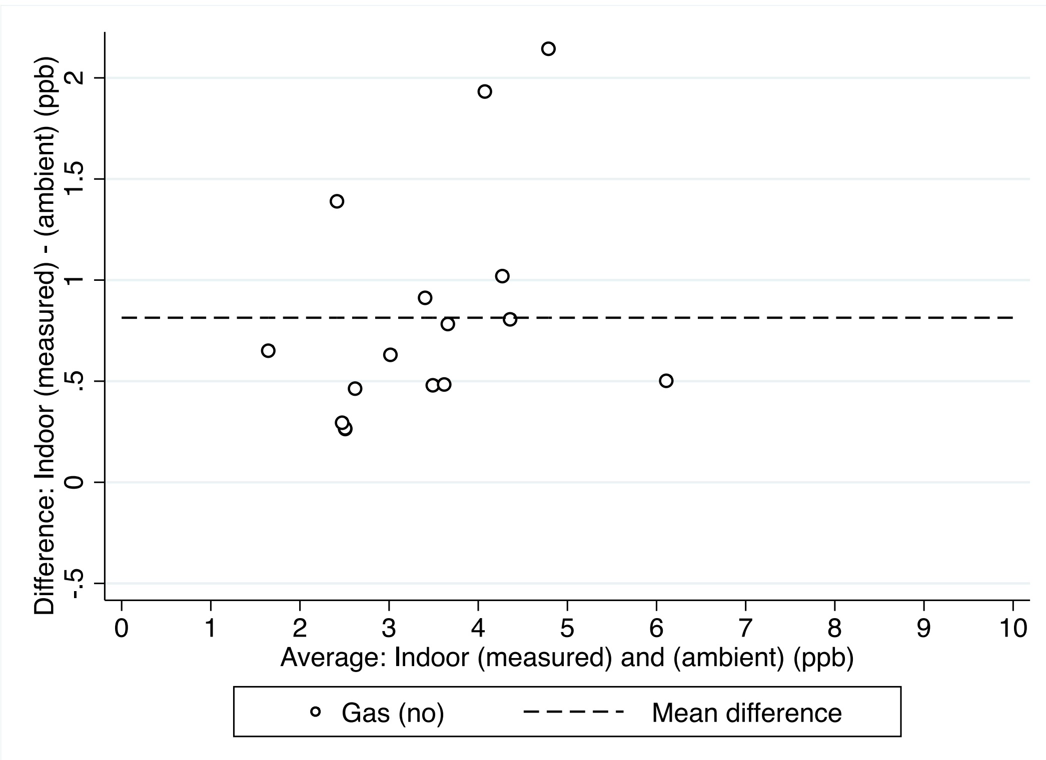

Figure II. Bland-Altman plot: comparison of average with difference in measured indoor NO_2 concentrations and indoor ambient source-derived NO_2 concentrations

Table VII. Results of Bland-Altman plot

Metric	**Result**
95% CI of agreement (ppb)	(-0.3, 1.9)
Outside 95% CI of agreement (%)	12.5
Mean difference (ppb)	0.8
Range of averages (ppb)	(1.6, 6.1)

Table VIII shows the calculated microenvironmental and individual ambient source-derived NO_2 exposure concentrations using a time-weighted model; this used participants' self-reported time-location diary data of the time spent within each microenvironment multiplied by their respective NO_2 concentrations, all divided by their time of participation. The indoor NO_2 exposure concentration was multiplied by the modeled I/O, which accounted for the ambient source-derived fraction of outdoor NO_2 concentrations that infiltrated the indoor microenvironment.

Table VIII. [a]Microenvironmental and individual ambient source-derived NO2 exposure concentrations (ppb)

Exposure concentration	Minimum	25th	Median	75th	Maximum	IQR	Mean	SD
[b]Indoor (ambient)								
[c][NO_2] (ppb)	1.3	2.7	3.2	3.6	5.9	0.9	3.2	0.8
[d]Time (h)	278.8	302.5	315.3	320.9	361.2	18.5	312.6	15.2
[e]Time-weighted [NO_2] (ppb)	1.3	2.6	3.1	3.4	5.0	0.9	3.0	0.7
[f]Indoor (measured)								
[NO_2]	2.0	3.7	5.0	10.7	98.1	7.0	13.5	19.5
Outdoor								
[NO_2]	3.9	8.0	9.4	10.7	17.2	2.7	9.3	2.3
Time	0.0	1.3	4.1	5.9	40.6	4.6	7.4	10.1
Time-weighted [NO_2]	0.0	0.1	0.1	0.2	2.1	0.1	0.2	0.4
In-vehicle								
[NO_2]	22.8	61.7	74.1	91.6	187.4	29.9	82.0	38.5
Time	5.3	8.8	13.1	17.7	36.2	9.0	14.8	7.4
Time-weighted [NO_2]	1.4	2.5	2.9	3.8	5.1	1.4	3.1	1.0
[g]Individual (ambient)								
Time-weighted [NO_2]	3.1	5.6	6.0	6.8	11.2	1.2	6.3	1.4
[h]Personal (measured)								
[NO_2]	2.9	4.8	6.7	9.5	93.8	4.7	12.2	16.6

[a]MESA Air participants (n=37), [b]Calculated indoor ambient source-derived NO_2 exposure concentration (ppb), [c]NO_2 concentration (ppb), [d]Time spent within each microenvironment (h), proportionally adjusted for the time of participation; [e]NO_2 exposure concentration (ppb), [f]Measured indoor NO_2 concentration (ppb), [g]Calculated individual ambient source-derived NO_2 exposure concentration (ppb), [h]Measured personal NO_2 concentration (ppb)

Table IX, Figure III, and Figure IV show the calculated microenvironmental contributions to each individual's ambient source-derived NO_2 exposure concentration, and we found that the in-vehicle microenvironment was responsible for the highest contribution at 48.9±10.4%. Although indoor NO_2 concentrations were lower than those measured in-vehicle (3.2±0.8 vs. 82.0±38.5

ppb), the indoor microenvironment demonstrated a nearly equivalent contribution since the mean time spent indoors was far higher than in-vehicle (312.6±15.2 vs. 14.8±7.4 h). The outdoor microenvironment was responsible for the lowest direct contribution; however, the indoor contribution represents an indirect contribution of the outdoor microenvironment through the ambient source-derived fraction of outdoor NO_2 concentrations that infiltrated the indoor microenvironment. The contribution of each individual's ambient source-derived NO_2 exposure concentrations to his or her measured personal NO_2 concentration was 90.2±46.9% (6.5-182.8%). The upper end of this range may have exceeded 100% due to a lack of participant compliance in wearing their personal badges. If these remained indoors for the two-week sampling period, measured personal NO_2 concentrations could be biased-low by not capturing higher-exposure microenvironments. However, no self-reported comments in the time-location diary data or field technician logs could substantiate this theory with empirical evidence.

Table IX. [a]Microenvironmental contributions to individual ambient source-derived NO_2 exposure concentration (%)

Contribution	Minimum	25th	Median	75th	Maximum	IQR	Mean	SD
Indoor (ambient)	25.4	41.7	47.0	54.1	65.3	12.5	47.7	8.8
Outdoor	0.0	0.6	1.9	2.7	18.5	2.1	3.4	5.0
In-vehicle	24.9	42.4	47.1	55.0	74.5	12.6	48.9	10.4
[b]Individual (ambient)	6.5	58.8	86.2	120.4	182.8	61.6	90.2	46.9

[a]MESA Air participants (n=37), [b]Individual ambient source-derived contribution to measured personal NO_2 concentration

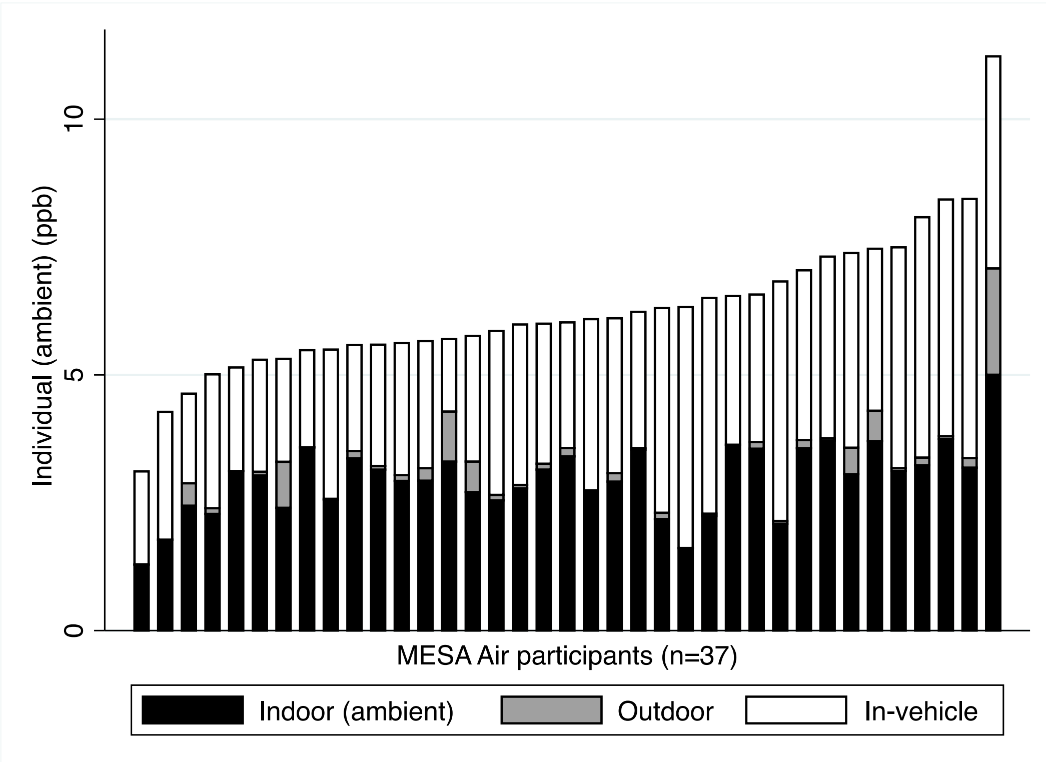

Figure III. Distribution of individual ambient source-derived NO_2 exposure concentration

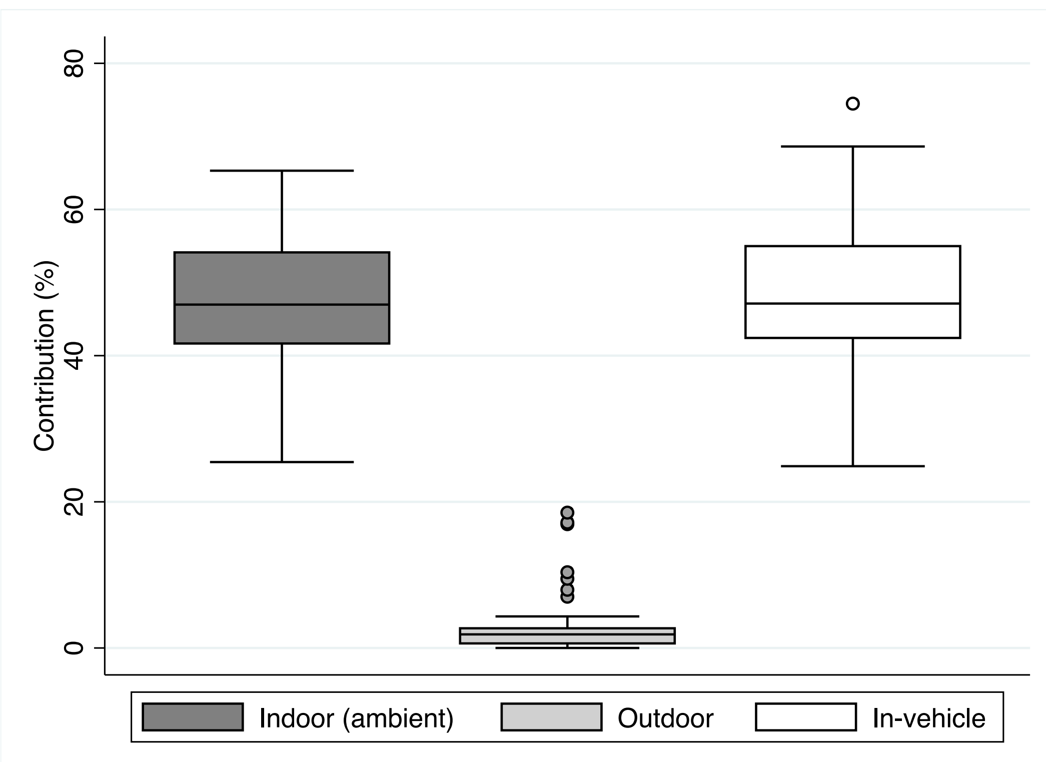

Figure IV. Distribution of microenvironmental contributions to individual ambient source-derived NO_2 exposure concentration

Table X shows calculated Pearson correlation coefficients testing the linear relationship between microenvironmental NO_2 concentrations and each individual's ambient source-derived NO_2 exposure concentration. We found that indoor ambient source-derived and outdoor NO_2 concentrations demonstrated the strongest significant linear relationships (r=0.73), as shown in Figure V. These correlations were identical because we multiplied the indoor NO_2 exposure concentration by the modeled I/O to account for the ambient source-derived fraction of outdoor NO_2 concentrations that infiltrated the indoor microenvironment. In-vehicle NO_2 concentrations demonstrated a moderate significant linear relationship (r=0.44), as shown in Figure VI. Four outliers at the far-right side of the plot demonstrated far higher in-vehicle NO_2 concentrations, and a review of the time-location diary data for these participants did not reveal noteworthy differences in their self-reported time spent in-vehicle, vehicle age, vehicle type, road types, traffic conditions, or window opening. These findings are important because they show that previous studies that used only indoor and outdoor NO_2 concentrations as surrogates of personal NO_2 exposures were not completely off the mark. These concentrations demonstrated a strong, but not perfect, linear relationship, indicating that concentrations originating from other microenvironments also contribute to personal NO_2 exposures. While in-vehicle NO_2 concentrations demonstrated a more moderate linear relationship, our participants only spent an average of one hour per day in-vehicle, and this microenvironment made up for more than the difference found in the previous relationship. These microenvironments were good surrogates of personal NO_2 exposures in our participants, and advanced previous studies through considering in-vehicle NO_2 concentrations.

Table X. [a]Correlations between microenvironmental NO_2 concentrations with individual ambient source-derived NO_2 exposure concentration (ppb)

Microenvironment	r
Indoor (ambient) and Outdoor	0.73§
In-vehicle	0.44¶

§ = for these values, $p<0.01$; ¶ = for these values, $p<0.05$, [a]MESA Air participants (n=37)

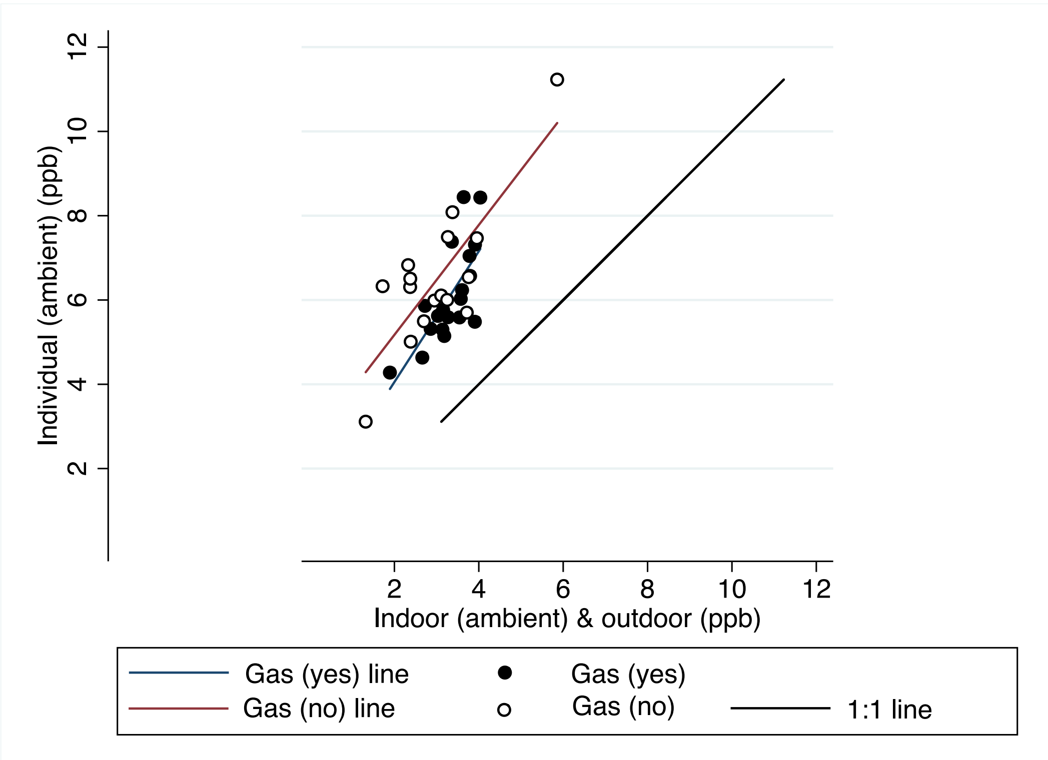

Figure V. Comparison of indoor ambient source-derived and outdoor NO_2 concentrations with individual ambient source-derived NO_2 exposure concentration

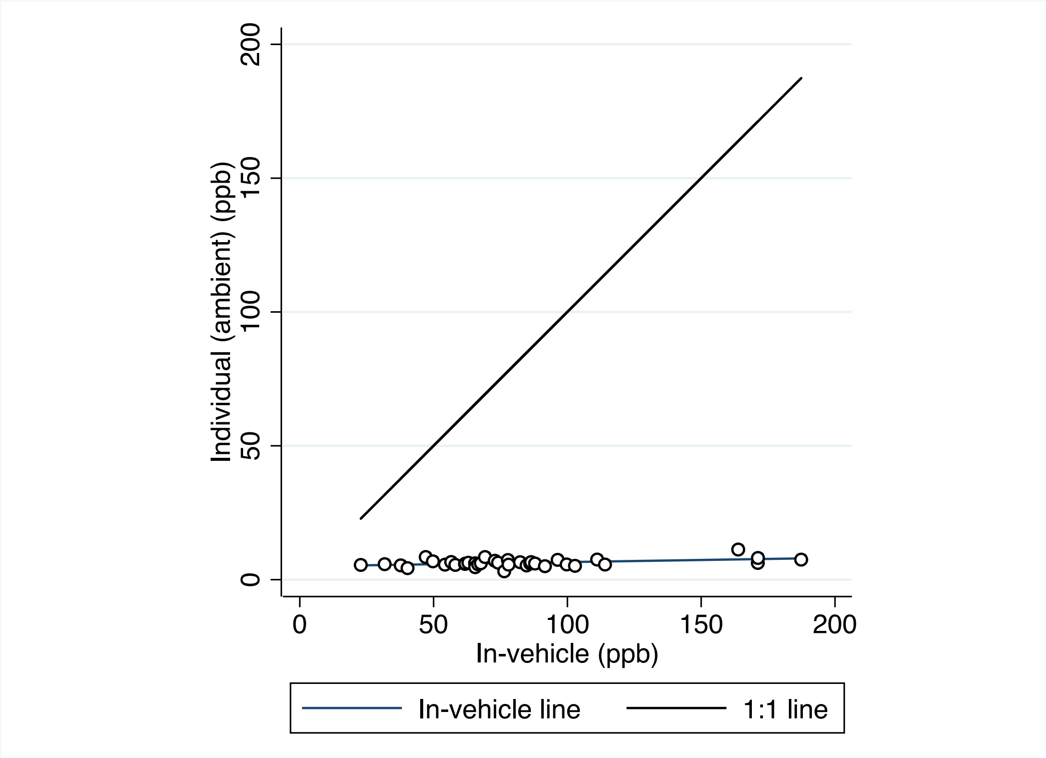

Figure VI. Comparison of in-vehicle NO_2 concentrations with individual ambient source-derived NO_2 exposure concentration

To study in-vehicle NO_2 concentrations further, we used time-location diary data to predict in-vehicle NO_2 masses, which were used to calculate in-vehicle NO_2 concentrations, using the time spent in different travel conditions in a person-level analysis. But first, we aggregated complete time-location diary data for each participant. We calculated proportionally adjusted missing data of self-reported road types and traffic conditions for participants who self-reported greater than 50% of these data. For participants who self-reported less than 50% of road types (n=2), we used ArcGIS (ESRI, Redlands, CA) to review their GPS data to determine if they were driving on a major road during the indicated dates and times of their self-reported trips with missing data. The relationship between GPS and time-location diary data was inconsistent, as these participants did not always bring their GPS unit on trips for which they self-reported missing data. We identified as many instances possible of driving on major roads for these two participants, and then calculated proportionally adjusted missing values of their self-reported road types. For participants who self-reported less than 50% of traffic conditions (n=3), we calculated proportionally adjusted missing values for the first two participants and assumed light traffic during all trips driven for the third participant, since they did not self-report any traffic conditions during the two-week sampling period. This was a reasonable assumption, since all participants self-reported an average of 66% of time spent in light traffic. After adjusting the time-location diary data, we calculated each participant's number of trips, time spent for the average trip (h), as well as percent of time spent during rush hour, on major roads, in heavy traffic, and with open windows during the two-week sampling period, as shown in Table XI. Table XII shows calculated Pearson correlation coefficients testing the linear relationship between percent of time spent during rush hour, on major roads, and in heavy traffic with the time spent for the average trip (h); all of which were found to be very low, and demonstrated no significant relationships. There were instances of participants who had self-reported forgetting to close their in-vehicle sampler; however, these were short durations and not associated with a specific trip, and such trips could not be excluded.

Table XI. [a]Travel conditions derived from self-reported time-location diary data

Travel conditions	Minimum	25th	Median	75th	Maximum	IQR	Mean	SD
Time spent in-vehicle (h)								
[b]Number of trips	6.0	23.0	36.0	45.0	56.0	22.0	33.0	13.3
[c]Average trip (h)	0.2	0.3	0.4	0.6	1.1	0.3	0.5	0.2
[d]Rush hour (%)	6.2	18.0	25.2	35.3	71.1	17.3	26.7	13.6
[e]Major roads (%)	0.0	5.3	23.5	65.9	100.0	60.6	35.7	32.8
[f]Heavy traffic (%)	0.0	2.6	10.6	32.1	84.1	29.5	20.7	23.4
[g]Open windows (%)	0.0	0.0	0.0	4.1	66.7	4.1	6.7	15.1

[a]MESA Air participants (n=38), [b]Number of trips driven during the two-week sampling period, Average time spent in-vehicle across all individual trips for each participant (h), [c]Percent of time spent for trips driven during assumed morning and evening rush hours (6:00-9:00 and 16:00-19:00, respectively), [d]Percent of time spent for trips driven on major roads, using the road type coding of 1 for "major roads", [e]Percent of time spent for trips driven in heavy traffic, using aggregated traffic condition coding of 2, 3, and 4 for "heavy traffic", [f]Percent of time spent for trips driven with open window, using the window coding of 1 for "open windows"

Table XII. [a]Correlations between percent of time spent during rush hour, on major roads, and in heavy traffic with the time spent for the average trip

Travel conditions	r
Time spent in-vehicle (h)	
Rush hour (%)	0.11
Major roads (%)	-0.10
Heavy traffic (%)	0.05

§ = for these values, $p<0.01$; ¶ = for these values, $p<0.05$, [a]MESA Air participants (n=38)

Table XIII shows person-level predicted estimates of in-vehicle NO_2 masses using travel conditions derived from self-reported time-location diary data using multiple linear regression, whose covariates were centered with respect to their mean values. One participant's in-vehicle NO_2 mass fell below the LOD of 0.25 µg; half this value was imputed, since it was also used to calculate their in-vehicle NO_2 concentration. Travel conditions predicted 44% of the in-sample variation within in-vehicle NO_2 masses. We found one statistically significant association with the number of trips driven during the two-week sampling period. Compared to the mean number of trips driven across all participants, each one additional trip driven collected adjusted 0.01 (95% CI: 0.01, 0.02) µg higher in-vehicle NO_2 masses ($p<0.0001$; partial R^2=0.33). Since the goal of our model was to predict in-vehicle NO_2 masses, we used cross-validation to estimate how accurately this predictive model would perform out of sample. Due to a small sample size (n=38), we used a more conservative type of cross-validation called "leave-one-out cross-validation" on the original model in order to train on as many participants as possible, which predicted 42% of the out-of-sample variation within in-vehicle NO_2 masses. The RMSE for the original model (0.25 µg) and for the cross-validated model (0.16 µg) sets were similar; however, the RMSE for the cross-validated model was lower, demonstrating that we did not over fit the data (e.g., create a model that tests well in sample, but demonstrates limited predictive value when tested out of sample). We plotted the measured against the predicted in-vehicle NO_2 masses from leave-one-out cross validation, and found that the cross-validated model demonstrated good predictive value (R^2=0.42), which could have been diminished by an outlier at the far-left side of the plot, as shown in Figure VII. Regression diagnostics of its jackknife residual confirmed it was over-predicted; its measured value was that for the participant who fell below the LOD. Ultimately, the use of time-location diary data enhanced the resolution of the time spent in-vehicle, and revealed that the number of trips driven during the two-week sampling period explained change and variation within in-vehicle NO_2 masses. We also used a five-fold cross-validation to test our predictions out-of-sample, and did not find deviations from our results of the leave-one-out cross-validation. These results demonstrated predictive value when tested out of sample, but could potentially be improved using a larger sample size.

Table XIII. [a]Predicted and cross-validated estimates of in-vehicle NO_2 masses (µg), adjusted for travel conditions derived from self-reported time-location diary data

	[b]Model					[c]CV	
	β	**95% CI**	**Partial R^2**	**R^2**	**RMSE**	**CV R^2**	**CV RMSE**
In-vehicle NO_2 (µg)				0.44	0.25	0.42	0.15
β_0	0.86	(0.78, 0.95)	-				
Number of trips	0.01§	(0.01, 0.02)	0.33				
Average trip (h)	0.23	(-0.22, 0.68)	0.03				
Rush hour (%)	0.00	(-0.01, 0.00)	0.04				
Major roads (%)	0.00	(0.00, 0.00)	0.05				
Heavy traffic (%)	0.00	(0.00, 0.01)	0.05				
Open windows (%)	0.00	(0.00, 0.01)	0.01				

Results of ANOVA: § = for these values, $p<0.01$; ¶ = for these values, $p<0.05$, [a]MESA Air participants (n=38), [b]Model (β, 95% CI, Partial R^2, R^2, and RMSE) = change and 95% confidence interval (µg), partial and total variation (%), and root mean square error (µg) of model, adjusted for the time spent in different travel conditions, [c]CV (CV R^2 and CV RMSE) = total variation (%) and root mean square error (µg) of leave-one-out cross-validation, adjusted for time spent for the average trip and percent of time spent with open windows

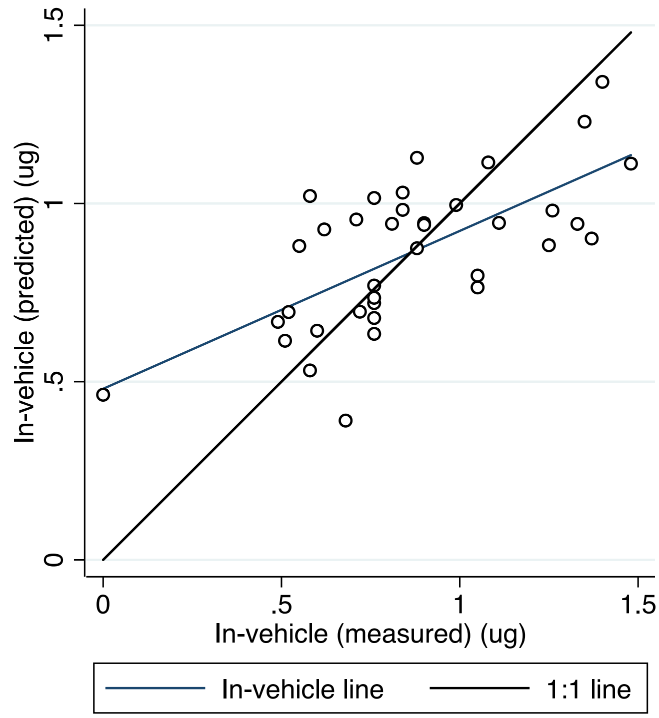

Figure VII. Comparison of measured in-vehicle NO_2 masses and predicted in-vehicle NO_2 masses using leave-one-out cross-validation

Discussion

I. Previous studies

Our mean in-vehicle NO_2 concentration falls within the range of those reported in previous studies, and our sampling time falls below their 17 day average, as shown in Table XIV (Chan et al. 1991; Rodes et al. 1998; Chan et al. 1999; Lee et al. 2000; Zagury et al. 2000; Farrar et al. 2001; Riediker et al. 2003; Sabin et al. 2004; Son et al. 2004). The studies agree that the in-vehicle microenvironment is a key contributor to personal NO_2 exposures, but sampling and seasonal differences might reduce the comparativeness of their results.

Table XIV. [a]In-vehicle NO_2 concentrations as reported in previous studies (ppb)

Study	Location	Subjects	Samples	Time	Season	In-vehicle [NO_2]
MESA Air	Winston-Salem	Participants	40	[b]2 w	Winter	82.0±38.5
Chan et al. 1991	Raleigh	Transit (cars)	35	5 w	Summer	[e]164.1±80.1
Chan et al. 1999	Hong Kong	Transit (cars)	8	[c]20-90 m	Fall-Summer	69.0 (15.0, 205.0)
Farrar et al. 2001	Perth	Transit (taxis)	7	1 w	-	15.0±6.0
Lee et al. 2000	Brisbane	Office workers	57	[d]2 d	Summer	32.0±13.2
Riediker et al. 2003	Wake County	NCSHP troopers	10	25 d	Summer-Fall	[f]156.6±78.4
Rodes et al. 1998	Sacramento	Transit (cars)	6	120 m	Fall	78.3±63.5
Sabin et al. 2004	Los Angeles	Schoolchildren	3,627	24 d	Spring	[g]227.5±92.1
Son et al. 2004	Asan, Chunan	Taxi drivers	14, 17	2 d	Summer	27.4±11.0
Zagury et al. 2000	Paris	Taxi drivers	29	2 m	Winter-Spring	[h]261.3±80.8

[a]In-vehicle NO_2 concentration (ppb), [b]Weeks, [c]Minutes, [d]Days, [e-h]Converted to ppb from μg/m^3, original values: [d]87.3±42.6 μg/m^3, [e]83.3±41.7 μg/m^3, [f]121.0±49.0 μg/m^3, and [g]139.0±43.0 μg/m^3

In-vehicle studies are becoming more common, but data are still limited since they are challenging to conduct properly. Microenvironmental, GIS, and personal monitoring studies have also been conducted to assess TRAP/NO_2 exposures. As shown in our study, others have shown that outdoor NO_2 concentrations do not entirely predict personal NO_2 exposures due to concentrations from other microenvironments (Spengler et al. 1994; Liard et al. 1999; Adgate et al. 2002; Han et al. 2006; Kousa et al. 2001). An alternative to microenvironmental studies is the use of GIS to predict TRAP exposures. GIS is better at capturing high-resolution spatial variability of TRAP concentrations in a large area than microenvironmental studies or stationary monitoring, but is not always effective at predicting TRAP exposures (Hoek et al., 2002; Brauer et al., 2003; Han et al. 2006; Bellander et al. 2012; Steinle et al. 2013). While personal monitoring has made it possible to measure TRAP exposures directly, it is costly, and unsuitable for prospective cohort studies such as MESA Air. However, it can be used to identify susceptible populations, such as taxi drivers or children transported in school buses (Zagury et al. 2000; Son et al. 2004; Sabin et al. 2004).

II. Strengths and limitations

Our study combines personal and stationary monitoring of multiple surrogates of TRAP with a rich array of time-location data to estimate microenvironmental and individual ambient source-derived NO_2 exposure concentrations. Using this novel approach, we will be able to incorporate these exposures into MESA Air. While MESA Air has measured a number of pollutants, it is not designed around a multi-pollutant model, and currently does not focus on TRAP or in-vehicle exposures. The major strength of our study lies in its ability to bridge this gap, while providing an understanding of exposure misclassification when utilizing time-location dairy data to estimate these exposures. Inaccurate or missing self-reported data are limitations of the time-location diary data; however, we did observe averages of 89%, 87%, and 100% completeness in self-reported road types, traffic conditions, and window opening for all trips driven during the two-week sampling period. The use of time-location diary data enabled us to enhance the resolution of the time spent in-vehicle by estimating the time spent in different travel conditions. However, these travel conditions were not reflective of the time spent in vehicle for the average trip, which was one of the most important predictors of in-vehicle NO_2 concentrations. Most participants lived in rural or suburban areas, and longer average trips could have occurred on rural roads with light traffic or in between rush hours, since approximately two-thirds were retired. Participants had also self-reported that they drive their vehicle for at least 30 minutes per day, and they might not be fully representative in terms of heath status.

Our exposure measurement was tested through two pilot studies and validated through a series of sensitivity analyses (Appendix). The entirety of each individual's ambient source-derived NO_2 exposure concentration could not be captured through just a two-week sampling period, which has the potential to result in Berkson measurement error. This type of error does not generally introduce bias and can safely be ignored in simple cases, but it tends to inflate the standard error of health effect estimates, which was not an aim of our analyses.

While our modeled I/O reasonably approximated the measured I/O of participants without indoor gas sources, we were unable to construct a generalizable model of I/O specific to NO_2 due to the time constraints of our study. In the future, we could collect predictors of I/O specific to NO_2, similar to those collected for $PM_{2.5}$ by Allen et al. (e.g., indoor gas sources, indoor and outdoor temperatures and relative humidity, AC use, force-air heat use, building type, and building age), which could help to better generalize to MESA Air or even larger populations (Allen et al. 2012). Our approximation; however, was impressive because it fell within one standard deviation of the measured I/O for participants without indoor gas sources. It was also a strong estimate because air exchange rates are likely to be lower in the winter due to closed windows and no AC use.

We only measured analytes at participants' homes, and did not measure them at every indoor and outdoor microenvironment they visited during the two-week sampling period (e.g., their place of work), and thus assumed that their measured home outdoor NO_2 concentrations was a reasonable approximation of their other outdoor NO_2 concentrations, and that their home indoor NO_2 concentration (derived from the modeled I/O) was a reasonable approximation for other indoor NO_2 concentrations. This assumption is more likely to be true for participants who spent more time at home and less likely to be true for participants that spent more time away from home (e.g., participants who worked full-time).

We found that our cross-validated model demonstrated good predictive value, whose regression diagnostics helped us to understand an outlier by determining whether there were improvements to the model could fix it. However, a small sample size limited our ability to select a model that could identify all of the important determinants of exposure for the remaining participants.

III. Implications

Our participants spent an average of one hour per day in-vehicle; their mean in-vehicle NO_2 concentration of 82.0±38.5 ppb is below the NAAQS one-hour standard of 100.0 ppb for NO_2, but exceeds the annual-average standard of 53.0 ppb for NO_2 (USEPA, 2011).

IV. Future studies

The time spent in different traffic conditions predicted in-vehicle NO_2 concentrations; however, other predictors might contribution to their variation. A few might include, but are certainly not limited to: vehicle I/O, age, speed, ventilation mode, and/or meteorological conditions. We did not assess for vehicle I/O or ventilation mode in our study, but Chan et al. found that the vehicle I/O is subject to significant short-term variability due to differences outdoor NO_2 concentrations across road types and traffic conditions as well as the use of different ventilation modes (Chan et al. 2003). This parameter should be better characterized in future studies, but could possibly be used in a modified version of our time-weighted model to consider short-term variability after being reviewed through a probabilistic analysis integrating GIS, GPS, and time-location diary data that considers the use of different ventilation modes for each trip. Vehicle age was recorded on the field technician observation forms, but will be considered in future analyses since participants drove in multiple vehicles during the two-week sampling period. Vehicle speed was recorded using GPS data, but will be considered in future analyses after the completed processing of these data. Meteorological data were also recorded, but will also be considered in future analyses to make seasonal comparisons. This analysis only utilized data from one of four two-week sampling periods; three additional two-week sampling periods in Winston-Salem, NC (summer 2013) and Los Angeles, CA (winter and summer 2014) will allow for municipal and seasonal comparisons using a larger sample size (n=144).

Conclusions

The in-vehicle microenvironment was a major contributor to each individual's ambient source-derived NO_2 exposure concentration, accounting for an estimated 48.9±10.4%. Using microenvironmental NO_2 concentrations, time-location diary data, and the modeled I/O, we developed a time-weighted model to calculate microenvironmental contributions to an individual's ambient source-derived NO_2 exposure concentration. The use of time-location diary data enhanced the resolution of the time spent in-vehicle, revealing that the number of trips driven during the two-week sampling period was the most important predictor of in-vehicle NO_2 masses, whose predictions tested well out of sample. These preliminary results suggest the need to account for in-vehicle exposures in studies of traffic-related air pollution.

Appendix

Our exposure measurement was tested through two pilot studies that aimed to: ensure nothing inside the in-vehicle sampler container was producing gases (using four tests with duplicate samplers for each, nine samplers total), determine whether the Teflon acted as a sorbant for the VOCs and if the trapping of gas in the container was a major contributor to in-vehicle VOC concentrations (using four samplers with duplicate VOC badges), and determine whether the in-vehicle samplers were capturing the time spent in-vehicle (using four samplers with uncovered Teflon and duplicate NO_x badges). To meet these aims, we collected three types of samples: office blanks, new vehicle blanks, and driving time samples. There were at least two participants (or locations, for office blanks) for each sample type, and all primary samples had a duplicate sample. The office blanks were never opened and were deployed to determine if any of the TRAP constituents of interest were present in the in-vehicle samplers. The new vehicle blanks were opened and closed immediately upon entry to the vehicle and remained unopened while driving. The driving time samples were divided into three categories, with two participants in each category: 30 minutes of driving per day, 45 minutes of driving per day, and more than 45 minutes of driving per day. One of the primary concerns we aimed to address in these pilot studies was whether TRAP constituents could be detected within in-vehicle samples taken for short driving times, and our results indicated that 30 minutes of driving per day was sufficient to detect many of the TRAP constituents of interest, especially NO_2 and NO_x.

In our pilot studies for NO_2, three of the four blank samples, either in the offices or in the new vehicles, were below the LOD. The blank samples that were above the LOD were at concentrations lower than any of the primary samples. Duplicate samples with concentrations less than the LOD were excluded from analysis, since additional information on the LODs for these samples was still needed at the time the pilot studies were conducted. The precision across the three blank samples with detectable results was 3%, ranged from 1% to 5%, and met the DQO of less than 10%. After excluding these blank samples, assigning the LODs to the values of the lab blank sample values of 0.18 μg/sample, excluding the blank sample accidentally left open, and averaging the duplicate samples, the correlation between the amount of time the samplers were open and in-vehicle NO_2 masses was found to be strong (r=0.86). In summary, and as shown in Table XV, the office blanks and new vehicle blanks demonstrated concentrations below the LOD, and met our DQO; the duplicate samples demonstrated good agreement, whose precision met our DQO, and the time the samplers were open and in-vehicle NO_2 masses were strongly correlated.

Our pilot studies were conducted with fewer participants (n=7) in a different location (Seattle, WA) from the location of our study (Winston-Salem, NC), and we found differences in our study results for these reasons. For instance, we found that in-vehicle NO_2 masses demonstrated a weaker positive correlation with the time spent in-vehicle (r=0.50). This was possibly due to a greater number of participants (n=38) that inevitably self-reported greater variability in their time spent in-vehicle. In our analysis, we found that the number of trips driven during the two-week sampling period was the most important predictor of in-vehicle NO_2 masses (partial R^2=0.33).

Table XV. Results of pilot studies for NO_2

[a]**Office Blanks**	[b]**New Vehicles**	[c]**Precision (%)**	**r**
Less than LOD	Less than LOD	3	0.86

[a]Equal to or less than LOD meets DQO, [b]Compared to driving time participants, [c]Less than 10% meets DQO

As an analysis of sensitivity, we included two participants in Aims 1-3. The first spent 12 hours on a bus (but provided better data than the other participant who also spent 12 hours on a bus), and the second spent about half of the two-week sampling period away from home; their measured personal NO_2 concentration was anticipated to not represent if they had been home during the whole two-week sampling period. This participant was previously included only in Aim 3. Their inclusion resulted in no noteworthy changes in our results for Aims 1-2.

As a second analysis of sensitivity, we recalculated our modeled I/O, which used an ACH of 0.50 h^{-1} (that ranged from 0.37-0.63 h^{-1}) and a K of 0.99±0.19 h^{-1} (that ranged from 0.80-1.18 h^{-1}). These values were used as measures of central tendency, and we recalculated our modeled I/O using permutations of the lower, central, and higher values of ACH and K to assess its variability, as shown in Table XVI. Table XVII shows recalculated the microenvironmental contributions using the minima (0.24) and maxima (0.44) modeled I/O, and each one fell within one standard deviation of its counterpart calculated using the modeled I/O of central tendency.

Table XVI. Modeled I/O, recalculated using permutations of the lower, central, and higher values of ACH and K

		[a]ACH		
		Lower	**Central**	**Higher**
[b]**K**	**Lower**	0.32	0.38	0.44
	Central	0.27	0.34	0.39
	Higher	0.24	0.30	0.35

[a]ACH (h^{-1}): lower = 0.37; central = 0.5; higher = 0.63, [b]K (h^{-1}): lower = 0.80; central = 0.99; higher = 1.18

Table XVII. [a]Microenvironmental contributions to individual ambient source-derived NO_2 exposure concentration (%), recalculated using minima and maxima modeled I/O

Contribution	Minimum	25th	Median	75th	Maximum	IQR	Mean	SD
I/O = 0.24								
Indoor	19.3	33.4	38.4	45.3	56.9	11.9	39.3	8.3
Outdoor	0.0	0.7	2.1	3.2	21.4	2.4	4.0	5.8
In-vehicle	30.1	49.8	55.5	63.4	80.6	13.6	56.7	10.5
I/O = 0.34								
Indoor	25.4	41.7	47.0	54.1	65.3	12.5	47.7	8.8
Outdoor	0.0	0.6	1.9	2.7	18.5	2.1	3.4	5.0
In-vehicle	24.9	42.4	47.1	55.0	74.5	12.6	48.9	10.4
I/O = 0.44								
Indoor	30.7	48.1	53.5	60.5	70.9	12.4	54.0	8.8
Outdoor	0.0	0.5	1.7	2.3	16.4	1.8	3.0	4.3
In-vehicle	21.2	36.4	41.0	48.6	69.3	12.2	43.0	10.1

[a]MESA Air participants (n=37)

As a third analysis of sensitivity, we excluded participants (n=5) who self-reported driving less than seven hours during the two-week sampling period, or less than 30 minutes per day on average. Table XVIII shows recalculated microenvironmental contributions excluding these participants, and each one only changed by a few percent.

Table XVIII. [a]Microenvironmental contributions to individual ambient source-derived NO_2 exposure concentration (%), recalculated excluding participants who drove <7 hours

Contribution	Minimum	25th	Median	75th	Maximum	IQR	Mean	SD
Including <7 hours								
Indoor	25.4	41.7	47.0	54.1	65.3	12.5	47.7	8.8
Outdoor	0.0	0.6	1.9	2.7	18.5	2.1	3.4	5.0
In-vehicle	24.9	42.4	47.1	55.0	74.5	12.6	48.9	10.4
Excluding <7 hours								
Indoor	25.4	41.5	46.4	52.7	65.3	11.2	46.8	8.8
Outdoor	0.0	0.6	1.9	2.7	18.5	2.1	3.5	5.1
In-vehicle	24.9	42.4	49.6	57.6	74.5	15.2	49.6	10.8

[a]MESA Air participants (n=5)

As a fourth analysis of sensitivity, we calculated the microenvironmental contributions for participants with primary and duplicate in-vehicle samples (n=4), and each one only differed by a few percent, as shown in Table XIX.

Table XIX. [a]Microenvironmental contributions to individual ambient source-derived NO_2 exposure concentration (%), difference between participants with primary and duplicate in-vehicle samples

Contribution	Minimum	25^{th}	Median	75^{th}	Maximum	IQR	Mean	SD
Primary								
Indoor	37.8	41.1	49.3	55.3	56.5	14.2	48.2	8.7
Outdoor	0.5	1.3	2.1	2.5	2.7	1.2	1.9	0.9
In-vehicle	40.8	42.3	49.4	57.5	60.0	15.2	49.9	9.1
Duplicate								
Indoor	38.4	39.1	45.7	53.6	55.6	14.5	46.3	8.5
Outdoor	0.5	1.3	2.1	2.4	2.5	1.1	1.8	0.9
In-vehicle	42.4	44.2	52.6	59.5	59.7	15.4	51.9	9.0

[a]MESA Air participants (n=4)

As a final analysis of sensitivity, we generated bootstrapped estimates of 95% CI, bias, and bias-corrected 95% CI in the model R^2 (Efron and Tibshirani 1994), as shown in Table XX. This was performed through unrestricted random sampling of 500 bootstrap datasets at a sampling rate of one, so that each bootstrap dataset was the same size as our original dataset. The multiple linear regression was run separately for each of the 500 bootstrap datasets, and our estimates were created using normal distribution theory, which assumes that the bootstrap R^2 values follow a t-distribution. The 95% CI was wide but symmetric about the model R^2, indicating that our model's estimate of in-sample variation was imprecise, but normally distributed. We calculated the bias in our model R^2 as the difference between this value and the mean of the bootstrap R^2 values. We also generated the bias-corrected 95% CI to check the assumption of the model R^2 as an unbiased estimate of the true R^2. The bias-corrected 95% CI provided a similar interpretation to the uncorrected 95% CI, indicating that our results were robust to two different methods of calculating a 95% CI.

Table XX. [a]Predicted and bootstrapped estimates of in-vehicle NO_2 masses (μg), adjusted for travel conditions derived from self-reported time-location diary data

	[b]Model				[c]Bootstrap			
	β	**95% CI**	**Partial R^2**	**R^2**	**R^2**	**95% CI**	**Bias**	**Bias-corrected 95% CI**
In-vehicle NO_2 (μg)				0.44	0.44	(0.22, 0.67)	0.07	(0.19, 0.60)
β_0	0.86	(0.78, 0.95)	-					
Number of trips	0.01	(0.01, 0.02)	0.33					
Average trip (h)	0.23	(-0.22, 0.68)	0.03					
Rush hour (%)	0.00	(-0.01, 0.00)	0.04					
Major roads (%)	0.00	(0.00, 0.00)	0.05					
Heavy traffic (%)	0.00	(0.00, 0.01)	0.05					
Open windows (%)	0.00	(0.00, 0.01)	0.01					

Results of ANOVA: § = for these values, $p<0.01$; ¶ = for these values, $p<0.05$, [a]MESA Air participants (n=38), [b]Model (β, 95% CI, Partial R^2, R^2, and RMSE) = change and 95% confidence interval (μg), partial and total variation (%), and root mean square error (μg) of model, adjusted for the time spent in different travel conditions, [c]Bootstrap (R^2, 95% CI, Bias, and Bias-corrected 95% CI) = bootstrap estimates of total variation and 95% confidence interval (%), bias (%), and bias-corrected 95% confidence interval (%) in model total variation

Figure VIII. Time-location diary

CCAR Time – Location Diary

Date at Noon: ____________________ **Day of Week at Noon:** _________________________

Participant ID:________________________ **Site:**______________

Start Time	End Time	Home		Away from Home		Motor Vehicle
		Indoor	Outdoor	Indoor	Outdoor	
Midnight						

Vehicle Type	Traffic Cond.	Road Type	Windows Open?

Locations Legend	
Home Indoor	Inside your home
Home Outdoor	Outdoors near your home (yard, deck, driveway, etc.)
Away from Home Indoor	Indoors other than your home (workplace, grocery store, movie theater, etc.)
Away from Home Outdoor	Outdoors other than your home (workplace, park, waiting for the bus, etc.)
Motor Vehicle	Car, bus, taxi, motorcycle, subway, etc.

Travel Legend	
Vehicle type	Car (write make & model of car), bus, taxi, motorcycle, subway, train, etc.
Traffic Cond.	1: Light traffic, moving at speed limit
	2: Heavy traffic, moving at or above speed limit
	3: Heavy traffic, moving below speed limit
	4: Congested or stop and go
	5: N/A, I travel by train or subway
Road Type	A: Freeways, expressways, highways, toll roads, etc.
	B: Other major, heavily traveled roads or streets
	C: Residential or lightly traveled roads, streets, or paths

Event Start Date:_______________________

City:_______________ Page ______ of _______

CCAR Time-Location Diary, Version 2.0

NOTES:

REFERENCES

Adar, S. D., and J. D. Kaufman. "Cardiovascular disease and air pollutants: evaluating and improving epidemiological data implicating traffic exposure." Inhalation Toxicology 19, no. S1 (2007): 135-149.

Adgate, John L., Gurumurthy Ramachandran, G. C. Pratt, L. A. Waller, and Ken Sexton. "Spatial and temporal variability in outdoor, indoor, and personal $PM_{2.5}$ exposure." Atmospheric Environment 36, no. 20 (2002): 3255-3265.

Agency, US Environmental Protection. "Office of Air and Radiation." Office of Air Quality Planning and Standards: Research Triangle Park, NC (2011).

Allen, Ryan W., Sara D. Adar, Martin Cohen Avol, Cynthia L. Curl, Timothy Larson, L-J. Sally Liu, Lianne Sheppard, and Joel D. Kaufman. "Modeling the residential infiltration of outdoor $PM_{2.5}$ in the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air)." Environmental health perspectives 120, no. 6 (2012): 824.

Bellander, Tom, Janine Wichmann, and Tomas Lind. "Individual exposure to NO2 in relation to spatial and temporal exposure indices in Stockholm, Sweden: the INDEX study." PloS one 7, no. 6 (2012): e39536.

Chan, Andy T., and Michael W. Chung. "Indoor–outdoor air quality relationships in vehicle: effect of driving environment and ventilation modes." Atmospheric Environment 37, no. 27 (2003): 3795-3808.

Chan, Chang Chuan, Haluk Ozkaynak, John D. Spengler, and Linda Sheldon. "Driver exposure to volatile organic compounds, carbon monoxide, ozone and nitrogen dioxide under different driving conditions." Environmental Science & Technology 25, no. 5 (1991): 964-972.

Chan, L. Y., C. Y. Chan, and Y. Qin. "The effect of commuting microenvironment on commuter exposures to vehicular emission in Hong Kong." Atmospheric Environment 33, no. 11 (1999): 1777-1787.

Chao, Christopher YH, and Anthony Law. "A study of personal exposure to nitrogen dioxide using passive samplers." Building and Environment 35, no. 6 (2000): 545-553.

Chen, Hong, Mark S. Goldberg, Richard T. Burnett, Michael Jerrett, Amanda J. Wheeler, and Paul J. Villeneuve. "Long-term exposure to traffic-related air pollution and cardiovascular mortality." Epidemiology 24, no. 1 (2013): 35-43.

Cho, Seung-Hyun, Haiyan Tong, John K. McGee, Richard W. Baldauf, Q. Todd Krantz, and M. Ian Gilmour. "Comparative toxicity of size-fractionated airborne particulate matter collected at different distances from an urban highway." Environmental health perspectives 117, no. 11 (2009): 1682.

Cohen, Martin A., Sara D. Adar, Ryan W. Allen, Edward Avol, Cynthia L. Curl, Timothy Gould, David Hardie et al. "Approach to estimating participant pollutant exposures in the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air)." Environmental Science & Technology 43, no. 13 (2009): 4687-4693.

Dimitroulopoulou, C., M. R. Ashmore, M. A. Byrne, and R. P. Kinnersley. "Modelling of indoor exposure to nitrogen dioxide in the UK." Atmospheric Environment 35, no. 2 (2001): 269-279.

Dockery, Douglas W., C. Arden Pope, Xiping Xu, John D. Spengler, James H. Ware, Martha E. Fay, Benjamin G. Ferris Jr, and Frank E. Speizer. "An association between air pollution and mortality in six US cities." New England journal of medicine 329, no. 24 (1993): 1753-1759.

Dubowsky, Sara D., Lance A. Wallace, and Timothy J. Buckley. "The contribution of traffic to indoor concentrations of polycyclic aromatic hydrocarbons." Journal of Exposure Analysis & Environmental Epidemiology 9, no. 4 (1999).

Efron, Bradley, and Robert J. Tibshirani. "An introduction to the bootstrap." (1994).

ESRI. "ArcGIS, version 9.2." (2006).

Farrar, D., P. Dingle, and R. Tan. "Exposure to nitrogen dioxide in buses, taxis, and bicycles in Perth, Western Australia." Bulletin of environmental contamination and toxicology 66, no. 4 (2001): 433-438.

Frampton, Mark W., Joseph Boscia, Norbert J. Roberts, Mitra Azadniv, Alfonso Torres, Christopher Cox, Paul E. Morrow et al. "Nitrogen dioxide exposure: effects on airway and blood cells." American Journal of Physiology-Lung Cellular and Molecular Physiology 282, no. 1 (2002): L155-L165.

Gill, Edward A., Cynthia L. Curl, Sara D. Adar, Ryan W. Allen, Amy H. Auchincloss, Marie S. O'Neill, Sung Kyun Park, Victor C. Van Hee, Ana V. Diez Roux, and Joel D. Kaufman. "Air pollution and cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis." Progress in cardiovascular diseases 53, no. 5 (2011): 353-360.

Han, Xianglu, and Luke P. Naeher. "A review of traffic-related air pollution exposure assessment studies in the developing world." Environment international 32, no. 1 (2006): 106-120.

Heal, M. R., M. A. O'Donoghue, R. M. Agius, and I. J. Beverland. "Application of passive diffusion tubes to short-term indoor and personal exposure measurement of NO_2." Environment international 25, no. 1 (1999): 3-8.

Hoek, Gerard, Bert Brunekreef, Sandra Goldbohm, Paul Fischer, and Piet A. van den Brandt. "Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study." The lancet 360, no. 9341 (2002): 1203-1209.

Hoffmann, Barbara, Susanne Moebus, Andreas Stang, Eva-Maria Beck, Nico Dragano, Stephan Möhlenkamp, Axel Schmermund et al. "Residence close to high traffic and prevalence of coronary heart disease." European Heart Journal 27, no. 22 (2006): 2696-2702.

Jerrett, Michael, Murray M. Finkelstein, Jeffrey R. Brook, M. Altaf Arain, Palvos Kanaroglou, Dave M. Stieb, Nicolas L. Gilbert et al. "A cohort study of traffic-related air pollution and mortality in Toronto, Ontario, Canada." Environ Health Perspect 117, no. 5 (2009): 772-7.

Kaufman, Joel D., Sara D. Adar, Ryan W. Allen, R. Graham Barr, Matthew J. Budoff, Gregory L. Burke, Adrian M. Casillas et al. "Prospective Study of Particulate Air Pollution Exposures, Subclinical Atherosclerosis, and Clinical Cardiovascular Disease The Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air)." American journal of epidemiology 176, no. 9 (2012): 825-837.

Kornartit, C., R. S. Sokhi, M. A. Burton, and Khaiwal Ravindra. "Activity pattern and personal exposure to nitrogen dioxide in indoor and outdoor microenvironments." Environment international 36, no. 1 (2010): 36-45.
Kousa, Anu, Christian Monn, Tuulia Rotko, Sari Alm, Lucy Oglesby, and Matti J. Jantunen. "Personal exposures to NO_2 in the *EXPOLIS*-study: relation to residential indoor, outdoor and workplace concentrations in Basel, Helsinki and Prague." Atmospheric Environment 35, no. 20 (2001): 3405-3412.

Künzli, Nino, Reinhard Kaiser, Sylvia Medina, M. Studnicka, Olivier Chanel, Paul Filliger, Max Herry et al. "Public-health impact of outdoor and traffic-related air pollution: a European assessment." The Lancet 356, no. 9232 (2000): 795-801.

Laden, Francine, Lucas M. Neas, Douglas W. Dockery, and Joel Schwartz. "Association of fine particulate matter from different sources with daily mortality in six US cities." Environmental health perspectives 108, no. 10 (2000): 941.

Lee, Kiyoung, Jianping Xue, Alison S. Geyh, Haluk Ozkaynak, Brian P. Leaderer, Charles J. Weschler, and John D. Spengler. "Nitrous acid, nitrogen dioxide, and ozone concentrations in residential environments." Environmental health perspectives 110, no. 2 (2002): 145.

Lee, Kiyoung, Jonathan I. Levy, Yukio Yanagisawa, John D. Spengler, and Irwin H. Billick. "The Boston residential nitrogen dioxide characterization study: classification and prediction of indoor NO2 exposure." Journal of the Air & Waste Management Association 48, no. 8 (1998): 736-742.

Lee, Kiyoung, Wonho Yang, and Neville D. Bofinger. "Impact of microenvironmental nitrogen dioxide concentrations on personal exposures in Australia." Journal of the Air & Waste Management Association 50, no. 10 (2000): 1739-1744.

Lee, Kiyoung, Wonho Yang, Chungsik Yoon, Busun Son, Jun Min Jeon, Joung Yoon Kim, and Jiseon Yeom. "Relationship Between Personal Exposures and Microenvironmental Concentrations of NO_2 in Korea." Epidemiology 22, no. 1 (2011): S118-S119.

Levy, J. I. "Impact of residential nitrogen dioxide exposure on personal exposure: an international study." Journal of the Air & Waste Management Association 48, no. 6 (1998): 553-560.

Liard, Renata, Mahmoud Zureik, Yvon Le Moullec, David Soussan, Marie Glorian, Alain Grimfeld, and Françoise Neukirch. "Use of Personal Passive Samplers for Measurement of NO_2, NO, and O_3 Levels in Panel Studies." Environmental research 81, no. 4 (1999): 339-348.

Monn, Ch, O. Brändli, C. Schindler, U. Ackermann-Liebrich, and Ph Leuenberger. "Personal exposure to nitrogen dioxide in Switzerland." Science of the Total Environment 215, no. 3 (1998): 243-251.

Monn, Christian. "Exposure assessment of air pollutants: a review on spatial heterogeneity and indoor/outdoor/personal exposure to suspended particulate matter, nitrogen dioxide and ozone." Atmospheric Environment 35, no. 1 (2001): 1-32.

Ogawa, C. "NO, NO_2, NO_x and SO_2 sampling protocol using the Ogawa sampler." (2002).

Peters, Annette, Stephanie Von Klot, Margit Heier, Ines Trentinaglia, Allmut Hörmann, H. Erich Wichmann, and Hannelore Löwel. "Exposure to traffic and the onset of myocardial infarction." New England Journal of Medicine 351, no. 17 (2004): 1721-1730.

Release, S. A. S. "SAS/STAT 9.3." User's Guide. SAS Institute Inc., Cary, NC (2011).

Riediker, Michael, Ronald Williams, Robert Devlin, Thomas Griggs, and Philip Bromberg. "Exposure to particulate matter, volatile organic compounds, and other air pollutants inside patrol cars." Environmental science & technology 37, no. 10 (2003): 2084-2093.

Ryan, P. Barry, Mary Lou Soczek, Robert D. Treitman, John D. Spengler, and Irwin H. Billick. "The Boston residential NO_2 characterization study—II. Survey methodology and population concentration estimates." Atmospheric Environment (1967) 22, no. 10 (1988): 2115-2125.

Sabin, Lisa D., Eduardo Behrentz, Arthur M. Winer, Seong Jeong, Dennis R. Fitz, David V. Pankratz, Steven D. Colome, and Scott A. Fruin. "Characterizing the range of children's air pollutant exposure during school bus commutes." Journal of Exposure Science and Environmental Epidemiology 15, no. 5 (2005): 377-387.

Schwarzenegger, Governor Arnold. "Review of the California Ambient Air Quality Standard For Nitrogen Dioxide." (2006).

Sheldon, L., D. Whitaker, A. Clayton, K. Fitzgerald, J. Flanagan, F. DiGenova, S. Hering, and C. Frazier. "Measuring concentrations of selected air pollutants inside California vehicles: final report." (1998).

Sherman, Max H., and Jennifer A. McWilliams. "Air Leakage of US Homes: Model Prediction." (2007).

Son, Busoon, Wonho Yang, Patrick Breysse, Taewoong Chung, and Youngshin Lee. "Estimation of occupational and nonoccupational nitrogen dioxide exposure for Korean taxi drivers using a microenvironmental model." Environmental research 94, no. 3 (2004): 291-296.

Spengler, John D., Colin P. Duffy, Richard Letz, Theodore W. Tibbitts, and Benjamin G. Ferris. "Nitrogen dioxide inside and outside 137 homes and implications for ambient air quality standards and health effects research." Environmental science & technology 17, no. 3 (1983): 164-168.

Spengler, John, Margo Schwab, P. Barry Ryan, Steven Colome, A. L. Wilson, Irwin Billick, and Edward Becker. "Personal exposure to nitrogen dioxide in the Los Angeles Basin." Air & Waste 44, no. 1 (1994): 39-47.

Stata Corporation. "Stata Statistical Software Release 12.1: Reference Su-Z." (2012).

Steinle, Susanne, Stefan Reis, and Clive Eric Sabel. "Quantifying human exposure to air pollution—moving from static monitoring to spatio-temporally resolved personal exposure assessment." Science of the Total Environment 443 (2013): 184-193.

Stephens, Brent, Elliott T. Gall, and Jeffrey A. Siegel. "Measuring the penetration of ambient ozone into residential buildings." Environmental science & technology 46, no. 2 (2011): 929-936.

Thatcher, Tracy L., and David W. Layton. "Deposition, resuspension, and penetration of particles within a residence." Atmospheric Environment 29, no. 13 (1995): 1487-1497.

Tonne, Cathryn, Jeff Yanosky, Alexandros Gryparis, Steve Melly, Murray Mittleman, Robert Goldberg, Stephanie von Klot, and Joel Schwartz. "Traffic particles and occurrence of acute myocardial infarction: a case–control analysis." Occupational and environmental medicine 66, no. 12 (2009): 797-804.

Tonne, Cathryn, Steve Melly, Murray Mittleman, Brent Coull, Robert Goldberg, and Joel Schwartz. "A case–control analysis of exposure to traffic and acute myocardial infarction." Environmental health perspectives 115, no. 1 (2007): 53.

Van Hee, Victor C., Sara D. Adar, Adam A. Szpiro, R. Graham Barr, David A. Bluemke, Ana V. Diez Roux, Edward A. Gill, Lianne Sheppard, and Joel D. Kaufman. "Exposure to traffic and left ventricular mass and function: the Multi-Ethnic Study of Atherosclerosis." American journal of respiratory and critical care medicine 179, no. 9 (2009): 827.

Vedal, Sverre. "Traffic and cardiovascular disease: the challenge of estimating exposure." Occupational and environmental medicine 66, no. 12 (2009): 787-788.

Villeneuve, Paul J., Michael Jerrett, Jason Su, Richard T. Burnett, Hong Chen, Jeffrey Brook, Amanda J. Wheeler, Sabit Cakmak, and Mark S. Goldberg. "A cohort study of intra-urban variations in volatile organic compounds and mortality, Toronto, Canada." Environmental Pollution 183 (2013): 30-39.

Yamanaka, Shin'ichi. "Decay rates of nitrogen oxides in a typical Japanese living room." Environmental science & technology 18, no. 7 (1984): 566-570.

Yang, W., K. Lee, and M. Chung. "Characterization of indoor air quality using multiple measurements of nitrogen dioxide." Indoor Air 14, no. 2 (2004): 105-111.

Zagury, Emmanuelle, Yvon Le Moullec, and Isabelle Momas. "Exposure of Paris taxi drivers to automobile air pollutants within their vehicles." Occupational and environmental medicine 57, no. 6 (2000): 406-410.

Zhang, Kai, and Stuart Batterman. "Air pollution and health risks due to vehicle traffic." Science of The Total Environment 450 (2013): 307-316.

Zhou, Ying, and Jonathan I. Levy. "Factors influencing the spatial extent of mobile source air pollution impacts: a meta-analysis." BMC Public Health 7, no. 1 (2007): 89.