Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Cassandra Ruth O'Lenick Date

Ambient Air Quality and Pediatric Asthma Morbidity: Sociodemographic Influences

By

Cassandra Ruth O'Lenick
Doctor of Philosophy
Environmental Health Sciences

Stefanie Ebelt Sarnat, ScD
Advisor

Howard H. Chang, PhD
Committee Member

Michael R. Kramer, PhD, MMSc
Committee Member

James A. Mulholland, PhD
Committee Member

Andrea Winquist, MD, PhD
Committee Member

Accepted:

Lisa A. Tedesco, Ph.D. Dean of the James T. Laney School of Graduate Studies

---

Date

Ambient Air Quality and Pediatric Asthma Morbidity: Sociodemographic Influences

By

Cassandra Ruth O'Lenick
MS, University of North Carolina at Chapel Hill, 2008
BS, University of North Carolina at Wilmington, 2001

Advisor: Stefanie Ebelt Sarnat, ScD

An abstract of
A dissertation submitted to the Faculty of the James T. Laney School of Graduate Studies of Emory University in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Environmental Health Sciences
2016

Abstract

Ambient Air Quality and Pediatric Asthma Morbidity: Sociodemographic Influences

By Cassandra Ruth O'Lenick

Introduction. Increasing evidence suggests that ambient air quality (e.g., ambient air pollution and high ambient temperature) is associated with asthma morbidity among children. Susceptibility to the health effects of ambient air quality may be influenced by sociodemographic factors at both the individual (e.g. sex, race/ethnicity, insurance status) and neighborhood level, such as neighborhood socioeconomic status (SES). However, epidemiologic research has provided inconsistent findings on whether individual- and/or neighborhood-level factors modify short-term associations between ambient air quality and respiratory morbidity, particularly across different study areas. In this dissertation I examined the degree to which individual- and/or neighborhood-level factors influence air quality-related respiratory emergency department (ED) visits among children 5-18 years old.

Methods. In **Chapter 1**, conditional logistic regression (CLR) was used to estimate associations between air pollution and pediatric asthma ED visits in Atlanta. Effect modification by ZIP Code Tabulation Area (ZCTA) SES was examined via stratification. In **Chapter 2**, a 2-stage modeling approach (CLR followed by a Bayesian hierarchical meta-regression) was used to estimate associations between ozone-related pediatric respiratory ED visits and to examine effect modification by neighborhood SES across multiple US cities (Atlanta, Dallas, and St. Louis). In **Chapter 3**, Poisson regression was used to estimate associations between high temperature and asthma ED visits. Effect modification by sex, race/ethnicity, insurance status (a proxy for individual-level SES), and neighborhood SES was examined via stratification.

Results. Findings from Chapters 1 and 2 suggest that air pollution is associated with pediatric respiratory morbidity in multiple US cities and that neighborhood SES may modify this association in a non-linear manner. Findings from Chapter 3 suggest stronger associations between high temperature and asthma morbidity among males compared to females, non-white children compared to white children, children with private insurance compared to children with Medicaid, and among children living in high compared to low SES neighborhoods.

Conclusion. Short-term ambient air quality is associated with increases in pediatric respiratory morbidity in multiple US cities; individual and neighborhood-level sociodemographic factors may confer vulnerability. Findings from this research can help identify vulnerable subpopulations in our study areas and may inform risk assessment and targeted prevention strategies.

Ambient Air Quality and Pediatric Asthma Morbidity: Sociodemographic Influences

By

Cassandra Ruth O'Lenick
MS, University of North Carolina at Chapel Hill, 2008
BS, University of North Carolina at Wilmington, 2001

Advisor: Stefanie Ebelt Sarnat, ScD

A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Environmental Health Sciences
2016

Acknowledgements:

I am profoundly grateful for the wonderful people who have supported me throughout my doctoral training. I will strive to recognize them here, but words cannot adequately thank them or repay the debt I owe them for helping make this dissertation possible. Because of the vital contribution so many have made to my doctoral training, this dissertation means so much more to me than just a body of research–it is an accomplishment that I share with my family, friends, and mentors, and a worthwhile endeavor made possible by their love and encouragement.

I would not be where I am today were it not for the tireless support and countless sacrifices of my parents, Brenda Murphy and Frank O'Lenick. My parents instilled in me a strong work ethic, insatiable curiosity, and the knowledge that I was never alone in my endeavors. Most importantly, my parents allowed me to fail so that I could learn from my missteps. In doing so, they taught me how to be resilient and how to persevere in times of adversity. My sister, Franceska Bailey, has always been my greatest advocate and a steadfast companion throughout my life. She is also the funniest person I've ever known; if I have managed to surface from graduate school with a sense of humor, it is entirely due to her. I want to thank my partner, Maggie Hodges, for being ever-present and encouraging throughout this process, for keeping me grounded, for daily doses of laughter, for knowing when to let me keep working and when to wrench me from the depths of this dissertation, and for being willing to peer-edit everything I've written since starting my doctoral program. I would also like to thank Cindy and Mike Hodges who brought me into the fold of their family and who have been generous with their advice and time. Being a part of their family has been a great source of strength for me throughout my doctoral training.

My doctoral training has been an exceedingly rewarding and positive experience primarily due to the invaluable guidance, support, and mentorship of my dissertation committee. I am eternally grateful to Stefanie Sarnat, Howard Chang, Michael Kramer, James Mulholland, and Andrea Winquist for helping me develop the necessary tools to complete this dissertation as well as fostering

a rich sense of camaraderie that gave this journey more meaning. Immense thanks go to my committee Chair and advisor, Stefanie Sarnat, for giving so generously of her time, for the rapidity of her feedback, and for engaging fully in my doctoral training.

I would like to thank all of my friends and mentors who have been a part of this journey and who are too numerous to name individually. Thank your for your friendship, for being my extended family, for housing me, for taking caring of Timo during my travels, for help with my research, and for keeping me sane.

Additionally, this dissertation was supported by a Clean Air Research Center grant to Emory University and Georgia Institute of Technology from the US Environmental Protection Agency (US EPA; Grant, RD834799) and by grants to Emory University from the US EPA (Grant R82921301), the National Institute of Environmental Health Sciences (Grants R01ES11294 and R21ES023763), and the Electric Power Research Institute (Grants EP-P27723/C13172, EP-P4353/C2124, EP-P34975/C15892, EP-P45572/C19698, and EP-P25912/C12525).

Finally, I would like to honor the memory of my dog, Timo, who was my companion for over 14 years and whose boundless enthusiasm for walks was contagious; our daily walks together were always the best part of my day.

Table of Contents

List of Tables

CHAPTER 1

CHAPTER 2

CHAPTER 3

List of Figures

INTRODUCTION

CHAPTER 1

CHAPTER 2

CHAPTER 3

PREAMBLE

Greetings, dear readers: I am delighted to present to you a detailed account of my dissertation research. This body of work has been very fulfilling for me, and I hope that my enthusiasm for this research and for the environmental health science discipline is evident throughout these pages.

Broadly, my dissertation research examines whether sociodemographic influences at the individual or neighborhood level confer vulnerability to the adverse effects of ambient air pollution and high temperatures on respiratory health among children. In the Introduction, I take you on a brief tour of the relevant literature to provide the context in which my research takes place and to emphasize the significance of my work within the air pollution/climate-health discipline. Within the introduction, I also outline the specific research questions that have motivated this dissertation, and summarize the three aims that constitute the substantive work presented in each chapter

Following the introduction are three chapters (chapters 1-3) that represent the three discrete aims of my dissertation research. These chapters are the pith of this dissertation and each chapter is a completed study, formatted for publication in a scientific journal. Currently, Chapter 1 is under review at the *Journal of Epidemiology and Community Health* (JECH), and has been formatted based on JECH requirements. Chapters 2 & 3 are formatted as complete manuscripts for submission to *Environmental Health*. Finally, the Discussion recounts the overarching strengths and limitations of this research, and distills the main findings from each study into a discussion on the contribution of this work to the broader air pollution and climate health research fields.

INTRODUCTION

Asthma is characterized by chronic inflammation of the airways, recurrent episodes of wheezing, breathlessness, chest tightness, coughing, obstructed airflow, and bronchial hyper-responsiveness.[1, 2] In 2010, the US Centers for Disease Control and Prevention estimated that 25.7 million people suffer from asthma in the US (approximately 18.7 million adults and 7 million children).[3, 4] Annually, asthma exacerbations are responsible for over 12 million medical visits and approximately 3,300 deaths.[4] In the US, studies have consistently shown that asthma exacerbation disproportionately affects children, racial/ethnic minorities, and socioeconomically disadvantaged populations.[1, 4-10] The burden of asthma on individual lives and the US health care system translates into a considerable economic impact. A recent study estimated that direct and indirect expenditures associated with asthma cost the US economy over $56 billion US dollars in 2007.[11]

Numerous studies have found that asthma symptoms and related respiratory disorders (e.g. wheeze, cough, bronchoconstriction) are exacerbated by a variety of environmental stimuli, including ambient air pollution, high ambient temperature, low ambient temperature, tobacco smoke, pollen, mold, pet dander, cockroach allergen, dust, and psychosocial stress.[1, 6, 9, 10] Children are among the most vulnerable to environmentally induced respiratory morbidity because their respiratory systems are not yet fully developed and, compared to adults, children breathe more air per unit of body mass, have higher ventilation rates, and anatomically smaller peripheral airways that predispose them to airway inflammation and obstruction.[12-16] In addition, children generally spend more time outdoors and are frequently exposed to communicable diseases in school settings. The unique time-activity patterns of children may translate into greater exposures to ambient pollutants, facilitate the spread of communicable airway diseases, or place children in contact

with environmental triggers of asthma. Because of their physiological and behavior-related risk factors, children are especially sensitive to environmental insults of the respiratory system. Gaining a better understanding of environmental mediators of childhood asthma morbidity and identifying vulnerable subpopulations remain primary objectives in pediatric respiratory health research.

A large body of research has demonstrated associations between respiratory morbidity and ambient air pollutants, including ozone (O_3), nitrogen oxides (NOx), nitrogen dioxide (NO_2) sulfur dioxide (SO_2), carbon monoxide (CO), and fine particles ($PM_{2.5}$).[17, 18] Air pollution associated exacerbations of respiratory disease have been observed using emergency department (ED) visit and hospitalization data,[16, 19-27] self-reported illness surveys,[28-33] and asthma medication prescription trends.[34, 35] A much smaller body of literature has examined associations between high temperatures and respiratory morbidity. Among these studies, there is mounting epidemiologic evidence for an effect of high temperature on respiratory morbidity, especially among children and the elderly compared to other age groups.[36-40] Furthermore, several studies have found that the effects of temperature on respiratory morbidity persist despite controlling for ambient air pollution, [36, 41-44] suggesting a strong effect of high temperature on respiratory morbidity that occurs through pathways other than through the effect of temperature on air pollution. Additional studies on the respiratory effects of high temperature are needed, as climate change is expected to cause higher warm-season ambient temperatures, especially in large metropolitan cities where temperatures are amplified by the urban heat island effect.[45-47]

Within the air pollution/climate-health literature there is suggestive evidence that intrinsic factors (e.g. sex, race/ethnicity), extrinsic factors (e.g. socioeconomic status), and differential exposures may potentiate susceptibility to the respiratory health effects of

ambient air quality (defined here as ambient air pollution and ambient temperature).[1, 9, 10, 20, 48-58] However, epidemiologic research has provided inconsistent findings on whether individual factors and/or neighborhood-level indicators of SES modify short-term associations between ambient air quality and respiratory morbidity.[35, 38, 41, 50, 59-68] Indeed, disentangling the relative influence of these vulnerability factors is conceptually and analytically challenging.

Conceptually, vulnerability can operate at both the individual- and neighborhood levels and may modify health associations through promoting higher exposures to harmful ambient air quality and/or by causing the emergence of additional sources of vulnerability. Figure 1 represents a conceptual framework of the key pathways through which individual and neighborhood vulnerability factors can modify associations between ambient air quality and respiratory morbidity among children. Figure 1 illustrates how individual-level factors such as sex, race/ethnicity, and socioeconomic status (e.g. household income, parental education, access to health care) can convey vulnerability through greater exposures to indoor and outdoor ambient air quality, greater psychosocial stress associated with their home environment, and through reduced access to resources (e.g. nutritious food, health care, transportation). Concurrently, social inequalities at the neighborhood level may cultivate unhealthy residential environments and further compound vulnerability. For example, poorer neighborhoods may be clustered near roadways or industrial centers, and children living within these neighborhoods likely experience greater exposures to ambient air pollution. Additionally, a neighborhood with a high poverty rate may lack public parks and healthy food options. An inability to exercise regularly and eat a balanced diet may ultimately undermine proper immune function, leading to increased airway sensitivity to environmental insults.[9, 13, 49, 69-71]

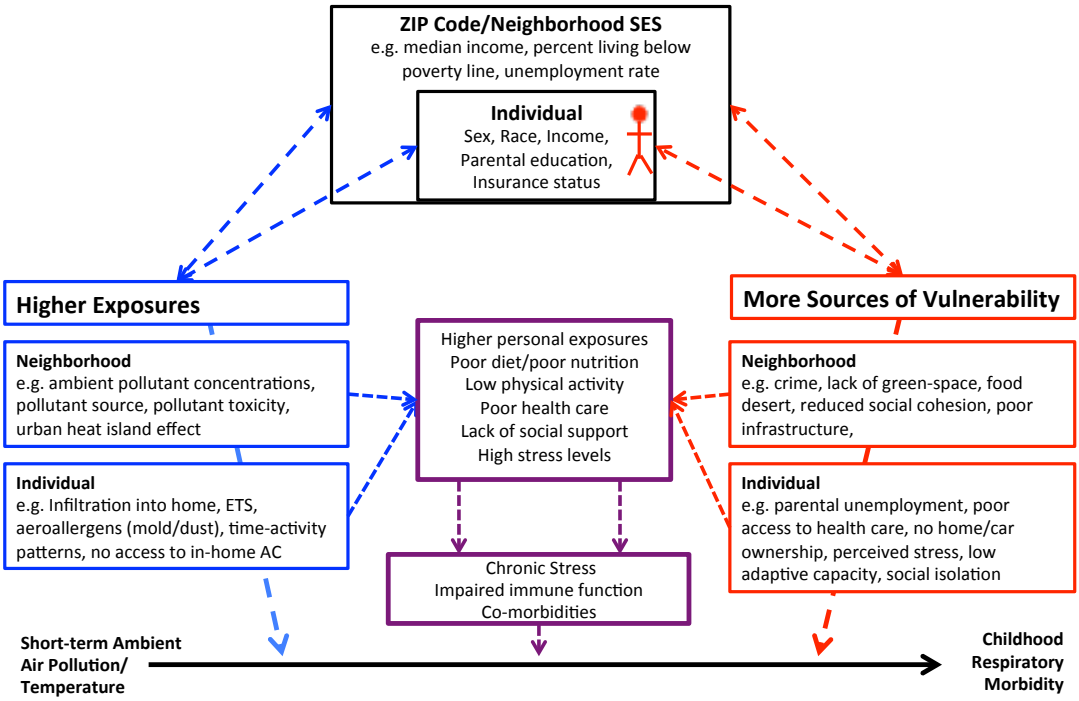


Figure 1: Conceptual framework illustrating the key pathways through which individual and neighborhood vulnerability factors and their downstream effects can modify associations between ambient environments and respiratory morbidity among children

Notably, Figure 1 emphasizes that socioeconomic hardships can be experienced at both the individual- and neighborhood-level and may result in numerous adverse impacts that are more proximal to the health outcome. One key impact related to respiratory health is the experience of persistently high levels of psychosocial stress, which can lead to altered cellular function.[50, 54, 55, 72-76] Due to physiological responses to stress that impair cellular growth and repair mechanisms, recurring stress may shape both lifelong health and the susceptibility of a child's cardio-pulmonary system to the effects of harmful ambient air quality.[77-84]

As evidenced in this conceptual framework, the vulnerability factors typically evaluated in epidemiological research are far upstream (distal) of the health outcome and are therefore only a proxy for the more downstream effects that truly actuate individual health outcomes.

Conceptually, we can envision how intrinsic and extrinsic vulnerability operate at both the individual and neighborhood levels, but specifying these relationships analytically is a formidable methodological challenge for environmental epidemiology.

DISSERTATION AIMS

The need to further understand environmental mediators of childhood asthma morbidity and to better identify vulnerable subpopulations is evident. This dissertation research was conceived within this context and motivated by a desire to better understand the potential reasons for inconsistent findings reported in the air pollution-respiratory morbidity literature and to better identify vulnerability factors among children in relation to ambient air quality related respiratory morbidity.

This dissertation is organized into three main chapters that represent the three aims of this dissertation research. Common objectives within each chapter are (1) to assess the degree to which neighborhood SES modifies associations between ambient air quality and respiratory health among children and (2) to assess the impact of investigator decisions on observed effect modification. Additionally, each chapter addresses its own set of unique research questions outlined below:

1. **Chapter 1:** To what extent do investigator decisions with regard to SES indicator choice and stratification criteria influence observed effect modification? Is it plausible that these choices are partially responsible for the reporting of incongruent findings on neighborhood SES as an effect modifier in the literature?
2. **Chapter 2:** Is there evidence of non-linear effect modification by neighborhood SES? Can spatial mapping of health risk provide qualitative information on how

health risk varies across urban populations? Are results generalizable across geographically diverse study locations?

3. **Chapter 3:** To what extent do individual factors (sex, race/ethnicity, insurance status) and neighborhood SES modify associations between high temperature and pediatric asthma? Does there appear to be a stronger modifying effect at one scale compared to another? Do indicators of individual-level SES and neighborhood SES produce similar patterns of effect modification?

In Chapter 1, we investigate associations between air pollution and pediatric asthma and conducted a detailed assessment of the potential for neighborhood SES [defined as ZIP Code Tabulation Area (ZCTA) environments] to modify short-term air pollution-pediatric asthma associations in Atlanta. Results from Chapter 1 advance our current understanding of how investigator decisions affect observed effect modification and further advance our understanding of how neighborhood SES influences air pollution-pediatric respiratory morbidity. To our knowledge Chapter 1 provides the first comprehensive assessment of neighborhood SES as an effect modifier in this setting.

In Chapter 2, we select ozone as a candidate environmental exposure to extend our work from Chapter 1 and investigate the generalizability of results across geographically diverse US cities (Atlanta, Dallas, St. Louis). Chapter 2 provides an assessment of the consistency and generalizability of social-environmental pathways underlying childhood respiratory morbidity in US cities. A unique aspect of the study design in Chapter 2 is assessment of associations between ozone and respiratory disease at the neighborhood level and spatial mapping of estimated associations. Results within this chapter suggest non-linear effect modification by neighborhood SES and the implications of these findings are

discussed in detail.

In Chapter 3, we leverage a 20-year health dataset for Atlanta to assess the influence of individual- and neighborhood-level factors on high temperature related pediatric asthma. Chapter 3 evaluates vulnerability at both the individual- and neighborhood-level and assesses whether indicators of individual-level SES and neighborhood SES produce similar patterns of effect modification. Findings from Chapter 3 are inherently valuable, as few studies have ever examined vulnerability factors among children in relation to high temperature related asthma.

REFERENCES

1. Gold DR, Wright R. Population disparities in asthma. *Annu Rev Public Health* 2005;26:89-113.

2. National Asthma Education and Prevention Program TEPotDaMoA. Expert panel report 3: Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute (US), Aug. 2007.

3. Akinbami LJ, Moorman JE, Bailey C, et al. Trends in asthma prevalence, health care use, and mortality in the united states, 2001–2010. CDC report. Hyattsville, MD: National Center for Health Statistics, 2012.

4. Moorman JE, Akinbami LJ, Bailey CM, et al. National surveillance of asthma: United states, 2001–2010. Hyattsville, Maryland: National Center for Health Statistics, 2012.

5. Gwynn RC, Thurston GD. The burden of air pollution: Impacts among racial minorities. *Environ Health Perspect* 2001;109(Suppl 4):501-06.

6. Pearlman DN, Zierler S, Meersman S, et al. Race disparities in childhood asthma: Does where you live matter? *J Natl Med Assoc* 2006;98(2):239-47.

7. Smith LA, Hatcher-Ross JL, Wertheimer R, et al. Rethinking race/ethnicity, income, and childhood asthma: Racial/ethnic disparities concentrated among the very poor. *Public Health Reports* 2005;120(2):109-16.

8. Volmer T. The socio-economics of asthma. *Pulm Pharmacol Ther* 2001;14(1):55-60.

9. Williams DR, Sternthal M, Wright RJ. Social determinants: Taking the social context of asthma seriously. *Pediatrics* 2009;123(Suppl):S174-84.

10. Wright RJ, Subramanian SV. Advancing a multilevel framework for epidemiologic research on asthma disparities. *Chest* 2007;132(5 Suppl):757S-69S.

11. Barnett SB, Nurmagambetov TA. Costs of asthma in the united states: 2002-2007. *J Allergy Clin Immunol* 2011;127(1):145-52.

12. Bateson TF, Schwartz J. Children's response to air pollutants. *J Toxicol Environ Health A* 2007;71(3):238-43.

13. Makri A, Stilianakis NI. Vulnerability to air pollution health effects. *Int J Hyg Environ Health* 2008;211(3-4):326-36.

14. Selgrade MK, Plopper CG, Gilmour MI, et al. Assessing the health effects and risks associated with children's inhalation exposures--asthma and allergy. *J Toxicol Environ Health A* 2008;71(3):196-207.

15. Sharma G, Goodwin J. Effect of aging on respiratory system physiology and immunology. *Clin Interv Aging* 2006;1(3):253-60.

16. Strickland MJ, Darrow LA, Klein M, et al. Short-term associations between ambient air pollutants and pediatric asthma emergency department visits. *Am J Respir Crit Care Med* 2010;182(3):307-16.

17. U.S. Environmental Protection Agency. Air quality criteria for particulate matter (final report, oct 2004). Washington, DC: U.S. Environmental Protection Agency, 2004.

18. U.S. Environmental Protection Agency. Air quality criteria for ozone and related photochemical oxidants (2006 final). Washington, DC: U.S. Environmental Protection Agency, 2006.

19. Darrow LA, Hess J, Rogers CA, et al. Ambient pollen concentrations and emergency department visits for asthma and wheeze. *J Allergy Clin Immunol* 2012;130(3):630-38 e4.

20. Grineski SE, Staniswalis JG, Peng Y, et al. Children's asthma hospitalizations and relative risk due to nitrogen dioxide (no2): Effect modification by race, ethnicity, and insurance status. *Environ Res* 2010;110(2):178-88.

21. Samoli E, Nastos PT, Paliatsos AG, et al. Acute effects of air pollution on pediatric asthma exacerbation: Evidence of association and effect modification. *Environ Res* 2011;111(3):418-24.

22. Sarnat SE, Sarnat JA, Mulholland J, et al. Application of alternative spatiotemporal metrics of ambient air pollution exposure in a time-series epidemiological study in atlanta. *J Expo Sci Environ Epidemiol* 2013;23(6):593-605.

23. Villeneuve PJ, Chen L, Rowe BH, et al. Outdoor air pollution and emergency department visits for asthma among children and adults: A case-crossover study in northern alberta, canada. *Environ Health* 2007;6:40.

24. Winquist A, Klein M, Tolbert P, et al. Comparison of emergency department and hospital admissions data for air pollution time-series studies. *Environ Health* 2012;11(1):70.

25. Peel JL, Tolbert PE, Klein M, et al. Ambient air pollution and respiratory emergency department visits. *Epidemiology* 2005;16(2):164-74.

26. Darrow LA, Klein M, Flanders WD, et al. Air pollution and acute respiratory infections among children 0-4 years of age: An 18-year time-series study. *Am J Epidemiol* 2014;180(10):968-77.

27. Yang Q, Chen Y, Shi Y, et al. Association between ozone and respiratory admissions among children and the elderly in vancouver, canada. *Inhal Toxicol* 2003;15(13):1297-308.

28. Basagana X, Sunyer J, Kogevinas M, et al. Socioeconomic status and asthma prevalence in young adults: The european community respiratory health survey. *Am J Epidemiol* 2004;160(2):178-88.

29. Peters A, Dockery DW, Heinrich J, et al. Short-term effects of particulate air pollution on respiratory morbidity in asthmatic children. *Eur Respir J* 1997;10(4):872-9.

30. Zmirou D, Gauvin S, Pin I, et al. Traffic related air pollution and incidence of childhood asthma: Results of the vesta case-control study. *J Epidemiol Community Health* 2004;58(1):18-23.

31. Schwartz J, Dockery DW, Neas LM, et al. Acute effects of summer air-pollution on respiratory symptoms reporting in children. *Am J Respir Crit Care Med* 1994;150(5):1234-42.

32. Zhang JJ, Hu W, Wei F, et al. Children's respiratory morbidity prevalence in relation to air pollution in four chinese cities. *Environ Health Perspect* 2002;110(9):961-7.

33. Jerrett M, Shankardass K, Berhane K, et al. Traffic-related air pollution and asthma onset in children: A prospective cohort study with individual exposure measurement. *Environ Health Perspect* 2008;116(10):1433-8.

34. Klot Sv, Wolke G, Tuch T, et al. Increased asthma medication use in association with ambient fine and ultrafine particles. *European Respiratory Journal* 2002;20(3):691-702.

35. Laurent O, Pedrono G, Filleul L, et al. Influence of socioeconomic deprivation on the relation between air pollution and beta-agonist sales for asthma. *Chest* 2009;135(3):717-23.

36. Cheng J, Xu Z, Zhu R, et al. Impact of diurnal temperature range on human health: A systematic review. *Int J Biometeorol* 2014;58(9):2011-24.

37. Bunker A, Wildenhain J, Vandenbergh A, et al. Effects of air temperature on climate-sensitive mortality and morbidity outcomes in the elderly; a systematic review and meta-analysis of epidemiological evidence. *EBioMedicine* 2016.

38. Xu Z, Huang C, Su H, et al. Diurnal temperature range and childhood asthma: A time-series study. *12* 2013;12.

39. Michelozzi P, Accetta G, De Sario M, et al. High temperature and hospitalizations for cardiovascular and respiratory causes in 12 european cities. *Am J Respir Crit Care Med* 2009;179(5):383-9.

40. Kovats RS, Hajat S, Wilkinson P. Contrasting patterns of mortality and hospital admissions during hot weather and heat waves in greater london, uk. *Occup Environ Med* 2004;61(11):893-8.

41. Li S, Baker PJ, Jalaludin BB, et al. Are childrens asthmatic symptoms related to ambient temperature? A panel study in australia. *Environ Res* 2014;133:239-45.

42. Winquist A, Grundstein A, Chang HH, et al. Warm season temperatures and emergency department visits in atlanta, georgia. *Environ Res* 2016;147:314-23.

43. Anderson GB, Dominici F, Wang Y, et al. Heat-related emergency hospitalizations for respiratory diseases in the medicare population. *Am J Respir Crit Care Med* 2013;187(10):1098-103.

44. Lin S, Luo M, Walker RJ, et al. Extreme high temperatures and hospital admissions for respiratory and cardiovascular diseases. *Epidemiology* 2009;20(5):738-46.

45. Conlon K, Monaghan A, Hayden M, et al. Potential impacts of future warming and land use changes on intra-urban heat exposure in houston, texas. *PLoS One* 2016;11(2):e0148890.

46. Luber G, McGeehin M. Climate change and extreme heat events. *Am J Prev Med* 2008;35(5):429-35.

47. Stone B, Hess JJ, Frumkin H. Urban form and extreme heat events: Are sprawling cities more vulnerable to climate change than compact cities? *Environ Health Perspect* 2010;118(10):1425-8.

48. Chang J, Delfino RJ, Gillen D, et al. Repeated respiratory hospital encounters among children with asthma and residential proximity to traffic. *Occup Environ Med* 2009;66(2):90-8.

49. Clougherty JE, Kubzansky LD. A framework for examining social stress and susceptibility to air pollution in respiratory health. *Environ Health Perspect* 2009;117(9):1351-8.

50. Clougherty JE, Levy JI, Kubzansky LD, et al. Synergistic effects of traffic-related air pollution and exposure to violence on urban asthma etiology. *Environ Health Perspect* 2007;115(8):1140-6.

51. Lee JT, Son JY, Kim H, et al. Effect of air pollution on asthma-related hospital admissions for children by socioeconomic status associated with area of residence. *Arch Environ Occup Health* 2006;61(3):123-30.

52. Watson JP, Cowen P, Lewis RA. The relationship between asthma admission rates, routes of admission, and socioeconomic deprivation. *Eur Respir J* 1996;9(10):2087-93.

53. Wissow LS, Gittelsohn AM, Szklo M, et al. Poverty, race, and hospitalization for childhood asthma. *Am J Public Health* 1988;78(7):777-82.

54. Wright R, Rodriguez M, Cohen S. Review of psychosocial stress and asthma: An integrated biopsychosocial approach. *Thorax* 1998;53(12):1066-74.

55. Miller G, Chen E. Unfavorable socioeconomic conditions in early life presage expression of proinflammatory phenotype in adolescence. *Psychosomatic Medicine* 2007;69(5):402-09.

56. Seagrave J, McDonald JD, Bedrick E, et al. Lung toxicity of ambient particulate matter from southeastern u.S. Sites with different contributing sources: Relationships between composition and effects. *Environ Health Perspect* 2006;114(9):1387-93.

57. Bell ML, Zanobetti A, Dominici F. Evidence on vulnerability and susceptibility to health risks associated with short-term exposure to particulate matter: A systematic review and meta-analysis. *Am J Epidemiol* 2013;178(6):865-76.

58. Vinikoor-Imler LC, Owens EO, Nichols JL, et al. Evaluating potential response-modifying factors for associations between ozone and health outcomes: A weight-of-evidence approach. *Environ Health Perspect* 2014;122(11):1166-76.

59. Kim SY, O'Neill MS, Lee JT, et al. Air pollution, socioeconomic position, and emergency hospital visits for asthma in seoul, korea. *Int Arch Occup Environ Health* 2007;80(8):701-10.

60. O'Neill MS, Jerrett M, Kawachi I, et al. Health, wealth, and air pollution: Advancing theory and methods. *Environ Health Perspect* 2003;111(16):1861-70.

61. Yap P-S, Gilbreath S, Garcia C, et al. The influence of socioeconomic markers on the association between fine particulate matter and hospital admissions for respiratory conditions among children. *Am J Public Health* 2013;103(4):695-702.

62. Bell ML, O'Neill MS, Cifuentes LA, et al. Challenges and recommendations for the study of socioeconomic factors and air pollution health effects. *Environmental Science & Policy* 2005;8(5):525-33.

63. Sacks JD, Rappold AG, Davis JA, Jr., et al. Influence of urbanicity and county characteristics on the association between ozone and asthma emergency department visits in north carolina. *Environ Health Perspect* 2014;122(5):506-12.

64. Shmool JL, Kubzansky LD, Newman OD, et al. Social stressors and air pollution across new york city communities: A spatial approach for assessing correlations among multiple exposures. *Environ Health* 2014;13:91.

65. Newman NC, Ryan PH, Huang B, et al. Traffic-related air pollution and asthma hospital readmission in children: A longitudinal cohort study. *J Pediatr* 2014;164(6):1396-402e1.

66. Gronlund CJ. Racial and socioeconomic disparities in heat-related health effects and their mechanisms: A review. *Curr Epidemiol Rep* 2014;1(3):165-73.

67. Clougherty JE. A growing role for gender analysis in air pollution epidemiology. *Environ Health Perspect* 2010;118(2):167-76.

68. Nauenberg E, Basu K. Effect of insurance coverage on the relationship between asthma hospitalizations and exposure to air pollution. *Public Health Reports* 1999;114(2):135-48.

69. Krieger N, Williams DR, Moss NE. Measuring social class in us public health research: Concepts, methodologies, and guidelines. *Annu Rev Public Health* 1997;18:341-78.

70. Bernard P, Charafeddine R, Frohlich KL, et al. Health inequalities and place: A theoretical conception of neighbourhood. *Soc Sci Med* 2007;65(9):1839-52.

71. Galobardes B, Lynch J, Smith GD. Measuring socioeconomic position in health research. *Br Med Bull* 2007;81-82:21-37.

72. Eisenberger NI, Cole SW. Social neuroscience and health: Neurophysiological mechanisms linking social ties with physical health. *Nat Neurosci* 2012;15(5):669-74.

73. McEwen BS, Gianaros PJ. Central role of the brain in stress and adaptation: Links to socioeconomic status, health, and disease. *Ann N Y Acad Sci* 2010;1186:190-222.

74. Shankardass K, McConnell R, Jerrett M, et al. Parental stress increases the effect of traffic-related air pollution on childhood asthma incidence. *Proc Natl Acad Sci U S A* 2009;106(30):12406-11.

75. Cohen S, Doyle WJ, Skoner DP. Psychological stress, cytokine production, and severity of upper respiratory illness. *Psychosomatic Medicine* 1999;61(2):175-80.

76. Clougherty JE, Shmool JLC, Kubzansky LD. The role of non-chemical stressors in mediating socioeconomic susceptibility to environmental chemicals. *Curr Envir Health Rpt* 2014;1(4):302-13.

77. Chen E, Hanson MD, Paterson LQ, et al. Socioeconomic status and inflammatory processes in childhood asthma: The role of psychological stress. *J Allergy Clin Immunol* 2006;117(5):1014-20.

78. Chen E, Miller GE. Stress and inflammation in exacerbations of asthma. *Brain, behavior, and immunity* 2007;21(8):993-99.

79. Foley P, Kirschbaum C. Human hypothalamus-pituitary-adrenal axis responses to acute psychosocial stress in laboratory settings. *Neurosci Biobehav Rev* 2010;35(1):91-6.

80. Hansel A, Hong S, Camara RJ, et al. Inflammation as a psychophysiological biomarker in chronic psychosocial stress. *Neurosci Biobehav Rev* 2010;35(1):115-21.

81. Juster RP, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neurosci Biobehav Rev* 2010;35(1):2-16.

82. Miller GE, Chen E, Sze J, et al. A functional genomic fingerprint of chronic stress in humans: Blunted glucocorticoid and increased nf-kappab signaling. *Biol Psychiatry* 2008;64(4):266-72.

83. Miller GE, Cohen S, Ritchey AK. Chronic psychological stress and the regulation of pro-inflammatory cytokines: A glucocorticoid-resistance model. *Health Psychology* 2002;21(6):531-41.

84. Tsigos C, Chrousos GP. Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress. *J Psychosom Res*;53(4):865-71.

CHAPTER 1

Assessment of neighborhood-level socioeconomic status as a modifier of air pollution-asthma associations among children in Atlanta

Cassandra R. O'Lenick, Andrea Winquist, James A. Mulholland, Mariel D. Friberg, Howard H. Chang, Michael R. Kramer, Lyndsey A. Darrow, Stefanie Ebelt Sarnat

Disclaimer: *Please note, this chapter was submitted for publication to the* Journal of Epidemiology and Community Health *on February 15, 2016. At the time of submission of this dissertation to Laney Graduate School this chapter was still under review by the journal.*

ABSTRACT

Background. A broad literature base provides evidence of association between air pollution and pediatric asthma. Socioeconomic status (SES) may modify these associations; however, previous studies have found inconsistent evidence regarding the role of SES. **Methods:** Effect modification of air pollution-pediatric asthma morbidity by multiple indicators of neighborhood SES was examined in Atlanta, GA. Emergency department (ED) visit data were obtained for 5-18 year olds with a diagnosis of asthma in 20-county Atlanta during 2002-2008. Daily ZIP-Code Tabulation Area (ZCTA)-level concentrations of ozone, nitrogen dioxide, fine particulate matter, and elemental carbon were estimated using ambient monitoring data and emissions-based chemical transport model simulations. Pollutant-asthma associations were estimated using a case-crossover approach, controlling for temporal trends and meteorology. Effect modification by ZCTA-level (neighborhood) SES was examined via stratification. **Results.** We observed stronger air pollution-pediatric asthma associations in "deprivation areas" (e.g., ≥20% of the ZCTA population living in poverty) compared to "non-deprivation areas". When stratifying analyses by quartiles of neighborhood SES, odds ratios indicated stronger associations in the highest and lowest SES quartiles and weaker associations among the middle quartiles. **Conclusion.** Our results suggest that neighborhood-level SES is a factor contributing vulnerability to air pollution-related pediatric asthma morbidity in Atlanta. Children living in low SES environments appear to be especially vulnerable given positive odds ratios and high underlying asthma ED rates. Inconsistent findings of effect modification among previous studies may be partially explained by choice of SES stratification criteria, and the use of multiplicative models combined with differing baseline risk across SES populations.

INTRODUCTION

Ambient air pollutants are well-documented causes of respiratory morbidity.[1, 2] A broad literature base provides evidence of association between asthma morbidity and diverse classes of air pollutants including ozone (O_3), nitrogen oxides, nitrogen dioxide (NO_2), and fine particulate matter ($PM_{2.5}$); children are especially sensitive to the respiratory effects of air pollution due to physiological and behavior-related risk factors.[3, 4] Increasing evidence suggests that socioeconomic factors may further influence vulnerability to the health effects of air pollution among children.[5-9]

Pathways through which low socioeconomic status (SES) may potentiate susceptibility to air pollution-related childhood asthma include higher exposures to outdoor and indoor air pollutants, greater psychosocial stress associated with the social environment (e.g., neighborhood poverty, neighborhood crime levels, parental unemployment), and reduced access to local resources (e.g., healthy food options, green-space, health care access).[10-12] However, toxicological studies focusing on such mechanisms are limited[13-15] and epidemiologic research has provided inconsistent findings on whether individual factors and/or neighborhood-level indicators of SES modify short-term air pollution-asthma associations. Notably, among population-based studies that have specifically examined modification of air pollution-asthma associations by neighborhood SES, 7 reported no evidence of effect modification,[16-22] 8 reported results suggesting stronger associations in lower SES populations,[23-30] and 2 reported stronger associations in high SES populations.[29, 31]

Differences in analytical choices by investigators may partially explain these inconsistent findings.[32] While of similar study design, these studies assessed associations at different scales (region, county, ZIP code, census block, and census block group), considered

different indicators of SES, and used different cut-points to stratify populations by neighborhood SES (e.g. median,[25-31] tertile,[24] quartile,[20] or quintile[16-18, 30] values of neighborhood SES indicators). Among these studies, education, household income, and poverty were most commonly used as indicators of neighborhood SES; however, reported conclusions about effect modification by SES were contradictory between studies using similar indicators[16, 30, 31, 33] as well as between different SES indicators within the same study.[28-31]

Previous work in Atlanta has identified strong associations between air pollution and pediatric asthma ED visits.[34-37] Here, we present a comprehensive assessment of neighborhood SES as a modifier of air pollution-pediatric asthma ED visit associations in Atlanta with a specific focus on the influence of SES indicator choice and stratification criteria on observed associations and interpretations.

METHODS

Asthma emergency department visit data

Patient-level emergency department (ED) visit data from January. 1, 2002 to December. 31, 2008 were acquired from hospitals located within the 20-county metropolitan area of Atlanta; ED visit data were acquired directly from hospitals (2002-2004 period) and the Georgia Hospital Association (2005-2008 period). Relevant data elements included admission date, International Classification of Diseases, 9th Revision (ICD-9) diagnosis codes, age, and ZIP code of patient residence. ED visits for asthma were identified using primary and secondary ICD-9 diagnosis codes for asthma (493.0–493.9) or wheeze (786.07). We restricted our analyses to the pediatric population (5–18 years old) and to patients with a residential ZIP code (defined as US Postal Service delivery areas) located wholly or partially in 20-county Atlanta (232 ZIP codes).

To facilitate merging with air quality and Census-based SES data, which were estimated for all Atlanta ZIP Code Tabulation Areas (ZCTA, 2010 Census Bureau boundaries, created from census blocks to approximate ZIP codes), each ZIP code in the ED visit dataset was assigned to one of 191 ZCTAs. Assignments were accomplished by matching ZIP-to-ZCTA ID numbers and verifying locations of ZIP code centroids via ZCTA map shapefiles in ArcGIS. ZIP code change reports facilitated ZCTA assignments for 31 ZIP codes that were altered or eliminated within the study period. ED data were excluded from 10 ZCTAs with no SES data (e.g., businesses, university campuses).

Air quality data

Daily concentrations of ambient air pollutants for each ZCTA in 20-county Atlanta were estimated from January 1, 2002 to December 31, 2008. Pollutant concentration estimates were obtained by fusing observational data from available network monitors with pollutant concentration simulations from the CMAQ (Community Multi-Scale Air Quality) emissions-based chemical transport model at 12x12 km grids over Atlanta.[38] Pollution concentrations were estimated for each ZCTA by determining the fraction of a ZCTA's area within each 12x12 km grid cell and area weighting the observation-simulation data fusion estimates to get the ZCTA-specific value. Supplemental Figure S1.1 illustrates the Atlanta study area with 12x12 km pollution estimate grid cells overlaid onto ZCTAs. The following pollutants and daily temporal metrics were evaluated: 1-hour maximum nitrogen dioxide (NO_2); 8-hour maximum ozone (O_3); 24-hour average fine particulate matter ($PM_{2.5}$); and 24 hour average major $PM_{2.5}$ component, elemental carbon (EC). Daily meteorological data measured at the Atlanta Hartsfield International Airport were acquired from the National Climatic Data Center.

Neighborhood-level socioeconomic data

Estimates of ZCTA-level socioeconomic status (SES) were obtained from the 2000 US Census long form and the American Community Survey (ACS) 5-year (2007-2011) summary file, all normalized to 2010 ZCTA borders ("The Time-Series Research Package", GeoLytics, Inc., East Brunswick, NJ, 2013). To examine the influence of SES indicator choice on air pollution health associations, we evaluated six single indicators that included education, household type, income, poverty, transportation, and unemployment socioeconomic domains (Table 1.1). In addition, to capture the multifaceted nature of neighborhood SES,

we included two composite indices of material and social deprivation, the Neighborhood Deprivation Index (NDI)[39] and the Townsend index[40] (Table 1.1). We used linear interpolation (by year) between Census 2000 and ACS (2007-2011) to obtain yearly SES indicators and account for possible changes in neighborhood-level SES over the 2002-2008 study period.

To examine the influence of SES stratification criteria on observed effect modification, we categorized ZCTAs based on "deprivation area" status [i.e. "poverty areas" were defined as ≥20% of the population living below the federal poverty line, and "undereducated areas" were defined as ≥25% of the adult population (≥25 years old) with less than a 12^{th} grade education][12, 39] and also based on several *a priori* cut-points of continuous ZCTA-level SES data (above/below the 90^{th} percentile, above/below the median, and quartiles).

Table 1.1. Indicators of Neighborhood Socioeconomic Status, Indicator Descriptions and Summary Statistics Across Atlanta Metropolitan Area Neighborhoods[a] (n=191 Zip Code Tabulation Areas), Atlanta, Georgia, 2002-2008.

SES Domain	SES Indicator Description	Census/ACS Variable Code[b]	Freq. of ZCTA-days[c]	Min	p25[c]	p50[c]	p75[c]	Max
1. Education	**1a. % <12th grade:** Percentage (%) of adult population (≥25 yrs) with < 12th grade education	P37 / B15		0.1	9.4	14.8	21.5	39.1
	1b. Undereducated area (yes/no): ZCTA with ≥ 25% of the adult population (≥25 yrs.) with < 12th grade education	P37 / B15	Yes: 15.1% No: 84.9%					
2. Household	**2a. Median Home Value ($)**	H76 / B25		76,153	127,548	157,541	208,800	774,900
	2b. % Renter occupied households (HH)	H07 / B25		5.27	17.7	25.4	42.8	92.1
	2c. % Female headed HH	P01 / B11		0.7	9.1	12.9	18.5	45.0
	2d. % HHs living in crowding	H02 / B25		0	1.5	2.5	4.0	17.5
3. Income	**3a. Median Income**	P53 / B19		20,397	44,186	53,663	66,846	130,270
	3b. % HHs on public assistance	P06 / B19		0	1.0	1.5	2.3	9.13
4. Poverty	**4a. % HHs living below the federal poverty line**	P87 / B17		1.7	7.6	11.4	16.2	45.9
	4b. Poverty area (yes/no): ZCTA with ≥ 20% of HHs living below the federal poverty line	P87 / B17	Yes: 15.6% No: 84.4%					
5. Transportation	**5a. % HHs that do not own or lease a car**	H44 / B25		0.1	2.5	4.2	7.4	43.8
6. Unemployment	**6a. % Civilian population (≥ 16 yrs.) unemployed**	P43 / B23		0.8	5.8	8.0	10.9	50.6
7. Composite Indices	**7a. Neighborhood deprivation index (NDI):** Principle component analysis of 8 indicators: % HH low income (<$30,000), % males not in management, and indicators 1a, 2c, 2d, 3b, 4a, 6a (above). Z-score standardized.			-2.0	-0.8	-0.1	0.6	3.41
	7b. Townsend Index: Summary metric that combines data on indicators 2b, 2d, 5a, 6a (above). Z-score standardized.			-4.4	-2.3	-0.8	1.3	16.6

Abbreviations: ACS, American Community Survey (2007-2011); Census, Census 2000; HH, households; Max, maximum value; Min, minimum value; NDI, Neighborhood Deprivation Index; p25, 25th percentile; p50, 50th percentile; p75, 75th percentile; SES, socioeconomic status; ZCTA, Zip Code Tabulation Area.

[a] Neighborhoods are identified by Zip Code Tabulation Area Boundaries.

[b] Census/ACS variable codes identify which variable groups were used to create indicators of neighborhood SES within Census 2000 and ACS 2007-2011 data tables.

[c] SES frequencies and percentiles based on distribution of the yearly values (2002-2008) across 191 ZCTAs in Atlanta (n=488,387 ZCTA days).

Bold typeface indicates variables evaluated for effect modification in stratified models.

Statistical analyses

Associations between 3-day moving average (lag days 0-2) pollutant concentrations and pediatric asthma ED visits were assessed using conditional logistic regression in single-pollutant case-crossover models, matching on ZCTA of patient residence, year, month, and day of week of the ED visit. By design, the case-crossover approach controls for individual-level time-invariant confounders since case and control days are compared for the same person. Models included additional control for time-varying factors: indicator variables for season (4-levels), periods of hospital participation and holidays; cubic polynomials for 3-day moving average (lags 0-2) maximum temperature and mean dew point; interaction terms between season and maximum temperature; and a cubic spline on day of year (5 degrees of freedom) to control smoothly for recurrent within-window seasonal trends. See Appendix 1 for the full conditional logistic regression equation.

To evaluate effect measure modification, models were stratified by SES categories. Odds ratios (ORs) and 95% confidence intervals (CIs) are presented for associations between air pollution and pediatric asthma ED visits for each SES stratum, scaled to each pollutant's approximate interquartile range. Difference between strata-specific ORs was tested in pairwise comparisons. To evaluate the robustness of results to different model specifications, we performed a series of sensitivity analyses, described in more detail in Appendix 2. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Descriptive analysis results: ED visits and air pollution data

Our ED visit database included 1,624,572 total ED visits of children aged 5-18 years, with 128,758 ED visits for asthma during the years 2002-2008 in 20-county Atlanta (191 ZCTAs). Supplemental Table S1.1 presents descriptive statistics for the ED visit database and Supplemental Table S1.2 presents descriptive statistics and Spearman correlations for air pollutants.

Epidemiological results: air pollution–asthma associations

Overall associations (per interquartile range) between short-term exposure to ambient air pollutants and pediatric asthma are reported in Table 1.2. Ozone exhibited the highest overall association with pediatric asthma, followed by $PM_{2.5}$, and EC.

Table 1.2. Odds Ratios From Case-Crossover Analyses Between 3-day Moving Average ZCTA-Level Pollutant Concentrations (per Interquartile Range Increase) and Asthma-Related Emergency Department Visits in Atlanta, Georgia, 2002-2008

Air Pollutant	IQR	Odds Ratio	95% CI	*P* value
O_3	25 ppb	1.073	1.043, 1.104	< 0.001
NO_2	15 ppb	1.012	0.994, 1.030	0.18
$PM_{2.5}$	10 μg/m^3	1.027	1.012, 1.043	< 0.001
EC	0.5 μg/m^3	1.013	1.005, 1.022	0.002

Abbreviations: CI, Confidence Intervals; EC, elemental carbon fraction of $PM_{2.5}$; IQR, interquartile range; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter < 2.5 μm in diameter (fine particulate matter); ZCTA, Zip Code Tabulation Area.

Descriptive analysis results: socioeconomic subpopulation characterization

Table 1.1 presents summary statistics for each SES indicator and Supplementary Table S1.3 presents Spearman correlations between indicators. In summary, we found that socioeconomic composition varied widely across the 191 Atlanta ZCTAs (e.g., % living below the poverty line varied from 1.7% to 45.9%) and we observed moderate- to high-

correlations between many but not all SES indicators (Supplemental Table S1.3), suggesting these indicators describe similar SES constructs and have similar spatial patterning. Appendix 3 provides further characterization of air quality and ED visits by neighborhood SES.

Epidemiological results: effect measure modification

Analyses stratified by deprivation area status (areas of extremely low SES were characterized as 'poverty areas' or 'undereducated areas') suggested stronger magnitudes of association in deprivation areas compared to areas of higher SES (non-deprivation areas). Differences in observed associations by deprivation area status were more apparent for ozone and the traffic-related pollutants (NO_2 and EC) than for $PM_{2.5}$ (Table 1.3). As an alternative definition of extremely low SES, we stratified neighborhoods using the 90^{th} percentiles of continuous SES variables (or 10^{th} percentiles for median income and median home value) as the categorical cut-points. In general, results from the $90^{th}/10^{th}$ percentile analysis were similar to the deprivation area results, as we observed stronger effect estimates in extremely low SES neighborhoods compared to areas of higher SES (Table 1.3). However, this pattern of effect modification was only consistent for NO_2, across all SES indicators. In most analyses, differences in ORs between strata were not statistically significant due to the wide CIs in the low SES strata resulting from low ED visit counts.

Table 1.3. Odds Ratios From Case-Crossover Models Stratified by Deprivation Area and 90th/10th Percentiles for Interquartile Range Increases in 3-day Moving Average ZCTA-Level Pollutant Concentrations and Asthma Emergency Department Visits in Atlanta, Georgia, 2002-2008

SES Indicator	Stratification Criteria	SES Strata[a]	# Asthma ED Visits	O_3 (per 25 ppb)		NO_2 (per 15 ppb)		$PM_{2.5}$ (per 10 µg/m³)		EC (per 0.5 µg/m³)	
				OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Stratification by Deprivation Area											
Undereducated Area (UA)	< 25% < 12th grade*	High*	111,446	**1.067**	**1.035, 1.099**	1.008	0.989, 1.028	**1.027**	**1.011, 1.044**	**1.012**	**1.003, 1.021**
	≥ 25% < 12th grade	Low	17,312	**1.116**	**1.033, 1.207**	1.038	0.990, 1.088	1.023	0.983, 1.066	1.020	0.999, 1.042
Poverty Area (PA)	< 20% below poverty*	High*	99,069	**1.067**	**1.034, 1.102**	0.999	0.979, 1.022	**1.020**	**1.003, 1.038**	1.010	0.999, 1.021
	≥ 20% below poverty	Low	29,689	**1.099**	**1.034, 1.168**	**1.038§**	**1.003, 1.074**	**1.048**	**1.017, 1.081**	**1.018**	**1.004, 1.033**
Stratification by 90th (or 10th) Percentile											
% <12th Grade	≤ 90th %tile (27.3%)*	High*	117,765	**1.067**	**1.036, 1.099**	1.010	0.991, 1.029	**1.028**	**1.012, 1.044**	**1.013**	**1.004, 1.022**
	> 90th %tile (27.3%)	Low	10,993	**1.134**	**1.030, 1.248**	1.029	0.969, 1.093	1.020	0.969, 1.074	1.015	0.990, 1.041
Median home value	≥ 10th %tile ($109,011)*	High*	118,110	**1.074**	**1.042, 1.106**	1.009	0.990, 1.028	**1.028**	**1.012, 1.044**	**1.012**	**1.003, 1.021**
	< 10th %tile ($109,011)	Low	10,617	1.068	0.970, 1.175	1.038	0.980, 1.100	1.011	0.960, 1.065	1.023	0.997, 1.050
Median income	≥ 10th %tile ($36,680)*	High*	109,786	**1.074**	**1.042, 1.107**	1.002	0.982, 1.023	**1.023**	**1.007, 1.040**	**1.010**	**1.001, 1.020**
	< 10th %tile ($36,680)*	Low	18,972	1.070	0.993, 1.152	**1.050§**	**1.006, 1.095**	**1.049**	**1.010, 1.090**	**1.023**	**1.005, 1.041**
% Living in poverty	≤ 90th %tile (22.5%)*	High*	107,547	**1.069**	**1.037, 1.102**	1.005	0.984, 1.025	**1.023**	**1.006, 1.040**	**1.013**	**1.003, 1.022**
	> 90th %tile (22.5%)	Low	21,211	**1.103**	**1.026, 1.187**	1.032	0.992, 1.074	**1.048**	**1.011, 1.086**	1.014	0.998, 1.031
% HH no vehicle	≤ 90th %tile (14.1%)*	High*	104,255	**1.086**	**1.052, 1.120**	1.004	0.983, 1.026	**1.023**	**1.006, 1.040**	**1.011**	**1.001, 1.021**
	> 90th %tile (14.1%)	Low	24,503	1.022	0.956, 1.091	1.028	0.991, 1.067	**1.044**	**1.010, 1.079**	**1.018**	**1.002, 1.034**
% Unemployed	≤ 90th %tile (14.1%)*	High*	104,594	**1.078**	**1.045, 1.112**	1.008	0.988, 1.029	**1.026**	**1.009, 1.043**	**1.016**	**1.006, 1.026**
	> 90th %tile (14.1%)	Low	24,158	1.057	0.987, 1.132	1.018	0.980, 1.058	**1.035**	**1.000, 1.071**	1.004	0.988, 1.021
NDI	≤ 90th %tile (1.3)*	High*	105,329	**1.073**	**1.040, 1.106**	1.001	0.980, 1.022	**1.023**	**1.006, 1.040**	**1.012**	**1.002, 1.022**
	> 90th %tile (1.3)	Low	23,429	**1.076**	**1.006, 1.151**	1.037	0.999, 1.077	**1.043**	**1.008, 1.079**	**1.016**	**1.000, 1.032**
Townsend Index	≤ 90th %tile (4.4)*	High*	105,873	**1.077**	**1.044, 1.111**	1.003	0.982, 1.024	**1.025**	**1.009, 1.042**	**1.013**	**1.003, 1.023**
	> 90th %tile (4.4)	Low	22,885	1.057	0.987, 1.131	**1.038**	**1.000, 1.079**	1.033	0.998, 1.069	1.014	0.998, 1.030

Abbreviations: CI, Confidence Interval; EC, elemental carbon fraction of $PM_{2.5}$; HH, Households; NDI, Neighborhood Deprivation Index; NO_2, nitrogen dioxide; O_3, ozone; OR, odds ratio; PA, Poverty Area; $PM_{2.5}$, particulate matter < 2.5 µm in diameter (fine particulate matter); SES, socioeconomic status; UA, Undereducated Area; ZCTA, Zip Code Tabulation Area.

[a]Column denotes which stratum was designated as 'high [SES]' and 'low [SES]'

Bold typeface indicates stratum specific confidence intervals that do not include the null value.

* indicates referent group used in assessment of heterogeneity of stratum-specific ORs (i.e. referent strata is 'High [SES]')

§ indicates significant difference (one-sided $P < 0.05$) from referent group. Heterogeneity between stratum-specific ORs was tested in pairwise comparisons by dividing the difference in log odds ratio by the square root of the sum of the variances and computing a Z-statistic.

To assess the influence of SES stratification criteria on observed effect modification, we compared results of analyses stratified by deprivation area and $90^{th}/10^{th}$ percentiles (Table 1.3) to results of analyses stratified using the median (Supplemental Table S1.4) or quartiles as cut-points (Supplemental Table S1.5). Figure 1.1 presents representative findings from our cut-point comparison for % $<12^{th}$ grade education and % below the poverty line for NO_2 and $PM_{2.5}$.

As Figure 1.1A shows, when using % $<12^{th}$ grade education to indicate neighborhood SES, patterns of effect modification differed by pollutant (NO_2 and $PM_{2.5}$), but patterns were similar across the different stratification criteria (undereducated area, or using cut points based on the $90^{th}/10^{th}$ percentile, median, or quartiles). Specifically, we observed stronger associations between NO_2 and asthma ED visits in low SES compared to high SES strata for all stratification criteria based on % $<12^{th}$ grade education; however, significant differences between strata-specific ORs were only observed in the quartile analysis (Figure 1.1A). In contrast, for $PM_{2.5}$, slightly weaker associations with asthma ED visits were observed in low SES strata compared to high SES strata; differences between observed ORs across strata were not significant (Figure 1.1A). Similar patterns of effect modification (and differences between pollutants) were found when stratifying by median home value (Supplemental Table S1.5).

When using % below the poverty line to indicate neighborhood SES, patterns of effect modification differed across the different stratification criteria, but were generally consistent across pollutants (Figure 1.1B). In particular, we observed less pronounced patterns of effect modification when stratifying at the median compared to when using deprivation area or 90^{th} percentile stratification criteria for both NO_2 and $PM_{2.5}$ (Figure 1.1B). Stratifying by quartile values of % below poverty provided insight into these findings, as odds ratios across strata

followed a U-shaped pattern, indicating stronger magnitudes of air pollution-pediatric asthma associations in the highest and lowest SES quartiles (Figure 1.1B). Similar U-shaped effect modification was consistently observed for all pollutants for several other indicators (median income, NDI, Townsend Index) when stratifying by quartiles (Supplemental Table S1.5). In sensitivity analyses, patterns of effect modification were similar by SES indicator, stratification criterion, and pollutant to those observed in main analyses (Appendix 2).

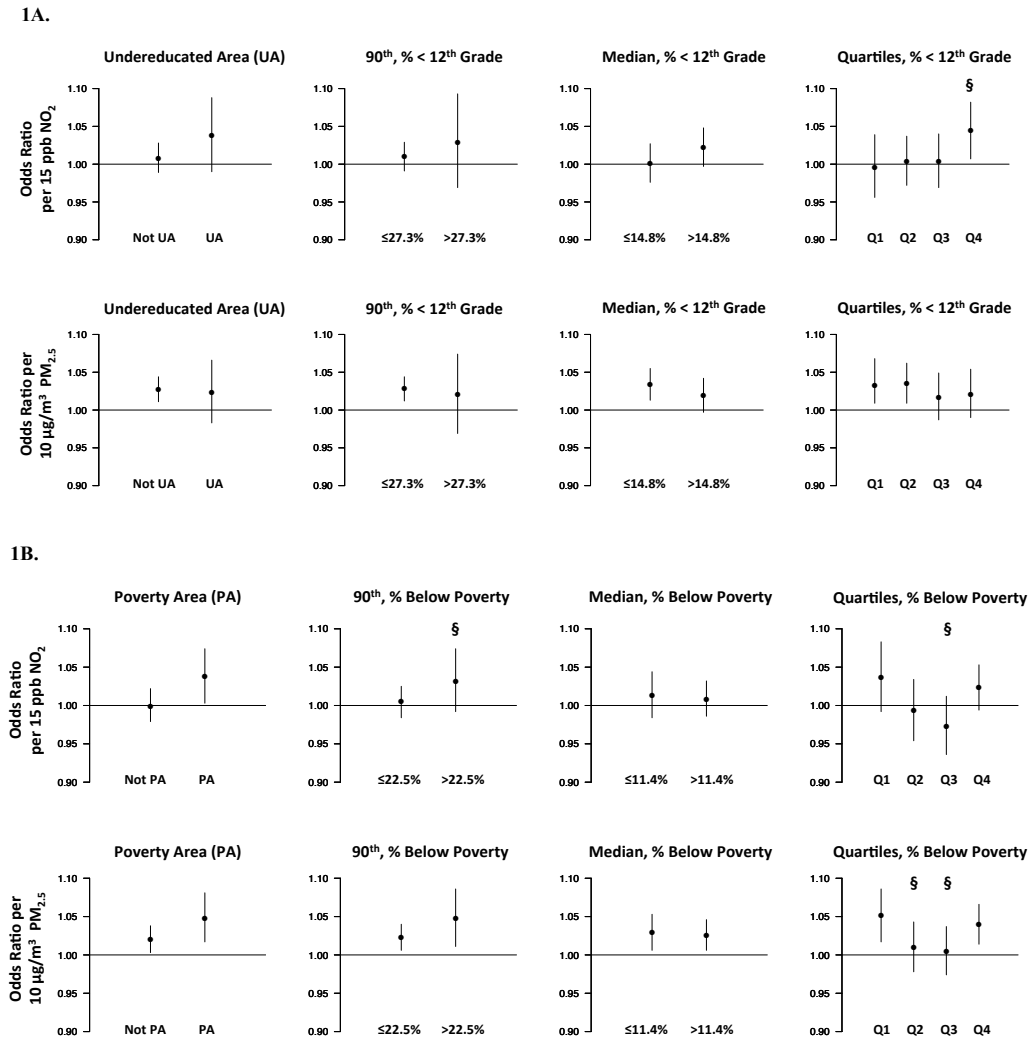


Figure 1.1. Comparison of alternative stratification criteria in relation to observed effect modification of associations between asthma emergency department (ED) visits and 3-day moving average ZCTA-level pollutant concentrations in Atlanta, Georgia (2002-2008). Odds ratios and 95% confidence intervals (CIs) per interquartile range (IQR) increase are shown for 1A) associations between asthma ED visits, nitrogen dioxide (NO_2) and fine particulate matter ($PM_{2.5}$), stratified by undereducated area, or by categories defined by cut points based on the 90th percentile, median, and quartile values of % <12th grade education; 1B) associations between asthma ED visits, nitrogen dioxide (NO_2) and fine particulate matter ($PM_{2.5}$), stratified by poverty area, or by categories defined by cut points based on the 90th percentile, median, and quartile values of % below poverty. Interquartile range values are as follows: NO_2=15 ppb and $PM_{2.5}$=10 µg/m³. Quartile values of % <12th grade education: Q1 = <9.4%; Q2 = ≥ 9.4% to <14.8; Q3 = ≥14.8% to <21.5%; Q4 = >21.5%. Quartile values of % below poverty: Q1 = <7.6%; Q2 = ≥ 7.6% to <11.4; Q3 = ≥11.4% to <16.2%; Q4 = >16.2%. § indicates significant difference (one-sided $P < 0.05$) from referent group. Heterogeneity between strata-specific ORs was tested in pairwise comparisons by dividing the difference in log odds ratio by the square root of the sum of the variances and computing a Z-statistic. Abbreviations: % <12th grade, % of persons (25 and older) with < 12th grade education; % below poverty, % of households living below the federal poverty line; CI, Confidence Interval; ED, emergency department, IQR, Interquartile Range; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter < 2.5 µm in diameter (fine particulate matter); ZCTA, Zip Code Tabulation Area

DISCUSSION

In this analysis of over 128,000 ED visits for pediatric asthma, we assessed neighborhood SES as a potential modifier of acute air pollution-pediatric asthma associations over a 7-year period. Our comprehensive assessment considered multiple indicators of SES as well as multiple ways to categorize socioeconomic strata.

In overall models we observed statistically significant associations between air pollutants and pediatric asthma, particularly for 3-day average concentrations of O_3. When assessing the impact of living in a neighborhood characterized by extremely low SES, we generally observed stronger associations between air pollution and pediatric asthma in extremely low SES neighborhoods compared to areas of higher SES. Our results were particularly consistent across SES indicators when evaluating NO_2, a traffic-related pollutant; these findings support similar results in the literature and a common hypothesis in the health disparities field that low SES environments confer vulnerability to a variety of health outcomes, including traffic pollution-related pediatric asthma morbidity.[6, 8]

Patterns of effect modification of air pollution-asthma associations differed depending on our SES indicator choice and stratification approach. Notably, when indicating SES by % $<12^{th}$ grade education and median home value, we consistently observed stronger associations between asthma and traffic-related pollutants (NO_2 and EC) in low SES strata, for all cut-point definitions. Conversely, for other SES indicators (e.g., % below poverty), results from analyses stratified by median cut-points contradicted results from deprivation area analyses (Figure 1.1B). Defining strata more finely through quartile values of neighborhood SES provided some insight into the differences observed. In particular, for several SES indicators (median income, % below poverty, NDI, Townsend Index) we observed a distinct U-shaped pattern in OR estimates across quartiles, with stronger

associations in high and low SES quartiles and weaker associations in the middle quartiles (Figure 1.1B, Supplemental Table S1.5). This pattern of effect modification could be responsible for the null and unanticipated patterns observed with median cut-points. Complex spatial patterning of neighborhood SES (e.g. location being an important determinant of home value), as well as the possibility that single measures of SES are poor proxies for nuanced socioeconomic environments, may partially account for the different patterns of effect modification observed by SES indicator and pollutants. In our assessment, SES indicators based on % below poverty and the NDI provided the most consistent results across pollutants for the stratification criteria we examined.

Although a U-shaped pattern of effect modification was consistently observed across multiple SES indicators and pollutants, it is important to consider the interpretation of our findings with respect to the mathematical scale of effect measures. Modeling of air pollution health effects on a multiplicative scale is common,[41, 42] however, the true nature of the effect of air pollution on asthma ED visits may be additive. In this scenario it is possible that low baseline risk in the highest SES strata could explain apparent stronger relative effects of air pollution. If air pollution increases the risk of ED visits on an absolute (i.e., additive) scale, and the highest SES strata has lower baseline risk compared to the lowest SES strata [an assumption supported by the literature[43] and our data (Figure 1.2)], we would expect an odds ratio from a multiplicative model to appear larger for the population with the lowest baseline risk (i.e. the highest SES strata). However, assuming strict additivity, we would expect the high baseline risk in the lowest SES strata to result in weaker apparent effects on a multiplicative scale compared to the highest SES strata. Instead, in many analyses, we consistently observed strong, positive associations in both the highest and lowest SES strata. It is therefore possible that higher odds ratios in high SES strata reflect their lower baseline

risk, whereas higher odds ratios in low SES strata reflect supra-additive effects of SES and air pollution.

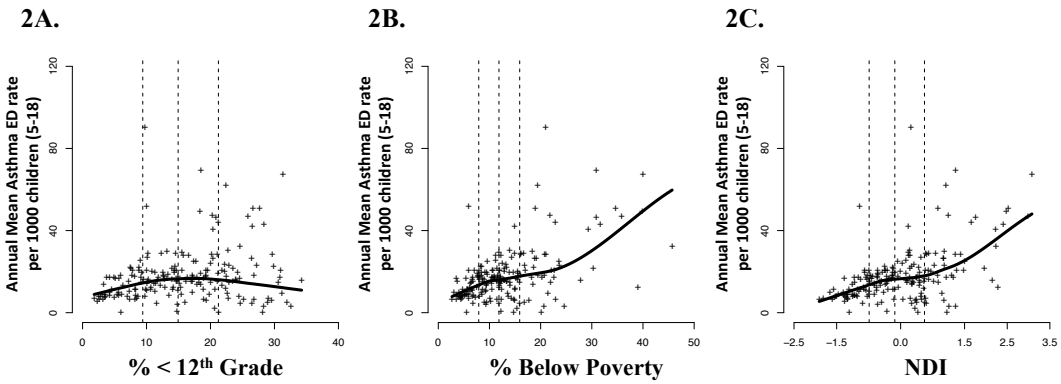


Figure 1.2. Annual mean ED visit rates of pediatric asthma by neighborhood SES for each ZCTA in Atlanta, GA (2002-2008). Asthma ED rates are reported per 1000 children (5-18 years old) and were calculated for each ZCTA by dividing the annual total number of asthma ED visits by annual estimates of the 5-18 year old population. Annual ED Rates were then averaged over the entire study period (2002-2008). ED visit rates for each ZCTA are represented by the "+" symbol and shown in Figure 1.2A by percentage (%) of the adult population (≥ 25 years old) with less than a 12th grade education (% < 12th grade), in Figure 1.2B by % of households living below the federal poverty line (% below poverty), and in Figure 1.2C by the Neighborhood Deprivation Index (NDI). The solid black line represents local polynomial regression using weighted least squares to fit a line through the data. The dotted gray lines represent the 1st, 2nd, and 3rd quartile values of each SES indicator. In each panel, neighborhood SES decreases from left to right. Abbreviations: ED, Emergency Department; NDI, Neighborhood Deprivation Index; SES, socioeconomic status; ZCTA, Zip Code Tabulation Area.

Synthesizing the results from our deprivation area and quartile analyses, and taking into account the high baseline risk in Atlanta's lowest SES populations (Figure 1.2), we believe the data support our main conclusion that children living in low SES environments in Atlanta suffer from a higher burden of asthma due to air pollution compared to their counterparts living in wealthier SES environments.

Our study had several limitations that should be acknowledged. First, differences in ORs across strata were small for some analyses (e.g. ORs for EC stratified by increasing quartile of % below poverty: 1.029, 1.004, 1.001, 1.016); while statistically different, these small ORs indicate that the contribution of air pollution to asthma ED visits may be small relative to other risk factors. Second, by assessing neighborhood SES effects at the ZCTA level, we assumed that ZCTA boundaries are relevant socioeconomic environments with regards to air pollution vulnerability. However, other scales may also be relevant, and the relevance of

specific scales may vary by geographical location due to regional patterns of urban development.[44] Third, our study utilized 12 x12 km pollution grids (the spatial resolution at which CMAQ was run) to estimate daily ZCTA-level air pollution concentrations. A 12x12 km grid is a relatively large area to assess exposure to air pollutants, especially for spatiotemporally-variable primary pollutants (NO_2 and EC). For these pollutants, concentrations vary over small scales due to influences of local traffic sources. The possibility of differential exposure error between SES strata could affect observed patterns of effect modification. Our exposure assignment approach, based on modeled ZCTA-specific pollution estimates, was chosen to minimize the possibility of such differential error compared to common approaches in time-series studies which typically assign daily pollution values to an entire study area based on central monitor estimates. Finally, although we had large numbers of daily ED visits overall, we had low power to detect associations with air pollution in some socioeconomic strata.

Overall, our findings suggest that neighborhood-level SES is a factor contributing vulnerability to air pollution-related pediatric asthma morbidity in Atlanta, and this study provides important insights on how the choice of neighborhood SES indicator and stratification criteria influence results. Published studies investigating SES effect modification of air pollution-health associations commonly define strata based on median cut-points of continuous SES.[25, 27, 30, 31] Given our current findings, it is possible that stratifying at the median may be partially responsible for the inconsistent reports in the literature of effect modification by neighborhood SES on air pollution-health associations. Inconsistent findings of effect modification may also be due to the use of multiplicative models and differing baseline risk across SES populations. We recommend evaluating multiple indicators of SES, using multiple stratification criteria including consideration of

strata indicating extremely low SES environments, and estimating baseline risks across diverse socioeconomic populations. Going forward, it will be critical to explore additive interaction models and whether diverse study areas have similar patterns of effect modification across multiple SES indicators and categorization criteria.

REFERENCES

1. U.S. Environmental Protection Agency. Air quality criteria for particulate matter (final report, oct 2004). Washington, DC: U.S. Environmental Protection Agency, 2004.

2. U.S. Environmental Protection Agency. Air quality criteria for ozone and related photochemical oxidants (2006 final). Washington, DC: U.S. Environmental Protection Agency, 2006.

3. Bateson TF, Schwartz J. Children's response to air pollutants. *J Toxicol Environ Health A* 2007;71(3):238-43.

4. Makri A, Stilianakis NI. Vulnerability to air pollution health effects. *Int J Hyg Environ Health* 2008;211(3-4):326-36.

5. Bell ML, Ebisu K. Environmental inequality in exposures to airborne particulate matter components in the united states. *Environ Health Perspect* 2012;120(12):1699-704.

6. Gold DR, Wright R. Population disparities in asthma. *Annu Rev Public Health* 2005;26:89-113.

7. O'Neill MS, Jerrett M, Kawachi I, et al. Health, wealth, and air pollution: Advancing theory and methods. *Environ Health Perspect* 2003;111(16):1861-70.

8. Williams DR, Sternthal M, Wright RJ. Social determinants: Taking the social context of asthma seriously. *Pediatrics* 2009;123(Suppl):S174-84.

9. Wright RJ, Subramanian SV. Advancing a multilevel framework for epidemiologic research on asthma disparities. *Chest* 2007;132(5 Suppl):757S-69S.

10. Adler NE, Newman K. Socioeconomic disparities in health: Pathways and policies. *Health Affairs* 2002;21(2):60-76.

11. Bernard P, Charafeddine R, Frohlich KL, et al. Health inequalities and place: A theoretical conception of neighbourhood. *Soc Sci Med* 2007;65(9):1839-52.

12. Krieger N, Williams DR, Moss NE. Measuring social class in us public health research: Concepts, methodologies, and guidelines. *Annu Rev Public Health* 1997;18:341-78.

13. Bolton JL, Huff NC, Smith SH, et al. Maternal stress and effects of prenatal air pollution on offspring mental health outcomes in mice. *Environ Health Perspect* 2013;121(9):1075-82.

14. Clougherty JE, Levy JI, Kubzansky LD, et al. Synergistic effects of traffic-related air pollution and exposure to violence on urban asthma etiology. *Environ Health Perspect* 2007;115(8):1140-6.

15. Clougherty JE, Rossi CA, Lawrence J, et al. Chronic social stress and susceptibility to concentrated ambient fine particles in rats. *Environ Health Perspect* 2010;118(6):769-75.

16. Burra TA, Moineddin R, Agha MM, et al. Social disadvantage, air pollution, and asthma physician visits in toronto, canada. *Environ Res* 2009;109(5):567-74.

17. Laurent O, Pedrono G, Segala C, et al. Air pollution, asthma attacks, and socioeconomic deprivation: A small-area case-crossover study. *Am J Epidemiol* 2008;168(1):58-65.

18. Laurent O, Pedrono G, Filleul L, et al. Influence of socioeconomic deprivation on the relation between air pollution and beta-agonist sales for asthma. *Chest* 2009;135(3):717-23.

19. Norris G, YoungPong SN, Koenig JQ, et al. An association between fine particles and asthma emergency department visits for children in seattle. *Environ Health Perspect* 1999;107(6):489-93.

20. Sacks JD, Rappold AG, Davis JA, Jr., et al. Influence of urbanicity and county characteristics on the association between ozone and asthma emergency department visits in north carolina. *Environ Health Perspect* 2014;122(5):506-12.

21. Winquist A, Klein M, Tolbert P, et al. Comparison of emergency department and hospital admissions data for air pollution time-series studies. *Environ Health* 2012;11:70.

22. Yang Q, Chen Y, Shi Y, et al. Association between ozone and respiratory admissions among children and the elderly in vancouver, canada. *Inhal Toxicol* 2003;15(13):1297-308.

23. Kim SY, O'Neill MS, Lee JT, et al. Air pollution, socioeconomic position, and emergency hospital visits for asthma in seoul, korea. *Int Arch Occup Environ Health* 2007;80(8):701-10.

24. Lee JT, Son JY, Kim H, et al. Effect of air pollution on asthma-related hospital admissions for children by socioeconomic status associated with area of residence. *Archives of Environmental & Occupational Health* 2006;61(3):123-30.

25. Lin M, Chen Y, Villeneuve PJ, et al. Gaseous air pollutants and asthma hospitalization of children with low household income in vancouver, british columbia, canada. *Am J Epidemiol* 2004;159(3):294-303.

26. Neidell MJ. Air pollution, health, and socio-economic status: The effect of outdoor air quality on childhood asthma. *J Health Econ* 2004;23(6):1209-36.

27. Sarnat SE, Sarnat JA, Mulholland J, et al. Application of alternative spatiotemporal metrics of ambient air pollution exposure in a time-series epidemiological study in atlanta. *J Expo Sci Environ Epidemiol* 2013;23(6):593-605.

28. Shmool JL, Kubzansky LD, Newman OD, et al. Social stressors and air pollution across new york city communities: A spatial approach for assessing correlations among multiple exposures. *Environ Health* 2014;13:91.

29. Wilhelm M, Qian L, Ritz B. Outdoor air pollution, family and neighborhood environment, and asthma in la fans children. *Health Place* 2009;15(1):25-36.

30. Yap P-S, Gilbreath S, Garcia C, et al. The influence of socioeconomic markers on the association between fine particulate matter and hospital admissions for respiratory conditions among children. *Am J Public Health* 2013;103(4):695-702.

31. Delfino RJ, Chang J, Wu J, et al. Repeated hospital encounters for asthma in children and exposure to traffic-related air pollution near the home. *Annals of Allergy, Asthma & Immunology* 2009;102(2):138-44.

32. Galobardes B, Lynch J, Smith GD. Measuring socioeconomic position in health research. *Br Med Bull* 2007;81-82:21-37.

33. Lin S, Bell EM, Liu W, et al. Ambient ozone concentration and hospital admissions due to childhood respiratory diseases in new york state, 1991-2001. *Environ Res* 2008.

34. Alhanti BA, Chang HH, Winquist A, et al. Ambient air pollution and emergency department visits for asthma: A multi-city assessment of effect modification by age. *J Expo Sci Environ Epidemiol* In press.

35. Gass K, Balachandran S, Chang HH, et al. Ensemble-based source apportionment of fine particulate matter and emergency department visits for pediatric asthma. *Am J Epidemiol* 2015;181(7):504-12.

36. Strickland MJ, Darrow LA, Klein M, et al. Short-term associations between ambient air pollutants and pediatric asthma emergency department visits. *Am J Respir Crit Care Med* 2010;182(3):307-16.

37. Tolbert PE, Mulholland JA, MacIntosh DL, et al. Air quality and pediatric emergency room visits for asthma in atlanta, georgia, USA. *Am J Epidemiol* 2000;151(8):798-810.

38. Friberg MD, Zhai X, Holmes HA, et al. Method for fusing observational data and chemical transport model simulations to estimate spatiotemporally resolved ambient air pollution. *Environ Sci Technol* 2016;50(7):3695-705.

39. Messer LC, Laraia BA, Kaufman JS, et al. The development of a standardized neighborhood deprivation index. *J Urban Health* 2006;83(6):1041-62.

40. Townsend P, Phillimore P, Beattie A. *Health and deprivation: Inequality in the north*. London; New York: Croom Helm, 1988.

41. Bell ML, Zanobetti A, Dominici F. Evidence on vulnerability and susceptibility to health risks associated with short-term exposure to particulate matter: A systematic review and meta-analysis. *Am J Epidemiol* 2013;178(6):865-76.

42. Bell ML, Zanobetti A, Dominici F. Who is more affected by ozone pollution? A systematic review and meta-analysis. *Am J Epidemiol* 2014;180(1):15-28.

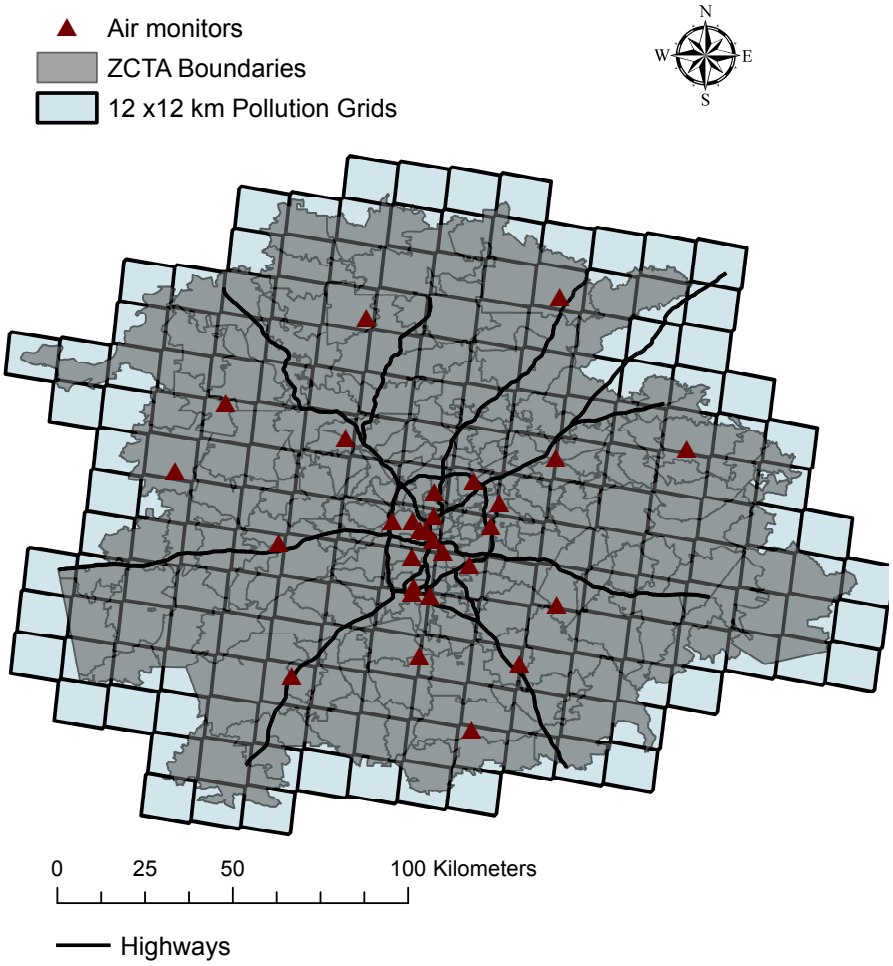
43. Largent J, Nickerson B, Cooper D, et al. Paediatric asthma hospital utilization varies by demographic factors and area socio-economic status. *Public Health* 2012;126(11):928-36.

44. Kramer MR, Cooper HL, Drews-Botsch CD, et al. Do measures matter? Comparing surface-density-derived and census-tract-derived measures of racial residential segregation. *Int J Health Geogr* 2010;9:29.

SUPPLEMENTAL MATERIAL

Chapter 1: Assessment of neighborhood-level socioeconomic status as a modifier of air pollution-asthma associations among children in Atlanta

Contents



Supplemental Figure S1.1 Map of Atlanta study area with 12 x12 km pollution estimate grids overlaid onto ZCTAs. Abbreviations: ZCTA, Zip Code Tabulation Area.

Supplemental Table S1.1. Summary of Emergency Department Visit Data, Overall Visits and Visits by Zip Code Tabulation Area[a], Atlanta, Georgia, 2002-2008.

	Total ED Visit Number				Mean Daily ED Visit Number			
	Overall	Per ZCTA			Overall	Per ZCTA		
		Mean	Min	Max		Mean	Min	Max
All ED visits	1,624,572	8,505.61	40	28,414	635.3	3.33	0	41
Asthma[b] ED	128,758	674.13	4	3,269	50.4	0.26	0	9
Primary Asthma[c] ED	62,308	326.22	1	1,984	24.4	0.13	0	7

Abbreviations: ED, Emergency Department; ICD-9, International Classification of Diseases, 9th Revision; ZCTA, Zip Code Tabulation Area.

[a] 191 Zip Code Tabulation Areas (ZCTAs) in 20-county Atlanta.

[b] Main asthma outcome of interest: primary and secondary diagnoses of asthma (ICD-9 codes 493.0 493.9) or wheeze (ICD-9 code 786.07).

[c] Primary asthma: primary diagnoses of asthma (ICD-9 codes 493.0–493.9) or wheeze (ICD-9 code 786.07).

Supplemental Table S1.2. Daily ZCTA-Level Pollutant Descriptive Statistics and Spearman Correlation Coefficients, Atlanta, Georgia (2002-2008; n=488,387 ZCTA days)

				Spearman Correlation Coefficients			
Pollutant	Mean (SD)	Median	IQR	O_3	NO_2	$PM_{2.5}$	EC
8-hr max O_3, ppb	42.2 (17.3)	40.4	26.0	1	-0.11	0.54	0.07
1-hr max NO_2, ppb	19.4 (12.4)	17.5	19.1		1	0.21	0.75
24-hr avg. $PM_{2.5}$, $\mu g/m^3$	15.2 (7.33)	14.0	9.21			1	0.53
24-hr avg. EC, $\mu g/m^3$	1.02 (0.68)	0.85	0.77				1

Abbreviations: EC, elemental carbon fraction of $PM_{2.5}$; IQR, interquartile range; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter < 2.5 μm in diameter (fine particulate matter); SD, standard deviation; ZCTA, Zip Code Tabulation Area.

Supplemental Table S1.3. Spearman Correlation Coefficients Among ZCTA-Level Indicators of Socioeconomic Status, Atlanta, GA, 2002-2008 (n=191 ZCTAs)

	% <12th Grade	Median Home Value	% Renter Occup.	% Female Headed	% Crowded Living	Median Income	% Public Assist.	% Below Poverty	% No Vehicle	% Un-Employed	NDI	Townsend Index
1a. % <12th Grade	1	-0.76	0.14	0.43	0.53	-0.79	0.60	0.60	0.36	0.41	0.78	0.40
2a. Median Home Value		1	0.02	-0.58	-0.42	0.71	-0.61	-0.42	-0.21	-0.45	-0.69	-0.27
2b. % Renter Occupied			1	0.44	0.57	-0.49	0.29	0.69	0.80	0.35	0.53	0.88
2c. % Female Headed Household				1	0.55	-0.66	0.61	0.63	0.52	0.68	0.77	0.64
2d. % Crowded Living					1	-0.63	0.56	0.63	0.61	0.36	0.68	0.77
3a. Median Income						1	-0.70	-0.83	-0.65	-0.64	-0.95	-0.72
3b. % Public Assistance							1	0.57	0.44	0.50	0.71	0.51
4a. % Below Poverty								1	0.74	0.71	0.90	0.85
5a. % No Vehicle									1	0.42	0.68	0.86
6a. % Unemployed										1	0.75	0.63
7a. NDI											1	0.79
7b. Townsend Index												1

Abbreviations: NDI, Neighborhood Deprivation Index; ZCTA, Zip Code Tabulation Area.

Supplemental Table S1.4. Odds Ratios From Case-Crossover Models Stratified by Median Values of Neighborhood Socioeconomic Status for IQR Increases in 3-day Moving Average ZCTA-Level Pollutant Concentrations and Pediatric Asthma Emergency Department Visits in Atlanta, Georgia, 2002-2008

SES Indicator	Median Values	SES Strata[a]	O_3 (per 25 ppb)		NO_2 (per 15 ppb)		$PM_{2.5}$ (per 10 μg/m³)		EC (per 0.5 μg/m³)	
			OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
% <12th Grade	≤14.8*	High*	**1.075**	**1.035, 1.116**	1.001	0.976, 1.027	**1.034**	**1.013, 1.055**	1.011	0.999, 1.023
	>14.8	Low	**1.072**	**1.028, 1.118**	1.022	0.997, 1.048	1.019	0.997, 1.042	**1.015**	**1.003, 1.027**
Median home value ($)	≥ 157,541*	High*	**1.079**	**1.033, 1.126**	0.996	0.969, 1.024	**1.036**	**1.013, 1.059**	1.007	0.994, 1.020
	<157,541	Low	**1.068**	**1.029, 1.109**	**1.024**	**1.000, 1.049**	1.020	0.999, 1.040	**1.018**	**1.006, 1.029**
Median HH income ($)	≥ 53,663*	High*	**1.092**	**1.047, 1.139**	1.013	0.985, 1.043	**1.037**	**1.014, 1.060**	**1.015**	**1.001, 1.029**
	< 53,663	Low	**1.060**	**1.020, 1.101**	1.008	0.985, 1.032	1.019	0.999, 1.040	**1.012**	**1.001, 1.023**
% Living in poverty	≤ 11.4*	High*	**1.105**	**1.059, 1.153**	1.013	0.984, 1.044	**1.029**	**1.006, 1.053**	**1.016**	**1.001, 1.030**
	> 11.4	Low	**1.052**§	**1.013, 1.092**	1.008	0.986, 1.032	**1.026**	**1.006, 1.046**	**1.012**	**1.001, 1.022**
%HH no vehicle available	≤ 4.2*	High*	**1.076**	**1.031, 1.122**	1.024	0.994, 1.055	**1.036**	**1.013, 1.060**	**1.021**	**1.007, 1.036**
	> 4.2	Low	**1.073**	**1.033, 1.114**	1.003	0.981, 1.027	**1.020**	**1.000, 1.040**	1.009	0.998, 1.019
% Population unemployed	≤8.0*	High*	**1.102**	**1.053, 1.154**	1.032	0.999, 1.065	**1.039**	**1.013, 1.065**	**1.021**	**1.006, 1.036**
	>8.0	Low	**1.061**	**1.023, 1.100**	0.998§	0.977, 1.020	**1.021**	**1.002, 1.040**	1.009	0.999, 1.019
NDI	≤ -0.1*	High*	**1.082**	**1.037, 1.129**	1.017	0.989, 1.047	**1.032**	**1.009, 1.055**	**1.014**	**1.001, 1.028**
	> -0.1	Low	**1.068**	**1.028, 1.109**	1.004	0.981, 1.028	**1.023**	**1.003, 1.044**	**1.012**	**1.001, 1.023**
Townsend Index	≤ -0.8*	High*	**1.079**	**1.032, 1.128**	1.029	0.998, 1.062	**1.025**	**1.001, 1.049**	**1.020**	**1.005, 1.035**
	> -0.8	Low	**1.072**	**1.033, 1.111**	1.001	0.979, 1.024	**1.029**	**1.009, 1.048**	**1.010**	**1.000, 1.020**

Abbreviations: CI, Confidence Interval; EC, elemental carbon fraction of $PM_{2.5}$; HH, Household; IQR, Interquartile Range; NDI, Neighborhood Deprivation Index; NO_2, nitrogen dioxide; O_3, ozone; OR, odds ratio; $PM_{2.5}$, particulate matter < 2.5 μm in diameter (fine particulate matter); SES, socioeconomic status; ZCTA, Zip Code Tabulation Area.

[a]Column denotes which stratum was designated as 'high [SES]' and 'low [SES]'

Bold typeface indicates confidence intervals that do not include the null value.

*Indicates referent group used in assessment of heterogeneity of stratum-specific ORs (i.e. referent strata is 'High [SES]'.

§ indicates significant difference (one-sided $P < 0.05$) from referent group. Heterogeneity between strata-specific ORs was tested in pairwise comparisons by dividing the difference in log odds ratio by the square root of the sum of the variances and computing a Z-statistic.

Supplemental Table S1.5. Odds Ratios From Case-Crossover Models Stratified by Quartile Values of Socioeconomic Status for IQR Increases in 3-day Moving Average ZCTA-Level Pollutant Concentrations and Pediatric Asthma Emergency Department Visits in Atlanta, Georgia, 2002-2008

SES Indicator	Quartile Values	SES Strata	O_3 (per 25 ppb)		NO_2 (per 15 ppb)		$PM_{2.5}$ (per 10 µg/m³)		EC (per 0.5 µg/m³)	
			OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
% <12th Grade	<9.4*	Q1*	**1.133**	**1.065, 1.207**	0.996	0.956, 1.039	1.033	0.999, 1.068	1.001	0.982, 1.020
	≥9.4; <14.8	Q2	1.042§	0.993, 1.093	1.004	0.972, 1.037	**1.035**	**1.009, 1.062**	**1.018**	**1.003, 1.034**
	≥14.8; <21.5	Q3	1.039§	0.979, 1.102	1.003	0.969, 1.040	1.017	0.987, 1.049	1.010	0.993, 1.027
	≥21.5	Q4	**1.103**	**1.040, 1.171**	**1.044§**	**1.007, 1.082**	1.021	0.990, 1.054	**1.020**	**1.004, 1.037**
Median Home Value ($)	≥208,800*	Q4*	**1.139**	**1.060, 1.224**	0.969	0.925, 1.015	1.031	0.994, 1.070	0.993	0.973, 1.014
	≥157,541; <208,800	Q3	1.044§	0.989, 1.102	1.009	0.975, 1.044	**1.039**	**1.010, 1.068**	1.015§	0.999, 1.032
	≥127,548; <157,541	Q2	**1.060**	**1.009, 1.113**	1.024§	0.992, 1.057	**1.028**	**1.002, 1.055**	**1.021§**	**1.006, 1.037**
	<127,548	Q1	**1.076**	**1.015, 1.141**	1.024§	0.987, 1.062	1.006	0.974, 1.039	1.013	0.997, 1.030
Median HH Income ($)	≥66,846*	Q4*	**1.105**	**1.042, 1.173**	1.021	0.980, 1.064	**1.034**	**1.003, 1.067**	1.013	0.994, 1.032
	≥53,663; <66,846	Q3	**1.077**	**1.014, 1.143**	1.007	0.967, 1.049	**1.040**	**1.006, 1.074**	1.017	0.997, 1.038
	≥44,186; <53,663	Q2	**1.064**	**1.006, 1.126**	0.973§	0.937, 1.010	0.988§	0.959, 1.018	0.994	0.976, 1.012
	<44,186	Q1	**1.055**	**1.002, 1.111**	1.030	0.999, 1.061	**1.042**	**1.015, 1.070**	**1.021**	**1.008, 1.034**
% Living in poverty	<7.6*	Q1*	**1.099**	**1.034, 1.168**	1.037	0.992, 1.083	**1.051**	**1.017,1.086**	**1.029**	**1.008, 1.050**
	≥7.6%; <11.4	Q2	**1.114**	**1.050, 1.182**	0.993	0.954, 1.034	1.010§	0.978,1.043	1.004§	0.985, 1.024
	≥11.4%; <16.2	Q3	1.030	0.971, 1.094	0.973§	0.936, 1.012	1.005§	0.974, 1.037	1.001§	0.983, 1.020
	≥16.2	Q4	**1.068**	**1.017, 1.121**	1.023	0.994, 1.053	**1.040**	**1.014, 1.066**	**1.016**	**1.003, 1.029**
%HH no vehicle available	<2.5*	Q1*	**1.082**	**1.022, 1.145**	1.024	0.983, 1.066	**1.031**	**1.000, 1.062**	1.019	0.999, 1.039
	≥2.5; <4.2	Q2	**1.070**	**1.004, 1.141**	1.025	0.981, 1.070	**1.044**	**1.008, 1.080**	**1.024**	**1.002, 1.045**
	≥4.2; <7.4	Q3	**1.070**	**1.005, 1.140**	0.963§	0.923, 1.005	1.001	0.968, 1.036	1.004	0.984, 1.025
	≥7.4	Q4	**1.078**	**1.028, 1.130**	1.013	0.985, 1.042	**1.030**	**1.005, 1.055**	1.010	0.998, 1.022
% Population unemployed	<5.8*	Q1*	**1.126**	**1.050, 1.208**	1.004	0.955, 1.055	1.024	0.985, 1.065	1.004	0.982, 1.027
	≥5.8; <8.0	Q2	**1.082**	**1.018, 1.149**	**1.051**	**1.007, 1.096**	**1.047**	**1.014, 1.082**	**1.034§**	**1.014, 1.054**
	≥8.0; <10.9	Q3	**1.066**	**1.009, 1.126**	0.975	0.940, 1.011	1.003	0.975, 1.032	1.004	0.987, 1.022
	≥10.9	Q4	**1.058**	**1.009, 1.110**	1.014	0.986, 1.043	**1.035**	**1.009, 1.060**	1.012	0.999, 1.025
NDI	<-0.8*	Q1*	**1.133**	**1.064, 1.206**	**1.048**	**1.003, 1.095**	**1.055**	**1.021, 1.090**	**1.027**	**1.007, 1.048**
	≥-0.8; <-0.1	Q2	1.040§	0.982, 1.102	0.996§	0.958, 1.035	1.011§	0.981, 1.043	1.004	0.986, 1.022
	≥-0.1; <0.6	Q3	**1.074**	**1.009, 1.143**	**0.931§**	**0.893, 0.972**	0.993§	0.960, 1.027	0.988§	0.967, 1.009
	≥0.6	Q4	**1.064**	**1.014, 1.116**	**1.033**	**1.004, 1.063**	**1.039**	**1.014, 1.066**	**1.020**	**1.007, 1.032**
Townsend Index	<-2.3*	Q1*	**1.105**	**1.038, 1.177**	1.014	0.969, 1.061	**1.045**	**1.010, 1.080**	1.018	0.996, 1.040
	≥-2.3; <-0.8	Q2	1.056	0.992, 1.125	1.040	0.996, 1.086	1.006	0.973, 1.040	**1.022**	**1.001, 1.044**

≥-0.8; <1.3	Q3	**1.068**	**1.007, 1.133**	**0.956**§	**0.919, 0.994**	1.001§	0.970, 1.033	0.993§	0.974, 1.012
≥1.3	Q4	**1.075**	**1.026, 1.126**	1.022	0.994, 1.051	**1.045**	**1.020, 1.070**	**1.017**	**1.005, 1.029**

Abbreviations: CI, Confidence Interval; EC, elemental carbon fraction of $PM_{2.5}$; HH, Household; IQR, Interquartile Range; NDI, Neighborhood Deprivation Index; NO_2, nitrogen dioxide; O_3, ozone; OR, odds ratio; $PM_{2.5}$, particulate matter < 2.5 μm in diameter (fine particulate matter); SES, socioeconomic status; ZCTA, Zip Code Tabulation Area.

Bold typeface indicates confidence intervals that do not include the null value.

*Indicates referent group used in assessment of heterogeneity of stratum-specific ORs [i.e. referent strata is 'Q1' (or 'Q4' for median income and median home value)].

§ indicates significant difference (one-sided $P < 0.05$) from referent group. Heterogeneity between strata-specific ORs was tested in pairwise comparisons by dividing the difference in log odds ratio by the square root of the sum of the variances and computing a Z-statistic.

APPENDICES

Chapter 1: Assessment of neighborhood-level socioeconomic status as a modifier of air pollution-asthma associations among children in Atlanta

Contents

Appendix 1: Conditional Logistic Regression Equation

Short-term associations between air pollution and pediatric asthma emergency department (ED) visits were assessed via a case-crossover model. The general form of the model was conditional logistic regression, matching on year, month, day of week of the ED visit (time-stratified), and patient Zip Code Tabulation Area (ZCTA) of residence, as follows:

$$\begin{aligned}\text{Logit}[\text{pr}(Y_{kt}=1)] = {} & \beta_0 + \sum_{k=1}^{x} \zeta_k V_k \\ & + \beta(\text{pollution}_{ti}) \\ & + \Sigma_s \Omega_s(\text{SEASON}_{ts}) + \Sigma_m \lambda_m(\text{DOW}_{tm}) + \Sigma_n \nu_n(\text{hosp\_period}_{tn}) \\ & + g(\gamma 1,\ldots, \gamma n;\text{time}_t) + \Sigma_z \psi_z(\text{meteorology}_{tz})\end{aligned}$$

We let Y_{kt} indicate whether person k had the event at time t (1 = event; 0 = no event). V_k denotes the dummy variables that distinguish the case-control set, conditioned on the individual and x is the total number of case-control sets. ζ_k denotes parameters specific to the case-control set V_k. We defined pollution_{ti}, as the exposure for subject k at time t in ZCTA i. The air pollutant variable (pollution) included daily ZCTA-level data on single pollutants from traffic-related sources [nitrogen dioxide (NO_2) and the elemental carbon (EC) fraction of fine particulate matter] and secondary pollutants [ozone (O_3) and fine particulate matter ($PM_{2.5}$)]. For each air pollutant variable, we used a 3-day moving average of lags 0, 1, and 2 as the *a priori* lag structure. Other model covariates included indicator variables for season (SEASON, 4-levels), day of week and holidays (DOW), and indicator variables (hosp_period) for periods of hospital participation during the study period. A cubic spline on day of year (5 degrees of freedom) was included to control smoothly for recurrent within-window seasonal trends. Meteorology was controlled with cubic polynomials for 3-

day moving average (lags 0-2) of maximum temperature and mean dew point; interaction terms between season and maximum temperature were also included.

Appendix 2: Sensitivity Analyses

Methodology. A series of sensitivity analyses were performed to test the consistency of observed results to different model and data specifications. Case-crossover model results were compared with those from traditional Poisson time-series models. In the Poisson models, the outcome was specified as daily counts of pediatric asthma emergency department (ED) visits for each Zip Code Tabulation Area (ZCTA) in the Atlanta metropolitan area. Exposure and covariate control was similar to the case-crossover approach: cubic polynomials for 3-day moving average (lags 0-2) maximum temperature and mean dew point; interaction terms between season and maximum temperature; monthly time splines to control for time trends; indicator variables for season, day of week and holidays; and indicator variables for periods of hospital participation during the study period. The sensitivity of our stratified results to socioeconomic status (SES) assignment [Census 2000 or American Community Survey (ACS) 2007-2011] was examined by assigning ZCTA-level SES values from Census data for the 2002-2005 period and ACS data for the 2005-2008 period rather than a weighted average (linear interpolation) of both sources. The influence of the asthma outcome specification was examined by comparing results from models predicting asthma ED visits identified using both primary and secondary International Classification of Diseases, 9th Revision (ICD-9) codes with results from models predicting asthma ED visits identified using only primary ICD-9 codes (specified as 'primary asthma'). Sensitivity of our results to potential errors in assigning ZCTAs to the 31 ZIP codes that were changed or eliminated during the study period was evaluated by excluding visits from these ZIP codes altogether. Finally, to examine the impact of potentially different lag structures in the air pollution-asthma association between SES strata, models were specified using 5- and 7-day moving average (lags 0-4 and 0-6, respectively) pollutant concentrations

(with maximum temperature and mean dew point temperature control similarly extended), to compare with results for 3-day moving average concentrations.

Results. Sensitivity analysis results are summarized here and not presented quantitatively. Poisson regression results were consistent with the effect estimates and patterns of effect modification observed in case-crossover analyses. Patterns of effect modification were not sensitive to how Census 2000 and ACS 2007-2011 data were linked with ED databases; these analyses generated results with identical interpretations as those based on interpolated SES values. ZIP codes that changed or were eliminated during the study period contributed very few ED visits to the overall study population; therefore, removing these ZIP codes from our database in sensitivity analyses had minimal impact on odds ratio estimates. In both Poisson and case-crossover models, we observed similar patterns of association when primary asthma (instead of primary and secondary asthma) was used as our health outcome definition. In stratified analyses that used alternate pollutant lag structures (5- and 7-day moving averages) we observed slightly stronger associations across all strata with wider confidence intervals. However, patterns of effect modification were similar to patterns observed using 3-day moving averages of pollutant concentrations.

Appendix 3: Neighborhood Characterization

We further characterized neighborhood air quality and emergency department (ED) visit rates by neighborhood socioeconomic status (SES) for select SES indicators: percentage with less than 12th grade education (% <12th grade education), percentage living below the federal poverty line (% below poverty), and the Neighborhood Deprivation Index (NDI). These indicators were selected based on the frequency of their use in the literature and because at least one of them was at least moderately correlated (Spearman's ρ>0.65) with the other SES indicators of interest (see online material, Supplemental Table S1.3).

ED visit data and neighborhood SES. We observed a greater number of ED visits in low SES quartiles, except for when evaluating quartiles of % <12th grade education (Appendix Table A1.1). Few Zip Code Tabulation Areas (ZCTAs) were identified as deprivation areas (i.e. undereducated areas and poverty areas) and therefore deprivation areas contributed fewer ED visits to stratified analyses than non-deprivation areas (Appendix Table A1.1).

Air quality data and neighborhood SES. With regard to spatial distribution of pollutants across socioeconomic groups, ozone and $PM_{2.5}$ concentrations were relatively homogenous across ZCTAs, with similar mean concentrations across SES quartiles (Appendix Table A1.1). Though ozone levels were largely similar across SES strata, we observed slightly lower concentrations in poverty as compared to non-poverty areas due to slightly lower levels of ozone in central Atlanta (Appendix Figure A1.1) where most poverty area ZCTAs are located (Appendix Figure A1.2). Conversely, for % below poverty and the NDI, mean NO_2 and EC concentrations were generally higher in low SES strata compared to high SES strata

(Appendix Table A1.1). However, when considering % <12th grade education as an indicator of neighborhood SES, we observed, on average, lower concentrations of NO_2 and EC in low SES compared to high SES neighborhoods because ZCTAs at the periphery of our study area are characterized by low concentrations of traffic related pollutants (Appendix Figure A1.1) and high percentages of adults with <12th grade education (Appendix Figure A1.3)

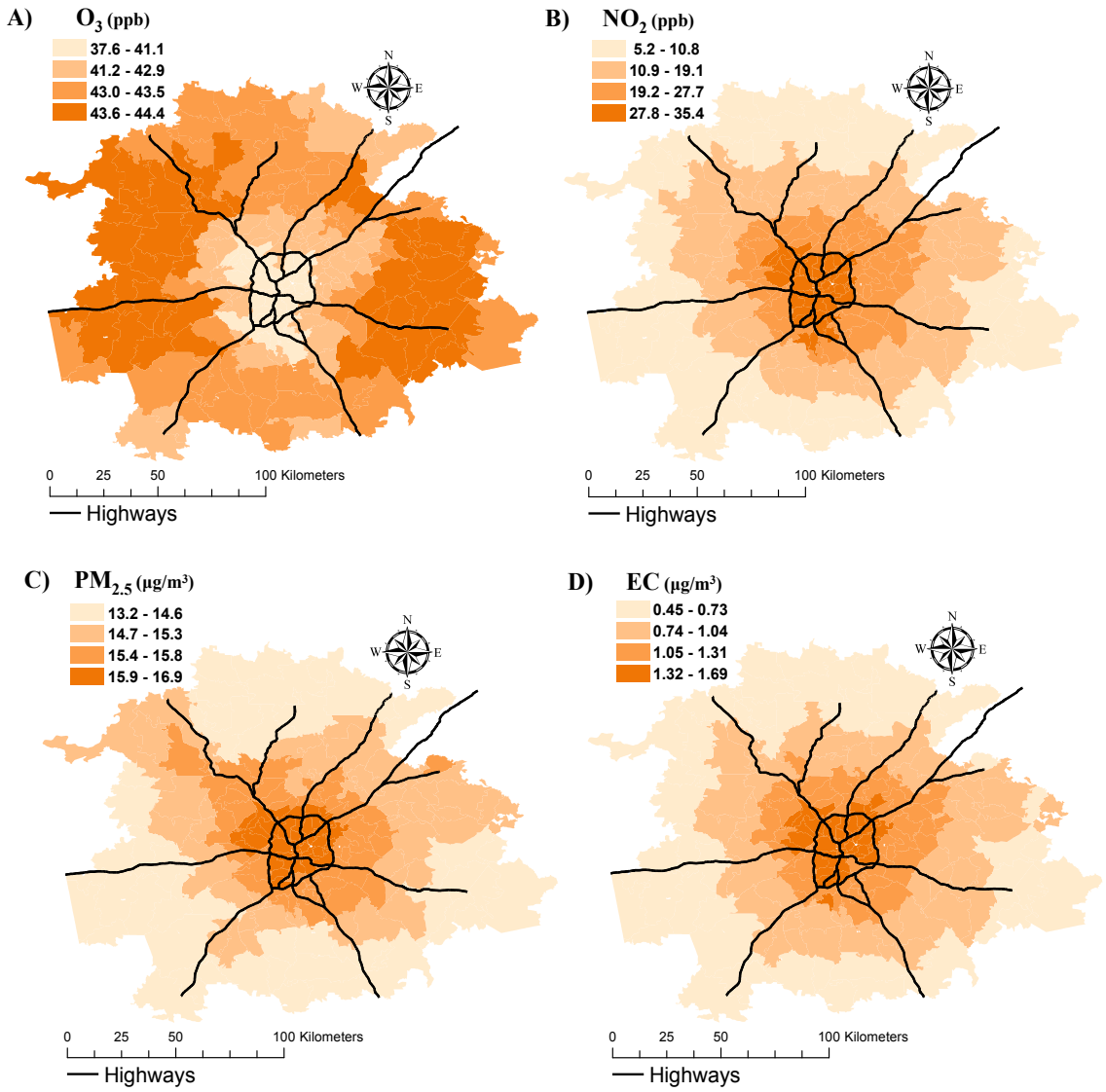
Appendix Table A1.1. Mean ZCTA-Level Pollutant Concentrations and Counts of Emergency Department Visits by Socioeconomic Strata, Atlanta, Georgia (2002-2008; n=488,387 ZCTA days)

SES Indicator	O_3 (ppb)	NO_2 (ppb)	$PM_{2.5}$ ($\mu g/m^3$)	EC ($\mu g/m^3$)	# Primary Asthma ED visits[a]	# Asthma ED visits[b]	# All ED visits
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Total Count	Total Count	Total Count
% < 12th Grade (Quartiles)							
<9.4 (High SES)	42.1 (17.9)	23.1 (11.4)	15.5 (7.39)	1.17 (0.70)	12,895	25,934	361,234
≥9.4 to <14.8	42.6 (17.7)	20.2 (11.1)	15.3 (7.36)	1.06 (0.65)	20,621	43,858	527,570
≥14.8 to <21.5	42.3 (17.0)	18.3 (12.6)	15.1 (7.34)	0.97 (0.66)	14,745	30,208	383,906
≥21.5 (Low SES)	42.0 (16.8)	16.0 (13.2)	14.9 (7.22)	0.88 (0.65)	14,047	28,758	351,862
Undereducated Area (≥ 25% < 12th grade)							
No	42.3 (17.5)	20.0 (12.1)	15.3 (7.35)	1.05 (0.68)	53,490	111,446	1,423,111
Yes	42.0 (16.7)	16.0 (13.1)	14.8 (7.22)	0.87 (0.65)	8,818	17,312	201,461
% Below Poverty (Quartiles)							
<7.6 (High SES)	42.7 (17.5)	17.5 (10.2)	15.1 (7.20)	0.96 (0.60)	10,915	26,053	393,489
≥7.6% to <11.4	42.6 (17.3)	17.7 (11.3)	15.1 (7.29)	0.96 (0.63)	11,884	27,938	380,936
≥11.4% to <16.2	42.5 (17.1)	18.0 (12.2)	15.1 (7.33)	0.97 (0.66)	14,113	29,152	374,259
≥16.2 (Low SES)	41.1 (17.5)	24.5 (13.9)	15.5 (7.48)	1.19 (0.78)	25,396	45,615	475,888
Poverty Area (≥ 20% below poverty)							
No	42.6 (17.3)	17.9 (15.1)	15.1 (7.29)	0.97 (0.63)	45,540	99,069	1,328,766
Yes	40.2 (17.6)	27.8 (15.8)	15.8 (7.51)	1.31 (0.82)	16,768	29,689	295,806
NDI (Quartiles)							
<-0.8 (High SES)	42.5 (17.6)	19.9 (11.1)	15.3 (7.32)	1.06 (0.65)	11,359	26,060	382,463
≥-0.8 to <-0.1	42.5 (17.3)	18.6 (11.7)	15.2 (7.35)	1.00 (0.65)	12,740	30,152	404,920
≥-0.1 to <0.6	42.7 (16.9)	15.7 (11.5)	14.9 (7.26)	0.89 (0.61)	11,584	25,677	339,765
≥0.6 (Low SES)	41.1 (17.5)	23.4 (13.9)	15.4 (7.38)	1.14 (0.76)	26,625	46,869	497,424

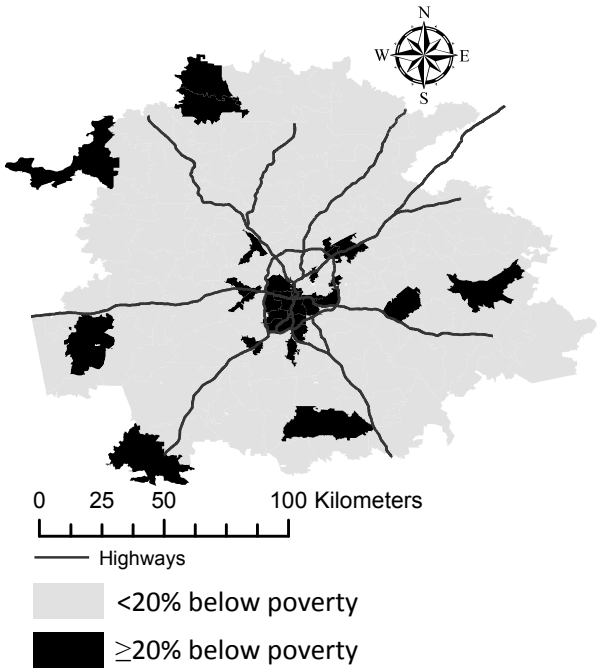
Abbreviations: EC, elemental carbon fraction of $PM_{2.5}$; ED, Emergency Department; ICD-9, International Classification of Diseases, 9th Revision; NDI, Neighborhood Deprivation Index; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter < 2.5 μm in diameter (fine particulate matter); SD, standard deviation; SES, socioeconomic status; ZCTA, Zip Code Tabulation Area.

[a] Primary asthma: primary diagnoses of asthma (ICD-9 codes 493.0–493.9) or wheeze (ICD-9 code 786.07).

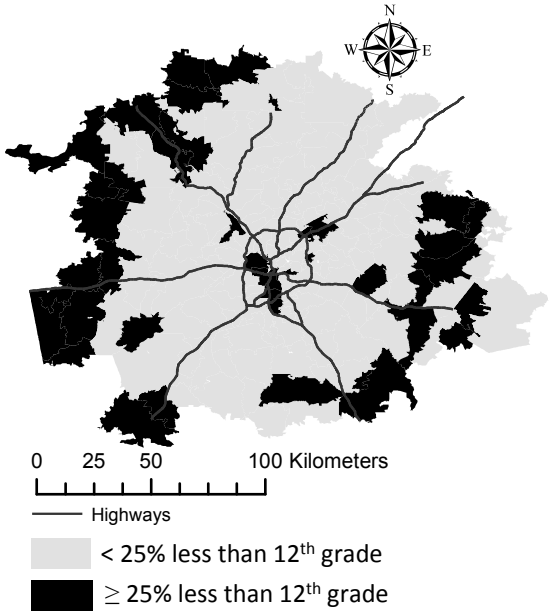
[b] Main asthma outcome of interest: primary and secondary diagnoses of asthma (ICD-9 codes 493.0–493.9) or wheeze (ICD-9 code 786.07).



Appendix Figure A1.1. Average ZCTA-level Concentrations of Ambient Air Pollutants in 20-County Atlanta, Georgia (2002-2008). A) Spatial representation of ozone levels across metropolitan Atlanta by quartiles of average ZCTA-level O_3 concentrations (ppb); B) Spatial representation of NO_2 levels across metropolitan Atlanta by quartiles of average ZCTA-level NO_2 concentrations (ppb); C) Spatial representation of $PM_{2.5}$ levels across metropolitan Atlanta by quartiles of average ZCTA-level $PM_{2.5}$ concentrations (µg/m^3); D) Spatial representation of EC levels across metropolitan Atlanta by quartiles of average ZCTA-level EC concentrations (µg/m^3). Abbreviations: EC, elemental carbon fraction of $PM_{2.5}$; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter < 2.5 µm in diameter (fine particulate matter); ZCTA, Zip Code Tabulation Area.



Appendix Figure A1.2. Spatial Representation of ZCTAs Ever Designated as a Poverty Area in Atlanta, Georgia Between 2002 and 2008. Atlanta ZCTA categorized as a 'poverty area' if ≥20% of the households are living below the Federal Poverty Line. Abbreviations: ZCTA, Zip Code Tabulation Area.



Appendix Figure A1.3. Spatial Representation of ZCTAs Ever Designated as an Undereducated Area in Atlanta, Georgia Between 2002 and 2008 (Atlanta ZCTA categorized as an 'undereducated area' if ≥25% of the population has less than a 12th grade education). Abbreviations: ZCTA, Zip Code Tabulation Area.

Chapter 2

Ozone and childhood respiratory disease in three US cities: evaluation of effect measure modification by neighborhood socioeconomic status using a Bayesian hierarchal approach

Cassandra R. O'Lenick, Howard H. Chang, Michael R. Kramer, Andrea Winquist, James A. Mulholland, Mariel D. Friberg, Stefanie Ebelt Sarnat

[Formatted for submission to *Environmental Health*]

ABSTRACT

Background. Ground-level ozone is a potent airway irritant and a determinant of respiratory morbidity. Susceptibility to the health effects of ambient ozone may be influenced by both intrinsic and extrinsic factors, such as neighborhood socioeconomic status (SES). Questions remain regarding the manner and extent that factors such as SES influence ozone-related health effects, particularly across different study areas. **Methods.** Using a 2-stage modeling approach we evaluated neighborhood SES as a modifier of ozone-related pediatric respiratory morbidity in Atlanta, Dallas, & St. Louis. We acquired multi-year data on emergency department (ED) visits among 5-18 year olds with a primary diagnosis of respiratory disease in each city. Daily concentrations of 8-hour maximum ambient ozone were estimated for all ZIP Code Tabulation Areas (ZCTA) in each city by fusing observed concentration data from available network monitors with simulations from an emissions-based chemical transport model. In the first stage, we used conditional logistic regression to estimate ZCTA-specific odds ratios (OR) between ozone and respiratory ED visits, controlling for temporal trends and meteorology. In the second stage, we combined ZCTA-level estimates in a Bayesian hierarchical model to assess overall associations and effect modification by neighborhood SES considering categorical and continuous SES (e.g., ZCTA-specific levels of poverty) indicators. We estimated ORs and 95% posterior intervals (PI) for a 25 ppb increase in ozone. **Results.** The hierarchical model combined effect estimates from 179 ZCTAs in Atlanta, 205 ZCTAs in Dallas, and 151 ZCTAs in St. Louis. The strongest overall association of ozone and pediatric respiratory disease was in Atlanta (OR=1.08, 95% PI: 1.06, 1.11), followed by Dallas (OR=1.04, 95% PI: 1.01, 1.07) and St. Louis (OR=1.03, 95% PI: 0.99, 1.07). Patterns of association across levels of neighborhood SES in each city suggested stronger ORs in low compared to high SES areas, with some

evidence of non-linear effect modification. **Conclusions.** Results suggest that ozone is associated with pediatric respiratory morbidity in multiple US cities; neighborhood SES may modify this association in a non-linear manner. In each city, children living in low SES environments appear to be especially vulnerable given positive ORs and high underlying rates of respiratory morbidity.

BACKGROUND

Ground-level ozone, a criteria pollutant regulated by the US Environmental Protection Agency (EPA), is a potent airway irritant and well-known determinant of adverse health outcomes, including respiratory morbidity and mortality.[1] Increasing evidence suggests that intrinsic factors (e.g. age, sex, genetics), extrinsic factors (e.g. low socioeconomic status), and differential exposure among populations may potentiate susceptibility to the health effects of ambient ozone.[2] However, questions remain as to the degree of influence these factors exert on ozone-related health effects.[3]

Intrinsically, children are considered more vulnerable than adults to the health effects of ozone due to their higher ventilation rates, a developing respiratory system, and time activity patterns that generally increase their exposures to ambient ozone. Concomitantly, physiological differences in airway structure and function cause greater doses of pollutants to be delivered into airways and predispose children to airway inflammation and obstruction.[4-6] Extrinsically, low socioeconomic status (SES) may exacerbate vulnerabilities among children through greater exposure to indoor and outdoor air pollutants, greater psychosocial stress associated with their social environment, and reduced access to local resources (e.g., healthy food options, green-space, adequate health care options).[7-9] However, vulnerability to ozone-related respiratory morbidity among children has not been consistently observed between study locations, and findings to date have not conclusively identified SES as a modifier of ozone-related respiratory disease.[2, 3] These observed incongruences call into question whether findings from individual studies, often conducted in single cities or communities, can be generalized.

Previous findings from our research team in Atlanta have identified robust associations between ground level ozone and pediatric respiratory health outcomes.[10-16] Analyses

examining effect modification of ozone-related pediatric asthma ED visits by neighborhood-level SES suggest non-linear patterns of effect modification by neighborhood SES in Atlanta; for example, in some analyses we observed stronger associations between ozone and pediatric asthma ED visits in the highest and lowest SES strata and weaker associations in middle SES strata.[12] However, the generalizability of these findings to other study areas or other respiratory health outcomes has not been established.

Several studies have utilized Bayesian hierarchical models to explore associations between air pollution and adverse health outcomes across multiple study locations, in a computationally efficient manner.[17-21] Furthermore, analyzing multicity data using Bayesian hierarchical models allows for assessment of factors that may help to explain between-location heterogeneity and ultimately ascertain population-level vulnerability factors.[17, 18] Here, we use a two-stage Bayesian hierarchical approach to examine effect modification of ozone-related pediatric respiratory disease by categorical and continuous measures of neighborhood SES in three diverse cities (Atlanta, Dallas, and St. Louis). By applying a consistent analytic approach we assess the generalizability of associations between ozone and pediatric respiratory disease across diverse study areas and evaluate whether patterns of effect modification differ by city.

METHODS

Asthma emergency department visit data

Multi-year ED visit data were collected from three diverse study locations, which included the metropolitan areas of Atlanta, Dallas, and St. Louis. These data have been used previously in air pollution health effects investigations [16, 22-24]. For the current analysis, ED data were available for 2002-2008 from 41 hospitals in 20-county Atlanta; data through 2004 were collected from individual hospitals directly while 2005-2008 data were collected through the Georgia Hospital Association. ED data were available for 2006-2008 from the Dallas-Fort Worth Hospital Council Foundation for 36 hospitals in the 12-county Dallas metro area. In St. Louis, ED data were available for 2002-2007 from the Missouri Hospital Association for 36 hospitals in the 16-county metro area. ED visits for respiratory outcomes (upper respiratory infections, bronchiolitis, pneumonia, asthma, and wheeze) were identified using primary International Classification of Diseases, 9th Revision (ICD-9) codes 460-486, 493, 786.07. We restricted our analyses to the pediatric population (5–18 years old) and to patients with a residential Zone Improvement Plan (ZIP) code located wholly or partially in 20-county Atlanta (232 ZIP codes), 12-county Dallas (271 ZIP codes), or 16-county St. Louis (264 ZIP codes). The Emory University Institutional Review Board approved this study and granted exemption from informed consent requirements.

To create spatial scales compatible with air quality and census-based data, each ZIP code in the ED visit database was assigned to a 2010 Zip Code Tabulation Area (ZCTA, Census Bureau boundaries, created from census blocks to approximate ZIP codes). Assignments were accomplished by matching each ZIP code to a 2010 ZCTA based on 5-digit Census ID numbers. ZIP code change reports helped facilitate ZCTA assignments for ZIP codes that were altered or eliminated during the study period. ZCTAs that were classified as businesses

or university campuses were excluded from the study. The resulting study areas included 191 ZCTAs in Atlanta, 253 ZCTAs in Dallas, and 256 ZCTAs in St. Louis.

Neighborhood-level socioeconomic data

Estimates of ZCTA-level socioeconomic status (SES) were obtained from the 2000 US Census long form and the American Community Survey (ACS) 5-year (2007-2011) summary file, all normalized to 2010 ZCTA borders ("The Time-Series Research Package", GeoLytics, Inc., East Brunswick, NJ, 2013). In our analyses, ZCTA boundaries were used to represent neighborhoods of patient residence and yearly values of neighborhood-level (i.e. ZCTA-level) SES were estimated by linear interpolation of Census 2000 and ACS 2007-2011 values. We then averaged the yearly values across the study periods of each city (2002-2008 in Atlanta; 2006-2008 in Dallas, and 2002-2007 in St. Louis) to estimate a mean SES value for each neighborhood. We chose percentage of the population (≥25 years old) with less than a 12^{th} grade education (% < 12^{th} grade), percentage of households living below the poverty line (% below poverty), and the Neighborhood Deprivation Index (NDI), a composite index comprised of 8 single indicators of SES that were summarized using principle components analysis[25], to represent neighborhood-level SES and to enable comparison of results across different SES indicators.

Ambient ozone concentration data

Our study used daily estimates of ambient 8-hour maximum ozone for each ZCTA in Atlanta, Dallas, and St. Louis. Daily concentrations of ambient 8-hour maximum ozone were estimated by combining observational data from network monitors in each city with pollutant concentration simulations from an emissions-based chemical transport model, the

Community Multi-Scale Air Quality version 4.5 (CMAQ) model at 12x12 km grids over Atlanta, Dallas, and St. Louis[26]. Ozone concentrations were estimated for each ZCTA by determining the fraction of a ZCTA's area within each 12x12 km grid cell and area-weighting the observation-simulation data fusion estimates to get the ZCTA-specific value. Although a 12x12 km grid is a relatively large area to assess exposure to air pollutants, ozone is a spatially homogenous secondary pollutant and concentrations are unlikely to vary substantially over the 12x12km grids used in each city. We specifically chose ambient ozone and our exposure modeling approach to minimize the potential for exposure measurement error in each city. Daily meteorological data were obtained from National Climatic Data Centers at Atlanta Hartsfield International Airport, Dallas/Ft. Worth International Airport, and St. Louis Lambert International Airport.

Statistical analyses

We applied a two-stage modeling approach to estimate associations between daily ZCTA-specific ozone concentrations and pediatric respiratory ED visits, as well as to evaluate effect modification by neighborhood SES across multiple locations. In the first stage, associations between 3-day moving average (lag days 0-2) ZCTA-specific ozone concentrations and pediatric respiratory disease were estimated for every ZCTA in Atlanta, Dallas, and St. Louis in case-crossover analyses using conditional logistic regression, matching on year, month, and day of the week of the ED visit. We chose a 3-day moving average of ozone as our a priori lag structure based on previous work.[10, 12, 27] We included additional control for time-varying factors: indicator variables for season (4-levels), periods of hospital participation and holidays; cubic polynomials for 3-day moving average (lags 0-2) maximum temperature and mean dew point; interaction terms between season and

maximum temperature; and a cubic spline on day of year (5 degrees of freedom) to control smoothly for recurrent within-window seasonal trends. The general structure of each ZCTA-specific model was:

$$\text{Logit}[\text{pr}(Y_{kt}=1)] = \beta_0 + \sum_{k=1}^{x} \zeta_k V_k + \beta(\text{ozone}_{tz}) + \Sigma_s \Omega_s(\text{season}_{ts}) + \quad \textbf{Eq. 1}$$

$$\Sigma_m \lambda_m(\text{DOW}_{tm}) + \Sigma_n \nu_n(\text{hosp\_period}_{tn}) + g(\gamma 1,\ldots,\gamma n;\text{time}_t) + \Sigma_q \psi_q(\text{meteorology}_{tq})$$

where, Y_{kt} indicates whether person k had the event at time t (1 = event; 0 = no event) and t indexes the event and control days. V_k denotes the indicator variables that distinguish the case-control sets for the various individuals, x is the total number of case-control sets, and ζ_k denotes parameters specific to the case-control sets (which are not estimated in conditional logistic regression). We defined ozone_{tz}, as the ozone exposure for subject k at time t in ZCTA z. Other model covariates included indicator variables for season (4-levels), day of week and holidays (DOW), and indicator variables (hosp_period) for periods of hospital participation during the study period. We note that the above model assumes all confounder effects are ZCTA-specific. Using Eq. 1 (stage 1), we estimated the log odds ratio, $\hat{\beta}_z$, of ozone on respiratory disease for ZCTA z, and its estimated variance, $\hat{V}_z$. Stage 1 models with fewer than 50 total ED visits per ZCTA during the study period did not converge; therefore, these ZCTAs were excluded from the second stage of our modeling approach.

In the second stage, we fit two-level Bayesian hierarchical models via the R package TLnise with noninformative priors.[28] Similar to a meta-regression analysis, ZCTA-specific effect estimates (log odds ratios, $\hat{\beta}_z$) were combined to generate city-specific estimates of the short-term association between ozone and pediatric respiratory ED visits, accounting for (1) uncertainty associated with each ZCTA-specific log odds ratio as measured by its asymptotic

standard error, and (2) between-ZCTA variability of the true unobserved ZCTA-specific log odds ratio.[18, 29, 30] Specifically, we fit the following Bayesian hierarchical model:

$$\beta_z \mid \theta_z, \hat{V}_z \sim N\left(\theta_z, \hat{V}_z\right) \qquad \textbf{Eq. 2}$$

$$\theta_z \mid \alpha_0, \gamma, \tau^2 \sim N(\alpha_0 + \sum_j \gamma_j X_{zj}, \tau^2)$$

where,

θ_z = the unobserved true log odds ratio in each ZCTA

X_{zj} = ZCTA-specific values of ZCTA-level covariates (j) in ZCTA z

α_0 = the average log odds ratio for ZCTAs

Υ_j = the change in the log odds ratio for a change in X_{zj}

τ^2 = heterogeneity variance across ZCTAs of the unobserved log odds ratio, θ_z, unexplained by ZCTA-level characteristics, X_{zj}. τ reflects the standard deviation and is the parameter we used to assess whether ZCTA-level characteristics explained heterogeneity in the effect of ozone on pediatric respiratory disease across ZCTAs.

To estimate overall associations between ozone and pediatric respiratory disease, we used Eq. 2 to fit 'combined' meta-regressions which pooled data from all three cities (535 ZCTAs) and included indicator variables for each city, represented by X_{zj} in Eq. 2 [i.e. $\mathbf{X}_{(535x3)}$ = ($\mathbf{X}_{Atlanta(z)}$, $\mathbf{X}_{Dallas(z),}$ $\mathbf{X}_{St.Louis(z)}$]. In secondary analyses, we used Eq. 2 to fit "city-specific" meta-regressions which pooled ZCTA-specific data from each city individually (179 ZCTAs in Atlanta; 205 ZCTAs in Dallas; and 151 ZCTAs in St. Louis).

To examine modification of ozone-related respiratory disease by neighborhood SES, we further included X_{zj} covariates in Eq. 2 that characterized ZCTAs with respect to their SES. In these analyses, ZCTAs of extremely low SES were identified using the following SES

indicators: undereducated area (yes/no)' [≥25% of the population aged at least 25 years with <12th grade education; 'poverty area status (yes/no)' (≥20% of households living below the federal poverty line); and 'above the 90th percentile of the NDI (yes/no)'. We also characterized ZCTAs by continuous values of SES and examined linear and non-linear effect modification through linear, quadratic, and cubic functions of neighborhood SES (indicated by continuous values of % <12th grade education, % below poverty, and the NDI).

For our main effect modification analyses we fit 'combined' meta-regressions with the assumption that the effect of neighborhood SES on ozone-related respiratory disease is the same for each city. In combined models, X_{zj} covariates included an intercept, indicators for city, and categorical or continuous ZCTA-level SES. For example, the X_{zj} matrix from a combined meta-regression examining effect modification by linear % below poverty was $\mathbf{X}_{(535x4)} = (1, \mathbf{X}_{Dallas(z)}, \mathbf{X}_{St.Louis(z)}, \mathbf{X}_{\%poverty(z)})$, where '1' is the intercept and represents a ZCTA in Atlanta with 0% poverty. Consequently, all associations reported from combined models are interpreted as a summary estimate of effect modification by neighborhood SES based on data from three cities. In secondary analyses we assessed deviation from our assumption that the effect of neighborhood SES on ozone-related respiratory disease is the same for each city by fitting 'city-specific' meta-regressions, which pooled ZCTA-specific data from each city individually, and thus enabled each city to have its own ozone effect modification by SES.

All associations between ozone and pediatric respiratory disease are reported as odds ratios (OR) and 95% posterior intervals (PI) scaled to a 25 ppb increase in ozone. Additionally, model parameter estimates were considered significant if the absolute value of the estimate divided by its posterior standard error was greater than 1.96 (analogous to a Z-score). All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) and R version

3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Three cities characterization

The three study sites assessed in this analysis are large, urban cities located in three distinct US regions: the Southeast (Atlanta), Southwest (Dallas), and Midwest (St. Louis). Table 2.1 presents descriptive statistics for each study site including mean temperature, number of ozone monitors, ozone concentration, and socioeconomic composition of the population.

Daily mean temperatures during the study period were on average higher in Dallas (68.8 F) compared to Atlanta (63.1 F) and St. Louis (57.9 F). On average, Atlanta and Dallas had slightly greater daily concentrations of ozone across their respective study periods (42.2 and 42.0 ppb) compared to St. Louis (40.0 ppb). With regard to socioeconomic composition, Dallas had the highest mean values of % below poverty (14.0%) and % $<12^{th}$ grade education (17.5%) across ZCTAs, indicative of lower SES neighborhoods, on average, in Dallas compared to Atlanta and St. Louis. Supplemental Figure S2.1 presents additional summary statistics and density distribution plots of % $<12^{th}$ grade, % below poverty, and the NDI for each city. Note, NDI values were standardized to mean neighborhood deprivation in each city, hence means of 0 and standard deviations of 1 in each city.

Pediatric respiratory ED visits

Our complete ED visit database for respiratory disease among children aged 5-18 years included 211,530 ED visits during the years 2002-2008 in Atlanta, 96,983 ED visits during the years 2006-2008 in Dallas, and 113,285 ED visits during the years 2002-2007 in St. Louis.

Due to model convergence issues in the first stage of our analysis, we excluded all ZCTAs that reported fewer than 50 ED counts over their respective study periods. This resulted in the exclusion of 12 ZCTAs in Atlanta, 48 ZCTAs in Dallas, and 105 ZCTAs in St. Louis; these ZCTAs contributed very few ED visits to our overall study and the exclusion of these ZCTAs from analyses resulted in less than 2% of the total number of ED visits from each city to be excluded. Figure 2.1 presents spatial maps of the included and excluded ZCTAs of the Atlanta, Dallas, and St. Louis study areas. Table 2.2 summarizes differences in ED data between our complete ED database and the analytical ED database, restricted to data from ZCTAs with at least 50 ED counts.

Table 2.1: Descriptive statistics of temperature, ozone concentrations, and population socioeconomic composition in Atlanta, Georgia (2002-2008); Dallas, Texas (2006-2008); and St. Louis, Missouri/Illinois (2002-2007)

City	# Counties	# ZCTAs	Temp. (F)	8-hr max Ozone* (ppb)					Socioeconomic Composition	
				# Monitors	Mean (SD)	Min	Max	IQR	% <12th Grade Mean (SD)	% Below Poverty Mean (SD
Atlanta	20	191	63.1	12	42.2 (17.3)	2.21	125	26.0	15.7 (8.1)	13.1 (7.84)
Dallas	12	253	68.8	19	42.0 (14.6)	2.23	118	19.7	17.5 (12.1)	14.0 (9.75)
St. Louis	16	256	57.9	18	40.0 (17.3)	0.15	115	25.4	15.9 (8.14)	12.5 (9.45)

* Daily ZCTA-specific concentrations of ambient 8-hour maximum ozone. Mean, SD, min., max., and IQR are summarized across days and ZCTAs.

Abbreviations: % <12th grade, percentage of the adult population (≥25 years old) with less than a 12th grade education; % below poverty, percentage of households living below the Federal Poverty Line; #, number; IQR, interquartile range; Max, maximum; Min, minimum; SD, standard deviation; Temp, average daily mean temperature in degrees Fahrenheit; ZCTA, Zip Code Tabulation Area.

Table 2.2. Summary of respiratory ED visit counts among children aged 5–18 years, overall visits, and visits by ZIP code tabulation areas for Atlanta, Georgia (2002-2008); Dallas, Texas (2006-2008); and St. Louis, Missouri/Illinois (2002-2007)

	Complete ED Database (data from all ZCTAs)		**Analytical ED Database** (data from ZCTAs with ≥50 ED visits)					
						ED visits per ZCTA		
City	Number of ZCTAs	ED visit Number	Number of ZCTAs	ED visit Number	% of total ED visits[b]	Min	Mean	Max
Atlanta	191	211,530	179	211,207	99.8%	54	1,180	4,883
Dallas	253	96,983	205	96,108	99.1%	51	469	2,237
St. Louis	256	113,285	151	111,949	98.8%	55	741	5,052

[a] primary diagnosis of respiratory disease (ICD-9 codes 460-486,493,786.07)

[b] Total ED visits are represented by ED visit number from the Complete ED Dataset

Abbreviations: ED, Emergency Department; ICD-9, International Classification of Diseases, 9th Revision; ZCTA, Zip Code Tabulation Area.

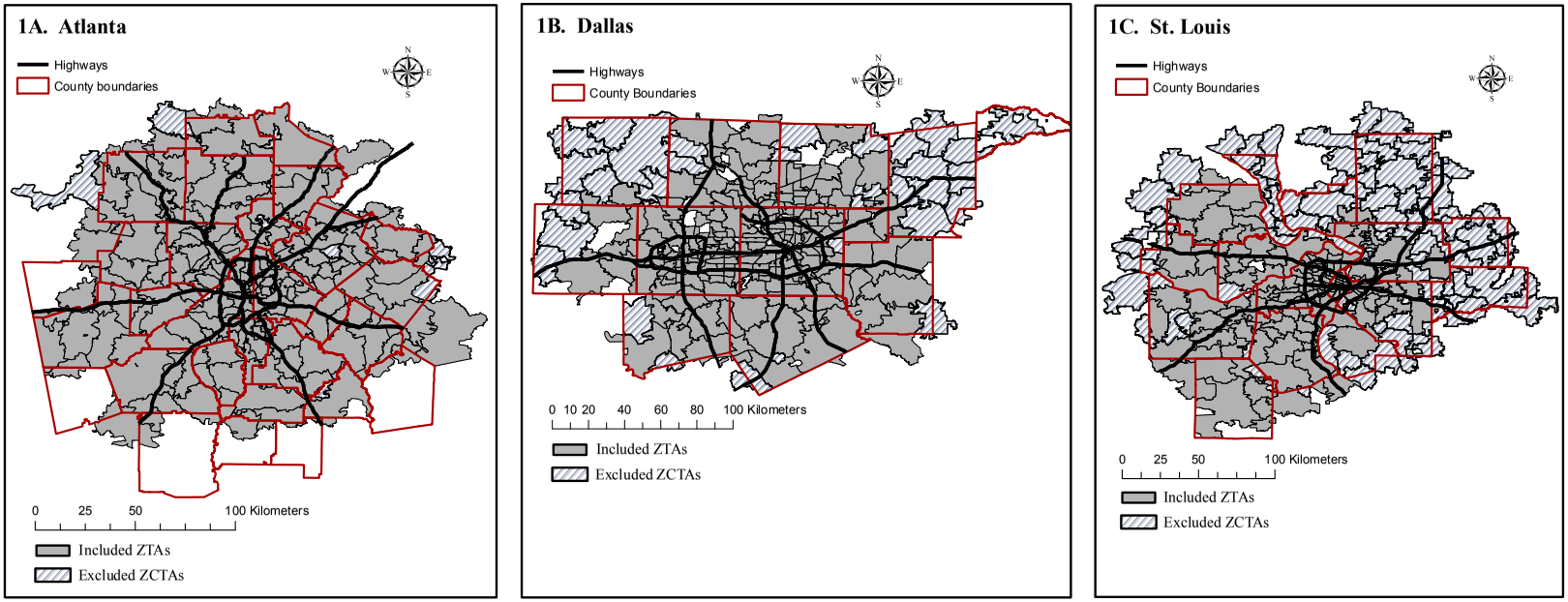


Figure 2.1: Study area maps for main analyses. Gray areas represent the ZCTAs included in analyses (≥ 50 respiratory disease ED visits). Hash mark areas represent excluded ZCTAs (< 50 respiratory disease ED visits). Figure 2.1A represents the Atlanta study area; Figure 2.1B represents the Dallas study area; Figure 2.1C represents the St. Louis study area. Abbreviations: ED, Emergency Department; ZCTA, ZIP Code Tabulation Area.

Epidemiological results: association between ozone and pediatric respiratory disease

The combined meta-regression, which pooled data from all three cities (535 ZCTAs), and city-specific meta-regressions, which pooled ZCTA-specific data from each city individually (179 ZCTAs in Atlanta; 205 ZCTAs in Dallas; and 151 ZCTAs in St. Louis), produced identical overall associations between ozone and pediatric respiratory disease. Ozone exhibited the strongest overall association with pediatric respiratory disease in Atlanta [(OR= 1.08 (95% PI = 1.06-1.11)], followed by Dallas [OR=1.04 (95% PI = 1.01, 1.07)] and St. Louis (OR=1.03 (95% PI= 0.99, 1.07)].

Epidemiological results: effect measure modification

Categorical effect modification

Categorical ZCTA-level variables were used in the second stage of our modeling approach to assess effect measure modification by neighborhood SES (undereducated area, poverty area, >90th percentile NDI). We did not observe differences in associations between ozone and pediatric respiratory ED visits by undereducated area status when using combined or city-specific models (Figure 2.2A). However, when assessing other indicators of neighborhood SES, we observed stronger associations between ozone and pediatric respiratory ED visits in poverty areas for all cities in both the combined and city-specific meta-regressions (Figure 2.2B) and stronger associations in areas designated as above the 90th percentile of the NDI with the exception of Dallas in city-specific models (Figure 2.2C). These differences in association between SES strata were not statistically significant; ORs in low SES groups had very wide posterior intervals resulting from very few ZCTAs designated as extremely low SES (Supplementary Table S2.1).

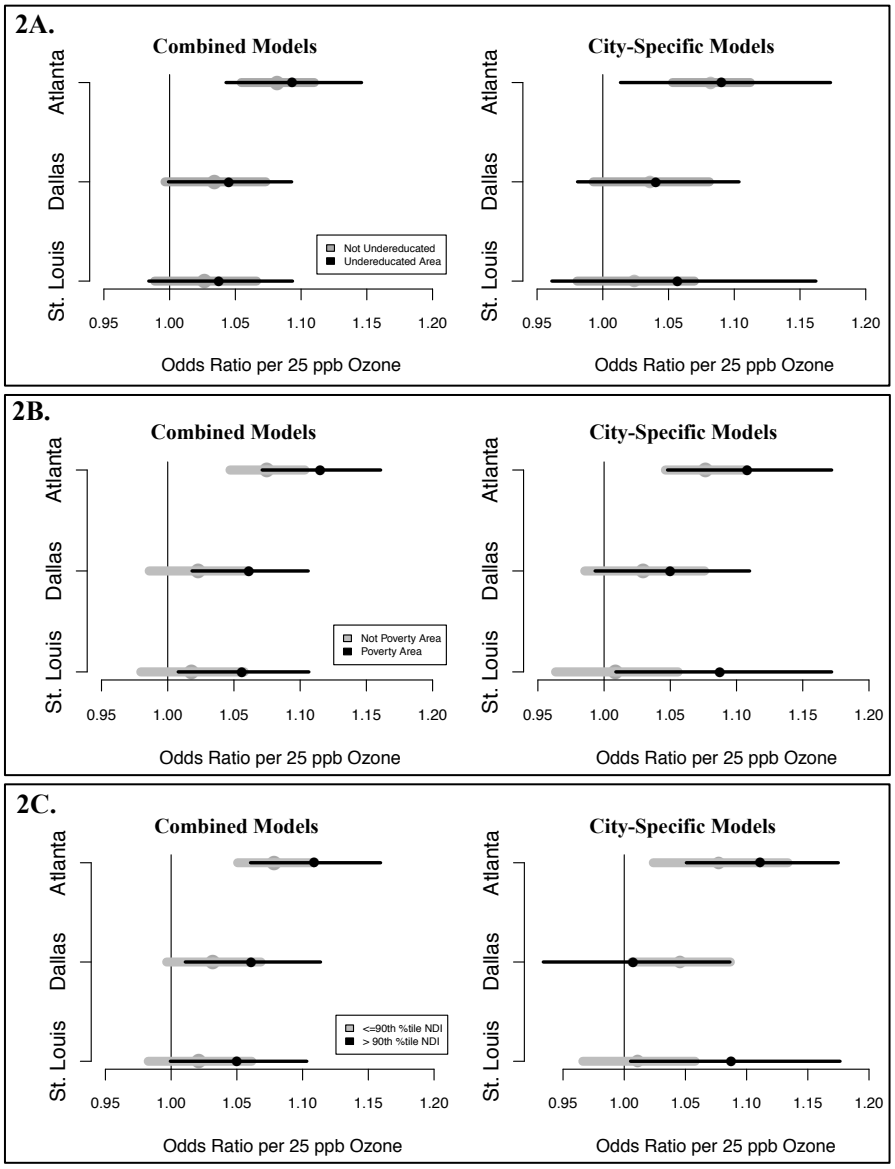


Figure 2.2: Effect modification by categorical indicators of neighborhood SES using combined and city-specific models. Figure 2.2A: association between ozone and pediatric respiratory ED visits in undereducated areas (low SES) and non-undereducated areas (high SES). Figure 2.2B: association between ozone and pediatric respiratory ED visits in poverty areas (low SES) and non-poverty areas (high SES). Figure 2.2C: association between ozone and pediatric respiratory ED visits in areas above the 90th percentile of the NDI (low SES) and in areas below the 90th percentile (higher SES). Odds ratios and 95% posterior intervals per 25 ppb ozone are presented. Black points and error bars represent ORs and 95% PIs in low SES areas; gray points and bars represent ORs and 95 % PIs in areas of higher SES. Undereducated areas: ≥ 25% the adult population (≥ 25 years old) with less than a 12th grade education. Poverty area: ≥ 20% households living below the Federal Poverty Line. Abbreviations: ED, Emergency Department; NDI, Neighborhood Deprivation Index; SES, socioeconomic status; ZCTA, Zip Code Tabulation Area.

Linear and non-linear effect modification

For each city, linear and non-linear effect modification by neighborhood SES was evaluated through the use of linear, quadratic, and cubic functions of % <12th grade education, % below poverty, and the NDI. We present results from combined and city-specific models for estimated ORs across the entire range of neighborhood SES values in each city; interpretations of these results were based on estimated ORs falling between the 2.5th and 97.5th percentiles of neighborhood SES due to data sparseness at the extremes of the SES distributions outside of these bounds.

In combined modes, estimated ORs tended to increase with decreasing SES, regardless of the continuous function specified in models (linear, quadratic, cubic); this pattern was observed across all SES indicators and in each city (Figure 2.3). In Atlanta, robust associations between ozone and pediatric respiratory disease were observed regardless of the socioeconomic environment in which children live. In Dallas and St. Louis, significantly positive estimated ORs were only observed in areas characterized as low to very low SES (i.e. above approximately 16% below poverty in Dallas and 20% below poverty in St. Louis). However, in many models specified with quadratic or cubic functions of SES we also observed a decrease in the magnitude of estimated ORs at the lowest extremes of the SES distribution (Figure 2.3).

In combined models, we found no evidence of linear effect modification by neighborhood SES, but found some evidence of non-linear effect modification. Specifically, the parameter estimate for the cubic function of the NDI was nearly significant at the 0.05 level (P = 0.052, 2-tailed) and the estimated mean ORs varied across NDI levels in a non-linear manner (Figure 2.3). Note that in combined models, the relative similarity across cities in linear and non-linear patterns of effect modification reflects the underlying assumption

that the effect of neighborhood SES on ozone-related respiratory disease is the same in each city. To assess deviation from this assumption, we also fit city-specific models (Supplementary Figure S2.2). In city-specific analyses, patterns of estimated ORs generally reflected those of the combined models, however, some qualitative differences were observed. The differences between combined and city-specific models were primarily observed when comparing the shape of the nonlinear curve from models fit with quadratic functions of neighborhood SES. For example, when combined and city-specific models were fit with quadratic functions of neighborhood SES, estimated ORs in Dallas followed an inverted U-shape across levels of SES that was not observed in the other cities; however, this pattern was much more dramatic in city-specific models compared to the combined model (Supplementary Figure S2.2).

Although our assessment suggested effect modification by neighborhood SES, inclusion of neighborhood SES in both combined and city-specific models did not substantively explain variability in the unobserved true effects of ozone across ZCTAs as measured by the between-ZCTA heterogeneity parameter, τ (results not shown); these findings imply unexplained heterogeneity across ZCTAs and warrant further inquiry.

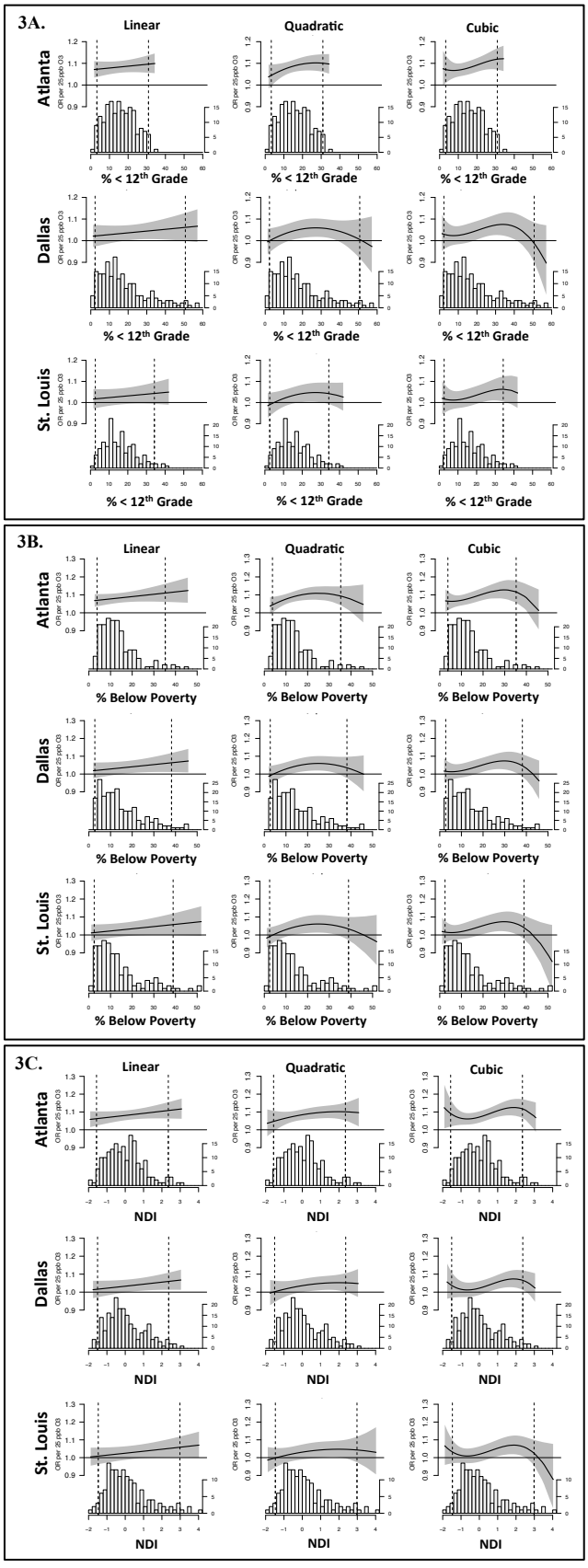


Figure 2.3: Associations between ozone and pediatric respiratory ED visits by continuous neighborhood SES. Combined meta-regressions were used to examine effect modification of the association between ozone and pediatric respiratory disease by neighborhood SES. Linear, quadratic, and cubic functions of % <12th grade education (3A), % below poverty (3B), and the NDI (3C) were included in combined meta-regressions to examine linear and non-linear effect modification. Solid black lines represent estimated ORs between ozone and pediatric respiratory disease ED visits by ZCTA-specific values of neighborhood SES. Gray polygons represent 95% PIs of the estimated ORs. Histograms below each plot represent the distribution of ZCTA-specific SES values in each city. Dotted black lines represent the 2.5th and 97.5th percentile values of neighborhood SES in each city. The y-axis scale on the right side of each graph represents the frequency count of ZCTAs.

Abbreviations: Abbreviations: ED, Emergency Department; NDI, Neighborhood Deprivation Index; OR, odds ratio; PI, Posterior Intervals; SES, socioeconomic status; ZCTA, Zip Code Tabulation Area. Plots adapted from R code available at http://www.ag-myresearch.com/lancet2015.html

Spatial mapping and risk visualization

To visually and qualitatively explore spatial patterning, we transferred estimated mean ORs from combined models that included cubic functions of the NDI (Figure 2.3C) onto spatial maps (Figure 2.4). The spatial maps presented in Figure 2.4 reveal strong spatial patterning of the ORs and this mapping exercise allowed us to qualitatively assess commonalities among cities. For example, ORs tended to be greater in areas clustered near urban centers and along major roadways, suggesting common areas of concern in each city. We also observed distinct patterns of clustering in each city (e.g. a cluster of high ORs in southwest St. Louis); these differences may be related to patterns of urban development and socio-demographic clustering unique to each city.

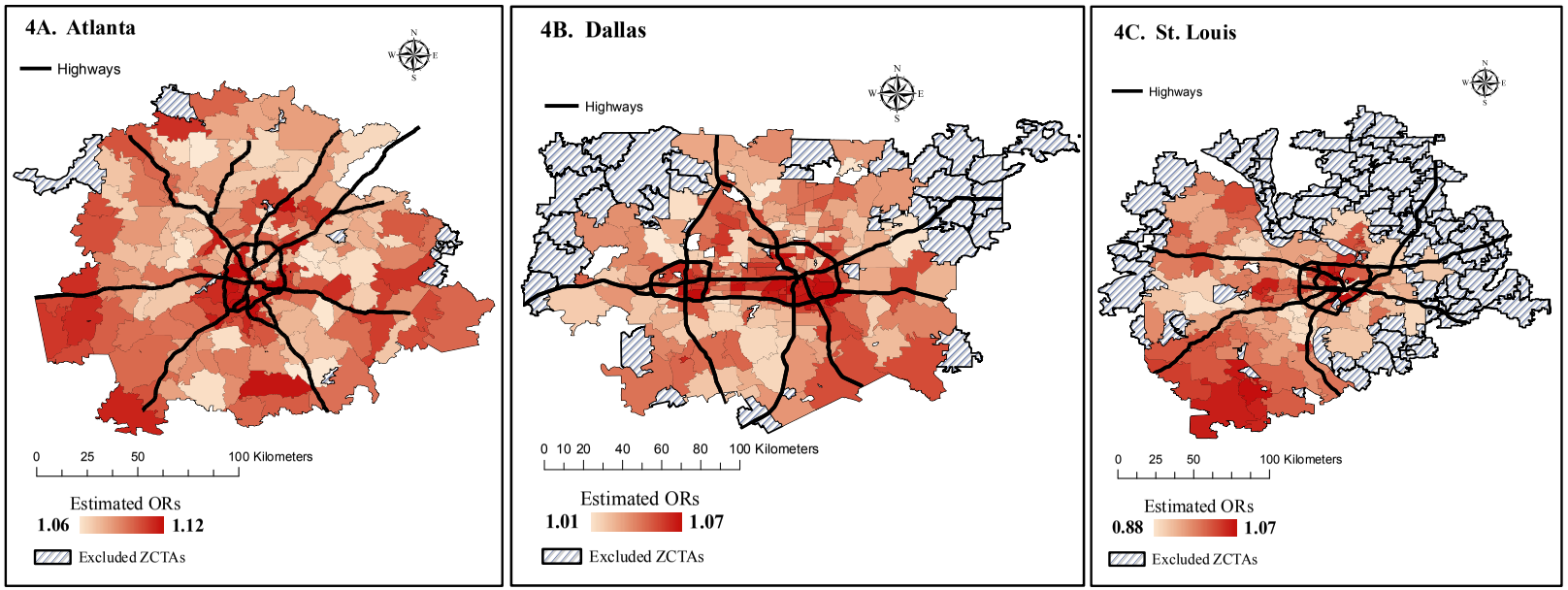


Figure 2.4: Spatial representation of estimated mean ORs accounting for ZCTA-specific NDI values in each city. In Figure 2.4, average ORs between ozone and respiratory disease accounting for ZCTA-specific NDI values were estimated for each ZCTA in Atlanta (4A), Dallas (4B), and St. Louis (4C) using a combined model that included a cubic function of the NDI. Abbreviations: NDI, Neighborhood Deprivation Index; OR, odds ratio; SES, socioeconomic status; ZCTA, ZIP Code Tabulation Area.

DISCUSSION

In this study, we assessed the short-term effects of ozone on respiratory ED visits among children in three US cities. We used a 2-stage Bayesian hierarchical approach to examine modification by neighborhood SES and we used information from three cities to improve the representativeness of our results. Our methodology is similar to previous work in this field, but extends that work in two key ways: (1) we specifically focused our meta-regression on ozone-related respiratory disease in the pediatric population, a subpopulation with known sensitivities; and (2) by pooling effects at the ZCTA-level (instead of the city or county-level as is commonly done,[17-21] we were able to quantitatively and qualitatively (through spatial mapping) assess socioeconomic influences at a finer scale resolution than was done previously. Our findings add new insights, and new questions, to the burgeoning knowledge base on neighborhood socioeconomic modifiers of air pollution-health effects.

In overall analyses we observed statistically significant associations between 3-day average concentrations of ozone and pediatric respiratory disease in Atlanta and Dallas. Associations were non-significant in St. Louis, but were similar in magnitude to observed associations in Dallas. These results and their respective magnitudes of association are in line with our previous findings from these cities [11, 16, 23, 24] and with work by others on ozone related respiratory disease.[31-34]

A primary objective of our study was to examine effect modification by neighborhood SES in each city and to evaluate whether patterns of effect modification differed by city. We primarily assessed effect modification through the use of combined meta-regressions that pooled information across ZCTAs in our three cities. By combining information from all ZCTAs we were able to more generally assess the presence of linear and non-linear effect modification across study areas. Another advantage of the combined model approach was

greater power to detect effect modification versus city-specific models that had fewer ZCTAs contributing data; however, combined models forced the effect of neighborhood SES on ozone-related respiratory disease to be uniform across all cities. Because neighborhood SES may represent a confluence of extrinsic vulnerability factors and because these factors may differ by city, this is a strong assumption and therefore we also fit city-specific models to assess this assumption. Comparison of results from combined and city-specific models did not yield substantially different interpretations; in fact, patterns of effect modification were largely similar across cities and observed differences could have been due to limited power in city-specific models as well as observed sensitivity of the city-specific models to sparse data at extreme values of neighborhood SES. Therefore, results from combined meta-regressions were used to facilitate interpretations.

In each city, results from combined meta-regressions fit with categorical SES indicators suggested stronger associations between ozone and pediatric respiratory disease in neighborhoods characterized as poverty areas and in neighborhoods above 90^{th} percentile values of the NDI. However, differences between groups were not statistically significant due to wide posterior intervals. Similar patterns were found in Atlanta and St. Louis in previous studies that examined neighborhood SES as a modifier of associations between air pollution and pediatric asthma.[12, 24, 35] When using % $<12^{th}$ grade to indicate SES we did not observe differences between strata, suggesting that observed effect modification depends on the way in which neighborhood SES is measured.

In combined meta-regressions fit with continuous values of neighborhood SES, we found some evidence of non-linear patterns of effect modification across levels of SES, particularly for the NDI; overall, these results reflected those observed with categorical indicators of SES in that ORs tended to increase with decreasing neighborhood SES. Our

investigation of modification by continuous SES also resulted in the following key observations: (1) we observed robust associations between ozone and pediatric respiratory disease in Atlanta regardless of the socioeconomic environment in which children live (i.e. nearly all ZCTA-specific ORs were significantly positive between the 2.5th and 97.5th percentiles of neighborhood SES). However, in both Dallas and St. Louis, significantly positive associations between ozone and pediatric respiratory disease were only observed in areas that are characterized as low to very low SES (i.e. between the 75th and 95th percentile of neighborhood SES); and (2) in some analyses we observed weak associations in the lowest SES neighborhoods [i.e., neighborhoods at or above the 95th percentile of % below poverty (the extreme right-tail of the SES distribution)].

Non-linear effect modification by continuous neighborhood SES has not been examined previously and findings from this study add to the knowledge base on neighborhood SES as a modifier of air pollution-respiratory disease associations among children. While stronger associations between ozone and respiratory disease have been consistently observed in children compared to adults,[2, 16, 34] the evidence on extrinsic factors (e.g. low socioeconomic status) and their potential to modify ozone-health associations is limited. A recent systematic review by Vinikoor-Imler et al. designates the weight of evidence, regarding neighborhood SES as a modifier as suggestive only, citing "inconsistencies within a discipline" or "lack of coherence across disciplines" as reasons for not being able to make more definitive inferences.[2] Our results suggest potential non-linearity in effect modification, different patterns of effect modification depending on choice of neighborhood SES indicator, and spatial patterning of risk. The non-linear patterns and different findings with different SES indicators may account for some of the inconsistencies observed in the studies reviewed by Vinikoor-Imler et al.

However, our results also raise additional questions worthy of investigation. For example, why are ORs weak in the lowest SES neighborhoods? These observations are in stark contrast with our intuition and belief that children from impoverished neighborhoods would be more vulnerable to the respiratory effects of ozone, compared to children living in wealthy neighborhoods. Our study is not designed to answer this question directly, but one possible reason for this observation may be that children living in wealthier neighborhoods have few component causes of air pollution-health effects; therefore, ozone has a substantial relative influence (i.e. a large piece of the 'causal pie') on air pollution-health associations[36]. Whereas children in living in lower SES neighborhoods may have a multitude of exposures that could exacerbate respiratory disease, and ozone is only one of many factors (i.e. exposure to ozone constitutes a small piece of the 'causal pie').

Another plausible reason for having observed weaker associations in low SES populations may be due to our use of multiplicative models and the mathematical scale of effect measures. While multiplicative models are used in the vast majority of air pollution-health studies,[3, 37] the true nature of the effect of ozone on ED visits may be additive. In our own data, we observed a marked increase in ED rates from high SES to low SES in each city and for each SES indicator (Figure 2.5). Assuming additive effects, low baseline risk could explain stronger relative effects of ozone in the highest SES populations and apparent weaker relative effects in the lowest SES populations.[12, 38] However, in many analyses we observed strong, positive associations in low SES areas, which may reflect supra-additive effects of SES and ozone.[12] While there are methods for estimating additive interaction based on results of multiplicative models (e.g. the Relative Excess Risk due to Interaction (RERI) and the Synergy Index), these methods cannot be straightforwardly applied to our models, and the validity of applying these methods to models with multiple covariates and a

continuous exposure is uncertain.

Another potential factor influencing observed associations is complex spatial patterning of respiratory disease risk and socioeconomic status. Our modeling approach enabled us to qualitatively assess similarities and differences in spatial patterning of ozone-health associations across cities by transferring estimated ZCTA-specific ORs onto a spatial canvas to visualize locations of low- and high-risk areas. Findings from this qualitative assessment show that spatial influences are apparent in each city. The observed clustering of health risk around urban centers and roadways (seen in all cities), as well as spatial patterning that is unique to each city, may partially account for the patterns of effect modification observed.

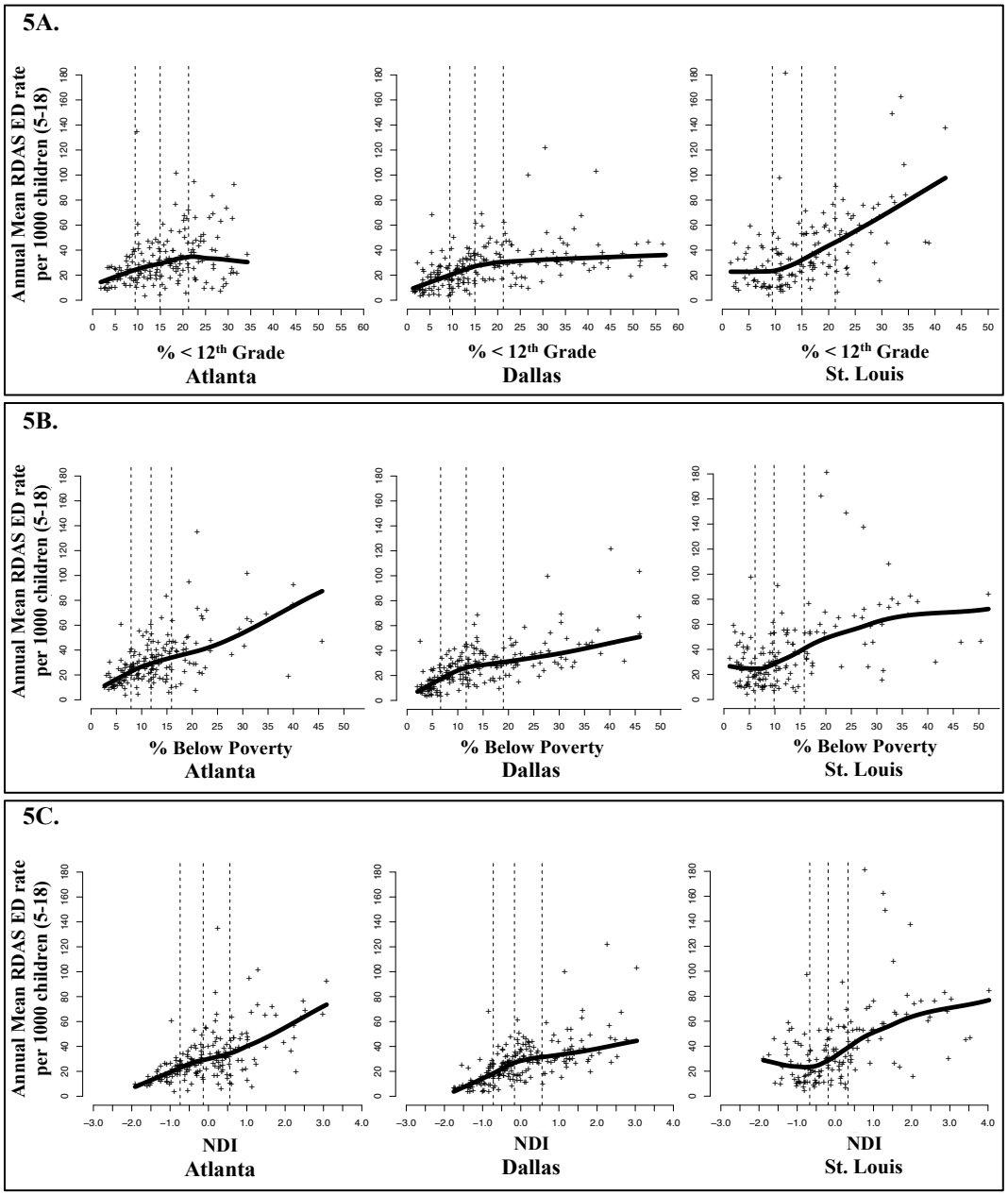


Figure 2.5: Annual mean pediatric respiratory disease ED visit rates by neighborhood SES for each ZCTA in Atlanta (2002-2008), Dallas (2006-2008), and St. Louis (2007-20008). Respiratory disease ED rates are reported per 1000 children (5-18 years old) and were calculated for each ZCTA by dividing the annual total number of respiratory disease ED visits by annual estimates of the 5-18 year old population for each year in the study period. Annual ED Rates were then averaged over the study period of each city. ED visit rates for each ZCTA are represented by the "+" symbol and shown in Figure 2.5A by percentage (%) of the adult population (≥ 25 years old) with less than a 12th grade education (% < 12th grade), in Figure 2.5B by % of households living below the federal poverty line (% below poverty), and in Figure 2.5C by the Neighborhood Deprivation Index (NDI). The solid black line represents local polynomial regression using weighted least squares to fit a line through the data. The dotted gray lines represent the 1st, 2nd, and 3rd quartile values of each SES indicator. In each panel and city, neighborhood SES decreases from left to right. Abbreviations: ED, Emergency Department; NDI, Neighborhood Deprivation Index; RDAS, respiratory disease; SES, socioeconomic status; ZCTA, ZIP Code Tabulation Area.

In our study, inclusion of neighborhood SES in models did not appear to significantly explain heterogeneity in ozone-related pediatric respiratory disease across ZCTAs. There are several limitations that could have contributed to this observation. First, by assessing neighborhood SES effects at the ZCTA level, we assumed that ZCTA boundaries are relevant socioeconomic environments with regards to air pollution vulnerability. However, previous studies using similar methods have only assessed city or county-level effects;[17-21] given that neighborhood SES often varies over smaller spatial scales than counties, our approach, which assessed neighborhood effects at the ZCTA-level, is an improvement over these previous studies. Second, we used neighborhood SES values that were averaged across the study periods to evaluate effect modification of ozone-health associations. While these averages accounted for any shifts in socioeconomic composition that may have occurred during the respective study periods of our three cities, use of these averages in epidemiologic analyses assumed that the SES of all ZCTAs were constant. Due to Dallas' relatively short study period, we expect this type of exposure misclassification to be less of an issue for Dallas than Atlanta or St. Louis. Finally, although we have large numbers of daily ED visits within each city, power to detect effect modification by socioeconomic factors may have been limited.

CONCLUSION

It is well established that ozone is a potent oxidizer and highly toxic to the epithelial cells of the entire respiratory tract. In toxicological studies, acute exposures to ozone induce transient physiological and biochemical changes while chronic exposures lead to cumulative damage or permanent decreases in airway function.[39] Continued efforts to better identify individual- and population-level vulnerabilities, while producing generalizable findings, are imperative.

Our findings suggest that neighborhood-level SES is a factor contributing short-term vulnerability to ozone-related pediatric respiratory morbidity in Atlanta, Dallas, and St. Louis. While nuanced relationships between neighborhood SES and ozone-respiratory health were observed in each city, overall findings were largely generalizable. Synthesizing our results from combined meta-regressions and taking into account the high baseline risk in low SES populations (Figure 2.5), we conclude that children living in low SES environments in Atlanta, Dallas, and St. Louis suffer from a higher burden of respiratory disease due to ozone compared to their counterparts living in wealthier SES neighborhoods.

REFERENCES

1. U.S. Environmental Protection Agency. Final report: Integrated science assessment of ozone and related photochemical oxidants. Washington, DC: U.S. Environmental Protection Agency, 2013.

2. Vinikoor-Imler LC, Owens EO, Nichols JL, et al. Evaluating potential response-modifying factors for associations between ozone and health outcomes: A weight-of-evidence approach. *Environ Health Perspect* 2014;122(11):1166-76.

3. Bell ML, Zanobetti A, Dominici F. Who is more affected by ozone pollution? A systematic review and meta-analysis. *Am J Epidemiol* 2014;180(1):15-28.

4. Bateson TF, Schwartz J. Children's response to air pollutants. *J Toxicol Environ Health A* 2007;71(3):238-43.

5. Makri A, Stilianakis NI. Vulnerability to air pollution health effects. *Int J Hyg Environ Health* 2008;211(3-4):326-36.

6. Klepeis NE, Nelson WC, Ott WR, et al. The national human activity pattern survey (nhaps): A resource for assessing exposure to environmental pollutants. *J Expo Anal Environ Epidemiol* 2001;11(3):231-52.

7. Adler NE, Newman K. Socioeconomic disparities in health: Pathways and policies. *Health Affairs* 2002;21(2):60-76.

8. Bernard P, Charafeddine R, Frohlich KL, et al. Health inequalities and place: A theoretical conception of neighbourhood. *Soc Sci Med* 2007;65(9):1839-52.

9. Krieger N, Williams DR, Moss NE. Measuring social class in us public health research: Concepts, methodologies, and guidelines. *Annu Rev Public Health* 1997;18:341-78.

10. Strickland MJ, Darrow LA, Klein M, et al. Short-term associations between ambient air pollutants and pediatric asthma emergency department visits. *Am J Respir Crit Care Med* 2010;182(3):307-16.

11. Tolbert PE, Mulholland JA, MacIntosh DL, et al. Air quality and pediatric emergency room visits for asthma in atlanta, georgia, USA. *Am J Epidemiol* 2000;151(8):798-810.

12. O'Lenick CR, Winquist A, Mulholland JA, et al. Assessment of neighborhood socioeconomic status as a modifier of air pollution-asthma associations among children in atlanta. *J Epidemiol Community Health* 2016;In Review.

13. Strickland MJ, Klein M, Flanders WD, et al. Modification of the effect of ambient air pollution on pediatric asthma emergency visits: Susceptible subpopulations. *Epidemiology* 2014;25(6):843-50.

14. Peel JL, Tolbert PE, Klein M, et al. Ambient air pollution and respiratory emergency department visits. *Epidemiology* 2005;16(2):164-74.

15. Darrow LA, Klein M, Flanders WD, et al. Air pollution and acute respiratory infections among children 0-4 years of age: An 18-year time-series study. *Am J Epidemiol* 2014;180(10):968-77.

16. Alhanti BA, Chang HH, Winquist A, et al. Ambient air pollution and emergency department visits for asthma: A multi-city assessment of effect modification by age. *J Expo Sci Environ Epidemiol* 2016;26(2):180-8.

17. Bell ML, Dominici F. Effect modification by community characteristics on the short-term effects of ozone exposure and mortality in 98 us communities. *Am J Epidemiol* 2008;167(8):986-97.

18. Dominici F, Samet JM, Zeger SL. Combining evidence on air pollution and daily mortality from the 20 largest us cities: A hierarchical modelling strategy. *Journal of the Royal Statistical Society: Series A (Statistics in Society)* 2000;163(3):263-302.

19. Levy JI, Diez D, Dou Y, et al. A meta-analysis and multisite time-series analysis of the differential toxicity of major fine particulate matter constituents. *Am J Epidemiol* 2012;175(11):1091-99.

20. Chen R, Kan H, Chen B, et al. Association of particulate air pollution with daily mortality: The china air pollution and health effects study. *Am J Epidemiol* 2012;175(11):1173-81.

21. Peng RD, Bell ML, Geyh AS, et al. Emergency admissions for cardiovascular and respiratory diseases and the chemical composition of fine particle air pollution. *Environ Health Perspect* 2009;117(6):957-63.

22. Sarnat SE, Winquist A, Schauer JJ, et al. Fine particulate matter components and emergency department visits for cardiovascular and respiratory diseases in the st. Louis, missouri-illinois, metropolitan area. *Environ Health Perspect* 2015.

23. Winquist A, Kirrane E, Klein M, et al. Joint effects of ambient air pollutants on pediatric asthma emergency department visits in atlanta, 1998–2004. *Epidemiology* 2014;25(5):666-73.

24. Winquist A, Klein M, Tolbert P, et al. Comparison of emergency department and hospital admissions data for air pollution time-series studies. *Environ Health* 2012;11(1):70.

25. Messer LC, Laraia BA, Kaufman JS, et al. The development of a standardized neighborhood deprivation index. *J Urban Health* 2006;83(6):1041-62.

26. Friberg MD, Zhai X, Holmes HA, et al. Method for fusing observational data and chemical transport model simulations to estimate spatiotemporally resolved ambient air pollution. *Environ Sci Technol* 2016;50(7):3695-705.

27. Strickland MJ, Darrow LA, Mulholland JA, et al. Implications of different approaches for characterizing ambient air pollutant concentrations within the urban airshed for time-series studies and health benefits analyses. *Environ Health* 2011;10:36.

28. Everson PJ, Morris CN. Inference for multivariate normal hierarchical models. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)* 2000;62(2):399-412.

29. Peng RD, Chang HH, Bell ML, et al. Coarse particulate matter air pollution and hospital admissions for cardiovascular and respiratory diseases among medicare patients. *JAMA* 2008;299(18):2172-79.

30. Dominici F, Peng RD, Bell ML, et al. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *JAMA* 2006;295(10):popost1127-34.

31. Villeneuve PJ, Chen L, Rowe BH, et al. Outdoor air pollution and emergency department visits for asthma among children and adults: A case-crossover study in northern alberta, canada. *Environ Health* 2007;6:40.

32. Choi M, Curriero FC, Johantgen M, et al. Association between ozone and emergency department visits: An ecological study. *Int J Environ Health Res* 2011;21(3):201-21.

33. Yang Q, Chen Y, Shi Y, et al. Association between ozone and respiratory admissions among children and the elderly in vancouver, canada. *Inhal Toxicol* 2003;15(13):1297-308.

34. Sacks JD, Rappold AG, Davis JA, Jr., et al. Influence of urbanicity and county characteristics on the association between ozone and asthma emergency department visits in north carolina. *Environ Health Perspect* 2014;122(5):506-12.

35. Sarnat SE, Klein M, Sarnat JA, et al. An examination of exposure measurement error from air pollutant spatial variability in time-series studies. *J Expo Sci Environ Epidemiol* 2010;20(2):135-46.

36. Rothman KJ. Causes. *Am J Epidemiol* 1976;104(6):587-92.

37. Bell ML, Zanobetti A, Dominici F. Evidence on vulnerability and susceptibility to health risks associated with short-term exposure to particulate matter: A systematic review and meta-analysis. *Am J Epidemiol* 2013;178(6):865-76.

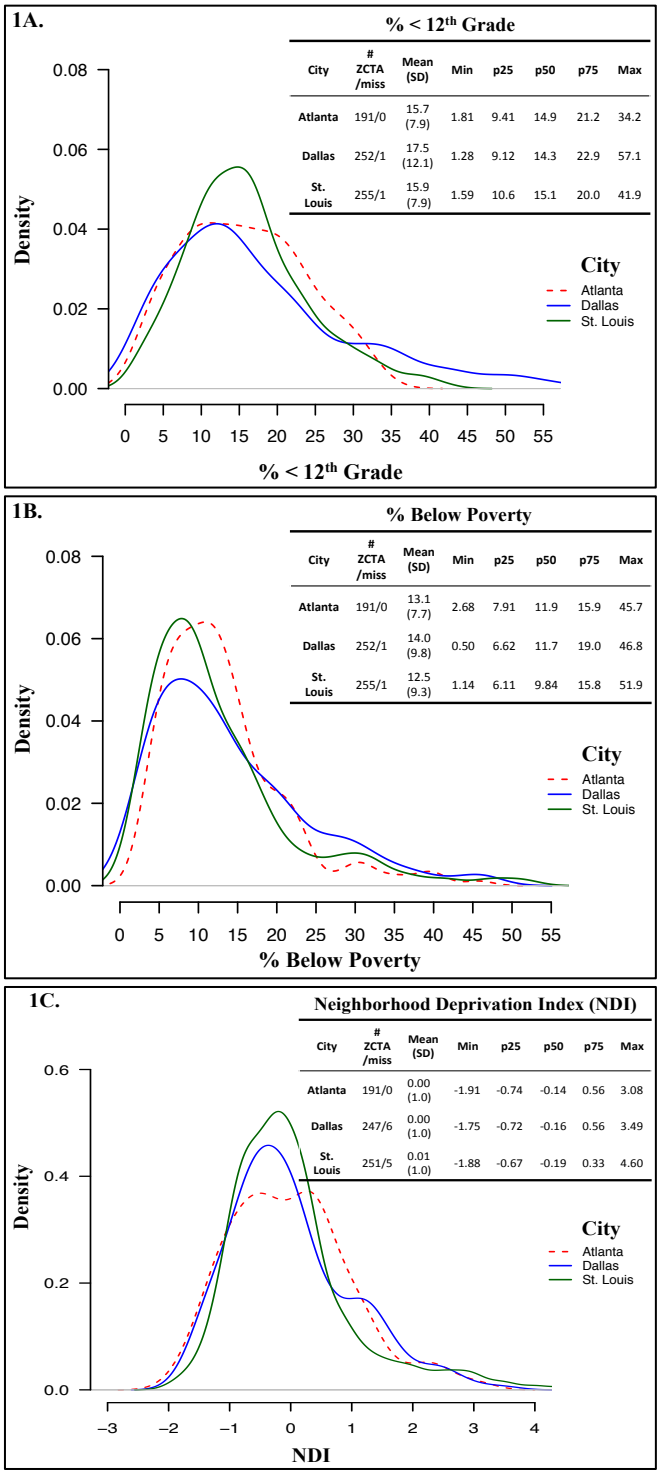
38. Burra TA, Moineddin R, Agha MM, et al. Social disadvantage, air pollution, and asthma physician visits in toronto, canada. *Environ Res* 2009;109(5):567-74.

39. Curtis D. Klaassen, Louis J. Casarett, Doull J. *Casarett and doull's toxicology : The basic science of poisons*. 8th ed: New York : McGraw-Hill Education, c2013.

SUPPLEMENTAL MATERIAL

Chapter 2: Ozone and childhood respiratory disease in three US cities: evaluation of effect measure modification by neighborhood socioeconomic status using a Bayesian hierarchal approach

Contents

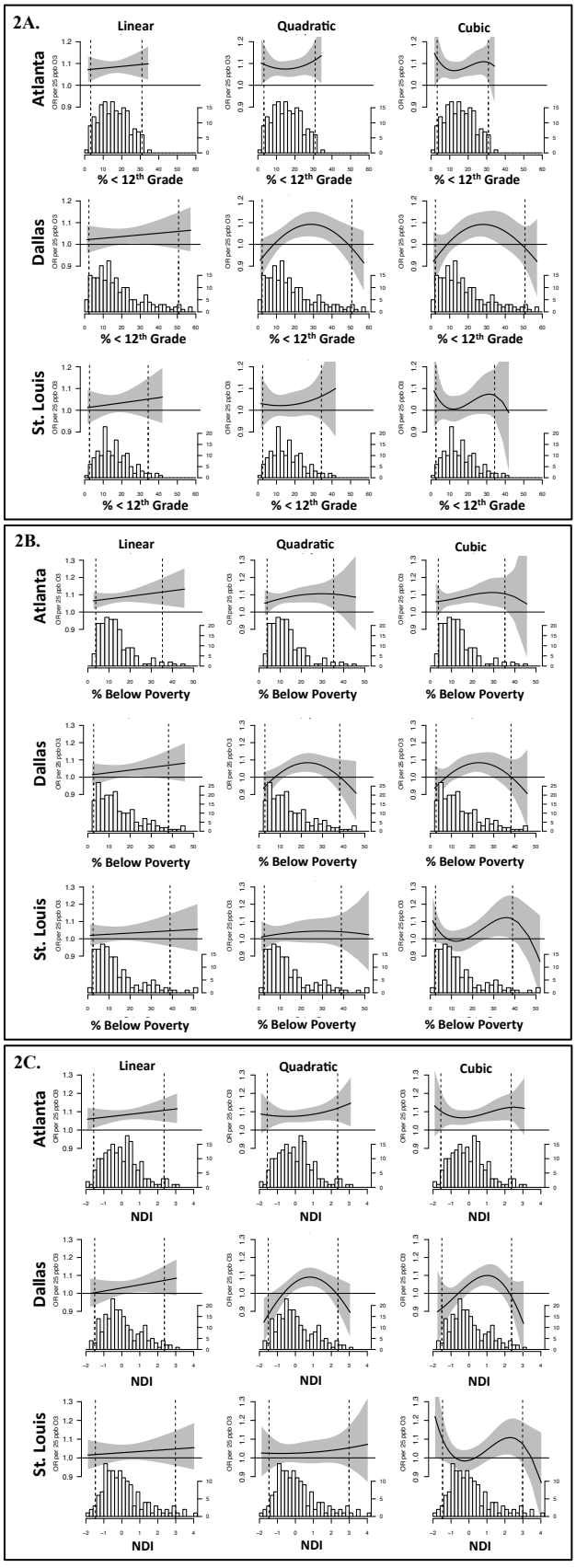


Supplemental Figure S2.1. Distribution and summary statistics of ZCTA-level SES for % below poverty (1A), % <12th grade education (1B), and the NDI (1C) in each city. Descriptive results include data from the complete ED database (data from all ZCTAs). Abbreviations: % <12th grade, percentage of the adult population (≥25 years old) with less than a 12th grade education; % below poverty, percentage of households living below the Federal Poverty Line; Max, maximum; Min, minimum; n miss., number missing; NDI, Neighborhood Deprivation Index; p25, 25th percentile; p50, 50th percentile (median), p75, 75th percentile; SD, standard deviation; SES, socioeconomic status, ZCTA, Zip Code Tabulation Area.

Supplemental Table S2.1. Number of respiratory disease ED visits and number of ZCTAs contributing data to high and low SES neighborhoods in each city[a]

			Undereducated Area (UA) Status		Poverty Area (PA) Status		Deprivation Area Status (≤ or > 90th %tile NDI)	
City	Metric	Total #	Not UA (high SES)	UA (low SES)	Not PA (high SES)	PA (low SES)	≤ 90th %tile NDI (high SES)	> 90th %tile NDI (low SES)
Atlanta	#ED visits	211,207	183,156	28,051	163,880	47,327	173,169	38,038
	#ZCTAs	179	155	24	153	26	162	17
Dallas	#ED visits	96,108	62,105	34,003	58,181	37,927	76,623	19,485
	#ZCTAs	205	158	47	155	50	182	23
St. Louis	#ED visits	111,949	92,261	19,688	80,236	31,713	82,739	29,210
	#ZCTAs	151	131	20	122	29	128	23

[a] Descriptive results limited to data from Analytical ED database (ZCTAs with at least 50 ED counts)



Supplemental Figure S2.2: Associations between ozone and pediatric respiratory ED visits by continuous neighborhood SES. City-specific meta-regressions were used to examine effect modification of the association between ozone and pediatric respiratory disease by neighborhood SES. Linear, quadratic, and cubic functions of % <12th grade education (2A), % below poverty (2B), and the NDI (2C) were included in city-specific meta-regressions to examine linear and non-linear effect modification. Solid black lines represent estimated ORs between ozone and pediatric respiratory disease ED visits by ZCTA-specific values of neighborhood SES. Gray polygons represent 95% PIs of the estimated ORs. Histograms below each plot represent the distribution of ZCTA-specific SES values in each city. Dotted black lines represent the 2.5th and 97.5th percentile values of neighborhood SES in each city. The y-axis scale on the right side of each graph represents the frequency count of ZCTAs.

Abbreviations: Abbreviations: ED, Emergency Department; NDI, Neighborhood Deprivation Index; OR, odds ratio; PI, Posterior Intervals; SES, socioeconomic status; ZCTA, Zip Code Tabulation Area. Plots adapted from R code available at http://www.ag-myresearch.com/lancet2015.html

CHAPTER 3

Evaluation of individual and neighborhood factors as modifiers of the association between warm-season temperature and pediatric asthma morbidity in Atlanta, GA

Cassandra R. O'Lenick, Andrea Winquist, Howard H. Chang, Michael R. Kramer, James A. Mulholland, Andrew Grundstein, Stefanie Ebelt Sarnat

ABSTRACT

Introduction. Previous studies have found associations between respiratory morbidity and high temperatures; however, few studies have explored associations in potentially sensitive subpopulations. **Methods.** We evaluated individual and neighborhood factors as modifiers of the association between warm-season (May-Sept.) temperature and pediatric respiratory morbidity in Atlanta during 1993-2012. We used emergency department (ED) visit data among 5-18 year-olds with a diagnosis of asthma or respiratory disease. Daily maximum temperature (Tmax) was acquired from the observing station at Atlanta Hartsfield International Airport. Poisson generalized linear models were used to estimate rate ratios (RR) between daily Tmax and asthma or respiratory disease ED visits, controlling for time and meteorology. Tmax was estimated for single-day lags of 0-6 days and modeled with cubic terms to allow for non-linear relationships. Effect modification by individual factors (race, sex, insurance status) and neighborhood socioeconomic status (SES; ZIP code levels of poverty, education, and the neighborhood deprivation index) was examined via stratification. **Results.** Estimated RRs for Tmax and pediatric asthma ED visits were positive and significant for lag days 0-4 and strongest on lag day 2 (RR=1.06, 95% CI: 1.03, 1.09 for a change in Tmax from 27 °C to 32 °C (25th to 75th percentile). We observed stronger RRs between Tmax and asthma among males compared to females, non-white children compared to white children, children with private insurance compared to children with Medicaid, and among children living in high compared to low SES neighborhoods, defined by poverty levels. Associations between Tmax and respiratory disease ED visits were weak and non-significant. **Conclusions.** Results suggest individual-level socio-demographic factors confer vulnerability to temperature-related pediatric asthma morbidity, and may aid in risk assessment and targeted prevention strategies.

INTRODUCTION

Global surface temperatures have risen steadily and rapidly for the past several decades, resulting in location-specific variation in ambient temperatures and more frequent episodes of extreme heat.[1, 2] Climate change is expected to cause higher warm-season ambient temperatures, especially in large metropolitan cities where temperatures are amplified by the urban heat island effect.[3-5] Although high ambient temperature is a well-documented cause of cardiorespiratory mortality, particularly among the elderly,[6-12] much less is known about the effects of high ambient temperature on respiratory morbidity and the influence of modifying factors among sensitive subpopulations remains largely unexplored.

Among the studies that have investigated high temperature-related respiratory morbidity, there is mounting epidemiologic evidence for a lagged effect of temperature[10, 13-17], and stronger associations among children and the elderly compared to other age groups[10, 14, 15, 18, 19]; several studies have also found that the effects of temperature on respiratory morbidity remain after controlling for ambient air pollution [10, 17, 20-22] suggesting a strong, independent effect of high temperature that does not only occur through the effect of air pollution. However, there is less agreement on whether thresholds or non-linear exposure-response functions exist regarding the effects of high temperature on respiratory outcomes[10, 16, 23]. Some studies have reported threshold or non-linear exposure-response functions[15, 18, 19, 22], while others have not [13, 20, 24, 25], and multi-city studies have reported heterogeneity in the exposure-response function between study areas.[18, 21]

Inconsistencies between studies may be due to a variety of factors including differences in the climate of the study area, different adaptive strategies employed in cities (e.g. high utilization of AC, cooling centers, early warning systems), differences in population-level acclimation to climate, and the use of disparate temperature metrics to capture exposure to

high ambient temperature (e.g. daily minimum temperature, daily mean temperature, daily maximum temperature, diurnal temperature ranges, heat waves, and heat stress indices).[23, 26] Despite a small body of literature, and some inconsistencies, commonalities among studies have emerged: (1) high temperatures are generally associated with increases in respiratory morbidity; (2) health impacts vary across population subgroups and study areas; (3) exposure-response functions may vary by location; and (4) children are among the most vulnerable.

Children are considered a susceptible population to respiratory morbidity due to higher ventilation rates, developing respiratory and immunological systems, and anatomically smaller peripheral airways that predispose children to airway inflammation and obstruction.[27-30] Children are also uniquely susceptible to the adverse health effects of temperature due to an underdeveloped thermoregulatory system that results in a diminished capacity to maintain optimal internal temperatures under heat stress.[31] Impaired thermoregulation and prolonged heat exposure can result in hyperthermia and lead to increases in core body temperature, systemic inflammation, protein damage, increased cardiac output, and increases in tidal volume, respiratory rate, and pulmonary ventilation[21, 31-33]. Additionally, inhalation of hot, humid air was shown to trigger bronchoconstriction in patients with mild asthma [34, 35] and airway hypersensitivity in toxicological studies.[36] Given the impacts of high temperature on lung function via hyperthermia and bronchoconstriction and the physiological susceptibility of children, exposure to high temperature poses a serious health concern for children, especially those with underlying diseases or vulnerabilities.

In addition to physiological factors, other intrinsic (e.g. sex, race) and extrinsic [e.g. socioeconomic status (SES), health care access] factors may confer susceptibility and

vulnerability to temperature related pediatric respiratory disease. Extrinsic factors can operate at multiple scales (such as the individual- or neighborhood-level); therefore, it is important for epidemiological studies, when feasible, to evaluate both individual- and neighborhood-level factors for their ability to modify temperature-respiratory health associations. Improved understanding of modifying factors will serve to enhance climate change adaptation efforts and help protect vulnerable populations from life-threatening environmental exposures. Furthermore, identification of vulnerable populations in large urban areas is critical: populations living in large metropolitan areas will be disproportionately impacted by climate change due to the urban heat island effect,[3-5] and emerging research has shown that sprawling cities, like Atlanta, are experiencing a rapid increase in the number of extreme heat events occurring annually (double the rate of increase observed in compact cities).[5, 17]

Our study builds on previous work in Atlanta from an extensive assessment of heat-related morbidity for 17 different health outcomes across 4 different age groupings (0-4 years, 5-18 years, 19-64, and >65)[17]. One sub-analysis of this comprehensive study identified positive and significant associations between high warm-season temperature and asthma ED visits among children, 5-18 years old; associations were non-significant across other age groupings[17]. Here, using a similar methodology, we focus on this previously observed association between high temperature and respiratory morbidity among children (5-18 years) to specifically examine the degree to which individual-level factors (sex, race/ethnicity, insurance status) and neighborhood (SES) modify associations, and to examine the non-linear effects of temperature across different modifying factors.

METHODS

Data sources

Hourly meteorological data for 20-county Atlanta for the period January 1, 1993 through December 31, 2012 were obtained from the automated surface observing station located at Atlanta Hartsfield International Airport. Hourly observations were used to create daily ambient meteorological metrics including daily maximum temperature and dew-point temperature (defined as the highest recorded hourly temperature or dew-point temperature in a 24 hour period), and daily total precipitation. We selected daily maximum temperature (in degrees Celsius, °C) as our primary exposure of interest based on our previous work[17] and use of this metric by others in related health studies.[26, 37-41]

Patient-level emergency department (ED) visit data for the period January 1, 1993 to December 31, 2012 were acquired from hospitals located within the 20-county metropolitan area of Atlanta; ED visit data from 1993-2004 were acquired directly from individual hospitals and ED data from 2005-2012 were acquired from the Georgia Hospital Association. Relevant data elements included admission date, age, sex, race/ethnicity, method of ED visit payment, ZIP code of patient residence, and International Classification of Diseases, 9th Revision (ICD-9) diagnosis codes. ED visits for asthma were identified using primary ICD-9 diagnosis codes for asthma (493.0–493.9) or wheeze (786.07) and ED visits for respiratory disease were identified using primary ICD-9 codes 460-466, 477, 480-486, 491-493, 496, 786.07, which indicated diagnoses of upper respiratory infections, bronchiolitis, pneumonia, chronic obstructive pulmonary disease, asthma, and wheeze. Data were restricted to the pediatric population (5–18 years old) and to patients with a residential ZIP code located wholly or partially in 20-county Atlanta. Data were aggregated to daily counts of asthma and respiratory ED visits by strata defined by individual factors [sex,

race/ethnicity, insurance status (a proxy for individual-level SES)] and neighborhood SES variables of interest. The Emory University Institutional Review Board approved this study and granted exemption from informed consent requirements.

Neighborhood SES was evaluated using census data at the ZIP code level. To create spatial scales compatible with census based data, each ZIP code in the ED visit database was assigned to a 2010 Zip Code Tabulation Area (ZCTA, Census Bureau boundaries, created from census blocks to approximate ZIP codes). Assignments were accomplished by matching each ZIP code to a 2010 ZCTA based on 5-digit ZCTA ID numbers. ZIP code change reports helped facilitate ZCTA assignments for 31 ZIP codes that were altered or eliminated during the study period. ZCTAs that represented locations of businesses, P.O. boxes, and university campuses were excluded from the study. The resulting study area included 191 ZCTAs in Atlanta.

ZCTA-level (neighborhood) SES was estimated from the 1990 US Census long form, the 2000 US Census long form, and the American Community Survey (ACS) 5-year (2007-2011) summary file, all normalized to 2010 ZCTA borders ("The Time-Series Research Package", GeoLytics, Inc., East Brunswick, NJ, 2013). We estimated annual values of neighborhood SES between 1993 and 2006 by linear interpolation of Census 1990, Census 2000, and ACS 2007-2011 data. Neighborhood SES from 2007-2012 was estimated using only ACS 2007-2011 data. To represent neighborhood-level SES we chose percentage of the population (≥25 years old) with less than a 12^{th} grade education (% < 12^{th} grade), percentage of households living below the poverty line (% below poverty), and the Neighborhood Deprivation Index (NDI), a composite index comprised of five socio-demographic domains (income/poverty, education, employment, housing, and occupation) that were summarized with principle components analysis.[42] The 1990 Census did not include all of the variables

that constitute the NDI; therefore, ED visit data from 1993-1999 were assigned NDI values based on data from the 2000 Census.

Statistical analyses

Poisson generalized linear models were used to estimate associations between daily maximum temperature and daily counts of pediatric asthma or pediatric respiratory disease ED visits. All analyses were restricted to the warm-season, defined here as May through September, and daily maximum temperature values were estimated for single-day lags of 0-6 days. Poisson models were fit with cubic functions of maximum temperature (using a combination of linear, squared, and cubic terms) to allow for non-linear relationships. Associations between maximum temperature and ED visits were assessed for lag days 0 to 6, using separate models for each lag day and for each health outcome (asthma or respiratory disease). Models accounted for Poisson overdispersion, and included additional control for days with any precipitation (yes/no) and maximum dew-point temperature using cubic terms at the same lag period as maximum temperature. Time-varying factors were controlled for using indicator variables for day of the week, holidays, periods of hospital participation, year of the study period, year-specific linear trend of day-of-year, and a cubic spline for day of the warm season with monthly knots to control smoothly for time-trends.

In stratified analyses, we evaluated whether individual factors (sex, race/ethnicity, and insurance status) or neighborhood SES modified associations between maximum temperature and pediatric respiratory morbidity. For the individual factors, daily ED visit counts were aggregated for the following strata: male or female sex; white or non-white race (a consolidated category that included African American, Hispanic, and other race/ethnicity); and private insurance or Medicaid insurance. ED visit records with missing

information on sex, race/ethnicity, or insurance status were excluded from these analyses, and ED visits paid by worker's compensation or paid for directly by the patient were also excluded from analyses examining modification by insurance status. For neighborhood SES, daily ED visit counts were aggregated for strata based on several *a priori* cut-points of continuous ZCTA-level education, poverty, and NDI values including median, tertile, quartile, and 90th percentile cut-points.

For all models, we estimated rate ratios (RR) and 95% confidence intervals (CI) for changes in maximum temperature relative to a maximum temperature value of 27 °C, the 25th percentile value of daily maximum temperature during the study period. The primary temperature increment evaluated was 27-32 °C, representing an interquartile range increase in maximum temperature from the 25th to 75th percentile; other temperature increments were considered for evaluating non-linearity in effects. RRs for a given temperature relative to 27°C were estimated by contrasting linear, squared, and cubic terms of the chosen maximum temperature value to the referent value. Evidence of significant effect modification by individual factors and neighborhood SES was assessed by estimating the degree of heterogeneity between stratum-specific RRs in pairwise comparisons for the primary temperature increment (27-32 °C).[43] All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) and R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Descriptive results

During 1993-2012, year-round daily maximum temperatures ranged from -7.80 °C to 40.6°C and were highly correlated with maximum dew-point temperature (Spearman's ρ of 0.89, Table 3.1). Monthly average distributions of maximum temperature from 1993 to 2012 indicated that the 5 warmest months in Atlanta were May to September, defined here as the warm-season, with peak temperatures observed in July and August (Figure 3.1). During the warm-season, maximum temperature values ranged from 13.3 °F to 40.6 °C (Table 3.1); previous findings in Atlanta reported no apparent trend in daily warm-season maximum temperature from year to year between 1993 and 2012.[17]

Our warm-season health outcome database included 1,528,145 total ED visits among children aged 5-18 years with 51,360 ED visits for asthma and 161,301 ED visits for respiratory disease during the years 1993-2012 in 20-county Atlanta (191 ZCTAs). Although nearly all asthma ED visits recorded information on patient sex and insurance status (missing for <1% and 5% of ED visits, respectively), approximately 50% of ED visits did not have information on race/ethnicity; this was primarily due to complete missingness of race/ethnicity data from 2007-2009 (Table 3.2). A greater number of ED visits were made by male compared to female children, non-white compared to white children, and children paying for their visit using Medicaid compared to private insurance (Table 3.2).

Table 3.1: Descriptive statistics for relevant meteorological metrics, Atlanta 1993-2012

Meteorological Metrics	# days*	Mean	SD	Min	p25	p50	p75	Max	Spearman Correlations		
									Tmax	Tdmx	Precip
Max temperature, °C (year-round)	7,305	22.1	8.35	-7.80	16.1	23.3	28.9	40.6	1.00	0.84	-0.08
Max dew-point temperature, °C (year-round)	7,305	12.8	8.47	-17.2	7.20	15.0	20.0	28.0		1.00	0.23
Total daily precipitation, mm (year-round)	7,305	4.62	15.2	0.00	0.00	0.00	1.00	290			1.00
Max temperature, °C (warm season)	3,060	29.4	3.71	13.3	27.2	30	32.0	40.6	1.00	0.47	-0.18
Max dew-point temperature, °C (warm season)	3,060	19.6	3.57	2.20	17.8	20.6	22.2	28.0		1.00	0.32
Total daily precipitation, mm (warm season)	3,060	4.84	16.0	0.00	0.00	0.00	1.00	290			1.00

* Number of days for which temperature data was available

Abbreviations: #, number; max, maximum; min, minimum; SD, p25, 25th percentile; p50, 50th percentile; p75, 75th percentile; precip, total daily precipitation; standard deviation; Tdmax, daily maximum dew-point temperature °C; Tmax, daily maximum temperature °C

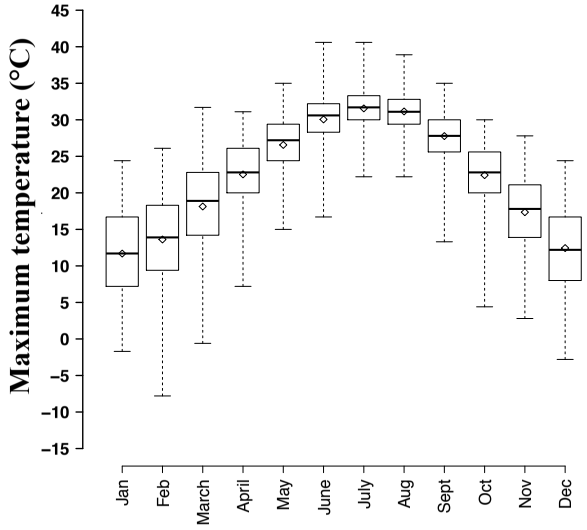


Figure 3.1. Monthly distribution of maximum temperature values during 1993-2012. Each box represents the distribution of daily maximum temperature values by month across all years. Solid black lines represent 50th percentile values and hollow diamonds represent monthly means. Boxes represent the 25th to 75th percentile values of maximum temperature and whiskers range from minimum to maximum values for each month.

Table 3.2. Summary of Emergency Department Visit Data and Visits Stratified by Response Modifying Factors, Warm Season, 1993-2012

				Asthma/wheeze[a]		Respiratory disease[b]		All ED visits	
	Stratification Criteria	SES category	# Days	Total # ED visits	Mean # ED visits/day	Total # ED visits	Mean # ED visits/day	Total # ED visits	Mean # ED visits/day
Overall	N/A	-	3,060	51,360	16.8	161,301	52.7	1,528,145	499
Sex	Female	-	3,060	20,000	6.54	78,057	25.5	726,290	237
	Male	-	3,060	30,929	10.1	81,601	26.7	785,842	257
Race / Ethnicity[c]	White	-	2,601[c]	6,552	2.52	33,125	12.7	445,333	171
	Non-white	-	2,601 [c]	19,771	7.60	58,366	22.4	466,356	179
Insurance status	Private	High SES	3,060	18,489	6.04	54,767	17.9	658,815	215
	Medicaid[d]	Low SES	3,060	23,536	9.94	75,049	32.3	564,737	260
% < 12th grade*	≤16.6%	High SES	3,060	30,258	9.89	91,620	29.9	923,210	302
	<16.6%	Low SES	3,060	21,102	6.90	69,681	22.8	604,935	198
% below poverty*	≤10.2%	High SES	3,060	18,150	5.93	59,631	19.5	684,636	224
	<10.2%	Low SES	3,060	33,210	10.9	101,670	33.2	843,509	276
NDI*	≤ -0.08	High SES	3,060	19,955	6.52	66,050	21.6	751,075	245
	< -0.08	Low SES	3,060	31,405	10.3	95,251	31.1	777,070	254

Abbreviations: % <12th grade, percentage of the adult population (≥25 years old) with less than a 12th grade education; % below poverty, percentage of households living below the Federal Poverty Line; #, number; ED, emergency department; NDI, Neighborhood Deprivation Index; SES, socioeconomic status

[a] primary diagnosis of asthma/wheeze (ICD-9 codes 493.0–493.9/786.07)

[b] primary diagnosis of respiratory disease (ICD-9 codes 460-486, 493.0–493.9,786.07)

[c] Race/ethnicity data completely missing during 2007-2009

[d] Medicaid category included ED visits paid for by Medicaid insurance

* Categorized by median values of continuous neighborhood SES

During our study period, socioeconomic composition of the population varied widely across the 191 Atlanta ZCTAs (e.g., in 2010, % below poverty varied from 1.66% to 45.5%) and large variability was observed consistently during each year of our study period (Figure 3.2). Between 1993 and 2012, maximum and mean values of % <12th grade education declined, indicating an increase in educational attainment for Atlanta neighborhoods during our study period (Figure 3.2). Conversely, mean values of neighborhood % below poverty increased from 1993 to 2012, suggesting, on average, an increase over time in the number of households in Atlanta neighborhoods that were living in poverty (Figure 3.2). Across indicators of neighborhood SES, we observed moderate-correlations between % <12th grade education and the other SES indicators, and high-correlation between % below poverty and the NDI (Spearman's ρ>0.87), suggesting that % below poverty and the NDI describe similar SES constructs and have similar spatial patterning (Table 3.3).

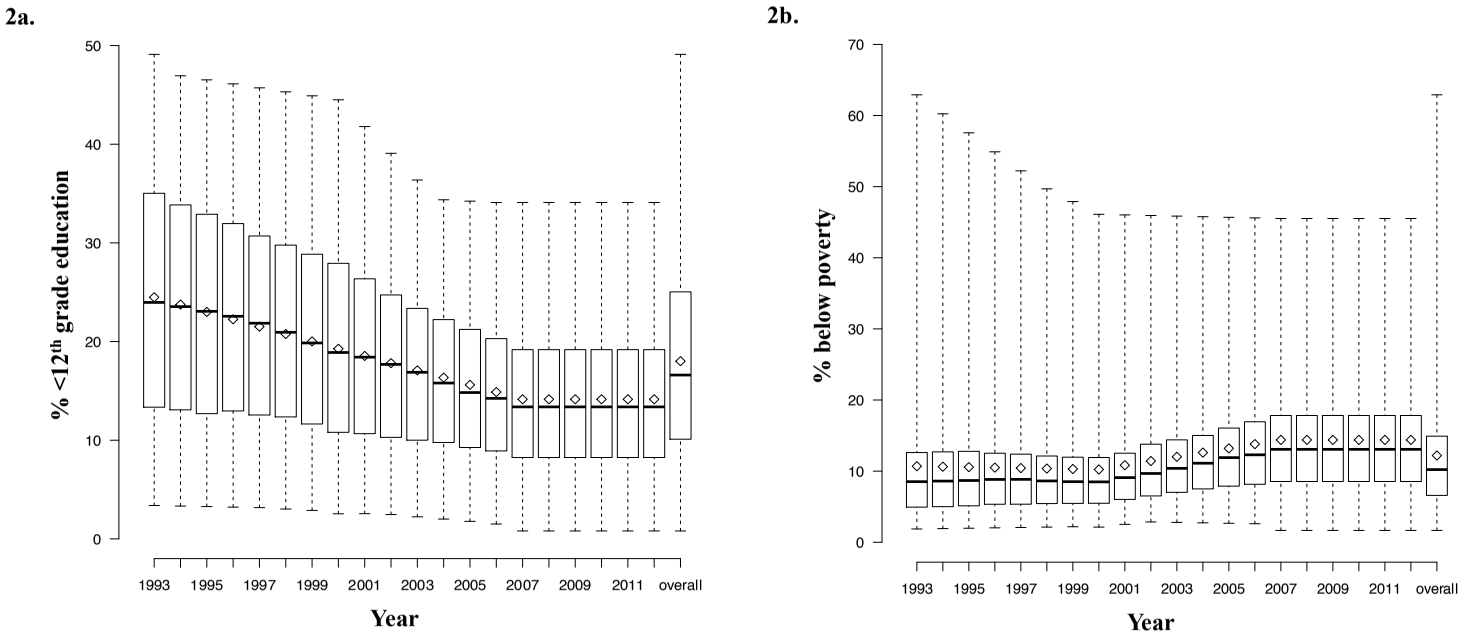


Figure 3.2. Distributions of yearly neighborhood SES values by year and overall distributions across all years during 1993-2012. Boxes represent the 25th to 75th percentile values of % <12th grade education (2a) and % below poverty (2b) by year and overall across all years. Solid black lines represent 50th percentile values and hollow diamonds represent means. Whiskers range from minimum to maximum values within a given time period.

Table 3.3. Summary of Neighborhood Socioeconomic Status Data during 1993-2012 for all ZCTAs (n=191) in Atlanta[a]

Neighborhood SES Metrics	Mean	SD	Min	p25	p50	p75	p90	Max	Spearman Correlations		
									% <12th grade	% below poverty	NDI
% < 12th grade education	18.0	9.96	0.80	10.1	16.6	25.0	32.1	49.1	1.00	0.49	0.72
% below poverty	12.2	8.19	1.66	6.59	10.2	14.9	22.0	62.9		1.00	0.87
NDI	0.00	15.2	-2.00	-0.76	-0.08	0.55	1.28	3.71			1.00

[a] Data are summarized across all Atlanta ZCTAs (n=191) and across all years of the study period (1993-2012)

Abbreviations: % <12th grade, percentage of the adult population (≥25 years old) with less than a 12th grade education; % below poverty, percentage of households living below the Federal Poverty Line; Max, maximum value; Min, minimum value; NDI, Neighborhood Deprivation Index; p25, 25th percentile; p50, 50th percentile; p75, 75th percentile; SD, standard deviations; SES, socioeconomic status

Overall associations

Associations between maximum temperature and pediatric respiratory morbidity for lag days 0 to 6 are reported in Table 3.4. Significant associations between maximum temperature and pediatric asthma ED visits were observed across lag days 0-5, with the strongest association observed on lag day 2 [RR = 1.059 (95% CI: 1.030, 1.088) for an increase in maximum temperature from 27 °C to 32 °C]. Associations between maximum temperature and pediatric respiratory disease ED visits were weak and non-significant for all lag days examined.

Table 3.4: Associations between maximum temperature and pediatric respiratory outcomes on lag days 0 to 6 per increase in maximum temperature from 27 °C to 32 °C

Tmax	Asthma[a] ED			Respiratory Disease [b] ED		
Lag day	**RRs**	**95% CI**		**RRs**	**95% CI**	
0	1.037	1.006	1.069	1.008	0.988	1.029
1	1.043	1.014	1.073	0.997	0.978	1.016
2	1.059	1.030	1.088	1.008	0.990	1.027
3	1.058	1.030	1.088	1.006	0.987	1.024
4	1.038	1.010	1.067	0.987	0.970	1.006
5	1.037	1.009	1.065	0.988	0.970	1.006
6	1.025	0.997	1.053	0.989	0.971	1.007

[a] primary diagnosis of asthma/wheeze (ICD-9 codes 493.0–493.9/786.07)
[b] primary diagnosis of respiratory disease (ICD-9 codes 460-486, 493.0–493.9,786.07)
Abbreviations: RR, rate ratio; CI, confidence interval; Tmax, daily maximum temperature °C

Effect modification

For all analyses examining effect modification, we focused on results for lag day 2 (Figures 3.3-3.5); results for lag days 0 to 6 are presented in the Supplemental Material. Unless otherwise noted, stratum-specific RRs are scaled to an increase in maximum temperature from 27°C to 32°C.

Effect modification: Individual factors

Analyses stratified by sex (male verses female) suggested somewhat stronger associations between maximum temperature and asthma ED visits in males compared to females for lag days 0 to 4 [e.g. lag 2 RR among males = 1.064 (95% CI: 1.029, 1.100); lag 2 RR among females = 1.054 (95% CI: 1.015,1.095)] (Figure 3.3a, Supplemental Figure S3.1a); however,

confidence intervals were wide and the differences in RRs between strata were not significant at the 0.05 level. Similarly, associations between maximum temperature and pediatric respiratory disease ED visits did not differ by patient sex, and associations among both males and females were non-significant for all lag days (Figure 3.3b, Supplemental Figure S3.1b).

In analyses stratified by race/ethnicity (white verses non-white), results suggested stronger associations between maximum temperature and asthma ED visits in non-white children compared to white children for lag days 0 to 3 (Supplemental Figure S3.1a), with near significant (P=0.07) differences in RRs between strata on lag day 2 suggesting potential effect modification of temperature-related asthma by race/ethnicity (Figure 3.3a). We did not find evidence that race/ethnicity modified the association between maximum temperature and respiratory disease. Note that significant associations between temperature and respiratory disease were observed within each race stratum for lag days 0-3 (Supplemental Figure S3.1b); these observations were different from the weak overall associations we observed between maximum temperature and pediatric respiratory disease ED visits (Table 3.4) and are likely due to missingness among the race data in the later time period of our study (our data on race/ethnicity was more complete prior to 2007). In sensitivity analyses, we observed stronger associations between maximum temperature and respiratory outcomes (asthma and respiratory disease) in the years prior to 2007 (e.g., for respiratory disease ED visits prior to 2007, lag 2 RR = 1.052 (95% CI: 1.030,1.075 per 27-32 C increase) compared to the later time period (for respiratory ED visits between 2007-2012, lag 2 RR = 0.961 (95% CI: 0.931, 0.992). Although the reason for attenuated RRs in the later time period is unknown, these findings agree with previous findings from Atlanta[17].

Results from analyses stratified by insurance status (private insurance verses Medicaid insurance) showed consistently stronger associations between maximum temperature and respiratory outcomes in children whose ED visit was paid by private insurance compared to those who used Medicaid insurance [e.g. for asthma, lag day 2 RR by private insurance = 1.095 (95% CI: 1.053,1.140); lag day 2 RRs by Medicaid = 1.064 (95% CI: 1.007, 1.075)] (Figures 3.3a-3.3b). This pattern was observed consistently across all lag days and significant differences between strata were detected (Supplemental Figure S3.1), suggesting insurance status modifies the effect of maximum temperature on asthma and respiratory disease among children.

To visualize the non-linear effects of maximum temperature and assess differences in the shape of maximum temperature effects across individual factors, we also estimated RRs and 95% CIs for several temperature changes from a reference maximum temperature of 27 °C. Maximum temperature changes of -8 °C to +10 °C relative to 27 °C were chosen to capture values between the 1st and 99th percentiles of the maximum temperature distribution during our study period and represent a temperature range of 19 °C to 37 °C. Through this assessment we observed striking differences in the shape of the effect of maximum temperature on asthma and respiratory disease, particularly when stratifying by race/ethnicity and insurance status (Figures 3.3c-3.3d; Supplemental Figure S3.2). These graphs illustrate distinct, stratum-specific relationships with maximum temperature and, for some comparisons (i.e. white versus non-white race), differences between strata were more apparent at the lower and upper temperature extremes compared to mid-range temperatures, as represented by the main 27-32 °C (25th-75th percentile) increment for example.

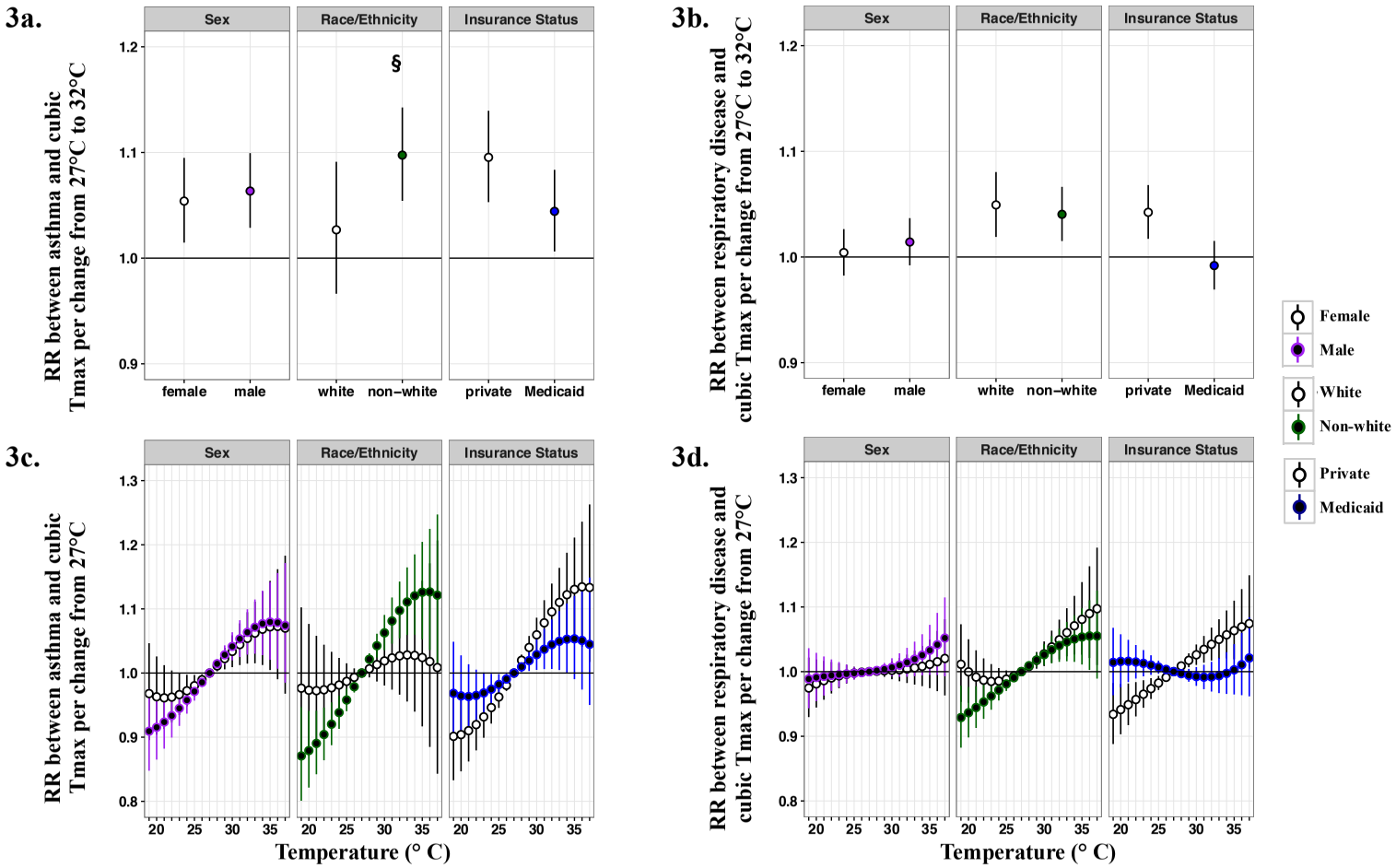


Figure 3.3. Estimated RRs and 95% CIs between maximum temperature at lag 2 and asthma and maximum temperature at lag 2 and respiratory disease stratified by individual factors. Figure 3.3a represents associations between maximum temperature (Tmax) at lag 2 and asthma across individual factors for a change from 27°C to 32°C. Figure 3.3c shows the non-linear effects of Tmax at lag 2 on pediatric asthma across individual factors by graphing associations for a given temperature relative to 27°C. Figure 3.3b and 3.3d represent associations between Tmax at lag 2 and pediatric respiratory disease across individual factors for a given change in Tmax relative to 27°C. * indicates significant statistical difference (two-sided $P < 0.05$) from referent group (i.e. female sex, white race, or private insurance) and § indicates $P = 0.07$ for test of significant difference from referent group.

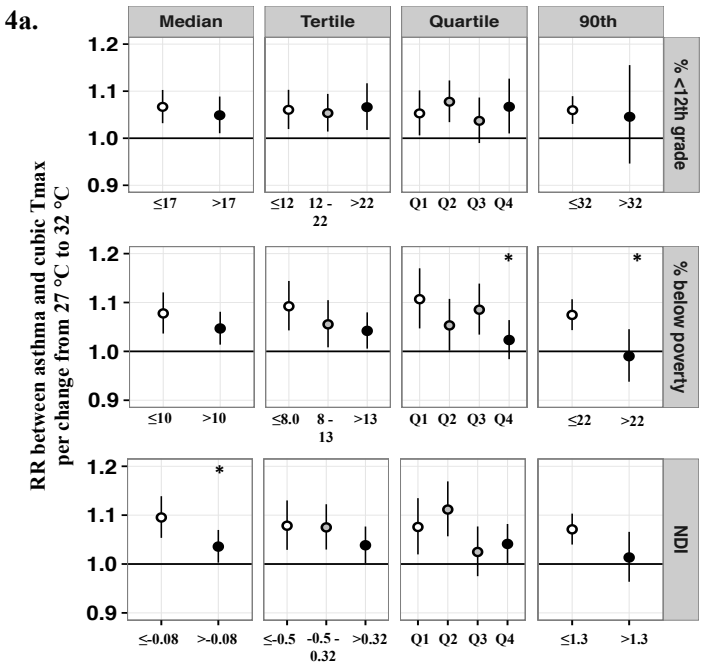
Effect modification: Neighborhood SES

Neighborhood SES was examined for its potential to modify associations between maximum temperature and pediatric respiratory outcomes. In general, observed patterns of effect modification (determined by differences between strata per change in maximum temperature from 27°C to 32°C) were consistent across stratification criteria (median, tertile, quartile, or 90th percentiles values of continuous neighborhood SES), indicating that models stratified by median SES values sufficiently captured patterns of effect modification observed across other stratification approaches (lag day 2 results presented in Figure 3.4; results for all lag days presented in Supplemental Figures S3.3-S3.5).

However, effect modification was inconsistently observed depending on the choice of SES indicator. For example, when examining effect modification by gradations of % < 12th grade as an indicator of neighborhood SES, magnitudes of associations between maximum temperature and pediatric respiratory outcomes (asthma and respiratory disease) were very similar across all strata, demonstrating no modification by %<12th grade (Figures 3.4a-b; 3.5a-5b). Conversely, when neighborhood SES was characterized by % below poverty or the NDI, we observed weaker associations between maximum temperature and respiratory outcomes among children living in low SES neighborhoods compared to children living in areas of higher SES (Figures 3.4a-b; 3.5a-b). This pattern was observed for both asthma and respiratory disease and across most lag days (Supplemental Figures S3.3-S3.5).

In models stratified by median values of neighborhood SES, we also graphed the non-linear effects of maximum temperature by plotting RRs and 95% CIs per maximum temperature changes of -8°C to +10°C relative to 27°C for each strata (maximum temperature range of 19°C to 37°C). The shape of the maximum temperature-response function differed between high and low SES strata when neighborhood SES was defined by

% below poverty or the NDI, and differences in RRs between strata increased at higher increments in maximum temperatures compared to the 27 C reference (Figures 3.5c-3.5d).



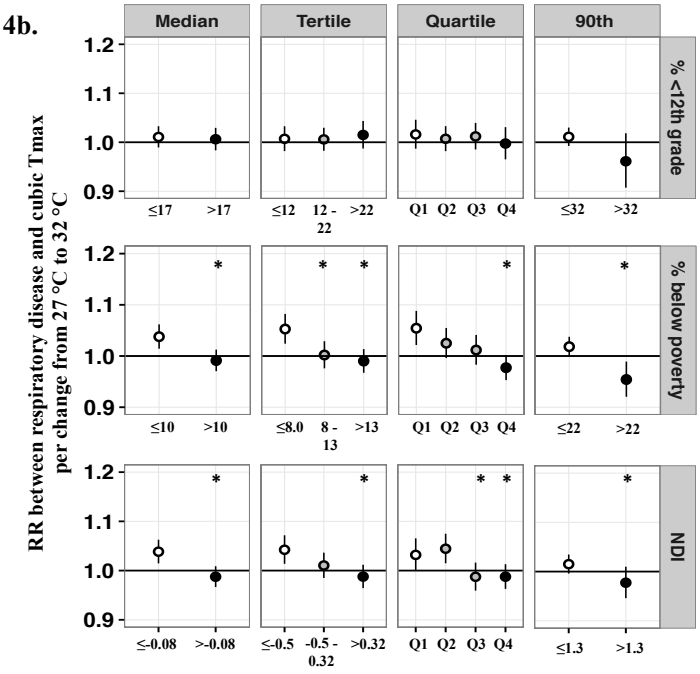


Figure 3.4. Associations and 95% CIs between maximum temperature at lag 2 and asthma and maximum temperature at lag 2 and respiratory disease stratified by categories of neighborhood socioeconomic status. Figure 3.4a represents associations between maximum temperature (Tmax) at lag 2 and pediatric asthma across SES strata for a change from 27°C to 32°C. Figure 3.4b represents associations between maximum temperature (Tmax) at lag 2 and pediatric respiratory disease across SES strata for a change from 27°C to 32°C. * indicates significant statistical difference (two-sided $P < 0.05$) from referent group (i.e. the highest SES strata). Quartiles values are reported in Table 3.3. Abbreviations: CI, confidence interval; SES, socioeconomic status; Tmax, daily maximum temperature.

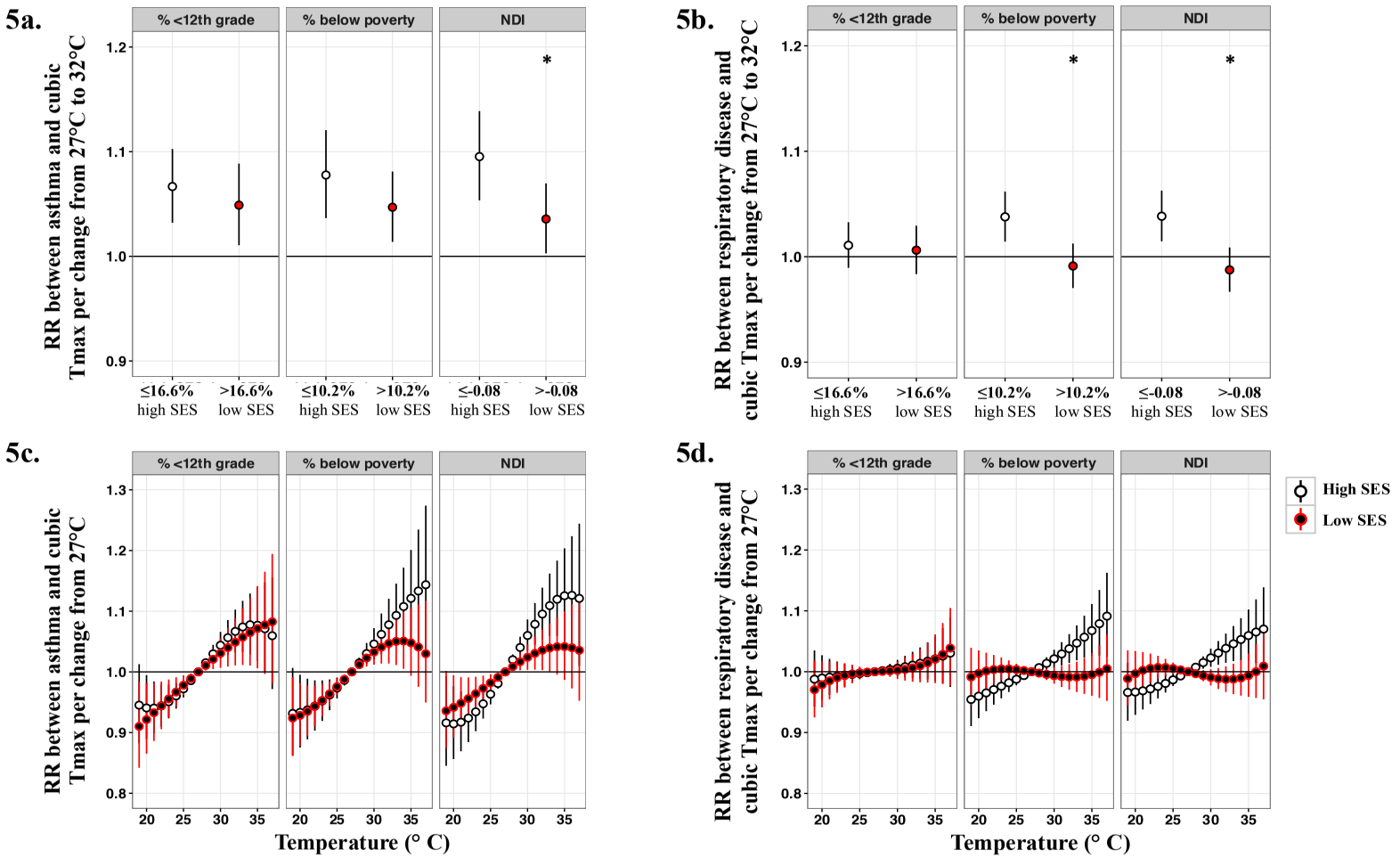


Figure 3.5. Associations and 95% CIs between maximum temperature at lag 2 and asthma and maximum temperature at lag 2 and respiratory disease stratified by median values of neighborhood socioeconomic status. Figure 3.5a represents associations between maximum temperature (Tmax) at lag 2 and asthma across SES strata for a change from 27°C to 32°C. Figure 3.5c shows the non-linear effects of Tmax at lag 2 on pediatric asthma across SES strata by graphing associations for a given temperature relative to 27°C. Figure 3.5b and 3.5d represent associations between Tmax at lag 2 and pediatric respiratory disease across SES strata for a given change in temperature relative to 27°C. ***** indicates significant statistical difference (two-sided $P < 0.05$) from referent group ('high SES').

DISCUSSION

In this 20-year time-series study, we evaluated the short-term effects of maximum temperature on respiratory ED visits among children in Atlanta, and assessed the degree to which individual or neighborhood factors act as effect modifiers. Only a few studies have examined vulnerability to temperature-related respiratory outcomes among children and our findings add to the small, yet growing body of literature on climate-related health effects among sensitive subpopulations.

In overall analyses, we found significant associations between maximum temperature and pediatric asthma ED visits across several lag days. Conversely, we observed weak, non-significant associations between maximum temperature and pediatric respiratory disease. Observed differences in effect across these health outcomes may be due in part to greater specificity of the asthma/wheeze health outcome compared to general respiratory disease, which included upper respiratory infections, bronchiolitis, pneumonia, COPD, asthma, and wheeze. Previous studies have also reported larger magnitudes of associations between temperature and asthma/wheeze compared to other respiratory outcomes.[17, 20, 21] Studies exploring the mechanistic causes of temperature-related respiratory morbidity suggest that inhalation of hot air activates airway sensory nerves, the cholinergic reflex pathway, and transient bronchoconstriction[34, 35]; therefore, it is possible that asthma/wheeze and related cough disorders may have a more direct relationship with high temperature compared to other respiratory illnesses such as upper or lower respiratory infections.

We found a lagged effect of high ambient temperature on asthma, with the strongest associations observed on lag days 2 and 3. Previous studies have also reported lagged effects for temperature-related respiratory morbidity[10, 13-17, 20]; plausible reasons for a lagged

effect include delayed onset of respiratory symptoms, failed attempts at personal management of respiratory symptoms, reduced access to health care for some of our ED population, and/or the concurrence of high maximum temperatures during the day with relatively high ambient minimum temperatures at night, (i.e. a narrow diurnal temperature range), preventing adequate physiological thermoregulation and recovery from high daytime temperatures.[10, 31]

A primary objective of this study was to identify susceptibility and vulnerability factors among children in relation to temperature and respiratory health. In stratified analyses, we evaluated both individual- and neighborhood-level factors for their ability to modify associations because these factors can operate at multiple scales and predispose children to temperature-related respiratory disease due to differences in airway physiology, immunological responses, time-activity patterns, cultural practices (e.g. burning of incense indoors), differential indoor and outdoor exposures, and/or reduced access to adequate health care[28, 44-49],

Effect modification by individual-level factors

At the individual-level, we examined potential effect modification by sex, race/ethnicity, and insurance status (a proxy for individual-level socioeconomic status). When assessing modification of temperature-related asthma by sex, we observed significant RRs among males for lag days 0-4, while RRs were typically weaker and non-significant among females on the same lag days; however, these differences in effect between males and females were not statistically significant. Previous studies focusing on temperature-related pediatric respiratory health have also reported slightly stronger effects between temperature and respiratory symptoms among male children compared to female children.[15, 20] Male

children may be more susceptible to respiratory morbidity due to sex differences in airway maturation and function (young males tend to have greater airway resistance), a greater propensity for atopy, differences in immunological function, and time-activity patterns that increase their exposure to environmental triggers.[50-52] While physiological differences and gendered behaviors may confer vulnerability among young males, distinguishing sex effects among children is challenging due to changes in lung development and pubertal maturation that occur with age and differ by sex.[51, 52] For example, young males have more physiological disadvantages than young females, but these disadvantages are less apparent by adolescence and by adulthood women may have greater physiological susceptibility.[50, 51] Given little evidence in the literature on the potential for modification of temperature-respiratory morbidity by sex, and the analytical difficulties of examining a sex effect among children, additional studies examining modification by sex are needed.

When we stratified models based on patient race/ethnicity (white or non-white), we found suggestive evidence that race/ethnicity modifies associations between temperature and asthma ED visits, with stronger RRs observed among non-white compared to white children. Similar findings have been observed in other temperature-health studies[22, 53-56] and previous research in Atlanta has reported similar findings concerning modification by race/ethnicity of air pollution related-health effects.[57] Our results lend further support to findings across multiple disciplines that report non-white race as a risk factor for adverse health outcomes. Although the underlying etiology of effect modification by race/ethnicity is unclear, racial/ethnic differences of home environments (e.g. pets, environmental tobacco smoke, incense burning), and racial/ethnic differences in adherence to medication and/or asthma control may be contributing factors to the observed vulnerability to temperature-related asthma morbidity in this study.[58-61]

To examine effect modification by individual-level SES, we used the patient's insurance status as a proxy for household SES. Children were considered from a low SES household if their ED visit was paid using Medicaid insurance and from a high SES household if their ED visit was paid with private insurance. In stratified analyses, we observed statistically stronger associations between temperature and respiratory outcomes (asthma and respiratory disease) among children whose visits were paid through private insurance (high SES) compared to children whose visits were paid through Medicaid for changes in maximum temperature from 27°C to 32°C, indicating evidence of effect modification by insurance status. Because Medicaid eligibility in Georgia is based on family size and income limits at or below the Federal Poverty Line (https://dch.georgia.gov/eligibility-criteria-chart), we assumed that individual-level health insurance status is a meaningful indicator of low household socioeconomic status for children, and we assumed it would have been directly related to a child's vulnerability through reduced access to health care, medications, or healthy food options. However, our findings suggested otherwise. Interestingly, similar findings were reported in a comprehensive study examining effect modification of nitrogen dioxide (NO_2)-related asthma exacerbation by insurance status and race[62]. In that study, Grineski *et al.* disaggregated insurance status into three categories: private insurance, Medicaid, and no insurance. They found significantly lower relative risks to NO_2-related asthma, among children on Medicaid compared to children on private insurance,[62] and significantly greater relative risks among uninsured children compared to those using Medicaid or private insurance. Grineski *et al.* also examined the combined modifying effect of race and insurance status, and reported no racial disparities in the effect of air pollution among children on Medicaid, but did find racial disparities in the effect of air pollution among children on private insurance. Their findings may be due to differences in asthma control among

children with private insurance, and/or due to the possibility that some children have more barriers to adequate health care despite being insured. Due to low numbers of ED visits we were unable to estimate associations by race and insurance status. However, in light of the findings by Grineski *et al.,* our results may have been more interpretable had we been able to disaggregate our ED data further, exploring associations among the uninsured population and distinguishing insurance status based on race/ethnicity.

Further disaggregation by race and insurance status would have also enabled us to better understand why the directionality of the race/ethnicity effect seems to be in conflict with that of the insurance status effect given that non-white race was associated with Medicaid insurance in our population [i.e. associations between high temperature and asthma ED visits were stronger among non-white children compared to white children, while associations between high temperature and asthma ED visits were stronger among children on private insurance (high SES children), compared to children on Medicaid insurance (low SES children)]. Although our study cannot directly address this discrepancy, the racial composition of our ED data may be partially responsible for the observed patterns of effect modification: non-white children accounted for approximately 85% of asthma ED visits paid by Medicaid insurance and approximately 61% of asthma ED visits paid by private insurance. If racial disparities in exposure-response relationships are not apparent among children on Medicaid insurance, but are apparent among children on private insurance, as suggested by Grineski *et. al.*, then having a majority of non-white children among our private insurance subgroup could have driven the stronger associations observed within this strata compared to the Medicaid strata. Note, that we are only able to assess racial composition across insurance status categories for asthma ED visits with information on race/ethnicity and insurance status (about 50% of asthma ED visits).

Effect modification by neighborhood-level SES

We also explored the influence of low SES at the neighborhood level by characterizing neighborhood (ZCTA) of patient residence by gradations of neighborhood % <12th grade education, % below poverty, and the NDI. There was no evidence that associations varied across SES strata based on gradations of %<12th grade. However, when using % below poverty and the NDI to indicate neighborhood SES, we observed weaker associations among children living in low SES compared to high SES ZCTAs, regardless of the stratification approach used (e.g. median, tertile, quartile, and 90th percentiles). These results echoed our findings of effect modification by insurance status, an indicator of individual-level SES. With regard to data source, indicators of individual SES and neighborhood SES were completely independent in these analyses and yet the same patterns of effect modification were observed. If being insured through Medicaid is a good proxy for individual low SES and if the ZCTA-level is a suitable scale to assess the social environment of one's neighborhood then the similarities in effect modification (i.e. weak associations in low SES populations) for both individual and neighborhood level SES effects lend strength to our findings, especially given that observed modification was not in the expected direction (i.e. we would have expected to observe stronger associations in low SES groups). We did not have sufficient power to stratify on both individual and neighborhood SES, and as such it is unclear whether neighborhood SES, individual SES, or a joint effect of both were drivers of the observed modification.

Although weaker associations in low SES populations run counter to our belief that children from impoverished households or neighborhoods would be more vulnerable to the respiratory effects of temperature, similar patterns of effect modification (or no evidence of effect modification) have been observed in air pollution-health studies. [63-74] Plausible

reasons for observing weaker associations among low SES populations compared to high SES populations include 1) complex spatial patterning of health risk and neighborhood level SES; 2) the possibility that single measures of SES are poor proxies for nuanced home or neighborhood socioeconomic environments; 3) the use of multiplicative models on health outcomes that tend to have differing baseline risks across socioeconomic subpopulations (i.e. asthma); and 4) children from wealthier households or living in wealthier neighborhoods may have few component causes of respiratory morbidity; therefore, temperature would have a substantial relative influence (i.e. a large piece of the 'causal pie').[75] Children from low SES households or living in low SES neighborhoods may have many different exposures that could exacerbate respiratory disease; in this context, high ambient temperatures may only be one of many contributing factors, thus exerting little relative influence on respiratory morbidity (i.e. a small piece of the 'causal pie').

While, these myriad reasons may limit the interpretability of our results on SES effect modification, acknowledging them can be useful for informing future research and understanding inconsistent findings already reported in the literature. Based on our results, future studies could consider (1) modeling temperature-health effects on the additive scale, (2) evaluating individual and neighborhood effects within the same model, (3) examining effect modification by multiple indicators of SES, including composite indices, and (4) using health, exposure, and socioeconomic data with enhanced spatial resolution.

A major contribution of this study was our examination of the non-linear effect of maximum temperature on health associations across individual- and neighborhood-level factors. By plotting a continuum of effect estimates relative to a reference value we observed differences in the shape of the maximum temperature-morbidity functions across strata of sex, race/ethnicity, insurance status, and neighborhood SES. Although we did not test for

statistical differences between strata along the entire range of the non-linear maximum temperature curve, differences in estimated RRs between strata of individual factors were greater at low and high ambient temperature extremes, while differences in RRs between neighborhood SES strata were greater at high ambient temperature extremes.

Our ability to examine modification by individual and neighborhood SES factors was facilitated by the long 20-year study period, and rich, patient-level data. However, there are several limitations that we took into consideration when interpreting results. First, daily maximum temperature data were only available at the city-level and may have induced exposure misclassification error. However, a recent study found that models using non-spatially resolved temperatures were equally as good as spatiotemporal models at estimating associations between daily temperature and mortality.[76] Second, we did not include control for air pollution in our temperature-health models; by not controlling for air pollution, our RRs represent the total effect of maximum temperature, including that which may be mediated by air pollution or aeroallergens[77]. However, previous studies by our research group[17] and others[10, 20-22] have shown that control for air pollution made a nominal impact on effect estimates, usually increasing the magnitude of the temperature effect. Third, 50% of our ED visit data were missing information on race/ethnicity which may have severely limited the interpretability and generalizability of the observed pattern of effect modification. Forth, by assessing neighborhood SES effects at the ZCTA level, we assumed that ZCTA boundaries were relevant socioeconomic environments. However, other scales may also be relevant, and the relevance of specific scales may vary by geographical location due to regional patterns of urban development.[78] Fifth, SES variables were not available for every year of our study period and in some cases we had to impute SES data from later time periods; these imputed data would not be able to capture important shifts in

socioeconomic composition that may have occurred during the study period. Finally, although we had large numbers of daily ED visits during our 20-year study period, we had limited power to assess individual and neighborhood factors in models together.

CONCLUSION

As warm season temperatures rise due to climate change, populations living within large, sprawling metropolitan areas, like Atlanta, will become exceedingly exposed and vulnerable to high temperatures. Our results demonstrate that short-term exposures to maximum temperature significantly increase pediatric asthma ED visits in Atlanta, and observed lagged (delayed) effects suggest that health impacts can be observed for several days after exposure to high temperatures. We also identified race/ethnicity and insurance status as potential vulnerability factors at the individual-level. At the neighborhood level, results suggest that neighborhood-level SES (specifically poverty-related SES) is a factor contributing short-term vulnerability to temperature-related pediatric asthma in Atlanta. However, it is unclear whether neighborhood effects were influenced by individual-level SES effects (indicated by insurance status) or were independent of them. Our findings on vulnerability factors contribute new insights to the growing knowledge base on climate-related health effects and can be used to help tailor climate change adaptation and public health interventions strategies.

REFERENCES

1. McMichael AJ, Lindgren E. Climate change: Present and future risks to health, and necessary responses. *J Intern Med* 2011;270(5):401-13.

2. Meehl GA, Tebaldi C. More intense, more frequent, and longer lasting heat waves in the 21st century. *Science* 2004;305.

3. Conlon K, Monaghan A, Hayden M, et al. Potential impacts of future warming and land use changes on intra-urban heat exposure in houston, texas. *PLoS One* 2016;11(2):e0148890.

4. Luber G, McGeehin M. Climate change and extreme heat events. *Am J Prev Med* 2008;35(5):429-35.

5. Stone B, Hess JJ, Frumkin H. Urban form and extreme heat events: Are sprawling cities more vulnerable to climate change than compact cities? *Environ Health Perspect* 2010;118(10):1425-8.

6. Basu R. High ambient temperature and mortality: A review of epidemiologic studies from 2001 to 2008. *Environ Health* 2009;8:40.

7. Basu R, Malig B. High ambient temperature and mortality in california: Exploring the roles of age, disease, and mortality displacement. *Environ Res* 2011;111(8):1286-92.

8. Benmarhnia T, Deguen Sv, Kaufman JS, et al. Vulnerability to heat-related mortality a systematic review, meta-analysis, and meta-regression analysis. *Epidemiology* 2015;26:781–93.

9. Laaidi K, Zeghnoun A, Dousset B, et al. The impact of heat islands on mortality in paris during the august 2003 heat wave. *Environ Health Perspect* 2012;120(2):254-9.

10. Cheng J, Xu Z, Zhu R, et al. Impact of diurnal temperature range on human health: A systematic review. *Int J Biometeorol* 2014;58(9):2011-24.

11. Basu R. Relation between elevated ambient temperature and mortality: A review of the epidemiologic evidence. *Epidemiol Rev* 2002;24(2):190-202.

12. Braga AsLF, Zanobetti A, Schwartz J. The effect of weather on respiratory and cardiovascular deaths in 12 u.S. Cities. *Environ Health Perspect* 2002;110:859–63.

13. Li S, Baker PJ, Jalaludin BB, et al. Ambient temperature and lung function in children with asthma in australia. *Eur Respir J* 2014;43(4):1059-66.

14. Bunker A, Wildenhain J, Vandenbergh A, et al. Effects of air temperature on climate-sensitive mortality and morbidity outcomes in the elderly; a systematic review and meta-analysis of epidemiological evidence. *EBioMedicine* 2016.

15. Xu Z, Huang C, Su H, et al. Diurnal temperature range and childhood asthma: A time-series study. *12* 2013;12.

16. Ye X, Wolff R, Yu W, et al. Ambient temperature and morbidity: A review of epidemiological evidence. *Environ Health Perspect* 2012;120(1):19-28.

17. Winquist A, Grundstein A, Chang HH, et al. Warm season temperatures and emergency department visits in atlanta, georgia. *Environ Res* 2016;147:314-23.

18. Michelozzi P, Accetta G, De Sario M, et al. High temperature and hospitalizations for cardiovascular and respiratory causes in 12 european cities. *Am J Respir Crit Care Med* 2009;179(5):383-9.

19. Kovats RS, Hajat S, Wilkinson P. Contrasting patterns of mortality and hospital admissions during hot weather and heat waves in greater london, uk. *Occup Environ Med* 2004;61(11):893-8.

20. Li S, Baker PJ, Jalaludin BB, et al. Are childrens asthmatic symptoms related to ambient temperature? A panel study in australia. *Environ Res* 2014;133:239-45.

21. Anderson GB, Dominici F, Wang Y, et al. Heat-related emergency hospitalizations for respiratory diseases in the medicare population. *Am J Respir Crit Care Med* 2013;187(10):1098-103.

22. Lin S, Luo M, Walker RJ, et al. Extreme high temperatures and hospital admissions for respiratory and cardiovascular diseases. *Epidemiology* 2009;20(5):738-46.

23. Turner LR, Barnett AG, Connell D, et al. Ambient temperature and cardiorespiratory morbidity: A systematic review and meta-analysis. *Epidemiology* 2012;23(4):594-606.

24. Carreras H, Zanobetti A, Koutrakis P. Effect of daily temperature range on respiratory health in argentina and its modification by impaired socio-economic conditions and pm10 exposures. *Environ Pollut* 2015;206:175-82.

25. Green RS, Basu R, Malig B, et al. The effect of temperature on hospital admissions in nine california counties. *Int J Public Health* 2010;55(2):113-21.

26. Davis RE, Hondula DM, Patel AP. Temperature observation time and type influence estimates of heat-related mortality in seven u.S. Cities. *Environ Health Perspect* 2016;124(6):795-804.

27. Bateson TF, Schwartz J. Children's response to air pollutants. *J Toxicol Environ Health A* 2007;71(3):238-43.

28. Makri A, Stilianakis NI. Vulnerability to air pollution health effects. *Int J Hyg Environ Health* 2008;211(3-4):326-36.

29. Selgrade MK, Plopper CG, Gilmour MI, et al. Assessing the health effects and risks associated with children's inhalation exposures--asthma and allergy. *J Toxicol Environ Health A* 2008;71(3):196-207.

30. Sharma G, Goodwin J. Effect of aging on respiratory system physiology and immunology. *Clin Interv Aging* 2006;1(3):253-60.

31. Hanna EG, Tait PW. Limitations to thermoregulation and acclimatization challenge human adaptation to global warming. *Int J Environ Res Public Health* 2015;12(7):8034-74.

32. Leon LR, Helwig BG. Heat stroke: Role of the systemic inflammatory response. *J Appl Physiol (1985)* 2010;109(6):1980-8.

33. White MD. Components and mechanisms of thermal hyperpnea. *J Appl Physiol (1985)* 2006;101(2):655-63.

34. Hayes D, Jr., Collins PB, Khosravi M, et al. Bronchoconstriction triggered by breathing hot humid air in patients with asthma: Role of cholinergic reflex. *Am J Respir Crit Care Med* 2012;185(11):1190-6.

35. Khosravi M, Collins PB, Lin RL, et al. Breathing hot humid air induces airway irritation and cough in patients with allergic rhinitis. *Respir Physiol Neurobiol* 2014;198:13-9.

36. Lin YJ, Lin RL, Khosravi M, et al. Hypersensitivity of vagal pulmonary c-fibers induced by increasing airway temperature in ovalbumin-sensitized rats. *Am J Physiol Regul Integr Comp Physiol* 2015;309(10):R1285-91.

37. Saha S, Brock JW, Vaidyanathan A, et al. Spatial variation in hyperthermia emergency department visits among those with employer-based insurance in the united states - a case-crossover analysis. *Environ Health* 2015;14:20.

38. Ye F, Piver WT, Ando M, et al. Effects of temperature and air pollutants on cardiovascular and respiratory diseases for males and females older than 65 years of age in tokyo, july and august 1980–1995. *Environ Health Perspect* 2001;109(4):355–59

39. Hondula DM, Barnett AG. Heat-related morbidity in brisbane, australia: Spatial variation and area-level predictors. *Environ Health Perspect* 2014;122(8):831-6.

40. Ebi KL, Exuzides KA, Lau E, et al. Weather changes associated with hospitalizations for cardiovascular diseases and stroke in california, 1983–1998. *Int J Biometeorol* 2004;49(1):48-58.

41. Linares C, Diaz J. Impact of high temperatures on hospital admissions: Comparative analysis with previous studies about mortality (madrid). *Eur J Public Health* 2008;18(3):317-22.

42. Messer LC, Laraia BA, Kaufman JS, et al. The development of a standardized neighborhood deprivation index. *J Urban Health* 2006;83(6):1041-62.

43. Kaufman JS, MacLehose RF. Which of these things is not like the others? *Cancer* 2013;119(24):4216-22.

44. Clougherty JE, Kubzansky LD. A framework for examining social stress and susceptibility to air pollution in respiratory health. *Environ Health Perspect* 2009;117(9):1351-8.

45. Krieger N, Williams DR, Moss NE. Measuring social class in us public health research: Concepts, methodologies, and guidelines. *Annu Rev Public Health* 1997;18:341-78.

46. Williams DR, Sternthal M, Wright RJ. Social determinants: Taking the social context of asthma seriously. *Pediatrics* 2009;123(Suppl):S174-84.

47. Bernard P, Charafeddine R, Frohlich KL, et al. Health inequalities and place: A theoretical conception of neighbourhood. *Soc Sci Med* 2007;65(9):1839-52.

48. Galobardes B, Lynch J, Smith GD. Measuring socioeconomic position in health research. *Br Med Bull* 2007;81-82:21-37.

49. Adler NE, Newman K. Socioeconomic disparities in health: Pathways and policies. *Health Affairs* 2002;21(2):60-76.

50. Becklake MR, KauVmann F. Gender diverences in airway behaviour over the human life span. *Thorax* 1999;54:1119–38.

51. Clougherty JE. A growing role for gender analysis in air pollution epidemiology. *Environ Health Perspect* 2010;118(2):167-76.

52. Sheffield PE, Zhou J, Shmool JL, et al. Ambient ozone exposure and children's acute asthma in new york city: A case-crossover analysis. *Environ Health* 2015;14:25.

53. O'Neill MS. Modifiers of the temperature and mortality association in seven us cities. *Am J Epidemiol* 2003;157(12):1074-82.

54. Uejio CK, Wilhelmi OV, Golden JS, et al. Intra-urban societal vulnerability to extreme heat: The role of heat exposure and the built environment, socioeconomics, and neighborhood stability. *Health Place* 2011;17(2):498-507.

55. Schwartz J. Who is sensitive to extremes of temperature?: A case-only analysis. *Epidemiology* 2005;16(1):67-72.

56. Gronlund CJ. Racial and socioeconomic disparities in heat-related health effects and their mechanisms: A review. *Curr Epidemiol Rep* 2014;1(3):165-73.

57. Alhanti BA, Chang HH, Winquist A, et al. Ambient air pollution and emergency department visits for asthma: A multi-city assessment of effect modification by age. *J Expo Sci Environ Epidemiol* In press.

58. Alhanti BA, Chang HH, Winquist A, et al. Ambient air pollution and emergency department visits for asthma: A multi-city assessment of effect modification by age. *J Expo Sci Environ Epidemiol* 2016;26(2):180-8.

59. Crocker D, Brown C, Moolenaar R, et al. Racial and ethnic disparities in asthma medication usage and health-care utilization: Data from the national asthma survey. *Chest* 2009;136(4):1063-71.

60. Law HZ, Oraka E, Mannino DM. The role of income in reducing racial and ethnic disparities in emergency room and urgent care center visits for asthma-united states, 2001-2009. *J Asthma* 2011;48(4):405-13.

61. Roy A, Wisnivesky JP. Racial and ethnic differences in the use of environmental control practices among children with asthma. *J Asthma* 2010;47(5):507-12.

62. Grineski SE, Staniswalis JG, Peng YL, et al. Children's asthma hospitalizations and relative risk due to nitrogen dioxide: Effect modification by race, ethnicity, and insurance status. *Environ Res* 2010;110(2):178-88.

63. Burra TA, Moineddin R, Agha MM, et al. Social disadvantage, air pollution, and asthma physician visits in toronto, canada. *Environ Res* 2009;109(5):567-74.

64. Laurent O, Pedrono G, Segala C, et al. Air pollution, asthma attacks, and socioeconomic deprivation: A small-area case-crossover study. *Am J Epidemiol* 2008;168(1):58-65.

65. Laurent O, Pedrono G, Filleul L, et al. Influence of socioeconomic deprivation on the relation between air pollution and beta-agonist sales for asthma. *Chest* 2009;135(3):717-23.

66. Norris G, YoungPong SN, Koenig JQ, et al. An association between fine particles and asthma emergency department visits for children in seattle. *Environ Health Perspect* 1999;107(6):489-93.

67. Winquist A, Klein M, Tolbert P, et al. Comparison of emergency department and hospital admissions data for air pollution time-series studies. *Environ Health* 2012;11:70.

68. Yang Q, Chen Y, Shi Y, et al. Association between ozone and respiratory admissions among children and the elderly in vancouver, canada. *Inhal Toxicol* 2003;15(13):1297-308.

69. O'Lenick CR, Winquist A, Mulholland JA, et al. Assessment of neighborhood socioeconomic status as a modifier of air pollution-asthma associations among children in atlanta. *J Epidemiol Community Health* 2016;In Review.

70. O'Lenick CR, Chang HH, Kramer MR, et al. Ozone and childhood respiratory disease in three us cities: Evaluation of effect measure modification by neighborhood socioeconomic status using a bayesian hierarchal approach. *in progress*.

71. Delfino RJ, Chang J, Wu J, et al. Repeated hospital encounters for asthma in children and exposure to traffic-related air pollution near the home. *Annals of Allergy, Asthma & Immunology* 2009;102(2):138-44.

72. Wilhelm M, Qian L, Ritz B. Outdoor air pollution, family and neighborhood environment, and asthma in la fans children. *Health Place* 2009;15(1):25-36.

73. Sacks JD, Rappold AG, Davis JA, Jr., et al. Influence of urbanicity and county characteristics on the association between ozone and asthma emergency department visits in north carolina. *Environ Health Perspect* 2014;122(5):506-12.

74. Sarnat SE, Sarnat JA, Mulholland J, et al. Application of alternative spatiotemporal metrics of ambient air pollution exposure in a time-series epidemiological study in atlanta. *J Expo Sci Environ Epidemiol* 2013;23(6):593-605.

75. Rothman KJ. Causes. *Am J Epidemiol* 1976;104(6):587-92.

76. Guo Y, Barnett AG, Tong S. Spatiotemporal model or time series model for assessing city-wide temperature effects on mortality? *Environ Res* 2013;120:55-62.

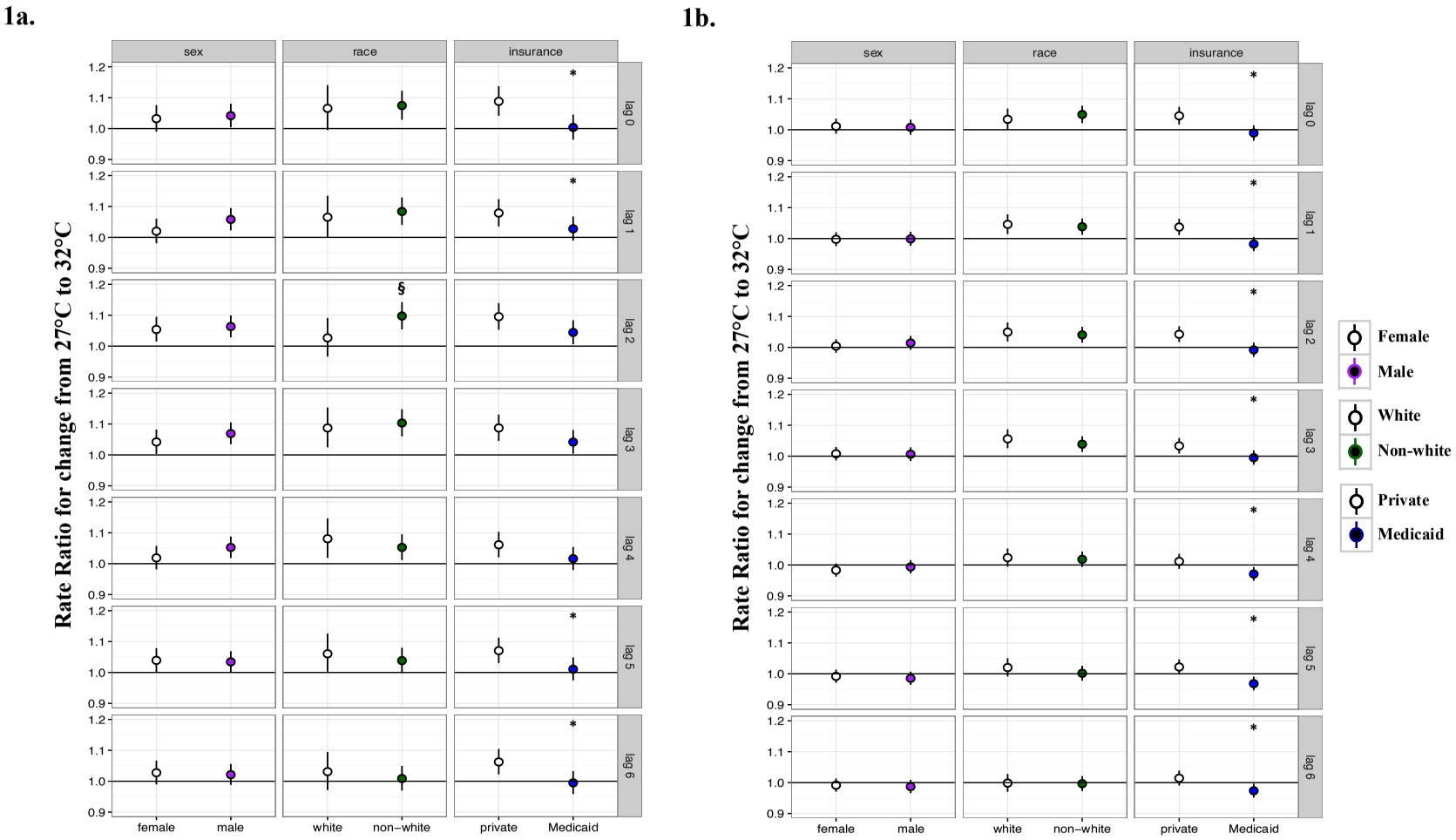
77. Buckley JP, Richardson DB. Seasonal modification of the association between temperature and adult emergency department visits for asthma: A case-crossover study. *Environmental Health* 2012;11(55).

78. Kramer MR, Cooper HL, Drews-Botsch CD, et al. Do measures matter? Comparing surface-density-derived and census-tract-derived measures of racial residential segregation. *Int J Health Geogr* 2010;9:29.

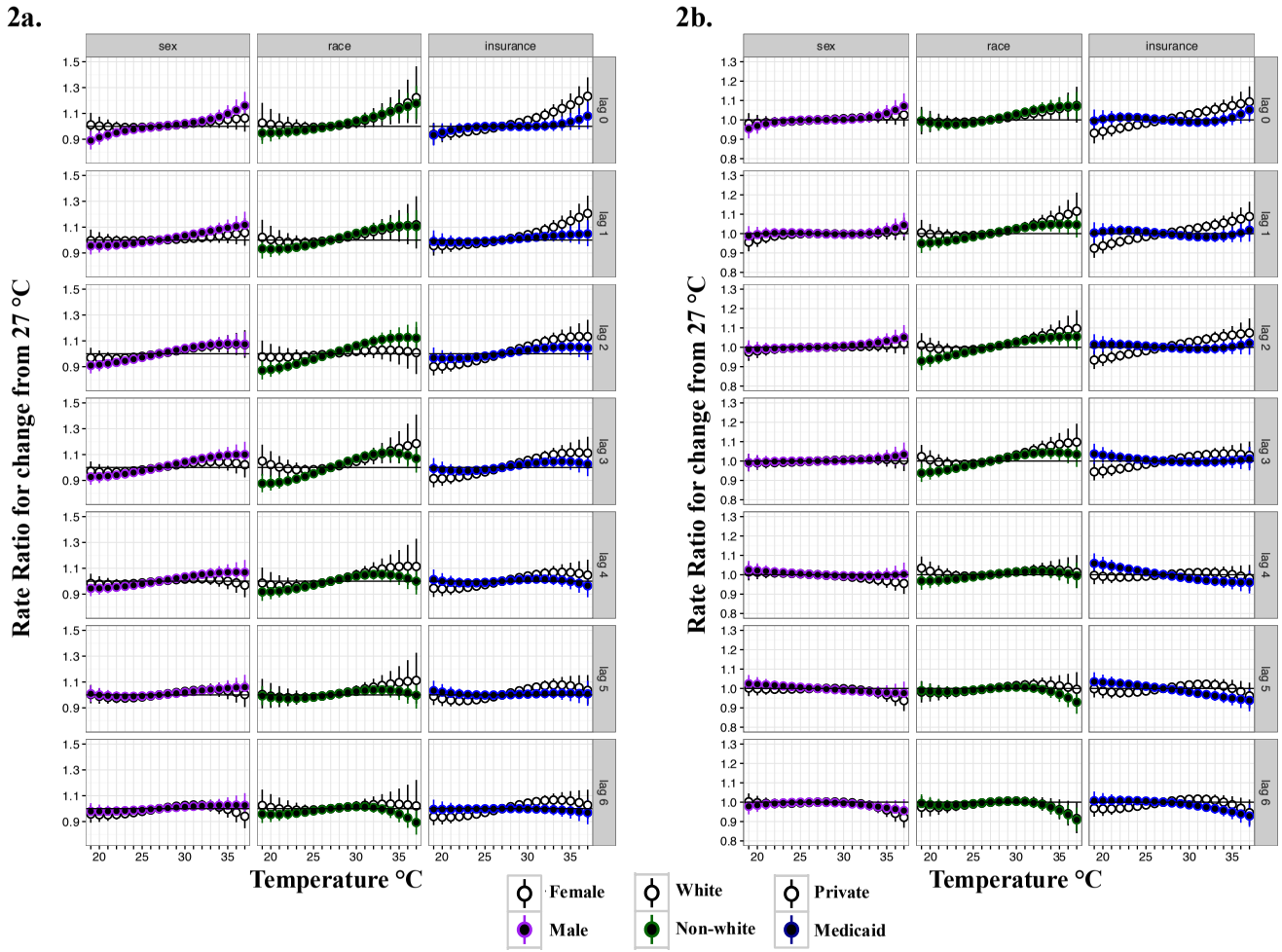
Supplemental Material

Chapter 3: Evaluation of individual and neighborhood factors as modifiers of the association between warm-season temperature and pediatric asthma morbidity in Atlanta, GA

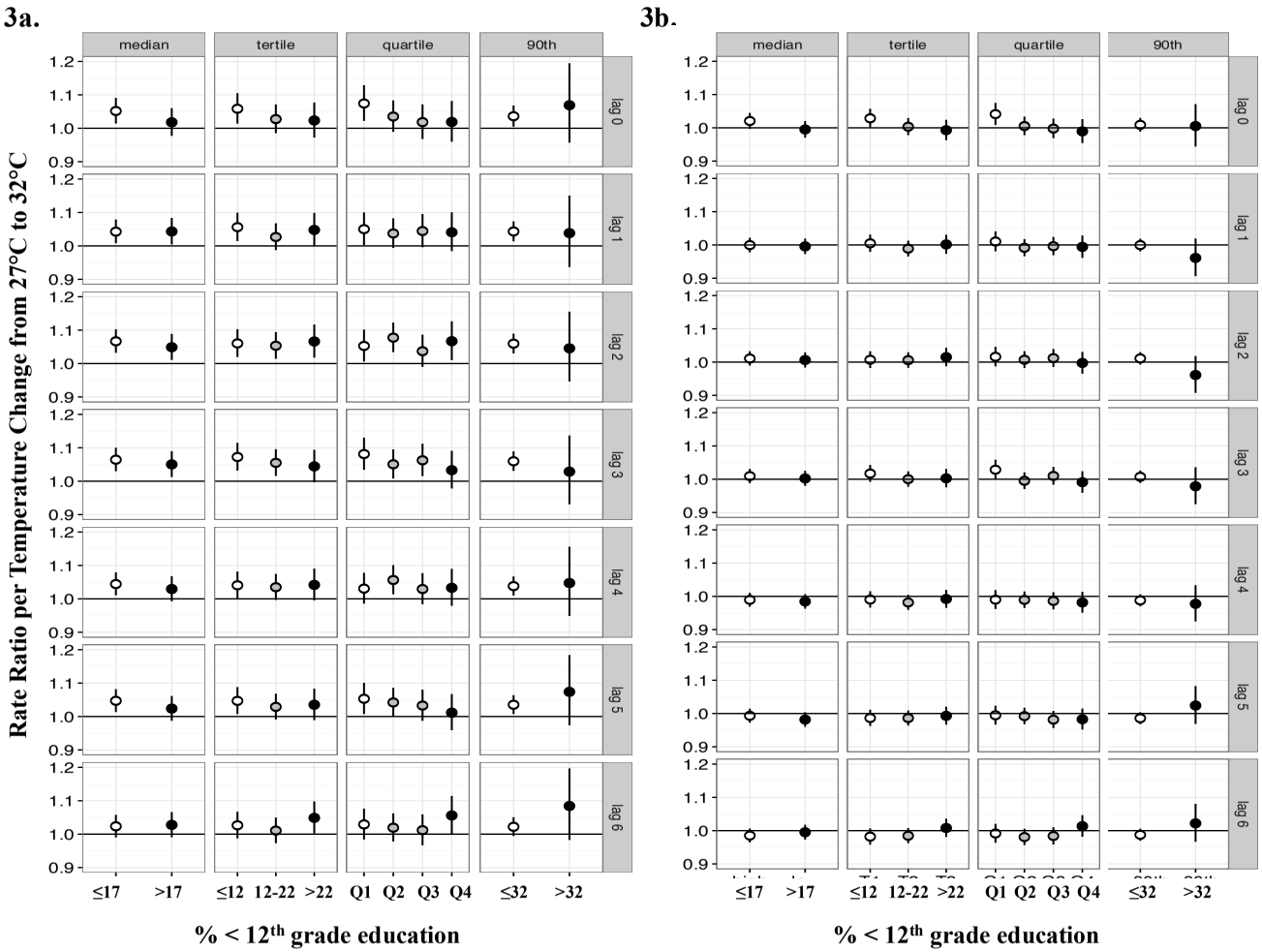
Contents



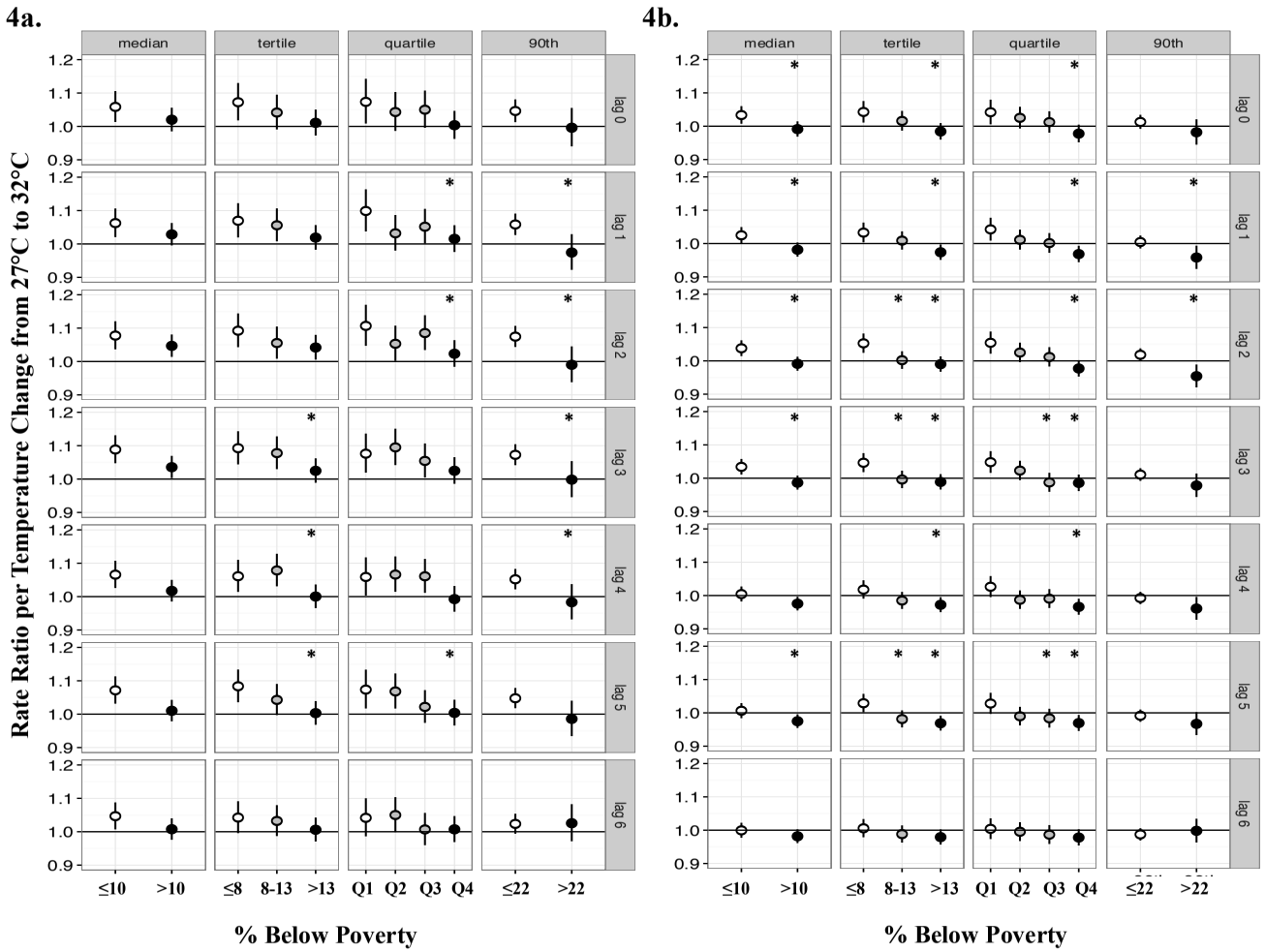
Supplemental Figure S3.1. Associations between cubic maximum temperature and pediatric asthma (1a) or pediatric respiratory disease (1b) by individual factors per change in maximum temperature from 27°C to 32°C. * indicates significant statistical difference (two-sided $P < 0.05$) from referent group (i.e. female sex, white race, or private insurance) and § indicates nearly significant difference ($P = 0.07$) from referent group. Heterogeneity between stratum-specific ORs was tested in pairwise comparisons by dividing the difference in log odds ratio by the square root of the sum of the variances and computing a Z-statistic.



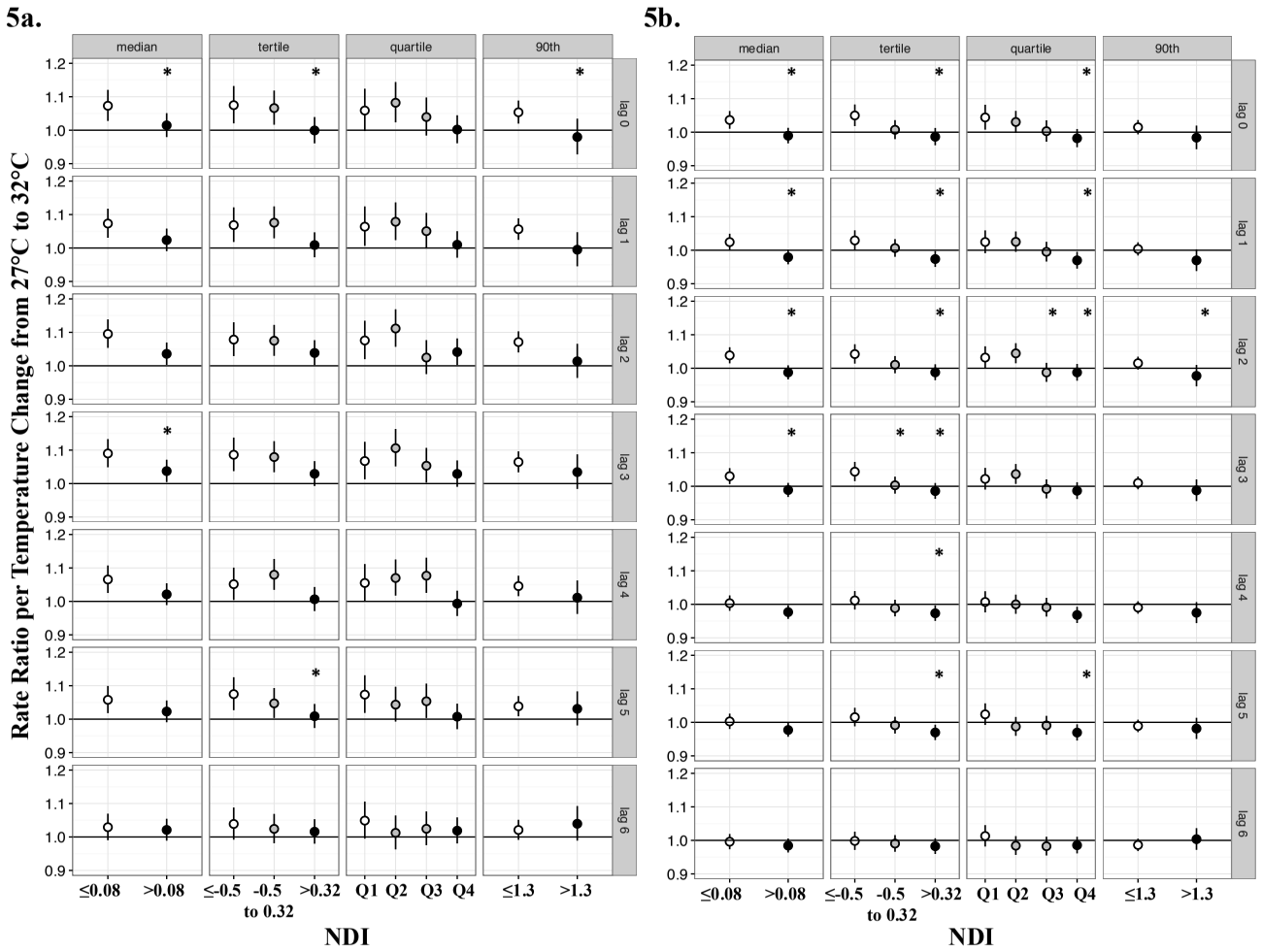
Supplemental Figure S3.2. Associations between cubic maximum temperature and pediatric respiratory outcomes by individual factors per change in maximum temperature from 27°C. Figure S3.2a represents associations between cubic maximum temperature and pediatric asthma. Figure S3.2b represents associations between cubic maximum temperature and pediatric respiratory disease.



Supplemental Figure S3.3. Associations between cubic maximum temperature and pediatric asthma (3a) or pediatric respiratory disease (3b) by % <12th grade education per change in maximum temperature from 27°C to 32°C. % <12th grade quartiles: Q1: < 10.1; Q2: ≥ 10.1 - < 16.6; Q3: ≥ 16.6 - <25; Q4: > 25.



Supplemental Figure S3.4. Associations between cubic maximum temperature and pediatric asthma (4a) or pediatric respiratory disease (4b) by % below poverty per change in maximum temperature from 27°C to 32°C. * indicates significant statistical difference (two-sided $P < 0.05$) from referent group (i.e. the highest SES strata). Heterogeneity between stratum-specific ORs was tested in pairwise comparisons by dividing the difference in log odds ratio by the square root of the sum of the variances and computing a Z-statistic. % below poverty quartiles: Q1: < 6.59; Q2: ≥ 6.59 - < 10.2; Q3: ≥ 10.2 - <14.9; Q4: > 14.9.



Supplemental Figure S3.5. Associations between cubic maximum temperature and pediatric asthma (5a) or pediatric respiratory disease (5b) by the NDI per change in maximum temperature from 27°C to 32°C. * indicates significant statistical difference (two-sided $P < 0.05$) from referent group (i.e. the highest SES strata). Heterogeneity between stratum-specific ORs was tested in pairwise comparisons by dividing the difference in log odds ratio by the square root of the sum of the variances and computing a Z-statistic. NDI quartiles: Q1: < -0.76; Q2: ≥ -0.76 - < -0.08; Q3: ≥ -0.08- <0.55; Q4: > 0.55.

CONCLUSION

Sociodemographic inequalities are posited to be key mechanisms through which environmental exposures induce respiratory health disparities across subpopulations. However, toxicological studies focusing on mechanisms of susceptibility are limited, and epidemiologic research has provided inconsistent findings on whether individual factors and/or neighborhood SES modify short-term associations between ambient air pollution or ambient high temperature and respiratory morbidity. From the outset, this body of work has endeavored to better understand the reasons underlying inconsistent reports of effect modification by sociodemographic factors in air pollution/climate health literature. Our investigation focused on the pediatric population and on the respiratory health effects of air pollution and high temperature because these exposures disproportionately impact vulnerable populations in urban settings and are also expected to increase with climate change.

To some extent, the individual studies included within this dissertation were successful in answering our specific research questions. In other cases, findings from these studies raised new questions instead of answering those we focused upon initially. However, this body of work helped clarify the impact investigator decisions have on observed effect modification by neighborhood SES, while also offering analytical design recommendations for future evaluations.

CONTRIBUTIONS

This body of work offers several important findings. The comprehensive assessment performed in Chapter 1 revealed that observed modification by neighborhood SES of associations between air pollution and pediatric asthma depends heavily on investigator

decisions regarding choice of neighborhood SES indicator and SES stratification criteria. Furthermore, these decisions may be partially responsible for the inconsistent reporting of modification by neighborhood SES in this field. Based on the findings from Chapter 1, recommendations for future studies included (1) evaluating multiple indicators of neighborhood SES, including composite indices that may better capture the multifaceted nature of neighborhood SES, (2) use of nuanced stratification criteria to examine possible non-linearity in effect modification, (3) consideration of neighborhood SES indicators that identify extremely low SES environments (i.e. poverty area status), and (4) estimation of baseline ED rates within neighborhoods and across socioeconomic strata to facilitate the interpretation of results. Additionally, results from Chapter 1 suggested non-linear effect modification by neighborhood SES in Atlanta, a finding that had not been explicitly reported or discussed in the literature.

Work performed in Chapter 1 was extended to multiple study areas for the purposes of investigating the generalizability of results across geographically diverse US cities (Atlanta, Dallas, St. Louis) and to test for the presence of non-linear effect modification. In Chapter 2, we estimated ZCTA-level associations between ozone and pediatric respiratory disease across three cities and examined effect modification by ZCTA-level characteristics. Previous studies using similar methods have only examined associations at the city and county-level. Results from the multi-city assessment detailed in Chapter 2 further bolster the recommendations discussed above. In addition, results from Chapter 2 provided further support for potential non-linear effect modification by neighborhood SES. Observed non-linear effect modification may be due to a variety of factors and the implications of these findings are discussed in detail in Chapter 2. Despite having found evidence of effect modification by neighborhood SES, it was somewhat surprising that inclusion of

neighborhood (ZCTA) level characteristics in our models did not significantly explain heterogeneity in the true effect of ozone on pediatric respiratory disease across ZCTAs. These findings imply unexplained heterogeneity across neighborhoods and warrant further inquiry. In general, results from Chapter 2 raised several additional questions worthy of investigation in future studies.

Another contribution of Chapter 2 stemmed from the spatial mapping procedure and our qualitative assessment of similarities and differences in spatial patterning of ozone-health associations across cities. Findings from this assessment indicated that spatial influences on ozone-related respiratory morbidity were apparent in each city: on average, estimated associations between ozone and pediatric respiratory morbidity were greater in neighborhoods clustered near urban centers and along major roadways, suggesting common areas of concern in all of our study areas. While we did not undertake a quantitative assessment of spatial effects (i.e. our results are based on temporal contrasts of environmental exposures), these findings underscore the importance of considering spatial influences on air pollution-health associations. This study is the first to spatially map estimated associations between ozone and pediatric respiratory morbidity at the ZCTA level.

Findings from Chapters 1 and 2 clearly demonstrated an increase in both asthma and respiratory ED visit rates as neighborhood SES decreased. This trend was observed across all study areas (Atlanta, Dallas, and St. Louis) and for each indicator of SES examined (% $<12^{th}$ grade, % below poverty, and the NDI), underscoring three important findings that are also important contributions to the literature: (1) low SES populations have a greater baseline burden of asthma and respiratory morbidity, (2) low SES populations experience a greater burden of air pollution-related asthma than do their counterparts living in areas of higher SES, and (3) it is critical to consider differing baseline ED rates across socioeconomic

strata when interpreting results generated from models that estimate associations on the multiplicative scale.

Finally, the study detailed in Chapter 3 corroborated our previous findings on investigator choices and provided further support that observed modification is dependent on the choice of neighborhood SES indicator. Additionally, individual-level factors, race/ethnicity and insurance status, appeared to modify associations between high temperature and asthma among children. However, the directionality of the race/ethnicity effect was opposite that of the insurance status effect (insurance status was used as a proxy for individual-level SES). This is an important finding as it supports the assertion that although race/ethnicity and socioeconomic status are linked in the US, they are not interchangeable variables, and this work emphasizes that this discordance is an important theoretical and analytical distinction to make within this field. It is also worth noting that patterns of effect modification were similar between our indicators of individual level SES (insurance status) and neighborhood SES. However, we were not able to determine the underlying reasons for this similarity and these results warrant further investigation. Other important contributions from Chapter 3 are the findings themselves. As very few studies have examined vulnerability factors among children in relation to high temperature and respiratory morbidity, the work performed in Chapter 3 inherently adds to the growing base of climate-health literature.

LIMITATIONS

The methodological challenges discussed in each chapter are also pervasive limitations of the air pollution/climate health field. These limitations primarily stem from the data themselves due to low spatial resolution of the health, environmental exposure, and

sociodemographic data. Until improved access to spatially resolved data is made more readily available to researchers, these inherent limitations will continue to be problematic for this field.

Within the context of this dissertation research, we were unable to assess the influence of neighborhood SES at finer scales such as the census track or census block level because information on patient residence was only available at the ZIP code level. Related to this limitation is the possibility that ZCTAs may not be the most relevant social environments to assess effect modification of air pollution/climate effects on respiratory morbidity among children. Indeed, there may be too much social heterogeneity within a ZCTA to infer an individual's experience with his or her social environment. In addition, we were unable to account for the uncertainty surrounding Census and ACS data. Finally, our studies were not powered to stratify models on both individual- and neighborhood-level factors, thereby limiting our ability to discern independent or joint effects of these variables.

CONCLUSIONS

As evidenced in this work, as well as the work of others, environmental, social, and spatial influences on health are tethered together. To ultimately understand the environmental and social mechanisms underlying susceptibility and vulnerability to respiratory disease, enhanced spatial resolution of data is necessary as well as improved generalizability. This field would benefit greatly from more multicity studies with access to fine-scale resolution data.

This body of work has highlighted the importance of using multiple lenses through which to characterize the socioeconomic composition of neighborhoods. Furthermore, during the course of this dissertation it became evident that individual and neighborhood

factors should be considered together for a more unified understanding of vulnerability. Related to this point is our finding on modification by insurance status, which suggested a possible protective effect of being on Medicaid. Future studies would be well served to examine the role of health care access among children as it may provide important insights into health disparity and may be a channel through which interventions can be actualized. Additionally, complex spatial patterning of area-level SES and area-level health risk may hinder efforts to ascertain an independent effect of neighborhood level SES on air pollution/climate-health associations; greater utilization of spatio-temporal analyses may provide valuable insights into spatial influences on air pollution/climate-health associations. Finally, this work underscores the importance of accounting for differing baseline risk across socioeconomic subpopulations.

Ultimately, these results may be leveraged to advance the study design of future analyses, inform policy, and facilitate the implementation of targeted health interventions by identifying vulnerable populations within our study areas. Going forward, it will be critical to explore additive models and multi-level models that can combine information at both the individual and neighborhood level. I hope the results presented in this dissertation research will help motivate other studies to examine diverse SES characterization methods and further explore mechanistic pathways that may potentiate vulnerability to air pollution/climate-related health effects across diverse socioeconomic populations.