Can the Effects of Outdoor Air Pollution on Asthma be Mitigated?

by

Erica L. Stevens

BS, University of Southern Indiana, 2010

MD, Indiana University School of Medicine, 2014

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This essay is submitted

by

Erica L. Stevens

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and approved by

Essay Advisor:
Juan C. Celedon, MD, DrPH
Professor
Departments of Medicine, Epidemiology and Human Genetics
School of Medicine, Graduate School of Public Health
University of Pittsburgh

Essay Reader:
David Finegold, MD
Professor
Department of Human Genetics
Graduate School of Public Health
University of Pittsburgh

Juan C. Celedón, MD, DrPH

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Erica L. Stevens, MPH

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Abstract

Outdoor air pollution affects lung development, asthma morbidity, and early life exposure to outdoor pollutants has been linked with development of asthma. Recent findings suggest that several non-modifiable and modifiable factors may diminish or augment the harmful effects of outdoor air pollution on asthma. While genetic studies have been limited by sample size and or issues with replication, interactions have been demonstrated between the *GSTM1*-null genotype and ozone, along with NO_2 and adenylate cyclase 2. Co-exposure to psychosocial stress and air pollutants is associated with asthma and reduced lung function in children, particularly among males. Cigarette smoking is associated with incident asthma among adults with outdoor pollutant exposure, but studies examining a potential interaction between second-hand smoke and outdoor pollutants are lacking. Concurrent exposure to aeroallergens and air pollutants is associated with increased airway inflammation in adults and asthma in atopic children. Some studies support an interaction between obesity and air pollution on lung function in adults and respiratory symptoms in children. Nutritional factors, including antioxidants, may attenuate the detrimental effects of air pollution by reducing airway inflammation. Vitamin E was associated with decreased airway inflammation in adults with asthma, while reductions in lung function in children exposed to ozone were attenuated with supplementation of vitamins C and E. Vitamin D supplementation reduced the effects of TRAP and allergen exposure in a murine model examining airway inflammation and vitamin D deficiency or insufficiency is associated with increased asthma morbidity in children. Diets rich in fruit and vegetables and the Mediterranean diet are associated with greater lung function among children exposed to ozone.

Conclusions: Policy measures related to improved air quality have been effective at improving respiratory symptoms and objective measures such as lung function. The findings of our review suggest that public health policies related to modifiable risk factors such as smoking, second-hand smoke exposure or obesity may both significantly reduce the harmful effects of air pollution and greatly benefit overall health. Further, certain populations that remain exposed to air pollution may benefit from identification of key interventions that mitigate the harmful effects of pollutants via well-designed clinical trials.

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Acknowledgement

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1.0 Introduction

Outdoor air pollution affects lung development and leads to morbidity from asthma in children and adults, and current evidence supports a causal link between pre- and early-postnatal exposure to outdoor pollutants and childhood asthma.[1] Recent findings suggest that several factors attenuate or enhance the detrimental effects of outdoor pollutants on asthma, including genetic variants, exposure to violence and chronic psychosocial stress, indoor pollutants, diet, and obesity (**Figure 1**).

2.0 Possible Mitigating or Augmenting Factors

2.1 Genetics

Candidate-gene studies have identified gene-by-pollutant interactions on asthma (i.e. between the *GSTM1* null genotype and ozone), but no firm conclusions can be drawn due to inconsistent results or insufficient replication.[2] A recent genome-wide interaction study in 1,534 European children identified gene by NO_2 interactions on asthma, but only those for adenylate cyclase 2 were partially replicated in one of two North American cohorts.[3] Similarly, candidate-gene studies of pollutant-related methylation markers have been limited by small sample size or inadequate replication.[4,5]

2.2 Psychosocial Stress

Air pollution and chronic psychosocial stress can increase oxidative stress, and pre- or post-natal stress and pollutants may have synergistic detrimental effects on asthma and lung function in children.[6–10] In a birth cohort study, prenatal exposure to nitrate or $PM_{2.5}$ was significantly associated with asthma and reduced lung function at age 6 years in boys exposed to chronic stress, but not in girls.[6–8] In another birth cohort, post-natal NO_2 exposure was associated with asthma in children with high lifetime exposure to violence but not in those with lower lifetime exposure to violence.[9] Similarly, longitudinal studies found that postnatal exposure to total oxides of nitrogen and other forms of traffic-related air pollution (TRAP) were linked to asthma and reduced lung function in children whose parents were highly stressed.[10,11] There have been no clinical trials of stress reduction to reduce pollutant effects on asthma.

2.3 Tobacco Smoke

Cigarette smoking may modify the effect of air pollution on asthma in adults, as current or former smokers appear to be more prone to develop incident asthma related to outdoor pollutants than never smokers.[12,13] Although SHS increases the risk of childhood asthma and may thus worsen the effects of air pollution on asthma, few studies have directly examined this potential interaction.[14] [15] Since eliminating active smoking and SHS has beneficial effects not only on asthma but on general health, vigorous efforts to help prevent or quit smoking must continue.

2.4 Aeroallergens

Concurrent exposure to aero-allergens and air pollutants may enhance airway inflammation and lead to asthma exacerbations. A cross-sectional study using population-level data showed that high exposure to fungal and pollen allergens may interact with $PM_{2.5}$ or PM_{10} to increase the risk of hospitalizations for asthma.[16] In another study, co-exposure to DEP and dust mite allergen increased T_H2 cytokines and airway responsiveness in a murine model, and high exposure to DEP was associated with asthma in atopic children but not in non-atopic children.[17] Small clinical trials in adults have demonstrated enhanced allergen-induced airway inflammation in participants exposed to DEP.[18,19] Whether modifying outdoor activity during high pollen season or reducing indoor allergen levels attenuates pollutant effects on asthma merits further study.

2.5 Obesity

Obesity has been reported to modify the effects of air pollution on asthma in most, but not all, published studies. A large cross-sectional study of European adults found that $PM_{2.5}$ exposure was significantly associated with wheeze and shortness of breath, without any significant interaction between obesity and air pollution on respiratory symptoms.[13] In contrast, a longitudinal 10-year study of Swiss adults found that improved air quality reduced the rates of age-related decline in FEF_{25-75}, FEF_{25-75}/FVC and FEV_1/FVC in participants with low to normal weight, but not in overweight or obese participants.[20] Moreover, a large cross-sectional study of Chinese children found that the estimated effect of NO_2 and SO_2 on respiratory symptoms or asthma was significantly greater in overweight or obese children than in children of normal weight.[21] In addition, two studies reported that short- or long-term exposure to ozone was significantly associated with greater reductions in lung function in overweight or obese adults than in non-overweight adults, with one of these studies showing this interaction only in women.[22,23] Obesity is a major public health problems, and thus campaigns to prevent obesity in childhood have benefits that extend beyond any amelioration of pollution effects on asthma.

2.6 Diet and Nutrition

Diet and certain vitamins may attenuate the effects of air pollution on asthma. For example, gamma-tocopherol (an isoform of vitamin E) was recently shown to reduce sputum eosinophils and mucins, as well as airway responsiveness after lipopolysaccharide challenge, in a clinical trial in 15 adults with mild asthma.[24] Another clinical trial examined the effects of antioxidants, including vitamin C and vitamin E, on lung function in Mexican children exposed to high levels of air pollutants. In that study, ozone levels were associated with lower FEF_{25-75} (-13.32 ml/second/10 ppb, $P<0.001$) and FEV_1 (-4.59 ml/10 ppb, $P=0.04$) in children with moderate to severe asthma in the placebo arm, but not in those in the intervention arm.[25] Regarding vitamin D, a murine model showed that vitamin D supplementation reduces the combined effects of TRAP and allergen exposure on airway responsiveness and T_{H2} and T_{H17} immune responses in the lung.[26] Moreover, a prospective study of urban children found that higher exposure to $PM_{2.5}$ was only associated with asthma symptoms in obese and vitamin D deficient children.[27] This is partly consistent with results from a cross-sectional study that showed that children with vitamin D insufficiency who lived near a major highway (a marker of TRAP) had nearly fivefold higher odds of severe asthma exacerbations than those without either risk factor.[28] With regard to diet, a prospective study demonstrated that dietary intake of fruits and vegetables was significantly and positively associated with FEV_1 and FVC, particularly among children exposed to ozone.[29] Similar findings were reported for a Mediterranean diet and FVC among children exposed to ozone.[29] Thus, current evidence suggests that a healthy diet and, perhaps, vitamins with antioxidant properties could protect against pollution effects on asthma.

3.0 Discussion

3.1 Public Health Implications

A large longitudinal study of children in California demonstrated that improved air quality is associated with positive effects on lung function growth and reduced bronchitic symptoms during childhood,[30,31] emphasizing that the most effective way to eliminate the detrimental effects of air pollution on asthma is through health policies to ensure "clean air" for all. Such policies should address not only pollutant levels but factors that could increase pollution, including climate change and wildfires. Similarly, public health policies designed to prevent or eliminate smoking and obesity would have beneficial effects on general health, beyond those of reducing pollutant effects on respiratory health. This said, identifying other modifiable factors that mitigate the effects of air pollution could be beneficial to populations that remain exposed to pollutants due to lack of effective policies. Moreover, studies of genetic and epigenetic modifiers of the effects of air pollution on asthma could not only identify high-risk individuals but also provide novel insights into asthma pathogenesis.

3.2 Future Directions

Current evidence suggests that chronic stress and an unhealthy diet or low levels of antioxidant vitamins interact with air pollution to cause or worsen asthma. Well-designed randomized clinical trials should help determine the extent to which dietary interventions or vitamin supplementation mitigate the harmful effects of air pollution on asthma. Because of the complex etiology of asthma, multifactorial trials examining several interventions (i.e. reducing SHS, weight loss, stress reduction, and a healthy diet) may be best suited to identify the most effective modifiers of pollutant-related effects.

Appendix Figure

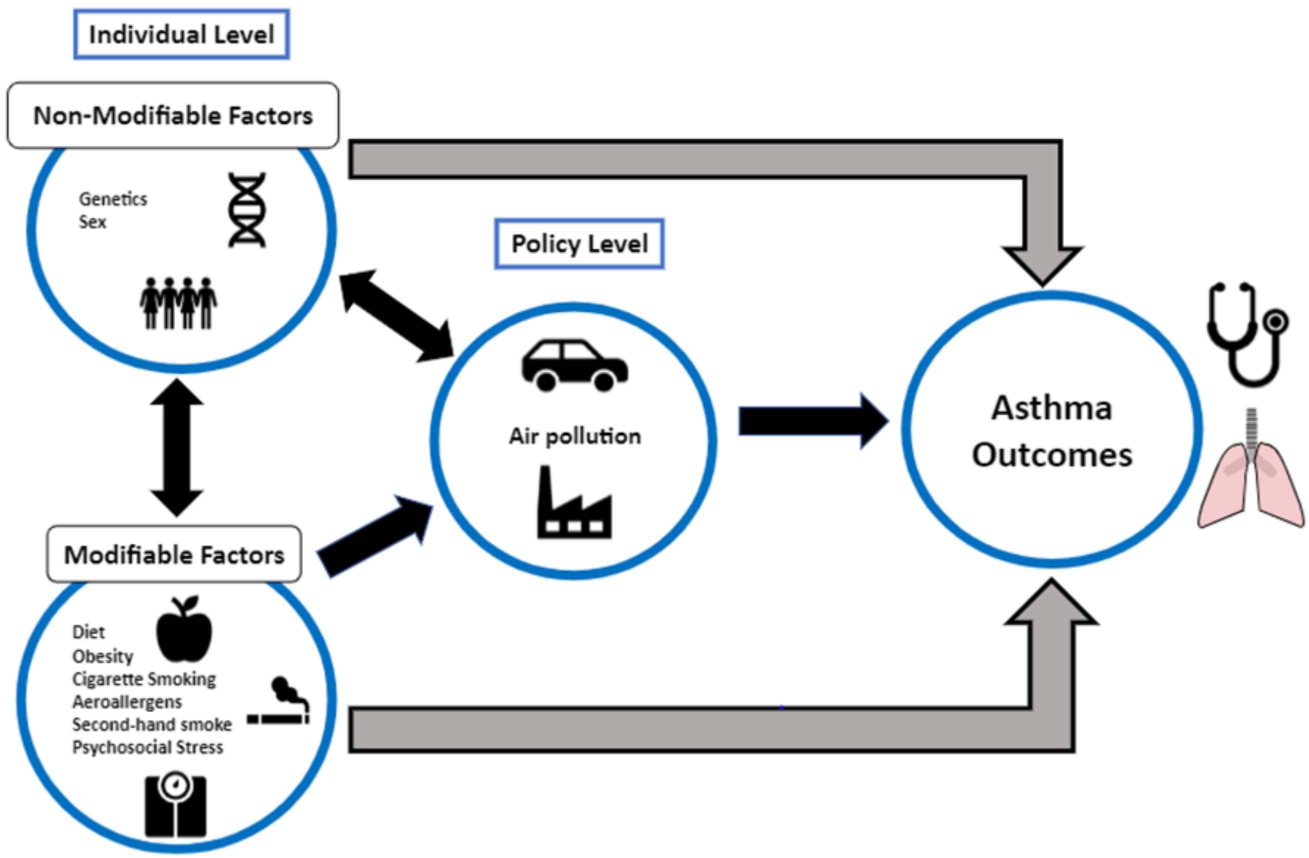

Figure 1 Mitigating and Augmenting Factor

Factors that may mitigate or augment the harmful effects of air pollution on asthma are shown. Non-modifiable factors can interact with modifiable factors, and both can in turn interact with air pollution. Modifiable and non-modifable factors should be considered when addressing air pollution at the policy level.

Bibliography

1. Burbank AJ, Sood AK, Kesic MJ, Peden DB, Hernandez ML. Environmental determinants of allergy and asthma in early life. J Allergy Clin Immunol 2017;140:1–12.

2. Romieu I, Moreno-Macias H, London SJ. Gene by environment interaction and ambient air pollution. Proc Am Thorac Soc 2010;7:116–122.

3. Gref A, Merid SK, Gruzieva O, Ballereau S, Becker A, Bellander T, et al. Genome-Wide Interaction Analysis of Air Pollution Exposure and Childhood Asthma with Functional Follow-up. Am J Respir Crit Care Med 2017;195:1373–1383.

4. de F C Lichtenfels AJ, van der Plaat DA, de Jong K, van Diemen CC, Postma DS, Nedeljkovic I, et al. Long-term Air Pollution Exposure, Genome-wide DNA Methylation and Lung Function in the LifeLines Cohort Study. Environ Health Perspect 2018;126:027004.

5. Jung KH, Lovinsky-Desir S, Yan B, Torrone D, Lawrence J, Jezioro JR, et al. Effect of personal exposure to black carbon on changes in allergic asthma gene methylation measured 5 days later in urban children: importance of allergic sensitization. Clin Epigenetics 2017;9:61.

6. Bose S, Chiu Y-HM, Hsu H-HL, Di Q, Rosa MJ, Lee A, et al. Prenatal nitrate exposure and childhood asthma. influence of maternal prenatal stress and fetal sex. Am J Respir Crit Care Med 2017;196:1396–1403.

7. Lee A, Leon Hsu H-H, Mathilda Chiu Y-H, Bose S, Rosa MJ, Kloog I, et al. Prenatal fine particulate exposure and early childhood asthma: Effect of maternal stress and fetal sex. J Allergy Clin Immunol 2018;141:1880–1886.

8. Bose S, Rosa MJ, Mathilda Chiu Y-H, Leon Hsu H-H, Di Q, Lee A, et al. Prenatal nitrate air pollution exposure and reduced child lung function: Timing and fetal sex effects. Environ Res 2018;167:591–597.

9. Clougherty JE, Levy JI, Kubzansky LD, Ryan PB, Suglia SF, Canner MJ, et al. Synergistic effects of traffic-related air pollution and exposure to violence on urban asthma etiology. Environ Health Perspect 2007;115:1140–1146.

10. Islam T, Urman R, Gauderman WJ, Milam J, Lurmann F, Shankardass K, et al. Parental stress increases the detrimental effect of traffic exposure on children's lung function. Am J Respir Crit Care Med 2011;184:822–827.

11. Shankardass K, McConnell R, Jerrett M, Milam J, Richardson J, Berhane K. Parental stress increases the effect of traffic-related air pollution on childhood asthma incidence. Proc Natl Acad Sci USA 2009;106:12406–12411.

12. Burte E, Nadif R, Jacquemin B. Susceptibility Factors Relevant for the Association Between Long-Term Air Pollution Exposure and Incident Asthma. Curr Environ Health Rep 2016;3:23–39.

13. Doiron D, de Hoogh K, Probst-Hensch N, Mbatchou S, Eeftens M, Cai Y, et al. Residential Air Pollution and Associations with Wheeze and Shortness of Breath in Adults: A Combined Analysis of Cross-Sectional Data from Two Large European Cohorts. Environ Health Perspect 2017;125:097025.

14. Sonnenschein-van der Voort AMM, de Kluizenaar Y, Jaddoe VWV, Gabriele C, Raat H, Moll HA, et al. Air pollution, fetal and infant tobacco smoke exposure, and wheezing in preschool children: a population-based prospective birth cohort. Environ Health 2012;11:91.

15. Rabinovitch N, Silveira L, Gelfand EW, Strand M. The response of children with asthma to ambient particulate is modified by tobacco smoke exposure. Am J Respir Crit Care Med 2011;184:1350–1357.

16. Cakmak S, Dales RE, Coates F. Does air pollution increase the effect of aeroallergens on hospitalization for asthma? J Allergy Clin Immunol 2012;129:228–231.

17. Brandt EB, Biagini Myers JM, Acciani TH, Ryan PH, Sivaprasad U, Ruff B, et al. Exposure to allergen and diesel exhaust particles potentiates secondary allergen-specific memory responses, promoting asthma susceptibility. J Allergy Clin Immunol 2015;136:295–303.e7.

18. Carlsten C, Blomberg A, Pui M, Sandstrom T, Wong SW, Alexis N, et al. Diesel exhaust augments allergen-induced lower airway inflammation in allergic individuals: a controlled human exposure study. Thorax 2016;71:35–44.

19. Rider CF, Yamamoto M, Günther OP, Singh A, Hirota JA, Tebbutt SJ, et al. Effects of Controlled Diesel Exhaust and Allergen Exposure on microRNA and Gene Expression in Humans. Modulation of Lung Inflammatory Markers Associated with Asthma. Annals of the American Thoracic Society 2018;15:S130–S131.

20. Schikowski T, Schaffner E, Meier F, Phuleria HC, Vierkötter A, Schindler C, et al. Improved air quality and attenuated lung function decline: modification by obesity in the SAPALDIA cohort. Environ Health Perspect 2013;121:1034–1039.

21. Dong GH, Qian Z, Liu MM, Wang D, Ren WH, Fu Q, et al. Obesity enhanced respiratory health effects of ambient air pollution in Chinese children: the Seven Northeastern Cities study. Int J Obes 2013;37:94–100.

22. Alexeeff SE, Litonjua AA, Suh H, Sparrow D, Vokonas PS, Schwartz J. Ozone exposure and lung function: effect modified by obesity and airways hyperresponsiveness in the VA normative aging study. Chest 2007;132:1890–1897.

23. Bennett WD, Hazucha MJ, Folinsbee LJ, Bromberg PA, Kissling GE, London SJ. Acute pulmonary function response to ozone in young adults as a function of body mass index. Inhal Toxicol 2007;19:1147–1154.

24. Burbank AJ, Duran CG, Pan Y, Burns P, Jones S, Jiang Q, et al. Gamma tocopherol-enriched supplement reduces sputum eosinophilia and endotoxin-induced sputum neutrophilia in volunteers with asthma. J Allergy Clin Immunol 2018;141:1231–1238.e1.

25. Romieu I, Sienra-Monge JJ, Ramírez-Aguilar M, Téllez-Rojo MM, Moreno-Macías H, Reyes-Ruiz NI, et al. Antioxidant supplementation and lung functions among children with asthma exposed to high levels of air pollutants. Am J Respir Crit Care Med 2002;166:703–709.

26. Bolcas PE, Brandt EB, Zhang Z, Biagini Myers JM, Ruff BP, Khurana Hershey GK. Vitamin D supplementation attenuates asthma development following traffic-related particulate matter exposure. J Allergy Clin Immunol 2019;143:386–394.e3.

27. Bose S, Diette GB, Woo H, Koehler K, Romero K, Rule AM, et al. Vitamin D status modifies the response to indoor particulate matter in obese urban children with asthma. J Allergy Clin Immunol Pract 2019;

28. Rosser F, Brehm JM, Forno E, Acosta-Pérez E, Kurland K, Canino G, et al. Proximity to a major road, vitamin D insufficiency, and severe asthma exacerbations in Puerto Rican children. Am J Respir Crit Care Med 2014;190:1190–1193.

29. Romieu I, Barraza-Villarreal A, Escamilla-Núñez C, Texcalac-Sangrador JL, Hernandez-Cadena L, Díaz-Sánchez D, et al. Dietary intake, lung function and airway inflammation in Mexico City school children exposed to air pollutants. Respir Res 2009;10:122.

30. Berhane K, Chang C-C, McConnell R, Gauderman WJ, Avol E, Rapappport E, et al. Association of Changes in Air Quality With Bronchitic Symptoms in Children in California, 1993-2012. JAMA 2016;315:1491–1501.

31. Gauderman WJ, Urman R, Avol E, Berhane K, McConnell R, Rappaport E, et al. Association of improved air quality with lung development in children. N Engl J Med 2015;372:905–913.