Module 3: Activity 1

Scientific Literacy: Health Problems and Air Pollution

IT'S OUR AIR

INDEX OF ARTICLES AND PAPERS

This activity includes four general-audience articles and four scientific papers. Divide the class into eight groups. Assign each group a different article or paper. Have each group answer the questions about their assigned article/paper, then make a short presentation to the class summarizing what they read. Next, pair up each group that read a general audience article with a group that read the related scientific paper. Have them exchange papers and add to the answers given by the first group. (Pair Article 1 with the Paper 1, and so forth.)

For the purposes of this activity, *It's Our Air* received permission to post some of the articles and papers on the It's Our Air website. Those articles and papers are included in this document. There were several articles for which we were unable to obtain this permission, but teachers can download the documents from their original source. The links to the sources for those articles are provided in this document.

ARTICLES

SCIENTIFIC PAPERS

ARTICLE 1: "Duke Scientists Report Air Pollution Controls Linked to Lower NC Death Rates"
by S. Wheeler *Reproduced courtesy of the Charlotte Observer.*

JUNE 23, 2014

Duke scientists report air pollution controls linked to lower NC death rates

HIGHLIGHTS

State and federal air pollution standards that require fewer emissions are linked to lower death rates in North Carolina, Duke University scientists report today in the International Journal of COPD.

BY SARAH WHEELER - SWHEELER@NEWSOBSERVER.COM

Stronger emission controls in North Carolina may have saved lives by reducing deaths from respiratory illness, according to an academic study published Monday.

During the past few decades, the state has tightened its air quality standards through adherence to federal legislation such as the Clean Air Act and the state's 2002 Clean Smokestacks Act. The state's success in reducing air pollution may explain a substantial decline in deaths from the respiratory illnesses asthma and emphysema during corresponding periods, reported Duke University scientists in the International Journal of COPD on Monday.

The release of the study comes as state lawmakers are considering legislation this week that eliminates some of the state's air-quality stations, part of the framework for measuring pollution across the state.

"This research tends to show that environmental policies work, if the goal of those policies is not only to improve the environment but also to improve public health," said the study's lead author, Dr. H. Kim Lyerly from Duke University.

State and Environmental Protection Agency air quality measurements and public health records from 1993-2010 allowed researchers to connect improved air quality to reduced death rates from asthma and emphysema. In their analysis, scientists correlated death rates and exposure to levels of nitrogen dioxide, sulfur dioxide, airborne particulate matter and other pollutants. Researchers factored out the effects of age or smoking history in determining changes in subjects' health.

The research established that the improvements in health coincided with the reduction in pollution. But researchers said the data could not conclusively show the reduction in pollution caused the health improvements because there are other potentially influential factors – such as medical history or allergies – they did not account for in their analysis.

Sheila Holman, the director of the Division of Air Quality at the N.C. Department of Environment and Nature Resources, documented the decline in emissions and improvement to air quality since the passage of the Clean Smokestacks Act. She partnered with Duke researchers on the project and believes the improvements to air quality have improved health.

“Here was some evidence that we did have an impact on the public health of North Carolina,” Holman said.

Scientists also explored whether overall medical advances could explain the decline in death rates in North Carolina but concluded that it was unlikely. Death rates in the state fluctuated along with seasonal concentrations of pollutants within a year, a time frame too short for medical advances to have an effect. Unlike the changes in mortality seen in North Carolina, deaths from respiratory illness at the national level remained relatively constant from 1999-2010, according to National Vital Statistics System records.

Duke, DENR collaborate

Partnerships across multiple disciplines at Duke University and the state DENR made the study possible.

“There was a great opportunity to bridge the gap in information by bringing together environmental data and health-related data, something that hadn’t been done before,” Lyerly said.

Few studies are able to evaluate the health consequences of chronic air pollution over a long period, mostly because consistent long-term records of such factors are seldom kept. Duke researchers capitalized on existing health and environmental data. They used records from both state and federal EPA air-quality devices. And they gathered public-health information from the Vital Statistics National Center for Health Statistics, the Centers for Disease Control and Prevention, and other databases.

The study was supported with funding from Fred and Alice Stanback to the cancer and environment program of the Nicholas School of the Environment-Duke Cancer Center.

“Our study leverages these collected data in a way that it can contribute to the dialogue on whether pollution controls are effective in improving public health,” Lyerly said.

Bill would remove monitors

The presence of devices that measure air quality has created ongoing discussion in this year's session of the General Assembly.

Senate Bill 734 – sponsored by Republican Sens. Trudy Wade, Brent Jackson and Andrew C. Brock – would change long-term air quality monitoring in the state. The bill passed the Senate on May 29 and has been referred to two House committees. It would require the state DENR to request removal of any air monitors not required by federal regulations in its next report to the EPA.

The bill does not threaten the department's ability to install temporary air monitors for targeted investigations. The House has sent its own environmental bill to the Senate that does not include a provision to remove monitoring stations.

Currently, 56 air quality monitoring sites scattered across the state house devices to measure pollutants. Each device costs approximately $12,540 per year to operate, with additional costs for maintenance and data management, according to the DENR.

Costs, benefits weighed

Health care costs from respiratory illness in North Carolina may outweigh the cost to improve air quality. In addition to increasing death rates evaluated in this study, air pollution can trigger asthma attacks, according to the CDC. Asthma cost the U.S. $56 billion in direct and indirect costs in 2007, the CDC reported in May 2011.

Duke Energy estimates it costs citizens roughly $250 million per year to meet emissions standards after the Clean Smokestacks Act took effect.

The energy company and the state have worked together to dramatically reduce emissions of carbon monoxide, nitrogen dioxide, sulfur dioxide and particulate matter. Sulfur dioxide emissions have dropped 92 percent since 2005 in North Carolina and South Carolina, and half of the aging coal plants in North Carolina have shut down.

"It has been a very successful process. It is a great example of private industry working with the state to bring environmental benefits to citizens," said Jeff Brooks, a Duke spokesman.

Lyerly will continue to research the health consequences of air pollution by refocusing his analysis to the county level.

"Now we have some opportunities to make more accurate equations of the pros and cons of policies that improve air quality."

ARTICLE 2: "Take-Home Message is Clear" by T. Lucas *Reproduced courtesy of Dukenvironment Magazine, Fall 2014, Nicholas School of the Environment at Duke.*

dukenvironment fall 2014

COVER STORY

Scientific Literacy: Health Problems and Air Pollution

Article 2

During the 2008 Summer Olympics in Beijing, while the rest of the world was watching swimmers, gymnasts and other athletes go for gold, **Junfeng "Jim" Zhang** and his team had their eyes on a different prize.

Zhang, an expert in the field of exposure science, had temporarily set up shop in the Chinese capital to measure how improvements in the city's air quality during the Olympics affected its residents' cardiovascular and respiratory health.

Beijing is one of the world's most polluted cities, but the Chinese government had promised to reduce pollution by shutting down factories and limiting traffic for a six-week period leading up to and encompassing the games.

"This was something no one had attempted to do on such a large scale before," Zhang says. "We wanted to take advantage of such a huge intervention and look at what happens in people's bodies when their exposure to pollution drops."

To conduct the study, he and his colleagues measured blood clotting, heart rate, lung and systemic inflammation and other biomarkers of cardiovascular health in 125 young, healthy, nonsmoking medical residents who worked at a central Beijing hospital. They examined each volunteer six times: twice before the pollution-control measures began; twice while they were in play; and twice after the games ended and air quality measures were relaxed.

The results were golden.

Zhang's study, published four years later in the prestigious *Journal of the American Medical Association*, became the first to identify a biological link between air pollution and cardiovascular health.

"Inflammation, oxidative stress and other risk factors for heart disease were significantly reduced while pollution-control measures were in play but rose again sharply when the measures were relaxed," he says. "This was evidence that physiological changes occur rapidly in our bodies when we are exposed to changing levels of pollution."

The take-home message was clear: Even short-term improvements in air quality can yield significant reductions in disease risks, not just among children and other higher-risk groups but in healthy young adults, too.

It was the latest in a series of breakthroughs that have catapulted Zhang, who joined the Nicholas School faculty in 2013, to the forefront of his field.

Since 1994, he's published more than 150 studies examining the environmental and human health impacts of air pollution. His work has shed light not only on *what* the effects of exposure to pollutants are, but also *how* they alter the physical and biochemical processes that affect Earth's climate and reduce or increase disease risks in our bodies.

He was among the first scientists to investigate hydrocarbon emissions and health risks from cookstoves in developing countries, and has led pioneering studies on a long list of other pollutants, as well, including diesel fumes on the streets of London; lead dust from pottery production in Mexico; volatile organic compounds from paint manufacturing in Kenya; hydrocarbon emissions from mosquito coils in China and Malaysia; perchlorate exposures in lactating women in New Jersey; greenhouse gas emissions and other airborne pollutants from charcoal making in Brazil and Kenya; and, most recently, engineered silver and carbon nanoparticles in consumer products in the United Kingdom and the United States.

"Indoor exposures, outdoor exposures—I'm interested in them all, particularly in cases where people work and live very close to the source of pollution," says Zhang, 49, of his globe-spanning interests.

In recognition of his early work to characterize sources of non-methane greenhouse gases, Zhang was officially recognized as a contributor to the 2007 Nobel Peace Prize awarded to the United Nations' Intergovernmental Panel on Climate Change.

In 2012, he received the Jeremy Wesolowski Award, the highest professional honor bestowed by the International Society of Exposure Science. In 2013, he was named a Fellow of the American Association for the Advancement of Science.

A follow-up study to his 2008 Beijing research may yield additional accolades.

The study, which Zhang and colleagues recently submitted to a leading environmental health journal, examines the impact of pollution reductions on pre-term birth rates and birth weights – another scientific first.

"We find that babies' birth weights increased significantly if their mothers' eighth month of pregnancy was during the 2008 Olympics, when air pollution was reduced for six weeks," he says. "Even a temporary reduction made a statistically significant difference."

It's further proof, he says, that from birth to death, our health and the environment are inextricably linked.

A GROWING GLOBAL THREAT

The urgency of Zhang's work is underscored by a World Health Organization (WHO) report released earlier this year. The report estimates that in 2012 about 7 million deaths, or roughly one in eight premature deaths worldwide, were caused by air pollution—more than from malaria, tuberculosis and AIDS combined.

The new estimate of pollution-related deaths is more than twice that of previous WHO estimates, and establishes airborne pollutants as the world's single largest environmental threat to human health, particularly in developing countries and large cities.

Emissions from carbon-based fuels account for most of the risk. But new threats may be emerging.

"Manufactured nanoparticles are being used in all kinds of consumer products, from fuel additives to sunscreens to sporting equipment, but we're only beginning to understand how they interact with the environment or might affect human health," says Zhang, who is heading two major research initiatives to find answers.

With $4 million in funding from the U.S. Environmental Protection Agency and the United Kingdom's National Environmental Research Council, he's directing a four-year laboratory study to assess the risks posed by engineered nanoparticles used in consumer products.

With $5 million in funding from the National Institute of Environmental Health Sciences, he's leading a five-year lab study to understand the link between the physiochemical properties of nanoparticles and their toxicity.

"Our goal is to produce well-defined measurements of nanoparticle properties so we can better determine their risks," he explains. "It's not possible to test nanoparticles side by side, one to one, as we can with other pollutants. They're too tiny and there's too many of them. But if we know their basic properties—such as their sizes, shapes and structures, and if they're water soluble or not—we can figure out relationships between those properties and toxicity, and provide guidance on how to design and manufacture safer alternatives."

One of the initiatives' most widely cited findings so far has been on the use of nanosized ceria additives in diesel fuel.

Ceria, or cerium oxide, is a metallic powder. Nanosized ceria has been used in recent years as a catalyst to improve combustion and increase fuel efficiency in diesel engines. Zhang's team's analysis, published in 2013 in the journal *Environmental Science & Technology*, suggests the jury is still out on whether the environmental benefits outweigh the possible risks.

"Nanosized ceria additives do reduce fuel use by 10 to 15 percent, meaning engines emit 10 to 15 percent less carbon dioxide emissions," he says. But there's a catch. "Even though we see a reduction in particle mass, we also see a shift from larger particles to smaller ones."

These particles are so small they resemble a gas and not only can be inhaled into lungs but also can shoot directly into a person's blood.

"We've essentially changed the emissions' profile and the pathways they can take into our bodies," Zhang says. "It's too early to tell if this is a good thing or not."

While lab studies on nanoparticles and other emerging sources of pollution occupy more and more of his time now, Zhang continues to pursue the meticulously constructed field studies on real-life exposures that have long been his hallmark.

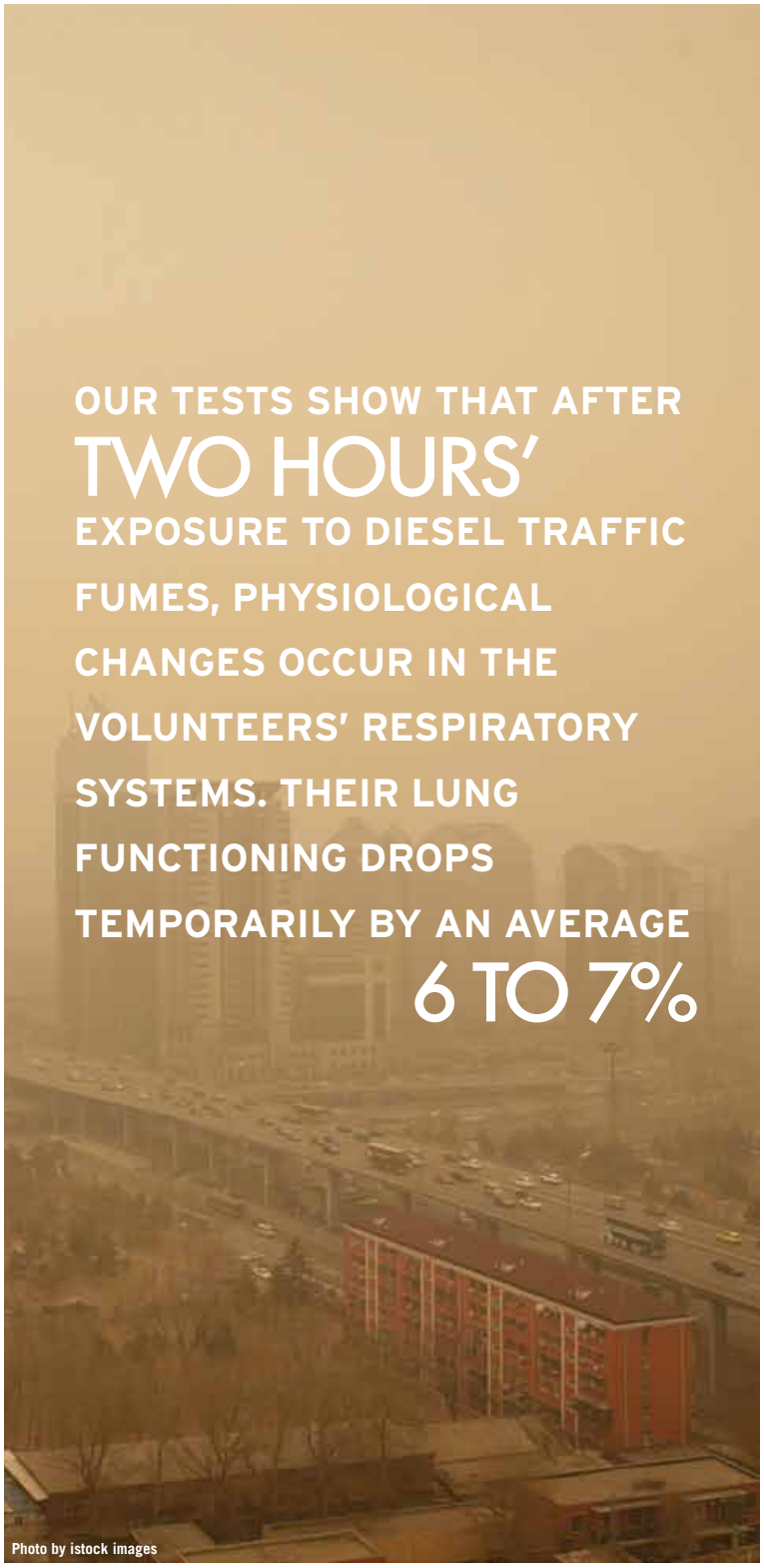


Photo by istock images

A case in point is his ongoing study, first reported in 2007 in the *New England Journal of Medicine*, on how short-term exposure to big-city traffic exhaust alters lung functioning.

The project, which Zhang began in 2000, measures changes in biomarkers of respiratory health in people with asthma after they spend two hours walking along London's busy Oxford Street.

"Our tests show that after two hours' exposure to diesel traffic fumes, physiological changes occur in the volunteers' respiratory systems. Their lung functioning drops temporarily by an average of 6 to 7 percent," he says.

By comparison, rescue workers who responded to the 9/11 bombings of New York City's World Trade Center lost an average of 10 percent of their lung functioning. The rescue workers' decrease was far more debilitating and long-lasting, Zhang says, but it serves to illustrate "how serious the effects of even short-term exposure to big-city traffic exhaust can be, especially for people with a mild to moderate pre-existing respiratory disease. Biology does not lie."

SMALL BEGINNINGS

These days, new research findings by Zhang and other leaders in the field can generate widespread buzz in medical, scientific and policy circles.

But it wasn't always the case.

"My early presentations on cookstove emissions attracted very small crowds. Sometimes, it was just me, my mentor Kirk Smith and maybe one other person in the room," Zhang recalls with a laugh. "It was the mid-1990s. Exposure science, especially indoor air science, was just emerging. I was one of only a few researchers worldwide looking at the cookstove exposure issue."

And even he came to it somewhat circuitously.

After earning a bachelor's degree in applied chemistry in 1985 from Peking University in Beijing, Zhang stayed on to pursue a master's degree in atmospheric chemistry. He planned to study ozone pollution, which was a growing problem in many of China's large cities.

"I was more interested in environmental applications than human health exposures," he says. "But by the time I graduated with my master's in 1988, my interests had broadened. I was becoming more aware of the human health impacts of air pollution, so decided I wanted to do something that bridged human health, environmental science and physical science."

He enrolled at Rutgers University in New Jersey to pursue a second master's degree in environmental science. He stayed at Rutgers for his doctoral studies, earning his PhD in exposure science in 1994 before heading west for a two-year postdoctoral fellowship with renowned global environmental health researcher **Kirk R. Smith** at the University of California at Berkeley.

"My training in exposure science up to that point had mostly been in hardcore theoretical science, but Professor Smith transformed my thinking," Zhang says. "He helped me understand what is really important, and I began working much more on the applied side."

Zhang's earliest work focused on characterizing the sources of greenhouse gas emissions, but he increasingly became fascinated with the issue of indoor air quality.

"It was a new field, there were lots of opportunities, and the number of people affected was huge, especially women and children in developing countries," Zhang says. "I started looking at the issue anywhere there was considerable exposure."

A rapid-fire succession of peer-reviewed papers followed, along with a steady rise up the ranks of some of the world's leading centers for environmental health, including Rutgers and the University of Southern California's Keck School of Medicine.

In 2013, he joined the Duke faculty with joint appointments as professor of environmental and global health at the Nicholas School of the Environment, the Duke Global Health Institute (DGHI) and Duke Kunshan University in China.

Today, he divides his time between the Durham and Kunshan campuses, managing research labs and teaching students at both.

In Durham, he teaches a master's-level course on air pollution and will co-teach a doctoral-level course on exposure measurement and assessment next fall. In China, he teaches an "Introduction to Global Health" course.

When he's not busy teaching, traveling, giving talks, managing research, writing papers, or writing grant proposals for new projects, Zhang enjoys spending time at home in Durham with his wife, Gloria, and their two sons, Charles, 14, and Barry, 12, photos of whom are among the few personal items on display in his still half-unpacked office in the Levine Science Research Building.

If he had spare time, he'd also like to take up a favorite old pastime again: writing poetry.

"When I was younger, I published numerous poems, mostly in Chinese but also a few in English," he says. "I enjoy playing with language, the challenge it presents."

A poem that he wrote in 1990 about his parents, "Memory: a Serenade," won first place in the National Hongyu (Rainbow and Rain) Cup Contest of Poetry and Words in Beijing. The honor is prominently listed on page two of Zhang's 44-page curriculum vitae, the same page as his Nobel Prize citation.

"It's been years since I've written anything like that. I miss it, but after writing grants all day, you don't have room in your brain to write something different," he says as he politely turns and eyes the stacks of unfinished grant proposals on his desk and the ever-growing number of emails accumulating in his inbox. "You make your choice about what's truly important.

"Someday, perhaps, I'll have time to pursue poetry again. But if not, it's okay," he says contentedly. "I have more than enough to keep me challenged."

Tim Lucas is senior writer for Dukenvironment magazine and is the Nicholas School's director of marketing communications.

ARTICLE 3: "Air Pollution, Climate and Heart Disease" by D.R. Gold and J.M. Samet

This article cannot be posted on the website, but teachers may download it from the following link and print it out for their students: http://circ.ahajournals.org/content/128/21/e411.full.

ARTICLE 4: FAQ Regarding Public Health and Wildfires by the North Carolina Department of Public Health

Frequently Asked Questions Regarding Public Health and Wildfires

Q: ***What is the health threat from wildfire smoke?***
A: Smoke from wildfires is a mixture of gases and fine particles from burning trees and other plant materials. Smoke can irritate your eyes or your respiratory system, and worsen chronic heart and lung diseases. How much and how long you are exposed to the smoke, as well as your age and degree of susceptibility play a role in determining whether or not someone will experience smoke-related health problems. If you are experiencing serious medical problems for any reason, seek medical treatment immediately.

Q: ***How can I tell if the smoke is affecting my family or me?***
A: • Smoke can cause coughing, scratchy throat, irritated sinuses, shortness of breath, chest pain, headaches, stinging eyes and runny nose.

• If you have heart or lung disease, smoke might make your symptoms worse.

• People who have heart disease might experience chest pain, rapid heartbeat, shortness of breath and fatigue.

• Smoke may worsen symptoms for people who have pre-existing respiratory conditions, such as respiratory allergies, asthma, and chronic obstructive pulmonary disease (COPD), in the following ways:

- Inability to breathe normally
- Cough with or without mucus
- Chest discomfort
- Wheezing and shortness of breath

• When smoke levels are high, even healthy people may experience some of these symptoms.

Q: ***How can I protect myself and my family from the harmful effects of smoke?***
A: The best thing to do is to limit your exposure to the smoke. Specific strategies to decrease exposure to smoke include staying indoors whenever possible, using air conditioners (air conditioned homes usually have lower air exchange rates than homes that use open windows for ventilation), using mechanical air cleaners, keeping windows closed while driving in a vehicle, and minimizing other sources of air pollution such as smoking tobacco, using wood burning stoves, burning candles or incense and vacuuming.

Q: ***Will I suffocate in my house?***
A: No. The most common call for evacuation during a wildfire is due to the direct threat of the fire, not smoke. Leaving the area of thick smoke may be an option for those who are sensitive to smoke. But it is often difficult to predict the duration, intensity and direction of smoke, making this an unattractive choice to many people. Those without air conditioning must also remember not to become overheated by closing all windows .

Q: ***Should I wear a dust mask or N95 respirator?***
A: N95 respirators and dust masks are masks made of filtering material that fit over the nose and mouth. The filter material will filter out some of the small particles that may be found in smoke, but only if there is a good fit to the wearer's face. It is also important to know that N95 particulate respirators and dust masks only filter particles, **not toxic gases and vapors**.

Most people will find it difficult to use the respirators and masks correctly for general use. For instance, it is impossible to get a good seal on individuals with facial hair. **As a result, the respirator will provide little if any protection, and may offer the wearer a false sense of protection.**

Filtering face-piece respirators and masks can make the work of breathing more difficult and can lead to increased breathing rates and heart rates. They can also contribute to heat stress. **Because of this, respirator use by those with heart and respiratory diseases can be dangerous, and should only be done under a doctor's supervision.** Even healthy adults may find that the increased effort required for breathing makes it uncomfortable to wear a respirator for more than short periods of time. Decisions on whether to use respirators or masks as personal protection for people who must work outside should be made on a case by case, day by day basis.

Q: ***What is the difference between an N95 respirator and dust mask?***
A: In terms of being used by the public for wildfires and for people that have not been trained and fitted to use respirators, the difference between a dust mask and an N95 respirator is not great. N-95 respirators are tested and approved by the National Institute of Occupational Safety and Health (NIOSH) for use in certain work places. N-95 respirators are tested to filter particles efficiently and are likely to filter small particles like those found in smoke, more effectively than dust masks, which are not tested. If an employer requires an employee to wear a respirator, the employee must be trained and fitted to wear a respirator and may only use a NIOSH approved respirator.

Q: ***Will a wet towel or bandana provide any help?***
A: A wet towel or bandana may provide some help but it will be very limited. Since wet towels or bandanas may not be sealed to the face and their capacity to filter very small particles is unknown, they will likely provide little protection.

Q: ***What should I do if I must drive to work?***
A: Individuals can reduce the amount of smoke particles in their vehicles by keeping the windows closed and using the air conditioner. The car's ventilation systems typically remove a portion of the particulate coming in from outside. For best results, individuals may also want to use the re-circulate air feature found in most cars, which will help keep the particulate levels lower.

Q: ***Our community has an outdoor game scheduled for this evening, should we cancel it?***
A: All persons in areas affected by the wildfire smoke are being advised to limit outdoor activity and stay indoors whenever possible to minimize exposure to the smoke. Contact your local emergency management and sports association officials for more guidance.

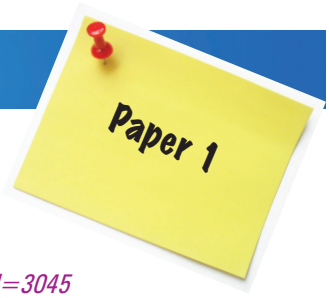
Q: ***Do air-purifying machines help remove smoke particles inside buildings?***
A: Some air cleaners may be effective at reducing indoor particle levels, but most are not effective at removing gases and odors, and also tend to be expensive. Some devices, known as ozone generators, personal ozone devices, "energized oxygen", "diatomic oxygen", "activated oxygen" and "pure air" generators are sold as air cleaners, but they are not recommended for use in occupied buildings. Ozone does not remove particles from the air, and would not be effective during smoke events. Ozone itself is toxic and a regulated outside air pollutant. We advise the public to avoid exposure to ozone indoors by not using air cleaners that produce ozone. For additional information consider reviewing the US Environmental Protection Agency document: "Ozone Generators That Are Sold As Air Cleaners" available at www.epa.gov/iaq/pubs/ozonegen.html
Also, humidifiers or de-humidifiers are not technically air cleaners and will not significantly reduce the amount of particles in the air during a smoke event.

Q: ***What should I do about closing up my house when it is so hot in there?***
A: If you do not have an air conditioner and if it is too warm to stay inside with the windows closed, seek alternative shelter by visiting family members or neighbors who have air conditioning. You may also be able to visit an air conditioned location for a few hours such as a mall.

Q: ***If I have respiratory problems and can't reach my doctor, where should I go?***
A: If you have a medical emergency you should call 911 or go to the hospital emergency room immediately.

Q: ***I operate a nonresidential building with outside air intakes. Should I close the outside air intakes during a wildfire smoke event?***
A: Every nonresidential building has a uniquely designed ventilation system, where any changes even temporary ones, can have an impact on building occupants and indoor air quality. If your building is strictly an office environment it may be wise to cut back or eliminate outside intake into the building during a wildfire smoke event. If the building has labs or special ventilation systems in may not be wise to reduce outside air flow as harmful exposures may be generated by such processes that need ventilation to prevent the build up of chemicals in the building. We recommend you consult with a heating, ventilation and air-conditioning professional or some one who knows your special ventilation needs for guidance on this issue.

Q: ***Where can I find information about the air quality in the area I live?***
A: The NC Department of Environment and Natural Resources, Division of Air Quality provides updated information on outdoor air quality in North Carolina. You can access this information by logging into the following website: http://www.ncair.org/



PAPER 1: "Long-Term Dynamics of Death Rates of Emphysema, Asthma, and Pneumonia and Improving Air Quality" by J. Kravchenko et al *Reproduced courtesy of J. Kravchenko and Dove Press, publisher of the International Journal of COPD. The open access license is available here: http://www.dovepress.com/why_publish_with_dove.php?content_id=3045*

Long-term dynamics of death rates of emphysema, asthma, and pneumonia and improving air quality

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Background: The respiratory tract is a major target of exposure to air pollutants, and respiratory diseases are associated with both short- and long-term exposures. We hypothesized that improved air quality in North Carolina was associated with reduced rates of death from respiratory diseases in local populations.

Materials and methods: We analyzed the trends of emphysema, asthma, and pneumonia mortality and changes of the levels of ozone, sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), and particulate matters ($PM_{2.5}$ and PM_{10}) using monthly data measurements from air-monitoring stations in North Carolina in 1993–2010. The log-linear model was used to evaluate associations between air-pollutant levels and age-adjusted death rates (per 100,000 of population) calculated for 5-year age-groups and for standard 2000 North Carolina population. The studied associations were adjusted by age group-specific smoking prevalence and seasonal fluctuations of disease-specific respiratory deaths.

Results: Decline in emphysema deaths was associated with decreasing levels of SO_2 and CO in the air, decline in asthma deaths–with lower SO_2, CO, and PM_{10} levels, and decline in pneumonia deaths–with lower levels of SO_2. Sensitivity analyses were performed to study potential effects of the change from *International Classification of Diseases* (ICD)-9 to ICD-10 codes, the effects of air pollutants on mortality during summer and winter, the impact of approach when only the underlying causes of deaths were used, and when mortality and air-quality data were analyzed on the county level. In each case, the results of sensitivity analyses demonstrated stability. The importance of analysis of pneumonia as an underlying cause of death was also highlighted.

Conclusion: Significant associations were observed between decreasing death rates of emphysema, asthma, and pneumonia and decreases in levels of ambient air pollutants in North Carolina.

Keywords: chronic obstructive pulmonary disease, sulfur dioxide, carbon monoxide, nitrogen dioxide, particulate matter

Introduction

Air pollution has a deleterious impact on human health,[1–6] with global outdoor air pollutants estimated to account for approximately 1.4% of total mortality and 2% of all cardiopulmonary mortality.[7] Both ambient particles[4,8,9] and such gases as nitrogen dioxide (NO_2), ozone (O_3), and carbon monoxide (CO) have been shown to increase total, cardiovascular, and respiratory (predominantly due to lung cancer and chronic obstructive pulmonary disease [COPD]) mortality and morbidity.[3,10,11] While the impact on any individual's risk of death has been thought to be relatively modest per se, the overall impact of air pollution on the health of an exposed population makes it a major public health concern.[12]

While more studies on short-term impacts of changes of air quality are available (such as the legislated traffic holidays during the 1996 Atlanta Olympic Games[13] and the 2008 Beijing Olympic Games[14]), less is known about the long-term effects of changing air quality on the health of exposed populations. For example, a ban on heating-coal sales in Dublin was thought to be associated with both reduced pollution from airborne particulate matters (PMs) and 5.7% reduction in all-cause, 15.5% reduction in respiratory, and 10.3% reduction in cardiovascular mortality.[15] However, these results were considered inconclusive, due to the complexity and expense of evaluating the health effects of air pollution on populations.[16,17] Since the 1990s, a variety of acts, standards, and requirements in the US have been adopted to improve air quality. For example, increasingly stringent national gasoline and automotive engine requirements have been applied, resulting in a decrease of CO, NO_x, PM, and volatile organic compounds in the air. At the state level, North Carolina in 1992 entered into the Southern Appalachian Mountains Initiative, leading to the development of the Clean Smokestacks Act[18] to mandate reduced emissions from coal-fired power plants.[19]

While few studies have analyzed the associations of both air quality and health over a long period, and they were typically limited to analysis of a specific air pollutant or a couple of pollutants, we were able to study longitudinally a number of air contaminants, including both PMs and noxious gases. In addition, we analyzed both air quality and health outcomes over almost two decades (1993–2010). Because respiratory morbidity and mortality are affected by changes in air quality,[20–22] we evaluated the associations between the changes of the levels of PM_{10} and $PM_{2.5}$, ozone, CO, NO_2, and SO_2 in the air and death rates of emphysema, asthma, and pneumonia.

Materials and methods

Data

We analyzed mortality rates for emphysema (*International Classification of Diseases* [ICD]-9 code 492, ICD-10 code J43), asthma (ICD-9 code 493, ICD-10 codes J45, J46), and pneumonia (ICD-9 codes 480.0, 480.1, 480.2, 480.9, 485, 486, 487.0, 487.1, ICD-10 codes J11.00, J11.1, J12.0, J12.1, J12.2, J12.9, J18.0, J18.9) in North Carolina from 1983 to 2010 using the data from the Vital Statistics National Center for Health Statistics Multiple Cause of Death dataset. We started the mortality analysis with the data from 1983, but could only analyze air quality when monitoring data were available, ie, 1993–2010. The mortality data enabled an analysis of a longer period of death-rate dynamics, thus allowing to observe the dynamics of disease-specific mortality before the measured reduction in particulate and gaseous emissions in North Carolina. Age-adjusted death rates (per 100,000 of population) were calculated using 5-year age-groups and standard 2000 North Carolina population. The data on population were provided by the Surveillance Epidemiology and End Results Registry (SEER) at http://www.seer.cancer.gov/popdata/download.html.

Data on concentrations of $PM_{2.5}$ (μg/m^3), PM_{10} (μg/m^3), ozone (ppb), CO (ppb), NO_2 (ppb), and SO_2 (ppb) in the air in 1993–2010 were obtained from the US Environmental Protection Agency (EPA) (http://www.epa.gov/ttn/airs/airsaqs/detaildata/downloadaqsdata.htm). We used the averaged month-specific concentrations of air pollutants for North Carolina to further analyze them for associations with the dynamics of cause-specific monthly mortality in the state. A two-stage averaging procedure was used to avoid heterogeneity in the numbers of measurements made in certain days of the month: first, we calculated the day-specific means, and then these values were averaged, resulting in month-specific means. Negative values were excluded, and measurements with various units were converted to μg/m^3 for $PM_{2.5}$ and PM_{10}, and to ppb for ozone, CO, NO_2, and SO_2. Since the data on air pollutants represented different methods of registration during different durations of sample collection (ie, the length of time used to acquire a sample measurement), an auxiliary analysis was performed to check whether the specific method could be considered as an outlier and therefore excluded from the analyses.

Also, data on the prevalence of tobacco use for 1995–2010 were obtained from the Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System survey for age–groups 18–24, 25–34, 35–44, 45–54, 55–64, and 65+ years (http://www.cdc.gov/brfss).

Ethics statement

The data used in this study have no individual identifiable information. No specific procedures were required for de-identification of the records. All data analyses were designed and performed in accordance with the ethical standards of the committee on human experimentation and with the Helsinki Declaration (1975, revised in 1983), and were approved by the Duke University Health System Institutional Review Board.

Methods

Trends of cause-specific death rates and of levels of air contaminants were analyzed for correlations. Adjustment by

smoking prevalence and seasonal fluctuations in respiratory deaths (for monthly death rates of emphysema, asthma, and pneumonia) were included in a log-linear model that was used to evaluate the associations between the level of each studied air pollutant and the death rates, as follows:

$$\log(r) = u + \beta_1 c + \beta_2 s + \sum_{m=1}^{11} \mu_m I_m + \varepsilon, \qquad (1)$$

where u was the intercept, β_1 represented the effect of each studied air pollutant depending on its concentration (denoted by c) measured in its units (as described in the Data section), β_2 represented the effect of smoking prevalence (denoted by s), μ_m represented the effects of 11 months (January to November for each year) in respect of December (I_m is the month indicator), and ε stood for random residuals. Note that if the air-pollutant concentration changes by one unit of its measured level in the air, the rate r changes by the factor of $\exp(\beta_1)$. For multiple comparisons, the Bonferroni correction was applied.

Sensitivity analysis

The potential effect of ICD code changes (from ICD-9 to ICD-10), the seasonal fluctuation of air pollutants and mortality during summer and winter, and the analysis validity when only the underlying causes of deaths contributed to the cause-specific death rates were tested. In addition, sensitivity analysis was performed for county-level data on respiratory mortality and air-pollutant levels. Only counties for which the data on air quality were directly measured by monitoring stations were included in the analysis: 37 counties for ozone measurements, 11 counties for NO_2, 22 counties for SO_2, 16 counties for CO, and 37 counties for $PM_{2.5}$ and PM_{10} measurements. As in the main analysis, dynamics of smoking prevalence (on state level) and seasonal fluctuations in respiratory mortality were used for adjustments of the results.

Results

We analyzed up to 180 month-specific measurements of each of the studied air pollutants recorded at multiple monitoring sites in North Carolina (see Table 1 for detailed air pollutant-specific information). We found air quality in North Carolina gradually improving over time, primarily due to decreasing PM_{10}, NO_2, and CO levels. These decreases became more pronounced from 2002 (see Figure 1; note that individual pollutants were placed onto a single graph by utilizing the arbitrary units to enable a collective visualization of the trends). The following seasonal fluctuations of pollutants levels were observed (Figure 2): levels of ozone, $PM_{2.5}$, and PM_{10} were higher in summer, while levels of SO_2, NO_2, and CO were higher in winter.

Table 1 Measurements of air pollutants used in the study, 1993–2010

Air pollutant	Number of monitored sites	Number of month-specific measurements
Ozone	69	148
Nitrogen dioxide	15	180
Sulfur dioxide	35	180
Carbon monoxide	41	180
PM_{10}	68	180
$PM_{2.5}$	60	132

Abbreviation: PM, particulate matter.

Since 1983, the death rates of three studied diseases have been decreasing (Figure 3), with declines in emphysema death rates more dramatic since 1998, for asthma since 1995, and for pneumonia since 1990. From 1993 to 2010, 101,374 deaths in North Carolina were caused by pneumonia, 13,187 by emphysema, and 5,509 by asthma. The detailed description of the studied population is presented in Table 2. Among those who died from emphysema and from pneumonia, 80.7% and 85.9%, respectively, were older than 65 years. For asthma, ages at death were younger: 9.7% were younger than 40 years, and 31.3% were aged 40–64 years old. However, the declining trends of pollutant concentrations and death rates during 1993–2010 do not essentially confirm causality.

The association between the changes of air-pollutant levels and dynamics of disease-specific death rates after being adjusted for smoking prevalence (for respective year and age-group), and by monthly fluctuations in respiratory disease-specific death rates are shown in Table 3, for each air pollutant. The disease-specific death rate (number of deaths per 100,000 population) decreased by a factor calculated based on the value of estimate presented in Table 3 (ie, per decrease of concentration of each pollutant by one unit of measurement: per 1.0 ppb for ozone, SO_2, NO_2, CO, and per 1.0 $\mu g/m^3$ for $PM_{2.5}$ and PM_{10}). For example, the estimate for emphysema in Table 3 means that if the SO_2 level decreases by 1 ppb, the emphysema death rate (per 100,000 population) can be predicted to decrease by a factor of $\exp(0.0547) = 1.056$. Similar interpretation can be developed for smoking estimates, keeping in mind that smoking is represented by its prevalence in population measured in percentages, and thus the respective exponential factor corresponds to a change in smoking prevalence by 1%.

Among gaseous pollutants, the estimates for associations between reduction of air-pollutant levels and reduction of death rates were significant for SO_2 and emphysema (0.0547 ± 0.0106, $P < 0.0001$), asthma (0.0598 ± 0.0173,

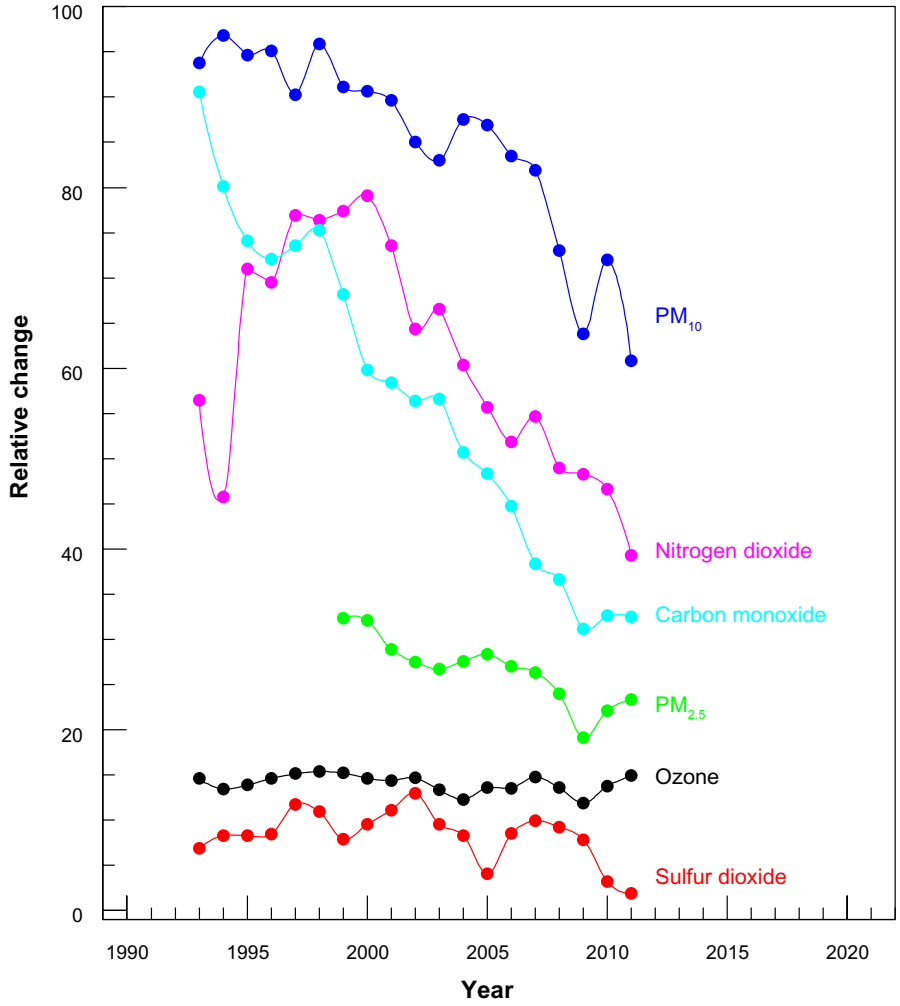

Figure 1 Levels of six air pollutants in North Carolina, 1993–2011. Individual pollutants were placed onto a single graph by utilizing arbitrary units to enable a collective visualization of the trends.
Abbreviation: PM, particulate matter.

$P<0.001$), and pneumonia (0.0309±0.0093, $P<0.001$), and for CO and emphysema (0.0004±0.0001, $P<0.0001$) and asthma (0.0006±0.0001, $P<0.001$). For PM, reduced $PM_{2.5}$ levels were associated with reduction of emphysema mortality (0.0155±0.0066, $P<0.05$) and reduced PM_{10} levels, with reduction of asthma mortality (0.0204±0.0058, $P<0.001$). As expected, smoking significantly affected the mortality of each disease.

Sensitivity analysis

The sensitivity analysis demonstrated good stability of obtained results (see Table S1 for detailed information). In the sensitivity analysis, the association between pneumonia mortality and CO levels became significant (P=0.0655 in main versus $P<0.0001$ in sensitivity analysis) when pneumonia was analyzed as an underlying cause of death. Recent studies have demonstrated that separation of comorbid conditions to underlying and secondary causes can be unreliable;[23–25] however, for certain diseases with a predominantly acute course (eg, pneumonia), that may not be the case, and additional information can also be obtained from analysis of underlying causes of death. In addition, sensitivity analysis showed that during summer decreased mortality from emphysema was associated with lower levels of PM_{10} (P=0.2554 in main versus P=0.017 in sensitivity analysis), and statistical significance was observed for associations between pneumonia mortality and CO levels when ICD code changes were taken into account (P=0.0655 in main versus P=0.018 in sensitivity analysis).

A county-level analysis also demonstrated the stability of most observations in the main analysis. Among associations

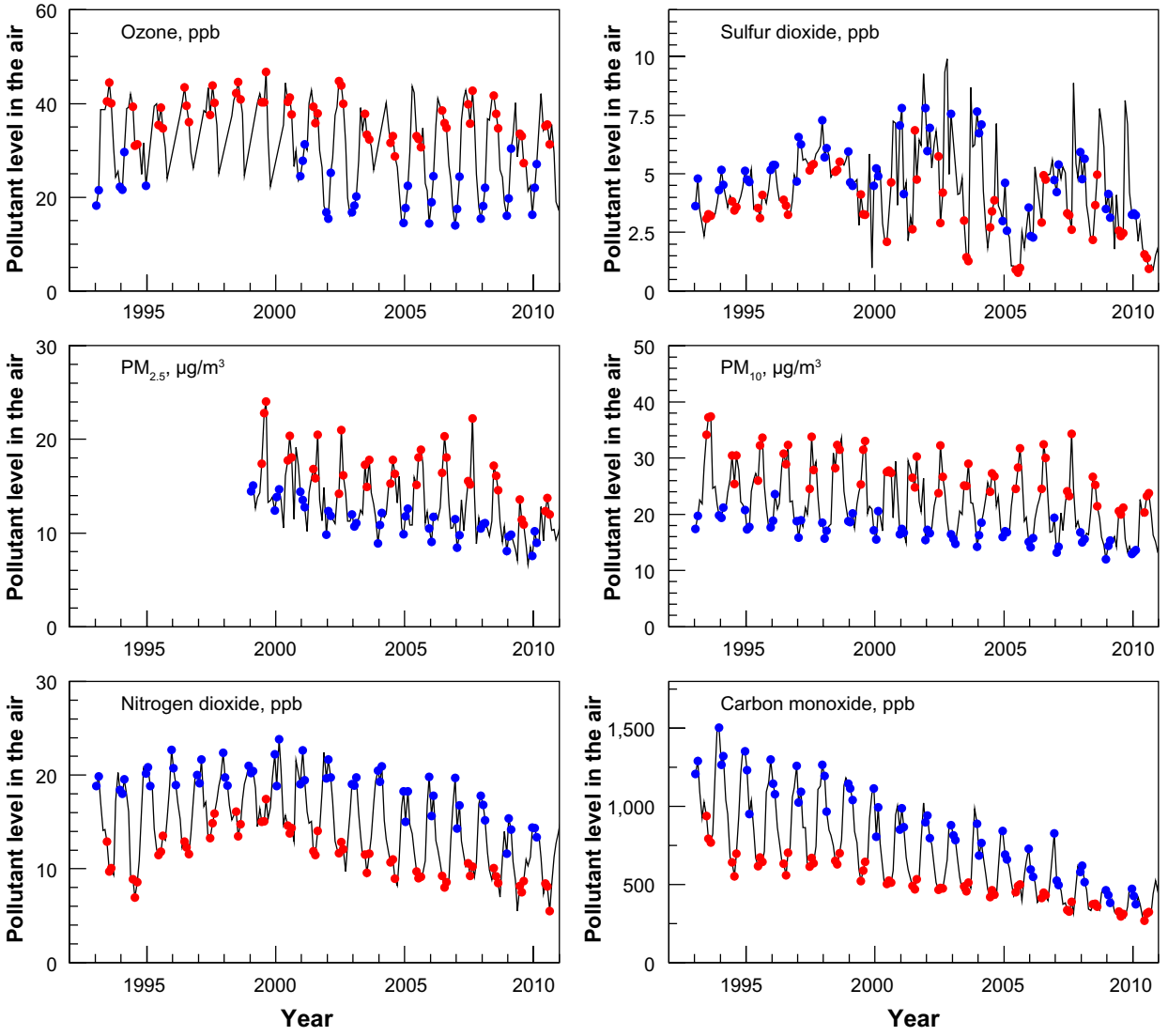

Figure 2 Seasonal fluctuations of air-pollutant levels: summer (red, 3 months) and winter (blue, 3 months), 1993–2011.
Abbreviation: PM, particulate matter.

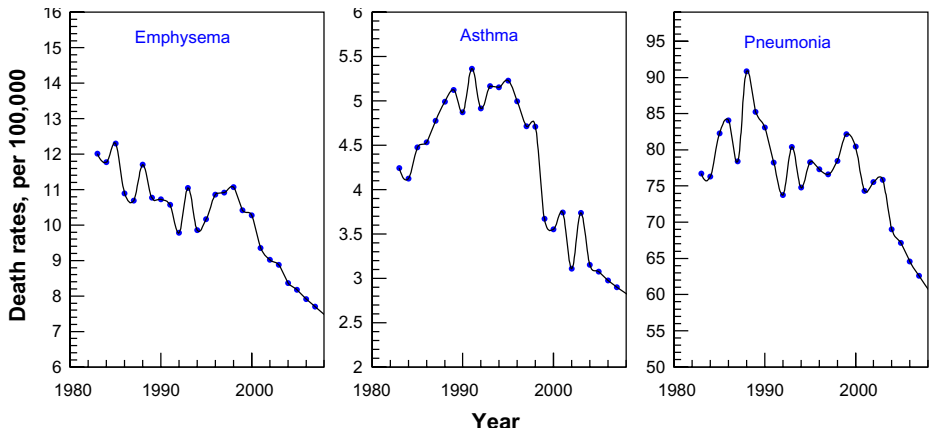

Figure 3 Trends in death rates for emphysema, asthma, and pneumonia in North Carolina, 1983–2010. Mortality rates were age-adjusted to the 2000 North Carolina population.

Table 2 Demographic characteristics of North Carolina population with cause-specific respiratory mortality, 1993–2010

Demographic characteristic	Cause of death		
	Emphysema	Asthma	Pneumonia
Number of deaths	13,187	5,509	10,1374
Sex, n			
Males	7,951 (60.3%)	1,806 (32.8%)	48,517 (47.9%)
Females	5,236 (39.7%)	3,703 (67.2%)	52,857 (52.1%)
Race, n			
Caucasians	11,866 (90.0%)	3,567 (64.8%)	82,759 (81.6%)
African-Americans	1,237 (9.4%)	1,853 (33.6%)	17,665 (17.4%)
Other	84 (0.6%)	89 (1.6%)	950 (1.0%)
Age, n			
<15 years old	7 (0.1%)	103 (1.9%)	595 (0.6%)
15–39 years old	40 (0.3%)	429 (7.8%)	1,633 (1.6%)
40–64 years old	2,504 (19.0%)	1,723 (31.3%)	12,054 (11.9%)
65+ years old	10,636 (80.7%)	3,254 (59.1%)	87,091 (85.9%)

that were significant under Bonferroni correction in the main analysis, associations between dynamics of SO_2 and mortality from emphysema (0.1399, $P<0.001$) and pneumonia (0.0698, $P<0.001$), and associations between changes of CO levels and asthma mortality (0.0004, $P<0.05$) were also significant in the sensitivity analysis. The association between CO and pneumonia mortality was also significant when analysis was performed on a county level (0.0002, $P<0.001$). Recall that this association was significant in the analysis using state-level data in two cases: when being corrected for changes of ICD codes and when only underlying causes of deaths were considered as contributing to the cause-specific death (see detailed results in Table S1). The effects of dynamics of SO_2 and PM_{10} on asthma mortality became nonsignificant ($P>0.05$), likely due to the small number of county-specific asthma deaths and due to the large fraction of zeroth death rates that were not successfully described by Equation 1.

Discussion

We found significant correlations between reduction of air pollutants and dynamics of deaths due to respiratory diseases during the period we studied. We need to contextualize these findings, particularly in regard to the multifactorial contributors to respiratory mortality. In general, COPD has been shown to correlate highly with air pollution linked to global urbanization,[26] eg, higher prevalence of chronic bronchitis (odds ratio [OR] 2.26, confidence interval [CI] 1.54–3.31), asthma (OR 1.57, CI 1.25–1.98), and emphysema (OR 2.98, CI 1.95–4.54) were observed in the meta-analyses of individuals exposed to urban air.[27] Little is known about whether chronic, low-dose exposure to ambient air pollutants can exacerbate COPD progression.[28,29] Several recent studies related respiratory symptoms to long-term rather than short-term effects of ambient particles,[30] with the long-term exposure to PM_{10} increasing the risk of COPD.[31]

Changing air quality in North Carolina could be a good example of analysis of the trends of both improved air quality and respiratory mortality over almost two decades of observations. Improved air quality in North Carolina since the mid-1990s is related to a series of federal and state acts and regulations (see Table 4), including the national heavy-duty truck engine standards, reduction of NO_x emissions, the Clean Smokestacks Act, and new engine standards. Regulations of emissions of NO_x, PM_{10}, and CO appeared to be very effective in improving air quality in the state. Observed seasonal fluctuations of air-pollutants levels could be due to season-dependent local dispersive conditions, breeze dynamics,

Table 3 Associations between trends in emphysema, asthma, and pneumonia death rates and dynamics of air pollutants in North Carolina, 1992–2010

Potential health-impact factor	Emphysema	Asthma	Pneumonia
Ozone, ppb	0.0061±0.0030, $P<0.05$	0.0082±0.0056*	–0.0011±0.0019*
Smoking	0.0493±0.0056†, $P<0.0001$	0.0649±0.0105†, $P<0.0001$	0.0413±0.0034†, $P<0.0001$
SO_2, ppb	0.0547±0.0106†, $P<0.0001$	0.0598±0.0173†, $P<0.001$	0.0309±0.0093†, $P<0.001$
Smoking	0.0399±0.0074†, $P<0.0001$	0.0563±0.0121†, $P<0.0001$	0.0360±0.0063†, $P<0.0001$
NO_2, ppb	0.0153±0.0062, $P<0.01$	0.0270±0.0094, $P<0.005$	0.0030±0.0053*
Smoking	0.0456±0.0090†, $P<0.0001$	0.0511±0.0140†, $P<0.001$	0.0455±0.0076†, $P<0.0001$
CO, ppb	0.0004±0.0001†, $P<0.0001$	0.0006±0.0001†, $P<0.0001$	0.0001±0.0001*
Smoking	0.0300±0.0083†, $P<0.001$	0.0349±0.0129, $P<0.01$	0.0388±0.0074†, $P<0.0001$
$PM_{2.5}$, μg/m³	0.0155±0.0066, $P<0.05$	0.0116±0.0083*	0.0044±0.0063*
Smoking	0.0414±0.0072†, $P<0.0001$	0.0329±0.0093†, $P<0.001$	0.0462±0.0067†, $P<0.0001$
PM_{10}, μg/m³	0.0045±0.0039*	0.0204±0.0058†, $P<0.001$	–0.0015±0.0035*
Smoking	0.0583±0.0069†, $P<0.0001$	0.0644±0.0109†, $P<0.0001$	0.0499±0.0057†, $P<0.0001$

Notes: For each air pollutant, the effect of smoking was evaluated. The effects of month-to-month fluctuations in disease-specific mortality for emphysema, asthma, and pneumonia are not shown in the table, but they also were evaluated for each month. *$P>0.05$; †significant under Bonferroni correction for multiple comparisons.
Abbreviation: PM, particulate matter.

Table 4 Timeline of key federal and North Carolina state-specific air regulations and actions

Year	Acts and regulations	Federal or North Carolina acts and regulations	Description of the act or regulation	Pollutant(s) under regulation	Level of targeted pollutant in North Carolina at the time of act/regulation (as shown in Figure 1)
1970	Congress passes the Clean Air Act, which called for the first tailpipe-emission standards	Federal	The new standards go into effect in 1975 with NO_x standard for cars and light-duty trucks of 3.1 g/mile (gpm)	NO_x	NA
1977–1988	Tightened emission standards in the Clean Air Act	Federal	For cars, in 1977–1979 the NO_x standard became 2.0 gpm; in 1981, it was reduced to 1.0 gpm For light-duty trucks, in 1979 the standard became 2.3 gpm; in 1988, the standard became 1.2 gpm For heavier trucks, in 1988 the standard became 1.7 gpm	NO_x	NA
1990–1994	Tier 1 tailpipe standards	Federal	For cars, the NO_x standard reduced from 1.0 gpm to 0.6 gpm For light-duty trucks, the standard ranged from 0.6 to 1.53 gpm, depending on truck's weight	NO_x	↑ NO_2 level
1990–1998	National Heavy Duty Truck Engine Standards	Federal	NO_x rate drops from 6.0 g/bhp-h to 4.0 g/bhp-h for both diesel and gasoline heavy-duty vehicles PM rate lowered from 0.6 to 0.1 g/bhp-h for diesel	NO_x, PM	↑ NO_2 level ↓ PM_{10} level
1994	EPA issued new standards for chemical plants to reduce toxic air pollutants	Federal	To reduce the emission of toxic air pollutants* at or near industrial locations by more than 0.5 million tons each year	188 toxic air pollutants to be regulated by EPA, including dioxins, benzene, arsenic, beryllium, mercury, and vinyl chloride	NA
1995	EPA launches an incentive-based acid-rain program, Phase I	Federal	To reduce SO_2 and NO_x emissions, ie, 2 million-ton reduction in NO_x emissions and reduction of SO_2 emissions by 40% below their required level Under regulation were 110 mostly coal-burning electric utility plants located in 21 Eastern and Midwestern states	SO_2, NO_x	↑ NO_2 level ↑ SO_2 level
1998	EPA promulgates the NO_x State Implementation Plan (SIP) Call	Federal	To identify the states in which the NO_x emissions from certain sectors were significantly contributing to nonattainment in or interfering with maintenance in downwind states	NO_x	↑ NO_2 level
1999–2001	National Low Emission Vehicles (NLEV) Program	Federal	To reach a 50% reduction in NO_x emissions from light-duty vehicles and 17% for light-duty trucks	NO_x	↑ NO_2 level
2000	EPA launches an incentive-based acid-rain program, Phase II	Federal	To reduce SO_2 and NO_x emissions	SO_2, NO_x	↑ NO_2 level ↓ SO_2 level
2001	NC EMC adopted rules to reduce ozone-forming NO_x emissions from coal-fired power plants and other large industrial sources	North Carolina	To reduce NO_x by 68% between 2000 and 2006	NO_x	↓ NO_2 level
2002	Clear Skies Initiative and alternative regulations	Federal	To reduce SO_2 emissions by 70% and NO_x emissions by 65% below current levels	SO_2, NO_x	↓ NO_2 level ↑ SO_2 level

(*Continued*)

Table 4 (*Continued*)

Year	Acts and regulations	Federal or North Carolina acts and regulations	Description of the act or regulation	Pollutant(s) under regulation	Level of targeted pollutant in North Carolina at the time of act/regulation (as shown in Figure 1)
2002	North Carolina General Assembly passed Session law 2002–4 (Senate Bill 1078), called Clean Smokestacks Act	North Carolina	To control multiple air pollutants from old coal-fired power plants; under the act, coal-fired power plants must achieve a 77% cut in NO_x emissions by 2009 and a 73% cut in SO_2 emissions by 2013. North Carolina's two largest utility companies, Duke Power and Progress Energy, must achieve these emissions cuts through actual reductions at their 14 power plants in the state; requires Duke Energy to limit NO_x emissions to 35,000 tons per year and Progress Energy to 25,000 tons per year for certain coal-fired units by 2007; to limit SO_2 emissions to 150,000 tons per year and 100,000 tons per year from Duke Energy and Progress Energy, respectively, by 2009	NO_x, SO_2. The act does not set caps on mercury; however, when NO_x and SO_2 limits are met, it will also reduce mercury by about 60%–90%; also, that will lead to reduction of PM levels	↓ NO_2 level ↑ SO_2 level
2003	Clean Bus USA program	Federal	EPA provides funds for more than 4,000 school buses to be retrofitted to remove 200,000 pounds of particulate matter from the air over the next 10 years	PM	↓ PM_{10} level ↓ $PM_{2.5}$ level
2004	Tier 2 tailpipe standards	Federal	New emissions standards requiring cars, sport utility vehicles, minivans and light-duty trucks to be 77%–95% cleaner than in 1999; the new standard is 0.07 gpm for NO_x; also, reduction in average SO_2 levels to 30 ppm	SO_2, NO_x, CO	↓ NO_2 level ↓ SO_2 level ↓ CO level
2005	EPA issues the Clean Air Act Interstate Rule (CAIR)	Federal (for the eastern US)	To achieve the largest reduction in air pollution in more than a decade by permanently capping SO_2 and NO_x emissions	SO_2, NO_x	↓ NO_2 level ↓ SO_2 level
2006	North Carolina 1998 Clean Air Plan	North Carolina	Low sulfur gasoline requirements go in place statewide	SO_2	↑ SO_2 level
2007	Additional regulations in the Smokestacks Act	North Carolina	Requires Duke Energy to limit NO_x emissions to 31,000 tons per year and Progress Energy to 25,000 tons per year for certain coal-fired units	NO_x	↓ NO_2 level
2007–2010	New heavy-duty engine standards	North Carolina	90%–95% lower emissions expected	CO	↓ CO level
2009	EPA approved North Carolina Clean Air Interstate Rules into the State Implementation Plan	North Carolina	NO_x and SO_2 emission allowances for North Carolina utilities to be lower than those set by the Clean Smokestacks Act	NO_x, SO_2	↓ NO_2 level ↓ SO_2 level
2009	Additional regulations in the Smokestacks Act	North Carolina	Requires Duke Energy to limit NO_x emissions to 31,000 tons per year and Progress Energy to 25,000 tons per year for certain coal-fired units; the act also requires SO_2 limits of 150,000 tons per year and 100,000 tons per year from Duke Energy and Progress Energy, respectively	NO_x, SO_2 Mercury, PM	↓ NO_2 level ↓↓ PM_{10} level ↑ $PM_{2.5}$ level ↓ SO_2 level
2011	North Carolina, the Tennessee Valley Authority (TVA), and several other parties agreed to a comprehensive settlement on the caps for all TVA coal-fired facilities	North Carolina and Tennessee	To decline annual basis to permanent levels of 110,000 tons of SO_2 in 2019 and 52,000 tons of NO_x in 2018; it requires TVA to install modern pollution controls or shutdown several of its coal-fired units	NO_x, SO_2	↓ NO_2 level ↓ SO_2 level
2013	Additional regulations in the Smokestacks Act	North Carolina	Requires Duke Energy to limit SO_2 emissions to 80,000 tons per year and Progress Energy to 50,000 tons per year for certain coal-fired units by 2013	SO_2	NA

Notes: The acts and regulations that had a major impact on air quality in North Carolina are highlighted in gray. *Toxic air pollutants are those pollutants known or suspected to cause cancer or other serious health effects, such as birth defects or reproductive effects (http://www.epa.gov/airtrends/aqtrnd95/tap.html). Up and down arrows mean an increase or decrease of respective air pollutant level as compared with the years before the date of the act/regulation became effective.
Abbreviations: PM, particulate matter; NA, not applicable; EPA, Environmental Protection Agency; NC EMC, North Carolina Environmental Management Commission.

differences in concentration process (eg, caused by the thinning of the air mixing layer in winter), and season-specific higher formation of certain compounds, eg, higher nitrate formation in the cold season leads to higher levels of NO_x in the air.[32] Higher PM levels observed in North Carolina during the summer are of additional concern for health effects being exacerbated by hot humid weather, especially during heat waves.[33] For respiratory mortality, no threshold effect has been identified;[34,35] therefore, detailed economic analysis is required to evaluate the expenses and benefits of keeping the levels of air pollutants extra low. For current regulations in the US, it has been shown that control of $PM_{2.5}$ emissions could result in $100 billion of benefits annually.[36]

Air quality and emphysema

In our study, the association between reduced levels of ozone, SO_2, NO_2, CO, and $PM_{2.5}$ and decreased mortality from emphysema were observed, with associations for SO_2 and CO remaining significant under Bonferroni correction. In other studies, emphysema outcomes were usually analyzed as a part of COPD; nonetheless, our findings on emphysema are in general agreement with these publications. For example, higher prevalence of visits to emergency departments for COPD and emphysema have been observed for higher SO_2 levels[37] (especially among older adults[38]); however, some studies showed that these associations may be attributable to SO_2 serving as a surrogate of other substances.[39] Few studies are available on the effects of outdoor CO on COPD.[40,41] Our results on associations between lower CO levels and lower emphysema mortality are in agreement with studies that showed increased morbidity and mortality risks among patients with COPD.[42–45] Note that the impacts of CO could be effectively minimized by controlling transportation activities, which accounts for more than three-quarters of CO emissions in the US.[42,46] While in our study associations with $PM_{2.5}$ became nonsignificant under Bonferroni correction, in other studies higher levels of $PM_{2.5}$ have been associated with higher admissions for COPD exacerbation[47] and with increased COPD mortality.[48–50] These differences could be due to the fact that the aforementioned studies were performed outside the US, had different patterns of seasonal fluctuations of PM levels in the air, and also were focused on specific populations (ie, older adults).

Air quality and asthma

We observed decreasing asthma mortality associated with lower levels of NO_2, SO_2, CO, and PM_{10}, with the latter three pollutants remaining significant under Bonferroni correction. These results are in agreement with other studies. For example, correlations have been reported between asthma mortality and SO_2[51] and NO_2[52–56] levels, and between asthma severity (in children) and CO levels.[43,44,57] Other studies reported that asthma mortality decreased earlier in response to improvement of air quality (eg, when compared to emphysema or chronic bronchitis),[51] with a decrease of asthma deaths occurring approximately 5 years earlier.

The effects of PMs on respiratory health and, in particular, on asthma have been studied predominantly for associations with prevalence of respiratory symptoms[58–60] and emergency department visits or hospital admissions.[28,61–63] It has been shown that asthma symptoms were exacerbated even at PMs concentrations being 60% below the safety limits for PMs (ie, that supposed not to affect the healthy population).[64] However, information on associations of asthma mortality with long-term exposure to PMs is sparse. In our study, reduction of PM_{10} (and its seasonal fluctuations) was associated with decreased asthma mortality in North Carolina. Previous studies on PM_{10} showed that elevated levels of PM_{10} were correlated with hospital admissions for asthma among patients aged 65+ years[65] and children,[44,57] and also with increased use of asthma medications among patients aged from 8 to 72 years old.[66]

Because air-quality and asthma-aggravation associations are reported from the studies typically performed in a single geographic region over a single season, individual study results may not be applicable to different populations and to longer weather/season cycles.[43] Also, different components of PMs (eg, sulfates, nitrates, organic chemicals, metals, and soil or dust particles)[12] may have different effects on the respiratory system.[16,34,67] This makes comparisons between the studies challenging and may explain the diversity of results on health effects of PMs on both geographic and temporal scales.[68]

Air quality and pneumonia

In our study, a decrease in pneumonia deaths was associated with decreasing SO_2 levels. Also, when pneumonia was considered as the underlying cause of death, lower pneumonia death rates were observed for lower CO levels. Some studies have linked an acute respiratory disease with higher levels of SO_2 pollution, independently of cigarette smoking,[69] while later studies have not confirmed these associations (however, some results were sensitive to the methods used to estimate air-pollutant levels).[70,71] For CO, an association has been reported between its increased concentrations and higher pneumonia hospitalization.[45]

While some epidemiological and experimental studies have suggested relationships between NO_2, ozone, and PMs and increased risk for viral respiratory infections,[72] we

in agreement with another study that did not find positive associations between PMs and pneumonia deaths (they found associations only for the group of never-smokers).[73] However, most of the studies were performed on pneumonia morbidity (including hospitalizations and emergency department visits), while our study was on mortality. Also, multiple reports on associations between pneumonia risk and PMs levels come from international studies, eg, from Europe (where PMs levels peak in winter), while on the East Coast of the US they typically peak in summer,[74] as we also observed in our study. While pneumonia is more frequent in late fall and winter, the relationships between outdoor air quality and health are supposed to be stronger in summer, when people spend more time outdoors. A study from Boston also supports our findings: no associations with pneumonia hospital admissions were found in summer, while in winter the largest effect on pneumonia morbidity was reported not for PMs but for black carbon (a surrogate for traffic particles: 14.3% increase of pneumonia hospitalizations for 1.7 $\mu g/m^3$ increase of black carbon).[45] Higher risk of morbidity and mortality from acute respiratory infections has been also reported for children exposed to PM_{10}.[22,75–85] In our study, we did not estimate mortality risks specifically for children; future studies will be performed for age-groups that are potentially at highest risk (ie, children and older adults).

Methodological aspects and study limitations

In our approach, the number of observations sufficient to estimate model parameters was achieved by incorporating monthly changes of air-pollutant levels and respiratory mortality. One advantage of this approach is that the unobserved heterogeneity due to other factors (such as socioeconomic status, quality of health care, migration) is minimal, because these factors do not essentially vary from month to month. In contrast, this unobserved heterogeneity is typical for ecological studies with area-based design, and could result in the occurrence of additional biases if these variables are not sufficiently controlled.

One example of such a factor is the time trend describing improvements in the treatment of respiratory disease that occurred during the recent two decades and which contributed to decreasing trends of mortality from emphysema, asthma, and pneumonia. Both improved air quality and vaccinations against pneumonia could lead to fewer hospital admissions, eg, pneumonia age-adjusted death rates started declining in the late 1990s, while the hospital than 15 years.[86–88] Although our approach with measurements at the month level minimizes the bias from this time trend (because only a 12th of our measurements reflect the annual time trend), improvements in treatment (as well as factors other than air pollution and smoking with significant time trends) should be taken into account in further studies. For example, further analysis of disease-specific visits to emergency departments would be important to validate the role of improved medical care in observed respiratory disease trends.

Other factors, such as changes in socioeconomic status, can also impact the dynamics of disease-specific mortality rates. However, it has been reported that for social factors, as well as for race, the effects of modification, eg, of PMs (ie, PM_{10}) on total mortality were weak.[20]

In our study, the time pattern of smoking was chosen to reflect annual trends in respiratory mortality in addition to air pollution. Inclusion of one additional variable measured annually (ie, not on a monthly basis) could result in difficulty in distinguishing the effect of this variable and smoking. Smoking was chosen because its patterns are concordant with patterns of respiratory mortality, and because of many substantive results on the role of smoking in respiratory mortality (eg, findings that both smoking and exposure to air pollutants [eg, $PM_{2.5}$] could exacerbate respiratory diseases).[28,73] In our study, smoking had a significant stable effect on the dynamics of respiratory mortality from all three studied diseases. However, it can also reflect possible impacts of other variables with similar to smoking time trends and associations with respiratory mortality. Better evaluation of smoking effects (including synergistic effects of smoking and air pollutants) could be achieved in studies with individual records on smoking status.

Study designs based on individual measurements of environmental exposure and health outcomes (which are classic epidemiologic approaches) would be helpful for improvement of the quality of estimates. However, such approaches are expensive and complex, in part due to the difficulty of measuring subjects' exposure to the relatively low levels of pollutants in the air. Some studies on the use of outdoor monitoring-station data (compared with the personal indoor/outdoor-exposure monitors) demonstrated that personal exposure to pollutants of outdoor origin was more closely related to outdoor air-pollutant levels than interpretations of personal monitoring data.[58,89] Furthermore, the frequently high correlations between levels of certain pollutants in the air also make it difficult to identify the impact of a single agent on human health.[17]

Changes in diagnostic criteria of respiratory diseases that happened during last two decades primarily affected the trends of disease incidence; however, in part, mortality trends were also affected. In children, diagnoses can transfer from chronic bronchitis and pneumonia to asthma, thus contributing to increasing trends in asthma prevalence (with its recent stabilization) and health care utilization.[90] If the person dies from pneumonia, but also had an underlying condition of which the pneumonia was probably a result, than that underlying disease but not pneumonia is considered the cause of death in the death certificate, and thus fewer deaths are directly attributable to pneumonia.[86] Although asthma death rates increased from 1980 to the mid-1990s, replaced ICD codes from the ninth to the tenth revision makes it challenging to evaluate the decline in asthma mortality since the late-1990s.[91,92] With regard to this problem, it has been shown that decline in asthma mortality that occurred from 1998 to 1999 included approximately 11% of decline that resulted from the changes during the ICD codes transition; then, under ICD-10, asthma death rates continued declining.[91] Because no definitive asthma laboratory tests exist, asthma estimates rely on the physician, who also should accurately attribute the cause of death to asthma; therefore, the reliability of the death certificates has been questioned (eg, for the chance of misreporting the cause of death in older persons with comorbid conditions). Large well-designed studies have concluded that asthma death coding has 99% specificity and low sensitivity (42%), and asthma as a cause of death was underreported in preference to COPD in all age-groups.[91,93]

Conclusion

We observed temporal regional associations between long-term dynamics of decreasing death rates of emphysema, asthma, and pneumonia and reductions of the levels of certain air pollutants in North Carolina. Our results support the hypothesis that improvement in air quality, especially declines in SO_2, CO, and PM_{10} levels in the air, contributed to the improved respiratory health of the North Carolina population. Since other factors (in addition to the studied air pollutants) might also account for improved health outcomes, ultimately caution should be exercised in inferring cause–effect relations.

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Author contributions

JK, WGR, and HKL developed the concept behind the study; JK and IA designed the study and carried out the data analysis with help from APA, SH, and HKL; JK wrote the paper with help from IA, and SH; APA, WGR, and HKL provided critical reviews of the manuscript. All authors have read and approved the final manuscript.

Disclosure

The authors report no competing conflicts of interest in this work.

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Supplementary material

Table S1 Results of the sensitivity analysis

Potential health-impact factor	Emphysema	Asthma	Pneumonia
	Analysis 1 (ICD-9/10)	Analysis 1 (ICD-9/10)	Analysis 1 (ICD-9/10)
Ozone, ppb	0.0056±0.0029, $P>0.05$	0.0052±0.0050, $P>0.05$	–0.0011±0.0019, $P>0.05$
Smoking	0.0433±0.0057, $P<0.0001$	0.0427±0.0097, $P<0.0001$	0.0411±0.0036, $P<0.0001$
	Analysis 2 (summer)	Analysis 2 (summer)	Analysis 2 (summer)
Ozone, ppb	0.0043±0.0069, $P>0.05$	–0.0004±0.0085, $P>0.05$	–0.0046±0.0024, $P>0.05$
Smoking	0.0777±0.0159, $P<0.0001$	0.1140±0.0205, $P<0.0001$	0.0403±0.0051, $P<0.0001$
	Analysis 3 (winter)	Analysis 3 (winter)	Analysis 3 (winter)
Ozone, ppb	0.0092±0.0037, $P<0.01$	0.0004±0.0098, $P>0.05$	0.0052±0.0056, $P>0.05$
Smoking	0.0377±0.0066, $P<0.0001$	0.0104±0.0153, $P>0.05$	0.0241±0.0101, $P<0.05$
	Analysis 4 (underlying)	Analysis 4 (underlying)	Analysis 4 (underlying)
Ozone, ppb	0.0039±0.0031, $P>0.05$	–0.0003±0.0084, $P>0.05$	0.0054±0.0049, $P>0.05$
Smoking	0.0524±0.0056, $P<0.0001$	0.0682±0.0156, $P<0.0001$	0.0814±0.0097, $P<0.0001$
	Analysis 1 (ICD-9/10)	Analysis 1 (ICD-9/10)	Analysis 1 (ICD-9/10)
SO_2, ppb	0.0502±0.0108, $P<0.0001$	0.0289±0.0159, $P>0.05$	0.0331±0.0094, $P<0.001$
Smoking	0.0361±0.0075, $P<0.0001$	0.0375±0.0109, $P<0.001$	0.0379±0.0064, $P<0.0001$
	Analysis 2 (summer)	Analysis 2 (summer)	Analysis 2 (summer)
SO_2, ppb	0.0551±0.0189, $P<0.05$	0.0535±0.0231, $P<0.05$	0.0027±0.0077, $P>0.05$
Smoking	0.0651±0.0145, $P<0.0001$	0.0978±0.0188, $P<0.0001$	0.0345±0.0052, $P<0.0001$
	Analysis 3 (winter)	Analysis 3 (winter)	Analysis 3 (winter)
SO_2, ppb	0.0823±0.0243, $P<0.001$	0.0298±0.0357, $P>0.05$	0.0596±0.0250, $P<0.05$
Smoking	0.0386±0.0167, $P<0.0001$	0.0432±0.0247, $P>0.05$	0.0194±0.0170, $P>0.05$
	Analysis 4 (underlying)	Analysis 4 (underlying)	Analysis 4 (underlying)
SO_2, ppb	0.0358±0.0126, $P<0.005$	0.0387±0.0259, $P>0.05$	0.1094±0.0193, $P<0.0001$
Smoking	0.0471±0.0087, $P<0.0001$	0.0724±0.0180, $P<0.0001$	0.0666±0.0140, $P<0.0001$
	Analysis 1 (ICD-9/10)	Analysis 1 (ICD-9/10)	Analysis 1 (ICD-9/10)
NO_2, ppb	0.0159±0.0062, $P<0.01$	0.0281±0.0084, $P<0.001$	0.0029±0.0053, $P>0.05$
Smoking	0.0367±0.0094, $P<0.0001$	0.0179±0.0129, $P>0.05$	0.0469±0.0079, $P<0.0001$
	Analysis 2 (summer)	Analysis 2 (summer)	Analysis 2 (summer)
NO_2, ppb	0.0434±0.0114, $P<0.0001$	0.0160±0.0163, $P>0.05$	0.0049±0.0051, $P>0.05$
Smoking	0.0410±0.0167, $P<0.01$	0.0987±0.0235, $P<0.0001$	0.0306±0.0067, $P<0.0001$
	Analysis 3 (winter)	Analysis 3 (winter)	Analysis 3 (winter)
NO_2, ppb	0.0135±0.0149, $P>0.05$	0.0224±0.0196, $P>0.05$	–0.01101±0.0145, $P>0.05$
Smoking	0.0621±0.0203, $P<0.005$	0.0352±0.0263, $P>0.05$	0.0591±0.0199, $P<0.005$
	Analysis 4 (underlying)	Analysis 4 (underlying)	Analysis 4 (underlying)
NO_2, ppb	0.0024±0.0072, $P>0.05$	0.0385±0.0133, $P<0.005$	0.0098±0.0114, $P>0.05$
Smoking	0.0590±0.0104, $P<0.0001$	0.0477±0.0204, $P<0.05$	0.0986±0.0171, $P<0.0001$
	Analysis 1 (ICD-9/10)	Analysis 1 (ICD-9/10)	Analysis 1 (ICD-9/10)
CO, ppb	0.0004±0.0001, $P<0.0001$	0.0002±0.0001, $P>0.05$	0.0002±0.0001, $P<0.05$
Smoking	0.0299±0.0084, $P<0.001$	0.0342±0.0120, $P<0.01$	0.0386±0.0073, $P<0.0001$
	Analysis 2 (summer)	Analysis 2 (summer)	Analysis 2 (summer)
CO, ppb	0.0013±0.0003, $P<0.0001$	0.0017±0.0004, $P<0.0001$	0.0002±0.0001, $P>0.05$
Smoking	0.0510±0.0149, $P<0.001$	0.0766±0.0179, $P<0.0001$	0.0298±0.0057, $P<0.0001$
	Analysis 3 (winter)	Analysis 3 (winter)	Analysis 3 (winter)
CO, ppb	0.0005±0.0001, $P<0.001$	0.0007±0.0002, $P<0.0001$	0.0001±0.0002, $P>0.05$
Smoking	0.0267±0.0202, $P>0.05$	–0.0173±0.0258, $P>0.05$	0.0454±0.0211, $P<0.05$
	Analysis 4 (underlying)	Analysis 4 (underlying)	Analysis 4 (underlying)
CO, ppb	0.0001±0.0001, $P>0.05$	0.0008±0.0002, $P<0.0001$	0.0010±0.0001, $P<0.0001$
Smoking	0.0501±0.0101, $P<0.0001$	0.0334±0.0194, $P>0.05$	0.0352±0.0150, $P<0.05$
	Analysis 1 (ICD-9/10)	Analysis 1 (ICD-9/10)	Analysis 1 (ICD-9/10)
$PM_{2.5}$, $\mu g/m^3$	0.0155±0.0066, $P<0.05$	0.0116±0.0083, $P>0.05$	0.0044±0.0063, $P>0.05$
Smoking	0.0414±0.0072, $P<0.0001$	0.0329±0.0093, $P<0.001$	0.0462±0.0067, $P<0.0001$
	Analysis 2 (summer)	Analysis 2 (summer)	Analysis 2 (summer)
$PM_{2.5}$, $\mu g/m^3$	0.0207±0.0113, $P>0.05$	0.0014±0.0105, $P<0.05$	0.0016±0.0045, $P>0.05$
Smoking	0.0578±0.0152, $P<0.0001$	0.0797±0.0141, $P<0.0001$	0.0352±0.0060, $P<0.0001$

(*Continued*)

Table S1 (*Continued*)

Potential health-impact factor	Emphysema	Asthma	Pneumonia
	Analysis 3 (winter)	Analysis 3 (winter)	Analysis 3 (winter)
$PM_{2.5}$, μg/m³	0.0224±0.0168, $P>0.05$	0.0195±0.0186, $P>0.05$	0.0039±0.0214, $P>0.05$
Smoking	0.0498±0.0154, $P<0.001$	0.0049±0.0168, $P>0.05$	0.0446±0.0193, $P<0.05$
	Analysis 4 (underlying)	Analysis 4 (underlying)	Analysis 4 (underlying)
$PM_{2.5}$, μg/m³	0.0030±0.0072, $P>0.05$	0.0030±0.0137, $P>0.05$	–0.0047±0.0101, $P>0.05$
Smoking	0.0560±0.0078, $P<0.0001$	0.0366±0.0154, $P<0.05$	0.0667±0.0106, $P<0.0001$
	Analysis 1 (ICD-9/10)	Analysis 1 (ICD-9/10)	Analysis 1 (ICD-9/10)
PM_{10}, μg/m³	0.0025±0.0039, $P>0.05$	0.0125±0.0053, $P<0.05$	–0.0012±0.0035, $P>0.05$
Smoking	0.0521±0.0072, $P<0.0001$	0.0395±0.0101, $P<0.0001$	0.0508±0.0059, $P<0.0001$
	Analysis 2 (summer)	Analysis 2 (summer)	Analysis 2 (summer)
PM_{10}, μg/m³	0.0169±0.0071, $P<0.05$	0.0243±0.0083, $P<0.05$	–0.0029±0.0026, $P>0.05$
Smoking	0.0714±0.0142, $P<0.0001$	0.1020±0.0176, $P<0.0001$	0.0377±0.0050, $P<0.0001$
	Analysis 3 (winter)	Analysis 3 (winter)	Analysis 3 (winter)
PM_{10}, μg/m³	–0.0104±0.0143, $P>0.05$	0.0407±0.0180, $P<0.05$	–0.0135±0.0143, $P>0.05$
Smoking	0.0828±0.0170, $P<0.0001$	0.0297±0.0213, $P>0.05$	0.0569±0.0162, $P<0.0005$
	Analysis 4 (underlying)	Analysis 4 (underlying)	Analysis 4 (underlying)
PM_{10}, μg/m³	–0.0063±0.0047, $P>0.05$	0.0256±0.0084, $P<0.005$	0.0140±0.0074, $P>0.05$
Smoking	0.0662±0.0078, $P<0.0001$	0.0679±0.0163, $P<0.0001$	0.0993±0.0133, $P<0.0001$

Notes: The following factors were tested: the potential effect of *International Classification of Diseases* (ICD) code changes (from ICD-9 to ICD-10) (analysis 1), the effects of air pollutants on mortality during the summer (analysis 2) and winter (analysis 3), and the association when only underlying causes of death contributed to the cause-specific death rates (analysis 4).
Abbreviation: PM, particulate matter.

Paper 2

PAPER 2: "Coarse Particulate Matter (PM 2.5-10) Affects Heart Rate Variability, Blood Lipids, and Circulating Eosinophils in Adults with Asthma" by K. Yeatts et al

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Coarse Particulate Matter ($PM_{2.5–10}$) Affects Heart Rate Variability, Blood Lipids, and Circulating Eosinophils in Adults with Asthma

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Introduction: We investigated whether markers of airway and systemic inflammation, as well as heart rate variability (HRV) in asthmatics, change in response to fluctuations in ambient particulate matter (PM) in the coarse [PM with aerodynamic diameter 2.5–10 μm ($PM_{2.5–10}$)] and fine ($PM_{2.5}$) size range.

Methods: Twelve adult asthmatics, living within a 30-mile radius of an atmospheric monitoring site in Chapel Hill, North Carolina, were followed over a 12-week period. Daily $PM_{2.5–10}$ and $PM_{2.5}$ concentrations were measured separately for each 24-hr period. Each subject had nine clinic visits, at which spirometric measures and peripheral blood samples for analysis of lipids, inflammatory cells, and coagulation-associated proteins were obtained. We also assessed HRV [SDNN24HR (standard deviation of all normal-to-normal intervals in a 24-hr recording), ASDNN5 (mean of the standard deviation in all 5-min segments of a 24-hr recording)] with four consecutive 24-hr ambulatory electrocardiogram measurements. Linear mixed models with a spatial covariance matrix structure and a 1-day lag were used to assess potential associations between PM levels and cardiopulmonary end points.

Results: For a 1-μg/m^3 increase in coarse PM, SDNN24HR, and ASDNN5 decreased 3.36% (p = 0.02), and 0.77%, (p = 0.05) respectively. With a 1-μg/m^3 increase in coarse PM, circulating eosinophils increased 0.16% (p = 0.01), triglycerides increased 4.8% (p = 0.02), and very low-density lipoprotein increased 1.15% (p = 0.01). No significant associations were found with fine PM, and none with lung function.

Conclusion: These data suggest that small temporal increases in ambient coarse PM are sufficient to affect important cardiopulmonary and lipid parameters in adults with asthma. Coarse PM may have underappreciated health effects in susceptible populations.

Key words: asthma, coarse PM, heart rate variability, inflammatory markers, lipids, systemic inflammation. *Environ Health Perspect* 115:709–714 (2007). doi:10.1289/ehp.9499 available via *http://dx.doi.org/* [Online 18 January 2007]

In a recent review article of the health effects of coarse airborne particles on health, Brunekreef and Forsberg (2005) call for special consideration in studying and regulating coarse particulate matter [PM with aerodynamic diameter 2.5–10 μm ($PM_{2.5–10}$)] separately from fine particulate matter ($PM_{2.5}$). Epidemiologic evidence indicates that coarse PM had as strong a short-term effect (or stronger) as fine PM on asthma, chronic obstructive pulmonary disease (COPD), cardiac, and respiratory hospital admissions (Brunekreef and Forsberg 2005; Burnett et al. 1997, 1999; Chen et al. 2004; Sheppard et al. 1999). There is a growing body of work examining the mechanisms of effect of fine PM on heart rate variability (HRV) and systemic inflammation in susceptible populations such as the elderly, individuals with COPD, and individuals with recent myocardial infarction, hypertension, diabetes, or ischemic heart disease (Chuang et al. 2005; Liao et al. 1999; O'Neill et al. 2005; Park et al. 2005; Sullivan et al. 2005; Wheeler et al. 2006). However, few if any studies have examined potential mechanisms of effect of coarse PM to explain the epidemiologic associations between increased mortality/morbidity and exposure to ambient coarse PM.

Coarse PM can be distinguished from other particulate sizes by the content of bioactive microbial products. Becker et al. have reported that coarse PM activates macrophages and monocytes *in vitro* in a toll-like receptor (TLR)2- and TLR4-dependent fashion, with a significant fraction of this biologic activity being ascribed to endotoxin (Becker et al. 2002; Soukup and Becker 2001). Alexis et al. (2006) recently showed that in healthy individuals, endotoxin on inhaled coarse PM elicits innate immune responses *in vivo* on airway macrophages. Likewise, endotoxin found in ambient PM samples (Mueller-Anneling et al. 2004), indoor dust samples (Michel et al. 1996; Pacheco et al. 2003; Thorne et al. 2005), and via personal ambient air monitoring (Rabinovitch et al. 2005) was linked to increased respiratory morbidity in children, demonstrating the likely importance of endotoxin containing coarse PM. Adachi et al. (2006) found that intraperitoneally administered endotoxin decreases heart rate variability measures such as rMSSD (root mean square of successive differences in normal-to-normal R-R intervals) and spectral density at low and high frequencies in a mouse model. Moreover, we and others have found that bronchial challenge with endotoxin also induces systemic inflammatory effects in asthmatics, even at inhaled doses that do not cause overt airway or systemic symptoms (Alexis et al. 2004; Michel et al. 1992, 1997).

Collectively, these observations led to the hypothesis that coarse PM has the ability to induce respiratory, cardiovascular, and systemic effects in humans and perhaps more so in those with preexisting airway disease such as asthma. As in our previous panel study on the effects of ambient PM on highway patrol officers (Riediker et al. 2004), we employed a repeated-measures design and examined a

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panel of 12 adults with asthma to determine the effects of two PM size fractions on *a*) circulating immune cells and prothrombotic factors, *b*) the induction of airway inflammation, and *c*) changes in cardiac autonomic function. Asthmatics were studied because they were considered more likely to demonstrate cardiopulmonary and systemic effects from ambient PM than healthy populations.

Materials and Methods

Population and study design. Twelve adults with persistent asthma (ranging from mild to severe disease), living within a 30-mile radius of the PM ambient exposure monitor located at the U.S. Environmental Protection Agency (EPA) research facility in Chapel Hill, North Carolina, were each monitored over a 12-week period. The study was designed to evaluate a range of ambient PM concentrations. Each subject made nine clinic visits, five the first week and four spaced randomly over the subsequent 6–11 weeks. Enrollment occurred from 9 September 2003 to 19 July 2004. Subjects were excluded from the study if they had a medical history of cystic fibrosis, COPD, chronic bronchitis, recurrent pneumonia, pulmonary embolism, congestive heart failure, vocal cord dysfunction, chest wall deformity, autoimmune disease, diabetes, existing heart disease, or any health problem that precluded following study protocol. Potential study subjects were excluded if they smoked more than two packs of cigarettes in the year before study enrollment. The University of North Carolina (UNC) Biomedical Institutional Review Board reviewed and approved the research protocol as did the U.S. EPA. All study subjects gave informed consent before participation.

Study logistics. At enrollment, we obtained demographic information and medical histories using a standardized questionnaire. During the first clinic visit, participants underwent a physical exam, phlebotomy, electrocardiogram (ECG), and a pulmonary function test. The subsequent eight clinic visits included a phlebotomy, physical examination, and pulmonary function testing. Eight of 12 volunteers consented to epicutaneous skin testing during the study period. Four volunteers were unwilling to discontinue antihistamine therapy and were not skin tested. Skin prick tests (SPT) for house dust mites, German cockroach, an Eastern tree mix, grass mix, two mold mixes, guinea pig, rat, cat, and mouse were performed, with four of the eight tested subjects having a positive response to at least one allergen, three persons having completely negative skin tests, and one having invalid results due to a nonreactive histamine control test. Use of asthma medications was recorded, including anti-inflammatory controller medication (inhaled corticosteroids, oral corticosteroids, oral leukotriene inhibitors), and rescue medication (short-acting beta$_2$ agonist, albuterol). Asthma severity was classified using the National Heart, Lung, and Blood Institute (NHLBI) Asthma Guidelines (NHLBI 2003). Daily asthma symptoms and medication use were recorded electronically in a personal digital assistant (PDA).

PM air pollution measurements. Daily ambient coarse ($PM_{2.5–10}$) and fine ($PM_{2.5}$) size PM were measured separately for each 24-hr period using a Dichotomous Partisol-Plus Sequential Air Sampler (Model 2025-D; Rupprecht & Patashnick Co., Inc., Albany, NY) located on the roof of the U.S. EPA Human Studies Facility on the UNC campus in Chapel Hill. Coarse PM is usually not directly measured, only calculated as the difference between PM_{10} and $PM_{2.5}$. However, we directly measured coarse PM and fine PM separately within the same air stream using a method that first separates the particles according to their size fraction before collecting them. PM mass retained on the Teflon filters (47 mm 2.0 µm; Teflo Pallflex Gelman Scientific; Pall Corporation, Ann Arbor, MI) was weighed on a microbalance in an EPA weight chamber.

Lung function, airway inflammation, and airway cell surface marker expression. Lung function was measured at each clinic visit using a spirometer (Sensormedics Corporation, Yorba Linda, CA). Pre-bronchodilator values were used. Induced sputum was performed according to previously published procedures (Alexis et al. 2001, 2004, 2005), and airway inflammation measures included enumeration of inflammatory cells (neutrophils, eosinophils, monocytes, macrophages). Flow cytometry was performed using a FACSORT (Becton Dickinson, Franklin Lakes, NJ) as previously described (Alexis et al. 2005, 2006). Macrophages, monocytes, neutrophils, and lymphocytes in sputum were labeled with fluorescent monoclonal antibodies, identified, and gated based on light scatter properties (FSC: cell size; SSC: cell granularity) and positive expression for CD45 (panleukocyte marker), HLA-DR/CD14 (macrophages/monocytes), CD16/FcgRIII (neutrophils), CD16-/FcgRIII (eosinophils), and CD3 (lymphocytes). The appropriate isotypic controls were used. Analysis was performed using the Cell Quest software (Becton Dickinson) and receptor expression was expressed as mean fluorescence intensity (MFI).

Circulating cells, lipids, and proteins. During each clinic visit, blood was drawn using standardized procedures for phlebotomy, collection, and storage. Blood samples were taken from antecubital veins and collected into vacuum tubes. Blood samples were sent to LabCorp (Burlington, NC) for a complete blood count analysis that included differential leukocyte analysis.

Plasma from these samples was distributed into aliquots and stored at –80°C until assayed in our laboratory using commercially available ELISA kits. Analytes of interest included interleukin-6, (R&D Systems, Minneapolis, MN), protein C, prothrombin, plasminogen, Factor VII, Factor IX (Enzyme Research Labs, South Bend, IN), plasminogen activator inhibitor type 1 (Oncogene Science, Cambridge, MA), von Willebrand factor (Diagnostica Stago, Asnières-sur-Seine, France), and fibrinogen (DiaSorin, Stillwater, MN).

HRV assessment using ambulatory ECG. During the first week of the study, changes in HRV parameters were measured using an ambulatory ECG (Zymed Inc., Camarillo, CA). After a 20-min rest, ECG R-waves were recorded from participants in a supine position. Subjects wore the ambulatory ECG recorders for four 24-hr periods. Each morning, at the beginning of the clinic visit, volunteers rested quietly in a supine position for 20 min followed by a specific 10-min period of recording (again in the supine position). The final 10-min period was used specifically for frequency domain analysis of HRV. Each 24-hr period of ECG data was analyzed by a cardiac electrophysiology nurse specialist and reviewed by a cardiologist. We measured ASDNN5 (the mean of the standard deviation in all 5-min segments of a 24-hr recording), SDANN5 (the standard deviation of the average of normal-to-normal intervals in all 5-min segments of a 24-hr recording), SDNN24HR [the standard deviation of all normal-to-normal R-R intervals in a 24-hr recording (milliseconds)], SDNN7min taken from the 7-min rest period each morning, and rMSSD. Additional measurements in the time domain included pNN50 [the percentage of differences between adjacent normal to normal intervals that are > 50 msec for both a 24-hr period (pNN50_24), and a 7-min period (pNN50_7), measured after 20 min supine] and the mean cycle length of normal R-R intervals (MCL). Mean heart rate (beats per minute), a general marker of autonomic function, was derived from the RR-interval record.

SDNN24HR was used to estimate the overall modulation of autonomic nervous system function and reflects total variability, whereas rMSSD estimates high-frequency variations in heart rate and primarily reflects parasympathetic activity. ASDNN5 includes respiratory-mediated parasympathetic input as well as baroreceptor-mediated sympathetic and parasympathetic input. To address the issue of HRV circadian cycles, we examined several HRV parameters from the same time each day, pNN50 measured for 7 min, and SDNN measured for a 7-min period during the 20-min rest period at the same time each morning.

We used a fast Fourier transformation to calculate the power spectral density curve.

We used the area under the curve in the high-frequency range (0.15–0.40 Hz) to estimate parasympathetic modulation of variability. And we used low-frequency (LF) power (0.04–0.15 Hz) to estimate the joint contribution of parasympathetic and sympathetic influences on HRV, although it reflects primarily sympathetic modulation.

Statistical analyses. We used linear mixed models with restricted maximum-likelihood estimation to assess potential time-varying associations of coarse and fine PM with sputum measurements, lung function, measures of HRV, proteins associated with plasma coagulation, hemostatic and inflammatory markers, and serum lipids. A 24-hr or 1-day lag of effect was assumed; the daily 24-hr PM concentrations were matched with the outcome measurements of the subsequent day. We also evaluated 2- and 3-day lags (Peel et al. 2005; Pekkanen et al. 2002; Peters et al 2004; Ruckerl et al. 2006; Timonen et al. 2006; Zeka et al. 2005) for all outcomes.

Models included the time-varying factors of atmospheric average daily temperature, humidity, and pressure. Time-invariant subject specific characteristics (such as age and sex) were not included in the final models because no differences in main effect estimates were seen with the time-invariant variables. Each subject served as his or her own control by study design. Daily PM concentrations and atmospheric variables were modeled as fixed effects.

The models included a random intercept for each subject to help account for between-subject variability. The correlation matrix structure with the repeated measures statement was specified as a spatial power function with an exponential time term of the form $f(d_{ijj'}) = \rho^{d_{ijj'}}$. This parameterization accounts for the variable time between clinic visits for each individual; in particular, for the ith person $\text{corr}(Y_{ij}, Y_{ij'}) = \rho^{d_{ijj'}}$, where $d_{ijj'}$ is the time (in days) between responses Y_{ij} and $Y_{ij'}$ for the ith person. All statistical computations were performed with SAS software version 8.2 (SAS Institute Inc., Cary, NC) using the "proc mixed" (mixed models) procedure. To evaluate potential outliers we examined the regression residuals. Plots of the residuals versus predicted values were constructed and examined for outliers. In addition, we also used the interactive data analysis feature in SAS to construct crude bivariate plots of coarse PM and main outcomes variables for all study subjects and for each individual. There was no evidence of significant influence by outliers or the models being driven by one or two subjects.

Results

Environmental measures. The mean (± SD) coarse PM concentration for the 284 days sampled was 5.3 ± 2.8 μg/m^3 with a range of 0–14.6 μg/m^3; for fine PM, the mean concentration was 12.5 ± 6.0 μg/m^3 with a range of 0.6–37 μg/m^3. The average temperature was 17.6°C, and the relative humidity 49.1%. Coarse and fine PM were not strongly correlated with relative humidity or barometric pressure, although temperature was statistically significantly correlated (0.48 and 0.61, respectively, $p < .01$). The fine PM and PM_{10} levels never exceeded the 1990 U.S. National Ambient Air Quality 24-hr standard of 65 μg/m^3 and 150 μg/m^3, respectively (U.S. EPA 1990). Summary statistics for air pollution and weather characteristics are presented in Table 1. Subsequent results are presented for a 1-day lag. We evaluated 2- and 3-day lags and did not find any patterns of statistically significant associations with the 2- or 3-day lags with measures of HRV, blood lipids, coagulation, or lung function and markers of inflammation.

Subjects. The 12 subjects (3 male, 9 female) ranged in age from 21 to 50 years, with a mean of 33 years. Three subjects were African American (Table 2). Most asthmatics had mild disease severity (7 persistent, 2 intermittent), two had moderate disease and one severe. Percent predicted FEV_1 (forced expiratory volume at 1 sec) values for the subjects ranged from 65 to 118%, with a mean of 96%. Four of 12 subjects were atopic (positive skin prick test), four were unable/unwilling to withdraw from antihistamine use but had previously tested positive for allergies before study enrollment, and four had invalid skin prick test results (negative histamine result or positive saline result) but reported allergic symptoms. All subjects took short acting beta-agonist rescue medication, and 10 of the 12 were taking controller medication (9 inhaled corticosteroids, 1 leukotriene inhibitor). Summary statistics (means, standard deviations, and range) of the HRV, circulating proteins, and lipids for the twelve study subjects are presented in the Supplemental Material Table 1 (available online at http://www.ehponline.org/docs/2007/9499/suppl.pdf). They are within the normal range of healthy individuals, and comparable to other recently published studies (Liao et al. 2004).

Changes in spirometry, symptoms, induced sputum parameters, and total particle size fractions. No consistent associations between either coarse PM or fine PM were found with spirometric measurements, rescue beta-agonist use, or reported symptoms; nor were associations found with measures of airway inflammation [see Supplemental Material Tables 2 and 3, (including sputum macrophages, monocytes, and neutrophils) available online at http://www.ehponline.org/docs/2007/9499/suppl.pdf].

HRV and total particle size fractions. We observed statistically significant changes in HRV associated with $PM_{2.5-10}$ (Table 3). For a 1-μg/m^3 increase in $PM_{2.5-10}$, heart rate variability as measured by SDANN5, SDNN24HR, and ASDNN5 decreased 3.76% ($p = 0.02$), 3.360% ($p = 0.02$), and 0.77% ($p = 0.05$), respectively. We found a borderline association with pNN50_7min ($p = 0.07$), and no association with the 7-min SDNN (SDNN7min). High-frequency power, a measure of parasympathetic modulation,

Table 1. Ambient air characteristics and PM concentrations ($n = 284$ days).

Variable	Concentration (mean ± SD)	Range	Spearman ρ correlation coefficients $PM_{2.5-10}$	Spearman ρ correlation coefficients $PM_{2.5}$
$PM_{2.5-10}$ (coarse)	5.3 ± 2.8	(0 to 14.6)	1	0.46*
$PM_{2.5}$ (fine)	12.5 ± 6.0	(0.6 to 37.1)	0.46*	1
PM_{10} (total)	17.5 ± 7.8	(1.4 to 45.6)	0.73*	0.90*
Temperature (°C)	17.6 ± 8.5	(–5.0 to 32.9)	0.60*	0.48*
Relative humidity (%)	49.1 ± 14.5	(10.5 to 91.6)	0.13**	0.16
Barometric pressure (mm Hg)	756.1 ± 5.9	(741 to 770)	0.11	–0.01

*$p < 0.01$. **$p < 0.05$.

Table 2. Demographic characteristics of study participants ($n = 12$).

Category	No. (%)[a]
Sex	
Female	9 (75)
Race/ethnicity	
African American	3 (25)
White	7 (58)
Latino	1 (8)
Asian	1 (8)
NHLBI severity classification	
Severe	1 (8)
Moderate persistent	2 (17)
Mild persistent	7 (58)
Mild intermittent	2 (17)
Asthma medication	
Antiinflammatory controller medication	10 (83)
Inhaled corticosteroids	
Fluticasone/salmeterol	5 (42)
Budesonide	3 (25)
Fluticasone	1 (8)
Leukotriene inhibitor (montelukast)	1 (8)
Beta-agonists (albuterol)	12 (100)
Allergies	
Antihistamine therapy	4 (33)
Subjects SPT	8 (67)
SPT positive	4 (33)
Symptoms, SPT negative	3 (25)
Uninterpretable SPT	1 (8)
IgE concentration (IU/mL)	166.7 (3–755)
Percent predicted FEV1 [%, mean (range)]	0.96 (65–118)
Age [years, mean (range)]	33.17 (21–50)

[a]Percentages are rounded to the near whole number.

decreased 0.46% (p = 0.01) per 1-μg/m^3 increase in coarse PM, indicating a decrease in vagal autonomic input to the heart associated with coarse PM. Similar patterns were not seen for fine PM (see Supplemental Material Tables 4 and 5, available online at http://www.ehponline.org/docs/2007/9499/suppl.pdf).

Circulating proteins, cells, and lipids and total particle size fractions. Estimated regression coefficients (percent) and p-values for circulating proteins, cells, and lipids associated with coarse and fine PM are presented in Table 4. For a 1-μg/m^3 increase in coarse PM, a 0.16% increase in circulating eosinophils (p = 0.01) was found. Ambient coarse PM was also associated with changes in blood lipids. For a 1-μg/m^3 increase in coarse PM, an increase of 4.8% in triglycerides (milligrams per deciliter) (p = 0.02) and a 1.15% increase in very low-density lipoprotein (VLDL) (milligrams per deciliter) (p = 0.01) were found. After adjusting for ambient temperature, relative barometric pressure, and relative humidity, the association of the levels of blood coagulation–related proteins (fibrinogen and plasminogen) with coarse PM were of borderline significance (p = 0.07, p = 0.08). For a 1-μg/m^3 increase in coarse PM, a decrease of 0.01% in plasminogen (international units per milliliter) and 0.04% in fibrinogen concentration (milligrams per milliliter) were found.

Other blood proteins and lipids revealed no associations with either size fraction of PM. Other circulating inflammatory cells (basophils, monocytes, lymphocytes, or neutrophils) were not significantly associated with coarse PM concentrations. C-reactive protein was not statistically significantly associated with increases in ambient coarse or fine PM concentrations. No consistent statistically significant relationships were seen for fine PM (Table 5, Supplemental Material, available online at http://www.ehponline.org/docs/2007/9499/suppl.pdf).

Discussion

We examined airway and systemic responses to exposure to ambient coarse ($PM_{2.5–10}$) and fine ($PM_{2.5}$) PM in a cohort of adult asthmatics. Recent reports suggest that coarse PM initiates responses from airway cells *in vivo* in healthy volunteers (Alexis et al. 2006) and may be an underappreciated cause for respiratory and systemic inflammation (Brunekreef and Forsberg 2005). This study is the first to report that relatively low concentrations of coarse PM are associated with decreases in HRV, increases in circulating eosinophils, and serum triglycerides in adult asthmatics.

We were somewhat surprised that we did not observe any relationship between coarse or fine PM with rescue medication use, asthma symptoms, lung function, or airway inflammatory markers in sputum samples. However, 10 of the 12 adult asthmatics in the present study were treated with anti-inflammatory controller medication for their disease, and 9 of the 12 had mild disease. It is possible that anti-inflammatory treatment mitigated the effect of PM in their airways, or that adults with asthma are less susceptible to the effects of PM than children with asthma [in whom associations have been reported with coarse PM and increased asthma admissions to hospitals (Lin et al. 2002)]. Indeed, we have observed that inhaled corticosteroids minimizes the effect of inhaled endotoxin in asthmatics (Alexis et al. 2001). Mar et al. (2004) have reported that health outcomes associated with coarse PM were more notable in children with asthma than in adults with asthma. All the ambient fine and coarse PM concentrations in this panel study were well below the current 1997 National Ambient Air Quality Standards (U.S. EPA 1990), and the variability in PM measurements was not very large over the course of the study; this may not have been sufficient to induce acute lung inflammation in adults with well-controlled asthma. We did observe, however, a significant increase in circulating eosinophils in this cohort that was associated with coarse PM, suggesting a general pro-allergic effect of coarse PM in asthmatics, even in the absence of airway effects.

Despite the lack of short-term effect of PM on respiratory-tract biology in these asthmatics, we found that both coarse and fine PM had a significant effect on cardiac autonomic function as reflected by changes in heart rate variability. However, the associations between coarse PM and HRV were stronger and more consistent than with fine PM. In particular, greater effects were noted between coarse PM exposure and decreased high-frequency power (and percent high-frequency power) in the frequency domain, and decreased ASDNN5, SDANN5, and SDNN24HR parameters in the time domains. These measures are consistent with decreased parasympathetic influence and vagal tone. With respect to fine PM, there was a modest association with two heart rate variability parameters (SDANN5 and rMSSD).

Our HRV findings are consistent with those of Gong et al. (2004), who reported that mild asthmatic and normal volunteers undergoing a controlled exposure to particulate

Table 3. Change in HRV indices[a] per 1-μg/m^3 increase in $PM_{2.5–10}$ and $PM_{2.5}$.

	$PM_{2.5–10}$				$PM_{2.5}$			
	Estimated regression coefficient	SE	p-Value	95% CI	Estimated regression coefficient	SE	p-Value	95% CI
HRV								
Max heart rate	−1.95	0.88	0.03	−3.67 to −0.23	0.40	0.43	0.36	−0.45 to 1.24
ASDNN5	−0.77	0.37	0.05	−1.50 to −0.04	−0.07	0.15	0.63	−0.37 to 0.22
SDANN5	−3.76	1.53	0.02	−6.76 to −0.76	1.66	0.65	0.02	0.39 to 2.93
SDNN24HR (msec)	−3.36	1.38	0.02	−6.06 to −0.65	1.16	0.58	0.06	0.02 to 2.29
rMSSD	−0.75	0.53	0.16	−1.79 to 0.28	0.53	0.20	0.01	0.14 to 0.91
pNN50_24hour	−0.50	0.27	0.07	−1.03 to 0.03	−0.06	0.11	0.58	−0.27 to 0.15
pNN50_7min	−1.88	0.55	0.07	−2.95 to −0.81	0.47	0.42	0.27	−0.35 to 1.29
Low-frequency power	−0.19	0.42	0.65	−1.01 to 0.63	−0.23	0.14	0.11	−0.51 to 0.05
Percent low frequency	0.57	1.08	0.60	−1.55 to 2.69	−0.78	0.41	0.07	−1.59 to 0.03
High-frequency power	−0.46	0.17	0.01	−0.79 to −0.14	0.14	0.07	0.07	−0.01 to 0.28
Percent high frequency	−2.14	0.94	0.03	−3.98 to −0.30	0.64	0.36	0.09	−0.07 to 1.34

Abbreviations: Max, maximum; pNN50_24hour and pNN50_7min, percentage of differences between adjacent normal-to-normal intervals that are > 50 msec for either 24 hr or 7 min during resting period each morning.
[a]Adjusted for relative temperature, pressure, and humidity.

Table 4. Change in circulating proteins and hematologic and lipid indices[a] per 1-μg/m^3 increase in $PM_{2.5–10}$ and $PM_{2.5}$.

	$PM_{2.5–10}$				$PM_{2.5}$			
Outcome	Estimated regression coefficient	SE	95% CI	p-Value	Estimated regression coefficient	SE	95% CI	p-Value
Blood lipids								
Triglycerides	4.78	2.02	0.81 to 8.74	0.02	−0.63	0.84	−2.29 to 1.02	0.46
VLDL	1.15	0.44	0.29 to 2.02	0.01	−0.17	0.22	−0.61 to 0.26	0.44
Total cholesterol	0.78	0.54	−0.28 to 1.84	0.15	−0.06	0.22	−0.49 to 0.36	0.77
Hematologic factors and circulating immune cells								
Circulating eosinophils	0.16	0.06	0.04 to 0.28	0.01	−0.02	0.00	−0.02 to −0.02	0.27
Platelets	−1.71	1.11	−3.89 to 0.47	0.13	−0.01	0.45	−0.88 to 0.86	0.98
Circulating proteins								
Plasminogen	−0.01	0.01	−0.02 to 0.00	0.08	0.00	0.00	−0.01 to 0.00	0.82
Fibrinogen	−0.04	0.02	−0.08 to 0.00	0.07	0.00	0.01	−0.01 to 0.02	0.59
Von Willibrand factor	−1.23	0.66	−2.53 to 0.06	0.07	−0.31	0.29	−0.87 to 0.25	0.28
Factor VII	−0.90	0.85	−2.58 to 0.77	0.29	−0.65	0.33	−1.29 to −0.01	0.05

[a]Adjusted for relative temperature, pressure, and humidity.

matter (80% of which was coarse PM by mass) had a small but significant increase in heart rate with decreased HRV in both normal volunteers and asthmatics, though the effects in normal volunteers were somewhat more pronounced. Similarly, the decreases in HRV measurements were comparable in magnitude to decreases associated with fine PM in other susceptible populations (Gold et al. 2000; Holguin et al. 2003; Liao et al. 1999, 2004; Park et al. 2005; Pope et al. 1999, 2004). For example, in our study the estimated regression coefficient for high frequency was a –4.6 [95% confidence interval (CI), –7.9 to –1.4] percent change with a 10-μg/m^3 increase in coarse PM; Liao et al. (2004) reported an estimated regression coefficient for high frequency of 5.1 (95% CI, –8.0 to –2.1) with a 10-μg/m^3 increase in fine PM.

There was also a near significant decrease of plasma plasminogen, fibrinogen, and von Willebrand factor (suggesting metabolic consumption of these agents), and a significant increase in triglycerides and VLDL related to increased exposure to coarse PM. Recently published clinical and epidemiologic studies support the plausibility of the increased triglycerides and VLDL association with elevated PM as a potential mechanism for atherosclerotic plaque progression (Chen and Nadziejko 2005; Kunzli et al. 2005; Sun et al. 2005; Suwa et al. 2002; Tomao et al. 2002).

Animal models and epidemiologic studies have shown an association between PM exposure and modified lipid levels. Suwa et al. (2002) demonstrated in Watanabe heritable hyperlipidemic rabbits that exposure to PM_{10} increased the total amount of lipids in aortic lesions. Sun et al. (2005) showed in a murine model that the lipid content in the aortic arch increased 1.5-fold in mice fed a high-fat chow diet and exposed to PM versus filtered air. In an epidemiologic case–control study of traffic-exposed police officers, the average values of HDL cholesterol and triglycerides were elevated in the exposed group versus an unexposed control group (Tomao et al. 2002). With respect to HRV, lipids, and other circulating markers of inflammation and PM exposure, several recent studies have begun to report an association that involves systemic inflammation as a possible mechanism underlying the association. Yue et al. (2006) found an association between abnormal HRV and blood markers of inflammation in coronary artery disease patients, and Sajadieh et al. (2004) reported earlier that reduced HRV is associated with subclinical inflammation in middle-aged and elderly subjects with no apparent heart disease. Consistent with these reports are our findings in asthmatics that ambient coarse PM is associated with increased serum triglycerides, decreased HRV, and increased circulating granulocytes (eosinophils), suggesting a complex network of interrelated pathways at work with respect to the health effects of PM exposure.

This study is one of few with daily gravimetric measurements of both the coarse and fine PM size fractions. Daily ambient fine PM and coarse concentrations were measured with a dichotomous Partisol-Plus Sequential Air Sampler at the central site for 11 months. To address potential spatial variation in coarse PM, we conducted a validation study with samplers at the site of the subject's residence (Chen et al. 2007). The correlation between residential outdoor coarse PM mass concentrations and those obtained from the central ambient monitoring site were typically greater than $r = 0.75$. These results show that although coarse PM mass concentrations were temporally variable, they were relatively consistent spatially for distances up to 50 km (Chen et al. 2007). Thus, we are reasonably confident that for this panel study, the central-site exposure is an acceptable proxy for residential exposure of coarse PM. Fine PM measured at a central site is recognized as a good proxy for personal exposure (Koutrakis et al. 2005; Sarnat et al. 2000; Williams 2003a, 2003b). The recent Williams et al. studies (2003a, 2003b), conducted in Research Triangle Park, North Carolina, over the course of a 1-year period, indicate that fine PM concentrations are highly homogeneous with respect to mass at distances approaching 70 km.

Given that coarse PM is rich in biologic material, particularly endotoxin, it may not be surprising that we found effects of ambient coarse PM exposure that mimic those seen with systemic endotoxin challenge. Intravenous challenge with endotoxin is associated with decreased HRV (associated with increased risk for cardiac events), systemic inflammation, and increases in serum triglycerides and VLDL in human volunteers and in animal models (Godin et al. 1996; Goldstein et al. 1995; Hardardottir et al. 1995; Hudgins et al. 2003; Levels et al. 2003; Voss et al. 2004). We and others have found that bronchial challenge with endotoxin induces systemic inflammatory effects as well, even at inhaled doses that do not cause overt airway or systemic symptoms (Alexis et al. 2004; Michel et al. 1992, 1997). We have also observed reduced airway cytokine and macrophage responses in healthy volunteers when they were exposed to coarse PM that had been heated to deactivate biologic agents (including denature endotoxin) versus PM that had not been heated (Alexis et al. 2006). These observations are consistent with our hypothesis that persons with chronic inflammatory diseases of the airway have increased responsiveness to biologic materials contained in coarse particulates.

Our panel study design allowed us to examine both low-level ambient PM exposures and their associated daily variability while at the same having repeated intensive clinical monitoring that would be impossible in field epidemiologic studies. In summary, we found that in repeated measures on a panel of 12 well-controlled asthmatics, 1-day lagged 24-hr concentrations of ambient coarse PM were significantly associated with decreased HRV, increased circulating eosinophils, and increases in serum triglycerides, indicating that coarse PM may play an underappreciated role in pollutant-induced cardiovascular events, even in asthmatics using anti-inflammatory therapy. We also report that neither low levels of ambient coarse nor fine PM had an effect on respiratory symptoms, airway inflammation, or lung function. Further study is needed to identify the mechanisms of effect of coarse and fine PM on systemic endpoints in healthy and susceptible populations as well as the role of endotoxin and other biologic components of coarse PM on these outcomes.

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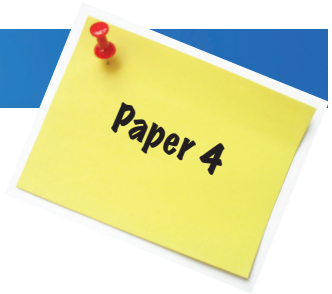

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