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ORIGINAL RESEARCH

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]

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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:

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

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,

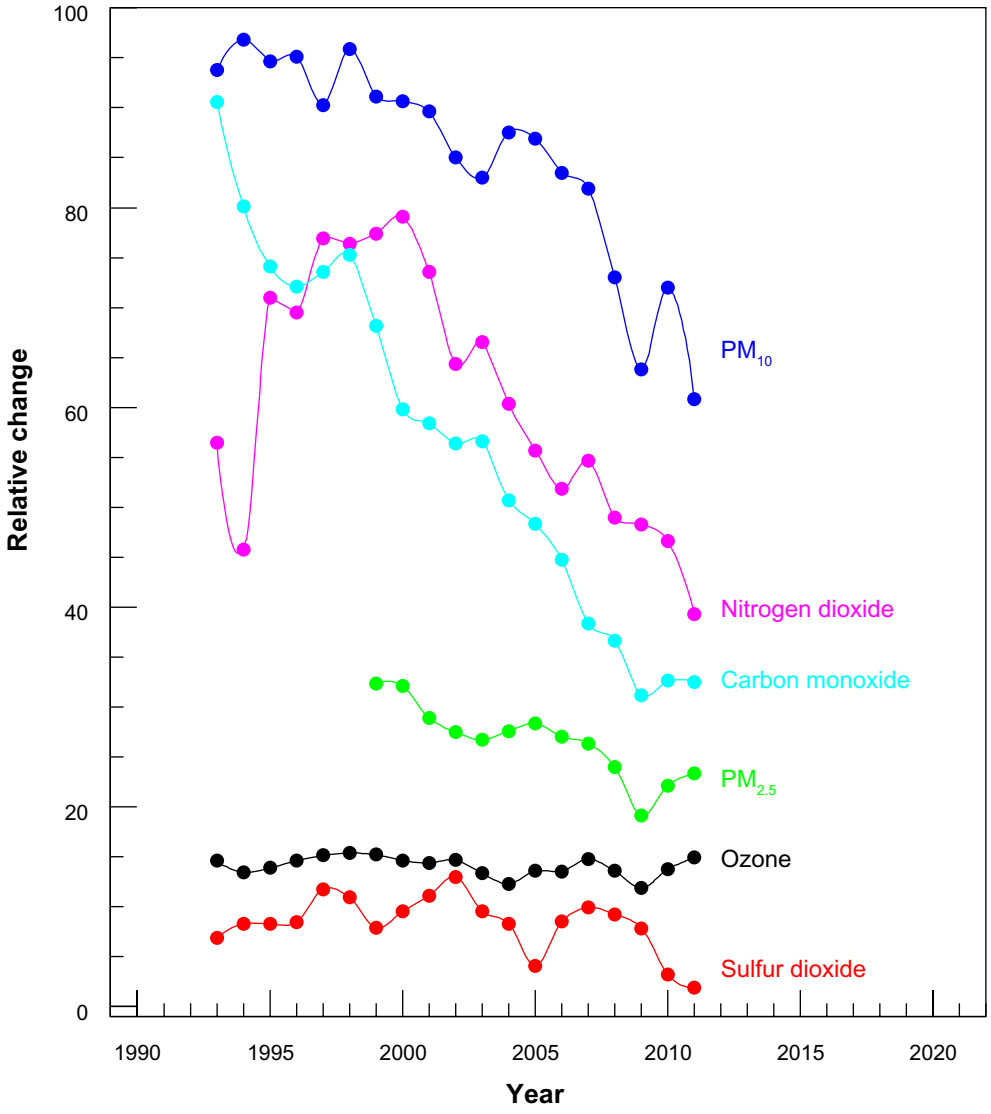

Figure 1 Levels of six air pollutants in North Carolina, 1993–2011. Individual pollutants were placed onto a single graph by utilizing arbitrary units to enable a collective visualization of the trends.
Abbreviation: PM, particulate matter.

$P<0.001$), 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

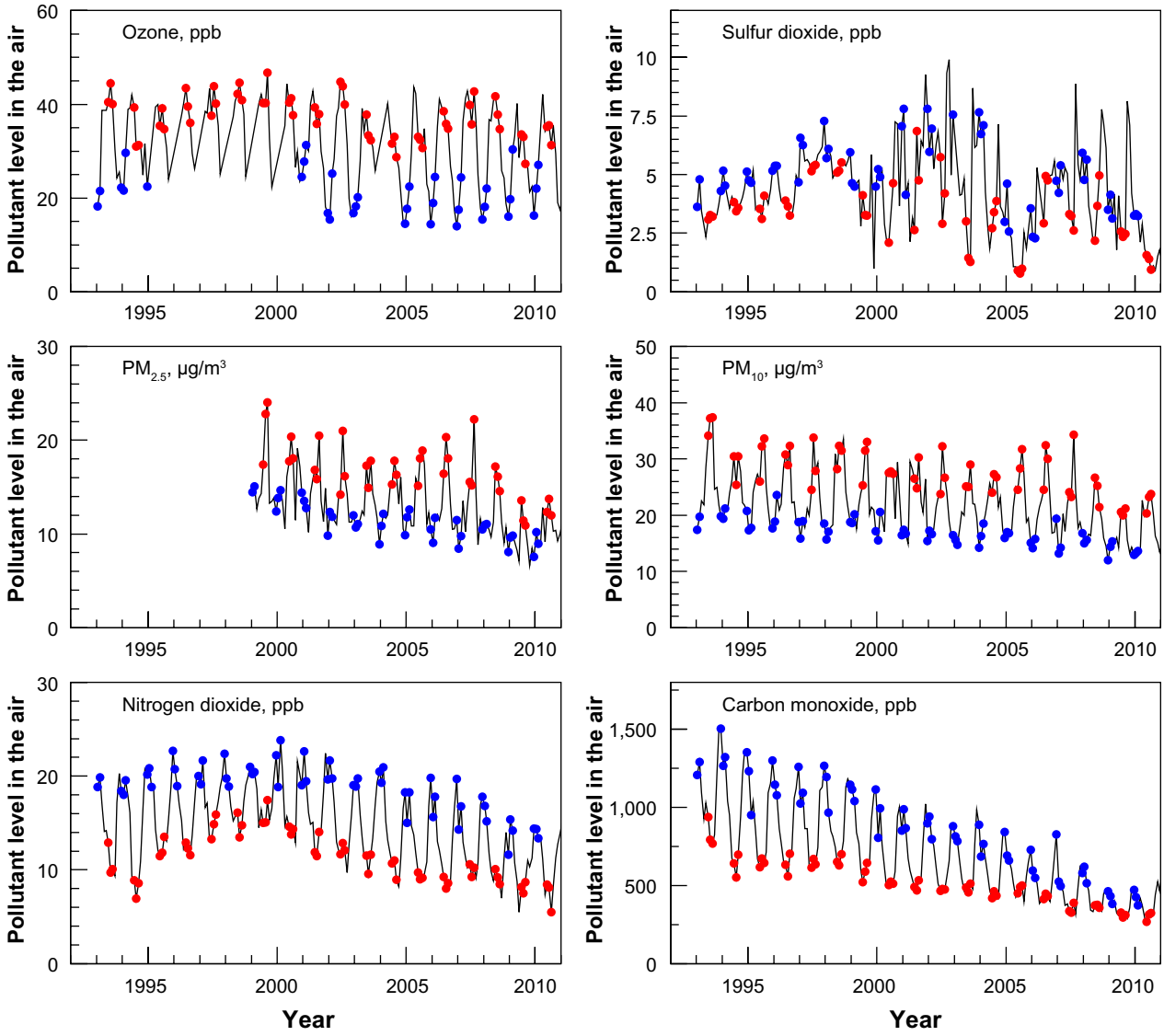

Figure 2 Seasonal fluctuations of air-pollutant levels: summer (red, 3 months) and winter (blue, 3 months), 1993–2011.
Abbreviation: PM, particulate matter.

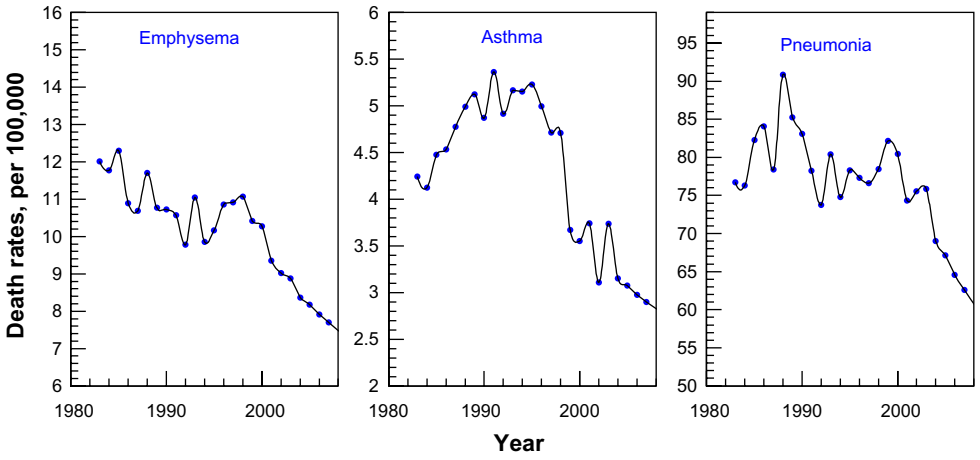

Figure 3 Trends in death rates for emphysema, asthma, and pneumonia in North Carolina, 1983–2010. Mortality rates were age-adjusted to the 2000 North Carolina population.

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/m^3	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/m^3	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

did not find these associations in our study. Our results are 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 discharge rate did not change significantly for patients older 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)
$PM_{2.5}$, μg/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)
$PM_{2.5}$, μg/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.