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The Influence of Improved Air Quality on Mortality Risks in Erfurt, Germany

Annette Peters, Susanne Breitner, Josef Cyrys, Matthias Stölzel, Mike Pitz, Gabriele Wölke, Joachim Heinrich, Wolfgang Kreyling, Helmut Küchenhoff, and H.-Erich Wichmann

Includes a Commentary by the Institute's Health Review Committee

The Influence of Improved Air Quality on Mortality Risks in Erfurt, Germany

Annette Peters, Susanne Breitner, Josef Cyrys, Matthias Stölzel, Mike Pitz, Gabriele Wölke, Joachim Heinrich, Wolfgang Kreyling, Helmut Küchenhoff, and H.-Erich Wichmann

with a Commentary by the HEI Health Review Committee

Research Report 137

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Research Report 137

ABOUT HEI

The Health Effects Institute is a nonprofit corporation chartered in 1980 as an independent research organization to provide high-quality, impartial, and relevant science on the effects of air pollution on health. To accomplish its mission, the institute

- Identifies the highest-priority areas for health effects research;
- Competitively funds and oversees research projects;
- Provides intensive independent review of HEI-supported studies and related research;
- Integrates HEI's research results with those of other institutions into broader evaluations; and
- Communicates the results of HEI research and analyses to public and private decision makers.

HEI receives half of its core funds from the U.S. Environmental Protection Agency and half from the worldwide motor vehicle industry. Frequently, other public and private organizations in the United States and around the world also support major projects or certain research programs. HEI has funded more than 280 research projects in North America, Europe, Asia, and Latin America, the results of which have informed decisions regarding carbon monoxide, air toxics, nitrogen oxides, diesel exhaust, ozone, particulate matter, and other pollutants. These results have appeared in the peer-reviewed literature and in more than 200 comprehensive reports published by HEI.

HEI's independent Board of Directors consists of leaders in science and policy who are committed to fostering the public–private partnership that is central to the organization. The Health Research Committee solicits input from HEI sponsors and other stakeholders and works with scientific staff to develop a Five-Year Strategic Plan, select research projects for funding, and oversee their conduct. The Health Review Committee, which has no role in selecting or overseeing studies, works with staff to evaluate and interpret the results of funded studies and related research.

All project results and accompanying comments by the Health Review Committee are widely disseminated through HEI's Web site (*www.healtheffects.org*), printed reports, newsletters, and other publications, annual conferences, and presentations to legislative bodies and public agencies.

ABOUT THIS REPORT

Research Report 137, *The Influence of Improved Air Quality on Mortality Risks in Erfurt, Germany,* presents a research project funded by the Health Effects Institute and conducted by Annette Peters, of the GSF–National Research Center for Environment and Health in Neuherberg, Germany, and her colleagues. This study is the first of those funded by HEI's Accountability Research program to be completed and published. See the Preface for more about this program.

This report contains three main sections.

The HEI Statement, prepared by staff at HEI, is a brief, nontechnical summary of the study and its findings; it also briefly describes the Health Review Committee's comments on the study.

The Investigators' Report, prepared by Peters et al., describes the scientific background, aims, methods, results, and conclusions of the study.

The Commentary is prepared by members of the Health Review Committee with the assistance of HEI staff; it places the study in a broader scientific context, points out its strengths and limitations, and discusses remaining uncertainties and implications of the study's findings for public health and future research.

This report has gone through HEI's rigorous review process. When an HEI-funded study is completed, the investigators submit a draft final report presenting the background and results of the study. This draft report is first examined by outside technical reviewers and a biostatistician. The report and the reviewers' comments are then evaluated by members of the Health Review Committee, an independent panel of distinguished scientists who have no involvement in selecting or overseeing HEI studies. During the review process, the investigators have an opportunity to exchange comments with the Review Committee and, as necessary, to revise their report. The Commentary reflects the information provided in the final version of the report.

PREFACE

HEI's Accountability Research Program

The goal of most air-quality regulations is to protect the public's health by implementing regulatory actions or providing economic incentives that help reduce the public's exposure to air pollutants. If this goal is met, air pollution should be reduced, and indicators of public health should improve or at least not deteriorate. Evaluating the extent to which air-quality regulations succeed in protecting public health is part of a broader effort—variously termed accountability research, research on regulatory effectiveness, or outcome studies—designed to assess the performance of environmental regulatory policies in general. In recent decades, air quality in the United States and Western Europe has improved substantially, and this improvement is attributable to a number of factors, including increasingly stringent air-quality regulations. However, the cost of the pollution-control technologies and mechanisms needed to implement and enforce these regulations is often high. It is therefore prudent to ask whether the regulations have in fact yielded demonstrable improvements in public health and provided information to inform future efforts to do so.

Several U.S. government agencies have concluded that there is a lack of direct evidence about the extent to which air-quality regulations have improved health (measured as a decrease in premature mortality and excess morbidity). This finding is well documented by the National Research Council (NRC) in its report *Estimating the Public Health Benefits of Proposed Air Pollution Regulations* (NRC 2002), as well as by the California Air Resources Board, the U.S. Environmental Protection Agency (EPA), the U.S. Centers for Disease Control and Prevention (CDC), and other agencies.

In 2003, the Health Effects Institute (HEI) published a monograph on accountability, Communication 11, *Assessing Health Impact of Air Quality Regulations: Concepts and Methods for Accountability Research* (HEI 2003). This monograph was written by the members of HEI's multidisciplinary Accountability Working Group after a 2001 workshop on the topic. Communication 11 set out a conceptual framework for accountability research and identified the types of evidence required and the methods by which the evidence should be obtained. It has also guided the development of the HEI Accountability Research program, which is discussed below.

Between 2002 and 2004, HEI issued four requests for applications (RFAs) for studies to evaluate the effects of actions taken to improve air quality. Two studies were ultimately funded under RFA 02-1, "Measuring the Health Impacts of Actions That Improve Air Quality," one of which was the study by Dr. Annette Peters and colleagues described in this Research Report. HEI also funded seven additional accountability studies resulting from subsequent RFAs (see table).

This preface describes both the framework of accountability research as it relates to air-quality regulations and HEI's Accountability Research program.

BACKGROUND

The first step in assessing the effectiveness of air-quality regulations is to measure emissions of the targeted pollutants to see whether they have in fact decreased as intended. A series of intermediate assessments, described in detail below, are needed in order to accurately measure the adverse health effects associated with air pollution to see whether they, too, decreased in incidence or severity relative to emissions. Some accountability studies to date have used hypothetical scenarios (comparing estimated outcomes under existing and more stringent regulations) and risk estimates obtained from epidemiologic studies in an attempt to quantify past effects on health and to predict future effects (U.S. EPA 1999). However, more extensive validation of these estimates with data on actual outcomes would be helpful.

HEI's Accountability Research Program[a]

RFA	Investigator (Institution)	Study Title	Intervention
RFA 02-1			
	Douglas Dockery (Harvard School of Public Health, Boston, Mass.)	"Effects of Air Pollution Control on Mortality and Hospital Admissions in Ireland" (underway)	Coal ban in Irish cities
	Annette Peters (GSF–National Research Center for Environment and Health, Neuherberg, Germany)	"Improved Air Quality and Its Influences on Short-Term Health Effects in Erfurt, Eastern Germany" (published as HEI Research Report 137, 2009)	Switch from brown coal to natural gas for home heating and power plants, changes in motor vehicle fleet after reunification of Germany
RFA 04-1			
	Frank Kelly (King's College London, London, U.K.)	"Congestion Charging Scheme in London: Assessing Its Impact on Air Quality and Health" (in press)	Measures to reduce traffic congestion in the inner city of London
RFA 04-4			
	Frank Kelly (King's College London, London, U.K.)	"The London Low Emission Zone Baseline Study" (in press)	Measures to exclude most-polluting vehicles from entering greater London
	Richard Morgenstern (Resources for the Future, Washington, D.C.)	"Accountability Assessment of Title IV of the Clean Air Act Amendments of 1990" (underway)	Measures to reduce sulfur emissions from power plants east of the Mississippi River
	Curtis Noonan (University of Montana, Missoula, Mont.)	"Assessing the Impact on Air Quality and Children's Health of Actions Taken to Reduce $PM_{2.5}$ Levels from Woodstoves" (underway)	Woodstove change-out program
	Jennifer Peel (Colorado State University, Fort Collins, Colo.)	"Impact of Improved Air Quality During 1996 Atlanta Olympic Games on Multiple Cardiorespiratory Outcomes" (in review)	Measures to reduce traffic congestion during the Atlanta Olympics
	Chit-Ming Wong (University of Hong Kong, Hong Kong)	"Impact of the 1990 Hong Kong Legislation for Restriction on Sulfur Content in Fuel" (underway)	Measures to reduce sulfur content in fuel for motor vehicles and power plants
RFPA 05-3			
	Junfeng (Jim) Zhang (University of Medicine and Dentistry of New Jersey, Piscataway, N.J.)	"Molecular and Physiological Responses to Drastic Changes in PM Concentration and Composition" (underway)	Measures to improve air quality during the Beijing Olympics

[a] Abbreviations: RFA, Request for Application; RFPA, Request for Preliminary Application. As of 2008, GSF–National Research Center for Environment and Health is now the Helmholtz Zentrum München–German Research Center for Enfironmental Health.

The long-term improvements in U.S. air quality have been associated with improved health in retrospective epidemiologic studies (Chay and Greenstone 2003; Laden et al. 2006; Pope et al. 2009). Considerable challenges, however, are inherent in the assessment of the health effects of air-quality regulations. Different regulations go into effect at different times, for example, and may be implemented at different levels of government (e.g., national, regional, or local). Their effectiveness therefore needs to be assessed in ways that take into account the varying times of implementation and

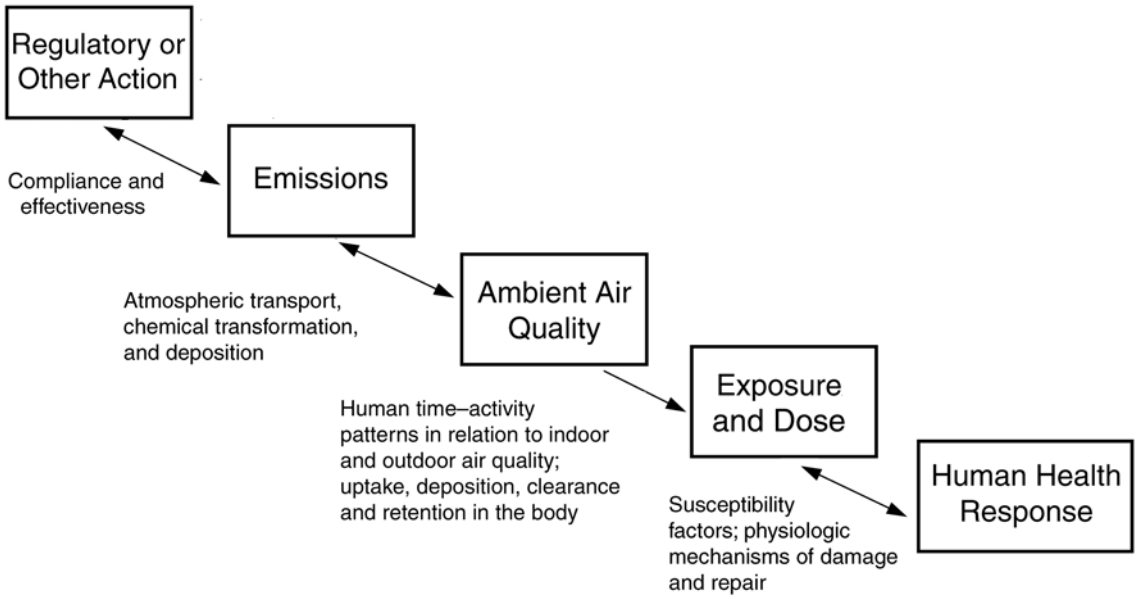
levels of regulation. In addition, other changes at the same time and place might have confounded an apparent association between pollution reduction and improved health, such as economic trends (e.g., in changes in employment), improvements in health care, and behavioral changes (e.g., staying indoors when government warnings indicate pollution concentrations are high). Moreover, adverse health effects that might have been caused by exposure to air pollution can also be caused by other environmental risk factors (some of which changed over the same time periods as the air-pollution concentrations). These challenges become more pronounced when regulations are implemented over long periods and when changes in air quality and health outcomes are not seen immediately, thus increasing the chance for confounding by other factors. For these reasons, scenarios in which regulations are expected to have resulted in rapid changes in air quality tend to be among the first, and most likely, targets for investigation, rather than evaluations of complex regulatory programs implemented over the long term. Studies in Ireland by Clancy and colleagues (2002) and in Hong Kong by Hedley and colleagues (2002) are examples of such scenarios.

These inherent challenges are well documented in Communication 11 (HEI 2003), which was intended to advance the concept of accountability research and to foster the development of accountability methods and studies throughout the relevant scientific and policy communities. In addition, recent advances in data collection and analytic techniques provide an unprecedented opportunity to improve our assessments of the effects of air-quality interventions.

THE CHAIN OF ACCOUNTABILITY

The NRC's Committee on Research Priorities for Airborne Particulate Matter set out a conceptual framework for linking air-pollution sources to adverse health effects (NRC 1998). This framework can be used to identify factors along a "chain of accountability" (see figure), each stage of which affords its own opportunities for making quantitative measurements of the intended improvements.

At the first stage (regulatory action), one can assess whether controls on source emissions have in fact been put into place. At the second stage (emissions), one can determine whether controls on sources have indeed reduced emissions, whether emitters have changed their practices, and whether there have been unintended consequences. At the third stage (ambient air quality), one can assess whether controls on



The Chain of Accountability. Each box represents a stage in the process between regulatory action and human health responses to air pollution. Arrows connecting the stages indicate possible directions of influence. The text below the arrows identifies factors affecting the effectiveness of regulatory actions (referred to as "accountability") at each stage. At several stages, knowledge gained from accountability studies can provide valuable feedback for improving regulatory or other action. (Adapted from HEI 2003.)

sources and reductions in emissions have resulted in improved air quality. At the fourth stage (personal or population exposure), one can assess whether the improvement in air quality has reduced people's actual exposure and whether susceptible subpopulations (those most likely to experience adverse health effects) have benefited. At this stage, it is important to take into account changes in time–activity patterns that could either increase or reduce exposure. The actual dose that an individual's organs may be exposed to should also be considered (i.e., whether reductions in exposure have led to reductions in concentrations in body tissues such as the lung). Finally, at the fifth stage (human health response), one can assess whether risks to health have declined, given the evidence about changes in health outcomes such as morbidity and mortality that have resulted from changes in exposure. The challenge at this stage is to investigate the health outcomes that are most directly related to exposure to air pollution.

At each stage in the chain of events, the opportunity exists to collect evidence that either validates the assumptions that motivated the intervention or points to ways in which the assumptions were incorrect. The collection of such evidence can thus ensure that future interventions are maximally effective.

Ultimately, the framework for accountability research will need to encompass investigations of the broader consequences of regulations, not just the intended consequences. Unintended consequences should also be investigated, along with the possibility that risks to public health in fact increased, as discussed by Wiener (1998) and others who have advanced the concept of a so-called portfolio of effects of a regulation.

HEI'S ACCOUNTABILITY RESEARCH PROGRAM

HEI's Accountability Research program currently includes nine studies. The study by Dr. Annette Peters and colleagues that is presented in this report is the first of the nine to be completed; three additional studies are in review and are expected to be published in 2009 or early 2010. The remaining five studies are still underway and are expected to be completed during 2010.

These studies involve the measurement of indicators along the entire chain of events, from regulatory or other interventions to human health outcomes. Some of the studies are investigating interventions that are implemented over relatively short periods of time, such as a ban on the sale of coal, the replacement of old wood stoves with more efficient, cleaner ones, reductions in the sulfur content of fuels, and measures to reduce traffic. Other groups are focusing on longer-term, wider-ranging interventions or events; for instance, Peters and colleagues assessed complex changes associated with the reunification of the former East and West Germany, including a switch from brown coal to natural gas for fueling power plants and home-heating systems and an increase in the numbers of modern diesel-powered vehicles in eastern Germany. HEI is also supporting research, including the development of methods, in an especially challenging area — namely, the effects of regulations that are implemented incrementally over extended periods of time, such as those resulting from Title IV of the 1990 Clean Air Act Amendments (U.S. EPA 1990), which aimed at reducing sulfur dioxide emissions from power plants by requiring compliance with prescribed emission limitations. A summary of studies on accountability funded by HEI to date is provided in the table.

FUTURE DIRECTIONS

In addition to the completion, review, and publication of these nine accountability studies, HEI has also funded the development of two Web sites intended to enhance transparency and provide other researchers with access to extensive data and software from HEI-funded studies:

1. Data and software from the National Morbidity, Mortality, and Air Pollution Study (NMMAPS), as described by Zeger and colleagues (2006) (data available at the Johns Hopkins Bloomberg School of Public Health Web site *http://www.ihapss.jhsph.edu*) and
2. Data from the National Particle Components Toxicity Initiative (NPACT) on concentrations of components of particulate matter with an aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$) collected at or near the 54 sites in the EPA's $PM_{2.5}$ Chemical Speciation Trends Network (STN) (data available at the Atmospheric and

Environment Research, Inc., Web site *http://hei.aer.com*).

The data on pollution and health from a large number of U.S. cities, as documented and regularly updated by the NMMAPS team and made available on the Internet-Based Health and Air Pollution Surveillance System (iHAPSS) Web site, constitute a valuable resource that allows other researchers to undertake additional analyses, possibly including further accountability studies. The STN Web site provides scientists an opportunity to investigate specific questions about concentrations of $PM_{2.5}$ components and their association with adverse health effects in regions covered by the STN network and to address questions related to accountability when interventions in these regions are being planned.

In January 2008, HEI co-organized and co-sponsored, with the CDC's Environmental Public Health Tracking Program and the EPA, a workshop entitled "Methodologic Issues in Environmental Public Health Tracking of Air Pollution Effects." The workshop was part of an effort to implement the initiative outlined in HEI's Strategic Plan for 2005 through 2010 (HEI 2005) to "build networks with the U.S. Centers for Disease Control and Prevention and state public health tracking programs to facilitate accountability research." Building on the work of the CDC's Environmental Public Health Tracking Program (see the CDC Web site *http://www.cdc.gov/nceh/ tracking/*) in the development of standardized measures of air-pollution–related effects on health at the state and local levels in the United States, the workshop brought together representatives of state and federal agencies and academic researchers to discuss methodologic issues in the development of such measures and made recommendations for their further development and application. The recommendations were provided in a September 2008 report to the CDC, and the proceedings will be published in the journal *Air Quality, Atmosphere & Health* in mid to late 2009. HEI will continue to seek opportunities to work with the CDC and the EPA to apply methods newly developed for tracking public health to the assessment of the effectiveness of environmental regulations.

As a part of its upcoming Strategic Plan for 2010 through 2015, HEI will look closely at opportunities for unique new contributions to accountability research. Investigators who have identified a distinctive opportunity to evaluate the effects of environmental regulations on air pollution and human health are encouraged to contact HEI.

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HEI STATEMENT

Synopsis of Research Report 137

The Influence of Improved Air Quality on Mortality Risks in Erfurt, Germany

BACKGROUND

In 2002, as part of the Accountability Research program of the Health Effects Institute, HEI solicited research proposals to evaluate the effectiveness of measures intended to improve air quality, including proposals for research that focused on "real world experiments or measurement of the health impact of planned or unplanned actions that improve air quality." When East and West Germany were reunified, in October 1990, the city of Erfurt, in the former East Germany, underwent sweeping changes in its economy and energy use as a result of stricter environmental controls and the modernization of industry, transportation, and household heating. Over the next 11 years, the resulting changes in the sources and emissions of air pollution in the city affected its ambient air quality, and the mixture of pollutants changed from that associated with widespread coal combustion to one more similar to that of most Western European countries. However, the resulting changes in health impacts were difficult to predict, as there had been little published research on the consequences for mortality when pollution sources or emissions change so dramatically. However, data on mortality and measurements of pollution concentrations in Erfurt were available for this transition period, making it possible to evaluate the health impacts of such sweeping changes in air quality.

APPROACH

Dr. Annette Peters of the Institute of Epidemiology at Germany's GSF–National Research Center for Environment and Health (which, as of 2008, is now the Helmholtz Zentrum München–German Research Center for Environmental Health) with her colleagues performed a study of daily mortality and pollutant concentrations in Erfurt spanning the period of modernization that followed German reunification. Peters and colleagues had previously studied data from Erfurt on air pollution and health effects as part of an HEI-funded study of ultrafine particles (UFP) and mortality conducted by Dr. H.-Erich Wichmann and colleagues (HEI Research Report 98, 2000).

For the current study, Peters and her colleagues used daily measurements of concentrations of various air pollutants, available from 1990 to 2002, to study how the association between air pollution and risk of death (toxicity per unit of air pollutant) in Erfurt changed as the city's air quality changed. They presented relative risk (RR) results from Poisson models for each pollutant, as was done in Wichmann et al.'s time-series study, but the primary innovation of the study was the use of a complex statistical method known as time-varying coefficient modeling. Time-varying coefficient models were originally used to track insurance and investment risks and are at their most effective when used to study a series of changes that occur over a period of time rather than as a single event. The investigators used time-varying coefficient models to calculate the RR of death from various causes for a fixed change in the concentration of a pollutant in ambient air over the study period as a whole, thus providing a picture of how the unit toxicity of complex pollutants, such as $PM_{2.5}$ (particulate matter [PM] less than or equal to 2.5 µm in aerodynamic diameter) or gaseous mixtures, might have changed as fuels and pollutant sources changed and overall pollution levels declined.

RESULTS AND INTERPRETATION

Overall air-pollution concentrations in Erfurt decreased during the study period, with the largest reduction occurring for sulfur dioxide (SO_2; from 64 µg/m^3 in 1992 to 4 µg/m^3 in 2001). PM less than or equal to 10 µm (PM_{10}) or $PM_{2.5}$ and carbon monoxide

This Statement, prepared by the Health Effects Institute (HEI), summarizes a research project funded by HEI and conducted by Dr. Annette Peters of the Institute of Epidemiology at the GSF–National Research Center for Environment and Health in Neuherberg, Germany, and colleagues. Research Report 137 contains both the detailed Investigators' Report and a Commentary on the study prepared by HEI's Health Review Committee.

(CO) concentrations decreased by more than 50%. High degrees of correlation were found between concentrations of nitric oxide (NO), nitrogen dioxide (NO_2), CO, and ultrafine particles—pollutants commonly associated with combustion in motor vehicles.

Results from the study's Poisson time-series models for individual pollutants are somewhat puzzling. Over the study period as a whole, RRs for all-cause mortality varied substantially from little or no association at some lags (the number of days between exposure and death) to significant associations at selected lags with an interquartile range (IQR) change in pollutant concentrations. All-cause mortality was associated with ultrafine particles (RR at lag 4 = 2.9%; 95% confidence interval [CI], 0.3% to 5.5%), CO (RR at lag 4 = 1.9%; 95% CI, 0.2% to 3.6%), and ozone (O_3; RR at lag 2 = 4.6%; 95% CI, 1.1% to 8.3%) and was marginally associated with NO_2 (RR at lag 3 = 1.6%; 95% CI, –0.4% to 3.5%). The investigators concluded that the results for ultrafine particles, NO_2, and CO, taken together, pointed to an association between mortality and local combustion sources. The lack of association between these pollutants and mortality at other lags is noteworthy, given the substantial drop in SO_2 and predominance of emissions from the combustion of coal in the early years of the study.

The time-varying coefficient models estimated RRs per IQR for pollutant exposures and all-cause and cause-specific mortality that had varied continuously across the study period. The models suggested that the RRs of mortality per unit of exposure to O_3, CO, ultrafine particles, and NO_2 varied during the period.

The investigators observed that the highest RRs per unit of pollutant concentrations occurred in the transition period and noted that this transient increase in risk occurred when pollutant sources were changing and the full benefits of the rapidly improving air quality had yet to be realized in mortality reduction. The HEI Health Review Committee noted that the observed variations in pollutant–mortality coefficients could also be due to chance, as the study had relatively low statistical power because of the low number of daily deaths in Erfurt. Methods for selecting the time lags between exposure and death were entirely based on a statistical analysis of the available data, rather than on any specific understanding of physiologic mechanisms linking exposure and death from various causes. The time lags between exposure and death were limited to the selection of a single day lag, as multi-day or distributed lags were not explored in this study. Other methodologic sources of uncertainty included the selection of confounders and methods for the control of confounding.

The observed pattern of variations over time in the toxicity per unit of the studied pollutants did not correspond to the known trends in the pollutants' concentrations or sources. Current scientific understanding is insufficient to predict what happens to unit toxicity as sources change from coal combustion to motor-vehicles emissions. Changes in risk over time might relate not only to changes in unit toxicity but also to changes in the effects of misclassification of exposure or in the vulnerability of the population. The extent or nature of exposure misclassification seems unlikely to have changed to a large extent over time in Erfurt, given the quality of the monitoring data, but the Review Committee noted that the report discussed variables associated with potential changes in the vulnerability of the population, such as its age structure and the prevalence of chronic cardiopulmonary disease and smoking; other potential variables could include diet and lifestyle. These variables were not explicitly included in the analysis, making epidemiologic inferences problematic.

Because of the limitations noted above — in particular the restricted power of the study — the Review Committee considered the investigation of dynamic risk by Dr. Peters et al. more valuable as an exploration of methods for tracking changes in unit toxicity during periods of changing air quality than as a source of substantive information on this issue.

A number of the study's conclusions were based on estimated effects on mortality of individual pollutants when analyzed over the study period as a whole. Considerable caution should be used in interpreting these overall effect estimates because of the factors mentioned above. The ongoing measurements of ultrafine particles by Dr. Peters and colleagues during a time of rapid change in Erfurt provided a unique opportunity to explore concurrent changes in mortality risks in this accountability study. The study's finding of an association between exposure to ultrafine particles and mortality may be important, given the paucity of other epidemiologic evidence on the health effects of ultrafine particles, despite intensive laboratory research. However, there is considerable uncertainty in the findings for ultrafine particles as the biologic

basis for an association between mortality and exposure to ultrafine particles 3 or 4 days earlier (and not for other lag times) is not known, and previously reported associations between ultrafine particle exposure and mortality and nonfatal cardiac events from this research group are contradictory (Wichmann et al. 2000; Peters et al. 2005).

Given the extensive literature on associations between mortality and air pollution, it is puzzling that no consistent effects of $PM_{2.5}$ or PM_{10} were observed over the study period, although the null $PM_{2.5}$ results are consistent with an earlier report by the same investigators. Neither $PM_{2.5}$ nor PM_{10} daily mean concentrations were highly correlated with concentrations of ultrafine particles, which were associated with mortality risk. The investigators also observed effects on mortality of gaseous pollutants of vehicular origin (NO_2 and CO) at selected lags. Because of the high degree of correlation between the concentrations of ultrafine particles and the two gaseous pollutants, the effects were interpreted by the investigators as surrogates for particle effects, in particular the effects of ultrafine particles. The Review Committee noted that this interpretation was based on toxicologic grounds and was not strongly supported by the epidemiologic evidence presented in the report.

HEI considers this study to be an accountability study, in that it explores innovative, advanced methods to evaluate some subtle consequences of improving air quality. The situation in Erfurt differed from that in Dublin (which involved a ban on coal sales) or Hong Kong (which involved a regulation to reduce sulfur in motor fuel). In Dublin and Hong Kong, a permanent change in air quality enabled changes in health outcomes to be linked directly to the intervention. In the case of the slower, less well defined changes in air pollution seen in Erfurt, investigating changes in unit toxicity rather than overall changes in the risk of health outcomes clearly had interesting potential. However, the innovative methods that Dr. Peters and her colleagues used make severe demands on statistical power, as demonstrated in the report. Any future research that uses the methodologic work on time-varying coefficients developed by Peters and colleagues should first determine that the study population is of sufficient size to permit the methods to detect changes in unit toxicity over time with an appropriate degree of statistical certainty. The innovative methodologic work on time-varying coefficients carried out in this study could have an important part to play in a study of a sufficiently large population.

INVESTIGATORS' REPORT

The Influence of Improved Air Quality on Mortality Risks in Erfurt, Germany

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ABSTRACT

Around the world, daily variations in ambient air pollution have been consistently associated with variations in daily mortality. The aim of the study presented here was to assess the effects of ambient air pollution on daily mortality during a period of tremendous changes in air quality in the city of Erfurt, in eastern Germany, from October 1991 to March 2002.

Data on particle size distributions were obtained from September 1995 to March 2002 at a research monitoring station. For particles from 0.01 µm to 2.5 µm in diameter, number concentrations (NCs)* and mass concentrations (MCs) were calculated. Particles with diameters less than or equal to 0.10 µm are defined as ultrafine particles (UFP). Data on the gaseous pollutants NO_2, CO, SO_2, and O_3 and on PM_{10} (particulate matter [PM] with aerodynamic diameter less than or equal to 10 µm) were obtained from a government air-monitoring station. Data on changes in energy consumption, car fleet composition, and population were collected from local authorities. Death certificates of persons living in and dying in Erfurt were abstracted, and daily mortality counts were calculated. Poisson regression models were used to analyze the data, applying penalized splines (also known as P-splines) to model nonlinear relationships in the confounders. Model selection was done without air pollutants in the models, based on a combination of goodness-of-fit criteria and avoidance of autocorrelation in error terms. Final models included P-splines of time trend, meteorologic data, and influenza epidemics as well as day of the week with an indicator variable. Results are presented as change per interquartile range (IQR), i.e., change in the relative risk of mortality associated with a change in the concentration from the 25th to the 75th percentile of a given pollutant. Air pollutants were considered both as linear terms and as P-splines to assess the exposure–response functions. Changes in effect estimates over time were calculated using fully Bayesian time-varying coefficient models. This method was selected over four other approaches tested in simulation studies.

Air-pollution concentrations decreased substantially in Erfurt during the decade under observation. The strongest changes were observed for SO_2, for which annual concentrations decreased from 64 µg/m^3 in 1992 to 4 µg/m^3 in 2001. Concentrations of PM_{10}, $PM_{2.5}$ (particulate matter with aerodynamic diameter less than or equal to 2.5 µm), and CO decreased by more than 50%. NO_2, O_3, and ultrafine particles also decreased, though to a lesser extent. Based on visual inspection of the data on the changes in ambient air-pollution concentrations during the study period, we defined three study subperiods: A first subperiod from 1991 to 1995; a second, transitional subperiod from 1995 to 1998; and a third subperiod from 1998 to 2002. Generally, air-pollution concentrations decreased substantially from the first subperiod to the second, and some additional decreases occurred from the second subperiod to the third. During the second, transitional subperiod, natural gas replaced coal as the main energy source in Erfurt. In addition, the number of cars with catalytic converters increased over time, as did the number of cars in general. To facilitate

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* A list of abbreviations and other terms appears at the end of the Investigators' Report.

the interpretation of the results, we organized the air pollutants into four groups: (1) NO_2, CO, and ultrafine particles, (2) PM_{10} and $PM_{2.5}$, (3) SO_2, and (4) O_3.

We observed a 1.6% increased risk for daily mortality (CI, −0.4% to 3.5%) for an increase of 19.7 μg/m^3 in NO_2 (lag day 3), a 1.9% increased risk (CI, 0.2%–3.6%) for an increase of 0.48 mg/m^3 in CO (lag day 4), and a 2.9% increased risk (CI, 0.3%–5.5%) for an increase of 9743/cm^3 in ultrafine particles (lag day 4). No consistent associations were observed for PM_{10}, $PM_{2.5}$, or SO_2. For O_3, a 4.6% increased risk for daily mortality (CI, 1.1%–8.3%) was associated with a 43.8 μg/m^3 maximum 8-hr concentration of O_3 per day (lag day 2). For all four pollutants, exposure–response functions suggested no deviation from linearity. However, in time-varying models the strongest associations were observed for NO_2, CO, and ultrafine particles during the transition subperiod, from 1995 to 1998, when O_3 concentrations were lowest. Changes in source characteristics or ambient air-pollution concentrations were not able to explain these observations in a straightforward manner. However, the observations suggested that changes such as the introduction of three-way catalytic converters in cars and the substitution natural gas for coal might have been beneficial.

Overall we concluded that:

1. Economic and political changes and the adoption of new technologies in eastern Germany resulted in distinct improvements in ambient air quality;
2. Urban air pollution in Erfurt changed within one decade from the eastern mixture toward that of western Europe ("western mixture"), which is dominated by concentrations of NO_x, O_3, fine particles, and ultrafine particles with low concentrations of SO_2;
3. There was an association between daily mortality and ultrafine particles and combustion-related gases (lag days 3 or 4);
4. Ultrafine particles seemed to be the best pollution indicator and to point to the role of local combustion in the pollution mixture;
5. Regression coefficients showed variation over time for NO_2, CO, ultrafine particles, and O_3 that could not be explained by nonlinearity in the exposure–response functions;
6. Mortality associated with pollution was lower at the end of the 1990s than during the 1990s, except for mortality associated with O_3; and
7. Mortality associated with pollution was strongest in the second, transitional subperiod, from 1995 to 1998, when changes in source characteristics had taken place but the benefits of improved ambient air quality had not yet been completely achieved.

INTRODUCTION AND SPECIFIC AIMS

The U.S. National Ambient Air Quality Standards (NAAQS) set limits on the criteria pollutants $PM_{2.5}$ (particulate matter with aerodynamic diameters of 2.5 μm or less), PM_{10}, SO_2, NO_2, CO, and O_3 in order to help reduce short- and long-term effects on human health in the United States. In recent years, air-pollution concentrations have been reduced by emission controls and fuel replacement. Accountability research (i.e., research that assesses the effectiveness of environmental regulatory policies and actions in reducing air-pollution exposure and protecting public health) on these pollution-control measures is a major concern for regulating agencies as well as for the regulated entities. This is of particular interest as some areas in the United States and Europe are still out of compliance with enacted or suggested guideline values (U.S. Environmental Protection Agency [EPA] 2004; World Health Organization [WHO] 2005).

This report assesses changes in the concentrations of several pollutants in the ambient air of Erfurt, Germany, and their effects on daily mortality in the city.

Ambient concentrations of PM and O_3 have been consistently associated with daily mortality (Samet et al. 2000a; Katsouyanni et al. 2001; Health Effects Institute [HEI] 2003; Gryparis et al. 2004; Bell et al. 2004, 2005). Associations between ambient concentrations of NO_2 and daily mortality have also been observed (Stieb et al. 2002; Burnett et al. 2004; Samoli et al. 2006), but the causality of the associations is still under debate (WHO 2005). Recent studies have also discerned associations between SO_2 and daily mortality even at rather low SO_2 concentrations (Hedley et al. 2002).

Political changes in Central and Eastern Europe have resulted in the restructuring of industries in the former Eastern Bloc countries, improved emission controls, and a changed car fleet. They have also led to a nearly complete change in fuels used in power plants and homes: natural gas replaced brown coal in the course of a decade. These changes have led to improved air quality in the region and can be considered as a natural experiment in the effect of dramatic air-quality changes on human health. Particle size distributions[†] were monitored in Erfurt during the winter of 1991/92 and from 1995 to 2002 (Kreyling et al. 2003). As a result, it was possible to assess the health

[†] Particles in the size range between 0.01 μm and 2.5 μm were measured with an aerosol spectrometer and summarized as number concentrations and mass concentrations in the following size classes: $NC_{0.01–0.1}$, $NC_{0.01–0.03}$, $NC_{0.01–2.5}$, $NC_{0.03–0.05}$, $NC_{0.05–0.1}$, $MC_{0.01–2.5}$, $MC_{0.1–0.5}$, $MC_{0.5–1.0}$, and $MC_{1.0–2.5}$. $MC_{0.01–2.5}$ is nearly equivalent to $PM_{2.5}$ and is referred to as $PM_{2.5}$ in this report.

implications of the changes in these particle size distributions and in the concentrations of criteria pollutants while the improvements in air-quality control were being implemented.

The study had the following specific aims:

1. (a) To relate ambient concentrations of SO_2, NO_2, CO, and O_3 to daily mortality for the period between October 1991 and March 2002 and (b) to relate the mass concentrations of PM_{10} and $PM_{2.5}$ and the number concentrations of ultrafine particles to daily mortality for the periods between October 1991 and March 1992 and between September 1995 and March 2002;
2. To test whether the relative risks (RR) for daily mortality in association (a) with SO_2, NO_2, CO, and O_3 and (b) with PM_{10}, $PM_{2.5}$, and ultrafine particles remained unchanged over the respective time periods; and
3. To test whether changes (a) in concentrations of the gaseous pollutants and (b) in emissions affected the RRs for PM_{10}, $PM_{2.5}$, and ultrafine particles.

Nearly all time-series studies published until 2003 had assumed that exposure–response functions were constant over time. For the current study, we hypothesized that the exposure–response functions changed over time as the air-pollution mixture and source characteristics changed. Although the city of Erfurt presented us with a unique natural experimental site and one of the largest data sets with continuous measurements of particle size distribution, it was also limited: Erfurt had only about 200,000 inhabitants in the years studied, with on average only 4.6 deaths per day from natural causes. Time-series studies in small cities such as Erfurt face a severe limitation in the small size of the population studied, because the power for statistical analyses is limited, and the assessment of time-varying coefficients is a rarely used and novel approach.

Estimation of the functional (algebraic) form of time-varying exposure–response relationships as well as their variance can depend heavily on the constraints of the statistical model selected for their estimation. Chiogna and Gaetan (2002), for example, allowed the effect of air pollution to change, in principle, freely over time, applying a dynamic generalized linear model based on a likelihood analysis using the iteratively reweighted Kalman filter and smoother. To enforce smoothness, the amount by which the time-varying effect could change was restricted by constraining it to follow a first-order random walk. However, this approach can result in roughness of the estimated exposure–response function. A smoother change over time might be more realistic; it can be obtained with other approaches (see *Methods* section). Under the circumstances, we considered it prudent to select the time-varying coefficient models based on a simulation study rather than comparing different models in our application.

The study was carried out in three stages: (1) the collection of air-pollution data, daily mortality data, and data on source characteristics from 1991 to 2002; (2) the selection of suitable models for time-varying exposure–response functions and the comparison of these models in a simulation study; and (3) statistical analyses addressing specific aims 1 to 3.

In the *Methods* section, we present the methods for data collection and selected statistical models for estimating time-varying coefficients. We then present results of the simulation study and the methods used to assess effects on daily mortality.

In the *Results* section, we describe the data collected and present the results of the statistical analyses, addressing specific aims 1 to 3.

These results are considered in the *Discussion and Synthesis* section in the context of the current state of the art for time-variant coefficient modeling and for the health effects of the criteria pollutants ($PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3) and ultrafine particles.

METHODS

STUDY DESIGN AND STUDY PERIOD

The study analyzed day-to-day variations in daily mortality counts in association with day-to-day variations in the concentrations of gaseous and particulate air pollutants.

To investigate whether incremental changes in air-pollution concentrations reflected changes in the contributions of specific sources to the ambient air pollutant mixture, we divided the study period into the following three subperiods:

- First subperiod: from October 1, 1991, to August 31, 1995;
- Second subperiod: from September 1, 1995, to February 28, 1998 (the start of this subperiod was chosen to coincide with the time when measurements of particle size distribution started); and
- Third subperiod: from March 1, 1998, to March 31, 2002.

To organize the interpretation of the data on the measured air pollutants, which represented different aspects of the ambient pollution mixture, the air pollutants under consideration were divided into the following four groups:

- NO, NO_2, CO, and ultrafine and fine particles in several size classes measured as number concentrations ($NC_{0.003–0.064}$, $NC_{0.01–0.03}$, $NC_{0.01–0.1}$, and $NC_{0.01–2.5}$);
- $PM_{2.5}$ and PM_{10};

- SO_2; and
- O_3.

The pollutants belonging to the first group were in general strongly correlated with each other. One of the major sources of these pollutants was motor-vehicle traffic. In urban areas, NO and CO can be the most abundant primary air pollutants because they are produced by fuel combustion and industrial activities. NO is rapidly converted to NO_2 by reaction with O_3 or peroxy radicals; CO has a relatively long lifetime in the atmosphere. NO_2 is emitted by traffic, in part, and also derived chemically through the reaction of NO and O_3. Ultrafine particles are formed in local combustion processes and from the gas-to-particle conversion of atmospheric gases (see, for example, Clement and Ford 1999).

$PM_{2.5}$ and PM_{10} were strongly correlated with each other but were, in general, less correlated with the traffic-related pollutants, such as nitrogen oxides (NO_x), CO, and ultrafine particles.

SO_2 is a prominent anthropogenic pollutant and contributes to the formation of sulfuric acid and sulfate aerosols. The main source of SO_2 is the combustion of fossil fuels in general, principally coal and diesel, and not traffic.

O_3 is formed in the atmosphere by the reaction of atomic oxygen with molecular oxygen when O_3 precursors (NO_x, CO, and volatile organic compounds [VOCs]) react in the presence of sunlight. Although the precursors often originate in urban areas, winds can carry NO_x hundreds of kilometers, with the result that O_3 formation can occur in less populated regions as well. Because of the complex cycles in which O_3 precursors are oxidized, diurnal and seasonal O_3 patterns are completely different from those of the other air pollutants.

Although NO does not belong to the criteria air pollutants (and was therefore not included in the mortality analysis in this study), we included it in the descriptive analysis of air pollutants because it might provide further insights into the changes in Erfurt's air-pollution sources during the study period. We measured NCs and MCs, stratified by particle size, at a central monitoring station. Air-pollution data from official stations in the city were also obtained. Anonymized death certificates were obtained from the local health authorities. Influenza data were obtained from an independent source.

Poisson regression methods were used for specific aim 1. For specific aims 2 and 3, time-varying coefficient models were developed, tested in simulations, and applied.

STUDY AREA

The study was conducted in Erfurt, Germany, using data for the period from October 1, 1991, to March 31, 2002. Erfurt is the capital of the German federal state of Thuringia, which is in the southernmost part of the former German Democratic Republic (GDR) (Figure 1). The population of Erfurt declined from 219,713 in December 1991 to 199,967 in December 2002 (Thüringer Landesamt für Statistik [Statistical Office of Thuringia] 2004), even though an administrative reform enacted in April and July 1994 incorporated 18 adjoining villages with 15,876 additional inhabitants into the city. In the course of this reform, the area of Erfurt increased from 107.63 km^2 to 269.08 km^2.

Erfurt is surrounded on three sides by hills approximately 100 m higher than the city itself. The land opens up to the north-northwest. But several tall buildings located in the direction of the opening probably further reduce air exchange between the city and rural areas. As a result, temperature inversions, which are frequent in winter, can cause increased concentrations of ambient air pollutants in the city.

Figure 1. Map of Germany and its federal states. The state of Thuringia is shown in black. The states of the former German Democratic Republic are shown in light gray.

MORTALITY DATA

In Germany, access to death certificates is restricted because of data-privacy rules in the Bundesstatistikgesetz (a federal law that regulates access to individual death-certificate data for scientific purposes). Daily mortality counts in Erfurt from August 1995 to December 1998 were already available from an earlier HEI study, *Daily Mortality and Fine and Ultrafine Particles in Erfurt, Germany* (Wichmann et al. 2000). All death certificates for the period from October 1991 to July 1995 as well as from January 1999 to March 2002 were obtained from local health authorities, with names and addresses of the deceased removed, and entered into a database.

The following information was recorded for each subject:

- date of birth;
- sex;
- date of death;
- hour of death;
- type of death (natural, nonnatural, unclear, or missing [i.e., not filled in]);
- place of death (i.e., at home, in the hospital, etc.);
- postal codes of place of residence and place of death;
- immediate, primary, and contributing causes of death as given by the doctor who filled in the death certificate (autopsy results were considered when available on the death certificate; causes of death were coded according to ICD-9 [*International Classification of Diseases*, 9th revision] through 1999 and, from 2000 onward, according to ICD-10 [*International Classification of Diseases*, 10th revision]); and
- ICD code for "external" (i.e., nonnatural) causes of death.

Data were entered twice, as in the study by Wichmann and colleagues (2000). In cases where autopsy data were available (3.7% of cases), only the autopsy results were considered.

Plausibility Checks

The following implausible cases were assessed:

1. Cases for which nonexistent ICD codes were reported.
2. Cases for which implausible causes of death were reported (such as male causes of death in females, or vice versa, and diseases specific to children reported in the elderly, or vice versa).
3. Cases for which no ICD codes were reported.
4. Cases for which an external (i.e., nonnatural) cause of death was reported but the box for nonnatural death was not filled in (or vice versa) or a natural or nonexistent ICD code was filled in.
5. Cases for which the box for nonnatural cause of death was filled in but only natural ICD codes were filled in, or vice versa.
6. Cases with unclear causes of death, comprising those for which an ICD-9 code 798 (unattended death) or 799 (other ill-defined and unspecified causes of mortality) or the corresponding ICD-10 codes R98 or R99 were reported and the box for nonnatural or unclear cause of death was filled in.

The implausible death certificates were reviewed. On the basis of all available information on the certificate (which was sometimes handwritten as additional comments and could not be entered in the database), we recoded the implausible information and decided whether to consider the death as natural or nonnatural.

Inclusion and Exclusion Criteria

Deaths were included or excluded according to the following criteria:

1. Deaths were included for which the places of death and last residence were in Erfurt. A number of small, outlying villages were incorporated into the city in an administrative reform in 1994. Before this date, the death certificates for the deceased inhabitants of these villages were archived in the villages and were not available to us. After the reform, the certificates were collected by the health authorities of Erfurt. On the basis of postal codes, we were able to identify cases of people who had lived or died in one of these formerly independent villages. For the period 1991–2002, we defined Erfurt as the area before the incorporation of the villages (postal codes 99084, 99085, 99086, 99087, 99089, 99091, 99092, 99094, 99096, 99097, 99098, and 99099). For the analysis of particle size distribution over the period 1995–2002, we defined Erfurt as the area after the incorporation of the villages (i.e., including village postal codes 99100, 99102, 99189, 99192, 99195, and 99198).
2. Deaths of infants (< 1 year of age) were excluded.
3. Deaths from natural causes were included (i.e., those for which the ICD codes for the immediate, primary, or contributing causes of death were less than 800 (ICD-9) or S00 (ICD-10). Cases with a V code (ICD-9; "Factors influencing health status and contact with health services") or the corresponding Z code (ICD-10) were included unless they violated other inclusion criteria.
4. Deaths from external (i.e., nonnatural) causes were excluded.

Table 1. ICD Codes for Causes of Death

	ICD-9	ICD-10
Cardiovascular	390–459, 785	I00–I99, R00–R03, R09
Respiratory	460–519, 786	J00–J99, R04–R06, R09
Lung cancer	162	C34
Diabetes	250	E10–E14
Nonnatural	≥800	≥S00, except Z00–Z99

Cause-Specific Mortality

Table 1 shows the ICD codes for causes of death. Note that ICD-10 code R09 ("Other symptoms and signs involving the circulatory and respiratory systems") is assigned to both cardiovascular and respiratory diseases.

In the course of the earlier HEI study in Erfurt from 1995 to 1998 (Wichmann et al. 2000), a small validation study of the ICD codes was performed. Two hundred randomly chosen death certificates with ICD-9 codes were reanalyzed by a nosologist at the Academy of Public Health in Düsseldorf, the institution that teaches coding principles to official coders. The validation study revealed that very few of the errors made by physicians concerned the actual ICD codes. The most frequent errors were the misplacement of immediate, primary, and contributing causes of death. When the errors involved codes, most corrected codes were still within the same ICD group.

We therefore disregarded the placement of information and just looked for any mention of a cardiovascular or respiratory disease. The validation study showed that these prevalent conditions were rarely reassigned by the nosologist: after recoding, only 3.4% of prevalent conditions were found in a different category (Wichmann et al. 2000).

OTHER HEALTH-RELATED DATA

Descriptive data on the city and the state, age distribution, health-care data, and cause-of-death distribution were taken from official federal, state, or community statistical publications.

Data on influenza epidemics were provided by the Arbeitsgemeinschaft Influenza ([Influenza Working Group] 2005), an institute set up to collect data on cases of acute respiratory infection and actively monitor for short-term increases indicative of possible influenza outbreaks from September to April of each year. The data are provided in the form of a doctors' practice index, which provides measures of the average relative deviation in the observed number of cases of acute respiratory infection from a background level determined for all doctors' practices participating in the system. The index has been published every winter since 1992/93 for calendar weeks 40 through 15 (September through April). We used the doctors' practice index for the whole of Germany because only a small number of practices in Thuringia participated in the system.

EXPOSURE

Location of the Monitoring Stations

Air-pollution and daily meteorologic data were compiled from three different monitoring stations in Erfurt: our GSF–National Research Center for Environment and Health[§] monitoring station, a network monitoring station operated by the State of Thuringia, and a meteorologic station operated by the German Meteorologic Service (Deutscher Wetterdienst). The location of the stations is shown in Figure 2.

The GSF monitoring station was located about 200 m above sea level in a residential area approximately 2 km from the city center. It was surrounded by homes, offices, a school, and a hospital and was approximately 40 m from a major road (Figure 2). From this station, we obtained detailed data on particulate air pollutants.

The network monitoring station was located on Krämpferstraße 2 km from the GSF monitoring station and at the same elevation. We obtained data on gaseous pollutants (NO, NO_2, CO, SO_2, and O_3), total suspended particles (TSP) until 2000, and PM_{10} (from 2001 onward) from this station.

The German Meteorologic Service station was located at an airport 5 km northwest of the GSF monitoring station, at 316 m above sea level (i.e., approximately 100 m higher than the other two monitoring stations). The meteorologic data we used came from this station. We selected it because it provided a complete record for the entire study period and because it reflected the general weather pattern on a daily basis better than the weather monitoring conducted at the GSF station.

Air-Pollution Measurement Methods

At the network monitoring station, SO_2 concentrations were measured using a UV-fluorescence monitor (model AF21M, Environnement S.A., Poissy, France). Concentrations of nitrogen oxides (NO and NO_2) were measured using a chemiluminescence monitor (model AC31M, Environnement S.A.). The manufacturer checked both monitors before the measuring period. CO concentrations were measured using infrared-light absorption. TSP and PM_{10} concentrations were measured using the beta-absorption method.

[§] Since 2008, the Center has been known as the Helmholtz Zentrum München – German Research Center for Environmental Health. However, it will be referred to as GSF (its name at the time of the study) in this report.

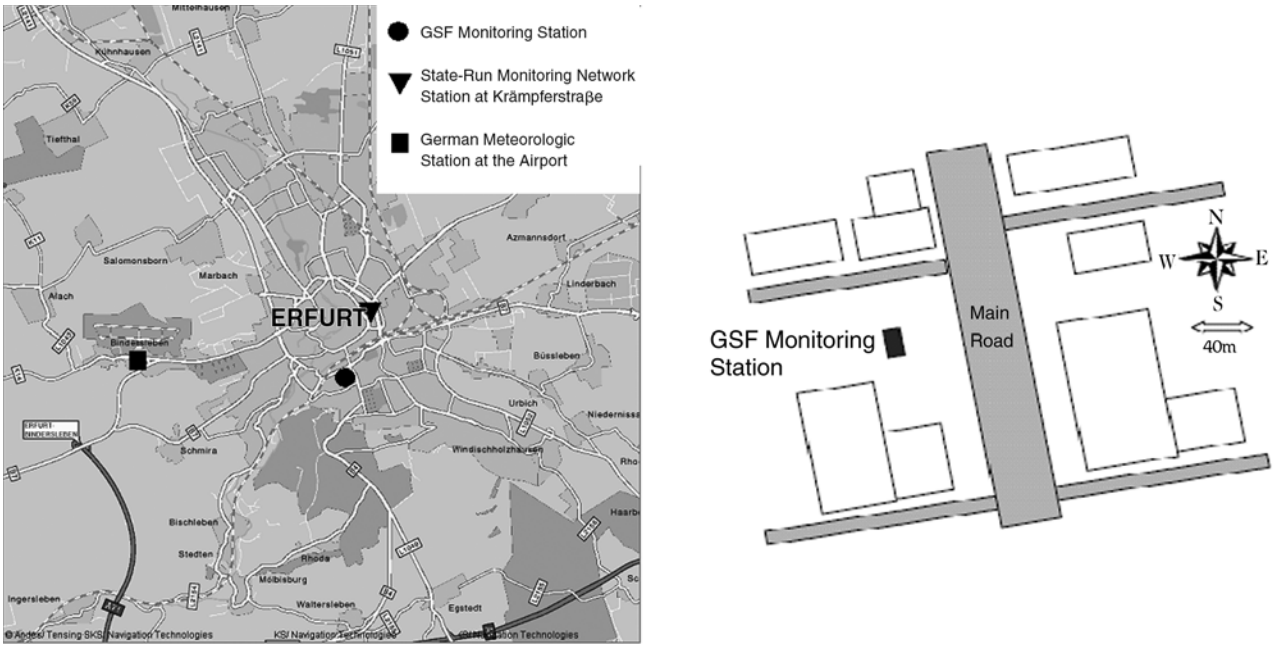

Figure 2. Locations of the two air monitoring stations and the meteorological station in Erfurt, Germany (*left*). Detail of location of the GSF monitoring station (*right*).

Data from the GSF monitoring station had already been used in a previous study (Wichmann et al. 2000; Brand et al. 2005). We measured PM_{10} and $PM_{2.5}$ using Harvard impactors (Air Diagnostics and Engineering Inc., Harrison, Maine, USA). Total particle NCs were measured using a condensation particle counter (model TSI 3025A, TSI Incorporated, Shoreview, Minn., USA). Particle size distribution was measured using an aerosol spectrometer for particles between 0.01 µm and 2.5 µm and a scanning mobility particle sizer (model TSI 3085, TSI Incorporated) for particles between 0.003 µm and 0.064 µm.

The mobile aerosol spectrometer was described in detail by Wichmann and colleagues (2000). It consisted of two devices: a differential mobility particle sizer to measure particles between 0.01 µm and 0.5 µm and a laser aerosol spectrometer to measure particles between 0.1 µm and 2.5 µm. The upper differential-mobility-particle-sizer channels, which measure particles between 0.1 µm and 0.5 µm, were used for mobility calibration of the spectrometer.

From each spectrum, total NCs and NCs for various particle-size ranges were calculated. Daily mean NCs were calculated for several ranges of particle sizes ($NC_{0.003–0.064}$, $NC_{0.01–0.03}$, $NC_{0.01–0.1}$, $NC_{0.01–2.5}$, $NC_{0.03–0.05}$, and $NC_{0.05–0.1}$). ($NC_{x–y}$ represents the NC for a specific range of particle sizes, measured in microns: $NC_{0.01–0.03}$, for example, represents the NC for ultrafine particles from 0.01 µm to 0.03 µm in diameter.) A mean density of 1.53 g/cm^3 of ambient aerosol was estimated, based on 700 simultaneous measurements of total particle number and $PM_{2.5}$ particle mass (Tuch et al. 2000). Daily MCs were calculated for several ranges of particle sizes ($MC_{0.1–0.5}$, $MC_{0.5–1.0}$, $MC_{1.0–2.5}$, and $MC_{0.01–2.5}$). ($MC_{x–y}$ represents the MC for a specific range of particle sizes, measured in microns.) Calculations assumed spherical particles of the estimated mean density (Wichmann et al. 2000). Calculated in this way, $MC_{0.01–2.5}$ is therefore a close approximation to $PM_{2.5}$. Note that a geometric diameter of 2.5 µm measured with the laser aerosol spectrometer corresponded to an aerodynamic diameter of 3.1 µm in Erfurt's ambient aerosol; the MC for particles between 0.01 and 2.5 µm ($MC_{0.01–2.5}$) therefore slightly exceeded the concentration of $PM_{2.5}$.

Imputation of data

The availability of air pollutant data measured at the GSF monitoring station varied from 80% to 91% (see *Exposure and Emission Data*). The missing data were missing as a result of malfunctions in the measurement devices or of the setting aside of certain implausible data after plausibility checks. In the case of the particle-mass measurements made with a manually operated Harvard impactor, some missing values can be attributed to the time fieldworkers were away on vacation or holidays. To reduce the number of missing values, we developed an imputation strategy using values obtained from parallel measurements made by other instruments.

Table 2 summarizes how missing $NC_{0.01–0.1}$, $NC_{0.01–2.5}$, $MC_{0.01–2.5}$, and PM_{10} values were imputed. The approaches for the various parameters are described in

more detail below. In general, we used semiparametric models to predict the missing values from existing concurrent measurements. This approach allows the inclusion of a smooth function of time to account for possible changing relationships between the two measurement periods over time. However, we could not use this approach at the ends of the measurement periods because the smooth functions of time tended to fray out. Linear regressions alone were therefore used under these circumstances.

Imputation of Values for $NC_{0.01–0.1}$ Missing values for $NC_{0.01–0.1}$ (which were to have been measured by a mobile aerosol spectrometer) were imputed for the period from December 12, 2000, to March 31, 2002, from concurrent measurements of the NC for ultrafine particles from 0.003 to 0.064 µm in diameter ($NC_{0.003–0.064}$) (Table 2). A scanning mobility particle sizer put into operation in December 2000 made the concurrent measurements. The imputation was made using a semiparametric model that allowed inclusion of a smooth function of time to account for temporal variations in the relationship between the measurements made with the differential mobility particle sizer and the scanning mobility particle sizer. Using measurements for $NC_{0.003–0.064}$ made from December 12, 2000,

Table 2. Measurement Periods and Imputation Methods for Particulate Pollutants

Pollutant	Measurement Period	Measurement Days		Imputation Period	Model	Predictor	Model-Fitting Period	Number of Imputed Values	Goodness of Fit (R^2)
		Scheduled	Actual						
$NC_{0.01–0.1}$ (MAS)	10/01/1991–5/25/1992 8/26/1995–3/31/2002	2648	2233 (84.3%)	12/12/2000–03/31/2002	GAM	$NC_{0.003–0.064}$ (SMPS)	12/12/2000–3/31/2002	126	0.94
$NC_{0.003–0.064}$ (SMPS)	12/12/2000–3/31/2002	475	424 (89.3%)						
$NC_{0.01–2.5}$ (MAS)	10/01/1991–5/25/1992 08/26/1995–3/31/2002	2648	2123 (80.2%)	02/25/1996–08/14/2001	GAM	$NC_{0.01–2.5}$ (CPC)	2/25/1996–8/14/2001	180	0.85
				08/15/2001–03/31/2002	Linear regression	$NC_{0.01–2.5}$ (CPC)	8/15/2000–8/14/2001	218	0.89
$NC_{0.01–2.5}$ (CPC)	2/25/1996–3/31/2002	2227	1848 (83.0%)						
$MC_{0.01–2.5}$ (MAS)	10/01/1991–5/25/1992 8/26/1995–3/31/2002	2648	2123 (80.2%)	09/01/1995–10/06/1999	GAM	$PM_{2.5}$ HI lags 0 and 1	9/12/1995–10/06/1999	72	0.75
				10/07/1999–08/14/2001	GAM	$PM_{2.5}$ HI lag 0	10/07/1999–8/14/2001	114	0.88
				08/15/2001–03/31/2002	Linear regression	$PM_{2.5}$ HI lag 0	8/15/2000–8/14/2001	207	0.90
$PM_{2.5}$ (HI)	9/12/1995–3/31/2002	2393	2184 (91.3%)						
PM_{10} (HI)	10/01/1991–6/27/1992 9/15/1995–3/31/2002	2661	2406 (90.4%)	10/01/1991–06/27/1992	GAM	TSP[a]	10/01/1991–6/27/1992	1	0.71
				06/28/1992–09/14/1995	Linear regression	TSP[a]	10/01/1991–12/31/1999	1143	0.72
				09/15/1995–12/31/2000	GAM	TSP[a]	9/15/1995–12/31/2000	101	0.76
				01/01/2001–03/31/2002	GAM	PM_{10}[a]	1/01/2001–3/31/2002	151	0.92
TSP[a]	10/01/1991–4/02/2001	3472	3421 (98.5%)						
PM_{10}[a]	12/21/2000–3/31/2002	466	455 (97.6%)						

[a] Measured at state-run monitoring station at Krämpferstraße.

through March 31, 2002, we predicted 126 missing $NC_{0.01–0.1}$ values (Table 2).

Imputation of Values for $NC_{0.01–2.5}$ Missing values for $NC_{0.01–2.5}$ (which were to have been measured by a mobile aerosol spectrometer) were imputed for two periods (February 25, 1996, through August 14, 2001, and August 15, 2001, through March 31, 2002) from concurrent measurements of the NC for particles from 0.01 to 2.5 μm in size ($NC_{0.01–2.5}$). A condensation particle counter in operation from February 25, 1996, onward measured the $NC_{0.01–2.5}$. Again, the imputation was made using a semiparametric model that allowed inclusion of a smooth function of time to account for temporal variations in the relationship between the measurements by the mobile aerosol spectrometer and the condensation particle counter. The measurements from the mobile aerosol spectrometer ended on August 14, 2001. From August 15, 2001, onward, $NC_{0.01–2.5}$ measurements were predicted by a linear regression based on condensation particle counter measurements made between August 15, 2000, and August 14, 2001. Using these measurements, we predicted 398 missing $NC_{0.01–2.5}$ values (Table 2).

Imputation of Values for $MC_{0.01–2.5}$ Values for $MC_{0.01–2.5}$ were derived from mobile aerosol spectrometer measurements made from October 1991 to June 1992 and from August 1995 to March 2002. Missing values were caused by malfunctions of a component, the laser aerosol spectrometer, that could no longer be repaired in 2001. Harvard impactor measurements for $PM_{2.5}$ were started in 1995. Missing $MC_{0.01–2.5}$ values were predicted based on concurrent $PM_{2.5}$ Harvard impactor measurements. Until October 6, 1999, the Harvard impactor collected $PM_{2.5}$ from 11 a.m. the day before to 11 a.m. on the same day; daily means for $MC_{0.01–2.5}$ derived from the aerosol spectrometer were computed from midnight to midnight. From October 7, 1999, onward, Harvard impactor filters were changed automatically at midnight to match the whole day as the basic time unit used in the epidemiologic analysis and the collection period of the aerosol spectrometer.

The imputation period was thus split into three subperiods. In the first imputation subperiod, from October 1, 1991, to October 7, 1999, the imputation of $MC_{0.01–2.5}$ values was based on Harvard impactor $PM_{2.5}$ values from the same day and the day before. In the second imputation subperiod, from October 7, 1999, to August 14, 2001, only same-day measurements were used. In both of these subperiods, a smooth function of time and a smooth function of an interaction between time and the Harvard impactor measurements were included in the semiparametric model. Because $MC_{0.01–2.5}$ measurements made by the aerosol spectrometer ceased on August 14, 2001, values for $MC_{0.01–2.5}$ for the third imputation subperiod, from August 15, 2001, to March 31, 2002, were predicted based on a linear regression using Harvard impactor $PM_{2.5}$ measurements made between August 15, 2000, and August 14, 2001 (i.e., one year). Using the $PM_{2.5}$ measurements, we predicted 393 missing $MC_{0.01–2.5}$ values (Table 2).

Imputation of Values for PM_{10} Missing values for PM_{10} measurements made with a Harvard impactor were imputed from measurements of TSP (through December 2000) or PM_{10} (from January 2001 onward) obtained from the network monitoring station, which was located near the GSF monitoring station. A semiparametric model was fitted based on TSP measurements made between September 15, 1995, and December 31, 2000, and PM_{10} measurements made between January 1, 2001, and March 31, 2002. In addition to a smooth function of time, a smooth interaction between time and the TSP or PM_{10} measurements was included in the semiparametric model. For missing Harvard impactor measurements of PM_{10}, we predicted 101 missing PM_{10} values using TSP measurements and 151 using PM_{10} measurements from the network monitoring station.

During an earlier measurement campaign (from October 1, 1991, to June 27, 1992), one missing value was predicted based on a semiparametric model that included the TSP measurements at the network monitoring station along with a smooth function of time and a smooth interaction between time and the TSP value.

Because there were no Harvard impactor measurements of PM_{10} between June 28, 1992, and September 14, 1995, TSP measurements from the network monitoring station were scaled according to a linear regression based on data collected between October 1991 and December 1999. Using these TSP measurements, we predicted 1143 missing PM_{10} values (Table 2).

POISSON REGRESSION ANALYSIS

Confounder Model and Regression Analysis

The counts of daily deaths were considered to be Poisson distributed. We used Poisson regression in a generalized additive model to allow for smooth functions of the confounders. Models were built in a manner similar to that in the Air Pollution and Health: A European Approach (APHEA) study (Touloumi et al. 2004). Trend, seasonality, influenza epidemics, calendar effects, and meteorology were considered as potential confounders. These variables were included stepwise into the model, which was then assessed by the Akaike information criterion.

First, a preliminary model was developed with the statistical software package S-plus® (Insightful Corporation, Seattle, WA, USA), in which nonparametric smooth functions were used to adjust for the confounders. We started with trend and seasonality, which were included using a smoothing spline. The number of knots was chosen to remove residual autocorrelation. Next, influenza epidemics were included using LOESS (locally weighted smoothing scatterplot) smoothers. Because the influenza epidemics might have peaked in Erfurt at a time different from the peak time in Germany as a whole, shifts of up to plus or minus three weeks were tested. Only influenza epidemics that improved the model fit in terms of the Akaike information criterion and that had a plausible exposure–response relationship (i.e., the doctors' practice index and the count of daily deaths were positively associated) were included in the model. The lag days and the number of degrees of freedom were chosen to minimize the Akaike information criterion.

We also controlled for the effects of immediate and lagged temperature as well as humidity. The lag days and spans were chosen to minimize the Akaike information criterion. After that, indicator variables for day of the week and public holidays were tested.

The last step of the model building consisted of readjusting the number of knots for the smoothing spline that adjusted for trend and seasonality. Because other confounders, particularly temperature, also partially account for seasonality, the model is usually overestimated, indicated by the presence of negative autocorrelation in the residuals. This can be overcome by reducing the number of knots in the smoothing spline that adjusts for trend and seasonality, as suggested by Touloumi and colleagues (2004).

To properly determine the standard errors of the linear terms included in the confounder model (Dominici et al. 2002; Ramsay et al. 2003), the model was afterward replicated in R statistical software using penalized splines with the same number of degrees of freedom. The R-based model was considered to be the final one. In the next step, the pollutants were included in this final model as linear predictors. We evaluated the associations of the pollutants with daily mortality for lag times of up to five days.

We built separate confounder models for the periods of analysis 1991–2002 and 1995–2001. In the first model, the effects of gaseous pollutants were investigated. In the second model, the effects of particle size distribution were investigated. Table 3 summarizes the confounders included in the final models for each analysis period.

The same confounder models were used for the analysis of cause-specific mortality. The penalties for the penalized splines were slightly adjusted to yield the same number of degrees of freedom as in the final model for total mortality.

A number of sensitivity analyses were performed to assess the effects of confounder-model specification on the associations between air-pollutant concentrations and daily mortality (see *Sensitivity Analyses*).

Time-Varying Coefficient Models

Time-varying coefficient models are a special type of varying coefficient models. These models allow a response variable to depend linearly on some regressors, with coefficients as smooth functions of some other

Table 3. Comparison of the Confounder Models Built for Two Periods of Analysis

Variable	Model for 1991–2002	Model for 1995–2001
Offset	Log(population)	Log(population)
Trend and season	P-spline (df = 22)	P-spline (df = 8)
Influenza epidemics	1993/94: P-spline, df = 2.7	
	1994/95, lag minus 3 weeks: P-spline, df = 2.7	
	1995/96, lag minus 1 week: P-spline, df = 3.5	1995/96, lag minus 1 week: P-spline, df = 3.8
		1998/99, lag 2 weeks: linear
	1999/00, lag 2 weeks: P-spline, df = 2.8	1999/00, lag 2 weeks: linear
	2000/01, lag 3 weeks: P-spline, df = 3	2000/01, lag 3 weeks: P-spline, df = 3
Meteorology	Temperature: P-spline, df = 4	Temperature: P-spline, df = 5
	Temperature, lag 1: linear	Temperature, lag 1: linear
	Relative humidity, lag 2: P-spline, df = 3	Relative humidity, lag 2: P-spline, df = 2.8
Day of week	Sunday	Sunday

predictor variables, called effect modifiers. Their additive-linear structure enables simple interpretation and avoids the "curse of dimensionality" problem in high-dimensional cases.

Varying coefficient models, which were systematically introduced by Hastie and Tibshirani (1993), have in general a predictor of the form

$$\eta = \beta_0 + f_1(r_1)x_1 + \ldots + f_p(r_p)x_p. \quad (1)$$

The model described in equation 1 says that $r_1,\ldots,r_p$ change the coefficients of the $x_1,\ldots,x_p$ through the (unspecified) functions $f_1,\ldots,f_p$. The dependence of f_j on r_j implies a special kind of interaction between each r_j and x_j, $j = 1,\ldots,p$.

Varying coefficient models arise from various statistical contexts in slightly different forms. The vast amount of literature includes, among many others, approaches based on local regression (Kauermann and Tutz 1999; Fan and Zhang 1999, 2000), functional data analysis (Ramsay and Silverman 2002), generalized linear models with varying coefficients (Cai et al. 2000a; Galindo et al. 2001), and mixed models for longitudinal data (Hoover et al. 1998; Tutz and Kauermann 2003; Zhang 2004).

Here we considered time-varying coefficient models as a special case of the varying coefficient model with the effect modifier being time t. Further, we considered a model where some of the functions f_j were assumed to be constant, $f_j(\bullet) = \beta_j$, which meant that this term was linear. It was also assumed that the confounders were modeled as nonlinear time-invariant functions. In this case the jth term was simply $f_j(x_j)$, an unspecified function in x_j. Altogether, this led to a semiparametric time-varying coefficient model with a predictor of the following form:

$$\eta = \beta_0 + \sum_{j=1}^{l} \beta x_j + \sum_{j=l+1}^{k} f_j(x_j) + \sum_{j=k+1}^{p} f_j(t)x_j \; . \quad (2)$$

In the following sections, five different approaches fitting semiparametric time-varying coefficient models are illustrated.

Model A: Time-Varying Coefficient Model with Regression Splines One possibility, mentioned in Hastie and Tibshirani (1993), was estimating an interaction term $f_j(t)\,x_j$, where the unknown function $f_j(t)$ was approximated by a polynomial regression spline in time.

A polynomial spline for the functions $f_j(t)$ can, for example, be constructed by using truncated power series bases:

$$f_j(t) = \gamma_{j0} + \gamma_{j1}t + \ldots + \gamma_{jp}t^p + \sum_{m=1}^{M-1} \gamma_{jm}(t-\xi_m)_+^p \; , \quad (3)$$

where $(t-\xi_m)_+ = \max\{0,(t-\xi_m)\}$, and $\xi_1, \ldots, \xi_{M-1}$ are fixed knots.

We chose $p = 3$ here, which means we were using a cubic regression spline. Thereby, $f_j(t)$ could be parameterized in terms of a linear combination of $M + 3$ ($M \in N$) basis functions such that the spline function was also twice continuously differentiable at knots $\xi_1,\ldots,\xi_{M-1}$. Thus, a time-varying coefficient term could be modeled by

$$f_j(t)\,x_j = \left(\gamma_{j0} + \gamma_{j1}t + \gamma_{j2}t^2 + \gamma_{j3}t^3 + \sum_{m=1}^{M-1} \gamma_{jm}(t-\xi_m)_+^3\right)x_j, \quad (4)$$

where $\gamma = (\gamma_{j0}, \gamma_{j1},\ldots,\gamma_{jM-1})$ denoted the vector of unknown regression coefficients. The terms $1, t, t^2, t^3, (t-\xi_1)^3,\ldots,(t-\xi_{M-1})^3$ in equation 4 were the basis functions. The basis functions were defined by a vector of knots $\xi_1, \ldots, \xi_{M-1}$ that lay within the domain of the respective effect modifier t. If regression splines had also been used for all of the other nonlinear functions f_j, then the analyses would have been completely parametric.

Model B: Bayesian Time-Varying Coefficient Model with P-Splines A second approach was the use of fully Bayesian time-varying coefficient models with penalized splines, as described in Lang and Brezger (2004).

Bayesian-type models are defined hierarchically: In the first step, an observation model for the response given the covariates must be specified. Here, we considered the predictor expressed in equation 2 as the observation model. In the next step, we formulated prior distributions (the probability distributions of parameter values based on prior knowledge; also known as priors) for the unknown parameters of the model.

Prior Distributions Prior distributions should account for available information and reflect prior knowledge about the parameters. Often, these priors will depend on further parameters, called hyperparameters, for which additional hyperpriors must be defined.

Continuous Covariates and Interactions

Priors for the unknown functions $f_{l+1},\ldots, f_p$ depended on the type of covariates as well as on prior beliefs about

the smoothness of f_j. Several alternatives have been proposed for specifying smoothness priors for continuous covariates or time scales. These are random-walk priors or more generally autoregressive priors (Fahrmeir and Lang 2001), Bayesian smoothing splines (Hastie and Tibshirani 2000), and Bayesian versions of penalized splines based on B-spline basis functions (Bayesian P-splines) (Lang and Brezger 2004), the last of which being the ones used in this study.

We assumed that an unknown function f_j of a covariate x_j, $j = l + 1,\ldots,k$ could be approximated by a third-order polynomial spline, which could be written in terms of a linear combination of B-spline basis functions

$$f_j\left(x_j\right) = \sum_{d=1}^{S} \gamma_{jd} \mathbf{B}_{jd}^3\left(x_j\right),\ j = l+1,\ldots,k, \tag{5}$$

where $\gamma_{jd} = (\gamma_{j1},\ldots,\gamma_{jS})^T$ corresponded to a vector of unknown regression coefficients.

By defining the $T \times S$ design matrices $\mathbf{X}_j$, where the element in row t and column d was given by $\mathbf{X}_j(t,d) = \mathbf{B}_{jd}(x_{tj})$, we could rewrite the P-spline formulation in matrix notation as

$$f_j\left(x_j\right) = \mathbf{X}_j \gamma_j. \tag{6}$$

A moderate number of knots (between 20 and 40) was chosen, and the resulting estimate was smoothed by penalizing differences between the parameters of the spline. For our analysis, we used second-order random walks as priors for γ_{jd} defined by

$$\gamma_{jd} = 2\gamma_{j,d-1} - \gamma_{j,d-2} + u_{jd}, \tag{7}$$

with Gaussian errors $u_{jd} \sim N(0,\tau_j^2)$. Diffuse priors $p(\gamma_{j1}) \propto const$ and $p(\gamma_{j2}) \propto const$ were chosen for initial values. This specification was the stochastic analogue of difference penalties (Eilers and Marx 1996) and could be interpreted as a prior for the regression coefficients. In the case of a second-order random-walk model, this meant that deviations from the linear trend were penalized. The amount of smoothness was controlled by an additional variance parameter τ_j^2, which corresponded to the inverse smoothing parameter in the classical approach. Thus, the Bayesian version of P-splines allowed for considering the smoothing parameters as random and, hence, for simultaneous estimation with the other model parameters.

As to the time-varying coefficient terms, we used the priors already defined above for the nonlinear functions f_j and adapted them to the time variable t:

$$f_j(t) = \mathbf{X}_j^* \gamma_j,\ j = k+1,\ldots,p. \tag{8}$$

Only the design matrices $\mathbf{X}^*_j$ in equation 8 had to be redefined by multiplying each element in row t of $\mathbf{X}^*_j$ with x_{tj}. Hence, the overall matrix formulation for the varying terms was given by

$$f_j\left(t,x_j\right) = f_j(t)\,x_j = \text{diag}\left(x_{1j},\ldots,x_{Tj}\right)\mathbf{X}_j^* \gamma_j = \mathbf{X}_j \gamma_j, \tag{9}$$

where $\mathbf{X}^*_j$ was the usual design matrix for splines composed of the basis functions evaluated at the observations t as given above.

The priors for γ_j in the case of continuous covariates and interactions could be equivalently written in the form of global smoothness priors

$$p\left(\gamma_j \mid \tau_j^2\right) \propto \exp\left(-\frac{1}{2\tau_j^2}\gamma_j' \mathbf{K}_j \gamma_j\right), \tag{10}$$

where $\mathbf{K}_j$ was the precision matrix of the multivariate Gaussian distribution. This precision matrix was of the form $\mathbf{K}_j = \mathbf{D}'\mathbf{D}$ where $\mathbf{D}$ was, in our analysis, a second-order difference matrix of the form

$$\mathbf{D} = \begin{pmatrix} 1 & -2 & 1 & & & \\ & 1 & -2 & 1 & & \\ & & \ddots & \ddots & \ddots & \\ & & & 1 & -2 & 1 \end{pmatrix}.$$

Fixed Effects

In the absence of any prior knowledge, diffuse priors were an appropriate choice for fixed parameters, i.e., $p\left(\beta_j\right) \propto const$, where the priors were supposed to be independent for each $j = 1,\ldots,l$.

Hyperparameters

In addition to the coefficients, the variance parameters τ_j^2 had to be supplemented with a prior distribution as well. Thus, these parameters were also assumed to be random and were estimated simultaneously with the coefficients. The advantage of this procedure was that the problem of choosing a smoothing parameter was avoided. The prior distribution for the variance parameters, also called hyperparameters, is often chosen to be a highly dispersed but proper inverse gamma prior $p(\tau_j^2) \sim IG(a_j,b_j)$. A

common choice for the parameters a_j and b_j are small values, e.g., $a_j = b_j = 0.001$.

Bayesian Inference Bayesian inference is based on the posterior distribution of values in the model, which was given by

$$\begin{aligned} & p\left(\gamma_{l+1}, \ldots, \gamma_p, \tau_{l+1}^2, \ldots, \tau_p^2, \beta\right) \\ & \propto \mathrm{L}\left(y, \gamma_{l+1}, \ldots, \gamma_p, \tau_{l+1}^2, \ldots, \tau_p^2, \beta\right) \\ & \quad \prod_{j=l+1}^{p} p\left(\gamma_j \mid \tau_j^2\right) p\left(\tau_j^2\right), \end{aligned} \tag{11}$$

where L(•) denoted the likelihood, which was the product of individual likelihood contributions.

In many practical applications, this high-dimensional posterior will not have a known closed form but rather a complicated high-dimensional density, known only up to the proportionality constant. Inference can therefore be done by using Markov chain Monte Carlo (MCMC) simulation methods.

For updating the parameters in the MCMC sampler, a Metropolis-Hastings (MH) algorithm was used, based on iteratively weighted least squares (IWLS) proposals introduced by Gamerman (1997). The basic idea behind IWLS proposals is to combine the MH algorithm with Fisher scoring or IWLS (see, for example, Fahrmeir and Lang 2001) for estimating regression parameters in generalized linear models. More precisely, the goal is to approximate the full conditionals of regression parameter vectors β and γ by a Gaussian distribution, obtained by accomplishing one Fisher scoring step in each iteration step of the sampler. A detailed description of this algorithm and its implementation can be found in Brezger and Lang (2006).

Model C: Time-Varying Coefficient Model with Penalized Linear Splines Based on a Generalized Mixed-Model Framework Recent applications in spline smoothing make use of a convenient connection between penalized linear splines and mixed models (Brumback et al. 1999).

Mixed-model approaches to penalized splines based on truncated power series representations have been described in Wand (2003), Ruppert and colleagues (2003), and Ngo and Wand (2004). Ngo and Wand also described the estimation of varying coefficient models but only for the case of Gaussian distributed responses. Here, we extended this estimation approach to a generalized setting, though we followed the suggestions of Ngo and Wand and used penalized linear splines.

Before addressing the estimation of regression coefficients as well as variance parameters in a (generalized) mixed model, we will first show how the model (as described in equation 2) was reformulated as a generalized linear mixed model.

Mixed-Model Representation The linear spline estimator for a function f_j of a variable x_j is of the form (see earlier section *Model A: Time-Varying Coefficient Model with Regression Splines*)

$$f_j\left(x_j\right) = \alpha_{j0} + \alpha_{j1} x_j + \sum_{m=1}^{M_j - 1} u_{jm}\left(x_j - \xi_m^j\right)_+. \tag{12}$$

Equivalently, a linear spline version of a time-varying coefficient term is given by

$$f_j(t) x_j = \left(a_{j0} + a_{j1} t + \sum_{m=1}^{M_t - 1} u_{jm}\left(t - \xi_m\right)_+\right) x_j, \tag{13}$$

where $\xi_1, \ldots, \xi_{M_t - 1}$ are knots over the range of the t values.

Using these two formulas, the model (see equation 2) could be written as

$$\begin{aligned} \eta = \beta_0 + \sum_{j=1}^{l} \beta_j x_j + \sum_{j=l+1}^{k} \left(a_{j1} x_j + \sum_{m=1}^{M_j - 1} u_{jm}\left(x_j - \xi_m^j\right)_+\right) \\ + \sum_{j=k+1}^{p} \left(\left(a_{j0} + a_{j1} t + \sum_{m=1}^{M_t - 1} u_{jm}\left(t - \xi_m^j\right)_+\right) x_j\right). \end{aligned} \tag{14}$$

To implement spline smoothing in practice, the coefficient vectors $\alpha = (\alpha_{l+1}, \ldots, \alpha_{p1})^T$ and $\boldsymbol{u} = (u_{l+1,\,1}, \ldots, u_{p,\,M_t - 1})^T$ had to be estimated. In principle, we could apply the usual methods as described earlier in the section *Model A: Time-Varying Coefficient Model with Regression Splines*, but we expected that this would tend to result in a rather rough estimate of the function. A greater degree of smoothing could be achieved by shrinking the estimated coefficients toward zero.

Smoothing was now achieved by regarding the $\boldsymbol{u_{jm}}$ as random coefficients, distributed independently as

$$\begin{aligned} & u_{l+1,1}, \ldots, u_{l+1,M_{l+1}-1}, \\ & iid\ \mathrm{N}\left(0, \sigma_{l+1}{}^2\right), \ldots, u_{p,1}, \ldots, u_{p,M_t - 1}\ \ iid\ \mathrm{N}\left(0, \sigma_p^2\right), \end{aligned} \tag{15}$$

as suggested by Brumback and colleagues (1999), with σ_j^2 controlling the amount of smoothing. Constraining the coefficients $u_{l+1,1}, \ldots, u_{l+1,M_{l+1}-1}, \ldots, u_{p,1}, \ldots, u_{p,M_t - 1}$ to come from a common distribution had the effect of damping changes in the gradient of fitted line segments from one knot point to the next. Thus, the resulting estimator was a type of penalized spline smoother.

Then we set the design matrix to take the following form:

$$\mathbf{X} = \left(1\ x_{tl},\ \ldots,\ x_{tk-l}\ t\ x_{tk+1}\ tx_{tk+j},\ \ldots,\ x_{tp}\ tx_{tp}\right)_{1\le t\le T}.$$

The random-effects matrix **Z** was constructed as

$$\mathbf{Z} = \Bigg[\underset{1\le m\le M_{l+1}-1}{\left(x_{tl+1} - \xi_m^{l+1}\right)_+} \ \ldots\ \underset{1\le m\le M_k-1}{\left(t - \xi_m^{k}\right)_+} \ \underset{1\le m\le M_k-1}{x_{tk+l}\left(t - \xi_m^{k+1}\right)} + \ \ldots\ \underset{1\le m\le M_k-1}{x_{tp}\left(t - \xi_m^{p}\right)_+}\Bigg]_{1\le t\le T}.$$

By defining

$$b = \left[u_{l+1,l},\ \ldots,\ u_{l+1,M_{l+1}-1},\ \ldots,\ u_{p,l},\ \ldots,\ u_{p,M_t-1}\right]^T \quad (16)$$

and

$$\mathrm{Cov}(b) = \mathbf{D} = \begin{bmatrix} \sigma_{l+1}^2\mathbf{I} & 0 & \ldots 0 \\ 0 & \sigma_{l+2}^2\mathbf{I} & \ldots 0 \\ \vdots & \vdots & \ddots 0 \\ 0 & 0 & \ldots \sigma_p^2\mathbf{I} \end{bmatrix} \quad (17)$$

we were then able to write the model (expressed in equation 14) in matrix notation as

$$\eta = \mathbf{X}\beta + \mathbf{Z}b \quad (18)$$

Thereby, we divided the functions f_j and the varying coefficient terms $f_j(t)x_j$ into a fixed-effects and a random-effects part and thus got a generalized linear mixed model:

$$\begin{aligned} &y \mid b \sim \mathrm{Poisson}_0(\mu) \\ &\log(\mu) = \mathbf{X}\beta + \mathbf{Z}b \\ &b \sim \mathrm{N}(0,\mathbf{D}) \end{aligned} \quad (19)$$

Fitting the linear splines therefore amounted to minimization of the penalized spline criterion.

Knot specification

The location of the knots had to be specified before fitting the model. Wand (2003) commented that knot specification is "very much a minor detail for penalized splines." Thus, we followed Wand's suggestion that a reasonable default rule for the location of the knots was

$$\begin{aligned} u_m = &\frac{(s+1)}{S+2}\text{th sample quantile of the} \\ &\text{unique } x_t, 1 \le s \le S, \end{aligned} \quad (20)$$

where S = max{5; min(1/4 × number of unique x_t; 35)}. Some additional algorithms, empirical results, and comments on the topic of knot selection were supplied in Ruppert (2002).

Estimation Parameters in this model were estimated through pseudolikelihood procedures, as described in Wolfinger and O'Connell (1993). The generalized linear mixed model was approximated by a linear mixed model based on current values of the covariance parameter estimates. β and **b** were estimated from Henderson's mixed-model equations, and **D** and **V** were estimated with restricted pseudolikelihood (REPL).

Model D: Time-Varying Coefficient Model with Bayesian P-Splines Based on Empirical Bayes Inference An alternative approach was the use of time-varying coefficient models with P-splines based on empirical Bayes inference, as described in Fahrmeir and colleagues (2004). The differences between this approach and the one used in Model C were, first, that penalized splines based on B-spline bases were used in this model and, second, that the estimation procedure used in this model was slightly different. Finally, this model had a different, namely a Bayesian, perspective.

Observation Model and Prior Assumptions As with the fully Bayesian model (Model B), an observation model had to be specified, for which we again used the model defined in equation 2. As noted above, in a Bayesian approach the unknown functions $f_j(x_j)$ and $f_j(t)$ in the observation model as well as the parameter vectors β and γ are considered random variables and must be supplemented by appropriate prior assumptions, for which we chose the same prior distributions as for Model B.

Mixed-Model Representation As shown in the *Prior Distributions* section for Model B, the functions $f_j(x_j)$, $j = l + 1,\ldots,k$ and $f_j(t)\ x_j$, $j = k + 1,\ldots, p$ could be expressed as the matrix product of a design matrix $\mathbf{X}_j$ and a vector of unknown parameters γ_j, i.e.,

$$\begin{aligned} &f_j\left(x_j\right) = \mathbf{X}_j\gamma_j \text{ and} \\ &f_j(t)\,x_j = \mathrm{diag}\left(x_{1j},\ \ldots,\ x_{Tj}\right)\mathbf{X}_j^*\gamma_j = \mathbf{X}_j\gamma_j\ , \end{aligned} \quad (21)$$

respectively.

In order to express the functions $f_j(x_j)$ and $f_j(t)$ as the sum of fixed and random effects, we needed to decompose the vectors of the regression coefficient γ_j, where $j = l + 1,\ldots,p$,

into an unpenalized (*unpen*) part and a penalized (*pen*) part:

$$\boldsymbol{\gamma}_j = \boldsymbol{\Psi}_j^{unpen}\boldsymbol{\gamma}_j^{unpen} + \boldsymbol{\Psi}_j^{pen}\boldsymbol{\gamma}_j^{pen}. \tag{22}$$

For P-splines with a second-order random walk, $\boldsymbol{\Psi}_j^{unpen}$ was specified as a two-column matrix, where the first column was the identity vector and the second was composed of the (equidistant) knots of the spline. The matrices $\boldsymbol{\Psi}_j^{pen}$ were given by $\boldsymbol{\Psi}_j^{pen} = \mathbf{D}^T(\mathbf{D}\mathbf{D}^T)^{-1}$, Using the decomposition of the vectors of the regression coefficient shown in equation 22, we got for the general prior (see equation 10).

$$\begin{aligned} p\left(\gamma_j \mid \tau_j^2\right) &\propto \exp\left(-\frac{1}{2\tau_j^2}\gamma_j^T\mathbf{K}_j\gamma_j\right) \\ &= \exp\left(-\frac{1}{2\tau_j^2}{\gamma_j^{pen}}^T\gamma_j^{pen}\right). \end{aligned} \tag{23}$$

In the next step, we defined the matrices $\tilde{\mathbf{X}}_j = X_j{\boldsymbol{\Psi}_j}^{unpen}$ and $\tilde{Z}_j = X_j{\boldsymbol{\Psi}_j}^{pen}, j = l+1, \ldots, p$. Using these matrices, equation 22 could be rewritten as

$$\eta = X\beta + \sum_{j=l+1}^{p}\left(\tilde{\mathbf{X}}_j{\boldsymbol{\gamma}_j}^{unpen} + \tilde{Z}_j{\boldsymbol{\gamma}_j}^{pen}\right). \tag{24}$$

This, however, could be further simplified by specifying $\tilde{\mathbf{X}} = \left(\tilde{\mathbf{X}}_{l+1}, \ldots, \tilde{\mathbf{X}}_p, \mathbf{X}\right)$ and the vector $\boldsymbol{\gamma}^{unpen} = \left(\left(\boldsymbol{\gamma}_{l+1}^{unpen}\right)^T, \ldots, \left(\boldsymbol{\gamma}_p^{unpen}\right)^T, \boldsymbol{\beta}^T\right)^T$. Similarly, we made the specifications $\tilde{Z} = (\tilde{Z}_{l+1}, \ldots, \tilde{Z}_p)$ and , $\boldsymbol{\gamma}^{pen} = \left(\left(\boldsymbol{\gamma}_{l+1}^{pen}\right)^T, \ldots, \left(\boldsymbol{\gamma}_p^{pen}\right)^T\right)^T$, obtaining a generalized linear mixed model

$$\boldsymbol{\eta} = \tilde{\mathbf{X}}\boldsymbol{\gamma}^{unpen} + \tilde{Z}\boldsymbol{\gamma}^{pen} \tag{25}$$

with fixed effects γ^{unpen} and random effects γ^{pen}, where $\gamma^{pen} \sim N(\mathbf{0}, \Lambda)$, and $\Lambda = \text{diag}(\tau_{l+1}{}^2, \ldots, \tau_{l+1}{}^2, \ldots, \tau_p{}^2, \ldots, \tau_p{}^2)$.

Estimation Based on the generalized mixed-model representation (see equation 25), we got the following posterior distribution:

$$\begin{aligned} &P\left(\boldsymbol{\gamma}^{unpen}, \boldsymbol{\gamma}^{pen} \mid y\right) \\ &\propto L\left(y, \boldsymbol{\gamma}^{unpen}, \boldsymbol{\gamma}^{pen}\right) \prod_{j=l+1}^{p}\left(p\left({\boldsymbol{\gamma}_j}^{pen} \mid \boldsymbol{\tau}_j^2\right)\right), \end{aligned} \tag{26}$$

where $p({\gamma_j}^{pen} \mid \tau_j{}^2)$ was defined as above. Note that for empirical Bayes inference, no priors $p(\tau_j^2)$ for the variances were specified, because the variances τ_j^2 were considered as constants, but the τ_j^2 were estimated from the data.

Updated estimates for the unknown functions and covariate effects were obtained using the IWLS algorithm, resulting in posterior mode estimates. Variance parameters $\tau_j{}^2$ were estimated by maximizing the (approximate) restricted log-likelihood (REML) with respect to the variance parameters $\tau_{l+1}{}^2, \ldots, \tau_p{}^2$. Consequently, we again got a data-driven smoothing parameter selection.

A detailed description of empirical Bayes inference can be found in Fahrmeir and colleagues (2004). This approach is included in BayesX (*http://www.stat.uni-muenchen.de/~bayesx/bayesx.html*), a software package for Bayesian inference (Brezger et al. 2005).

Model E: Adaptive Generalized Varying-Coefficient Linear Models In contrast to the approaches based on spline estimation described earlier, a model based on local likelihood estimation was the fifth model considered. Fan and colleagues (2003) proposed a class of adaptive varying-coefficient linear models of the form

$$Y = \sum_{j=0}^{p} g_j\left(\beta_0{}^T X\right)x_j + \epsilon, \tag{27}$$

where $X = (x_0, \ldots, x_p)$ and $x_0 = 1$. In these models, the parameter vector β_0 is unknown, and the functions g_j are also unknown. Fan and colleagues used the term "adaptive model" to indicate that the coefficients are functions of an unknown index $\beta_0{}^T X$, in contrast to, for example, the functional-coefficient models of Cai and colleagues (2000b).

To be applicable in the context of count data, this approach was extended to allow, for example, for a Poisson response. Then the following predictor was obtained:

$$\begin{aligned} \log(\mu) &= \sum_{j=0}^{p} g_j\left(\beta_0{}^T X\right)x_j \\ &= g_0\left(\beta_0{}^T X\right) + X^T\, g\left(\beta_0{}^T X\right). \end{aligned} \tag{28}$$

It was easy to see that the model described in equation 28 was not identifiable, as we could replace the (g_0, g) with

$(g_0 + c\,\beta_0{}^T X,\ g - c\,g_0)$ for any $c \in R$. Therefore, the model could be represented in a reduced form

$$\log(\mu) = \sum_{j=0}^{p-1} g_j\left(\beta_0{}^T X\right) x_j\,, \tag{29}$$

(see Theorem 1 in Fan and colleagues [2003]). More details about the identifiability of models such as that described in equation 29 were given in Fan and colleagues (2003) and Lu and colleagues (2007).

The estimation procedure could be formally split into two parts: the estimation of functions g_j with β_0 given and the estimation of the index coefficient β_0 with functions g_j given. Unlike Fan and colleagues (2003), we did not apply backward deletion to choose locally significant variables.

Estimation of the Varying Coefficients $g_j(\bullet)$ We used a local linear modeling scheme to get an estimator for the functions g_j, $j = 1,\ldots, p-1$.

The method described here used a given estimator of β_0 that is called $\hat{\boldsymbol{\beta}}_0$. We therefore wrote for the index $\hat{Z} = \hat{\boldsymbol{\beta}}_0{}^T X$.

Suppose g_j has a continuous second derivative. For each given z, $z, g_j(\hat{Z})$ was approximated locally by a linear function $g_j\left(\hat{Z}\right) \approx a_{j0} + a_{j1}\left(\hat{Z} - z\right)$ for $\hat{Z}$ in the neighborhood of z.

Computing the local maximum likelihood estimate can be very time-consuming, especially for more complex models such as varying coefficient models. Therefore, we followed Cai and colleagues (2000a), who proposed replacing iterative local maximum likelihood estimation with a one-step Newton-Raphson estimator, which has been frequently used in parametric models. Cai and colleagues also demonstrated that the one-step estimator was statistically efficient provided that the initial estimate is good enough.

Given an initial estimate $\hat{g}_0 = \hat{g}(z) = \left(\hat{a}_0(z)^T, \hat{a}_1(z)^T\right)^T$, the updated estimator for a Poisson-distributed response was given by

$$\hat{g}_{os} = \hat{g}_0 + \begin{pmatrix} \mathbf{H_{t0}}\ \mathbf{H_{t1}} \\ \mathbf{H_{t1}}\ \mathbf{H_{t2}} \end{pmatrix}^{-1} + \begin{pmatrix} u_{t0} \\ u_{t1} \end{pmatrix}, \tag{30}$$

where

$$\mathbf{H}_{tj} = \sum_{t=1}^{T} \mathrm{K}_h\left(\hat{Z}\right) \mathrm{w}\left(\hat{Z}\right) \exp\left\{\sum_{j=0}^{p-1}\left[\hat{a}_{j0} + \hat{a}_{j1}\left(\hat{Z} - z\right)\right] X_{tj}\right\} \left(\hat{Z} - z\right)^l \mathrm{X}_t \mathrm{X}_t{}^{\mathrm{T}},\ l = 0, 1, 2\,. \tag{31}$$

In the above expressions, $\mathrm{K}(\bullet)$ is a kernel function, $\mathrm{K_h}(\bullet) = \mathrm{h}^{-1}\mathrm{K}(\bullet/\mathrm{h})$, $\mathrm{h} > 0$ is the bandwidth, and $\mathrm{w}(\bullet) = \mathrm{I}_{[-\mathrm{L},\,\mathrm{L}]}(\bullet)$ is a bounded weight function controlling the edge effect in the estimation. Furthermore, u_{tj} is given by

$$u_{tj} = \sum_{t=1}^{T} \mathrm{K}_h\left(\hat{Z}\right) \mathrm{w}\left(\hat{Z}\right) \left(Y_t - \exp\left\{\sum_{j=0}^{p-1}\left[\hat{a}_{j0} + \hat{a}_{j1}\left(\hat{Z} - z\right)\right] \mathrm{X}_{tj}\right\}\right) \left(\hat{Z} - z\right)^l \mathrm{X}_t\,,\ l = 0, 1\,. \tag{32}$$

As the matrix described in equation 30 can be singular or nearly singular, one could use a ridge parameter to attenuate the problem, as proposed by Cai and colleagues (2000a).

Estimation of the Index β_0 with $g_j(\bullet)$ Fixed Again, a one-step estimation scheme was used to estimate the index coefficients β_0. We searched for β_0 to minimize

$$R(\beta_0) = \frac{1}{T}\sum_{t=1}^{T}\left[Y_t - \exp\left(\sum_{j=0}^{p-1} g_j\left(\beta_0^T X - z\right) x_{tj}\right)\right]^2 w\left(\beta_0^T X\right) \tag{33}$$

For any initial value $\beta_0{}^{(0)}$ close to $\hat{\beta}$, one has the approximation

$$R'\left(\hat{\beta}_0\right) \approx R'\left(\beta_0{}^{(0)}\right) + R''\left(\beta_0{}^{(0)}\right)\left(\hat{\beta}_0 - \beta_0{}^{(0)}\right), \tag{34}$$

where R' is the derivative and R'' is the Hessian matrix of $R(\bullet)$. Thus, we got the one-step iterative estimator

$$\beta_0{}^{(1)} = \beta_0{}^{(0)} - R''\left(\beta_0{}^{(0)}\right)^{-1} R'\left(\beta_0{}^{(0)}\right) \tag{35}$$

As with the matrix described in equation 30, the matrix R'' can be singular or nearly so. If this is the case, one again must add a ridge regression parameter (Fan et al. 2003).

Simulation Study

We conducted a simulation study to evaluate which of the five approaches for fitting semiparametric time-varying coefficient models would be best for our study. We investigated models with one or some (but not all) coefficients varying with time. A model under the null hypothesis was estimated by time-varying estimation methods, which means that the true effect was in fact time-invariant. We further investigated how well different components in the predictor could be identified and separated from each other.

Description of the Simulation Study The general framework for our simulated time series of mortality counts was based on the following model. Death counts were simulated from a Poisson distribution

$$\begin{aligned} &Y_t \sim \text{Poisson}(\lambda_t) \\ &\log(\lambda_t) = \log(4.62) \\ &*\left(\beta_1\, relhum_t + f(t_t) + f(temp_t) + f_{SO_2}(t)\, SO_{2,t}\right), \end{aligned} \tag{36}$$

where $relhum_t$, $temp_t$, and $SO_{2,t}$ are the time series of relative humidity, temperature, and SO_2, respectively. Data were used from the Erfurt data set for the years 1991 to 2002. The approximate mean death count in Erfurt between September 1991 and March 2002 was 4.62.

Relying on simulated data, we investigated, among others, the following three scenarios:

1. Constant effect $f_{poll}(t) = 0.002$, and no confounders were considered. This scenario reflected a mode under the null hypothesis, which means that the true effect was time-constant.
2. The effect of $f_{poll}(t)$ was curvilinear (see Figure 3A):

   $$f_{poll}(t) = 0.002 * (1 + (2t/T) - (t^2/T^2)),$$

   and no additional confounders were considered.
3. Testing whether the methods were able to distinguish time-varying from time-invariant coefficients when some but not all of the coefficients were time-varying. The effect of $f_{poll}(t)$ was defined as a sine function:

   $$f_{poll}(t) = 0.002 * (1 + 0.2 * \sin(2\pi(t/365))),$$

   (see Figure 3B). Additionally, the effect of the confounder time trend $f(t)$ was considered as the product of a sine function with constant amplitude and a linear pattern (see Figure 3C):

   $$f(t) = 0.02 * ((1 + (t/3835)) * (1 + 0.6 * \sin(\pi(t/365))).$$

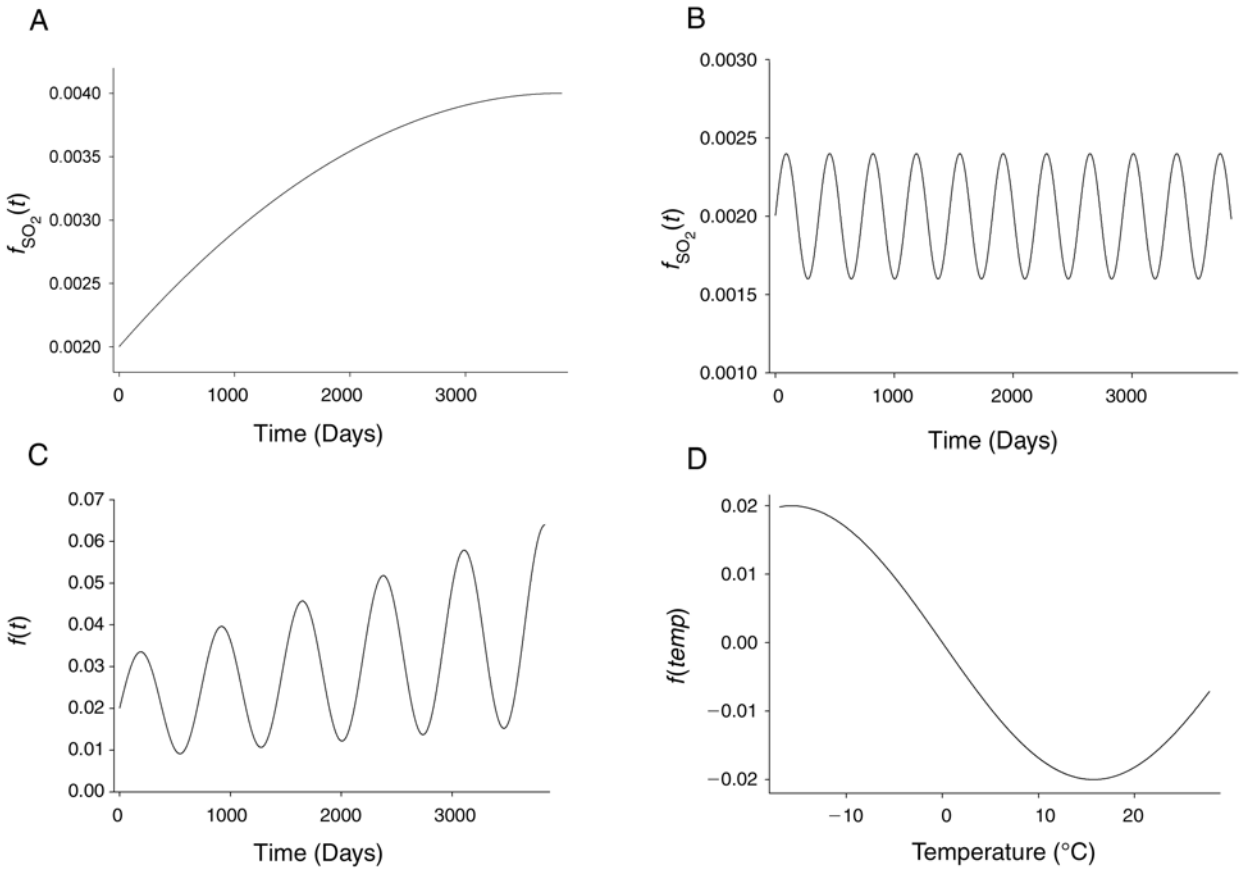

Figure 3. Simulated effects. The simulated effects of $f_{SO_2}(t)$ (curvilinear [**A**], sinusoidal [**B**]) and of time trend $f(t)$ (**C**) and temperature, $f(temp)$, (**D**) are shown.

Further, effects of temperature and relative humidity were included. The effect of temperature was defined as the sine function $f(temp) = -0.02 * \sin(0.1 * temp)$, as shown in Figure 3D. A constant effect of -0.0015 was considered for relative humidity.

For each of the three scenarios, we generated death counts $Y_t^{(n)}, t = 1, \ldots, 3835$ for simulation runs $n = 1, \ldots, N = 250$ using equation 36. We assessed the performance of the five models using the following specifications:

Model A: Time-varying coefficient models with regression splines. For estimation, we first chose the optimal degrees of freedom of the splines by using the Akaike information criterion.

Model B: Bayesian time-varying coefficient models with P-splines. The MCMC specification for each model was 20,000 iterations, of which the first 4000 iterations were discarded as burn-in. Every fifteenth subsequent sample point was saved for estimation of posterior means. We specified the number of knots for the unknown functions to be 20.

Model C: Time-varying coefficient models with penalized linear splines based on a generalized mixed-model framework.

Model D: Time-varying coefficient models with Bayesian P-splines based on empirical Bayes inference. In cases of no convergence in the empirical Bayes approach, we used the final values after the maximum number of iterations (400) to compute empirical root mean squared errors (RMSEs). Fahrmeir and colleagues (2004) stated that "a closer inspection of estimates with and without convergence showed that differences in terms of MSE are negligible and the choice of the final values leads to reasonable estimates." As in the fully Bayesian approach, the number of knots was specified to be 20.

Model E: Adaptive generalized varying-coefficient models. For estimation, an Epanechnikov kernel was used. Further, the number of the bandwidth values was chosen to be $q = 15$, and the range was $h_k = 0.2 \times 1.2^{k-1}$. To speed up computation, the functions $f_j(\bullet)$ were estimated on 200 grid points.

The performance of the estimators was compared based on the empirical RMSE defined as

$$\mathrm{RMSE}\left(\hat{f}_{poll}(t)\right) = \sqrt{T^{-1}\sum_{t=1}^{T}\left(f_{poll}(t) - \hat{f}_{poll}(t)\right)^2}, \qquad (37)$$

where $t = 1, \ldots,$ and T was the number of observations.

Note that our simulation framework did not address the issue of measurement error in the pollutant variable.

Results of the Simulation Study Using simulated data in the three scenarios described earlier, results were obtained that could be used to compare the performance of the five models. The results are presented as boxplots of the RMSEs from each of the models: Model A, the time-varying coefficient model with an interaction term between the pollutant and a regression spline in time; Model B, the Bayesian time-varying coefficient model with P-splines using MCMC estimation methods; Model C, the time-varying coefficient model with penalized linear splines based on a generalized mixed-model framework; Model D, the time-varying coefficient model with Bayesian P-splines based on empirical Bayes inference; and Model E, the adaptive generalized varying-coefficient linear models.

Scenario 1 The consequences of estimating a time-varying coefficient when the true effect is time-constant were examined in Scenario 1. If one wrongly estimates a time-varying coefficient model, there is the danger of

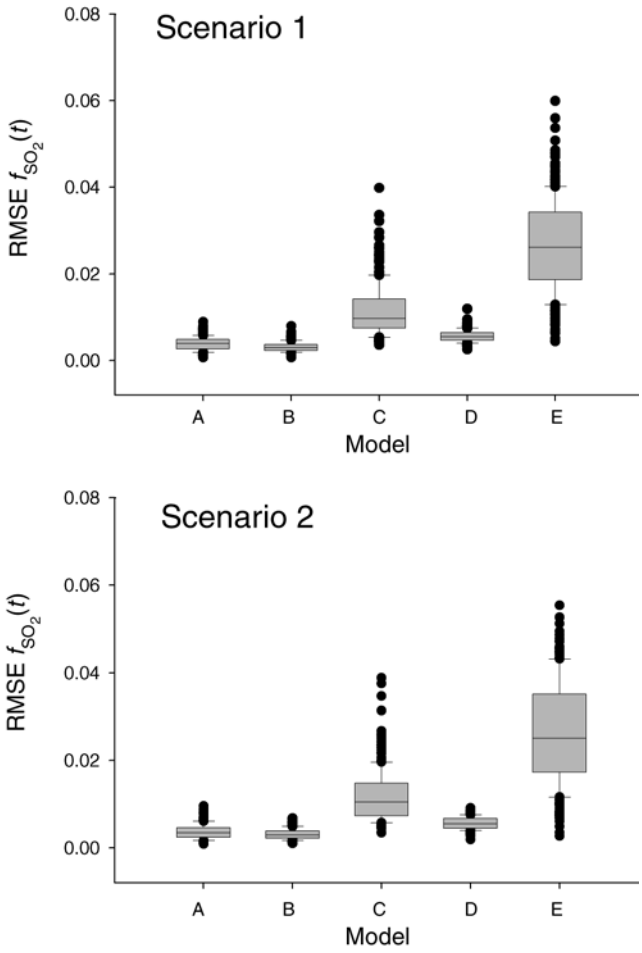

Figure 4. Boxplots of RMSEs of $f_{SO_2}(t)$ for Models A through E for scenario 1 and scenario 2.

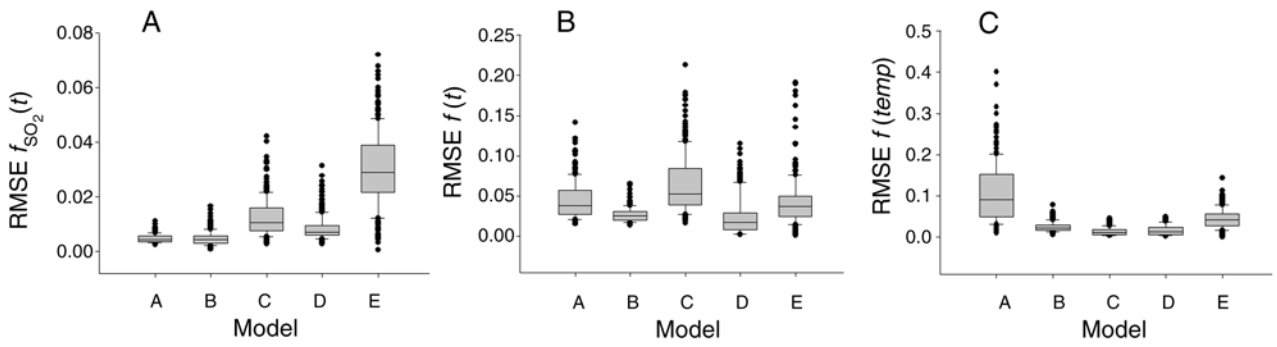

Figure 5. Boxplots of RMSEs for Models A through E for scenario 3. Effects of $f_{SO_2}(t)$ (**A**), $f(t)$ (**B**), and $f(temp)$ (**C**) are shown.

deriving time variation in the coefficients when they are in fact time-constant. The boxplots of the RMSE in this scenario are given in Figure 4. The time-varying estimates for $f_{poll}(t)$ were relatively stable for models A, B, and D. Hence, estimating a time-varying coefficient when the effect was time-invariant, as seen in this scenario, did not seem to produce significant coefficient variation for these three models. The RMSEs of models C and E suggested that the estimates resulting from these models were more variable. Altogether, we obtained the most stable estimates from Model B, which was the fully Bayesian model.

Scenario 2 In Scenario 2, the simulated effect of $f_{poll}(t)$ was assumed to be curvilinear. The boxplots of the RMSEs of the five models (Figure 4) revealed a pattern similar to that in Scenario 1. Again, the most stable time-varying estimates for $f_{poll}(t)$ resulted from models A, B, and D.

Scenario 3 In Scenario 3, the five models were tested to determine if time-varying and time-invariant terms could be distinguished when some but not all of the terms were time-varying. This scenario was of particular interest for the applied work of air-pollution analysis, because it contained confounding effects of time and temperature. Figure 5A shows the boxplots of the RMSEs for the time-varying coefficients $f_{SO_2}(t)$. The estimates from models A, B, and D seemed to exploit the variation quite well. The most stable estimates were obtained from Model B. The boxplots of the RMSEs for $f(t)$ (Figure 5B) and for $f(temp)$ (Figure 5C) showed that Model D best reestimated the simulated effects of both confounders (time and temperature), followed by Model B, which showed the second smallest RMSE values.

Selected Time-Varying Coefficient Models

Altogether, the simulations suggested that Model B, the fully Bayesian varying-coefficient model with P-splines, and Model D, the varying coefficient model with P-splines based on empirical Bayes inference, performed best in all the simulated scenarios. For this study, then, we made use only of Model B, the Bayesian time-varying coefficient model with P-splines. The reasons for this selection are discussed below in *Results*, in the section *Comparison of the Two Models that Performed Best in the Simulations Studies.*

RESULTS

MORTALITY DATA

All-Cause Mortality

The basic statistics on daily death counts in Erfurt are presented in Table 4. On average, 4.6 deaths per day were observed during the study period. About 10% of all cases occurred in the outlying communities incorporated into Erfurt in 1994.

Annual death counts are summarized in Table 5. During the study period, the population of Erfurt declined until 2000, after which it remained stable. The total number of deaths obtained from the Statistical Office of Thuringia for each year usually exceeded the study's numbers by about 20% because of the restriction to subjects who had lived and died inside the old city limits of Erfurt.

With the exception of a slight dip on Sundays, there was no distinct weekly pattern in the mean number of daily deaths (Figure 6A). However, the mean daily death counts were higher during the winter months (Figure 6B).

Cause-Specific Mortality

Figure 7 presents the causes of death as percentages for the entire study period, 1991–2002. In our data set, the percentages for each category, based on the primary cause

Table 4. Daily Death Counts in Erfurt

Year	Number of Days	Old City Limits[a] Mean	Old City Limits[a] SD	New City Limits[b] Mean	New City Limits[b] SD
1991	92	5.7	2.4		
1992	366	5.1	2.4		
1993	365	5.0	2.4		
1994	365	4.5	2.1		
1995	365	4.7	2.2	4.9	2.3
1996	366	4.5	2.2	5.0	2.2
1997	365	4.6	2.2	4.9	2.3
1998	365	4.2	2.1	4.6	2.2
1999	365	4.4	2.1	4.9	2.2
2000	366	4.6	2.2	5.0	2.3
2001	365	4.3	2.2	4.7	2.2
2002	90	4.8	2.2	5.3	2.2
1991–2002	3835	4.6	2.2		

[a] Comprises areas with postal codes 99084, 99085, 99086, 99087, 99089, 99091, 99092, 99094, 99096, 99097, 99098, 99099, i.e., within Erfurt's city limits as of 1991.

[b] Comprises areas with postal codes as in footnote a plus postal code areas 99100, 99102, 99189, 99192, 99195, 99198, which belong to the communities incorporated into Erfurt in 1994.

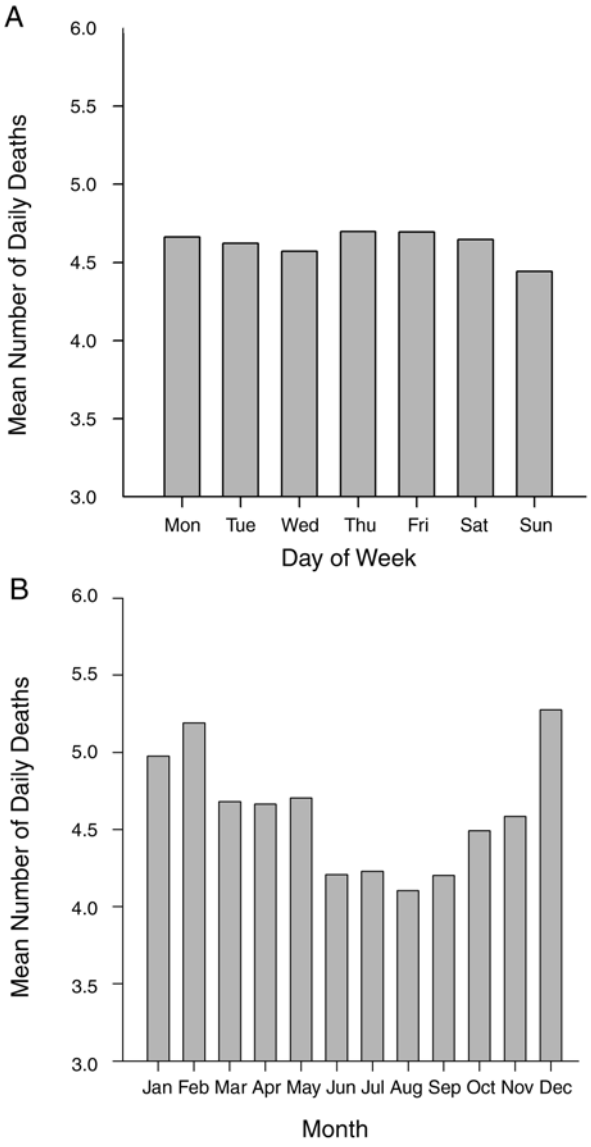

Figure 6. Patterns of mean daily death counts in Erfurt (old city limits) by day of the week (A) and calendar month (B).

of death, were in very good agreement with official data obtained from the Statistical Office of Thuringia. According to the official data, between 1995 and 2002 49.9% of all deaths were caused by cardiovascular diseases, 4.6% by respiratory diseases, 40.6% by other natural causes, and 4.9% by nonnatural causes (Thüringer Landesamt für Statistik [Statistical Office of Thuringia] 2004).

When assigning deaths to categories based on a cardiovascular or respiratory disease in any of the given ICD codes for immediate, primary, or contributing causes of death, the fraction of cardiovascular cases was higher than when looking only at the primary cause of death (Table 6 and Figure 8). There were fewer cases in the category of respiratory cause without a cardiovascular condition. A considerable number of cases were in the category of both cardiovascular and respiratory conditions.

It should be noted that, although diabetes mellitus was listed as the immediate, the primary, or a contributing cause of death in a substantial number of cases, it was treated as a subcategory for the purposes of this study. For instance, if diabetes was listed as a contributing cause of death, and a cardiovascular condition as the immediate or primary cause of death, the death was assigned to the cardiovascular category. The same was true for lung cancer. Because diabetes and lung cancer were treated as subcategories, they are not represented in Figure 8.

From 1991 to 2002, the number of deaths from all causes, cardiovascular and respiratory causes, cardiovascular causes, and cardiovascular-only causes followed a Poisson distribution, with means of 4.6, 3.7, 3.6, and 3.0, respectively. Note that the number of deaths from respiratory causes also followed a Poisson distribution, with a mean

Table 5. Annual Death Counts in Erfurt and Thuringia

	City of Erfurt[a]					State of Thuringia			
	Total Deaths[b]		Natural Deaths[c]				Total Deaths[f]		
Year	*N*	Per 100,000 Inhabitants	*N*	Per 100,000 Inhabitants	Nonnatural Deaths[d] (*N*)	Population[e]	*N*	Per 100,000 Inhabitants	Natural Deaths[f] (*N*)
1991	572[g]		526[g]		46[g]	219,713	2315		
1992	2022	926.8	1853	849.4	169	218,164	2244		
1993	1945	900.6	1826	845.5	119	215,978	2331		
1994	1753	821.2	1657	776.2	96	213,472	2230		
1995	1809	856.9	1703	806.7	106	211,108	2235	1059	2122
1996	1747	839.2	1657	795.9	90	208,179	2103	1010	1992
1997	1785	869.2	1671	813.7	114	205,361	2077	1011	1954
1998	1595	786.0	1530	754.0	65	202,931	1952	962	1868
1999	1703	846.1	1617	803.4	86	201,267	2025	1006	1926
2000	1751	873.0	1685	840.1	66	200,564	2050	1022	1973
2001	1633	816.0	1556	777.5	77	200,126	1943	970	1851
2002	454[h]		432[h]		22[h]	199,967	2037	1019	1926

[a] Data obtained from Gesundheitsamt Erfurt (Erfurt Health Authority) (Wichmann et al. 2000).

[b] Residence and place of death in Erfurt (postal code between 99000 and 99099), age at death ≥ 365 days.

[c] Deaths for which residence and place of death were both in Erfurt (old city limits); age at death was ≥ 365 days; the underlying, contributing, or immediate cause of death was given as ICD-9 code < 800 or ICD-10 code < S00; and no external cause of death was given.

[d] External cause of death or ICD-9 code ≥ 800 or ICD-10 code ≥ S00 as underlying, contributing, or immediate cause of death.

[e] Total population as of December 31 (Thüringer Landesamt für Statistik [Statistical Office of Thuringia] 2004).

[f] Thüringer Landesamt für Statistik (Statistical Office of Thuringia) 2004.

[g] October through December.

[h] January through March.

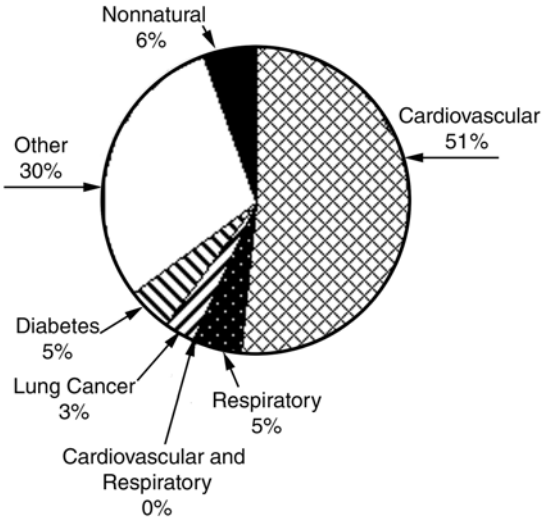

Figure 7. Percentage of deaths from 1991 to 2002 in Erfurt for each major cause of death. Categories are based on ICD-9 codes for primary cause of death.

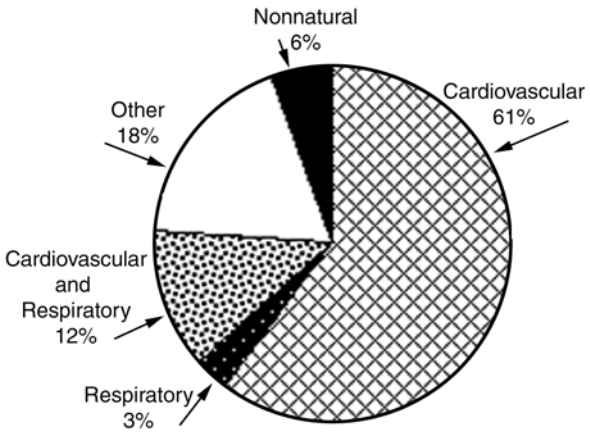

Figure 8. Percentage of deaths from 1991 to 2002 in Erfurt for each major cause of death. Categories are based on ICD-9 codes for immediate, primary, and contributing causes of death.

Table 6. Deaths per Category for All ICD Codes

	Natural Causes						
	Main Categories				Subcategories		
Year	Cardiovascular	Respiratory	Cardiovascular and Respiratory	Other Natural Causes	Lung Cancer[a]	Diabetes[b]	Nonnatural Causes
1991[c]	330	16	87	93	22	82	46
1992	1199	67	268	319	63	345	169
1993	1153	63	303	307	59	339	119
1994	1115	46	190	306	62	282	96
1995	1112	45	213	333	67	288	106
1996	1064	56	182	355	80	288	90
1997	1081	42	210	338	84	329	114
1998	945	56	199	330	75	261	65
1999	1040	61	180	336	93	282	86
2000	1043	57	230	355	84	305	66
2001	981	76	213	286	80	321	77
2002[d]	269	17	63	83	18	77	22
1991–2002	11,332	602	2338	3441	787	3199	1056

[a] Lung cancer as immediate, primary, or contributing cause of death.

[b] Diabetes as immediate, primary, or contributing cause of death.

[c] October through December.

[d] January through March.

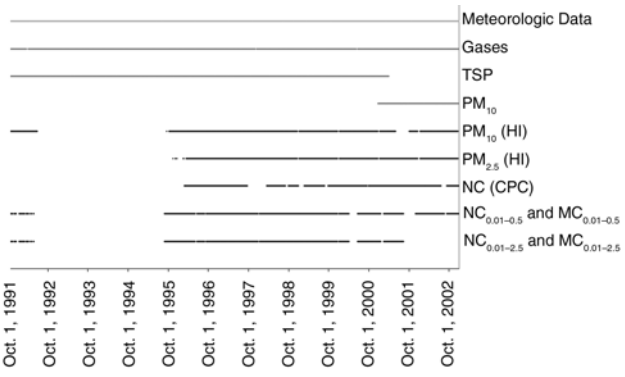

Figure 9. Measurement periods for meteorologic (light gray) and air-pollution data measured at the network monitoring station (gray) and the GSF monitoring station (black).

of 0.8. From 1995 to 2001, the means for the number of deaths from all causes, cardiovascular and respiratory causes, cardiovascular causes, cardiovascular-only causes, and respiratory causes were 4.9, 3.9, 3.7, 3.1, and 0.8, respectively.

EXPOSURE AND EMISSION DATA

An overview of the available air-pollution and meteorologic data is given in Figure 9. A visual inspection of the data on measured gaseous air pollutants over time, especially the SO_2 time-series data (see below), suggests that there were significant incremental changes in air-pollution concentrations during the study period. To investigate whether these changes reflected changes in the contributions of specific sources to the ambient air pollutant mixture, we divided the study period into three subperiods and the pollutants into four groups, as described in *Methods*.

Table 7 shows the numbers of measurement days and the daily mean air pollutant concentrations in Erfurt from October 1991 to March 2002.

The limit of detection (LOD) was 0.5 ppb for NO, NO_2, and O_3; 1 ppb for SO_2; and 50 ppb for CO. Of the gaseous pollutants, only SO_2 had measured values below the LOD (i.e., undetectable concentrations). Because of the dramatic decrease in SO_2 emissions in eastern Europe in the 1990s, 42% of the SO_2 concentrations measured in 2000 were below the LOD. In the following two years, more than

Table 7. Daily Mean Air Pollutant Concentrations and Measurement Days

	Air Pollutant Concentration			Measurements Days		
	Mean	SD	*N* below LOD[a]	Scheduled	Actual	Measurement Period
Gaseous Pollutants						
NO (μg/m^3)	22.7	27.6	0	3835	3727 (97.2%)	10/01/91–3/31/02
NO_2 (μg/m^3)	33.8	18.5	0	3835	3771 (98.3%)	10/01/91–3/31/02
NO_2 (μg/m^3)[b]	35.2	18.5	0	3835	3467 (90.4%)	10/01/91–3/31/02
CO (mg/m^3)	0.6	0.5	0	3835	3761 (98.1%)	10/01/91–3/31/02
SO_2 (μg/m^3)	23.9	47.5	809 (21.1%)	3835	3772 (98.4%)	10/01/91–3/31/02
O_3 (μg/m^3)	39.1	23.4	0	3835	3779 (98.5%)	10/01/91–3/31/02
Ultrafine Particles (Measured as Number Concentrations)						
$NC_{0.01–0.03}$ (MAS) (particles/cm^3)[c]	6902	4628	0	238	159 (66.8%)	10/01/91–5/25/92
	8743	5886	0	2410	2074 (86.1%)	8/26/95–3/31/02
$NC_{0.01–0.1}$(MAS) (particles/cm^3)[c]	13,428	9097	0	238	159 (66.8%)	10/01/91–5/25/92
	13,163	8786	0	2410	2074 (86.1%)	8/26/95–3/31/02
$NC_{0.003–0.064}$ (SMPS) (particles/cm^3)[c]				475	424 (89.3%)	12/12/00–3/31/02
$NC_{0.01–2.5}$ (MAS) (particles/cm^3)[c]	18,686	12,109	0	238	159 (66.8%)	10/01/91–5/25/92
	15,417	9807	0	2410	1964 (81.5%)	8/26/95–3/31/02
$NC_{0.01–2.5}$ (CPC) (particles/cm^3)[c]	16,670	10,298	0	2227	1848 (83.0%)	2/25/96–3/31/02
Particulate Matter Pollutants						
TSP (μg/m^3)	51.5	36.1	0	3472	3421 (98.5%)	10/01/91–4/02/01
PM_{10} (μg/m^3)	26.2	16.1	0	466	455 (97.6%)	12/21/00–3/31/02
PM_{10} (HI) (μg/m^3)[c]	58.3	39.6	0	271	270 (99.6%)	10/01/91–6/27/92
	31.4	22.9	0	2390	2136 (89.4%)	9/15/95–3/31/02
$PM_{2.5}$ (MAS) (μg/m^3)[c]	80.7	78.9	0	238	159 (66.8%)	10/01/91–5/25/92
	22.7	19.7	0	2410	1964 (81.5%)	8/26/95–3/31/02
$PM_{2.5}$ (HI) (μg/m^3)[c]	20.9	17.2	0	2393	2184 (91.3%)	9/12/95–3/31/02
Air Temperature and Relative Humidity						
Temperature (°C)	8.3	7.6	0	3835	3823 (99.7%)	10/01/91–3/31/02
Relative humidity (%)	79.5	11.2	0	3835	3823 (99.7%)	10/01/91–3/31/02

[a] Number of measurement days for which pollutant concentrations were below LOD.

[b] Implausible data from April 1, 1994 to January 31, 1995, omitted.

[c] Measured at GSF monitoring station.

50% of measured SO_2 concentrations were below the LOD. As a result, the total percentage of undetectable SO_2 concentrations for the study period as a whole was more than 20%. All undetectable SO_2 values were automatically set to the respective LOD. This unequal distribution of low values should be kept in mind when interpreting the statistical analyses of the data.

Another problem occurred with regard to questionable NO_2 data from the network monitoring station on Krämpferstraße. NO_2 concentrations between April 1, 1994, and February 1, 1995, were remarkably low and showed much less variability day to day compared with time periods before and after this questionable period (see Figure 10B). Regional authorities were unable to provide additional information on these measurements. We therefore decided to run analyses with and without the questionable period.

As can be seen in Table 7, the available data on particulate air pollutants measured at the GSF station varied from 67% to 99% of scheduled measurement days for most of the pollutants. As described in detail in *Methods*, we developed an imputation strategy to fill in the missing values with values obtained from parallel measurements using other instruments. Table 8 shows a comparison of

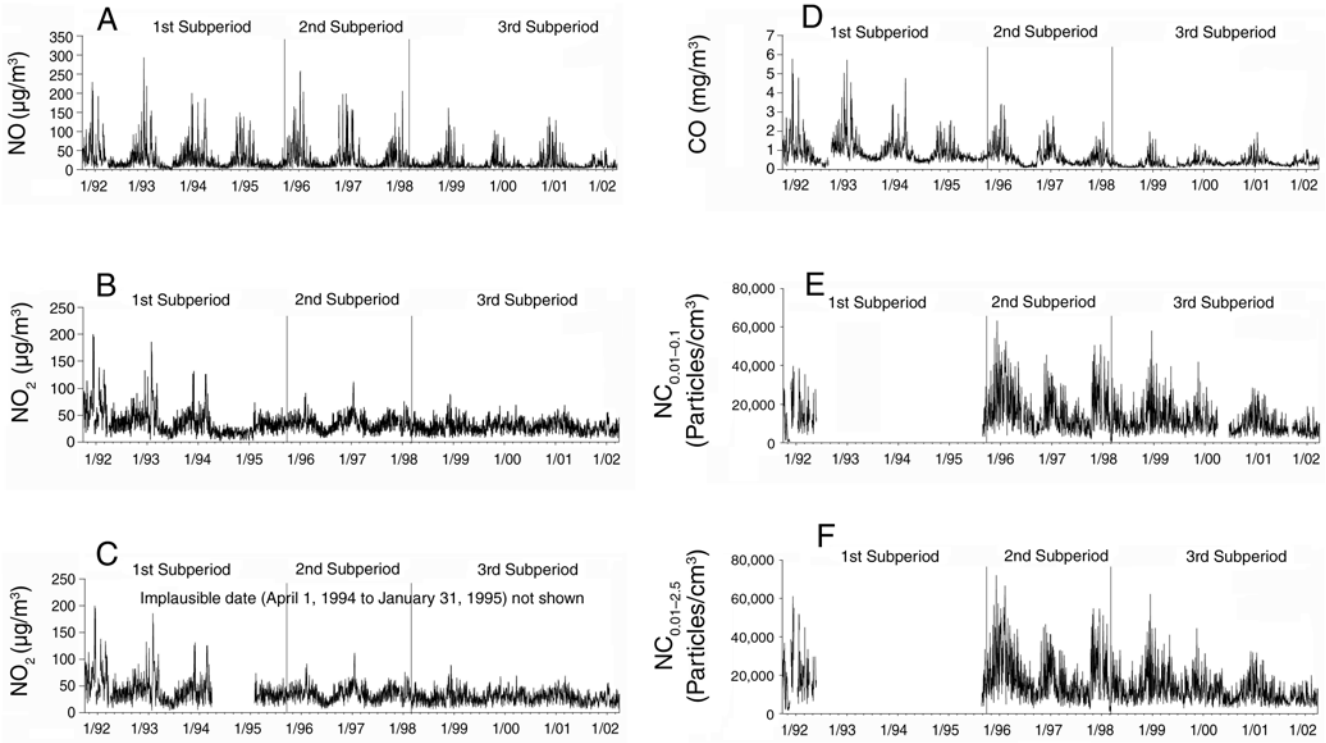

Figure 10. Daily average concentrations of traffic-related air pollutants in Erfurt. Pollutants shown are NO (**A**), NO_2 (**B**), NO_2 with implausible data omitted (**C**), CO (**D**), $NC_{0.01–0.1}$ (**E**), and $NC_{0.01–2.5}$ (**F**).

Table 8. Actual and Imputed Air-Pollution Data for Erfurt

	Air Pollutant Concentration				Measurements Days	
	Mean	SD	Minimum	Maximum	Scheduled	Actual
PM_{10} (HI) (µg/m³)	34.4	26.7	2.2	255.2	2661	2406 (90.4%)
PM_{10} imputed (µg/m³)	38.0	28.3	2.2	292.2	3835	3802 (99.1%)
$PM_{2.5}$ (MAS) (µg/m³)	27.0	32.5	1.6	458.6	2648	2123 (80.2%)
$PM_{2.5}$ imputed (µg/m³)	25.6	30.4	1.6	458.6	2648	2516 (95.0%)
$NC_{0.01–2.5}$ (MAS) (particles/cm³)	15,662	10,032	1202	72,089	2648	2123 (80.2%)
$NC_{0.01–2.5}$ imputed (particles/cm³)	14,801	9625	1202	72,089	2648	2521 (95.2%)
$NC_{0.01–0.1}$ (MAS) (particles/cm³)	13,182	8806	564	63,181	2648	2233 (84.3%)
$NC_{0.01–0.1}$ imputed (particles/cm³)	12,910	8685	564	63,181	2648	2359 (89.1%)

the actual and the imputed data. With the exception of PM_{10}, the imputed time series tended to have somewhat smaller means than the actual time series. Also, the variation in the imputed time series was a bit smaller.

NO, NO_2, CO, and Ultrafine and Fine Particles

Daily mean concentrations of the traffic-related air pollutants (NO, NO_2, CO, $NC_{0.01–0.1}$, and $NC_{0.01–2.5}$) are shown in Figure 10. A clear seasonal pattern could be observed for all these pollutants. Pollutant concentrations were higher in winter than in summer.

Whereas annual concentrations of NO_2 and CO decreased continuously over the entire study period, no clear trend could be observed for NO. NO concentrations decreased continuously in the first subperiod, increased from winter 1994/95 to winter 1995/96, and remained at similar concentrations during the second subperiod. In the third subperiod, they decreased again.

Table 9. NO, NO_2, CO, and NC Data Stratified for the Three Subperiods[a]

		Measurement Days		Pollutant Concentration				Ratio of Subperiods		
Pollutant	Subperiod	Actual (*N*)	Missed (%)	Median	Mean	5th Percentile	95th Percentile	1:3	1:2	2:3
NO ($\mu g/m^3$)	1	1395	2.5	17.0	27.3	3.7	89.0	1.77[b]	1.00	1.77[b]
	2	885	3.0	15.4	27.3	4.7	87.0			
	3	1447	3.0	9.6	15.4	4.0	48.2			
	Total	3727	2.8	13.3	22.7	4.1	75.6			
NO_2 ($\mu g/m^3$)	1	1405	1.8	31.4	37.3	10.4	85.0	1.27[b]	1.05	1.21[b]
	2	901	1.2	34.0	35.5	15.0	59.5			
	3	1465	1.8	28.2	29.4	11.7	49.7			
	Total	3771	1.7	30.6	33.8	11.8	63.5			
NO_2[c] ($\mu g/m^3$)	1	1101	23.1	38.2	42.8	14.7	91.0	1.46[b]	1.20[b]	1.21[b]
	2	901	1.2	34.0	35.5	15.0	59.5			
	3	1465	1.8	28.2	29.4	11.7	49.7			
	Total	3467	9.6	31.9	35.2	13.1	65.2			
CO (mg/m^3)	1	1362	4.8	0.7	0.9	0.4	2.2	2.67[b]	1.47[b]	1.82[b]
	2	912	0.0	0.5	0.6	0.2	1.6			
	3	1487	0.3	0.3	0.4	0.1	0.8			
	Total	3761	1.9	0.5	0.6	0.1	1.6			
$NC_{0.01–0.1}$ ($particles/cm^3$)	1	165	88.5	11,308	13,198	968	30,396	1.23[b]	0.80[b]	1.54[b]
	2	837	8.2	13,217	16,434	4435	37,625			
	3	1357	9.0	9051	10,702	3717	23,823			
	Total	2359	38.5	10,464	12,910	3743	30,654			
$NC_{0.01–2.5}$ ($particles/cm^3$)	1	165	88.5	15,352	18,301	2840	42,933	1.51[b]	0.98	1.54[b]
	2	882	3.3	15,374	18,639	5706	42,166			
	3	1474	1.2	10,424	12,112	4639	25,667			
	Total	2521	34.3	12,128	14,801	4812	34,033			

[a] Subperiod 1: October 1, 1991, to August 31, 1995; subperiod 2: September 1, 1995, to February 28, 1998: and subperiod 3: March 1, 1998, to March 31, 2002. Mean values of pollutant concentrations were used for ratios of subperiods.

[b] Statistically significant (*t* test for independent variables, $P < 0.05$)

[c] Period with implausible data from April 1, 1994, to January 31, 1995, omitted.

There was a large gap in the data for $NC_{0.01–0.1}$ and $NC_{0.01–2.5}$ during the first study subperiod, so the trend in this subperiod could not be described adequately. During the second subperiod, the concentrations for both $NC_{0.01–0.1}$ and $NC_{0.01–2.5}$ remained stable (much as NO concentrations did). The concentrations decreased in the middle of the third subperiod (i.e., after 1999).

The descriptive statistics for these traffic-related air pollutants were stratified for the three study subperiods and are summarized in Table 9.

Mean NO_2 concentration (without the implausible period from April 1, 1994, to February 1, 1995) decreased 31.3%, from 42.8 $\mu g/m^3$ in the first subperiod to 29.4 $\mu g/m^3$ in the third subperiod. The decrease in ambient CO concentrations over the same time period was more pronounced (from 0.9 mg/m^3 to 0.4 mg/m^3, or 55.5%). As shown in Table 9, NO concentrations in the first and second subperiods were comparable. They decreased remarkably only during the third subperiod.

In the first subperiod, ultrafine and fine particle number concentrations ($NC_{0.01–0.1}$ and $NC_{0.01–2.5}$) were measured only during winter 1991/92, with the result that more than 80% of the values for this subperiod were missing. Hence, comparisons between the first and the other subperiods shown in Table 9 should be interpreted with care. However, a comparison between the first and the second subperiods suggests that $NC_{0.01–2.5}$ concentrations remained constant over this period, while $NC_{0.01–0.1}$ concentrations

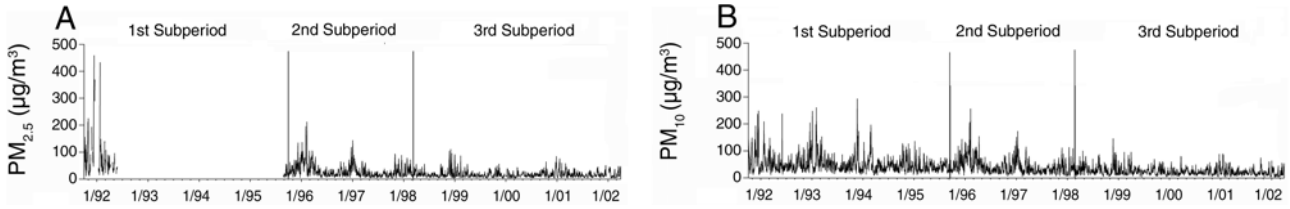

Figure 11. Daily average concentrations of $PM_{2.5}$ (A) and PM_{10} (B) in Erfurt.

increased. During the third subperiod, both concentrations were significantly lower than during the second subperiod, and the decrease was similar for $NC_{0.01–0.1}$ and $NC_{0.01–2.5}$.

$PM_{2.5}$ and PM_{10}

The time series of $PM_{2.5}$ and PM_{10} are shown in Figure 11. Particularly high $PM_{2.5}$ and PM_{10} concentrations were observed during the winter months of the early 1990s. Like the traffic-related air pollutants, $PM_{2.5}$ and PM_{10} showed a clearly seasonal pattern, with higher concentrations in winters than in summers. The low PM_{10} concentrations in winter 1994/95 were remarkable. However, during this winter, air pollutant concentrations in general were lower than in winter 1993/94 and winter 1995/96 (this was also true for NO and CO concentrations; see Figure 10A and D).

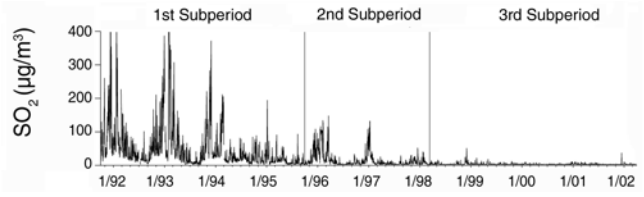

Figure 12. Daily average concentrations of SO_2 in Erfurt.

PM_{10} concentrations were especially high during the first subperiod. The annual mean of PM_{10} was 52.8 µg/m^3 for 1992 and 54.7 µg/m^3 for 1993. This means that the U.S. PM_{10} standard for the annual mean (50 µg/m^3) was exceeded for those 2 years. From 1994 on, the U.S. PM_{10} standard was no longer exceeded. However, the annual means for 1994 and 1996 were close to the U.S. standard (46.3 and 47.5 µg/m^3, respectively), and the U.S. standard for 24-hour PM_{10} (150 µg/m^3) was still exceeded on 3 days in 1994, 6 days in 1996, and 2 days in 1997.

The descriptive statistics for $PM_{2.5}$ and PM_{10} were stratified for the three subperiods and are summarized in Table 10.

SO_2

The SO_2 time series is shown in Figure 12. As with the other air pollutants, a clear seasonal pattern could be observed, with higher SO_2 concentrations in winters than in summers. The overall decrease in SO_2 was the steepest

Table 10. Particulate Matter Data Stratified for the Three Subperiods[a]

		Measurement Days		Pollutant Concentration				Ratio of Subperiods		
Pollutant	Subperiod	Actual (*N*)	Missed (%)	Median	Mean	5th Percentile	95th Percentile	1:3	1:2	2:3
$PM_{2.5}$ (µg/m^3)	1	165	88.5	54.3	78.2	14.5	224.5	4.50[b]	2.68[b]	1.68[b]
	2	899	1.4	21.2	29.2	6.9	77.2			
	3	1452	2.7	13.7	17.4	5.4	40.5			
	Total	2516	34.4	16.9	25.6	6.0	71.0			
PM_{10} (µg/m^3)	1	1400	2.2	42.3	50.6	19.5	111.5	2.08[b]	1.23[b]	1.69[b]
	2	912	0.0	33.2	41.1	12.0	100.3			
	3	1490	0.1	20.2	24.3	8.1	53.4			
	Total	3802	0.9	30.6	38.0	9.9	91.8			

[a] Subperiod 1: October 1, 1991, to August 31, 1995; subperiod 2: September 1, 1995, to February 28, 1998; and subperiod 3: March 1, 1998, to March 31, 2002. Mean values of pollutant concentrations were used for ratios of subperiods.

[b] Statistically significant (*t* test for independent variables, $P < 0.05$).

observed among the gaseous pollutants. SO_2 concentrations decreased rapidly immediately after Germany's reunification (i.e., after 1989; data not shown). Only a few years later, there was another pronounced decrease in SO_2 concentration. The last winter with fairly high SO_2 concentration in Erfurt was in 1993/94, with a mean SO_2 concentration of 69 $\mu g/m^3$. Thereafter, mean SO_2 winter concentrations were significantly lower (25.4, 37.2, 19.1, and 9.8 $\mu g/m^3$ SO_2 for the winters of 1994/95, 1995/96, 1996/97, and 1997/98, respectively). Since the late 1990s, a large percentage of daily SO_2 concentrations were below the LOD (42% in 2000, 52% in 2001, and almost 60% in 2002).

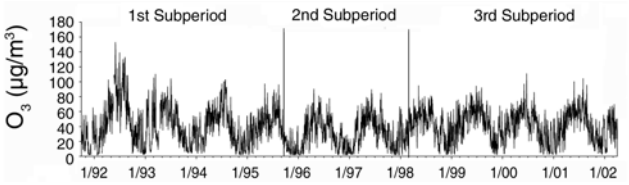

Figure 13. Daily average concentrations of O_3 in Erfurt.

The descriptive statistics for SO_2 were stratified for the three subperiods and are summarized in Table 11.

O_3

The daily average concentrations of O_3 are shown in Figure 13. A continuous decrease in annual O_3 concentrations was observed during the first subperiod. During the second subperiod, O_3 concentrations remained stable. In the third subperiod, a slight increase in O_3 concentrations was observed. O_3 concentrations were higher in summers than in winters.

The descriptive statistics for O_3 were stratified for the three subperiods and are summarized in Table 12.

Table 11. Summary of SO_2 Data Stratified for the Three Subperiods[a]

		Measurement Days		Pollutant Concentration				Ratio of Subperiods		
Pollutant	Subperiod	Actual (*N*)	Missed (%)	Median	Mean	5th Percentile	95th Percentile	1:3	1:2	2:3
SO_2 ($\mu g/m^3$)	1	1395	2.5	26.9	50.2	4.4	188.7	12.62[b]	3.17[b]	3.98[b]
	2	911	0.1	6.3	15.8	3.0	73.7			
	3	1466	1.7	3.0	4.0	3.0	8.1			
	Total	3772	1.6	6.0	23.9	3.0	99.6			

[a] Subperiod 1: October 1, 1991, to August 31, 1995; subperiod 2: September 1, 1995, to February 28, 1998; and subperiod 3: March 1, 1998, to March 31, 2002. Mean values of pollutant concentrations were used for ratios of subperiods.

[b] Statistically significant (*t* test for independent variables, $P < 0.05$).

Table 12. Summary of O_3 Data Stratified for the Three Subperiods[a]

		Measurement Days		Pollutant Concentration				Ratio of Subperiods		
Pollutant	Subperiod	Actual (*N*)	Missed (%)	Median	Mean	5th Percentile	95th Percentile	1:3	1:2	2:3
O_3 ($\mu g/m^3$)	1	1387	3.1	40.3	42.6	5.0	89.7	1.02	1.46[b]	0.70[b]
	2	910	0.2	26.4	29.1	2.3	64.8			
	3	1482	0.7	43.1	41.9	6.3	73.0			
	Total	3779	1.5	38.5	39.1	4.0	77.8			

[a] Subperiod 1: October 1, 1991, to August 31, 1995; subperiod 2: September 1, 1995, to February 28, 1998; and subperiod 3: March 1, 1998, to March 31, 2002. Mean values of pollutant concentrations were used for ratios of subperiods.

[b] Statistically significant (*t* test for independent variables, $P < 0.05$).

Correlations between Air Pollutants

Correlations between the pollutants are shown in Table 13. The highest correlations were observed among the traffic-related air pollutants, i.e., NO, NO_2, CO, and ultrafine- and fine-particle number concentrations ($NC_{0.01–0.1}$ and $NC_{0.01–2.5}$, respectively). $PM_{2.5}$ and PM_{10} were strongly correlated with each other and also with NO_2 and CO. The correlation of $PM_{2.5}$ with $NC_{0.01–0.1}$ and $NC_{0.01–2.5}$ was weaker. SO_2 was strongly correlated with CO, $NC_{0.01–0.1}$ and $NC_{0.01–2.5}$, and $PM_{2.5}$ and PM_{10}. O_3 had negative correlations with all the other air pollutants, the strongest with NO.

Correlations varied in the various study subperiods, as shown in Table 14. Correlation coefficients obtained for the traffic-related air pollutants were high throughout all subperiods. However, during the third subperiod, CO was no longer strongly correlated with NO, NO_2, $NC_{0.01–0.1}$, or $NC_{0.01–2.5}$. In the second subperiod, $NC_{0.01–0.1}$ and $NC_{0.01–2.5}$ were strongly correlated with CO and SO_2; during the third subperiod, they were strongly correlated with NO_2 but not with CO or SO_2. The correlations of $NC_{0.01–0.1}$ and $NC_{0.01–2.5}$ with $PM_{2.5}$ were also slightly higher during the second subperiod than during the third. The correlations of CO with the other air pollutants were stronger in the second subperiod compared with the first and third. In general, the correlations between the various air pollutants were strongest in the second subperiod of the study. The relatively strong correlation of SO_2 with other pollutants in the first and second subperiods is noteworthy. The correlation in the third subperiod was weak because of the clearly lower SO_2 concentrations (near the LOD) in this subperiod and consequently lower SO_2 day-to-day variations. An inspection of the correlations and ratios between pollutants on an annual basis provided further insights into changes in the air-pollution mixtures over the study period as a whole (see Appendix B). In brief, correlations differed between winter and summer, and in general they were higher during the winter months.

Changes in the Sources of Pollutants from 1991 to 2002

After reunification, two major sources of air pollutants—power plants and domestic heating systems as well as mobile sources—underwent significant changes in eastern Germany.

Power Plants and Domestic Heating Systems Power plants and domestic heating systems were prominent stationary sources of air pollution in Erfurt before reunification. As was common throughout East Germany before reunification, brown coal (lignite) was the principal fuel in Erfurt, meeting almost 80% of the region's energy requirements (**Figure 14A**). Brown coal has a high sulfur content, and its combustion results in high emissions of SO_2 and particulate matter. At the time of reunification, coal-fired power plants in the former East Germany operated with only minimal emission controls.

In May 1996, the one coal-fired power plant in Erfurt that remained in operation after reunification was retrofitted to use natural gas as a fuel. This resulted in a dramatic decrease in the use of coal in Erfurt between 1996

Table 13. Spearman Rank Correlation for Daily Mean Concentrations of Air Pollutants and Meteorologic Conditions for the Entire Study in Erfurt[a]

	NO_2	NO_2[b]	CO	$NC_{0.01–0.1}$	$NC_{0.01–2.5}$	$PM_{2.5}$	PM_{10}	SO_2	O_3	Temperature	Relative Humidity
NO	0.76	0.84	0.72	0.61	0.65	0.55	0.53	0.49	−0.72	−0.36	0.28
NO_2	1	1.00	0.57	0.62	0.66	0.63	0.55	0.42	−0.50	−0.26	0.13
NO_2[b]		1	0.68	0.62	0.66	0.63	0.64	0.54	−0.55	−0.28	0.14
CO			1	0.51	0.55	0.62	0.65	0.75	−0.58	−0.49	0.25
$NC_{0.01–0.1}$				1	0.98	0.48	0.57	0.55	−0.45	−0.32	0.07
$NC_{0.01–2.5}$					1	0.57	0.64	0.62	−0.46	−0.33	0.06
$PM_{2.5}$						1	0.85	0.69	−0.46	−0.31	0.18
PM_{10}							1	0.73	−0.31	−0.12	0.00
SO_2								1	−0.26	−0.31	0.02
O_3									1	0.59	−0.63
Temperature										1	−0.53

[a] The study started on October 1, 1991, and ended on March 31, 2002. Correlation coefficients between 0.61 and 0.80 are single-underlined and those between 0.81 and 1.00 are double-underlined.

[b] Implausible data from April 1, 1994, to January 31, 1995, were omitted.

Table 14. Spearman Rank Correlation for Daily Mean Concentrations of Air Pollutants and Meteorologic Conditions Stratified by Subperiod in Erfurt[a]

	NO_2	NO_2[b]	CO	$NC_{0.01–0.1}$	$NC_{0.01–2.5}$	$PM_{2.5}$	PM_{10}	SO_2	O_3	Temperature	Relative Humidity
Subperiod 1											
NO	0.69	0.86	0.82	(0.41)	(0.56)	(0.77)	0.48	0.55	−0.75	−0.49	0.39
NO_2[b]	1	1.00	0.64	(0.48)	(0.64)	(0.83)	0.53	0.57	−0.41	−0.29	0.15
NO_2		1	0.73	(0.48)	(0.64)	(0.83)	0.63	0.62	−0.60	−0.35	0.25
CO			1	(0.50)	(0.65)	(0.85)	0.59	0.69	−0.77	−0.65	0.46
$NC_{0.01–0.1}$				1	(0.95)	(0.52)	(0.63)	(0.53)	(−0.27)	(−0.18)	(0.09)
$NC_{0.01–2.5}$					1	(0.72)	(0.78)	(0.68)	(−0.40)	(−0.27)	(0.08)
$PM_{2.5}$						1	(0.90)	(0.84)	(−0.66)	(−0.44)	(0.21)
PM_{10}							1	0.67	−0.34	−0.15	0.02
SO_2								1	−0.44	−0.54	0.21
O_3									1	0.66	−0.66
Temperature										1	−0.54
Subperiod 2											
NO	0.82		0.77	0.61	0.64	0.50	0.55	0.56	−0.78	−0.37	0.33
NO_2	1		0.75	0.54	0.59	0.55	0.64	0.60	−0.61	−0.35	0.20
CO			1	0.63	0.65	0.63	0.64	0.72	−0.74	−0.63	0.46
$NC_{0.01–0.1}$				1	0.99	0.52	0.54	0.66	−0.46	−0.48	0.19
$NC_{0.01–2.5}$					1	0.59	0.61	0.71	−0.48	−0.49	0.20
$PM_{2.5}$						1	0.87	0.77	−0.49	−0.45	0.38
PM_{10}							1	0.77	−0.47	−0.36	0.27
SO_2								1	−0.54	−0.66	0.38
O_3									1	0.54	−0.65
Temperature										1	−0.54
Subperiod 3											
NO	0.82		0.60	0.62	0.63	0.45	0.45	0.37	−0.71	−0.23	0.23
NO_2	1		0.61	0.70	0.71	0.58	0.58	0.47	−0.52	−0.17	0.09
CO			1	0.34	0.38	0.46	0.28	0.34	−0.65	−0.52	0.31
$NC_{0.01–0.1}$				1	0.98	0.42	0.53	0.50	−0.38	−0.19	−0.01
$NC_{0.01–2.5}$					1	0.48	0.57	0.53	−0.37	−0.20	−0.02
$PM_{2.5}$						1	0.81	0.51	−0.34	−0.12	0.11
PM_{10}							1	0.52	−0.22	0.08	−0.05
SO_2								1	−0.25	−0.22	−0.03
O_3									1	0.55	−0.60
Temperature										1	−0.52

[a] Subperiod 1: October 1, 1991, to August 31, 1995; subperiod 2: September 1, 1995 to February 28, 1998; and subperiod 3: March 1, 1998 to March 31, 2002. Correlation coefficients between 0.61 and 0.80 are single-underlined and those between 0.81 and 1.00 are double-underlined.

[b] Implausible data from April 1, 1994, to January 31, 1995, were omitted.

[c] Note that for $PM_{2.5}$, $NC_{0.01–0.1}$ and $NC_{0.01–2.5}$ only a limited number of measurements in the first subperiod are available ($N = 165$ compared with $N > 1360$ for the other pollutants); therefore the correlation coefficients for these are in parentheses.

and 1997 (Figure 14A). After 1996, only small amounts of surface coal (which has 1.7% sulfur) were used as fuel (mainly as short-term supplements when energy demand increased because of very cold temperatures). Since January 1999, natural gas completely replaced coal. In addition, the power plant was equipped with desulfurization systems.

As a result of these changes, the proportion of coal used for heating in Erfurt decreased to 2% in 2001, when natural gas was used to meet almost 79% of the city's energy requirements (Figure 14A). Other fuels were used to a lesser extent. The proportion of electricity used was 7%, and the proportion of oil used to meet energy requirements

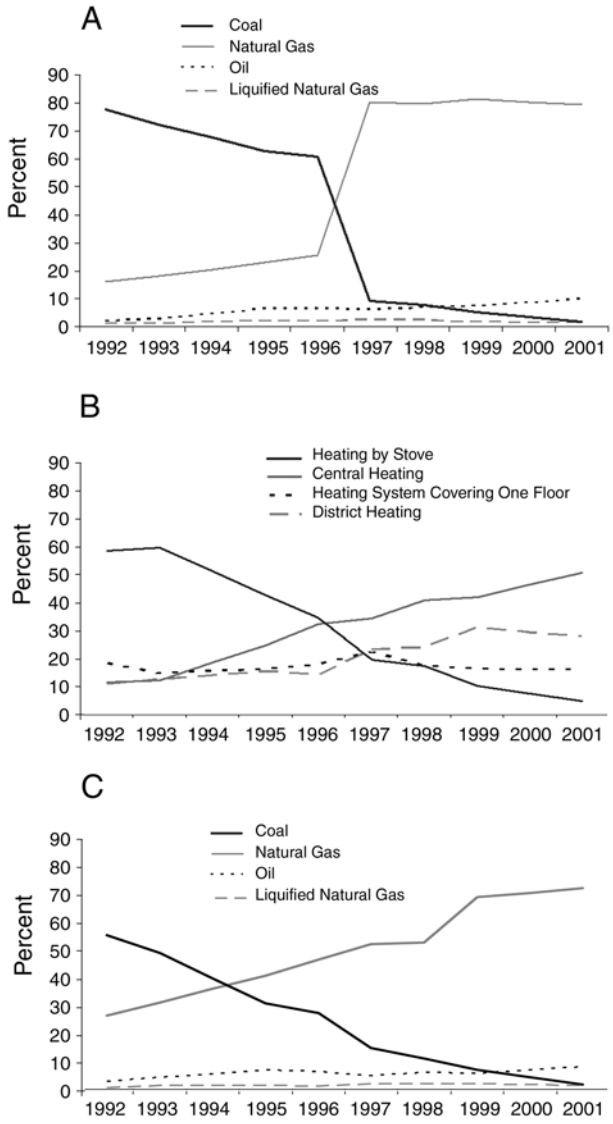

Figure 14. Changes in heating-fuel consumption and in heating systems in Erfurt. Changes in fuels used for heating (**A**); heating systems in the city's older urban areas (**B**); and fuels used for heating in the city's older urban areas (homes supplied by district heating are not included) (**C**) are shown. Data courtesy of the city of Erfurt, Department of Urban Development.

decreased from 10% to 8% in 2001. The changes illustrated in Figure 14A were mostly driven by the changes in fuel used in the power plant. The plant was located several kilometers northeast of the city center and was equipped with a tall stack. Because the most prominent wind in Erfurt was from the west, air pollution produced by the plant would be expected to influence air quality in the city only during days with calm weather or with stationary temperature inversions.

It is possible that the changes in energy use for Erfurt's domestic heating played a more important role in influencing the city's air quality than the changes in the type of fuel used by the power plant. The changes in energy use for domestic heating reflect changes in the two main types of fuel used in the city (brown coal and natural gas), changes in the four main types of heating systems (individual stoves heating a kitchen and nearby rooms, boilers heating a floor of a building, central heating serving an entire building, and district heating serving a group of nearby buildings), and the three main types of residential areas in Erfurt (an older urban area, concrete high-rise areas, and a rural area).

The older urban area comprises the heavily populated city center as well as the immediately surrounding districts. Because of the type of buildings in this area, many homes used individual coal stoves for domestic heating before reunification. This practice has been nearly eliminated since reunification, as the stoves were replaced mostly by natural-gas heating systems (Figure 14B). Between 1992 and 2001, the proportion of homes in the city heated by individual stoves decreased from 59% to 5%, while the proportion of homes heated by central heating increased from 12% to 51%. The proportion of homes heated by district heating also increased, from 11% to 28%.

These changes affected fuel use as well (Figure 14C). The proportion of homes heated by coal in the older urban area decreased from 55% in 1992 to 2% in 2001, while the proportion of homes heated by natural gas increased from 26% to 72%. However, these changes occurred steadily, compared with the dramatic drop in the use of coal shown in Figure 14A. The steadier changes might have been more representative of the overall changes in air quality in Erfurt.

In the areas of concrete high-rise buildings, domestic heating systems didn't change much. These buildings, situated mostly on the outskirts north and south of the city center, were supplied by district heating systems. The proportion of district heating in these areas was greater than 95% during the study period.

In the suburban-rural area, comprising small communities with large green areas between them, changes in domestic heating systems were similar to those of the older urban area. These communities are the former villages that were incorporated into the city in the course of several administrative reorganizations. The area is located partly on hills around the city and is less influenced by air pollution emitted in the city. As in the urban areas, most of the coal-burning stovesin the former villages were replaced by natural-gas heating systems, and energy-use patterns underwent similar changes (data not shown).

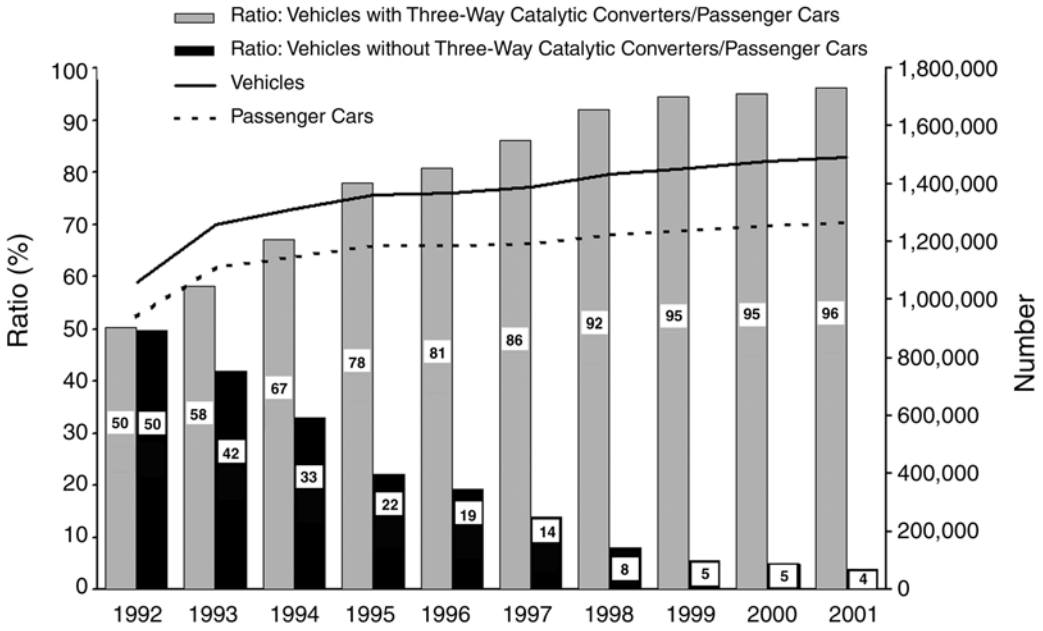

Figure 15. Changes in vehicle and passenger car fleets in Thuringia, Germany. Data courtesy of the Thüringer Landesanstalt für Umwelt und Geologie (Thuringian Regional Office for Environment and Geology).

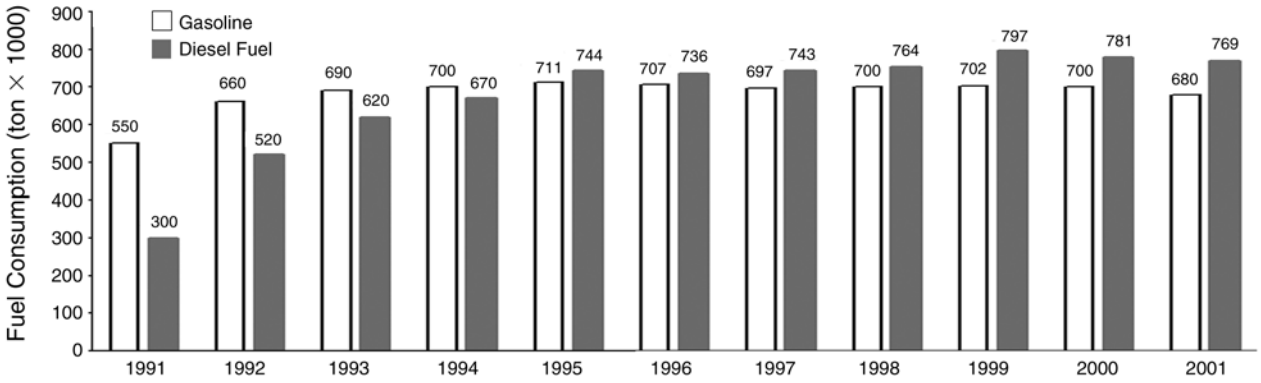

Figure 16. Changes in vehicle-fuel consumption in Thuringia. Data courtesy of the Mineralölwirtschaftsverband (Association of the German Petroleum Industry).

Mobile Sources Mobile sources, another major source of air pollution in eastern Germany, also underwent changes after reunification. Prior to reunification, Trabants were the predominant brand of passenger car in the German Democratic Republic (the former East Germany). The Trabant is a small car with a 26-horsepower, two-stroke engine and visibly high exhaust emissions. After reunification, cars with comparatively modern engine technology, including three-way catalytic converters, gradually replaced the Trabants. Diesel-powered vehicles also became more common because of the lower costs and improved fuel efficiency associated with diesel fuel.

We collected supplementary data on vehicles in Thuringia to explain the reductions in NO and CO concentrations (for Erfurt, data are available only from 1997 onward). As shown in Figure 15, the number of cars in Thuringia as a whole increased by 40%; in Erfurt the number increased only slightly (15%) between 1990 and 1998 (Ebelt et al. 2001). Even with the slight increase in numbers, the character of the car fleet became more modern and included more vehicles with diesel engines. In eastern Germany, the proportion of cars equipped with three-way catalytic converters increased from 50% to 96% during the study period.

Figure 16 shows the changes in annual diesel-fuel and gasoline consumption in Thuringia between 1991 and 2001. Annual consumption of diesel fuel and gasoline increased by 156% (to 469,000 tons) and 24% (to 130,000 tons),

respectively. The increase in diesel-fuel consumption was mostly driven by two factors: the growth of the truck fleet and the increase in the ratio of diesel-powered cars among the passenger cars in the fleet. In the former East Germany, nearly all goods were transported by rail to junctions and distributed by a small number of trucks. After reunification, a conversion from mainly rail to mainly truck transportation took place.

REGRESSION RESULTS FOR POLLUTANTS AND ALL-CAUSE AND CAUSE-SPECIFIC MORTALITY

For each of the four groups of pollutants, regression results for associations between the pollutant and all-cause and cause-specific mortality were obtained.

The percent changes in daily mortality per IQR (i.e., an increase in pollutant concentration equivalent to the magnitude of the IQR for the observed distribution of values for the pollutant measurements) for cardiorespiratory or cardiovascular mortality and CO and NO_2, both at lag day 3, were of the same magnitude, as were the percent changes in daily mortality per IQR for all-cause mortality and CO and NO_2.

Regression Results for NO_2, CO, and Ultrafine Particles

All-Cause Mortality Table 15 and Table 16 present regression results for NO_2, CO, and ultrafine particles (in several size classes) and all-cause mortality. For NO_2 and CO, the strongest associations were observed at lag days 3 and 4 (Table 15). The association was statistically significant for CO at lag day 4. The associations for NO_2 were somewhat stronger when the implausible values for the period between April 1, 1994, and February 1, 1995, were excluded.

For ultrafine particles, consistent associations with mortality were observed at lag day 4 for all size classes ($NC_{0.01–0.03}$, $NC_{0.03–0.05}$, $NC_{0.05–0.1}$, and $NC_{0.01–0.1}$; Table 16). The associations were statistically significant, except for $NC_{0.05–0.1}$. A small increase at lag day 0 was observed for all size classes but was not statistically significant.

The effect of ultrafine particle concentrations on daily mortality counts was greater for the time period 1995–2002 (including imputed values for the last 7 months) than for the time period 1995–2001 (Table 16).

The magnitude of the effect estimates for the gaseous pollutants during the period 1995–2001 was very similar to that for 1991–2002 except that the lag-day effect for CO changed slightly: during the period 1995–2001, lag day 2 had an effect estimate similar to that for lag day 4. In addition, the 95% CIs were broader than in the longer study period. No significant effect estimates were observed for the gaseous pollutants in 1995–2001.

Table 15. Percent Changes in Daily Deaths Associated with NO_2 and CO in Erfurt[a]

Pollutant / Lag (Days)	IQR	Change in Daily Deaths (%)[b]	CI	*P*
NO_2 (µg/m^3)				
0	20.5	−0.8	−3.0 to 1.4	0.46
1	20.5	0.8	−1.2 to 2.9	0.42
2	20.5	0.8	−1.1 to 2.8	0.41
3	20.5	1.4	−0.5 to 3.4	0.15
4	20.5	1.3	−0.6 to 3.3	0.18
5	20.5	0.3	−1.6 to 2.2	0.78
NO_2 (µg/m^3)[c]				
0	19.7	−0.6	−2.7 to 1.6	0.58
1	19.7	1.0	−1.0 to 3.0	0.34
2	19.7	0.8	−1.1 to 2.8	0.40
3	19.7	1.5	−0.4 to 3.5	0.12
4	19.7	1.4	−0.5 to 3.3	0.14
5	19.7	0.2	−1.7 to 2.1	0.85
CO (mg/m^3)				
0	0.48	−0.5	−2.4 to 1.4	0.57
1	0.48	0.5	−1.4 to 2.3	0.62
2	0.48	0.5	−1.3 to 2.3	0.57
3	0.48	1.4	−0.4 to 3.2	0.12
4	0.48	1.9	0.2 to 3.7	0.03
5	0.48	1.2	−0.6 to 2.9	0.19

[a] Data were gathered from 1991 to 2002 and included daily deaths in the old city limits of Erfurt.

[b] Percent change in daily deaths calculated per IQR.

[c] Plausible data only. Implausible data from April 1, 1994, to January 31, 1995, omitted.

Cause-Specific Mortality Table 17 presents regression results for associations between NO_2, CO, and ultrafine particles and cause-specific mortality. Results are also shown for lags where associations with all-cause mortality were detected.

At lag day 4, both CO and NO_2 exhibited somewhat greater percent changes in daily mortality per IQR for cardiorespiratory or cardiovascular mortality than for all-cause mortality.

The percent changes in daily mortality per IQR for ultrafine particles were highest for cardiovascular-only mortality, then cardiovascular, cardiorespiratory, and finally all-cause mortality. For respiratory mortality, the

Table 16. Percent Changes in Daily Deaths Associated with NO_2, CO, and Ultrafine Particles in Erfurt[a]

Pollutant / Lag (Days)	IQR	Change in Daily Deaths[b] (%)	CI	*P*
NO_2 (µg/m^3)				
0	17.2	−0.8	−3.8 to 2.4	0.62
1	17.2	0.7	−2.1 to 3.6	0.63
2	17.2	0.2	−2.5 to 3.0	0.88
3	17.2	1.2	−1.5 to 4.0	0.39
4	17.2	0.7	−2.0 to 3.5	0.62
5	17.2	−0.6	−3.3 to 2.1	0.66
CO (mg/m^3)				
0	0.35	0.0	−2.3 to 2.3	0.99
1	0.35	0.2	−2.0 to 2.4	0.87
2	0.35	1.3	−0.9 to 3.5	0.26
3	0.35	0.7	−1.4 to 2.9	0.52
4	0.35	1.2	−1.0 to 3.4	0.29
5	0.35	−0.5	−2.6 to 1.7	0.67
$NC_{0.01–0.03}$ (Particles/cm^3)				
0	6861	2.3	−0.5 to 5.3	0.11
1	6861	−0.1	−2.9 to 2.7	0.94
2	6861	−1.1	−3.8 to 1.6	0.42
3	6861	1.2	−1.5 to 3.9	0.38
4	6861	2.8	0.2 to 5.6	0.04
5	6861	0.5	−2.1 to 3.2	0.69
$NC_{0.03–0.05}$ (Particles/cm^3)				
0	2088	1.5	−1.0 to 4.0	0.25
1	2088	0.8	−1.6 to 3.2	0.52
2	2088	0.5	−1.8 to 2.9	0.66
3	2088	1.2	−1.0 to 3.5	0.29
4	2088	2.7	0.4 to 4.9	0.02
5	2088	0.6	−1.7 to 2.9	0.62

Table continues next column

Table 16 (*Continued*). Percent Changes in Daily Deaths Associated with NO_2, CO, and Ultrafine Particles in Erfurt[a]

Pollutant / Lag (Days)	IQR	Change in Daily Deaths[b] (%)	CI	*P*
$NC_{0.05–0.1}$ (Particles/cm^3)				
0	1265	1.4	−1.0 to 3.8	0.26
1	1265	0.9	−1.4 to 3.2	0.43
2	1265	1.1	−1.1 to 3.3	0.32
3	1265	0.8	−1.4 to 2.9	0.49
4	1265	1.9	−0.2 to 4.1	0.07
5	1265	0.2	−1.9 to 2.3	0.88
$NC_{0.01–0.1}$ (Particles/cm^3)[c]				
0	9743	2.1	−0.7 to 4.9	0.15
1	9743	0.1	−2.5 to 2.9	0.92
2	9743	−0.3	−2.9 to 2.4	0.83
3	9743	1.2	−1.4 to 3.8	0.36
4	9743	2.9	0.3 to 5.4	0.03
5	9743	0.6	−1.9 to 3.2	0.65
$NC_{0.01–0.1}$ (Particles/cm^3)[d]				
0	9419	2.0	−0.7 to 4.7	0.14
1	9419	0.4	−2.2 to 3.0	0.78
2	9419	−0.2	−2.6 to 2.3	0.89
3	9419	1.3	−1.1 to 3.8	0.29
4	9419	3.2	0.7 to 5.7	0.01
5	9419	1.1	−1.4 to 3.5	0.39

[a] Data were gathered from 1995 to 2001, except where noted, and included daily deaths in the new city limits of Erfurt as well as concentrations of ultrafine particles in several size classes (measured as number concentrations [NC]).

[b] Percent change in daily deaths calculated per IQR.

[c] Imputed time series.

[d] Imputed time series gathered from 1995 to 2002.

Table 17. Percent Changes in Daily Cause-Specific Deaths Associated with NO_2, CO, and Ultrafine Particles in Erfurt[a]

Pollutant / Lag (Days)	Cause of Death[b]	IQR	Change in Daily Deaths[c] (%)	CI	*P*
NO_2 (µg/m^3)[d]					
3	Cardiorespiratory	19.7	1.2	−0.9 to 3.4	0.25
3	Cardiovascular	19.7	1.5	−0.7 to 3.7	0.19
3	Cardiovascular only	19.7	1.6	−0.7 to 4.0	0.18
4	Cardiorespiratory	19.7	1.9	−0.2 to 4.1	0.07
4	Cardiovascular	19.7	2.2	0.1 to 4.4	0.05
4	Cardiovascular only	19.7	2.3	0.0 to 4.7	0.05
CO (mg/m^3)					
3	Cardiorespiratory	0.48	1.2	−0.8 to 3.1	0.24
3	Cardiovascular	0.48	1.3	−0.7 to 3.3	0.20
3	Cardiovascular only	0.48	0.9	−1.3 to 3.1	0.43
4	Cardiorespiratory	0.48	2.2	0.3 to 4.1	0.02
4	Cardiovascular	0.48	2.4	0.4 to 4.3	0.02
4	Cardiovascular only	0.48	2.3	0.2 to 4.4	0.03
$NC_{0.01–0.1}$ (Particles/cm^3)[e]					
4	Cardiorespiratory	9743	3.0	0.2 to 5.9	0.04
4	Cardiovascular	9743	3.1	0.2 to 6.0	0.03
4	Cardiovascular only	9743	3.9	0.7 to 7.0	0.02

[a] Data were gathered from 1991 to 2002 and included daily deaths in the old city limits of Erfurt, except where noted. Ultrafine particles were measured as number concentrations (NC).

[b] **Cardiorespiratory death** is any mention of a cardiorespiratory cause of death on the death certificate (ICD-9 codes 390–459, 460–519, 785 and 786; and ICD-10 codes I00–I99, J00–J99, R00–R06 and R09). **Cardiovascular death** is any mention of a cardiovascular cause of death on the death certificate (ICD-9 codes 390–459, 785; ICD-10 codes I00–I99, R00–R03, R09). **Cardiovascular only death** is any mention of a cardiovascular cause of death on the death certificate (ICD-9 codes 390–459, 785; ICD-10 codes I00–I99, R00–R03), and no mention of respiratory death causes (ICD-9 codes 460–519, 786; ICD-10 codes J00–J99, R04–R06, R09).

[c] Percent change in daily deaths calculated per IQR.

[d] Plausible data only. Implausible data from April 1, 1994, to January 31, 1995, omitted.

[e] Imputed time series for data gathered from 1995 to 2001 for deaths in the new city limits of Erfurt.

lag-day effect was different from that for all-cause and cardiovascular mortality, as there were immediate associations at lag days 0 and 1 for ultrafine particles (data not shown). However, the percent changes in daily mortality per IQR were not statistically significant.

Regression Results for PM_{10} and Fine Particles

All-Cause Mortality Table 18 presents regression results for particulate matter measured as mass concentrations in several size classes ($MC_{0.1–0.5}$, $MC_{0.5–1.0}$, $MC_{1.0–2.5}$, and $MC_{0.01–2.5}$ [which is nearly equivalent to $PM_{2.5}$]) and all-cause mortality during two periods of analysis. No significant associations were found.

Cause-Specific Mortality No significant associations between particle mass concentrations and cardiorespiratory, cardiovascular, or cardiovascular-only mortality were found during the period 1995–2001 (data not shown). A slight, though nonsignificant, increase in respiratory mortality was observed at lag days 0 to 2 for particles with an aerodynamic diameter of less than 2.5 µm. No significant associations between PM_{10} and cause-specific mortality were observed (data not shown).

Regression Results for SO_2

Regression results for all-cause mortality (Table 19) and cause-specific mortality (data not shown) were not associated with increases in SO_2 concentrations during the study period.

Table 18. Percent Changes in Daily Deaths Associated with Particulate Matter in Erfurt[a]

Pollutant / Lag (Days)	IQR ($\mu g/m^3$)	Change in Daily Deaths[b](%)	CI	*P*
$MC_{0.1–0.5}$				
0	13.1	1.0	−1.5 to 3.4	0.44
1	13.1	0.6	−1.7 to 2.9	0.61
2	13.1	0.7	−1.5 to 2.9	0.54
3	13.1	−0.6	−2.7 to 1.6	0.60
4	13.1	0.2	−1.9 to 2.3	0.88
5	13.1	−0.3	−2.4 to 1.8	0.79
$MC_{0.5–1.0}$				
0	2.8	0.2	−1.2 to 1.6	0.78
1	2.8	−0.2	−1.5 to 1.1	0.76
2	2.8	−0.6	−1.9 to 0.7	0.37
3	2.8	−0.9	−2.2 to 0.5	0.20
4	2.8	−0.8	−2.1 to 0.5	0.24
5	2.8	−0.3	−1.6 to 1.0	0.64
$MC_{1.0–2.5}$				
0	1.0	1.4	−0.2 to 3.0	0.08
1	1.0	0.3	−1.3 to 2.0	0.69
2	1.0	−0.5	−2.1 to 1.2	0.60
3	1.0	−2.0	−3.7 to −0.3	0.02
4	1.0	−1.4	−3.1 to 0.3	0.10
5	1.0	0.1	−1.5 to 1.7	0.93
$PM_{2.5}$[c]				
0	16.7	0.7	−1.5 to 3.0	0.52
1	16.7	0.5	−1.6 to 2.6	0.66
2	16.7	0.3	−1.7 to 2.3	0.79
3	16.7	−1.1	−3.0 to 0.9	0.28
4	16.7	0.2	−1.8 to 2.2	0.85
5	16.7	−0.2	−2.1 to 1.8	0.88

Table continues next column

Table 18 (*Continued*). Percent Changes in Daily Deaths Associated with Particulate Matter in Erfurt[a]

Pollutant / Lag (Days)	IQR ($\mu g/m^3$)	Change in Daily Deaths[b](%)	CI	*P*
$PM_{2.5}$[c,d]				
0	16.3	0.8	−1.3 to 2.9	0.47
1	16.3	0.5	−1.5 to 2.5	0.65
2	16.3	0.4	−1.6 to 2.3	0.72
3	16.3	−0.8	−2.7 to 1.1	0.39
4	16.3	0.4	−1.5 to 2.2	0.72
5	16.3	0.1	−1.8 to 2.0	0.95
PM_{10}[e]				
0	27.8	−0.8	−2.7 to 1.1	0.40
1	27.8	−0.2	−2.0 to 1.6	0.84
2	27.8	0.0	−1.7 to 1.8	0.98
3	27.8	−1.0	−2.7 to 0.8	0.27
4	27.8	0.5	−1.2 to 2.3	0.56
5	27.8	0.7	−1.0 to 2.5	0.41

[a] Data were gathered from 1995 to 2001 and included daily deaths in the new city limits of Erfurt, except where noted. Particulate matter was measured as mass concentration (MC) of several size classes of particles.

[b] Percent change in daily deaths calculated per IQR.

[c] Imputed time series.

[d] Data were gathered from 1995 to 2002 and included daily deaths in the new city limits of Erfurt.

[e] Data were gathered from 1991 to 2002 and included daily deaths in the old city limits of Erfurt.

Table 19. Percent Changes in Daily Deaths Associated with SO_2 in Erfurt[a]

Lag (Days)	Change in Daily Deaths[b](%)	CI	*P*
0	−0.8	−1.6 to 0.1	0.08
1	−0.7	−1.5 to 0.2	0.14
2	−0.4	−1.3 to 0.4	0.34
3	−0.4	−1.2 to 0.5	0.40
4	0.2	−0.6 to 1.0	0.64
5	0.3	−0.5 to 1.0	0.52

[a] Data were gathered from 1991 to 2002 and included daily deaths in the old city limits of Erfurt.

[b] Percent change in daily deaths calculated per IQR (IQR = 19.3 $\mu g/m^3$).

Table 20. Percent Changes in Daily Deaths Including Cause-Specific Deaths Associated with O_3 in Erfurt[a]

Mortality / Pollutant	Lag (Days)	IQR ($\mu g/m^3$)	Change in Daily Death[b] (%)	CI	*P*
All-Cause Mortality					
O_3 (daily mean)					
	0	34.7	2.1	−1.5 to 5.8	0.26
	1	34.7	1.5	−2.0 to 5.2	0.40
	2	34.7	3.2	−0.4 to 6.8	0.08
	3	34.7	−0.7	−3.9 to 2.5	0.65
	4	34.7	0.0	−3.0 to 3.1	0.99
	5	34.7	−1.5	−4.4 to 1.6	0.35
O_3 (maximum 8-hr mean)					
	0	43.8	0.8	−2.5 to 4.2	0.64
	1	43.8	1.4	−2.0 to 4.9	0.42
	2	43.8	4.6	1.1 to 8.3	0.01
	3	43.8	−0.9	−3.8 to 2.2	0.57
	4	43.8	−0.3	−3.0 to 2.6	0.85
	5	43.8	−1.3	−4.0 to 1.4	0.34
Cause-Specific Mortality[c]					
Cardiorespiratory	2	43.8	4.7	0.8 to 8.8	0.02
Cardiovascular	2	43.8	5.1	1.1 to 9.2	0.01
Cardiovascular only	2	43.8	5.1	0.8 to 9.7	0.02

[a] Data were gathered from 1991 to 2002 and included daily deaths in the old city limits of Erfurt.

[b] Percent change in daily deaths calculated per IQR.

[c] **Cardiorespiratory death** is any mention of a cardiorespiratory cause of death on the death certificate (ICD-9 codes 390–459, 460–519, 785 and 786; and ICD-10 codes I00–I99, J00–J99, R00–R06 and R09). **Cardio-vascular death** is any mention of a cardiovascular cause of death on the death certificate (ICD-9 codes 390–459, 785; ICD-10 codes I00–I99, R00–R03, R09). **Cardiovascular only** death is any mention of a cardiovascular cause of death on the death certificate (ICD-9 codes 390–459, 785; ICD-10 codes I00–I99, R00–R03), and no mention of respiratory death causes (ICD-9 codes 460–519, 786; ICD-10 codes J00–J99, R04–R06, R09).

Regression Results for O_3

All-Cause Mortality For O_3, a statistically significant increase in all-cause mortality was observed at lag day 2 for the maximum 8-hour moving mean O_3 concentration (Table 20). Borderline significant associations were found for the daily mean concentration.

Cause-Specific Mortality For O_3, slightly stronger, statistically significant associations were found for cardiorespiratory, cardiovascular, and cardiovascular-only mortality, each at lag day 2, than for all-cause mortality (Table 20). The risk estimate for respiratory mortality was lower than for all-cause mortality and was not statistically significant.

Two-Pollutant Models

When we adjusted for gaseous pollutants in two-pollutant models (for the 1995–2001 period), risk estimates for all-cause mortality in association with the ultrafine-particle size class $NC_{0.01–0.1}$ increased (Table 21), while risk estimates for NO_2 and CO decreased. The change in daily mortality associated with a one-IQR increase in concentrations of both $NC_{0.01–0.1}$ and O_3 increased slightly, compared with the daily mortality increase associated with a one-IQR increase of either pollutant taken alone.

Sensitivity Analyses

A number of analyses were performed to test the sensitivity of the chosen confounder model with respect to changes in its parameters. Table 22 presents results for the ultrafine-particle size class $NC_{0.01–0.1}$ during the period 1995–2001. The risk estimate did not change when we excluded imputed values for $NC_{0.01–0.1}$. It increased when we included indicators for all days of the week instead of indicators for Sundays only or when we used the same temperature model as in an earlier Erfurt study (Wichmann et al. 2000). The previously used temperature model included smooth functions of same-day temperature (2.8 df),

Table 21. Effects of Ultrafine Particles ($NC_{0.01–0.1}$), NO_2, CO, and O_3 in Two-Pollutant Models[a]

Two-Pollutant Model	Lag (Days)	IQR	Change in Daily Death[b] (%)	CI	*P*
$NC_{0.01–0.1}$ (particles/cm^3)	4	9743	4.0	0.9 to 7.3	0.01
NO_2 (μg/m^3)	4	17.2	−2.5	−5.7 to 0.9	0.15
$NC_{0.01–0.1}$ (particles/cm^3)	4	9743	3.3	0.3 to 6.5	0.03
CO (mg/m^3)	4	0.35	−0.9	−3.5 to 1.8	0.52
$NC_{0.01–0.1}$ (particles/cm^3)	4	9743	3.1	0.5 to 5.7	0.02
O_3 (μg/m^3)	2	43.5	4.8	−1.3 to 11.1	0.12

[a] Data are gathered from 1995 to 2001 and include daily deaths in the new city limits of Erfurt. Ultrafine particles are measured as number concentrations (NC). All ultrafine particle NC data are from imputed series.

[b] Percent change in daily deaths calculated per IQR.

temperature lagged 3 days (3.9 df), and same-day relative humidity (4 df). The risk estimate also increased slightly when we restricted the analysis to the old city limits. When the spline that adjusts for trend and seasonality had more degrees of freedom, the risk estimate decreased and became borderline significant. However, this also introduced negative residual autocorrelation, which points to overfitting of the model.

Similar consistent results were observed in sensitivity analyses for other pollutants (Appendix C).

Exposure–Response Relationships We also looked at the shape of the exposure–response relationship for the main pollutants. Two models were used: The first included the pollutant using a LOESS smoother in the final model in S-plus software. The span was chosen to minimize the Akaike information criterion. The second model permitted R statistical software to determine the shape of the relationship using its built-in generalized cross-validation score. Selected details of the model that fitted best are presented in Table 23.

For CO, NO_2, and the ultrafine-particle size class $NC_{0.01–0.1}$, both models yielded a nearly linear exposure–response relationship except at the boundaries, where it tended to fray out (Figure 17). Models that included NO_2 and CO as linear predictors decreased the Akaike information criterion even further. The model using the generalized cross-validation score also led to an exact linear exposure–response relationship for NO_2, CO, and ultrafine particles ($NC_{0.01–0.1}$).

For PM_{10}, a linear exposure–response relationship was observed with a small, positive slope only at concentrations below 50 μg/m^3 (Figure 18A). For $PM_{2.5}$, a linear exposure–response relationship was observed (Figure 18B).

No clear effect was observed for SO_2 (Figure 18C). The lowest Akaike information criterion, however, was observed when SO_2 was included as a linear predictor.

For O_3, both methods yielded a very similar, nearly linear exposure–response relationship (Figure 18D).

TIME-VARYING MODELS

In the following section, the results of the analysis using the Bayesian models are presented for all-cause mortality and the four pollutant groups. Confounder models were

Table 22. Sensitivity Analysis of Confounder Models and Effects of Ultrafine Particle Number Concentrations ($NC_{0.01–0.1}$)[a]

Type of Model	Lag (Days)	IQR	Change in Daily Death[b] (%)	CI	*P*
Original model (7 df for trend)	4	9743	2.9	0.3 to 5.5	0.03
Excluded imputed values	4	9864	2.9	0.3 to 5.5	0.03
Indicator for all days of the week instead of Sunday indicator	4	9743	3.2	0.5 to 6.0	0.02
14 df for trend (more than in original model)	4	9743	2.3	−0.3 to 5.0	0.08
Temperature model (Wichmann et al. 2000)	4	9743	3.2	0.6 to 5.9	0.02
Included deaths in old city limits only	4	9743	3.1	0.5 to 5.9	0.02

[a] Data were gathered from 1995 to 2001 and are from imputed series, except where noted.

[b] Percent change in daily deaths calculated per IQR.

Table 23. Exposure–Response Relationships Estimated by Two Time-Varying-Coefficient Models

Pollutant	Lag (Days)	Models: Span (Pollutant)[a]	Models: df (Pollutant)[b]
NO_2[c]	3	Best AIC: Linear	Linear ($P = 0.00$)
		2nd best AIC: span = 0.6 (df = 3.9, $P = 0.21$, Figure 17B)	
CO	4	Best AIC: Linear	Linear ($P = 0.02$)
		2nd best AIC: span = 0.95 (df = 2.2, $P = 0.81$, Figure 17A)	
$NC_{0.01–0.1}$[d]	4	0.9 (df = 2.3, $P = 0.17$, Figure 17C)	Linear ($P = 0.03$)
PM_{10}[d]	0	0.9 (df = 2.5, $P = 0.05$, Figure 18A)	4.5 ($P = 0.16$, Figure 18A)
$PM_{2.5}$[d]		Best AIC: Linear	Linear ($P = 0.52$)
		2nd best AIC: span = 0.95 (df = 2.1, $P = 0.67$, Figure 18B)	
SO_2	0	Best AIC: Linear	4.8 ($P = 0.13$, Figure 18C)
		2nd best AIC: span = 0.6 (df = 4.3, $P = 0.23$, Figure 18C)	
O_3	2	0.95 (df = 1.9, $P = 0.06$, Figure 18D)	2.0 ($P = 0.04$, Figure 18D)

[a] The span was chosen to minimize the Akaike information criterion (AIC). S-Plus is the software used. The best Akaike information criterion is the one with the lowest value.

[b] Model used R statistical software to determine shape of relationship using its built-in generalized cross-validation score.

[c] Plausible data only. Implausible data from April 1, 1994, to January 31, 1995, omitted.

[d] Imputed series.

adopted as described in Table 3. The lag days for each pollutant and time periods were chosen based on results of our regression analysis (see regression results below).

Figures 19 through 21 show the results of Bayesian analyses estimating a different effect of air pollution for each year of the study. Results are presented as relative risk (RR) for mortality per IQR, together with the corresponding 95% Bayesian credible intervals. For 1991 and 2002, only three months of data were available. Annual RRs of mortality are therefore shown only for 1992–2001.

We also show the smooth time-varying RR of mortality per IQR in association with the specific pollutant, together with the corresponding 95% Bayesian credible intervals. Results of the cause-specific mortality analysis are given in Appendix D.

Time-Varying Regression Results for NO_2, CO, and Ultrafine Particles

Results of the time-varying regression analysis for associations between the pollutants CO, NO_2, and ultrafine particles in several size classes and all-cause mortality are presented in this section. A delayed association was found for all pollutants.

Associations for CO were strongest with a lag of 4 days (Figure 19); associations for NO_2 were strongest with a lag of 3 days (Figure 20). For the ultrafine-particle size classes, associations were strongest with a lag of 4 days (Figures 21 and 22).

Figure 19A shows the annual RRs of mortality per IQR increase in CO. The RRs increased until 1997, with a clear positive effect in 1997. Afterward, a sharp decline was observed. At the end of the study period, pollution concentrations, and especially the variation in pollution concentrations, were quite low (see Figure 10, for example). There was therefore larger uncertainty in the later years, as indicated by the (considerable) widening of the 95% credible intervals (Figure 19A). The time-varying curve (Figure 19B) showed a long-term trend for CO (lag day 4) that increased until the middle of 1997 and then decreased. Again, the low pollution concentrations and low variation in pollutant concentrations resulted in a widening of the 95% credible intervals. When the time-smoothed risks are compared with the annualized risks, the same pattern could be observed.

Unlike the long-term trend in the association between CO (lag day 4) and all-cause mortality, time-varying effect estimates for all the other pollutants showed some seasonal patterns (Figure 20B, Figure 21B, and Figure 22). For the association between NO_2 and mortality, we saw a period with an elevated effect between 1995 and mid-1997

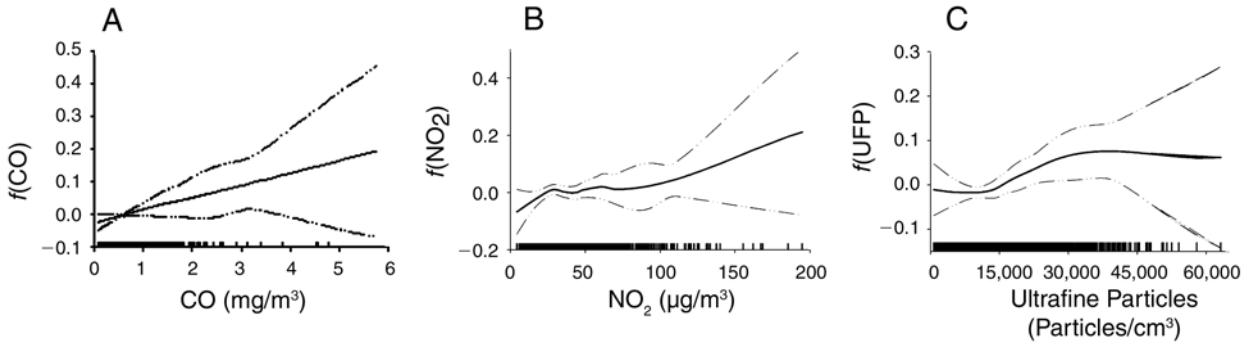

Figure 17. Exposure–response relationships of CO (A), NO_2 (B), and ultrafine particles (UFP defined as $NC_{0.01–0.1}$) (C), with LOESS smoothing. The solid lines indicate the LOESS fit. The dashed lines are the respective 95% CI. Bars along the *x* axis represent the number of observations used in the analysis.

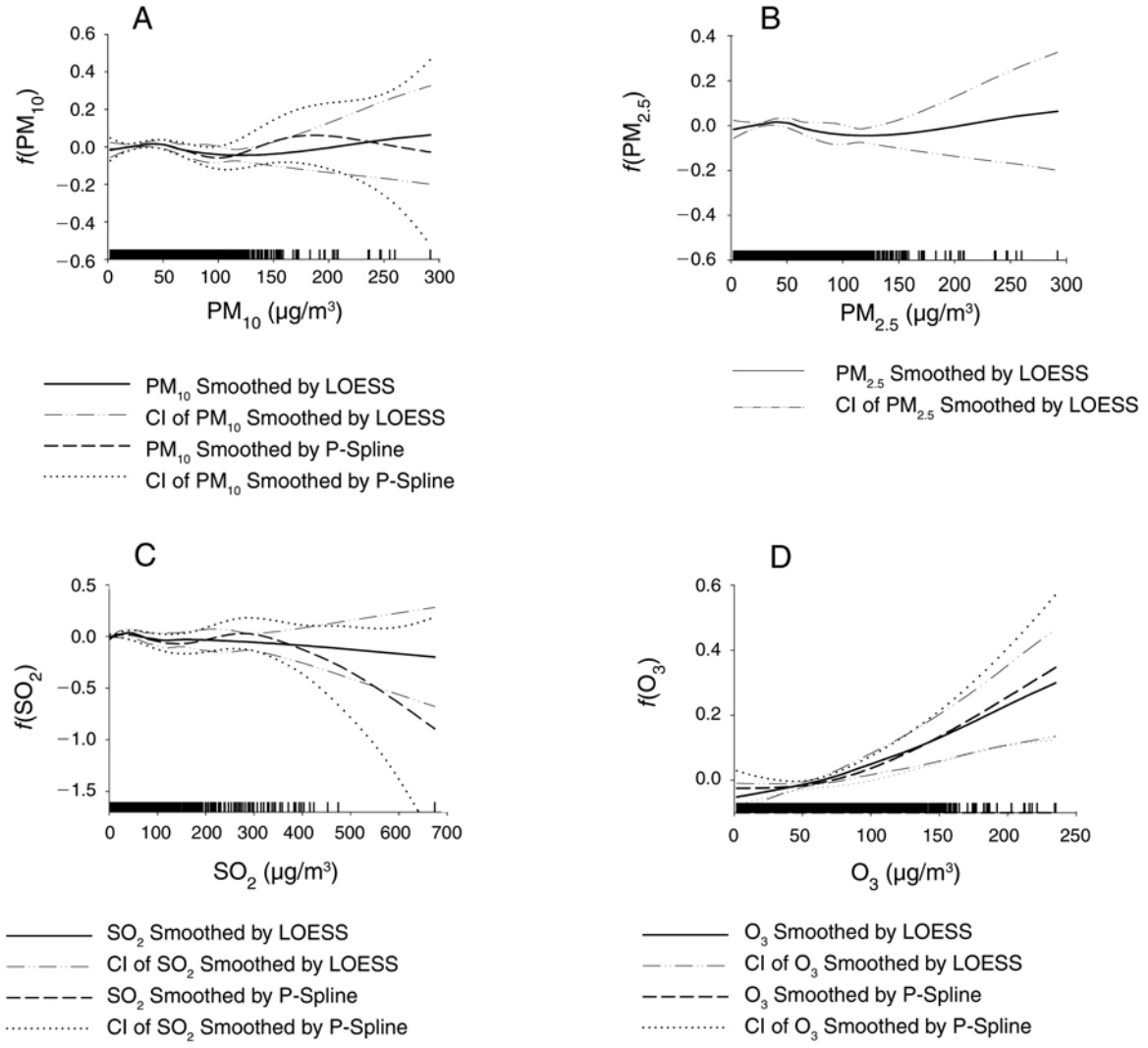

Figure 18. Exposure–response relationships of PM_{10} (imputed data series) (A), $PM_{2.5}$ (imputed data series) (B), SO_2 (C), and O_3 (D), LOESS and P-spline smoothing. Bars along the *x* axis represent the number of observations used in the analysis.

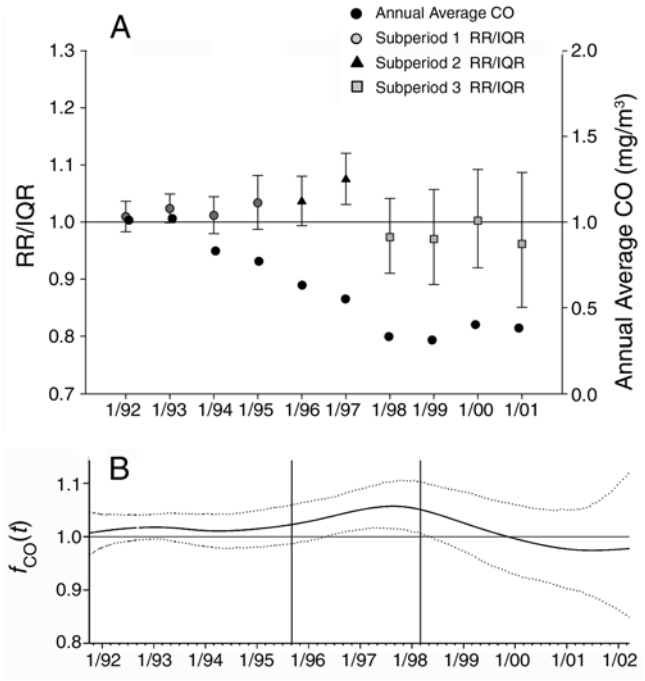

Figure 19. RR of mortality per IQR increase of CO, lag day 4 in Erfurt (old city limits). Annual RR of mortality per IQR increase of CO, lag day 4. Bars indicate 95% CI. Annual average CO concentrations are also shown (**A**). Smoothed time-varying association of CO at lag day 4 using Bayesian P-spline smoothing (**B**). The solid line indicates the fit. Dotted lines are the 95% credible intervals.

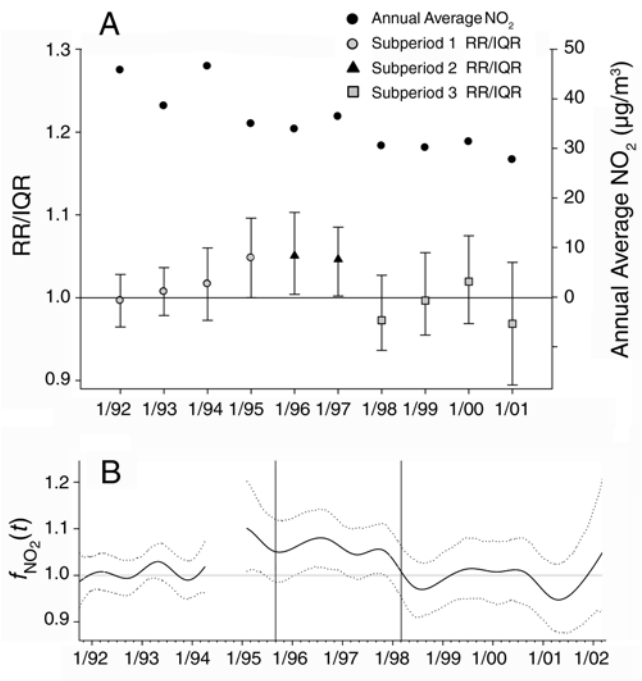

Figure 20. RR of mortality per IQR increase of NO_2, lag day 3 in Erfurt (old city limits). Annual RR of mortality per IQR increase of NO_2, lag day 3. Bars indicate 95% CI. Annual average NO_2 concentrations are also shown (**A**). Smoothed time-varying association of NO_2 at lag day 3 using Bayesian P-spline smoothing (**B**). The solid line indicates the fit. Dotted lines are the 95% credible intervals.

in both the yearly risk estimates and the time-varying curves (Figure 20). The time-varying curves for all ultrafine-particle size classes had very similar patterns, as shown in Figures 21B and 22. In general, the time-varying effect estimates for these pollutants were higher in subperiod 2 and decreased afterward; this was also reflected in the plot of the annual risk estimates obtained for $NC_{0.01–0.1}$ (Figure 21A). At the end of the study period, the time-varying curves increased again. These increases, however, should be evaluated in view of the wide 95% credible intervals. Especially on days with missing values, the 95% credible intervals are wider because of the uncertainty in the corresponding estimates.

We further examined the time-varying estimates by calculating the median percent change in the risk of daily mortality for the three subperiods. The results of this analysis are shown in Table 24.

An increase in CO (lag day 4) per IQR of 0.48 mg/m^3 was associated with a median percent change in daily deaths that ranged from −0.9% for the third subperiod (95% credible interval, −7.8 to 6.9) to 4.9% for the second subperiod (95% credible interval, 1.0–8.8). Similar results were observed for NO_2 (lag day 3). We observed a median 5.3% increased risk for daily mortality for an increase in NO_2 of 19.7 µg/m^3 for the second subperiod (95% credible interval, −0.2 to 10.8); the weakest associations were seen for the third subperiod, with a median change of −0.1% (95% credible interval, −6.9 to 6.8).

An increase of 9419 particles/cm^3 in ultrafine particles (lag day 4) was associated with a median percent change in daily deaths that ranged from −0.9% for the third subperiod (95% credible interval, −9.1 to 7.9) to 4.2% for the second subperiod (95% credible interval, −0.8 to 10.3). Results for the various size classes of ultrafine particles are shown in Table 24. The largest median percent increased risk was observed for $NC_{0.01–0.03}$.

Time-Varying Regression Results for PM_{10} and $PM_{2.5}$

Results for the time-varying regression analysis of PM_{10} and $PM_{2.5}$ were obtained, and Figures 23 and 24 show the time-varying effect estimates, together with the corresponding point-wise 95% Bayesian credible intervals.

In general, no clear association between PM_{10} or $PM_{2.5}$ and mortality could be seen, which agreed with the results of the regression analyses described earlier. The time-varying estimates for both PM_{10} and $PM_{2.5}$ showed some seasonal patterns (see Figure 23B, for example, which shows the estimated time-varying curve for PM_{10} [lag day 5]).

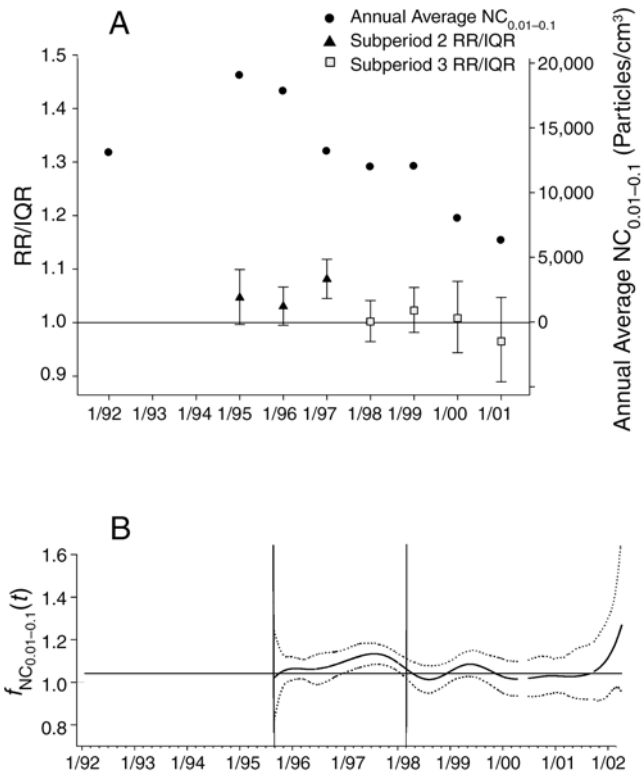

Figure 21. RR of mortality per IQR increase of ultrafine particles ($NC_{0.01–0.1}$), lag day 4 in Erfurt (new city limits). Annual RR of mortality per IQR increase of $NC_{0.01–0.1}$, lag day 4. Bars indicate 95% CI. Annual average $NC_{0.01–0.1}$ concentrations are also shown (**A**). Smoothed time-varying association of $NC_{0.01–0.1}$ at lag day 4 using Bayesian P-spline smoothing (**B**). The solid line indicates the fit. Dotted lines are the 95% credible intervals.

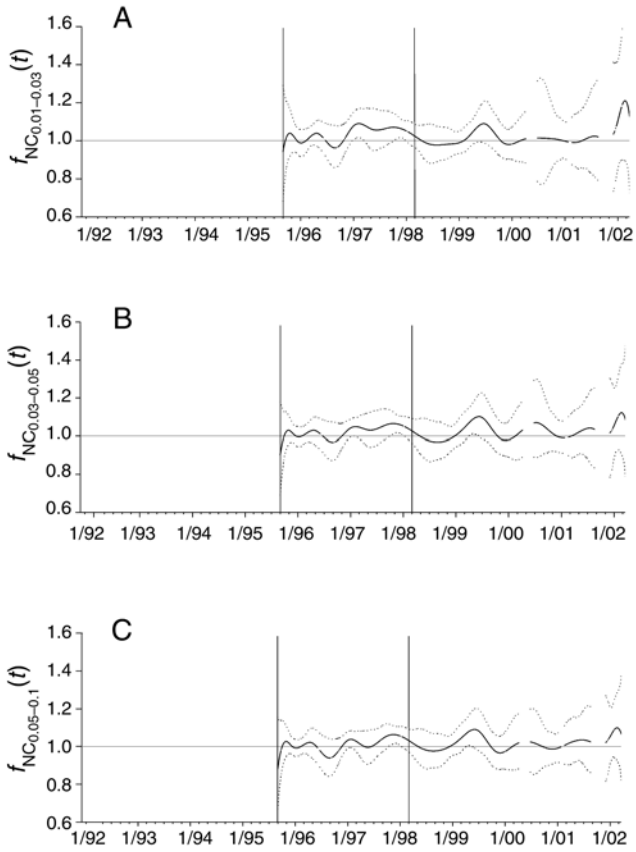

Figure 22. Time-varying associations of ultrafine particles at lag day 4 in Erfurt (new city limits) using Bayesian P-spline smoothing. Associations were estimated for three size classes of ultrafine particles: $NC_{0.01–0.03}$ at lag day 4 (**A**), $NC_{0.03–0.05}$ at lag day 4 (**B**), and $NC_{0.05–0.1}$ at lag day 4 (**C**). The solid lines indicate the fit. Dotted lines are the 95% credible intervals.

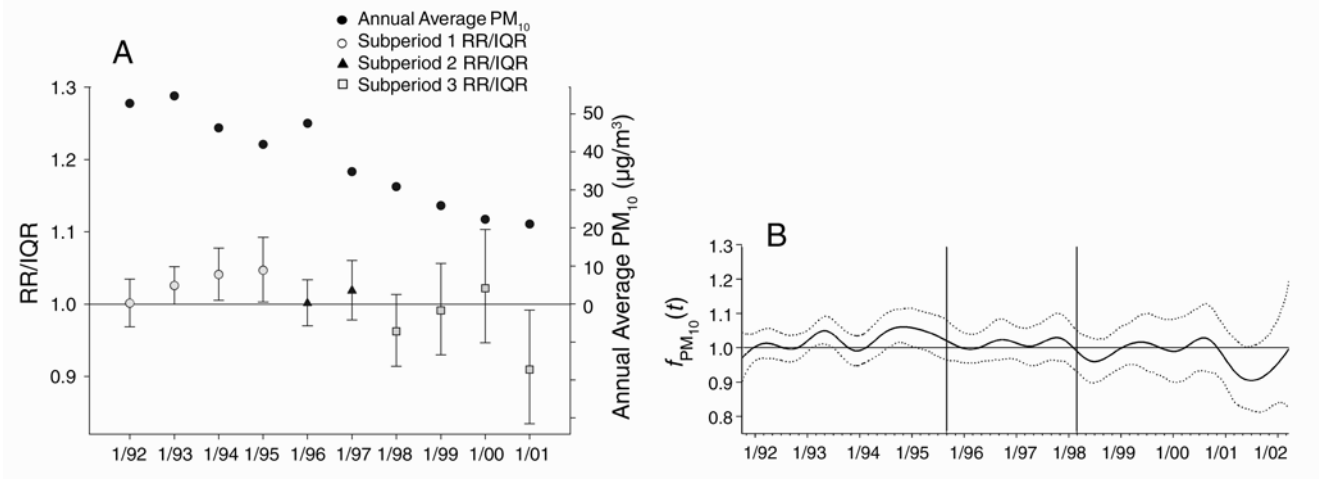

Figure 23. RR of mortality per IQR increase of particulate matter (PM_{10}), lag day 5 in Erfurt (old city limits). Annual RR of mortality per IQR increase of PM_{10}, lag day 5. Bars indicate 95% CI. Annual average PM_{10} concentrations are also shown (**A**). Smoothed time-varying association of PM_{10} at lag day 5 using Bayesian P-spline smoothing (**B**). The solid line indicates the fit. Dotted lines are the 95% credible intervals.

Table 24. Median Percent Changes in Daily Deaths Associated with an IQR Change in Concentrations of CO, NO_2, and Ultrafine Particles per Subperiod, in Erfurt[a]

Pollutant / Subperiod	Study Period	City Limits	Lag (Days)	IQR	Median Change in Daily Death[b] (%)	95% Credible Interval[c]
CO (mg/m^3)	1991–2002					
1		Old	4	0.48	1.5	−1.6 to 4.3
2		Old	4	0.48	4.9	1.0 to 8.8
3		Old	4	0.48	−0.9	−7.8 to 6.9
NO_2 ($\mu g/m^3$)[d]	1991–2002					
1		Old	3	19.7	0.9	−2.8 to 4.8
2		Old	3	19.7	5.3	−0.2 to 10.8
3		Old	3	19.7	−0.1	−6.9 to 6.8
Ultrafine Particles						
$NC_{0.01–0.1}$ ($particles/cm^3$)[e]	1995–2002					
2		New	4	9419	4.2	−0.8 to 10.3
3		New	4	9419	−0.9	−9.1 to 7.9
$NC_{0.01–0.03}$ ($particles/cm^3$)	1995–2001					
2		New	4	6861	3.9	−3.7 to 11.4
3		New	4	6861	0.6	−10.3 to 12.5
$NC_{0.03–0.05}$ ($particles/cm^3$)	1995–2001					
2		New	4	2088	2.9	−3.8 to 9.8
3		New	4	2088	1.7	−9.4 to 12.6
$NC_{0.05–0.10}$ ($particles/cm^3$)	1995–2001					
2		New	4	1265	1.4	−4.9 to 8.3
3		New	4	1265	1.2	−9.5 to 11.5

[a] Subperiod 1: October 1, 1991, to August 31, 1995; subperiod 2: September 1, 1995, to February 28, 1998; and subperiod 3: March 1, 1998, to March 31, 2002.

[b] Percent change in daily deaths calculated with median of time-varying estimates per IQR.

[c] 95% pointwise Bayesian credible interval.

[d] Implausible data from April 1, 1994, to January 31, 1995 omitted.

[e] Imputed time series.

Table 25. Median Percent Changes in Daily Deaths Associated with an IQR Change in Concentrations of PM_{10} and $PM_{2.5}$ per Subperiod, in Erfurt[a]

Pollutant / Subperiod	Study Period	City Limits	Lag (Days)	IQR	Median Change in Daily Death[b] (%)	95% Credible Interval[c]
PM_{10} ($\mu g/m^3$)[d]	1991–2002					
1		Old	5	27.8	2.3	−2.5 to 6.3
2		Old	5	27.8	1.2	−4.0 to 6.7
3		Old	5	27.8	−1.1	−9.1 to 7.4
$PM_{2.5}$ ($\mu g/m^3$)[d]	1995–2002					
2		New	0	16.3	1.5	−3.6 to 7.1
3		New	0	16.3	−2.3	−10.6 to 7.0
2		New	1	16.3	2.3	−3.0 to 8.6
3		New	1	16.3	−2.2	−10.3 to 5.9

[a] Subperiod 1: October 1, 1991, to August 31, 1995; subperiod 2: September 1, 1995, to February 28, 1998; and subperiod 3: March 1, 1998, to March 31, 2002.

[b] Percent change in daily deaths calculated with median of time-varying estimates per IQR.

[c] 95% pointwise Bayesian credible interval.

[d] Imputed time series.

Figure 23 indicates an increasing time-varying association between PM_{10} (lag day 5) and all-cause mortality that was highest and even significant at the end of the first subperiod (Figure 23A). From then on, a general decreasing effect for PM_{10} was observed. The results for $PM_{2.5}$ (measured as $MC_{0.01–2.5}$) pointed to a rather immediate association. Figure 24 shows the time-varying associations for lag day 0 (Figure 24B) and lag day 1 (Figure 24C). For both lags, the largest effects were observed at the end of the second subperiod. This pattern was also seen in the annual risk estimates obtained for $PM_{2.5}$ concentrations at lag day 0 (Figure 24A). Afterward, the time-varying estimates decreased until mid-2001 and then increased again (Figure 24 B and C).

Again, we analyzed the percent change in daily deaths for the three subperiods (Table 25).

Time-Varying Regression Results for SO_2

We saw the largest positive association between all-cause mortality and SO_2 at lag day 5 (Figure 25 A and C). Annual risk estimates and the smooth curve indicated an

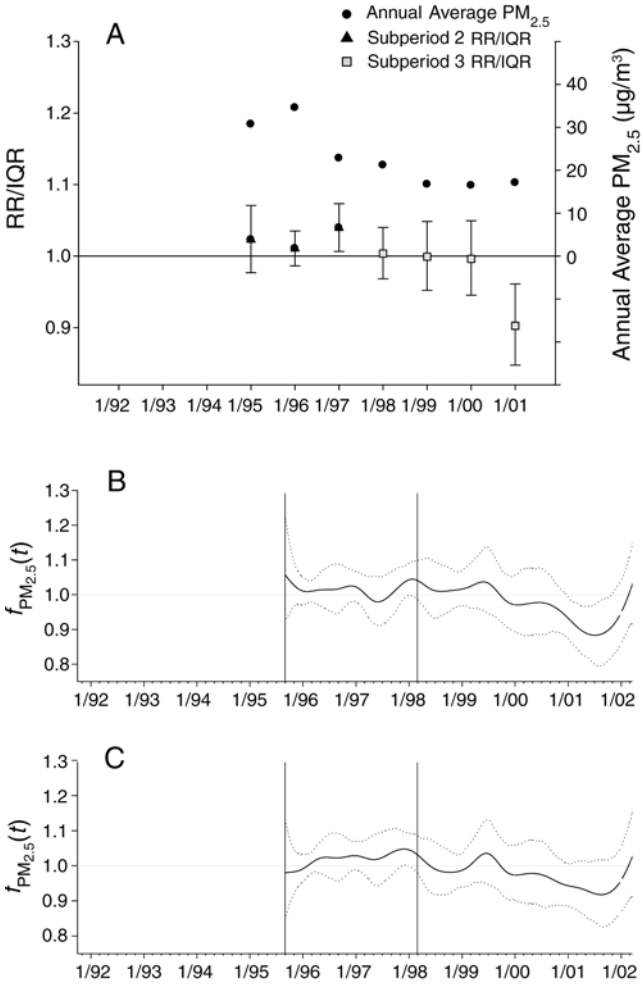

Figure 24. RR of mortality per IQR increase of particulate matter ($PM_{2.5}$), lag day 0, in Erfurt (new city limits). Annual RR of mortality per IQR increase in $PM_{2.5}$, lag day 0. Bars indicate 95% CI. Annual average $PM_{2.5}$ concentrations are also shown (**A**). Smoothed time-varying associations of $PM_{2.5}$ at lag day 0 (**B**) and at lag day 1 (**C**) using Bayesian P-spline smoothing. The solid lines indicate the fit. Dotted lines are the 95% credible intervals.

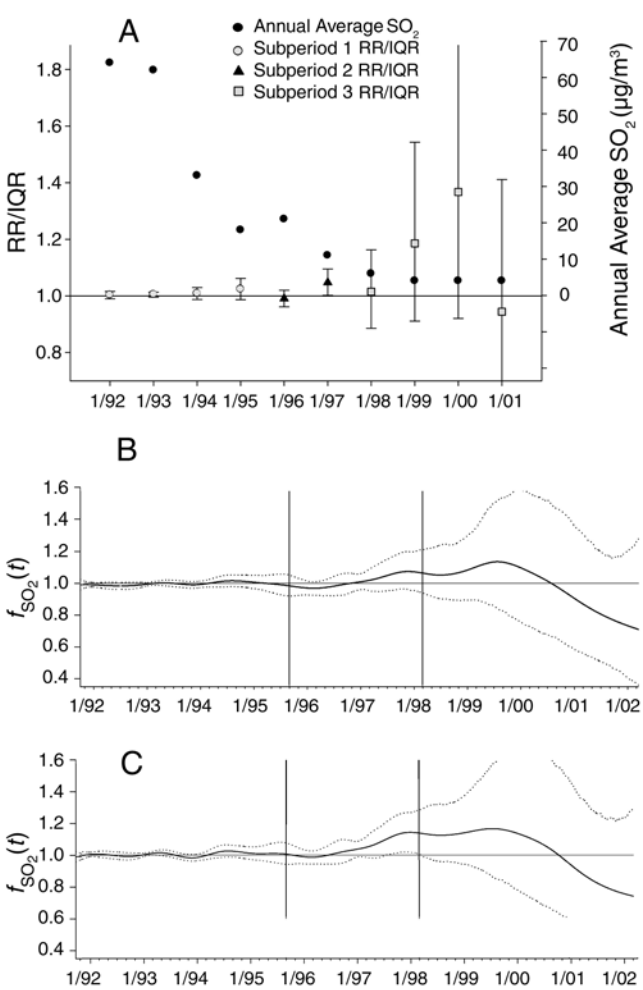

Figure 25. RR of mortality per IQR increase of SO_2 at lag day 5, in Erfurt. Annual RR of mortality per IQR increase of SO_2, lag day 5. Bars indicate 95% CI. Annual average SO_2 concentrations are also shown (**A**). Smoothed time-varying association of SO_2 at lag day 0 (**B**) and lag day 5 (**C**) using Bayesian P-spline smoothing. The solid lines indicate the fit. Dotted lines are the 95% credible intervals.

increase in the effect estimate through the end of 1997. The later increase, and especially the steep decline in the curve and annual estimates, should be evaluated with regard to the very wide 95% credible intervals. The time-varying curve can take almost any shape in that region of the curve. This is because of the extremely low variation in pollution concentrations in the third subperiod, when measured SO_2 was close to the LOD from the beginning of 2000 onward.

Because Wichmann and colleagues (2000) reported the strongest associations for SO_2 at lag day 0, this lag was also examined. We saw a pattern similar to that for the association at lag day 5 but with weaker effects (Figure 25B).

An increase in SO_2 of 19.3 µg/m^3 at lag day 5 was associated with a median change in daily deaths ranging from 11.1% for the third subperiod (95% credible interval, −25.1% to 38.7%) to 0.6% for the first subperiod (95% credible interval, −2.3% to 0.4%). The median change for the second subperiod was 3.1% (95% credible interval, −2.3% to 9.3%). In association with an increase of 19.3 µg/m^3 in concentrations of SO_2 (lag day 0), the largest median change (5.2%) was observed in the third subperiod (95% credible interval, −27.5% to 32.3%); the weakest association (−0.5%) was observed in the first subperiod (95% credible interval, −2.7% to 1.8%).

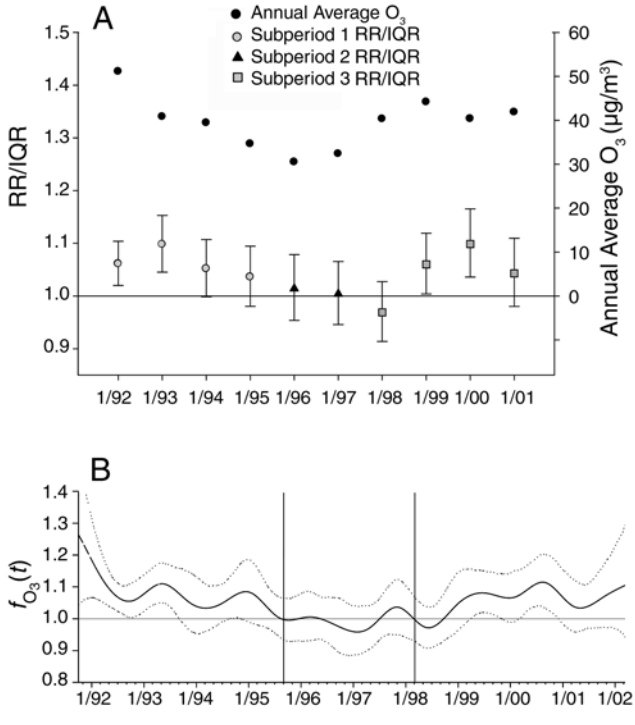

Figure 26. RR of mortality per IQR increase of O_3 at lag day 2 in Erfurt (old city limits). Annual RR of mortality per IQR increase of O_3, lag day 2. Bar indicate 95% CI. Annual average O_3 concentrations are also shown (**A**). Smoothed time-varying association of O_3 at lag day 2 using Bayesian P-spline smoothing (**B**). The solid line indicates the fit. Dotted lines are the 95% credible intervals.

Time-Varying Regression Results for O_3

A time-varying association was observed between maximum 8-hour concentrations of O_3 (lag day 2) and mortality (Figure 26). The time-varying curve (Figure 26B) shows that this association had some seasonal pattern. The overall pattern was a long-term decrease until 1997 and 1998, then an increase until the beginning of 1999, and then a leveling off. The same pattern was found in the annual RR estimates (Figure 26A). In contrast to the other gaseous pollutants and most of the particulate pollutants, the risk estimates were lowest in the second subperiod. The largest median increase in daily deaths per 43.8-µg/m^3 increase in O_3 was 6.9% (95% credible interval, 0.1%–14.3%), in the first subperiod; the smallest effect was −0.3%, seen in the second subperiod (95% credible interval, −7.0% to 6.8%). The median change for the third subperiod was 6.8% (95% credible interval, −2.7% to 14.8%).

Sensitivity Analyses

Time-Varying Effects of Exposure–Respones Sensitivity analyses examined the time-varying effects of the pollutants to see if the effects were real.

Figure 27A shows, for example, the time-varying association between CO (lag day 4) and daily mortality, and the time series of CO concentrations. The largest effects did not occur when concentrations were highest. The exposure–response relationship between CO (lag day 4) and mortality was clearly linear (see Figure 17).

In Figure 18, the exposure–response relationship between O_3 and mortality was examined using various

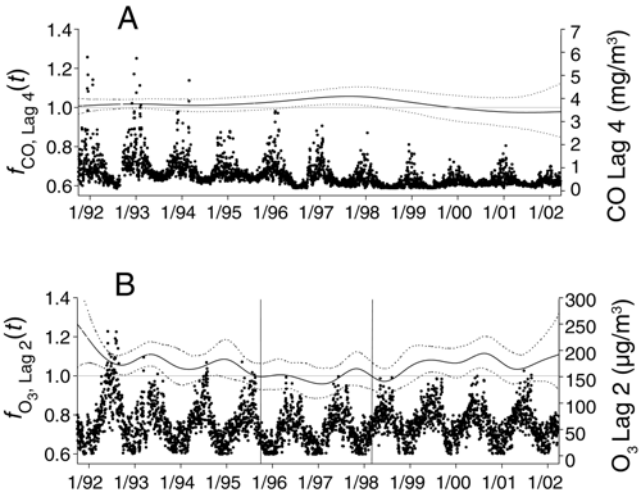

Figure 27. Time series and time-varying associations of CO at lag day 4 (A) and O_3 at lag day 2 (B) with Bayesian P-spline smoothing. The solid lines indicate the fit. Dotted lines are the 95% credible intervals.

smoothing approaches. One could argue that the figure shows a slightly nonlinear relationship. So the time-varying effect might have been driven by this relationship. Figure 27B shows the time-varying association of O_3 at lag day 2 and the time series of O_3 concentrations. Again, the largest effects did not occur when concentrations were highest.

Sensitivity within Markov Chain Monte Carlo Estimation The estimated nonlinear function $f_j(t)$ can in some situations depend considerably on the choice of hyperparameters, such as the parameters a_j and b_j defining the inverse gamma prior of the variances of nonparametric effects. It is therefore often recommended that the models under consideration be estimated using a (small) number of choices of a_j and b_j to check how sensitive the results are to changes in the hyperparameters. The standard choices for a and b used in BayesX are $a = b = 0.001$. We reestimated the model with different choices for a and b for each effect in the model. The values chosen were: $a = 0.00001$, $b = 0.00001$; $a = 1$, $b = 0.005$; and $a = 1$, $b = 0.00005$. Figure 28 shows, for example, the results for the time-varying effect of CO with $a = b = 0.001$ (Figure 28A, standard choice); $a = 0.00001$, $b = 0.00001$ (Figure 28B); and $a = 1$, $b = 0.005$ (Figure 28C). Obviously, the estimated function was somewhat smoother for $a = 0.00001$, $b = 0.00001$, and the function for $a = 1$, $b = 0.005$ showed slightly more curvature. But neither of these two functions differed much from the estimate made using the standard choice.

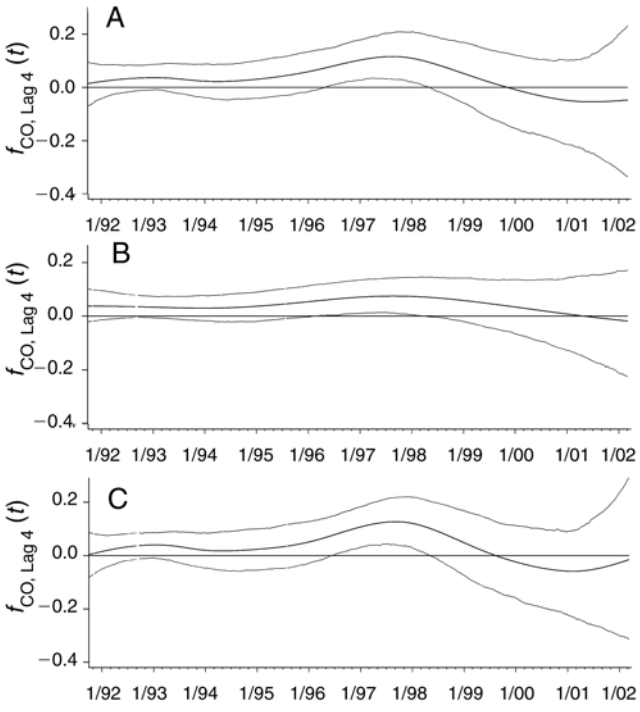

Figure 28. Time-varying association of CO at lag day 4 with various hyperparameters. Hyperparameter choices are: $a = b = 0.001$ (standard choice) (**A**); $a = 0.00001$, $b = 0.00001$ (**B**); and $a = 1$, $b = 0.005$ (**C**). Bayesian P-spline smoothing was used. Black lines indicate the fit. Gray lines are the 95% credible intervals.

Comparison of the Two Models that Performed Best in the Simulation Studies The two models that performed best in our simulation studies (see *Methods*) were applied to a regression model relating CO (lag day 4) to all-cause mortality, and the results were compared. The two models used were Model B, the fully Bayesian time-varying coefficient models with P-splines, and Model D, the time-varying coefficient model with P-splines based on empirical Bayes inference.

The estimated coefficients $f_{CO,\ lag\ 4}(t)$ using the two models are shown in Figure 29. Figure 29A shows the time-varying posterior mean estimated using the fully Bayesian Model B, together with 95% point-wise credible intervals; Figure 29B shows the results for Model D, the empirical Bayes model, and gives the time-varying posterior mode, again with appropriate 95% point-wise credible intervals. Both estimates had similar shapes, showing a long-term trend with a time-varying effect that increased until mid-1997 and then decreased. From mid-1996 to the beginning of 1998, the effect was statistically significant. The estimate made using Model B showed slightly more curvature. This indicates that the effect estimates for the mid-1990s were consistently estimated by both models,

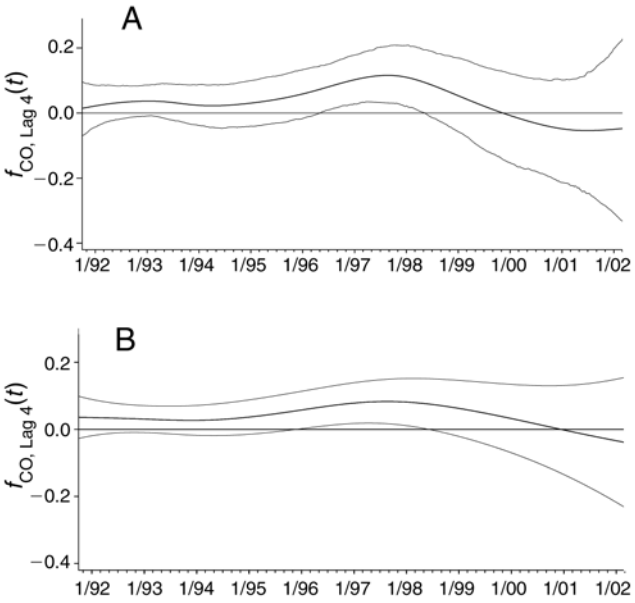

Figure 29. Time-varying effect of CO at lag day 4 estimated using two models. Model A, the fully Bayesian approach (**A**), and Model B, the empirical Bayes method (**B**). Bayesian P-spline smoothing was used. Black lines indicate the fit. Gray lines are the 95% credible intervals.

Table 26. Percent Change in Daily Deaths Associated with CO, NO_2, and Ultrafine Particle Number Concentration per Subperiod, in Erfurt[a]

Pollutant / Subperiod	Study Period	City Limits	Lag (Days)	IQR	Change in Daily Deaths (%)[b]	95% Credible Interval[c]
CO (mg/m³)	1991–2002					
1		Old	4	0.48	1.5	−0.5 to 3.4
2		Old	4	0.48	4.5	1.3 to 7.6
3		Old	4	0.48	−2.1	−7.5 to 3.9
NO_2 (µg/m³)[d]	1991–2002					
1		Old	3	19.7	1.0	−1.1 to 3.1
2		Old	3	19.7	4.3	0.9 to 7.7
3		Old	3	19.7	−1.0	−4.6 to 2.9
Ultrafine Particles						
$NC_{0.01–0.1}$ (particles/cm³)[e]	1995–2002					
2		New	4	9419	5.0	2.1 to 7.9
3		New	4	9419	0.6	−3.2 to 4.8
$NC_{0.01–0.03}$ (particles/cm³)	1995–2001					
2		New	4	6861	4.8	1.4 to 8.2
3		New	4	6861	0.5	−3.5 to 4.4
$NC_{0.03–0.05}$ (particles/cm³)	1995–2001					
2		New	4	2088	4.3	1.6 to 7.0
3		New	4	2088	1.5	−2.5 to 5.5
$NC_{0.05–0.10}$ (particles/cm³)	1995–2001					
2		New	4	1265	3.3	0.8 to 5.8
3		New	4	1265	1.3	−2.3 to 5.1

[a] The percent change in daily deaths per IQR is shown for three subperiods. Subperiod 1: October 1, 1991, to August 31, 1995; subperiod 2: September 1, 1995, to February 28, 1998; and subperiod 3: March 1, 1998, to March 31, 2002. Indicator variables were used in the regression to denote data from each subperiod.

[b] Percent change in daily deaths calculated per IQR.

[c] 95% pointwise Bayesian credible interval.

[d] Implausible data from April 1, 1994, to January 31, 1995, omitted.

[e] Imputed time series.

Table 27. Percent Change in Daily Deaths Associated with O_3 per Subperiod, in Erfurt[a]

Pollutant / Subperiod	IQR	Change in Daily Death (%)[b]	95% Credible Interval[c]
O_3 (µg/m³) (Lag days = 2)			
1	43.8	5.6	2.2 to 9.4
2	43.8	2.1	−3.2 to 7.3
3	43.8	3.1	−1.0 to 7.4

[a] Subperiod 1: October 1, 1991, to August 31, 1995; subperiod 2: September 1, 1995, to February 28, 1998; and subperiod 3: March 1, 1998, to March 31, 2002. Data were gathered from 1991 to 2002 and included daily deaths in the old city of Erfurt. Indicator variables were used in the regression to denote data from each subperiod.

[b] Percent change in daily deaths calculated per IQR.

[c] 95% pointwise Bayesian credible interval.

when there was more uncertainty about the effect estimates in the beginning of the study period.

Results per Subperiod Table 26 and Table 27 show the results of an analysis for pollutants in which indicator variables were used for the three subperiods of the study. The results for CO, NO_2, and the various size classes of ultrafine particles are shown in Table 26; the results for O_3 are shown in Table 27.

The magnitude of the percent changes in daily deaths for CO and NO_2 were comparable to the median percent changes shown in Table 24. However, the percent changes for ultrafine particles were considerably larger in the second subperiod, and statistically significant (Table 26). The percent change for O_3 was smaller in the first and third subperiods (compared with the median percent change described earlier in the results of the time-varying

regression analyses of O_3) but larger in the second subperiod. Table 27 shows a statistically significant 5.6% increase for the first subperiod (95% credible interval, 2.2%–9.4%).

Results by Season The results of seasonality tests are shown in Table 28. The seasons were defined as follows: winter, November 16 to February 28; spring, March 1 to May 31; summer, June 1 to August 31; and fall, September 1 to November 15. Analyses were made using indicator variables for the seasons.

For all pollutants examined, associations were always weakest or not observable at all in summer, when, except for O_3, pollution concentrations were low. Associations for O_3, ultrafine particles, and CO were strongest in winter and, for ultrafine particles, CO, and NO_2, in spring.

Among the pollutants, maximum 8-hour O_3 and ultrafine particles had the strongest associations, with an 11.9% increase in daily deaths (95% credible interval, 5.1%–19.0%) per IQR increase in maximum 8-hour O_3 (lag day 2) in winter and a 4.4% increase in daily deaths per

Table 28. Regression Results for Daily Mortality per Season in Erfurt[a]

Pollutant / Season	Study Period	City Limits	Lag (Days)	IQR	Change in Daily Death (%)[b]	95% Credible Interval[c]
CO (mg/m³)	1991–2002					
Winter		Old	4	0.48	2.2	0.5 to 3.9
Spring		Old	4	0.48	2.7	−0.4 to 5.7
Summer		Old	4	0.48	−3.7	−10.2 to 3.1
Fall		Old	4	0.48	−0.7	−3.6 to 2.0
NO_2 (µg/m³)[d]	1991–2002					
Winter		Old	3	19.7	2.1	−0.1 to 4.5
Spring		Old	3	19.7	2.1	−0.5 to 4.6
Summer		Old	3	19.7	−3.2	−7.1 to 1.2
Fall		Old	3	19.7	−0.8	−3.2 to 1.8
Ultrafine particles ($NC_{0.01–0.1}$) (particles/cm³)[e]	1995–2002					
Winter		New	4	9419	3.2	0.3 to 6.0
Spring		New	4	9419	4.4	0.7 to 8.0
Summer		New	4	9419	−2.8	−8.8 to 3.9
Fall		New	4	9419	3.2	−0.8 to 7.3
$PM_{2.5}$ ($MC_{0.01–2.5}$) (µg/m³)[e]	1995–2002					
Winter		New	0	16.3	0.9	−1.3 to 3.5
Spring		New	0	16.3	0.0	−3.0 to 3.0
Summer		New	0	16.3	−6.7	−12.7 to −0.3
Fall		New	0	16.3	1.5	−1.7 to 4.7
O_3 8-hr maximum (µg/m³)	1991–2002					
Winter		Old	2	43.8	11.9	5.1 to 19.0
Spring		Old	2	43.8	6.0	1.1 to 10.8
Summer		Old	2	43.8	−0.7	−6.0 to 4.6
Fall		Old	2	43.8	1.7	−5.9 to 9.7

[a] Results from regression model using indicator variables for season. Seasons were defined as: winter, November 16 to February 28; spring, March 1 to May 31; summer, June 1 to August 31; and fall, September 1 to November 15.

[b] Percent change in daily deaths calculated per IQR.

[c] 95% pointwise Bayesian credible interval.

[d] Implausible data from April 1, 1994, to January 31, 1995, omitted.

[e] Imputed time series.

IQR (95% credible interval, 0.7%–8.0%) for ultrafine particles ($NC_{0.01–0.1}$) in spring (Table 28).

A comparison of the effects for an increase of one IQR for the various pollutants in winter again revealed the strongest associations for maximum 8-hour O_3 and ultrafine particles ($NC_{0.01–0.1}$) (Figure 30A). Similar effects for O_3 and ultrafine particles ($NC_{0.01–0.1}$) in summer are also shown (Figure 30B).

IQRs in winter were 0.70 mg/m^3 for CO, 23.3 µg/m^3 for NO_2, 14,308 particles/cm^3 for ultrafine particles ($NC_{0.01–0.1}$ [imputed]), 32.0 µg/m^3 for $PM_{2.5}$, and 35.1 µg/m^3 for maximum 8-hour O_3. IQRs in summer were 0.27 mg/m^3 for CO, 14.5 µg/m^3 for NO_2, 6004 particles/cm^3 for ultrafine particles ($NC_{0.01–0.1}$ [imputed]), 9.0 µg/m^3 for $PM_{2.5}$, and 44.6 µg/m^3 for maximum 8-hour O_3.

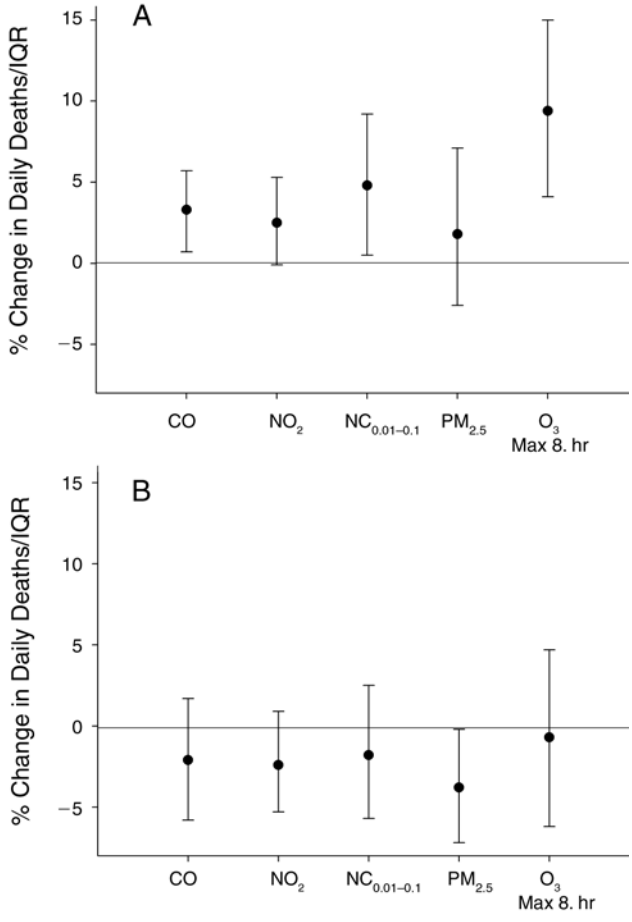

Figure 30. Percent change in daily deaths in winter and summer per IQR for five pollutants. In winter (**A**), IQR values were 0.70 mg/m^3 for CO, 23.3 µg/m^3 for NO_2, 14,308 particles/cm^3 for ultrafine particles ($NC_{0.01–0.1}$), 32.0 µg/m^3 for particulate matter ($PM_{2.5}$), and 35.1 µg/m^3 for O_3 (maximum 8-hr concentration). In summer (**B**), IQR values were 0.27 mg/m^3 for CO, 14.5 µg/m^3 for NO_2, 6004 particles/cm^3 for ultrafine particles ($NC_{0.01–0.1}$), 9.0 µg/m^3 for particulate matter ($PM_{2.5}$), and 44.6 µg/m^3 for O_3 (maximum 8-hr concentration). Bars indicate 95% CI.

INTERACTIONS BETWEEN POLLUTANTS AND OTHER VARIABLES

We employed Model B, the fully Bayesian time-varying coefficient model, to assess whether changes in effect estimates observed over time could be attributed to changes in other air pollutants (specific aim 3). The confounder model for this analysis is shown in Table 3. Further, interactions between ultrafine particles ($NC_{0.01–0.1}$ [lag day 4]) and one P-spline of the effect modifier (i.e., CO, NO_2, PM_{10}, $PM_{2.5}$, SO_2, and O_3 [lag day 4]) were included. In contrast with the time-varying regression analyses described earlier, the number of knots was chosen to be 10, as the concentration range of the effect modifiers was smaller. Figure 31A shows that, as CO concentrations increased in the 0.9–1.5 mg/m^3 range, there was a linear increase in the effect of ultrafine particles on mortality. However, at lower and higher concentrations, there was no evidence for a systematic change in effect. A similar result was observed for NO_2 (Figure 31B). In the 40–60-µg/m^3 concentration range, there seemed to be a linear increase in the effect of ultrafine particles on mortality, but not at lower or higher concentrations. Figure 32 shows a slightly decreasing effect of ultrafine particles on mortality when PM_{10} and $PM_{2.5}$ concentrations increased up to about 100 µg/m^3. This might be interpreted as an independent effect of ultrafine particles on mortality. The increase of the ultrafine-particle effect when PM_{10} was in

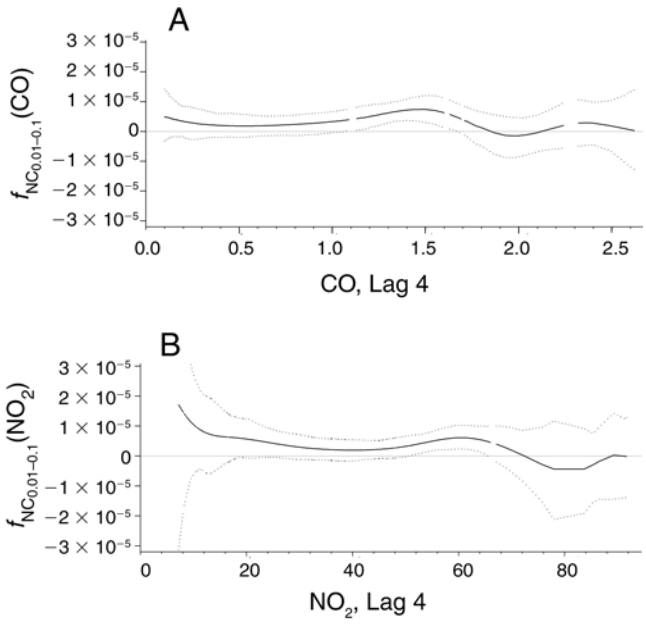

Figure 31. Effects of ultrafine particles ($NC_{0.01–0.1}$) at lag day 4 ($f_{NC_{0.01–0.1}}$ (poll, lag 4)) over the ranges of CO at lag day 4 (A) and NO_2 at lag day 4 (B). Bayesian P-spline smoothing was used. The solid lines indicate the fit. Dotted lines are the 95% credible intervals.

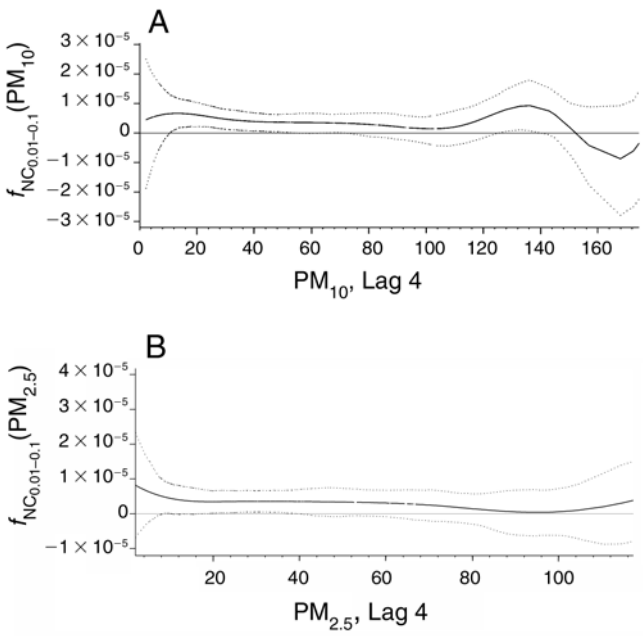

Figure 32. Effects of ultrafine particles ($NC_{0.01–0.1}$) at lag day 4 ($f_{NC_{0.01–0.1}}$ (poll, lag 4)) over the ranges of PM_{10} at lag day 4 (A) and $PM_{2.5}$ at lag day 4 (B). Bayesian P-spline smoothing was used. The solid lines indicate the fit. Dotted lines are the 95% credible intervals.

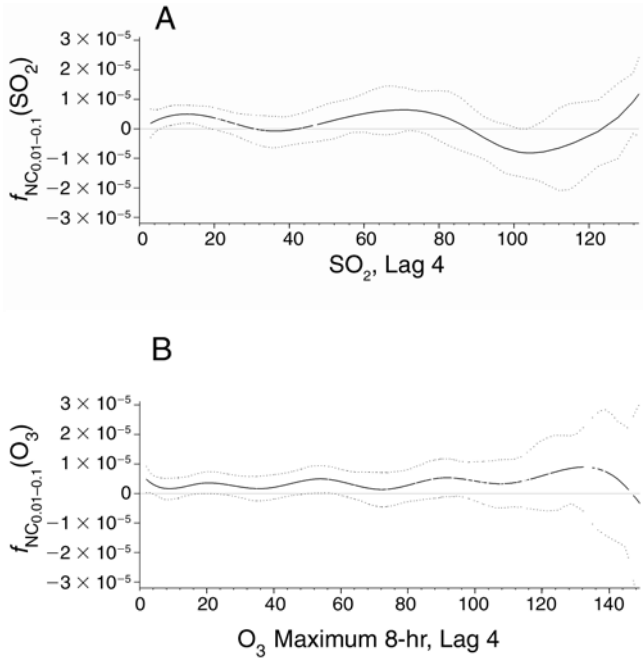

Figure 33. Effects of ultrafine particles ($NC_{0.01–0.1}$) at lag day 4 ($f_{NC_{0.01–0.1}}$ (poll, lag 4)) over the ranges of SO_2 at lag day 4 (A) and O_3 at lag day 4 (B). O_3 was measured as maximum 8-hr concentrations. Bayesian P-spline smoothing was used. The solid lines indicate the fit. Dotted lines are the 95% credible intervals.

the 120–140-µg/m^3 concentration range might have been caused by winter inversions. But the role of inversions cannot be assessed with certainty because of the limited number of days (10) in which measurements fell in that range. Changes in SO_2 or O_3 concentrations did not affect the association between ultrafine particles and mortality (Figure 33).

Interactions between the other pollutants were assessed as well, but no evidence for systematic changes in effects was observed (data not shown).

Annual effect estimates for the associations between air pollutants and mortality were calculated and plotted against information on the sources of the pollutants (which was available on an annual basis). We hypothesized a priori that an increased number of cars with catalytic converters should be associated with a reduced effect estimate for traffic-related pollutants on mortality. Figure 34 shows that, while the percentage of cars with catalytic converters increased, the effects of traffic-related air pollutants on mortality decreased. Annual average NO_2 concentrations changed least over time, and the effect estimates for NO_2 did not change systematically with increases in the percentage of cars with catalytic converters.

Figure 35 shows the estimates of the effects of ultrafine particles ($NC_{0.01–0.1}$ [lag day 4]) on mortality as a function of the percentage of various fuels used in heating systems. The switch from coal to natural gas was not immediately followed by a reduction in effect estimates for ultrafine particles (Figure 35). Also, the increased use of oil, natural gas, and electricity was not consistently associated with a reduction in effect estimates for ultrafine particles. Figure 36 shows the effect estimates for ultrafine particles for the switch from coal-stove heating to central heating, indicating that the effects of ultrafine particles on mortality decreased while the proportion of central heating increased. In all of these figures, the prevailing feature is the sharp drop in the effects of ultrafine particles on mortality during subperiod 2. None of the sources of pollution changed rapidly during this time period, nor were ultrafine-particle concentrations dramatically reduced. The switch from coal to natural gas as the fuel for district heating had already occurred in 1996, i.e., a year earlier. The annual effect estimates for PM_{10} or $PM_{2.5}$ and mortality were all close to null, with the result that it was not meaningful to assess their variations with respect to sources of pollution.

We also examined the effects of CO (lag day 4) and ultrafine particles ($NC_{0.01–0.1}$ [lag day 4]) on mortality as a function of the size of Erfurt's population (Figure 37) and as a function of the number of natural deaths per

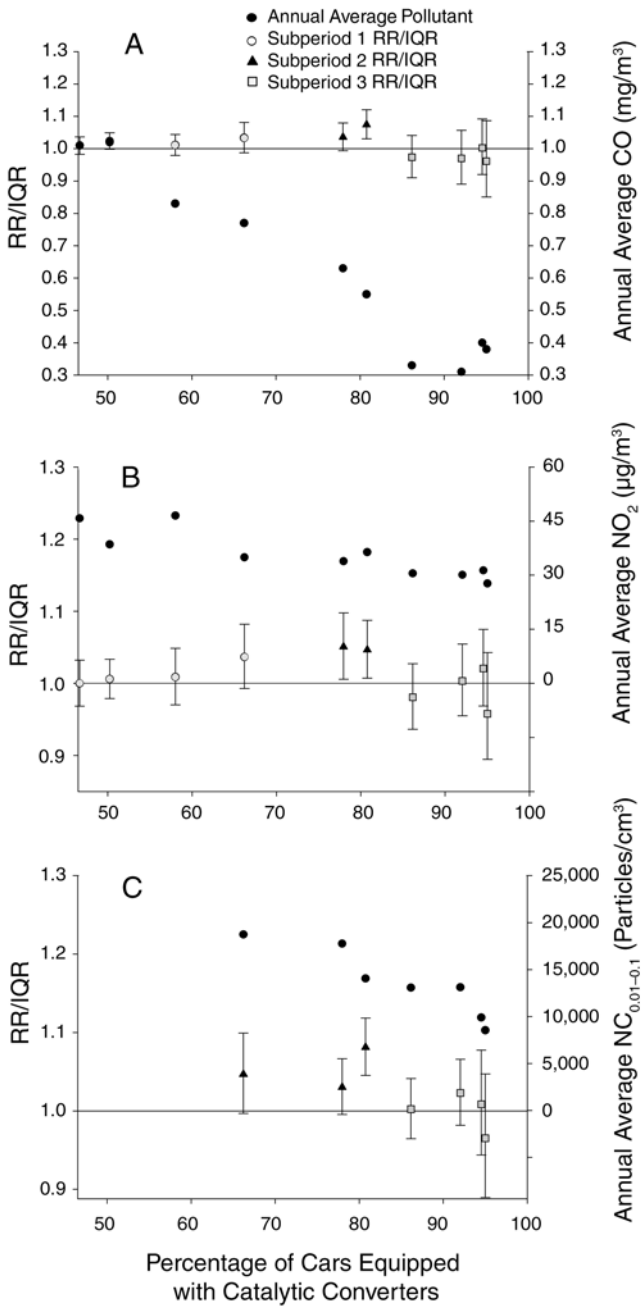

Figure 34. Annual associations between three pollutants and mortality as a function of the percentage of cars equipped with three-way catalytic converters. The annual associations of CO at lag day 4 (**A**), NO_2 at lag day 3 (**B**), ultrafine particles ($NC_{0.01–0.1}$) at lag day 4 (**C**), and mortality as a function of the percentage of cars equipped with three-way catalytic converters in Thuringia, Germany. Corresponding annual averages of CO (mg/m^3), NO_2 ($\mu g/m^3$), and ultrafine particles ($NC_{0.01–0.1}$) ($particles/cm^3$) are also shown. Bars indicate 95% CI.

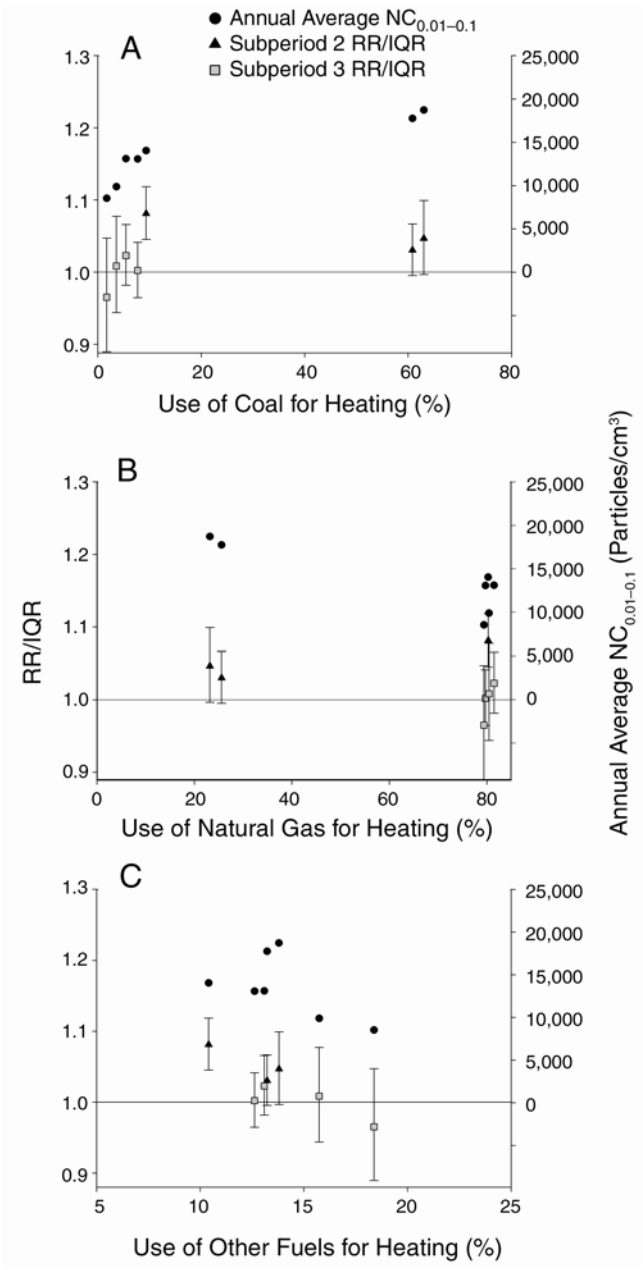

Figure 35. Annual associations between ultrafine particles ($NC_{0.01–0.1}$) and mortality as a function of heating-fuel use. The annual association of $NC_{0.01–0.1}$ at lag day 4 and mortality is shown as a function of the percentage of heating systems using coal (**A**), natural gas (**B**), and other heating fuels and electricity (**C**). Corresponding annual averages of $NC_{0.01–0.1}$ ($particles/cm^3$) are also shown. Bars indicate 95% CI.

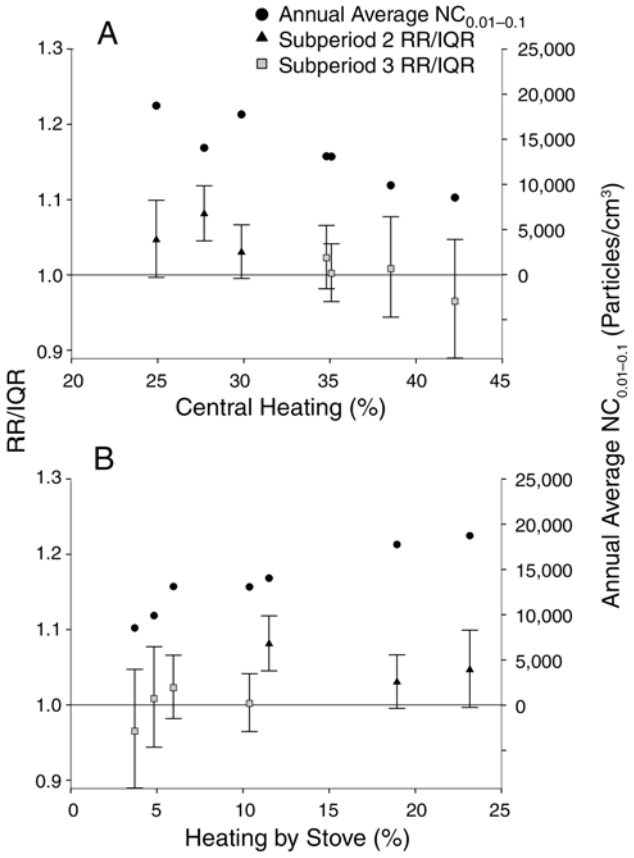

Figure 36. Annual associations between ultrafine particles ($NC_{0.01–0.1}$) and mortality as a function of heating systems. The annual association of $NC_{0.01–0.1}$ at lag day 4 and mortality is shown as a function of changes in the use of coal-burning stoves (**A**) and central heating (**B**). Corresponding annual averages of $NC_{0.01–0.1}$ (particles/cm^3) are also shown. Bars indicate 95% CI.

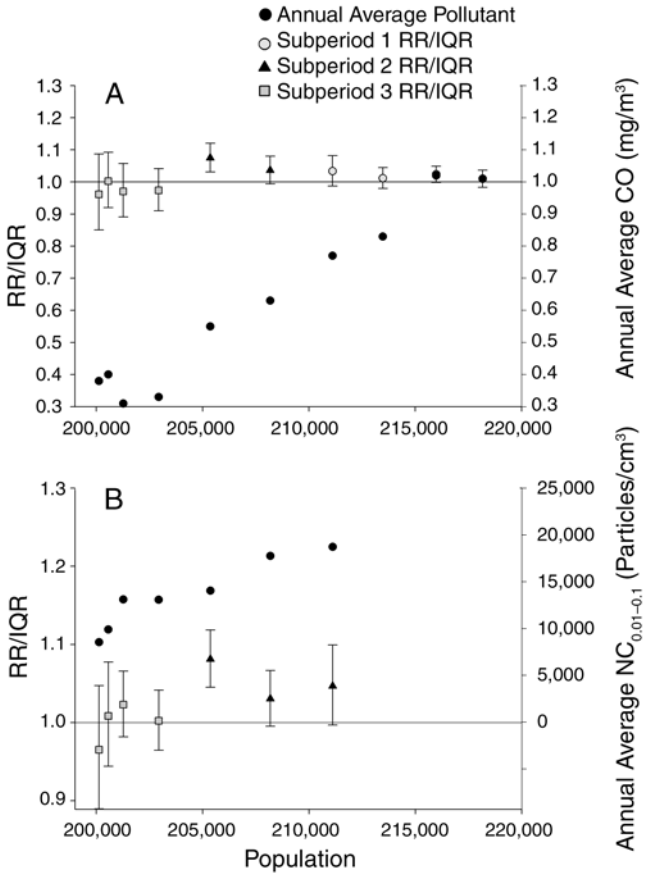

Figure 37. Annual association between CO, ultrafine particles, and mortality as a function of population. The annual association between CO at lag day 4 (**A**), ultrafine particles ($NC_{0.01–0.1}$) at lag day 4 (**B**), and mortality is shown as a function of the changes in the number of inhabitants in Erfurt between 1992 and 2001. Corresponding annual averages of CO (mg/m^3) and $NC_{0.01–0.1}$ (particles/cm^3) are also shown. Bars indicate 95% CI.

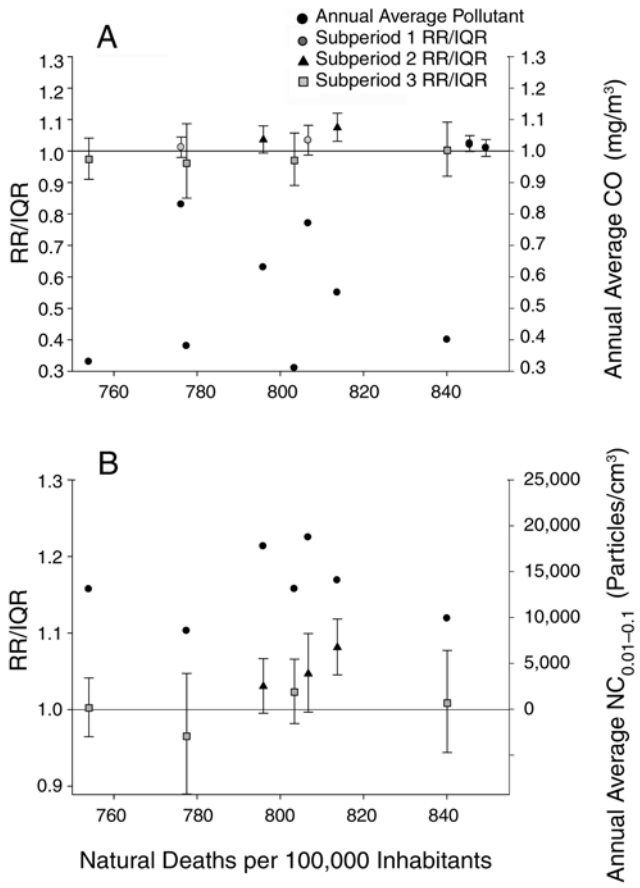

Figure 38. Annual association between CO, ultrafine particles, and mortality as a function of natural deaths. The annual association between CO at lag day 4 (**A**), ultrafine particles ($NC_{0.01–0.1}$) at lag day 4 (**B**), and mortality is shown as a function of the number of natural deaths per 100,000 inhabitants of Erfurt between 1992 and 2001. Corresponding annual averages of CO (mg/m^3) and of $NC_{0.01–0.1}$ ($particles/cm^3$) are also shown. Bars indicate 95% CI.

100,000 inhabitants (Figure 38). Figures 37 and 38 show convincingly that neither population nor natural-death rates influenced the associations between CO or ultrafine particles and mortality.

A transient increase in the association between SO_2 and mortality was not associated with the prevalence of coal use (data not shown).

DISCUSSION

The key findings of this study are summarized in Table 29. We observed clear improvements in air quality caused by continuing changes in the sources of air pollutants. Traffic-related pollutants and O_3 were associated with mortality. The effects decreased as air quality improved.

Table 29. Summary of Key Findings

Pollutant	More Than Twofold Decrease[a]	Overall Effect on Mortality	Subperiod with Effects on Mortality[b]
NO_2[c]	No	At lag day 3 to 4	Transition period, 1995–1997
CO	Yes	At lag day 3 to 4	Transition period, 1995–1997
Ultrafine particles	No	At lag day 3 to 4	Transition period, 1995–1997
$PM_{2.5}$	Yes	No	Transition period, 1995–1997
PM_{10}	Yes	No	Transition period, 1995–1997
SO_2	Yes	No	Transition period, 1995–1997
O_3	No	At lag day 2	Subperiods 1 and 3

[a] Minimum and maximum annual mean concentration, with at least 66% of all measurements available.

[b] Subperiod 1: October 1, 1991, to August 31, 1995; subperiod 2: September 1, 1995, to February 28, 1998; and subperiod 3: March 1, 1998, to March 31, 2002.

[c] Implausible data from April 1, 1994, to January 31, 1995, omitted.

In the following section, we discuss the changes in air-pollution concentrations and in the nature of the sources of air pollution in Erfurt. The air pollutants were divided into four groups according to their putative sources to facilitate the interpretation of the study results (especially with regard to effects on mortality risk); however, because the correlations between the pollutants were investigated for all pollutants (see *Results* and *Appendix B*), we discuss all the pollutants in an integrated manner. An added argument for this approach is the chemical coupling of O_3, NO, and NO_2 and the partly shared emission sources of the majority of the anthropogenic air pollutants (CO, NO_x, ultrafine particles, and fine particles).

Finally, we discuss the risk of mortality, the changes in risk over time, and the strengths and limitations of this study.

EXPOSURE AND SOURCE EMISSION DATA

The air pollution measured at the GSF monitoring station and the network monitoring station was primarily

produced by small-scale industry, domestic heating, and mobile sources. Hence, the measured pollution mixture was typical of air pollution in Erfurt. The generation of electricity for air conditioning in summer was not investigated as a source of pollution because it was not prevalent in Erfurt (and wasn't considered necessary).

Changes in Air-Pollution Concentrations

Pollution concentrations (except for O_3) exhibited a distinct seasonal pattern, i.e., lower in summers and higher in winters. This is the usual pattern for air pollutants, as atmospheric dispersion is typically at a minimum in winter, and pollutants are therefore dispersed into the troposphere to a lesser extent than in summer. Also, in summer the average planetary boundary layer is typically at its thickest, and thus the troposphere has more volume, which leads to increased mixing and hence lower concentrations of pollutants. Another seasonal factor is the lack of precipitation in winter, which reduces the potential for wet deposition and associated cleaning mechanisms. In some winters, unusual meteorologic conditions, such as extreme cold, inversions, and high winds, affected pollution concentrations as well. These effects for the winters of 1992/93, 1995/96, and 2001/02 are also discussed in detail in this section.

Apart from the seasonal variations, the concentrations of all pollutants under consideration decreased continuously over the study period, from October 1991 to March 2002. However, the pattern of decrease was different for different pollutants. In Figure 39 the annual mean concentrations of air pollutants from 1992 to 2001 are expressed as a percentage of their 1992 concentrations (with the 1992 concentrations set to 100%).

The most rapid decrease was seen for SO_2 concentrations. This dramatic decrease was seen not only in Erfurt but throughout the entire state of Thuringia. The annual mean concentrations of SO_2 from 1991 to 2004 measured at various network monitoring stations in Thuringia and the locations of these stations are shown in Figure 40.

The network monitoring stations in Erfurt, Gera, and Greiz were located in urban areas. Before reunification, Erfurt and Gera were home mainly to small-scale industry; Greiz was an important center of the chemical industry. The monitoring stations in Dreißigacker, Neuhaus, and Leinefelde were located in forested areas and reflected rural background concentrations of SO_2. It can be clearly seen that there were large differences in SO_2 concentrations in the early 1990s, depending on the location (urban, industrial, or rural) of the monitoring station. However, from the end of the 1990s on, only very low SO_2 concentrations were measured at all monitoring stations. An increasing number of days with SO_2 concentrations below the LOD were seen countrywide. Note that the increase in mean annual SO_2 concentration in 1996 compared with

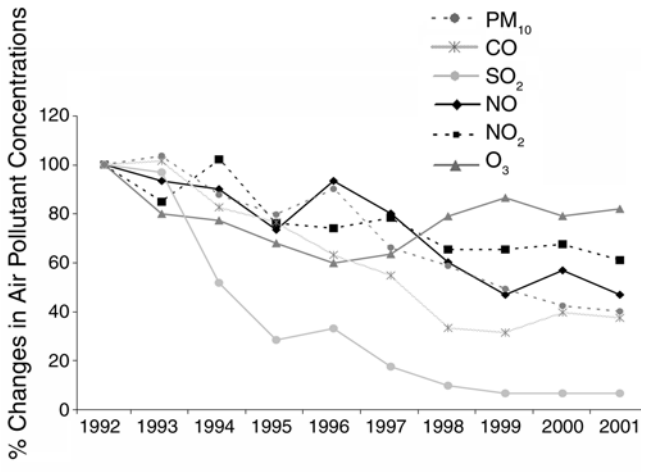

Figure 39. Percent changes in the annual average concentrations of air pollutants in Erfurt, 1992 to 2001. Concentrations for 1992 are indexed as 100%.

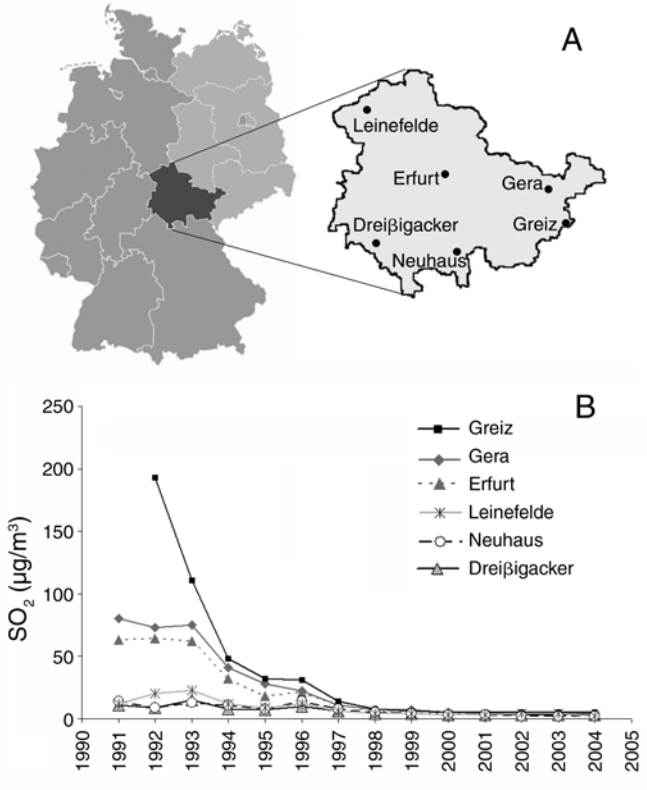

Figure 40. Selected network monitoring stations in Thuringia, Germany. Locations (**A**) and annual averages of SO_2 measured at each station (**B**).

1995 was observed not only at the monitoring station in Erfurt, but also at other monitoring stations across Thuringia. This is supported the hypothesis that the SO_2 increase was driven by meteorologic conditions occurring across the country as a whole rather than by local SO_2 sources.

The SO_2 time-series data measured at the network monitoring station on Krämpferstraße suggested that the changes in SO_2 concentrations occurred stepwise. This observation was one of the reasons for dividing the study period into three subperiods, in the belief that they might correspond to stepwise changes in the contributions from various sources. The first sharp decrease of emissions occurred countrywide between 1989 and 1991. Between 1989 and 1992, total SO_2 emissions in the former East Germany dropped from 48,500 to about 23,600 kg/km^2 per year (Acker et al. 1998). But this was not caused by managed changes in air-pollution control. It was caused solely by the collapse of nearly all industry and agriculture in the former East Germany. From 1991 to 1993, the decrease in SO_2 emissions was smaller for urban areas with no large industrial emission sources (see the trend in Erfurt or Gera, Figure 40). From 1994 to 1998, air-pollution control — including more efficient removal of particulate emissions in power plants, the use of coal with lower sulfur content, the installation of flue-gas desulfurization equipment, and the replacement of coal by natural gas — resulted in a further, though comparatively less spectacular, reduction in emissions. From the end of the 1990s on, no further significant changes in sources of pollution occurred. The year-to-year variation in gaseous air-pollution concentrations in this period was probably driven by local and regional meteorologic conditions rather than by changes in source contributions.

The downward trend in SO_2 concentrations was observed not only in eastern Germany but also in other economies in transition. Hunova and colleagues (2004) reported a statistically significant decrease in SO_2 concentrations at selected rural sites in the Czech Republic, a country neighboring eastern Germany. They explained this trend as having been caused by the combined effects of political and economic changes in the Czech Republic in the early 1990s and of the adoption of new technologies, resulting in remarkable SO_2 decreases.

Annual mean concentrations of CO and PM_{10} were also reduced by more than 50% during the decade under observation (see Figure 39). Like the decrease in SO_2, the decrease in CO and PM_{10} can be traced to the above-mentioned changes in emission sources in eastern Germany. However, insofar as CO concentrations remained stable from 1998 onward, one can speculate that the downward trend was eventually balanced by large increases both in the number of cars and of miles driven. In addition, because CO has a long lifetime of 1 to 3 months and can therefore be transported long distances in the atmosphere, a substantial portion of the CO in Erfurt could have been produced in more polluted areas in eastern Europe and still have contributed to the city's air quality.

A similar downward trend in concentration was observed for PM_{10}. Particulate matter is emitted directly into ambient air as primary particles and is produced in the atmosphere from precursor gases (such as NO_x, SO_2, and ammonia) as secondary particles. The decreasing concentrations of the precursor gases contributed to the decrease in the formation of particulate matter as secondary particles.

Apart from the GSF station at Erfurt, there are only a few monitoring stations in Europe (most are in Great Britain) that measure PM_{10} over longer time periods. These stations, like the GSF station, documented a decreasing trend in PM_{10} concentration during the study period (van Aalst 2002). Spindler and colleagues (2004) reported a decrease in PM_{10} from a maximum value of 39 µg/m^3 in 1996 to a mean of 23 µg/m^3 for 1999–2002 at a monitoring station downwind of Leipzig, Germany. At the same station, no significant changes in PM_{10} concentrations were observed from 1993 to 1995 (Müller 1999).

In contrast to these decreases in SO_2, CO, and PM_{10}, decreases in ambient concentrations of NO and NO_2 were less pronounced. Again, the major political and economic changes in central and eastern European countries after 1990 played key roles in the decrease in emissions and lower ambient concentrations of NO_x. The decrease in NO_x emissions was caused by the modification of combustion conditions and introduction of modern denitrification processes (i.e., selective catalytic and noncatalytic reduction and activated carbon processes). However, the reduction of NO_2 emissions from power plants and other industrial sources was accompanied by increasing NO_x emissions from traffic. Between 1990 and 1993, private transportation by passenger car and transportation of goods by truck increased rapidly in eastern Germany, by 16% and 100%, respectively (Acker et al. 1998). During the same period, the total number of passenger cars increased by 27%, and the number of trucks increased by 133%. In contrast, in western Germany the increase was only 6% for both cars and trucks. Nevertheless, the increase in the percentage of gasoline-powered motor vehicles with catalytic converters compensated somewhat for this increase in numbers.

In contrast to the concentrations of the other primary urban pollutants, O_3 concentrations did not decrease much in spite of reductions in O_3 precursors. As described earlier, O_3 can be formed locally or from transported pollutants;

however, if meteorologic parameters show a high correlation with measured concentrations (as was the case in Erfurt; see *Correlations between Air Pollutants* in *Results*), then O_3 concentrations at the monitoring station were more heavily influenced by local conditions. The flat response in O_3 to decreased NO concentrations suggests that local reductions in O_3 precursors had relatively little effect on O_3 concentrations. Similar observations were made in Switzerland by Kuebler and colleagues (2001).

Because of the data gap for fine particles ($PM_{2.5}$) and ultrafine particles (NCs) between May 1992 and September 1995, comparisons of annual means were only possible for the years 1996–2001. However, comparisons of winter means were possible, including winter 1991/92 as a reference point (see Figure 41). The mean decrease in particulate matter during the winter seasons of the study period was very marked in Erfurt (80% for $PM_{2.5}$ and 70% for PM_{10}). Note that the mean decrease in PM_{10} was greater in winter than for the year as a whole (70% compared with 40%). The trend was similar for $PM_{2.5}$. Unlike PM_{10} data, however, $PM_{2.5}$ data from other monitoring stations in Germany or elsewhere in Europe were available only for time periods that were too short for trends to be detected.

The trends for ultrafine particles were less clear. First, there was a strong increase in ultrafine particles in winter 1995/96 compared with winter 1991/92. This was followed by a period of rather stable concentrations and finally by a considerable decrease in winter 2001/02 (the end of the study period). It should be noted that meteorologic data indicated that wind conditions were unusual during the winters of 1995/96 and 2001/02. Winds at the GSF monitoring station were most often from the north and west (250°–320°) and least often from the south and east (100°–190°). For easterly winds, the monitoring station was downwind of Erfurt's principal roadway. For westerly winds, the influence of the roadway was reduced (see Figure 2). The average ratio of the two wind directions (easterly and westerly) was 0.4 in winter 1991/92 and 1.2 in winter 1995/96. This meant that the monitoring station was downwind of the major roadway much more often in winter 1995/96 than in winter 1991/92, which could have contributed significantly to the extraordinarily high concentrations of ultrafine particles in the period 1995–1996. For the next five winters (1996/97 to 2000/01), the ratio ranged from 0.3 to 0.7 and was thus similar to the ratio for the first winter (0.4). In the final winter of the study period (2001/02), the ratio was unusually low (0.1), which might explain the low concentrations of ultrafine particles measured that winter.

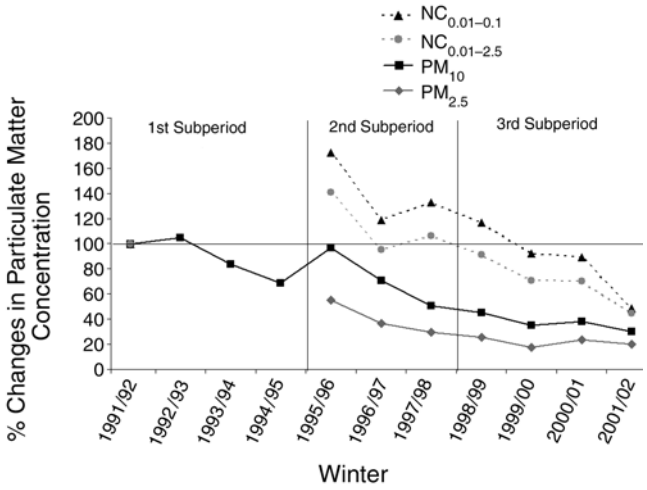

Figure 41. Changes in the mean concentrations of particulate air pollutants in Erfurt in winter from 1991/92 to 2001/02. The mean concentrations for winter 1991/92 are indexed as 100%.

In addition, the vertical temperature difference between the GSF monitoring station and the official German Weather Service station (which is situated approximately 100 m higher than the GSF station) served to detect stationary temperature inversions in the Erfurt basin. The average temperature measured at our station was usually about 1°C higher than the average temperature measured at the weather station. This value is close to the theoretical adiabatic temperature gradient of −1 K/100 m. During inversions, if the temperature difference is < 0 K, vertical air exchange is inhibited, which leads to an accumulation of ultrafine and fine particles from local emissions. On average, the air temperature in Erfurt's higher atmospheric layer was higher than at the ground level for 20% of winter hours. Therefore, it can be assumed that for 20% of winter hours there was a stable inversion. In winter 2001/02, the proportion of hours with inverse temperature conditions was unusually low (8%); this might have contributed to the low concentrations of ultrafine particles that winter.

As a result, the strikingly high concentrations of ultrafine particles in winter 1995/96 and the low concentrations in winter 2000/01 could be considered extreme values attributable to unusual meteorologic conditions and should therefore be excluded from the description of the trend of ultrafine-particle concentrations. The remaining ultrafine-particle concentrations ranged from 130% to 90% of the concentrations measured in winter 1991/92. Fine-particle concentrations ranged from 106% to 70% of the concentrations measured in winter 1991/92. This means that ultrafine particles decreased less than the other air pollutants. Note that within the same time period,

the size distribution of particles in Erfurt shifted strongly toward smaller particles (Kreyling et al. 2003).

In conclusion, Erfurt had some of the worst ambient air pollution in East Germany before reunification. This was not attributable solely to heavy industry but to a rather typical mix of industrial activity, coal-fueled domestic-heating systems, and a fleet of high-emission cars as well as to geographic and meteorologic conditions that frequently trapped the pollutants in inversions. The economic and political changes since reunification have led to changes in the nature of air pollution in eastern Germany as a result of the restructuring and modernization of production systems, the shutdown of inefficient facilities, and the effects of new environmental legislation and regulations.

These changes led to a downward trend in ambient concentrations of all air pollutants. However, the decrease was especially pronounced for historically important air pollutants, such as SO_2 and PM_{10}. As shown in Figures 39 and 41, the pollution mixture in Erfurt changed during the 1990s toward a mixture much like that of urban areas in western Europe. This mixture is characterized by low concentrations of SO_2 and PM_{10} and higher concentrations of NO_x, O_3, and ultrafine particles.

Long-term trends in pollutant concentrations in Erfurt and the effects of changes in emission sources could only be characterized on a descriptive basis. One reason for this was the very high correlations found in several cases between annual mean concentrations of air pollutants and annual mean emissions (e.g., 0.89 between NO and the use of coal for heating and −0.89 between NO and the percentage of cars equipped with a three-way catalytic converter). This made it impossible to identify the emission source with the largest effect on the concentration of a specific air pollutant based only on correlation coefficients. Moreover, the patterns of air-pollution concentrations measured at a single monitoring station (as in Erfurt) are affected not only by local anthropogenic sources but also by long-distance transport of pollutants by wind. As shown by Giannitrapani and colleagues (2006), additional data on wind trajectories could show a statistically significant effect of neighboring countries' emissions on monitored SO_2 concentrations for 6 of 11 stations located across Europe. Other research revealed that the official emission figures for NO_x, CO, and PM could account for only about one-half of all local anthropogenic emissions in, for example, Estonia (Kimmel et al. 2002).

Correlations and Ratios of Ambient Air-Pollution Concentrations in Erfurt

The consideration of correlations and ratios between air pollutants was another possible method of characterizing changes in the sources of air pollution. As with correlation coefficients, the ratios of pollutant concentrations are less dependent on temporal variation in sources and meteorologic conditions than are concentrations of individual pollutants.

In general, correlations between the various air pollutants were rather strong, which supported the hypothesis that the GSF monitoring station could be considered an urban monitoring station located in the immediate vicinity of local sources of air pollutants. It was striking that the correlations in the first subperiod were stronger than those in subsequent subperiods. This indicated that the influence of local emission sources decreased over the study period. A similar pattern could be observed in the differences between correlation coefficients in winter and summer. The generally higher correlations in winter showed the stronger influence of seasonally important emission sources (such as domestic heating), boosted by frequent stationary temperature inversions. As described earlier, atmospheric dispersion is typically at a minimum in winter, when stagnant air masses allow more pollutants to accumulate, causing higher correlations between them.

As expected, the highest correlations were observed between NO, NO_2, CO, and ultrafine particles. These correlations remained strong for all pollutants during the whole study period, except for CO, which supports the hypothesis that these pollutants were traffic-related. In the third subperiod, CO was more weakly associated with the other traffic-related air pollutants (mostly as a result of weaker correlations in summers). This means that the proportion of CO transported long distances from other regions by wind might have been higher in this subperiod and that almost all the CO in the first two subperiods was produced locally.

The distinctly weaker correlation coefficients between NO and NO_2 and between NO and PM_{10} in winter 1995/96 were notable in comparison with adjacent winters. The same could be seen for the associations between CO and the other air pollutants (see *Appendix B*). The weak correlation between these pollutants in winter 1995/96 can probably be traced to the unusually low temperatures in this winter. In winter 1995/96, the mean temperature measured at the German Meteorologic Service station was 0.4°C. The second coldest winter was in 1992/93, with a mean temperature of 2.4°C. The mean temperature for all winter seasons was 3.0°C.

The dramatic decrease in SO_2 concentrations during the 1990s and the resulting lower day-to-day variations in SO_2 led to clearly lower correlations with the other air pollutants in the third subperiod of the study.

The ratios between pollutants yielded additional insight into the characteristics of the sources of air pollution in

Erfurt. It is known that mobile-source emissions are characterized by high CO and NO_x concentrations and that point-source emissions are characterized by high SO_2 and NO_x emissions. As a result, mobile-source emissions typically have high CO/NO_x ratios and low SO_2/NO_x ratios, and point-source emissions typically have lower CO/NO_x ratios and higher SO_2/NO_x ratios (Aneja et al. 2001).

Parrish and colleagues (1991) reported values of 8.4, 7.8, and 10.2 for mobile sources of CO/NO_x in the eastern U.S., the state of Pennsylvania, and the western U.S., respectively. The average CO/NO_x ratio was 16.3 in Raleigh, North Carolina (Aneja et al. 1997), and 50 in New Delhi, India (Aneja et al. 2001). Aneja and colleagues (1997) concluded that a high CO/NO_x ratio (> 7) indicated that mobile sources were dominant and that low ratios (< 1) indicated that point sources were dominant. The high CO/NO_x ratios in Erfurt, then, demonstrated that the pollution mix was dominated by mobile sources. The increase in the annual CO/NO_x averages in the third subperiod showed that the effect of traffic on the pollutant mix increased during the period.

SO_2/NO_x ratios reported for areas dominated by point sources range from 0.44 to 2.3; typical values for areas dominated by mobile sources are about 0.05 (Parrish et al. 1991). From 1995 onward, the SO_2/NO_x ratios measured in Erfurt were always lower than 0.2. This indicated that after 1995, the contribution of point sources to the pollution mix in Erfurt was negligible.

Kimmel and colleagues (2002) estimated the NO/NO_2 ratio at six Estonian monitoring stations. At rural stations, where most of the pollutants measured were not locally produced, the estimated ratios were below 0.1. The ratios at stations close to emission sources were about 1. Kuhlbusch and colleagues (2001) stated that at monitoring stations located close to combustion sources the NO/NO_2 ratio was normally greater than 2 and that, as the distance between the monitoring stations and the combustion sources increased, the ratio decreased because of the oxidation of NO to NO_2. At the monitoring station in Erfurt, the estimated NO/NO_2 ratio was between 0.5 and 1.0 in winters and between 0.3 and 0.5 in summers. However, the NO/NO_2 ratio showed a pronounced diurnal pattern, with the highest values in the morning and the lowest at night. The average NO/NO_2 ratio was about 1 between 7:00 and 9:00 a.m. in winter and 0.8 at 7:00 a.m. and 0.7 at 8:00 a.m. in summer. This showed that during the morning hours the monitoring station was mainly measuring pollutants from sources in the vicinity, i.e., from traffic.

The increases in $PM_{2.5}/PM_{10}$ ratios for the last two years of the study period (2000 and 2001), in both summer and winter, were noteworthy. The increases indicated that the fraction of coarse particles decreased at the end of the study period, supporting our assumption that the composition of Erfurt's air pollutants changed from the eastern toward the western urban mixture (which, again, is characterized by elevated concentrations of NO_x, O_3, and fine and ultrafine particles and lower concentrations of SO_2 and coarse particles).

HEALTH EFFECTS

Regression results pointed to delayed short-term associations of NO_2, CO, and ultrafine particles with all-cause mortality, cardiorespiratory mortality, and cardiovascular mortality with lags of 3 to 4 days. Regression results also pointed to a delayed association of O_3 with all-cause mortality, cardiorespiratory mortality, and cardiovascular mortality with a lag of 2 days. No clear associations were found for $PM_{2.5}$, PM_{10}, or SO_2.

Health Effects and Mortality Risks of NO_2, CO, and Ultrafine Particles

Large multicenter studies in Europe (Samoli et al. 2006), Canada (Burnett et al. 2004), and the United States (Samet et al. 2000b) as well as a comprehensive meta-analysis (Stieb et al. 2002) provided evidence of short-term associations of NO_2 with mortality. A 10-$\mu g/m^3$ increase in NO_2 concentrations (average of lag days 0 and 1 of the 1-hr maxima of NO_2) was significantly associated with a 0.3% increase in daily deaths in Europe. In Canada, a 10-$\mu g/m^3$ increase in the 3-day moving average of NO_2 concentrations was significantly associated with a 0.5% increase in daily deaths. In the U.S., no consistent, significant associations at lag days 0 or 1 were found, but a highly significant association was found at lag day 2, with a magnitude similar to that of the study in Canada (Samet et al. 2000b). According to the meta-analysis by Stieb and colleagues (2002) of 32 studies investigating NO_2 associations with mortality in cities around the world, a 24-ppb increase in NO_2 concentrations was associated with a 2.8% increase in mortality (95% CI, 2.1%–3.5%).

In the present study, no NO_2 association was observed at lag day 0, and the association at lag day 1 had a magnitude similar to that of the study in Canada. In Erfurt, however, NO_2 associations were observed mainly in winter and spring; in Canada they were observed in the warm season. This might be attributable to the differences in sources of NO_2 and in meteorologic conditions in Europe and Canada.

The largest NO_2 associations in this study were observed at lag days 3 and 4. These results were similar to those of an earlier 3.5-year study by Wichmann and colleagues (2000). Samoli and colleagues (2006) reported that

the cumulative effect of NO_2 over 6 days was larger than the immediate effects, which suggested a considerably delayed effect. Because NO_2 and ultrafine particles showed a high correlation in Erfurt, the observed NO_2 association might have been confounded by the association observed for ultrafine particles. Seaton and Dennekamp (2003) also suggested this type of confounding. The association for ultrafine particles was stronger than the association for NO_2. In our two-pollutant model of NO_2 and ultrafine particles ($NC_{0.01–0.1}$), the association of NO_2 weakened. Also, Samoli and colleagues (2006) could not completely rule out the role of NO_2 as a surrogate for other, unmeasured pollutants. No data on ultrafine particles were available in their analysis. After adjustment for particulate matter and O_3, the NMMAPS study (Samet et al. 2000b) in the United States also could not provide evidence of a significant mortality effect of NO_2. Although NO_2 concentrations in Erfurt (annual mean of 35.2 µg/m^3) were low, and below the recommended WHO standard (WHO 2005), mortality effects were nevertheless detected. In agreement with the WHO (2005), we concluded that the NO_2 associations were considerably confounded by ultrafine particles.

The situation for CO seemed to be similar. CO was shown to have statistically significant associations with mortality counts in the United States (Samet et al. 2000b). The associations tended to decrease when adjusted for other pollutants, with the result that there was little evidence of a significant association of CO with mortality (Samet et al. 2000a). Burnett and colleagues (2004) reported a significant 0.68% increase in mortality for a 1.02-ppm increase in CO concentration that was highly sensitive to adjustments for NO_2. In the current study, the strongest CO association was again observed with a lag of 4 days, as in the previous Erfurt study (Wichmann et al. 2000). As with NO_2, there was also a considerable (though somewhat smaller) correlation between CO and ultrafine particles. However, the CO associations were robust in a two-pollutant model with ultrafine particles.

The evidence on associations of ultrafine particles with mortality is limited. Forastiere and colleagues (2005) found a significant 7.6% increase (95% CI, 2.0%–13.6%) in out-of-hospital coronary deaths in Rome, Italy, in association with a 27,790-particles/cm^3 increase in number concentrations of fine particles (which included a substantial ultrafine particle fraction). Previous analyses of data from Erfurt for 1995–1998 indicated associations of ultrafine particles with daily mortality that were independent of associations with fine particles (measured as mass concentration) (Wichmann et al. 2000). Wichmann and colleagues reported that a 12,690-particles/cm^3 increase in number concentrations of ultrafine particles was associated with a 4.5% increase in mortality (lag day 4). One of the aims of the present study was to examine possible associations of particles in various size classes with mortality for a study period extended for an additional three years.

The strongest association between ultrafine particles and daily mortality was observed at lag day 4. The magnitude of this association (2.9% more daily deaths per 9748-particles/cm^3 increase in ultrafine particles [$NC_{0.01–0.1}$]) was somewhat smaller than that in previous analyses using data only for 1995–1998 (Wichmann et al. 2000; Stölzel et al. 2003). However, it was consistent with results from the time-varying models. These showed the largest effect estimates for ultrafine particles, NO_2, and CO in the period 1995–1997, which by chance was about the same time period as that of the earlier Erfurt study by Wichmann and colleagues (2000). The time periods before and after these years showed smaller effect estimates per unit change in the respective air pollutants, based on the time-varying models and the models using an indicator for the three subperiods. All three correlated pollutants showed evidence of linear exposure–response relationships when smoothing techniques were applied, which added to the consistency of the associations.

A number of potential ways in which ultrafine particles could affect the human body have been suggested (Donaldson et al. 2001; Frampton 2001; Kreyling et al. 2004; Schulz et al. 2005): (1) ultrafine particles are biologically more reactive than larger particles, (2) ultrafine particles at the same mass concentration as larger particles have a much higher number concentration and surface area than the larger particles (Oberdörster 2001), (3) inhaled ultrafine particles have a very high deposition efficiency in the respiratory system (International Commission on Radiological Protection 1994), and (4) ultrafine particles have a propensity to penetrate the epithelium, reach interstitial sites, and enter the bloodstream. All of these factors might contribute to the adverse health effects of ultrafine particles observed in humans. It takes time for ultrafine particles to penetrate the epithelium and, in particular, to enter the interstitium, which provides a possible explanation for the delayed effects observed in the present study. Other epidemiologic studies have also showed delayed effects of ultrafine particles. For example, in a study with asthma patients, the cumulative effect of ultrafine particles on decreases in peak expiratory flow was strongest over 5 days (Peters et al. 1997). Medication use in people with asthma also increased in association with cumulative exposure to ultrafine particles over 5 or even 14 days (von Klot et al. 2002). Rückerl and colleagues (2006) observed the largest increases in certain blood

markers in patients with coronary heart disease at a lag of 48 to 71 hours. However, other studies observed immediate associations of ultrafine particles with mortality or morbidity. In Rome, Italy, increased concentrations of particulate matter in which ultrafine particles were the principal component were significantly associated with increases in out-of-hospital coronary deaths on the day of exposure (Forastiere et al. 2005). In five European cities, the risk of readmission to the hospital for myocardial-infarction survivors in association with increased ultrafine particle concentrations was highest on the day of exposure (von Klot et al. 2005).

Health Effects and Mortality Risks of PM_{10} and $PM_{2.5}$

The association between particulate matter and all-cause mortality has been consistently observed (Pope and Dockery 1999; Samet et al. 2000a; Katsouyanni et al. 2001; Health Effects Institute 2003; Dominici et al. 2005). A 10-μg/m^3 increase in the concentration of PM_{10} was associated with a 2.7% increase in mortality in the United States (Dominici et al. 2002) and by a 0.6% increase in Europe (Katsouyanni et al. 2002). In the present study, a 10-μg/m^3 increase in $PM_{2.5}$ (measured as a mass concentration) was associated with a 0.4% increase in daily deaths, which was not significant. However, the magnitude of this risk estimate was within the 95% confidence limit of the 0.6% risk estimate found for PM_{10} in the APHEA study (95% CI, 0.4–0.8, Katsouyanni et al. 2002).

Previous analyses of data from Erfurt, Germany, pointed to independent associations of mortality with concentrations of both fine particles and ultrafine particles (Wichmann et al. 2000). A 19.9-μg/m^3 increase in $PM_{2.5}$ was significantly associated with 3.0% more daily deaths (lag day 0). Time-varying models indicated that, during the 1995–1997 subperiod, positive effect estimates were observed; in the other subperiods, effect estimates were indistinguishable from the null.

Health Effects and Mortality Risks of SO_2

In this study, we did not observe associations of SO_2 with changes in mortality. SO_2 concentrations were very low and often close to the LOD, especially during the last three years of the study period. At such low concentrations, effects of SO_2 on health were not expected. Effects were observed in Erfurt during the 1980s, when SO_2 concentrations were higher by a factor of nearly 100. A 10-μg/m^3 increase in SO_2 was then associated with a 0.11% increase in mortality (lag day 2) (Spix et al. 1993). A study in the 1990s (Wichmann et al. 2000) with much lower SO_2 concentrations observed a 4.3% mortality increase associated with a 10-μg/m^3 increase in SO_2; the magnitude of the risk increase for total suspended particles remained remarkably constant. Time-varying models showed an increase in effect estimates during the period 1995–1997; before 1995, effect estimates alternated around the null. At the end of the study period, concentrations of SO_2 were repeatedly close to or below the LOD, and hence day-to-day variation was extremely low. This was reflected in the extremely wide confidence limits around the time-varying effect estimates. Also, the exposure–response functions estimated by smoothing methods showed no evidence of a linear or other consistent relationship across the concentration ranges observed in Erfurt over the decade. These inconsistencies suggested that SO_2 was not the causal agent. Similarly, no consistent associations between SO_2 and mortality were reported for the Netherlands by Buringh and colleagues (2000).

However, SO_2 was significantly associated with mortality in a study in 12 Canadian cities, with an average concentration of only 5 μg/m^3 (Burnett et al. 2004). In Hong Kong, a major reduction in sulfur content in fuels over a very short period of time showed a substantial reduction in effects on health, such as childhood respiratory disease and all-age mortality outcomes (Hedley et al. 2002). In the United States, the association of SO_2 with mortality observed in univariate models decreased tremendously when adjusted for other pollutants, thus suggesting confounding (Samet et al. 2000b).

Health Effects and Mortality Risks of O_3

Evidence of small but substantial short-term effects of O_3 on mortality came from large multicenter studies in Europe (Gryparis et al. 2004) and the United States (Bell et al. 2004). In Europe, a 10-μg/m^3 increase in maximum 8-hour O_3 concentrations (lag days 1 and 0) was associated with a 0.31% (CI, 0.17%–0.52%) increased all-cause mortality risk, a 0.46% (CI, 0.22%–0.73%) increased cardiovascular mortality risk, and a 1.13% (CI, 0.74%–1.51%) increased respiratory mortality risk in summer, i.e., the O_3 season (Gryparis et al. 2004). In the United States, a 20-μg/m^3 increase in the previous week's O_3 concentrations was associated with a 0.52% (CI, 0.27%–0.77%) increased all-cause mortality risk and a 0.64% (CI, 0.31%–0.98%) increased cardiovascular and respiratory mortality risk (Bell et al. 2004). Results for lag days 0 and 1 were smaller but also statistically significant. The results from both continents, then, are comparable. The O_3 association is unlikely to be confounded by temperature (Schwartz 2005).

These numbers have been largely confirmed in recent meta-analyses (Bell et al. 2005; Ito et al. 2005; Levy et al. 2005). The risk increase associated with a 20-μg/m^3 increase in daily average O_3 concentration was estimated

to be 0.83% (CI, 0.53%–1.12%) by Bell and colleagues (2005), 0.8% (CI, 0.55%–1.0%) by Ito and colleagues (2005), and 0.82% (CI, 0.62%–1.0%) by Levy and colleagues (2005).

The magnitude of the risk estimate per 20-μg/m^3 increase in mean daily O_3 amounted to 1.8% in the present study and was therefore somewhat larger than those of the meta-analyses cited above. The risk estimate was even higher for the maximum 8-hour mean concentration. Like other researchers, we observed slightly higher risk estimates for cardiovascular mortality but not, surprisingly, for respiratory mortality, even though the respiratory tract is more likely to be affected by O_3. In contrast to most other studies, our study found that the O_3 risk was highest in winter, i.e., when O_3 concentrations were lowest. Only a few other studies have reported substantial associations of O_3 with health outcomes in winter (see, for example, Hoek et al. 1997). Time-varying models indicated that the effects of O_3 were observed at the beginning and end of our study period but not between 1995 and 1998. The exposure–response functions suggested a linear relationship between O_3 (lag day 2) and mortality, adding internal consistency to the observed associations.

DO CHANGES IN THE SOURCES OF AIR POLLUTION EXPLAIN THE VARIATION IN MORTALITY RISKS?

Two principal competing factors might explain changes in effect estimates during times of drastic change in pollutant concentrations. The first is that there is a nonlinear exposure–response relationship that might be detected as changes in effect estimates over time as pollutant concentrations change. The second possible factor is that there is a linear exposure–response relationship but that, because the measured pollutant serves as an indicator for changes in sources, source emission, or the air-pollution mixture, associations with daily mortality vary.

We therefore assessed the exposure–response functions and estimated the variation in coefficients over time using time-varying models. The time-varying models revealed some variation in effect estimates, which was reflected in seasonal variation as well as in overall variation of the effect estimates over time. A striking observation was that the effect estimates were largest for ultrafine particles, NO_2, and CO during the period 1995–1997. Also, other pollutants, such as PM and SO_2, that generally did not show strong associations with mortality showed positive effect estimates during this time period, when the change in major fuel sources occurred. Air-pollution concentrations were reduced, but it seems the benefits of the improved air quality had not yet been fully achieved. It was also striking that for O_3 some significant effects were observed during most of subperiods 1 and 3, and no significant effects were observed from 1995 through the end of 1998. O_3 concentrations were at their minimum during stagnant air conditions, when other pollutant concentrations had increased. One might speculate that the air-pollution mix was more reactive, as indicated by low O_3 concentrations in 1995–1997, leading to higher effect estimates during this period.

Plotting annual regression coefficients against indicators of the changes in the characteristics of the sources of air pollution, such as reduced coal use, increased natural-gas use, or changes in the percentage of cars with catalytic converters, might guide the interpretation of our findings. At the end of the study period, when the implementation of air-quality measures was complete, the pollutants were no longer associated with mortality. This observation was consistent with the interpretation that traffic-related pollutants and local combustion products seemed to be most closely associated with increased mortality risk. Positive associations persisted only for ultrafine particles during the final year of the study. When we used changes in the concentrations of other pollutants to try to explain the variations in the effect estimates between ultrafine particles and mortality, we did not find a discernible pattern. Though we observed an increase in effect estimates for ultrafine particles and mortality around the median concentrations of NO_2 and CO, this relationship broke down at concentrations below the 10th percentile and above the 90th.

While it seemed difficult to disentangle the effects of gaseous and particulate pollutants, the study demonstrated several things: First, the effects of the pollutants were variable over time to a much greater extent than generally appreciated. Second, the implementation of measures to improve air quality resulted in reduced risk estimates. Third, the observed patterns indicated a surrogate status for most of the pollutants, as the exposure–response functions were linear, and the concentration changes did not explain the variation in the coefficients. Fourth, results obtained elsewhere around the world might need to be interpreted with respect to the time period considered as well as to the air-quality-control measures in place at the time.

DO CHANGES IN SOCIOECONOMIC FACTORS OR OVERALL HEALTH EXPLAIN THE VARIATION IN MORTALITY RISKS?

The interpretation of temporal changes in morbidity rates in terms of improvements in air quality are often criticized, or at least debated, because changed patterns in other factors might also affect changes in health outcomes (Brunekreef 2002; Heinrich et al. 2002). Assessment of the

health effects of improved air quality in eastern Germany in the 1990s called for a thoughtful discussion of potential cofactors, such as changes in the political system, economy, and society on a large scale.

The reunification of Germany in 1990 was a natural experiment in rapid changes for an entire society. Over the course of a few months, a struggling communist country merged with a country with one of the world's leading capitalist economies. Massive financial injections and the introduction of democratic structures created tremendous social changes. This fundamental transformation in the east led initially to a 49% decline in industrial output over the course of 1990 (Sinn and Sinn 1992). By 1991 the gross national product had fallen by a third, and by the end of 1992 about 3.5 million jobs (35% of the labor force) had been lost. Unemployment rose from almost zero at the beginning of 1990 to 15.4% of the labor force in 1992 (Nolte 2000, Bach et al. 1998). However, after 1992 there was a strong, steady increase in the gross national product and in income levels in eastern Germany as well as a general convergence of the economies of eastern and western Germany (Nolte and McKee 2004). Social and living conditions also changed dramatically. Therefore, it is important not to draw conclusions about the relationships between temporal trends in health and air-pollution concentration changes without considering these important concurrent socioeconomic and political trends.

In time-series studies, the focus is on short-term variations in exposure driven primarily by variations in weather. The number of potential confounders is limited; everything that changes over a time period of less than a couple of weeks is filtered out by smoothing techniques or by the application of linear or nonlinear trend adjustments (Brunekreef 2002). We had no means of determining the extent to which these socioeconomic and political trends have modified the observed exposure and mortality risk relationships. In terms of long-term effects on health, a large study of children in eastern Germany showed decreased respiratory symptoms and increased lung function when air quality was improving (Heinrich et al. 2002; Frye et al. 2003). In addition to changes in medical care, a rapid change in diet, reflecting a greater availability of fruit and vegetable oils, was also discussed as a driving force for improved health after reunification (Nolte and McKee 2004). Repeated dietary surveys before and after reunification (e.g., in 1987–1988 and 1991–1992) showed a very rapid change in diet and in particular a strong increase in the consumption of fruit and fresh vegetables (Winkler et al. 1997). However, these rapid changes were already completed at the beginning of the 1990s, and it seems unlikely that they could account for the transient increase in risk associated with air-pollution exposure in the mid-1990s.

In addition, doubts were raised that the effects of changes in air quality could be disentangled from the changes in several other factors that might contribute to changes in morbidity rates over time. Specifically, it was argued that associations between improvements in respiratory health and the decline in air-pollution concentrations in eastern Germany could have been confounded by other, unmeasured factors (Brunekreef 2002). A recent study on the decline in ambient air-pollution concentrations and changes in respiratory health in Swiss children (Bayer-Oglesby et al. 2005) must be considered. In nine Swiss communities, nearly 10,000 children participated in repeated cross-sectional health assessments between 1992 and 2001. Bayer-Oglesby and colleagues (2005) found a declining prevalence of chronic cough, bronchitis, common cold, nocturnal dry cough, and conjunctivitis symptoms similar to that reported by Heinrich and colleagues (2002). These changes were in line with a reduction in ambient air pollution (PM_{10}). Changes in the prevalence of sneezing during pollen season, asthma, and hay fever were not associated with PM_{10} reductions. Bayer-Oglesby and colleagues concluded that the reduction in air-pollution concentrations contributed to the improved respiratory health of the children. This study is of particular importance because it confirmed previous findings in children in eastern Germany. But, in contrast to eastern Germany, where there was a tremendous decline in air pollution in the 1990s because of political and social changes, Switzerland had had stable political and social systems for many decades (Bayer-Oglesby et al. 2005). The findings of the Swiss study did not support the criticism that the improvements in respiratory health in residents of eastern Germany after reunification were driven mainly by factors other than air pollution. These studies on the long-term effects of air pollution gave us no reason to suppose that factors other than temporal changes in the concentration and composition of air pollution had had a substantial influence on changes in mortality risk in Erfurt. On the other hand, we also could not prove that change in air pollution was the only driving force behind change in mortality effect estimates.

STRENGTHS AND LIMITATIONS

Erfurt is a small city with fewer than 5 deaths per day on average. This limited the statistical power of the present study's analyses. However, because of Erfurt's geography and uniquely long record of air-pollution measurements, the city could nevertheless be studied as a natural experiment

in the transition to modern energy technologies and vehicles and its effects on air pollution and health.

Exposure Assessment

The use of a single monitoring station to measure the various pollutants for the whole city of Erfurt might have proved to be a limitation of the study. However, Cyrys and colleagues (1998) showed that the air measured at the station was representative of the city's air with respect to PM_{10} and sulfate.

Also, the air measured at a station in a carefully chosen site can represent the air of an entire city when the air pollutants have strong spatial correlations, as they do in Erfurt because of the city's geography. As described in *Methods*, Erfurt is surrounded by hills on three sides and is open only to the northwest, where several tall buildings are located. As a result, the rate of air exchange between the city and the surrounding rural areas is reduced on more days than in most other German cities, which leads to more days with increased concentrations of ambient air pollutants. Because ultrafine particles are produced mostly by local traffic, more local spatial variation in ultrafine particles was expected. Concurrent measurements of ultrafine particles at various sites within one city often show good correlations despite differing magnitudes and suggest, again, that a background site might well be able to represent the exposure of the average population to ultrafine particles if the site is carefully chosen (Buzorius et al. 1999; Aalto et al. 2005; Peters et al. 2005). Furthermore, the area of the city of Erfurt, including the surrounding communities incorporated in 1994 (which doubled the city's area), is small, measuring only 21 km from north to south and 22 km from east to west. This doubling might have led to less precise exposure assessments for the inhabitants of the newly incorporated communities. However, about 90% of the inhabitants of Erfurt live within a rectangular area measuring only 5 km by 3 km around the old city center. The study's measurement station was located in this area.

Mortality Data

We compiled a data set of the annual total numbers of deaths for Erfurt. The corresponding annual total numbers of deaths obtained from the Statistical Office of Thuringia exceeded our numbers, usually by around 20%. This was because we excluded all deaths of residents who had died outside of Erfurt.

The number of deaths per 100,000 inhabitants declined; this trend was especially pronounced in the early 1990s. A similar trend was observed for the whole of Germany, with 11.4 deaths per 1,000 inhabitants in 1991 and 10.2 in 2002 (Statistisches Bundesamt Deutschland [Federal Statistical Office Germany] 2005); for the neighboring state of Saxony, which had been part of the former East Germany, with 13.9 deaths per 1,000 inhabitants in 1991 and 11.5 in 2002 (Statistisches Landesamt Sachsen [Statistical Office of the Free State of Saxony] 2005); and for the neighboring state of Hesse, which had been part of West Germany, with 11.3 deaths per 1,000 inhabitants in 1990 and 9.9 in 2002 (Hessisches Statistisches Landesamt [Statistical Office of the State of Hesse] 2005).

There was uncertainty about the classification of some of the deaths as cardiorespiratory or cardiovascular. A nosologic expert's examination of a randomly selected subset of 200 death certificates revealed that the doctors who filled in the certificates tended to get the required order of the immediate, primary, and contributing causes of death wrong. Far fewer errors were made with respect to the actual causes of death (Wichmann et al. 2000). Therefore, the placement of cause-of-death information was ignored. A death was classified as cardiorespiratory, for example, if a cardiorespiratory ICD code appeared at least once on the death certificate, i.e., either as the immediate, the primary, or a contributing cause of death. Cardiovascular deaths were classified in the same way. It is possible that the numbers of deaths classified as cardiorespiratory and cardiovascular were overestimated. According to our classification criteria, around 80% of all natural deaths were attributable to cardiorespiratory causes. The correlation between cardiorespiratory and all-cause mortality was around 0.90.

Many studies on the associations between particulate matter and mortality report higher risk estimates for respiratory or cardiovascular mortality than for all-cause mortality (e.g., Dominici et al. 2005). This pattern was also observed in previous analyses in Erfurt over a shorter time period (Wichmann et al. 2000), especially for respiratory diseases. In the present study, risk estimates for all-cause and cardiorespiratory mortality in association with ultrafine particles were almost identical. As for all-cause mortality, no associations were found between $PM_{2.5}$ or PM_{10} and cause-specific mortality, except for a suggestive association of $PM_{2.5}$ with respiratory mortality that was not statistically significant. Two reasons might explain the observed equality of the risk estimates for all-cause mortality and cardiorespiratory mortality: (1) overestimation of the fraction of cardiorespiratory mortality in all-cause mortality, as discussed earlier, and (2) the overlap in the large CIs for the risk estimates for all-cause and cause-specific mortality, such that no difference between the estimates could be detected.

When the analysis was restricted to cardiovascular mortality, the risk estimate for ultrafine particles was somewhat increased compared with all-cause mortality. This increase seemed to be caused by an increase in cardiovascular mortality, an observation similar to that reported in many studies of particulate matter (Clancy et al. 2002; Zeka et al. 2005; Ostro et al. 2006).

Statistical Modeling

In the present study, models were built according to the principles of the APHEA study (Touloumi et al. 2004). Confounders were smoothed using penalized splines instead of the LOESS smoothers used by Wichmann and colleagues (2000) and Stölzel and colleagues (2003). This was done because of recent concerns about biased estimates of the standard errors when using LOESS smoothers in the statistical software package S-plus in the presence of concurvity (Ramsay et al. 2003). Our results were internally consistent and agreed qualitatively with ultrafine-particle results from previous analyses (Wichmann et al. 2000; Stölzel et al. 2003), despite the slightly different modeling strategy described above. The confidence limits for the RR estimates were somewhat smaller because of the larger amount of data.

Additional sensitivity analyses indicated that the final model tested seemed to be conservative and stable with respect to the choice of parameters. The model ultimately chosen was the one that fitted the data best, in terms of the Akaike information criterion and the autocorrelation of error terms. The process of selecting the model was purposely conducted without including the air pollutants in the model. This strategy had three advantages: (1) it did not favor one air pollutant over another, because air-pollutants have different seasonal patterns and different correlations with weather; (2) it allowed for blind model building, as the investigators were unaware of changes in air-pollution estimates; and (3) it reduced the number of tests, as the model-building process was strictly separated from the estimation of air-pollution effects.

Missing data for PM_{10}, $PM_{2.5}$, and ultrafine particles were imputed using concurrent measurements made by particle-measurement devices other than the primary device. We conducted sensitivity analyses comparing regression analyses using the imputed data and the original data and found no substantial differences between the results. However, to assess the effect of this process correctly, measurement-error models considering the imputation procedures would be needed.

In the present study, five models were chosen for fitting time-varying coefficients and were tested in simulation studies. Based on the results of the simulations, we selected the fully Bayesian time-varying coefficient model with P-splines (Model B) as the best model for the applications. The model performed quite well in terms of RMSE and of bias (data not shown) and especially outperformed the model using local likelihood smoothing (Model B) and the two models based on truncated power series (Models A and C). Nearly comparable results were obtained with a model using Bayesian P-splines based on empirical Bayes inference (Model D). This might have been expected, as Eilers and Marx (2004), among others, have shown that P-splines have better numerical properties than splines based on truncated power series.

Based on the simulation results, the coverage of point-wise credible intervals obtained with the fully Bayesian model (Model B) was investigated. Empirical coverage probabilities were calculated, meaning that relative frequencies were calculated, which showed how often the true simulated functions were covered by the credible intervals of the corresponding estimates. Considering the coverage properties of point-wise credible intervals for a nominal level of 95%, average coverage rates were always at least slightly above the nominal level, ranging from 95.2% to 98%. This indicated that the fully Bayesian approach yielded rather conservative credible intervals, an observation already made for other Bayesian applications (see, for example, Fahrmeir et al. 2004 or Lang and Brezger 2004).

Model B, the fully Bayesian time-varying coefficient model, extended previous work. Chiogna and Gaetan 2002 applied a dynamic generalized linear model based on a likelihood analysis using the iteratively reweighted Kalman filter and smoother. They allowed the effect of air pollution to change, in principle, freely over time; but to enforce smoothness of this time-varying effect, the amount by which it could change was restricted by constraining it to follow a first-order random walk. Lee and Shaddick (2005) replaced the assumption of a first-order random walk with an autoregressive process of higher order and based their inference on Markov chain Monte Carlo simulation methods. The Bayesian time-varying coefficient models with P-splines used in the present study extended both previous approaches.

Additional advantages of the fully Bayesian model were that the shape of the time-varying effect was determined by the data and not by a parametric form assumed a priori by the investigators. The model furthermore allowed for the inclusion of the uncertainty associated with the smoothing parameters, leading to more realistic estimates of the variability in the effects of air pollution. This resulted in generally wider Bayesian credible intervals. Additionally, the Bayesian models enabled further

investigation of possible nonlinear relationships with other co-pollutants.

Computationally, the fully Bayesian model was demanding, and there were issues related to determining whether or not the Markov chain Monte Carlo simulations had properly converged. Another limitation of the fully Bayesian models was the assumption of global variances for each function, corresponding to inverse global smoothing parameters. This assumption might have been inappropriate in functions with rapidly varying curvature. The results of the simulation studies showed that in these scenarios estimation performed well in terms of RMSEs but showed larger bias as the Bayesian methods estimated much smoother curves (data not shown). Thus, an alternative might be to replace the global variances with locally adaptive variances (or smoothing parameters) to improve the estimation of rapidly varying functions. Another possibility might be to increase the number of knots.

In a sensitivity analysis, the results of the fully Bayesian approach were compared with those obtained by using Bayesian P-splines based on empirical Bayes inference. In these models, questions about the convergence of Markov chain Monte Carlo samples or sensitivity to hyperparameters did not arise. The results showed very good agreement.

Additional sensitivity analyses using different knot specifications as well as different specifications for the hyperparameters indicated that Model B seemed to be conservative and stable.

A comparison with the results of estimating a different effect of air pollution for each year showed good agreement. In principle, this simple approach, which is equivalent to constraining the air-pollution effect to step functions, could have been used. However, a step function is not an ideal model, as it is implausible that the effects of air pollution are constant for a year and then make a discontinuous jump at the end of each year.

It should be noted that there were some severe limitations in the study in interpreting trends and variations in the short-term effects of air pollutants. These include power limitations caused by the small population size. Because there were only five deaths per day on average, the power for statistical analyses was limited, and therefore the assessment of time-varying air-pollution effects was a challenging task. A further limitation was the lack of a formal significance test to assess the strength of evidence for any change over time. To get a clear indication whether the time-varying coefficient approach in the applications was really necessary, a test of the fixed-parameter hypothesis against a time-varying coefficient alternative is called for. In principle, such a test would be based on a likelihood ratio test statistic. However, in contrast to parametric models, where the likelihood ratio statistic asymptotically follows an χ^2 distribution, the analytic form of the null distribution of an appropriate test for time-varying applications is hard to find, and therefore bootstrap procedures have to be adopted (see, for example, Fahrmeir and Mayer 2001). An implementation and assessment of the properties of such a bootstrap procedure is underway.

We regard the results obtained from the Erfurt data as reliable, despite these limitations, and have found no evidence for inconsistencies in sensitivity analyses. The results indicated that the effect estimates can be highly variable over time. In particular, we tried to estimate seasonal differences based on varying coefficient models but found that these models reflected subtle variations in season onset and progression from year to year over the 11-year period. These variations might have been caused by a combination of residual confounding and statistical variation in a nonstationary Poisson process. Because of the limited power of the study, we also did not extend the varying coefficient models to interactions with higher dimensions.

Finally, power considerations within the time-varying effects framework were challenging and, to our knowledge, have not been addressed in the literature. Calculation of the optimal sample size must be based on simulations, a task for future research.

CONCLUSIONS

Economic and political changes and the adoption of new technologies in eastern Germany have resulted in clear improvements in ambient air quality. Urban air pollution in the city of Erfurt changed within one decade from the mixture formerly characteristic of Eastern Bloc countries to that of western Europe, with high concentrations of NO_x, O_3, and ultrafine particles and low concentrations of SO_2, $PM_{2.5}$, and PM_{10}.

Regression results pointed to associations of ultrafine particles and of the gaseous pollutants NO_2 and CO with an increased number of daily deaths (lag days 3 and 4). All three pollutants can be considered to be markers of local combustion, in particular combustion from mobile sources. Specifically, the consistent effects observed for the relatively short-lived ultrafine particles—especially for particles in the 0.01 to 0.05 μm size ranges—point to the role of local combustion. Regression coefficients revealed variation over time for ultrafine particles, NO_2, CO, and O_3 that could not be explained by nonlinearity in the exposure–response functions. The highest mortality risks were observed in the transition period 1995–1997, when changes in the sources of air pollution took place and the benefits of improved air quality had not yet been completely achieved. Effects on health were lower at the end of

the 1990s than during the 1990s, except for effects associated with O_3.

The Bayesian time-varying coefficient framework presented in this study provides a valuable addition to the existing methodology for gaining insight into the temporal features of air-pollution time-series data. Additional epidemiologic research suggested by the results of this study would involve a comparison with larger communities and in communities in which the amount and type of air pollution did not change, so that the effect modification of risk over time could be tested with more power. As only limited information can be obtained from a single city and it is difficult to identify the temporal confounders of risk clearly, the Bayesian time-varying coefficient models could be extended to incorporate multiple-city temporal-risk models. The methodology presented here can also be used to further investigate possible nonlinear relationships with other co-pollutants.

Despite the limitations caused by the low number of daily deaths in Erfurt, the study might indicate that new combustion technologies can reduce air-pollution emissions and help improve human health.

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APPENDIX A: HEI Quality-Assurance Report

The conduct of this study was subject to periodic, independent quality-assurance audits by a team from Hoover Consultants. The team consisted of auditors with experience in toxicology, epidemiology, and air-quality data and instrumentation. The audits included in-process monitoring of study activities for conformance to the study protocol and examination of records and supporting data. The audits are presented below by date of each audit along with the phase of the study examined.

Written reports of each inspection were provided to the Director of Science of the Health Effects Institute, who transmitted the findings to the Principal Investigator. The audits demonstrated that the study was conducted by experienced professionals in accordance with the original study protocal. The report appears to be an accurate representation of the study.

DATE AND PHASE OF STUDY AUDITED

June 28–30, 2004

Data for mortality, air-quality parameters, and meteorology were audited. Personnel qualifications and experience were discussed. An audit of 300 death certificates was conducted (1.6% sample) for comparison with the electronic files for 47 different variables (14,100 data points). Air-quality monitoring data parameters in the final SAS air data set were audited for all criteria gases and $PM_{2.5}$ for two, one day from early in the study and one day from the last two years.

Data files used in this audit were the most basic level of data available on-site in Erfurt. These data were compared to the data in the investigators' final SAS data set. (SAS is a statistical software package by SAS Institute Inc., Cary, N.C., USA.) Validation of the construction of the database was examined. Methods used for the imputation of mass size for $PM_{2.5}$ were examined.

However, when local meteorology data from the GSF station were examined, some of the gaseous pollutant data were in the same files and some questionable data were serendipitously identified. Meteorology data from both the GSF station and the German Weather Service (Deutscher Wetterdienst) station were reviewed for wind speed and temperature, as these parameters are inversion indicators. (The meteorology data used in the study were entirely from the meteorology station.)

June 21–22, 2007

An audit of 100% of the numbers appearing in the report tables was conducted against electronic files available at the GSF station using S-Plus, R, and SAS databases. Original data from this study have been audited previously.

Many of the values appearing in the text were compared with the numbers in the study records and/or data tables. Data tables in the study records were compared with those in the report. As time permitted, figures were compared with the data. Spot checks of the spreadsheet of air pollution data (e.g., correlations and imputations based on linear regression) were made, and statements about these data were compared with the text of the report.

When a potential discrepancy in a set of records was identified, it was discussed with study personnel.

B. Kristin Hoover

Hoover Consultants

APPENDICES AVAILABLE ON THE WEB

The following appendices are available on the HEI Web site at *www.healtheffects.org* or upon request by contacting the Health Effects Institute at 101 Federal Street, Suite 500, Boston MA 02110, +1-617-488-2300, fax +1-617-488-2335, or email (*pubs@healtheffects.org*). Please give (1) the first author, full title, and number of the Research Report and (2) the title of the appendix or appendices requested.

Appendix B. Correlations and Ratios Between Pollutants on an Annual Basis

Appendix C. Sensitivity Analyses of Other Pollutants

Appendix D. Time-Varying Models and Cause-Specific Mortality

Appendix E. Additional Sensitivity Analyses for Time-Varying Models

ABOUT THE AUTHORS

Annette Peters is a senior scientist leading the Air Pollution Health Effects working unit at the Institute of Epidemiology of the Helmholtz Zentrum München–German Research Center for Environmental Health in Neuherberg, Germany. In addition, she is an assistant professor (Privatdozent) at Ludwig-Maximilians-Universität München, in Germany. She received her doctoral degree from Ludwig-Maximilians-Universität München and a master's degree in epidemiology from the Harvard School of Public Health in Boston, Massachusetts. Her research focuses on the health effects of ambient air pollution. She has pioneered work on the cardiovascular health effects of particles and the health effects of ultrafine particles. She has received the American Thoracic Society David Bates Award for outstanding young scientists.

Susanne Breitner is a postdoctoral research fellow at the Institute of Epidemiology of the Helmholtz Zentrum München–German Research Center for Environmental Health in Neuherberg, Germany. She finished her Ph.D. in 2007 at the Department of Statistics at Ludwig-Maximilians-Universität München, in Germany, where she studied statistics with a focus on biometrics and stochastics. Her research interests include time-varying coefficient models and their use in modeling the effects of fine and ultrafine particles on health as well as measurement errors in air-pollution exposure measurements.

Josef Cyrys is a scientist at the Institute of Epidemiology of the Helmholtz Zentrum München–German Research Center for Environmental Health in Neuherberg, Germany. He studied chemistry at Ludwig-Maximilians-Universität München, in Germany, and received his Ph.D. from the agriculture faculty of the Technical University of Munich. At the Institute of Epidemiology he is responsible for exposure assessment, including developing and validating sampling strategies for determining short- and long-term exposures of study populations to various gaseous and particulate air pollutants. Since 1998 he has supervised the GSF air pollution monitoring station in Erfurt and, since 2001, the monitoring station in Augsburg.

Matthias Stölzel is a postdoctoral research fellow at the Institute of Epidemiology of the Helmholtz Zentrum München–German Research Center for Environmental Health in Neuherberg, Germany. He studied mathematics with a focus on mathematical statistics at the University of Mining and Technology in Freiberg, Germany. He received a doctoral degree in epidemiology from Ludwig-Maximilians-Universität München, in Germany. His research focuses on the source apportionment and short-term health effects of particulate matter.

Mike Pitz studied environmental engineering and medical technology at the University of Applied Sciences in Jena, Germany. Since 1998 he has been an engineer at the Institute of Epidemiology of the Helmholtz Zentrum München–German Research Center for Environmental Health in Neuherberg, Germany. He is responsible for the technical coordination and supervision of indoor and outdoor measurements of air pollutants, for the development and implementation of standard operating procedures and other quality-assurance standards, and for data management and analysis.

Gabriele Wölke received a degree in sociology from the University of Berlin, in Germany. Later she specialized in medical sociology, in which she received her degree in 1985. Her working experience includes eight years as a sociologist at the Forschungszentrum des Binnenhandels Berlin (Research Center for Domestic Trade), Erfurt office, and 11 years as a scientist at the Institute for Environmental Hygiene in Erfurt, where she was involved in projects analyzing the effects of smog and noise. In 1991, she began working with Erich Wichmann at the University of Wuppertal in Wuppertal, Germany. Among other projects, she has been involved in the investigation of short-term effects of air pollution. From 1996, she was employed at the Ludwig-Maximilians-Universität München–Institute of Medical Data Management, Biometrics, and Epidemiology Chair (LMU-IBE), of Epidemiology, working with Dr. Wichmann's group on indoor radon studies and the investigation of short-term effects of ambient air pollution on mortality and morbidity. Since

2001, she has worked for the Institute of Epidemiology, where she has been involved in studies on asthma and allergies as well as in genetic studies on lung cancer and atrial fibrillation.

Joachim Heinrich studied mathematics at the University of Jena in Jena, Germany. He has also had special training in biomathematics. Afterward, he began working at the Medical School of Erfurt in the fields of cardiovascular and nutritional epidemiology. He then worked in the department of labor safety and environmental medicine at the University of Wuppertal in Wuppertal, Germany, where he established an epidemiologic research unit in eastern Germany, including a measurement station for ambient particles. His main research interests are related to air-pollution epidemiology (short- and long-term effects), nutrition, and the epidemiology of asthma.

Wolfgang Kreyling studied physics at Johann Wolfgang Goethe University in Frankfurt, Germany, and received a M.Sc. in physics at Ludwig-Maximilians-Universität München, in Germany. After obtaining his Ph.D. from the Technical University of Munich, he joined the Institute for Radiation Protection. His main research interests are aerosol biophysics, respiratory cell biology, and the interaction of inhaled particles with fluids, cells, and tissues of the respiratory tract of humans and various animal species. In 1987, Dr. Kreyling joined the newly founded Projekt Inhalation, which became the current Institute for Inhalation Biology in 1994. He broadened his research to include particle–lung interactions associated with exposure to sulfur-related air pollutants and, more recently, with exposure to ultrafine surrogate particles. For the present study, he supervised the ambient air measurements at Erfurt.

Helmut Küchenhoff is a professor and the head of the statistical consulting unit of the Department of Statistics at Ludwig-Maximilians-Universität München, in Germany. After studying mathematics in Zürich, Switzerland, he earned his doctoral degree in statistics at Ludwig-Maximilians-Universität München. His main research interests are regression models with measurement error and misclassification. Other issues of research relate to assessment of threshold limiting values for health effects. He has been a consultant in many epidemiologic and other research projects at Ludwig-Maximilians-Universität München.

H.-Erich Wichmann is a professor and the chairman of the Department of Epidemiology at Ludwig-Maximilians-Universität München, in Germany. He is also the director of the Institute of Epidemiology at the Helmholtz Zentrum München–German Research Center for Environmental Health. He received his doctoral degree in physics and his medical degree from the University of Düsseldorf in Düsseldorf, Germany. His research has focused on environmental and occupational agents; currently, it ranges from allergy development in newborn infants and children to chronic diseases in older persons. His principal focus is on the application of molecular and genetic tools in epidemiologic studies.

OTHER PUBLICATIONS RESULTING FROM THIS RESEARCH

Breitner S. 2007. Time-Varying Coefficient Models and Measurement Error [dissertation]. Ludwig-Maximilians-Universität München, Munich, Germany.

Breitner S, Stölzel M, Cyrys J, Pitz M, Wölke G, Kreyling W, Küchenhoff H, Heinrich J, Wichmann HE, Peters A. 2008. Short-term mortality rates during a decade of improved air quality in Erfurt, Germany. Environ Health Perspect doi: 10.1289/ehp.11711. [Available online October 7, 2008.]

Stölzel M, Breitner S, Cyrys J, Pitz M, Wölke G, Kreyling W, Heinrich J, Wichmann HE, Peters A. 2007. Daily mortality and particulate matter in different size classes in Erfurt, Germany. J Expo Sci Environ Epidemiol 17(5):458–467.

ABBREVIATIONS AND OTHER TERMS

AIC	Akaike information criterion
CI	confidence interval
CO	carbon monoxide
CPC	condensation particle counter
DDR	Deutsche Demokratische Republik
df	degrees of freedom
DMPS	differential mobility particle sizer
GAM	generalized additive model
GSF	National Research Center for Environment and Health (Germany)
HI	Harvard impactor
ICD-9	*International Classification of Diseases*, 9th Revision
ICD-10	*International Classification of Diseases*, 10th Revision
imp	imputed time series
IQR	interquartile range
IWLS	iteratively weighted least squares

LOD	limit of detection
LOESS	locally weighted smoothing scatterplot
MAS	mobile aerosol spectrometer
MC	mass concentration
NAAQS	National Ambient Air Quality Standards (U.S.)
NC	number concentration
NO	nitric oxide
NO_2	nitrogen dioxide
O_3	ozone
PM	particulate matter
$PM_{2.5}$	PM with aerodynamic diameter $\leq$ 2.5 μm
PM_{10}	PM with aerodynamic diameter $\leq$ 10.0 μm
P-spline	penalized spline
REML	restricted log-likelihood
REPL	restricted pseudolikelihood
RMSE	root mean squared error
RR	relative risk
SD	standard deviation
SO_2	sulfur dioxide
SMPS	scanning mobility particle sizer
TSP	total suspended particles
TVCM	time-varying coefficient model
UFP	ultrafine particles
EPA	Environmental Protection Agency (U.S.)
VOC	volatile organic compound
WHO	World Health Organization

COMMENTARY
Health Review Committee

HEI

Research Report 137, *The Influence of Improved Air Quality on Mortality Risks in Erfurt, Germany,* A. Peters et al.

INTRODUCTION

The Accountability Research program of the Health Effects Institute (HEI*) aims to assess the effects of environmental regulatory policies and interventions in terms of their success in reducing exposure to air pollution and in improving or protecting public health. As part of the Winter 2002 Research Agenda, HEI issued Request for Applications (RFA) 02-1, "Measuring the Health Impacts of Actions That Improve Air Quality." This RFA solicited research proposals that focused on "real world experiments or measurement of the health impact of planned or unplanned actions that improve air quality."

In response to the RFA, Dr. Annette Peters of the GSF–National Research Center for Environment and Health (now known as the Helmholtz Zentrum München–German Research Center for Environmental Health), in Neuherberg, Germany, submitted an application that proposed to make use of existing data on air quality (daily measurements beginning in 1990) and on mortality obtained during the post-reunification period in Erfurt, Germany. Erfurt is a city in the German state of Thuringia, one of five states in the former Deutsche Demokratische Republik (DDR), or East Germany. When East and West Germany were reunified, in October 1990, the city of Erfurt underwent rapid changes in its economy and energy-use patterns as a result of new, stricter environmental controls and the modernization of industry, transportation, and household heating. The resulting changes in pollution sources and emissions affected ambient air quality (pollutant concentrations and mixtures) and, in turn, population exposures.

The availability of both daily mortality data and daily air-pollution monitoring data made it possible to analyze changes in mortality with respect to changes in pollutant concentrations over time using a time-series study design. A time-series study estimates the changes in daily mortality risk associated with specified incremental changes in pollutant concentrations. Dr. Peters and her colleagues proposed to use time-varying coefficient models to explore how associations between mortality and air quality changed over the course of the time period studied. Time-varying coefficient models had been used in fields that use statistics intensively, such as economics, to model phenomena that vary over time (e.g., changes in actuarial risks over time and variability in investment risks given the fluctuating behavior of stock markets) but had not been used in environmental epidemiology.

Dr. Peters' initial application also included a proposed study of repeated measures of biomarkers of inflammation associated with cardiovascular disease. HEI's Health Research Committee asked Dr. Peters for a revised application omitting the biomarker study because of the expense and uncertainty of the methods. The committee also asked her to include a biostatistician in the time-series study team and to provide more specific details about her data-analysis plan. Dr. Peters and her team submitted a revised application that addressed these concerns, and the Research Committee recommended it for funding. The Influence of Improved Air Quality on Mortality Risks in Erfurt, Germany, by Dr. Peters and colleagues, is the first of seven accountability-research reports to be funded through RFA 02-1 and published by HEI.

SCIENTIFIC BACKGROUND

TIME-SERIES STUDIES

Daily time-series studies have rarely been used to assess the health effects of changes in pollutant exposure resulting from an intervention. Recently, however, several studies have used time-series methods to investigate changes in health effects over time, including studies in the United States (Dominici 2007) and Canada (Burnett 2005). The time-series design allows investigators to estimate the relative risks of daily mortality associated with

Dr. Peters' 3-year study, "Improved Air Quality and Its Influences on Short-Term Health Effects in Erfurt, Eastern Germany," began in February 2003. Total expenditures were $346,294. The draft Investigators' Report from Peters and colleagues was received for review in July 2006. A revised report, received in January 2007, was accepted for publication in February 2007. During the review process, the HEI Health Review Committee and the investigators had the opportunity to exchange comments and to clarify issues in both the Investigators' Report and in Review Committee's Commentary.

* A list of abbreviations and other terms appears at the end of the Investigators' Report.

increments in pollution concentrations. Trends in time-series coefficients point to changes in the unit toxicity (the change in mortality or another health outcome per fixed incremental increase or decrease of exposure) of a given pollution mixture for a given population, provided that the methods of measuring the population's exposure do not change over the measuring period.

A previous HEI-funded study, in which Dr. Peters participated, made use of the time-series study design to analyze data on pollution and cardiovascular and respiratory mortality from September 1995 to December 1998 in Erfurt (Wichmann et al. 2000). Wichmann's team investigated the relationships between mortality and exposure concentrations measured 1 to 5 days prior to death (daily lag days) and exposure concentrations mathematically combined across the 5 days prior to death (distributed lag). Results for the relative risk (RR) of all-cause mortality per interquartile-range (IQR) increase in the concentrations studied are shown in Commentary Table 1.

Dr. Mattias Stölzel, with assistance from Dr. Peters, conducted a revised time-series study of daily mortality and ambient air pollution in Erfurt using the same exposure data as Wichmann and colleagues. This reanalysis explored the effect of applying stricter convergence criteria when using S-Plus statistical software for generalized additive models and was published as part of HEI's Special Report *Revised Analyses of Time-Series Studies of Air Pollution and Health* (HEI 2003). Stölzel's results for all-cause mortality were fully consistent with the results of Wichmann and colleagues from the earlier Erfurt study for all pollutants of interest and thus are not shown.

Commentary Table 1. All-Cause Mortality Results in Erfurt, Germany as reported by Wichmann et al. (2000)[a]

Pollutant	Lag (Days)	IQR for Pollutant Concentration	Percent Change in RR of Mortality per IQR (95% CI)
Ultrafine particles	4	12,690 (particles/cm^3)	4.6 (−0.3 to 9.7)
$PM_{2.5}$	3	18.5 (μg/m^3)	−0.3 (−5.9 to 0.0)
PM_{10}	0	27.7 (μg/m^3)	3.5 (0.1 to 6.9)
CO	4	0.5 (mg/m^3)	1.9 (0.3 to 11.0)
NO_2	3	20.0 (μg/m^3)	2.9 (−0.8 to 6.7)
SO_2	0	14.3 (μg/m^3)	6.0 (1.1 to 11.2)

[a] Data from the initial HEI-funded time series study of mortality and pollutant exposures in Erfurt, Germany (Wichmann et al. 2000). Ozone exposure risks were not analyzed in this study.

[b] IQR indicates interqartile range; RR, relative risk; and CI, confidence interval.

In the current study, Peters and colleagues examined the changes in concentrations of other pollutants of importance: sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), ozone (O_3), particulate matter (PM) with aerodynamic diameter less than or equal to 10 μm (PM_{10}), PM with aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$ or fine particles), and PM with aerodynamic diameter less than or equal to 0.1 μm (ultrafine particles). Daily measurements of these pollutants were available in Erfurt for most or all of the study period. These pollutants are included because of their known associations with daily mortality, their relationships to the various sources of pollutant emissions discussed in the study, and their possible correlations and interactions with fine-particle pollutant concentrations.

TIME-VARYING COEFFICIENT MODELS

Rather than repeat the time-series study for Erfurt by Wichmann and colleagues, with mortality data and exposure measurements from 1991 to 2002, the current study used time-varying coefficient models to provide a running assessment of the effects of the changing mixture of pollutants and overall pollution concentrations and of the associated risk of mortality. Introduced by Hastie and Tibshirani in 1993, time-varying coefficient models are used wherever it is desirable to track variations in the probability of events over time in concert with other time-dependent variables. Such models are used by insurance companies, economists, and stock-market analysts, for example, as well as by those interested in tracking time-varying risks for public-health purposes. When used for public-health studies, the methods used in time-varying coefficient modeling differ from those of time-series studies in that they estimate how the risk of mortality for a given increment of concentration changes over time, instead of simply calculating a summary RR for the entire period. Tracking changes in mortality risks of air-pollution exposure over time also allows for an assessment of the influence of cultural, social, economic, energy-use, and atmospheric factors that changed as air-pollution concentrations declined in Erfurt during the study period.

PREVIOUS ACCOUNTABILITY STUDIES

The most direct evaluations of the effect of a pollution-control measure on the health of a population consider how health-outcome rates compare before and after the control measure is put in place. All intervention studies encounter problems in evaluating changes in the health of a population that are associated with changes in the concentrations

and nature of ambient air pollution resulting from the intervention. These problems become much more severe if the changes in air pollution caused by the intervention are gradual, because changes in health outcomes that accompany gradual changes in pollutant concentrations can also result from concurrent changes in social, economic, and other factors. For this reason, the most convincing accountability studies to date have been those that evaluated a discrete, stepwise change in pollution. When HEI was first considering the Peters application, the most important time-series pollution studies known or underway were of daily mortality before and after a regulatory order forcing the removal of sulfur from motor fuel in Hong Kong (Hedley et al. 2002); a ban on coal sales in Dublin, Ireland (Clancy et al. 2002); and the shutdown of a smelter during a strike in Utah (Pope 2007). These studies are summarized in Commentary Table 2; although they examined changes over time, none used a time-series study design to evaluate the effects of the changes.

STUDIES IN THE LITERATURE

Unlike the earlier studies, the current study by Dr. Peters and colleagues could not use a stepwise analysis because of the complex timing and nature of the changes in Erfurt during the 1990s. Three of Erfurt's four coal-fired electric-power generating plants were shut down between 1990 and 1993 (Ebelt et al. 2001), and the remaining plant was retrofitted to burn natural gas in May 1996. With improving natural-gas supply and distribution in Erfurt after reunification, residents replaced stoves burning local high-sulfur brown coal with modern natural-gas heating systems. As in other areas of the former East Germany, obsolete industrial complexes were shut down, further

Commentary Table 2. Summary of Key Air-Pollution Interventions and Health Outcomes

Investigators	Intervention Scenario	Objective	Study Design	Key Findings
Pope, Rodermund, Gee	Closure of a Utah smelter during a labor dispute, July 15, 1967, to early April 1968. The closure removed approximately 90% of sulphate emissions in the airshed.	Retrospectively compare mortality rates before, during, and after the labor dispute (mortality data for years 1960–1975).	Poisson regression model that controlled for time trends, mortality counts in bordering states, and nationwide death counts for influenza and pneumonia, cardiovascular, and other respiratory deaths.	The estimated strike-related decrease in mortality was 2.5% (95% CI, 1.1% to 4.0%).
Clancy, Goodman, Sinclair, Dockery	September 1, 1990, implementation of a ban on sales of coal in Dublin, Ireland.	Assess effect of the coal ban on particulate pollution and death rates in Dublin	Concentrations of air pollution and directly standardized nontrauma, respiratory, and cardiovascular death rates were compared for 72 months before and after the ban.	Average black smoke concentrations in Dublin declined by 35.6 $\mu g/m^3$ (70%) after the ban. Adjusted nontrauma death rates decreased by 5.7% (95% CI, 4% to 7%) $P < 0.0001$.
Hedley, Wong, Thach, Ma, Lam, Anderson	July 1990 implementation of strict limits on sulfur content of fuel oil used in power plants and road vehicles in Hong Kong.	Compare monthly mortality before and after the advent of sulfur-restriction regulations.	Poisson regression model of monthly mortality rates between 1985 and 1995. Changes in seasonal deaths rates immediately after the intervention were measured by the increase in deaths from warm to cool season.	The intervention led to a significant decline in the average annual trend in deaths from all causes (2.1%; $P = 0.001$).

reducing brown-coal use in the region. The resulting reduction in emissions from coal burning was expected to reduce the burden of associated health effects on Erfurt's population and potentially to result in lower death rates.

Erfurt's aging diesel-truck fleet was steadily modernized with replacement lower-emissions vehicles during the post-reunification period, although increased demand for consumer goods resulted in increased numbers of trucks and more truck traffic overall. Similarly, high-emission cars from the Soviet era, many with two-stroke engines, were scrapped in favor of modern cars with three-way catalytic converters. Car ownership and use expanded during the study period, while emissions from industry sources declined. Changes in fuel use and vehicle fleets are described in Figures 14 and 15 of the Investigators' Report.

Clancy and colleagues (2002), Hedley and colleagues (2002), and Pope and colleagues (2007) compared daily exposure concentrations and mortality before and after an abrupt regulatory event or labor action. Dr. Peters and her colleagues used time-varying coefficient models to track fluctuations in the RR of daily mortality per unit of pollutant exposure over the study period, examining whether there is epidemiologic evidence that toxicity per unit of exposure had changed as a result of changes in the sources over time. If the changes had reduced pollutant concentrations but not pollutant toxicity, health would benefit, but the RR of an adverse health event per unit of exposure would not change. In Erfurt, such changes in toxicity were a plausible outcome because of the tremendous changes in the mixture of air-pollution sources and the characteristics of air pollution during the study period.

SPECIFIC AIMS AND METHODS

SPECIFIC AIMS

The investigators pursued the following specific aims:

1. (a) To relate ambient concentrations of the criteria pollutants SO_2, NO_2, CO, and O_3 to daily mortality for the period from October 1991 to March 2002 and (b) to relate the mass concentrations of PM_{10} and $PM_{2.5}$ and the number concentrations of ultrafine particles to daily mortality for the periods from October 1991 to March 1992 and from September 1995 to March 2002;
2. To test whether the RR of daily mortality in association (a) with the gaseous criteria pollutants SO_2, NO_2, CO, and O_3 and (b) with PM_{10}, $PM_{2.5}$, and particle size distribution remained unchanged over the respective time periods; and
3. To test whether changes (a) in concentrations of the gaseous criteria pollutants and (b) in emissions affected the RR associated with PM_{10}, $PM_{2.5}$, and ultrafine particles.

To address specific aim 1 and provide the basis for addressing specific aims 2 and 3, the investigators collected existing data on daily concentrations of the pollutants as well as on meteorologic conditions and mortality. They divided the study into three subperiods that reflected changes in pollutant sources. The first subperiod, from October 1, 1991, to August 31, 1995, was characterized by the effects of heavy use of brown coal for domestic and industrial purposes. The second subperiod, from September 1, 1995, to February 28, 1998, was characterized by the effects of a rapid change from brown-coal to natural-gas combustion. By the time of the third subperiod, from March 1, 1998, to March 31, 2002, air quality in the Erfurt area had stabilized, and the mixture and concentrations of pollutants resembled those now found in Western European cities.

METHODS

Pollutant Concentrations

The investigators obtained data on daily concentrations of the gaseous pollutants NO, NO_2, CO, SO_2, and O_3, as well as on several size classes of particulates, including PM_{10}, $PM_{2.5}$, and ultrafine particles. Daily measurements of NO, NO_2, CO, SO_2, and O_3 were obtained from a government-run monitoring station at Krämpferstraße, in Erfurt, for the entire study period. The station also provided data on daily total suspended particles (TSP) until 2000 and on PM_{10} thereafter. Daily measurements of $PM_{2.5}$ and PM_{10} as well as mass concentrations and number concentrations of airborne particulates were made at a GSF monitoring station in central Erfurt, about 2 km from the government monitoring station. Monitoring data were incomplete or missing for certain pollutants during certain portions of the study period and were therefore imputed, or interpolated, using various methods deemed appropriate by the investigators. Table 2 of the Investigators' Report details the periods for which data were imputed (derived from other data) for each pollutant that had significant gaps in measurements.

Mortality Data

Peters and colleagues obtained mortality data for Erfurt from death-certificate information provided by local authorities. Immediate, primary, and contributing causes of death were coded from the death certificates using the *International Classification of Diseases, 9th revision*

(ICD-9), for deaths occurring before January 1, 2000; deaths occurring on January 1, 2000, or later were coded using the *International Classification of Diseases, tenth revision* (ICD-10).

In preparation for the time-varying coefficient modeling, the investigators used Poisson time-series regression models to evaluate associations between pollutant concentrations and mortality. The methods used for such analyses have become quite standard, although certain aspects remain controversial, as we discuss below.

Recognizing that there might be a delay between the day of exposure and the associated health outcome, the investigators performed preliminary analyses to select lag days (the number of days after exposure to a pollutant) for the analysis of each mortality outcome. They performed Poisson time-series regressions using concentrations measured from 0 to 5 days before the day of death. For each pollutant, the model with the lowest *P* value determined the number of lag days used for subsequent investigations.

Time-Varying Coefficient Models

Specific Aims 2 and 3 were concerned with estimating how the coefficients of the Poisson time-series regression model varied over time between 1991 and 2002. No new data were needed for this analysis, but statistical extensions to the regression model were necessary. The review, development, and comparison of such time-varying coefficient models were an important part of the study and an important innovation in public-health investigation.

Peters and colleagues used time-varying coefficient models to study how changes in daily non-accidental mortality risk in Erfurt were associated with concentrations of gaseous pollutants and particulates of various size classes. This dynamic estimation of risk is different from calculating a summary RR over the study period. The time-varying estimates of risk derived from the time-varying coefficient models developed by Dr. Peters and her colleagues provide a possible indicator of changes in the toxicity of the pollution mixture during the study period.

Peters and colleagues selected the time-varying coefficient models to be used for the study through a complicated process involving simulations with data extracted from the actual Erfurt data. They altered the simulation data to include trends that were not related to the exposure–response relationship and that could introduce bias into the analysis, producing three test data sets, or "scenarios." Having selected five different time-varying coefficient models to evaluate, the investigators used the three test data sets to assess each model according to its ability to produce high-quality statistical results despite the presence of the problematic trends. They then selected a final time-varying coefficient model that performed best (i.e., that produced the least biased results overall) in the three simulations. This process is summarized in more detail below.

The shape of the pattern of variation over time in the association between daily pollutant concentrations and daily deaths was modeled using semiparametric time-varying coefficient regression methods. Several modeling approaches were considered initially using parametric cubic regression splines or semiparametric penalized splines with fully Bayesian, empirical Bayesian, or mixed generalized linear model formulations. An additional approach was considered in which an adaptive generalized varying-coefficient linear model was postulated. Here, a temporally local linear model of risk was considered. All these approaches allowed the data to select the shape of the variation over time in the risk function within certain constraints, such as cubic spline formulation and the amount of smoothing required.

The statistical properties of these modeling approaches were evaluated in a study in which time series of daily deaths were simulated based on a Poisson model with selected time-varying functions of risk (constant or curvilinear without additional confounders such as time and weather) and a sinusoidal risk function of time with nonlinear functions of time and weather. Data on daily SO_2 concentrations in Erfurt were used in this simulation study. The use of real air-pollution data was important, because a feature of the overall study was the dramatic decline in some of the pollutants, including SO_2, over time, and it was useful for the models to be capable of capturing changes in risk under such extreme conditions. The five modeling approaches were compared using the empirical root-mean-squared-error (RMSE) statistic, which evaluates both bias and uncertainty in the model estimates.

RESULTS

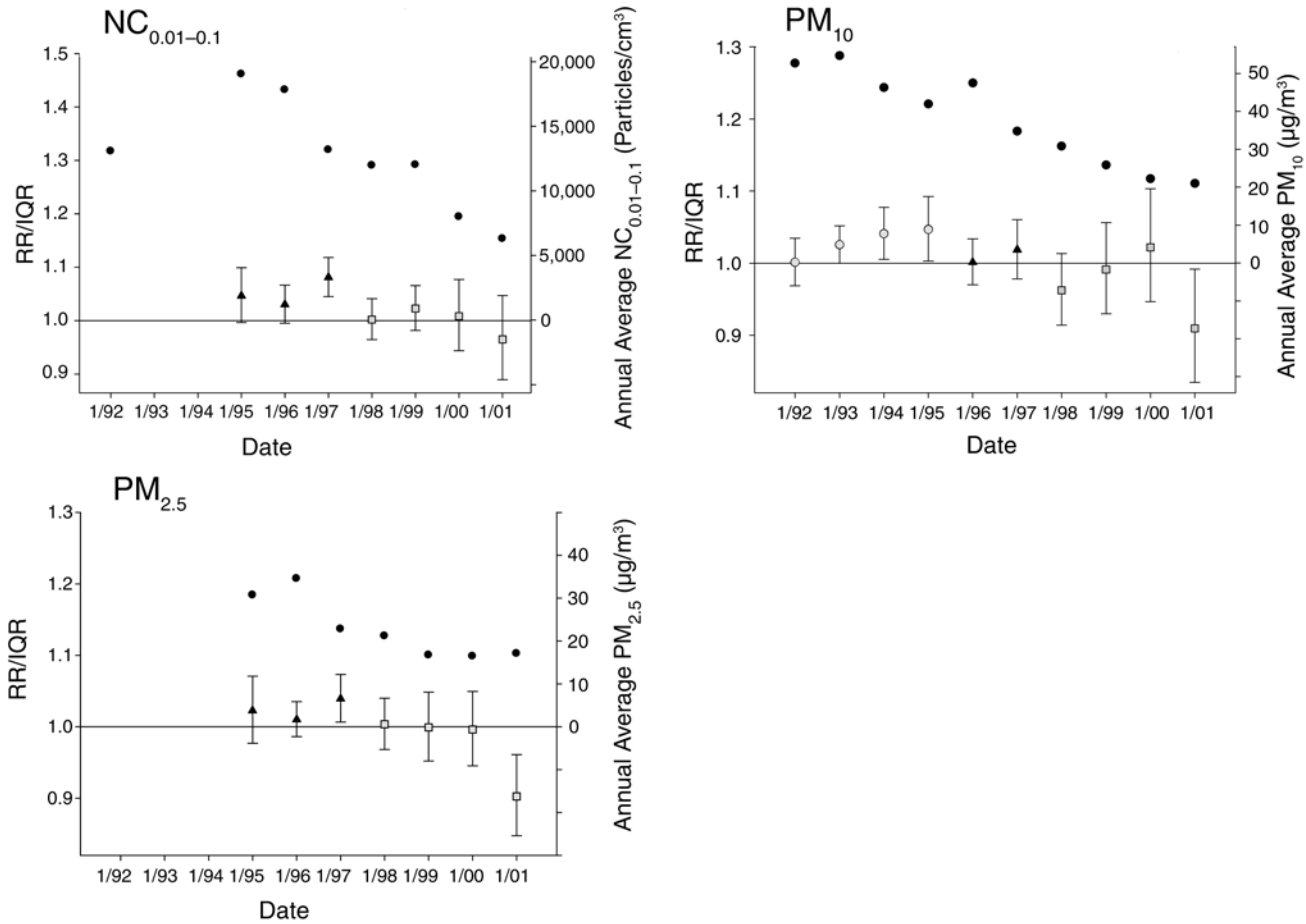
Overall air-pollution concentrations in Erfurt decreased during the study period. The largest change was in SO_2, whose annual concentrations decreased from 64 $\mu g/m^3$ in 1992 to 4 $\mu g/m^3$ in 2001. PM_{10}, $PM_{2.5}$, and CO concentrations decreased by more than 50%. These reductions were probably caused by the decrease in the burning of coal for electrical power, industrial use, and domestic heating as the use of natural gas increased. Although O_3 concentrations initially dropped, between 1992 and 1997, they remained stable or increased thereafter, possibly because of emissions of increased vehicular traffic.

High correlations were found between concentrations of NO, NO_2, CO, and ultrafine particles, pollutants commonly

Commentary Table 3. Summary of RRs for All-Cause Mortality in Erfurt per IQR of Selected Pollutants (Poisson Time-Series Model)[a]

Pollutant	Lag (Days)	IQR for Pollutant Concentration	Percent Change in RR of Mortality per IQR (95% CI)
Ultrafine particles	4	9743 (particles/cm^3)	2.9 (0.3 to 5.5)
$PM_{2.5}$ ($MC_{0.1–2.5}$)	3	16.3 ($\mu g/m^3$)	−0.8 (−2.7 to 1.1)
PM_{10}	3	27.8 ($\mu g/m^3$)	−1.0 (−2.7 to 0.8)
CO	4	0.48 (mg/m^3)	1.9 (0.2 to 3.6)
NO_2	3	19.7 ($\mu g/m^3$)	1.6 (−0.4 to 3.5)
SO_2	0	19.3 ($\mu g/m^3$)	−0.8 (−1.6 to 0.1)
O_3	2	43.8 ($\mu g/m^3$) (maximum 8-hr concentration)	4.6 (1.1 to 8.3)

[a] Lags selected are those showing the strongest associations.



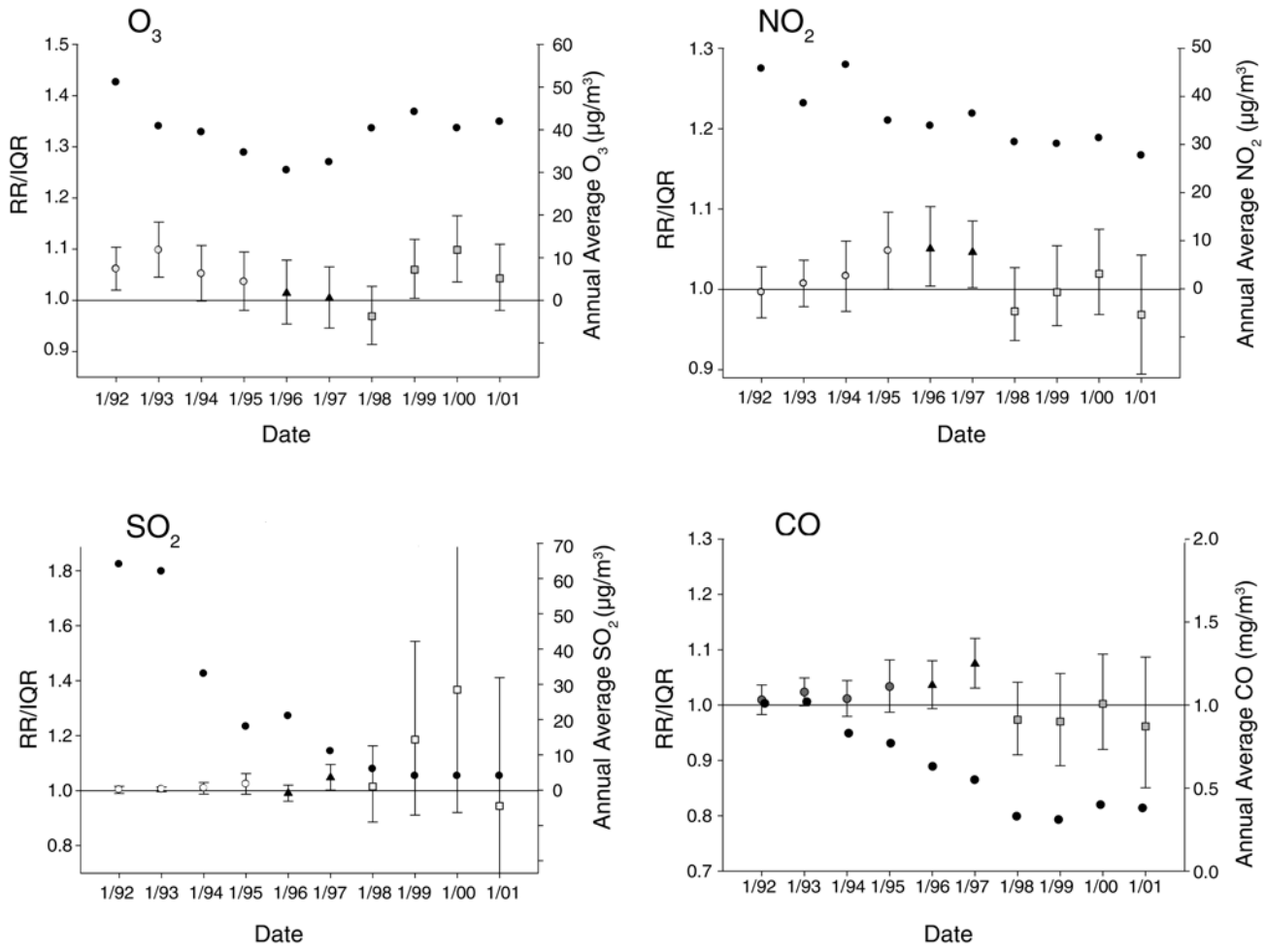
Commentary Figure 1. Annualized RR/IRQ values for all-cause mortality and particulate pollutants. Black dots indicate annual average pollutant concentrations. Gray dots, black triangles, and gray boxes indicate RR/IQR values for subperiods 1, 2, and 3, respectively. Bars indicate 95% CI.

associated with traffic-related combustion. Particle number concentrations of various particle size classes were highly correlated with each other and with NO_2 and CO. SO_2 was strongly correlated with CO and particle number concentrations. Although CO is produced in all combustion processes, large quantities of it are produced in coal combustion, a known source of the correlated SO_2 emissions. Correlations between the concentrations of the various pollutants also varied in relation to the study subperiod (see Table 14 in the Investigators' Report).

Summary results of the analysis of associations of mortality with levels of particles, CO, NO_2, and O_3 for the study period as a whole are shown in Commentary Table 3.

The time-varying coefficient models estimated RRs per interquartile range (IQR) for the pollutant concentrations and mortality types that varied continuously across the study period. These results are best viewed graphically and are easier to interpret when the pollutant concentrations and RR per IQR are annualized. Annualized results from the time-varying coefficient models are shown in Commentary Figures 1 and 2. Because IQRs for each pollutant were calculated for the entire period, each year's RR reflects the same incremental exposure. The lag days used are those the investigators selected as having the highest overall significance (Commentary Table 3).

Most notable among these figures is the decrease in pollutant concentrations over the study period for nearly all pollutants investigated. By contrast, the RRs (i.e., estimated unit toxicity) were more varied. For two pollutants (NO_2 and CO), RRs were higher in the middle period



Commentary Figure 2. Annualized RR/IRQ values for all-cause mortality and gaseous pollutants. Black dots indicate annual average pollutant concentrations. Gray dots, black triangles, and gray boxes indicate RR/IQR values for subperiods 1, 2, and 3, respectively. Bars indicate 95% CI.

(1995–1997) than before or after. For ultrafine particle counts, the RRs were also higher in 1995–1997 than later (no measurements were available before 1995). For O_3, the pattern of variation in RRs was reversed: higher in the beginning and final years of the study period than in the middle. The patterns for PM_{10} and $PM_{2.5}$ (which showed little evidence of associations with mortality overall) were different from those for NO_2, CO, and O_3: the RRs associated with PM_{10} were highest in 1994 and 1995 and the RRs associated with $PM_{2.5}$, were highest in 1997. For SO_2, the RRs were highest in 1999 and 2000, although it should be noted that the confidence intervals were wide then, reflecting the very low concentrations measured at the time. The smoothly time-varying coefficient models showed the same patterns as the RR/IQR values calculated on an annualized basis.

DISCUSSION

The work of Peters and colleagues is groundbreaking and contributes to accountability research in a number of ways. The group has successfully applied a statistical method developed in another field to model time-varying relationships between air pollutant concentrations and the RR of mortality. By applying time-varying coefficient modeling to cases in which both the concentrations and the composition of airborne pollution were changing over time, they have demonstrated how variations in the risk of mortality per unit of exposure over time can be investigated. This research expands the way we think about how interventions that reduce pollution might relate to health effects and mortality. Although the results of the study lack certainty because of their limited statistical power, they raise interesting questions for accountability-research initiatives, such as what factors resulting from or accompanying an intervention might change the risk per unit of exposure. Social or economic changes as well as changes to the pollutant mixture are examples of such factors.

POLLUTANT CONCENTRATION DATA

The pollution concentration data used by Peters and colleagues were of high quality, with relatively few gaps in time (although some were quite long and required extensive imputation). Consequently, the specific method chosen to impute values to fill the gaps was not likely to be critical. The imputation methods, which included the use of comparative information from the two sites measuring particulates, appear to be sound. A number of reviewers suggested that the imputation methods could have been more completely validated with simulations in which actual data from existing measurement series were removed and then compared with values independently imputed for the same periods.

CONFOUNDER CONTROL

The modeling methods used by Peters and colleagues follow the modeling procedures used by investigators participating in the APHEA (Air Pollution and Health: A European Approach) study, in which air-pollution and mortality data from 29 cities throughout Europe were aggregated. The APHEA and APHEA2 studies advanced the development of analytic methods for time-series modeling and were informed by much expert discussion (Atkinson et al. 2001). The methods used for APHEA represented the state of the art for time-series modeling in the early 2000s, when Dr. Peters originally proposed the current study to HEI. However, debate on the proper choice of models continues (HEI 2003, Peng 2006), and some of the details of the approach used by Dr. Peters and her colleagues remain controversial. Specifically, the use of residual autocorrelation statistics to choose the degree of smoothness of the "time smooth" has never been theoretically justified and was shown in simulations by Peng (2006) to lead to bias in some realistic scenarios. Similar concerns apply to the use of the Akaike information criterion (AIC) to build confounder models to control for time-varying trends linked to both pollution and mortality, such as season, meteorologic variables, and influenza epidemics. It would be unfair to criticize the investigators for failing to take into account developments not published when the analysis was planned, but these sources of uncertainty should inform our interpretation of the study results.

In the study, the final models for temperature (4 df spline at lag day 0 and a linear term at lag day 1) are quite standard in these sorts of studies, but concern about residual confounding remains. Substantially longer lag-day effects have routinely been reported for temperature, especially for periods of unusually cold weather in Europe. The robustness of the study's results with the addition of temperature terms up to lag day 3 in sensitivity analyses was, however, reassuring.

Dr. Peters and her team used techniques that were state of the art at the time of their research and performed sensitivity testing to assess the effect on the pollution–mortality relationships of some changes in the confounder models. Although the Review Committee still has concerns over the possibility of residual confounding in light of recently published work, we do not have a specific view as to the likelihood or direction of such confounding.

Commentary Table 4. Percent Change in Daily Deaths per IQR for Exposures Lagged 0 to 5 Days Before Death[a]

Pollutant	Percent Change in Daily Deaths per IQR (95% CI)					
	Lag Day 0	Lag Day 1	Lag Day 2	Lag Day 3	Lag Day 4	Lag Day 5
NO_2	−0.8 (−3.8 to 2.4)	0.7 (−2.1 to 3.5)	0.2 (−2.5 to 3.0)	**1.2 (−1.5 to 4.0)**	0.7 (−2.0 to 3.5)	−0.6 (−3.3 to 2.1)
SO_2	**−0.8 (−1.6 to 0.1)**	−0.6 (−1.5 to 0.2)	−0.4 (−1.3 to 0.4)	−0.4 (−1.2 to 0.5)	0.2 (−0.6 to 1.0)	0.3 (−0.5 to 1.0)
CO	0.0 (−2.3 to 2.3)	0.2 (−2.0 to 2.4)	1.3 (−0.9 to 3.5)	0.7 (−1.4 to 2.9)	**1.2 (−1.0 to 3.4)**	−0.5 (−2.6 to 1.7)
Ultrafine particles	2.0 (−0.7 to 4.9)	0.1 (−2.5 to 2.9)	−0.3 (−2.8 to 2.3)	1.2 (−1.4 to 3.8)	**2.9 (0.3 to 5.5)**	0.6 (−1.9 to 3.2)
PM_{10}	−0.8 (−2.7 to 1.1)	−0.2 (−2.0 to 1.6)	0.0 (−1.7 to 1.8)	**−1.0 (22.7 to 0.8)**	0.5 (−1.2 to 2.3)	0.7 (−1.0 to 2.5)

[a] Boldface type indicates the change for the lag days that were selected as producing the most significant results. Data from Investigators' Report Tables 16 (for NO_2, CO, and ultrafine particles), 18 (for SO_2), and 19 (for PM_{10}).

CHOICE OF LAG DAY FOR POLLUTION VARIABLES

In their initial analyses (Specific Aim 1), the investigators used six models to explore the associations between pollutant concentrations and mortality for exposures lagged from 0 to 5 days before death. For each pollutant, the investigators then focused on the lag day with the largest RR of mortality and used this value exclusively in the time-varying coefficient models (Specific Aims 2 and 3). Although this approach to lag-day selection is systematic, it poses challenges when the time dependence of biologic mechanisms linking exposure to mortality is not well understood. Statistically speaking, a choice of lag day based on the strength of association found in the data suffers from upward bias, because even random data exhibit some positive associations by chance alone; and an a priori choice can suffer from downward bias if the choice was incorrect (i.e., in overlooking a genuine association at another lag day). Commentary Table 4, which shows results for all of the lag-day values examined in the study for several of the pollutants, illustrates some of these challenges. The differences in the "effects" associated with the various lag-day values are seen to be small relative to the size of their confidence intervals and thus could well have been caused by chance. Selection of the most significant values would be expected to introduce values that are high at least in part by chance. Also, even if the 30 associations in Commentary Table 4 were entirely random, we would still expect roughly one to appear "significant" by chance alone, making the association of ultrafine particles and mortality at lag day 4 seem less remarkable. The investigators' single-day lag results for several pollutants (ultrafine particles, CO, NO_2, and SO_2) were, however, consistent with the single-day lags reported in the earlier Erfurt study (Wichmann et al. 2000), which contained fewer years of data (1995–1998), though within the same period of time as this study (1991–2002). This consistency with earlier work reduces our concern over the post hoc selection of lag days, albeit minimally due to the substantial overlap of data. The use of "distributed lag" models avoids problems of lag-day selection to some extent, and it was disappointing not to see distributed-lag models used in the study, as the results might have better represented the true temporal relationships between exposure and mortality.

TIME-VARYING COEFFICIENT ANALYSIS

The results of the simulations with the five candidate time-varying coefficient models were evaluated by calculating the RMSE, a summary statistic that compares actual data with values predicted by a model for an entire data set. A summary statistic such as RMSE cannot depict the behavior of a complex function over a range of values. The investigators' selection process for an appropriate time-varying coefficient model for use with the study data would have been improved if they had evaluated the shape of the risk function over time (averaged over the simulations) for the various models considered. The issue of having sufficient statistical power to detect potentially complex risk functions, given the relatively few deaths (approximately 4) per day on average reported for Erfurt, is also a concern.

As part of the analysis of the data, mortality risks associated with air pollution and based on a constant function were obtained for each year separately and plotted over time to express annual risk. This simple assessment of the time course of risk mimicked the shape of the risk function estimated by the time-varying coefficient model. The similarity is reassuring, in that a statistically complex approach (i.e., the time-varying coefficient model) yielded results similar to those of a relatively simple, intuitive, and empirical approach (i.e., the annual risks).

Although various penalized-spline models of time-varying risk were fitted to the data, with some sensitivity analysis as to the amount of smoothing to be used, no formal statistical tests were undertaken to find out whether the estimated risk functions were different from a constant or simple linear function of time. The absence of such statistical comparisons again raises the issue of statistical power to detect time-varying risk functions in the study.

Dr. Peters and her colleagues employed graphical techniques to identify external factors that might vary along with risk over time, such as changes in fuel use, traffic, and household heating. The possibility of such external factors underscores the need to develop formal statistical methods that incorporate these potential risk-modifying factors directly into time-varying coefficient models, particularly for public-health studies. In this manner, statistical tests can be proposed to identify important factors that modify risk over time — a major purpose of the study.

RESULTS

Dr. Peters and her colleagues concluded that their results pointed to an association between daily mortality and exposure to ultrafine particles (and correlated gaseous pollutants) with a lag time of 3 to 4 days and that the results for ultrafine particles, NO_2, and CO, taken together, pointed to an association between mortality and local combustion sources. Using the time-varying coefficient model to demonstrate dynamic changes in RR, the investigators concluded that the RRs of mortality per unit of pollutant concentration were lowest near the end of the study period. They also concluded that the highest RRs per unit of pollutant concentration occurred in the transition period (1995–1997), when pollution sources were changing rapidly and the benefits of improved air quality had yet to be realized.

The main problem in interpreting these results (both the observations of overall pollutant–mortality associations and their variations over time) is in distinguishing "real" patterns from chance ones. We begin by considering the results pertaining to changes in risk over time — the main innovation of the study — then turn to an interpretation of the evidence for overall pollution effects.

As noted earlier in this commentary (and as acknowledged by the investigators), the variations observed in pollutant–mortality associations could have been largely, if not entirely, caused by chance. This possibility is mostly due to the limited statistical power resulting from the low number of daily deaths in Erfurt. Other methodologic sources of uncertainty relate to the broader, continuing debate about the "best" way to do time-series studies of this type. The points of contention include the choice of confounders and how best to control for them, how to deal with single pollutants in a varying multipollutant mixture, and the best way to deal with lag days. Even without these concerns, the study's relatively limited statistical power makes it very difficult to evaluate how "real" any reported changes in toxicity were across the study period.

If the changes were indeed real and not caused by chance, bias, or confounding, how would we interpret the temporal variation in unit toxicity? The observed pattern does not correspond to known trends in the sources or concentrations of Erfurt's pollution. In a recent World Health Organization (WHO) workshop on the health effects of particulates, it was concluded that, although it is likely that the toxicity of particles in the inhalable fraction varies by their size, source, and chemistry, it was not possible to quantify these variations sufficiently to give firm guidance for policy (WHO workshop March 2007**)**. The particulate and gaseous mixture of pollutants in Erfurt underwent major quantitative and qualitative changes, but apart from limited evidence that the exposure–response relationship might flatten at higher concentrations (Schwartz and Marcus 1990), current knowledge is insufficient to formulate confidently an a priori hypothesis about what should happen to unit toxicity as pollution sources change from coal combustion to motor-vehicle combustion. Thus, the study by Peters and colleagues is best considered as exploratory.

A further consideration in interpreting changes in coefficients over time is that they might relate not only to changes in unit toxicity but also to changes in the effects of exposure misclassification or in population vulnerability. Exposure misclassification seems unlikely to have changed in some important way over time in Erfurt; but we note that the report discusses — without explicitly including — variables associated with potential changes in the vulnerability of the population. Variables reported by others that can affect the risk of daily mortality per unit of air pollution include the population's age structure and the prevalence of chronic cardiopulmonary disease and smoking; such variables can potentially include other factors as well, such as diet and lifestyle.

A number of the report's conclusions related to the estimated effects of individual pollutants when analyzed over the study period as a whole, with particular attention being drawn to the suggestive conclusion that ultrafine particles (lagged 3 to 4 days) had the largest effects on daily mortality. These estimates are also limited by the statistical power of the study, though not as much as the estimates of variations in pollutant effects over time. Compounding the uncertainty is the post hoc selection, from a large number of analyses, of pollutant–lag-day combinations when the biologic basis for

the selected lag days (and not for other days) is unknown. Together with the uncertainty about the adequacy of control for confounding, discussed above (in particular, the very limited control for variation in mortality over time caused by factors other than air pollution), considerable caution should be exercised in interpreting the report's overall effect estimates.

The research group at GSF was the first to obtain long-term daily series of measurements of ultrafine particles that relate to a population (residents of the city of Erfurt) and to have published widely on the relationship between ultrafine particles and health outcomes. The coincidence of the measurements of ultrafine particles and the rapid changes that had occurred in Erfurt over the same time period therefore provided a unique opportunity to explore changes in time-series coefficients in an accountability study. The finding regarding ultrafine particle is important in view of the paucity of epidemiologic evidence on the health effects and mortality risks associated with ultrafine particles (which contrasts with the intense interest in laboratory research on the topic), but only if we put the uncertainties aside. As noted in the HEI Statement accompanying the report by Wichmann and colleagues (2000), "This [Wichmann et al.'s] study was the first to suggest that [ultrafine particles] may be associated with human mortality," even though the RRs it reported, while larger, were not significantly larger than those reported in the current study. In contrast, the HEI-funded study by Peters and colleagues of nonfatal cardiac events in Augsburg, Germany (2005), found no significant associations between nonfatal myocardial infarctions and ultrafine-particle exposure 1 to 6 hours earlier. However, these contradictory findings for ultrafine particles from the same research group underscore the concern that methodologic uncertainties, such as those noted for lag-day selection, can easily produce artificially reduced or magnified associations. They also highlight the problematic nature of inference from current research into the role of ultrafine particles in health outcomes.

It is unusual that no consistent effects of $PM_{2.5}$ or PM_{10} were observed over the study period. Null $PM_{2.5}$ results are consistent with those from the earlier report from Erfurt (Wichmann et al. 2000) and with reports that have studied $PM_{2.5}$ and daily mortality in two other European cities (Anderson et al. 2001 and Peters et al. 2000). But a study by Spix and colleagues (1993) of suspended particulates (with no size cut-off, thus approximating TSP) and daily mortality in Erfurt observed significant effects for the period 1988–1989. Why, then, were effects not observed for $PM_{2.5}$ or PM_{10} in 1991–2002? Was there an earlier reduction in the unit toxicity of particles that had flattened by the time of the study period? Or was some important element of the particle mixture captured in measurements of TSP, but not of PM_{10} or $PM_{2.5}$? The absence of coherence in these patterns, along with other considerations, increases our suspicion that they might have been caused by chance or bias. Effects of mobile-source gaseous pollutants (NO_2 and CO) on mortality at selected lag days were also observed, and these were interpreted by the investigators as surrogates for particle effects, especially the ultrafine-particle effects, because of the high degree of correlation between measures of ultrafine particles and the gaseous pollutants. This interpretation is based on toxicologic grounds and not on the epidemiologic evidence presented. While the interpretation is plausible, current knowledge is not sufficient to be entirely confident about it.

Implications for Accountability Research

The main objective of the study related to accountability research (i.e., assessing the effectiveness of environmental regulatory policies, interventions, and changes in reducing exposure to air pollution and improving human health). As have many other cities, Erfurt has undergone gradual yet major changes in the concentrations of its airborne pollutants as a result of changes in its pollution sources. In addition, these changes were contemporaneous with many other factors affecting the health of the population and possibly its vulnerability to air pollution. This makes causal inferences relating to changes in risk estimates problematic. Erfurt's epidemiologic scenario contrasts with those in Dublin and Hong Kong, for example, in which abrupt regulatory actions caused sharp and sustained changes in air quality that allowed changes in health outcomes to be linked more convincingly to the interventions.

In circumstances of more gradual change in air pollution, investigating mortality risk relative to changes in unit toxicity (as was done in Erfurt), instead of changes in health per se (as was done in Dublin and Hong Kong), has a clear advantage. But this choice does make severe demands on statistical power. In hindsight, a city the size of Erfurt was probably too small for such a study. If similar studies are contemplated in the future, it would be prudent to make a careful assessment of sample sizes needed to detect convincing changes. The innovative methodologic work on time-varying coefficients carried out in this study could have an important part to play in a study of a sufficiently large population.

Finally, it should be emphasized that, irrespective of the study's inconclusive findings on trends in daily mortality risks per unit of pollution over the study period, it is very likely that deaths attributable to air pollution have diminished in Erfurt because of the absolute decline in the population's exposure to air pollutants.

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