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Effects of Long-Term Exposure to Traffic-Related Air Pollution on Respiratory and Cardiovascular Mortality in the Netherlands: The NLCS-AIR Study

Bert Brunekreef, Rob Beelen, Gerard Hoek, Leo Schouten, Sandra Bausch-Goldbohm, Paul Fischer, Ben Armstrong, Edward Hughes, Michael Jerrett, and Piet van den Brandt

Includes a Commentary by the Institute's Health Review Committee

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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.

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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 139, *Effects of Long-Term Exposure to Traffic-Related Air Pollution on Respiratory and Cardiovascular Mortality in the Netherlands: The NLCS-AIR Study,* presents a research project funded by the Health Effects Institute and conducted by Dr. Bert Brunekreef of the Institute for Risk Assessment Sciences at Utrecht University, the Netherlands, and his colleagues. 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 Brunekreef 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.

HEI STATEMENT

Synopsis of Research Report 139

Long-Term Exposure to Traffic-Related Air Pollution and Mortality

BACKGROUND

Increases in urbanization and motor vehicle use have raised questions about the health effects of exposure to pollutants, such as oxides of nitrogen and black smoke (a measure of fine particulate matter), that are emitted from motor vehicle exhaust pipes. Measurements at regional monitoring stations, however, may not reflect the actual concentrations of pollutants related to automobile, bus, and truck traffic to which the surrounding population is exposed. Some studies indicate that living near roads with heavy traffic may increase the risk of adverse health effects associated with air pollution. In Europe, most studies of traffic-related air pollution and health before 2000 focused on short-term variations in pollutant concentrations and acute outcomes in very young populations. Assessments of the risks of long-term exposure were often based on ambient air pollution levels and on results from large cohort studies that did not include specific information on traffic exposure.

In the current study, which began in July 2001, Dr. Bert Brunekreef and colleagues examined associations between long-term exposure to pollution from motor vehicles and mortality in a large cohort in the Netherlands. This expanded the work of a pilot study, reported in the *Lancet* in 2002, in which Gerard Hoek, Bert Brunekreef, and others used state-of-the-art methods based on geographic information systems to estimate black smoke and nitrogen dioxide (NO_2) concentrations at the home addresses of 5000 older adults, a randomly selected subcohort within the ongoing Netherlands Cohort Study (NLCS) on diet and cancer. The investigators found variations in concentrations of these traffic-related pollutants among the addresses of study participants; however, the results for the two pollutants were highly correlated at both regional and local levels. In 8 years of follow-up, the relative risk of cardiopulmonary mortality was found to be significantly higher for those who lived near a major road. For the current study, the investigators refined the methods of exposure assessment, included more traffic data, and extended the mortality analysis to the full NLCS cohort. They also added exposure estimates for several other pollutants, collected pollutant data for the 10 years before the NLCS began, and extended the follow-up to 10 years.

STUDY SUMMARY

The objectives of this study were to estimate exposure to traffic-related air pollution for all subjects in the full NLCS cohort, to evaluate associations between exposure and mortality, as well as the incidence of lung cancer, to determine whether exposure was associated with death from specific causes, and to determine whether mortality risks were influenced by the characteristics of individual subjects. The NLCS was originally created to study possible connections between nutritional patterns and the development of cancer. The cohort used for the current study, known as NLCS-AIR, contained 120,852 subjects, who were 55 to 69 years of age in September 1986. During the follow-up period from January 1, 1987, through December 31, 1996, there were 17,674 deaths from natural causes recorded for this cohort.

For the NLCS-AIR study, Dr. Brunekreef's team conducted full-cohort analyses, in which they examined exposure information and mortality data for the entire cohort, but computerized information on potential individual-level confounding variables was very limited. Detailed personal information from questionnaires completed when the cohort was formed was available for the 5000-person NLCS subcohort on which their pilot study had

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr. Bert Brunekreef of the Division of Environmental Epidemiology, Institute for Risk Assessment Sciences, at Utrecht University in the Netherlands, and colleagues. Research Report 139 contains both the detailed Investigators' Report and a Commentary on the study prepared by the Institute's Health Review Committee.

been based and was also entered for all cohort members who died during follow-up. The investigators used this information in case–cohort analyses in which data for the subcohort were compared with data for study participants who died (cases), with adjustment for a substantial number of potential confounders, to estimate relative risk of mortality. They also analyzed data for the subcohort alone, using the current study methods, to generate results that can be directly compared with those of their pilot study.

Exposure assessment was the most complicated aspect of data collection and analysis. Using available measurements from 1976 through 1996, the investigators calculated long-term exposure levels for black smoke, NO_2, sulfur dioxide (SO_2), and particulate matter equal to or less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$), at the 1986 home address of each study participant. Calculations were based on a complex system, including regional, urban, and local components of overall exposure for each pollutant. The investigators also used indicators of traffic-related air pollution, including traffic intensity on the nearest road, living near a major road, and sum of traffic intensity in a surrounding 100-m buffer, as variables for local exposure. For analyses including the local variables, a combination of the regional and urban components (called the background exposure) was also included to control for the effects of exposure from sources that were not local.

The health endpoints analyzed in this study were death from all natural causes and death from cardiovascular or respiratory causes, lung cancer, or other natural causes, as well as lung cancer incidence. For the full cohort, analyses were adjusted for age, sex, and smoking status at baseline, determined from the questionnaire, and for information on socioeconomic status in the participant's neighborhood and regional area, derived from public sources.

Brunekreef and his team chose the well-known Cox proportional hazards method to calculate relative risks of mortality associated with traffic-related air pollution. They also used a newly developed method of Cox-Poisson mixed model analysis, which enabled them to incorporate statistical corrections for spatial autocorrelation (the nonindependence of exposure and health-status observations for people living close together) in the results.

RESULTS AND INTERPRETATIONS

The results discussed here, unless stated otherwise, are of the full-cohort analyses, which displayed greater statistical precision than those of the case–cohort analyses because of the much larger number of subjects. Of particular interest are analyses of associations between specific traffic variables and the relative risk (RR) of death from cardiopulmonary causes. In a model that included two variables, reflecting exposure to background air pollution and to local traffic-related air pollution, the RR (95% confidence interval [CI]) was 1.13 (0.99–1.29) for exposure to background black smoke and 1.07 (0.96–1.19) for living near a major road (defined as a road with traffic intensity of more than 10,000 motor vehicles/day). In a model with one variable for exposure to the overall concentration of black smoke, calculated from estimated background exposure and local exposure from traffic using a land-use regression model, the RR was 1.07 (95% CI, 0.98–1.15).

In the pilot study, Brunekreef and colleagues previously reported considerably higher risks for death from cardiopulmonary causes, obtained using similar models: for exposure to background black smoke, the RR was 1.34 (95% CI, 0.68–2.64); for living near a major road, the RR was 1.95 (1.09–3.51); and for overall black smoke exposure, the RR was 1.71 (1.10–2.67). These results were obtained for 8 years of follow-up in the 5000-person NLCS subcohort, compared with 10 years of follow-up in the full cohort of 120,852 members for the current study. Though the relative risks of mortality were higher in the pilot study, the confidence intervals were much wider than those in the current study, reflecting less precision in the estimated risks. The discrepancy between the results is partially due to the difference in statistical power between the two studies resulting from their sample sizes, although other factors such as the longer follow-up period are also likely to have been important. Given the prominence of the pilot study results, the lower risk estimates in the current study, especially for the traffic variable, are noteworthy.

Of further interest are the relative risks of cardiopulmonary mortality for the subjects who lived in the three largest cities, which were higher, for the most part, than those reported for the full cohort. This finding raises questions about whether the higher risk esimates in these three cities are related to the effects of traffic and urbanization, or reflect exposure estimates that were more precisely modeled in urban areas than in other areas.

DISCUSSION

A spatial relationship between air pollution and mortality has been reported for decades, both in the United States and in Europe, but attempts to assign risk based on spatial patterns have the potential for serious confounding from local social and economic factors. Though excess mortality due to pollutant exposure has been observed in cohort studies in the United States, evidence from Europe has been sparse. Consequently, European assessments of the health effects of air pollution have relied on results from U.S. studies. The current study in the Netherlands adds to the available information about exposures encountered by European populations.

The large size of the cohort makes the study by Brunekreef and his team noteworthy, in part because effects are detected with greater statistical precision than in a small cohort. Well-designed cohort studies also have the potential to be able to control for confounding factors at the individual level. In the current study control for potential individual-level confounders was very limited in the full-cohort analyses. In contrast, the case–cohort and subcohort analyses were adjusted for an extensive list of potential confounders, but the risk estimates were less precise because of the smaller sample sizes. Sensitivity analyses suggested, however, that the inclusion of the more detailed individual variables would not have substantially changed the risk estimates for the full cohort.

One of the most challenging aspects of this study was the modeling of exposure for specific addresses with limited primary data on local pollutant concentrations and traffic. Several methods were used, including interpolation from pollutant measurements of the national monitoring network and land-use regression models to characterize exposure at residences. The calculations involved considerable manipulation of data and incorporated regression models developed in other studies. Taken as a whole, the data and methods used for exposure assessment result in some uncertainty about the exposure estimates and, consequently, about the associations between exposure and mortality. This is particularly true when quantitative exposure estimates at participants' residences were not calculated using data from quantitative studies, but based instead on default assumptions about traffic intensity on nearby roads. Uncertainty resulting from a chain of assumptions about exposure (rather than measurement of exposure) may be an issue in this study, particularly when traffic intensity was converted to quantitative local estimates of traffic-related pollutant exposures. Despite these concerns, the exposure assessment in this study was innovative and based on sound principles. Brunekreef's team made excellent use of advanced technology involving geographic information systems and a wide variety of data sources and types, pushing available techniques for modeling exposure to their limits.

Overall, the results of the mortality analyses should be regarded as suggestive rather than conclusive. The estimates of relative risk were small, in many cases not statistically significant, and often consistent with chance. Also, in any observational study in which the exposure is estimated, rather than measured, residual confounding by unknown factors is possible. Internal inconsistencies in the study are the higher risks of mortality for residents of the three largest cities and for subjects who had a lower level of education or ate less fruit. These results could be explained by differences in these subjects' vulnerability to air pollution or in the toxicity of the air pollutants to which they were exposed, or they may point toward some type of confounding specific to these groups.

There are also features of the study that might bias the results toward a smaller effect. The authors concluded that exposure misclassification was likely to be higher for subjects who did not live in the major urban areas where more traffic information was available, and might be responsible for their lower risk estimates. Consistent with this theory is the greater risk of death estimated for those who had not changed residence over the period of observation and were thus assumed to have more accurate exposure assessments.

The most intriguing difference is the considerably lower risk of cardiopulmonary mortality associated with measures of traffic-related air pollution in the current study of the full NLCS cohort compared with the pilot study of 5000 persons drawn from the same cohort. The exposure assessment in the current study was more refined. In particular, changes in the way subjects were classified with respect to living near a major road led to substantial changes in exposure assignment for this variable. It

seems reasonable to accept the authors' conclusion that the main explanation for the discrepancy in results lies in the random variation in the selection of the pilot study cohort from the full cohort, and in the longer follow-up period in the current study – although the findings remain puzzling. This experience indicates that caution is necessary in analyzing results from small cohort studies.

Two previous studies of the health effects of traffic-related air pollution in large U.S. cohorts, the American Cancer Society Study and the Harvard Six Cities Study, found stronger associations with cardiovascular mortality than with respiratory mortality, but little association with death from other causes. In contrast, the current study in a large Dutch cohort found higher risks for respiratory mortality than for cardiovascular mortality, and the risks for cardiovascular mortality were similar to those for deaths not related to either respiratory or cardiovascular causes. All three cohort studies found associations with lung cancer mortality, although the risks in the Dutch cohort were not significant. As mentioned above, the precision of the estimates should be taken into account when interpreting such patterns.

The Netherlands, a country half the size of the state of South Carolina, is exposed to a high and fairly homogeneous regional background concentration of particulate matter. This background pollution constituted by far the greatest proportion of the Dutch cohort's exposure to the pollutants investigated in this study. Though the variation in air pollution exposure estimates was mainly related to traffic sources, the traffic-related variability in exposure was small. Therefore, the estimated mortality risks associated with air pollution were based on a narrower range of exposures than was the case in the U.S. studies, in which average estimates for cities, rather than individuals, were derived directly from measurements of air pollution concentrations.

This major cohort study provides evidence that long-term exposure to air pollution is likely to reduce life expectancy in Europe. The study found evidence of an increased risk of death in subjects living near a busy road, albeit at much lower levels of risk than were found in the pilot study. Though the study did not estimate the city-specific effects of the cohort's exposure to air pollution, and in this respect differs from cohort studies based on city-level differences in exposure, the estimated effects of air pollution on mortality appear similar in scale to those observed in large U.S. cohort studies. The findings of this study are potentially important for environmental policy decisions and pollution prevention and warrant further investigation.

INVESTIGATORS' REPORT

Effects of Long-Term Exposure to Traffic-Related Air Pollution on Respiratory and Cardiovascular Mortality in the Netherlands: The NLCS-AIR Study

Bert Brunekreef, Rob Beelen, Gerard Hoek, Leo Schouten, Sandra Bausch-Goldbohm, Paul Fischer, Ben Armstrong, Edward Hughes, Michael Jerrett, and Piet van den Brandt

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ABSTRACT

Evidence is increasing that long-term exposure to ambient air pollution is associated with deaths from cardiopulmonary diseases. In a 2002 pilot study, we reported clear indications that traffic-related air pollution, especially at the local scale, was related to cardiopulmonary mortality in a randomly selected subcohort of 5000 older adults participating in the ongoing Netherlands Cohort Study (NLCS)* on diet and cancer. In the current study, referred to as NLCS-AIR, our objective was to obtain more precise estimates of the effects of traffic-related air pollution by analyzing associations with cause-specific mortality, as well as lung cancer incidence, in the full cohort of approximately 120,000 subjects.

Cohort members were 55 to 69 years of age at enrollment in 1986. Follow-up was from 1987 through 1996 for mortality (17,674 deaths) and from late 1986 through 1997 for lung cancer incidence (2234 cases). Information about potential confounding variables and effect modifiers was available from the questionnaire that subjects completed at enrollment and from publicly available data (including neighborhood-scale information such as income distributions). The NLCS was designed for a case–cohort approach, which makes use of all the cases in the full cohort, while data for the random subcohort are used to estimate person-time experience in the study. Full information on confounders was available for the subjects in the random subcohort and for the emerging cases of mortality and lung cancer incidence during the follow-up period, and in NLCS-AIR we used the case–cohort approach to examine the relation between exposure to air pollution and cause-specific mortality and lung cancer. We also specified a standard Cox proportional hazards model within the full cohort, for which information on potential confounding variables was much more limited.

Exposure to air pollution was estimated for the subjects' home addresses at baseline in 1986. Concentrations were estimated for black smoke (a simple marker for soot) and nitrogen dioxide (NO_2) as indicators of traffic-related air pollution, as well as nitric oxide (NO), sulfur dioxide (SO_2), and particulate matter with aerodynamic diameter $\leq$ 2.5 μm ($PM_{2.5}$), as estimated from measurements of particulate matter with aerodynamic diameter $\leq$ 10 μm (PM_{10}). Overall long-term exposure concentrations were considered to be a function of air pollution contributions at regional, urban, and local scales. We used interpolation from data obtained routinely at regional stations of the National Air Quality Monitoring Network (NAQMN) to

This Investigators' Report is one part of Health Effects Institute Research Report 139, which also includes a Commentary by the Health Review Committee and an HEI Statement about the research project. Correspondence concerning the Investigators' Report may be addressed to Dr. Bert Brunekreef, Division of Environmental Epidemiology, Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands.

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

estimate the regional component of exposure at the home address. Average pollutant concentrations were estimated from NAQMN measurements for the period 1976 through 1996. Land-use regression methods were used to estimate the urban exposure component. For the local exposure component, geographic information systems (GISs) were used to generate indicators of traffic exposure that included traffic intensity on and distance to nearby roads. A major effort was made to collect traffic intensity data from individual municipalities. The exposure variables were refined considerably from those used in the pilot study, but we also analyzed the data for the full cohort in the current study using the exposure indicators of the pilot study. We analyzed the data in models with the estimated overall pollutant concentration as a single variable and with the background concentration (the sum of regional and urban components) and the local exposure estimate from traffic indicators as separate variables.

In the full-cohort analyses adjusted for the limited set of confounders, estimated overall exposure concentrations of black smoke, NO_2, NO, and $PM_{2.5}$ were associated with mortality. For a 10-μg/m^3 increase in the black smoke concentration, the relative risk (RR) (95% confidence interval [CI]) was 1.05 (1.00–1.11) for natural-cause (nonaccidental) mortality, 1.04 (0.95–1.13) for cardiovascular mortality, 1.22 (0.99–1.50) for respiratory mortality, 1.03 (0.88–1.20) for lung cancer mortality, and 1.04 (0.97–1.12) for noncardiopulmonary, non–lung cancer mortality. Results were similar for NO_2, NO, and $PM_{2.5}$. For a 10-μg/m^3 increase in $PM_{2.5}$ concentration, the RR for natural-cause mortality was 1.06 (95% CI, 0.97–1.16), the same as in the results of the American Cancer Society Study reported by Pope and colleagues in 2002. The highest relative risks were found for respiratory mortality, though confidence intervals were wider for this less-frequent cause of death. No associations with mortality were found for SO_2.

Some of the associations between the traffic indicator variables used to assess traffic intensity near the home and mortality reached statistical significance in the full cohort. For an increase in traffic intensity of 10,000 motor vehicles in 24 hours (motor vehicles/day) on the road nearest a subject's residence, the RR was 1.03 (95% CI, 1.00–1.08) for natural-cause mortality, 1.05 (0.99–1.12) for cardiovascular mortality, 1.10 (0.95–1.26) for respiratory mortality, 1.07 (0.96–1.19) for lung cancer mortality, and 1.00 (0.94–1.06) for noncardiopulmonary, non–lung cancer mortality. Results were similar for traffic intensity in a 100-m buffer around the subject's residence and living near a major road (a road with more than 10,000 motor vehicles/day). Distance in meters to the nearest major road and traffic intensity on the nearest major road were not associated with any of the mortality outcomes. We did not find an association between cardiopulmonary mortality and living near a major road as defined using the methods of the pilot study.

In the case–cohort analyses adjusted for all potential confounders, we found no associations between background air pollution and mortality. The associations between traffic intensity and mortality were weaker than in the full cohort, and confidence intervals were wider, consistent with the smaller number of subjects. The lower relative risks of mortality associated with traffic variables in the case–cohort study population could be related to the particular subcohort that was randomly selected from the full cohort, as the risks estimated with the actual subcohort were well below the average estimates obtained for 100 new case–cohort analyses with 100 alternative subcohorts of 5000 subjects each that we randomly selected from the full cohort. Differences in adjusted relative risks between the full-cohort and the case–cohort analyses could be explained by random error introduced by sampling from the full cohort and by a selection effect resulting from the relatively large number of missing data for variables in the extensive confounder model used in the case–cohort analyses. More complete control for confounding probably did not contribute much to the lower relative risks in the case–cohort analyses, especially for the traffic variables, as results were similar when the limited confounder model for the full cohort was used in analyses of the subjects in the case–cohort study population.

In additional analyses using black smoke concentrations as the exposure variables, we found that the association between overall black smoke and cardiopulmonary mortality was somewhat stronger for case–cohort subjects who did not change residence during follow-up, and in the full cohort, there was a tendency for relative risks to be higher for subjects living in the three major cities included in the study. Adjustment for estimated exposure to traffic noise did not affect the associations of background black smoke and traffic intensity with cardiovascular mortality. There was some indication of an association between traffic noise and cardiovascular mortality only for the 1.6% of the subjects in the full cohort who were exposed to traffic noise in the highest category of > 65 A-weighted decibels (dB(A); decibels with the sound pressure scale adjusted to conform with the frequency response of the human ear).

Examination of sex, smoking status, educational level, and vegetable and fruit intake as possible effect modifiers showed that for overall black smoke concentrations, associations with mortality tended to be stronger in case–cohort subjects with lower levels of education and those with low fruit intake, but differences between strata were not statistically significant. For lung cancer incidence, we

found essentially no relation to exposure to NO_2, black smoke, $PM_{2.5}$, SO_2, or several traffic indicators. Associations of overall air pollution concentrations and traffic indicator variables with lung cancer incidence were, however, found in subjects who had never smoked, with an RR of 1.47 (95% CI, 1.01–2.16) for a 10-μg/m^3 increase in overall black smoke concentration.

In the current study, the mortality risks associated with both background air pollution and traffic exposure variables were much smaller than the estimate previously reported in the pilot study for risk of cardiopulmonary mortality associated with living near a major road (RR, 1.95; 95% CI, 1.09–3.51). The differences are most likely due to the extension of the follow-up period in the current study and to random error in the pilot study related to sampling from the full cohort. Though relative risks were generally small in the current study, long-term average concentrations of black smoke, NO_2, and $PM_{2.5}$ were related to mortality, and associations of black smoke and NO_2 exposure with natural-cause and respiratory mortality were statistically significant. Traffic intensity near the home was also related to natural-cause mortality. The highest relative risks associated with background air pollution and traffic variables were for respiratory mortality, though the number of deaths was smaller than for the other mortality categories. As a whole, the results of this study add to the evidence that long-term exposure to ambient air pollution is associated with increased mortality.

INTRODUCTION

In the past decade numerous epidemiologic studies have reported associations between short-term variations in ambient concentrations of particulate matter and mortality from cardiovascular and respiratory diseases (Samet et al. 2000; Katsouyanni et al. 2001). Two prospective studies in large U.S. cohorts, one conducted by Harvard researchers in six cities (Dockery et al. 1993) and the other based on American Cancer Society data linked to pollution levels in 51 metropolitan areas (Pope et al. 1995), found associations between long-term exposure to particulate matter air pollution and mortality. An independent reanalysis of these studies confirmed the associations (Krewski et al. 2000). In an extended follow-up of the American Cancer Society Study cohort, associations between particulate matter air pollution and cardiopulmonary mortality were still observed, although effect estimates were smaller than those originally reported (Pope et al. 2002). An extended follow-up of the Harvard Six Cities Study cohort also confirmed the findings of the earlier analyses (Laden et al. 2006).

In the Harvard Six Cities and the American Cancer Society studies, researchers estimated long-term exposure to ambient air pollution as the average concentration within a city or metropolitan area, ignoring small-scale variations within that area. Studies based on air pollution monitoring have shown, however, that concentrations of traffic-related air pollutants such as black smoke, NO_2, and ultrafine particles, when assessed on a small scale, vary widely within cities (Fischer et al. 2000; Jerrett et al. 2005a). Three European cohort studies (Hoek et al. 2002; Nafstad et al. 2004; Filleul et al. 2005) and several studies in North America (Finkelstein et al. 2004; Jerrett et al. 2005b; Miller et al. 2007) have evaluated health effects related to intraurban contrasts in air pollution.

In a pilot study conducted in the Netherlands, we found an association between long-term exposure to traffic-related air pollution by living near a major road and cardiopulmonary mortality (RR, 1.95; 95% CI, 1.09–3.51) in a subcohort of 5000 individuals randomly selected from a large cohort of older men and women (Hoek et al. 2002). In a cohort of 16,209 Norwegian men living in Oslo, Nafstad and colleagues (2004) found associations between long-term exposure to urban air pollution and increased mortality, with the strongest associations being for mortality caused by respiratory diseases other than lung cancer. Results of the prospective French study Pollution Atmospherique et Affections Respiratoires Chroniques (PAARC), which started in 1974 with 14,284 adults, showed that mortality over the next 25 years was associated with urban air pollution as assessed from 1974 through 1976 (Filleul et al. 2005). These European studies characterized air pollution by concentrations of NO_2, nitrogen oxides (NO_x), and black smoke. They did not include information about $PM_{2.5}$; however, a study of intraurban contrasts in NO_2 and $PM_{2.5}$ levels in three European areas showed generally high correlations between the two pollutants (Lewne et al. 2004).

Finkelstein and colleagues, using the same indicator variable for exposure to traffic-related air pollution (residence within 50 m of a major road or 100 m of a freeway) as we used in the Dutch pilot study (Hoek et al. 2001), found that mortality from all natural causes was increased for Canadian subjects who lived near a major road (RR, 1.18; 95% CI, 1.02–1.38) (Finkelstein et al. 2004). Jerrett and colleagues (2005b), in an analysis of the Los Angeles area within the American Cancer Society Study, concluded that the association between health effects and intraurban gradients in $PM_{2.5}$ concentrations may be even greater than associations previously reported for metropolitan areas. The Women's Health Initiative Study among women in 36 U.S. communities also suggested that within-city gradients

of $PM_{2.5}$ exposure had a stronger association with health effects than between-city gradients of exposure (Miller et al. 2007).

Within-community contrasts in long-term average ambient air pollutant concentrations have been assessed by a variety of approaches (Jerrett et al. 2005a). Several recent cohort studies have estimated pollution exposure by interpolation of measurement data (Abbey et al. 1999; Jerrett et al. 2005b; Miller et al. 2007). Studies have also documented that land-use regression models can be utilized to predict long-term average concentrations of air pollutants (Briggs et al. 1997; Briggs et al. 2000; Brauer et al. 2002; Gilbert et al. 2005; Hochadel et al. 2006; Ross et al. 2006; Ross et al. 2007). Other studies have used dispersion models to calculate the concentration of gaseous pollutants at a particular address (Nyberg et al. 2000; Nafstad et al. 2004; Naess et al. 2007).

In the current study we used a combination of exposure indicators, interpolation of measurements, and land-use regression to assess outdoor air pollution concentrations at the home address for each individual. As in the pilot study, we sought to reflect the processes governing air pollution contrasts at three different spatial scales, regional, urban, and local (Hoek et al. 2001). On the local scale, we used traffic variables and then calculated pollutant concentrations resulting from local traffic, very similar to the approach used in the Children's Health Study in California (Gauderman et al. 2007). Indicators of air pollution exposure such as distance to a major road or traffic intensity on the nearest road or nearest major road have been widely used in epidemiologic studies of health effects related to motorized traffic (Brunekreef et al. 1997; Hoek et al. 2002; Finkelstein et al. 2004; Gehring et al. 2006).

The pilot study (Hoek et al. 2002) had several limitations, including the relatively small study population of approximately 5000. Lung cancer mortality and respiratory mortality could not be analyzed separately because of the small numbers of deaths in these categories. The small study size also prevented us from assessing effect modification with reasonable precision. Long-term exposure to traffic-related air pollution was separated into background exposure and local exposure. Background exposure was calculated as the sum of pollutant contributions from regional and urban sources. Local exposure was characterized by an indicator variable for living near a major road. In reality, the local exposure component is also dependent on traffic intensity, traffic composition, and other factors (Hoek et al. 2001) for which data were not collected in the pilot study.

In the current study on the association between long-term exposure to traffic-related air pollution and mortality, we included all of the approximately 120,000 subjects in the NLCS cohort and improved the method of exposure assessment compared with that in the pilot study.

SPECIFIC AIMS

The objectives of this study were as follows:

1. To estimate exposure to traffic-related air pollution for all subjects in a large, ongoing cohort study on diet and cancer in the Netherlands
2. To evaluate the associations between exposure to traffic-related air pollution and natural-cause mortality and lung cancer incidence in this cohort
3. To evaluate whether these associations vary with specific causes of death (respiratory, cardiovascular, and noncardiopulmonary, non–lung cancer) and with subject characteristics such as smoking habits, educational level, sex, and occupational exposures

METHODS

STUDY DESIGN

The association between air pollution and cause-specific mortality was examined in an existing cohort from the NLCS, a large study in the Netherlands on the relation between diet and cancer. In contrast to the pilot study (Hoek et al. 2002), we examined data for the full cohort of approximately 120,000 adults aged 55–69 years at enrollment. For each subject the baseline home address in 1986 and information on residential history were used to generate indicators of long-term exposure to air pollutants.

As indicators of traffic-related air pollution, we used black smoke and NO_2. Exposures to NO, SO_2, and $PM_{2.5}$ were assessed as well. Using GISs, we generated traffic exposure variables that included traffic intensity on nearby roads and distances to these roads. A major effort was made to collect data on traffic intensity from individual municipalities. Follow-up for mortality and lung cancer incidence covered the 10-year period from 1987 through 1996. Information about potential confounding variables and effect modifiers was available from the NLCS baseline questionnaire and from public databases (including neighborhood-scale confounders, such as income).

The NLCS was designed for a case–cohort approach that makes use of all the cases in the full cohort and a randomly selected subcohort (n = 5000) of the full cohort to estimate person-time in the study for participants. This approach was selected for several reasons, including efficiency of

data entry. In NLCS-AIR we used the case–cohort approach (with full information on confounders) to study the relation between exposure to air pollution and cause-specific mortality, as well as lung cancer incidence. In addition, we specified a standard Cox proportional hazards model within the full cohort; however, information on potential confounders was limited for the full cohort. The latter approach is more comparable to the analysis approach in several North American and other European cohort studies of long-term air pollution exposures than the case–cohort approach.

STUDY POPULATION

The NLCS began in 1986, with 120,852 subjects who were 55 to 69 years of age at enrollment (van den Brandt et al. 1990). The cohort study population is drawn from throughout the Netherlands, so there is ample variation in the air pollution conditions to which subjects are exposed. The study is being conducted by the Department of Epidemiology at Maastricht University, under the direction of Prof. Piet van den Brandt, and at the Nutrition and Food Research Institute of the Netherlands Organization for Applied Scientific Research (abbreviated TNO for Toegepast-Natuurwetenschappelijk Onderzoek) in Zeist, under the direction of Dr. Sandra Bausch-Goldbohm. Study subjects were recruited in 1986 from municipalities that had computerized population registries at that time. This was so for 323 of the 714 municipalities in the Netherlands, with no apparent relation to the magnitude of the respective populations. Of these municipalities, 300 agreed to make data available to the study; however, only 204 of them were adequately covered by cancer registries at the time, and these 204 communities were included in the study.

In the initial NLCS questionnaire, information was collected about a large number of risk factors for the development of cancer, besides diet. Many of these risk factors, such as smoking habits, passive exposure to smoke, and occupation, are also of potential importance for the development of respiratory and cardiovascular diseases and mortality from these diseases.

The exact address of each study subject in 1986 was known. In addition, the questionnaire allowed space for identification of up to four previous cities of residence. For the purpose of the current study, we also identified changes of residence during follow-up for subjects who died. Follow-up for the NLCS subcohort of approximately 5000 individuals is conducted by communication with both the individuals and the municipalities at regular intervals, to determine the residential and vital status of its members, and the information is used to estimate the person-time experience of the full cohort.

EXPOSURE ASSESSMENT

Exposure assessment in general followed the approach taken in the pilot study (Hoek et al. 2001), but we refined the estimates of air pollution exposure. The basic approach was that long-term average exposure to outdoor air pollution was considered to be a function of the regional pollutant concentration ($C_{regional}$), additional pollution from urban sources (C_{urban}), and additional pollution from local sources—in this case, nearby roads (C_{local}). In formula:

$$Exposure = C_{regional} + C_{urban} + C_{local}$$

In the pilot study (Hoek et al. 2001), long-term exposures to black smoke and NO_2 were assessed by separate estimations of regional, urban, and local (traffic) contributions to concentrations of these pollutants at the centroids of the six-digit postal code areas in which the subjects' home addresses were located. Interpolation by inverse distance weighting was used to estimate the regional concentration from measured air pollutant concentrations at regional stations of the national monitoring network. A regression model was used to estimate the urban background concentration by relating the address density of the four-digit postal code area in which a subject lived to measured air pollution concentrations at urban monitoring sites. Distance from a subject's residence to major roads was calculated to characterize local traffic contributions, using a GIS and a digital road network (Basisnetwerk, 1993 version). The result was a dichotomous variable indicating whether or not the subject lived within 50 m of a major road or within 100 m of a freeway (Hoek et al. 2001).

For the current study, we extended exposure assessment by obtaining data for more air pollutants, over a longer period of time, and added spatial determinants to the characterization of air pollution. The specific refinements were as follows:

1. Long-term exposure to outdoor air pollution was again estimated for the components black smoke and NO_2, but exposures to NO and SO_2 were also estimated, and data on ozone and PM_{10} were collected as well. PM_{10} data were used to estimate $PM_{2.5}$ concentrations.
2. Data were collected from 1976 (start of the NAQMN) through 1996 (end of follow-up), as compared with 1987 through 1991 for the pilot study.
3. Exposure estimates were based on the exact 1986 residential addresses of study participants, which were geocoded into standard Dutch geographic coordinates using a database from the year 2000. In the pilot study the six-digit postal code, which comprises about 25 addresses, was used for geocoding.

4. We evaluated kriging as a method for interpolation of regional pollutant concentrations in addition to the inverse-distance-weighting method used previously.
5. We evaluated more potential determinants and a more appropriate spatial scale (using circular buffers) to assess the urban pollutant concentrations, compared with using address density in the four-digit postal code area as in the pilot study.
6. We used the national road database (Nationaal Wegen Bestand, NWB) for the year 2000, which provides a more complete and geographically more precise road network than that used for the pilot study.
7. We made a major effort to collect complete data on traffic intensity to link to the national road database, whereas the pilot study used classification of road types, without traffic intensity data, in exposure estimates.

Thus, in the current study estimates of exposure are more precise than those determined in the pilot study. For comparison, we also estimated exposures by the same methods as were used in the pilot study.

Measurements from the NAQMN have been used to document that the contrast in PM_{10} concentrations across the Netherlands is small (30% to 40%), and that there is virtually no contrast in long-term average ozone concentrations within the Netherlands. However, as our pilot study documented, there are considerable regional differences in measured concentrations of black smoke and NO_2, air pollution components that are more specifically related to traffic (Hoek et al. 2001).

Black smoke is measured by light absorbance of exposed filters and is mostly related to elemental carbon emissions from diesel engines. Black smoke is not a good proxy for PM_{10} or $PM_{2.5}$ but has been shown to be closely related to the elemental carbon content of particles (Edwards et al. 1983; Chow 1995). Therefore, it is a more direct indicator of exposure to particles related to diesel traffic than either PM_{10} or $PM_{2.5}$. In the Netherlands, road traffic contributes 65% of the black smoke concentrations in urban environments (Bloemen et al. 1998).

In contrast to black smoke, NO_2 reflects emissions from all motorized vehicles. Approximately 50% of the national NO_2 emissions in the Netherlands are due to motorized traffic. Because of the low emission height of traffic-related air pollutants, and the concentration of traffic in urban environments, the contribution of traffic to the ambient NO_2 concentrations to which human beings are actually exposed is higher than 50%. In primary traffic emissions NO_2 is only 5% of the total NO_x emissions. NO_2 is therefore largely a secondary pollutant. Nevertheless, the Small Area Variation in Air Pollution and Health (SAVIAH) study has shown that within urban environments, a large part of the spatial variation in NO_2 concentrations can be explained by traffic intensity and by the characteristics of buildings on the street (Briggs et al. 1997).

Exposure Assessment Process

We used a combination of exposure indicators, interpolation of measurements, and land-use regression to assess outdoor air pollution concentrations at the subject's home address. We chose these different methods to reflect the processes governing air pollution contrasts at different spatial scales. We distinguished regional, urban, and local scales of air pollution for exposure assessment, as in the pilot study (Hoek et al. 2001). This distinction between spatial scales is very common; for example, stations in the monitoring network are also described in these terms.

To describe variations at the regional scale, we used interpolation of air pollution measurements at monitoring stations, since air pollutant concentrations at this scale are expected to vary smoothly in space. We preferred to base these calculations on actual measurements of air pollution, rather than use dispersion models. Dispersion models for PM_{10} are not as developed as those for gaseous pollutants. In the pilot study, we documented that interpolation errors were small compared with the range of regional pollutant concentrations in the Netherlands (Hoek et al. 2001).

To assess variations in air pollution at the urban scale, we used land-use regression methods. We did not use dispersion models because no validated model for assessing small-scale spatial variation (for example, in grids of 500 m $\times$ 500 m) was available in the Netherlands. In addition, we preferred to utilize actual measurements and develop a stochastic model based on them. Finally, in the pilot study we had documented that the prediction errors that occurred when we used very simple land-use regression models were small compared with the range of urban and regional pollutant concentrations in the Netherlands (Hoek et al. 2001). Several studies have now documented that land-use regression models can be used to predict long-term average air pollution concentrations (Brauer et al. 2002).

To assess variations in air pollution at the local scale, we used traffic indicators and then calculated the pollutant concentrations due to local traffic, an approach very similar to that used in the Children's Health Study (Gauderman et al. 2007). Relevant information was obtained through GISs. These traffic indicators do not yield quantitative air pollutant concentrations and do not capture effects such as pollutant dispersion related to street configuration, traffic speed, and traffic composition. However, they do provide a direct link to a specific source of pollution. There is also

evidence that in the Netherlands these traffic indicators are related to substantial contrasts in ambient concentrations of NO_2, black smoke, and to a lesser extent PM_{10} and $PM_{2.5}$ (Janssen et al. 1997; Roorda-Knape et al. 1998; Fischer et al. 2000; Janssen et al. 2001; Roemer and van Wijnen 2001; Hoek et al. 2002; Lewne et al. 2004).

To calculate the local contribution to exposure, we developed stochastic models using data from specific monitoring campaigns conducted near major roads and freeways in the Netherlands (Janssen et al. 2001; Brauer et al. 2003). We did not use dispersion models for this calculation because the one publicly available model in the Netherlands capable of calculating traffic contributions, the CAR-2 model, only takes into account emissions in the street of residence. It does not account for contributions of nearby major roads. And for urban streets, the CAR-2 model only calculates concentrations up to 30 m from the street. Finally, data on relevant factors such as street configuration, for example, were less available than the traffic intensity data used in the regression modeling.

In the epidemiologic analysis we considered the background (regional and urban) contribution and the local contribution, both separately and together, and referred to the sum of the two as overall air pollution. The motivation for separating them is that the regional and urban scales reflect more aged traffic emissions and the local scale reflects primary, fresh traffic emissions. The health effects of aged and fresh emissions may differ, for example, because of changes in the composition and overall abundance of ultrafine particles in emissions over time.

Figure 1 summarizes the steps in our exposure assessment. In the following sections we provide information regarding the data sources used for exposure assessment and explain the use of these data for assessing exposure at regional, urban, and local scales.

Data Sources

Geocoding The exact 1986 residential addresses of study participants were geocoded into standard Dutch geographic coordinates according to the Address Coordinates of the Netherlands (ACN) database from the year 2000, available at the National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu, or RIVM). The ACN database consists of all coordinates of all addresses registered by the Dutch postal service. It includes more than 7 million addresses, which is approximately 95% of all addresses in the Netherlands. The accuracy of the ACN database was previously evaluated in 27 sample areas throughout the Netherlands. In that analysis, 93.5% of all postal address coordinates were located at the centroid of the correct building, 6.0% were located at the centroid of the correct land parcel, and only 0.5% of all coordinates were not located in the correct building or parcel (VIG/Kadata 2001).

For 21,868 (97.9%) of the 22,337 subjects in the case–cohort study population (case subjects and subcohort members), the home address could be geocoded and an exposure assessment could be made. When geocoding data were missing for a subject's recorded address, we checked the original address and corresponding postal code. This process resulted in a small number of changes: 34 postal codes were changed on the basis of address. Reasons for missing data included a missing postal code (n = 1) and missing house numbers (n = 7). The vast majority of missing data could not be traced to errors and probably resulted from incompleteness of the database. In the full cohort, the address could be geocoded for 117,528 (97%) of the 120,852 subjects.

A procedure was developed that minimized the risk that confidential information about cohort members would become available to outsiders. The ACN database was brought from RIVM to Maastricht University, where the database of complete addresses for study subjects is held. The exact address for each subject was transformed into geographic coordinates and stored with the subject's ID in a file. Next, university staff changed the ID. This temporary ID and the geographic coordinates were then taken to RIVM and linked to the GIS information and air pollution data to create an exposure file for each subject's address. These files were then returned to Maastricht University, where university staff linked them to the health and confounder data for each subject.

RIVM personnel had previously geocoded NAQMN monitoring locations on paper maps. The coordinates they reported for these locations were rounded to 100 m. Since we used data from these monitoring locations for interpolation of regional pollutant concentrations and estimation of urban pollutant concentrations using buffers with GIS predictors of 300 m and more, this level of precision was considered acceptable.

National Air Pollution Measurements Air pollutant concentrations for the years 1976 through 1996 measured by the National Air Quality Monitoring Network (NAQMN, or Landelijk Meetnet Luchtkwaliteit), which was designed for nationwide monitoring of air pollution, were obtained from RIVM. All available 24-hour average concentrations were obtained for NO_2, NO, black smoke, SO_2, PM_{10}, carbon monoxide (CO), and ozone (O_3). Measurements were available starting in 1976 for SO_2, followed by measurements for NO_2, NO, and CO in 1977

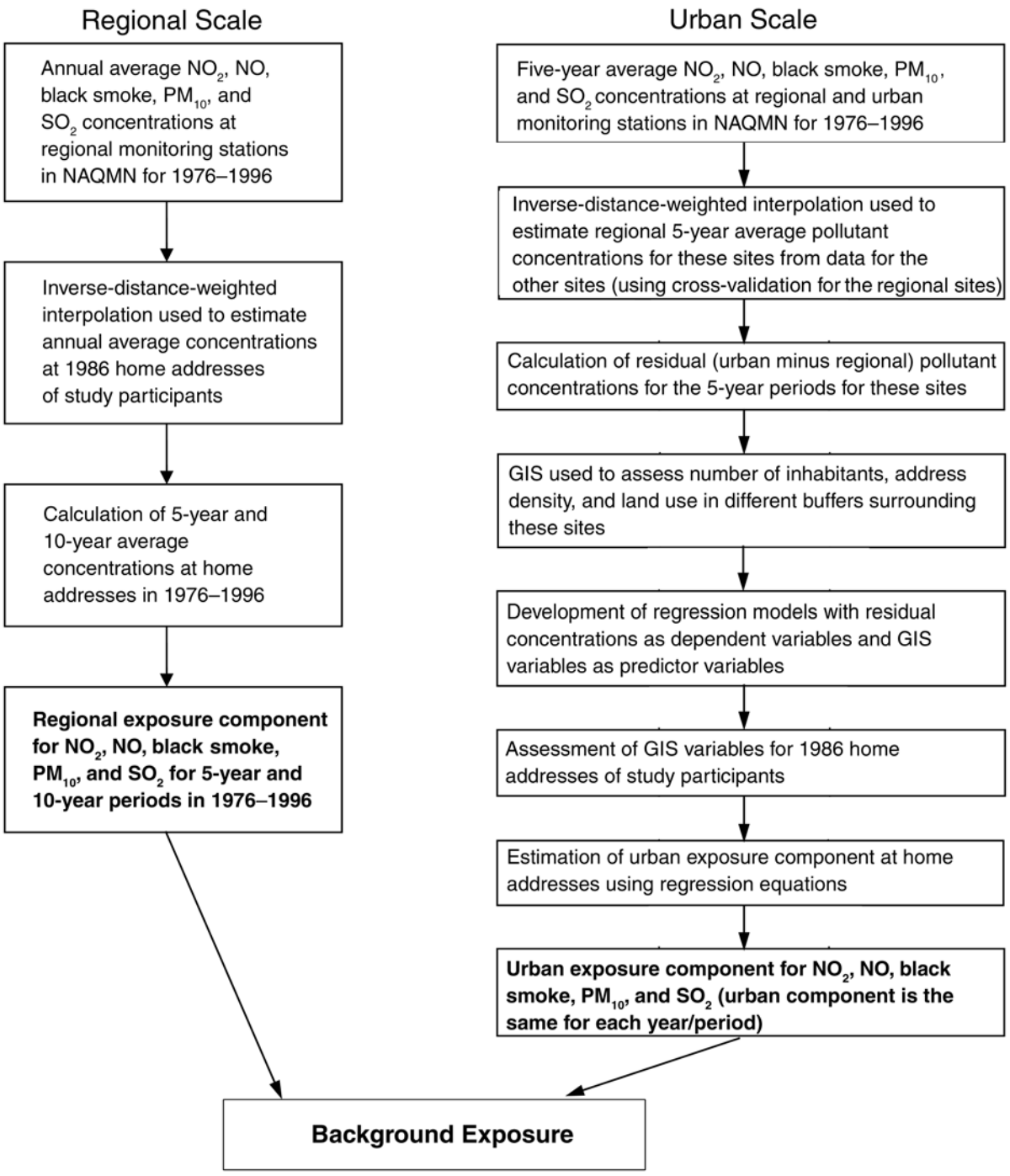

Figure 1. Exposure assessment methods at regional, urban, and local scales. PM_{10} data were only available for 1992–1996. (*Figure continues next page*)

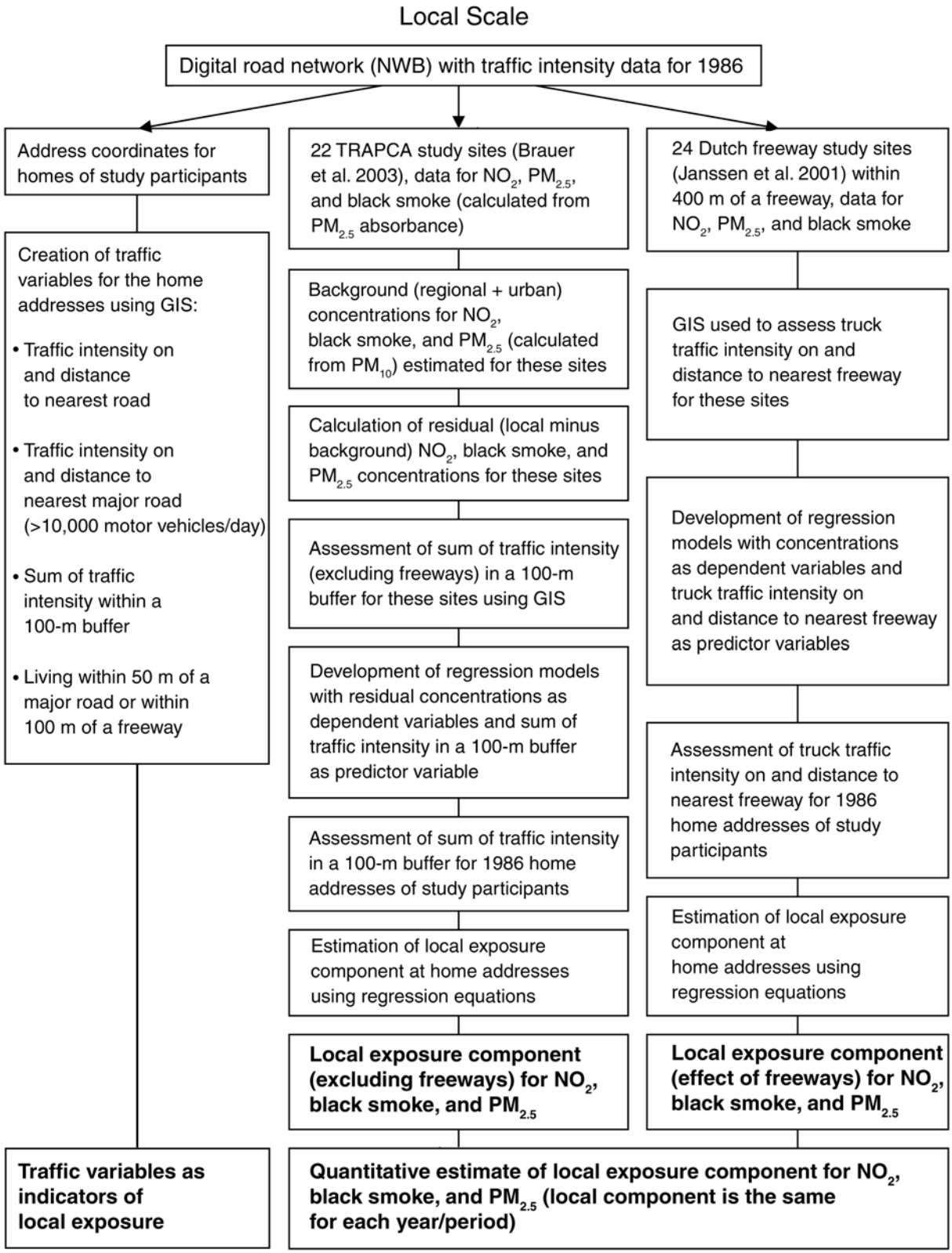

Figure 1 (*Continued*).

(Table 1). Measurement of black smoke began in 1984, at seven locations. Measurement of PM_{10} started in 1992. During the study period, $PM_{2.5}$ was not measured. In Table 1, the total number of monitoring stations that measured in each year is shown for each pollutant.

Complete modernization of the monitoring network was begun during the study period, on January 1, 1985, and the new network was put into operation on April 1, 1986 (Elskamp 1989). The number of monitoring stations was reduced (see Table 1), with the rationale that accurate air pollution patterns for the Netherlands could still be determined. In the years after 1986, however, the total number of monitoring stations increased gradually (Buijsman 1994).

In Table 1, the maximum number of stations that measured on any one day in a year is also shown for each pollutant. In 1986, the maximum number of stations that measured some of the pollutants on any day was much lower than the total number of stations measuring those pollutants. Many of the stations in the old network stopped measuring on January 1, 1985, but some of these started measuring again on April 1, 1986. Other stations of the old network stopped measuring in March 1986. A few stations of the old network continued measuring as part of the new network, and several new stations began measuring on April 1, 1986. During the year 1993–1994, another revision of the NAQMN took place that reduced the number of monitoring locations from 105 to 56 (Buijsman 1994). The 1993–1994 revision was primarily aimed at reducing the large network of regional SO_2-monitoring stations (see Table 1) (Buijsman 1994). (As an example, Figure 3 in Appendix C shows the configuration of the NAQMN on January 1, 1994; see section Appendices Available on the Web.)

RIVM classified the monitoring stations that measured in the period 1986–1996 as follows (Elskamp 1989):

1. Regional (spatially representative) stations are located in areas that are not highly developed and placed so as to avoid the influence of local sources on pollutant measurements.
2. City (urban) stations are sited in streets that are within the built-up area of a city or town, but where there are fewer than 2750 motor vehicles/day passing within a circle of 35 m around the station.
3. Street stations are located in streets with heavy traffic of different types (i.e., trucks, buses, and automobiles), and where there are at least 10,000 motor vehicles/day passing within a circle of 35 m around the station.

Table 1. Total Number of Monitoring Stations with Pollutant Measurements per Year (and Maximum Number on Any Day)[a]

Year	NO_2	NO	Black Smoke	SO_2	PM_{10}	CO	O_3
1976	—	—	—	209 (207)	—	—	NC
1977	72 (71)	72 (72)	—	215 (210)	—	26 (26)	NC
1978	91 (91)	91 (91)	—	215 (213)	—	37 (36)	NC
1979	92 (90)	92 (91)	—	216 (209)	—	38 (37)	NC
1980	91 (90)	91 (90)	—	216 (212)	—	38 (37)	NC
1981	91 (90)	91 (91)	—	216 (212)	—	38 (38)	NC
1982	91 (90)	91 (91)	—	216 (206)	—	38 (38)	NC
1983	92 (90)	92 (91)	—	213 (206)	—	38 (38)	NC
1984	91 (91)	91 (91)	7 (7)	208 (208)	—	37 (37)	NC
1985	40 (40)	40 (40)	7 (7)	70 (69)	—	21 (21)	13 (13)
1986	57 (35)	57 (35)	12 (12)	133 (74)	—	34 (19)	31 (31)
1987	36 (35)	36 (35)	15 (15)	82 (82)	—	27 (27)	31 (31)
1988	40 (40)	40 (40)	15 (15)	82 (82)	—	31 (31)	35 (35)
1989	46 (43)	46 (43)	21 (20)	84 (83)	—	26 (26)	39 (37)
1990	43 (43)	43 (43)	20 (20)	83 (83)	—	26 (26)	37 (37)
1991	43 (43)	43 (43)	20 (20)	83 (83)	—	26 (26)	32 (32)
1992	49 (46)	49 (46)	21 (20)	84 (83)	13 (13)	27 (26)	40 (38)
1993	47 (46)	47 (46)	18 (18)	86 (82)	18 (17)	22 (22)	39 (38)
1994	45 (45)	45 (45)	14 (14)	40 (40)	19 (19)	22 (22)	38 (38)
1995	46 (46)	46 (46)	14 (14)	40 (40)	20 (19)	22 (22)	39 (38)
1996	47 (46)	47 (46)	15 (15)	40 (40)	19 (19)	23 (23)	39 (39)

[a] Stations that measured in a limited period of time and "street" stations are included. A dash indicates the pollutant was not measured that year. NC indicates data were not collected. Values in parentheses are the maximum number of stations that measured on any day that year.

There is no corresponding classification of the monitoring stations that measured in the period 1976–1986. In consultation with air quality managers from RIVM, we therefore developed a procedure to classify the stations that obtained measurements in that period according to the degree of urbanization (using 1993 data) of the postal code areas in which they were located. The degree of urbanization in the Netherlands is described by classes ranging from 1 (very urban) to 5 (not urban). Monitoring sites in postal code areas classified as 1 or 2 were assumed to be city (urban) stations, and monitoring sites in postal code areas classified as 3, 4, or 5 were assumed to be regional stations. To assess whether a monitoring site was a street station, regardless of the degree of urbanization, we calculated the ratio between NO and NO_2. NO_x emissions from motor vehicles generally contain about 95% NO and 5% NO_2. NO_2 is more often a secondary pollutant. If the NO/NO_2 ratio was higher than 1 for one or more years at a monitoring site, we classified it as a street station. Monitoring sites that did not measure NO and NO_2 were assumed not to be street stations. The vast majority of those sites were measuring only SO_2, a component not very sensitive to local traffic emissions.

Monitoring methods used in the national air pollution monitoring network are presented in Table 2, which includes a brief description of calibration procedures (Elskamp 1989). All measurements were made according to specific national regulations, usually derived from European Union guidelines. The same equipment and procedures were used at all sites. Although the specific air-monitoring instruments used at each site changed during the study period of 1976–1996 (van de Wiel et al. 1977; Elskamp 1989; van Elzakker 2001), the principle behind the method remained the same. Since the calibration procedures did not change, data from throughout the study period are most likely directly comparable, with the exception of the CO data.

The instrument for measuring CO was changed in 1989, and CO values measured with the new instrument were approximately twice as high as those measured previously (Figure 2). There has been no comparison of the two methods for measuring CO concentrations, so it is not possible to correct the data for this change in measurement method. Furthermore, relatively few of the monitoring stations measured CO concentrations. For these reasons, we did not include CO data in the exposure assessment. Data for O_3 were also not included in the final exposure assessment, because data before 1985 were not available in the original NAQMN data set; furthermore, NAQMN measurements have documented that there is virtually no contrast in long-term average O_3 concentrations in the Netherlands.

The only other adjustment of data that was necessary was for average PM_{10} concentrations, which we multiplied by 1.33 for all monitoring sites to account for losses of volatile components. This is a standard correction used within the European Union if continuous particle monitors are used.

Table 2. Monitoring Methods Used in the National Air Quality Monitoring Network[a]

Pollutant	Method	Calibration Procedure
NO_2, NO	Chemiluminescence	Zero air and span gas daily
Black smoke	Reflectance[b]	White and gray tile checked during reflectance measurement
PM_{10}	Beta gauge	Foils with known mass every 3 months
SO_2	UV fluorescence	Zero air daily, span gas weekly
O_3	Chemiluminescence	—[c]
CO	Gas filter correlation spectrometry	Zero air daily, span gas weekly

[a] Adapted from Elskamp (1989).

[b] Standard method specified by the Organization for Economic Cooperation and Development (OECD), 1964.

[c] No information about procedures for calibrating O_3 measurements was available.

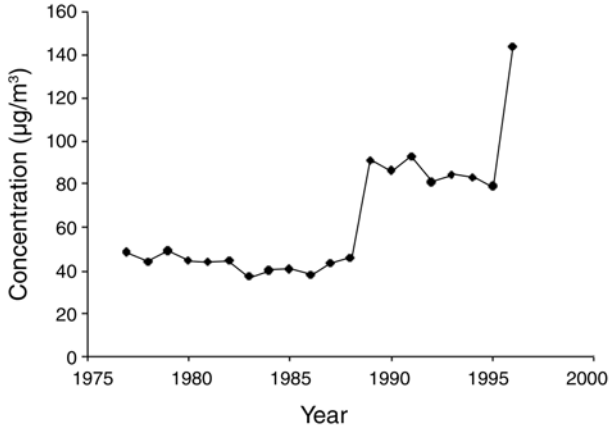

Figure 2. National average CO concentrations for 1977–1996, by year. The instrument used to measure CO in the national monitoring network was changed in 1989.

Geographic Information System Predictor Variables

To assess background concentrations of pollutants at the urban scale, regression models were developed with the measured concentrations at NAQMN sites as dependent variables and several potential predictor variables based on data collected using GISs as independent variables. All the databases we used were available at RIVM. The potential predictor variables were number of inhabitants (in a 1995 database) and address density (in a 1998 database) within three different buffers (300 m, 1000 m, and 5000 m) surrounding a subject's address. Address density is a standardized variable that the Dutch Central Bureau of Statistics developed as a proxy for the intensity of human activities in an area. The buffer sizes were based on earlier work in the Netherlands that was part of the Traffic-Related Air Pollution and Childhood Asthma (TRAPCA) study (Brauer et al. 2002). In the pilot study (Hoek et al. 2001, 2002), we used an average pollutant concentration for the subject's postal code area. A limitation of this method is that a subject may live near the border of another postal code area with a completely different address density. Other potential predictor variables included in the current study were land-use variables that indicated whether a monitoring site was located in the center of a city or town, a rural area, an industrial area, or near traffic. A complete list of potential predictor variables with their spatial scale and the year of the data used is presented in Table 3.

National Road Database At the local scale, pollutant concentrations were assessed using a digital road network to which data on traffic intensity were linked. Compared with the pilot study (Hoek et al. 2001, 2002), in the current study we used a more detailed, more complete, and geographically more accurate national road database (the NWB, 2001 version). The NWB includes all streets and roads in the Netherlands that have a street name or road number or both. This means that more than 98% of the Dutch roads are included. More than 95% of all locations for road sections in the NWB do not differ from the true location by more than 10 m (Ministry of Transport, Public Works, and Water Management 2001).

Geographic attributes are linked to each road section in the NWB, which makes it possible to link other information, such as traffic intensity data, to the road network. For the linkage of traffic intensity data, we made use of the following attributes that are linked to each road section in the NWB: a unique identification number for each road section ("WVK_ID"), street name ("STT_NAAM"), road number ("WEGNUMMER"), municipality code ("GME_ID"), starting kilometer of a road section ("BEGINKM"), ending kilometer of a road section ("EINDKM"), and the organization that manages the road ("WEGDEELLETTER"). Road sections in the NWB are divided into those that are managed by national, provincial, and municipal administration.

The NWB does not include information on road function or traffic intensity. Therefore, we collected traffic intensity data for the years 1986–1996 and linked them to the NWB by road name, road number, and road section.

Traffic intensity data were available for each separate section of roads managed by the national government (referred to as freeways in this study). We linked traffic data to national roads by the road number and to sections of national roads by the starting and ending kilometers. Traffic intensity data for provincial and municipal roads were only available for the road as a whole. We linked traffic data to provincial roads by the road name or road number. Traffic data were linked to municipal roads by the road name and municipality code because roads with the same name may be present in different municipalities.

Table 3. Potential Predictor Variables for Modeling the Urban Exposure Component

GIS Coverage[a]	Potential Predictor Variable	Spatial Scale	Year
Postcode register	Address density	4-position postal code areas	1998
Stedelijk ruimtegebruik	Use of urban space: land-use variables that indicate whether a site is located in the center of a city or town, a rural area, an industrial area, or near traffic	250 m × 250 m	1999
Aantal inwoners	Number of inhabitants	300 m, 1000 m, and 5000 m	1995

[a] Dutch names for the geographic data sets used in land-use regression analyses of urban-scale air polllution.

Traffic Intensity Data We aimed to obtain data on both total traffic intensity and truck traffic intensity for the study period 1986–1996. The road network in the Netherlands has a total length of more than 100,000 km. The national roads and provincial roads have total lengths of approximately 3200 and 9000 km, respectively. Thus, the municipalities are responsible for the largest part of the total road network. Traffic intensity data were not readily available for all roads.

For national roads, traffic intensity data for 1986–1996 were available from the Transport Research Center of the Ministry of Transport, Public Works, and Water Management. Data were available for all road sections between two junctions. Total traffic intensity data were available for the years 1986–2000, but data on truck traffic intensity (the sum of medium-duty and heavy-duty truck traffic intensities) were only available for 1992–2000.

Although traffic is counted on all provincial roads in the Netherlands, this information is not available in a central database. Therefore, we contacted all 12 provinces individually to obtain traffic intensity data. Data were available for all provincial roads, however, not always for the full period of 1986–2000. Table 4 lists the years for which data were available by province. Data on total traffic intensity were available for all of the provinces; however, data on truck traffic intensity were only available for 23% of the provincial roads.

Obtaining traffic intensity data for municipal roads, especially in small municipalities, was the most difficult. We used a standard questionnaire to obtain information from all 204 municipalities included in the study. Environmental Traffic Maps, used to assess traffic-related air pollution and noise, were another source of municipal data.

Table 4. Years for Which Data on Traffic Intensity Were Available for Each Province

Province	Years
Groningen	1986; 1990–2000
Limburg	1985; 1990–2001
Noord-Brabant	1995–1999
Friesland	1986; 1990–2000
Utrecht	1986; 1999; 2000
Noord-Holland	1986–1996; 1999
Drenthe	1986; 1990–2001
Overijssel	1986–2001
Gelderland	1993–2001
Zuid-Holland	1990–2000
Zeeland	1986–2001
Flevoland	1999

In the Netherlands, municipalities with more than 40,000 inhabitants are obliged to develop these maps for all roads on which there are at least 2450 motor vehicles/day (Harms 2000). For the municipalities with Environmental Traffic Maps, traffic data were available for all major roads. Data on total traffic intensity on municipal roads were obtained for 121 (59%) of the 204 municipalities in the study. Table 5 lists the municipalities with more than 40,000 residents for which traffic intensity data were available. No traffic data were available for many of the municipalities with a small number of study participants, most of which were small towns. Of the 21,868 deceased and subcohort subjects in the study for whom geocoding was possible, 17,912 (82%) lived in the 121 municipalities for which traffic data were available.

Not all municipalities had traffic counts for their municipal roads, and the municipalities that reported traffic counts did not have this information for all of their roads. On average, traffic intensity data were available for 14.3% of the municipal roads. This percentage varied substantially, however, between municipalities. Municipal roads without traffic intensity data were assumed not to be major roads, and a background traffic intensity value of 1225 motor vehicles/day was assigned to those roads to avoid underestimation of exposure on the local scale, for example, when calculating total traffic intensity in a buffer. This is half of the value of 2450 motor vehicles/day that municipalities with Environmental Traffic Maps used as a traffic intensity cutoff below which roads were not assessed for air pollution (Harms 2000).

Once traffic intensity data were obtained, several methodologic issues needed to be resolved before average traffic intensities could be linked to the NWB. For six of the municipalities and for four of the twelve provinces, traffic intensities were only available for workdays (Monday–Friday). There are no standards for the conversion of average workday traffic intensity into average whole-week traffic intensity (Monday–Sunday). However, for five municipalities and four provinces, both average workday and whole-week traffic intensities were available for several years. From this information, we calculated ratios between average whole-week and workday traffic intensities. To this end, the whole-week traffic intensities were expressed in counts per day, as for the workday intensities. The overall average ratios were 0.94 (SD = 0.03) for municipal roads and 0.93 (SD = 0.02) for provincial roads. The ratios did not change over time and did not depend on the size of a municipality or the intensity of workday traffic. Average workday traffic intensities were therefore multiplied by 0.94 and 0.93 for municipal and provincial roads, respectively, to estimate daily averages of whole-week traffic intensities.

Table 5. Number of Cohort Members in Municipalities with More than 40,000 Inhabitants and Availability of Municipal Traffic Data

Municipality	Number of Cohort Members	Number of Inhabitants in 1990	% of Roads with Traffic Data[a]
The Hague	10,611	441,506	30.5
Rotterdam	6,761	579,179	14.7
Utrecht	4,380	230,358	13.5
Eindhoven	4,015	191,467	12.3
Arnhem	2,844	139,220	18.0
Tilburg	2,667	156,421	11.8
Nijmegen	2,589	144,748	17.8
Maastricht	2,532	117,008	6.7
Enschede	2,477	146,010	9.5
Hilversum	2,388	84,608	—
Heerlen	2,183	94,046	19.5
Dordrecht	1,974	109,285	18.6
Leeuwarden	1,916	85,570	18.0
Amersfoort	1,831	99,403	4.3
Hertogenbosch, 's-	1,688	91,113	4.7
Velsen	1,654	58,520	11.5
Ede	1,605	93,377	3.7
Schiedam	1,605	69,417	17.4
Delft	1,535	88,739	7.5
Zeist	1,500	59,469	21.3
Leiden	1,474	110,423	10.7
Hengelo	1,427	75,993	8.6
Haarlemmermeer	1,402	95,782	11.6
Voorburg	1,293	40,116	9.0
Venlo	1,273	63,918	—
Rheden	1,213	45,691	25.5
Almelo	1,097	62,190	13.6
Kerkrade	1,050	53,127	18.9
Gouda	1,037	64,611	14.2
Zoetermeer	1,012	96,292	8.6
Helmond	1,004	68,159	11.6
Assen	887	49,650	10.3
Smallingerland	884	50,229	—
Zwijndrecht	760	41,884	6.9
Doetinchem	747	41,647	7.6
Lelystad	703	57,638	23.5
Veenendaal	667	48,343	24.6
Huizen	606	41,966	14.1
Weert	592	40,262	4.1
Nieuwegein	556	58,774	13.8
Barneveld	501	42,335	—
Communities of ≤ 40,000 with traffic data (N = 82)	22,946		17.2
Communities of ≤ 40,000 without traffic data (N = 80)	18,128		—

[a] Dash indicates no traffic data.

For two of the municipalities, only daytime traffic intensities (between 7:00 am and 7:00 pm) were available. A previous study had found, however, that 77.8% of the total daily traffic intensity in the Netherlands occurred during daytime hours (Dassen et al. 2000). We assumed that this percentage did not change over time and was independent of the traffic intensity on a road. For municipal roads, we therefore multiplied the daytime traffic intensity by 1.29 (= 1/0.778) to calculate the average daily traffic intensity.

Figure 3 shows the correlation between 1996 and 1986 traffic intensities on municipal, provincial, and national roads. The regression equations in Figure 3 show that the increase in traffic intensity over time was substantially larger for national and provincial roads than for municipal roads. Correlations between 1996 traffic intensities and 1986, 1987, 1988, 1989, and 1990 traffic intensities were all greater than 0.92 for all three road types, supporting the use of traffic intensities from one year to represent a long-term average.

Traffic data for individual municipalities were not always available for the same years. To account for temporal trends for the three road types, trends in traffic intensity were estimated using roads with data for several years and mixed modeling procedures. The estimated trends (percentage increases per year) in traffic intensity on national, provincial, and municipal roads within different traffic intensity classes are shown in Table 6. A linear trend for the whole period was assumed. These trends were used to estimate traffic intensities for roads that did not have data available for all years in the study period 1986–1996. (More details are provided in Appendix D; see section Appendices Available on the Web.)

Table 6. Estimated Trends (Percentage Increase per Year) in Traffic Intensity on National, Provincial, and Municipal Roads in 1986–1996, by Traffic Intensity Class

Traffic Intensity Class (motor vehicles/day)	Number of Observations	Trend (%)
National roads		
< 20,000	323	2.7
20,000–50,000	343	3.9
> 50,000	301	3.6
Provincial roads		
All intensities	2362	2.0
Municipal roads		
< 4,000	161	0.1
4,000–11,000	131	1.0
> 11,000	78	1.1

Regional, Urban, and Local Scales of Exposure

Regional Scale The regional component of exposure at the home address was estimated using interpolation of annual average air pollutant measurements obtained at regional monitoring stations in the NAQMN. Original measurement data (as 24-hour averages) were downloaded from a validated database. Original data were checked for

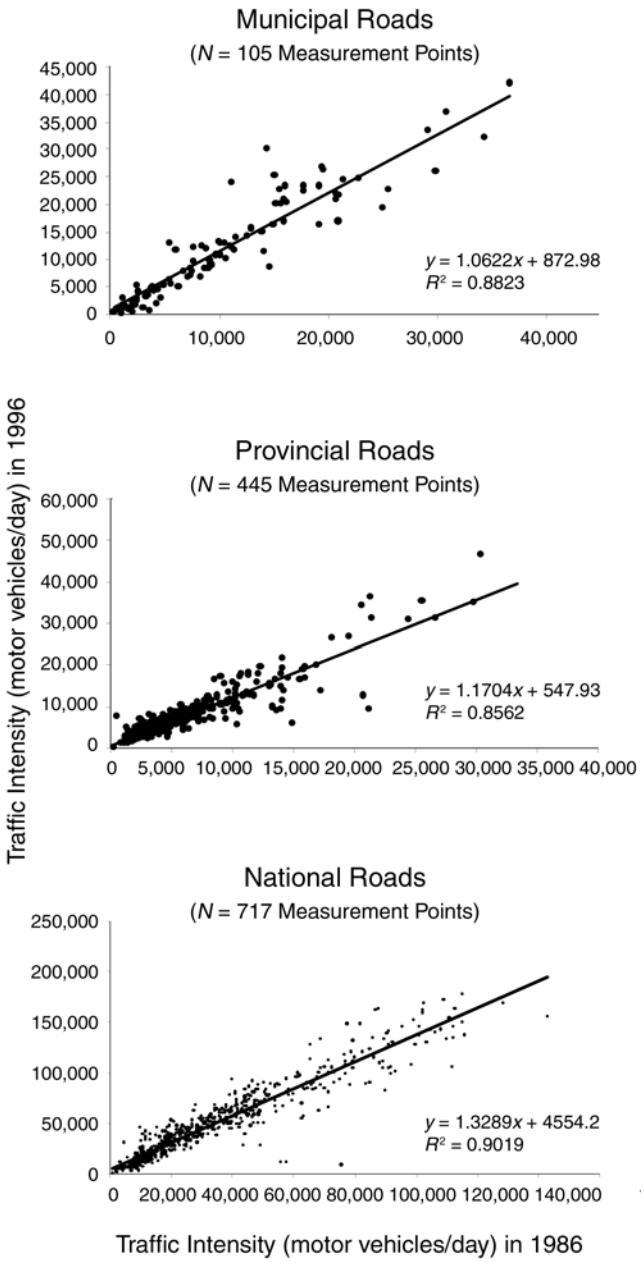

Figure 3. Correlation between 1986 and 1996 traffic intensities for municipal, provincial, and national roads. For each road type, a regression equation shows the relation between 1986 values (x) and 1996 values (y), and the coefficient of determination (R^2).

outliers using graphical methods, and after consultation with the RIVM network manager about unlikely concentration data, a few errors were corrected. Data from a few stations were not used because they were too close to major roads to be spatially representative of regional concentrations. We did not use data from stations that measured during fewer than half of the maximum number of years that measurements were obtained by the NAQMN. This was analyzed separately for the old network (1976–1985) and the new network (1987–1996). These stations were removed from the analysis so that for each analysis period there would be a consistent set of stations that all measured a considerable amount of the time. (More details are provided in Appendix C; see section Appendices Available on the Web.)

To prevent bias in comparisons across monitoring stations, imputed values were used for days on which measurements were missing. To estimate concentrations, daily ratios were calculated for each monitoring station by dividing the measured concentrations of pollutants at that site by the daily average concentrations at all regional and urban background monitoring stations. Average ratios were then calculated for summer and winter. For days with missing measurements, values were estimated by multiplying the seasonal average ratio for the monitoring station by the corresponding daily average of concentrations at all other monitoring stations. For each monitoring station, annual average pollutant concentrations were calculated, as well as the number of values (i.e., days) that contributed to the average concentrations. With these data, average concentrations over multiyear periods were calculated. To determine the annual average concentration for a station, values had to be available for at least 292 (80%) of 365 days; otherwise, the annual average concentration was considered as missing. The correlation between the unadjusted annual average concentrations and the adjusted annual average concentrations (i.e., those with imputed values) was greater than 0.9 for all pollutants and all stations, so imputation had a modest impact, as observed in the pilot study (Hoek et al. 2001).

We evaluated two methods to interpolate concentrations: ordinary kriging using the GSTAT package within the R statistical software environment (Pebesma 2004), and inverse distance weighting as in the pilot study (Hoek et al. 2001). Kriging is an optimal interpolation method that produces unbiased predictions which have minimal variance. The technique is based on the theory of regionalized variables and utilizes the spatial structure of the data. It involves the construction of a covariance function and the fitting of an appropriate model. The kriging interpolation predicts values by local weighted averaging, where the weights have been determined by the covariance function and the configuration of the data (Collins 1998).

Inverse-distance-weighted interpolation, with a power of 2, was also used to estimate concentrations at the home addresses. We studied the dependence of the prediction error on the distance criterion used for inclusion of network sites. Prediction errors were estimated by cross-validation: the pollutant concentration at a monitoring station was estimated using data from the other stations in the network, and the estimate was compared with the actual measured concentration. Exclusion of SO_2 measurements from monitoring sites more than 75 km away and exclusion of NO_2, NO, and black smoke measurements from sites more than 100 km away resulted in the lowest prediction errors in the cross-validation. Therefore, we used these distance criteria when we estimated the regional contribution to pollutant concentrations at the home addresses by inverse-distance-weighted interpolation.

Urban Scale The urban component of exposure at the home address was estimated using regression models, in which we evaluated land use, address density, and number of inhabitants in different buffers surrounding the home address as potential predictor variables. In the pilot study only the address density in the four-digit postal code area in which a subject resided was used as a predictor variable for exposure at the urban scale (Hoek et al. 2001). For each pollutant, regression models with mixed modeling were developed with residual concentrations as dependent variables. Residual concentrations for each regional and urban monitoring station in the NAQMN (Elskamp 1989) were calculated as the average measured concentration at that station minus the interpolated regional concentration (using cross-validation for regional sites). The average residual concentrations for each of four 5-year periods (1976–1980, 1981–1985, 1987–1991, and 1992–1996) were used as dependent variables in separate models. In 1986 the NAQMN was remodeled, resulting in only a limited number of days with valid measurements, so this year was excluded. We used 5-year periods because these were the planned exposure periods of interest for the NLCS-AIR study.

For each pollutant and each 5-year period separately, an initial model was developed with the predictor variable that had the highest adjusted explained variance (R^2) value in univariate regression analyses. Each of the other variables was added separately to this initial model, and the effect on the adjusted R^2 value was evaluated. If the effect was greater than 1% and the direction of the effect was as defined a priori, then the predictor variable with the highest addition to the previous regression model was

added to the model. This was repeated until there were no predictor variables that added more than 1% to the adjusted R^2 value of the previous regression model.

To assess whether a single regression coefficient for each predictor variable could be applied for the whole period 1976–1996, we tested interaction terms between different 5-year periods within this time span and the predictor variables in the final models. No significant differences between the coefficients for the different time periods were found for the predictor variables. Therefore, an overall coefficient was estimated for each predictor variable by using mixed modeling and combining the data of the different 5-year periods.

We used GISs to obtain values for the predictor variables at the coordinates of the home addresses of study participants. These values were multiplied by the coefficients of the regression models to calculate a concentration for the urban exposure component.

This urban exposure component was added to the regional component, resulting in a total background concentration. Background concentrations were estimated for all individual years in the period 1976–1996 for which data were available, and average exposure estimates were made for the 5-year periods 1976–1980, 1981–1985, 1987–1991, and 1992–1996.

Local Scale In the current study the availability of data on traffic intensities provided an opportunity to estimate continuous indicators for exposure at the local scale. The indicators were total traffic intensity in 1986 on what was determined by GIS to be the nearest residential road, and on the nearest major road (defined as a road with more than 10,000 motor vehicles/day), and the distances to these roads. Because of GIS limitations, the maximum distance to a nearby road that could be calculated was 500 m.

Buffer calculations were made by determining the sum of traffic intensity in 1986 within buffers of 100 m and 250 m around each home address per day. Each buffer was divided into cells of 10 m $\times$ 10 m, and for each cell the traffic intensity (motor vehicles/day) was assessed. Then, the traffic intensities of all cells within the specified buffer were added together. A buffer of 100 m was used because in the densely built Dutch cities, the largest contrast in traffic-related air pollutants is likely to occur within distances of less than 100 m (Briggs et al. 1997). We also calculated total traffic intensity in buffers of 100 m and 250 m while excluding roads on which traffic intensity was less than 5000 motor vehicles/day, and separately while excluding freeways.

Quantitative estimates of the local component concentrations were calculated using data from traffic-specific sites. In the NAQMN, however, there were only a limited number of traffic-specific sites, which were all concentrated in urban areas except for one site that was close to a freeway. We therefore used data from monitoring sites of the TRAPCA study (Brauer et al. 2003), which were not located close to freeways, to estimate the local component concentrations related to urban roads. To estimate the local pollutant concentrations resulting from nearby freeways, data from a Dutch study on air pollution near freeways was used (Janssen et al. 2001).

In the TRAPCA study, 40 monitoring sites were selected throughout the Netherlands. At each site NO_2, $PM_{2.5}$, and $PM_{2.5}$ filter absorbance were measured for four 2-week periods between February 1999 and July 2000 (Brauer et al. 2003). We transformed the annual average $PM_{2.5}$ filter absorbance at TRAPCA sites into a black smoke concentration using the equation: Black smoke ($\mu g/m^3$) = -3.663 + 9.897 $PM_{2.5}$ filter absorbance (Roorda-Knape et al. 1998). Then we estimated background concentrations of NO_2, black smoke, and PM_{10} (sums of the regional and urban concentrations) for the TRAPCA sites using the methods described above. The NAQMN did not measure $PM_{2.5}$ concentrations; therefore, we transformed estimated background PM_{10} concentrations at TRAPCA sites into $PM_{2.5}$ concentrations using the formula: $PM_{2.5}$ = 0.6739 PM_{10} $-$ 0.1038 (Cyrys et al. 2003). The residual (traffic-related) NO_2, black smoke, and $PM_{2.5}$ concentrations at each site were calculated (as measured concentrations minus estimated background concentrations), and regression models were developed with the sum of traffic intensity, excluding the traffic intensities of freeways, in a buffer of 100 m as the predictor variable. Of the 40 TRAPCA sites, 22 were used to develop regression models; the excluded sites were in cities or municipalities for which traffic intensity data were not available.

To estimate the local component of exposure, the coefficient of a regression model was multiplied by the total traffic intensity in 1986, excluding the traffic intensities of freeways, in a buffer of 100 m around each home address. When the traffic intensity in a 100-m buffer around a home address was higher than that at the TRAPCA site with the highest value, the exposures for that address were estimated using the sum of traffic intensity in a 100-m buffer around that TRAPCA site.

A study to estimate exposures near freeways in the Netherlands used weekly average concentrations of NO_2, $PM_{2.5}$, and black smoke measured at 24 schools located within 400 m of a freeway. Measurements were obtained 5 to 10 times between January 1997 and May 1998 (Janssen et al. 2001). For the same 24 schools, we assessed the truck traffic intensity on and the distance to the nearest freeway. Regression models were developed with the average concentrations at these 24 sites as dependent variables and

Table 7. Availability of Pollutant Data for Each Exposure Component in 1976–1985 and 1987–1996[a]

	Exposure Component				
Pollutant	Regional	Urban	Background (Regional + Urban)	Local	Overall (Regional + Urban + Local)
NO_2	Yes	Yes	Yes	Yes	Yes
NO[b]	Yes	Yes	Yes	No	No
Black smoke	Yes	Yes	Yes	Yes	Yes
SO_2[c]	Yes	Yes	Yes	No	No
$PM_{2.5}$[d]	No	No	No	Yes	Yes
PM_{10}[e]	Yes	Yes	Yes	No	No

[a] Periods used in the epidemiologic analyses.

[b] No data were available to assess NO concentrations on the local scale.

[c] Traffic (local) contributions to SO_2 concentrations were assumed to be negligible.

[d] No direct $PM_{2.5}$ background measurements were available; concentrations were estimated from PM_{10} background concentrations. Overall $PM_{2.5}$ concentrations were only available for 1987–1996.

[e] PM_{10} data were only available for 1992–1996; therefore, concentrations were estimated only for the study period 1987–1996.

truck traffic intensity on and distance to the nearest freeway in three categories (< 100 m; 100 to 300 m; and > 300 m, reference category) as predictor variables. For each home address, the local component of exposure to NO_2, black smoke, and $PM_{2.5}$ was estimated using the coefficients of the regression models. If a home address was more than 500 m from a freeway, the local pollutant concentration caused by nearby freeways was set to 0 $\mu g/m^3$.

Estimated local pollutant concentrations resulting from freeways and from other roads were added to the estimated background pollutant concentration to obtain an overall concentration. In most of the epidemiologic analyses, we added the background (regional and urban) concentration and the local traffic indicator variable to the model as separate exposure variables. However, we also specified models with the overall concentration as a single variable. Table 7 summarizes the available data for each pollutant.

Residential Mobility The exact address for each study subject in 1986 was known. In addition, the baseline questionnaire allowed space for identification of up to four previous cities of residence (but not the addresses within those cities). We used the residential histories to restrict the analysis to subjects who had lived at their current address for more than 10 years.

During the HEI quality assurance audit (see Appendix B. HEI Quality Assurance Report), it became clear that it was possible to identify the exact addresses of the deceased study participants from 1986 till death, as well as their exact residential history before 1986. This residential information is available from the Dutch Central Bureau of Genealogy, which has an archive of municipal registration cards for subjects that died before October 1994. For persons that died after October 1994, it also has computer files containing residential history. Residential information on these municipal registration cards for cohort members who had died was entered in a database.

Residential information for living cohort members was not available through this source. For the subcohort members, biennial follow-up questionnaires were used to determine residential mobility.

For data analysis, we created a variable to indicate whether a subject moved from his or her 1986 address during follow-up and used this variable to restrict the analysis to subjects with a stable address.

Traffic Noise Motor vehicle traffic results in both air pollution and noise. Previously reported associations of traffic with adverse health effects could thus be due to noise or air pollution or both. Therefore, we attempted to disentangle the effects of these two exposures.

Modeled road-traffic noise levels for the year 2001 were available from RIVM. Noise levels were calculated for grids of 25 m × 25 m using the Environmental Model for Population Annoyance and Risk Analysis (EMPARA; module NOISTOOL, version 4), which was developed to evaluate the size and the effects of traffic-related noise on a national scale (Dassen et al. 2001). Noise levels were calculated as daily averages because traffic intensity data were mostly available as 24-hour averages.

HEALTH ENDPOINTS

The study cohort was followed from January 1, 1987, through 1996, for a total of 10 years. Data on deaths of cohort members were obtained from the Dutch Central Bureau of Genealogy. Until October 10, 1994, the relevant data were obtained manually and entered on individual paper file cards. After that date, the transfer of data was automated. Data on cause of death were obtained from the Dutch Central Bureau of Statistics. Maastricht University supplied the following information: death certificate code, municipality of death, sex, and birth date. To these data, the Central Bureau of Statistics added the exact cause of death (expressed as *International Classification of Diseases,* 9th revision [ICD-9] codes for 1986–1995 deaths and *International Classification of Diseases,* 10th revision [ICD-10] codes for 1996 deaths). During the study, a procedure was developed to allow the data files with causes of death included to be transferred to Maastricht University. In the pilot study, these data remained at the Central Bureau of Statistics, and data analyses had to be conducted there. In the current analyses, we have used only the primary cause of death (that is, the underlying cause of death according to World Health Organization protocols) as coded on the death certificate. For 99.7% of the deceased subjects, the cause of death was available.

In accordance with previous cohort studies of the association between air pollution and mortality, we grouped the deaths by major causes (Table 8). Deaths by cardiovascular and respiratory causes were analyzed together and separately. In the attribution of effects related to traffic noise, it is important to separate respiratory and cardiovascular deaths, as a relation to noise is plausible only for cardiovascular deaths. Mortality from other causes (noncardiopulmonary, non–lung cancer mortality) was also analyzed as a separate variable. The hypothesis was that the latter mortality variable would not be associated with air pollution exposure.

We also investigated the relation between air pollution exposure and lung cancer incidence. Data on cancer incidence are routinely collected in the NLCS, including data from the municipal cancer registries, which are more accurate than data from death certificates. The follow-up period for lung cancer incidence was 11.3 years (September 1986 through December 1997).

CONFOUNDING VARIABLES

Data on potentially confounding variables were available mostly from the baseline questionnaires that cohort members filled out in 1986. Information on area-level covariates was available in databases from Statistics Netherlands.

Data Entry and Management

Before the current study began, the data from the full questionnaires for the subcohort (n = 4971) and for subjects with cancer had been entered in a separate database. For the current study, data from the full questionnaires also were entered for participants who died during follow-up.

The data-entry and data-management procedures described here are identical to procedures used in NLCS in general. The full questionnaire consists of 11 pages. The first page of the questionnaire is called an optical mark reading (OMR) form, which is machine-readable. Data from the first page consist of a search number (which is used to locate the questionnaires of people who have died), an ID number, demographic data, and basic data about smoking. The information about smoking on the first page is used to check for consistency with answers to the questions on these subjects that appear in the remainder of the questionnaire (pages 2–11). Therefore, for approximately 120,000 subjects data were available on age, sex, and smoking status. On the OMR form, subjects describe their smoking status by choosing a category of current smoker, "ex" (former) smoker, or never smoker, separately for cigarettes, cigars, and pipes. No information was available about the total number of years the subject smoked or the quantity of tobacco smoked. This more detailed information was available within the full questionnaire only. The data on pages 2–11 are entered when a subject develops cancer or dies.

Data Entry For each data-entry task, 100 to 200 questionnaires (pages 2–11) of cohort members (approximately as many men as women) who developed cancer or died are randomly selected, then entered and sorted on the basis of their ID numbers. The procedure used for entering the data from pages 2–11 of the questionnaire is described in a

Table 8. Mortality Categories Analyzed and Corresponding ICD Codes

Mortality Category	ICD-9 Codes	ICD-10 Codes
Natural cause	< 800	< V01
Cardiopulmonary	400–440 and 460–519	I10–I70 and J00–J99
Cardiovascular	400–440	I10–I70
Respiratory	460–519	J00–J99
Lung cancer	162	C33–C34
Noncardiopulmonary, non–lung cancer	Not 400–440, not 162, not 460–519, and < 800	Not I00–I70, not J00–J99, not C33–C34, and < V01

manual (Bethlehem et al. 2000). Blinding of the persons who enter the data is accomplished by enriching the group of questionnaires of subjects who have died with questionnaires of a random sample of subjects from the subcohort. Per data-entry task, approximately 10% to 20% of the total questionnaires from which data are entered are those of subcohort members.

Data entry for the NLCS takes place at three different places (Table 9). The same software (Pascal, Gebroeders Van Montfort, Heerlen/Maastricht) is used at the three locations (Bethlehem et al. 2000), and data from the three locations are merged at Maastricht University.

Table 9. Organization of Data Entry and Management

TNO Nutrition and Food Research, Zeist

- Entry of questionnaire data about food and nutrition (questions 11–36), smoking (questions 37–39), educational level (question 40), and occupation (question 42).
- Data cleaning of questions related to food and nutrition.
- Nutrient calculations, product-group calculations, and calculation of product-group and nutrient combinations based on the entered questionnaires.
- Biennial follow-up of the subcohort.

TNO Work and Employment, Hoofddorp

- Entry of questionnaire data about occupation (question 41).

Maastricht University, Maastricht

- Entry of questionnaire data about medical information (questions 43–50) and other questions (51–56).
- Repeated entry of a selection of questions in the questionnaire.
- Check for differences between the first entry and repeated data entry. Quick check of questions that are only entered once.
- Data cleaning of questions not related to food, except questions related to occupation. Data on food questions are cleaned based on the use of vitamins.
- Mortality follow-up: linkage of cohort to mortality data of Dutch Central Bureau of Genealogy (in earlier follow-up years manual linkage by CBG, in later years computerized linkage).
- Entry and management of mortality data in NLCS database.
- Management of data from NLCS questionnaires and mortality data.
- Management of cancer follow-up data (linkage to cancer registries and national database of pathology records).

The statistical program SPSS (version 12.0.1 for Windows; SPSS Inc., Chicago, IL) was used to determine which questions had the highest frequencies of errors at data entry. For men, they were questions 32, 37–39, and 48–50; for women, they were questions 47–51. Data from these questions are entered twice for all questionnaires, and the duplicate entries are checked for differences. Repeated entry of questionnaire data takes place only at Maastricht University, by the same three persons who entered the data the first time; however, for a specific questionnaire, the person who enters the data the second time differs from the person who entered the data the first time. The data manager, who does not enter data, compares the duplicate entries. When there are differences between the first and repeated data entries, a person who is also involved in the data entry checks the database entries against the questionnaires and, if necessary, corrects errors in the database. The same person has done this for more than 10 years. If necessary, a physician or dietitian or other expert is consulted. In the NLCS-AIR study, repeated data entry was not conducted for budgetary reasons.

Data Management First, inconsistencies between answers or strange answers are checked with the SPSS program. The output consists of the ID number and the questions that have to be checked. This takes place at Maastricht University and is conducted by several different people.

Data cleaning takes place at two places. All questions with inconsistencies between answers or strange answers, and those related to food and nutrition (questions 11–36), are sent to the TNO Nutrition and Food Research Institute, where a dietitian checks these questions and decides whether the answers have to be adjusted in the database (Breeijen et al. 1990). Changes are sent back to Maastricht University and are adjusted in the database. Data about smoking habits (questions 37–39) and about medical information (questions 43–48) are cleaned in a similar way at Maastricht University. Data that are not cleaned are, for example, answers to questions about residential history and about sports participation.

After data cleaning and correction of errors, several different people conduct a final check to determine whether adjustment has been done correctly (Breeijen et al. 1990).

After this step, data from page 1 of the questionnaire (the OMR form) and cancer and mortality data are added to the cleaned file of data from pages 2–11. Postal codes and more detailed information about food and nutrition, such as calculations of nutrient intake (Breeijen et al. 1990), are also added to the file.

The final analysis file consists of approximately 2500 variables.

Definition of Confounding Variables

Confounding variables were selected a priori as those considered in our pilot study (Hoek et al. 2002), in the initial two large U.S. cohort studies (Dockery et al. 1993; Pope et al. 1995), in the reanalysis of these two U.S. cohort studies (Krewski et al. 2000), and in previous analyses of the relationship between lung cancer and diet in the NLCS subjects, or were identified from the literature on risk factors for the causes of death under study. Potential confounding variables for the case–cohort analyses are described in Table 10 and for the full-cohort analyses in Table 11.

Table 10. Confounding Variables in the Case–Cohort Analyses

Individual Variables
Sex
Indicator variable
Age
Continuous variable (years)
Quetelet index (weight/height squared)
Categorical variable (kg/m^2)
1 = < 20
2 = 20–25
4 = 25–30
8 = > 30
Smoking status
Currently smoking cigarettes (yes/no), number of cigarettes per day, and years of smoking cigarettes
Currently smoking cigars (yes /no), number of cigars per day, and years of smoking cigars
Currently smoking pipes (yes/no), number of pipes per day, and years of smoking pipes
Passive smoking status
Partner is current smoker, former smoker, or never smoker
Educational level
Highest educational level of the household, coded as low (only primary school); middle (lower vocational education, such as technical or domestic science school); or high (junior high school, senior high school, higher vocational education, and university)
Occupation
EGP score of the last occupation, coded as
1 = blue collar (manual labor)
2 = lower white collar
3 = higher white collar
4 = other
5 = last occupation longer than 40 years ago
88 = never had paid work
Occupational exposure
ALOHA (JEM) used to assign exposure of the last occupation to biological dust, mineral dust, and gases and fumes, coded in three variables as 0 = no exposure, 1 = low exposure, or 2 = high exposure

Table continues next column

Table 10 (*Continued*). Confounding Variables in the Case–Cohort Analyses

Individual Variables (*Continued*)
Marital status
Married versus never married, divorced or widowed
Alcohol use
Categorical variable (g/day)
1 = 0
2 = 0.1–4
3 = 5–14
4 = 15–29
5 = ≥ 30
Total vegetable intake
Continuous variable (g/day)
Fruit intake
Continuous variable (g/day)
Energy intake
Continuous variable (kJ)
Saturated fatty acids intake
Continuous variable (g/day)
Monounsaturated fatty acids intake
Continuous variable (g/day)
Polyunsaturated fatty acids intake
Continuous variable (g/day)
Trans fatty acids intake
Continuous variable (g/day)
Total fiber intake
Continuous variable (g/day)
Folic acid intake
Continuous variable (µg/day)
Fish consumption
Continuous variable (g/day)
Area-Level Covariates
% persons with income below 40th percentile[a]
Continuous variable
% persons with income above 80th percentile[a]
Continuous variable

[a] Percentages were determined for two spatial scales: neighborhood and COROP (Coordinatie-Commissie Regionaal Onderzoeksprogramma) area. COROP values reflect mostly regional variation. Percentiles are of the national income distribution for the Netherlands.

Table 11. Confounding Variables in the Full-Cohort Analyses

Individual Variables
Sex
Indicator variable
Age
Continuous variable (years)
Smoking status
Cigarette smoking (never, former, or current smoker)
Cigar smoking (never, former, or current smoker)
Pipe smoking (never, former, or current smoker)
Area-Level Covariates
% persons with income below 40th percentile[a]
Continuous variable
% persons with income above 80th percentile[a]
Continuous variable

[a] Percentages were determined for two spatial scales: neighborhood and COROP area. COROP values reflect mostly regional variation. Percentiles are of the national income distribution for the Netherlands.

Sex Sex was modeled as an indicator variable.

Age Age was specified as a continuous variable, as this models the generally observed exponential increase of mortality rates with age. The age range of the cohort (55–69 years at baseline) is quite narrow when compared, for example, with that of the American Cancer Society Study cohort. As a sensitivity analysis, associations between mortality rates and age were examined using 1-year age classes.

Quetelet Index Body weight and height were used to calculate the Quetelet index, which was entered as a categorical variable because both low and high values may be associated with increased mortality. Categories were defined as 0–20 kg/m^2, 20–25 kg/m^2, 25–30 kg/m^2, and > 30 kg/m^2.

Smoking Status The baseline questionnaires provided detailed information on the number of cigarettes, cigars, or pipes that subjects smoked per day, the years they had smoked, and the years they started and stopped smoking. We used the questions that have been used in the analyses of lung cancer incidence in the NLCS (see Table 10).

To assess the sensitivity of associations between mortality and air pollution to adjustment for smoking, we used analyses stratified for smoking status and also specified models with quadratic smoking terms for continuous variables to allow for potential nonlinear relationships (Pope et al. 2002; Krewski et al. 2003).

Furthermore, we used the method from the pilot study (Hoek et al. 2002) and the American Cancer Society Study (Pope et al. 2002): that is, we used indicator variables for current smoker or former smoker versus never smoker; number of cigarettes smoked per day, separately for former and current smokers; and number of years of smoking, separately for former and current smokers.

Passive Smoking Status Passive smoking status was characterized by the question on whether the study participant's partner could be classified as a current smoker, former smoker, or never smoker. The questionnaire also provides information about number of hours of passive exposure to smoke and passive exposure at work. However, there were many missing values for these variables, and therefore they were not used in the analyses.

Educational Level Level of education was used as an indicator of cohort members' socioeconomic status. The level of education was classified as low (only primary school), middle (lower vocational education, such as technical school or domestic science school), or high (junior high school, senior high school, higher vocational education, and university). However, because the educational level may not be a good indicator for the socioeconomic status of a study participant when the educational level of the partner is much higher, the highest educational level in the household was used to define the educational level of the study participant.

Occupation Occupation was used as a second indicator for socioeconomic status and as an indicator for occupational exposures and for physical activity.

As an indicator for socioeconomic status, the last occupation was evaluated according to the EGP score, an international classification for socioeconomic status described by Erikson, Goldthorpe, and Portocarero (Erikson et al. 1979). A large proportion of the cohort was already retired at the onset of the study. Few people actually work until age 65 in the Netherlands. The last occupation (coded using the standard occupation coding of the Dutch Central Bureau of Statistics) was classified as not codable, never paid for work, blue collar, lower white collar, higher white collar, and last occupation longer than 40 years ago (a new category added because the last occupation is not a good indicator of socioeconomic status for someone who stopped working at an early age — which describes many Dutch women in this age group).

Occupational exposure may be an important confounder of the association between air pollution and mortality or lung cancer incidence, and therefore was evaluated in more

detail in the reanalysis of the two U.S. cohort studies (Krewski et al. 2000), compared with the original analyses (Dockery et al. 1993; Pope et al. 1995). In the current study, we used the ALOHA job-exposure matrix (JEM) (Kromhout et al. 2004) to account for possible occupational exposures. The question regarding occupational exposure to dust, fumes, and gases that was used in the two U.S. cohort studies is not included in the NLCS-AIR study.

A JEM can be defined as any cross-tabulation of a classification of jobs against a classification of chemical, biological, or physical agents, with, in each cell, a score for (potential) exposure (Kromhout and Vermeulen 2001). When linked with the occupational and industrial codes of the study subjects, a JEM can place subjects from different industry–occupation combinations in the same exposure category. A JEM can be constructed for the general population and include all possible occupations that occur in the population, or it can be industry-specific ('t Mannetje and Kromhout 2003).

The first consideration before using a general-population JEM is the exposure of interest. Another consideration is the fit between the occupational and industrial classifications used in the JEM and those in the study. To make optimal use of the information in a JEM, the level of detail in the study's occupational classification should be equal to or greater than the level of detail in the JEM ('t Mannetje and Kromhout 2003).

On the basis of these considerations, we decided to use the ALOHA JEM. First developed by Professor Hans Kromhout (Institute for Risk Assessment Sciences, Utrecht University) and Dr. J. P. Zock (Municipal Institute of Medical Research, Barcelona) for the follow-up of the European Community Respiratory Health Survey (ECRHS) on chronic obstructive pulmonary disease among young adults, the ALOHA JEM was used to establish occupational exposures to biological dusts, mineral dusts, gases, vapors, and fumes, in three categories: none, low, and high (Kromhout et al. 2004). In the Harvard Six Cities Study the baseline questionnaire included a question about occupational exposures to dust, gases, or fumes (Dockery et al. 1993), and in the American Cancer Society Study the baseline questionnaire included a question about occupational exposure to asbestos; chemicals, acids, or solvents; coals or stone dusts; coal tar, pitch, or asphalt; diesel engine exhaust; or formaldehyde (Pope et al. 1995). Estimation of occupational exposure using the ALOHA JEM is largely comparable to estimations in the Harvard Six Cities Study and the American Cancer Society Study. However, the automatic assignment of exposure by the ALOHA JEM avoids recall bias and differential misclassification of exposure ('t Mannetje and Kromhout 2003).

Another advantage of using the ALOHA JEM is that it was developed for a European study and therefore covers more of the occupations of NLCS-AIR study participants than JEMs developed for U.S. populations, such as the Hoar JEM (Hoar et al. 1980), which we considered but did not use.

Occupational exposure using the ALOHA JEM was assessed for the study participant's last occupation. As a sensitivity analysis, the occupational exposure of the longest-held occupation also was assessed.

Marital Status Marital status was included as a potential confounder in the cohort studies of Pope and colleagues (1995) and Abbey and colleagues (1999). In the current study, marital status was specified as a single indicator variable for never married, divorced, or widowed versus married.

Alcohol Use Alcohol use was entered as a categorical variable to allow for nonlinear associations such as higher mortality in nonusers and those consuming large amounts of alcohol compared with those consuming moderate amounts of alcohol.

Total Vegetable and Fruit Intake Vegetable and fruit intake were modeled as continuous variables. The questionnaire provides detailed information about dietary habits, such as use of antioxidant vitamins A, C, and E and intake of carotenoids, retinol, and folate. However, we only used total fruit intake and total vegetable intake, because previous NLCS studies found inverse associations for both vegetable and fruit intake with cancer, but no specific type of vegetable or fruit or nutrient was found to be particularly responsible for the associations (Voorrips et al. 2000).

Total Energy-Adjusted Fat Intake Total energy-adjusted fat intake was modeled as a continuous variable (grams per day). To allow for major differences in health effects of different types of fats, we also included intake of saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, and trans fatty acids separately in the model.

Other Dietary Information Finally, we adjusted separately for intake of total fiber, folic acid, and fish.

Area-Level Covariates The potential area-level covariates evaluated in our study were average annual income of individual inhabitants in the area, percentage of persons with low annual income (below the 40th percentile of the Dutch income distribution), percentage of persons with

high annual income (above the 80th percentile of the Dutch income distribution), and percentage of persons who depended on financial benefits from the state, in 1995. All variables were initially assessed at the neighborhood scale, in contrast to the metropolitan scale used in the American Cancer Society Study (Pope et al. 2002). Differences in mortality rates in the Netherlands can be larger between poor neighborhoods and wealthy neighborhoods than they are between urban areas and rural areas. Large differences in demographic factors exist between neighborhoods in urban areas and those in nonurban areas. There is no meaningful variation in climate and altitude within the Netherlands, so these variables were not of interest. Gaseous air pollutants were included as additional exposure variables in the analysis and not treated as confounding covariates. We ultimately decided to include in the analyses the percentage of persons with a low income and percentage of persons with a high income in a neighborhood, because these variables had the least amount of missing data. (More detail is presented in Appendix E; see section Appendices Available on the Web.)

In initial data analyses, we observed that the associations between air pollution and mortality were sensitive to the inclusion of a four-level indicator variable for the region of the country. In the final analyses, we therefore included an area-level variable defined at a larger spatial scale, the COROP (Coordinatie-Commissie Regionaal Onderzoeksprogramma) area, which is an administrative district linked to regional health services. The Netherlands is divided into 40 COROP areas. The inclusion in the analysis of percentages of persons with low and high income at the COROP level is supported by a map of life expectancy in the Netherlands (Figure 4), as lower-income rural areas in the northeast and east of the Netherlands demonstrate reduced life expectancy relative to more urbanized areas in the west.

Confounding Variables Not Used We did not adjust for some of the confounders used in the U.S. cohort studies. In particular, though information was available on whether subjects had high blood pressure or diabetes before 1986, we did not adjust for preexisting disease at baseline, because we regard this more as a potential marker for susceptibility to mortality related to air pollution. We also did not adjust for physical activity in general or physical activity at work. This was partly because of the difficulty in adequately defining meaningful categories, and partly because of the relation between physical activity level and the inhaled dose of air pollutants, as well as the possible association of low levels of physical activity with underlying disease.

One limitation was that information on changes in potential confounders during the study period was available only for the subcohort. For the rest of the full cohort, only information at baseline in 1986 was available. However, temporal patterns of variation in potential confounders in the subcohort may give an indication of temporal patterns in the full cohort.

EFFECT MODIFIERS

We evaluated the following potential effect modifiers: sex, smoking status, educational level, fruit intake, and vegetable intake. Educational level was assessed because in the two initial U.S. cohort studies (Dockery et al. 1993; Pope et al. 1995), educational attainment significantly modified the associations between air pollution and mortality. Sex and smoking status were evaluated for effect modification both in the full cohort and in the case–cohort study population. Educational level, fruit intake, and vegetable intake were evaluated only in the case–cohort sample because data on these variables were obtained from the full questionnaire, which was not available for the full cohort. We used stratified analyses to assess effect modification. Differences of effect estimates between strata were tested with the Cochran Q test, a method commonly used in meta-analysis (DerSimonian and Laird 1986)

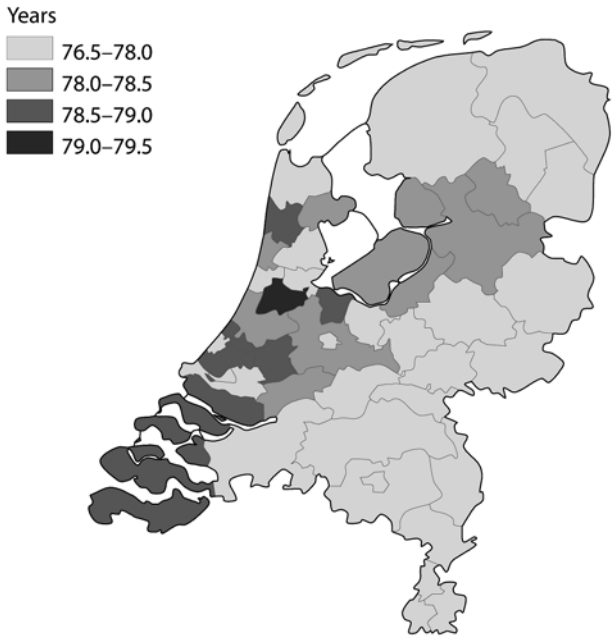

Figure 4. Life expectancy in the Netherlands, 1995–1999. The map is divided into areas of administration for the Municipal Health Services, which are broadly similar to the COROP areas for which data were obtained in this study. (Adapted from Volksgezondheid Toekomst Verkenning, Nationale Atlas Volksgezondheid, RIVM, Bilthoven.)

DATA ANALYSIS

Main Analyses

The case–cohort data were analyzed with a multivariate case–cohort approach adjusting for major potential confounders. The basic approach was the method developed for the NLCS (Volovics and Brandt 1997). Briefly, a random subcohort of approximately 5000 was sampled from the full cohort of approximately 120,000 older adults, while cases were enumerated in the full cohort. Person-years of follow-up were calculated for the subcohort members from January 1, 1987, until the date of death or the end of follow-up on December 31, 1996. Relative risks and corresponding 95% confidence intervals were estimated using the Cox proportional hazards model, processed with the STATA statistical software package. Standard errors were estimated using the robust Huber-White sandwich estimator to account for variance introduced by sampling from the full cohort.

Data for the full cohort were analyzed using the standard Cox proportional hazards model. The same STATA procedure was used; however, in this instance person-time in the study was taken from all cohort members.

We assessed three models that differed in their treatment of confounders. The first model adjusted only for age and sex (unadjusted model). The second model included all potential confounders identified in Tables 10 and 11. Approximately 40% of observations were lost because values were missing for one or more of the covariates, so we also specified an unadjusted model for the subjects that did not have missing information for any of the covariates included in the second model. This model was specified to assess potential selection effects.

In the data analysis, we included the estimated background concentration of an air pollutant and a traffic indicator variable (which represents the local exposure component) as separate variables in one model. Because of the high correlation between background air pollution concentrations during different periods, we decided to assess only the average concentrations for the 10-year periods before the start of follow-up (1976–1985) and during follow-up (1987–1996), excluding 1986, when the monitoring network was remodeled. In the main analyses, we estimated exposures for all combinations of background pollutant concentrations, the two 10-year periods of exposure, and variables related to local pollutant exposure. The main models all include linear exposure terms. As a sensitivity analysis, we conducted additional analyses examining separate categories of data for some of the variables related to the local exposure component (Table 12). For comparisons

Table 12. Overview of Main and Additional Air Pollution Analyses for 1976–1985 and 1987–1996[a]

Main Analyses	Additional Analyses
Background Exposure Component	
Estimated background concentrations of NO_2, NO, black smoke, SO_2, and $PM_{2.5}$ at home addresses	
Local Exposure Component	
Living near a major road (pilot study)	
Living near a major road (current study)	
Traffic intensity on the nearest road	Traffic intensity on the nearest road as a categorical variable (< 1225, 1225–5000, 5000–10,000, > 10,000 motor vehicles/day) Highest five intensities excluded Natural logarithm of distance added Product of traffic intensity and ln (501 − distance)
Traffic intensity in a 100-m buffer	
Traffic intensity on *and* natural logarithm of distance to the nearest major road	Traffic intensity on the nearest major road as a categorical variable (< 10,000, 10,000–20,000, > 20,000 motor vehicles/day) and natural logarithm of distance to the nearest major road Product of traffic intensity and ln (501 m − distance) Restricted to freeways and to roads with < 10,000 motor vehicles/day
Quantitative estimate of local exposure (NO_2, black smoke, and $PM_{2.5}$) added to the background concentration	Only background concentration Background concentration and quantitative estimate of local exposure component separately

[a] No consistent data were available for 1986, when the air pollution monitoring network was remodeled.

with other studies, we also included models with the estimated background and local pollutant concentrations added (overall exposure). These models were only used for assessments of NO_2, black smoke, and $PM_{2.5}$ concentrations during the follow-up period 1987–1996.

Calculation of Relative Risks

Calculations of relative risks associated with continuous variables were based on the change from the 5th to the 95th percentile in the distribution of values for that variable (Table 13). Relative risks associated with categorical variables were calculated relative to the reference variable in the category.

Spatial Autocorrelation

The HEI-sponsored reanalysis of the Harvard Six Cities and American Cancer Society cohort studies documented that it is necessary to account for spatial autocorrelation in health and pollution exposure data. One important difference between the current study and the American Cancer Society Study is that we estimated exposure to air pollution on an individual level by using local GIS and urbanization data in addition to regional air pollution data. In comparison, the American Cancer Society Study used exposure data that were identical for each of the subjects living in one of the communities included in the study. The approach we took was similar to the HEI reanalysis approach (Krewski et al. 2000), in which spatial clustering of the data was assessed progressively in a set of separate analyses.

The HEI reanalysis of the two U.S. cohort studies used a two-stage approach. The first step involved calculation of community-specific mortality rates from a regression model including indicator variables for city, but not for air pollution, while adjusting for individual-level confounders. The second step involved regression of these adjusted community-specific mortality rates on air pollution and other ecologic variables, using different weights. This approach was not possible for the current study because we used individual-level exposure variables.

We therefore established contacts with Drs. Michael Jerrett (University of California–Berkeley) and Richard Burnett (Health Canada, Ottawa, Ontario), who developed one-stage models taking into account spatial autocorrelation. Geocoded data on neighborhoods and municipalities were transformed into weight matrices to assess spatial

Table 13. Increments Used to Calculate Relative Risk

Variable	Change
Background and overall exposure components[a]	
NO_2 concentration	30 μg/m^3
NO concentration	30 μg/m^3
Black smoke concentration	10 μg/m^3
SO_2 concentration	20 μg/m^3
$PM_{2.5}$ concentration	10 μg/m^3
Traffic variables	
Total traffic intensity on nearest road as continuous variable	10,000 motor vehicles/day
Natural logarithm of distance to this nearest road	−1.77[b]
Product term of total traffic intensity on nearest road as continuous variable *and* natural logarithm of converted distance to this nearest road as continuous variable	26,500
Total traffic intensity on nearest major road (defined as a road with >10,000 motor vehicles/day) as continuous variable	20,000 motor vehicles/day
Natural logarithm of distance to this nearest major road	−2.3[b]
Product term of total traffic intensity on nearest major road as continuous variable *and* natural logarithm of converted distance as continuous variable	40,000
Sum of traffic intensity in a 100-m buffer	335,000 motor vehicles/day
Local exposure component[a]	
NO_2 concentration	6 μg/m^3
Black smoke concentration	6 μg/m^3
$PM_{2.5}$ concentration	2.5 μg/m^3

[a] Pollutant concentrations are quantitative estimates.

[b] A negative value to obtain RR above 1 if subjects living closer to major roads experienced higher mortality.

autocorrelation on these two levels. Analyses within the case–cohort framework were more complicated than anticipated because of the small number of cases in the subcohort, especially in the neighborhood analyses. The method requires that each cluster at the finest level of analysis have a sufficient number of members from the subcohort for stable statistical computations. There were many neighborhoods and some municipalities having zero, one, or two subcohort members, with consequent instability of random effects. This is an inherent difficulty of random effects models with a case–cohort study design. The only real solution is to select the subcohort by sampling that is stratified on the clusters. This was not possible here, as the subcohort already existed. Therefore, we decided to perform the spatial autocorrelation analyses only for the analyses of the full cohort (which use standard Cox proportional hazards models and do not use the subcohort).

Cox-Poisson random effects survival software, as described by Jerrett and colleagues (2005b), was used to incorporate spatial clustering at the municipal or neighborhood scale in the full-cohort analyses. Both one-level analyses of either municipality or neighborhood and two-level analyses of both municipality and neighborhood were conducted, using distance-decay random effects models. In addition, we specified a random effects model that takes into account clustering but ignores which areas are adjacent to each other (i.e., clusters are independent). Analyses were performed in R.

Figure 5. Municipalities of the Netherlands represented in the full study cohort, in black.

RESULTS

STUDY POPULATION

Figure 5 shows the municipalities represented in the full cohort. They are distributed throughout the Netherlands and include small rural communities as well as the major cities of Rotterdam, The Hague, and Utrecht. Amsterdam is not included because it did not have an automated population registry in 1986 when the NLCS was initiated. Table 14 lists the individual municipalities that each contributed at least 1% of the subjects in the full cohort. The three major cities contributed 18% of the cohort, and 35% of the cohort members lived in the 11 municipalities with more than 100,000 inhabitants. The distribution of the case–cohort study population was similar.

Table 14. Municipalities with At Least 1% of the Subjects in the Full Cohort (N = 120,227)

Municipality	Number of Inhabitants in 1990	Subjects in Full Cohort	Percentage of Full Cohort
The Hague	441,506	10,611	8.8
Rotterdam	579,179	6,761	5.6
Utrecht	230,358	4,380	3.6
Eindhoven	191,467	4,015	3.3
Arnhem	139,220	2,844	2.4
Tilburg	156,421	2,667	2.2
Nijmegen	144,748	2,589	2.2
Maastricht	117,008	2,532	2.1
Enschede	146,010	2,477	2.1
Hilversum	84,608	2,388	2.0
Heerlen	94,046	2,183	1.8
Dordrecht	109,285	1,974	1.6
Leeuwarden	85,570	1,916	1.6
Amersfoort	99,403	1,831	1.5
Hertogenbosch, 's-	91,113	1,688	1.4
Velsen	58,520	1,654	1.4
Ede	93,377	1,605	1.3
Schiedam	69,417	1,605	1.3
Delft	88,739	1,535	1.3
Zeist	59,469	1,500	1.2
Leiden	110,423	1,474	1.2
Hengelo	75,993	1,427	1.2
Haarlemmermeer	95,782	1,402	1.2
Voorburg	40,116	1,293	1.1
Venlo	63,918	1,273	1.1
Rheden	45,691	1,213	1.0

Table 15. Characteristics of the Municipalities Represented and Those Not Represented in the NLCS[a]

Variable / Municipality in NLCS	Minimum Value	Percentile					Maximum Value
		5th	25th	50th	75th	95th	99th	
Address density[b]								
Yes	71	157	398	693	1162	2218	3593	4656
No	96	135	260	442	768	1550	2672	5637
% Age > 65 yr								
Yes	7	9	12	14	17	22	24	25
No	5	11	12	14	17	22	25	28
% Low income								
Yes	26	31	35	39	43	48	49	59
No	23	32	35	37	40	45	48	51
% High income								
Yes	12	13	17	20	24	31	38	39
No	11	15	18	21	25	31	36	51

[a] Data source: Dutch Central Bureau of Statistics, 1993. There were 199 municipalities included in the NLCS (in 1993 four of the 1986 municipalities were no longer independent municipalities) and 445 municipalities were not included.

[b] Number of addresses per km^2.

Table 16. Number of Deaths in the Study Populations, by Mortality Category

Mortality Category	Full Cohort (N = 120,227)	Case–Cohort (N = 21,911)[a]	Subcohort (N = 4,971)
Natural cause	17,674	17,674	734
Cardiopulmonary	7,325	7,325	309
Cardiovascular	6,279	6,279	264
Respiratory	1,046	1,046	45
Lung cancer	1,935	1,935	73
Noncardiopulmonary, non–lung cancer	8,749	8,749	360

[a] The number in the case–cohort population depends on cause of death. N = 21,911 for analyses of all natural causes of death; this also includes participants for whom the residential address could not be geocoded.

One of the original 204 municipalities in the NLCS was excluded because no subjects from this small town were included in the cohort. The remaining 203 municipalities were not a random sample of all municipalities of the Netherlands. Statistically significant differences in address density and percentage of subjects with a low income were found between municipalities participating in the NLCS and those not participating (Table 15). However, the difference in address density is small compared with the range of densities across municipalities. Because the NLCS is a prospective cohort study, bias due to these small differences in baseline characteristics is unlikely. No difference was found in the percentage of subjects with a high income, or in the number of persons older than 65, between municipalities participating and those not participating in the NLCS.

Table 16 lists the number of deaths that occurred during follow-up in the full cohort and in the subcohort. For the epidemiologic analyses we excluded 426 subjects with special dietary habits that had been recruited for the original NLCS study on diet and cancer. Of the 120,227 subjects in the full cohort, 17,674 (14.8%) died during the 10-year follow-up period. All deaths in the full cohort are used in the case–cohort analyses. Consistent with their relative sizes, 24 times more deaths occurred in the full cohort than in the subcohort. Compared with our pilot study, the larger numbers and longer follow-up in the current study provided substantially more statistical power to estimate associations between air pollution and mortality with good precision. Of all natural-cause (nonaccidental) deaths, 41% were due to cardiopulmonary disease, and the vast majority of these were cardiovascular deaths. More than 1000 of the deaths were due to respiratory causes, allowing separate analyses of respiratory and cardiovascular deaths. Eleven percent of the deaths were due to lung cancer. Thus, the number of deaths was sufficient to allow analysis of associations with lung cancer mortality, in contrast to the pilot study.

The remaining 49% of all deaths from natural causes were deaths from noncardiopulmonary, non–lung cancer causes. Major diseases in this category were cancers other than lung cancer (5723 cases) and diseases of the digestive tract (467 cases). The category also included a number of diseases that are potentially associated with air pollution, such as bladder cancer (180 cases) and some diseases related to the cardiovascular system and the circulatory system (449 cases), including acute rheumatic fever and chronic rheumatic heart disease (ICD-9 codes 390–400; ICD-10 codes I00–I09) and diseases of arteries, arterioles, and capillaries, as well as diseases of veins and lymphatics (ICD-9 codes 441–460; ICD-10 codes I71–I99). As the number of these cases was relatively small, we retained the original definition of this category.

There were 2234 incidences of lung cancer during the 11.3 years of follow-up for this health endpoint and 1935 lung cancer deaths during the 10 years of follow-up for mortality analyses. The similarity of these numbers is consistent with the high fatality rate of lung cancer.

Tables 17 and 18 give population characteristics of the subjects who died of natural causes and of the subcohort members. Tables 19 and 20 present data on the same characteristics in the full cohort, for which the available information was less complete. Case subjects differed from the other subjects in the full cohort and from subcohort members with respect to several potential confounders, such as age, sex, smoking status, and occupation, consistent with the expected impact of these variables on mortality. Nontrivial percentages of values were missing, especially for occupation, passive smoking status, fat intake, and number of cigarettes smoked per day. The percentage of missing values was slightly higher among the case subjects than among the subcohort members, an issue that is further addressed below (see section Air Pollution and Mortality: Main Analyses).

EXPOSURE

For 97% of the study subjects in the full cohort, the home address could be geocoded and exposure could be assessed.

Background Air Pollution Concentrations

We evaluated ordinary kriging and inverse-distance-weighted interpolation as methods to estimate concentrations for the regional contribution to pollutant exposure at the home addresses. We used the distance squared in interpolation, as in the pilot study. As documented previously (Hoek et al. 2001), differences in prediction errors were small between different power parameters used for inverse-distance-weighted interpolation (higher power parameters assign greater influence to values closest to the interpolated point). Especially for black smoke, the number of monitoring sites available was limited (nine sites in the period 1992–1996), so it was not possible to develop a variogram model suitable for kriging. Correlations between estimates obtained with inverse-distance-weighted interpolation and with kriging were greater than 0.92 for NO_2 and SO_2, indicating that ordinary kriging and inverse-distance-weighted interpolation performed similarly. To be consistent, inverse-distance-weighted interpolation was used for all air pollutants. Exclusion of SO_2 measurements from sites that were more than 75 km away and exclusion of NO_2, NO, and black smoke measurements from sites more than 100 km away resulted in the lowest prediction errors in the cross-validation; therefore, these distance criteria were used in the estimation of regional concentrations at the home addresses by inverse-distance-weighted interpolation. Table 21 lists the prediction errors related to interpolation, expressed as the average root mean square error (RMSE) over the different years of interpolation for each pollutant.

For NO_2 and NO, the RMSE was lowest when the distance criterion was 75 km. However, not all home addresses were within 75 km of a monitoring site, resulting in missing values for the regional concentration estimate. Therefore, we used a distance criterion of 100 km for NO_2 and NO; furthermore, the RMSE values for 75 km and 100 km were only slightly different (see Table 21).

In Table 22, the regression models and coefficients used to estimate the urban exposure component are shown for NO_2, NO, black smoke, and SO_2. The predictor variables that are included in the NO model are also included in the NO_2 model, and the coefficients in the two models are similar.

In Table 23, the R^2 and RMSE values of the regression models in the current study are shown together with those of the models used in the pilot study to estimate the urban exposure component (Hoek et al. 2001). The R^2 values are higher and the RMSE values are lower for the current study than for the pilot study.

Additional model calculations for NO_2 and NO in which the number of inhabitants in a 5000-m buffer was the only predictor variable resulted in R^2 values of 56.4% (RMSE = 4.42) for NO_2 and 40.8% (RMSE = 6.15) for NO. This suggests that the explained variance of the NO_2 regression model of the current study is higher mainly because the number of predictor variables is larger than in the NO_2 model of the pilot study. The regression model for NO in the current study has a higher explained variance compared with the model of the pilot study owing to the combination of an extra predictor variable and a scale for the predictor variables that is geographically more accurate in

Table 17. Valid Observations for Confounding Categorical Variables in the Case–Cohort Study Population

Categroical Variable	Case Subjects (N = 17,674)[a]			Subjects in Subcohort (N = 4971)[a]		
	% of Total Subjects[b]	Number of Subjects[c]	% of Category	% of Total Subjects[b]	Number of Subjects[c]	% of Category
Sex	100			100		
Male		11,578	65.5		2397	48.2
Female		6,096	34.5		2574	51.8
Quetelet index (kg/m^2)	95			96		
< 20		776	4.6		179	3.7
20–25		8,107	48.0		2375	49.7
25–30		6,761	40.1		1901	39.8
> 30		1,232	7.3		325	6.8
Cigarette smoking status	100			100		
Never smoker		4,347	24.7		1807	36.4
Former smoker		6,283	35.7		1737	35.0
Current smoker		6,965	39.6		1415	28.5
Passive smoking status	90			90		
Never smoker		6,254	39.4		1485	33.2
Former smoker		3,911	24.7		1394	31.2
Current smoker		5,697	35.9		1592	35.6
Educational level	98			99		
Low		4,304	24.7		1017	20.7
Middle		8,971	51.6		2565	52.2
High		4,119	23.7		1330	27.1
Occupation	87			89		
Never had paid work		847	5.5		319	7.2
Blue collar		5,348	34.6		1340	30.3
Lower white collar		2,292	14.8		784	17.8
Higher white collar		3,456	22.3		955	21.6
Last occupation > 40 yr ago		843	5.5		249	5.6
Other		2,678	17.3		770	17.4
Exposure to biological dust	85			86		
No exposure		11,091	73.7		3059	71.6
Low exposure		2,788	18.5		943	22.1
High exposure		1,169	7.8		269	6.3
Exposure to mineral dust	85			86		
No exposure		10,819	71.9		3284	76.9
Low exposure		2,559	17.0		639	15.0
High exposure		1,670	11.1		348	8.1
Exposure to gases and fumes	85			86		
No exposure		8,983	59.7		2788	65.3
Low exposure		4,288	28.5		1104	25.8
High exposure		1,777	11.8		379	8.9
Marital status	100			100		
Married		13,790	78.2		3871	78.2
Never married, divorced, or widowed		3,835	21.8		1081	21.8
Alcohol intake (g/day)	93			94		
0		4,202	25.5		1120	23.9
0.1–4		4,024	24.4		1342	28.6
5–14		3,408	20.7		1068	22.7
15–29		2,750	16.7		732	15.6
≥ 30		2,107	12.8		434	9.2

[a] N indicates total number of subjects.

[b] Of total subjects, percentage with valid observations for the category.

[c] Number of subjects with valid observations for the categorical variable.

Table 18. Valid Observations and Distribution of Values for Confounding Continuous Variables in the Case–Cohort Study Population

Continuous Variable	Case Subjects (N = 17,674)[a]						Subjects in Subcohort (N = 4971)[a]					
	Minimum Value	Percentile			Maximum Value	n (%)[b]	Minimum Value	Percentile			Maximum Value	n (%)[b]
		25th	50th	75th				25th	50th	75th		
Age	54	60	64	67	70	17,674 (100)	55	58	62	65	70	4971 (100)
% persons with low income in a neighborhood	3	36	41	47	91	16,901 (96)	17	36	41	46	88	4759 (96)
% persons with high income in a neighborhood	3	12	18	24	74	16,833 (95)	3	13	19	25	67	4749 (96)
% persons with low income in a COROP area	32	36	41	45	50	17,373 (98)	32	36	41	45	50	4894 (98)
% persons with high income in a COROP area	13	18	19	23	28	17,373 (98)	13	18	19	23	28	4894 (98)
Number of cigarettes per day												
Former smoker	0	0	0	10	95	16,453 (93)	0	0	0	8	80	4746 (95)
Current smoker	0	0	0	12	95	16,453 (93)	0	0	0	3	75	4746 (95)
Years of smoking												
Former smoker	0	0	0	24	61	17,188 (97)	0	0	0	20	54	4866 (98)
Current smoker	0	0	0	41	62	17,188 (97)	0	0	0	56	59	4866 (98)
Vegetable intake (g/day)	0	124.1	168.6	222.5	1576.9	17,627 (100)	0	133.7	178.3	232.0	1252.0	4960 (100)
Fruit intake (g/day)	0	70.4	137.2	221.0	3444.1	17,627 (100)	0	89.0	153.3	233.5	961.6	4960 (100)
Saturated fatty acids intake (g/day)	3.3	29.3	33.9	38.9	78.1	15,762 (89)	7.9	27.9	32.5	37.6	82.9	4626 (93)
Monounsaturated fatty acids intake (g/day)	2.2	27.7	32.3	37.1	82.2	15,762 (89)	5.4	26.4	30.7	35.7	71.3	4626 (93)
Polyunsaturated fatty acids intake (g/day)	0	12.5	16.8	22.5	63.9	15,762 (89)	0	11.9	16.0	21.3	61.4	4626 (93)
Trans fatty acids intake (g/day)	0	1.8	2.5	3.5	35.2	17,627 (100)	0	1.8	2.6	3.5	21.4	4960 (100)
Total fiber intake (g/day)	0	19.8	24.7	30.4	135.9	17,627 (100)	0	20.8	25.8	31.3	77.8	4960 (100)
Folic acid intake (µg/day)	0	156.6	192.7	239.3	2332.6	17,627 (100)	0	160.6	197.2	241.0	1001.1	4960 (100)
Fish consumption (g/day)	0	0	8.7	19.9	287.1	17,627 (100)	0	0	8.2	19.9	181.6	4960 (100)

[a] N indicates total number of subjects.

[b] n indicates number of subjects with valid observations for the continuous variables (percentage of total subjects is shown in parentheses).

Table 19. Valid Observations for Confounding Categorical Variables in the Full Cohort

Categorical Variable	Case Subjects (N = 17,674)[a]			Other Subjects (N = 102,553)[a]		
	% of Total Subjects[b]	Number of Subjects[c]	% of Category	% of Total Subjects[b]	Number of Subjects[c]	% of Category
Sex	100			100		
Male		11,578	65.5		46,514	45.4
Female		6,096	34.5		56,039	54.6
Cigarette smoking status	93			94		
Never smoker		4,891	29.8		41,076	42.6
Former smoker		5,155	31.4		30,479	31.6
Current smoker		6,372	38.8		24,937	25.8
Cigar smoking status	96			96		
Never smoker		13,980	82.7		86,906	88.3
Former smoker		1,453	8.6		6,512	6.6
Current smoker		1,470	8.7		4,969	5.1
Pipe smoking status	96			96		
Never smoker		15,575	91.5		92,450	93.7
Former smoker		879	5.2		4,273	4.3
Current smoker		565	3.3		1,998	2.0

[a] N indicates total number of subjects.

[b] Of total subjects, percentage with valid observations for the category.

[c] Number of subjects with valid observations for the categorical variable.

Table 20. Valid Observations and Distribution of Values for Confounding Continuous Variables in the Full Cohort

Continuous Variable	Case Subjects (N = 17,674)[a]						Other Subjects (N = 102,553)[a]					
	Minimum Value	Percentile			Maximum Value	n (%)[b]	Minimum Value	Percentile			Maximum Value	n (%)[b]
		25th	50th	75th				25th	50th	75th		
Age	54	60	64	67	70	17,673 (100)	54	58	61	65	70	102,524 (100)
% persons with low income in a neighborhood	18	36	41	47	91	17,109 (97)	16	36	41	46	97	99,108 (97)
% persons with high income in a neighborhood	3	12	18	24	74	16,825 (95)	3	5	19	25	78	97,641 (95)
% persons with low income in a COROP area	32	36	41	45	50	17,373 (98)	32	36	41	45	50	99,566 (97)
% persons with high income in a COROP area	13	18	19	23	28	17,373 (98)	13	18	19	23	28	99,566 (97)

[a] N indicates total number of subjects.

[b] n indicates number of subjects with valid observations for the continuous variables (percentage of total subjects is shown in parentheses).

Table 21. Prediction Error with Interpolation of Data from Regional Monitoring Stations[a]

Distance Criterion (km)[b]	NO_2	NO	Black Smoke	SO_2
50	4.38	5.23	2.14	4.08
75	3.89	4.67	1.56	4.03
100	3.93	4.70	1.40	4.04
150	4.12	4.79	1.69	4.10
200	4.25	4.87	1.80	4.14
No criterion	4.32	4.91	1.83	4.17

[a] Values are RMSE in μg/m^3, derived from cross-validation. Data were interpolated for the years that measurements were available: NO_2 and NO, 1977–1996; black smoke, 1984–1996; SO_2, 1976–1996.

[b] Data from monitoring stations within this distance from the home address are included in the interpolation.

Table 23. Comparison Between Performance of Current Study and Pilot Study Methods for Estimation of the Urban Exposure Component

	Current Study[a]		Pilot Study[b]	
Pollutant	R^2(%)	RMSE	R^2(%)	RMSE
NO_2	67.3	3.57	54.0	4.21
NO	45.9	5.64	30.6	6.37
Black smoke	49.2	1.22	38.3	1.38
SO_2	34.8	3.23	18.1	3.62

[a] Predictor variables for the different pollutants in the current study are described in Table 22.

[b] Address density of the four-digit postal code area was used as the predictor variable in the pilot study.

Table 22. Coefficients for Estimating the Urban Exposure Component for Each Pollutant[a]

Variable[b]	Coefficient (SE)
NO_2 (N = 202)	
Intercept	−2.21 (0.50)
Number/1000 of inhabitants in a 5000-m buffer	0.31 (0.01)
Located in a nonrural area[c]	4.29 (1.01)
Located in the center of a city or town[c]	6.01 (1.93)
NO (N = 203)	
Intercept	−2.29 (0.78)
Number/1000 of inhabitants in a 5000-m buffer	0.39 (0.01)
Located in a nonrural area[c]	4.48 (1.56)
Black smoke (N = 23)	
Intercept	−0.72 (0.38)
Number/1000 of inhabitants in a 1000-m buffer	1.23 (0.04)
SO_2 (N = 508)	
Intercept	−1.26 (0.30)
Located in a nonrural area[c]	2.78 (0.58)
Located in an urban area[c]	3.31 (0.79)
Located in an industrial area[c]	6.25 (1.31)

a The urban exposure component is based on the residual concentrations at urban and regional monitoring sites and GIS-derived predictor variables.

[b] N indicates the number of observations on which the regression model is based; one site is represented in multiple five-year periods. The site is included as a random effect. R^2 and RMSE values of the models are described in Table 23.

[c] Indicator variable with 0 = no and 1 = yes.

the current study. As a primary pollutant, NO exhibits more local spatial variation than NO_2, which is mainly formed by atmospheric processes.

There were significant temporal trends in air pollution concentrations between 1976 and 1996 (Figure 6). No consistent data were available for 1986 because the monitoring network was being remodeled. Concentrations of SO_2, in particular, had decreased substantially to very low levels at the end of the follow-up period. These trends were similar when we assessed the measured air pollution concentrations at the monitoring locations.

Temporal trends were mostly due to large-scale changes in emissions that affected different locations in the Netherlands in similar proportions. As a result, the estimated air pollution concentrations at home addresses of the case–cohort study population for different time periods were highly correlated (Table 24). Correlations within the full cohort were similar; for example, correlations comparing the 10-year average concentrations for 1976–1985 and 1987–1996 were 0.95 for NO_2, 0.91 for NO, and 0.94 for SO_2. The high correlations were not artifacts of the estimation procedure in which we used the same estimated urban exposure component for all time periods, since correlations for annual measured concentrations at monitoring network sites were high as well (for $NO_2 > 0.91$; for NO > 0.85; for black smoke > 0.95, and for $SO_2 > 0.84$). Analyses disentangling the effects of different time periods were therefore not feasible. In analyses of the association between air pollution and mortality, we assessed the average concentration of the 10-year period before the start of follow-up and the 10-year period coinciding with follow-up.

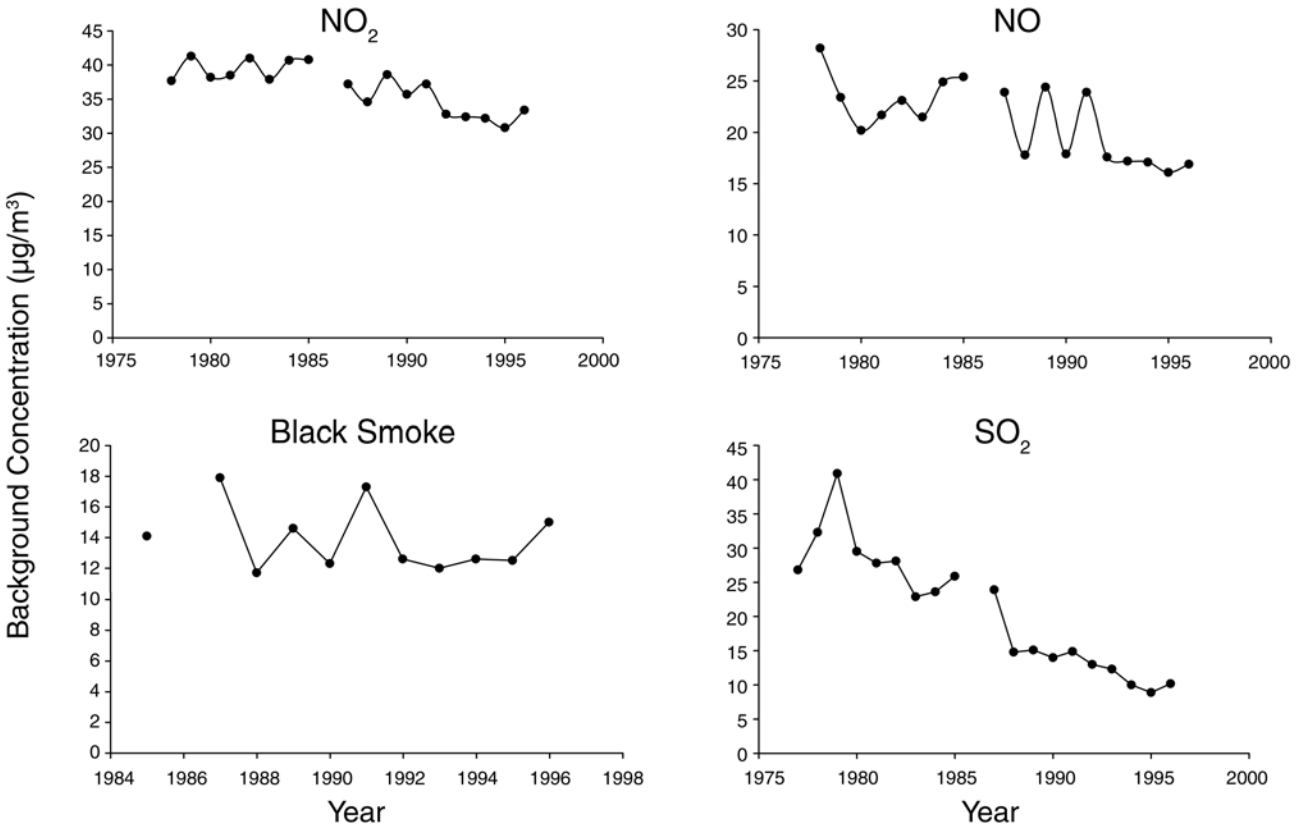

Figure 6. Average background concentrations of air pollutants during the study period (1976–1996) at home addresses of study participants (*N* = 117,528). No consistent data were available for 1986.

Table 24. Correlation of Background Pollutant Concentrations Between Different Periods at Home Addresses of the Case–Cohort Study Population (*N* = 21,868)

	1981–1985	1987–1991	1992–1996
NO_2			
1976–1980	0.99	0.92	0.93
1981–1985	1	0.93	0.94
1987–1991		1	0.98
NO			
1976–1980	0.98	0.91	0.91
1981–1985	1	0.88	0.89
1987–1991		1	0.96
Black smoke[a]			
1987–1991		1	0.97
SO_2			
1976–1980	0.97	0.96	0.88
1981–1985	1	0.95	0.84
1987–1991		1	0.94

[a] Black smoke data were not available for 1976–1980 and were available for only 2 years (1984 and 1985) in the period 1981–1985.

Table 25. Distribution of Estimated Long-Term Average (1987–1996) Pollutant Concentrations (μg/m^3) at 1986 Home Addresses of the Full Cohort, by Spatial Scale (N = 117,528)

Pollutant / Spatial Scale[a]	Minimum Value	Percentile						Maximum Value
		5th	25th	50th	75th	95th	99th	
NO_2								
Background	15	21	30	36	40	45	48	52
Background + local	15	22	32	38	43	49	55	66
Black smoke								
Background	9	9	12	14	15	17	18	19
Background + local	9	11	15	17	18	23	27	35
$PM_{2.5}$[b]								
Background + local	23	24	27	28	30	32	33	37
NO[c]								
Background	2	6	14	21	23	32	34	36
SO_2[d]								
Background	4	6	10	13	17	22	28	34

[a] "Background" refers to the sum of the estimated regional and urban exposure components. "Background + local" is the sum of the estimated regional, urban, and local exposure components, which is referred to as the overall concentration.

[b] For $PM_{2.5}$, there is little variation between "background" and "background + local."

[c] Data were not available to estimate local concentrations for NO.

[d] For SO_2, there is essentially no local (traffic) contribution to the exposure concentration.

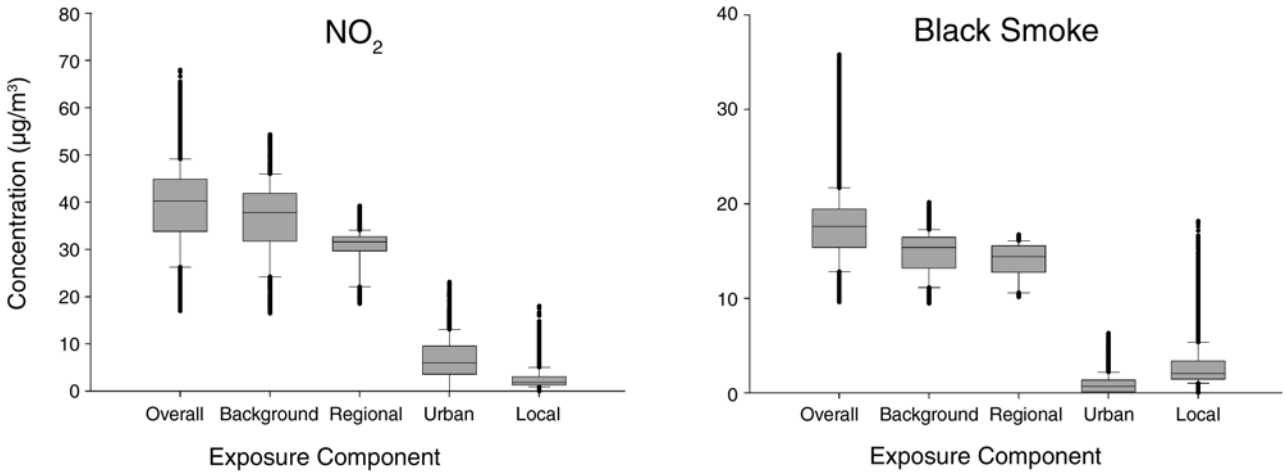

Figure 7. Distributions of estimated NO_2 and black smoke concentrations for 1987–1996 at home addresses of study participants (N = 117,528), by spatial scale. "Overall" is the sum of estimated regional, urban, and local concentrations. "Background" is the sum of estimated regional and urban concentrations. NO_2 and black smoke are the only pollutants for which quantitative exposure estimates are available for all spatial scales (regional, urban, and local scales). For each box the center line shows the median value, and the bottom and top lines show the 25th and 75th percentiles. The vertical bars extend from the 5th and 95th percentiles to the minimum and maximum values, respectively.

Estimated background (regional and urban) air pollution concentrations at home addresses varied substantially within the cohort (Table 25; Figures 7 and 8). The largest variability, relative to mean concentrations, was found for NO concentrations. Even with the local exposure component added, the range of $PM_{2.5}$ concentrations was small. Adding the local exposure component had a greater effect on the distribution of exposure concentrations for black smoke than for NO_2. The regional exposure component contributed most to the average background and overall concentrations. However, the urban and local exposure components contributed significantly to the variability in the background and overall air pollution concentrations (Figures 7 and 8).

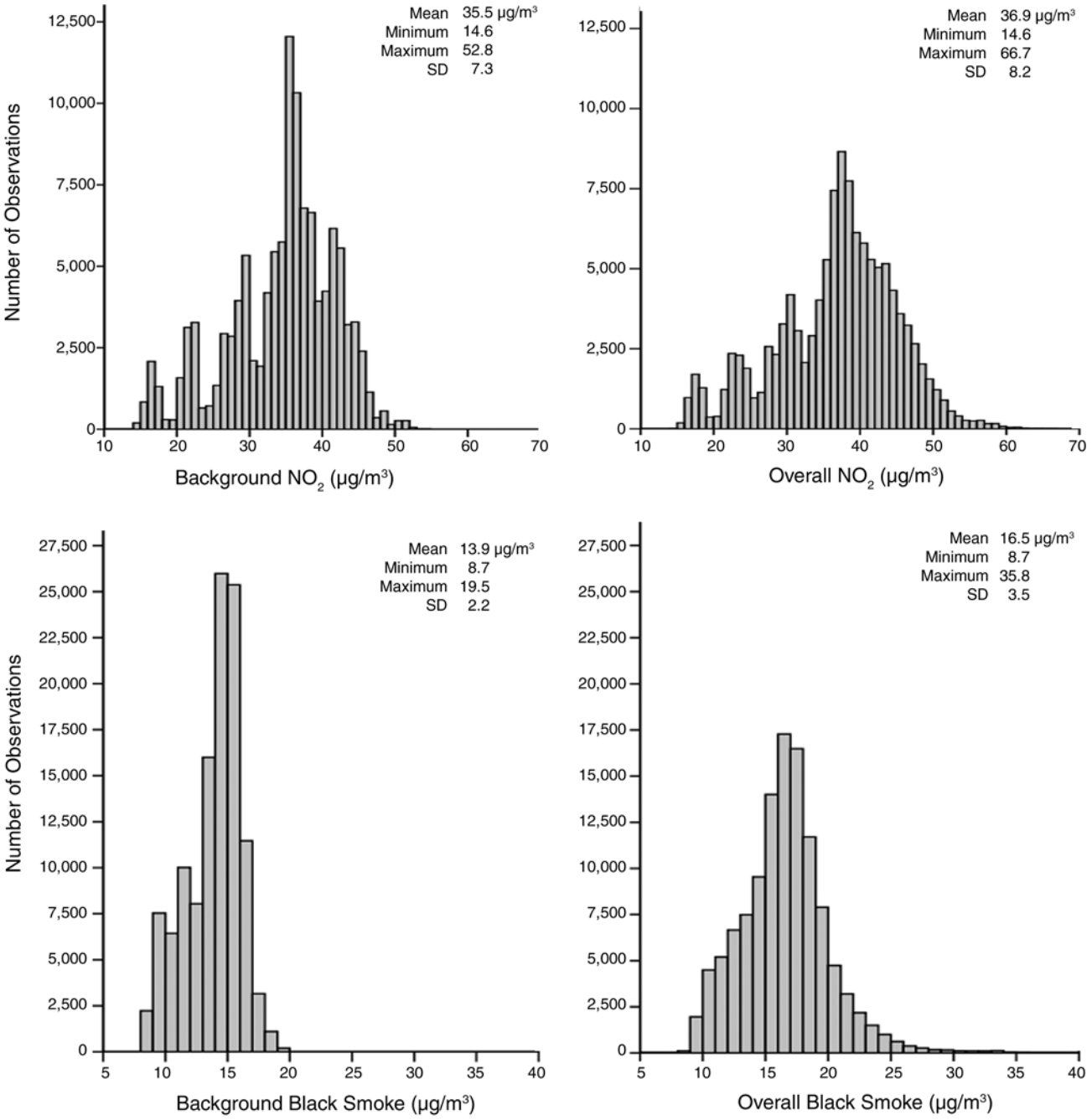

Figure 8. Distributions of estimated exposure components at the home addresses of study participants (N = 117,528): NO_2, black smoke, SO_2, and $PM_{2.5}$ concentrations for 1987–1996; traffic intensity on the nearest road for 1986; and sum of traffic intensity in a 100-m buffer for 1986. For SO_2, only background concentrations are shown; because there was virtually no local (traffic) contribution, background and overall concentrations are equivalent. For $PM_{2.5}$, only overall concentrations are shown because there was little variation in background concentrations. The data for the two traffic intensity variables were used to estimate the local exposure component. (*Figure continues next page*).

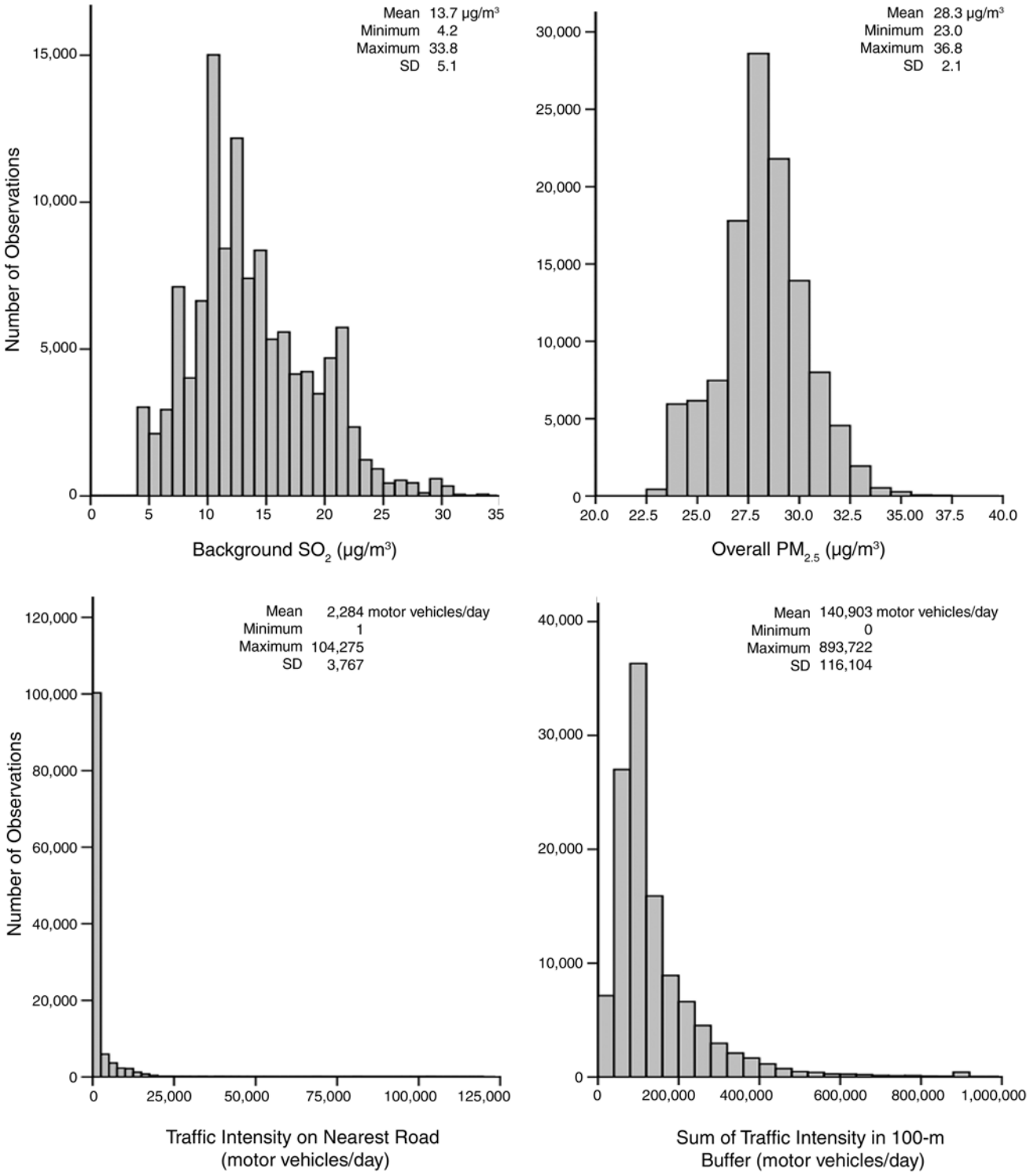

Figure 8 (*Continued*).

The correlation between the average background concentrations of the different pollutants was high for the home addresses (Table 26). This was largely due to the similarity of regional patterns for the different pollutants, with low concentrations in the north and higher concentrations in the more populated west of the country. We therefore had limited ability to disentangle the potential effects of individual pollutants. Correlations with SO_2 were moderately high. Correlations for the full cohort and the case–cohort study population were nearly identical.

Local Traffic Variables

Traffic Intensity Data Information on total traffic intensity was obtained for all national roads (for all years in the period 1986–1996) and all provincial roads (although not for all roads for all years in 1986–1996). For municipal roads, data were obtained for 121 (59%) of the total of 204 municipalities. Especially for municipalities with a small number of participants, most of which are small towns, no data were available. The 121 municipalities for which data were available contained 95,700 (81.4%) of the total 117,528 subjects in the study. Traffic intensity data were available for 14.3% of the municipal roads. Therefore, a background traffic intensity value of 1225 motor vehicles/day was assigned to a large proportion of the municipal roads in most of these municipalities, as explained previously. Data on truck traffic intensity were available for all national roads. However, data on truck traffic intensity were available for only 19% of the municipal roads and 23% of the provincial roads for which data on total traffic intensity were available.

As documented in Figure 3, the correlation between 1996 and 1986 traffic intensities on municipal, provincial, and national roads was high. Correlations between traffic intensities in 1996 and traffic intensities in the years 1986 through 1990 were all greater than 0.92 for the different road types. All traffic intensities were therefore transformed into 1986 intensities such that temporal trends did not bias comparisons across addresses. The increase in traffic intensity over time was substantially larger for national and provincial roads than for municipal roads (see Figure 3 and Table 6). This was due in part to municipal policies that limit automobile traffic in urban areas, for example, by imposing parking restrictions.

Traffic Intensity Variables With the methods used in the pilot study [Hoek et al. 2002), we found that 5893 (5%) of the 117,528 subjects in the full cohort lived near a major road (defined as living within 100 m of a freeway or within 50 m of a major urban road, using a less accurate and less complete road network compared with the road network used in the NLCS-AIR study). With the more refined methods of the current study, we found that 5784 (4.9%) of the 117,528 subjects lived within 100 m of a freeway or within 50 m of a major road (defined as a road with more than 10,000 motor vehicles/day). Despite the similar percentages of subjects living near a major road in the two analyses, there were considerable differences in classification (Table 27). By both methods, the majority of the subjects were classified as not exposed to pollution by living near a major road; however, of those classified as exposed by one of the two methods, only 17% were classified as exposed by both methods. The use of different definitions and cutpoints to define a road as major in the two studies contributed to the differences in classification. Of the 117,528 total addresses in the full cohort, 86,537 (73.6%) had an assigned traffic intensity on the nearest road of 1225 motor vehicles/day and 38,346 (32.6%) were located in municipalities with 100,000 or more inhabitants. Of the addresses in these larger municipalities, 24,888 (64.9%) had an assigned traffic intensity on the nearest road of 1225 motor vehicles/day. Of the 79,182 addresses in municipalities with fewer than 100,000 inhabitants, 61,649 (77.9%) had an assigned traffic intensity on the nearest road of 1225 motor vehicles/day. These results show that traffic intensity data were available for a higher percentage of the roads in the larger municipalities than in the small municipalities.

Table 26. Correlation Between Average Background Concentrations of Different Pollutants (1987–1996) at Home Addresses of the Full Cohort (N = 117,528)

	NO_2	Black Smoke	$PM_{2.5}$	NO	SO_2
NO_2	1	0.85	0.75	0.94	0.69
Black smoke		1	0.84	0.83	0.60
$PM_{2.5}$			1	0.69	0.43
NO				1	0.74

Table 27. Agreement Between Classifications of the Full Cohort (N = 117,528) as Living Near a Major Road or Not by Pilot Study and Current Study Methods[a]

Pilot Study	Current Study		Total
	No	Yes	
No	107,888	3747	111,635
Yes	3,856	2037	5,893
Total	111,744	5784	117,528

[a] "Yes" indicates subjects were classified as living near a major road. "No" indicates they were classified as not living near a major road.

Table 28. Distribution of Traffic Intensity Values for Home Addresses of Study Participants Living on Roads with Traffic Intensities Higher than 1225 Motor Vehicles per Day

Value	All Addresses (N = 22,417)	In Municipalities with ≥100,000 Inhabitants (N = 10,500)	In Municipalities with <100,000 Inhabitants (N = 11,917)
Minimum	1,226	1,229	1,226
5th percentile	1,458	1,513	1,425
25th percentile	2,619	2,927	2,458
50th percentile	5,062	6,035	4,228
75th percentile	9,536	11,192	7,817
95th percentile	17,553	20,353	14,620
Maximum	104,275	104,275	101,160

Table 29. Distribution of Values for Traffic Intensity on and Distance to the Nearest Major Road[a] for Home Addresses of the Full Cohort in 1986 (N = 117,528)

Value	Traffic Intensity (motor vehicles/day)	Distance (m)
Minimum	10,000	5
5th percentile	10,000	55
25th percentile	10,000	222
50th percentile	10,171	485
75th percentile	13,758	501
95th percentile	30,502	501
99th percentile	78,274	501
Maximum	114,968	501

[a] All subjects living more than 500 m from a major road were assigned a distance of 501 m to and a traffic intensity of 10,000 motor vehicles/day on that road.

Table 30. Distribution of Values for the Sum of Traffic Intensity in a Buffer Around the Home Address of Each Study Participant in 1986 (N = 117,528)

Value	Traffic Intensity in a 100-m Buffer (motor vehicles/day)
Minimum	0
5th percentile	35,525
25th percentile	75,557
50th percentile	104,125
75th percentile	166,787
95th percentile	363,519
Maximum	2,867,610

In Table 28 the distribution of the results for traffic intensity on the nearest road is shown for addresses on roads with traffic intensities higher than 1225 motor vehicles/day. Results are shown for all addresses together and separately for addresses in municipalities with at least 100,000 inhabitants and in those with fewer than 100,000 inhabitants. The roads in the more-populated municipalities for which traffic intensity data were available had, on average, higher traffic intensity. Overall, 9.6% of the subjects lived on a residential road with traffic intensity of at least 5000 motor vehicles/day, and 4.5% of the subjects lived on a road with at least 10,000 motor vehicles/day.

Owing to GIS computer limitations, we calculated exact distances only up to 500 m, as described previously (see section Methods / Exposure Assessment / Regional, Urban, and Local Scales of Exposure / Local Scale). For subjects within 500 m of the nearest road, the median distance to the nearest road was 16 m (interquartile range, 11–22 m), with a minimum value of 1 m and a maximum value of 466 m. For 14 subjects, the nearest road was located farther than 500 m away.

Of the 117,528 subjects in the full cohort, 60,026 (51.1%) lived within 500 m of a major road, defined as a road with traffic intensity > 10,000 motor vehicles/day, in 1986 (Table 29). The average distance to the nearest major road for these 60,026 subjects was 237 m, the minimum distance was 5 m, and the maximum distance was 500 m. Only 4.4% of study participants lived within 50 m of a major road, and 10.3% lived within 100 m of a major road.

Table 30 shows the distribution of results for the sum of traffic intensity in a buffer of 100 m around the home address of each study participant in 1986. A few of the values were extremely high. These were set to 893,722 motor vehicles/day, the maximum value found in the TRAPCA study, which was used to derive a quantitative

local air pollution estimate. The distributions of results for other variables indicating local air pollution exposure, traffic intensity on the nearest road (Figure 8), traffic intensity on the nearest major road (Table 29), and sum of traffic intensity in a 250-m buffer around the home address (data not shown), were also all highly skewed.

Local Air Pollution Estimates In the regression models for quantitatively estimating the local exposure component without taking into account air pollution effects of nearby freeways, the regression coefficients for pollutants, per 100,000 motor vehicles/day in a 100-m buffer, were as follows: for NO_2 the coefficient was 1.61 μg/m^3 (SE = 0.60 μg/m^3), and the R^2 of the model was 26.3% (RMSE = 5.70); for black smoke, 1.84 μg/m^3 (SE = 0.38 μg/m^3) with an R^2 of 54.5% (RMSE = 3.54); and for $PM_{2.5}$, 0.50 μg/m^3 (SE = 0.23 μg/m^3) with an R^2 of 18.7% (RMSE = 2.21). The 100-m buffer was the most significant predictor of the estimated local pollutant concentration (though the difference in explained variance when traffic intensity in a 250-m buffer and traffic intensity on the nearest road were used as predictors was small). The average local pollutant concentrations (minimum; maximum) predicted from traffic intensity in a 100-m buffer were 2.3 μg/m^3 (0; 14.4 μg/m^3) for NO_2, 2.6 μg/m^3 (0; 16.4 μg/m^3) for black smoke, and 0.7 μg/m^3 (0; 4.5 μg/m^3) for $PM_{2.5}$.

The coefficients for the regression models to estimate the contribution of nearby freeways to the local exposure component are shown in Table 31. No distance effect could be shown for $PM_{2.5}$. The R^2 values for the regression model were 11.6% (RMSE = 5.21) for NO_2, 59.7% (RMSE = 1.40) for black smoke, and 31.2% (RMSE = 1.92) for $PM_{2.5}$. Of the 21,911 case subjects, 1873 (8.6%) lived within 500 m of a freeway. For these individuals, the average contribution of nearby freeways to the local pollutant concentration (minimum; maximum) was predicted to be 2.7 μg/m^3 (0.2; 9.8 μg/m^3) for NO_2, 1.9 μg/m^3 (0.1; 7.7 μg/m^3) for black smoke, and 2.2 μg/m^3 (0.2; 7.0 μg/m^3) for $PM_{2.5}$.

The distributions of the local air pollution estimates, as sums of contributions from freeways and other roads, are shown in Figures 7 and 8. Especially for black smoke, a primary pollutant, the range of local concentration estimates was wide compared with the values for background (urban and regional) concentrations. For all of the pollutants, the average contribution of the estimated local air pollution concentration to overall estimated exposure was small, consistent with the small number of subjects living near major roads.

Table 31. Coefficients for Estimating the Local NO_2, Black Smoke, and $PM_{2.5}$ Concentrations Near Freeways[a]

	Coefficient (SE)		
Variable	NO_2	Black Smoke	$PM_{2.5}$
Truck traffic intensity[b]	3.86 (3.84)	1.90 (1.03)	4.01 (1.42)
Distance of <100 m	4.43 (3.73)	5.06 (1.00)	−0.02 (1.38)
Distance of 100–300 m	0.53 (2.65)	1.00 (0.71)	−0.07 (0.98)

[a] Regression models are based on pollutant measurements at 24 locations near freeways, with truck traffic intensity on the nearest freeway and distance to it in 3 categories (< 100 m, 100–300 m, and > 300 m as the reference category) as predictor variables.

[b] Truck traffic intensity is measured per 10,000 trucks in 24 hours.

Performance of the Exposure Assessment Method

Other studies (Brauer et al. 2003; Jerrett et al. 2005a) have reported R^2 values obtained by incorporating the three spatial scales in one overall regression method. To illustrate the overall performance of our exposure assessment method, we developed one overall regression model for each air pollutant using average concentrations for 1987–1991 measured at regional, urban, and street (local) monitoring stations in the NAQMN as dependent variables. For all pollutants, the regional component was described by an indicator variable (North, East, West, or South) as a proxy for the interpolated estimates for the regional exposure component, which cannot be used as predictors in the model. The urban exposure component was modeled using the procedures described in the Methods section. The sum of traffic intensity (excluding the traffic intensity of freeways) in a 100-m buffer around a home address, truck traffic intensity on the nearest freeway, and distance to this freeway in three categories were used as indicator variables for the local exposure component for all pollutants. However, none of the NAQMN sites in the period 1987–1991 was located within 500 m of a freeway; therefore, the contributing effect of the nearest freeway on the performance of the overall model could not be evaluated. The resulting models explained 84%, 44%, 59%, and 56% of the variability in concentrations for NO_2 (N = 36 sites), NO (N = 36 sites), black smoke (N = 16 sites), and SO_2 (N = 81 sites), respectively. One monitoring site was located in a street canyon with extremely high annual average concentrations of NO (248 μg/m^3) and black smoke (63 μg/m^3). Excluding this site resulted in models that explained 67% and 87% of the variance on NO and black smoke, respectively.

Table 32. Correlation of 1987–1996 Estimated Background Air Pollution Exposures with Local and Overall Exposures in the Full Cohort (N = 117,528)

	Background	
Pollutant	Local	Overall
NO_2	0.33	0.97
Black smoke	0.29	0.81
$PM_{2.5}$	0.17	0.90

Table 33. Correlation of 1987–1996 Estimated Background Air Pollution Exposures with Traffic Intensity Variables in the Full Cohort (N = 117,528)

	Traffic Intensity		
Pollutant	On the Nearest Road	In a 100-m Buffer	On the Nearest Major Road
NO_2	0.14	0.32	0.19
Black smoke	0.12	0.28	0.13
$PM_{2.5}$	0.11	0.21	0.12
NO	0.15	0.34	0.21
SO_2	0.12	0.27	0.17

Correlation Between Local and Background Exposure Variables The correlation between the traffic intensity on the nearest road and that on the nearest major road was 0.12; the correlations between the sum of traffic intensity in a 100-m buffer and traffic intensity on the nearest road and on the nearest major road were 0.62 and 0.16, respectively. The correlation between background and local air pollution variables was low but statistically significant (Tables 32 and 33). The overall air pollution estimate was dominated by the background estimate, consistent with the relatively small number of subjects that were living close to major roads.

AIR POLLUTION AND MORTALITY: MAIN ANALYSES

Several models were created to assess the association between exposure to air pollution and relative risk of mortality (see Table 12). We observed that the estimated risk associated with a specific traffic variable (local exposure component) did not depend on the estimated pollutant concentration (background exposure component) with which it was modeled simultaneously. To present results for traffic variables, we chose models with the background black smoke concentration for 1987–1996, because black smoke is a particle metric and correlates best with $PM_{2.5}$ (see Table 26). In general, effect estimates for the local traffic variables were slightly larger when combined with SO_2 concentrations. Local traffic emissions have a very limited impact on SO_2 concentrations. Because NO_2 and NO concentrations were highly correlated, we did not include the results of epidemiologic analyses for NO as relative risks for mortality were similar to those for NO_2.

Analyses were performed in the full cohort of 120,227 subjects and in the case–cohort study population. In the full cohort, we could adjust for a limited set of confounders (sex, age, smoking status, and area-level socioeconomic status), but we were able to use the mortality and exposure data for the entire cohort by utilizing methods comparable to those in previous cohort studies in the United States. In the case–cohort analyses, we used only information from the case subjects (cohort members who died) and the randomly selected subcohort of 4971 subjects. In these analyses we had information available for an extensive set of potential confounders that had been defined a priori. Associations between air pollution and mortality were generally smaller and less significant in case–cohort analyses. We extensively studied the reasons contributing to these differences between the full-cohort and the case–cohort analyses (see section Discussion / Full-Cohort Versus Case–Cohort Analyses).

Overall Air Pollution Concentrations and Mortality

In the analyses of overall (background and local) pollutant concentrations and mortality (Table 34), black smoke, NO_2, and $PM_{2.5}$ were associated with natural-cause, cardiovascular, and respiratory mortality, with some results of statistical significance or borderline statistical significance. Relative risks for noncardiopulmonary, non–lung cancer mortality were also increased and were similar to those for natural-cause mortality. The largest risk estimates were found for respiratory mortality, for which the case–cohort analyses supported the analyses in the full cohort. In the full cohort the RR for cardiopulmonary mortality was 1.05 (95% CI, 0.92–1.20) for a 10-$\mu g/m^3$ increase in $PM_{2.5}$ concentration.

There was no association between SO_2 concentration and any of the mortality categories. For SO_2 there is no difference between overall and background concentrations as there is virtually no local (traffic) contribution to this pollutant.

Background Air Pollution Concentrations and Mortality

Table 35 shows the associations of background black smoke and NO_2 exposure with mortality in a model that included traffic intensity on the nearest road as a variable. Relative risks were slightly higher with background air

Table 34. Adjusted Relative Risks (95% CI) for Associations Between Overall Pollutant Concentrations (1987–1996) and Cause-Specific Mortality in Case–Cohort and Full-Cohort Analyses[a]

Mortality Calegory[b]	Black Smoke		NO_2		$PM_{2.5}$		SO_2	
	Case–Cohort	Full Cohort	Case–Cohort	Full Cohort	Case–Cohort	Full Cohort	Case–Cohort	Full Cohort
Natural cause	0.97 (0.83–1.13)	1.05 (1.00–1.11)	0.87 (0.69–1.10)	1.08 (1.00–1.16)	0.86 (0.66–1.13)	1.06 (0.97–1.16)	0.91 (0.71–1.16)	0.97 (0.90–1.05)
Cardiovascular	0.98 (0.81–1.18)	1.04 (0.95–1.13)	0.88 (0.66–1.17)	1.07 (0.94–1.21)	0.83 (0.60–1.15)	1.04 (0.90–1.21)	0.88 (0.65–1.18)	0.94 (0.82–1.06)
Respiratory	1.29 (0.91–1.83)	1.22 (0.99–1.50)	1.26 (0.74–2.15)	1.37 (1.00–1.87)	1.02 (0.56–1.88)	1.07 (0.75–1.52)	0.88 (0.51–1.50)	0.88 (0.64–1.22)
Lung cancer	1.03 (0.77–1.38)	1.03 (0.88–1.20)	0.80 (0.52–1.23)	0.91 (0.72–1.15)	0.87 (0.52–1.47)	1.06 (0.82–1.38)	0.99 (0.62–1.58)	1.00 (0.79–1.26)
Noncardiopulmonary, non–lung cancer	0.91 (0.78–1.07)	1.04 (0.97–1.12)	0.83 (0.66–1.06)	1.09 (0.98–1.21)	0.85 (0.65–1.12)	1.08 (0.96–1.23)	0.93 (0.72–1.19)	1.00 (0.90–1.12)

[a] Analyses in the full cohort are adjusted for age, sex, smoking status, and percentage of persons with low income and percentage of persons with high income in a neighborhood, and in a COROP area. Case–cohort analyses are adjusted for all confounding variables (see Table 10). RRs were calculated for concentration changes of 10 $\mu g/m^3$ for black smoke and $PM_{2.5}$; 30 $\mu g/m^3$ for NO_2; and 20 $\mu g/m^3$ for SO_2. Overall concentrations are the sum of background and local exposure components. For SO_2, there is essentially no local (traffic) contribution to the exposure concentration.

[b] Number of observations in case–cohort analyses: for natural cause, 12,720; for cardiovascular, 6510; for respiratory, 3607; for lung cancer, 4075; and for noncardiopulmonary, non–lung cancer mortality, 7883. Number of observations for all full-cohort analyses, 105,296.

Table 35. Adjusted Relative Risks (95% CI) for Associations of Average Background Black Smoke and NO_2 Concentrations (1987–1996) with Cause-Specific Mortality in Case–Cohort and Full-Cohort Analyses[a]

Mortality Category[b]	Black Smoke		NO_2	
	Case–Cohort	Full Cohort	Case–Cohort	Full Cohort
Natural cause	0.99 (0.75–1.31)	1.09 (1.00–1.19)	0.86 (0.65–1.13)	1.08 (0.99–1.18)
Cardiovascular	1.00 (0.72–1.40)	1.11 (0.96–1.28)	0.86 (0.62–1.20)	1.08 (0.94–1.26)
Respiratory	1.52 (0.80–2.88)	1.22 (0.86–1.74)	1.24 (0.66–2.32)	1.36 (0.94–1.95)
Lung cancer	1.02 (0.61–1.71)	1.01 (0.78–1.32)	0.71 (0.43–1.19)	0.86 (0.66–1.11)
Noncardiopulmonary, non–lung cancer	0.95 (0.71–1.26)	1.09 (0.96–1.23)	0.85 (0.64–1.12)	1.11 (0.98–1.26)

[a] Analyses included traffic intensity on the nearest road as a variable. Analyses in the full cohort are adjusted for age, sex, smoking status, and percentage of persons with low income and percentage of persons with high income in a neighborhood, and in a COROP area. Case–cohort analyses are adjusted for all confounding variables (see Table 10). RRs were calculated for concentration changes of 10 $\mu g/m^3$ for black smoke and 30 $\mu g/m^3$ for NO_2.

[b] For the number of observations, see Table 34.

pollution exposure than with overall exposure in the analyses of natural-cause, cardiovascular, and noncardiopulmonary, non–lung cancer mortality. We did not specify these models for $PM_{2.5}$ because there was little variation in background $PM_{2.5}$ concentrations. For SO_2, only results for overall concentrations are presented (see Table 34).

Traffic Indicators and Mortality

Table 36 shows the adjusted associations between the traffic variables and mortality. We did not find any association between living near a major road, as defined in the pilot study (Hoek et al. 2002), and mortality. With the current study's more refined traffic variables indicating traffic near the home, associations of (borderline) statistical significance were found with natural-cause, cardiovascular, respiratory, and lung cancer mortality in the full cohort. For the association between cardiopulmonary mortality and traffic intensity on the nearest road (data not shown), the RR was 1.06 (95% CI, 1.00–1.12) for an increase of 10,000 motor vehicles/day. Appendix A provides a more detailed analysis of the differences between the large estimated relative risk reported in the pilot study (Hoek et al. 2002) and the much smaller relative risk found in the current study.

Relative risks associated with the traffic variables were larger for respiratory mortality than for cardiovascular mortality in the full cohort, as was observed for risks associated with background and overall pollutant concentrations. No associations were found with any of the traffic variables and noncardiopulmonary, non–lung cancer mortality. No association was found between any of the mortality outcomes

Table 36. Adjusted Relative Risks (95% CI) for Associations Between Traffic Variables and Cause-Specific Mortality in Case–Cohort and Full-Cohort Analyses[a]

Traffic Variable	Case–Cohort Analyses	Full-Cohort Analyses
Natural-Cause Mortality	*N* = 12,720	*N* = 105,296
Traffic intensity on nearest road	0.99 (0.88–1.11)	1.03 (1.00–1.08)
Traffic intensity in 100-m buffer	0.98 (0.85–1.13)	1.02 (0.97–1.07)
Living near major road (current study)	0.92 (0.74–1.15)	1.05 (0.97–1.12)
Living near major road (pilot study)	0.96 (0.76–1.21)	1.02 (0.95–1.09)
Cardiovascular Mortality	*N* = 6,510	*N* = 105,296
Traffic intensity on nearest road	1.03 (0.90–1.17)	1.05 (0.99–1.12)
Traffic intensity in 100-m buffer	0.98 (0.82–1.16)	1.00 (0.92–1.08)
Living near major road (current study)	0.93 (0.72–1.21)	1.05 (0.93–1.18)
Living near major road (pilot study)	0.91 (0.69–1.19)	0.96 (0.85–1.08)
Respiratory Mortality	*N* = 3,607	*N* = 105,296
Traffic intensity on nearest road	0.94 (0.71–1.25)	1.10 (0.95–1.26)
Traffic intensity in 100-m buffer	1.23 (0.89–1.68)	1.21 (1.02–1.44)
Living near major road (current study)	0.85 (0.50–1.43)	1.19 (0.91–1.56)
Living near major road (pilot study)	1.00 (0.71–1.40)	1.04 (0.79–1.38)
Lung Cancer Mortality	*N* = 4,075	*N* = 105,296
Traffic intensity on nearest road	1.03 (0.87–1.22)	1.07 (0.96–1.19)
Traffic intensity in 100-m buffer	1.10 (0.85–1.43)	1.07 (0.93–1.23)
Living near major road (current study)	1.07 (0.70–1.64)	1.20 (0.98–1.47)
Living near major road (pilot study)	1.38 (0.90–2.10)	1.13 (0.92–1.38)
Noncardiopulmonary, Non–Lung Cancer Mortality	*N* = 7,883	*N* = 105,296
Traffic intensity on nearest road	0.93 (0.82–1.06)	1.00 (0.94–1.06)
Traffic intensity in 100-m buffer	0.93 (0.80–1.07)	0.99 (0.93–1.06)
Living near major road (current study)	0.85 (0.68–1.07)	0.98 (0.88–1.09)
Living near major road (pilot study)	0.89 (0.70–1.12)	1.01 (0.92–1.12)

[a] Analyses in the full cohort are adjusted for age, sex, smoking status, and percentage of persons with low income and percentage of persons with high income in a neighborhood, and in a COROP area. Case–cohort analyses are adjusted for all confounding variables (see Table 10). RRs were calculated for traffic intensity on the nearest road, 10,000 motor vehicles/day; for the traffic intensity in a 100-m buffer, 335,000 motor vehicles/day. RRs for living near a major road were calculated with the reference category of not living near a major road. All models included average background black smoke concentration (1987–1996).

and traffic intensity on the nearest major road or distance to this road (indicators of traffic intensity potentially farther away from the home). For the association of cardiopulmonary mortality with traffic intensity on the nearest major road, the RR was 0.98 (95% CI, 0.93–1.02) for an increase of 20,000 motor vehicles/day and 1.03 (95% CI, 0.95–1.11) for a change in natural-logarithm-transformed distance of 2.3, corresponding to the difference between the 5th and the 95th percentiles of the distribution of distances to the nearest major road (55 m and 501 m, respectively).

Table 37 illustrates that associations between the overall NO_2 and SO_2 concentrations and mortality were similar for the two analyzed averaging periods (1976–1985 and 1987–1996). The same was true for background air pollutant concentrations (data not shown). Data on $PM_{2.5}$ and black smoke were available only for 1987–1996. The similarity of risk estimates is consistent with the high correlation between the exposure estimates for the two periods.

SENSITIVITY ANALYSES

In the full-cohort analyses, adjustment for the limited set of confounders that were available resulted in lower relative risks of mortality associated with overall concentrations of black smoke. Closer inspection of the data showed that this was related to adjustment for smoking status in particular (Table 38).

Municipal traffic data were available for about 80% of the subjects. When the analyses were restricted to the subjects living in municipalities for which traffic intensity data were available, relative risks were similar to those reported for the full cohort, as is illustrated for cardiopulmonary mortality in Table 39. Most municipalities with missing local traffic data were small communities. We assumed that no major roads were present in these small communities, other than provincial and national roads, for which data were available for all municipalities.

AIR POLLUTION AND MORTALITY: ADDITIONAL ANALYSES

In additional analyses of associations between air pollution and mortality, we evaluated separately the effects of residential mobility, spatial autocorrelation, living in the three major cities in the study, living near freeways, and exposure to traffic noise.

Residential Mobility

The effect of residential mobility could only be analyzed in the case–cohort study population because information about moving was available only for subjects who died and for the original subcohort. Of the 21,911 subjects in the case–cohort study population, 15,144 did not move between 1986 and the end of follow-up. There were only slight differences in residential mobility between the subjects who died and the subcohort members. Of the 17,674 subjects who died during follow-up, 12,381 (70%) had not moved; in the subcohort of 4237 subjects, 2763 (65%) had not moved. The results reported in Table 40 were adjusted for the confounders available for the full cohort only, to avoid the selection effect. This analysis shows that associations between air pollution exposure and mortality were stronger in the subjects who did not move than in the complete case–cohort study population. One explanation of this difference is that exposure assessment was more accurate for subjects who did not change residence during the study period.

Table 37. Adjusted Relative Risks (95% CI) for Associations of Overall NO_2 and SO_2 Concentrations with Cause-Specific Mortality in Full-Cohort Analyses[a]

Mortality Category	NO_2		SO_2	
	1976–1985	1987–1996	1976–1985	1987–1996
Natural cause	1.05 (0.99–1.12)	1.08 (1.00–1.16)	1.00 (0.96–1.04)	0.97 (0.90–1.05)
Cardiovascular	1.05 (0.94–1.16)	1.07 (0.94–1.21)	0.98 (0.91–1.05)	0.94 (0.82–1.06)
Respiratory	1.34 (1.04–1.73)	1.37 (1.00–1.87)	0.98 (0.82–1.17)	0.88 (0.64–1.22)
Lung cancer	0.90 (0.74–1.09)	0.91 (0.72–1.15)	1.01 (0.89–1.16)	1.00 (0.79–1.26)
Noncardiopulmonary, non–lung cancer	1.06 (0.97–1.16)	1.09 (0.98–1.21)	1.01 (0.95–1.07)	1.00 (0.90–1.12)

[a] Analyses are adjusted for age, sex, smoking status, and percentage of persons with low income and percentage of persons with high income in a neighborhood, and in a COROP area. Number of observations for all full-cohort analyses was 105,296. RRs were calculated for concentration changes of 30 $\mu g/m^3$ for NO_2 and 20 $\mu g/m^3$ for SO_2. Overall concentrations are the sum of background and local exposure components. For SO_2, there is essentially no local (traffic) contribution to the exposure concentration.

Table 38. Relative Risks (95% CI) for Associations of Overall Black Smoke, NO_2, and $PM_{2.5}$ Concentrations (1987–1996) with Cause-Specific Mortality in Full-Cohort Analyses by Confounder Model[a]

Confounder Model[b]	Natural-Cause Mortality	Cardiovascular Mortality	Respiratory Mortality	Lung Cancer Mortality	Noncardiopulmonary, Non–Lung Cancer Mortality
Black Smoke					
Unadjusted	1.10 (1.05–1.15)	1.09 (1.02–1.17)	1.31 (1.11–1.56)	1.10 (0.97–1.26)	1.07 (1.01–1.14)
Smoking	1.06 (1.01–1.10)	1.05 (0.97–1.13)	1.24 (1.03–1.48)	1.04 (0.91–1.19)	1.04 (0.98–1.11)
Smoking, area-level income	1.05 (1.00–1.11)	1.04 (0.95–1.13)	1.22 (0.99–1.50)	1.03 (0.88–1.20)	1.04 (0.97–1.12)
NO_2					
Unadjusted	1.08 (1.02–1.14)	1.06 (0.96–1.16)	1.26 (1.01–1.58)	0.98 (0.83–1.16)	1.09 (1.01–1.18)
Smoking	1.03 (0.98–1.09)	1.01 (0.92–1.12)	1.17 (0.92–1.48)	0.93 (0.78–1.10)	1.06 (0.98–1.15)
Smoking, area-level income	1.08 (1.00–1.16)	1.07 (0.94–1.21)	1.37 (1.00–1.87)	0.91 (0.72–1.15)	1.09 (0.98–1.21)
$PM_{2.5}$					
Unadjusted	1.11 (1.04–1.20)	1.09 (0.97–1.23)	1.23 (0.92–1.65)	1.17 (0.95–1.46)	1.10 (1.00–1.22)
Smoking	1.04 (0.96–1.13)	1.02 (0.90–1.16)	1.10 (0.81–1.50)	1.06 (0.85–1.33)	1.05 (0.94–1.16)
Smoking, area-level income	1.06 (0.97–1.16)	1.04 (0.90–1.21)	1.07 (0.75–1.52)	1.06 (0.82–1.38)	1.08 (0.96–1.22)

[a] RRs for continuous variables were calculated for concentration changes from the 5th to the 95th percentile; for black smoke and $PM_{2.5}$, 10 μg/m^3; for NO_2, 30 μg/m^3.

[b] The "unadjusted" model was adjusted only for age and sex (number of observations = 117,499). The "smoking" model was adjusted for age, sex, and smoking status (N = 109,986). The "smoking, area-level income" model was adjusted for age, sex, smoking status, percentage of persons with low income and percentage of persons with high income in a neighborhood, and in a COROP area (N = 105,296).

Table 39. Adjusted Relative Risks (95% CI) for Associations of Black Smoke Concentrations and Traffic Variables with Cardiopulmonary Mortality for Subjects Living in Municipalities with Local Traffic Data and for the Full Cohort[a]

Exposure Model[b]	Subjects in Municipalities with Traffic Data (N = 87,667)	Full Cohort (N = 105,296)
Background black smoke *and* Traffic intensity on the nearest road	1.12 (0.96–1.31) 1.06 (1.00–1.12)	1.12 (0.98–1.28) 1.06 (1.00–1.12)
Background black smoke *and* Living near a major road	1.13 (0.96–1.32) 1.08 (0.97–1.21)	1.13 (0.99–1.29) 1.07 (0.96–1.19)
Background black smoke *and* Traffic intensity in a 100-m buffer	1.12 (0.96–1.31) 1.03 (0.96–1.11)	1.12 (0.98–1.29) 1.03 (0.95–1.10)
Overall black smoke	1.07 (0.98–1.17)	1.07 (0.98–1.15)

[a] Analyses are adjusted for age, sex, smoking status, and percentage of persons with low income and percentage of persons with high income in a neighborhood, and in a COROP area. RRs were calculated for a concentration change of 10 μg/m^3.

[b] The first three exposure models each contain one of the three traffic indicator variables and the average background (regional and urban) black smoke concentration for 1987–1996. The "overall black smoke" model contains a quantitative estimate for the background and local exposure components combined.

Spatial Autocorrelation

The analyses presented so far have not taken into account the potential for bias due to spatial clustering. When we applied models developed to account for spatial autocorrelation in neighborhood and municipality, we observed that both the relative risk of mortality and the confidence interval from the standard Cox proportional hazards model were unaffected (Figure 9). The original estimates differ only very slightly from those presented in the main analyses because we did not originally adjust for the socioeconomic status associated with the COROP areas. As explained in the Methods section, this variable was added after we observed that inclusion of a crude variable for the region affected the risk estimates associated with background air pollution.

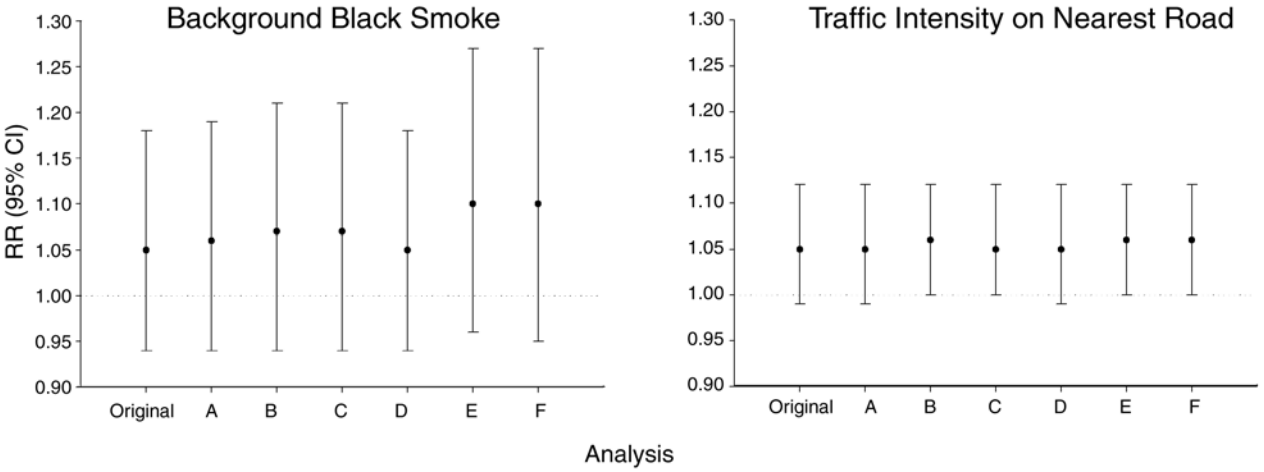

Figure 9. Effect of spatial autocorrelation on associations of background black smoke concentration (1987–1996) and traffic intensity on the nearest road with cardiopulmonary mortality in the full cohort (*N* = 107,005). RRs and 95% CIs are shown without adjustment for spatial correlation (**Original**). For comparison, they are shown with adjustment for spatial autocorrelation, using random effects models to analyze independent clusters on one level, within neighborhoods (**A**) or within municipalities (**B**); using random effects models to analyze clusters on two levels, within neighborhoods of municipalities (**C**); using distance-decay random effects models on one level, within neighborhoods (**D**) or within municipalities (**E**); and using distance-decay random effects models on two levels, within neighborhoods of municipalities (**F**). All analyses are also adjusted for age, sex, smoking status, and percentage of persons with low income and percentage of persons with high income living in a neighborhood, and in a COROP area. The vertical bars show 95% confidence intervals.

Table 40. Adjusted Relative Risks (95% CI) for Associations of Background Black Smoke Concentration, Traffic Intensity in a 100-Meter Buffer, and Overall Black Smoke Concentration in the Case–Cohort Analyses for Subjects Who Did Not Move During Follow-Up (1987–1996)[a]

Exposure Variable[b]	Natural-Cause Mortality (*N* = 14,035)	Cardiopulmonary Mortality (*N* = 7622)	Cardiovascular Mortality (*N* = 7053)	Respiratory Mortality (*N* = 3639)	Lung Cancer Mortality (*N* = 4307)	Noncardiopulmonary, Non–Lung Cancer Mortality (*N* = 8472)
Background black smoke	1.15 (0.89–1.50)	1.15 (0.84–1.56)	1.14 (0.84–1.55)	1.21 (0.69–2.12)	1.18 (0.76–1.84)	1.15 (0.88–1.51)
Traffic intensity in a 100-m buffer	1.08 (0.93–1.24)	1.13 (0.96–1.33)	1.09 (0.92–1.28)	1.38 (1.04–1.82)	1.10 (0.86–1.39)	1.03 (0.89–1.19)
Overall black smoke	1.13 (0.97–1.31)	1.16 (0.97–1.38)	1.12 (0.94–1.34)	1.39 (1.01–1.90)	1.14 (0.88–1.48)	1.10 (0.94–1.28)

[a] *N* indicates number of subjects. Analyses are adjusted for age, sex, smoking status, percentage of persons with low income and percentage of persons with high income in a neighborood, and in a COROP area (i.e., confounders that were also available for the full-cohort analyses).

[b] RRs were calculated for black smoke concentration, 10 μg/m^3; for the sum of traffic intensity in a buffer of 100 m, 335,000 motor vehicles/day.

Analyses for the Three Major Cities

To increase the comparability with previous cohort studies that were largely based on urban areas, we also performed analyses restricted to the three major cities represented in the cohort, Rotterdam, The Hague, and Utrecht. Analyses restricted to these cities showed slightly higher relative risks for the association between traffic variables and cardiopulmonary mortality (Table 41). Relative risks associated with the background black smoke concentration were increased as well, but with wide confidence intervals related to the small range of values for background air pollution. The relative risks associated with the overall black smoke concentration, which is the sum of the background and local exposure components and thus is less affected by reduction in exposure contrast, increased and became statistically significant. A statistical test of heterogeneity between the effect estimates for an association between overall air pollution and cardiopulmonary mortality, the Cochran Q test (DerSimonian and Laird 1986), did not show significant differences between subjects living in one the three major cities and members of the full cohort ($P = 0.31$). Effect estimates for overall air pollution were slightly higher among those living in the three major cities for total mortality ($P = 0.41$), cardiovascular mortality ($P = 0.35$), and respiratory mortality ($P = 0.75$); effect estimates were lower for lung cancer ($P = 0.91$) and for noncardiopulmonary, non–lung cancer mortality ($P = 0.03$).

Analyses of Freeway Exposures

No association was found between the traffic intensity on or distance to a major road from a cohort member's home address and mortality. This could be due to interference from buildings between the road and the home. Such potential interference is likely more important for urban roads than for freeways, which are usually located in more open terrain. Therefore, we performed some analyses that focused exclusively on local emissions from freeways. Analyses focusing on freeways did not show any association between traffic intensity on the freeway or distance to the freeway and cause-specific mortality (Table 42). For these analyses, subjects who did not live close to a freeway but did live close to another type of major road were excluded, as we did not want to include them in the reference category.

The results obtained with models that include traffic intensity on and distance to the nearest freeway are somewhat difficult to interpret as all subjects living farther than 500 m from a freeway were assigned values of 10,000 motor vehicles/day for traffic intensity and 501 m for distance, which resulted in negative correlation between the two variables. Analyses restricted to the two variables (traffic intensity on and distance to a freeway) resulted in risk estimates that did not differ from unity for both variables. This interpretation problem does not play a role in the quantitative estimate of exposure, as subjects more than 500 m away from a freeway were (appropriately) assigned the value 0. Restriction of the analysis to subjects living within 500 m of

Table 41. Adjusted Relative Risks (95% CI) for Associations of Black Smoke Concentrations and Traffic Variables with Cardiopulmonary Mortality for Subjects Living in the Three Major Cities and for the Full Cohort[a]

Exposure Model[b]	Subjects in the Three Major Cities[c] ($N = 21,430$)	Full Cohort ($N = 105,281$)
Background black smoke *and*	1.39 (0.87–2.23)	1.12 (0.98–1.28)
Traffic intensity on the nearest road	1.08 (1.00–1.18)	1.06 (1.00–1.12)
Background black smoke *and*	1.40 (0.87–2.24)	1.13 (0.99–1.29)
Living near a major road	1.07 (0.90–1.28)	1.07 (0.96–1.19)
Background black smoke *and*	1.34 (0.83–2.16)	1.12 (0.98–1.29)
Traffic intensity in a 100-m buffer	1.08 (0.97–1.21)	1.03 (0.95–1.1)
Overall black smoke	1.17 (1.00–1.36)	1.07 (0.98–1.15)

[a] N indicates number of subjects. There were 1366 cardiopulmonary deaths among subjects living in the three major cities and 5609 in the full cohort. Analyses are adjusted for age, sex, smoking status, percentage of persons with low income and percentage of persons with high income in a neighborhood, and in a COROP area. RRs were calculated for a concentration change of 10 $\mu g/m^3$.

[b] The first three exposure models each contain one of the three traffic indicator variables and the average background (regional and urban) black smoke concentration for 1987–1996. The "overall black smoke" model contains a quantitative estimate for the background and local exposure components combined.

[c] The three major cities are Rotterdam, The Hague, and Utrecht.

a freeway resulted in a small sample size (N = 9300) and thus wide confidence intervals (data not shown).

Traffic Noise and Cardiovascular Mortality

Estimated exposure to traffic noise, modeled on a scale of 25 m × 25 m, varied substantially within the full cohort (Table 43). To 45,773 (39%) of 117,487 subjects, an exposure to traffic noise of 50 dB(A) or less was assigned; 36,348 (31%) were assigned a value between 50 and 55 dB(A); 26,248 (22%), a value between 55 and 60 dB(A); 7492 (6%), a value between 60 and 65 dB(A); and 1626 (1.6%), a value above 65 dB(A).

Traffic noise was higher when subjects lived near a major road, according to the current study definition. The mean traffic noise level was 51 dB(A) for the 111,703 subjects who did not live near a major road and 60 dB(A) for the 5784 subjects who did live near a major road. However, the distributions overlapped substantially. This is reflected in the moderate correlations between traffic noise and variables for traffic intensity (Table 44). The moderate correlation between traffic noise and variables for air pollution and traffic allowed us to assess the independent effects of noise and air pollution.

Table 42. Adjusted Associations Between Exposure to Black Smoke Related to Freeways and Cause-Specific Mortality in the Full Cohort (N = 94,757)[a]

Exposure Model[b]	RR (CI)
Total Mortality (13,674 deaths)	
Local black smoke exposure contributed by freeways	1.00 (0.89–1.11)
Traffic intensity on nearest freeway *and*	0.90 (0.77–1.05)
ln-Transformed distance to nearest freeway	1.08 (0.95–1.23)
Truck traffic intensity on nearest freeway *and*	0.92 (0.81–1.04)
ln-Transformed distance to nearest freeway	1.08 (0.94–1.23)
Light-duty traffic intensity on nearest freeway *and*	0.90 (0.77–1.05)
ln-Transformed distance to nearest freeway	1.08 (0.94–1.23)
Cardiopulmonary Mortality (5609 deaths)	
Local black smoke exposure contributed by freeways	0.94 (0.78–1.12)
Traffic intensity on nearest freeway *and*	0.83 (0.65–1.07)
ln-Transformed distance to nearest freeway	1.07 (0.87–1.32)
Truck traffic intensity on nearest freeway *and*	0.82 (0.67–1.01)
ln-Transformed distance to nearest freeway	1.10 (0.89–1.35)
Light-duty traffic intensity on nearest freeway *and*	0.84 (0.66–1.08)
ln-Transformed distance to nearest freeway	1.06 (0.86–1.31)

[a] N indicates number of subjects. Analyses are adjusted for age, sex, smoking status, percentage of persons with low income and percentage of persons with high income in a neighborood, and in a COROP area.

[b] In the first exposure model for each mortality category, the variable is the quantitative estimate of the local black smoke exposure contributed by freeways. The other three models each contain a traffic indicator variable for the nearest freeway and the natural-log-transformed distance to the nearest freeway.

Table 43. Distribution of Average 2001 Traffic Noise at Home Addresses of the Full Cohort (N = 117,487)

Value	Traffic Noise in dB(A)
Minimum	29
1st percentile	29
5th percentile	41
10th percentile	44
25th percentile	48
50th percentile	52
75th percentile	56
90th percentile	60
95th percentile	62
99th percentile	66
Maximum	75

Table 44. Correlation of Traffic Noise with Air Pollution and Traffic Variables in the Full Cohort (N = 117,487)

Variable	Correlation with Traffic Noise
Background black smoke	0.23
Traffic intensity on nearest road	0.30
Traffic intensity on nearest major road	0.26
Natural log of distance to nearest major road	−0.35
Traffic intensity in 100-m buffer	0.38
Overall black smoke	0.41

When a continuous variable for traffic noise was added to a model containing background black smoke concentration and traffic intensity on the nearest road, we observed no change in the estimated effects of black smoke and traffic intensity on cardiovascular mortality (data not shown). The relative risk associated with the continuous variable for traffic noise was essentially unity. When we entered traffic noise as a categorical variable in models, there was some indication that exposure to traffic noise levels in the highest category was associated with cardiovascular mortality, especially when variables for air pollution and traffic intensity were not included in the model (Table 45). In particular, the effect of traffic noise was reduced when traffic intensity on the nearest road, the traffic variable with the strongest association with cardiovascular mortality, was included in the model. At the same time, relative risks associated with background black smoke concentration, overall black smoke concentration, and traffic intensity were essentially unchanged after inclusion of traffic noise in the model. This suggests that the association between traffic intensity and cardiovascular mortality is largely not due to traffic noise.

Table 45. Relative Risks (95% CI) for Associations Between Traffic Noise and Cardiovascular Mortality (5396 Cases), Adjusted for Potentially Confounding Variables, Including Air Pollution Indicators, in the Full Cohort (N = 105,254)[a]

Variable	Confounder Model With Noise[b]	Confounder Model Without Noise[b]
Traffic noise 50–55 dB(A)	1.00 (0.94–1.07)	
Traffic noise 55–60 dB(A)	1.00 (0.93–1.08)	
Traffic noise 60–65 dB(A)	0.91 (0.81–1.03)	
Traffic noise > 65 dB(A)	1.25 (1.01–1.53)	
Background black smoke *and*	1.11 (0.95–1.28)	1.11 (0.96–1.28)
Traffic intensity on nearest road	1.06 (0.99–1.13)	1.05 (0.99–1.12)
Traffic noise 50–55 dB(A)	1.00 (0.94–1.07)	
Traffic noise 55–60 dB(A)	0.99 (0.92–1.06)	
Traffic noise 60–65 dB(A)	0.88 (0.78–1.00)	
Traffic noise > 65 dB(A)	1.17 (0.94–1.45)	
Background black smoke *and*	1.11 (0.96–1.29)	1.11 (0.96–1.28)
Living near a major road	1.05 (0.93–1.19)	1.05 (0.93–1.08)
Traffic noise 50–55 dB(A)	1.00 (0.94–1.07)	
Traffic noise 55–60 dB(A)	0.99 (0.92–1.07)	
Traffic noise 60–65 dB(A)	0.90 (0.79–1.01)	
Traffic noise > 65 dB(A)	1.21 (0.98–1.5)	
Background black smoke *and*	1.12 (0.96–1.30)	1.11 (0.96–1.28)
Traffic intensity in a 100-m buffer	0.99 (0.91–1.08)	1.00 (0.92–1.08)
Traffic noise 50–55 dB(A)	1.00 (0.94–1.07)	
Traffic noise 55–60 dB(A)	1.00 (0.93–1.07)	
Traffic noise 60–65 dB(A)	0.91 (0.80–1.03)	
Traffic noise > 65 dB(A)	1.25 (1.00–1.55)	
Overall black smoke	1.04 (0.95–1.14)	1.04 (0.95–1.04)
Traffic noise 50–55 dB(A)	1.00 (0.94–1.07)	
Traffic noise 55–60 dB(A)	1.00 (0.93–1.07)	
Traffic noise 60–65 dB(A)	0.90 (0.79–1.02)	
Traffic noise > 65 dB(A)	1.22 (0.99–1.51)	

[a] RRs for traffic noise were calculated with traffic noise < 50 dB(A) as the reference category. RRs for continuous variables were calculated for background black smoke, 10 μg/m^3; for traffic intensity on the nearest road, 10,000 motor vehicles/day; for the sum of traffic intensity in a buffer of 100 m, 335,000 motor vehicles/day. RRs for living near a major road were calculated with the reference category of not living near a major road.

[b] All confounder models were adjusted for age, sex, smoking status, percentage of persons with low income and percentage of persons with high income in a neighborhood, and in a COROP area.

EFFECT MODIFICATION

We assessed effect modification by smoking status and sex in the full cohort. More detailed analyses were performed in the case–cohort study population as more data were available from the questionnaire.

Table 46 presents the results of analyses stratified by cigarette smoking status. The *P* value was determined by the Cochran *Q* test for heterogeneity. There were no significant differences in relative risks of mortality with exposure to black smoke between subjects of the different smoking status strata.

There also were no significant differences between results for men and women (data not shown). For an increase of 10 $\mu g/m^3$ in the overall black smoke concentration, the RR for natural-cause mortality was 1.07 (95% CI, 1.00–1.14) for women and 1.03 (95% CI, 0.95–1.12) for men.

More detailed analyses of effect modification were conducted using the case–cohort approach. To avoid the selection effect in these analyses, we adjusted only for the confounding variables that were used in the full cohort. There were no differences between men and women, or between subjects as stratified by smoking status or vegetable intake (data not shown). Low fruit intake was significantly associated with low educational levels (data not shown), and there was some indication that subjects in households with low educational levels and subjects with low fruit intake experienced stronger effects of air pollution; however, *P* values of the Cochran *Q* test for heterogeneity were not statistically significant (Figure 10). The relatively small number of cases of respiratory mortality and lung cancer mortality limits the interpretation of results for these outcomes.

ANALYSES OF LUNG CANCER INCIDENCE

We also assessed the association between air pollution exposure and lung cancer incidence, identified by computerized linkage of the records for the full cohort to regional cancer registries and to the Dutch national database of pathology records (Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief, or PALGA). The follow-up period was 11.3 years, from September 1986 through December 1997. We excluded subjects already diagnosed with cancers other than skin cancer at baseline. During follow-up, 2189 new cases of lung cancer were identified, of which 1887 were in men.

There was essentially no association between overall pollutant concentrations and lung cancer incidence (Table 47). Relative risk estimates for traffic variables were above unity, both in the full-cohort and in the case–cohort analyses, but none of the estimates was statistically significant (Table 48). The estimated relative risk for lung cancer incidence associated with the overall black smoke concentration was higher for subjects who had never smoked and for subjects with low fruit intake (Table 49). There was no difference in relative risk between men and women.

Table 46. Adjusted Associations Between Overall Black Smoke Concentration and Cause-Specific Mortality in the Full Cohort, Stratified by Cigarette Smoking Status[a]

Mortality Category	Never Smokers (*N* = 43,118)		Former Smokers (*N* = 34,110)		Current Smokers (*N* = 29,779)		*P*[b]
	n	RR (95% CI)	*n*	RR (95% CI)	*n*	RR (95% CI)	
Natural cause	4559	1.12 (1.02–1.23)	4928	0.98 (0.89–1.08)	6052	1.05 (0.97–1.14)	0.15
Cardiopulmonary	1725	1.10 (0.94–1.28)	2138	0.98 (0.85–1.13)	2541	1.11 (0.98–1.25)	0.38
Cardiovascular		1.13 (0.96–1.32)		0.96 (0.83–1.13)		1.03 (0.90–1.19)	0.35
Respiratory		0.86 (0.53–1.41)		1.09 (0.76–1.55)		1.51 (1.13–2.03)	0.11
Lung cancer	208	1.48 (0.97–2.25)	476	0.89 (0.66–1.21)	1021	0.97 (0.79–1.19)	0.14
Noncardiopulmonary, non–lung cancer	2731	1.11 (0.99–1.26)	2402	0.98(0.86–1.12)	2595	1.01 (0.89–1.15)	0.35

[a] *N* indicates the number of subjects in the category; *n* indicates the number of deaths.

[b] *P* value determined by the Cochran *Q* test for heterogeneity.

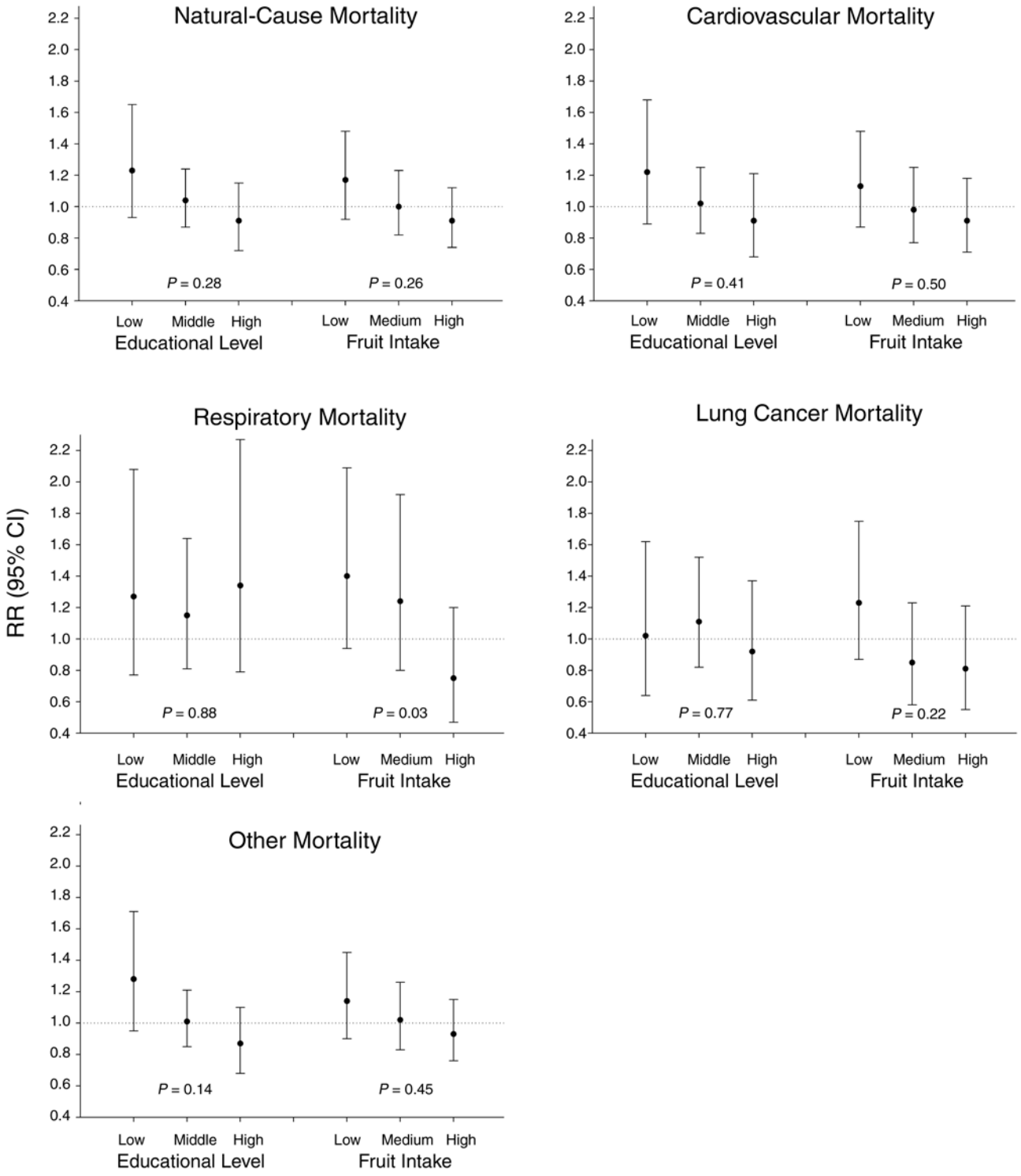

Figure 10. Association between overall black smoke concentration (1987–1996) and cause-specific mortality stratified by educational level and fruit intake in the case–cohort study population. "Other mortality" is noncardiopulmonary, non–lung cancer mortality. Educational level of the household is coded as low for only primary school; middle for lower vocational education; or high for junior high school, senior high school, higher vocational education, and university. Fruit intake is stratified in tertiles as low, 0–96.8 g/day; medium, 96.8–191.8 g/day; or high, >191.8 g/day. Associations are adjusted for age, sex, smoking status, and percentage of persons with low income and percentage of persons with high income living in a neighborhood, and in a COROP area. The *P* value is determined by the Cochran *Q* test for heterogeneity.

Table 47. Relative Risks (95% CI) for Associations Between Overall Pollutant Concentrations for 1976–1985 and 1987–1996 and Lung Cancer Incidence in Case–Cohort and Full-Cohort Analyses, by Confounder Model[a]

Pollutant / Confounder Model[b]	1976–1985[c]		1987–1996	
	Case–Cohort	Full Cohort	Case–Cohort	Full Cohort
Black smoke				
Unadjusted			1.09 (0.93–1.27)	1.07 (0.95–1.21)
Adjusted			1.01 (0.76–1.34)	0.96 (0.83–1.11)
Unadjusted complete			1.05 (0.85–1.29)	1.06 (0.93–1.20)
$PM_{2.5}$				
Unadjusted			0.93 (0.71–1.22)	0.96 (0.79–1.18)
Adjusted			0.67 (0.41–1.10)	0.81 (0.63–1.04)
Unadjusted complete			0.87 (0.60–1.25)	0.92 (0.74–1.15)
NO_2				
Unadjusted	1.07 (0.89–1.29)	1.02 (0.89–1.17)	1.00 (0.82–1.22)	0.96 (0.82–1.12)
Adjusted	0.96 (0.67–1.38)	0.91 (0.76–1.08)	0.79 (0.52–1.20)	0.86 (0.70–1.07)
Unadjusted complete	1.04 (0.81–1.34)	0.99 (0.86–1.15)	0.91 (0.70–1.18)	0.94 (0.80–1.11)
SO_2				
Unadjusted	1.05 (0.91–1.20)	0.97 (0.88–1.07)	1.04 (0.83–1.30)	0.92 (0.78–1.08)
Adjusted	0.94 (0.73–1.21)	0.94 (0.84–1.07)	0.95 (0.61–1.49)	0.90 (0.72–1.11)
Unadjusted complete	1.01 (0.85–1.21)	0.98 (0.88–1.09)	1.02 (0.76–1.36)	0.94 (0.79–1.12)

[a] RRs for continuous variables were calculated for concentration changes for black smoke and $PM_{2.5}$ of 10 $\mu g/m^3$; for NO_2, 30 $\mu g/m^3$; and for SO_2, 20 $\mu g/m^3$.

[b] The "unadjusted" model was adjusted for age and sex; the "adjusted" model was adjusted for all available potential confounders (for case–cohort analyses, see Table 10; for full-cohort anlayses, they were age, sex, smoking status, and percentage of persons with low income and percentage of persons with high income in a neighborhood, and in a COROP area). The "unadjusted complete" model was adjusted for age and sex but only included the subjects that had complete information for all possible confounders in the adjusted model. Number of observations in the case–cohort analyses: unadjusted, 6761; adjusted, 4101; unadjusted complete, 4101. Number of observations in the full-cohort analyses: unadjusted, 111,788; adjusted, 100,168; unadjusted complete, 100,168.

[c] Black smoke and $PM_{2.5}$ data were not available for the period 1976–1985.

Table 48. Relative Risks (95% CI) for Associations Between Traffic Variables and Lung Cancer Incidence in Case–Cohort and Full-Cohort Analyses[a]

Variable	Confounder Model[b]	Case–Cohort	Full Cohort
Traffic intensity on nearest road	Unadjusted	1.00 (0.89–1.12)	1.05 (0.94–1.16)
Traffic intensity on nearest road	Adjusted	1.02 (0.87–1.18)	1.05 (0.94–1.16)
Living near a major road	Unadjusted	1.05 (0.81–1.35)	1.12 (0.93–1.35)
Living near a major road	Adjusted	1.10 (0.74–1.62)	1.11 (0.91–1.34)
Traffic intensity in a 100 m buffer	Unadjusted	1.08 (0.92–1.28)	1.09 (0.97–1.24)
Traffic intensity in a 100 m buffer	Adjusted	1.07 (0.84–1.36)	1.05 (0.92–1.19)

[a] RRs for continuous variables were calculated for differences from the 5th to the 95th percentile; for the traffic intensity on the nearest road, 10,000 motor vehicles/day. For the sum of traffic intensity in a buffer of 100 m, 335,000 motor vehicles/day. RRs for living near a major road were calculated with the reference category of not living near a major road. Living near a major road is defined as living within 50 m of a road with traffic intensity > 10,000 motor vehicles/day or within 100 m of a freeway. All models included the background black smoke concentration for 1987–1996.

[b] The "unadjusted" model was adjusted only for age and sex. In the case–cohort analyses, the "adjusted" model was adjusted for all potential confounders (see Table 10); in the full-cohort anlayses, it was adjusted for age, sex, smoking status, and percentage of persons with low income and percentage of persons with high income living in a neighborhood, and in a COROP area.

Table 49. Adjusted Associations Between Overall Black Smoke Concentration (1987–1996) and Lung Cancer Incidence, Stratified by Educational Level, Fruit Intake, Cigarette Smoking Status, and Sex[a]

Variable	Number of Observations	Number of Cases	RR (95% CI)	P[b]
Educational level[c]				0.45
Low	1,373	514	0.80 (0.50–1.27)	
Middle	3,330	1114	1.10 (0.81–1.48)	
High	1,577	395	0.87 (0.59–1.29)	
Fruit intake[d]				0.04
Low	2,076	897	1.24 (0.88–1.75)	
Medium	2,199	634	0.67 (0.46–0.98)	
High	2,061	506	0.74 (0.50–1.09)	
Cigarette smoking status				0.04
Never smoker	40,114	252	1.47 (1.01–2.16)	
Former smoker	32,022	500	0.91 (0.68–1.23)	
Current smoker	28,030	1188	0.85 (0.70–1.03)	
Sex				0.92
Male	48,670	1668	0.95 (0.81–1.11)	
Female	51,496	272	0.93 (0.64–1.36)	

[a] Analyses for educational level and fruit intake were conducted in the case–cohort study population; analyses for cigarette smoking status and sex were conducted in the full cohort. All analyses were adjusted for age, sex, smoking status, and percentage of persons with low income and percentage of persons with high income living in a neighborhood, and in a COROP area.

[b] P value is determined by the Cochran Q test for heterogeneity.

[c] Educational level of the household is coded as low for only primary school; middle for lower vocational education; and high for junior high school, senior high school, higher vocational education, and university.

[d] Fruit intake is stratified in tertiles: low, 0–96.8 g/day; medium, 96.8–191.8 g/day; and high, >191.8 g/day.

DISCUSSION

In analyses of a large cohort of older adults in the Netherlands, we found that long-term average background air pollution concentrations of black smoke, NO_2, and $PM_{2.5}$ were associated with mortality from cardiovascular, respiratory, and other causes of death. With a change of 10 $\mu g/m^3$ in the black smoke concentration, RRs ranged from 1.09 (95% CI, 1.00–1.19) for natural-cause mortality to 1.22 (95% CI, 0.86–1.74) for respiratory mortality, and for noncardiopulmonary, non–lung cancer mortality, the RR was 1.09 (95% CI, 0.96–1.23). No association was found between mortality and SO_2 concentrations.

We also found associations between traffic intensity near the home and natural-cause, cardiovascular, lung cancer, and respiratory mortality. With a change of 10,000 motor vehicles/day in traffic intensity near the home, RRs ranged from 1.03 (95% CI, 1.00–1.08) for natural-cause mortality to 1.10 (95% CI, 0.95–1.26) for respiratory mortality. No association between traffic intensity and noncardiopulmonary, non–lung cancer mortality was found. Traffic noise did not explain the associations between traffic intensity and cardiovascular mortality.

In the case–cohort analyses, associations of air pollution and traffic intensity with mortality were generally weaker than in the full-cohort analyses.

Associations between air pollution and mortality were suggestively stronger in subjects that did not change residence during follow-up, those living in the three main cities represented in the cohort, those with low educational levels, and those with low fruit intake. Mortality risks did not differ between men and women. In subjects who had never smoked, relative risks associated with the overall black smoke concentration tended to be higher for incidence of lung cancer and death from lung cancer, but not for the other causes of death.

FULL-COHORT VERSUS CASE–COHORT ANALYSES

The NLCS-AIR project was started as a case–cohort study, following the general design of the NLCS, and then was expanded to include the full cohort. Associations between air pollution and mortality were generally smaller

and less significant in the case–cohort analyses. We studied the reasons contributing to these differences and concluded that more complete control for confounding in the case–cohort analyses probably did not contribute much to the lower risk estimates in this study population. We observed that similar results for case–cohort subjects with complete confounder data were obtained using a complete confounder model, a model with the more limited confounder data available for the full cohort, and a model including only potential confounders of borderline statistical significance (explained in detail in Appendix F; see section Appendices Available on the Web).

More likely explanations of the differences are increased random variability due to sampling from the full cohort and a selection effect due to the large number of missing data for the complete set of confounders. Confidence intervals were smaller in the full-cohort analyses, consistent with the larger number of subjects. We further observed that the specification of the complete confounder model in the case–cohort analysis resulted in a large number of missing data. Estimated relative risks of mortality for the subjects with complete confounder data were substantially smaller than those for the full cohort, pointing to a selection effect. In the case–cohort analyses, most of the difference in results between unadjusted and adjusted analyses was due to this selection. For these reasons, we focus our interpretation on the results for the full cohort.

COMPARISON WITH PREVIOUS STUDIES OF AIR POLLUTION AND MORTALITY

The estimated effects of exposure to air pollution and traffic on mortality in this study are much smaller than those we reported previously (Hoek et al. 2002). In the pilot study, living near a major road resulted in an RR for cardiopulmonary mortality of 1.95 (95% CI, 1.09–3.51). In the current study, we found no association with cardiopulmonary mortality for the exposure variable that was used in the pilot study. We did find RRs of between 1.05 and 1.10 for the more refined exposure variables of the current study, with some of these estimates being statistically significant or borderline significant. The smaller relative risks in the current study are due to the longer follow-up period and, most importantly, to much more precise exposure estimates. In the pilot study, we could only use the small subcohort of approximately 5000 subjects instead of the approximately 120,000 subjects of the full cohort. The confidence intervals of the pilot study estimates were therefore very wide and actually overlap with the current study estimates. Because the study population of the pilot study was a random sample of the current study population, factors such as exposures to air pollution or traffic were similar for the two groups. Differences in exposure assessment did not explain the current study's smaller risk estimates either, as the risks were even smaller when we analyzed the current study data using the (cruder) exposure variables of the pilot study. Small differences in the confounder models also did not contribute to the differences.

The relative risk estimates for the current study are more in line with estimates from other cohort studies than with the estimates from our pilot study. In the mid 1990s two large cohort studies in the United States found associations between long-term exposure to particulate matter air pollution and mortality (Dockery et al. 1993; Pope et al. 1995), while controlling for an extensive set of individual-level confounders. The associations in these cohort studies were confirmed in a reanalysis of these studies by independent analysts (Krewski et al. 2000). In an extended follow-up of the American Cancer Society Study (Pope et al. 2002), associations between particulate matter air pollution and (cardiopulmonary) mortality were still observed, although estimates were smaller than those originally reported. An extended follow-up of the Harvard Six Cities Study (Laden et al. 2006) also confirmed the findings of the earlier analyses. Results from the Seventh-Day Adventist Study found some associations between PM_{10} and respiratory, cardiovascular, and lung cancer deaths, especially in men (Abbey et al. 1999). A later report on the same study found stronger associations between $PM_{2.5}$ and fatal coronary heart disease, particularly for women (Chen et al. 2005). Some other studies have not been able to replicate these findings (Lipfert et al. 2000) or have argued that air pollution exposures were related to mortality in the more distant past, but not so in more recent years (Enstrom 2005).

Most of these studies have compared subjects living in different communities, assigning values for exposure to air pollution that are based on measurements taken at central sites. One exception is the Seventh-Day Adventist Study, which has used interpolation of data obtained from many monitoring stations as a basis for assigning exposure at home addresses (Abbey et al. 1999; Chen et al. 2005). An analysis of data from the Los Angeles population participating in the American Cancer Society–II Study has also assigned exposure values based on interpolation of data from many monitoring stations (Jerrett et al. 2005b). Recently, within-city contrasts in particulate matter air pollution were more closely related to cardiovascular mortality than between-city contrasts, in a large cohort study of postmenopausal women (Miller et al. 2007).

In Europe, five cohort studies published since 2002 have addressed the association between long-term exposure to air pollution and mortality (Hoek et al. 2002; Nafstad et al. 2004; Filleul et al. 2005; Gehring et al. 2006; Naess et al. 2007). These studies differ from the U.S. cohort studies in that their emphasis has been on investigating within-city contrasts in exposure rather than contrasts between communities. Within communities, major differences in ambient air pollution concentrations may result from differential distribution of sources (mostly traffic) or topographic features such as altitude. In general, European studies have not evaluated $PM_{2.5}$ and PM_{10} because of a lack of data.

In the Netherlands, we reported associations of NO_2 and black smoke with all-cause and cardiopulmonary mortality. Per 10-μg/m^3 change in NO_2 the RR for cardiopulmonary mortality was 1.27 (95% CI, 1.00–1.78) (Hoek et al. 2002).

In Norway, Nafstad and colleagues (2004) followed 17,000 men in Oslo from 1972 through 1998. SO_2 and NO_x concentrations were modeled at the home address level. No association was found between mortality and SO_2, whereas total, cardiovascular, respiratory, and lung cancer mortality were all significantly associated with NO_x. Per change of 10 μg/m^3 in NO_x, the RR for ischemic heart disease mortality was 1.08 (95% CI, 1.03–1.12). The NO_2/NO_x ratio was not given, but the relative risk of mortality would likely have been higher if they had calculated it for a 10-μg/m^3 change in NO_2 rather than NO_x.

In France, Filleul and colleagues (2005) followed 14,000 subjects for 25 years, from 1975 through 2000. This study was conducted in 24 areas in seven French cities. NO, NO_2, black smoke, total suspended particles (TSP), and SO_2 were all measured in the first phase of the study (1974–1976). The monitoring sites in 6 of the 24 areas were found to be heavily influenced by local traffic as evidenced by high NO/NO_2 ratios. After excluding these six areas, black smoke, TSP, and NO_2 were all significantly associated with total mortality. NO_2 was also associated with lung cancer and cardiopulmonary mortality. Per 10-μg/m^3 change in NO_2, the RR for cardiopulmonary mortality was 1.27. SO_2 concentrations were unrelated to any type of mortality.

In Germany, Gehring and colleagues (2006) studied mortality in a cohort of almost 5000 women living in urban areas in the industrialized Ruhr area, who were followed from either 1985 or 1990 to 2002. TSP and NO_2 were measured at seven locations. PM_{10} was estimated from TSP using a single 0.7 conversion factor. Both PM_{10} and NO_2 were associated with all-cause and cardiopulmonary mortality. Per 10-μg/m^3 change in the 1-year average NO_2 concentration, the RR of cardiopulmonary mortality was 1.36 (95% CI, 1.14–1.63).

In Oslo, Norway, Naess and colleagues (2007) used population registry data to follow all subjects who were between 51 and 90 years old on January 1, 1992. Deaths were counted between 1992 and 1998. On an individual level, data on educational level, occupational class, and sex were available. Concentrations of NO_2, PM_{10}, and $PM_{2.5}$ were modeled at the home address using dispersion models. Per 10-μg/m^3 of NO_2, the estimated RR of cardiovascular death was about 1.05 for both men and women 51 to 70 years old at baseline in 1992. Relative risks for those 71 to 90 years old at baseline were not significant for NO_2, but they were for $PM_{2.5}$. The estimated risks associated with $PM_{2.5}$ in this study, expressed per quartile, were RR of 1.10 (95% CI, 1.05–1.16) for men and 1.14 (95% CI, 1.06–1.21) for women aged 51–70 years, and 1.05 (95% CI, 1.01–1.08) for men and 1.03 (95% CI, 1.00–1.05) for women aged 71–90 years at baseline. The difference between quartiles was about 4 μg/m^3 in this study, so these estimates would translate into RRs of about 1.08 to 1.35 per 10 μg/m^3 of $PM_{2.5}$.

Following publication of our pilot study reporting an association between living near a major road and cardiopulmonary mortality in the Netherlands (Hoek et al. 2002), three studies have evaluated traffic exposure variables. For those living near a major road, the RR for all-cause mortality was 1.41 (95% CI, 0.94–2.12) in the pilot study. In a study by Finkelstein and colleagues (2004), the same indicator variable for traffic-related exposure as in the pilot study was used, that is, residence within 50 m of a major road or within 100 m of a freeway. Mortality from all natural causes was increased for subjects who lived close to a major road (RR, 1.18; 95% CI, 1.02–1.38). In a German cohort of 5000 women, living within 50 m of a major road was associated with increased cardiopulmonary mortality (RR, 1.70; 95% CI, 1.02–2.81). For all-cause mortality the RR was 1.29 (95% CI, 0.93–1.78) (Gehring et al. 2006). A case–control study in Worcester, Massachusetts, reported a significant association between acute myocardial infarction and cumulative traffic near the home (RR, 1.04; 95% CI, 1.02–1.07, expressed per interquartile range) and distance to the nearest major road (RR, 1.05; 95% CI, 1.03–1.06, expressed per kilometer). Although risk estimates of our current study are lower than those previously reported, the confidence intervals overlap with the estimates in the predominantly smaller studies conducted previously.

In summary, our study adds evidence that traffic-related air pollution increases mortality. Risk estimates differ substantially between studies, for reasons not well understood. Variations in methodology, population, composition of the air pollution mixture, and random error may all contribute to differences. The associations

between traffic-related air pollution and mortality are consistent with a growing body of evidence pointing to effects on morbidity indicators. The plausibility of an effect of air pollution on cardiovascular mortality has increased with recent findings of associations between long-term average exposure to ambient air pollution and measures of atherosclerosis (Künzli et al. 2005; Hoffmann et al. 2006, 2007).

RESPIRATORY MORTALITY

In contrast to the findings of the American Cancer Society Study (Pope et al. 2004), we found that variables representing air pollution and traffic intensity were associated with respiratory mortality, with some of the associations being statistically significant. The highest relative risk estimates were actually those for respiratory mortality, though interpretation should be cautious in light of the width of confidence intervals. We contend that our findings are consistent with the evidence of effects of air pollution.

First, numerous studies have found effects of long-term and short-term exposure to air pollution on respiratory morbidity (Brunekreef and Holgate 2002). Recent papers have strengthened this evidence (Gauderman et al. 2007). Second, time-series studies have found associations between short-term changes in air pollution and both cardiovascular and respiratory mortality. Third, other cohort studies also have reported significant associations between respiratory mortality and long-term average air pollution concentrations (Abbey et al. 1999; Nafstad et al. 2004).

In the Norwegian study by Nafstad and colleagues (2004), per 10-μg/m^3 increase in NO_x the RR for respiratory mortality was 1.16 (95% CI, 1.06–1.26). In the large ecologic study in Oslo, mortality from chronic obstructive pulmonary disease was associated with $PM_{2.5}$ and NO_2 (Naess et al. 2007). In the extended follow-up of the Harvard Six Cities Study, a nonsignificant relative risk of respiratory mortality was found, which was smaller than that for cardiovascular mortality (Laden et al. 2006).

Misclassification of underlying cause of death, between cardiovascular and respiratory deaths in particular, may have occurred. The consequence of misclassification is that associations for cardiovascular and respiratory deaths become more similar. Given that relative risks in the current study were higher for respiratory deaths than for cardiovascular deaths, it is unlikely that the associations observed for respiratory deaths were actually due to misclassified cardiovascular deaths.

LUNG CANCER

Air pollution has long been suspected to increase lung cancer rates. Vineis and colleagues (2004) summarized the evidence up to 2004 and concluded that air pollution may increase lung cancer. Case–control studies in Trieste (Barbone et al. 1995) and Stockholm (Nyberg et al. 2000) and cohort studies in the United States (Dockery et al. 1993; Abbey et al. 1999; Pope et al. 2002) and Europe (Nafstad et al. 2003) have significantly strengthened the evidence base. Since 2004, lung cancer was found to be associated with NO_2 in the French PAARC study (RR, 1.48; 95% CI, 1.05–2.06 per 10 μg/m^3) (Filleul et al. 2005). In the extended follow-up of the Harvard Six Cities Study, a nonsignificant association between $PM_{2.5}$ and lung cancer mortality was found (RR, 1.27; 95% CI, 0.96–1.69 per 10 μg/m^3) (Laden et al. 2006). In the European Prospective Investigation on Cancer and Nutrition cohort spread over nine European countries, lung cancer in never smokers was not significantly associated with living near a major road (RR, 1.46; 95% CI, 0.89–2.40) or with a change of 10 μg/m^3 in background NO_2 concentration (RR, 1.14; 95% CI, 0.78–1.67) (Vineis et al. 2006).

In the overall analyses, the relative risks associated with background and overall air pollutant concentrations were essentially unity for lung cancer mortality and lung cancer incidence in our study. Relative risks for the traffic variables were elevated, though none of them was statistically significant. The results for the never smokers agree more with findings in previous studies. Both for lung cancer mortality and for lung cancer incidence, associations with air pollution became (borderline) significant, with RRs per 10 μg/m^3 black smoke of 1.32 and 1.47, respectively.

OTHER CAUSES OF DEATHS

Traffic intensity was not associated with mortality from causes other than cardiopulmonary disease or lung cancer. For background air pollution, however, risk estimates for these other causes of death were similar to those for cardiovascular deaths. This is in contrast to the findings for effects of $PM_{2.5}$ in the American Cancer Society and Harvard Six Cities studies (Pope et al. 2002; Laden et al. 2006). In the American Cancer Society Study, associations between SO_2 and risks for other causes of death and for cardiopulmonary deaths were also similar.

Major noncardiopulmonary, non–lung cancer causes of death in the current study were cancer other than lung cancer (5723 cases) and diseases of the digestive tract (467 cases). Some of these other causes of deaths are conceivably related to air pollution, such as chronic rheumatic heart disease and other diseases of the circulatory system (449 cases), as well as bladder cancer (180 cases).

The finding of an association between background air pollution and other causes of death may be regarded as an argument against a causal interpretation of the associations

found for cardiopulmonary deaths. However, in recent years suggestive evidence of air pollution effects on organ systems other than the cardiorespiratory system has started to emerge, possibly related to passage of ultrafine particles into the blood stream.

EFFECT MODIFICATION

Our study provides only weak support for the observation in previous studies that estimates for the association of outdoor air pollution with health endpoints are higher in subjects with lower educational levels (Pope et al. 2002; Miller et al. 2007). It is unclear what is behind this observation. In the current study, we assigned individual exposure estimates, in contrast to the American Cancer Society Study (Pope et al. 2002), which assigned city-level averages. Thus it is unlikely that exposures were underestimated for subjects with lower levels of education. A potential explanation for the risk estimate in this group is the association between educational level and the consumption of fruit, a major source of antioxidants. Since oxidative stress probably plays an important role in the adverse health effects of air pollution (Donaldson et al. 2001; Brunekreef and Holgate 2002), low fruit intake might explain higher air pollution effects. In our study we found some evidence that low fruit intake was related to higher risks of mortality associated with air pollution. Subjects with lower educational levels consumed significantly less fruit.

Our study supports observations within the American Cancer Society Study (Pope et al. 2002) that there was no difference between men and women in the relative risks of cardiopulmonary mortality associated with air pollution. In the Seventh-Day Adventist Study, however, it was suggested that women were more affected than men (Chen et al. 2005). And in the Discussion section of the study by Miller and colleagues (2007), the inclusion of women is mentioned as one of the potential reasons for the high relative risks reported for cardiovascular events associated with air pollution.

TRAFFIC NOISE

To our knowledge this is the first study to assess the possible association between cardiovascular mortality and traffic-related noise at the same time as assessing the association with traffic-related air pollution. Our study suggests that the associations observed between cardiovascular mortality and local traffic intensity are not explained by traffic noise. Limitations of this assessment include the fact that noise exposure was modeled with data from a different year than the traffic intensity data and air pollution data. We also did not have information on the position of a subject's bedroom with respect to the road, a factor considered important in noise exposures (nighttime exposures probably play an important role in health effects). Further, no information on measures to insulate against sound in specific streets was available.

LIMITATIONS OF THE STUDY

This study has limitations related to exposure assessment, contrast between exposure values, control for confounding factors, and the study population.

We made a major effort to improve the assessment of exposure to outdoor air pollution compared with that in our pilot study. The collection of provincial and municipal data on traffic intensity turned out to be very time-consuming, as these data were not available in a central database. The use of a geographically more precise and more complete road network, the inclusion of traffic counts, the use of more predictor variables to model the urban background air pollution on a more appropriate spatial scale, and the use of multiple data periods were all improvements in the current study compared with the pilot study (Hoek et al. 2002).

Nevertheless, the limited availability of data on traffic intensity, both spatially and temporally, remained a problem for the current study. Procedures were developed to derive a consistent set of traffic variables, but some misclassification will have occurred due to incomplete traffic data. Because of the high correlation of data on traffic intensity collected 10 years apart, we do not think that temporal coverage is an important problem. Some municipalities did not have or did not provide traffic data. Since we assigned a standard low value for traffic intensity to roads without traffic count data, some subjects who actually had high exposure may have been classified as having low exposure. Because of the small fraction of subjects living close to major roads, this misclassification has probably not affected risk estimates substantially. An analysis restricted to municipalities that did provide traffic data, indeed, showed only slightly larger risks associated with the traffic variables. It should be noted that data on freeways and provincial roads were available for these predominantly smaller communities, and these are typically the only relevant (high traffic density) roads for these communities.

We do not think that the exact default number of vehicles per day assigned to each road segment is particularly important, as traffic intensities below about 5000 motor vehicles/day contribute very little to air pollution levels, with the possible exception of street canyons. We assumed that a street without data had a traffic intensity of less than

2450 motor vehicles/day and assigned 1225 motor vehicles/day as the default value. Assigning intensities randomly from a distribution with a mean of 1225 might have been more realistic, but would probably not have altered the results, as the range of traffic intensities evaluated was up to approximately 100,000 motor vehicles/day.

Traffic intensity data for municipal and provincial roads could only be linked to the road network by the road name and number. We were unable to account for variability of traffic within the length of a specific road. For national roads, data were linked per road section.

The estimations of $PM_{2.5}$ concentrations at the home address were less precise than estimations for black smoke and NO_2, as nationwide measurements of $PM_{2.5}$ were not available during the study period. Instead we transformed PM_{10} data into $PM_{2.5}$ values using a single ratio, established from monitoring data in the Netherlands, to estimate the background concentration at the home address. To this we added a local component based on actual measurements of $PM_{2.5}$ obtained at the end of the follow-up period. Much of the spatial contrast in $PM_{2.5}$ concentrations was due to this local component.

The number of monitoring sites available for developing the estimates of background air pollution concentrations at the residential addresses was limited, in particular, for black smoke and $PM_{2.5}$ (see Methods section). However, as documented in the Results section and in the pilot study using similar methods of exposure assessment (Hoek et al. 2002), prediction errors derived from cross-validation were small compared with the range in air pollution concentrations for all pollutants, including black smoke.

In developing land-use regression models for the urban exposure component, we used population density as one of the important predictors. Population density might be associated with other risk factors related, for example, to poor living conditions in urban areas and hence introduce confounding when the exposure variable is used in statistical analyses of the association with mortality (Moore et al. 2007). However, population density is not likely to be an independent risk factor, but might affect health because it is associated with area-level socioeconomic status, which has been recognized as an important determinant of health. Therefore, we adjusted for this variable at two spatial scales and do not think that using population density as a predictor for air pollution exposure has introduced appreciable confounding in the association between air pollution and mortality.

A further limitation of the study is that we only assessed outdoor pollutant concentrations at the home address. The questionnaire did not contain information about the work address. Since our cohort consisted of subjects aged 55–69 years at baseline, an age group in which many people in the Netherlands would no longer be working, the lack of work address is likely not an important limitation. Currently very little information is available about the validity of long-term average outdoor air pollution concentrations as estimates of personal exposure to air pollutants from ambient origin. In Amsterdam, personal soot exposure was 1.29 times higher for adults living on the main road network than for subjects living in quiet streets (Wichmann et al. 2005). Four studies in children found that higher ambient concentrations at the school or home address were associated with increased personal exposure to NO_2 (Rijnders et al. 2001) and soot (Wichmann et al. 2005; Van Roosbroeck et al. 2006; Van Roosbroeck et al. 2007). It is uncertain whether these findings in children apply to the older adults in our study.

We do not believe that the limited contrast in levels of exposure has contributed to an underestimation of the effect of air pollution. It certainly does not explain the difference between the results of the current study and the larger risk estimates reported previously for the pilot study (Hoek et al. 2002), as the pilot study population is a small random sample of the full cohort used in the current study. Histograms of the various exposure estimates in the cohort showed substantial variability of the concentrations of NO_2, black smoke, and SO_2 in particular. The range between the 5th percentile and the 95th percentile of the concentration distribution was 21 to 45 $\mu g/m^3$ for NO_2, 9 to 17 $\mu g/m^3$ for black smoke, and 6 to 22 $\mu g/m^3$ for SO_2. The contrast in $PM_{2.5}$ concentrations was smaller; the 5th and 95th percentiles were 24 and 32 $\mu g/m^3$ (minimum, 23 $\mu g/m^3$; maximum, 37 $\mu g/m^3$). In the U.S. cohort studies, the contrast in $PM_{2.5}$ values was somewhat larger; for example, in the Harvard Six Cities Study, the city-average $PM_{2.5}$ concentrations ranged from 11 to 29 $\mu g/m^3$ and from 10 to 22 $\mu g/m^3$ in the two evaluated periods (Laden et al. 2006). In the American Cancer Society Study, the range in city-average $PM_{2.5}$ concentration was from about 10 to 30 $\mu g/m^3$ in 1979–1983 and from 5 to 20 $\mu g/m^3$ in 1999–2000 (Pope et al. 2002). The somewhat smaller contrast in exposure concentrations in our study may have contributed to the wider confidence intervals found in our study compared with the American Cancer Society Study, for example.

For the traffic variables, a more skewed distribution was found, with relatively few subjects being highly exposed. This reflects actual conditions, as few people in the cohort lived near major roads. The low proportion of exposed subjects will have contributed to wider confidence intervals.

For the full cohort, we had limited information on potential confounders. As extensively discussed, we found some evidence that that this is unlikely to have affected our conclusions significantly — analyses within the case–cohort sample showed only modest differences between the various confounder models. However, we cannot be sure that this applies to the full cohort, so residual confounding in the full-cohort analyses remains a possibility.

When we compared the results of the standard Cox proportional hazards model in the full cohort with models taking into account clustering of the data at the neighborhood scale and municipality scale, or spatial autocorrelation at these scales, we observed that adjusted relative risks were very similar. Confidence intervals were also not widened when spatial clustering was accounted for. Apparently, the limited set of individual-level confounders and the four area-level indicators of socioeconomic status were sufficient to remove spatial clustering.

We specified a large number of models, and it can therefore be questioned whether the few significant associations we found reflect chance findings. We consider this unlikely, in light of the body of evidence that already exists. Further, the small relative risks found for traffic intensity near the home were consistently found in different models, for example, in models with background concentrations for different pollutants, models for different time periods, and models with slight modifications such as the use of indicator variables versus continuous variables.

CONCLUSIONS

Long-term average concentrations of black smoke, NO_2, and $PM_{2.5}$, but not SO_2, were associated with increased mortality. Relative risks were generally small. Associations of natural-cause and respiratory mortality with black smoke and NO_2 concentrations were statistically significant. Traffic intensity near the home was associated with increased natural-cause mortality. The associations of background air pollution and traffic variables were highest with respiratory mortality, though confidence intervals were wide for the relative risks of this less-frequent cause of death.

Overall (background and local) concentrations of air pollutants were associated with suggestively higher relative risks of mortality in subjects who did not move during follow-up, and with slightly higher relative risks for subjects living in the three main cities. Associations between overall air pollution and lung cancer incidence and mortality tended to be higher in subjects with low educational levels and low fruit intake, but differences between the strata for these variables were not statistically significant.

The association of background air pollution and traffic intensity variables with cardiovascular mortality remained after adjustment for traffic noise. Only traffic noise levels above 65 dB(A) were associated with cardiovascular mortality.

Relative risk estimates for mortality with background air pollution and local traffic variables were much smaller than those reported in our pilot study (Hoek et al. 2002), which was conducted in a 4% random sample of the full cohort. Confidence intervals in the current study were much smaller than those in the pilot study. The difference between our pilot study results and those in the current study cannot be explained by differences in methods of exposure assessment and data analysis. The most likely explanations are random variability related to sampling from the full cohort and the effect of a longer follow-up period. The relative risks of mortality associated with background air pollution and traffic variables in the current study are more in line with those in other cohort studies, such as the American Cancer Society Study (Pope et al. 2002).

The results of our study add to the evidence that long-term exposure to ambient air pollution is associated with increased mortality.

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APPENDIX A. Differences between Estimated Relative Risks in the Pilot Study and the Current Study

We previously reported that in a subcohort of the full NLCS cohort, cardiopulmonary mortality was associated with living near a major road, and also with estimated black smoke concentrations at the subcohort member's home address (Hoek et al. 2002). Some key results from that pilot study are presented in Table A.1. In the current study, referred to as NLCS-AIR, we found no association between cardiopulmonary mortality and exposure to traffic, as defined by the same variable as in the pilot study,

Table A.1. Associations Between Air Pollution Exposure Variables and Cardiopulmonary Mortality in the Subcohort ($n \sim 5000$), Pilot Study

Exposure Model[a]	RR (95% CI)[b]
Background black smoke *and*	1.34 (0.68–2.64)
Living near a major road	1.95 (1.09–3.51)
Overall black smoke	1.71 (1.10–2.67)

[a] The first model has two variables, the estimated background black smoke concentration and the traffic indicator variable (living near a major road) for local exposure. The second model has one variable, the estimated overall black smoke concentration (sum of background and local exposure components).

[b] For black smoke, RR is calculated per 10-μg/m^3 increment.

Table A.2. Associations Between Air Pollution Exposure Variables and Cardiopulmonary Mortality in the Full Cohort (n ~ 120,000), Current Study

Exposure Model[a]	RR (95% CI)[b]
Background black smoke *and* Living near a major road (defined as in pilot study)	1.12 (0.98–1.28) 0.97 (0.87–1.08)
Overall black smoke	1.07 (1.00–1.15)

[a] The first model has two variables, the estimated background black smoke concentration and the traffic indicator variable (living near a major road) for local exposure. The second model has one variable, the estimated overall black smoke concentration (sum of background and local exposure components).

[b] For black smoke, RR is calculated per 10-μg/m^3 increment.

Table A.3. Adjusted Associations Between Living Near a Major Road Defined as in the Pilot Study and Cardiopulmonary Mortality

Study Data	Study Population	Years of Follow-Up	RR (95% CI)
Pilot study	Subcohort[a]	8	1.95 (1.09–3.51)
Current study	Subcohort[b]	8	2.09 (1.15–3.82)
Current study	Subcohort	10	1.34 (0.75–2.40)
Current study	Full cohort[c]	8	0.94 (0.83–1.08)
Current study	Full cohort	10	0.97 (0.87–1.08)

[a] In the pilot study, subcohort analyses were adjusted for age, sex, Quetelet index, occupation, active and passive smoking, and neighborhood socioeconomic score.

[b] In the current study, subcohort anlayses were adjusted for age, sex, Quetelet index, active smoking, passive smoking, educational level, occupational exposure, marital status, alcohol use, vegetable intake, fruit intake, energy intake, fatty acids intake, folate intake, fish consumption, and area-level indicators of socioeconomic status (in neighborhood and COROP area).

[c] In the current study, full-cohort analyses were adjusted for age, sex, smoking status, and area-level indicators of socioeconomic status (in neighborhood and COROP area).

living near a major road (Table A.2 and Table 36 of the Investigators' Report), and much smaller relative risks than previously reported when more refined exposure estimates were used. In this appendix we first summarize differences between the pilot study and the current study and then provide some further analyses to aid in interpretation of the differences.

The pilot study results were based on the NLCS subcohort of approximately 5000 subjects, in which there were about 500 deaths from natural causes (including fewer than 200 deaths from cardiopulmonary causes). Follow-up was from September 17, 1986, to October 1, 1994. The results of the current study were based on the full cohort of approximately 120,000 subjects, and the follow-up period, from January 1, 1987, through December 31, 1996, was two years longer than that in the pilot study. Approximately 20,000 deaths were available for analysis in NLCS-AIR, or about 40 times the number on which the pilot study analysis was based.

For exposure assessment in the current study, we used more refined data and more advanced methods of analysis (see Methods section), but we also analyzed the data of the current study using the exposure variable of the pilot study. The confounder model used in the pilot study was adapted for the current study to incorporate new insights. In particular, we used the COROP area in which a subject lived to add area-level indicators of socioeconomic status. This is a larger area than was taken into account in the pilot study, and thus allowed for regional contrasts in life expectancy.

Table A.3 illustrates that when the current study methods are applied to the same exposure variable (living near a major road) and the same subcohort as were analyzed in the pilot study, the relative risk of cardiopulmonary mortality is similar to that obtained in the pilot study (compare rows 1 and 2). The estimates differ slightly because of differences in the confounder models and the follow-up periods and small differences in the number of subjects included in the analyses. When the results of the pilot study were reported, data management had not been completed for the entire subcohort, so the report included 185 (87%) of the 213 case subjects (study participants who died of cardiopulmonary causes) in the subcohort.

Extending follow-up by two years, through 1996, increased the number of cardiopulmonary deaths in the subcohort from 213 to 309. However, only 2 of the added case subjects were found to be living near a major road by the classification used in the pilot study (Table A.4). As a result, the estimated RR for cardiopulmonary mortality associated with this variable was sharply reduced to 1.34 from 1.95 as originally reported. This is important to note because it shows that a major part of the difference between the relative risks associated with living near a major road in the pilot study and the current study is explained simply by the addition of two more years of follow-up. The interpretation of this difference may also include random variability resulting from the small number of subjects who lived near a major road, as well as less-precise exposure characterization because more subjects changed residence. The interpretation of random error is supported by the fact that using the current study

Table A.4. Total Case Subjects and Number Living Near a Major Road in the Subcohort and Full Cohort for Each Study Year, by Pilot Study Method and Current Study Method

	Case Subjects in Subcohort			Case Subjects in Full Cohort		
		Number (%) Exposed[a]			Number (%) Exposed[a]	
Year	Total Number	Pilot Study	Current Study	Total Number	Pilot Study	Current Study
1987	26	1 (3.9)	5 (19.2)	474	25 (5.3)	31 (6.5)
1988	15	1 (6.7)	1 (6.7)	523	33 (6.3)	46 (8.8)
1989	33	1 (3.0)	4 (12.1)	573	25 (4.4)	50 (8.7)
1990	24	0 (0)	3 (12.5)	612	29 (4.7)	56 (9.2)
1991	26	4 (15.4)	3 (11.5)	684	32 (4.7)	49 (7.2)
1992	19	1 (5.3)	1 (5.3)	651	21 (3.2)	41 (6.3)
1993	33	3 (9.1)	4 (12.1)	822	35 (4.3)	55 (6.7)
1994	37	2 (5.4)	3 (8.1)	876	27 (3.1)	53 (6.1)
1995	47	2 (4.3)	4 (8.5)	1032	52 (5.0)	76 (7.4)
1996	49	0 (0)	7 (14.3)	1078	51 (4.7)	97 (9.0)

[a] "Exposed" indicates that the subject lived near a major road.

Table A.5. Associations Between Air Pollution Exposure Variables Used in the Current Study and Cardiopulmonary Mortality in the Subcohort and Full Cohort

	RR (95% CI)	
Variable	Subcohort	Full Cohort
Overall black smoke	1.44 (0.84–2.47)	1.07 (1.00–1.15)
Background black smoke	1.24 (0.46–3.33)	1.12 (0.98–1.28)
Traffic intensity on nearest road	1.27 (0.97–1.68)	1.06 (1.00–1.12)
Living near a major road	1.08 (0.51–2.26)	1.07 (0.96–1.19)
Traffic intensity in a 100-m buffer	1.29 (0.82–2.04)	1.03 (0.95–1.10)

method in the full cohort, we did not find the pattern of a small number of deaths among subjects living near a major road in the two additional years that was found using the pilot study method (Table A.4).

A second important difference between the two studies is that relative risks of cardiopulmonary mortality were much smaller in the full cohort than in the subcohort. This pattern was found for exposure variables other than living near a major road as well (Table A.5). This pattern could be explained by random variability introduced by using a small sample to represent the full cohort. With the exception of the 8-year analyses of the original exposure variable (Table A.3), the values for relative risk of the full cohort are included in the confidence intervals of the relative risks in the subcohort (Table A.5).

There was no evidence that the subcohort is a not a representative sample of the full cohort. We checked the procedures used to sample from the full cohort, and these were indeed random. In addition, we found no differences in distributions of estimated air pollution exposure values between the subcohort and the full cohort. The percentage of subjects living on a road with a traffic intensity of more than 10,000 motor vehicles/day was 4.8% in the subcohort and 4.5% in the full cohort minus the subcohort, with a χ^2-value of 1.31 (P value of 0.25). For the other traffic variables there were also no statistically significant differences between the subcohort and the full cohort minus the subcohort (data not shown). The estimated background black smoke concentrations for the period 1987–1996 also did not differ between the subcohort and the full cohort minus the subcohort (P value of t test was 0.71).

APPENDIX B. HEI Quality Assurance Report

The conduct of this study was subjected to independent audits by Dr. Richard Kwok (RTI International), an expert in quality assurance for air quality monitoring studies. The audits included on-site reviews of study activities for conformance to the study protocol and standard operating

procedures. The dates of the audits are listed below with the phase of the study examined.

Written reports of the inspection were provided to the HEI Project Manager, who transmitted the findings to the Principal Investigator. These quality assurance audits demonstrated that the study was conducted by a well-coordinated, experienced team according to the study protocol and standard operating procedures. Interviews with study personnel revealed a consistently high concern for data quality. The report appears to be an accurate representation of the study.

January 28–30, 2009: The auditor conducted an on-site audit at Utrecht University in the Netherlands to verify the integrity of the reported data. The audit reviewed the study's final report, the staffing, adequacy of equipment and facilities, internal quality assurance procedures, the air quality sampling methodology and data processing procedures, and responses to an earlier audit conducted in January 2003. Several data points for each parameter were traced through the entire data processing sequence to verify that the described procedures were being followed and to verify the integrity of the database. The audit also included a spot check of the hand-entered data cards for data entry errors. No errors were noted.

Richard K. Kwok, Ph.D.
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APPENDICES AVAILABLE ON THE WEB

Appendices C, D, E, and F contain supplemental material not included in the printed report. These appendices are available on the HEI Web site (www.healtheffects.org). You may also request these materials by contacting the Health Effects Institute at 101 Federal Street, Suite 500, Boston, MA 02110 (phone: +1-617-488-2300; fax +1-617-488-2335) or by e-mail (*pubs@healtheffects.org*). Please give (1) the first author, full title, and number of the Research Report and (2) the title of the appendix requested.

Appendix C. Data Management Air Pollution Concentrations of National Air Quality Monitoring Network

Appendix D. Assignment of Traffic Intensity Data

Appendix E. Motivation of Selection of Ecological Covariates

Appendix F. Full Cohort and Case–Cohort Analyses

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OTHER PUBLICATIONS RESULTING FROM THIS RESEARCH

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ABBREVIATIONS AND OTHER TERMS

ACN	Address Coordinates Netherlands
APHEA	Air Pollution and Health, a European Approach
CAFE	Clean Air For Europe
CI	confidence interval
CO	carbon monoxide
COROP	Coordinatie-Commissie Regionaal Onderzoeksprogramma
dB(A)	A-weighted decibels [decibels with the sound pressure scale adjusted to conform with the frequency of the human ear]
DEFRA	Department for Environment, Food, and Rural Affairs
EMPARA	Environmental Model for Population Annoyance and Risk Analysis
GIS	geographic information system
ICD-9	I*nternational Classification of Diseases*, 9th revision
ICD-10	*International Classification of Diseases*, 10th revision
JEM	job-exposure matrix
NAQMN	National Air Quality Monitoring Network
NLCS	Netherlands Cohort Study on diet and cancer
NLCS-AIR	study of average traffic-related air pollution concentrations and mortality in the NLCS cohort
NO	nitric oxide
NO_2	nitrogen dioxide
NO_x	nitrogen oxides
NWB	Nationaal Wegen Bestand (National Road Database)
O_3	ozone
PAARC	Pollution Atmospherique et Affections Respiratoires Chroniques [study]
PALGA	Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief (Pathologic-Anatomic National Automated Archive)
PM	particulate matter
$PM_{2.5}$	PM with aerodynamic diameter $\leq$ 2.5 µm
PM_{10}	PM with aerodynamic diameter $\leq$ 10 µm
RIVM	Rijksinstituut voor Volksgezondheid en Milieu (National Institute for Public Health and the Environment)
RMSE	root mean square error
RR	relative risk
SAVIAH	Small Area Variation in Air Pollution and Health [study]
SO_2	sulfur dioxide
TNO	Toegepast-Natuurwetenschappelijk Onderzoek (Netherlands Organization for Applied Scientific Research)
TRAPCA	Traffic-Related Air Pollution and Childhood Asthma [study]

Research Report 139, *Effects of Long-Term Exposure to Traffic-Related Air Pollution on Respiratory and Cardiovascular Mortality in the Netherlands: The NLCS-AIR Study,* B. Brunekreef et al.

INTRODUCTION

Increases in urbanization and motor vehicle use have raised questions about the health effects of exposure to emissions from motor vehicles. Pollutants such as oxides of nitrogen and black smoke (a measure of soot and fine particulate matter [PM]*) are emitted from motor vehicle exhaust pipes, affecting local and regional air quality. More general urban air pollutants that have been associated with adverse health effects, such as ozone, PM, and volatile organic compounds, are formed from emissions from many sources. For nitrogen dioxide (NO_2) and black smoke, however, researchers have found differences in concentrations within urban areas that are dependent on traffic intensity (Briggs et al. 1997; van Vliet et al. 1997). Roorda-Knape and colleagues (1998) found that concentrations of these two pollutants were higher when monitored near roads and declined with increasing distance from roads. Such findings have raised concerns that those living near roads traveled by high numbers of motor vehicles may have greater exposure to traffic-related air pollution than those living near less busy streets, and thus, may be at greater risk for associated health effects (Edwards et al. 1994; Oosterlee et al. 1996; van Vliet et al. 1997).

To better assess local exposure to traffic-related air pollution, some researchers have integrated information on road networks and traffic intensity with data from geographic information systems (GISs) and equations describing presumed chemical and physical behavior of emissions in the atmosphere into pollutant dispersion models (Gualtieri and Tartaglia 1998; Fedra 1999). Briggs and colleagues (1997) found that the incorporation of topographic and land-use information into these models increased their ability to predict spatial variations in traffic-related air pollution. As these investigators have shown, concentrations measured at regional monitoring stations may not reflect actual exposures of the surrounding population when local sources of air pollution dominate. Thus, approaches that make use of GIS and incorporate land-use and traffic data to estimate pollutant concentrations are useful to improve our understanding of where the population will potentially be affected the most by traffic-related air pollution, at far less cost than intensive neighborhood campaigns to measure air pollution.

In 2002, Gerard Hoek, Bert Brunekreef, and colleagues published an article in the *Lancet* (Hoek et al. 2002) describing the results of a pilot study, funded by the Netherlands Asthma Foundation, in which they used state-of-the-art GIS-based methods to assess long-term exposure to traffic-related air pollution. They examined associations between exposure to air pollution and mortality from 1986 to 1994 in a randomly selected sample of 5000 participants from the ongoing Netherlands Cohort Study (NLCS) on diet and cancer. In the pilot study, they found that estimated black smoke and NO_2 concentrations at the 1986 home addresses of study participants varied widely, though concentrations of the two pollutants were highly correlated at both regional and local levels. There was a significant association between living near a major road and all-cause mortality, which was even stronger and more significant for participants who had lived at their 1986 home address for more than 10 years. In a model they used to estimate the effect of "background pollution plus living near a major road," the relative risks for cardiopulmonary mortality were higher than the relative risks for all-cause mortality. The pilot study results suggested that further investigation into spatial and temporal contrasts in traffic-related air pollution and their associated health effects was both feasible and potentially valuable.

Each year, HEI issues a request for preliminary applications (RFPA) on the health effects of air pollution to seek proposals for new areas of research addressing the health effects of air pollutants derived from motor vehicle emissions. Brunekreef and colleagues responded to one of these

Dr. Bert Brunekreef's 4-year study, "Effects of Long-Term Exposure to Traffic-Related Air Pollution on Respiratory and Cardiovascular Mortality in the Netherlands: The NLCS-AIR Study," began in July 2001. Total expenditures were $949,426. The draft Investigators' Report from Brunekreef and colleagues was received for review in September 2006. A revised report was received in May 2007. A second revision of the report was received in September 2007 and was accepted for publication in October 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 the Review Committee's Commentary.

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

RFPAs with a preliminary application entitled, "Long-Term Effects of Traffic-Related Air Pollution on Respiratory and Cardiovascular Mortality." This study—which would advance the work of the pilot study—would use data for all participants enrolled in the NLCS (n = 120,852) to explore associations between local, urban, and regional levels of traffic-related pollutants and cause-specific mortality in the Netherlands.

On the basis of the pilot study results, the need for European studies that assess long-term exposure to air pollution, and the experience of the investigators, the HEI Health Research Committee asked the investigators to submit a full application. After evaluation of the full application, the Committee felt that clarification was needed on the type of longitudinal data that were available for analysis and the methods of exposure assessment and data analysis, as well as the expected precision of estimates of effect (statistical power). Brunekreef and colleagues submitted a more detailed application addressing these concerns. The Research Committee recommended the proposed study for funding in October 2000 because they believed that it would add new dimension to the investigation of health effects of air pollution. The investigators' approach to characterizing personal exposure was state-of-the art and had been well demonstrated in the pilot study. The proposed study was also based on a large amount of existing data, making it cost-effective for the investigators to obtain results with sufficiently high statistical power to detect subtle effects.

SCIENTIFIC BACKGROUND

Differences in meteorologic and climatic factors, types of industry, and degrees of urbanization have resulted in diverse air pollution mixtures and air pollutant levels across Europe. A project to determine the short-term health effects of air pollution, Air Pollution and Health, a European Approach (APHEA), examined pollutant measurements and meteorologic information from 15 cities in 10 European countries (Katsouyanni et al. 1995). Among the published findings based on the APHEA data are several reports in which black smoke and NO_2, both traffic-related pollutants, are associated with short-term effects on morbidity or mortality. Increases of 50 μg/m³ in daily mean levels of NO_2 and black smoke (as well as sulfur dioxide, ozone, and total suspended particles) on the previous 1 to 3 days were found to increase relative risks of daily hospital admissions for chronic obstructive pulmonary disease, defined as unspecified bronchitis, chronic bronchitis, emphysema, or chronic airways obstruction, for people of all ages (Anderson et al. 1997). Significant increases in the number of adults admitted to emergency departments for asthma were correlated with increases in ambient NO_2 (Sunyer et al. 1997). Increases in daily mean levels of black smoke and ozone also were shown to increase the relative risk of hospital admissions for respiratory disease among adults, and the association for black smoke was significantly stronger when NO_2 concentrations were high (Spix et al. 1998). In another study, daily mean levels of black smoke were significantly associated with all-cause mortality in both western and central-eastern European cities (Katsouyanni et al. 1997).

Several other European investigations have also focused on the association between traffic-related air pollution and respiratory morbidity. Commentary Table 1 provides the results of five European studies that examined the association between proximity to traffic and a variety of health outcomes. Investigators found that communities near major roads had higher prevalence rates of several respiratory symptoms and diseases, and children were found to be more sensitive to the effects of traffic exposure than adults (Oosterlee et al. 1996). Edwards and colleagues (1994) found that children living within 500 m of a major road had an increased risk of hospitalization for asthma. In a study of children who lived within 1000 m of a freeway, prevalence rates of chronic cough, wheezing, and rhinitis were higher among those who lived within 100 m (van Vliet et al. 1997).

Another method to estimate exposure to traffic-related air pollution uses measurements of traffic intensity on nearby roads. In one European study, an exposure variable based on traffic intensity was significantly associated with lung function and relative risks for croup, recurrent wheezing, and recurrent dyspnea in children (Wjst et al. 1993). In the study by Edwards and others (1994), children who lived near a road with a traffic count greater than 24,000 motor vehicles/day were significantly more likely to be admitted to a hospital for asthma than children living near a road with less traffic.

The type of traffic on nearby roads may also play a role in determining health effects. In Italy, Ciccone and colleagues (1998) found statistically significant associations between heavy truck traffic on the street of residence and several respiratory diseases in children. Interestingly, they did not find such associations for average traffic density without stratification by type of vehicle, or for exposure analyzed by residential zones rather than residential streets.

Though a number of studies of the possible health effects of traffic-related air pollution have been reported, there continue to be questions about the appropriate exposure metrics and also about possible confounding by factors such as the socioeconomic status of those who are most exposed. In recognition of these and other questions,

Commentary Table 1. Previous European Studies on Health Effects of Traffic-Related Air Pollution

Study	Study Population and Location	Methods and Outcome Measures	Main Results
Ciccone et al. 1998	Children aged 6–7 years and adolescents aged 13–14 years Northern and central Italy	Questionnaires used to collect information on type of traffic and traffic density on street of residence. Questionnaires used to determine history of respiratory disease and current respiratory conditions.	Residence on a street with heavy truck traffic significantly associated with bronchitis, pneumonia, bronchiolitis, and spastic laryngitis in the first 2 years of life; and with wheezing, shortness of breath with wheeze, dyspnea, dry cough, morning chest tightness, persistent cough, and persistent phlegm within the past year. Associations were not significant when traffic indicators were limited to average traffic density without stratifying for type of vehicle and when residential zones were used instead of residential streets.
Edwards et al. 1994	Children aged < 5 years Birmingham, U.K.	Distance from residence to major road determined by converting residential postal code to 10-figure Ordinance Survey grid reference. Information from Joint Planning and Transportation Data Team of the West Midlands Planning and Transportation Subcommittee used to determine major roads and traffic. Information from West Midlands Regional Health Authority inpatient data and Family Health Services Authority computer database used to determine cases, hospital controls, and community controls.	Residence within 500 m of a major road associated with increased risk of hospitalization for asthma. Residence within 200 m of a major road, regardless of traffic density, significantly associated with hospital admission for any cause. Residence near a road with traffic flow >24,000 motor vehicles/day significantly associated with hospital admission for asthma.
Oosterlee et al. 1996	Adults and children (birth–15 years) Haarlem, Netherlands	Environmental Traffic Maps and the Calculation of Air Pollution by Road Traffic (CAR) model used to estimate traffic density; streets classified as busy or quiet. Questionnaires used to collect information on respiratory conditions.	Residence on a busy road associated with higher prevalence rates of chronic cough, wheeze, attacks of dyspnea with wheeze, doctor's diagnosis of asthma, use of respiratory medication, and current use of asthma medication in children, with significant adjusted odds ratios for wheeze and respiratory medication Residence on a busy road associated with more frequent reports of dyspnea in adults.
van Vliet et al. 1997	Children attending 13 primary schools and living within 1000 m of a freeway South Holland	Distance from residence to major road determined by plotting residential address on 1:1000-scale maps. Information on 1993 freeway traffic counts from the Ministry of Public Works used to determine traffic density. Ambient air pollution and indoor air pollution measured in schools. Meteorologic data from Rotterdam airport used to determine how long schools were downwind from freeways during indoor measurements. Questionnaires used to collect information on respiratory conditions.	Residence within 100 m of a freeway associated with higher prevalence rates of chronic cough, wheeze, and rhinitis. Residence near roads with high truck traffic also associated with these respiratory conditions, as well as asthma attacks.
Wjst et al. 1993	Children aged 9–11 years who had lived in their current home ≥ 5 years Munich, Germany	Traffic density determined by assigning school districts the maximum traffic count from a nearby road. Questionnaires used to collect information on history of respiratory symptoms. Throughout the school year, children were asked about current respiratory conditions and then given lung function tests.	Traffic increase of 25,000 motor vehicles/day significantly associated with decreased adjusted average peak expiratory flow rates; decreased maximal expiratory flow at 25% and 50% of forced vital capacity expired; and increased risks for croup, recurrent wheezing, and recurrent dyspnea.

HEI has convened an expert panel to review all studies of exposure to and health effects of traffic-related air pollution; the results of that effort are expected to be published later in 2009.

Questions also remain about the effects of long-term exposure to air pollution in the general population. Before 2000 most studies of health and air pollution in Europe had focused on short-term variations in exposure and acute outcomes in very young populations. Although European studies provided useful information on the association between traffic and acute respiratory effects, attempts to assess potential risks of long-term exposure to air pollution in these countries were frequently based on ambient pollutant levels and on results from large cohort studies conducted in North America, such as the American Cancer Society Study (Krewski et al. 2000), and did not include specific information about traffic exposure.

The current study explores associations between long-term exposure to traffic-related pollution and patterns of cause-specific mortality over a 10-year period in the large NLCS cohort of older adults (aged 55 to 69 years at enrollment in 1986), drawn from throughout the Netherlands. Limited computerized information about subject characteristics was available for the full cohort. For the randomly selected subcohort of 5000 examined in the pilot study and for all subjects who died during follow-up, however, extensive information about potential confounders and effect modifiers was available from a questionnaire that subjects completed on enrollment. Sophisticated techniques that utilize GIS were used to produce finely varied estimations of exposure to pollution from traffic at each study participant's home address, based on estimated regional, urban, and local contributions to pollutant concentrations.

There are continuing questions about the most appropriate measures for capturing longer-term exposure to traffic-related air pollution. Measures based on the distance between a person's residence (or another location) and nearby roads and the classification of these roads by type of traffic are inexpensive to obtain from readily available data. They do provide the basis for estimates of the net effect of a wide range of exposures due to traffic, but they are nonspecific when compared with direct measurements of local pollutant concentrations. Exposure estimates based on traffic intensity may be more precise, but they are also nonspecific indicators of exposure to pollutants. Furthermore, the traffic counts used to calculate traffic intensity may be based on incomplete information or sporadic measurements that are not representative of long-term exposures, and these data often have been obtained for reasons other than health studies. Direct measurement of traffic-related pollutants is very expensive, and studies that have measured them often targeted specific pollutants that may or may not represent the complex mixture of air pollution and its associated health effects.

In addition to pollutant exposure, the stress caused by noise associated with heavy traffic areas is frequently mentioned as having a possible effect on health outcomes. As noise from traffic is proportional to traffic volume and distance to traffic, there is concern that studies of traffic-related pollution use average measures of noise that do not account for this variation. In the current study, Brunekreef and colleagues address the confounding potential of noise through a sensitivity analysis using combinations of traffic-related pollution and noise estimates for each cohort member's residence.

Other potential confounders of the association between air pollution and mortality in traffic studies are broadly referred to as "socioeconomic status" variables. In many countries, proximity to heavy traffic is associated with low socioeconomic status, which is further associated with adverse health outcomes and lower life expectancy. These factors are not necessarily individually determined: a person with high income who resides in a low-income neighborhood may share some of the risks of living in that neighborhood regardless of personal income. Summary variables for conditions in the neighborhood or region surrounding an individual residence are often called "ecologic" variables to reflect their geographic nature. In this study, the investigators address the effects of a suite of ecologic variables that reflect the socioeconomic status of the participants' local neighborhood and a larger regional area, ultimately including in the final models variables for the percentage of low-income persons and the percentage of high-income persons in these areas.

STUDY SUMMARY

SPECIFIC AIMS

After the successful completion of the pilot study, the investigators designed a much larger study of the full NLCS cohort. The specific aims of the study, referred to as NLCS-AIR, were as follows:

1. To estimate exposure to traffic-related air pollution for all subjects in a large, ongoing cohort study on diet and cancer in the Netherlands
2. To evaluate the associations between exposure to traffic-related air pollution and natural-cause mortality and lung cancer incidence in this cohort
3. To evaluate whether these associations vary with specific causes of death (respiratory, cardiovascular, and

noncardiopulmonary, non–lung cancer) and with subject characteristics such as smoking habits, educational level, sex, and occupational exposures

To carry out these objectives, Brunekreef's team expanded their study population to the full NLCS cohort and refined the exposure assessment methods that were used in the pilot study (Hoek et al. 2002). They further employed a case–cohort study design in which the data for the case subjects (those who had died) are compared with those for the 5000-member subcohort that was randomly selected within the full cohort. The information available for individual case subjects and subcohort members is more extensive than that available for the full cohort. The study data sets and methods are described below.

STUDY POPULATIONS

The NLCS was originally created to study possible connections between nutritional patterns in older Dutch citizens and the development of cancer. As with many large cohort studies, such as the American Cancer Society Study and the Framingham Heart Study in the United States, the NLCS became a potentially rich source of data for studies not directly related to its original purpose. Beginning with the previously described pilot study and continuing with the present NLCS-AIR study, Brunekreef and colleagues have used the cohort data to study associations between health outcomes and air pollution, referring to this subsequent use of the cohort data as the NLCS-AIR study.

The NLCS cohort contained 120,852 subjects who were 55 to 69 years of age at the inception of the cohort in September 1986. Participants were recruited from 204 municipalities that had computerized population registries in 1986 and were adequately covered by cancer registries. Subjects were followed from January 1, 1987, through December 31, 1996. There were 17,674 deaths recorded for this cohort during this 10-year follow-up period. Computerized data for participants in the full cohort included age, sex, location of residence in 1986, and information on smoking status.

For each of the 5000 persons in the randomly selected subcohort, information from an extensive questionnaire was entered into the study database. The questionnaire included questions about such risk factors as personal habits, passive smoking status, and occupation, some of which are relevant to the study of air pollution and associated diseases. For the current study, the full set of responses on the questionnaire completed by all subjects at study entry was also entered for subjects who died during follow-up, as well as information on changes of residential address during follow-up and cause of death.

The exact address of each subject at baseline in 1986 was known, and a residential history was available. Brunekreef's team used a GIS to map these addresses for all cohort participants. The spatial data and GIS were then used for pollutant exposure assessment and assignment of values of ecologic covariates based on the 1986 address for each participant. These residence locations were fairly well distributed in communities across the Netherlands, but were restricted to municipalities for which computerized population registries were available. Amsterdam was most notably excluded owing to the lack of such an electronic registry, but 18% of the cohort lived in three other large cities that were included (Rotterdam, The Hague, and Utrecht), and 35% lived in municipalities with more than 100,000 residents, with the remainder residing in numerous smaller municipalities and rural areas across the country.

Brunekreef's team analyzed their NLCS-AIR cohort data for three different study populations. The full-cohort analyses included exposure information and mortality data for the entire cohort, but had very limited information on potential individual-level confounding variables. The case–cohort analyses included detailed information for a substantial number of potentially confounding personal-level variables for both the randomly selected subcohort of 5000 and the 17,674 deceased members. Finally, the 5000-person subcohort was analyzed separately in order to generate results that would be directly comparable to those in the pilot study (Hoek et al. 2002).

POLLUTANT EXPOSURE DATA

The most complicated aspect of data collection and analysis was the assessment of exposure, which is described in detail in the Investigators' Report (see Exposure Assessment in Methods). The investigators calculated average long-term exposure levels for several air pollutants, including black smoke, NO_2, sulfur dioxide (SO_2), and PM with an aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$) at the 1986 home address of each study participant using data from 1976 through 1996. In addition, some analyses were conducted that directly incorporated the traffic variables "traffic intensity on the nearest road," "sum of traffic intensity in a 100-m buffer," and "living near a major road," which were calculated for the residence locations of cohort members.

Exposure levels were calculated based on a three-component system, described in detail in Figure 1 of the Investigators' Report. The regional exposure component for each pollutant species, which reflects large-scale transport of pollution from the Netherlands and all of northern Europe, was interpolated for each residence location from measurements at regional monitoring stations in the National Air Quality Monitoring Network.

The urban exposure component, calculated using data from monitoring stations classified as "urban background" in the same network, was intended to reflect nearer-scale emission and transport of pollutants than the regional component. To calculate the urban component of pollutant exposure for each cohort member, the urban monitoring data for pollutants were adjusted by subtracting the regional component of exposure, and the residual values were used in a land-use regression model with variables for land use and address density for each subject's residential location.

The local exposure component was similarly calculated by adjusting for the regional and urban components and using a land-use regression model with intensity of truck traffic and other traffic on nearby roads as variables. For analyses directly including the traffic variables mentioned above as a measure of local exposure, another variable was included for the sum of the regional and urban components, referred to as background exposure. Black smoke is the only pollutant for which analyses using these models are presented in the Investigators' Report.

HEALTH OUTCOME DATA

The health endpoints analyzed in this study were deaths due to specific causes (listed in Table 8 of the Investigators' Report) and the incidence of lung cancer. The cause of death, determined by codes from the *International Classification of Diseases,* 9th or 10th revision (ICD-9 or ICD-10), on death certificates, was available for 99.5% of the deceased subjects. Cause-of-death data were obtained from routine queries to government death registries in the study area. For the purposes of the current study, deaths were categorized according to the ICD codes on the death certificates as "natural cause," cardiovascular, cardiopulmonary, respiratory, lung cancer, and "noncardiopulmonary, non–lung cancer." Deaths from accidents or other nonnatural causes were excluded from the analysis as they were not likely to be associated with air pollution exposure.

CONFOUNDING VARIABLES

Subject characteristics recorded for the full cohort in the NLCS database utilized by Brunekreef's team were sex, age, smoking status, and information relating to socioeconomic status, based on the neighborhood of residence. This information was obtained from the questionnaire that each NLCS participant filled out at the beginning of the cohort study in 1986.

For the randomly selected subcohort of 5000 participants, all of the information on the original questionnaire was entered in a database. The subcohort was also followed at regular intervals to obtain information on change of address and vital status. In addition, for cohort members who died during the follow-up period, all of the data from the original questionnaire were entered in the study file. More detailed information on potential confounders was therefore available for the subcohort and the case subjects, including information on body weight divided by height squared (Quetelet index), passive smoking status, educational level, occupation, occupational exposure to air pollution, marital status, and a number of measures of food and alcohol intake. Complete lists of these potentially confounding individual variables are provided in Tables 10 and 11 of the Investigators' Report. Sex, smoking status, educational level, fruit intake, and vegetable intake were also assessed as potential effect modifiers for the case–cohort (and subcohort) analyses. The report also provides an excellent compilation of specific and detailed information on data management and quality control measures (see Data Entry and Management under Confounding Variables in the Methods section).

Ecologic variables for the cohort members were derived from the neighborhood in which they lived, rather than from individual attributes. They are included in the analysis of exposure and mortality because the circumstances of the community surrounding the participant's residence may modify the relation between air pollution exposure and mortality. They included average income in the neighborhood, percentages of persons with high income and with low income, and percentage of persons who were receiving government benefits. In addition, the percentages of residents with high income and with low income in a larger area surrounding the participant's address, the COROP (Coordinatie-Commissie Regionaal Onderzoeksprogramma) area, were included in the analysis as potentially confounding variables that are associated with life expectancy.

DATA ANALYSIS

Survival analyses are frequently used in long-term cohort studies of air pollution exposure and mortality. Participants are followed for a certain period, and comparisons are drawn between the estimated air pollution exposure of those who succumb to specific causes of death and those who survive (with adjustment for age, smoking status, and other variables known to affect longevity).

Brunekreef chose the Cox proportional hazards method to calculate relative risks of mortality associated with the levels of air pollution exposure experienced by the cohort. The newly developed method of Cox-Poisson mixed model analysis was also used, as it enabled the incorporation of statistical corrections for spatial autocorrelation (the nonindependence of exposure and health-status observations for people living close together) in the analysis.

For the full-cohort analyses, data on a limited number of potential confounders and effect modifiers were available and included in the study. A number of exposure variables were included in the models aimed at capturing both background and local pollutant exposure. A detailed summary of these variables, with the increments used for analysis, is given in Table 13 of the Investigators' Report.

For the case–cohort analyses, where the experience of the deceased participants is compared with that of the subcohort participants for whom there is more detailed information, Cox proportional hazards models were used with all the potential confounders as listed in Table 10. Again, detailed exposure estimates for both background and local sources were used as covariates in the model. The estimates of the standard errors of the relative risks were modified to account for the fact that the subcohort was sampled from the full cohort. Since data for the case–cohort analyses (and, hence, the subcohort analyses) had a large number of observations with data missing on one or more potential confounders, some analyses were conducted with only very limited information on confounders. The investigators also compared results from a case–cohort analysis with the restricted data set and a case–cohort analysis using all confounding variables.

An additional analysis restricted the full cohort to the residents of Rotterdam, The Hague, and Utrecht, the three largest cities. This analysis was intended to generate results that would be more directly comparable to other widely reported results of long-term pollution exposures in large cohorts, such as the reanalysis of the data from the Harvard Six Cities Study and the American Cancer Society Study (Krewski et al. 2000), which were conducted in urban areas.

SUMMARY OF KEY RESULTS

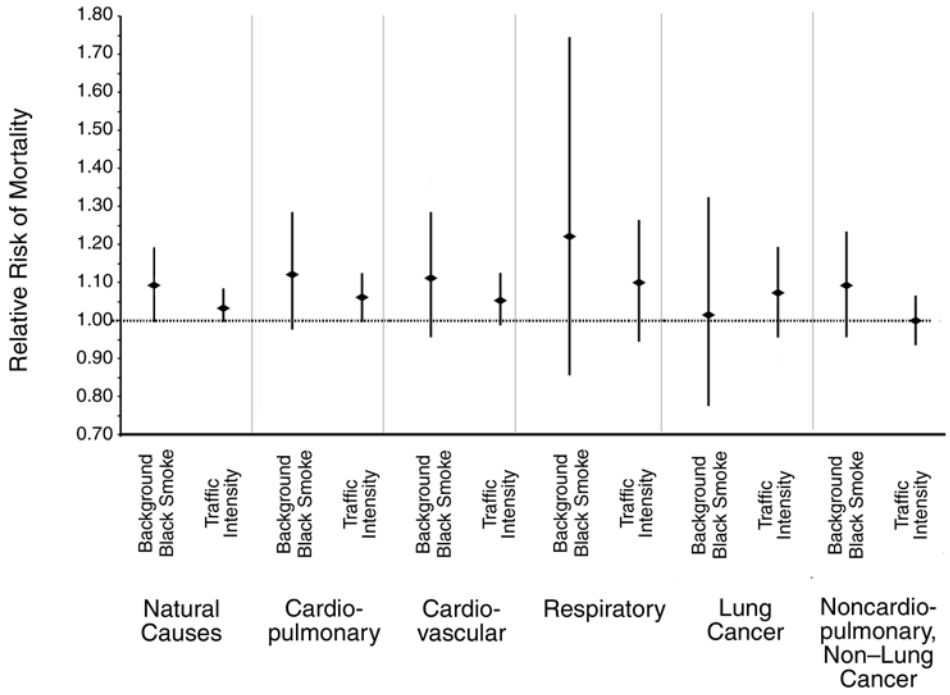
The relative risks of mortality estimated in the full-cohort analyses displayed greater precision (reflected in tighter confidence intervals) than estimates in the case–cohort analyses, a likely result of the much larger number of subjects in the full cohort. The results for the full cohort are also more comparable to the results of other large cohort studies of air pollution and mortality than results for the case–cohort study population. As a consequence, the results discussed in this section for each mortality category and exposure variable will be for the most highly controlled of the full-cohort analyses, which were adjusted for age, sex, smoking status, and neighborhood and area-level income, unless otherwise stated.

The primary objective of this study was to assess the association between traffic-related air pollution and mortality in a large cohort; therefore, the analyses containing specific traffic variables are of particular interest. Traffic data were handled in two ways: either a traffic variable was used in a model that also included a variable for background air pollution (black smoke), or traffic exposure data were converted to a pollutant concentration, which was added to the background concentration to produce an overall exposure concentration.

Commentary Figure 1 shows the relative risks for the studied mortality categories for a model with two exposure variables: the estimated background black smoke concentration and traffic intensity on the nearest road to a subject's residence. The generally lower relative risks associated with traffic intensity indicate that the background black smoke exposure explains more of the observed variability in mortality. The associations between mortality and background black smoke are not surprising, as most persons living in industrialized countries are exposed to air pollution that may be transported from sources in other areas and is unrelated to traffic. However, Commentary Figure 1 also shows that an increase in traffic intensity of 10,000 motor vehicles/day on the nearest road to a subject's residence was associated with significant increases in deaths from cardiopulmonary and natural causes, with nearly significant associations for deaths from cardiovascular and respiratory causes. Thus, traffic on the nearest road is still marginally associated with increased risk of mortality when the effect of background black smoke exposure from nonlocal sources is accounted for.

Only a small percentage of the population in this study lived within 50 m of a major road (defined as a road with traffic intensity of more than 10,000 motor vehicles/day) or 100 m of a freeway (defined as a road managed by the national government); therefore, the small number of subjects exposed to high traffic intensity on the nearest road resulted in wide confidence intervals in analyses with these traffic variables. Living near a major road often means living in a highly industrialized or urbanized area with high background black smoke exposure, and these results do not address concerns that background exposures from urban and regional sources may differ in toxicity from exposures from traffic sources.

Commentary Table 2 presents results of the current study for a two-variable model with the estimated background black smoke concentration and another traffic variable, living near a major road. It also presents results for a single-variable model with the estimated overall black smoke concentration. In the pilot study results (Hoek et al. 2002), Brunekreef and colleagues previously reported high relative risks for cardiopulmonary mortality associated with background black smoke and living near a major road in a two-variable model, and these results are included in the table for comparison purposes.



Commentary Figure 1. Relative risks for associations of background black smoke concentration and traffic intensity on the nearest road with cause-specific mortality in the full cohort. Associations are adjusted for age, sex, smoking status, and percentage of persons with high income and percentage of persons with low income living in a neighborhood, and in a COROP area. RR was calculated for a change from the 5th to the 95th percentile of estimated concentrations, rounded to 10 μg/m^3 for black smoke, and for an increase in traffic intensity of 10,000 motor vehicles/day. Vertical bars indicate 95% confidence intervals.

Commentary Table 2. Relative Risk (95% CI) for Cardiopulmonary Mortality Associated with Exposure Variables

		Investigators' Report	
Exposure Variable[a]	Pilot Study[b]	Full Cohort	Subjects in the Three Major Cities: Rotterdam, The Hague, and Utrecht
Background black smoke *and*	1.34 (0.68–2.64)	1.13 (0.99–1.29)	1.40 (0.87–2.24)
Living near a major road[c]	1.95 (1.09–3.51)	1.07 (0.96–1.19)	1.07 (0.90–1.28)
Overall black smoke	1.71 (1.10–2.67)	1.07 (0.98–1.15)	1.17 (1.00–1.36)

[a] For black smoke, RR is calculated per 10-μg/m^3 increment. For living near a major road, RR is calculated with the reference category of not living near a major road.

[b] For comparison with the pilot study, the investigators also conducted analyses in the same 5000-member subcohort as was used in the pilot study, albeit with 2 more years of follow-up and using the somewhat different exposure estimation methods of the current study. The new analysis, reported in Appendix A (Table A.5) of the Investigators' Report, also found substantially lower estimates of risk.

[c] Residence within 100 m of a freeway (national road), or 50 m of a major urban road (pilot study, defined according to a standard national classification system of Dutch roads), or 50 m of a road with > 10,000 motor vehicles/day (Investigators' Report).

The relative risks in the pilot study, although high, have wide confidence intervals and were obtained from the 5000-person NLCS subcohort. In the current study, which used data from around 25 times as many participants and nearly 40 times as many recorded deaths as the pilot study, the relative risks of cardiopulmonary mortality associated with background black smoke and living near a major road are much lower and the associated confidence intervals are much narrower. The differences between the results are partially due to the obvious differences in statistical power between the two studies. In their Investigators' Report, the investigators explain some methodologic

differences between the pilot study and the current study, and they provide possible explanations for this discrepancy in Appendix A. Nevertheless, with the prominence given to interpretation of the earlier pilot study results, the reduction in risk estimates, especially for the traffic variables, is noteworthy.

Also presented in Commentary Table 2 are results from the current study of an analysis restricted to the three largest cities represented in the cohort, Rotterdam, The Hague, and Utrecht. Despite the reduced statistical power in this model owing to the smaller number of subjects, the relative risks of cardiopulmonary mortality are higher than those reported for the full-cohort model.

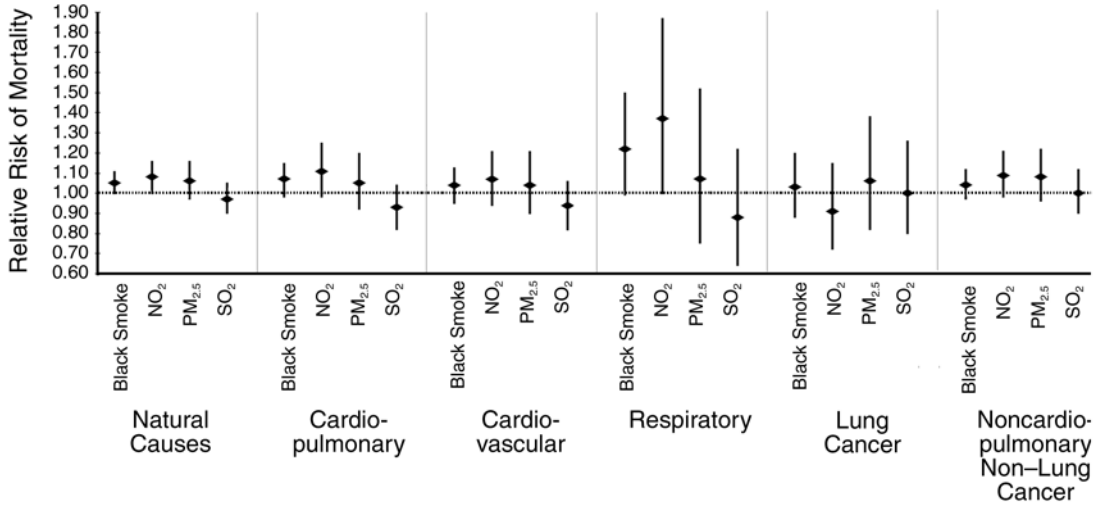
Commentary Figure 2 shows the relative risks for the specific mortality categories in association with estimated overall exposure concentrations for black smoke, NO_2, $PM_{2.5}$, and SO_2. Significant and nearly significant associations are shown between overall black smoke and NO_2 exposures and respiratory mortality, cardiopulmonary mortality, and natural-cause mortality. In addition, $PM_{2.5}$ is nearly significantly associated with noncardiopulmonary, non–lung cancer mortality and natural-cause mortality. The findings from this cohort study thus underscore the continuing risks of long-term exposure to air pollution from background and local sources.

The effect of traffic noise is often mentioned as a possible confounder in studies of traffic and human health. For people living near major roads, the noise generated by traffic may be high enough to cause stress and adverse effects on cardiovascular health. In this study, Brunekreef and colleagues perform some groundbreaking investigations into the potentially confounding effects of noise in conjunction with air pollution. The results, shown in Table 45 of the Investigators' Report, demonstrate that controlling for noise exposure did not change the strength of the association between black smoke exposure and cardiovascular mortality. The association between noise and cardiovascular mortality, when controlled for black smoke exposure, was significant only for the variable representing the highest noise levels (> 65 A-weighted decibels). These analyses, although preliminary, suggest that at high levels noise by itself might affect health, but that noise does not appear to affect or account for the observed associations between air pollution and cardiovascular mortality.

TECHNICAL EVALUATION

EXPOSURE ASSESSMENT

In this study, Brunekreef's team made an ambitious attempt to capture local variations in exposures to air pollution using emerging GIS-based methods. They attempted to account for many different contributors to and modifiers of personal exposure using both traditional and novel sources of data. The data sources ranged from airborne pollutant measurements from the national monitoring network to data from studies of traffic emissions, roadway traffic counts, and land-use data. These disparate data sources were integrated using GIS methods and combined and con-



Commentary Figure 2. Relative risks for associations of overall black smoke, NO_2, $PM_{2.5}$, and SO_2 concentrations with cause-specific mortality in the full cohort. Associations are adjusted for age, sex, smoking status, and percentage of persons with high income and percentage of persons with low income living in a neighborhood, and in a COROP area. RR was calculated for changes from the 5th to the 95th percentile of estimated concentrations, rounded to 10 μg/m^3 for black smoke and $PM_{2.5}$, 30 μg/m^3 for NO_2, and 20 μg/m^3 for SO_2. Vertical bars indicate 95% confidence intervals. For SO_2, the overall concentration is equivalent to the background concentration.

verted to exposure levels. The resulting estimates reflect the contributions of regional, urban, and local sources to exposure at the residential addresses of the participants.

As with any model of exposure, the reliability of the estimates is affected by the quantity and quality of the input data. The coverage and quality of the data used for exposure assessment in this study may have resulted in substantial uncertainty in the estimates. Table 1 of the Investigator's Report shows that coverage of the air pollutant monitoring network for the study period (1976 through 1996) was somewhat spotty, with varying numbers of monitors reporting results for the pollutants of interest. For example, black smoke measurements were available only from 1984 onward, and a maximum of 20 stations were measuring black smoke on any day during the study period. The study also included published data from 40 monitoring sites used in the Traffic-Related Air Pollution and Childhood Asthma (TRAPCA) study (Brauer et al. 2003), but each of these monitors had measured NO_2 and $PM_{2.5}$ for only four 2-week periods in a given year.

Of somewhat greater concern are the traffic count data for roads in the vicinity of subjects' home addresses. Traffic counts were available for all of the national roads, but only 23% of provincial roads and about 14% of municipal roads. Roads for which no traffic data existed were assigned a default value of 1225 motor vehicles per day, which is half the 2450 motor vehicles/day that some Dutch municipalities use as a cutoff below which they do not collect traffic data for a road. The default assumptions about traffic intensity, which may be too high or too low in reality, formed the basis of much of the assigned local component of exposure in this cohort.

Estimates of traffic intensity were converted to quantitative estimates of black smoke, NO_2, and $PM_{2.5}$ exposure using regression equations based on measurements obtained at schools near heavy and well-characterized traffic in another Dutch cohort study (Janssen et al. 2001). These data are also problematic, as they are based on only 5 to 10 measurements at 24 sites in high-traffic areas. This thinness of available data introduces further uncertainty when attempting to convert traffic data to quantitative estimates of pollution concentrations in low-traffic areas. Black smoke concentrations measured at monitoring sites were converted to $PM_{2.5}$ levels using a conversion factor based on published values from simultaneous measurements of both pollutants in the Netherlands (Cyrys et al. 2003).

Taken as a whole, the data, measurements, and methods used for exposure assessment in this study could result in uncertainty in the exposure estimates and, consequently, uncertainty in the associations between exposure and mortality. This is particularly true when quantitative exposure estimates at subjects' residences are calculated from data from other studies and based on default assumptions of traffic intensity on nearby roads. Further potential uncertainty results from the length of time between when the measurements used for the quantitative estimates were made and the study period, as motor vehicle emissions may have changed considerably between 1986 (baseline year of the study) and 1998, the last year for which follow-up data were obtained (Janssen et al. 2001). Uncertainty resulting from a chain of assumptions about exposure (rather than measurement of exposure) may be an issue in this study, particularly when traffic intensity is converted to quantitative local estimates of traffic-related exposures.

Brunekreef's team created a land-use regression model to assign exposure in the GIS. This group is quite experienced in building such models, which combine monitored pollutant values with land-use variables to estimate exposure, and their efforts produced a high-quality model. When estimates were validated against measured values at sites not used to produce the regression equations, the correlation between predicted and measured values (R^2) was approximately 35% for SO_2, 46% for NO, 49% for black smoke, and 67% for NO_2 (see Table 23 of the Investigators' Report). Although these correlations are not as high as those reported for more recent studies, they are impressive for a complex land-use regression model constructed on a national scale.

Aside from the issues of data quality and validation, there is a remaining concern about how the land-use regression was conducted in this study. One of the variables used to estimate exposure in this study is population density. Population density is also included in some later analyses as a potential confounding variable. This means that the same variable is used both to assign exposure and implicitly to predict mortality patterns in the Cox proportional hazards analysis. The statistical consequences of using variables in such a duplicate manner are neither obvious nor clearly understood, but they may be problematic given the assumptions made by the analysis methods.

Despite these concerns, the exposure assessment used in this study was innovative and based on sound principles. Brunekreef's team made reasonable if bold decisions, making excellent use of state-of-the-art GIS technology and methods and all available data sources to produce quantitative estimates of pollutant exposure for each study participant. They pushed the available exposure modeling techniques to their limits for this cohort study, integrating a wide variety of data sources and types. In some ways, their methods were more advanced and complete than the data sets they were working with.

STUDY DESIGN AND METHODS

The major strengths of this study are the detailed assessment of exposure information and health outcomes for a very large cohort and the prospective nature of the study design. Limitations include incomplete information on potential confounders in the full cohort and limitations associated with the method of assessing exposure.

Exposure Estimation

The regional component of exposure was estimated using inverse-distance-weighted interpolation of data from monitors within 75 or 100 km of the home address. The urban component was estimated by regression on population density and indicator variables for type of area in which a residence was located. Although both of these methods are subject to errors, they give a reasonably broad range of exposure levels for all pollutants (see Figure 8 of the Investigators' Report), and estimates of the exposure error are provided (see Table 21). For example, for NO_2, the interpolation error for the regional component is estimated to be about 4 $\mu g/m^3$, and the prediction error for the urban component is estimated to be about 4 $\mu g/m^3$ as well. The range of NO_2 values is approximately 55 $\mu g/m^3$. Estimates of exposure to the individual pollutants are highly correlated, as expected, which means that disentangling the effects of the individual pollutants is very difficult. Several different measures of traffic intensity and distance from roads are used to estimate the local component of exposure. The overall estimates of exposure are dominated by the regional exposure component, as is readily seen in Figure 7 of the Investigators' Report.

Main Analyses

The investigators found weak associations between estimates of overall exposure to pollutants (sum of background and local exposure) and mortality, particularly cardiovascular and respiratory mortality. When measures of traffic intensity and background exposure were included as separate variables in the models (instead of using overall exposure), the relative risks of mortality associated with exposure to pollution were slightly higher. In contrast to the pilot study, however, there was no observed association between living near a major road and cardiopulmonary mortality. These conclusions are all based on the full-cohort analyses; the case–cohort analyses led to similar conclusions, but the estimates are less precise owing to the smaller sample size. There did not appear to be any difference in effect estimates when the exposures were analyzed separately for two 10-year periods, 1976–1985 and 1987–1996.

Sensitivity Analysis

Results obtained in models including only subjects living in municipalities with detailed traffic measurements were consistent with models including the full cohort; this is consistent with the observation that traffic intensity information tends to be missing in the smaller municipalities, with fewer subjects and fewer deaths.

Additional Analyses

A number of additional analyses were conducted. One finding was that the association between pollution and mortality was stronger among subjects who did not change residence during the study period, perhaps because their exposure estimates were more accurate. The estimated relative risks of mortality were also larger when only the subjects who lived in the three major cities were included. There was no evidence of an effect due to distance of a subject's residence from a major road, or to traffic noise. Finally, incorporating spatial autocorrelation in the analyses did not affect the relative risks of mortality or their confidence intervals.

Effect Modification

The report presents extensive analyses of potential effect modification by sex and smoking status in the full cohort, and by educational level, fruit intake, and vegetable intake in the subcohort and the case subjects. As expected, there was an interaction between smoking status and the effect of air pollution (shown in Table 38 of the Investigators' Report by the difference in results obtained using models that were unadjusted and adjusted for smoking). The other covariates did not appear to be effect modifiers.

The investigators further explored the effects of a suite of socioeconomic status variables, including area-defined measures of income and poverty. These variables were defined and investigated for an area encompassing each participant's residence. Of these variables, the investigators chose "percentage of persons with low income" and "percentage of persons with high income" for use in their analyses of mortality and air pollution, as data for these variables were available for both the neighborhood and regional areas throughout the Netherlands.

DISCUSSION

A limited number of cohort studies have investigated the association between outdoor air pollution and mortality. In the United States there have been six major studies to date: the Harvard Six Cities Study (Dockery et al.

1993; Krewski et al. 2000), American Cancer Society Study (Pope et al. 1995; Krewski et al. 2000), Seventh-Day Adventist Study (Abbey et al. 1999), U.S. Veterans Study (Lipfert et al. 2006), Nurses' Health Study (Puett et al. 2008), and a Medicare cohort study (Zeger et al. 2008). Only the cohorts for the Harvard Six Cities and Seventh-Day Adventist studies were designed to study air pollution; the other studies were based on cohorts set up for different purposes. There have been fewer cohort studies on this topic in Europe (Nafstad et al. 2004; Filleul et al. 2005; Gehring et al. 2006; Naess et al. 2007). The current study by Brunekreef and colleagues is one of the largest long-term studies of air pollution exposure and mortality undertaken in northern Europe. As such, the cohort study results for traffic-related pollutant exposures and causes of death are important for comparison with results of U.S. studies and for use in health impact assessments.

A spatial relationship between air pollution and mortality has been reported for decades, both in the United States and in Europe, but attempts to assign risk to specific populations are subject to serious confounding by ecologic variables. Though evidence of excess risk of mortality due to pollutant exposure has been observed in cohort studies in the United States, the evidence from Europe has been sparse. Consequently, European assessments of the health effects of air pollution have relied on the results from U.S. studies. By far the most influential has been the American Cancer Society Study (Krewski et al. 2000), which has been used, for example, in analyses by the CAFE initiative (Clean Air For Europe 2005), DEFRA in the United Kingdom (Department for Environment, Food, and Rural Affairs 2005), and the World Health Organization (2006).

Cohort studies rank high in the hierarchy of methods used for observational epidemiology. This is not only because they are prospective in design and provide more convincing evidence of the existence of hazard than do other study designs, but also because the results can be applied to life tables to estimate potential years of life lost. The results of studies that compare time series of daily mortality data with pollution measurements, in contrast, cannot be directly translated into potential life years lost.

Well-designed cohort studies have the great advantage of having the potential to control for confounding factors at the individual level. The NLCS cohort used in the current study was originally set up to study the effects of nutrition on cancer incidence with a case–cohort approach, in which all the information on a questionnaire administered to participants at enrollment in 1986 was electronically available only for a random subcohort of 5000 subjects and the approximately 17,000 deceased members of the cohort. One dilemma of the present study was whether to focus on this subset or the whole cohort. The whole cohort of over 120,000 men and women provided much more statistical power, but with a more limited set of individual confounding variables. Sensitivity analyses presented in the Investigators' Report suggest that the inclusion of the more detailed individual variables would not have materially affected the results from the large cohort, so it is reasonably clear that the best approach was to use the whole cohort.

One of the most challenging aspects of this study was to model exposure at the address level with limited and patchy primary data on monitored pollutant concentrations and traffic density. This was done using a range of methods including interpolation of measured concentrations and land-use regression models and involved considerable manipulation of data and incorporation of regression models developed in other studies. The two main exposure metrics used as derived variables for estimating the relative risks of mortality were an estimate of individual exposure to the background concentrations of the studied pollutants and a measure or indicator of exposure to traffic-related air pollution. To determine associations with mortality, the data were analyzed by two approaches: in one, background black smoke exposure and a traffic exposure variable were included as separate variables; in the other, the background and local (traffic) contributions to exposure were combined into a quantitative estimate of overall black smoke exposure as one variable.

Taken alone, the results of this study would be regarded as suggestive rather than conclusive. The estimates of relative risk were small. Most were not statistically significant, and often they were consistent with the play of chance. Also, as in any observational study in which the exposure is estimated, rather than measured, the possibility remains of residual confounding by unknown factors. There are some unexplained internal inconsistencies in the results. For example, estimates were larger among subjects who had a lower educational level or ate less fruit. These results could be explained by differences in vulnerability, or they may point toward some uncontrolled confounding.

The associations between pollutant exposure and relative risks of cardiopulmonary mortality were also higher for subjects who lived in the three largest cities. When the conversion factors between $PM_{2.5}$ and black smoke (Cyrys et al. 2003), the tight range of exposures used for comparison (10 $\mu g/m^3$), and the reduced size of the data set used for the analysis restricted to these three cities are considered, however, the results from this sensitivity analysis are consistent with the PM findings from North American cohort studies, including the reported relative risk (RR) for cardiopulmonary mortality of 1.30 (95% confidence

interval [CI], 1.18–1.45) for a 24.5-μg/m^3 increase in $PM_{2.5}$ from the American Cancer Society Study (Krewski et al. 2000). The elevated relative risk for cardiopulmonary mortality associated with black smoke exposure in these three Dutch cities (RR, 1.17; 95% CI, 1.00–1.36) is also somewhat consistent with the results for an association between an 18.6-μg/m^3 increase in $PM_{2.5}$ exposure and cardiopulmonary mortality in the Harvard Six Cities Study (RR, 1.31; 95% CI, 1.07–1.61), considering the much larger interquartile range of exposures in that study, in which monitors were intentionally located near study populations (Krewski et al. 2000). The higher risk estimates for subjects living in the largest cities in the current study might be explained by differences in the toxicity of the air pollution in these cities compared with the nation as a whole. They also raise some interesting questions about the role of traffic and urbanization, and the possibility that exposures were more precisely modeled in urban areas because traffic count data were more complete and there was finer coverage by monitoring stations.

Land-use regression models, which were used to estimate the urban component of air pollution in this study, may also introduce confounding if they include variables that are themselves associated with the health outcome. In this case "address density" was used as a measure of population density, but we do not know if this is an independent risk factor for mortality. There are also some features of the study that might bias the results downward. In particular, exposure misclassification is highly likely given the many assumptions made for the exposure modeling. Greater exposure misclassification was the favored explanation of the authors for the lower estimates observed in those cohort members not living in the three largest urban areas in the study. Another observation consistent with the effects of exposure misclassification was a greater risk of mortality in those who had not moved during the study period.

Other aspects of the results were inconsistent with previous hypotheses. The estimates for noncardiopulmonary, non–lung cancer mortality, for example, were similar to those for cardiopulmonary mortality. However, the confidence intervals of the estimates for the specific mortality categories tended to overlap, so it may be inappropriate to read too much into differences between the results for specific causes of death.

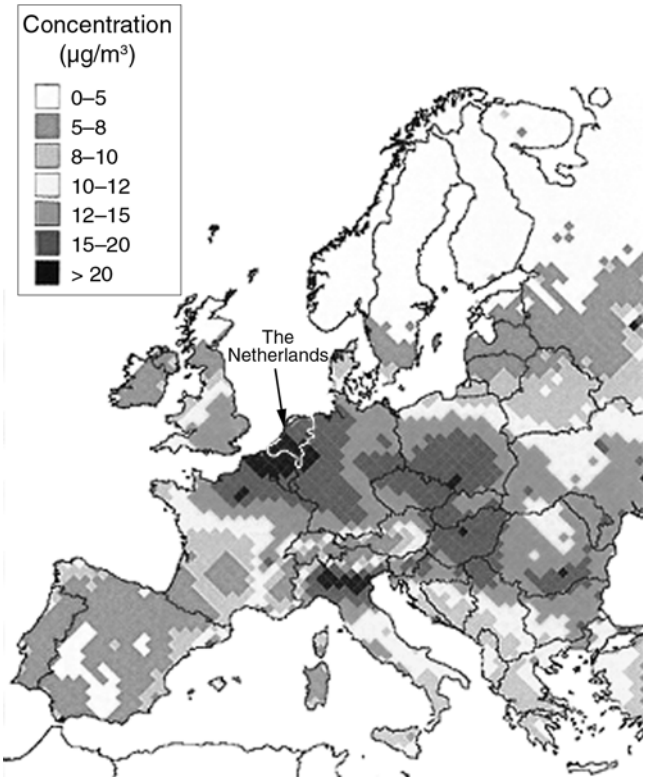
The most intriguing difference is between the results of the pilot study in the subcohort, with approximately 5000 subjects and 500 deaths, and the results for the full cohort in the current study. The pilot results found considerably higher risks of cardiopulmonary mortality associated with living near a major road and with the overall black smoke (background and local) exposure concentration (see Commentary Table 2). The current study included nearly 40 times the number of deaths and an extended follow-up period of 10 years (versus 8 years for the pilot study). The exposure assessment in the current study was more refined. In particular, changes in the way subjects were classified with respect to living near a major road led to substantial changes in exposure assignment for this variable. It also appears that where highly skewed variables are concerned, such as traffic intensity or living near a major road, the results may be particularly sensitive to random variation, and the authors postulate that this is one of the likely explanations for the disparity between the results of the pilot study and the current study. While the disparity in results remains puzzling, it seems reasonable to accept the authors' conclusion that the main explanation lies in the random variation and longer follow-up. This experience does, however, increase the caution with which the results from small cohort studies using regression-based methods of exposure assessment should be assessed. One approach would be to use a range of methods together with extensive sensitivity analyses, which Brunekreef's team details in extensive appendices (see Appendices Available on the Web listed in the Investigators' Report).

Another effect of traffic on health might be through exposure to noise. There was some evidence of an increase in cardiovascular mortality at levels of noise > 65 dB(A). However, there was no evidence that this factor explained any of the associations between air pollution and traffic intensity, as the effect estimate for black smoke does not change when noise is included.

Given that the results of this complex epidemiologic study are on the margins of what might be explained by chance, it is important to view them in relation to other studies done in different environments, by different investigators, using different methods. The other cohort studies (cited above) vary greatly in their environmental contexts, methods of exposure assessment, and the characteristics of the cohorts. It is therefore noteworthy that the relative risk of cardiopulmonary mortality with $PM_{2.5}$ exposure in the current study was of the same order of magnitude as estimates in the American Cancer Society, Medicare, and U.S. Veterans cohort studies, but somewhat lower than those in the Harvard Six Cities and Nurses' Health studies, and in the analysis of the Los Angeles area in the most recent study based on data from the American Cancer Society Study (Jerrett et al. 2005). Looking on the negative side, the lower bound of the 95% confidence interval for $PM_{2.5}$ and each cause of mortality (Commentary Figure 2) is less than unity; the result is thus also consistent with that of the Seventh-Day Adventist Study, which, alone among the U.S. studies, found no evidence of an association between

PM with an aerodynamic diameter ≤ 10 μm (PM_{10}) and mortality. However, the confidence intervals surrounding the risk estimates for mortality with $PM_{2.5}$ exposure in the current study reflect a great deal of uncertainty resulting from the way $PM_{2.5}$ levels were estimated from PM_{10} monitoring data, traffic measurements, and an extensive web of assumptions. There is some lack of consistency among the results for cause-specific mortality in the cohort studies. The American Cancer Society and Harvard Six Cities studies found stronger associations with cardiovascular mortality than with respiratory mortality, but little association with noncardiopulmonary mortality. In contrast, in the full-cohort study, Brunekreef et al. found higher risks associated with respiratory mortality than with cardiovascular mortality, although the results were less certain than those in the other studies. These three studies all found associations between air pollution and lung cancer mortality (although the associations in the current study were not significant). As mentioned above, in interpreting such patterns it is important to take the precision of the estimates into account.

In comparing the results of this study with results from other studies, and in considering whether they can be used to assess the impact of air pollution on health, it is important to recognize a fundamental difference between the studies. The Netherlands is exposed to a high and fairly homogeneous regional background concentration of fine particles, as shown in Commentary Figure 3. This background pollution constituted by far the greatest proportion of the cohort's exposure, as shown in Figure 7 of the Investigators' Report. So the heterogeneity of exposure on which these mortality estimates are based is largely restricted to the relatively small variability in exposure attributable to traffic emissions, together with the smaller amount of regional variability that exists within the Netherlands. Thus, from this study, it is not possible to draw any conclusions about the effect on mortality of the greater part of the population's exposure to air pollution.



Commentary Figure 3. Modeled annual mean $PM_{2.5}$ concentrations in Europe for emissions in 2000. (Source: *Health Risks of Particulate Matter from Lang-Range Transboundary Air Pollution,* WHO Regional Office for Europe, Copenhagen, Denmark, 2006, p. 2.)

In contrast, the exposure differentials exploited in the U.S. cohort studies, such as the American Cancer Society and Harvard Six Cities studies, are based on city-level estimates derived directly from measurements of air pollution concentrations for which the common regional background level is, at most, minimal. In the American Cancer Society Study, the range of annual $PM_{2.5}$ concentrations was from 9.0 to 33.5 μg/m³. In the current study, equivalent city-level concentrations were not available, but the 5th and 95th percentiles for estimated overall (background plus local) $PM_{2.5}$ concentrations were 24 and 32 μg/m³, respectively (Table 25 of the Investigators' Report). Therefore, there is no direct evidence concerning the mortality risk associated with concentrations below approximately 25 μg/m³.

Associations with mortality tend to dominate assessments of air pollution's health effects, and mortality risks estimated in cohort studies can be used directly to estimate years of life lost. Health impact assessments have been used both for estimating the size of the health burden of outdoor air pollution (e.g., Clean Air For Europe 2005; World Health Organization 2006) and for evaluating the relative benefits of different abatement policies (e.g., Department for Environment, Food, and Rural Affairs 2005; Clean Air For Europe 2005; U.S. EPA 2006). These assessments have used the American Cancer Society Study's mathematical functions to represent exposure response not only because it is the largest study, but also because the functions are based on an exposure metric ($PM_{2.5}$ at city level) that can be applied in other contexts. The application of this analysis outside of the United States involves the assumption that U.S. results can be translated to other populations. Given the possibility of differences in toxicity and vulnerability that may exist between areas and populations, this assumption may be questioned. The Dutch cohort results in the current study, together with other cohort evidence emerging from Europe, therefore provide valuable evidence of adverse

effects of air pollution on life expectancy in that continent. Further, because the estimates from this Dutch cohort are similar to those of the American Cancer Society Study, the use of the latter in European impact assessments to date appears to have been reasonable. Whether the Dutch cohort results themselves can be used for health impact assessment is, however, problematic because it would be difficult to replicate the methods of exposure assessment in other contexts.

In conclusion, this major cohort study provides evidence that air pollution in Europe is likely to reduce life expectancy. The variation in air pollution was mainly related to traffic sources, and the study was unable to estimate the effect of the greater concentrations of particles that form the background exposure of the region in which the cohort lived. In this respect the current study differs from cohort studies based on city-level differences in exposure. Nevertheless, the scale of the effect of air pollution on mortality appeared similar to that observed in large U.S. cohort studies. The study also found evidence of increased mortality in subjects living near a busy road, albeit at risk levels lower than those found in the pilot study. These findings are potentially important for environmental policy and reduction of health risks and merit further investigation.

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