Effects of long-term exposure to traffic-related air pollution on mortality and lung cancer

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Effects of long-term exposure to traffic-related air pollution on mortality and lung cancer

Effecten van lange-termijn blootstelling aan verkeersgerelateerde luchtverontreiniging op mortaliteit en longkanker

(met een samenvatting in het Nederlands)

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Chapter 1

General introduction

Chapter 1

Air pollution episodes

In the beginning of the 20th century, it was already predicted that "during winter, every city was in danger of catastrophe (of a smog episode) if certain weather conditions occurred with a combination of frost, fog and still air for days together".[1] Three major smog episodes, in which the concentrations of air pollutants were high for a period lasting up to several days, illustrated this prediction and drew attention to the effects of air pollution on health. During the smog episode of December 1930 in the Meuse Valley in Belgium, hundreds of people in the villages situated in the narrow portion of the Meuse Valley started to have severe respiratory signs and symptoms, and more than 60 people died in the days after the episode.[2] In October 1948, a fog laden with particulates and other industrial contaminants saturated the air of Donora, Pennsylvania. An estimated 5,000 to 7,000 persons in a town of 14,000 inhabitants became ill, and 20 died before the end of the smog episode.[3] In December 1952, a dense smog covered the Greater London area for four days. This led to an immediate increase in the number of deaths of about 3,000 – 4,000, but if the excess deaths in the months after the smog episode are related to air pollution, the mortality count would be approximately 12,000. Because of the scale of the disaster and because it allowed researchers to do the first detailed analysis of the relation between air pollution levels and increased morbidity and mortality, the London smog episode became a landmark in air pollution epidemiology in terms of its impact on science, public perception of air pollution, and government regulation.[2,4]

After these smog episodes, air pollution concentrations for the "classical" indicators such as particulate matter, sulfur dioxide, and black smoke decreased in Europe and North America in the last decades. The "newer" indicator pollutants nitrogen oxide and ozone have, however, generally not declined in Europe and North America. Therefore the air pollution mixture has also changed over time. Despite the decline in the concentrations of the "classical" indicator pollutants, both in studies on short-term exposure and long-term exposure to air pollution adverse health effects of air pollution have still been found.

Health effects of short-term and long-term exposure to air pollution

Effects on mortality dominate the health impact assessment of air pollution. For a proper assessment of the public health impact of air pollution, it is important to measure the extent to which shortening of the lifespan is attributable to short- and long-term exposure to pollution.[5] The health effects of smog episodes are short-term effects, with sharp increases in air pollution levels immediately followed by sharp

increases in mortality and morbidity, which returned to normal levels after the air pollution levels had returned to normal. In contrast, air pollution may also have long-term health effects after long-term exposure to (low) levels of air pollution.

Because of the decreasing levels of air pollution, the air pollution episodes became less clear in the last decades and more sophisticated methods were needed to study the effects of short-term exposure to air pollution. These so-called time-series analyses evaluated daily changes in air pollution at relatively low levels of air pollution in association with a broad array of health effects: daily mortality, respiratory and cardiovascular hospital admissions, use of respiratory and cardiovascular medications, and physiological changes (e.g. lung function).[6]

Studies on the association between daily mortality and short-term exposure to air pollution have been conducted as single-city studies and as multi-city studies. One major recent multi-city study was the National Morbidity, Mortality, and Air Pollution Study (NMMAPS), a study on fine particulate matter and daily mortality in 20 U.S. cities.[7] The estimated increase in the relative rate of death from all causes was 0.51% (95% confidence interval 0.07 – 0.93) for each increase in the fine particles level of 10 $\mu g/m^3$. A parallel research effort, the Air Pollution and Health: A European Approach (APHEA) project, studied the mortality effect of short-term exposure to particulate matter in 12 multiple European cities.[8] An extension of the APHEA project, APHEA-2, with data for 29 cities estimated an increase of 0.6% (95% confidence interval 0.4 – 0.8) in the daily number of deaths for a 10 $\mu g/m^3$ increase in daily particulate matter or black smoke concentrations.[9] Similar results were found in other studies on short-term exposure to air pollution and daily mortality. The World Health Organization[10] conducted a meta-analysis of time-series studies and showed a relative risk of 1.006 (95% confidence interval 1.004 – 1.008) for cause-specific mortality for each 10 $\mu g/m^3$ increase in particulate matter in urban air the same or next two days. For respiratory mortality, the equivalent figures were 1.013 (95% confidence interval 1.005 – 1.020); and for cardiovascular disease, they were 1.009 (95% confidence interval 1.005 – 1.013).[10] Although the effects of short-term changes in air pollution are small, associations between daily changes in air pollution concentrations and daily mortality counts continue to be fairly consistently observed.[11]

The health effects of short-term exposure to air pollution are well documented. However, compared to the many studies on the health effects of short-term exposure to air pollution, there have been much less studies conducted on the health effects of long-term exposure to air pollution.

The early studies on the effects of long-term exposure to air pollution were population-based cross-sectional mortality rate studies. The ecological nature of the study design means that individual level exposure data as well as individual level

confounder data were not available.[11] A major ecological study conducted by Özkaynak and Thurston analyzed the 1980 U.S. vital statistics and available ambient air pollution databases for sulfates and fine particles. Fine particles and sulfates were most consistently and significantly associated with the reported total annual mortality rates.[12] Results of these ecological studies were however controversial, because of concern that they could not control for individual risk factors, which raises the possibility of ecological bias and residual confounding.[11]

Emphasis has therefore been on cohort studies, which estimate chronic health effects associated with air pollution by examining risk of a health outcome in relation to long-term average pollution exposure, and which can control for individual risk factors. Cohort studies on the mortality effects of long-term exposure to air pollution have been initially conducted in the United States. The first cohort study on the long-term effects of air pollution was the Six Cities study,[13] which followed a cohort of 8,111 adults living in six U.S. cities for 14 to 16 years beginning in the mid-1970s. Higher ambient levels of fine particles and sulfate were associated with a 26% increase in mortality from all causes when comparing the most polluted to the least polluted city (fine particle concentrations differed 18.6 $\mu g/m^3$ between the most and least polluted city). An increase in fine particles was also associated with increased cardiopulmonary mortality in the Six Cities study.

The Six Cities study was followed by the much larger American Cancer Society (ACS) study,[14] in which 555,138 adults in 151 cities were followed from 1982 to 1989. Higher air pollution concentrations were associated with increased mortality from all causes, from cardiopulmonary mortality, and from lung cancer mortality. The difference between mortality from all causes between the most polluted and least polluted city was 17% and 15% for fine particles and sulfate, respectively (with a difference of 24.5 $\mu g/m^3$ for fine particles between the most and least polluted city).

An independent reanalysis of the original Six Cities and ACS studies concluded that the results originally reported could be reproduced and validated, and that the results did not substantively differ from the original results.[15] In addition, the reanalysis team also made a number of innovative methodological contributions that substantially contributed to subsequent analyses. A major contribution was the recognition that both pollutant variables and mortality appear to be spatially correlated in the ACS dataset. If not identified and modeled correctly, spatial correlation could cause substantial errors in both the regression coefficients and their standard errors. Several methods were identified for dealing with this, all of which resulted in some reduction in the estimated regression coefficients.[15] Further, the reanalysis team identified a possible modifying effect of education on the relation between air quality and mortality in that estimated mortality effects increased in the subgroup with less than high school education.[15] Recent analyses of the Six City

study and the ACS study with an extended follow-up time and a larger number of deaths showed that mortality associations persisted.[16,17]

A third initial cohort study was the Adventist Health Study of Smog (AHSMOG) that followed a cohort of 6,338 nonsmoking California Seventh-day Adventists from 1977 to 1992.[18] Associations were found between fine particles and mortality from all causes in males and nonmalignant respiratory mortality in both sexes. Lung cancer mortality was associated with fine particles and ozone in males and with sulfur dioxide in both sexes. Elevated mortality risks with long-term exposure to air pollution were also found in several European cohort studies.[19,20]

Other health effects that have been attributed to long-term exposure to air pollution are chronic respiratory disease incidence and prevalence (asthma, COPD, chronic pathological changes), chronic changes in physiological functions, lung cancer, and chronic cardiovascular disease.[6,21]

Although current evidence suggests that both short- and long-term exposure to air pollution are associated with health effects, long-term exposure exhibits larger effects with greater relative risks. Whereas most studies on short-term exposure have estimated relative risks of mortality of less than 1% per 10 $\mu g/m^3$ increase in air pollution levels over the previous days, cohort studies on long-term exposure have revealed excess relative risk in the order of a 4 – 10% increase in mortality for the same change in air pollution on a long-term basis.[6]

For a health impact assessment, years of life lost can only be derived from cohort studies on long-term exposure, where time to death is the outcome, while in studies on short-term exposure, death is a once-only event (no dimension in time). Studies on short-term exposure underestimate therefore cases of death attributable to air pollution.[5] Because cohort studies on long-term air pollution exposure can estimate a change in age-specific mortality, they allow the ascertainment of life expectancy.[6] It has been estimated that the effect of long-term exposure to relatively low concentrations of air pollution may lead to a reduction of life expectancy of more than one year. Effects of relatively small differences in long-term exposure to air pollution on life expectancy could thus be substantial.[22] It is therefore recommended that assessment of the public health impact of air pollution on health should be based on the results of cohort studies on long-term exposure to air pollution.[5]

Assessment of small scale variations in air pollution concentrations

The Six Cities and ACS study have compared cities with different ambient air pollution concentrations, assuming homogeneous exposure within a city and not taking into account small scale variation in air pollution levels. However, studies have

shown that there are important variations in the concentrations of air pollutants on a small scale within cities for example due to busy roads, with the largest decline in concentrations of traffic-related air pollutants in the first 100–200 meters near high traffic intensity roads.[23-25] Further, there is the danger that (unmeasured) confounding factors that vary between cities, may bias the association between health effects and air pollution when using city averages.

Recent epidemiological studies have therefore focused more on spatial variation in pollutant concentrations within a city and on traffic-related air pollution to study health effects of air pollution. Studies have used dispersion modeling[26,27] and land use regression mapping[28,29] to assess exposure to air pollution on an intra-urban scale. Other studies have used a wide variety of indicator variables for proximity to busy roads as exposure variables to air pollution on an intra-urban scale: traffic intensity near the residence,[30-32] distance to nearby (major) roads,[33-34] or a combination of both traffic intensity and distance.[35] A limitation of these indicator variables is that the assumed pattern of exposure may not always be true, e.g. the assumption that the dispersion pattern is the same in all directions may be violated because of wind patterns or topographic conditions.[36] A further limitation is that outdoor exposures have been estimated while persons generally spend a large part of the day indoors. Limited indoor and personal exposure studies support however the validity of traffic exposure indicators.[37,38]

Dispersion modeling, regression mapping and assessing indicator variables for living near a busy road have commonly been used in conjunction with Geographic Information Systems (GIS). A GIS is a powerful computer mapping and analysis technology capable of integrating large quantities of geographic (spatial) data as well as linking geographic (e.g. coordinates of home addresses) with nongeographic data (e.g. air pollution levels or traffic intensities).[39] Advantages of using a GIS are that individual exposure may be estimated without the need for time-consuming and expensive exposure assessment, especially when the study population is large.[40] Examples of functions in a GIS are distance functions (e.g. distance to nearest busy road) and buffer analysis (e.g. total traffic intensity in a circle of 100 meter around a home address), which have been used in studies on the health effects of air pollution. Because of advances in GIS technology, GIS is being increasingly used in environmental epidemiology studies.

Cohort studies on air pollution and mortality taking into account small-scale variations in air pollution concentrations

A few recent cohort studies have estimated individual exposure to air pollution using GIS and separated the background and local component of exposure using an indicator variable for living near a major road.

The first cohort study that evaluated the health effects of background air pollution concentrations and living near busy roads separately was a pilot study in the Netherlands among a random sample of 5,000 participants in the Netherlands Cohort Study on Diet and Cancer (NLCS).[41] The association between mortality and long-term exposure to air pollution defined as background concentrations (sum of regional and urban concentrations) and an indicator variable for living near a major road (living within 100 m of a freeway and/or living within 50 m of a major urban road) was studied. The adjusted relative risk of cardiopulmonary mortality was nearly double (relative risk 1.95; 95% confidence interval 1.09 – 3.52) for subjects that lived near a major road, while the relative risk for all cause mortality was 1.41 (95% confidence interval 0.94 – 2.12) for living near a major road.[41]

Following the Dutch pilot study, new cohort studies were conducted to study the association between mortality and living near a major road. In a study among 5,228 persons living in Hamilton, Canada, subjects living within 50 m of a major urban road or within 100 m of a highway had an increased risk of mortality with relative risk 1.18 (95% confidence interval 1.02 – 1.38).[42] In a German study among approximately 4,800 women, cardiopulmonary mortality was associated with living within a 50 m radius of a major road (relative risk 1.70; 95% confidence interval 1.02 – 2.81).[43]

These studies suggested that traffic-related air pollution assessed as living near a major road was associated with elevated risk estimates for mortality, which were generally higher than the risk estimates found for estimated background air pollution concentrations. However, there have only been a few cohort studies that have taken into account small-scale variations in air pollution concentrations, and these studies had a relatively small number of study subjects.

NLCS-AIR study and aims of our study

We extended the work of the Dutch pilot study[41] to the full NLCS cohort with a much larger number of deaths in order to obtain more precise estimates of the effects of traffic-related air pollution. Further, the larger study population provided the possibility to study more specific causes of death and to evaluate the modifying effect of several

variables. In addition, exposure assessment methods were improved compared to the pilot study.

The NLCS study is a cohort study that was started in 1986 with 120,852 subjects who were aged 55-69 years at enrollment.[44] For all participants individual long-term exposure to traffic-related air pollution was estimated, taking into account small-scale variations in air pollution concentrations within cities, and the association between air pollution exposure and mortality was studied.

The specific aims of the NLCS-AIR study are:

1. To estimate exposure to traffic-related air pollution for all study subjects in a large, ongoing cohort study in the Netherlands
2. To evaluate the association between exposure to background and traffic-related air pollution and to road traffic noise and (occurrence of) mortality and lung cancer incidence in this cohort study
3. To evaluate whether this association varies with specific causes of death (respiratory, cardio-vascular, other) and subject characteristics (such as gender, smoking habits, dietary habits, and education)

Outline of the thesis

Chapter 2 describes the exposure assessment method we used to estimate long-term exposure to traffic-related air pollution for all participants.

In chapter 3, we describe the association between cause-specific mortality and long-term exposure to traffic-related air pollution.

Chapter 4 describes the association between air pollution exposure and lung cancer incidence.

In chapter 5, we address the joint effects of exposure to traffic-related air pollution and road traffic noise on cardiovascular mortality. This includes an analysis of more specific cardiovascular causes of death.

Chapter 6 discusses the main results and provides a comparison with previous studies.

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Chapter 2

Estimated long-term outdoor air pollution concentrations in a cohort study

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Abstract

Several recent studies associated long-term exposure to air pollution with increased mortality. An ongoing cohort study, the Netherlands Cohort Study on Diet and Cancer (NLCS), was used to study the association between long-term exposure to traffic-related air pollution and mortality. Following on a previous exposure assessment study in the NLCS, we improved the exposure assessment methods.

Long-term exposure to Nitrogen Dioxide (NO_2), Nitrogen Oxide (NO), Black Smoke (BS), and Sulphur Dioxide (SO_2) was estimated. Exposure at each home address (N=21,868) was considered as a function of a regional, an urban and a local component. The regional component was estimated using inverse distance weighed interpolation of measurement data from regional background sites in a national monitoring network. Regression models with urban concentrations as dependent variables, and number of inhabitants in different buffers and land use variables, derived with a Geographic Information System (GIS), as predictor variables were used to estimate the urban component. The local component was assessed using a GIS and a digital road network with linked traffic intensities. Traffic intensity on the nearest road and on the nearest major road, and the sum of traffic intensity in a buffer of 100 m around each home address were assessed. Further, a quantitative estimate of the local component was estimated.

The regression models to estimate the urban component explained 67%, 46%, 49% and 35% of the variances of NO_2, NO, BS, and SO_2 concentrations, respectively. Overall regression models which incorporated the regional, urban and local component explained 84%, 44%, 59% and 56% of the variability in concentrations for NO_2, NO, BS and SO_2, respectively.

We were able to develop an exposure assessment model using GIS methods and traffic intensities that explained a large part of the variations in outdoor air pollution concentrations.

Introduction

We recently reported an association between cardiopulmonary mortality and long-term exposure to traffic-related air pollution in a random subgroup of 5,000 of a cohort study of elderly people (NLCS study; N ~ 120,000).[1] Other recent studies also found associations between long-term exposure to air pollution and health effects.[2-4]

Two large cohort studies in the US also showed associations between long-term exposure to air pollution and mortality. However, in the Harvard Six Cities study and the American Cancer Society (ACS) study, exposure has been estimated as the average concentration within a city/metropolitan area, ignoring small-scale variations within cities.[5,6] Exposure studies have shown large variations in concentrations of traffic-related air pollutants on a small scale within cities.[7,8] A study by Jerrett et al. in a subpopulation of the ACS study suggested that the chronic health effects associated with intraurban gradients in fine particles may be even larger than previously reported associations across metropolitan areas.[9]

In our previous study, long-term exposure to traffic-related air pollution was therefore considered as a function of the regional background, an urban background and an indicator variable for living near a major road.[10] Following on this previous study, we conducted a study on the association between long-term exposure to traffic-related air pollution and mortality in the full NLCS cohort of ~120,000 subjects (NLCS-AIR study). In this new study we improve the exposure assessment compared to the previous study that had no traffic intensity data and a less accurate road network.

The purpose of this paper is to describe an improved method for the assessment of long-term outdoor air pollution concentrations in a cohort study.

Methods

Design

The design of the NLCS (Netherlands Cohort Study on Diet and Cancer)[11] and the exposure assessment method used in the previous study have been described in detail elsewhere.[10] Briefly, the NLCS started in September 1986 when 120,852 participants from 204 municipalities, spread out over the Netherlands, were enrolled. The residential address of all participants in 1986 is known.

The NLCS was designed as a case-cohort study, i.e. mortality cases are derived from the entire cohort of ~120,000 participants, while the person years at risk are estimated from a random sample of ~5,000 subjects.[11] The number of observations in a case-cohort analysis consists of the number of subcohort members plus the

number of mortality cases (which depends on the cause of death). For all cause mortality, which has the largest number of observations, the number of observations in the case-cohort analysis is 22,337 (4,991 subcohort members and 17,346 mortality cases). The entire cohort was followed-up for mortality until December 31, 1996 for the current study.

In the previous study, the assessment of long-term exposure to black smoke and nitrogen dioxide consisted of a separate estimation of regional background, urban background and local traffic contributions at the centroids of the six-digit postal code areas of the home addresses. Inverse distance weighed interpolation of concentration data from regional background sites in the National Air Quality Monitoring Network (NAQMN) was used to estimate the regional background concentration. A regression model relating address density in a four-digit postal code area to measured concentrations at urban background sites was used to estimate the urban background concentration. Local traffic contributions were estimated using a Geographic Information System (GIS) and a digital road network (Basisnetwerk – version year 1993), resulting in a variable indicating whether a subject lived close to a major road (within 50 m from a major urban road or within 100 m from a motorway).[10]

For the current study we extended the exposure assessment with additional air pollutants and additional spatial determinants. Long-term outdoor air pollution concentrations for Black Smoke (BS), Nitrogen Dioxide (NO_2), Nitrogen Oxide (NO), and Sulphur Dioxide (SO_2) were estimated based on the exact residential home address in 1986. Data were collected from 1976 (start of the NAQMN) until 1996 (end of follow-up). NO_2 and NO data were available for the years 1978-1996, BS data for the years 1985-1996 and SO_2 data for the years 1977-1996. In 1986 the NAQMN was rearranged resulting in only limited days with valid measurements in 1986. A limited assessment was made for fine particles measuring less than 2.5 μm ($PM_{2.5}$) and less than 10 μm (PM_{10}) in diameter, using NAQMN data from 1992-1996 and data from two specific monitoring studies in 1997/1998[12] and 1999/2000.[13]

As in the previous study, long-term exposure to outdoor air pollution was considered as a function of a regional component, an additional urban component, and an additional local component from nearby (busy) roads: Exposure = C(regional) + C(urban) + C(local).

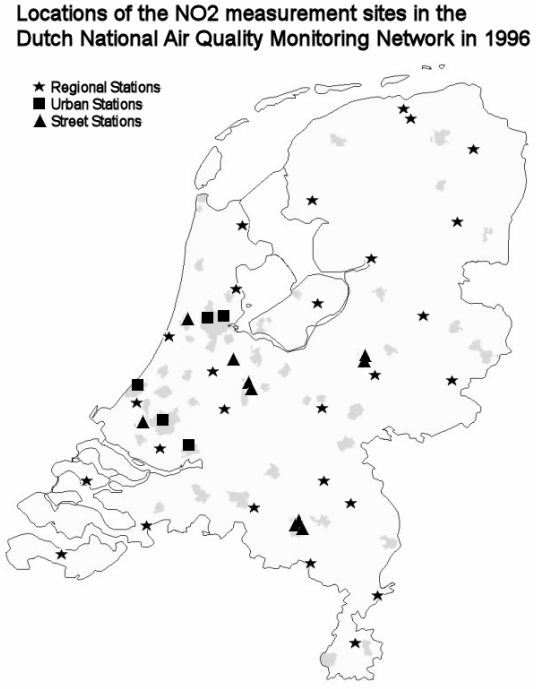
The exact 1986 residential addresses of participants were geocoded into standard Dutch geographical coordinates (Address Coordinates Netherlands (ACN)) using a database from the year 2000. For 21,868 of the 22,337 study subjects (97.9%), the home address could be geocoded.

Regional component

The regional component was estimated using average daily concentrations measured at regional background sites in the NAQMN.[14] Figure 1 shows the locations of NO_2 monitoring sites in the NAQMN in 1996. Before calculating the average concentration for a station, missing values were estimated to prevent bias in the comparison across sites. Missing values were estimated by calculating the seasonal means (summer/winter) of the daily ratios of the concentration at a station to the daily average concentration at the other sites. A seasonal mean ratio was used because differences in meteorological conditions between seasons can affect the mean ratio. These seasonal mean ratios were used to multiply the average concentration of all sites of a day with a missing value. Missing values were estimated for 0 – 17% of the days at a monitoring site. Correlations between unadjusted and adjusted annual averages were high (>0.9 for all pollutants), indicating that both unadjusted and adjusted data would results in similar exposure estimates.

In contrast with the previous study, we evaluated two methods to interpolate concentrations. Ordinary kriging using the GSTAT package within the R statistical software environment,[15] and inverse distance weighed interpolation as in the previous study, were used.

Figure 1. NO_2 monitoring sites in the national air quality monitoring network (1996).



Urban component

The urban component was estimated using regression models, in which we evaluated address density and number of inhabitants in different buffers as potential predictor variables while in the previous study only address density in a four-digit postal code area was used as predictor variable.[10] A possible limitation of the method in the previous study was that a subject can live near the border of a postal code area with a completely different address density. We also used a larger number of potential predictor variables compared with the previous study: number of inhabitants (GIS database available for 1995) and address density (available for 1998) in different buffers around the home address (300 m, 1,000 m, and 5,000 m), which were assessed using buffer calculations in which only cells within the buffer that have data values were used in determining the sum. For homes near the border of the Netherlands a (probably slight) underestimation thus occurred. Further, land use variables that indicated whether a site was located in a city center, in a rural background location, in an industrial location, or in a traffic location (available for 1999) were used. For each pollutant, regression models, using mixed modeling, were developed with residual concentrations as dependent variables. Residual concentrations for all regional background and urban monitoring sites in the NAQMN[14] were calculated as measured concentration minus estimated regional component concentration using cross-validation. The average residual concentrations for each 5-year period 1976-1980, 1981-1985, 1987-1991, and 1992-1996 were used as dependent variables in separate models. We used 5-year periods as these were the exposure variables of interest for the cohort study.

For each pollutant and each 5-year period separately, regression models were developed using a manual forward selection process. No restriction regarding the number of predictor variables was applied. Variables were only included when the direction of the effect was as defined a priori. First, univariate regression analyses were conducted for all possible predictor variables. The model with the highest adjusted explained variance (R^2) value was regarded as the start model. Second, to this start model the remaining variables were added separately and the effect on the adjusted R^2 was evaluated. If the effect on the adjusted R^2 value was greater than 1%, 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, interaction terms between time period and the predictor variables in the final models were tested. No significant interaction terms were found, indicating that regression coefficients did not differ for

different periods. Therefore, overall coefficients for each predictor variable were estimated using mixed modeling and combining data of the different 5-year periods.

Values for the predictor variables for the coordinates of the home addresses of the study participants were obtained using GIS and were multiplied with the coefficients of the regression models to calculate an urban component concentration.

This estimated urban component was added to the regional component resulting in a background concentration. Background concentrations were estimated for all separate years in the period 1976-1996 (if available), and average exposure estimates were made for the 5-year periods 1976-1980, 1981-1985, 1987-1991, and 1992-1996 (in 1986 the NAQMN was rearranged resulting in only limited days with valid measurements).

Local component

Traffic variables to characterize the local component were assessed using a digital road network to which average whole-week traffic intensity data (Monday – Sunday) were linked.

Compared to the previous study we used a more detailed, more complete and geographically more accurate digital road network: the National Road Database (Nationaal Wegen Bestand (NWB)), version year 2001, which was not yet available for use in the previous study.[16] Because the NWB has no road function or traffic intensity data attached, we collected traffic intensity data for national, provincial and municipal roads that were then linked to the road network. We aimed to obtain both total traffic and truck traffic intensity for the years 1986-1996 (= follow-up time of the study). More details about the collection of traffic intensity data and the linkage to the digital road network is described in the appendix.

Not all municipalities had traffic counts for their municipal roads, and municipalities that count traffic did not have traffic intensities for all roads in their municipality. To municipal roads without traffic intensities a background traffic intensity value of 1,225 mvh/24h was assigned assuming that these roads are not major. This was done to avoid underestimation of local scale exposure for example when calculating total traffic intensity in a buffer. A value of 1,225 mvh/24h was used, because this was half of the value of 2,450 mvh/24h that was used in Environmental Traffic Maps to distinguish between roads for which air pollution assessments were and were not made.[17]

Traffic intensities were available for different years on different roads. For some roads data were available for the years in the period 1986-1996, while for other roads data were available for isolated years. Because of time trends in traffic intensities, the comparability between roads with data for different years was limited. Therefore, we

developed extrapolation procedures to estimate traffic intensities for all years in the period 1986-1996 for which data were not available.

Continuous traffic variables for the local component of exposure were estimated using GIS calculations:

- Total daily average traffic intensity in 1986 on the nearest (mvh/24h) and distance to this road. If a road with traffic intensity > 10,000 mvh/24h was located within 30 m of the nearest road, the traffic intensity and distance to this road was used, covering situations were a major road was located close to a minor road (e.g. when roads run parallel).
- Total daily average traffic intensity in 1986 on the nearest major road (mvh/24h) (defined as a road with more than 10,000 mvh/24h) and distance to this road.

Because of GIS calculation limitations, distances to nearby (major) roads were calculated with a maximum distance of 500 m.

- The sum of the total daily average traffic intensity in 1986 (mvh/24h) in a buffer of 100 m and in a buffer of 250 m around each home address was calculated using buffer calculations. Each buffer was divided in 10x10 m cells and for each cell the traffic intensity was assessed. Then, the traffic intensities of all cells within the specified buffer were added together. A buffer of 100 m was used because especially in the densely built Dutch cities, the largest contrast in traffic-related air pollutants is likely to occur over distances less than 100 m.[18]

Further, quantitative estimates of the local component concentrations were estimated using regression models. Because there was only a limited number of traffic sites in the NAQMN which were concentrated in urban areas (only one motorway site), data from monitoring sites of the TRAPCA study were used.[13] Because the TRAPCA sites were not located close to motorways, they were used to estimate the local concentrations without taking into account the effect of motorways. To estimate the additional local concentrations caused by nearby motorways a Dutch study on air pollution near motorways was used.[12]

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 distributed over the period February 1999 and July 2000.[13] $PM_{2.5}$ filter absorbance at TRAPCA sites was transformed into BS concentrations using the equation: BS ($\mu g/m^3$) = -3.663 + 9.897* $PM_{2.5}$ filter absorbance.[19] Then, NO_2, BS and PM_{10} background concentrations (sum of regional and urban component) were estimated for the TRAPCA sites using the methods described above. $PM_{2.5}$ concentrations have not been measured in the NAQMN, therefore, estimated background PM_{10} concentrations at TRAPCA sites were transformed into $PM_{2.5}$ concentrations using the formula: $PM_{2.5} = 0.6739*PM_{10} - 0.1038$.[20] The residual (traffic) NO_2, BS and $PM_{2.5}$ concentrations at each site were calculated (measured

concentration minus estimated background concentration), and regression models were developed with the sum of traffic intensity, excluding the traffic intensities of motorways, in a buffer of 100 m as predictor. Because traffic intensities were not available for all municipalities, 22 sites were used to develop regression models. For addresses where the sum of traffic intensity in a 100 m buffer was higher than at the TRAPCA site with the highest buffer intensity (0.2%), the sum of traffic intensity in a 100 m buffer of this TRAPCA site was used as predictor variable, as unrealistically high local contributions were obtained for these addresses.

In the Dutch motorway study, weekly averaged measurements of NO_2, $PM_{2.5}$ and BS concentrations were conducted at 24 schools located within 400 m of a motorway in the Netherlands. Measurements were conducted 5 to 10 times in the period 1997 – May 1998.[12] For the 24 schools we assessed the truck traffic intensity on and the distance to the nearest motorway. Regression models were developed with the measured concentrations at these 24 sites as dependent variables and truck traffic intensity on nearest motorway and distance to this motorway in three categories (< 100 m, 100 – 300 m, and > 300 m (reference category)) as predictor variables. For addresses located further away than 500 m from a motorway, the quantitative local component concentration caused by nearby motorways was set to 0 $\mu g/m^3$.

Both estimated quantitative local component concentrations were added to the estimated background concentration.

GIS analyses were conducted using ArcGis at the National Institute of Public Health and the Environment (RIVM). Statistical analyses were performed using SAS 8.02.

Results

Regional component

We evaluated ordinary kriging and inverse distance weighed interpolation as methods to estimate regional background concentrations at the home addresses. However, there was only a limited number of BS sites (9 sites in the period 1992-1996), and therefore it was not possible to develop a suitable variogram for kriging. Further, the RIVM has used kriging procedures to decrease the density of the network during the rearrangement of the network in 1986. Therefore, it was less possible to estimate variograms for kriging for the periods after 1986.

For NO_2 and SO_2 both interpolation and kriging were possible and correlations between estimates with inverse distance weighed interpolation and kriging were all > 0.92, supporting that both methods performed similarly. To be consistent for all air pollutants, inverse distance weighed interpolation was used for all pollutants.

We studied how the prediction error depended on the distance criterion for inclusion of network sites. Prediction errors were estimated by cross-validation: the concentration at sites was estimated using data from the other network sites only and compared with the actually measured concentration. Table 1 lists the prediction errors related to interpolation (average root mean square error (RMSE) over the different years). For NO_2 and NO, RMSE was lowest when distance criterion was 75 km. However, not all home addresses were located within 75 km of a monitoring site. Therefore, we used for NO_2 and NO a distance criterion of 100 km (RMSE values for 75 km and 100 km were only slightly different). Distance criteria of 75 km (SO_2) and 100 km (NO_2, NO and BS) were used to estimate regional background concentrations using inverse distance weighed interpolation.

Table 1. Prediction errors (RMSE[a]) of interpolation of regional background monitoring stations using different distance criteria for inclusion of monitoring stations.

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

[a] RMSE in $\mu g/m^3$, derived from cross-validation

Urban component

In table 2, regression models to estimate the urban component are shown for NO_2, NO, BS and SO_2. As a sensitivity analysis we used for NO_2 a manual forward selection process, with as inclusion criterion whether the t-statistic of a variable was statistically significant, resulting in the same predictor model.

Table 2. Regression models for estimating the urban component for each pollutant based on residual concentration at urban and regional sites and GIS derived predictor variables: parameter estimates and standard errors (SE) (N = number of observations on which regression model is based). R^2- and RMSE-values of the models are described in table 3.

Variable	Parameter estimate (SE)
NO_2 (N = 202)	
Intercept	-2.21 (0.50)
(Number of inhabitants/1,000) in a 5,000m buffer	0.31 (0.01)
Located in a non-rural area[a]	4.29 (1.01)
Located in the center of a town[a]	6.01 (1.93)
NO (N = 203)	
Intercept	-2.29 (0.78)
(Number of inhabitants/1,000) in a 5,000m buffer	0.39 (0.01)
Located in a non-rural area[a]	4.48 (1.56)
BS (N = 23)	
Intercept	-0.72 (0.38)
(Number of inhabitants/1,000) in a 1,000m buffer	1.23 (0.04)
SO_2 (N = 508)	
Intercept	-1.26 (0.30)
Located in a non-rural area[a]	2.78 (0.58)
Located in an urban area[a]	3.31 (0.79)
Located in an industrial area[a]	6.25 (1.31)

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

In table 3, the R^2-values and RMSE of the regression models are shown together with the results of the regression models based on the previous study method.[10] The R^2-values are higher and the RMSE values are lower for the current study compared to the previous study.

Table 3. Comparison between performance of new exposure assessment (NLCS-AIR study) and previous study exposure assessment for estimation of the urban component (R^2-value and Root Mean Squared Error (RMSE)) (predictor variables for the different components in the NLCS-AIR method are described in table 2).

	NLCS-AIR method		**Previous study method[a]**	
	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
BS	49.2	1.22	38.3	1.38
SO_2	34.8	3.23	18.1	3.62

[a] address density of the four-digit postal code area used as predictor variable.

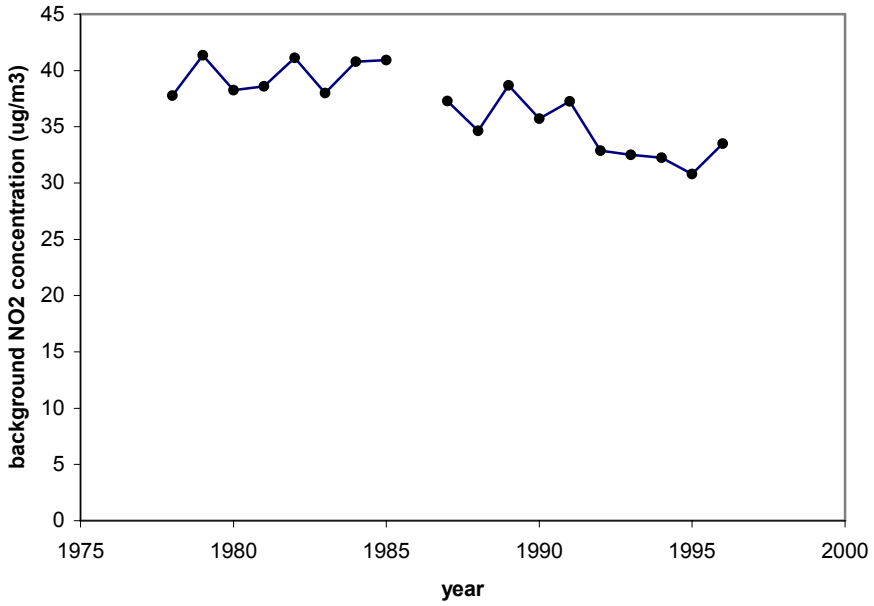
The correlations between the average background concentrations (sum of regional and urban component) in different 5-year periods at the home address of study participants are shown in table 4. The correlation between estimated concentrations for different periods is high. Because we added the same urban component to the regional component for each of the 5-year periods, this could result in artificially high correlations between background concentrations of different periods. However, this was not the case since correlations for annual measured concentrations of network sites were high as well (for NO_2 > 0.91; for NO > 0.85; for BS > 0.95; and for SO_2 > 0.84). In figure 2, the trend in background concentrations at the home addresses is shown for the components NO_2, NO, BS, and SO_2. SO_2 concentrations show a clear decrease over time, while for NO_2 and NO concentrations a more gradual decline is shown. BS concentrations appear to be more or less stable over time in the period 1976-1996, but showed a clear decline over a longer period of time.

Table 4. Correlations of background concentrations between different periods at addresses of study participants (N = 21,868).

	Period		
	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
BS[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] No data available for the periods 1976-1980 and 1981-1985.

Figure 2. Trends in average background concentrations at addresses of study participants (N = 21,868) (no data available for year 1986).



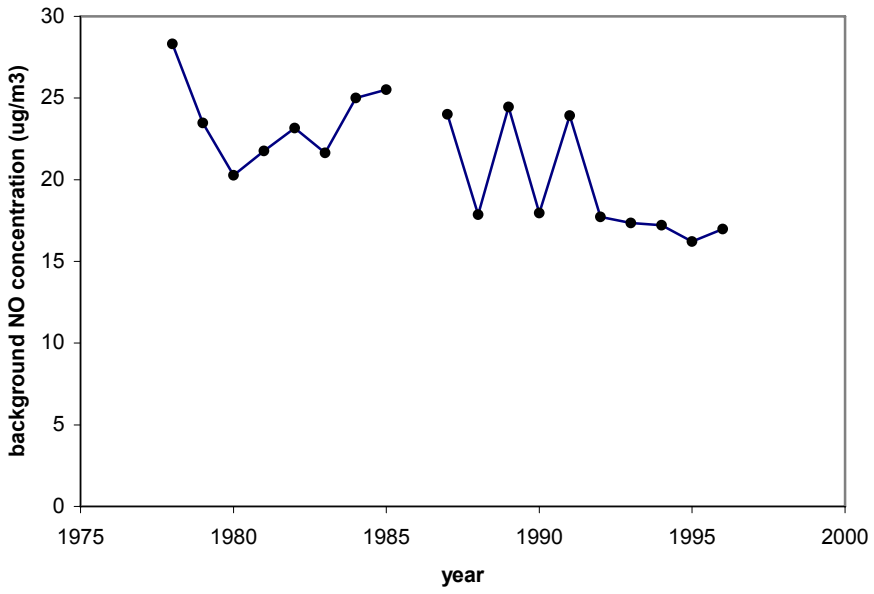
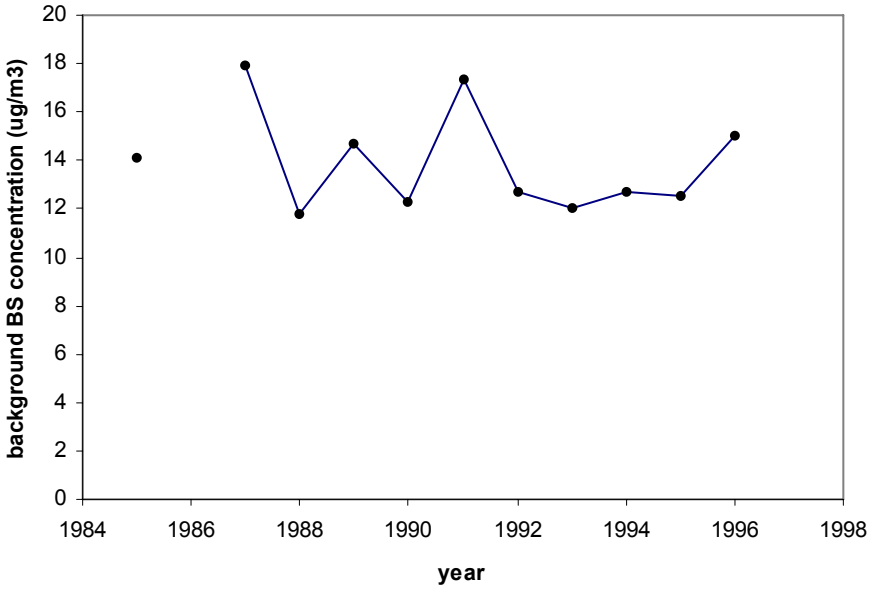
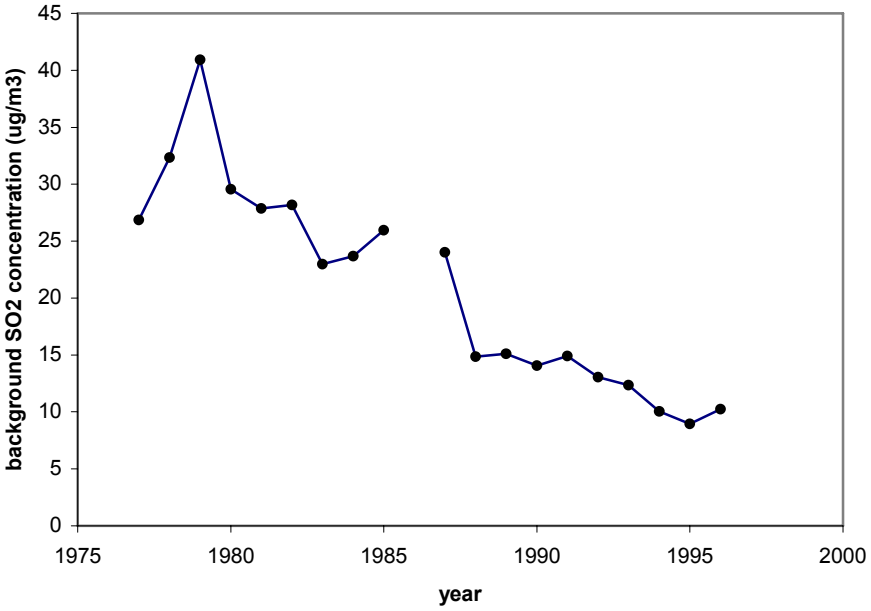


Figure 2 continued





Local component

Completeness

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 the period 1986-1996) total traffic intensity data were obtained. For municipal roads, total traffic intensity data were obtained for 121 of the in total 204 municipalities (~59%). Especially for municipalities with a small number of participants, no data were available. These 121 municipalities contained 17,912 subjects, i.e. approximately 82% of the total number of subjects in the study (N=21,868). The percentage of municipal roads for which traffic intensity data were available was 14.3%. For most of these municipalities, to a large part of the municipal roads a background traffic intensity value of 1,225 mvh/24h was therefore assigned. For all national roads truck traffic intensity data were available. For the municipal roads and provincial roads for which total traffic intensity data were available, truck traffic intensity data were available for only 19% and 23%, respectively.

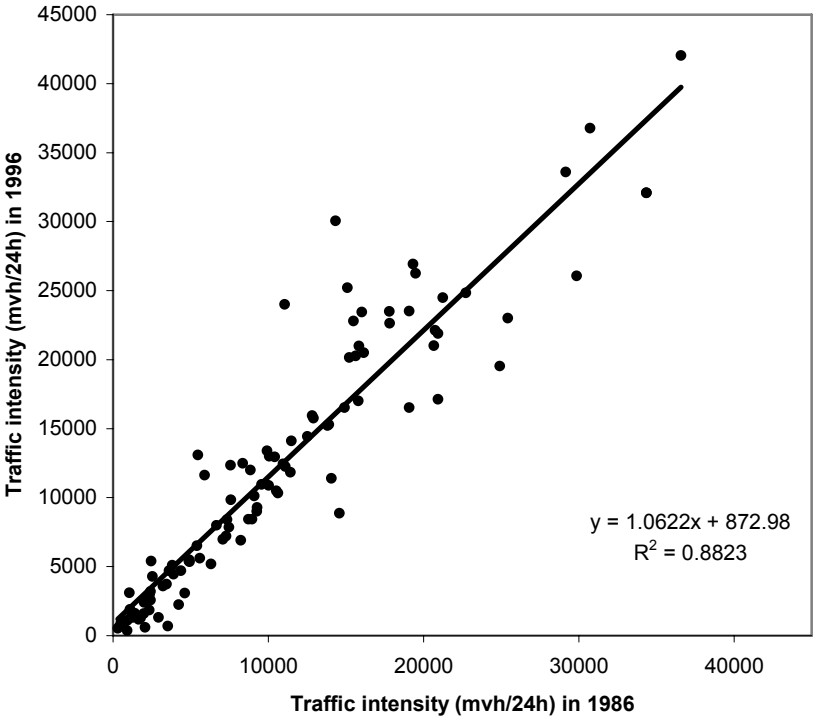
Of the in total 21,868 addresses, 17,592 (80.5%) had an assigned traffic intensity on nearest road of 1,225 mvh/24h. 9,632 addresses were located in municipalities with more than 100,000 inhabitants, and 7,282 of these addresses (75.6%) had an assigned traffic intensity on nearest road of 1,225 mvh/24h. Of the 12,236 addresses in municipalities with less than 100,000 inhabitants, 10,310 addresses (84.3%) had an assigned traffic intensity on nearest road of 1,225 mvh/24h. These data show that for the larger municipalities for a higher percentage of the roads traffic intensity data were available compared with small municipalities.

Temporal trends

In figure 3, the correlation between 1996 and 1986 traffic intensities on municipal, provincial and national roads is shown. The regression equations in figure 3 show that the increase in traffic intensity over time is substantially larger for national and provincial roads compared with municipal roads. Correlations between 1996 traffic intensities and traffic intensities from other years were all > 0.92 for the different road types, supporting the use of traffic intensities from one year to represent a long-term average. Because municipal data were not always available for the same year, trends in traffic intensity were estimated using roads with traffic intensity data for several years and mixed modeling procedures. The estimated trends (percentages increase per year) in traffic intensities on national, provincial and municipal roads within different traffic intensity classes are shown in table 5. A linear trend for the whole period was assumed. These trends were used to estimate traffic intensities for roads that did not have data for all years in the period 1986-1996.

Figure 3. Correlation between 1986 and 1996 traffic intensities and regression equation for municipal, provincial and national roads.

Municipal roads (N = 105 measurement points)



Provincial roads (N = 445 measurement points)

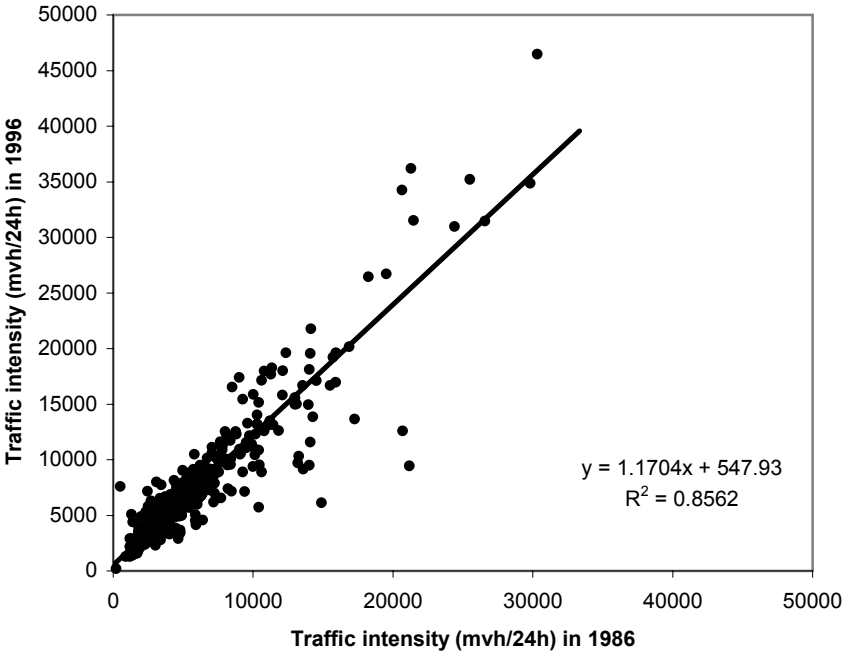


Figure 3 continued

National roads (N = 717 measurement points)

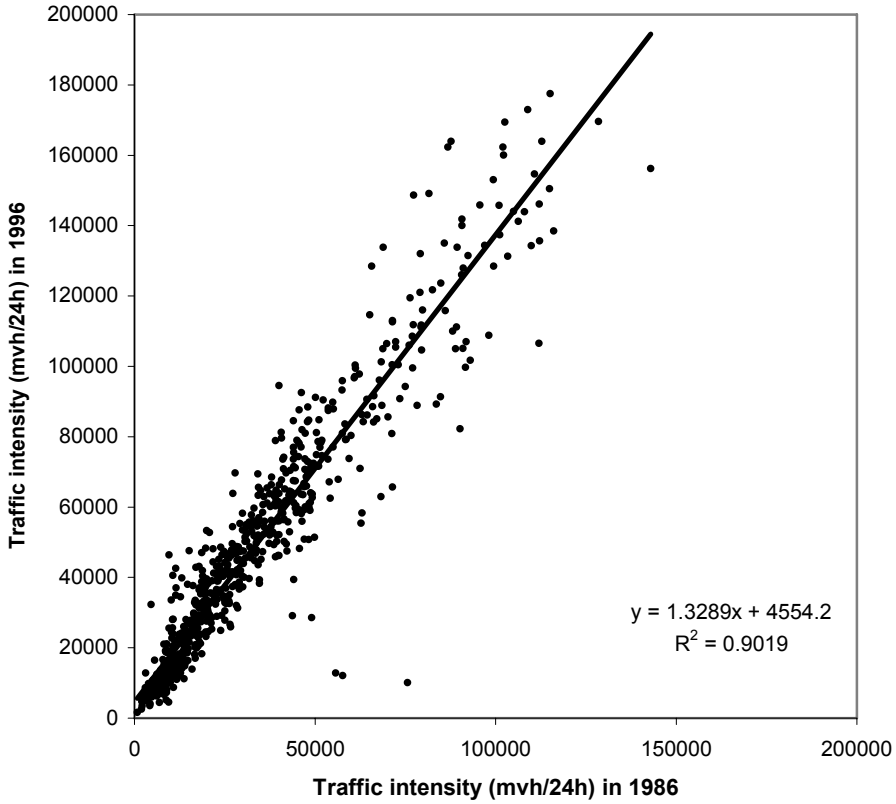


Table 5. Estimated trends (percentage increase per year) in traffic intensities on national, provincial and municipal roads within different traffic intensity classes in period 1986-1996 (N = number of observations on which trend is based).

National roads		**Provincial roads**		**Municipal roads**	
Intensity class	*Trend*	*Intensity class*	*Trend*	*Intensity class*	*Trend*
< 20,000 mvh/24h (N = 323)	2.7%	All intensities (N = 2,362)	2.0%	< 4,000 mvh/24h (N = 161)	0.1%
20,000 – 50,000 mvh/24h (N = 343)	3.9%			4,000 – 11,000 mvh/24h (N = 131)	1.0%
> 50,000 mvh/24h (N = 301)	3.6%			> 11,000 mvh/24h (N = 78)	1.1%

Distributions in cohort

In table 6 the distribution of the traffic intensities on the nearest road is shown for addresses located at roads with traffic intensities higher than 1,225 mvh/24h, for all addresses together and separately for addresses in municipalities with more than and less than 100,000 inhabitants. Table 6 shows that roads in municipalities with more than 100,000 inhabitants for which traffic intensity data were available had on average a higher traffic intensity compared with addresses in municipalities with less than 100,000 inhabitants.

The average distance to the nearest road was 19 m, with a minimum of 0 m and a maximum of 457 m. For only 3 subjects the nearest road was located further than 500 meters away.

Of the 21,868 subjects 11,229 (51.3%) lived within 500 m of a major road, defined as a road with traffic intensity > 10,000 mvh/24h in 1986. The average distance to the nearest major road was for these 11,229 subjects 233 m, and the minimum and maximum distance were 5 and 500 m, respectively. The percentage of participants who lived within 50 m of a major road was 4.7%, and 10.8% lived within 100 m of a major road.

Table 7 shows the distribution of the sum of total traffic intensity in 1986 in a buffer of 100 m around the home addresses of the study participants.

The distributions of the traffic variables were all highly skewed. The correlation between the traffic intensity on the nearest road and the nearest major road was 0.14, while the correlations with the sum of traffic intensity in a 100 m buffer were 0.64 and 0.20 for the traffic intensity on the nearest road and the nearest major road respectively.

Table 6. Distribution of traffic intensities on nearest roads for addresses of study participants located at roads with traffic intensities higher than 1,225 mvh/24h, for all addresses together and separately for addresses in municipalities with more or less than 100,000 inhabitants (mvh/24h).

Percentile	All addresses (N = 4,276)	Addresses in municipalities with more than 100,000 inhabitants (N = 2,350)	Addresses in municipalities with less than 100,000 inhabitants (N = 1,926)
Minimum	1,227	1,229	1,227
5%	1,484	1,536	1,425
25%	2,609	2,946	2,282
Median	5,137	6,039	4,004
75%	9,915	10,972	7,722
95%	19,192	20,889	15,385
Maximum	104,275	104,275	80,143

Table 7. Distribution of the sum of total traffic intensity in 1986 in a buffer of 100 m around each home address of a study participant (N = 21,868) (mvh/24h).

Percentile	Traffic intensity in a 100 m buffer (mvh/24h)
Minimum	0
5%	35,525
25%	77,175
Median	107,800
75%	182,977
95%	453,810
Maximum	2,867,610

Quantitative estimates

In the regression models for quantitatively estimating the local component without taking into account air pollution effects of nearby motorways, the regression coefficient of the local component was 1.61 (SE 0.60) μg/m^3 per 100,000 mvh in a 100 m buffer for NO_2, and the R^2 of the model was 26.3% (RMSE 5.70). For BS the regression coefficient was 1.84 (SE 0.38) μg/m^3 per 100 000 mvh in a 100 m buffer with an R^2 of 54.5% (RMSE 3.54). For $PM_{2.5}$, the regression coefficient was 0.50 (SE 0.23) μg/m^3 per 100,000 mvh in a 100 m buffer with a R^2 of 18.7% (RMSE 2.21). This resulted in average predicted local component concentrations (minumum; maximum) of 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 BS, and 0.7 μg/m^3 (0; 4.5 μg/m^3) for $PM_{2.5}$.

The parameter estimates for the regression models to estimate the contribution of nearby motorways to the local component are shown in table 8. No distance effect could be shown for $PM_{2.5}$. The R^2-values (RMSE values) for the regression model were for NO_2, BS and $PM_{2.5}$ 11.6% (5.21), 59.7% (1.40) and 31.2% (1.92), respectively. 1,873 participants (8.6%) lived within 500 m of a motorway. For these 1,873 participants the predicted average local component concentration caused by nearby motorways (minimum; maximum) were 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 BS, and 2.2 μg/m^3 (0.2; 7.0 μg/m^3) for $PM_{2.5}$.

Table 8. Regression models for estimating the local NO_2, BS and $PM_{2.5}$ concentration near motorways based on measurements of 24 locations near motorways with truck traffic intensity on nearest motorway and distance to this motorway in 3 categories (< 100 m, 100 – 300 m, and > 300 m (reference category)) as predictor variables (truck traffic intensity per 10,000 trucks/24h).

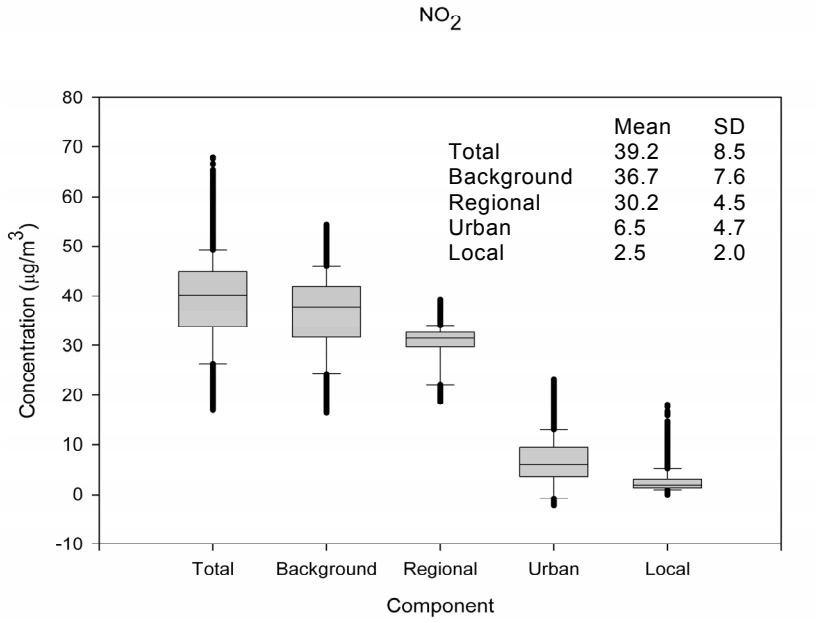
	Parameter estimates (Standard Error)		
Variable	*NO_2*	*BS*	*$PM_{2.5}$*
Truck traffic intensity	3.86 (3.84)	1.90 (1.03)	4.01 (1.42)
Distance < 100 m	4.43 (3.73)	5.06 (1.00)	-0.02 (1.38)
Distance 100 – 300 m	0.53 (2.65)	1.00 (0.71)	-0.07 (0.98)

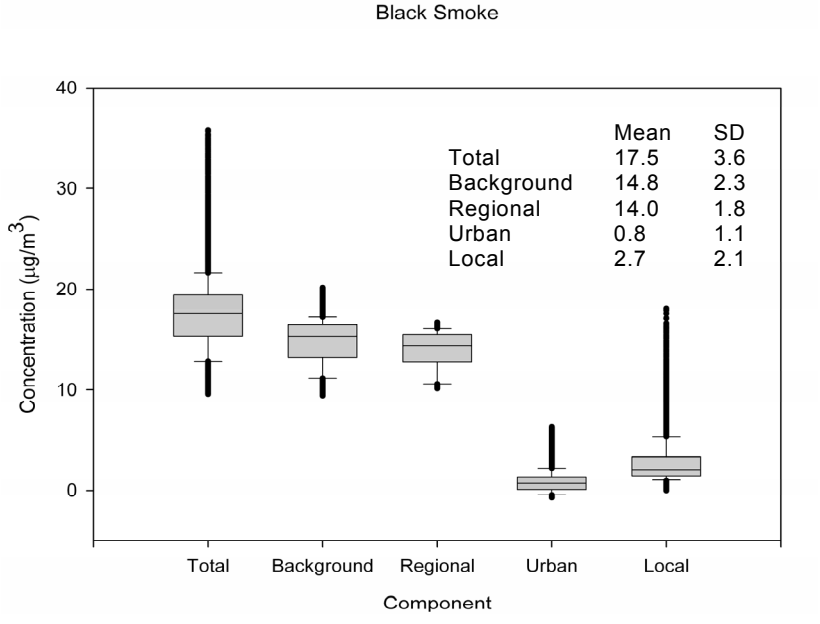
Performance of the exposure assessment method

Since other studies[8,13] have reported R^2-values incorporating the three spatial scales in one overall regression method, we illustrate the overall performance of our exposure assessment method by developing one overall regression model for each air pollutant with average concentrations for the period 1987-1991 measured at both regional background, urban background and street monitoring sites in the NAQMN as dependent variables. For all pollutants, the regional component was described by an indicator variable (North, East, West, and South) as proxy for the interpolation estimates, which cannot be used as predictors in the model. The urban component was modeled using the predictor variables for the different pollutants as described in table 2. The sum of traffic intensity, excluding the traffic intensity of motorways, in a 100 m buffer around a home address, and truck traffic intensity on nearest motorway and distance to this motorway in three categories were used as predictor variables for the local component for all pollutants. However, none of the NAQMN sites in the period 1987-1991 was located within 500 m of a motorway, and therefore the contributing effect of nearest motorway could not be evaluated. The models explained 84%, 44%, 59%, and 56% of the variability in concentrations for NO_2 (N = 36 sites), NO (N = 36 sites), BS (N = 16 sites) and SO_2 (N = 81 sites), respectively. One monitoring site was located in a street canyon with extremely high measured concentrations for NO (248 $\mu g/m^3$) and BS (63 $\mu g/m^3$). Excluding this site resulted in models which explained 67% and 87% of the variance of NO and BS, respectively.

Figure 4 shows the resulting distributions for the regional, urban, and local component for NO_2 and BS for the period 1987-1991 at addresses of participants. Further the distributions of the background concentrations (sum of regional and urban component) and total concentration (sum of regional, urban and local component) are shown. The estimated NO_2 and BS concentrations vary substantially over the home addresses of the study participants. The regional component contributes most to the total estimated concentration. Because only a small percentage of the study participants lived close to a major road, the effect for the local component is mostly in the highest concentrations.

Figure 4. Distributions of estimated NO_2 and BS concentrations (in $\mu g/m^3$) for the different components for the period 1987-1991 at addresses of study participants (N = 21,868).
(Total is sum of regional, urban and local; Background is sum of regional and urban)





Discussion

We described an improved method to estimate long-term outdoor air pollution concentrations in a Dutch cohort study. Using comprehensive data from existing air pollution monitoring stations, data on land use, population density, road networks and traffic density, we were able to develop exposure assessment models that explained a large part of the spatial variance in long-term averaged air pollution concentrations.

Spatial components

Ordinary kriging and inverse distance weighed interpolation procedures were evaluated as methods to estimate the regional component concentration. In general, all interpolation methods perform similarly when the data density is high and distributed relatively uniformly across the study area.[21] This similarity in performance was also shown by the high correlations (> 0.92) between estimates assessed with ordinary kriging and inverse distance interpolation procedures for those pollutants with large number of observations (NO_2 and SO_2).

Compared to our previous study the regression models to estimate the urban component concentrations were improved by 1) using varying buffer sizes around the exact home addresses instead of the postal codes, and 2) using a larger number of potential predictor variables. The results showed that the models of the current study resulted in more precise estimates of the urban component concentrations compared with the previous study. In the SAVIAH study[18] and a study by Stedman et al.[22] NO_2 concentrations were also estimated using regression modeling. In both studies land cover variables were used, *i.e.* area of built up land and percentage of urban and suburban land cover, which are equivalent with the variables we used. $PM_{2.5}$ filter absorbance, which can be transformed into BS concentrations, was predicted in the TRAPCA study.[13] In the TRAPCA regression models address density was used as predictor variable for the estimation of the urban component of exposure, which is similar with our urban component predictor variable for BS. In contrast with the other air pollutants, the number of inhabitants around a site was no predictor variable for SO_2 concentrations. However, whether a site was located in an industrial location was a significant predictor variable for SO_2, which is consistent with the fact that SO_2 is mainly emitted by industrial sources in the Netherlands.

Average background air pollution concentrations showed a decline during the measurement period. Average concentrations in different time periods were highly correlated ($r > 0.83$). A recent study by Pope et al. showed also a general decline in particulate air pollution in the United States, with a high correlation of 0.78 between average concentrations in the period 1979-1983 and the period 1999-2000.[23]

Exposure was estimated for the 1986 home address, as this is the baseline-address. Address history during the follow-up period was available for subcohort members and cases. For subcohort members, bi-annual follow-up questionnaires were used to determine residential history. The residential information of deceased subjects was available from the Central Bureau of Genealogy (CBG), which has an archive of municipal registration cards of subjects that deceased before October 1994. For persons that died after October 1994, the CBG has computer files on deaths containing however mostly incomplete address information. For most of these deceased subjects only the baseline address and the last address were available. Therefore, we did not assess total exposure for the entire period by estimating concentrations at different residential addresses. Approximately 30% of the participants moved between 1986 and end of follow-up. To take into account the effect of moving in the data-analysis, we used an indicator variable indicating whether a subject lived at the baseline address for the complete follow-up period.
Particulate matter was mainly characterized by BS. We had limited possibilities to evaluate PM_{10} and $PM_{2.5}$ exposures. Measurements of PM_{10} in the NAQMN started only in 1992, while $PM_{2.5}$ was not measured during the study period. PM_{10} measurements were thus available for only approximately half of the follow-up period. Measurements in the framework of the NAQMN of PM_{10} have documented that the contrast in PM_{10} concentrations in the Netherlands is relatively small.[24] Several studies have shown that BS or elemental carbon is better related to traffic than PM_{10} and $PM_{2.5}$.[12]

Traffic intensity is frequently used as an indicator for exposure to traffic-related air pollution.[25-28] One criticism of using traffic intensity as indicator of exposure is that data are often only available for only one point in time and not available for the relevant time period of interest.[29] Obtaining retrospective data on traffic intensity is laborious. We illustrated, however, that traffic intensity data obtained for different years were highly correlated, even over periods of 10 years.

A background traffic intensity value was assigned to roads for which no traffic data were available assuming that these were minor roads. This may have resulted in some (non-quantifiable) misclassification of exposure since some roads may actually have substantial counts. In the epidemiological study this may result in an underestimation of the effect because the ‘low exposed’ group contains some ‘exposed’ subjects. Because the vast majority (90-95%) of subjects is ‘low exposed’, this impact is likely small.

The trend in traffic intensity on municipal roads showed only a slight relative increase compared with the relative increase in traffic intensity on provincial and national roads. This suggests that the busy roads outside the city (provincial and national roads) became busier, but that traffic intensities on roads within cities did not

change much. This is due to the nation-wide introduction of regulations that prevent traffic in the more centrally located areas in municipalities and the increased development of employment facilities and other facilities at the borders of municipalities in the Netherlands.[17] Municipal roads with traffic intensities > 4,000 mvh/day showed a percentage increase in traffic intensity of 1% per year, while the traffic intensity on municipal roads with traffic intensities < 4,000 mvh/24h hardly increased. This is caused by municipal traffic regulations that prevent through traffic on minor municipal roads, with as consequence a concentration of traffic on the municipal main roads.[17]

Several Dutch urban traffic studies showed that concentrations of traffic-related air pollutants are substantially higher near busy roads compared to roads with low traffic intensities or at urban background locations.[7,30,31] We used therefore as first traffic variable the traffic intensity on the nearest road. This variable is however only based upon the characteristics of the nearest road, while a nearby busy road may also be important for local air pollution concentrations. Exposure studies near motorways showed that traffic-related air pollution concentrations depend on the traffic intensity on and the distance to motorways.[12,19] As a second traffic variable we used therefore the traffic intensity of the nearest major road, defined as a road > 10,000 mvh/24h, with the distance to this nearest major road. However, prediction of pollution values may be difficult in areas where there are a large number of intersecting line sources or where roads run parallel. Therefore, we used as third traffic variable the sum of traffic intensity in buffers of 100 m and 250 m around each home address. These variables use all traffic intensities within the specified buffer. A buffer of 100 m was used, because especially in urban areas with specific local topographic and building conditions marked variations in pollution levels can occur over distances less than 100 m.[18] Using buffer calculations has however limitations, e.g. the assumption that the dispersion pattern is the same in all directions may be violated because of wind patterns or topographic conditions.[8]

The used digital road network was from the year 2001 while home addresses of 1986 were used. The road network may have changed between 1986 and 2001. However, we focused mainly on busy roads that have likely been in place between 1986 and 2001. We used traffic intensities of 1986, while, for most municipal roads, these were estimated using traffic intensities of more recent years. The mixed modeling procedures to estimate trends in traffic intensities showed that for most roads the trend was not significantly different from the averaged fixed trend. We use therefore the assumption that while absolute traffic intensities may have changed, relative differences are likely to be stable. In addition, the 1986 addresses were geocoded with a database from 2000 and therefore the coordinates and digital road network are compatible.

Overall performance

The overall regression models predicted a large part of the variation in air pollution concentrations with explained variances of 84%, 44%, 59%, and 56% for NO_2, NO, BS, and SO_2, respectively. This is probably a (slight) underestimation because in the overall regression models an indicator variable for region was used as proxy for the interpolation results. It was not possible to predict concentrations for locations in street canyons. One monitoring site was located in a street canyon with a moderately high traffic intensity of 7,842 mvh/24h, but with extremely high measured concentrations for NO (248 $\mu g/m^3$) and BS (63 $\mu g/m^3$). Excluding this site resulted in models with substantially higher explained variances of the NO (67%) and BS (87%) concentrations.

Comparable to other studies which developed regression models to estimate exposure to air pollution using GIS derived variables, we found similar results.[13,18,32] The SAVIAH study used three key variables (traffic volume/road type, land cover and altitude) as predictors of NO_2 concentrations in three European cities (Amsterdam (NL), Huddersfield (UK), Prague (CR)). The explained variances of the annual mean NO_2 concentrations were 79%, 82% and 87% for the three cities respectively.[18] In the multicenter TRAPCA study, regression models using traffic-related variables were developed to estimate exposure to fine particles and filter absorbance. Regression models explained 81%, 67%, and 66% of the variability in annual average filter absorbance for the Netherlands, Munich and Stockholm, respectively.[13] These studies show that a large part of long-term averaged air pollution concentrations can be explained using a regression model with land use and traffic-related predictor variables and that it is a useful method to estimate exposure to air pollution for a large study population. However, to estimate concentrations using a regression-based approach both geographically relevant GIS data and concentration data from monitoring sites have to be available. These data may, however, not be available in all countries. GIS-based exposure assessment can be useful, but only when geo-referenced data are available at a relevant scale and with sufficient geographical accuracy.[29]

Conclusion

An improved method for assessment of long-term outdoor air pollution concentrations taking into account small-scale variations in air pollution concentrations was illustrated. Despite the limitations and methodological problems, we were able to develop an exposure assessment model using GIS-methods and traffic intensities that explained a large part of the variations in concentrations outdoor air pollutants and which can be used in epidemiologic studies to estimate air pollution levels at specified locations.

Appendix: Collection of and linkage of traffic intensity data to the digital road network

Traffic intensity data were collected for the different types of roads in the Netherlands: national, provincial and municipal roads. The road network in the Netherlands has a total length of more than 100,000 km. The national roads and provincial roads have a total length of approximately 3,200 and 9,000 km, respectively. The largest part of the total road network is thus the responsibility of the municipalities. Traffic intensity data were not readily available for all roads. Therefore, we put a major effort in obtaining as much traffic data as possible. For national roads, traffic intensity data for the period 1986-1996, both total traffic and truck traffic, 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. Although traffic intensities are counted on all provincial roads, traffic intensity data for provincial roads were not available in a central database. Therefore, we contacted all 12 provinces in the Netherlands individually to obtain total traffic and truck traffic intensity data for the years 1986-1996. Obtaining traffic intensity data for municipal roads was the most difficult, especially for small municipalities. To obtain data on total and truck traffic densities on municipal roads for the years 1986-1996 we contacted all 204 municipalities included in the study. Another source of municipal traffic intensity data were Environmental Traffic Maps. In the Netherlands, municipalities with more than 40,000 inhabitants are obliged to develop Environmental Traffic Maps to assess exposure to air pollution and noise for all roads with relevant traffic intensities defined as 2,450 motorvehicles/24h (mvh/24h).[17] For municipalities with an Environmental Traffic Map traffic data were available for all major roads.

For some provincial and municipal roads no average whole-week traffic intensities, but only average workday (Monday – Friday) or average daytime traffic intensities (traffic intensity between 7.00AM – 7.00PM) were available. We determined factors to convert these intensities to average whole-week traffic intensities by calculating ratios between whole-week and workday traffic intensities. For approximately 7% of the municipalities and for four of the twelve provinces only workday traffic intensities (Monday – Friday) were available. There are no standards for the conversion of average workday intensities into average whole-week traffic intensities (Monday – Sunday). However, for five municipalities and four provinces both average workday and whole-week traffic intensities were available for several years. Average ratios between whole-week and workday traffic intensities were calculated. To this end, the whole-week traffic intensities were expressed in counts per day as for the workday intensities. The overall average ratios for municipal and

provincial roads were 0.94 (SD 0.03) and 0.93 (SD 0.02), respectively. The ratios did not change over time and did not depend on the size of a municipality. Further, the ratio was not related to the workday traffic intensity. Average workday traffic intensities were therefore multiplied by 0.94 and 0.93 for municipal and provincial roads, respectively, to estimate daily average whole-week traffic intensities. Further, for two municipalities only daytime traffic intensities (traffic intensity between 7.00AM – 7.00PM) were available. From the literature information was available about the percentage of the total daily traffic intensity that occurs during daytime hours on municipal roads in the Netherlands; 77.8% of the total daily traffic intensity occurred during daytime hours.[33] We assumed that this percentage did not change over time and that the percentage is independent of the traffic intensity on a road. For municipal roads daytime traffic intensities were therefore multiplied by 1.29 (= 1/0.778) to calculate an average whole-week traffic intensity.

Average whole-week traffic intensities for the years 1986-1996 were linked to the National Road Database (Nationaal Wegen Bestand (NWB), based on road name and road number. The NWB includes all streets and roads in the Netherlands that have a street name and/or road number. This means that more than 98% of the Dutch roads have been included. More than 95% of all road sections in NWB have a maximum location difference of 10 m compared with the true location.[16]

Acknowledgements

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Chapter 3

Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study)

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Abstract

Several studies have found an effect of between-city contrasts in long-term exposure to air pollution on mortality. The effect of within-city contrasts is still poorly understood. We studied the association between long-term exposure to traffic-related air pollution and mortality in a Dutch cohort.

We used data from an ongoing cohort study on diet and cancer (NLCS) with 120,852 subjects who were followed from 1987 to 1996. Exposure to black smoke (BS), nitrogen dioxide (NO_2), sulfur dioxide (SO_2) and particulate matter ≤ 2.5 µm ($PM_{2.5}$), as well as various exposure variables related to traffic, were estimated at the home address. We conducted Cox analyses in the full cohort adjusting for age, gender, smoking and area-level socio-economic status.

Traffic intensity on the nearest road was independently associated with mortality. Relative risks (95% CI) for a 10 µg/m^3 increase in BS concentrations (difference between 5^{th} and 95^{th} percentile) were 1.05 (1.00 – 1.11) for natural cause, 1.04 (0.95 – 1.13) for cardiovascular, 1.22 (0.99 – 1.50) for respiratory, 1.03 (0.88 – 1.20) for lung cancer and 1.04 (0.97 – 1.12) for mortality other than cardiovascular, respiratory or lung cancer. Results were similar for NO_2 and $PM_{2.5}$, but no associations were found for SO_2.

Traffic-related air pollution and several traffic exposure variables were associated with mortality in the full cohort. Relative risks were generally small. Associations between natural cause and respiratory mortality were statistically significant for NO_2 and BS. These results add to the evidence that long-term exposure to ambient air pollution is associated with increased mortality.

Introduction

Although air pollution concentrations have decreased substantially over the last several decades, recent studies from the U.S. found associations between long-term exposure to air pollution and cardiopulmonary and lung cancer mortality.[1-7] Cohort studies from Europe have tended to confirm the U.S. findings,[8-11] but the emphasis has been on different pollutants, and on different exposure assessment methods. The U.S. studies have used data from single monitoring stations to characterize exposure of subjects living in that city, or spatial interpolation from multiple monitoring stations. Most European studies have estimated exposure at the home address using dispersion or stochastic modeling and variables such as living close to busy roads.

In a previous Dutch study in 5,000 subjects, a random sample from a full cohort (N ~ 120,000), cardiopulmonary and all cause mortality were associated with living close to a major road with relative risks of 1.95 (95% CI 1.09 – 3.52) and 1.41 (95% CI 0.94 – 2.12), respectively.[8] In this paper we extend this work to the full cohort with a much larger number of deaths, and with an improved exposure assessment method.

Materials and methods

Study Design

The cohort has been described in detail.[12] Briefly, the Netherlands Cohort Study on Diet and Cancer (NLCS) was initiated in September 1986 with the enrollment of 120,852 subjects (58,279 males and 62,573 females) aged 55-69 years living in 204 municipalities located throughout the country. The study was designed as a case-cohort study, i.e. cases are derived from the entire cohort, while the person years at risk are estimated from a random subcohort (N ~ 5,000).[13] This approach was selected for efficiency of baseline questionnaire processing and avoidance of active follow-up of the entire cohort.

At baseline, all participants completed an 11-page questionnaire on dietary habits and other risk factors for cancer. For all participants, data from one machine-readable page of the questionnaire were entered at baseline (with information about age, gender and smoking status). After recruitment, the entire cohort was followed up for cancer incidence by record linkage to cancer registries.[14] For the emerging cases and the randomly selected subcohort, the remaining 10 questionnaire pages (not machine readable) were manually entered, blinded with respect to case/subcohort

status. The exact residential address at baseline was available for all study participants.

Mortality was assessed between January 1, 1987 and December 31, 1996. Mortality data were obtained from the Dutch Central Bureau of Genealogy and the Dutch Central Bureau of Statistics. The cause of death was coded according to the International Classification of Disease, ninth revision (ICD-9) (for period 1986-1995) and tenth revision (ICD-10) (for 1996). Causes of death were grouped into natural cause, cardiopulmonary, cardiovascular, respiratory, lung cancer, and mortality other than cardiopulmonary or lung cancer (Table 1).

The NLCS study was approved by institutional review boards from Maastricht University and the Netherlands Organization for Applied Scientific Research (TNO). All cohort members consented to participation by completing a mailed, self-administered questionnaire.

Table 1. Number of deaths during follow-up.

Cause	ICD-9 codes	ICD-10 codes	Number of deaths
All cause	All	All	17,610
Natural cause	< 800	< V01	17,286
Cardiopulmonary	400 – 440 or 460 – 519	I10 – I70 or J00 – J99	7,153
Cardiovascular	400 - 440	I10 – I70	6,137
Respiratory	460 - 519	J00 – J99	1,016
Lung cancer	162	C33 – C34	1,888
Other than cardiopulmonary or lung cancer	Not 400-440, not 162, and not 460-519, and < 800	Not I00-I70, not J00-J99, not C33-C34, and < V01	8,569

Air pollution exposure assessment

Details of the exposure assessment method have been described previously.[15] In summary, long-term exposure to outdoor air pollution at the 1986 home address was estimated for all participants as the sum of regional, urban and local traffic contributions. The home addresses were geocoded into standard Dutch geographical coordinates (Address Coordinates Netherlands (ACN)) using a database from 2000 consisting of all registered addresses by the Dutch postal service. The accuracy of ACN is high with 93.5% of all coordinates located at the centroid of the correct building, 6.0% located at the centroid of the correct parcel, and only 0.5% not located in the correct building or parcel.[16] No information was available about the exact work addresses of participants.

Regional background concentrations were estimated using inverse distance weighed interpolation of concentrations measured at regional background sites in the

National Air Quality Monitoring Network (NAQMN). The additional urban component was estimated using regression models with residual concentrations for all regional background and urban monitoring sites in the NAQMN as dependent variable, calculated as measured concentration minus estimated regional component concentration using cross-validation. As predictor variables we used the number of inhabitants around a monitoring site and land-use variables that indicated whether a site was located in a city center, in a rural background location, or in an industrial location. The sum of the regional and urban contributions was defined as background concentration. Background concentrations were estimated for nitrogen dioxide (NO_2), black smoke (BS) and sulfur dioxide (SO_2). Average concentrations were estimated for 1976-1985 and 1987-1996 (in 1986 the NAQMN was rearranged resulting in only limited days with valid measurements in 1986). The background concentration for fine particles less than 2.5 μm ($PM_{2.5}$) in diameter was estimated by converting PM_{10} (particles less than 10 μm) concentrations, measured in the NAQMN from 1992 to 1996, into $PM_{2.5}$ concentrations using a single ratio, established from monitoring data in the Netherlands. This was done because $PM_{2.5}$ was not monitored in the Netherlands during the study period.

Local traffic contributions were characterized by traffic variables that were estimated using a Geographic Information System (GIS) from a digital road network to which traffic intensity data (average total number of motor vehicles per 24 hours (mvh/24h), including weekdays and weekend) from the year 1986 were linked. Because traffic intensity data were available for different years for municipal roads, we extrapolated traffic intensities to 1986 for roads for which 1986 traffic data were not available. Extrapolation was based upon trends estimated from traffic intensity data from municipalities with multiple years of data.[15] Traffic intensities were linked to the National Road Database (Nationaal WegenBestand – NWB), based on road name and/or road number. The NWB includes all roads in the Netherlands that have a street name and/or road number. More than 98% of the Dutch roads have been included. More than 95% of all road sections in the NWB have a maximum location difference of 10 m compared with the true location.[15] The digital road network and the coordinate database for geocoding addresses were from the same time period, and both used the same standard Dutch coordinate system, and therefore substantial error due to geographical differences between the two databases is unlikely.

We used as traffic variables: (1) traffic intensity on nearest road; (2) sum of traffic intensity in a 100 m buffer around each residential address; (3) traffic intensity on the nearest major road (with more than 10,000 mvh/24h) and distance to this road; and (4) an indicator variable 'living within 100 m of a motorway and/or within 50 m of a local road with traffic intensity > 10,000 mvh/24h'. Further, quantitative estimates for the local component were obtained for NO_2, BS and $PM_{2.5}$ from field monitoring

campaigns.[15] We estimated no local traffic contribution for SO_2 as there is virtually no traffic contribution to this pollutant. These local component concentrations were added to the background concentrations resulting in an overall exposure estimate for each pollutant.

Statistical analysis

Air pollution effects were analyzed for overall concentrations and for a combination of background concentrations and traffic variables to identify effects of living near busy roads separately.

Relative risks (RR) were calculated for concentration and traffic variable differences between the 5th and the 95th percentiles of the distributions. For NO_2 this was rounded to 30 µg/m^3, for BS 10 µg/m^3, for SO_2 20 µg/m^3, and for $PM_{2.5}$ 10 µg/m^3. For the traffic variables the differences between the 5th and the 95th percentile were 10,000 mvh/24h for the traffic intensity on the nearest road, 335,000 mvh/100 m for the sum of traffic intensity in a buffer of 100 m, 20,000 mvh/24h for the traffic intensity on the nearest major road, and 2.3 m for the natural logarithm of distance to this road.

We conducted analyses in the full cohort using Cox proportional hazards models. Person-years were calculated for all participants from baseline until death or end of follow-up. Person-years for subjects who died from causes other than those being analyzed were judged censored at time of death in cause-specific analyses.

We adjusted for gender, age at baseline, and smoking status coded as never, ex, and current smoker separately for cigarette, cigar and pipe smoking. We further adjusted for area-level indicators assessed using GIS data from the Central Bureau of Statistics (CBS): percentage of persons with a low and with a high income at the neighborhood scale and the COROP area scale. COROP areas have been defined in 1970 by the Coordination Commission for Regional Research Program such that each COROP area consists of a central point (e.g. a city) and the surrounding economic and social region. The Netherlands is divided in 40 COROP areas. We chose two scales for area-level socio-economic status because life expectancy varies significantly by COROP area,[17] and the neighborhood scale does not capture such regional variations adequately. Low income was defined by the CBS as below the 40th percentile and high income as above the 80th percentile of the Dutch income distribution (Table 2).

Cox-Poisson random effects survival software as described in Jerrett et al. 2005[5] was used to incorporate spatial clustering at the municipal and/or neighborhood scale in the full cohort analyses. Both 1-level (i.e. municipality or neighborhood) and 2-level (i.e. municipality and neighborhood) analyses were conducted, using independent-clusters and distance-decay random effects models.

Effect-modification by gender and cigarette smoking status in the full cohort was assessed by conducting separate analyses in subgroups. We also conducted separate subgroup analyses for the percentage of persons with a low income in a neighborhood and COROP area (in tertiles).

Heterogeneity in pollution relative risks across estimates from different subgroups was tested using Cochran's Q test.[18]

We also conducted case-cohort analyses, including only subcohort members and cases (deaths), which is the standard data analysis approach in the NLCS. Cases were enumerated from the entire cohort, whereas person-years for the entire cohort were estimated using the random subcohort of 4,971 participants. Data were analyzed with Cox proportional hazards models. To account for additional variance introduced by sampling from the cohort, standard errors were estimated using the robust Huber-White sandwich estimator.[19]

In the case-cohort analyses we adjusted for a priori chosen variables: gender; age at baseline; active cigarette, cigar and pipe smoking coded as never/ex/current and number of cigarettes/cigars/pipes and number of years of smoking; passive smoking defined as whether the partner smoked; educational level in three categories: primary school, lower vocational education and high school and higher; the last occupation of the participant was coded in six categories: never paid work, blue collar, lower white collar, upper white collar, other, and whether the last occupation was longer than 40 years ago; occupational exposure of the last occupation to biological dust, mineral dust, and gases and fumes coded as no, low and high exposure assessed using the ALOHA job exposure matrix;[20] marital status in two categories: married, and never married, divorced or widowed; Body Mass Index in categories <20, 20-25, 25-30, and >30 kg/m^2; alcohol consumption in five categories: none, 0-5, 5-15, 15-30, and >30 g/day; dietary habits as continuous variables: intake of vegetables, fruit, fish, and energy-adjusted intake of fiber, folate, and saturated, monounsaturated, polyunsaturated and trans fat; and for the area level indicators of socio-economic status. No methods were available for spatial autocorrelation analyses in a case-cohort setting.

We assessed effect-modification by educational level, fruit consumption (in tertiles) and vegetable consumption (in tertiles) in the case-cohort by conducting separate analyses in subgroups.

Information about moving during the follow-up period was only available in the case-cohort group. We conducted a separate analysis for subjects who did not move during the follow-up period.

We also conducted separate analyses in the case-cohort dataset for people who had a paid job and who did not have a paid job at baseline.

Data management was done using SPSS 12.0 (SPSS Inc, Chicago, US), and statistical analyses were conducted using STATA statistical software 8 (STATA Corporation, College Station, US). GIS calculations were conducted using ArcInfo (ESRI, Redlands, US). Spatial analyses were conducted using the R interface to the software described in Ma et al. 2003.[21]

Results

For 97% of the subjects a geographical coordinate for the home address was identified (N = 117,528). About 15% of the subjects died during follow-up (Table 1). Population characteristics of subjects for which a coordinate was available are summarized in Table 2.

Exposure data

Background concentrations estimated for the periods 1976-1985 and 1987-1996 were highly correlated (> 0.9) for each pollutant. The correlations between different air pollutants within the same period were all > 0.8, except for SO_2 (> 0.6).[15] Figure 1 illustrates that there is considerable contrast of exposure in the full cohort: 5,784 participants (4.9%) lived within 50 m of a road > 10,000 mvh/24h and/or within 100 m of a motorway; 4.4% lived within 50 m of a road > 10,000 mvh/24h, and 0.6% lived within 100 m of a motorway. Correlations between background BS and traffic intensity on the nearest road and sum of traffic intensity in a 100 m buffer were modest: 0.12 and 0.28, respectively.

Table 2. Descriptive characteristics of subjects who died and who were alive at end of follow-up in the full cohort (among subjects for which geographical coordinates of the home address were available (N = 117,528)). Values are number (%) or median (Inter Quartile Range).

Characteristic	**Cases (N = 17,286)**	**Non-cases (N = 100,242)**
Gender (men)	11,317 (65.5%)	45,484 (45.4%)
Age (years)	64 (60 – 67)	61 (58 – 65)
Cigarette smoking status		
Never	4,788 (29.8%)	40,113 (42.5%)
Ex	5,063 (31.5%)	29,899 (31.7%)
Current	6,207 (38.7%)	24,325 (25.8%)
Cigar smoking status		
Never	13,663 (82.7%)	84,935 (88.3%)
Ex	1,429 (8.6%)	6,394 (6.7%)
Current	1,438 (8.7%)	4,844 (5.0%)
Pipe smoking status		
Never	15,227 (91.5%)	90,351 (93.6%)
Ex	865 (5.2%)	4,200 (4.4%)
Current	552 (3.3%)	1,947 (2.0%)
% persons with low income in neighborhood	41 (36 – 47)	41 (36 – 46)
% persons with high income in neighborhood	18 (12 – 24)	19 (13 – 25)
% persons with low income in a COROP area	41 (36 – 45)	41 (36 – 45)
% persons with high income in a COROP area	19 (18 – 23)	19 (18 – 23)

Figure 1. Distribution of estimated NO_2 (background and overall estimate), black smoke (background and overall estimate), SO_2 (background) and $PM_{2.5}$ (overall estimate) concentrations (period 1987-1996), and of the traffic intensity on the nearest road and the sum of traffic intensity in a 100 m buffer, at the 1986 home address (N = 117,528).

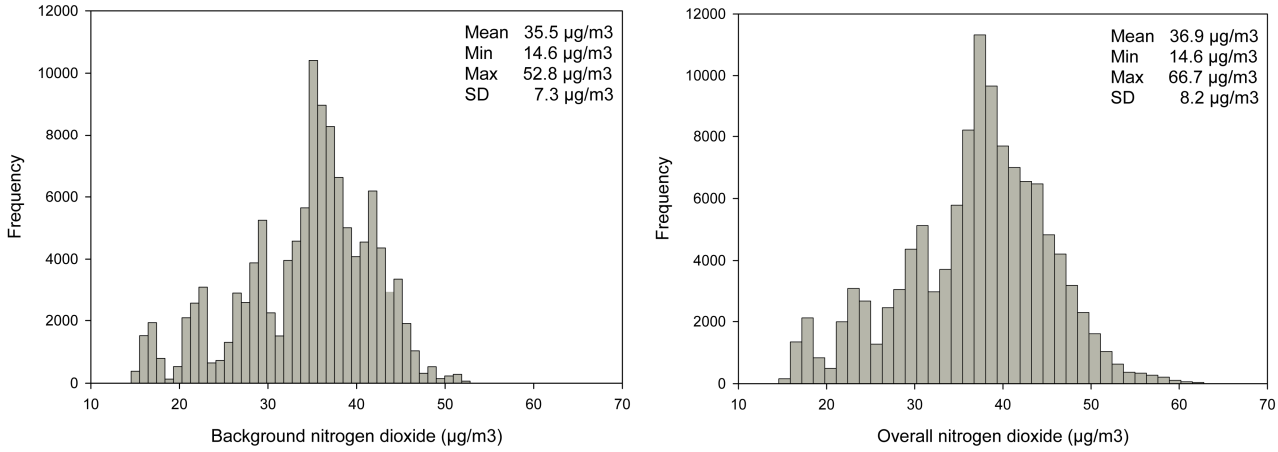
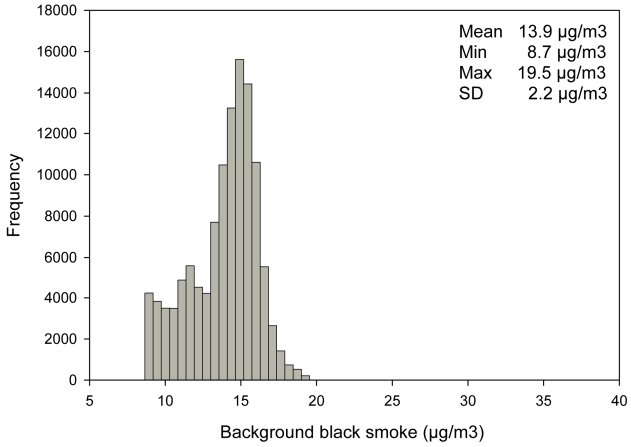
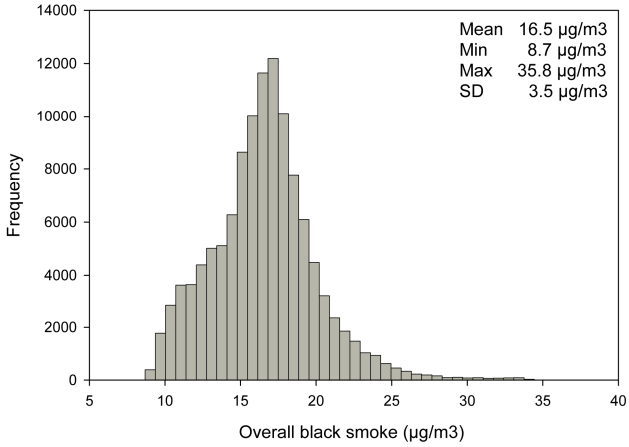
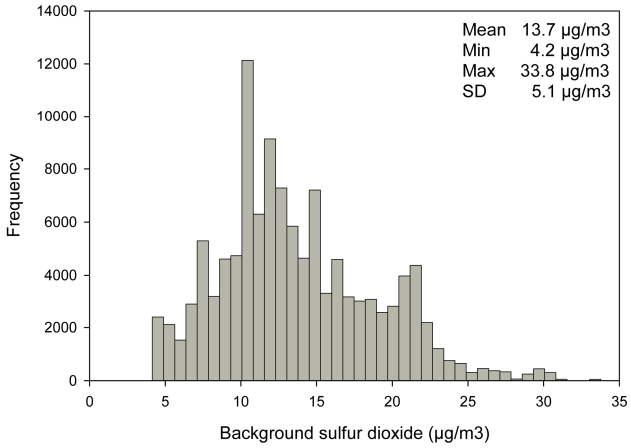
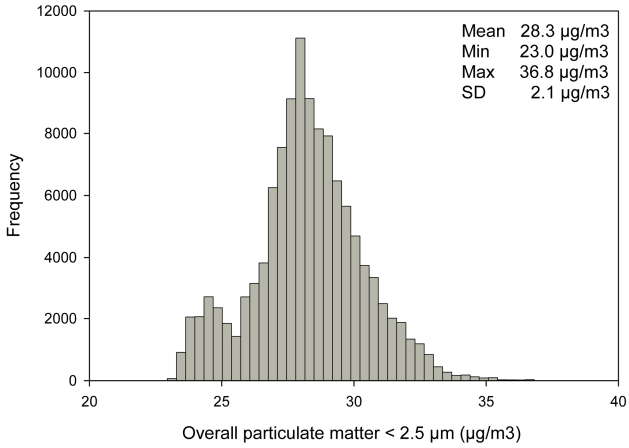


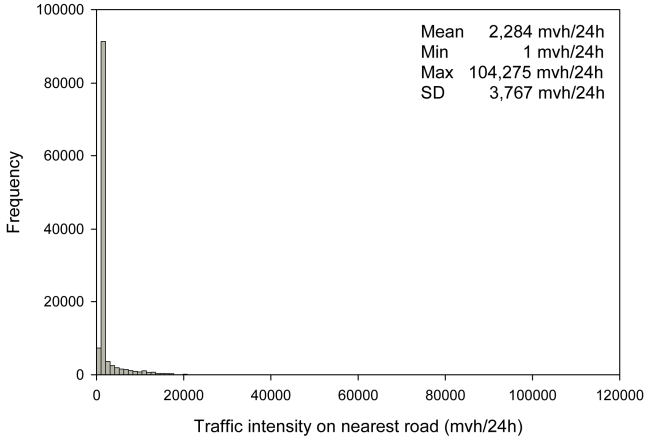
Figure 1 continued

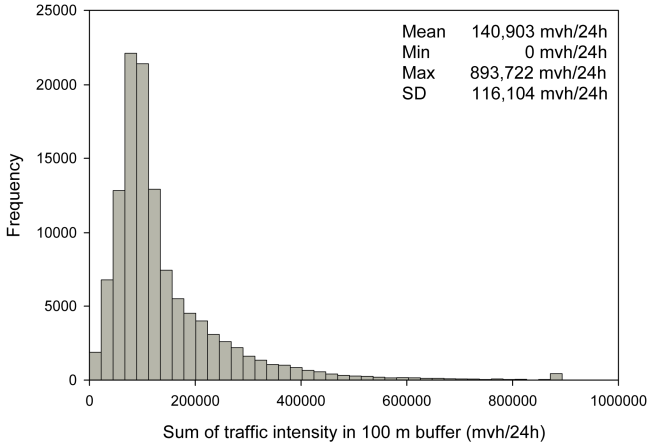












Associations between mortality and air pollution concentrations

Table 3 shows the associations between overall air pollution concentrations and mortality in the full cohort and case-cohort analyses.

In the full cohort analyses, there was no association between estimated SO_2 and mortality in any of the analyses. BS and NO_2 were significantly associated with natural cause and respiratory mortality. Effect estimates for other mortality were also increased with RRs similar to the effect estimates for natural cause mortality. The effect estimate in the full cohort for cardiopulmonary mortality was 1.07 (95% CI 0.98 – 1.15) for BS for a 10 $\mu g/m^3$ increase in concentration.

In the adjusted case-cohort analyses, there was no association between air pollution and mortality.

Further analyses showed that age-gender adjusted results between case-cohort and full cohort analyses were comparable, especially for BS and NO_2, but adjusted results were not. This was related to the loss of about 40% of subjects in the adjusted case-cohort analyses because of missing values in one or more confounder variables. Further analyses in the case-cohort sample showed little difference between the effect estimates adjusted for all available confounders and adjusted for only the limited set of confounders available in the full cohort, when the analysis was restricted to subjects without missing values. Because of these issues with the case-cohort analysis and evidence that residual confounding in the full cohort is unlikely to be substantial, in this paper we focus mainly on the full cohort results. The Appendix provides a more detailed discussion of these differences between case-cohort and full cohort results. Case-cohort analyses were, of course, also less precise, especially for the more frequent outcomes for which the ratio between subcohort size and number of cases was smaller.

Associations between mortality and traffic variables

Table 4 shows the adjusted associations between the traffic variables and cause-specific mortality in the full cohort and case-cohort analyses. Effect estimates for traffic variables were independent of background pollutant in the model, so we present relative risk estimates for traffic variables from models with BS background concentrations (1987-1996). Effect estimates were not sensitive to different confounder models for both full cohort and case-cohort analyses (data not shown).

In the full cohort analyses, risks for all traffic variables were elevated for all mortality outcomes, except for other mortality. The relative risk estimate for the association between cardiopulmonary mortality and traffic intensity on nearest road was 1.06 (95% CI 1.00 – 1.12) for an increase of 10,000 mvh/24h. No association was found with any of the mortality outcomes for traffic intensity on the nearest major road and distance to this road (data not shown).

Table 3. Adjusted relative risks (95% CIs) for the association between exposure to black smoke, $PM_{2.5}$, NO_2 and SO_2 (period 1987-1996) with cause-specific mortality in full cohort and case-cohort analyses (increment used to calculate RR).[a]

	Number of cases [b]		**BS (10 µg/m^3)**		**$PM_{2.5}$ (10 µg/m^3)**		**NO_2 (30 µg/m^3)**		**SO_2 (20 µg/m^3)**	
Mortality	*Full cohort*	*Case-cohort*	*Full cohort*	*Case-cohort*	*Full cohort*	*Case-cohort*	*Full cohort*	*Case-cohort*	*Full cohort*	*Case-cohort*
Natural cause	15,287	10,094	1.05 (1.00-1.11)	0.97 (0.83-1.13)	1.06 (0.97-1.16)	0.86 (0.66-1.13)	1.08 (1.00-1.16)	0.87 (0.69-1.10)	0.97 (0.90-1.05)	0.91 (0.71-1.16)
Cardiovascular	5,397	3,608	1.04 (0.95-1.13)	0.98 (0.81-1.18)	1.04 (0.90-1.21)	0.83 (0.60-1.15)	1.07 (0.94-1.21)	0.88 (0.66-1.17)	0.94 (0.82-1.06)	0.88 (0.65-1.18)
Respiratory	904	574	1.22 (0.99-1.50)	1.29 (0.91-1.83)	1.07 (0.75-1.52)	1.02 (0.56-1.88)	1.37 (1.00-1.87)	1.26 (0.74-2.15)	0.88 (0.64-1.22)	0.88 (0.51-1.50)
Lung cancer	1,670	1,059	1.03 (0.88-1.20)	1.03 (0.77-1.38)	1.06 (0.82-1.38)	0.87 (0.52-1.47)	0.91 (0.72-1.15)	0.80 (0.52-1.23)	1.00 (0.79-1.26)	0.99 (0.62-1.58)
Other	7,603	5,036	1.04 (0.97-1.12)	0.91 (0.78-1.07)	1.08 (0.96-1.23)	0.85 (0.65-1.12)	1.09 (0.98-1.21)	0.83 (0.66-1.06)	1.00 (0.90-1.12)	0.93 (0.72-1.19)

[a] *Full cohort analyses* adjusted for age, gender, smoking status, and area level indicators of socio-economic status.

Case-cohort analyses adjusted for age, gender, BMI, active smoking, passive smoking, education, occupational exposure, marital status, alcohol use, vegetable intake, fruit intake, energy intake, fatty acids intake, folate intake, fish consumption, and area level indicators of socio-economic status.

BS, $PM_{2.5}$ and NO_2 are quantitative overall concentrations. SO_2 is background concentration (including traffic intensity on nearest road in model).

Number of person years in full cohort analyses is 984,589 and number of person years in case-cohort analyses is 28,522.

[b] The number of cases between full cohort and case-cohort adjusted analyses differs due to the larger confounder model in the case-cohort analyses resulting in a higher number of subjects not available for analysis due to missing values.

Table 4. Adjusted relative risks (95% CIs) for the association between traffic variables with cause-specific mortality in full cohort and case-cohort analyses.[a]

Exposure model	Full cohort	Case-cohort
	Natural cause mortality	
Traffic intensity on nearest road	1.03 (1.00 – 1.08)	0.99 (0.88 – 1.11)
Traffic intensity in a 100 m buffer	1.02 (0.97 – 1.07)	0.98 (0.85 – 1.13)
Living near a major road	1.05 (0.97 – 1.12)	0.92 (0.74 – 1.15)
	Cardiovascular mortality	
Traffic intensity on nearest road	1.05 (0.99 – 1.12)	1.03 (0.90 – 1.17)
Traffic intensity in a 100 m buffer	1.00 (0.92 – 1.08)	0.98 (0.82 – 1.16)
Living near a major road	1.05 (0.93 – 1.18)	0.93 (0.72 – 1.21)
	Respiratory mortality	
Traffic intensity on nearest road	1.10 (0.95 – 1.26)	0.94 (0.71 – 1.25)
Traffic intensity in a 100 m buffer	1.21 (1.02 – 1.44)	1.23 (0.89 – 1.68)
Living near a major road	1.19 (0.91 – 1.56)	0.85 (0.50 – 1.43)
	Lung cancer mortality	
Traffic intensity on nearest road	1.07 (0.96 – 1.19)	1.03 (0.87 – 1.22)
Traffic intensity in a 100 m buffer	1.07 (0.93 – 1.23)	1.10 (0.85 – 1.43)
Living near a major road	1.20 (0.98 – 1.47)	1.07 (0.70 – 1.64)
	Other mortality	
Traffic intensity on nearest road	1.00 (0.94 – 1.06)	0.93 (0.82 – 1.06)
Traffic intensity in a 100 m buffer	0.99 (0.93 – 1.06)	0.93 (0.80 – 1.07)
Living near a major road	0.98 (0.88 – 1.09)	0.85 (0.68 – 1.07)

[a] The used confounders for the full cohort and case-cohort analyses are described in Table 3. RRs were calculated for differences from the 5th to the 95th percentile: for the traffic intensity on the nearest road: 10,000 mvh/24h, for the traffic intensity in a 100 m buffer: 335,000 mvh/100m. RRs for living near a major road were calculated with as reference category not living near a major road. All models included BS background concentration (1987-1996) as background concentration.
The number of person years and number of cases for the full cohort and case-cohort analyses are shown in Table 3.

The adjusted case-cohort analysis did not show any association with traffic variables. However, further analysis showed that this was not because of the additional adjustment (for the case-cohort analyses a larger number of confounders was available compared to the full cohort analyses) but because sampling the subcohort introduced random error in a downward direction, probably related to the small fraction of high exposed subjects and the skewness of the exposure distribution of the traffic variables (Figure 1). The Appendix provides a more detailed discussion of the effect of random variability in the case-cohort analyses.

Spatial analyses, effect modification, and moving

When spatial autocorrelation was taken into account, full cohort results did not change appreciably (Figure 2).

In the full cohort analyses, there were no significant differences in effect estimates between men and women. The effect estimates for respiratory mortality were higher among current smokers, while there was suggestive evidence that effect estimates

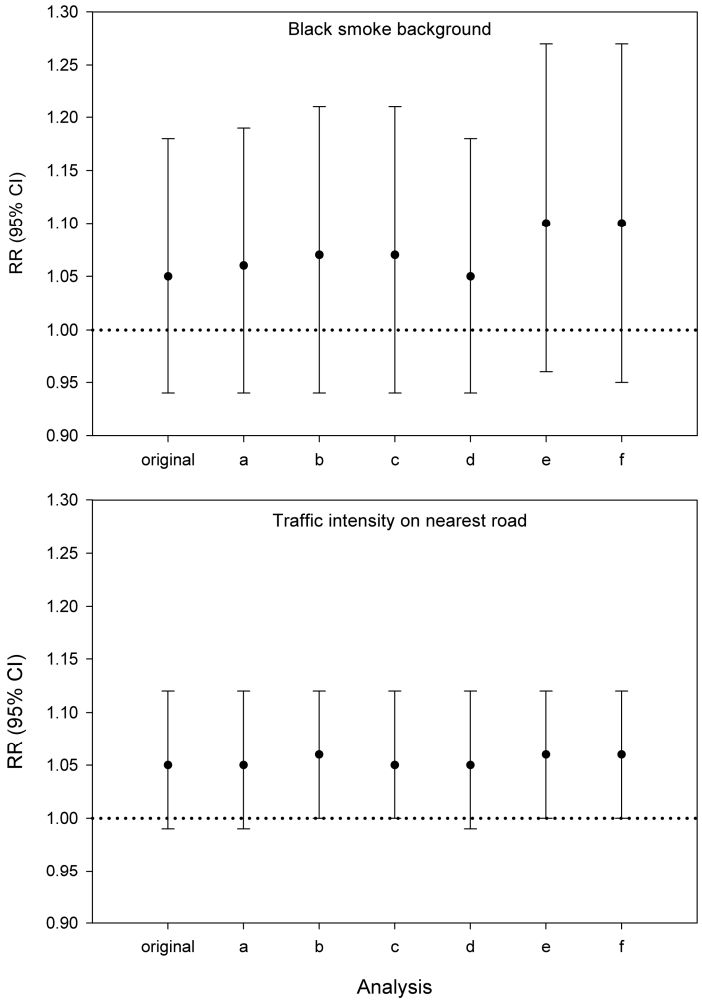
for natural cause and lung cancer mortality were higher among never smokers (Figure 3A). Air pollution effect estimates for natural cause mortality were significantly higher for people living in neighborhoods with the lowest percentage of persons with a low income. Differences between subgroups were however inconsistent for the different causes of death, e.g. for cardiovascular mortality the lowest and medium tertile had the same relative risk and for respiratory mortality the highest risk was found in the subgroup with the highest percentage of low-income subjects.

Subgroup analyses in the case-cohort dataset were adjusted for the limited number of confounders available for the full cohort to avoid the described selection effect that is present when the case-cohort analyses are adjusted for all available confounders. Effect estimates for the full case-cohort dataset adjusted for the limited confounder model used in the full cohort analyses were for BS overall concentrations 1.03 (95% CI 0.91 – 1.17) for natural cause mortality, 1.02 (95% CI 0.88 – 1.18) for cardiovascular mortality, 1.16 (95% CI 0.91 – 1.48) for respiratory mortality, 0.99 (95% CI 0.80 – 1.23) for lung cancer mortality, and 1.03 (95% CI 0.91 – 1.16) for other mortality. Figure 3B shows that the effect estimates for natural cause mortality for BS were higher in those with low education and in those with low fruit consumption in the case-cohort analyses. Relative risks for the different groups did however not differ significantly. Trends were similar for cardiovascular and other mortality (data not shown). Effects estimates for the different mortality outcomes for BS overall concentrations were not different for different tertiles of vegetable consumption (data not shown).

Approximately 30% of the participants moved between 1986 and end of follow-up.[15] Effect estimates from case-cohort analyses for the association between air pollution and mortality were higher for subjects who did not move during the follow-up period compared with all subjects, though not significantly so. Effect estimates for subjects who did not move during the follow-up period were for BS overall concentrations 1.13 (95% CI 0.97 – 1.31) for natural cause mortality, 1.12 (95% CI 0.94 – 1.34) for cardiovascular mortality, 1.39 (95% CI 1.01 – 1.90) for respiratory mortality, 1.14 (95% CI 0.88 – 1.48) for lung cancer mortality, and 1.10 (95% CI 0.94 – 1.28) for other mortality.

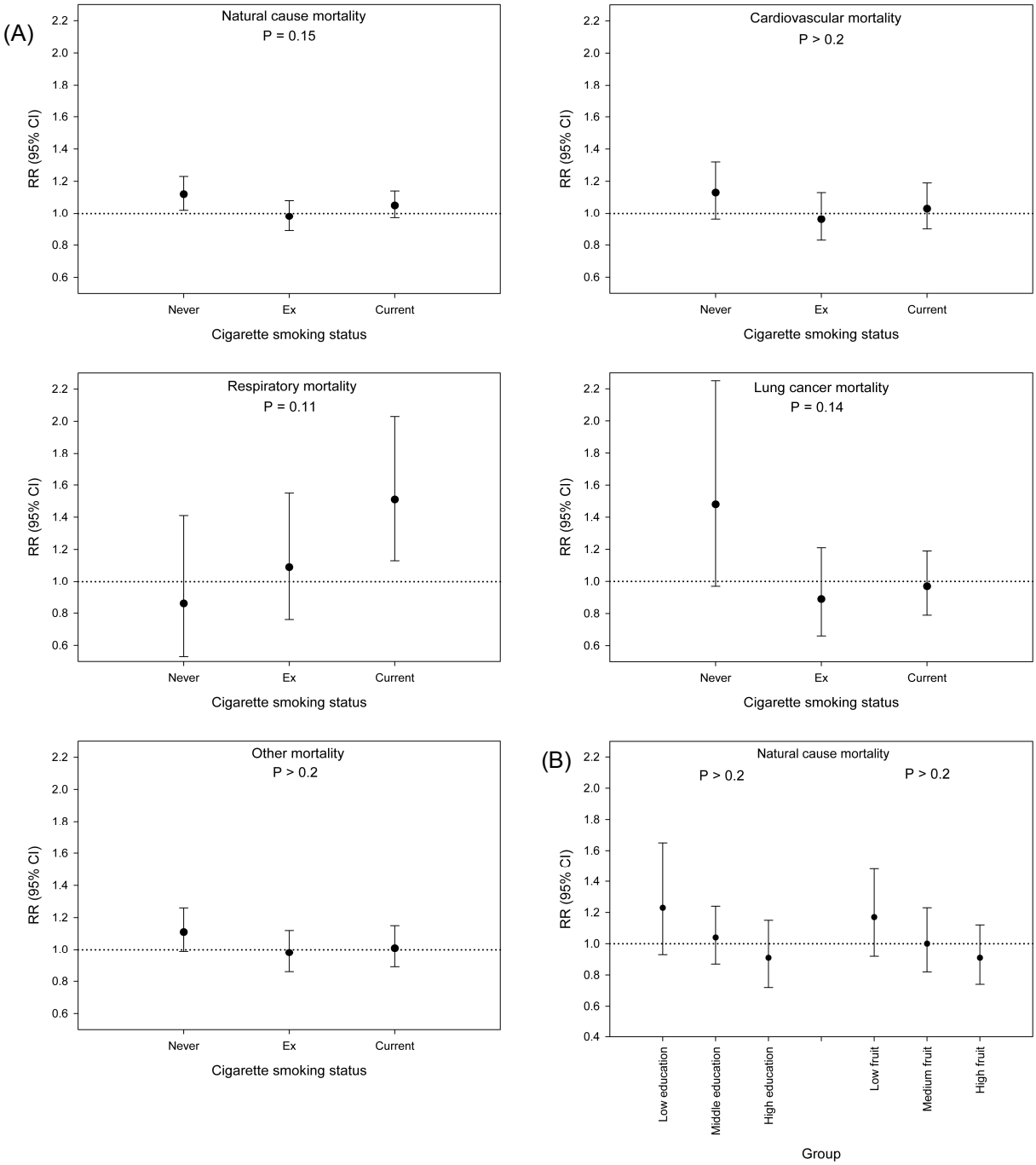
At baseline approximately 85% of the participants had no paid job. Effect estimates of case-cohort analyses for natural cause mortality were not different for participants who had no paid job at baseline (1.05 (95% CI 0.91 – 1.21) and for participants who had a paid job at baseline (0.97 (95% CI 0.74 – 1.29)), and did not differ with the results for the entire case-cohort sample. Results for the other mortality outcomes were similar.

Figure 2. Adjusted RRs and 95% CIs of spatial analyses for association between cardiopulmonary mortality and black smoke background concentration (period 1987 – 1996) and traffic intensity on the nearest road in the full cohort (N = 107,005).[a]



[a] RRs and 95% CIs are shown for the original, 1-level neighborhood independent-clusters (analysis a), 1-level municipality independent-clusters (analysis b), 2-level independent-clusters (analysis c), 1-level neighborhood distance-decay (analysis d), 1-level municipality distance-decay (analysis e), and 2-level distance-decay (analysis f) analyses (used confounders are age, gender, smoking status, and area level indicators of socio-economic status).

Figure 3. RRs and 95% CIs for association between black smoke overall concentration (period 1987-1996) and cause-specific mortality in subgroups for (A) cigarette smoking status in the full cohort dataset, and (B) by education and fruit consumption in the case-cohort dataset.[a]



[a] Education of the household coded as Low = Only primary school; Middle = Lower vocational education; and High = Junior high school, senior high school, higher vocational education, and university. Fruit consumption divided in tertiles: Low: 0 - 96.8 g/day; Medium: 96.8 - 191.8 g/day; and High: >191.8 g/day.
Adjusted for age, gender, smoking status, and area level indicators of socio-economic status.
P-value is p-value of Cochran's Q test for heterogeneity.

Discussion

In the full cohort, traffic-related air pollution and several traffic exposure variables were associated with mortality. Relative risks were generally small. Statistically significant associations between NO_2 and BS exposure and natural cause and respiratory mortality were found. The highest relative risks were found for respiratory mortality. Relative risks were also elevated but not significant for mortality other than cardiovascular, respiratory or lung cancer mortality.

For the first time in Europe, we now report a relative risk estimate for $PM_{2.5}$ based on $PM_{2.5}$ derived from monitored PM concentrations. Effect estimates for $PM_{2.5}$ for the full cohort analyses, although not statistically significant, were quantitatively comparable for natural cause mortality to those of the ACS study in the U.S.[4] In the ACS study strongest associations were found between cardiovascular mortality and fine particulate exposure, while we found only slightly, not significantly elevated risks for $PM_{2.5}$ exposure and this subcategory of mortality. The ACS study [22] and the extended follow-up of the Six Cities study [6] were unable to address traffic intensity variables for which we found some associations with especially respiratory mortality. Our findings are coherent with other cohort studies that reported significant associations between respiratory mortality and long-term exposure to air pollution.[3,9] Numerous studies have also found effects of long-term and short-term exposure to air pollution on respiratory morbidity.[23,24] Further, time-series studies have found associations between short-term changes in air pollution and both cardiovascular and respiratory mortality.

We also found non-significantly elevated risks for the association between mortality other than cardiopulmonary or lung cancer mortality and overall air pollution. This mortality outcome includes, however, several cancer types and other mortality outcomes that might also be associated with air pollution.

A study in a subpopulation of the ACS study in Los Angeles estimated exposure to $PM_{2.5}$ at an intraurban scale.[5] Relative risks associated with a 10 $\mu g/m^3$ increase of $PM_{2.5}$ concentrations were 1.17 (95% CI 1.05 – 1.30) for all-cause, 1.12 (95% CI 0.97 – 1.30) for cardiopulmonary, and 1.44 (95% CI 0.98 – 2.11) for lung cancer mortality. The results suggested that the health effects associated with within-city gradients in $PM_{2.5}$ concentrations may be larger than previously found across metropolitan areas.[5] A recent large cohort study on long-term exposure to fine particulate air pollution and cardiovascular events among postmenopausal women in 36 U.S. metropolitan areas also found that effect estimates within cities were larger than effect estimates between cities. The risk of cardiovascular death with higher levels of $PM_{2.5}$ was larger than the estimates reported in the previous U.S. cohort studies. A relative risk of 1.76 (95% CI 1.25 – 2.47) was found for cardiovascular mortality for an

increase of 10 μg/m^3 in $PM_{2.5}$ concentrations.[7] In the current study we assessed air pollution on an even finer spatial scale than the Jerrett[5] and Miller[7] studies, as we took traffic near the home into account, but we nevertheless found RR estimates for $PM_{2.5}$ that were more comparable to the national ACS study, which assessed between-city variability of concentrations.

In the current study, we refined the traffic exposure variables by using a more precise road network and adding actual traffic intensity data to the network compared to the previous study.[8] With these more refined traffic variables we did observe associations with cause-specific mortality, but the effect estimates were smaller than reported previously for the less refined exposure indicator in a random subgroup of the full cohort. This is related in part to sampling from the full cohort and to the difference in follow-up: adding an extra two years of follow-up reduced the relative risk for living near a major road in the subcohort from 1.95 to 1.34. The previous study results were based on about only 500 deaths and a small number of study subjects producing wide confidence intervals.

In a reanalysis of two US cohort studies, Krewski et al. found that persons with the lowest education experienced the largest health effects from air pollution.[25] We found in the case-cohort analyses suggestive evidence for higher effects for BS in those with low education and in those with low fruit consumption. Low fruit consumption occurred significantly more in low education households, suggesting that the possible modifying effect of education on air pollution estimates may result from differences in fruit consumption between subjects with different educational levels. Fruit consumption may protect against oxidative stress which is one of the main pathways from air pollution to health effects.[26] However, this is but one of a series of differences in potential risk factors that are related to educational level (e.g. physical activity patterns or other dietary habits).

Although not statistically significantly different, the effect estimates for natural cause and lung cancer mortality were higher among never smokers, while the effect estimates for respiratory mortality were higher among current smokers. We do not have an explanation for this. Stronger associations between air pollution and lung cancer mortality in never smokers have been observed in the large ACS study as well,[4] while for respiratory mortality the RRs for never, ex and current smokers were all close to unity.[22]

For subjects who did not move during the follow-up period, higher effect estimates were found for the BS overall concentrations than in all subjects. Such results could be related to more accurate exposure assessment for subjects who did not move. Because moving is a time-dependent variable, a limitation of this analysis is that we restricted the analysis only to the subjects who did not move during the follow-up period, ignoring the person-years that subjects lived at their baseline address before

they moved. This may have created bias.[27] The association between air pollution and mortality will still probably not differ for subjects who did not move and for subjects living at their baseline address before they moved.

Background concentrations showed a decrease over time,[15] but the correlations between the periods 1976-1985 and 1987-1996 were high (>0.9). Therefore it was difficult to evaluate which time period was most important in relation to health effects. The spatial correlation between different pollutants was also high.[15] This makes it very difficult to isolate the health effects of individual pollutants as they act as indicators of a mixture of air pollutants coming from the same sources.[28]

We only used traffic intensity data for the year 1986. Traffic intensities increased over time, but the correlations between traffic intensities from 1986 and traffic intensities from the years during follow-up were all > 0.92, supporting the use of traffic intensities from one year to represent a long-term average.[15] However, the high correlations made it difficult to assess which traffic intensity years are most important in relation to adverse health effects.

The results may not necessarily apply to current situations as emissions per vehicle have decreased in the last decades due to technical innovations and use of catalytic converters. However, the number of vehicles has increased in the same time period and important pollutants such as nitrogen dioxide, ultrafine particles and (diesel) soot are still being emitted.

A limitation of the exposure assessment method is that we only assessed outdoor concentrations at the baseline residential address, not taking into account factors related to infiltration of outdoor air pollution into the home such as air exchange rate. The questionnaire did not contain information about the work address. However, approximately 85% of the population had no paid job at baseline. Further, we had no information about the time participants spent at home or about the time commuting in traffic. The resulting misclassification is however likely to be non-differential.

In conclusion, we found that traffic-related air pollution and several traffic exposure variables were associated with mortality in the full cohort. Relative risks were generally small. Associations between natural cause and respiratory mortality were statistically significant for NO_2 and BS. These findings add to the evidence found in studies on the health effects of long-term exposure to air pollution concentrations. Although the relative risks were small, the public health impact of exposure to air pollution may be substantial due to the large exposed population.

Appendix: Differences between full cohort and case-cohort analyses

Essential in the NLCS-AIR study is that complete confounder information is only available for the subcohort and for subjects who died or developed cancer during follow-up. As a result, analyses adjusted for all available confounders from the questionnaire are only possible using the case-cohort approach. These potential confounders were chosen a priori (age, gender, BMI, active smoking, passive smoking, education, occupational exposure, marital status, alcohol use, vegetable intake, fruit intake, energy intake, fatty acids intake, folate intake, fish consumption, and area level socio-economic status variables). For the full cohort analyses only a limited number of confounders are available (age, gender, smoking status and area level socio-economic status variables).

Adjusting for all available confounders in the case-cohort analyses with the large confounder model led to a strong reduction of the number of subjects available for analysis (~60% of the original number) because of missing values in confounder variables. In the full cohort analyses this reduction was much smaller (~90% available for analysis) due to the limited number of confounders. This appendix includes the results of two sets of analyses we conducted to help interpret the results with the case-cohort and the full cohort approach. First, we assessed the impact of different models / populations on the effect estimates. Second, we assessed the role of random variability by repeating the case-cohort analyses after randomly drawing 100 new subcohorts from the full cohort.

Impact of confounder models and populations

We assessed four analysis models that differed in treatment of confounders: 1) adjusted for age and gender; 2) adjusted for all available confounders; 3) adjusted for age and gender, but only including the subjects that had complete information for all possible confounders included in model 2; and 4) adjusted only for the limited number of confounders available in the full cohort, but only including the subjects that had complete information for all possible confounders included in the model 2.

In the case-cohort dataset among the natural cause mortality cases 39.4% had a partner who never smoked, while 24.7% had a partner who was a former smoker and 35.9% had a partner who was a current smoker. For the subcohort members these percentages were 33.2%, 31.2% and 35.6%, respectively. Among the cases 18.5% was low exposed and 7.8% was high exposed to biological dust, with the remaining 73.7% being classified as non-exposed. Among the subcohort members 22.1% was low and 6.3% was high exposed to biological dust. For exposure to mineral dust the percentages low and high exposed were also slightly higher for the cases compared with the subcohort members: 17.0% versus 15.0% for low exposure, and 11.1% and

8.2% for high exposure. Among the cases 28.5% was low exposed to gases and fumes, and 11.8% was high exposed, while for the subcohort members these percentages were 25.9% and 8.9%, respectively. The median fruit consumption among cases was 137.2 g/day (interquartile range: 70.4 – 221.0 g/day); for subcohort members the median fruit consumption was 153.3 g/day (89.0 – 233.5 g/day). The median vegetable consumption was also slightly higher among subcohort members: 178.3 g/day (133.7 – 232.0 g/day), compared with the cases: 168.6 g/day (124.1 – 222.5 g/day).

Results of the confounder analyses are shown in Table 1 for the black smoke (BS) background concentration and the traffic intensity on the nearest road for the various mortality outcomes. Important differences between the effect estimates of the BS background concentrations in the age-gender adjusted model and the age-gender adjusted model with only subjects with complete confounder information were found in the case-cohort analyses for all mortality outcomes, showing that the occurrence of missing values introduced bias in the effect estimates of the background concentration. This difference was much smaller for the traffic variables in the case-cohort analyses. Similar analyses in the full cohort with the limited set of confounders showed much less evidence of such a selection effect for both background concentrations and traffic variables. The results also showed that in the case-cohort analyses there was little difference between the effect estimates adjusted for all available confounders and the effect estimates adjusted for the limited number of confounders in the full cohort, suggesting that inclusion of the full set of potential confounder variables in fact made little difference in the case-cohort analysis.

The biggest difference was for respiratory mortality where the effect estimate of the model adjusted for all available confounders for the background concentration in the case-cohort analysis was higher than for the age-gender adjusted models or the model adjusted for the limited number of confounders available in the full cohort. This does suggest, but not guarantee, that the pattern of adjustment would be the same in the full cohort analysis if data on all confounders had been available for analysis.

We investigated whether information of specific confounders in the case-cohort analysis were primarily responsible for this selection effect. However, not just one or two confounders were responsible for the reduction in the number of subjects available for analysis, and therefore responsible for the selection effect, but the combination of all available confounders in the case-cohort analysis was responsible for the selection effect.

Role of random variability

Table 1 also shows that the results of the age-gender adjusted model for the case-cohort and full cohort analyses produced nearly identical results for background concentrations but not for traffic intensity on the nearest road. The traffic variable was positively associated with natural cause, cardiovascular, respiratory and lung cancer mortality in the full cohort analyses, but there were no associations in the case-cohort analyses.

We further explored this issue by randomly generating one hundred subcohorts of 5,000 subjects from the complete study population, and then repeating the age-gender adjusted case-cohort analysis using each of these one hundred subcohorts in turn as reference. The results for cardiopulmonary mortality are shown in Table 2. The average RRs of the 100 case-cohort analyses were, as expected, very close to the RR obtained in the full cohort. According to expectations under normal sampling theory, the RRs of the 100 case-cohort analyses varied, with the effect estimates of the original case-cohort analyses clearly within the range of effect estimates of the 100 new case-cohort analyses. However, the results also indicate that for the variables “traffic intensity on the nearest road” and “living near a major road” the results of the age and gender adjusted case-cohort analysis using the original subcohort are different from what was found for the average of the 100 randomly drawn subcohorts. For the other exposure variables there was no such difference. These results suggest that the effect estimates in the case-cohort analyses can be sensitive to sampling variation, i.e. sensitive to the selection of the subcohort even though it was completely random, probably due to the small fraction of high exposed subjects (“living near a major road”) and the skewness of the exposure distribution (“traffic intensity on the nearest road” – see also Figure 1 in main text). This sampling variation results in effect estimates that do not reflect the underlying effect estimates in the study population as a whole.

Table 1. Relative risks (95% CIs) for the association between background concentration (period 1987-1996) and traffic intensity with cause-specific mortality in case-cohort and full cohort analyses, using different confounder models.

Exposure model	Confounder model [a]	Population [a]	Case-cohort analyses	N [b]	Full cohort analyses	N [b]
Natural cause mortality						
Black smoke background	Age-gender adjusted	All	1.15 (0.97 – 1.35)	21,457	1.14 (1.07 – 1.22)	117,499
Traffic intensity on nearest road			0.99 (0.91 – 1.08)		1.04 (1.00 – 1.08)	
Black smoke background	Fully adjusted	Complete confounder data	0.99 (0.75 – 1.31)	12,720	1.09 (1.00 – 1.19)	105,296
Traffic intensity on nearest road			0.99 (0.88 – 1.11)		1.03 (1.00 – 1.08)	
Black smoke background	Age-gender adjusted	Complete confounder data	1.03 (0.83 – 1.28)	12,720	1.15 (1.07 – 1.24)	105,296
Traffic intensity on nearest road			1.00 (0.90 – 1.12)		1.04 (1.01 – 1.09)	
Black smoke background	Partially adjusted	Complete confounder data	0.99 (0.76 – 1.19)	12,720	-	-
Traffic intensity on nearest road			0.98 (0.88 – 1.09)		-	-
Cardiovascular mortality						
Black smoke background	Age-gender adjusted	All	1.14 (0.94 – 1.38)	10,762	1.14 (1.02 – 1.28)	117,499
Traffic intensity on nearest road			1.00 (0.91 – 1.10)		1.06 (1.00 – 1.13)	
Black smoke background	Fully adjusted	Complete confounder data	1.00 (0.72 – 1.40)	6,510	1.11 (0.96 – 1.28)	105,296
Traffic intensity on nearest road			1.03 (0.90 – 1.17)		1.05 (0.99 – 1.12)	
Black smoke background	Age-gender adjusted	Complete confounder data	1.05 (0.81 – 1.36)	6,510	1.16 (1.03 – 1.31)	105,296
Traffic intensity on nearest road			1.02 (0.91 – 1.16)		1.06 (1.00 – 1.13)	
Black smoke background	Partially adjusted	Complete confounder data	1.01 (0.74 – 1.39)	6,510	-	-
Traffic intensity on nearest road			1.00 (0.88 – 1.13)		-	-
Respiratory mortality						
Black smoke background	Age-gender adjusted	All	1.42 (1.01 – 2.00)	5,847	1.41 (1.06 – 1.88)	117,499
Traffic intensity on nearest road			1.04 (0.91 – 1.19)		1.13 (0.99 – 1.27)	
Black smoke background	Fully adjusted	Complete confounder data	1.52 (0.80 – 2.88)	3,607	1.22 (0.86 – 1.74)	105,296
Traffic intensity on nearest road			0.94 (0.71 – 1.25)		1.10 (0.95 – 1.26)	
Black smoke background	Age-gender adjusted	Complete confounder data	1.31 (0.82 – 2.10)	3,607	1.34 (0.99 – 1.82)	105,296
Traffic intensity on nearest road			1.01 (0.80 – 1.27)		1.11 (0.97 – 1.27)	
Black smoke background	Partially adjusted	Complete confounder data	1.33 (0.77 – 2.31)	3,607	-	-
Traffic intensity on nearest road			0.97 (0.77 – 1.21)		-	-

Table 1 continued

Exposure model	Confounder model [a]	Population [a]	Case-cohort analyses	N [b]	Full cohort analyses	N [b]
Lung cancer mortality						
Black smoke background	Age-gender adjusted	All	1.17 (0.89 – 1.53)	6,692	1.15 (0.94 – 1.42)	117,499
Traffic intensity on nearest road			1.00 (0.89 – 1.13)		1.06 (0.95 – 1.18)	
Black smoke background	Fully adjusted	Complete confounder data	1.02 (0.61 – 1.71)	4,075	1.01 (0.78 – 1.32)	105,296
Traffic intensity on nearest road			1.03 (0.87 – 1.22)		1.07 (0.96 – 1.19)	
Black smoke background	Age-gender adjusted	Complete confounder data	1.03 (0.71 – 1.48)	4,075	1.09 (0.87 – 1.37)	105,296
Traffic intensity on nearest road			1.07 (0.92 – 1.24)		1.09 (0.97 – 1.21)	
Black smoke background	Partially adjusted	Complete confounder data	0.93 (0.59 – 1.48)	4,075	-	-
Traffic intensity on nearest road			1.01 (0.86 – 1.17)		-	-
Other mortality						
Black smoke background	Age-gender adjusted	All	1.12 (0.94 – 1.33)	13,098	1.11 (1.01 – 1.22)	117,499
Traffic intensity on nearest road			0.97 (0.89 – 1.05)		1.00 (0.95 – 1.06)	
Black smoke background	Fully adjusted	Complete confounder data	0.95 (0.71 – 1.26)	7,883	1.09 (0.96 – 1.23)	105,296
Traffic intensity on nearest road			0.93 (0.82 – 1.06)		1.00 (0.94 – 1.06)	
Black smoke background	Age-gender adjusted	Complete confounder data	0.98 (0.78 – 1.23)	7,883	1.13 (1.02 – 1.26)	105,296
Traffic intensity on nearest road			0.96 (0.85 – 1.08)		1.00 (0.95 – 1.06)	
Black smoke background	Partially adjusted	Complete confounder data	0.96 (0.73 – 1.25)	7,883	-	-
Traffic intensity on nearest road			0.94 (0.84 – 1.06)		-	-

[a] Used confounder models: *Age-gender adjusted*: adjusted for age and gender; *Fully adjusted*: adjusted for all available potential confounders; and *Partially adjusted*: adjusted only for confounders of the limited full cohort confounder model.
Populations: *All*: All subjects; and *Complete confounder data:* Only including the subjects that had complete information for all possible confounders included in the fully adjusted confounder model.
Used confounders in fully adjusted confounder model:
Case-cohort analysis: age, gender, BMI, active smoking, passive smoking, education, occupational exposure, marital status, alcohol use, vegetable intake, fruit intake, energy intake, fatty acids intake, folate intake, fish consumption, and area level indicators of socio-economic status.
Full cohort analysis: age, gender, smoking status, and area level indicators of socio-economic status.
RRs were calculated for concentration changes from the 5th to the 95th percentile: 10 µg/m^3 for BS and 10,000 mvh/24 h for traffic intensity on the nearest road.
[b] N is the number of observations available for analysis. The number of observations in case-cohort analyses is the sum of subcohort members and the number of mortality cases of the studied cause.

Table 2. Distribution of RR estimates and 95% CIs for cardiopulmonary mortality from case-cohort analyses of 100 randomly drawn subcohorts, and RRs of the case-cohort analyses with original subcohort and RRs of the full cohort analyses (adjusted for age and gender).[a]

Exposure model	RR (95%-CI) for case-cohort with original subcohort	RR (95%-CI) for full cohort	Average RR (min – max) [SD] of 100 case-cohort analyses
Black smoke background	1.17 (0.97 – 1.42)	1.17 (1.05 – 1.30)	1.16 (0.97 – 1.38) [0.09]
Traffic intensity on nearest road	1.01 (0.92 – 1.11)	1.07 (1.02 – 1.13)	1.08 (0.90 – 1.26) [0.05]
Black smoke background	1.13 (0.93 – 1.38)	1.16 (1.04 – 1.29)	1.15 (0.94 – 1.41) [0.09]
Traffic intensity in a 100 m buffer	1.08 (0.95 – 1.22)	1.06 (0.99 – 1.14)	1.07 (0.89 – 1.21) [0.06]
Black smoke background	1.18 (0.97 – 1.42)	1.18 (1.06 – 1.31)	1.17 (0.98 – 1.39) [0.09]
Living near a major road	1.00 (0.83 – 1.21)	1.10 (0.99 – 1.22)	1.10 (0.84 – 1.37) [0.09]

[a] RRs were calculated for concentration changes from the 5th to the 95th percentile: 10 µg/m^3 for BS background/overall estimate; for the traffic intensity on the nearest road: 10,000 mvh/24h, for the sum of traffic intensity in a buffer of 100 m: 335,000 mvh/100m. RRs for living near a major road were calculated with as reference category not living near a major road.

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Chapter 4

Long-term exposure to traffic-related air pollution and lung cancer risk in a Dutch cohort

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Abstract

Most studies on the association between lung cancer and air pollution investigated mortality, but fewer investigated lung cancer incidence. We investigated the influence of traffic-related air pollution on lung cancer incidence.

We used data from an ongoing cohort study on diet and cancer (NLCS) with 120,852 subjects with follow-up from September 1986 to December 1997. Exposure to black smoke (BS), nitrogen dioxide (NO_2), sulfur dioxide (SO_2) and particulate matter ≤ 2.5 μm ($PM_{2.5}$) for the periods 1976-1985 and 1987-1996 and various traffic intensity variables were estimated at the home address. We conducted Cox proportional hazard analyses in the full cohort adjusting for age, gender, smoking status and area-level socio-economic status, and case-cohort analyses using more potential confounders.

Relative risks (RR) for the overall air pollution concentrations were slightly below unity, but not statistically significant. RRs for the traffic variables were slightly elevated. In the full cohort, the RRs (95% CI) were 1.05 (0.94 – 1.16) for traffic intensity on the nearest road and 1.11 (0.91 – 1.34) for living near a major road. RRs were elevated among never smokers, with RRs of 1.47 (1.01 – 2.16) for overall BS concentration, 1.11 (0.88 – 1.41) for the traffic intensity, 1.55 (0.98 – 2.43) for living near a major road.

We found evidence for an association between black smoke and lung cancer incidence in never smokers. Exposure to traffic was also associated with borderline elevated risks among never smokers. No associations were found for the full cohort or other smoking categories.

Introduction

Most studies on long-term exposure to air pollution and lung cancer risk have investigated the association with lung cancer *mortality*. Fine particles were predictors of the risk of lung cancer mortality in the extended follow-ups of the Six Cities cohort study[1] and the ACS cohort study.[2] Evidence that air pollution is a (moderate) risk factor for lung cancer mortality was also found in several case-control studies,[3,4] with effect estimates that were of the same order of magnitude as the ones estimated from the limited number of cohort studies.[5]

Few studies have investigated the association between air pollution and lung cancer *incidence*.[6-9] Advantages of using cancer incidence data instead of mortality data are that mortality data are more often misclassified (e.g. metastasis in the lung recorded as lung cancer), and not all patients with cancer die (although this is less applicable to lung cancer for which the prognosis is bad).

In the AHSMOG cohort, incident lung cancer was associated with long-term exposure to ambient concentrations of fine particles and sulfur dioxide.[6] The AHSMOG study is conducted in adult Seventh Day Adventists, who are largely non-smoking. A nested case-control study within EPIC among non-smokers found associations between the nitrogen dioxide concentration and lung cancer incidence.[7] Two studies in Scandinavia found elevated relative risks for traffic-related air pollution assessed by nitrogen dioxide concentration at the home address and lung cancer incidence.[8,9]

We conducted a study on the effects of long-term exposure to traffic-related air pollution and lung cancer incidence using an ongoing Dutch cohort study.

Methods

Study design

The cohort has been described in detail.[10] Briefly, the Netherlands Cohort Study on Diet and Cancer (NLCS) was initiated in September 1986 with the enrollment of 120,852 subjects (58,279 males and 62,573 females) aged 55-69 years living in 204 municipalities located throughout the country. The study was designed as a case-cohort study, i.e. cases are derived from the entire cohort, while the person years at risk are estimated from a random subcohort (N ~ 5,000).[11] This approach was chosen for efficiency of baseline questionnaire processing.

At baseline, all participants completed an 11-page questionnaire on dietary habits and other potential risk factors for cancer. For all participants, data from one machine-readable page of the questionnaire were entered at baseline (with

information about smoking status). Further, for all participants information about gender and age at baseline was known. After recruitment, the entire cohort was followed up for cancer. For the emerging cases and the randomly selected subcohort, the remaining 10 questionnaire pages (not machine-readable) were manually entered, blinded with respect to case/subcohort status. The exact residential address at baseline was available for all study participants. We did not have information on the work address or on previous residential addresses. We did have information on the previous cities of residence, but as we assessed exposure to air pollution at the exact address, we did not use this information.

Incident lung cancer cases (International Classification of Diseases for Oncology code (ICD-O-3): C34) were identified by computerized record linkage of the entire cohort to the Netherlands Cancer Registry and the nationwide network and registry of histopathology and cytopathology in the Netherlands (PALGA).[12] The completeness of cancer follow-up was estimated to be over 96%.[13] The follow-up period was 11.3 years, from September 1986 to December 1997. We excluded prevalent cancer cases at baseline other than skin cancer resulting in 114,378 subjects available for analyses.[10]

The NLCS study was approved by institutional review boards from Maastricht University and the Netherlands Organization for Applied Scientific Research (TNO). All cohort members consented to participation by completing the mailed, self-administered questionnaire.

Air pollution exposure assessment

Details of the exposure assessment methods have been described previously, and they were shown to explain a large part of the variations in outdoor air pollution concentrations.[14] In summary, long-term exposure to outdoor air pollution at the geographical coordinate of the 1986 home address was estimated for all participants as the sum of regional, urban and local scale air pollution contributions. We documented that 90% of the participants had lived for 10 years or longer in their 1986 municipality. Mean duration of residence was 35 years (SD 19.8).[15] Regional background concentrations were estimated using inverse distance weighted interpolation of concentrations measured at regional background sites in the National Air Quality Monitoring Network (NAQMN). The additional urban component was estimated using regression models with residual concentrations for all regional background and urban monitoring sites in the NAQMN as dependent variable, calculated as measured concentration minus estimated regional component concentration using interpolation. As predictor variables we used the number of inhabitants around a monitoring site and land-use variables that indicated whether a site was located in a city center, in a rural background location, or in an industrial

location. The sum of the regional and urban contributions was defined as background concentration. Background concentrations were estimated for nitrogen dioxide (NO_2), black smoke (BS) and sulfur dioxide (SO_2). Average concentrations were estimated for 1976-1985 and 1987-1996 (in 1986 the NAQMN was rearranged resulting in only limited days with valid measurements in 1986). Correlations between estimated concentrations for different years were high, even over a period of 20 years (>0.8).[14] The background concentration for fine particles less than 2.5 μm ($PM_{2.5}$) in diameter was made by converting PM_{10} (particles less than 10 μm) concentrations, measured in the NAQMN from 1992 to 1996, into $PM_{2.5}$ concentrations using a single ratio, established from monitoring data in the Netherlands. This was done because $PM_{2.5}$ was not monitored in the Netherlands during the study period.

Local traffic contributions were characterized by traffic variables that were obtained through a Geographic Information System (GIS) from a digital road network to which traffic intensity data from the year 1986 were linked. We used: (1) traffic intensity on nearest road; (2) sum of traffic intensity in a 100 m buffer around each residential address; and (3) an indicator variable 'living within 100 m of a motorway and/or within 50 m of a local road with traffic intensity > 10,000 motor vehicles per 24 hours (mvh/24h)'. We documented that while absolute traffic intensities increased during the follow-up period, traffic intensity data obtained for different years were highly correlated (>0.9), even over a period of 10 years.[14] Further, quantitative estimates for the local component were estimated for NO_2, BS and $PM_{2.5}$ using data from field monitoring campaigns and regression models with traffic variables as predictor variables.[14] We estimated no local traffic contribution for SO_2 as there is virtually no traffic contribution to this pollutant. These local component concentrations were added to the background concentrations resulting in an overall exposure estimate for each pollutant.

Statistical analysis

Air pollution effects were analyzed for overall concentrations of pollutants and for a combination of background concentrations of the pollutants and traffic variables to identify effects of living near busy roads separately.

Relative risks (RR) and 95% confidence intervals (95% CI) were calculated for concentration and traffic variable differences between the 5^{th} and the 95^{th} percentiles of the distributions. For NO_2 this was rounded to 30 μg/m^3, for BS 10 μg/m^3, for SO_2 20 μg/m^3, and for $PM_{2.5}$ 10 μg/m^3. For traffic intensity on the nearest road we used 10,000 mvh/24h and for the sum of traffic intensity in a buffer of 100 m 335,000 mvh/100 m.

We initially conducted analyses in the full cohort using Cox proportional hazards models. Person-years were calculated for all participants from baseline until the date

of lung cancer diagnosis, death or end of follow-up. We adjusted for gender, age at baseline, and smoking status coded as never, ex, and current smoker separately for cigarette, cigar and pipe smoking. We further adjusted for area-level indicators assessed using GIS data from the Central Bureau of Statistics (CBS): percentage of persons with a low and with a high income at the neighborhood scale and the COROP area scale. COROP areas have been defined in 1970 by the Coordination Commission for Regional Research Program such that each COROP area consists of a central point (e.g. a city) and the surrounding economic and social region. The Netherlands is divided in 40 COROP areas. We chose two scales for area-level socio-economic status because life expectancy varies significantly by COROP area,[16] and the neighborhood scale does not capture such regional variations adequately. Low income was defined by the CBS as below the 40th percentile and high income as above the 80th percentile of the Dutch income distribution (Table 1).

For more complete confounder control at the cost of some power loss, we also conducted case-cohort analyses, including only subcohort members and cases. Cases were enumerated from the entire cohort, whereas person years for the entire cohort were estimated using the random subcohort of 4,755 participants. Data were again analyzed with Cox proportional hazards models, but to account for additional variance introduced by sampling from the cohort, standard errors were estimated using the robust Huber-White sandwich estimator.[17]

In the case-cohort analyses we adjusted for the variables chosen a priori for studying the association between air pollution and lung cancer incidence: gender; age at baseline; active cigarette, cigar and pipe smoking coded as current/non-current and number of cigarettes/cigars/pipes and number of years of smoking; passive smoking defined as whether the partner smoked; educational level in three categories: primary school, lower vocational education and high school and higher; occupational exposure during the last occupation to biological dust, mineral dust, and gases and fumes coded as no, low and high exposure assessed using the ALOHA-JEM;[18] alcohol consumption in two categories: 0-30 and > 30 g/day; dietary habits: intake of vegetables (continuous), fruit (in quintiles) and folate (continuous); and the area level indicators of socio-economic status.

As in other cohort studies of air pollution and lung cancer,[6,19] we conducted subgroup analyses for gender, educational level (three categories: primary school, lower vocational education and high school and higher), and fruit consumption (three categories based on tertiles: low (0 – 96.8 g/day), medium (96.8 – 191.8 g/day), and high (>191.8 g/day)). Further, we conducted subgroup analyses for cigarette smoking status (never/ex/current), because the never-smoker group is of particular interest in not being subject to possible residual confounding by the number of cigarettes and number of years of smoking cigarettes. Subgroup analyses for gender and smoking

status were assessed in the full cohort, and subgroup analyses for educational level and fruit consumption were assessed in the case-cohort (information about education and fruit consumption was only available in the case-cohort sample). Heterogeneity in pollution relative risks across estimates from different subgroups was tested using Cochran's Q test.[20]

We conducted sensitivity analyses in the case-cohort for BS and the traffic variables to evaluate the potential confounding effect of the number of cigarettes, cigars and pipe, and the number of years of smoking as no information about this was available in the full cohort. Further, we conducted sensitivity analyses adjusting for occupational exposure to biological dust, mineral dust, and gases and fumes during the longest held occupation instead of the last occupation, as occupational exposure earlier in life may also be important compared with more recent exposure of the last occupation. We also conducted case-cohort analyses adjusted only for the limited confounder model used in the full cohort analyses and compared the RRs with the RRs obtained with the complete set of potential confounders.

Data management was done using SPSS 12.0 (SPSS Inc, Chicago, US), and statistical analyses were conducted using STATA statistical software 8 (STATA Corporation, College Station, US). GIS calculations were conducted using ArcInfo (ESRI, Redlands, US).

Results

During 11.3 years of follow-up, 2,183 lung cancer cases occurred. For 98% of the subjects a geographical coordinate at baseline was identified (N = 111,816 in full cohort). Table 1 shows the characteristics of the subjects in the full cohort for which a coordinate was available. Lung cancer cases were older, predominantly men and more likely current smoker compared to non-cases. Lung cancer cases did not differ from non-cancer cases in the are-level socio-economic status.

Air pollution exposure data

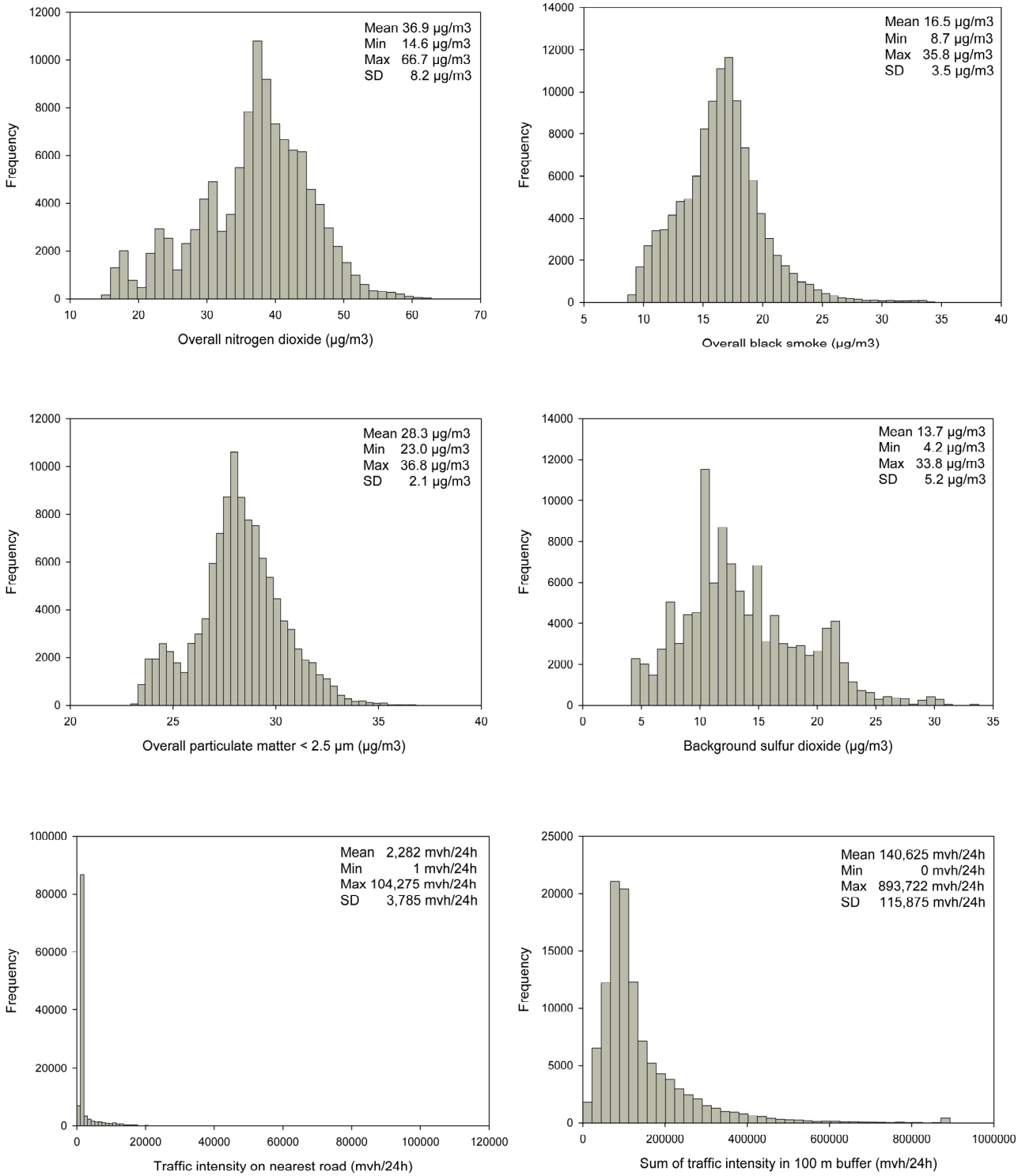
There was a considerable air pollution exposure contrast in the full cohort (Figure 1). Distributions were similar for different time periods. Estimated concentrations between the periods 1976-1985 and 1987-1996 were highly correlated (> 0.9) for each pollutant. The correlations between different pollutants within the same period were all > 0.8, except for SO_2 for which correlations were > 0.6.[14] 5,481 subjects (4.9%) lived within 50 m of a road > 10,000 mvh/24h and/or within 100 m of a motorway. Correlations between background BS and traffic intensity on the nearest

road and sum of traffic intensity in a 100 m buffer were modest: 0.12 and 0.28, respectively. More detail on the exposure variables has been reported before.[14]

Table 1. Descriptive characteristics of lung cancer incidence cases and non-lung cancer cases in the full cohort (among subjects for which a coordinate was available (N = 111,816)). Values are number (%) or median (Inter Quartile Range).

Characteristic	**Cases (N = 2,183)**	**Non-cases (N = 109,633)**
Men	1,882 (86.2%)	53,028 (48.4%)
Age at baseline (years)	63 (59 – 66)	61 (58 – 65)
Cigarette smoking status		
Never	278 (13.5%)	42,315 (41.1%)
Ex	520 (25.3%)	32,733 (31.8%)
Current	1,256 (61.2%)	27,929 (27.1%)
Cigar smoking status		
Never	1,616 (76.4%)	92,007 (87.5%)
Ex	156 (7.4%)	7,356 (7.0%)
Current	344 (16.3%)	5,741 (5.5%)
Pipe smoking status		
Never	1,922 (90.2%)	98,427 (93.3%)
Ex	80 (3.8%)	4,794 (4.5%)
Current	128 (6.0%)	2,282 (2.2%)
% persons with low income in neighborhood	41 (37 – 48)	41 (36 – 46)
% persons with high income in neighborhood	18 (12 – 24)	19 (13 – 25)
% persons with low income in a COROP area	41 (36 – 45)	41 (36 – 45)
% persons with high income in a COROP area	19 (18 – 23)	19 (18 – 23)

Figure 1. Distributions of estimated black smoke, NO_2, $PM_{2.5}$ and SO_2 concentrations (period 1987-1996), and of the traffic intensity on the nearest road and the sum of traffic intensity in a 100 m buffer, at the 1986 home address (N = 111,816).



Association between lung cancer incidence and air pollution concentrations
Table 2 shows the relative risks for exposure to average BS, $PM_{2.5}$, NO_2 and SO_2 concentrations during the period 1987-1996. In both the full cohort and case-cohort analyses, effect estimates for all pollutants were below one, but not significantly different from unity. Average concentrations for the period 1976-1985 were only available for NO_2 and SO_2. The RRs for NO_2 were 0.91 (95% CI 0.76 – 1.08) and 0.98 (95% 0.69 – 1.40) for full cohort and case-cohort analyses, respectively. Corresponding figures for SO_2 for the period 1976-1985 were 0.94 (95% CI 0.84 – 1.07) and 0.96 (95% CI 0.75 – 1.21). There were no differences between the RRs for the two periods, consistent with the high correlation of the concentrations for the two time periods.

The RRs for the traffic variables were slightly elevated for both the full cohort and case-cohort analyses, but not statistically significant (Table 3). Risk estimates of the traffic variables did not depend on the specific background exposure with which it was modeled simultaneously, so we present for the traffic relative risks from models with just one pollutant - BS concentrations for the period 1987-1996.

Table 2. Adjusted relative risks (95% CI) for association between lung cancer incidence and average BS, NO_2, $PM_{2.5}$ and SO_2 concentrations during the period 1987-1996 in full cohort and case-cohort analyses (increment used to calculate RRs for each pollutant).[a]

Pollutant	Full cohort	Case-cohort
Number of cases (total person years)	*1,940 (1,053,330)*	*1,295 (31,536)*
BS (10 µg/m^3)	0.96 (0.83-1.11)	1.03 (0.78 – 1.34)
NO_2 (30 µg/m^3)	0.86 (0.70-1.07)	0.86 (0.57 – 1.29)
$PM_{2.5}$ (10 µg/m^3)	0.81 (0.63-1.04)	0.65 (0.41 – 1.04)
SO_2 (20 µg/m^3)	0.90 (0.72-1.11)	1.01 (0.67 – 1.54)

[a] *Full cohort analyses* adjusted for age, gender, cigarette, cigar and pipe smoking status, and area level indicators of socio-economic status.
Case-cohort analyses adjusted for age, gender, active cigarette, cigar and pipe smoking, passive smoking, educational level, occupational exposure to biological dust, mineral dust, and gases and fumes, alcohol consumption, intake of vegetables, fruit and folate, and area level indicators of socio-economic status.
BS, $PM_{2.5}$ and NO_2 are quantitative overall concentrations. SO_2 is background concentration (including traffic intensity on nearest road in model).

Table 3. Adjusted relative risks (95% CI) for association between lung cancer incidence and traffic variables in full cohort and case-cohort analyses.[a]

Traffic variable	Full cohort	Case-cohort
Traffic intensity on nearest road	1.05 (0.94 – 1.16)	1.02 (0.87 – 1.18)
Living near a major road	1.11 (0.91 – 1.34)	1.10 (0.74 – 1.62)
Traffic intensity in a 100 m buffer	1.05 (0.92 – 1.19)	1.07 (0.84 – 1.36)

[a] Increment used to calculate RRs: for the traffic intensity on the nearest road: 10,000 mvh/24h, and for the sum of traffic intensity in a buffer of 100 m: 335,000 mvh/100m. RRs for living near a major road were calculated with as reference category not living near a major road. All models included the black smoke background concentration for the period 1987-1996 as background concentration.
The used confounders and number of cases (person years) for the full cohort and case-cohort analyses are shown in Table 2.

Subgroup analyses

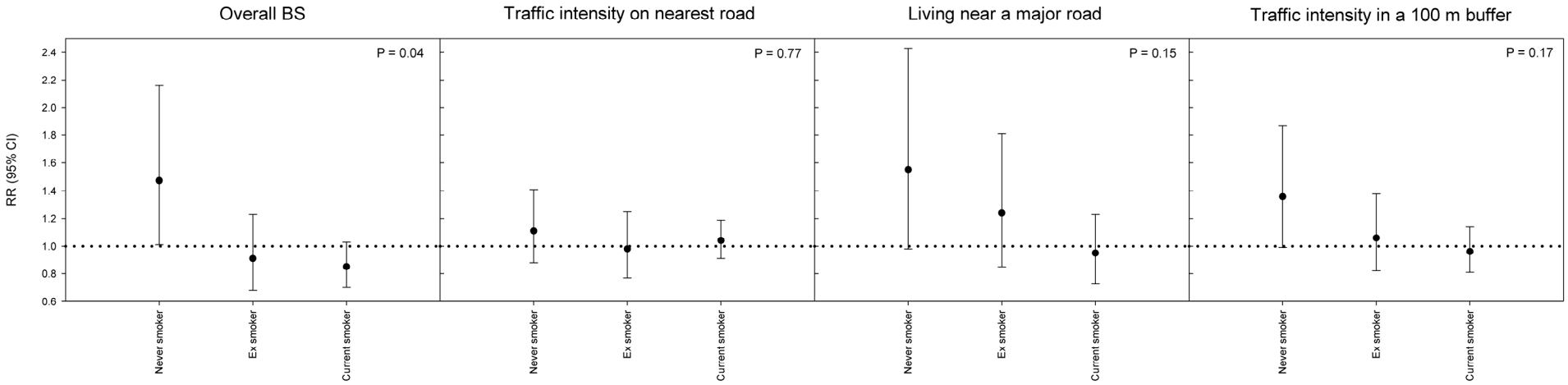
RR estimates for BS overall concentrations and traffic variables tended to differ for never (40,115 participants; 252 cases), ex (32,032; 500) and current smokers (28,031; 1,188) in the full cohort, with some of the differences being statistically significant (Figure 2A). Elevated relative risks among never smokers were found: 1.47 (95% CI 1.01 – 2.16) for BS overall, 1.11 (95% CI 0.88 – 1.41) for traffic intensity on the nearest road, 1.55 (95% CI 0.98 – 2.43) for living near a major road, and 1.36 (95% CI 0.99 – 1.87) for the traffic intensity in a 100 m buffer. A similar pattern was found for BS background concentrations.

There were no differences between the effect estimates for men and women for both BS concentrations and traffic variables (data not shown).

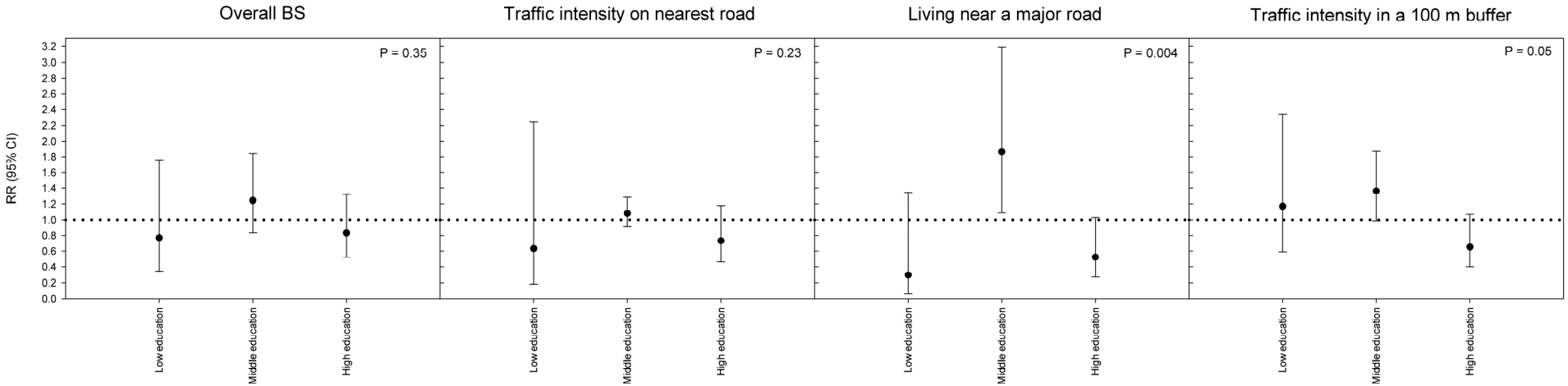
In the case-cohort analyses, no consistent differences in effect estimates were found for different educational levels (Figure 2B). Effect estimates for different fruit consumption groups tended to be higher for subjects with low fruit consumption, except for living near a major road for which no differences in effect estimates were found (Figure 2C).

Figure 2. Association (RR (95% CI)) between lung cancer incidence and black smoke overall concentration (period 1987-1996) and traffic variables in subgroups: A) cigarette smoking status (in the full cohort dataset); B) education (in the case-cohort dataset); and C) fruit consumption (in the case-cohort dataset).[a]

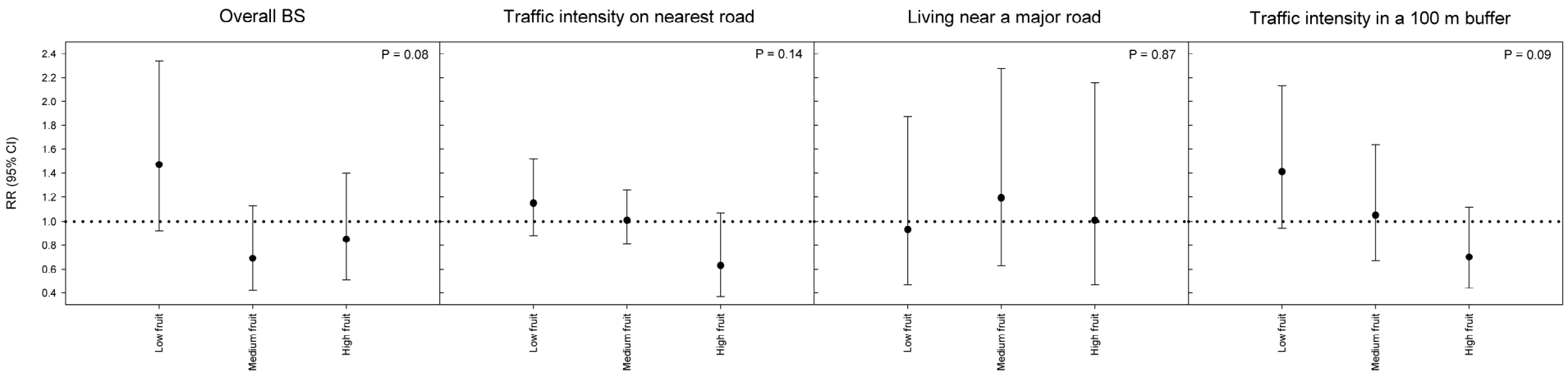
A) Subgroup analyses for cigarette smoking status



B) Subgroup analyses for education



C) Subgroup analyses for fruit consumption



[a] Highest education of the household coded as Low = Only primary school; Middle = Lower vocational education; and High = Junior high school, senior high school, higher vocational education, and university. Fruit consumption divided in tertiles: Low: 0 - 96.8 g/day; Medium: 96.8 - 191.8 g/day and High: >191.8 g/day. Used confounders are shown below Table 2.
P-value is p-value of Cochran's Q test for heterogeneity.

Sensitivity analyses

Adjusted case-cohort analyses showed that there were no differences in the effect estimates for overall BS concentrations for models with (RR 1.03; 95% CI 0.78 – 1.34) and without (RR 1.01; 95% CI 0.78 – 1.32) the number of cigarettes, cigars and pipes, and the number of years of smoking. There were also no differences between the effect estimates for the traffic variables.

There was no difference in the RRs for BS concentrations and traffic variables when including occupational exposure to biological dust, mineral dust, and gases and fumes during the longest held occupation in the confounder model (for BS: RR 1.03 (95% CI 0.78 – 1.34)) compared when including occupational exposure during the last occupation in the confounder model (for BS: RR 1.01 (95% CI 0.76 – 1.33)).

The RRs of case-cohort analyses adjusted for the limited confounder model used in the full cohort analyses were 0.92 (95% CI 0.74 – 1.13) for BS, 0.98 (95% CI 0.86 – 1.10) for the traffic intensity on the nearest road, 1.07 (95% CI 0.80 – 1.43) for living near a major road, and 1.10 (95% CI 0.83 – 1.22) for the traffic intensity in a 100 m buffer.

Discussion

In the full cohort, we found no association between air pollution concentrations, traffic intensity and lung cancer incidence. In never smokers, associations between black smoke concentrations and traffic variables with lung cancer incidence were (borderline) significant. No associations were found in the ex and current smokers. Associations between black smoke, traffic variables and lung cancer incidence were suggestively stronger in subjects with low fruit consumption.

Stronger associations between air pollution and lung cancer in never smokers have been observed in the large American Cancer Society study as well.[2] Relative risks associated with a 10 $\mu g/m^3$ increase of the concentration of fine particles were about 1.03, 1.09 and 1.13 in current, ex and never smokers respectively.[2] In a cohort study from Oslo, RRs per 10 $\mu g/m^3$ increase of the concentration of NO_x were 1.20, 1.25, 1.06 and 1.06 for never smokers, and current smokers smoking 1-9 cigarettes/day, 10-19 cigarettes/day and more than 20 cigarettes/day respectively.[9] In a case-control study from Stockholm, the RR for NO_2 above 29.3 $\mu g/m^3$ (the 90^{th} percentile) was similar in never smokers (RR 1.68), former smokers (RR 1.58) and those smoking 1-10 cigarettes per day (RR 1.36) but was smaller in current smokers smoking more than 20 cigarettes per day (RR 0.74).[8]

The lack of association found for ex or current cigarette smokers in our study could be due to the fact that the effect may be too small too measure in comparison

to the (strong) association between lung cancer incidence and cigarette smoking. In the full cohort analyses no information was available about the number of cigarettes, cigars and pipe, the number of years of smoking, the type of tobacco used, and the year when former smokers stopped smoking, which are all potentially important confounders. Sensitivity analyses in the case-cohort dataset showed that there were small differences in effect estimates for air pollution variables for models with and without the number of cigarettes, cigars and pipes, and the number of years of smoking. This agrees with observations in the Swedish case-control study, in which the confounding effect of smoking was adequately addressed by a categorical variable.[8] There was also little difference between the effect estimates adjusted for the complete confounder model used in the case-cohort analyses and adjusted for the limited confounder model used in the full cohort analyses. If the findings from the case-cohort analyses apply to the full cohort, it seems unlikely that residual confounding due to lack of detailed data on smoking and other potential confounders is the explanation of the lack of association in the ex and current smokers.

A few studies have investigated the association between lung cancer incidence and air pollution in study populations consisting entirely of non-smokers. A cohort study in the U.S. (AHSMOG) among 6,338 non-smoking adults found that incident lung cancer was significantly elevated with increased PM_{10} and SO_2 concentrations.[6] In a recent case-control study nested within EPIC among non-smokers, lung cancer incidence was non-significantly associated with residence nearby heavy traffic roads (odds ratio 1.46 (95% CI 0.89 – 2.40)). The odds ratio for NO_2 was 1.14 (95% CI 0.78 – 1.67) for an increase of 10 $\mu g/m^3$, and an odds ratio of 1.30 was found for concentrations greater than 30 $\mu g/m^3$. No clear association was found with PM_{10} and SO_2.[7] Our results in the full cohort analyses among never smokers are in agreement with the results among non-smokers of the AHSMOG and EPIC studies.

Some recent European studies investigated the association between lung cancer incidence and air pollution exposure using more individual level exposure assessments, with a focus on traffic-related air pollution. A case-control study in Stockholm on urban air pollution and lung cancer incidence found a RR of 1.05 (95% CI 0.93 – 1.18) for an increase of 10 $\mu g/m^3$ in 30-year average NO_2 concentrations from traffic, and a stronger RR of 1.10 (95% CI 0.97 – 1.23) when using a 20-year lag (i.e. using a 10-year average NO_2 concentration over 21-30 years ago).[8] In a cohort study among 16,209 men aged 40 to 49 year living in Oslo, the adjusted incidence risk ratio for lung cancer was 1.08 (95% CI 1.02 – 1.15) for a 10 $\mu g/m^3$ increase in average NO_x exposure between 1974 and 1978. The risk estimate for a 10 $\mu g/m^3$ increase in average SO_2 exposure between 1974 and 1978 was 1.01 (95% CI 0.94 – 1.08).[9] These studies suggested an increased risk of lung cancer from particularly traffic-related air pollution, assessed by either NO_x/NO_2 concentrations or indicator

variables for living near a major road.[7-9,21,22] In the study by Nyberg *et al.* heating-related SO_2 showed little effect in any time window, despite high exposure levels in the early years of the study period. Although averages of estimated individual SO_2 and NO_2 exposure showed reasonably high correlation, traffic-related NO_2 rather than heating-related SO_2 was consistently the stronger risk indicator.[8]

Previous studies showed that the association between lung cancer and air pollution became weaker when more recent exposures were used in the analyses, and that exposures 20 years before start of the study or even earlier in life were most important.[8,9] A limitation of our study is that we estimated exposure to air pollution during the latency period of lung cancer, i.e. we estimated exposure based on the baseline 1986 address for two periods (1976-1985 and 1987-1996) and we used traffic intensity data for 1986. Correlations between estimated concentrations for different years were however high, even over a period of 20 years (>0.8).[14] It was therefore not possible to evaluate the independent contributions of concentrations of different time periods. It is likely that the correlation with years and periods before 1976 would also be high. We further found that traffic counts from different years over a period of more than 10 years were highly correlated (>0.9) and we focused mainly on busy roads that have likely been in place for a long period of time. Only the baseline address was available for all subjects, but no complete residential history including exact addresses was available. It was however estimated that 90% of the participants had lived for 10 years or longer in their 1986 municipality. Mean duration of residence was 35 years (SD 19.8).[15] These results support the use of our exposure estimate as a proxy for time periods further back in time.

In a reanalysis of two US cohort studies on mortality and long-term exposure to air pollution, higher air pollution effect estimates for lung cancer mortality were found in subjects without high school education.[19] We did not find higher effect estimates among subjects with low educational level.

We did find that effect estimates for air pollution and traffic intensity tended to be higher for subjects with low fruit consumption compared to subjects with medium and high fruit consumption. Such results have not been reported before. An indication for elevated effect estimates was also found for all cause mortality among subjects with low fruit consumption.[23] Fruit consumption has been consistently inversely associated with lung cancer incidence, with the highest risks for the lowest quintile of fruit consumption.[24,25] One explanation for this finding is that diet is the only source of antioxidants which may protect against oxidative stress.[26] It is thought that one of the potential mechanisms of effect of air pollution is also through oxidative stress. Hence, low fruit consumption may be associated with a low protection against oxidative stress effects of air pollution.[26]

We previously presented results for the association between lung cancer mortality and air pollution in the NLCS cohort.[23] In the full cohort dataset, the adjusted risk estimate for lung cancer mortality for the BS overall concentration (period 1987-1996) was 1.03 (95% CI 0.88 – 1.20) and the adjusted RR for the traffic intensity on the nearest road was 1.07 (95% CI 0.96 – 1.19).[23] Among never smokers, RRs for lung cancer mortality were 1.48 (95 % CI 0.97 – 2.25) for BS overall; 1.15 (95% CI 0.92 – 1.46) for the traffic intensity on the nearest road; 1.44 (95% CI 0.86 – 2.42) for living near a major road; and 1.36 (95% CI 0.96 – 1.93) for the traffic intensity in a 100 m buffer.[23] Effect estimates for lung cancer mortality and lung cancer incidence were thus comparable, which is in agreement with the short time between diagnosis of lung cancer and death from lung cancer (on average 0.9 year (SD 1.0 year) in our study).

In conclusion, we found evidence for an association between black smoke and lung cancer incidence in never smokers. Exposure to traffic was also associated with borderline elevated risks among never smokers. No clear associations were found for the full cohort or other smoking categories.

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Chapter 5

The joint association of air pollution and noise from road traffic with cardiovascular mortality in a cohort study

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Abstract

Cardiovascular mortality has been associated with exposure to traffic-related air pollution and noise, but both exposures have previously been studied separately. We investigated associations between cardiovascular mortality and air pollution and noise together.

We used data from an ongoing cohort study on diet and cancer (NLCS, 120,852 subjects) with follow-up from 1987 to 1996. We evaluated cardiovascular causes of death. Exposure to black smoke (BS) and traffic intensity on the nearest road were assessed at the home address. Exposure to road traffic noise was modeled with a 25 x 25 m resolution. We conducted Cox proportional hazard analyses for the association between cardiovascular mortality and air pollution, traffic intensity and traffic noise.

Traffic intensity on the nearest road was associated with cardiovascular mortality, with highest relative risk (95% CI) for ischemic heart disease mortality: 1.11 (1.03 – 1.20). Relative risks for background BS concentrations were elevated for cerebrovascular (1.39 (0.99 – 1.94)) and heart failure mortality (1.75 (1.00 – 3.05)). The associations for background BS concentrations and traffic intensity were insensitive to adjustment for traffic noise. There was an excess of cardiovascular mortality in the highest noise category (>65 dB(A)), which was concentrated in ischemic heart disease and especially heart failure mortality (RR 1.99 (1.05 – 3.79). After adjustment for BS concentrations and traffic intensity noise effect estimates were reduced.

Associations between background BS concentrations and traffic intensity on the nearest road and specific cardiovascular causes of death were not explained by exposure to traffic noise.

Introduction

Cohort studies conducted in the U.S. have shown associations between long-term exposure to particulate matter air pollution and cardiovascular mortality.[1-4] Cohort studies which were mostly conducted in Europe have reported associations between traffic-related air pollution and cardiovascular mortality.[5-7] A cross-sectional study from Germany[8] and a case-control study from the U.S.[9] also reported associations between traffic-related air pollution and coronary heart disease. Exposure to traffic-related air pollution was assessed using dispersion modeling,[7] measured or modeled air pollution data and indicator variables for living near a busy road assessed with geographic information systems[5,6,8] or traffic intensities near the home.[9]

Motorized traffic is not only an important source of air pollution, but also of noise.[10] Exposure to traffic noise may be associated with increased blood pressure and ischemic heart disease.[10,11] Exposure to traffic noise is usually estimated using traffic intensity, composition of traffic, speed, distance to roads, surface roughness, noise barriers and other factors as input variables.

The joint association of long-term exposure to air pollution, traffic intensity and noise with cardiovascular mortality has not been studied before.

We earlier reported an association between traffic-related air pollution, traffic intensity and cardiovascular mortality in a Dutch cohort study.[12] In this paper, we study the joint association of long-term exposure to air pollution, traffic intensity and noise with cardiovascular mortality. Because air pollution and noise may be associated with different cardiovascular endpoints,[7,9-11,13,14] we studied overall as well as subcategories of cardiovascular mortality.

Methods

Study design

The cohort has been described in detail.[15] Briefly, the Netherlands Cohort Study on Diet and Cancer (NLCS) was initiated in September 1986 with the enrolment of 120,852 subjects (58,279 males and 62,573 females) aged 55-69 years living in 204 municipalities located throughout the country. The study was designed as a case-cohort study, i.e. cases are derived from the entire cohort, while the person years at risk are estimated from a random subcohort (N ~ 5,000).[16] This approach was chosen for efficiency of baseline questionnaire processing.

At baseline, all participants completed an 11-page questionnaire on dietary habits and other risk factors for cancer. For all participants, data from one machine readable page of the questionnaire were entered (with information about age, gender and

smoking status). The exact residential address at baseline was also available. After recruitment, the entire cohort was followed up for cancer incidence by record linkage to cancer registries.[17] For emerging cases and the randomly selected subcohort, the remaining 10 questionnaire pages (not machine readable) were manually entered, blinded with respect to case/subcohort status.

Mortality data for the 1987-1996 period were obtained from the Dutch Central Bureau of Genealogy and the Dutch Central Bureau of Statistics. The cause of death was coded according to ICD-9 for period 1986-1995 and ICD-10 for 1996. We studied cardiovascular mortality, which was grouped into ischemic heart disease (IHD), cerebrovascular, heart failure, and cardiac dysrhythmia mortality (Table 1).

The NLCS study was approved by institutional review boards from Maastricht University and the Netherlands Organization for Applied Scientific Research (TNO). All cohort members consented to participation by completing the mailed, self-administered questionnaire.

Air pollution

The air pollution exposure assessment method has been described previously.[18] Long-term exposure to outdoor air pollution at the geographical coordinate of the 1986 home address was estimated for all participants as the sum of regional, urban and local traffic contributions. In this paper we used average Black Smoke (BS) estimates for the period 1987-1996. We used BS as it is a measure of the traffic-related component of particles.

Regional concentrations were estimated using inverse distance weighed interpolation of concentrations measured at regional background sites in the National Air Quality Monitoring Network (NAQMN). The urban component was estimated using regression models relating measured urban concentrations to the number of inhabitants around a monitoring site. The sum of the regional and urban contributions was defined as background concentration.

Local traffic contributions were characterized by traffic variables which were assessed using a Geographic Information System (GIS) and a digital road network to which traffic intensity data from the year 1986 were linked.[18] We used traffic intensity on the nearest road because it had the strongest association with cardiovascular mortality.[12]

Traffic noise

Road traffic noise exposure at the home address was estimated for all subjects using EMPARA, a model for noise mapping in the Netherlands with a resolution of 25 x 25 m.[19] In EMPARA the roads are divided into small segments and the model successively calculates their contribution to the total noise level. Important input

variables for the model are the road network, traffic intensity on road segments, percentages of light, medium and heavy-duty traffic, location of noise barriers and quiet asphalt, and land use information.[19] These input data were collected for the period 2000-2001, whereas the relevant exposure period was from 1987-1996. Traffic intensities are the major input variable in these models. We documented that while absolute traffic intensities increased during the follow-up period, traffic intensity data obtained for different years were highly correlated (>0.9), even over a period of 10 years.[18]

As noise exposure indicator, we used the standard measure for noise exposure in the Netherlands. This is defined as the maximum of the annual average noise level during the day (7 to 19h), or the evening (19 to 23 h) or the night (23 to 7 h). The levels during the evening and during the night receive a penalty of respectively 5 and 10 decibel before assessing the maximum of the three periods. The indicator is modeled as equivalent A-weighted average sound pressure levels (dB(A)).[19]

Statistical analysis

We conducted analyses in the full cohort using Cox proportional hazards models. Person-years were calculated for all participants from baseline until death or end of follow-up. Person-years for subjects who died from causes other than those being analyzed were defined censored at the time of death in cause-specific analyses.

Air pollution effects were analyzed for the combination of BS background concentration and traffic intensity on the nearest road as continuous variables.

Effects of traffic noise exposure were analyzed with noise as a categorical variable, classified into categories of 5 dB(A), from ≤ 50 dB(A) to > 65 dB(A). These categories were chosen to address thresholds which have been observed in previous studies.[10]

Effects of air pollution and noise were investigated separately and in conjunction. Relative risks (RR) were calculated for air pollution concentration and traffic intensity differences between the 5th and the 95th percentile. For BS this was rounded to 10 μg/m^3 and for traffic intensity on the nearest road to 10,000 motor vehicles/24h (mvh/24h). RRs for the different noise categories were calculated with as reference category ≤ 50 dB(A).

We adjusted for gender, age at baseline, and smoking status coded as never, ex, and current smoking separately for cigarette, cigar and pipe smoking. We further adjusted for area-level indicators of socioeconomic status as in our previous paper (cf Table 2).[12]

As sensitivity analyses we investigated traffic intensity on the nearest road as categorical variable (≤ 1,225 mvh/24h (reference category); 1,225 – 10,000 mvh/24h; and > 10,000 mvh/24h), and traffic noise as continuous variable.

We conducted separate analyses for men and women because most previous studies investigated the cardiovascular effects of noise in men only.[10] Heterogeneity in relative risk estimates between different subgroups was tested using Cochran's Q test.[20]

Data management was done using SPSS 12.0 (SPSS Inc, Chicago, US), and statistical analyses were conducted using STATA statistical software 8 (STATA Corporation, College Station, US). GIS calculations were conducted using ArcInfo (ESRI, Redlands, US).

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

For 97% of the subjects we were able to estimate air pollution and noise at the home address (N = 117,528). The number of deaths from cardiovascular causes is shown in Table 1. About 57% of all cardiovascular deaths was caused by IHD. Characteristics of the study population are summarized in Table 2. Cardiovascular mortality cases were older and more likely to be male or current smoker compared to non-cases. There was no difference for area level socio-economic status.

Table 1. Number of deaths during follow-up.

Cause	ICD-9 codes	ICD-10 codes	Number of deaths
Cardiovascular mortality	400 – 440	I10 – I70	6,137
Ischemic heart disease mortality	410 – 414	I20 – I25	3,521
Cerebrovascular mortality	430 – 438	I60 – I69	1,175
Heart failure mortality	428	I50	422
Cardiac dysrhythmia mortality	427	I44 - I49	339

Table 2. Descriptive characteristics of cardiovascular mortality cases and non-cases according to various baseline characteristics (among subjects for which geographical coordinates of the home address were available (N = 117,528)). Values are number (%) or median (Inter Quartile Range).

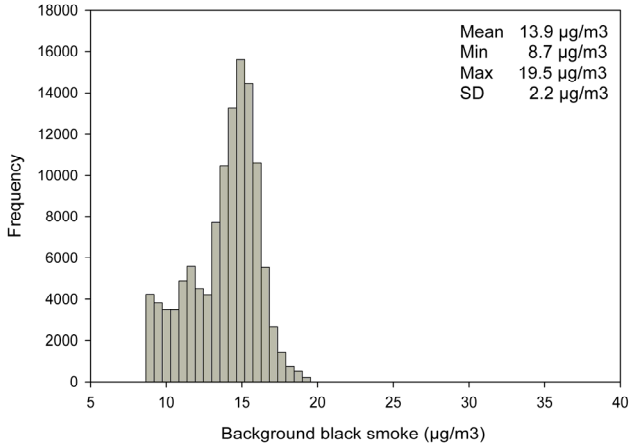
Characteristic	**Cases (N = 6,137)**	**Non-cases in full cohort (N = 111,391)**
Gender (men)	4,243 (69.1 %)	52,558 (47.2 %)
Age (years)	64 (61 – 67)	62 (58 – 65)
Cigarette smoking status		
Never	1,620 (28.6 %)	43,281 (41.3 %)
Ex	1,859 (32.8 %)	33,103 (31.6 %)
Current	2,182 (38.5 %)	28,350 (27.1 %)
Cigar smoking status		
Never	4,822 (82.4%)	93,776 (87.8%)
Ex	552 (9.4%)	7,271 (6.8%)
Current	475 (8.1%)	5,807 (5.4%)
Pipe smoking status		
Never	5,381 (91.3%)	100,197 (93.4%)
Ex	318 (5.4%)	4,747 (4.4%)
Current	194 (3.3%)	2,305 (2.2%)
% persons with low income in neighborhood	41 (36 – 47)	41 (36 – 46)
% persons with high income in neighborhood	18 (12 – 24)	19 (13 – 25)
% persons with low income in a COROP area	41 (36 – 45)	41 (36 – 45)
% persons with high income in a COROP area	19 (18 – 23)	19 (18 – 23)

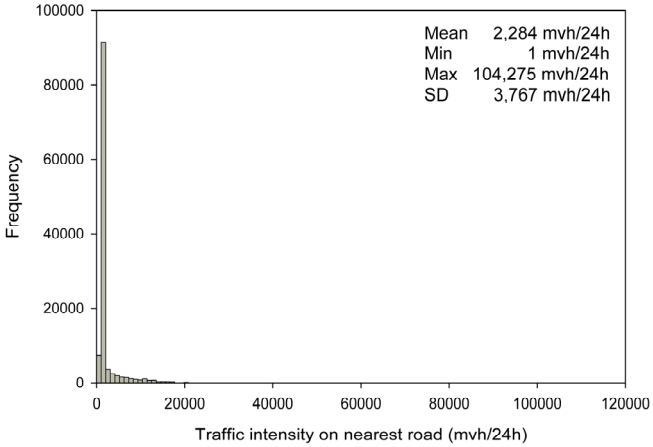
Air pollution and traffic noise

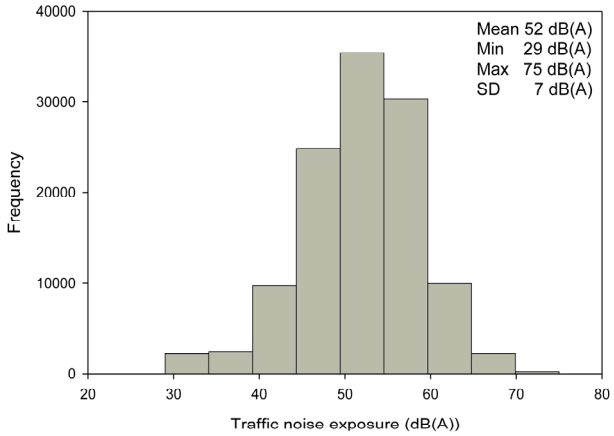
Figure 1 shows that background BS, traffic intensity on the nearest road and noise varied substantially within the cohort. 6.4% of the subjects were exposed to traffic noise between 60 and 65 dB(A), and 1.4% to more than 65 dB(A). For 4.5% of the subjects traffic intensity on the nearest road was > 10,000 mvh/24h.

Traffic noise exposure was higher for subjects who had a traffic intensity > 10,000 mvh/24h on the nearest road (mean 60 dB(A)) compared to subjects who had a traffic intensity ≤ 10,000 mvh/24h on the nearest road (mean 52 dB(A)). However, the correlations between traffic noise and background BS, and traffic intensity on the nearest road were moderate at: 0.24 and 0.30 respectively.

Figure 1. Distribution of estimated background black smoke concentrations (period 1987-1996), traffic intensity on the nearest road and traffic noise exposure, at the 1986 home address (N = 117,528).







Association of air pollution and traffic noise with cardiovascular mortality

Table 3 shows the associations between background BS, traffic intensity on the nearest road and traffic noise with cardiovascular mortality. Traffic intensity on the nearest road was associated with cardiovascular mortality, with highest relative risk for ischemic heart disease mortality: 1.11 (95% CI 1.03 – 1.20). Relative risks for background BS concentrations were elevated for cerebrovascular (1.39 (95% CI 0.99 – 1.94)) and heart failure mortality (1.75 (95% CI 1.00 – 3.05)). The associations for background BS concentrations and traffic intensity were insensitive to adjustment for traffic noise. There was an excess of cardiovascular mortality in the highest noise category (>65 dB(A)), which was concentrated in especially heart failure mortality (RR 1.99 (95% CI 1.05 – 3.79). After adjustment for BS concentrations and traffic intensity this association was slightly reduced and lost significance. Relative risks were non-significantly elevated for IHD mortality for the highest noise category, but reduced to unity after adjustment for background BS and traffic intensity.

Sensitivity analyses

After excluding the subjects who had a noise exposure > 65 dB(A), effect estimates for background BS and cardiovascular mortality did not change whereas they were slightly increased for traffic intensity on the nearest road to 1.09 (95% CI 1.02 – 1.17).

There was no interaction between traffic noise and background BS or traffic intensity on the nearest road.

When traffic intensity on the nearest road was modeled as a categorical variable, elevated relative risks were found only for the category > 10,000 mvh/24h for cardiovascular (1.12 (95% CI 0.99 – 1.28)) and IHD mortality (1.24 (95% CI 1.05 – 1.46)). After adjustment for background BS and traffic intensity as a categorical variable, RRs for traffic noise showed a similar pattern as when traffic intensity was modeled as a continuous variable.

The relative risks of traffic noise were essentially unity when traffic noise was included as a continuous exposure variable. RRs for background BS and traffic intensity on the nearest road were not affected (data not shown).

Effect estimates of background BS, traffic intensity and noise for cardiovascular mortality did not differ between men and women (results not shown).

Table 3. Adjusted relative risks (95% CI) for association between overall cardiovascular mortality and more specific cardiovascular mortality causes, and background black smoke (continuous), traffic intensity on the nearest road (continuous) and traffic noise exposure (in categories) which are assessed separately and in conjunction (N is number of cases).[a]

Model	Exposure	Cardiovascular (N = 6,137)	IHD (N = 3,521)	Cerebrovascular (N = 1,175)	Heart failure (N = 422)	Cardiac dysrhythmia (N = 339)
Only air pollution indicators	Background black smoke	1.11 (0.96 – 1.28)	1.01 (0.83 – 1.22)	1.39 (0.99 – 1.94)	1.75 (1.00 – 3.05)	0.96 (0.51 – 1.79)
	Traffic intensity on nearest road	1.05 (0.99 – 1.12)	1.11 (1.03 – 1.20)	0.82 (0.68 – 1.00)	1.07 (0.86 – 1.34)	1.04 (0.79 – 1.36)
Only traffic noise exposure	Traffic noise 50 – 55 dB(A)	1.00 (0.94 – 1.07)	1.00 (0.92 – 1.09)	0.90 (0.78 – 1.04)	1.08 (0.85 – 1.38)	1.03 (0.78 – 1.36)
	Traffic noise 55 – 60 dB(A)	1.00 (0.93 – 1.08)	1.02 (0.93 – 1.12)	0.89 (0.76 – 1.05)	1.00 (0.76 – 1.32)	1.08 (0.80 – 1.46)
	Traffic noise 60 – 65 dB(A)	0.91 (0.81 – 1.03)	0.95 (0.82 – 1.11)	0.59 (0.43 – 0.80)	1.04 (0.67 – 1.61)	1.08 (0.67 – 1.72)
	Traffic noise > 65 dB(A)	1.25 (1.01 – 1.53)	1.15 (0.86 – 1.53)	0.88 (0.52 – 1.50)	1.99 (1.05 – 3.79)	1.23 (0.50 – 3.01)
Both air pollution indicators and traffic noise exposure	Background black smoke	1.11 (0.95 – 1.28)	1.01 (0.83 – 1.22)	1.41 (1.01 – 1.97)	1.76 (1.01 – 3.08)	0.94 (0.50 – 1.76)
	Traffic intensity on nearest road	1.06 (0.99 – 1.13)	1.12 (1.04 – 1.21)	0.90 (0.74 – 1.10)	1.02 (0.79 – 1.32)	1.01 (0.75 – 1.36)
	Traffic noise 50 – 55 dB(A)	1.00 (0.94 – 1.07)	1.00 (0.91 – 1.09)	0.90 (0.78 – 1.04)	1.07 (0.83 – 1.37)	1.03 (0.78 – 1.36)
	Traffic noise 55 – 60 dB(A)	0.99 (0.92 – 1.06)	1.00 (0.91 – 1.10)	0.89 (0.76 – 1.05)	0.97 (0.73 – 1.29)	1.09 (0.80 – 1.47)
	Traffic noise 60 – 65 dB(A)	0.88 (0.78 – 1.00)	0.90 (0.76 – 1.06)	0.61 (0.44 – 0.84)	1.01 (0.64 – 1.59)	1.07 (0.66 – 1.76)
	Traffic noise > 65 dB(A)	1.17 (0.94 – 1.45)	1.01 (0.74 – 1.36)	0.95 (0.55 – 1.66)	1.90 (0.96 – 3.78)	1.23 (0.48 – 3.13)

[a] Adjusted for age, gender, smoking status, and area level indicators of socio-economic status

RRs for continuous variables were calculated for concentration changes from the 5^{th} to the 95^{th} percentile; for black smoke 10 $\mu g/m^3$, and for the traffic intensity on the nearest road 10,000 mvh/24h. RRs for traffic noise in categories were calculated with category ≤ 50 dB(A) as reference category.

Discussion

For the first time, the joint association between long-term exposure to air pollution, traffic intensity and road traffic noise with cardiovascular mortality has been studied. We observed an association between traffic intensity on the nearest road and overall cardiovascular mortality, which was driven by an association with IHD mortality. Relative risks for background BS were elevated for cerebrovascular and heart failure mortality. These associations were not affected by adjustment for traffic noise. There was an indication of an effect of traffic noise in the highest noise category (> 65 dB(A)) on cardiovascular mortality, which was concentrated in ischemic heart disease and especially heart failure mortality (RR 1.99 (95% CI 1.05 – 3.79). After adjustment for BS concentrations and traffic intensity, traffic noise effect estimates were reduced.

Traffic noise and air pollution effects

The moderate correlation between traffic noise with background BS (0.24) and traffic intensity on the nearest road (0.30), allowed an assessment of their independent effects despite the fact that traffic intensities were also included as predictor variables in the noise exposure model. The observed correlations between modeled traffic noise and air pollution were only slightly lower than in Oslo: 0.39 for $PM_{2.5}$, 0.46 for NO_2 and 0.46 for residential traffic intensity.[21] The moderate correlation is likely a result of the fact that different features of road traffic contribute to air pollution and noise, e.g. road surface and noise barriers affect noise much more than air pollution. Within urban areas, particle and NO_2 emissions increase with decreasing speed and noise emissions decrease with increasing speed. The use of traffic intensity on only the nearest road as exposure variable, while traffic on other nearby roads may also influence noise exposure, may have reduced correlations slightly. However, the correlation between traffic intensity in a 100 meter buffer and noise was only slightly larger (0.38).

The insensitivity of associations between BS concentrations and traffic intensity on the nearest road to adjustment for traffic noise was robust in analyses using continuous and categorical noise and traffic intensity variables. Exclusion of the observations with traffic noise exposure higher than 65 dB(A), the only noise category for which some independent effect was found in this study, also resulted in effect estimates for traffic intensity that were essentially the same as in the full population.

Limitations of the exposure assessment for air pollution and noise have to be considered in the interpretation of these findings. Background air pollution concentrations were estimated with a land use regression method combining

monitoring data and predictors available in a GIS.[18] Exposure was estimated for the 1986 home address, traffic intensities were estimated for the baseline year and a digital road network from the year 2001 was used. Traffic intensities were most accurate for motorways and major roads. However, the estimated misclassification of the air pollution exposures was relatively small.[18]

Similar limitations apply to estimation of traffic noise. The EMPARA model estimates traffic noise using traffic data from 2000-2001 whereas the relevant exposure period was from 1987-1996. This is likely not a major problem because we found that traffic counts from different years over a period of more than 10 years were highly correlated (>0.9) and time trends in traffic counts were similar.[18] Further, we focused mainly on busy roads that have likely been in place between 1987 and 2001.[18]

We did not have information about the bedroom location at the home addresses. Noise levels during the night are substantially reduced when the bedroom is at the back of the house. We also had no information about the time people spend at home or information about the work address. However, approximately 85% of the population had no paid job at baseline.

Traffic noise exposure was estimated as the maximum level of the modeled noise levels during the day, or evening or night, including penalties for evening- and nighttime. Other studies analyzed daytime and evening- or nighttime exposures separately. Our modeled noise levels may on average be 1 to 4 dB(A) higher. However, day-, evening- and nighttime noise levels are all highly correlated with 24h levels,[22] so that this likely does not introduce error.

As this is the first epidemiological study that evaluated the effects of exposure to air pollution, traffic intensity and traffic noise on mortality together in one study, further studies are required to confirm or refute our findings taking into account the limitations of our study. It is possible that in areas with higher traffic noise, noise effects are detected. Elevated risks of traffic noise on cardiovascular mortality were restricted to the highest noise category (> 65 dB(A)), but only 1.4% of our participants were exposed to such noise levels.

Specific causes of cardiovascular death

A few cohort studies also evaluated the effects of long-term exposure to air pollution on specific causes of cardiovascular mortality, which can be compared with our results for the background BS concentration. Pope *et al.* found an elevated relative risk of 1.12 (95% CI 1.08 – 1.15) for all cardiovascular diseases plus diabetes for a 10 $\mu g/m^3$ increase in long-term exposure to $PM_{2.5}$. Relative risks were 1.18 (95% CI 1.14 – 1.23) for IHD and 1.13 (95% CI 1.05 – 1.21) for dysrhythmia, heart failure and cardiac arrest. No elevated risk was found for cerebrovascular disease (RR 1.02;

95% CI 0.95 – 1.10).[13] A significantly elevated risk for IHD mortality was also found in the Los Angeles cohort of the American Cancer Society study with a RR of 1.39 (95% CI 1.12 – 1.73) for each increase of 10 μg/m^3 in $PM_{2.5}$.[23] A large cohort study in the U.S. among women found also significantly increased risks for overall cardiovascular mortality (RR 1.76; 95% CI 1.25 – 2.47) and for coronary heart disease (RR 2.21; 95% CI 1.17 – 4.16) for a 10 μg/m^3 increase in long-term exposure to $PM_{2.5}$.[4] However, in contrast with the Pope *et al.* study,[13] cerebrovascular mortality was also significantly associated with exposure to $PM_{2.5}$ in this study[4] as well as in our study. In a small cohort of Norwegian men no association between cerebrovascular mortality and NO_x was found whereas IHD mortality was significantly associated with a 10 μg/m^3 increase in NO_x concentrations (RR 1.08; 95% CI 1.03 – 1.12).[7] In general, an association between overall cardiovascular mortality and long-term exposure to air pollution concentrations was found. However, results for more specific cardiovascular causes varied between studies. It is possible that misclassification of specific cardiovascular causes on death certificates contributes to inconsistency of results. Death certificates may not be a perfect source of information of underlying causes, because there may be a convergence towards the most common cardiovascular causes of death.[24]

Traffic intensity near the home address was associated with only IHD mortality in our study. A recent study by Tonne *et al.* found that an increase in cumulative traffic near the home was associated with a 4% (95% CI 2 – 7%) increase per interquartile range in the odds of acute myocardial infarction, which is the most important cause of death within IHD.[9] Another study by Peters *et al.* found an association between exposure to traffic and acute myocardial infarction.[14] A German cross-sectional study found that living within 150 m of a major road was associated with the prevalence of coronary heart disease (odds ratio 1.85; 95% CI 1.21 – 2.84).[8] These results suggest that traffic intensity is associated especially with IHD.

The physical and chemical characteristics of fresh vehicle exhaust particles are different from those of urban background particles influenced by atmospheric transformation and coagulation. This may affect the mechanisms of effect. The proposed biological mechanisms linking air pollution to cardiovascular disease involve direct effects of pollutants on the cardiovascular system, blood, and lung receptors, and/or indirect effects mediated through pulmonary oxidative stress and inflammatory responses.[25] Subsequently, a cascade of physiological responses may follow which include alterations in blood rheology that favor thrombosis, cardiac dysrhythmias, acute vascular dysfunction, and the development of atherosclerosis.[25] A recent study among patients with stable coronary heart disease showed that brief exposure to dilute diesel exhaust promoted myocardial ischemia and inhibits endogenous fibrinolytic capacity.[26] These results are consistent with other

epidemiological studies showing associations between particulate air pollution and ST-depression, which possibly represents myocardial ischemia or inflammation.[27,28] These findings point to ischemic mechanisms that may explain the specific association found between exposure to traffic and ischemic heart disease. Cerebrovascular mortality is more likely due to a thrombotic process,[29] and possibly components of the urban background mixture are more related to thrombosis. The mechanisms of effect are however not exactly known yet and all of the mechanisms are likely inter-related.

Several epidemiological studies investigated the effects of road traffic noise exposure on different cardiovascular endpoints. Inconsistent effects were found for blood pressure and hypertension.[10,11] The evidence of an association between traffic noise and IHD is stronger.[10,11] The results of the cross-sectional studies on road traffic noise conducted in Caerphilly, Speedwell and Berlin, found an increase in IHD risk at outdoor noise levels above 60 dB(A) (estimated as day- and evening time noise levels) with increasing relative risks ranging from 1.1 to 1.4, although non-significant.[30-32] The relative risks for IHD in our study are in line with these previous results. However, there is a lack of epidemiological studies on the association between traffic noise exposure and cardiovascular mortality.

Our study had enough cases to evaluate more specific cardiovascular mortality causes. The effects of noise exposure on cardiovascular mortality in our cohort were largely driven by the association with heart failure mortality, but this association has not been evaluated in previous studies.

In conclusion, background BS concentrations, traffic intensity on the nearest road and traffic noise above 65 dB(A) were associated with specific cardiovascular causes of death. Associations with background BS and traffic intensity were insensitive to noise adjustment. Associations with traffic noise were reduced after adjustment for background BS and traffic intensity on the nearest road. As this is the first study that evaluated the effects of long-term exposure to air pollution, traffic intensity and traffic noise on mortality together in one study, further studies are required to confirm or refute our findings.

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Chapter 6

General discussion

Main findings

Evidence is increasing that exposure to current levels of ambient air pollution is associated with mortality.[1-7] Efforts have focused primarily on effects of short-term changes of air pollution. Only a limited number of longitudinal studies have evaluated the effects of long-term exposure to air pollution.

In this thesis we used the Netherlands Cohort on Diet and Cancer (NLCS) study[8] to investigate the effects of long-term exposure to traffic-related air pollution on mortality and lung cancer incidence in a Dutch cohort of ~120,000 persons aged 55-69 years. Further, we studied the joint effects of long-term exposure to air pollution and road traffic noise on cardiovascular mortality. We added an assessment of air pollution exposure at the individual baseline residential address, using a combination of interpolation of monitoring data, land use regression and geographic information system (GIS) calculations. Mortality follow-up was from 1987 to 1996. Data on individual confounders were taken from the baseline questionnaire. Area-level socio-economic status was taken from GIS databases. Cox proportional hazard models were used to study the association between air pollution and mortality.

Overall regression models which incorporated indicators for region, population density and land use for the urban and traffic intensities for the local component, explained 84%, 59% and 56% of the variability in measured concentrations for nitrogen dioxide (NO_2), black smoke (BS) and sulfur dioxide (SO_2), respectively. Our exposure assessment method thus explained a large part of the variations in outdoor air pollution concentrations. Air pollution concentrations decreased with time, but time trends were similar across the Netherlands. Due to the resulting high correlation of air pollution exposures of different 5-year time periods, we were unable to study the impact of different time lags on mortality. High correlations were observed between traffic count data collected in 1986 and 1996. Therefore we were able to make adjustments to especially municipal traffic count data that were available for different years.

After adjustment for potential confounders, mortality was associated with background air pollution concentrations of fine particles less than 2.5 μm ($PM_{2.5}$), NO_2 and black smoke. Relative risks were generally small. Natural cause and respiratory mortality were statistically significantly associated with NO_2 and black smoke exposure, with the highest relative risks for respiratory mortality. No associations were found with SO_2. Our study is the first European study that evaluated the effect of $PM_{2.5}$ on mortality. The relative risk for a change of 10 $\mu g/m^3$ in $PM_{2.5}$ concentrations was 1.06, identical to the estimate from the large American Cancer Society (ACS) study.[2] The results of our study differed from the ACS study in that we found higher relative risks for respiratory mortality compared to

cardiovascular mortality, whereas the opposite was the case in the ACS study. We also found associations between mortality and several traffic exposure variables. Effect estimates of traffic near the home address were much smaller than reported in the pilot study,[5] which was conducted in a 4% random sample of the current study population.

Lung cancer incidence was not associated with air pollution concentrations and traffic variables in the full study population. However, associations between black smoke concentrations and traffic variables with lung cancer incidence were (borderline) significant in never smokers.

We found an association between traffic intensity on the nearest road and overall cardiovascular mortality, which was driven by an association with ischemic heart disease mortality. Risk estimates for background black smoke concentrations were elevated for cerebrovascular and heart failure mortality. Associations with background black smoke and traffic intensity were insensitive to noise adjustment. There was an indication of an effect of the highest noise exposure category (> 65 dB(A)) on overall cardiovascular mortality, which was largely restricted to heart failure mortality. Associations with traffic noise were reduced after adjustment for background BS and traffic intensity on the nearest road.

In this chapter, the findings of this thesis will be discussed. The following topics will be discussed in more detail: 1) Comparison of our results with other studies assessing air pollution and traffic intensity 2) A discussion whether our results are attributable to short-term or long-term exposure to air pollution; 3) Impact on public health of long-term exposure to air pollution; 4) Methodological considerations of the exposure assessment method and in the statistical analyses; and 5) Conclusions.

Comparison with other cohort studies

Air pollution studies

The knowledge with regard to the long-term effects of air pollution exposure on mortality in adults is limited to a small number of studies in Northern America[1-3,7,9-12] and in Europe.[4,5,13,14] Table 1 compares the results of our study and of the previous cohort studies on the association between mortality and air pollution concentrations. Although these studies used different exposure assessment methods, collectively these studies demonstrated a positive association between long-term exposure to air pollution and mortality.

Table 1. Relative risks (95% CI) of studies on the association between mortality and long-term exposure to $PM_{2.5}$, NO_2, black smoke and SO_2 (increment used to calculate relative risks for each pollutant).

Study	Country	Study population	All cause mortality	Cardiopulmonary mortality	Cardiovascular mortality	Respiratory mortality	Lung cancer mortality
$PM_{2.5}$ (increment 10 µg/m^3)							
NLCS-AIR	Netherlands	120,852	1.06 (0.97 – 1.16)	1.05 (0.92 – 1.20)	1.04 (0.90 – 1.21)	1.07 (0.75 – 1.52)	1.06 (0.82 – 1.38)
Six Cities, original[1]	US	8,111	1.13 (1.04 – 1.23)	1.18 (1.06 – 1.32)	-	-	1.18 (0.89 – 1.57)
Six Cities, extended[10]	US	8,096	1.16 (1.07 – 1.26)	-	1.28 (1.13 – 1.44)	1.08 (0.79 – 1.49)	1.27 (0.96 – 1.69)
ACS, original[2]	US	552,138	1.06 (1.03 – 1.09)	1.11 (1.07 – 1.16)	-	-	1.01 (0.92 – 1.12)
ACS, extended[9,15]	US	552,138	1.06 (1.02 – 1.11)	1.09 (1.03 – 1.16)	1.12 (1.08 – 1.15)	0.92 (0.86 – 0.98)	1.14 (1.04 – 1.23)
ACS, Los Angeles[11]	US	22,905	1.17 (1.05 – 1.30)	1.12 (0.97 – 1.30)	-	-	1.44 (0.98 – 2.11)
AHSMOG[3,a]	US	6,338					
Males			1.04 (0.99 – 1.10)	1.04 (0.97 – 1.12)	-	1.09 (0.97 – 1.22)	1.65 (1.21 – 2.27)
Females			0.97 (0.93 – 1.02)	0.97 (0.91 – 1.02)	-	1.04 (0.94 – 1.15)	1.13 (0.81 – 1.57)
Miller et al.[7]	US	65,893	-	-	1.76 (1.25 – 2.47)	-	-
NO_2 (increment 30 µg/m^3)							
NLCS-AIR	Netherlands	120,852	1.08 (1.00 – 1.16)	1.11 (0.98 – 1.25)	1.07 (0.94 – 1.21)	1.37 (1.00 – 1.87)	0.91 (0.71 – 1.15)
AHSMOG[3,a]	US	6,338					
Males			1.02 (0.93 – 1.13)	1.01 (0.88 – 1.15)	-	0.90 (0.72 – 1.11)	1.61 (0.94 – 2.75)
Females			0.99 (0.91 – 1.09)	1.02 (0.92 – 1.14)	-	0.98 (0.81 – 1.18)	2.27 (1.11 – 4.63)
Hoek et al.[5]	Netherlands	4,492	1.36 (0.93 – 1.98)	1.81 (0.98 – 3.34)	-	-	-
PAARC[13,b]	France	14,284	1.48 (1.12 – 1.95)	2.05 (1.11 – 3.80)	-	-	3.24 (1.20 – 8.74)
Nafstad et al.[4,c]	Norway	16,209	1.26 (1.16 – 1.37)	-	-	1.56 (1.22 – 2.00)	1.37 (1.11 – 1.69)
Gehring et al.[14]	Germany	4,847	1.34 (1.04 0 1.73)	2.33 (1.48 – 3.67)	-	-	-
Black smoke (increment 10 µg/m^3)							
NLCS-AIR	Netherlands	120,852	1.05 (1.00 – 1.11)	1.07 (0.98 – 1.15)	1.04 (0.95 – 1.13)	1.22 (0.99 – 1.50)	1.03 (0.88 – 1.20)
Hoek et al.[5]	Netherlands	4,492	1.32 (0.98 – 1.78)	1.71 (1.10 – 2.67)	-	-	-
PAARC[13,b]	France	14,284	1.07 (1.03 – 1.10)	1.05 (0.98 – 1.12)	-	-	1.03 (0.92 – 1.15)
SO_2 (increment 20 µg/m^3)							
NLCS-AIR	Netherlands	120,852	0.97 (0.90 – 1.05)	0.93 (0.82 – 1.04)	0.94 (0.82 – 1.06)	0.88 (0.64 – 1.22)	1.00 (0.79 – 1.26)
AHSMOG[3,a]	US	6,338					
Males			1.10 (0.87 – 1.40)	1.02 (0.75 – 1.40)	-	0.75 (0.46 – 1.23)	4.02 (1.54 – 10.48)
Females			1.00 (0.82 – 1.21)	1.04 (0.82 – 1.33)	-	0.96 (0.61 – 1.52)	9.26 (3.55 – 24.18)
PAARC[13,b]	France	14,284	1.02 (0.96 – 1.08)	0.90 (0.80 – 1.02)	-	-	1.00 (0.81 – 1.23)
Nafstad et al.[4]	Norway	16,209	0.96 (0.90 – 1.02)	-	-	1.06 (0.87 – 1.30)	1.00 (0.86 – 1.17)

[a] PM_{10} concentrations, only separate results for males and females
[b] After exclusion six areas for which the monitoring sites were influenced by local traffic
[c] NO_x concentration

In our study, black smoke and NO_2 concentrations were significantly associated with natural cause and respiratory mortality. Relative risks in our study were elevated for $PM_{2.5}$ concentrations with mortality, but relative risks were small and not significant. There was no association between estimated SO_2 and mortality in any of our analyses. Our study is after the U.S. nation-wide ACS study[2] the largest cohort study conducted so far. The risk estimates of our study are in the lower end of the range in effect estimates found in other cohort studies. However, the relative risk for $PM_{2.5}$ for all cause mortality in the U.S. ACS study (RR 1.06; 95% CI 1.03 – 1.09)[2] is similar to the relative risk observed in our study, although our estimate was not significant (RR 1.06; 95% CI 0.97 – 1.16).

The first cohort study on long-term exposure to air pollution and mortality that had individual data on potential confounders was the Harvard Six Cities Study,[1] which reported on a 14- to 16-year follow-up of 8,111 adults living in six U.S. cities. $PM_{2.5}$ concentrations were associated with all cause, cardiopulmonary and lung cancer mortality.[1] In a recent extended analysis of the Six Cities Study with an additional 8 years of follow-up similar observations between mortality and $PM_{2.5}$ concentrations were found to those in the original analyses.[10] A second major cohort study conducted in the U.S. was the ACS study which followed 552,138 adults living in 151 metropolitan areas from 1982 to 1989.[2] Significant associations were found between $PM_{2.5}$ and all cause and cardiopulmonary mortality. No association with lung cancer mortality was observed. However, an extended analysis of the ACS study with follow-up until 1998,[10] showed a significant association between lung cancer mortality and $PM_{2.5}$ concentrations. Associations between all cause and cardiopulmonary mortality and $PM_{2.5}$ concentrations persisted in the extended analyses.[9] No association was found with respiratory mortality.[15] An intensive reanalysis of the original Six Cities[1] and ACS[2] studies by an independent research team reported that the results originally reported could be reproduced and validated.[16] A third study in the U.S. was the Adventist Health Study of Smog (AHSMOG) among 6,338 non-smoking California Seventh-day Adventists.[3] Air pollution exposure was estimated by interpolation of concentrations from network sites at the zip code centroid of the residential address. PM_{10} concentrations were associated with all cause, cardiopulmonary, respiratory and lung cancer mortality in males. PM_{10} concentrations were not associated with mortality in females. For NO_2 concentrations no associations were found with all natural cause, cardiopulmonary and respiratory mortality in both men and women, while relative risks for lung cancer were elevated.

More recently, also in Europe cohort studies on long-term exposure to air pollution concentrations and mortality have been conducted. Hoek et al. investigated a random sample of 4,492 subjects of the full cohort of the NLCS study.[5] Exposure to NO_2 and black smoke was estimated using a combination of interpolation, land use

regression and GIS-methods. Exposure to NO_2 and black smoke was associated with all cause and cardiopulmonary mortality, with highest risks for cardiopulmonary mortality. In the French PAARC survey 14,284 adults living in 24 areas in 7 cities were followed for 25 years.[13] Air pollution concentrations were measured in each area at a centrally located monitoring station. The areas varied in diameter from 0.5 to 2.3 km. Analyses were conducted before and after exclusion of six area monitors influenced by local traffic (NO/NO_2 ration > 3 in ppb). Before exclusion of these areas all relative risks for the various mortality outcomes were essentially unity. After exclusion of six areas for which the monitoring sites were influenced by local traffic, NO_2 concentrations were significantly associated with all cause, cardiopulmonary and lung cancer mortality. Black smoke concentrations were also associated with mortality, but effect estimates were much lower compared with the effect estimates for NO_2 concentrations. No associations were found between SO_2 concentrations and any of the mortality outcomes.[13] In a Norwegian cohort among 16,209 men with mortality from 1973-1973 until 1998,[4] annual average NO_x and SO_2 concentrations at the home address were estimated using a combination of dispersion model calculation, emission data and measurements.[17] Relative risks for NO_x concentrations were significantly elevated for all cause, respiratory and lung cancer mortality. Mortality was not associated with SO_2 concentrations.[4]

The Six Cities study[1] and the ACS study[2] compared cities with different ambient air pollution concentrations, assuming homogeneous exposure within a city and not taking into account small scale variation in air pollution levels. However, studies have shown that there are important variations in the concentrations of air pollutants on a small scale within cities.[18-20] Jerrett et al. conducted a study restricted to the 22,905 subjects of the ACS study who lived in the metropolitan Los Angeles area to study the within-city air pollution associations.[11] Exposure was estimated using interpolation of 23 $PM_{2.5}$ monitoring sites within the Los Angeles area. Effect estimates were elevated for all cause, cardiopulmonary and lung cancer mortality. The mortality associations were generally larger than those observed previously in the nation-wide ACS cohort.[2] These results may suggest that chronic health effects associated with within-city gradients in exposure may be larger than previously reported health effects between cities.[11] A recent study by Miller et al. on long-term association to air pollution and cardiovascular events among women found also that the between-city effect (relative risk 1.63 (95% CI 1.10 – 2.40) appeared to be smaller than the within-city effect (relative risk 2.28 (95% CI 1.10 – 4.75), although the difference was not significant ($p = 0.07$).[7] The risk estimates observed in the Miller et al. study are however high compared to the risk estimates found in the other U.S. cohort studies. Larger within-city effect estimates compared with between-city effect estimates have been attributed to measurement error due to the assignment of

the same area average concentration to all subjects living in that area. However, this is questionable because exposure measurement error can be of classical and Berkson type.[21] Classical measurement error occurs when exposure is measured and repeated measurements vary around the 'true' value. This usually results in bias towards the null, i.e. effect estimates underestimate the true effect estimate.[21] Berkson measurement error arises when the same approximate (group-average) exposure is used for many subjects, e.g. assigning the same exposure to all subjects living in the same city. Berkson error usually causes little to no bias of the effect estimates, but it decreases the precision, making it more likely that real associations are not detected.[21] As part of the measurement error is probably Berkson error when assigning the same area average concentration to all subjects living in that area, exposure error may not explain the larger within-city effect estimates compared with between-city effect estimates. Variations in air pollution concentrations between cities are mostly due to variations in secondary pollutants, while variations within cities are largely due to variations in primary pollutants, e.g. from traffic sources. The toxicity of primary and secondary pollutants may differ, and this may explain the differences between within-city and between-city effect estimates.

Traffic intensity studies

Despite the important contribution of traffic sources to reduced urban air quality, relatively few studies have evaluated the specific effects of traffic-related air pollution on mortality. In our study, air pollution effects were also analyzed for a combination of background concentrations and traffic variables to identify effects of living near busy roads separately. It has been shown that there are differences between the mortality effects of exposure to traffic-related NO_x concentrations and industrial- or heating-related SO_2 concentrations, and that traffic-related air pollution may be most important.[4] In none of the cohort studies an association between SO_2 concentrations and mortality was found, except for lung cancer mortality in the AHSMOG study,[3] for which the effect estimates were elevated but confidence intervals were wide (see Table 1). A recent cohort study on the effect of exposure to traffic on lung development among children also showed that effects of living near major roads were found independent of the background air pollution concentrations, which suggests that even in areas with low background concentrations, there are adverse health effects of living near a major road.[22] In addition, over the past 10 years advances in GIS have expanded into the field of exposure assessment and provided new possibilities to assess specific traffic-related exposure, e.g. by assessing traffic intensities near the home or developing indicator variables for living near a major road.[23]

Only a few prospective cohort studies studied the association between mortality and exposure to air pollution in a similar way as in our study, i.e. analyzing separately the mortality effects of background concentrations and living near a major road. Table 2 describes the cohort studies that specifically investigated the association between mortality and traffic near the home. The first cohort study that evaluated these effects on mortality was a pilot study in a subgroup of ~ 5,000 subjects of the full NLCS cohort.[5] Long-term exposure to air pollution was defined as background concentrations (sum of regional and urban concentrations) and an indicator variable for living near a major road (living within 100 m of a motorway and/or living within 50 m of a major road). Cardiopulmonary mortality was most strongly associated with living near a major road, but the association for all cause mortality was also borderline significantly elevated.[5] A study in Hamilton, Canada, among 5,228 subjects found also that living within 50 m of a major urban road or within 100 m of a highway was associated with all cause mortality.[24] They used the same indicator of traffic-related air pollution as Hoek et al.[5] A German cohort study among approximately 4,800 women found an association between mortality and living within 50 m of a major road, with the highest relative risk for cardiopulmonary mortality. However, the risk estimate for mortality other than cardiopulmonary or lung cancer mortality was elevated for living near a major road, though not significantly (RR 1.21; 95% CI 0.77 – 1.87).[14] This was in contrast with the results for mortality other than cardiovascular, respiratory or lung cancer in our study, for which the risk estimates for the various traffic variables were essentially unity.

The previous cohort studies that used traffic variables to assess air pollution effects on mortality have been relatively small (approximately 5,000 subjects), compared to our current study (~120,000 subjects). All of these studies used already existing cohorts. Effect estimates in the previous studies were based on a much smaller number of mortality cases producing wide confidence intervals. However, relative risks for the traffic variables found in our current study were much smaller than in the other cohort studies on mortality and living near a major road. These results could be interpreted as evidence for publication bias. A formal analysis whether publication bias exists is not possible due to the limited number of cohort studies in which the effects of background concentrations and traffic variables have been separately studied. In addition, it is unlikely that results of cohort studies, which have high costs and are time consuming, will not be submitted and/or published, but there is always the possibility that studies that find no associations will not be submitted or published. However, it is unlikely that publication bias has occurred.

Table 2. Relative risks (95% CI) of studies on the association between different mortality outcomes and living near a major road.[a]

Study	Exposure variable	All cause mortality	Cardiopulmonary mortality	Cardiovascular mortality	Respiratory mortality	Lung cancer mortality
NLCS-AIR	Traffic intensity on the nearest road	1.03 (1.00 – 1.08)	1.06 (1.00 – 1.12)	1.05 (0.99 – 1.12)	1.10 (0.95 – 1.26)	1.07 (0.96 – 1.19)
	Traffic intensity in a 100 m buffer	1.02 (0.97 – 1.07)	1.03 (0.95 – 1.10)	1.00 (0.92 – 1.08)	1.21 (1.02 – 1.44)	1.07 (0.93 – 1.23)
	Living near a major road	1.05 (0.97 – 1.12)	1.07 (0.96 – 1.19)	1.05 (0.93 – 1.18)	1.19 (0.91 – 1.56)	1.20 (0.98 – 1.47)
Hoek et al.[5]	Living near a major road	1.41 (0.94 – 2.12)	1.95 (1.09 – 3.51)	-	-	-
Finkelstein et al.[12]	Living near a major road	1.18 (1.02 – 1.38)	-	-	-	-
Gehring et al.[14]	Living near a major road	1.29 (0.93 – 1.78)	1.70 (1.02 – 2.81)	-	-	-

[a] Increment used to calculate relative risks: for the traffic intensity on the nearest road: 10,000 mvh/24h, and for the sum of traffic intensity in a buffer of 100 m: 335,000 mvh/100m. RRs for living near a major road were calculated with as reference category not living near a major road.

Relative contributions of short-term and long-term exposure on mortality effects

Air pollution may increase death rates by two principal mechanisms: by increasing the number of frail people, or by causing death in people who are already frail, or a combination of these two mechanisms. Künzli et al.[25] distinguished four categories of death associated with short-term and long-term exposure to air pollution: A) air pollution increases both the risk of underlying diseases leading to frailty and the short-term risk of death among the frail; B) air pollution increases the risk of chronic diseases leading to frailty but is unrelated to timing of death; C) air pollution is unrelated to risk of chronic diseases but short-term exposure increases mortality among persons who are frail; and D) neither underlying chronic disease nor the event of death is related to air pollution exposure. Studies on short-term variations in air pollution concentrations capture deaths from categories A and C, whereas cohort studies on long-term exposure assess mortality from categories A, B and C.[25]

This difference between studies on short-term and long-term exposure is also reflected in the mortality effect estimates for these two types of studies. Effect estimates for studies on short-term exposure are substantially lower, because these studies are only concerned with mortality effects following exposure within a few days. Two major recent multi-city studies on short-term exposure to air pollution and daily mortality are the National Morbidity, Mortality and Air Pollution Study (NMMAPS) in 20 cities the U.S.,[26] and the Air Pollution and Health: A European Approach (APHEA) study in 29 cities in Europe.[27] In the NMMAPS study the estimated relative risk for all cause mortality was 1.0051 (95% confidence interval 1.0007 – 1.0093) for each increase in the concentration of fine particles less than 10 µm (PM_{10}) of 10 µg/m^3.[26] The estimated relative risk in the APHEA project was 1.006 (95% confidence interval 1.004 – 1.008) for a 10 µg/m^3 increase in PM_{10} concentrations.[27] Further, a recent meta-analysis of time-series studies by the WHO estimated a relative risk of 1.006 (95% confidence interval 1.004 – 1.008) for each increase of 10 µg/m^3 in PM_{10} concentration.[28] In comparison, the risk estimates for all cause mortality were 1.06 (95% confidence interval 1.03 – 1.09) in the ACS cohort study,[2] and 1.13 (95% confidence interval 1.04 – 1.23) in the Six Cities cohort study[1] for an increase of 10 µg/m^3 in $PM_{2.5}$ concentrations.

A limitation of the studies on short-term exposure to air pollution and daily mortality is that only deaths within a maximum of 1-2 months after exposure can be considered, because seasonal variation of mortality may affect the effect estimates when longer time periods are evaluated. Two studies have assessed the mortality effects over 40 days rather than only a few days after air pollution exposure.[29,30] In a study by Goodman et al. total mortality increased by 0.4% (95% confidence interval

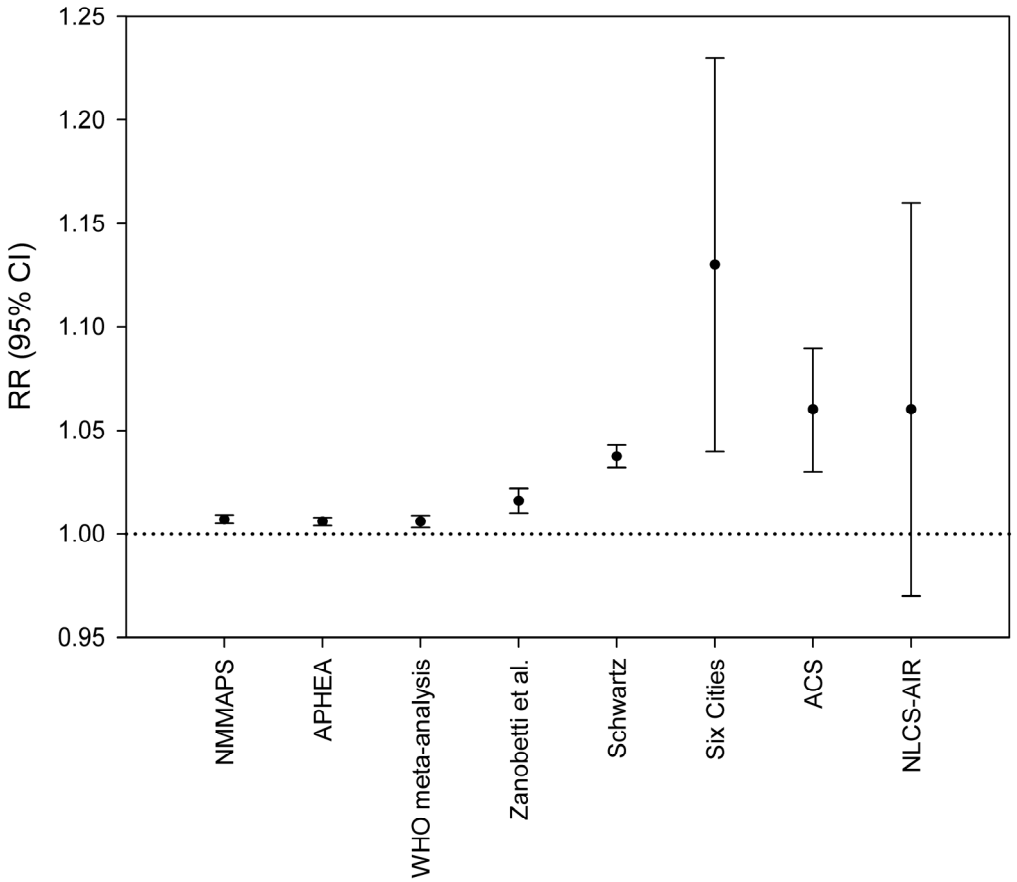
0.3 – 0.6%) for each 10 μg/m^3 increase in black smoke concentration when only acute effects (3-day mean) were considered. When deaths in the 40 days after exposure were considered, they found a 1.1% increase (95% confidence interval 0.8 – 1.3%).[30] In a study by Zanobetti et al. the extended air pollution effects for a period of 40 days were also twice as high as the short-term effects.[29] In a time-series study in Boston it was shown that the percentage increase in all deaths associated with a 10 μg/m^3 increase in $PM_{2.5}$ rose from 2.1% (95% confidence interval 1.5 – 4.3%) to 3.75 (95% confidence interval 3.2 – 4.3%) as the focus moved from daily patterns to monthly patterns.[31] Zeger et al. also showed that the increased mortality associated with higher air pollution levels is not restricted to very frail persons who die short after exposure to air pollution.[32] In addition, a reassessment of the lethal London smog episode of 1952 indicated also that the true scope and scale of the health effects linked with the smog episode extended over a longer period than the originally estimated effects within a few days. The smog episode led to an immediate increase in the number of deaths of about 3,000 – 4,000, but if the excess deaths in the 1-2 months after the smog episode are related to air pollution, the mortality count was about 12,000.[33]

Figure 1 shows the relative risks of the studies on short-term exposure in which both mortality effects within a few days and within a few weeks were assessed, together with the results of cohort studies on long-term exposure. The results of studies on the acute effects of short-term exposure to air pollution are much lower compared to the relative risks found in the cohort studies on long-term exposure to air pollution. The mortality effects within 40-60 days after short-term exposure to air pollution are at least twice as high as the acute effects. However, the studies on short-term exposure and the mortality effects within 40-60 days capture only a fraction of the mortality effects of long-term exposure to air pollution (Figure 1). The results of these studies suggest that studies on the acute effects of short-term exposure underestimate the mortality effects of air pollution, and that the effects observed in the daily time-series studies are not primarily due to short-term mortality displacement (‘harvesting’).

In the extended follow-up of the Six Cities study during a time of air pollution reductions, there was a unique opportunity to assess the effect of recent versus past exposures.[10] The results showed that particulate matter associated mortality decreased in the decade of the 1990s compared with the mid-1970s and 1980s, which is consistent with the decrease in ambient $PM_{2.5}$ concentrations. Furthermore, the similarity of effect for the annual air pollution concentration compared with the mean over the study period (1980 – 1998) suggests that air pollution during the last year may be important.[10] It was also shown that at least part of the $PM_{2.5}$ associated mortality may be partially reversible within a time scale of just a few years, and

further that the reductions in air pollution concentrations in the extended follow-up compared with the original study period were associated with improved survival.[10] Two intervention studies also showed that a reduction in air pollution concentrations lead to reduced death rate with a net benefit of the reduced death rate that was greater than predicted from results of previous time-series studies.[34,35] The finding that the mortality effect of air pollution is at least partially reversible suggests that ambient air pollution is likely associated with exacerbation of existing disease.

Figure 1. Relative risks (95% confidence intervals) for all cause mortality for studies on short-term exposure to air pollution and acute mortality effects within a few days (NMMAPS,[26] APHEA[27] and WHO meta-analysis[28]), for studies on short-term exposure to air pollution and mortality effects within a few weeks (40-60 days) (Zanobetti et al.,[29] Schwartz[31]), and for cohort studies on long-term exposure to air pollution (Six Cities,[1] ACS,[2] NLCS-AIR (this thesis)).
Relative risks were calculated for an increase of 10 μg/m^3 in PM_{10} (short-term studies) or $PM_{2.5}$ (long-term studies) concentrations.



In our current study we found associations between long-term exposure to air pollution and lung cancer incidence and mortality, with strongest associations within the group of never smokers. Other studies found also associations between air pollution and lung cancer (see also Table 1).[2,36-38] As the effect of long-term exposure to air pollution on lung cancer is a lifelong process, there also appears to be an effect that could be described as development of chronic disease in addition to the effect of exacerbation of existing disease.[10] In addition, recently a few studies have been conducted which showed that long-term exposure to air pollution is associated with chronic effects on the cardiovascular system. Two studies showed an association between long-term exposure to air pollution and well-established measures of atherosclerosis.[39,40] Künzli et al. studied the association between long-term exposure to $PM_{2.5}$ concentrations and atherosclerosis, assessed as carotid intimi-media thickness.[39] Carotid intimi-media thickness is a well-established quantitative measure of generalized atherosclerosis that correlates well with all of the major cardiovascular risk factors, with coronary artery atherosclerosis, and with clinical cardiovascular events. It is an established tool for investigating the contribution of long-term exposures such as smoking to subclinical stages of atherosclerosis.[39] Künzli et al. showed an increase of 5.9% (95% confidence interval 1.0 – 10.9%) in carotid intimi-media thickness for an exposure contrast in $PM_{2.5}$ of 10 $\mu g/m^3$. After adjustment for covariates the estimate became slightly lower in the range of 3.9 – 4.3%.[39] These results represent the first epidemiological evidence of an association between atherosclerosis and air pollution. A recent German study investigated the association between long-term residential exposure to traffic with the degree of coronary atherosclerosis.[40] The main outcome in this study was coronary artery calcification. Compared with participants who lived 200 m away from a major road, participants who lived closer to a major road had higher risks for a high coronary artery calcification. The odds ratio was 1.63 (95% confidence interval 1.14 – 2.33) for living within 50 m of a major road. The odds ratios for the associations between high $PM_{2.5}$ exposure and coronary artery calcification were consistently raised above 1, but the confidence intervals included the null effect.[40] These results suggest a role of air pollution in atherogenesis, but the epidemiological evidence is still scarce. Biological plausibility for a causal relationship between air pollution and atherosclerosis is supported by a few animal studies so far. In a study by Suwa et al. hyperlipidemic rabbits were exposed for four weeks to particulate matter exposure.[41] Exposure was associated with the progression of atherosclerotic lesions, and with an enhanced release of bone marrow monocytes. These precursors of macrophages play an important role in the atherogenic inflammatory responses.[41] Sun et al. studied mice that were exposed for six months to $PM_{2.5}$ concentrations. They found that exposure to low $PM_{2.5}$ concentration altered vasomotor tone, induced vascular inflammation,

and potentiated atherosclerosis.[42] These findings provide a potential biological basis for the association between atherosclerosis-related events observed in both time-series and cohort studies, but the precise mechanisms remain to be determined. The effects of air pollution on lung cancer and on the cardiovascular system are long-term processes and therefore reflect long-term exposure to air pollution. This provides evidence for chronic effects of air pollution that may in part explain the discrepancy between short-term and long-term risk estimates.

In summary, studies on the acute effects of short-term exposure on mortality capture a small fraction of the total mortality effects of long-term exposure to air pollution. A part of the effect of long-term exposure to air pollution may be reversible, but evidence is accumulating that long-term exposure to air pollution contributes to the development of chronic cardiovascular disease. There is more evidence linking long-term exposure to air pollution to respiratory morbidity including low lung function and bronchitis.[43]

Impact on public health

Health impact assessment provides quantitative information on the public health burden of air pollution exposure. In respect to the health consequences of air pollution levels, health impact assessment suggests what improvement in health can be expected through reductions in air pollution.[44] Mortality is of particular interest in health impact assessment for policy-makers, and in economic valuation, mortality-related costs are usually the dominant factor.[25] There is a consensus that health impact assessment should not rely on the results of time-series studies but rather should be based on long-term follow-up in cohort studies, because an assessment of the impact on public health of air pollution based on time-series studies would be incomplete and underestimate the number of early deaths that are associated with air pollution exposure.[25,45] Quantifying of the effect of air pollution on mortality based on cohort studies of effects of long-term exposure to air pollution on life expectancy has thus become a critical component in the policy discussion. Effects of long-term exposure to air pollution on mortality have been available so far from only a limited number of cohorts. Therefore, the ACS study[2,9] and the Six Cities study[1] have been the most important studies used in health impact assessment. It is now widely recognized that the effect estimates from the ACS study[2,9] are the best available for use in quantitative health impact assessment of the mortality effects of long-term exposure to ambient particles.[46]

Although the relative risks are small, the estimated effect on life expectancy can be substantial.[46-48] Life expectancy of a population can be estimated by using a life

table method. The life table approach follows up a study population over time into the future, under different assumptions about its mortality experience.[49,50] There are two scenarios:[49]

1. A baseline scenario, whereby age-specific death rates experienced by the study population are the same as those experienced currently by the target population at risk;
2. A population-changed scenario, whereby the baseline death rates are changed to reflect changes in levels of ambient air pollution.

The Clean Air For Europe (CAFE) program, funded by the European Commission, used the baseline scenario and compiled a set of baseline projections, to investigate the effects of current legislation on the future on health up to the year 2020.[49] The following scenarios have been analyzed: 1) Situation with baseline concentrations in 2000; 2) Situation with baseline concentrations for the CAFE baseline in 2020, under the assumption that current air pollution legislation is implemented in all countries of the European Union; and 3) The difference between these years, i.e. benefits of current policies up to 2020 from 2000. Estimations were made using the relative risk for all cause mortality observed in the extended ACS study.[9] Annual impacts across the European Union were estimated to be 3.6 million years of life lost each year based on the year 2000 and 2.5 million years of life lost each year based on the year 2020. The estimated gain in lost life years due to current legislation was 1.2 million years between 2000 and 2020. These results showed that large benefits are predicted to occur from current policies over this time.

Brunekreef[47] used the population-changed scenario and assessed the impact of air pollution on life expectancy based on effect estimates reported by the Six Cities[1] and ACS cohort studies.[2] He assumed a relative risk of 1.10 for men for a 10 $\mu g/m^3$ difference in long-term exposure to fine particles in the exposed and clean air group and applied this relative risk estimate to the 1992 table of mortality rates for Dutch men. A difference of 1.11 years (~13.1 months) in life expectancy was estimated between the exposed and the clean air groups in the Netherlands for Dutch men aged 25-90 years. The calculation has been restricted to ages 25-90, as the cohort studies have not gone beyond the age of 90 (the Six Cities study investigated a sample of persons 25-75 years old, who were followed up for about 15 years). When the calculation was extended to an age range of 25-100 year, the result was a difference in life expectancy of 1.51 years (~18.1 months) between the exposed and the clean air groups. These results show that the life-expectancy predictions are sensitive to extrapolation of cohort studies results to the older age groups.[47] Nevalainen and Pekkanen also used the population-changed scenario and estimated differences in life expectancy for a difference of 10 $\mu g/m^3$ in average fine particle levels in the less polluted and the more polluted areas.[48] They used the method of

competing causes of death, which were lung cancer, cardiopulmonary and other causes of death. The method of competing causes of death was used because the increase in the incidence of one cause of death does not directly increase mortality with the same impact, as the population at risk for the other causes will be reduced. Therefore the mortality due to these other causes of death will decline, even though the incidence has not changed. Mortality rates by age and cause of death in Finland in 1994 were used to estimate the number of deaths due to each cause of death in the life table, using cause-specific risk estimates from both the Six Cities[1] and the ACS study[2] (see Table 1 for effect estimates). In addition, calculations were also conducted using the all cause mortality risk estimates instead of the cause-specific risk estimates. The calculations were started from the age of 25, because the study population of the two cohort studies included only adults.[1,2] Life expectancy in the less polluted area was estimated to be 0.60 years (~7.2 months) higher than in the polluted area when the effect estimates of the ACS study[2] were used, and 1.01 years (~12.1 months) when the estimates of the Six Cities study[1] were used. If only the all cause mortality risk estimates had been used and the competing causes of death had been ignored, the losses in life expectancy would have been 0.70 years (~8.4 months) using the estimates of the ACS study,[2] and 1.37 years (~16.4 months) using the estimates of the Six Cities study.[1] These results indicate that the predictions of the health effects depend on the used risk estimates, and whether competing causes of death have been taken into account.[48] Miller and Hurley used a birth cohort from 2005 with mortality rates for England and Wales (for the year 1999) to estimate the gain in life expectancy for a reduction in $PM_{2.5}$ concentrations of 10 μg/m^3.[46] They used a relative risk of 1.06 for a 10 μg/m^3 difference in long-term exposure to $PM_{2.5}$, which was based on the extended ACS study.[9] The risk reduction was applied to the hazard rates for those who were aged 30 years or older only, because the ACS study included only people age 30 years or more at recruitment to the study. A 10 μg/m^3 reduction in $PM_{2.5}$ concentrations was estimated to results in a higher life expectancy of ~7 months.[46]

The described studies that used the population-changed scenario indicate that the life table estimates are sensitive to some uncertainties in input variables. These uncertainties may have an effect on the estimated life expectancy. All these studies estimated a difference in life expectancy for a difference of 10 μg/m^3 in average fine particle levels in less polluted and more polluted areas. Many epidemiological studies[2,9-11] and reviews[6] report risk estimates for an increase of 10 μg/m^3 in $PM_{2.5}$ concentrations. Although a change of 10 μg/m^3 in annual average $PM_{2.5}$ concentrations seems to be large in terms of possible pollutant reductions, it is not so large an amount that it is unrealistic to think about impact estimates based on a difference of 10 μg/m^3 $PM_{2.5}$.[46]

Following the method as used by Brunekreef,[47] the effect that long-term exposure to air pollution may have on life expectancy was estimated using the relative risk of 1.06 found in the NLCS-AIR study for a 10 μg/m^3 difference in $PM_{2.5}$ concentrations (which is the difference between the 5th and 95th percentile of the $PM_{2.5}$ distribution in the NLCS-AIR study). This relative risk was the same as the relative risk found in the ACS study for all cause mortality per 10 μg/m^3 increase in $PM_{2.5}$ concentrations.[2] In Table 3, this relative risk has been applied to the Central Bureau of Statistics (CBS) 1990 life table for Dutch men. The calculation has been restricted to ages 55-80, as this is the age range that was actually studied in the NLCS-AIR study (age at baseline 55-69 years at baseline and ten years of follow-up). The expected number of deaths for the different age categories was calculated over a 5-year period by subtraction of the number of survivors at age n + 5 from the number of survivors at age n. The expected number of deaths for each category over a period of 5 years decreases by a factor 1.06 in the "clean air" group, i.e. with $PM_{2.5}$ concentrations that are 10 μg/m^3 lower. To calculate average life expectancy between ages 55 and 80, the total number of years lived between 55 and 80 was calculated by multiplying the number of survivors in each of the 5-year age categories by 5. The result is the total number of years lived between ages 55 and 80 for men in the Netherlands. Life expectancy from age 55 is defined as the total number of years lived divided by the total number of subjects alive at age 55. The difference in life expectancy between the exposed and clean air groups was 0.34 years (~4.1 months). When using the same method to estimate the effect of air pollution exposure on mortality for women, the difference in life expectancy between the exposed and clean air groups was 0.21 years (~2.5 months). The difference in the estimated difference in life expectancy between men and women is caused by the lower underlying hazard rate among women in especially the lower ages. When the calculations were extended to an age range of 55-90 year, the difference in life expectancy between the exposed and clean air groups became 0.54 year (~6.5 months) for men and 0.45 year (~5.4 months). This shows how sensitive the results are to a wider age range, with wider age ranges leading to larger differences in life expectancy between the exposed and clean air groups.

Table 3. Estimated effect on life expectancy of Dutch men of a 10 μg/m^3 difference in long-term exposure to $PM_{2.5}$ between the exposed and clean air group (based on the Central Bureau of Statistics 1990 life table).

Age	Survivors (men)	Deaths in 5 years (n)	Expected deaths in 5 years in clean air (n)	Expected survivors in clean air (n)
55	91,475	4,749	4,480	91,475
60	86,726	7,223	6,835	86,995
65	79,503	11,159	10,614	80,160
70	68,344	15,326	14,713	69,545
75	53,018	17,595	17,167	54,833
80	35,423			37,665
	Total years lived: 2,072,445	Life expectancy between 55 and 80: 2,072,445 / 91,475 = 22.66	Life expectancy between 55 and 80: 2,103,363 / 91,475 = 23.00	Total years lived: 2,103,363

The estimated differences in life expectancy are lower compared with the 1.11 years for an age range of 25-90 estimated by Brunekreef.[47] However, the used relative risk estimate was slightly lower in our calculation (1.06 vs 1.10). When applying the same relative risk of 1.10 as used by Brunekreef[47] in our study, the differences in life expectancy between the exposed and clean air groups were for men 0.55 years (~6.6 months) for an age range of 55-80 years and 0.89 years (~10.7 months) for an age range of 55-90 year. Using a relative risk estimate of 1.10 instead of 1.06 explains a part of the difference in life time lost between our estimate and the estimate by Brunekreef.[47] Further, we did not take into account the number of deaths below age 55, so the life time lost for the full population will have been underestimated in our calculation.[46] Although the used age range and the used risk estimates had effects on the estimated life expectancy, our estimates of life expectancy were in agreement with estimates from previous studies.

In conclusion, the calculations in different studies suggest that the effect of long-term exposure to relatively low concentrations of air pollution may lead to a reduction of life expectancy of at least several months, which is a substantial public health impact. Several reservations need to be taken into account when interpreting the results of these calculations, because of uncertainties in input variables for the estimation of life expectancy. The calculations of the public health impact are still based on the relative risks of a limited number of studies, and differences between risk estimates can affect the estimates of life expectancy. Given the small number of prospective cohort studies, the shape of the exposure-response relation could not be explored in as much detail as in daily time-series studies. Further, as shown by the calculations, the results are sensitive to the used age range for which calculations have been made.

Methodological considerations

Exposure assessment

The ideal way to estimate an individual's personal exposure would be by personal monitoring. In large cohort studies, however, this would be not only extremely complex, but also extremely expensive and time-consuming.[51] Advances in methods such as land use regression modeling provided new possibilities to estimate air pollution exposure, also taking into account within-city air pollution contrasts, and a variety of approaches has been used to estimate air pollution exposure.[23] These include exposure indicators (traffic proximity variables) assessed using GIS, interpolation of measurements, land use regression modeling, dispersion modeling, and combinations of these methods. Because approximately 120,000 subjects were included in the NLCS-AIR study and because we had to estimate historical exposure for the years 1976-1996, personal monitoring was not possible in our study, and we used a combination of interpolation of measurements, land use regression and assessment of traffic intensity variables using GIS to assess long-term exposure to air pollution at different spatial scales. Exposure was considered to be a function of a regional, urban and local component. The regional component was assessed using interpolation of measurement data from regional background sites in a national monitoring network. Interpolation methods have been used in several recent cohort studies.[3,7,11] The urban component was estimated using land use regression modeling. Various studies have documented that land use regression models can be used to predict long-term average air pollution concentrations.[52-58] To assess the local scale component, we used traffic indicators (traffic intensity on nearest road, sum of traffic intensity in a 100 m buffer, and an indicator variable for living near a major road) and calculated concentrations due to local traffic. Indicators of traffic-related air pollution exposure have been widely used in epidemiological studies on the health effects related to motorized traffic.[5,14,24,59] A growing body of evidence supports the use of variables such as cumulative traffic near the home and distance from (major) roads as proxies for exposure to traffic-related air pollution. Distance from motorways as well as traffic density have been shown to be significant predictors of outdoor measurements of PM absorbance and NO_2.[56,60,61] Furthermore, previous studies have shown that concentrations of traffic-related air pollutants drop off to the local background concentration between 100 and 150 m from the roadside,[18] indicating that a 100 m buffer, as used in our study, is a reasonable distance to capture local traffic-related air pollution. A recent study by Hochadel et al. provides additional support for our choice of buffer size. After evaluating a wide range of buffer sizes, they found that cumulative traffic within a 100 m radius buffer was the most predictive of both measured $PM_{2.5}$ absorbance and NO_2.[56] The results

of our study showed that our regression models, which incorporated the regional, urban and local component, explained 84%, 44%, 59%, and 56% of the spatial variance for NO_2, NO, black smoke and SO_2, respectively. Our exposure assessment method takes thus small differences in long-term air pollution concentrations into account.

However, our exposure assessment method has relied on estimates of ambient outdoor air pollution concentrations at the home address, and home address exposure may not correctly estimate true personal exposure because people do not stay at home all the time and often stay indoors when they are at home. Personal exposure is influenced by factors such as time-activity patterns, indoor pollution sources, and time spent in locations other than at home, such as the workplace. In our study we did not have information about these factors. Participants in our study were 55-69 years old at baseline and approximately 85% of the population had no paid job anymore at baseline, which suggests that our participants may spent a relatively large amount of time at their home address. Time-activity studies provide support for this suggestion. In a German study, people who were older than 45 years were shown to spend on average 14.4 to 19.5 hours per day at home.[62] These results were in accordance with two North American time-activity studies, in which average time spent indoor at home was observed as 15.4 hours for Canadian adults and 15.5 hours for American adults.[63]

However, there is currently very little information about the validity of using long-term average outdoor air pollution as an estimate of personal air pollution exposure. In Amsterdam, personal soot exposure was 1.29 times higher in adults living on the main road network compared to subjects living in quiet streets.[64] Four studies in children found that higher ambient concentrations at the school and/or home address were associated with increased personal exposure to NO_2[19] and soot.[64-66] A recent study by Van Roosbroeck et al. among 47 older persons aged over 50 years showed that living in a high traffic intensity street was reflected in a small increase in personal exposure to soot (15%) and NO (16%).[67] However, no increase in personal exposure was found for $PM_{2.5}$, NO_2 and NO_x, despite demonstrable differences in outdoor concentrations between participants living in high and low traffic intensity streets, indicating that traffic intensity and personal exposure may not correlate well. The small contrast in personal exposure for subjects living in high and low traffic intensity streets can therefore not be explained by a small contrast in outdoor air concentrations. It is likely that three factors explain the smaller difference in personal exposure compared to the difference in outdoor concentrations: time activity patterns, incomplete penetration of outdoor air pollution in homes and indoor sources.[67] As there is only a limited number of studies on the validity of using long-term average outdoor air pollution as an estimate of personal exposure to air pollution, further

research is needed to evaluate the effects of measurement error in the exposure assessment on air pollution-health associations.

Statistical analyses

Associations between air pollution exposure and health may be influenced by a variety of confounding factors. In our study we conducted both case-cohort analyses, i.e. analyses using only cases and a randomly drawn subcohort, and analyses in the full cohort using all subjects. Complete confounder information was only available for the subcohort and for subjects who died or developed cancer during follow-up. As a result, analyses adjusted for all available confounders from the questionnaire were only possible using the case-cohort approach. For the full cohort analyses only a limited number of confounders were available (age, gender, smoking status and area level socio-economic status variables). The results showed that in the case-cohort analyses there was little difference between the effect estimates adjusted for all available confounders and the effect estimates adjusted for the limited number of confounders in the full cohort, suggesting that inclusion of the full set of potential confounder variables in fact made little difference in the case-cohort analysis. This does suggest, but not guarantee, that the effect of full adjustment would be the same in the full cohort analysis if data on all confounders had been available for analysis.

A potentially important confounder for the association between cardiovascular mortality and traffic-related air pollution is road traffic noise, as motorized traffic is not only an important source of air pollution, but also of noise, and because it has been suggested that both chronic exposure to air pollution and to traffic noise is associated with cardiovascular mortality.[6,68] In our study, associations between cardiovascular mortality and background black smoke concentrations and traffic intensity on the nearest road were insensitive to noise adjustment. Associations with traffic noise were however reduced after adjustment for background black smoke concentrations and traffic intensity on the nearest road. Hoffman et al. conducted a study on the association between long-term residential exposure to traffic and prevalence of coronary disease, comparing residents living within 150 m of major roads with those living further away.[69] Their definition of high exposure to traffic may also coincide with high traffic-related noise levels. Traffic noise levels were however not available, and analyses were therefore adjusted for hypertension, which is the hypothesized link between noise and cardiovascular disease. They concluded that residual confounding by traffic noise was small and presumably did not explain the observed observation.[69]

Health outcomes depend not only on the individual characteristics, but also on the area in which people live and work. “Area” effects occur when individual differences in health outcome are associated with the grouped variables that represent the

social, economic, and environmental setting where the individuals spent their time. These area effects often operate independently from (or interactively with) the individual variables.[70,71] Lack of statistical control for these area effects can bias the air pollution effect estimates and underestimate the associated standard errors.[71] First, we used four area-level confounders, the percentage of persons with a low and with a high income at the neighborhood and COROP area scale, to control for these area effects. We chose two scales for area-level socio-economic status because life expectancy varies significantly by COROP area (40 areas in the Netherlands),[72] and the neighborhood scale does not capture such regional variations adequately. After inclusion of these area-level confounders the effect estimates for background air pollution concentrations became slightly higher, while the effect estimates for the traffic variables did not change. Secondly, there are also spatial analytical models available to control for area effects. In the reanalysis of the ACS study spatial analytical models were used to take into account this spatial autocorrelation of air pollution, covariates and mortality. Control for spatial autocorrelation in the ACS study did not change the effect estimates substantially, but the standard errors became larger and therefore the confidence intervals became wider.[16] We also applied spatial analytical models in our study. When we compared the results of the standard Cox proportional hazard model in the full cohort with models taking into account spatial autocorrelation at the neighborhood and municipality scale, we observed that adjusted relative risks were very similar. Confidence intervals were also not widened when spatial clustering was accounted for. Apparently, the set of individual level confounders and the four area-level indicators of socio-economic status were sufficient to take into account spatial autocorrelation. In addition, spatial autocorrelation might be less influential on our results compared with the ACS study,[2,9] because our exposure was assessed on a smaller spatial scale and because we used traffic variables on an individual level.

In our study we assessed air pollution exposure using land use regression modeling with for example the number of inhabitants in a buffer around the residential address as predictor variable. Because this predictor variable might be related to other health factors such as socio-economic status in an area, using such a predictor variable for assessing air pollution exposure could introduce confounding when applied in epidemiological studies.[73] In addition to control for spatial autocorrelation, adjustment for area-level confounders that are more closely related to the disease of interest (e.g. percentage of people with a low income in a neighborhood) than the variable used in predicting air pollution (number of inhabitants in a buffer) is needed to ensure unbiased effect estimates of air pollution health effects.[73]

Conclusion

Our study is the second largest cohort study on the association between long-term air pollution with mortality and lung cancer conducted so far, after the ACS study.[2] In addition, the NLCS-AIR study is the largest cohort study that studied the separate effects of long-term exposure to background air pollution concentrations and living near a major road on mortality and lung cancer.

Within the NLCS-AIR study we developed an exposure assessment method to estimate long-term exposure to outdoor air pollution. Exposure was considered to be a function of a regional, an urban and a local component. Using GIS methods and traffic intensities our exposure assessment method explained a large part of the variations in outdoor air pollution concentrations.

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

Associations between black smoke concentrations and traffic variables with lung cancer incidence were (borderline) significant among never smokers. No associations were found for the complete study population or other smoking categories.

For the first time, the association between long-term exposure to air pollution, traffic intensity and road traffic noise and their respective impacts on mortality has been studied together. We observed an association between traffic intensity on the nearest road and overall cardiovascular mortality, which was driven by an association with ischemic heart disease mortality. Relative risks for background black smoke concentrations were elevated for cerebrovascular and heart failure mortality. The associations between black smoke concentrations and traffic intensity on the nearest road with overall cardiovascular mortality and ischemic heart disease mortality were not explained by modeled traffic noise in our study. There was an excess of overall cardiovascular mortality in the highest noise category (> 65 dB(A)), concentrated in deaths from heart failure and ischemic heart disease mortality. After adjustment for BS concentrations and traffic intensity these associations became lower and lost significance.

Our study adds evidence that long-term exposure to background and traffic-related air pollution increases mortality and lung cancer risk, and our results contribute to the still small database for quantifying the effects of long-term exposure

to air pollution on mortality and lung cancer risk. Although the individual health risks of air pollution are estimated to be relatively small, the public health consequences may still be substantial because of the large number of people exposed.

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Summary

Three major smog episodes (Meuse Valley, Belgium 1930; Donora, United States 1948; and London, United Kingdom 1952) drew attention to the effects of air pollution on health. Although the health effects of short-term exposure to air pollution, i.e. daily changes in air pollution at relatively low levels, are well documented, the health effects of long-term exposure to air pollution have been much less studied. Effects of long-term exposure to air pollution on mortality dominate the health impact assessment of air pollution, and more cohort studies of the association between long-term exposure to air pollution and mortality are needed.

The first cohort studies on mortality compared cities/metropolitan areas with different air pollution concentrations, assuming homogeneous exposure within a city not taking into account small-scale variations in air pollution levels. A few recent cohort studies have estimated individual exposure to air pollution and separated the background and local component of exposure by using an indicator variable for living near a major road. However, these studies included relatively small numbers of study subjects.

The NLCS-AIR study assessed the association between long-term exposure to background as well as traffic-related air pollution and mortality and lung cancer incidence using data from an ongoing cohort study: the Netherlands Cohort Study on Diet and Cancer (NLCS). The NLCS study was initiated in September 1986 with the enrollment of 120,852 subjects aged 55-69 years living in 204 municipalities located throughout the Netherlands.

The main aims of the NLCS-AIR study were:

1. To estimate exposure to traffic-related air pollution for all study subjects in a large, ongoing cohort study in the Netherlands
2. To evaluate the association between exposure to background and traffic-related air pollution and to road traffic noise and (occurrence of) mortality and lung cancer incidence in this cohort study
3. To evaluate whether this association varies with specific causes of death (respiratory, cardiovascular, other) and subject characteristics (such as gender, smoking habits, dietary habits, and education)

Details of the exposure assessment methods to estimate long-term exposure air pollution are described in chapter 2. Exposure at the baseline home address of all participants was considered as a function of a regional, an urban, and a local component. The regional component was estimated using inverse distance weighed interpolation of measurement data from regional background sites in the national monitoring network. The urban component was assessed using land use regression models with urban concentrations as measured by urban monitoring sites in the national monitoring network as dependent variables. Predictor variables were assessed using a geographic information system: number of inhabitants in different

buffers and land use variables. The sum of the regional and urban contributions was defined as background concentration. Background concentrations were estimated for nitrogen dioxide (NO_2), black smoke, fine particles less than 2.5 μm ($PM_{2.5}$) and sulfur dioxide (SO_2). The local component was assessed using a geographic information system including a digital road network with linked traffic intensities. Traffic intensity on the nearest (major) road and the sum of traffic intensity in a buffer of 100 m around each home address were estimated. Also an indicator variable for living near a major road was used. A quantitative estimate of the local component of the air pollution estimate was obtained using measurement data obtained from traffic sites and regression models with various traffic variables as predictor variables. It was added to the estimated background concentrations to create an overall exposure estimate for each pollutant. The methods that were developed were shown to explain a relatively large percentage of the spatial variance of the air pollution components that were studied.

In chapter 3, the association between mortality and long-term exposure to traffic-related air pollution is investigated. Background and traffic-related air pollution and several traffic exposure variables were associated with mortality, but the relative risks were generally small. Statistically significant associations between NO_2 and black smoke exposure and natural cause and respiratory mortality were found. The highest relative risks were found for respiratory mortality. Relative risks were also elevated but not significantly so for mortality other than cardiovascular, respiratory or lung cancer. We found suggestive evidence for larger effects of black smoke exposure in those with low education and in those with low fruit consumption.

As most studies on the association between lung cancer and air pollution investigated mortality only, we investigated the influence of traffic-related air pollution on lung cancer incidence in addition to mortality (chapter 4). We found no association between air pollution concentrations, traffic variables and lung cancer incidence in the full study population. In never smokers, associations between black smoke concentrations and traffic variables with lung cancer incidence were (borderline) significant, however. No associations were found in the ex and current smokers.

Chapter 5 focuses on the association between long-term exposure to air pollution, traffic intensity and road traffic noise and their respective impacts on cardiovascular mortality. This is the first time that the effects of air pollution, traffic intensity and traffic noise on cardiovascular mortality have been studied together. We observed an association between traffic intensity on the nearest road and overall cardiovascular mortality, which was driven by an association with ischemic heart disease mortality. Relative risks for background black smoke concentrations were elevated for cerebrovascular and heart failure mortality. These associations were not affected by adjustment for traffic noise. There was an indication of an effect of traffic noise in the

highest noise exposure category (> 65 dB(A)), which was largely restricted to heart failure mortality. The relative risk for the association between ischemic heart disease mortality and high traffic noise was reduced to unity after adjustment for background black smoke concentrations and traffic intensity. In the current study, associations between traffic intensity on the nearest road with overall cardiovascular mortality and ischemic heart disease mortality were not explained by traffic noise.

The results of this thesis provide evidence that exposure to background and to traffic-related air pollution increases the risk of cardiovascular, respiratory and lung cancer mortality.

Samenvatting

Drie grote smog episodes (Maas vallei, België 1930; Donora, Verenigde Staten 1948; en Londen, Groot-Brittannië 1952) zorgden voor aandacht voor de gezondheidseffecten van luchtverontreiniging. Alhoewel de gezondheidseffecten van korte-termijn blootstelling aan luchtverontreiniging, d.w.z. dagelijkse veranderingen in luchtverontreinigingniveaus bij relatief lage concentraties, goed zijn gedocumenteerd, zijn de gezondheidseffecten van lange-termijn blootstelling aan luchtverontreiniging veel minder onderzocht. Effecten van lange-termijn blootstelling aan luchtverontreiniging op mortaliteit domineren de 'health impact assessment' van luchtverontreiniging, en meer cohort studies naar de associaties tussen lange-termijn blootstelling aan luchtverontreiniging en mortaliteit zijn nodig.

De eerste cohort studies naar mortaliteit vergeleken steden met verschillende niveaus aan luchtverontreiniging, onder de aanname van homogene blootstelling binnen een stad en zonder rekening te houden met variaties in luchtverontreinigingsconcentraties op een kleine schaal. Enkele recente cohort studies hebben de blootstelling aan luchtverontreiniging op een individueel niveau geschat en hebben de achtergrond en lokale component van blootstelling van elkaar gescheiden door een indicator variabele voor wonen nabij een drukke weg te gebruiken. Deze studies bestonden echter maar uit een relatief klein aantal deelnemers.

De NLCS-AIR studie heeft de associatie tussen lange-termijn blootstelling aan zowel achtergrond als verkeersgerelateerde luchtverontreiniging met mortaliteit en longkanker incidentie onderzocht gebruikmakend van gegevens van een al bestaande cohort studie: de Nederlandse Cohort Studie naar Voeding en Kanker (NLCS). De NLCS studie is in september 1986 gestart met 120,852 deelnemers in de leeftijd 55-69 jaar die in 204 gemeenten verspreid over Nederland woonden.
De belangrijkste doelen van de NLCS-AIR studie waren:

1. Om de blootstelling aan verkeersgerelateerde luchtverontreiniging te schatten voor alle deelnemers in een grote, al bestaande cohort studie in Nederland
2. Om de associatie tussen blootstelling aan achtergrond en verkeersgerelateerde luchtverontreiniging en aan wegverkeergeluid met mortaliteit en longkanker incidentie te onderzoeken in deze cohort studie
3. Om te onderzoeken of deze associatie verschilt voor specifieke doodsoorzaken (respiratoir, cardiovasculair, anders) en voor individuele kenmerken (zoals geslacht, rookgewoonten, voedingsgewoonten en opleiding)

De details van de methoden om de blootstelling te schatten zijn beschreven in hoofdstuk 2. De blootstelling werd geschat voor elk huisadres bij het begin van het onderzoek en werd beschouwd als een functie van een regionale, een stedelijke en een lokale component. De regionale component werd geschat door gebruik te maken van interpolatie van meetdata van regionale achtergrondmeetstations in het

landelijke meetnetwerk. De stedelijke component werd geschat door gebruik te maken van regressie modellen met stedelijke concentraties gemeten door stadsmeetstations in het landelijke meetnetwerk als afhankelijke variabelen. De voorspellende variabelen werden bepaald met behulp van een geografisch informatie systeem: het aantal inwoners in verschillende buffers en landgebruik variabelen. De som van de regionale en stedelijke component werd gedefinieerd als de achtergrondconcentratie. Achtergrondconcentraties werden geschat voor stikstof dioxide (NO_2), zwarte rook, fijn stof deeltjes kleiner dan 2.5 µm ($PM_{2.5}$) en zwavel dioxide (SO_2). De lokale component werd geschat met behulp van een geografisch informatie systeem en een digitaal wegennetwerk met daaraan gekoppeld verkeersintensiteitsgegevens. De verkeersintensiteit op de dichtstbijzijnde (drukke) weg en de som van de verkeersintensiteit in een 100 m buffer rond het huisadres werden geschat. Er werd ook een indicator variabele voor wonen nabij een drukke weg gebruikt. Een kwantitatieve schatting van de lokale component werd geschat met behulp van meetdata van verkeersmeetstations en regressie modellen met verschillende verkeersvariabelen als voorspellende variabelen. Deze schatting werd toegevoegd aan de geschatte achtergrondconcentratie om een totale blootstellingschatting te creëren. De methoden die zijn ontwikkeld verklaarden een relatief hoog percentage van de ruimtelijke variatie in de niveaus van luchtverontreiniging.

In hoofdstuk 3 is de associatie tussen mortaliteit en lange-termijn blootstelling aan verkeersgerelateerde luchtverontreiniging onderzocht. Achtergrond en verkeersgerelateerde luchtverontreiniging als ook verschillende verkeersvariabelen waren geassocieerd met mortaliteit, maar de relatieve risico's waren over het algemeen klein. Statistisch significante associaties werden gevonden tussen blootstelling aan NO_2 en zwarte rook met natuurlijke doodsoorzaak en respiratoire mortaliteit. De hoogste relatieve risico's werden gevonden voor respiratoire mortaliteit. Relatieve risico's waren ook verhoogd, maar niet significant, voor mortaliteit anders dan cardiovasculair, respiratoir of longkanker. Er was suggestief bewijs voor hogere risico's voor zwarte rook blootstelling bij deelnemers met een laag opleidingsniveau en bij deelnemers met een lage fruitconsumptie.

Omdat de meeste studies naar de associatie tussen longkanker en luchtverontreiniging alleen mortaliteit hebben onderzocht, onderzochten wij de invloed van verkeersgerelateerde luchtverontreiniging op longkanker incidentie (hoofdstuk 4). Er werd geen associatie gevonden tussen blootstelling aan luchtverontreiniging, verkeersvariabelen en longkanker incidentie in de totale onderzoekspopulatie. Onder nooit-rokers waren de associaties tussen zwarte rook concentraties en verkeersvariabelen met longkanker incidentie echter significant. Er werden geen associaties gevonden voor ex- en huidige rokers.

Hoofdstuk 5 richt zich op de associatie tussen lange-termijn blootstelling aan luchtverontreiniging, verkeersintensiteit en wegverkeergeluid en hun effecten op cardiovasculaire mortaliteit. Dit is de eerste keer dat de effecten van luchtverontreiniging, verkeersintensiteit en verkeersgeluid op cardiovasculaire sterfte samen zijn onderzocht. Een associatie tussen de verkeersintensiteit op de dichtstbijzijnde weg en cardiovasculaire mortaliteit werd gevonden, en die werd voor een groot deel veroorzaakt door een associatie met ischemische hartziekte mortaliteit. Relatieve risico's voor achtergrond zwarte rook concentraties waren verhoogd voor cerebrovasculaire en hartfalen mortaliteit. Deze associaties veranderden niet na correctie voor verkeersgeluid. Er was een indicatie voor een effect van verkeersgeluid in de hoogste geluidscategorie (>65dB(A)), die voor het grootste deel beperkt bleef tot hartfalen mortaliteit. Het relatieve risico voor de associatie tussen ischemische hartziekte mortaliteit en blootstelling aan hoge verkeersgeluidsniveaus werd gereduceerd tot één na correctie voor achtergrond zwarte rook concentraties en verkeersintensiteit. In deze studie werden de associaties tussen de verkeersintensiteit op de dichtstbijzijnde weg met cardiovasculaire mortaliteit en met ischemische hartziekte mortaliteit niet verklaard door verkeersgeluid.

De resultaten van dit proefschrift laten bewijs zien dat blootstelling aan achtergrond en aan verkeersgerelateerde luchtverontreiniging het risico van cardiovasculaire, respiratoire en longkanker mortaliteit verhoogt.

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Curriculum Vitae

Rob Mathias Johannes Beelen was born in Weert (The Netherlands) on September 14, 1978. In 1996, he graduated secondary school (Gymnasium) at the Bisschoppelijk College in Weert, and started his study in Environmental Health Sciences at Maastricht University (The Netherlands). As part of his study he conducted in 1999 a 4-month research project on mortality from diabetes mellitus and rheumatoid arthritis in the paper and pulp mill industry at Linköping University (Sweden). After graduation in 2001, he started working as a PhD student at the Institute for Risk Assessment Sciences (IRAS) of Utrecht University (The Netherlands) on the study described in this thesis. This PhD project was embedded in the Netherlands Cohort Study on Diet and Cancer (NLCS), and was a collaboration between IRAS, the department of Epidemiology at Maastricht University (The Netherlands), TNO Quality of Life in Zeist (The Netherlands), and the Centre for Environmental Health Research at the National Institute for Public Health and the Environment (RIVM) (The Netherlands). In addition, from 2003 – 2005 he worked at a European project on Air Pollution Modeling for Support to Policy on Health and Environmental Risks in Europe (APMoSPHERE). Currently, he is working as a researcher at IRAS at a project on the use of geographic information for assessment of human exposure to air pollution within the framework of the Space for Geo-Information program (Ruimte voor Geo-Informatie (RGI)).

List of publications

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Mijn familie, pap, mam, Janneke en Tom, ook al heb ik jullie niet altijd even veel betrokken bij mijn onderzoek, jullie waren toch altijd benieuwd hoe het met mijn onderzoek ging en nu is het dan eindelijk zo ver dat jullie mij in pinguïn-pak kunnen zien! Ellemieke, nu we allebei onze scriptie en proefschrift af hebben, hebben we nog meer tijd om samen leuke dingen te doen!