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Long-term exposure to air pollution and mortality in the Danish population a nationwide study

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ABSTRACT

Background: Studies have shown higher mortality in association with exposure to air pollution. We investigated this association with focus on differences between socioeconomic groups.
Methods: We included all Danes born between 1921 and 1985 aged 30–85 years from 1991 to 2015 (N = 4,401,348). We applied a nested case-control design and identified those who died during follow-up and selected five controls per case. We modelled NO_2, fine particulate matter ($PM_{2.5}$), black carbon (BC) particles, and ozone (O_3) as five-year average concentrations at the residential addresses of 672,895 all natural cause mortality cases and 3,426,533 controls in conditional logistic regression with adjustment for individual and neighbourhood level socio-demographic variables.
Findings: In single pollutant models, a 10 $\mu g/m^3$ (BC: 1 $\mu g/m^3$) increase in NO_2, $PM_{2.5}$, BC, and O_3 was associated with natural cause mortality rate ratios (MRR) of 1·05 (95% confidence interval 1·04–1·06), 1·08 (1·04–1·13), 1·05 (1·02–1·08), and 0·96 (0·95–0·97), respectively. The patterns were similar for respiratory disease and lung cancer mortality. O_3 was associated with higher risk of CVD mortality. The rate differences for a unit increase in $PM_{2.5}$, NO_2, and BC were largest among those with the lowest income; this pattern was not detected when considering the relative risk measure, MRR.
Interpretation: Long-term concentration of air pollution at the residence was associated with higher natural cause mortality in the Danish population and the strength of the association differed by socioeconomic group. We recommend that future studies express socioeconomic differences in absolute rather than relative risk.

Introduction

It is well established that air pollution causes major diseases, including cardiovascular (CVD) and respiratory diseases [1,2]. In addition, studies have shown a higher mortality in association with exposure to the gaseous air pollutant NO_2, [3–7] fine particulate matter ($PM_{2.5}$), [4,8–11] black/elemental carbon (BC) particles, [4,7,12–14] and ozone (O_3) [15–18]. However, there is significant heterogeneity in the size of the observed risk estimates and the estimated differences between socioeconomic subgroups of the populations, which is probably related to differences in population characteristics, PM composition, exposure assessment method, and degree of confounder control. Statistical uncertainty due to limited size of the study population may also have played a role. The development of methods for air pollution exposure assessment over large areas has facilitated recent large-scale epidemiological studies of air pollution effects based on millions of individuals [5,9,11,16,19–22]. There is little statistical uncertainty of the risk estimates in such studies, but potential confounding is an important issue since information about individual lifestyle, e.g. smoking, alcohol, diet, and physical activity, is usually not available.

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Research in context

Evidence before this study

A review of 11 cohort studies from 2013 together with 10 more recent studies identified by a literature search in PubMed using the term "air pollution and mortality" show a pattern of higher all natural cause mortality among individuals living in locations with higher concentrations of fine particulate matter air pollution ($PM_{2.5}$). Many studies have investigated if the effect of $PM_{2.5}$ on mortality differs between subpopulations of different socioeconomic position but the results are far from consistent.

Added value of this study

This study confirms that higher exposure to $PM_{2.5}$, black carbon and NO_2 is associated with higher mortality. The rate differences for a unit increase in $PM_{2.5}$, NO_2, and BC were largest among those with the lowest income; that pattern was not detected when considering the relative risk measure, MRR.

Implications of all the available evidence

The results of this and previous studies collectively call for prevention strategies to reduce population exposure to air pollution and improve public health. Our results highlight the need of future studies to present results for different socioeconomic groups as absolute risk, taking into account the large differences in mortality rates between the different socioeconomic groups.

Ambient $PM_{2.5}$ air pollution was ranked as the 12th most important contributor to premature death in 2013 among all known environmental, occupational, and metabolic risk factors, [23] which might even be an underestimate.[24] There is a considerable interest in the distribution of this major public health burden across socioeconomic strata of populations and many studies have investigated if the association between air pollution and mortality differs between socioeconomic position (SEP) [4,9,10,16,21,25–33]. These studies compare *relative* risks across SEP typically expressed as hazard ratios or mortality rate ratios, i.e. a percentage increase in risk per a fixed increase in exposure. The meaning of such a percentage increase in risk depends on the number the percentage relates to; the same percentage in two different socioeconomic groups can represent very different absolute numbers of deaths for identical number of person-years at risk if the absolute mortality rate is different between the two groups. Also, differences between men and women in the air pollution related mortality have been investigated with inconsistent results [4,21,25,28–32,34–36].

It has been recognized for decades that Denmark has unique facilities for registry-based epidemiological research because of the many nation-wide, reliable registries including longitudinal information on vital status, health, mortality, emigration, address history, and many socioeconomic factors [37].

Based on the entire Danish population, we aimed to investigate associations between long-term exposure to air pollution and four mortality outcomes while subdividing the population by SEP and considering measures of both relative and absolute risk in different socioeconomic groups.

Methods

Population, data sources and study design

Since April 1st 1968, all persons living in Denmark have been registered in the Civil Registration System, [38] which records personal identification number (PIN), gender, date and place of birth, residential history, and continuously updates information on vital status. The unique PIN enables accurate linkage of individual data between the nation-wide registries. We defined a study base cohort consisting of all persons who have lived in Denmark at one point in time since April 2, 1968, who were born between 1921 and 1985, and aged 30–85 years (N = 4401,348). We followed up the cohort members for mortality outcomes in the nation-wide Danish Registry of Causes of Death, [39] and identified those who died from January 1st, 1991 to December 31st, 2015. We subdivided deaths by the underlying cause: All natural cause (ICD-8: 000–799; ICD-10: A00–R99), cardiovascular diseases (ICD-8: 390–459; ICD-10: I10–I99), respiratory diseases (ICD-8: 460–519; ICD-10: J00–J99), and lung cancer (ICD-8: 162.1; ICD-10: C34).

To limit the computation time of the analyses, we analysed the cohort in an individually time-matched nested case-control design with each case-control pair forming a separate stratum. For each death of a cohort member, we selected five controls at random among cohort members who were born within seven days of the case, were of the same sex, and were alive at the exact age at which the case died (index date). Only persons who lived in Denmark both at start of follow-up and at death/index date were included. Owing to the time-matching within each stratum and the density sampling of controls, this method provides results similar to a traditional time-to-event analysis of a cohort, i.e. mortality rate ratios [40].

Exposure assessment

We retrieved historical addresses of the study population from the Danish Civil Registration System, including geographical coordinates and exact dates of moving in and out.

The concentrations of $PM_{2.5}$, NO_2, BC, and O_3 at residential addresses were calculated with a multiscale integrated air pollution modelling system including contributions from urban and regional sources of the pollutants and their precursors, transport and chemistry in the atmosphere, and removal processes. The system enables calculation of ambient air pollution concentration at high temporal (hourly basis; summarized to yearly averages for this study) and spatial (1 km $\times$ 1 km) resolution.

The air pollution is modelled as the sum of the contributions from 1) regional background, i.e. from all natural and anthropogenic sources, such as residential heating, industry, and traffic, at distances of more than 25 km from the receptor point using emission inventories for the entire northern hemisphere and the Danish Eulerian Hemispheric Model (DEHM), [41] and 2) local scale, taking into account the emission density from all types of emissions such as traffic and residential heating estimated with the Spatial high resolution distribution model for emissions to air (SPREAD) methodology [42] and average building height and cover in 1 km $\times$ 1 km grid cells of Denmark, using the Urban Background Model (UBM) [43,44]. Comparisons between yearly average concentrations measured at monitoring stations in Denmark and concentrations modelled with the DEHM and UBM, as in the present study, at the monitoring station locations showed correlation coefficients of 0·87 for NO_2, 0·55–0·80 for $PM_{2.5}$, 0·64 for BC, and of 0·88 for O_3 (Appendix Table A1).

We *a priori* chose the five years preceding index date as our main exposure period and calculated time-weighted average concentrations (TWA) of air pollutants taking into account exact dates for moving in and out of each address during that period. We also calculated TWAs over one and ten years preceding index date for sensitivity analyses.

Individual level socio-demographic variables

For each individual, we included information from the registries at Statistics Denmark about socio-demography: marital status,

educational level, occupational status, country of origin, individual gross income, and number of children (Appendix p 2). To minimize potential effects of diseases (leading to death) on covariates, the covariate information was delineated five years before the index date.

Neighborhood level socio-demographic variables

We obtained nine socio-demographic indicators aggregated to the parish level from Statistics Denmark for each year: proportion of households (PH) without a car, PH in rented dwellings, proportion of inhabitants (PI) being unemployed, PI being single parents, PI with a criminal record, PI with only basic (mandatory) education, PI with a disposable family income in the lowest quartile, PI with a manual profession, and PI being immigrants or descendants from non-Western countries (Appendix p 2). Further, we used parish population density (inhabitants/km^2) for a sensitivity analysis. These parish-level characteristics five years before the index date were included as linear variables.

Statistical analyses

We used conditional logistic regression to estimate mortality rate ratios (MRRs) and 95% likelihood ratio based confidence intervals (CIs) for a fixed increase in air pollution assuming a linear exposure-response association. The linearity was investigated by comparing a linear model with a model including exposure deciles and using a likelihood ratio test. The association between the five-year TWA and natural cause mortality did not deviate statistically significantly from linearity for NO_2, O_3, or $PM_{2.5}$, whereas the association for BC did (Appendix Table A2). As a supplement, we therefore also calculated MRRs with 95% CIs for the nine upper exposure deciles using the lowest decile as comparison.

We undertook analyses of four endpoints: all natural cause, CVD, respiratory disease, and lung cancer mortality. We used three confounder models: 1) basic adjustment i.e. by design adjusting for age, sex and calendar time; 2) further adjustment for the individual level socio-demographic variables; 3) model two with further adjustment for the parish level socio-demographic variables (main model). All main model analyses used a robust sandwich covariance matrix in a two-level analysis specifying parish as the second level.

We included only individuals, for whom 100% of the ten-year period preceding index date had known air pollution exposure, thus ensuring maximum precision in exposure assessment and identical datasets for analyses of one-, five- and ten-year exposure-time windows. Further, we used complete case analyses including only participants with information about all potential confounders in the main model.

First, we fitted models with one air pollutant at a time. Secondly, we analyzed two-pollutant models. We investigated associations between air pollutants and mortality for subgroups defined by sex, age at index date, calendar year, income and education. We illustrated interactions graphically by plotting model three adjusted linear associations between air pollution and MRRs by population subgroups. Further, we used the study base cohort to calculate absolute mortality rates by population subgroup and plotted these rates by age. We calculated absolute rate differences for a 10 $\mu g/m^3$ change in air pollution (1 $\mu g/m^3$ for BC) by multiplying MRRs (minus one) with the absolute rates.

Sensitivity analyses included repeated analyses using 1) one-year and ten-year TWA exposure, 2) further adjustment of the main model for population density of the parish, 3) using summertime (April-September) O_3 instead of yearly means, 4) re-calculating the main results with additional adjustment for parish level incidence rates for lung cancer and diabetes as indicators for lifestyle habits (smoking, diet, physical activity), and 5) comparison of results obtained with our nested case-control design analyzed with conditional logistic regression and a traditional cohort design analyzed with Cox proportional hazards regression.

Individual lifestyle variables

Individual lifestyle factors such as smoking, physical activity, diet, and BMI were not available for the entire Danish population. We recently published on air pollution and mortality in the Diet Cancer and Health (DCH) cohort using an identical outcome definition and addressing the same air pollutants [4]. We repeated the analyses of the DCH cohort for five years TWA exposure using models with three different sets of co-variates:1) A basic model identical with the basic model one of the present study adjusting for sex, age, and calendar time, 2) additional adjustment for exactly the same individual and area level variables as adjusted for in the present nation-wide study and using identical sources and definitions of the variables, and 3) additional adjustment for questionnaire-based individual lifestyle variables: smoking (status, intensity, duration), passive smoking, physical activity, BMI, waist circumference, alcohol consumption, and fruit and vegetable intake. This served to evaluate the impact of individual lifestyle variables.

Ethics

Data access for this study was granted by Danish Data Protection Agency, the Danish Health Data Authority and Statistics Denmark. Because the study was based exclusively on registry data, according to Danish legislation, informed consent from cohort members was not required.

Role of funding source

The funding source had no involvement in the study design, collection, analysis, interpretation, writing or decision to submit for publication.

Results

We identified 702,539 cases and 3512,695 controls and excluded 12,803 (1·8%) cases and 30,736 (0·9%) controls for whom we did not have information about exposure for 100% percent of the time during the last ten years before index date, and 16,841 (2·4%) cases and 55,426 (1·6%) controls because of missing data in co-variates. Thus, we included 672,895 natural cause mortality cases and 3426,533 controls.

Table 1 shows similar distributions of sex, year of birth and death, and country of origin among cases and controls. Cases were more often never married/divorced/widowed and retired and had more often only mandatory education, no children, and low income. The distribution of the nine neighborhood level socio-demographic variables were similar among cases and controls (Appendix Table A3). The distribution of air pollution concentrations were also similar among cases and controls, with means of five-year TWA concentrations among controls of 17·5, 54·6, 12·2, and 0·7 $\mu g/m^3$ of NO_2, O_3, $PM_{2.5}$, and BC, respectively (Appendix Table A4-A6).

In our basic adjusted model, a 10 $\mu g/m^3$ (BC: 1 $\mu g/m^3$) increase in NO_2, $PM_{2.5}$, BC, and O_3 was associated with natural cause MRRs of 1·12 (1·12–1·13), 1·13 (1·10–1·17), 1·14 (1·12–1·15), and 0·89 (0·88–0·89), respectively (Table 2). Adjustment for the individual level socioeconomic variables affected only the MRRs for $PM_{2.5}$ and BC whereas adjustment for the parish socio-demographic variables affected the MRRs for all four pollutant. In our fully adjusted main model, a 10 $\mu g/m^3$ (BC: 1 $\mu g/m^3$) increase in NO_2, $PM_{2.5}$, BC, and O_3 was associated with natural cause MRRs of 1·05 (1·04–1·06), 1·08 (1·04–1·13), 1·05 (1·02–1·08), and 0·96 (0·95–0·97), respectively

Table 1
Distribution of individual level variables among the 672,895 cases and 3426,533 controls included in the analyses.*

	n (%)	
	Cases	Controls*
	672,895 (100)	3426,533 (100)
Cause of death		
Cardiovascular	185,947 (27.6)	939,146 (27.4)
Respiratory	66,958 (10.0)	339,108 (9.9)
Lung cancer	67,293 (10.0)	340,109 (9.9)
Other	352,697 (52.4)	1808,170 (52.8)
Year of death		
1991–1999	185,407 (27.6)	943,670 (27.5)
2000–2015	487,488 (72.4)	2482,863 (72.5)
Sex		
Men	372,489 (55.4)	1910,721 (55.8)
Women	300,406 (44.6)	1515,812 (44.2)
Birth year		
1920–1929	249,005 (37.0)	1247,237 (36.4)
1930–1939	224,423 (33.4)	1127,558 (32.9)
1940–1949	131,761 (19.6)	675,215 (19.7)
1950–1959	50,372 (7.5)	275,129 (8.)
1960–1969	14,470 (2.2)	84,660 (2.5)
1970–1985	2864 (0.4)	16,734 (0.5)
Age at index date		
30–39	7785 (1.2)	44,522 (1.3)
40–49	29,296 (4.4)	165,145 (4.8)
50–59	84,798 (12.6)	448,191 (13.1)
60–69	190,748 (28.3)	964,790 (28.2)
70–79	256,520 (38.1)	1285,232 (37.5)
80–85	103,748 (15.4)	518,653 (15.1)
Marital status		
Never married	67,094 (10.0)	212,816 (6.2)
Married	380,973 (56.6)	2299,963 (67.1)
Divorced	82,894 (12.3)	271,300 (7.9)
Widowed	103,790 (15.4)	452,831 (13.2)
Cohabitant/living together	38,144 (5.7)	189,623 (5.5)
Educational level		
Only mandatory	314,553 (46.7)	1382,749 (40.4)
Short	280,855 (41.7)	1476,884 (43.1)
Medium	11,995 (1.8)	77,999 (2.3)
Higher	65,492 (9.7)	488,901 (14.3)
Occupational status		
Employed, top level	20,388 (3.0)	200,367 (5.8)
Employed, medium level	43,619 (6.5)	353,541 (10.3)
Employed, basic level	93,316 (13.9)	625,153 (18.2)
Unemployed	18,360 (2.7)	80,653 (2.4)
Retired	497,212 (73.9)	2166,819 (63.2)
Country of origin (birth)		
Denmark	652,265 (96.9)	3310,265 (96.6)
Other OECD country	11,672 (1.7)	66,492 (1.9)
Non-OECD country	8958 (1.3)	49,776 (1.5)
Children		
None	168,785 (25.1)	658,890 (19.2)
One	141,938 (21.1)	682,121 (19.9)
Two	205,085 (30.5)	1204,014 (35.1)
Three	105,491 (15.7)	612,802 (17.9)
Four or more	51,596 (7.7)	268,706 (7.8)
Income quintile		
1st	199,195 (29.6)	830,670 (24.2)
2nd	199,451 (29.6)	819,261 (23.9)
3rd	123,459 (18.3)	652,222 (19.0)
4th	84,164 (12.5)	566,067 (16.5)
5th	66,626 (9.9)	558,313 (16.3)

* Controls were matched individually to cases by time of birth, age and sex thus showing nearly identical distributions of these covariates.

Table 2
Association between air pollution at the residence(s) 5 years before index date and mortality.

	MRR (95% CI)		
	Model 1*	Model 2†	Model 3‡
Natural cause mortality			
NO_2 (10 $\mu g/m^3$)	1.12 (1.12–1.13)	1.13 (1.12–1.13)	1.05 (1·04–1.06)
O_3 (10 $\mu g/m^3$)	0.89 (0.88–0.89)	0.88 (0.88–0.89)	0.96 (0.95–0.97)
$PM_{2.5}$ (10 $\mu g/m^3$)	1.13 (1.10–1.17)	1.31 (1.27–1.36)	1.08 (1.04–1.13)
BC (1 $\mu g/m^3$) §	1.14 (1.12–1.15)	1.18 (1.17–1.20)	1.05 (1.02–1.08)
Cardiovascular disease mortality			
NO_2 (10 $\mu g/m^3$)	1.03 (1.03–1.04)	1.06 (1·05–1.07)	1.00 (0·98–1.01)
O_3 (10 $\mu g/m^3$)	0.97 (0.96–0.98)	0.95 (0.94–0.96)	1.02 (1·01–1.04)
$PM_{2.5}$ (10 $\mu g/m^3$)	0.89 (0.84–0.94)	1.09 (1.02–1.15)	1.01 (0·95–1.08)
BC (1 $\mu g/m^3$)	0.99 (0·97–1.01)	1.06 (1.04–1.08)	0.97 (0·94–1.01)
Respiratory disease mortality			
NO_2 (10 $\mu g/m^3$)	1.12 (1.10–1.13)	1.17 (1.15–1.19)	1.08 (1·05–1·11)
O_3 (10 $\mu g/m^3$)	0.89 (0.87–0.90)	0.84 (0.82–0.86)	0.92 (0.90–0.94)
$PM_{2.5}$ (10 $\mu g/m^3$)	1.05 (0.95–1.17)	1.43 (1.29–1.58)	1.08 (0.97–1.20)
BC (1 $\mu g/m^3$)	1.11 (1.07–1·15)	1.26 (1.21–1.31)	1.07 (1.01–1.13)
Lung cancer mortality			
NO_2 (10 $\mu g/m^3$)	1.12 (1.10–1.14)	1.17 (1.15–1·18)	1.07 (1.04–1.09)
O_3 (10 $\mu g/m^3$)	0.89 (0.87–0.90)	0.85 (0.83–0.86)	0.94 (0.91–0.96)
$PM_{2.5}$ (10 $\mu g/m^3$)	1.10 (1.00–1.21)	1.36 (1.23–1.50)	1.08 (0.96–1.21)
BC (1 $\mu g/m^3$)	1.13 (1.09–1.16)	1.23 (1.18–1.27)	1.07 (1.03–1.11)

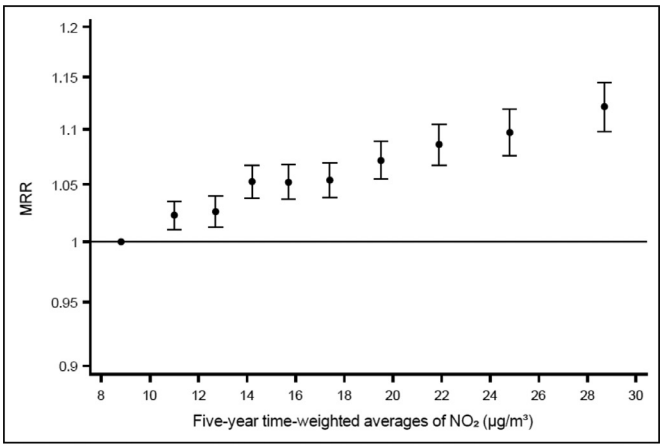
* Adjusted for sex, age, and calendar time, by match.
† Further adjusted for individual factors: marital status, educational level, occupational status, income, country of origin, and number of children.
‡ Further adjusted for neighborhood factors: car ownership, rented dwellings, unemployment, manual professions, education, income, one-parent households, immigrants, and criminal records.
§ For BC, the linearity assumption was not met and the results should be interpreted with caution (see Fig. 1 and Appendix Table A2).

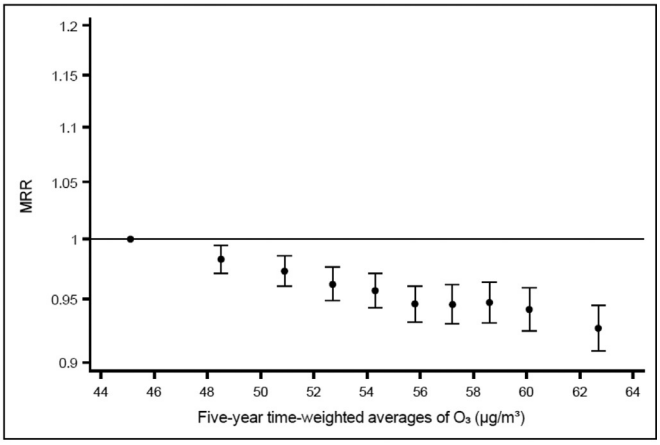
(Table 2). Decile-based results for NO_2, $PM_{2.5}$, and BC in association with natural cause mortality showed systematic increases of the MRR up through the ten exposure categories, and systematic decreases for O_3 (Fig. 1 and Appendix Table A7).

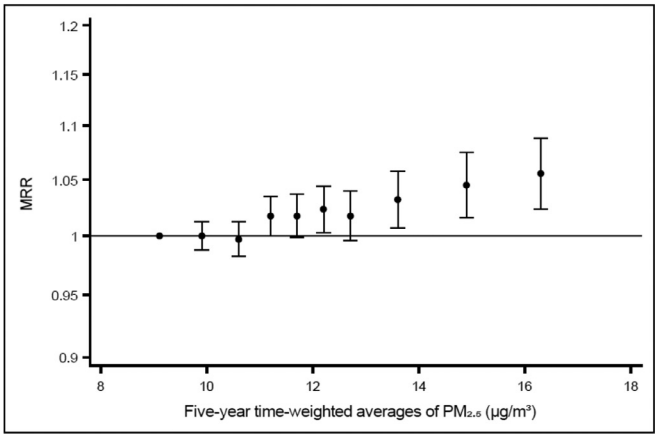
Higher concentrations of NO_2, $PM_{2.5}$, and BC were associated with higher rates of mortality due to both respiratory disease and lung cancer whereas O_3 showed associations in the opposite direction. O_3, but none of the other three pollutants, was associated with a higher risk of CVD mortality in the main model but not in the other models (Table 2). Among men, NO_2 and $PM_{2.5}$ were associated with CVD mortality (Appendix, Table A8).

Table 3 shows associations between natural cause mortality and NO_2, $PM_{2.5}$ and BC in different socio-demographic strata of the population. Men drove the higher overall MRR in association with these three pollutants. The highest MRRs were seen for the intermediate age group (60–69 y) and the lowest MRRs among the youngest (30–49 y) and oldest (80–84 y) age groups. The MRR in association with $PM_{2.5}$ was higher for deaths occurring between 1991 and 1999 than between 2000 and 2015 whereas MRRs in association with NO_2 and BC were similar in the two periods. For $PM_{2.5}$, the highest MRRs were found in association with higher educational and income levels. For NO_2 and BC, the highest MRRs were found in association with the lowest educational level and no clear pattern was evident in association with income level. Appendix Table A8 shows interaction results for cause specific mortality. Fig. 2 (upper) shows that at low $PM_{2.5}$ exposure, the mortality rate was highest for those with low education and lowest for those with highest education (reference category). At high $PM_{2.5}$ levels, however, the mortality rate was similar for the four educational level groups, reflecting the higher MRR (steeper slopes) among higher educational level groups (Table 3). Fig. 2 (lower) shows that at low $PM_{2.5}$ exposure, the lowest income quartile was associated with the highest mortality rates and the highest income quartile was associated with the lowest mortality rates. At high $PM_{2.5}$ exposure, the mortality rates were similar for the four upper quintiles whereas it remained highest for the lowest income quintile regardless of the $PM_{2.5}$ level.

Table 4, Fig. 3 and Appendix Figure A1 show higher natural cause mortality rates among those with lower education and income, and among men and older individuals. Table 4 illustrates the general pattern for all three pollutants that MRRs associated with air pollution







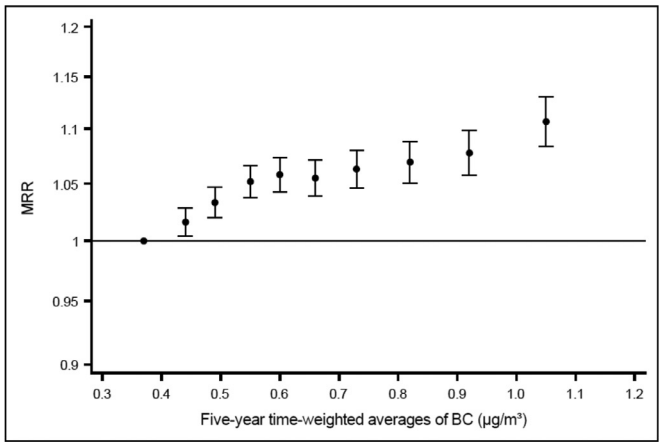


Fig. 1. Association between five-year average air pollution exposure and natural cause mortality in the fully adjusted Model 3. The vertical whiskers show mortality rate ratios with 95% confidence interval for each of the nine upper exposure deciles compared with the lowest decile (reference). The reference and the whiskers are placed at the median of each exposure decile.

Table 3
Associations between 5-year time-weighted air pollution concentrations and natural cause mortality rate ratio (MRR), by socio-demographic characteristics of the study population.

	Natural cause mortality		
	NO_2	$PM_{2.5}$	BC
	MRR (95% CI)	MRR (95% CI)	MRR (95% CI)
Sex			
Male	1.08 (1.07·1.10)	1.25 (1.18–1.32)	1.09 (1·05–1.13)
Female	1.02 (1.01–1.03)	0.91 (0.86–0.96)	0.98 (0.96–1·00)
Age at death			
30–49	1.04 (1.02–1.06)	0·96 (0·8·1·08)	1.01 (0.97–1.06)
50–59	1.07 (1·05–1.08)	1.07 (0.99–1.15)	1.05 (1.01–1.09)
60–69	1.08 (1.07–1.09)	1.14 (1.08–1.21)	1.08 (1.04–1.12)
70–79	1.04 (1.03–1.06)	1.08 (1.03–1.14)	1.03 (1.00–1.06)
80–84	1.02 (1.01–1.04)	1.02 (0.94–1.11)	1.00 (0.97–1.04)
Year of death			
1991–1999	1.06 (1.05–1.07)	1.11 (1.05–1.17)	1.05 (1.01–1.08)
2000–2015	1.05 (1.04–1.06)	1.07 (1.02–1.13)	1.05 (1.02–1.08)
Education, individual			
Mandatory	1.07 (1.06–1.08)	1.03 (0.98–1.07)	1.09 (1.05–1.12)
Short	1.05 (1.04–1.06)	1.12 (1.07–1.17)	1.02 (1.00–1.05)
Medium	1.06 (1.02–1.09)	1.26 (1.15–1.39)	1.03 (0.95–1·11)
High	1.03 (1.01–1.05)	1.32 (1.25–1.40)	0.98 (0.94–1.01)
Income, individual			
Q1 (lowest income)	1.06 (1.05–1·08)	1.11 (1.06–1.16)	1.06 (1.03–1.10)
Q2	1.03 (1.02–1.04)	0.98 (0.94–1.02)	1.01 (0.8–1·04)
Q3	1.05 (1.04–1·07)	1.04 (0.99–1.09)	1.06 (1.03–1.10)
Q4	1.06 (1.04–1.07)	1.17.(1.11–1.23)	1.06 (1.02–1.09)
Q5 (highest income)	1.09 (1.07–1.11)	1.49 (1.41–1.58)	1.09 (1.04–1.13)

All results are from our main model with adjustment for sex, age, and calendar time, by design, and individual factors: marital status, educational level, occupational status, income, country of origin and number of children, and neighborhood factors: car ownership, rented dwellings, unemployment, manual professions, education, income, one-parent households, immigrants, and criminal records.
MRRs are given per 10 $\mu g/m^3$ NO_2 and $PM_{2.5}$, and per 1 $\mu g/m^3$ BC.

were highest for the highest income group whereas the rate differences were highest for the lowest income group. Table 4 also shows a pattern of higher mortality rate differences per unit change in NO_2 and BC among those with lower education whereas the pattern was opposite for $PM_{2.5}$.

Table 5 shows results from the DCH cohort to illustrate the consequence of the lack of adjustment for individual lifestyle factors as in the present nation-wide study. The crude model (adjustment for sex, age, and calendar time) showed relatively high natural cause MRRs. Further adjustment for the same individual and neighborhood level socio-demographic variables as in the present nation-wide study reduced the MRRs substantially. Further adjustment for questionnaire-based individual lifestyle variables lowered the natural cause MRRs only moderately (22–33%). Appendix Table A9 shows similar results for CVD mortality whereas the reduction of the lung cancer MRR was larger (up to 50%).

Two pollutant models showed that the associations between NO_2 and BC, and lung cancer mortality was robust to adjustment for O_3 and $PM_{2.5}$; the size of the MRRs did not change much and the association remained statistically significant. Adjustment for each other, however, lowered the MRR for both NO_2 and BC. The association between NO_2 and natural cause mortality remained statistical significant when adjusted for the other pollutants, but the MRR was very sensitive to adjustment for O_3. The association between O_3 and CVD mortality remained statistically significant when adjusted for the other pollutants but was very sensitive to adjustment for NO_2 (Appendix Table A10). Apart from these results, the two pollutant

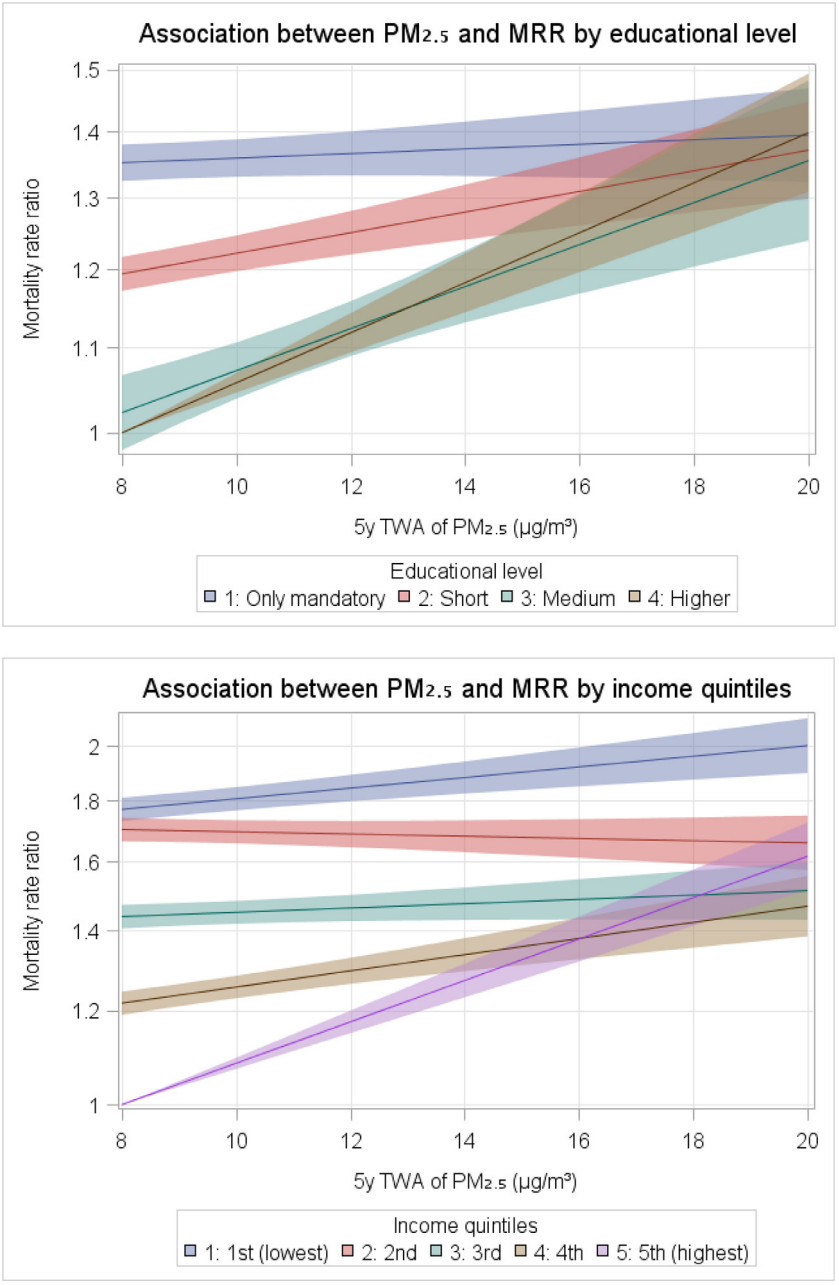


Fig. 2. Linear associations, with 95% confidence intervals, between time-weighted average (TWA) $PM_{2.5}$ exposure and mortality rate ratios for natural cause mortality (MRRs), by individual educational (upper) and income level (lower). The common reference is the combination of low exposure and highest, respectively, education and income category. The associations are adjusted for the co-variates of model 3.

models showed inconsistent and/or statistically insignificant results. The correlations between pollutants, especially that between NO_2 and O_3, was high (Appendix Table A11–13).

Sensitivity analyses showed 1) that our findings for natural cause mortality were not sensitive to choice of time-window for the TWA exposure (Appendix Table A14), 2) that the results of our main model was not sensitive to further adjustment for the population density of the neighborhood (results not shown), 3) that results based on summertime O_3 provided results similar to those based on yearly means (Appendix Table A15), 4) that adjustment for parish-level incidence rates of lung cancer and diabetes lowered the MRRs for natural cause mortality moderately and more for lung cancer mortality (Appendix Table A16), and 5) that analyzing our data in a nested case-control design with conditional logistic regression provided results identical to a traditional cohort design analyzed with Cox proportional hazards regression (Appendix pages 14–16, Appendix Table A17-A18).

Discussion

This study on air pollution and mortality, based on a population of an entire nation, shows that higher concentrations of NO_2, $PM_{2.5}$, and BC were associated with higher natural cause mortality, whereas ozone showed the opposite pattern. A similar risk pattern was seen for respiratory and lung cancer mortality. Higher concentrations of O_3, but none of the other three pollutants, was associated with a higher CVD mortality. The associations between natural cause mortality and $PM_{2.5}$, NO_2, and BC were driven by men and the MRR for $PM_{2.5}$ was higher in the early time period than in the later. For both BC, NO_2 and $PM_{2.5}$, the relative mortality measure (MRR) associated with a 10 $\mu g/m^3$ increase was highest among those with highest income, whereas the absolute mortality measure (rate difference) was highest among those with the lowest income.

Table 4
Natural cause mortality absolute rates (per 100,000 person-years)*, rate ratios (per 10 $\mu g/m^3$)†, and rate (per 100,000 person-years) differences‡ (per 10 $\mu g/m^3$ increase in NO_2 and $PM_{2.5}$, and 1 $\mu g/m^3$ increase in BC), by socio-demographic characteristics of the study population.

		NO_2		$PM_{2.5}$		BC	
	Mortality rate*	Mortality rate ratio†	Mortality rate difference‡	Mortality rate ratio†	Mortality rate difference‡	Mortality rate ratio†	Mortality rate difference‡
Sex							
Male	1078	1.08	86	1.25	270	1.09	97
Female	823	1.02	16	0.91	−74	0.98	−16
Age at death							
30–49	125	1.04	5	0.96	−5	1.01	1
50–59	557	1.07	39	1.07	39	1.05	28
60–69	1449	1.08	116	1.14	203	1.08	116
70–79	3453	1.04	138	1.08	276	1.03	104
80–84	7056	1.02	141	1.02	141	1.00	0
Education							
Mandatory	1628	1.07	114	1.03	49	1.09	147
Short	782	1.05	39	1.12	94	1.02	16
Medium	501	1.06	30	1.26	130	1.03	15
High	485	1.03	15	1.32	155	0.98	−10
Income							
Q1 (lowest income)	2282	1.06	137	1.11	251	1.06	137
Q2	2120	1.03	64	0.98	−42	1.01	21
Q3	741	1.05	37	1.04	30	1.06	44
Q4	394	1.06	24	1.17	67	1.06	24
Q5 (highest income)	351	1.09	32	1.49	172	1.09	32

* Calculated on the basis of our basic cohort population (excluding those with missing in education or income), i.e. 4101,889 individuals followed from last of January 1st, 1991 and 30 years birthday until first of December 31, 2015 and 85 years birthday, providing 686,311 deaths during 72,413,230 person-years· The crude incidence rates were based on number of cases and person-years summarized over all age groups. The contribution of cases and person-years to education and income was treated as time dependent variables measured 5 years ago.

† From Table 3.

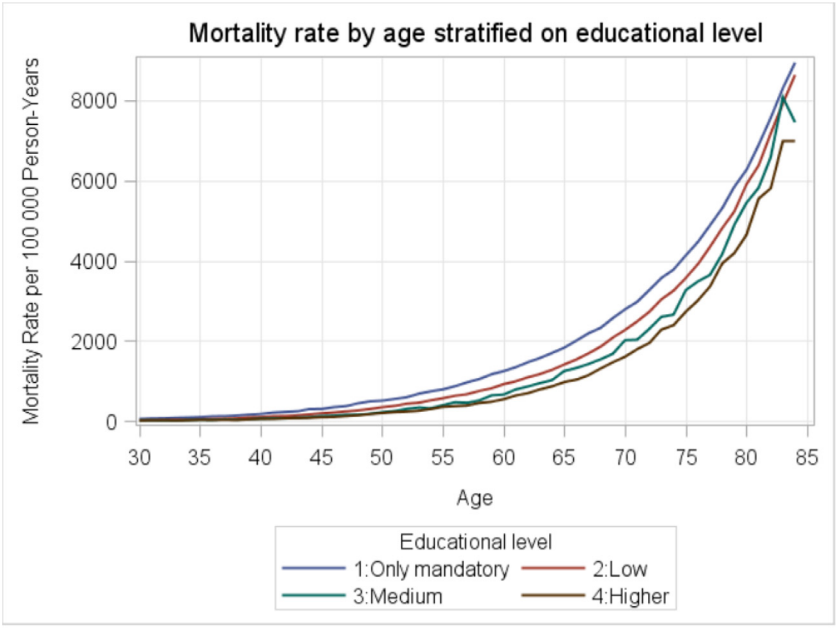
‡ The rate difference was calculated as "(mortality rate ratio − 1) × mortality rate", thus expressing the estimated change in mortality rate (per 100,000 person-years) in association with a 10 $\mu g/m^3$ increase in NO_2 and $PM_{2.5}$, and per 1 $\mu g/m^3$ BC.

Our results showed a natural cause MRR of 1·08 (1·04–1·13) for a 10 $\mu g/m^3$ increase in $PM_{2.5}$, which is similar to the hazard ratio (HR) of 1·06 (1·04–1·08) found in a meta-analysis of 11 cohort studies [12] and those of three recent studies [16,36,45] but lower than other recent studies [4,9,11,21,22,46,47]. Our null finding with a CVD MRR of 1·01 (0·95–1·08) per 10 $\mu g/m^3$ $PM_{2.5}$ is in line with a meta-analysis HR of 0·99 (0·91–1·08) based on 22 European cohorts, [32] whereas other cohort studies have found higher risk estimates. [4,9,10,12,22,30,45-47] The literature is inconsistent about a possible association between $PM_{2.5}$ and respiratory mortality; [4,12,22,29,30,46,47] the results of the present study indicated such an association (MRR=1·08; 0·97–1·20). Our finding of an increased lung cancer MRR (1·08; 0·96–1·21) in association with $PM_{2.5}$ is in line with most previous studies [4,22,45,47,48]. The present study found that a higher BC concentration was associated with higher MRRs for natural cause, respiratory and lung cancer mortality, but not with CVD mortality. This is in line with some, but not all, cohort studies. [4,7,12,14,29,31,32] A recent meta-analysis based on 48 articles showed associations between a 10 $\mu g/m^3$ increase in NO_2 concentrations and all-cause (HR = 1·02; 1·01–1·03), CVD (HR = 1·03; 1·02–1·05), respiratory (HR = 1·03; 1·01–1·05), and lung cancer mortality (HR = 1·05; 1·02–1·08) [3–7,15]. The present study found similar results except for our null finding for CVD mortality. A review of 14 articles found no evidence of an association between long-term O_3 exposure and mortality; [49] more recent studies have found both positive, negative, and no association [4,15–18,20]. Our present study found negative associations between O_3 and natural cause, respiratory and lung cancer mortality, but a positive association with CVD mortality.

A review from 2013 reported larger mortality HRs related to $PM_{2.5}$ among subjects with lower education [12] but studies since then provided no clear picture [4,9,10,16,21,30–32]. The present study found the highest $PM_{2.5}$-related MRRs among individuals with the highest education and income. An initial interpretation would be that $PM_{2.5}$ is more harmful to those of higher socioeconomic position. However, if we consider the results for the lowest income group, the MRR of 1.11 means an 11% higher mortality rate, which was 2282 deaths per 100,000 person-years in the low income group, resulting in 251 extra deaths per 10 $\mu g/m^3$ increase in $PM_{2.5}$ per 100,000 person-years. Considering similarly the highest income group, the MRR of 1.49, i.e. 49% higher mortality rate, which was 351 deaths per 100,000 person-years, resulted in 172 extra deaths per 10 $\mu g/m^3$ increase in $PM_{2.5}$ per 100,000 person-years. Is the relative risk measure (MRR) or the absolute risk measure (rate difference) most relevant? From an individual perspective, an absolute risk measure informs about the probability of death for a given exposure difference whereas the relative risk measure has no direct interpretation at the individual level; a meaningful interpretation requires calculations based on baseline mortality (or disease) rates. From a public health perspective, absolute risk measures also seem most relevant. In fact, health impact assessments for evaluation of the public health consequences of exposures usually translate the relative risk measures into absolute measures such as number of deaths or years of life lost in a population given an exposure contrast. Thus, when comparing risk in association with an exposure between sub-populations, we would recommend expressing risk in absolute terms, at least if the baseline mortality (or disease) rates differ much between the sub-populations, as is the case for socioeconomic groups.

We found a stronger association between $PM_{2.5}$ and risk of dying in the period 1991–1999 than in 2000–2015. An explanation could be that the PM composition has changed to be less harmful in the later period. Change over time in potentially interacting factors such as occupational exposures, dietary patterns or medical treatment could also be in play. The MRRs in association with NO_2 and BC were similar in the two periods; the composition of NO_2 and BC does not change over time.

In our study, men drove the association between air pollution and natural cause mortality with weaker, no, or even negative



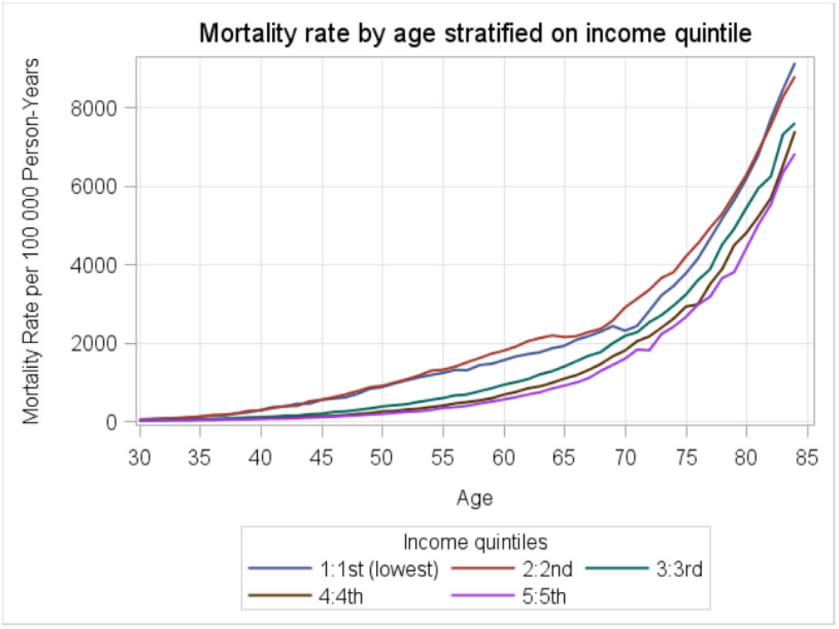


Fig. 3. Age-specific natural cause mortality rates, by educational level and income.

The figures were made on the basis of our basic cohort population (excluding those with missing in education or income), i.e. 4101,889 individuals followed from last of January 1st, 1991 and 30 years birthday until first of December 31, 2015 and 85 years birthday, providing 686,311 deaths during 72,413,230 person-years. Education and income were treated as time-dependent variables measuring the value five years ago.

Table 5
Associations between 5-year time-weighted average concentration of $PM_{2•5}$, BC and NO_2, and natural cause mortality in the Diet Cancer and Health cohort (N = 49,542), with different adjustment models.

Exposure	N cases	Model 1* MRR (95% CI)	Model 2† MRR (95% CI)	Model 3‡HR (95% CI)
$PM_{2•5}$ (10 $\mu g/m^3$ increment)	10,193	1.69 (1.45–1.97)	1.24 (1.05–1.45)	1.17 (0.99–1.38)
BC (1 $\mu g/m^3$ increment)	10,193	1.25 (1.18–1.32)	1.09 (1.02–1.16)	1.06 (0.99–1.13)
NO_2 (10 $\mu g/m^3$ increment)	10,193	1.16 (1.13–1.20)	1.04 (1.02–1.08)	1.03 (1.00–1.06)
O_3 (10 $\mu g/m^3$ increment)	10,193	0.82 (0.79–0.85)	0.95 (0.91–0.99)	0.97 (0.93–1.01)

* Model 1: Adjusted for age, sex, and calendar time.

† Model 2: Model 1 + all the socio-demographic variables available from Statistics Denmark for the nation-wide study a) at individual level: educational level, marital status, occupational status, income, number of children and country of origin, and b) at neighborhood level: car ownership, rented dwellings, unemployment, manual professions, education, income, one-parent households, immigrants, and criminal records.

‡ Model 3: Model 2 + mortality-related lifestyle factors from the baseline questionnaire of the Diet Cancer and Health cohort: smoking, alcohol consumption, physical activity, BMI, waist circumference, ETS, fruit, and vegetable consumption.

associations among women. Most previous studies have shown a similar pattern of higher risk estimates among men, [4,16,21,25,31,46] while others have not [9,28,36]. Such differences between sexes might relate to different biological responses to PM air pollution as suggested by a study showing associations between $PM_{2.5}$ and inflammation markers in men, but not in women [50]. Differences between sexes in time activity patterns leading to different exposure to air pollution or to potentially interacting occupational or other exposures might also play a role. The higher MRRs for men compared to women were consistent across pollutants for CVD mortality but inconsistent across pollutants for respiratory and lung cancer mortality (Appendix Table A8). It is uncertain if chance or other factors caused the inconsistent results.

The present study has several strengths including use of the population of an entire nation as the study base, which minimizes the risk for selection bias and provided an excellent statistical power. The nation-wide Danish registries are reliable and virtually complete impeding bias due to missing information. The registries also provided information on a wide range of socio-demographic data at the individual and at the parish level, which we used for adjustment and for interaction analyses. We retrieved information about residential history for the entire population four decades back in time to increase the precision of the exposure assessment, which was undertaken by use of a state-of-the-art, successfully validated multiscale air pollution modelling system. Although the air pollution modelling system has been successfully validated against independent measurements, [41,44] some degree of misclassification is inevitable. Such exposure misclassification would most likely be non-differential and attenuate risk estimates towards null. Another limitation is the lack of information about road traffic noise, which might confound estimated associations with traffic-related air pollutants such as NO_2 and BC. However, we would expect such potential confounding to apply particularly to CVD mortality because noise is an established risk factor for CVD, and given our null result for associations between these traffic-related air pollutants and CVD mortality, noise seems not to be an important confounder in the present study.

The main challenge of the present study was the lack of data about individual lifestyle, which potentially could confound our results. We met that challenge by adjustment for various individual and small area socio-demographic variables, which we would expect to account for at least part of the possible confounding from lifestyle factors such as smoking, diet, BMI, and physical activity. Analyses of data from the DCH cohort confirmed that when adjusting for socio-demographic variables at individual and neighborhood level, further adjustment for individual lifestyle would only change the estimated natural cause MRRs moderately towards the null, whereas lung cancer MRRs were reduced more. The DCH cohort participants were 50–64 years old at enrollment during 1993–1997, living in the two largest cities in Denmark, and were (self-)selected towards higher SEP [51]. Thus, the DCH is not a representative sample of the Danish population, which calls for caution when generalizing these results to the present nationwide study. However, adjusting our main model further for parish level incidence rates of lung cancer and diabetes (as indicators for lifestyle such as smoking, diet and physical activity) showed similar results, i.e. only a moderate reduction of MRRs for natural mortality and more reduction of the lung cancer MRRs. The larger reduction of lung cancer MRRs is probably because of the very strong association between smoking and lung cancer. Altogether, lack of adjustment for individual lifestyle factors in our nation-wide study, with extensive adjustment for socio-demographic variables from nationwide registries, seems to cause a slightly upwards biased MRR for natural cause mortality. Lung cancer MRRs were more affected by (lack of) adjustment for individual lifestyle and thus, associations between air pollution and lung cancer is probably best established in traditional cohort studies with detailed individual information about smoking.

Air pollution is a complex mixture of correlated pollutants. We fitted two pollutant models to try to identify single pollutants associated with mortality independently of the other pollutants. The results showed that the association between NO_2 and natural cause and lung cancer mortality persisted after adjustment for the other pollutants. NO_2 is an indicator of a mixture of air pollutants from local sources, such as traffic, and we interpret the result as an indication that air pollution from local sources, e.g. primarily emitted particles, increases the mortality. BC is another indicator for primary emissions from local sources and BC was also associated with natural cause and lung cancer mortality in the two-pollutant models. The high correlation between the pollutants made a meaningful interpretation of most of the two-pollutant models difficult and particularly the high correlation between NO_2 and O_3 seemed to influence the results. The finding of an apparently protective association with O_3 seems counterintuitive and is in contrast to previous results [15,16,18,20,52]. Therefore, it is likely that our negative O_3 association is a result of confounding by other, harmful pollutants being negatively correlated with O_3 (Appendix Tables A11-A13).

This study was based on the entire Danish population of which most are Caucasians exposed to relatively low concentrations of outdoor air pollution. We would expect that the results can be generalized to other Western populations although differences in genetic architecture, exposure levels, and PM composition could limit generalizability.

In conclusion, this nation-wide study showed that higher air pollution concentrations of $PM_{2.5}$, BC, and NO_2 at the residence were associated with higher natural cause, respiratory, and lung cancer mortality, but not with CVD mortality. Men drove these associations. Increases in $PM_{2.5}$, BC, and NO_2 were associated with the highest absolute increase in mortality rate among those with the lowest income; a pattern which was not detectable when considering the relative risk measure (MRR). We recommend that future studies focus on absolute risk measures when reporting associations with air pollution in different socioeconomic groups.

Declaration of Competing Interests

None

Data sharing statement

Access to individual-level data is governed by Danish authorities. These include the Danish Data Protection Agency, the Danish Health Data Authority and Statistics Denmark. Each scientific project must be approved before initiation, and approval is granted to a specific Danish research institution. Researchers at Danish research institutions may obtain the relevant approval and access data. International researchers may gain data access if governed by a Danish research institution having the needed approval and data access.

Author contribution

Conception: JB, ORN, CBP, TS, SA, CG, UAH. Design: ORN, CBP, UAH, JB, SA, TS. Data: CBP, SA, UAH, ORN, JB, CG, LFR, JHC. Analyses: ET, SA, UAH, CBP, ORN. Interpretation: All authors. Drafting manuscript: ORN, CBP, UAH. Critical revision of manuscript: All authors.

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analysis, interpretation, writing and decision to submit for publication.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2020.100605.

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