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Published in:
Environment International

DOI:
10.1016/j.envint.2018.12.010

Publication date:
2019

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (APA):
Hvidtfeldt, U. A., Sørensen, M., Geels, C., Ketzel, M., Khan, J., Tjønneland, A., Overvad, K., Brandt, J., & Raaschou-Nielsen, O. (2019). Long-term residential exposure to PM2.5, PM10, black carbon, NO2, and ozone and mortality in a Danish cohort. *Environment International*, *123*, 265-272. https://doi.org/10.1016/j.envint.2018.12.010

Environment International 123 (2019) 265–272

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Long-term residential exposure to $PM_{2.5}$, PM_{10}, black carbon, NO_2, and ozone and mortality in a Danish cohort

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ARTICLE INFO

Handling Editor: Xavier Querol

Keywords:
Particulate matter
NO_2
Black carbon
Ozone
CVD
Mortality
Epidemiology

ABSTRACT

Air pollutants such as NO_2 and $PM_{2.5}$ have consistently been linked to mortality, but only few previous studies have addressed associations with long-term exposure to black carbon (BC) and ozone (O_3).

We investigated the association between $PM_{2.5}$, PM_{10}, BC, NO_2, and O_3 and mortality in a Danish cohort of 49,564 individuals who were followed up from enrollment in 1993–1997 through 2015. Residential address history from 1979 onwards was combined with air pollution exposure obtained by the state-of-the-art, validated, THOR/AirGIS air pollution modelling system, and information on residential traffic noise exposure, lifestyle and socio-demography.

We observed higher risks of all-cause as well as cardiovascular disease (CVD) mortality with higher long-term exposure to $PM_{2.5}$, PM_{10}, BC, and NO_2. For $PM_{2.5}$ and CVD mortality, a hazard ratio (HR) of 1.29 (95% CI: 1.13–1.47) per 5 $\mu g/m^3$ was observed, and correspondingly HRs of 1.16 (95% CI: 1.05–1.27) and 1.11 (95% CI: 1.04–1.17) were observed for BC (per 1 $\mu g/m^3$) and NO_2 (per 10 $\mu g/m^3$), respectively. Adjustment for noise gave slightly lower estimates for the air pollutants and CVD mortality. Inverse relationships were observed for O_3. None of the investigated air pollutants were related to risk of respiratory mortality. Stratified analyses suggested that the elevated risks of CVD and all-cause mortality in relation to long-term PM, NO_2 and BC exposure were restricted to males.

This study supports a role of PM, BC, and NO_2 in all-cause and CVD mortality independent of road traffic noise exposure.

1. Introduction

Air pollution has consistently been linked to adverse health effects. The gaseous nitrogen oxide pollutants (NO_2 and NO_x), which are often used as indicators for traffic-related air pollution, have been related to some of the leading causes of premature death, namely cardiovascular diseases (CVD) and respiratory outcomes (Mills et al., 2015; Mills et al., 2016; Hamra et al., 2015).

Over the years, epidemiological evidence of an effect of particulate matter with the mass concentration of particles smaller than 2.5 or 10 μm ($PM_{2.5}$ and PM_{10}) has accumulated. A meta-analysis covering 11 cohort studies on long-term exposure to $PM_{2.5}$ reported a higher risk of all-cause and cardiovascular mortality with higher exposure (Hoek et al., 2013). However, the heterogeneity between studies was substantial. The large European Study of Cohorts for Air Pollution Effects (ESCAPE) project, including 22 European cohorts and > 350,000 individuals, also reported a higher overall mortality for $PM_{2.5}$ (Beelen et al., 2014a). The study, however, did not yield firm evidence of an association with CVD or non-malignant respiratory mortality (Beelen et al., 2014b; Dimakopoulou et al., 2014). Still, other studies have linked PM air pollution to cardiovascular disease incidence and mortality – on both short- and long-term exposure basis (Brook et al., 2010).

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https://doi.org/10.1016/j.envint.2018.12.010
Received 31 August 2018; Received in revised form 8 November 2018; Accepted 4 December 2018
Available online 12 December 2018

Black carbon (BC), which is a ubiquitous element of PM related to combustion-sources (e.g. diesel exhaust particle emissions), is hypothesized to play a key role in adverse health effects of particulate matter (Luben et al., 2017). The ESCAPE analysis on natural cause mortality did not find an overall association with $PM_{2.5}$ absorbance (a proxy for BC or soot) (Beelen et al., 2014a), but a newly published systematic review reported a consistent association between BC and cardiovascular disease hospital admissions and mortality (Luben et al., 2017). The authors, however, did not find merit for a causal interpretation due to potential for co-pollutant confounding by for instance $PM_{2.5}$. Likewise ozone (O_3) has been linked to overall mortality, CVD and respiratory mortality (Bell et al., 2005). Although focus has mainly been on short-term exposure, a systematic review of 14 studies on long-term exposure to O_3 did not find evidence of an association with CVD, respiratory or all-cause mortality (Atkinson et al., 2016). Recent large-scale prospective studies have, however, suggested a higher risk – even after adjustment for $PM_{2.5}$ and NO_2 (Turner et al., 2016; Crouse et al., 2015).

Road traffic noise is another important environmental exposure linked to CVD through mechanisms similar to those of air pollutants, such as systemic inflammation and oxidative stress (Münzel et al., 2017a). Since PM, NO_2, BC and noise share common sources (e.g. traffic), mutual adjustment is warranted. The majority of previous studies on air pollution and CVD, however, did not take into account road traffic noise exposure. A recent pooled analysis of three large British cohorts reported associations between PM and CVD, also after adjustment for road traffic noise (Cai et al., 2018).

The previous studies vary according to exposure assessment methods. Early studies have applied exposure estimates from centrally located monitoring stations with low spatial characterization of the pollutants, typically representing urban background conditions (Baxter et al., 2013). In recent years, many studies have used Land Use Regression (LUR) or dispersion modelling systems. Where LUR models rely on air pollution monitoring and land use data, the dispersion model requires detailed emission data input.

This study adds to the current evidence on PM, NO_2, BC, O_3 and mortality in a large cohort with detailed data on air pollution exposure and lifestyle factors and socio-demography at both individual and small-scale neighborhood level as well as decades of residential address history information. In addition, we were able to include information on residential traffic noise exposure several years prior to baseline and throughout the follow-up period. Associations between residential NO_2 exposure and all-cause mortality have been documented previously in this cohort, but with shorter follow-up and less detailed adjustments for confounders (Raaschou-Nielsen et al., 2012).

2. Methods

2.1. Study population

The Danish Diet, Cancer and Health cohort enrolled participants in the period of 1993–1997 (Tjønneland et al., 2007). Men and women aged 50–64 years residing in the areas of Copenhagen and Aarhus, who were born in Denmark and without a cancer diagnosis at the time of inclusion, were invited. In total, 57,053 agreed to participate (response ≈35%). All participants completed a self-administered questionnaire concerning lifestyle factors, diet, occupational and reproductive history. Physical examinations included anthropometric measures.

We linked participants to national registries from Statistics Denmark through the unique personal identification number. Sociodemographic information was available from 1980 and onwards.

2.2. Exposure assessment

We retrieved residential address history of each cohort member from the Danish Civil Registration System (CRS) (Bøcker Pedersen, 2011) in the period of January 1, 1979 to December 31, 2015, and geocoded 98.9% of these (within 5 m from the front door of the address) by linkage to the Danish address database. The PM, NO_2, BC, and O_3 concentrations at residential addresses of the cohort members were derived by a high-resolution dispersion modelling system which incorporates contributions from local, urban, and regional sources of precursors to PM, NO_2, BC, and O_3. This multiscale integrated model system (DEHM, UBM, and OSPM) is called the THOR system (Brandt et al., 2001), and when the OSPM is operated at individual addresses in GIS, this part is called AirGIS. The AirGIS system is a fully deterministic dispersion modelling system and its predictions are not dependent on any observed concentrations. The newly updated AirGIS has been described and validated in several papers and the geographical and temporal variations have been found to be predicted well (Hvidtfeldt et al., 2018; Ketzel et al., 2011; Khan et al., 2018). For $PM_{2.5}$, PM_{10} and BC the correlation coefficients between measured and modelled concentrations were in the range of 0.67–0.85, 0.70–0.74, and 0.77–0.79, respectively, across different locations and measurement periods (Hvidtfeldt et al., 2018). Correlations comparing modelled concentrations of NO_2, and O_3 to measurements from permanent stations from the Danish Monitoring Network and a measurement campaign were equally high (Ketzel et al., 2011). In brief, the system enables the calculation of ambient air pollution concentration at high temporal (hourly basis) and spatial (individual address) resolutions. The air pollution at a specific location is modelled as the sum of the contributions from 1) regional background, i.e. from sources outside the urban area such as power plants, industry, and long-range transport, using the Danish Eulerian Hemispheric Model (DEHM) (Brandt et al., 2012) 2) urban background, taking into account the emission density originating from all types of emissions (e.g. traffic and residential heating (Plejdrup and Gyldenkærne, 2011; Plejdrup et al., 2016)) and average building cover and height on a resolution of 1 km × 1 km, using the Urban Background Model (UBM) (Brandt et al., 2001; Brandt et al., 2003), and 3) local street traffic, including intensity, speed and type, emission factors for the car fleet, street and building geometry using the OSPM model (Ketzel et al., 2012), and meteorology using the WRF meteorological model (Skamarock et al., 2008). We calculated the full-year annual mean concentrations of $PM_{2.5}$, PM_{10}, NO_2, BC, and O_3 at all addresses between January 1, 1979 and end of follow-up.

2.3. Outcome

We established follow-up based on linkage to the CRS, which includes date of emigration and death, and the Danish Register of Causes of Death (Helweg-Larsen, 2011). We defined the cause of death according to the underlying cause of death recorded on death certificates. Participants who died from external causes such as injuries, accidents and suicides (ICD-10 codes S–Z) were censored at date of death. In addition, we investigated cardiovascular (ICD10 codes 'I00'–'I99') and respiratory (ICD10 codes 'J00'–'J99' and 'C34') subgroups of mortality.

2.4. Confounders

The following set of potential confounders of the relation between the exposures and mortality were selected through careful consideration of the underlying web of causation based on a priori knowledge and the method of Directed Acyclic Graphs (online Appendix Fig. S1) (Greenland et al., 1999): Age, sex, educational attainment, occupational status, marital status, smoking (status, intensity, and duration), environmental tobacco smoke (ETS), alcohol consumption, BMI, waist circumference, fruit consumption, vegetable consumption, physical activity, neighborhood level socioeconomic status (SES), and road traffic noise at the residence.

The neighborhood level SES variables are described in detail in the online Appendix. In brief, we classified neighborhoods according to the parish codes obtained from the Danish Geodata Agency and obtained

sociodemographic indicators aggregated to the parish level from Statistics Denmark. In 1996, a total of 2160 parishes existed with a median number of 1032 inhabitants (range 33–35,979) and a mean area of 16.2 km^2 (range 0.1–126.2). We obtained nine variables describing elements of neighborhood level SES from Statistics Denmark. These included: proportion of households (PH) without a car, PH living in rented dwellings, proportion of inhabitants (PI) being unemployed, PI being single parents (sole providers), PI with a criminal record, PI with only basic education, PI with a low disposable income, PI with a manual profession, and PI being immigrants or descendants from non-Western countries. We applied a shrinkage technique to address issues of large standard errors (McLennan et al., 2011), and performed a principal component analysis by use of the SAS (9.3) PROC FACTOR procedure with orthogonal (varimax) rotation in order to reduce the number of variables and to obtain the relative weights of each indicator. Two component scores were derived representing a linear composite of optimally weighted observed indicators for each parish at baseline (Meijer et al., 2013).

Road traffic noise was calculated by use of SoundPLAN (version 6.5, http://www.soundplan.dk/). For each residential address of cohort members in the period from 1987 to 2012, noise was calculated for the years 1990, 1995, 2000, 2005, and 2010, based on the following input: point for noise estimation (geographical coordinates and height); road links with information on annual average daily traffic, vehicle distribution (of light and heavy vehicles), travel speed, and road type; and building polygons with height for all buildings. Road traffic noise was calculated as the equivalent continuous A-weighted sound pressure level (L_{Aeq}) at the most exposed façade of the dwelling at each address for day (L_d; 07:00–19:00 h), evening (L_e; 19:00–22:00 h) and night (L_n; 22:00–07:00 h), and expressed as L_{den} (den = day, evening, night) by applying a 5-dB penalty for the evening and a 10-dB penalty for the night as follows: $L_{den} = 10 \times \log(1/24 \times (12 \times \exp(L_d/10) + 3 \times \exp((L_e + 5)/10) + 9 \times \exp((L_n + 10)/10)))$. A lower limit of 40 dB was applied (Sørensen et al., 2014).

2.5. Statistical methods

We applied Cox Proportional Hazards Models with age as the underlying time scale, following each cohort member from date of inclusion into the cohort until the date of death, emigration, or December 31, 2015. Persons, who moved during follow-up to an unknown address (N = 472, i.e. < 1%), were censored on the last date of the latest identified address.

We tested the proportional hazards (PH) assumption of the Cox Models for all covariates by a correlation test between the scaled Schoenfeld residuals and the rank order of event time. In addition, we compared air pollution associations across 10-year age categories. We detected deviation from the PH assumption for BMI, smoking status, smoking duration, alcohol, and occupational status and thus included these variables as strata. We formally tested the linearity of continuous variables by linear spline models (Greenland, 1995), with no deviation detected. The exposure-response function was plotted using smoothed splines with four degrees of freedom (Therneau, 2018).

The environmental exposures PM, NO_2, BC, O_3 and noise were modelled as time-dependent variables, thus recalculating exposure for survivors at the time of each death, with an exposure window of 15 years before death (5 years for noise). The time-weighted average concentrations were calculated based on the yearly concentrations at all addresses the last 15 years before death (and a similar exposure time window for non-censored cohort participants) and weights were calculated according to the exact days of living at each specific address.

$PM_{2.5}$, PM_{10}, NO_2, BC, and O_3 were modelled separately in three models of increasing levels of adjustment: Model 1: adjusted for age (underlying time-scale), sex and calendar time in order to account for time-trends in exposure and outcome (5-year groups entered as a time-dependent variable); Model 2: further adjusted for individual level factors educational attainment (8–11 yrs of basic schooling, 11–14 upper secondary/vocational training, and 15+), occupational status (strata of white collar, blue collar, unemployed, retired), marital status (married, divorced, single, widowed), smoking status (never, former, current), smoking duration (strata of < 10, 10–19, 20–29, and 30+ years), smoking intensity (g/day), exposure to environmental tobacco smoke (ETS, yes/no), alcohol intake (strata of < 1, 1–9, 10–19, 20–29, 30–39, and 40+ g/day), fruit intake (g/day), vegetable consumption (g/day), Body Mass Index (strata of < 25, 25–29, 30–34, and 35+), waist circumference (cm), sport during leisure time (yes/no); Model 3: further adjusted for neighborhood level SES (two components, grouped according to the quartiles of their distribution).

Sensitivity analyses included: 1) Adjustment for road traffic noise (dB, time-dependent, exposure window of 5 years before death) in the analyses of all-cause and CVD mortality, 2) further adjustment for parish population density (persons/km^2), 3) applying other air pollution exposure periods including the 1-year mean exposure at the baseline address as well as exposure time-windows of 1, 5, and 10 years preceding death, 4) investigating effect modification by sex, smoking status and education in relation to all-cause and CVD mortality by including an interaction term between the factors of interest and the time-weighted exposure under the null-hypothesis of no differences in the hazard ratios across the groups, 5) a further subdivision of respiratory mortality into lung cancer and non-malignant deaths, 6) investigating PM-coarse (as given by PM_{10} minus $PM_{2.5}$) in relation to the three outcomes of interest, and 7) exploring the association between the combined oxidant capacity of NO_2 and O_3 and mortality as suggested by recent studies (Yang et al., 2016; Williams et al., 2014; Weichenthal et al., 2017). If both pollutants affect health through a mechanism of oxidative stress, we would expect to observe higher effect estimates for the combined measure, O_x, than for the individual pollutants alone (Williams et al., 2014). We considered both a simple measure of O_x, given by the sum of NO_2 and O_3, as well as a weighted version which took into account the larger redox potential of O_3 compared to NO_2 (given by the equation $O_x^{wt} = [(1.07 \times NO_2) + (2.075 \times O_3)]/3.145$) (Williams et al., 2014; Weichenthal et al., 2017). The pollutants were converted from μg/m^3 to ppb prior to weighting with a conversion factor of 2.00 for O_3 and 1.88 for NO_2.

We used the function 'cox.zph' to test the proportional hazards assumption and the 'pspline' function of 'coxph' for the smoothed spline predictions in the statistical software package R, version 3.2.3. All other analyses were conducted in SAS, version 9.3 (SAS Institute Inc., Cary, NC).

3. Results

Of the 57,053 enrolled participants, we excluded 581 because of cancers prior to baseline, 2084 because residential address history - and thus exposure - were unavailable at some point in the period from 1979 to baseline, and 4624 because of missing information on the potential confounders. The total study population included 49,564 participants.

During a mean follow-up of 18.1 years (12.5 years among cases), a total of 10,193 deaths occurred. Descriptives of the cohort are given in Table 1. The median time-weighted averages of the $PM_{2.5}$, PM_{10}, NO_2, BC, and O_3 were 18.0, 25.1, 25.0, 0.92, and 55.4 μg/m^3, respectively. Persons exposed to higher levels of $PM_{2.5}$ were on average older than those living in areas of lower levels. The proportion of men, low educated, unmarried, unemployed, smokers, persons exposed to ETS, and physically inactive was higher in the high exposure group compared to the low exposure group. In addition, the highest exposure group had a higher mean BMI than the low exposure group, a higher proportion of persons with a low fruit and vegetable consumption, and a higher mean L_{den} exposure at their baseline address. Distributions and correlations matrices of the pollutants are provided in the online Appendix (Fig. S2 and Table S5). The baseline correlations between $PM_{2.5}$, PM_{10}, NO_2, and BC were in the range of 0.81–0.97 and a negative correlation with

Table 1
Baseline characteristics of participants in the Diet, Cancer, and Health Study across categories of residential $PM_{2.5}$ levels[a]. Median and 5–95 percentiles (continuous variables) and % (categorical variables).

	Total N = 49,564	Air pollution level, $PM_{2.5}$ (μg/m^3)		
		< 17.7 (N = 16,356)	17.7–18.4 (N = 16,356)	> 18.4 (N = 16,852)
$PM_{2.5}$, μg/m^3	18.0 (17.2, 21.5)	17.4 (17.0,17.6)	17.9 (17.7, 18.4)	19.5 (18.5, 23.3)
PM_{10}, μg/m^3	25.1 (23.7, 30.3)	24.2 (23.5, 25.1)	25.0 (24.3, 25.9)	27.2 (25.4, 33.3)
BC, μg/m^3	0.92 (0.68, 1.73)	0.80 (0.63, 0.91)	0.93 (0.77, 1.06)	1.18 (0.84, 2.23)
O_3, μg/m^3	55.4 (44.7, 60.8)	57.6 (54.0, 62.5)	55.5 (51.5, 59.7)	51.2 (39.7, 57.5)
NO_2, μg/m^3	25.0 (17.9, 39.4)	22.1 (16.3, 26.7)	24.8 (19.9, 30.5)	30.4 (22.1, 46.2)
Age at study entry, years	56.3 (50.8, 64.2)	55.6 (50.7, 63.9)	56.1 (50.7, 64.1)	57.1 (50.9, 64.5)
Males, %	47	46	45	50
Low educational level[b], %	28	26	26	31
Unmarried, %	28	22	27	35
Unemployed, %	8	7	8	9
Current smokers, %	36	30	33	45
Intensity[c], g/day	15.0 (5.0, 31.9)	14.2 (4.6, 31.4)	14.5 (4.6, 30.2)	15.9 (6.0, 33.2)
Duration, years	37 (22, 48)	36 (21, 46)	36 (21, 47)	38 (24, 48)
ETS ≥ 4 h per day, %	64	60	62	70
BMI, kg/m^2	25.5 (20.4, 33.4)	25.5 (20.6, 32.9)	25.4 (20.5, 33.2)	25.7 (20.2, 33.9)
Physically inactive, %	46	43	43	52
High risk alcohol intake[d], %	60	59	61	61
Low fruit intake[e], %	34	32	33	37
Low vegetable intake[e], %	24	22	22	28
Noise (L_{den}) at baseline address, dB	56.7 (48.6, 70.3)	53.8 (47.8, 64.9)	56.2 (48.8, 66.7)	62.0 (50.1, 72.7)

Abbreviations: PM, particle mass; BC, black carbon; O_3, ozone; NO_2, nitrogen dioxide; ETS, environmental tobacco smoke; BMI, body mass index; L_{den}, day-evening-night equivalent level.

[a] Time-weighted average from 1979 until death, censoring or end of follow-up.
[b] Defined as ≤11 years of basic schooling.
[c] Among current smokers.
[d] Defined as > 7/14 drinks per week for women and men, respectively.
[e] Defined as < 100 g/day.

O_3 in the range of 0.74–0.76 was observed.

Table 2 presents the associations between the time-weighted average exposure to air pollutants and all natural-cause, CVD and respiratory mortality. A graphical presentation of the functional form of the estimated exposure-response association is provided in the online Appendix (Fig. s3). In the analysis of a 15-year exposure to $PM_{2.5}$, a hazard ratio (HR) of 1.13 (95% CI 1.05–1.21) for all-cause mortality was observed per 5 μg/m^3 increase (Model 3). The corresponding HRs for CVD and respiratory mortality were 1.29 (95% CI 1.13–1.47) and 1.07 (95% CI 0.92–1.24), respectively. The results for PM_{10}, BC and

Table 2
Association between 15-year residential exposure to $PM_{2.5}$, PM_{10}, NO_2, O_3 and BC and risk of all-cause, CVD, and respiratory mortality.

Exposure	N cases	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)	Model 3 + noise[d] HR (95% CI)
$PM_{2.5}$ (5 μg/m^3 increment)					
All-cause	10,193	1.37 (1.29–1.47)	1.16 (1.08–1.24)	1.13 (1.05–1.21)	1.06 (0.98–1.15)
CVD	2319	1.58 (1.39–1.78)	1.32 (1.16–1.50)	1.29 (1.13–1.47)	1.24 (1.06–1.45)
Respiratory	2093	1.44 (1.25–1.65)	1.11 (0.96–1.29)	1.07 (0.92–1.24)	–
PM_{10} (10 μg/m^3 increment)					
All-cause	10,193	1.45 (1.34–1.56)	1.15 (1.06–1.25)	1.12 (1.03–1.22)	1.03 (0.94–1.14)
CVD	2319	1.69 (1.46–1.96)	1.34 (1.14–1.57)	1.30 (1.11–1.53)	1.23 (1.02–1.49)
Respiratory	2093	1.54 (1.30–1.82)	1.08 (0.91–1.29)	1.04 (0.87–1.24)	–
NO_2 (10 μg/m^3 increment)					
All-cause	10,193	1.19 (1.16–1.22)	1.09 (1.06–1.12)	1.07 (1.04–1.10)	1.05 (1.01–1.09)
CVD	2319	1.23 (1.16–1.29)	1.13 (1.07–1.20)	1.11 (1.04–1.17)	1.11 (0.99–1.25)
Respiratory	2093	1.22 (1.15–1.29)	1.07 (1.01–1.14)	1.03 (0.97–1.09)	–
BC (1 μg/m^3 increment)					
All-cause	10,193	1.27 (1.21–1.32)	1.12 (1.07–1.18)	1.09 (1.04–1.15)	1.04 (0.98–1.11)
CVD	2319	1.33 (1.22–1.46)	1.19 (1.08–1.30)	1.16 (1.05–1.27)	1.09 (1.01–1.18)
Respiratory	2093	1.27 (1.15–1.40)	1.05 (0.94–1.17)	1.00 (0.90–1.12)	–
O_3 (10 μg/m^3 increment)					
All-cause	10,193	0.79 (0.77–0.82)	0.89 (0.86–0.93)	0.92 (0.89–0.96)	0.95 (0.91–1.00)
CVD	2319	0.76 (0.71–0.81)	0.86 (0.79–0.92)	0.88 (0.82–0.96)	0.88 (0.82–0.96)
Respiratory	2093	0.76 (0.70–0.82)	0.91 (0.84–0.99)	0.97 (0.89–1.05)	–

[a] Adjusted for age, sex and calendar time.
[b] Model 1 + educational level, marital status, occupational status, smoking, alcohol consumption, physical activity, BMI, waist circumference, ETS, and fruit and vegetable consumption.
[c] Model 2 + neighborhood level SES.
[d] Model 3 adjusted for 5-year average L_{den}. The analyses of respiratory outcomes were not adjusted for noise because there was no a priori assumption of noise as a risk factor of this outcome.

Table 3
Association between 15-year exposure to $PM_{2.5}$, PM_{10}, NO_2, and BC and CVD mortality by sex, educational attainment and smoking status.

	N cases	$PM_{2.5}$ (per 5 μg/m^3)	*p*-Value*	PM_{10} (per 10 μg/m^3)	*p*-Value*	BC (per 1 μg/m^3)	*p*-Value*	NO_2 (per 10 μg/m^3)	*p*-Value*
		HR (95% CI)[a]		HR (95% CI)[a]		HR (95% CI)[a]		HR (95% CI)[a]	
All-cause									
Sex			< 0.01		< 0.01		0.02		< 0.01
Men	5848	1.20 (0.91–1.57)		1.21 (1.10–1.33)		1.15 (1.08–1.22)		1.10 (1.06–1.14)	
Women	4345	1.05 (0.97–1.14)		1.02 (0.91–1.13)		1.03 (0.96–1.11)		1.03 (0.99–1.07)	
Education			0.58		0.70		0.89		0.56
Low	3530	1.13 (1.04–1.23)		1.13 (1.01–1.26)		1.11 (1.02–1.19)		1.09 (1.04–1.14)	
Medium	4962	1.14 (1.06–1.23)		1.14 (1.03–1.26)		1.09 (1.02–1.17)		1.06 (1.02–1.10)	
High	1701	1.07 (0.95–1.28)		1.06 (0.90–1.25)		1.07 (0.94–1.21)		1.06 (0.99–1.13)	
Smoking status			0.53		0.30		0.15		0.58
Never	2120	1.08 (0.96–1.22)		1.03 (0.87–1.21)		1.04 (0.93–1.17)		1.04 (0.98–1.11)	
Former	2484	1.17 (1.06–1.30)		1.20 (1.05–1.38)		1.14 (1.02–1.25)		1.08 (1.03–1.14)	
Current	5589	1.13 (1.05–1.22)		1.14 (1.03–1.25)		1.10 (1.04–1.17)		1.08 (1.04–1.11)	
CVD									
Sex			< 0.01		< 0.01		0.09		0.01
Men	1549	1.41 (1.23–1.63)		1.49 (1.25–1.77)		1.22 (1.09–1.37)		1.16 (1.09–1.24)	
Women	770	1.03 (0.86–1.24)		0.98 (0.77–1.25)		1.03 (0.87–1.22)		1.01 (0.91–1.11)	
Education			0.49		0.66		0.86		0.91
Low	796	1.21 (1.03–1.43)		1.22 (0.98–1.52)		1.12 (0.96–1.30)		1.09 (1.00–1.19)	
Medium	1186	1.34 (1.15–1.65)		1.36 (1.12–1.64)		1.17 (1.03–1.34)		1.11 (1.03–1.20)	
High	337	1.31 (1.03–1.66)		1.33 (0.95–1.86)		1.19 (0.91–1.54)		1.13 (0.98–1.30)	
Smoking status			0.82		0.40		0.15		0.34
Never	430	1.21 (0.93–1.57)		1.09 (0.76–1.55)		1.03 (0.80–1.32)		1.04 (0.91–1.18)	
Former	602	1.24 (1.02–1.51)		1.21 (0.93–1.58)		1.00 (0.81–1.23)		1.06 (0.95–1.19)	
Current	1287	1.30 (1.12–1.50)		1.37 (1.14–1.65)		1.22 (1.09–1.37)		1.14 (1.06–1.22)	

[a] Adjusted for age, sex, calendar time, educational level, marital status, occupational status, smoking, alcohol consumption, physical activity, BMI, waist circumference, ETS, and fruit and vegetable consumption, and neighborhood level SES.
* *p* for interaction tested by the Wald's test.

NO_2 were similar. For O_3, we observed a HR of 0.92 (95% CI 0.89–0.96) for all-cause mortality and corresponding estimates of 0.88 (95% CI 0.82–0.96) and 0.97 (95% CI 0.89–1.05) for CVD and respiratory mortality, respectively. Further adjustment for population density did not change the estimates notably (data not shown).

In the analyses of the association between air pollutants and all-cause and CVD mortality adjusted for noise, lower HRs were observed across all pollutants compared to the main model (Table 2). The correlation coefficients between the different pollutants and noise were in the range of 0.48–0.68 (online Appendix Table S5).

Analyses of shorter exposure time-windows revealed results similar to those observed for 15-years of exposure for all pollutants, however, the estimates derived from analyses of the 1-year annual baseline exposures generally showed similar tendencies but were weaker in magnitude than those of the time-weighted exposures (online Appendix Table S6).

The sex-specific analyses revealed higher HRs of all-cause and CVD mortality in men than in women for $PM_{2.5}$, PM_{10}, NO_2, and BC (Table 3). We did not observe signs of heterogeneity across educational attainment level or smoking status.

The subdivision of respiratory mortality into lung cancer and non-malignant deaths revealed null-findings for both outcomes in relation to long-term exposure to NO_2, BC, and O_3. The estimates for $PM_{2.5}$ and PM_{10} were elevated in relation to lung cancer (e.g. HR = 1.14 (95% CI 0.95–1.37) per 5 μg/m^3 increments of $PM_{2.5}$) but close to unity for non-malignant respiratory mortality (HR = 0.95, 95% CI 0.74–1.23).

Further analyses of long-term exposure to PM-coarse in relation to all-cause, CVD and respiratory mortality did not reveal estimates distinctly different from those of $PM_{2.5}$ or PM_{10} (online Appendix Table s8).

The results of the additional analyses exploring the simultaneous impact of O_3 and NO_2 on mortality are provided in the online Appendix (Table s9). The simple combination of the two pollutants, O_x, showed a higher risk of all-cause and CVD mortality with higher levels of O_x, whereas the analysis based on the redox-weighted exposure indicated a lower risk with higher levels of O_x^{wt}.

4. Discussion

In this study, we observed an association between long-term exposure to $PM_{2.5}$, PM_{10}, BC, and NO_2 and all-cause mortality. A higher risk of CVD mortality was observed in the main model, which was slightly lower in a model adjusted for road traffic noise. Inverse associations were observed between O_3 and all-cause and CVD mortality. None of the investigated air pollutants were related to risk of respiratory mortality in general, however, in a sensitivity analysis a tendency for an association between PM2.5, PM10 and lung cancer mortality was observed. Stratified analyses according to sex suggested that the elevated risks of mortality in relation to long-term PM, NO_2 and BC exposure were restricted to males.

The biological mechanisms by which air pollutants could promote mortality include systemic inflammation and oxidative stress, increased blood pressure, as well as changes in serum metabolites such as stress hormones, insulin, glucose, amino acids, and lipids (Brook et al., 2010; Magalhaes et al., 2018; Li et al., 2017). Findings from previous studies on PM and mortality have been heterogeneous, but generally the literature is in support of an elevated risk of all-cause mortality with higher exposure to $PM_{2.5}$ (Hoek et al., 2013; Beelen et al., 2014a). A meta-analysis by Hoek et al. (Hoek et al., 2013) reported a relative risk of 1.03 (95% CI 1.02–1.04) for all-cause mortality per 5 μg/m^3 increments of $PM_{2.5}$ and the ESCAPE collaboration, reported a corresponding relative risk of 1.07 (95% CI 1.02–1.13) (Beelen et al., 2014a). However, whereas Hoek et al., as well as others, have reported evidence of a stronger association between $PM_{2.5}$ and CVD mortality (Hoek et al., 2013; Brook et al., 2010), the cause-specific analyses from ESCAPE did not yield firm evidence of an association with CVD mortality (Beelen et al., 2014b). In accordance with our findings, the summary estimate for all-cause mortality from the Hoek et al. meta-analysis for BC was

1.06 (95% CI 1.05–1.07) per 1 μg/m^3 increment, with estimates being generally consistent across the individual studies (Hoek et al., 2013). The lack of an association between long-term exposure to PM and respiratory mortality in our study is also in agreement with previous studies (Dimakopoulou et al., 2014; Cesaroni et al., 2013). However, as also implied by the sensitivity analysis of this study, the implication of $PM_{2.5}$ and PM_{10} may vary according to the specific subcategory of respiratory mortality. In the ESCAPE, no association was observed for non-malignant respiratory disease (Dimakopoulou et al., 2014), whereas a higher risk of lung cancer was observed among persons with a higher exposure to PM_{10} and $PM_{2.5}$ (Raaschou-Nielsen et al., 2013). Also, a meta-analysis conducted by the International Agency for Research on Cancer showed a higher risk of lung cancer both in relation to $PM_{2.5}$ and to PM_{10} (Hamra et al., 2014).

The association between NO_2 and mortality has been investigated previously in the Diet, Cancer and Health cohort (Raaschou-Nielsen et al., 2012). The tendencies were similar to those observed in the present study for both all-cause and CVD mortality, however, estimates were somewhat higher (HR = 1.08, 95% CI 1.01–1.14 per 10 μg/m^3 increment for all-cause mortality) in their fully adjusted model compared to our results. The present study differs on a range of parameters - e.g. 6 more years of follow-up, a different approach to exposure calculation (15 years before death vs. average from 1971 and onwards), more comprehensive adjustment for SES variables at both the individual and the area level, and a more detailed noise adjustment – which likely explains the difference.

Generally, the associations observed in our study were stronger than those observed in previous studies. This may be explained by differences in characteristics of source populations and thus in baseline hazards between our study and previously published studies (Hoek et al., 2013). Another reason may be methods of exposure assessment and the precision by which exposure is approximated, e.g. nearest monitor station measurements or different modelling approaches. A recent meta-analysis concluded that less error prone exposure assessments produced stronger associations (Vodonos et al., 2018). In continuation of this, the actual modelling approach of the exposure variable may also contribute to the observed differences (Hoek et al., 2013). In our study, exposure was available at a high spatial resolution for several decades. Rather than including a time-weighted average from the beginning of the available period (1979) throughout follow-up, we modelled the exposure for specific time-windows (i.e. 15 years before death), which may be more relevant for mortality. In our sensitivity analysis of different exposure-time windows, the estimates based on baseline exposure only - which is a crude approximation of the actual exposure during the study period - provided the weakest measures of association. In addition, the possibility of adjusting for several important confounders – not least SES at both the individual and the neighborhood level - may have contributed to stronger associations. The meta-analysis by Vodonos et al. mentioned above, suggested that failure to control sufficiently for such variables results in downward bias of the measures of association (Vodonos et al., 2018).

The tendency for a stronger association in men compared to women has been found previously for both $PM_{2.5}$ (Beelen et al., 2014a; Cesaroni et al., 2013; Di et al., 2017) and BC (Gan et al., 2011). In ESCAPE, the reported HR for all-cause mortality was 1.14 (95% CI 1.04–1.24) for men and 0.99 (95% CI 0.92–1.07) per 5 μg/m^3 increment in $PM_{2.5}$ for women (Beelen et al., 2014a). In the large Rome Longitudinal Study similar differences in $PM_{2.5}$-associations for men and women were observed for both natural cause mortality (overall) and CVD mortality (Cesaroni et al., 2013). Likewise, a large Canadian study reported a strong association between BC and coronary heart disease mortality in men - but not in women (Gan et al., 2011). Variations according to sex have been suggested in a study on the relation between $PM_{2.5}$ and systemic inflammatory markers where associations were found in men, but not in women (Hoffmann et al., 2009). The suggested explanations for these differences included variations in exposure patterns and sources between men and women, different mortality baseline hazards, and also a role of endogenous estrogen levels. The meta-analysis by Vodonos et al. mentioned above did not, however, support an effect-modifying role of sex in the association between $PM_{2.5}$ and mortality (Vodonos et al., 2018).

Results from previous studies on long-term exposure to O_3 and all-cause mortality have indicated minor or no effects (Atkinson et al., 2016; Turner et al., 2016; Di et al., 2017). A meta-analysis covering 14 studies reported HRs close to unity (Atkinson et al., 2016), and a later large cohort study of > 650,000 participants found a HR of 1.02 (95% CI 1.01–1.04) per 10 ppb (Turner et al., 2016). Previous studies have reported elevated risks of respiratory mortality in relation to O_3 exposure (Atkinson et al., 2016; Turner et al., 2016), which was not confirmed in our study. A meta-analysis on differential susceptibility to ozone across various population strata, showed that health implications of O_3 varied according to age, sex, and employment status (Bell et al., 2014), and thus, as also mentioned previously, differences in source populations may be one explanation for the deviation in effect sizes. In addition, the precision of exposure assessment, as mentioned above, may play a role. Another point to consider is that O_3 is often inversely correlated with pollutants such as NO_2, BC and PM due to the atmospheric chemical reaction between O_3 and NO forming NO_2; the inverse correlation is also evident in our data (online Table S5). Since a protective effect of O_3 on mortality seems little plausible, we consider the lower HRs in association with higher exposure to O_3 in our study to be a reflection of the inverse correlation between O_3 and truly harmful pollutants. As suggested by previous studies, we also explored the combination of NO_2 and O_3 – as a measure of the oxidative potential among them. The findings suggested a higher mortality risk associated with the simple sum of the two – whereas upweighting the O_3 contribution to account for the much larger oxidative potential, did not show a positive association with mortality. The differing results between the two approaches may imply that the association with mortality is not primarily driven by an oxidative stress mechanism. NO_2 has also been suspected to take effect via other mechanisms such as protein nitration (Williams et al., 2014). Such an effect would be underestimated by applying the weighted O_x.

Our study did not show positive associations between air pollutants and non-malignant respiratory mortality. One explanation could be that persons susceptible to developing respiratory diseases would tend to move away from highly polluted areas, and thus, people who remain in larger cities, are less sensitive to respiratory effects of air pollution – or that a potential effect would appear years later than in more susceptible individuals. The detailed residential history and corresponding air pollutant concentrations should, however, account for such differential movement patterns.

Traffic noise at the residence is correlated with traffic-related air pollution because traffic is a shared source. Noise is also associated with cardiovascular diseases (Cai et al., 2018; Vienneau et al., 2015; Münzel et al., 2017b; Babisch, 2014; Roswall et al., 2017), and therefore, a potential confounder of the association between air pollution and cardiovascular mortality. Unlike the majority of previous studies on air pollution and mortality, we were able to adjust the estimated associations between air pollution and mortality for noise at the residence. Such inclusion of correlated co-variates can cause unstable estimates difficult to interpret (Stansfeld, 2015). At the baseline address, noise correlated only moderately with the air pollutants (online Appendix Table S5). Adjustment for noise consistently provided lower HRs for CVD, yet all three PM measures and NO_2 still showed higher CVD mortality for higher concentrations after adjustment for noise. This could be interpreted as a causal role of both PM air pollution and noise in CVD mortality. The potential for a more precise exposure measurement of one over another correlated predictor of a health endpoint may complicate the interpretation (Münzel et al., 2017b). In such a situation, a mutual adjustment will cause the HR for the most precisely assessed predictor to increase more and the HR for the least precisely

assessed predictor to decrease more than what is related to biology. Although both the air pollution and the noise models are state-of-the-art and based on the same high quality input data, we cannot exclude such a situation when adjusting air pollution for noise. Because of inter-correlations (Table S5), we were not able to disentangle independent effects of each single air pollutant and determine potential causal agents in the relation between air pollution and mortality.

The strengths of this study include the large cohort with individual information on various potential confounders and the prospective design with a follow-up period of 20+ years, the ability to adjust for detailed traffic noise exposure history, and decades of air pollution exposure information at the individual residential address level. The air pollution exposures were modelled by the newly updated state-of-the-art, validated, THOR/AirGIS air pollution modelling system, which enabled calculations of both PM, BC, NO_2, and O_3. Spatial misalignment has been a concern in cohort studies of air pollution. The misalignment arises if exposure data are collected at a regulatory monitoring network location distinct from cohort participant locations (Keller et al., 2017). The exposure assessment method that we applied differs fundamentally from that referred above because we estimated exposure at each address. Our estimation was not based on monitoring stations at other locations. The deterministic AirGIS modelling system has as starting point an air pollution emission inventory and the modelling system was built to reflect best possible the physical and chemical processes leading to the air pollution concentration at a specific address. The model can estimate air pollution at any address point in Denmark taking into account also the very local circumstances which influence the air pollution concentration outside the front door of a dwelling, including amount, type and speed of traffic at the front door, the width of the street, the height of the buildings surrounding the address point and the meteorological conditions, which influence the dispersion of air pollution. Thus, the calculated air pollution concentration at two addresses separated by even a short distance can be very different. Because of this address level-spatial resolution, we do not believe that spatial misalignment in exposure assessment affects our results. However, exposure misclassification is inevitable when using a model for exposure assessment, in part because of uncertainties in input data and partly because we use modelled exposures at the front door façade of the participants' residence, which does not equal true personal exposure. In reality, an exposure scenario is more complex involving exposure indoors, at the work place, commuting patterns etc. We expect this potential misclassification to be non-differential, with a bias towards the null. In addition, the participation of the DCH study was only 35%, and non-participation has been found to be related to low SES (Tjønneland et al., 2007), and to a higher mortality rate compared to participation (Larsen et al., 2012). If non-participation was related to higher levels of air pollution and at the same time to poorer health than participation, the observed associations may be underestimations of the true effect in the source population. Also, we were only able to account for lifestyle confounding at baseline. Although we expect individuals in the included age ranges (50 to 64 years at enrolment) to have a relatively stable lifestyle, the occurrence of disease during follow-up may have affected their lifestyle and, thus, induced residual confounding. It would have been relevant to address residential area characteristics related to the built environment, such as presence of green space, which has been suggested as a confounder or effect-modifier of the health effects of air pollution - possibly through pathways of stress reduction, promoting social interaction or physical activity or as a buffer for air pollution or noise exposures (James et al., 2015). Depending on the setting and the specific air pollution component, green spaces may impact air quality in both positive and negative directions (Janhäll, 2015). Future studies should incorporate measures of access to and quality of green spaces.

In conclusion, the results of this study support a relationship between residential exposure to $PM_{2.5}$, PM_{10}, BC, NO_2 and all-cause and CVD mortality. The observed higher risks with higher levels of exposures are in line with previous studies.

Funding

The research was funded by NordForsk under the Nordic Programme on Health and Welfare (Project #75007: NordicWelfAir - Understanding the link between Air pollution and Distribution of related Health Impacts and Welfare in the Nordic countries). The funding source had no involvement in the study design, collection, analysis, interpretation, writing and decision to submit for publication.

Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.12.010.

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