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Published in:
Environment International

DOI:
10.1016/j.envint.2019.105268

Publication date:
2019

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

Citation for published version (APA):
Hvidtfeldt, U. A., Geels, C., Sørensen, M., Ketzel, M., Khan, J., Tjønneland, A., Christensen, J. H., Brandt, J., & Raaschou-Nielsen, O. (2019). Long-term residential exposure to PM2.5 constituents and mortality in a Danish cohort. *Environment International*, *133*(B), Article 105268. https://doi.org/10.1016/j.envint.2019.105268

Environment International 133 (2019) 105268

Contents lists available at ScienceDirect

Environment International

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

Long-term residential exposure to $PM_{2.5}$ constituents and mortality in a Danish cohort

Ulla Arthur Hvidtfeldt[a,*], Camilla Geels[c], Mette Sørensen[a,b], Matthias Ketzel[c,d], Jibran Khan[c,e], Anne Tjønneland[a,f], Jesper Heile Christensen[c], Jørgen Brandt[c], Ole Raaschou-Nielsen[a,c]

[a] Danish Cancer Society Research Center, Strandboulevarden 49, 2100 Copenhagen Ø, Denmark
[b] Department of Natural Science and Environment, Roskilde University, Universitetsvej 1, P.O. Box 260, 4000 Roskilde, Denmark
[c] Department of Environmental Science, Aarhus University, Frederiksborgvej 399, P.O.Box 358, 4000 Roskilde, Denmark
[d] Global Centre for Clean Air Research (GCARE), University of Surrey, Guildford GU2 7XH, United Kingdom
[e] Danish Big Data Centre for Environment and Health (BERTHA), Aarhus University, 4000 Roskilde, Denmark
[f] Department of Public Health, University of Copenhagen, Oester Farimagsgade 5, 1014 Copenhagen K, Denmark

ARTICLE INFO

Handling Editor: Hanna Boogaard

Keywords:
Particulate matter chemical constituents
Carbonaceous particles
Secondary inorganic aerosols
Secondary organic aerosols
Sea salt
Mortality

ABSTRACT

Studies on health effects of long-term exposure to specific $PM_{2.5}$ constituents are few. Previous studies have reported an association between black carbon (BC) exposure and cardiovascular diseases (CVD) and a few studies have found an association between sulfate exposure and mortality. These studies, however, relied mainly on exposure data from centrally located air-monitoring stations, which is a crude approximation of personal exposure.

We focused on specific chemical constituents of $PM_{2.5}$, i.e. elemental and primary organic carbonaceous particles (BC/OC), sea salt, secondary inorganic aerosols (SIA, i.e. NO_3^-, NH_4^+, and SO_4^{2-}), and secondary organic aerosols (SOA), in relation to all-cause, CVD and respiratory disease mortality.

We followed a Danish cohort of 49,564 individuals from enrollment in 1993–1997 through 2015. We combined residential address history from 1979 onwards with mean annual air pollution concentrations obtained by the AirGIS air pollution modelling system, lifestyle information from baseline questionnaires and socio-demography obtained by register linkage.

During 895,897 person-years of follow-up, 10,193 deaths from all causes occurred – of which 2319 were CVD-related and 870 were related to respiratory disease. The 15-year time-weighted average concentrations of $PM_{2.5}$, BC/OC, sea salt, SIA and SOA were 13.8, 2.8, 3.4, 4.9, and 0.3 $\mu g/m^3$, respectively. For all-cause mortality, a higher risk was observed with higher exposure to $PM_{2.5}$, BC/OC and SOA with adjusted hazard ratios of 1.03 (95% confidence intervals: 1.01, 1.05), 1.06 (1.03, 1.09), and 1.08 (1.03, 1.13) per interquartile range, respectively. The associations for BC/OC and SOA remained after adjustment for $PM_{2.5}$ in two-pollutant models. For CVD mortality, we observed elevated risks with higher exposure to $PM_{2.5}$, BC/OC and SIA. The results showed no clear relationship between sea salt and mortality.

In this study, we observed a relationship between long-term exposure to $PM_{2.5}$, BC/OC, and SOA and all-cause mortality and between $PM_{2.5}$, BC/OC, and SIA and CVD mortality.

1. Introduction

Associations between long-term exposure to particulate matter ($PM_{2.5}$ and PM_{10}) and mortality have been published previously (Hoek et al., 2013; Beelen et al., 2014; Vodonos et al., 2018; Pope et al., 2019). Recently, we added to this field of research with findings from the large Danish cohort study Diet, Cancer and Health showing an association between long-term exposure to $PM_{2.5}$ and all-cause and cardiovascular disease (CVD) mortality (Hvidtfeldt et al., 2019). $PM_{2.5}$, however, is comprised of a complex mixture of chemical components from different sources, and focused disease prevention strategies rely on more knowledge about which constituents of PM are most harmful to health.

* Corresponding author.
E-mail addresses: ullah@cancer.dk (U.A. Hvidtfeldt), cag@envs.au.dk (C. Geels), mettes@cancer.dk (M. Sørensen), mke@envs.au.dk (M. Ketzel), jibran@envs.au.dk (J. Khan), annet@cancer.dk (A. Tjønneland), jc@envs.au.dk (J.H. Christensen), jbr@envs.au.dk (J. Brandt), ole@cancer.dk (O. Raaschou-Nielsen).

https://doi.org/10.1016/j.envint.2019.105268
Received 11 September 2019; Received in revised form 11 October 2019; Accepted 14 October 2019
Available online 29 October 2019

Also, previous studies on health effects of $PM_{2.5}$ have shown differences in effect measure magnitude, which may in part be due to varying source mixtures of the $PM_{2.5}$ mass (Ostro et al., 2010; Thurston et al., 2016).

Previous studies have addressed the acute health effects of short-term exposure to several $PM_{2.5}$ constituents (Achilleos et al., 2017; Rohr and Wyzga, 2012; Franklin et al., 2008). A recent meta-analysis of these found an association between elemental/black carbon/black smoke (EC/BC/BS), organic carbon (OC), sodium (Na), silicon (Si), and sulfate (SO_4) and all-cause mortality (Achilleos et al., 2017). For CVD mortality, an association was observed for BS, EC, nitrate (NO_3), ammonium (NH_4), chlorine (Cl), and calcium (Ca). The included studies, however, varied in study designs and size of the effect measure estimates, which probably was affected by lack of adjustment for $PM_{2.5}$ mass in some studies. Analyses including both the constituent and $PM_{2.5}$ suggested that EC and potassium (K) had the strongest relation with mortality (Achilleos et al., 2017).

Studies on long-term exposure to $PM_{2.5}$ constituents and mortality are fewer. Two systematic reviews have reported consistent associations between BC and CVD hospital admissions and mortality (Hoek et al., 2013; Luben et al., 2017). A few previous American cohort studies have reported positive associations between long-term exposure to SO_4 and all-cause, cardiopulmonary disease and lung cancer mortality (Ostro et al., 2010; Pope et al., 2002; Dockery et al., 1993; Krewski et al., 2000). The exposure data in these studies were derived from centrally located air-monitoring stations. In the European Study of Cohorts for Air Pollution Effects (ESCAPE) project, an association between $PM_{2.5}$ sulfur and all-cause mortality was reported, which remained after adjustment for $PM_{2.5}$ mass (Beelen et al., 2015).

This study extends the findings of our previous paper on PM and mortality in a large Danish cohort (Hvidtfeldt et al., 2019), by focusing on specific chemical constituents of $PM_{2.5}$, namely the total primary emitted carbonaceous particles (BC/OC), sea salt, and chemically transformed particles grouped as secondary inorganic aerosols (SIA, i.e. NO_3^-, NH_4^+, and SO_4^{2-}, denoted as NO_3, NH_4, and SO_4 in the following) and secondary organic aerosols (SOA). The study differs from previously published papers on PM constituents and mortality by applying exposure data derived by high-resolution modelled data over a period of decades, using the Danish multiscale air pollution dispersion and human exposure modelling system DEHM/UBM/AirGIS (Brandt et al., 2001; Jensen et al., 2017; Khan et al., 2018); linked to decades of residential address history as well as more than 20 years of follow-up.

2. Methods

2.1. Study population

In the period of 1993–1997, Danish born men and women residing in the areas of Aarhus and Copenhagen aged 50–64 years, and who had not previously been diagnosed with cancer at the time of inclusion, were invited to take part in The Danish Diet, Cancer and Health cohort (Tjønneland et al., 2007). In total, 57,053 agreed to participate (response ≈ 35%). Participation involved a self-administered questionnaire on lifestyle factors, diet, reproductive and occupational history and a physical examination, including anthropometric measures. We were able to link participants to national registries from Statistics Denmark where sociodemographic information was available from 1980 and onwards.

2.2. Exposure assessment

We obtained residential address history of each participant from the Danish Civil Registration System (Bøcker Pedersen, 2011); in the period of January 1, 1979–December 31, 2015. We were able to geocode 98.9% of these addresses (within 5 m from the front door of the address) by linkage to the Danish address database.

The concentration of PM and its chemical components was modelled using the integrated multiscale air pollution model system, DEHM/UBM/AirGIS (Brandt et al., 2001). This is a comprehensive air pollution modelling system; which integrates three air pollution models in THOR, covering intercontinental, regional, local and street canyon scales, with different complexity. Overall, the particle constituents in the air pollution modelling system, giving the full $PM_{2.5}$ mass, consist of the primary emitted particles (BC, OC, sea salt and additional primary emitted particles which will be referred to as “dust”), SIAs and SOAs. The system is described in more detail in the online appendix A. In brief, the contribution from the intercontinental and regional background (due to non-local natural and anthropogenic sources) is calculated using the Danish Eulerian Hemispheric Model (DEHM), which is a 3D chemistry transport model covering the Northern hemisphere (Christensen, 1997; Brandt et al., 2012). DEHM includes all the above mentioned particle components, and especially handles the complex atmospheric chemistry involved in forming the SIA and SOA particles (Zare et al., 2012; Zare et al., 2014). The 5.6 km × 5.6 km resolution concentrations and meteorological fields from DEHM and the Weather Research and Forecasting Model (Skamarock et al., 2008), are used as input to the Urban Background Model (UBM) (Brandt et al., 2001; Brandt et al., 2003; Brandt et al., 2001). The UBM handles the local contribution from sources of primary anthropogenic emitted particles (dust, BC, OC) up to 25 km from all grid points and calculates concentrations with a 1 km × 1 km resolution. Lastly, the contribution from traffic at the street level is added by the OSPM® (Operational Street Pollution Model) (Ketzel et al., 2012; Kakosimos et al., 2010), whereby the local street traffic data (like intensity, speed and vehicle types) and the street and building geometry are taken into account. For the generation of the OSPM input parameters for human exposure estimates at a large number of addresses, the AirGIS system has been constructed using the Geographic Information System (GIS) (Jensen et al., 2017; Khan et al., 2019). All three models operate on an hourly basis and the output was subsequently averaged over time in order to provide yearly concentrations at all addresses in Denmark.

An evaluation of the DEHM performance against measured concentrations in Europe showed a correlation coefficient 0.66 for total $PM_{2.5}$ and correlation coefficients in the range of 0.77–0.81 for the SIA components and 0.78 for sea salt (based on daily values) (Brandt et al., 2012). Evaluation of SOA at European and US stations show temporal correlations in the range of 0.39–0.82, but a general underestimation (Zare et al., 2014). Analyses of the DEHM/UBM setup (Im et al., 2018), as well as the full DEHM/UBM/AirGIS (Khan et al., 2019), show that the overall long-term trend of the main air pollutants (NO_2, NO_x, $PM_{2.5}$ and PM_{10}) as observed at the Danish monitoring sites since the 1990s are captured well by the models. These trends are generally driven by similar trends in the Danish and international emissions. The performance of the models does not vary significantly over the years. In general, the models perform better for the individual components compared to the total $PM_{2.5}$ when compared to measurements. This could be due to the challenges related to measuring total PM. Recent evaluations of the DEHM/UBM/AirGIS comparing measured and modelled concentrations found correlation coefficients in the range of 0.67–0.85 for $PM_{2.5}$ and 0.77–0.79 for BC, across different locations and measurement periods (Hvidtfeldt et al., 2018).

2.3. Outcome

We followed participants by linkage to the Civil Registration System, which includes date of emigration and death, and the Danish

Register of Causes of Death (Helweg-Larsen, 2011). The outcome was defined according to the underlying cause of death recorded on death certificates. We censored participants who died from external causes such as injuries, accidents and suicides (ICD-10 codes S–Z) at the date of death. In addition to all natural-cause mortality, we investigated cardiovascular (ICD10 codes 'I00'–'I99') and respiratory (ICD10 codes 'J00'–'J99') subgroups of mortality.

2.4. Confounders

Potential confounders of the relation between the exposures and mortality were selected through the method of Directed Acyclic Graphs, (Greenland et al., 1999) and thus identified through careful consideration of the underlying causal relations based on the existing literature (online appendix Fig. B1). The confounders included in the main model were: Age, sex, occupational status, educational attainment, marital status, BMI, waist circumference, physical activity, alcohol consumption, smoking (status, intensity, and duration), environmental tobacco smoke (ETS), fruit consumption, vegetable consumption, and neighborhood level socioeconomic status (SES).

The neighborhood level SES variables have been described in detail previously (Hvidtfeldt et al., 2019). In brief, we obtained parish codes from the Danish Geodata Agency and linked these to sociodemographic indicators from Statistics Denmark aggregated to the parish level. We applied parish SES data from the year 1996. A total of 2160 parishes were included 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 included an index based on the following variables describing elements of neighborhood level SES: 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. The selection of neighborhood SES variables was based on previous demonstration of an association with mortality in Denmark (Meijer et al., 2013). We applied a shrinkage technique to address issues of large standard errors (McLennan et al., 2010), 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).

2.5. Statistical methods

We followed each cohort member from date of inclusion into the cohort until the date of death, emigration, or December 31, 2015 and applied Cox Proportional Hazards Models with age as the underlying time scale. Individuals, who moved to an unknown address during follow-up (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. We detected deviation from the PH assumption for smoking status, smoking duration, occupational status, BMI, and alcohol consumption, and thus included these variables as strata. We applied linear spline models to formally test the linearity of continuous variables (Greenland, 1995). We observed deviations from linearity for sea salt, and therefore we modelled this exposure in categories based on the quartiles of the distribution. We plotted the exposure-response function using smoothed splines with four degrees of freedom (Therneau, 2018).

We computed the air pollution exposure concentrations as a time-weighted average the last 15 years before death based on yearly concentrations at all addresses. We calculated weights according to the exact number of days of living at each address. We modelled these time-weighted concentrations as time-dependent variables, thus re-calculating exposure for survivors at the time of each death.

Initially, we modelled $PM_{2.5}$ and each constituent group (SIA, SOA, BC/OC and sea salt) 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/cohabiting, divorced, single, widowed), waist circumference (cm), Body Mass Index (strata of < 25, 25–29, 30–34, and 35+), sport during leisure time (yes/no), alcohol intake (strata of < 1, 1–9, 10–19, 20–29, 30–39, and 40+ g/day), 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), fruit intake (g/day), and vegetable intake (g/day). Model 3 (main model): further adjusted for neighborhood level SES (two components, grouped according to the quartiles of their distribution).

Subsequently, we performed different two-pollutant models based on the main model 3: (1) including $PM_{2.5}$ mass (PM_{10} for sea salt) in models with each constituent group and (2) models with BC/OC and SIA together with each of their specific chemical species.

Sensitivity analyses included: (1) stratifying main models according to sex, (2) further adjustment of the main model 3 for parish population density (persons/km^2) to account for degree of urbanicity, and (3) adjusting associations with $PM_{2.5}$, and BC/OC (for which the modelling include a contribution from local traffic) for residential road traffic noise (time-dependent variable based on a 5-year average before death). Road traffic noise was calculated by using the Nordic Prediction Method (SoundPLAN; version 6.5, http://www.soundplan.dk/) as the equivalent continuous A-weighted sound pressure level (L_{Aeq}) at the most exposed façade of the dwelling at each residential 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. The model included 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. Noise values below 40 dB were set to 40 as this is considered a realistic lower limit of ambient noise (Roswall et al., 2018).

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. We conducted all other analyses in SAS, version 9.3 (SAS Institute Inc., Cary, NC).

3. Results

Of the 57,053 enrolled participants, 538 were excluded because of a previous cancer diagnosis, 2084 were missing parts of their residential address history during the period from 1979 to baseline, and 4624 had missing information on confounders. In total, 49,564 participants remained eligible for analysis. During a mean follow-up of 18.1 years (12.5 years among cases), 10,193 deaths occurred. The median 15-year time-weighted averages of $PM_{2.5}$, SIA, SOA, BC/OC, and sea salt were 13.8, 4.9, 0.3, 2.8, and 3.4 $\mu g/m^3$, respectively (Table 1, see online appendix Fig. C1 for distributions). The correlation matrices of the pollutants are provided in the online appendix (Tables E1 and E2). We observed high baseline correlations between BC, OC and SOA and between the each of single SIA components. Moderate correlations between the SIAs overall and the other constituents were observed. Sea

Table 1
Baseline characteristics of participants in the Diet, Cancer, and Health Study across categories of residential $PM_{2.5}$ levels.

	$PM_{2.5}$ level[a] ($\mu g/m^3$)			
	Total N = 49,564	< 13.5 (N = 16,361)	13.5–14.2 (N = 16,352)	> 14.2 (N = 16,851)
$PM_{2.5}$, median (5, 95 pct) $\mu g/m^3$	13.8 (13.0, 18.8)	13.2 (12.8, 13.5)	13.8 (13.5, 14.2)	15.5 (14.3, 21.0)
SIA, median (5, 95 pct) $\mu g/m^3$	4.9 (4.8, 8.1)	4.9 (4.8, 5.1)	4.8 (4.8, 5.2)	5.3 (4.7, 9.6)
SOA, median (5, 95 pct) $\mu g/m^3$	0.3 (0.3, 0.4)	0.3 (0.3, 0.3)	0.3 (0.3, 0.3)	0.3 (0.3, 0.4)
BC/OC, median (5, 95 pct) $\mu g/m^3$	2.8 (1.8, 3.6)	2.5 (1.6, 3.0)	2.6 (1.9, 3.1)	3.1 (2.2, 4.0)
Sea salt, median (5, 95 pct) $\mu g/m^3$	3.4 (3.3, 4.2)	3.4 (3.3, 4.2)	3.4 (3.3, 4.2)	3.4 (3.3, 4.2)
Age at study entry, median (5, 95 pct) years	56.3 (50.8, 64.2)	55.4 (50.7, 63.7)	56.1 (50.7, 64.1)	57.4 (50.9, 64.5)
Males, %	47	45	45	51
Low educational level[b], %	28	27	26	30
Non-cohabitating, %	22	21	19	27
Unemployed, %	8	8	7	9
Former smokers, %	28	28	29	26
Current smokers, %	36	32	31	44
Intensity[c], median (5, 95 pct) g/day	15.0 (5.0, 31.9)	14.4 (4.6, 30.8)	14.4 (4.6, 30.1)	15.9 (6.0, 33.4)
Duration[c], median (5, 95 pct) years	37 (22, 48)	36 (20, 46)	36 (21, 47)	38 (24, 48)
ETS ≥ 4 h per day, %	64	62	61	69
BMI, median (5, 95 pct) kg/m^2	25.5 (20.4, 33.4)	25.5 (20.6, 33.1)	25.5 (20.5, 33.0)	25.7 (20.2, 33.9)
Physically inactive, %	46	44	43	51
Alcohol intake, median (5, 95 pct)	12.8 (0.7, 63.8)	12.3 (0.8, 59.9)	12.5 (0.8, 60.2)	13.8 (0.5, 72.4)
Fruit intake, median (5, 95 pct) g/day	145 (23, 471)	147 (25, 476)	150 (25, 468)	139 (19, 470)
Vegetable intake, median (5, 95 pct) g/day	157 (48, 351)	161 (51, 355)	161 (51, 353)	149 (43, 347)

Abbreviations: PM, particle mass; SIA, secondary inorganic aerosols; SOA, secondary organic aerosols; BC/OC, sum of primary emitted BC and OC; ETS, environmental tobacco smoke; BMI, body mass index.
[a] Time-weighted average 15 years prior to death, censoring or end of follow-up.
[b] Defined as ≤11 years of basic schooling.
[c] Among current smokers.

salt was strongly negatively correlated with OC and SOA, but only weakly correlated with BC and the SIAs. 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, non-cohabitating, unemployed, smokers, persons exposed to ETS, physically inactive and persons with a low fruit and vegetable consumption was higher in the high exposure group compared to the low exposure group (Table 1).

Table 2 shows a positive association between $PM_{2.5}$ mass and all-cause and CVD mortality, as reported previously (Hvidtfeldt et al., 2019). Higher levels of BC/OC and SOA were related to higher hazard ratios (HRs) for all-cause mortality with the highest HR per interquartile range (IQR) observed for SOA (HR = 1.08; 95% CI 1.03, 1.13). For BC/OC and SIA exposure, the results showed a positive association with CVD mortality, which was stronger in magnitude than the association with all-cause mortality. In addition, we observed a higher HR for SOA in relation to respiratory mortality (HR = 1.15; 95% CI 0.99, 1.35). For sea salt, we observed the highest HRs for all-cause and respiratory mortality in the two medium exposure groups and the lowest HR in the highest exposure group. A graphical presentation of the functional form of the exposure-response associations is provided in the online appendix (Fig. D1).

Table 3 shows the results of the two-pollutant models including $PM_{2.5}$ mass and each constituent. The association between $PM_{2.5}$ mass and all-cause and CVD mortality remained in models including SIA and SOA, but was not robust to inclusion of BC/OC. The HR for BC/OC in that model was 1.06 (95% CI 1.02, 1.11) for all-cause mortality, i.e. similar to the result obtained in the single-pollutant model. The associations observed for SIA and SOA in models including $PM_{2.5}$ mass were similar to those of the single-pollutant models. The HRs for sea salt adjusted for PM_{10} were also largely similar to those of the single-pollutant model.

Table 4 presents the results of the two-pollutant models in which BC/OC is modelled together with BC and OC. The associations between BC/OC and all-cause and CVD mortality were essentially unaffected by including BC or OC in a model. In the model including each of BC and OC – but not their sum (BC/OC), we observed independent associations with all-cause mortality for both constituents. For each 0.25 $\mu g/m^3$ increase in BC (estimated independently of OC), we observed a HR of 1.06 (95% CI 1.02, 1.11) for all-cause mortality and a corresponding HR of 1.02 (95% CI 1.00, 1.03) per 0.76 $\mu g/m^3$ increase in OC (estimated independently of BC). The estimates for respiratory mortality were unstable.

Table 5 shows that when SIA is modelled together with SO_4, the association between SIA and CVD mortality disappeared whereas the HR for SO_4 was 1.05 (95% CI 0.99, 1.11). HRs for NH_4 showed inverse associations when adjusted for SIA and HRs for NO_3 showed strong associations between NO_3 and all-cause and respiratory mortality in models with SIA, whereas corresponding HRs for SIA showed negative associations. Three-pollutant models with SO_4, NH_4 and NO_3 showed a CVD mortality HR of 1.03 (95% CI 1.00, 1.07) for SO_4; the HRs for all-cause and respiratory mortality were below 1.00 for NH_4 and above 1.00 for NO_3.

The sex-specific models did not show evidence of differences in all-cause or respiratory mortality between men and women. However, the analyses suggested higher HRs of CVD mortality in men than in women in relation to all three exposures (Table F1).

Adjustments of the main model 3 for road traffic noise, when analyzing exposures with contributions from local street traffic, revealed slightly lower HRs compared to those of Table 2 (Table F2). Adjustment of the main model 3 for population density also did not change the estimates notably (Table F2).

4. Discussion

The findings from this study suggested higher all-cause mortality in relation to higher long-term exposure to $PM_{2.5}$, BC/OC, and SOA. Exposure to $PM_{2.5}$, BC/OC, and SIA was associated with CVD mortality. In the two-pollutant analyses, results suggested an important role of BC/OC and SOA for the association between $PM_{2.5}$ and all-cause mortality. Two- and three pollutant models indicated a role of SO_4 in the observed association between SIA and CVD mortality. We did not observe a clear relationship between sea salt and mortality.

Table 2
Association between 15-year residential exposure to $PM_{2.5}$ and constituents of $PM_{2.5}$ and risk of all-cause, CVD, and respiratory mortality per IQR.

Exposure	N cases	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)
$PM_{2.5}$ (IQR = 1.36)				
All-cause	10,193	1.09 (1.07, 1.11)	1.04 (1.02, 1.06)	1.03 (1.01, 1.05)
CVD	2319	1.13 (1.09, 1.17)	1.08 (1.04, 1.12)	1.07 (1.03, 1.11)
Respiratory	870	1.09 (1.02, 1.16)	1.00 (0.93, 1.07)	0.99 (0.92, 1.06)
BC/OC (IQR = 0.83)				
All-cause	10,193	1.15 (1.12, 1.18)	1.08 (1.06, 1.11)	1.06 (1.03, 1.09)
CVD	2319	1.18 (1.13, 1.24)	1.12 (1.06, 1.18)	1.10 (1.04, 1.16)
Respiratory	870	1.19 (1.10, 1.30)	1.10 (1.01, 1.21)	1.04 (0.95, 1.15)
SIA (IQR = 0.26)				
All-cause	10,193	1.04 (1.03, 1.06)	1.01 (0.99, 1.02)	1.01 (0.99, 1.03)
CVD	2319	1.10 (1.07, 1.13)	1.05 (1.02, 1.08)	1.05 (1.02, 1.08)
Respiratory	870	1.09 (1.04, 1.15)	1.02 (0.97, 1.07)	1.02 (0.96, 1.07)
SOA (IQR = 0.05)				
All-cause	10,193	1.15 (1.10, 1.19)	1.12 (1.07, 1.16)	1.08 (1.03, 1.13)
CVD	2319	1.13 (1.04, 1.23)	1.12 (1.03, 1.22)	1.07 (0.98, 1.17)
Respiratory	870	1.26 (1.10, 1.45)	1.25 (1.09, 1.44)	1.15 (0.99, 1.34)
Sea Salt				
All-cause				
$< 3.33\ \mu g/m^3$	2104	(reference)	(reference)	(reference)
$3.33–3.37\ \mu g/m^3$	1619	1.04 (0.98, 1.12)	1.02 (0.95, 1.09)	1.02 (0.95, 1.09)
$3.38–4.07\ \mu g/m^3$	4402	1.12 (1.05, 1.19)	1.05 (0.98, 1.11)	1.06 (0.99, 1.12)
$\geq 4.08\ \mu g/m^3$	2068	0.95 (0.89, 1.01)	0.90 (0.84, 0.97)	0.94 (0.87, 1.00)
CVD				
$< 3.33\ \mu g/m^3$	459	(reference)	(reference)	(reference)
$3.33–3.37\ \mu g/m^3$	331	0.96 (0.83, 1.11)	0.94 (0.81, 1.09)	0.93 (0.80, 1.08)
$3.38–4.07\ \mu g/m^3$	1053	1.12 (0.99, 1.27)	1.06 (0.93, 1.21)	1.06 (0.93, 1.21)
$\geq 4.08\ \mu g/m^3$	476	0.94 (0.82, 1.08)	0.88 (0.76, 1.01)	0.91 (0.78, 1.05)
Respiratory				
$< 3.33\ \mu g/m^3$	212	(reference)	(reference)	(reference)
$3.33–3.37\ \mu g/m^3$	172	1.15 (0.94, 1.41)	1.09 (0.88, 1.34)	1.08 (0.87, 1.33)
$3.38–4.07\ \mu g/m^3$	333	1.19 (0.98, 1.44)	1.07 (0.88, 1.30)	1.09 (0.90, 1.33)
$\geq 4.08\ \mu g/m^3$	153	0.94 (0.75, 1.16)	0.83 (0.66, 1.04)	0.90 (0.71, 1.13)

Abbreviations: IQR, interquartile range; PM, particulate matter; SIA/SOA, secondary inorganic/organic aerosols; BC/OC, sum of primary emitted BC and OC; CVD, cardiovascular disease.

[a] Adjusted for age, sex and calendar time.

[b] Model 1 + educational level, marital status, occupational status, smoking, alcohol consumption, physical activity, body mass index, waist circumference, environmental tobacco smoke, and fruit and vegetable consumption.

[c] Model 2 + neighborhood level SES.

A range of different underlying biological mechanisms has been suggested to explain the potential adverse health effects of $PM_{2.5}$ constituents. BC may affect DNA methylation and induce oxidative stress (Niranjan and Thakur, 2017; Baccarelli et al., 2009; Baccarelli and Bollati, 2009), which in turn affects lung function and CVD risk (Mordukhovich et al., 2015; Santilli et al., 2015; Brook et al., 2010). BC and SO_4 have both been related to impaired vasodilatation as well as markers of systemic inflammation (O'Neill et al., 2005; Li et al., 2017). In a recent study, exposure to NO_3, NH_4, and SO_4 (SIA components) was associated with the activation of the hypothalamic-pituitaryadrenal (HPA) axis which may affect the cardiovascular system (Niu et al., 2018). Also, NO_3, NH_4, BC and OC have been associated with higher blood pressure (Brook et al., 2010; Lin et al., 2017; Magalhaes et al., 2018).

Previous studies on long-term $PM_{2.5}$ exposure and mortality generally support a positive association (Hoek et al., 2013; Beelen et al., 2014; Pope et al., 2019); yet, findings on mortality in relation to specific constituents of long-term exposure to $PM_{2.5}$ have been mixed (Stanek et al., 2011). In line with our results, analyses within the National Particle Component Toxicity (NPACT) initiative suggested an association between $PM_{2.5}$ mass, EC and all-cause mortality and between EC and Ischemic heart disease mortality (Lippmann et al., 2013). They did not, however, find evidence of an association with OC. Another NPACT report focusing specifically on CVD outcomes, showed associations with long-term exposure to sulfur, but also to OC exposure (Vedal et al., 2013). In the California Teacher's study, positive associations were found between NO_3, SO_4 and cardiopulmonary disease mortality which is in accordance with our results (Ostro et al., 2010, 2011). For Ischemic heart disease mortality, a positive relation was observed for EC, OC, SO_4, NO_3, and SOA (Ostro et al., 2010, 2011, 2015). A study within the large US Medicare population found the SIAs and OC to be less harmful in terms of all-cause mortality than other chemical components of $PM_{2.5}$ such as EC, aluminum, calcium, copper, iron, and vanadium (Wang et al., 2017). Another study based on Medicare enrollees, reported a positive association between EC, NO_3 and mortality, but an inverse association between SO_4 and mortality in models taking into account $PM_{2.5}$ mass (Chung et al., 2015). In our study, a positive association was observed between BC and NO_3 and all-cause mortality, but the SO_4 association was restricted to CVD mortality, for which the mentioned study did not provide separate estimates. The ESCAPE meta-analysis, which also included part of the Diet, Cancer and Health cohort, reported an association between $PM_{2.5}$ sulfur and all-cause mortality, which was independent of $PM_{2.5}$ mass exposure (Beelen et al., 2015). The mentioned studies differ according to study populations, exposure assessment methods, and statistical modelling approaches, which may explain some of the discrepancies. The California Teacher's study by Ostro et al. was solely based on women and exposure was derived from monitoring stations, but the analyses (in their erratum) resembles ours by modelling exposure data time-dependently with recalculation of exposure at each death occurrence. The Medicare study by Chung et al. covered an elderly population (65+ years) and relied on monitor exposure data in which $PM_{2.5}$ was

Table 3
Two-pollutant models of the association between 15-year residential exposure to $PM_{2.5}$ and constituents of $PM_{2.5}$ and risk of all-cause, CVD, and respiratory mortality per IQR.

Outcome	N cases	Model 3[a] HR (95% CI)	
		$PM_{2.5}$ (IQR = 1.36)	**BC/OC** (IQR = 0.83)
All-cause	10,193	1.00 (0.97, 1.03)	1.06 (1.02, 1.11)
CVD	2319	1.05 (0.99, 1.11)	1.03 (0.95, 1.13)
Respiratory	870	0.93 (0.84, 1.03)	1.13 (0.98, 1.30)
		$PM_{2.5}$ (IQR = 1.36)	**SIA** (IQR = 0.26)
All-cause	10,193	1.03 (1.01, 1.05)	1.00 (0.99, 1.02)
CVD	2319	1.06 (1.02, 1.10)	1.04 (1.01, 1.07)
Respiratory	870	0.98 (0.91, 1.05)	1.02 (0.97, 1.08)
		$PM_{2.5}$ (IQR = 1.36)	**SOA** (IQR = 0.05)
All-cause	10,193	1.03 (1.01, 1.05)	1.07 (1.02, 1.12)
CVD	2319	1.07 (1.03, 1.11)	1.04 (0.95, 1.14)
Respiratory	870	0.98 (0.91, 1.05)	1.16 (0.99, 1.36)
		PM_{10} (per IQR = 1.86)	**Sea Salt** (categorical)
All-cause			
Sea salt < 3.33 μg/m^3	2104	1.02 (1.01, 1.04)	(reference)
Sea salt 3.33–3.37 μg/m^3	1619		1.01 (0.95, 1.09)
Sea salt 3.38–4.07 μg/m^3	4402		1.05 (0.99, 1.12)
Sea salt ≥ 4.08 μg/m^3	2068		0.93 (0.87, 0.99)
CVD			
Sea salt < 3.33 μg/m^3	459	1.05 (1.02, 1.08)	(reference)
Sea salt 3.33–3.37 μg/m^3	331		0.93 (0.80, 1.08)
Sea salt 3.38–4.07 μg/m^3	1053		1.05 (0.91, 1.20)
Sea salt ≥ 4.08 μg/m^3	476		0.89 (0.77, 1.04)
Respiratory			
Sea salt < 3.33 μg/m^3	212	0.98 (0.93, 1.04)	(reference)
Sea salt 3.33–3.37 μg/m^3	172		1.08 (0.88, 1.34)
Sea salt 3.38–4.07 μg/m^3	333		1.10 (0.90, 1.34)
Sea salt ≥ 4.08 μg/m^3	153		0.90 (0.71, 1.14)

Abbreviations: IQR, interquartile range; PM, particulate matter; SIA/SOA, secondary inorganic/organic aerosols; BC/OC, sum of primary emitted BC and OC; CVD, cardiovascular disease.

[a] Adjusted for age, sex and calendar time, educational level, marital status, occupational status, smoking, alcohol consumption, physical activity, BMI, waist circumference, ETS, fruit and vegetable consumption, and neighborhood level SES.

Table 4
Two-pollutant models of the association between 15-year residential exposure to BC/OC , BC and OC and risk of all-cause, CVD, and respiratory mortality per IQR.

Outcome	N cases	Model 3[a] HR (95% CI)	
		BC/OC (IQR = 0.83)	**BC** (IQR = 0.25)
All-cause	10,193	1.07 (1.02, 1.12)	1.00 (0.98, 1.02)
CVD	2319	1.08 (0.98, 1.19)	1.01 (0.97, 1.05)
Respiratory	870	1.15 (0.98, 1.35)	0.94 (0.88, 1.02)
		BC/OC (IQR = 0.83)	**OC** (IQR = 0.76)
All-cause	10,193	1.06 (1.02, 1.11)	1.01 (0.94, 1.07)
CVD	2319	1.11 (1.02, 1.21)	0.98 (0.86, 1.11)
Respiratory	870	0.95 (0.80, 1.11)	1.20 (0.95, 1.51)
		BC (IQR = 0.25)	**OC** (IQR = 0.76)
All-cause	10,193	1.06 (1.02, 1.11)	1.02 (1.00, 1.03)
CVD	2319	1.08 (0.98, 1.17)	1.03 (1.01, 1.06)
Respiratory	870	1.14 (0.98, 1.32)	0.98 (0.94, 1.03)

Abbreviations: IQR, interquartile range; BC/OC, sum of primary emitted BC and OC; CVD, cardiovascular disease.

[a] Adjusted for age, sex and calendar time, educational level, marital status, occupational status, smoking, alcohol consumption, physical activity, body mass index, waist circumference, environmental tobacco smoke, fruit and vegetable consumption, and neighborhood level SES.

measured at different sites than the constituents. The ESCAPE study applied baseline exposures derived from LUR models.

The strengths of this study include the large cohort with individual information on several potential confounders and the prospective design with a follow-up period of 20+ years. The exposures were modelled by a state-of-the-art air pollution modelling system, which enabled calculations of decades of individual residential address level exposures of both $PM_{2.5}$ and the main constituents. Unlike many of the previous studies within this field, our study did not rely on monitor station input (Keller et al., 2017). Instead, the starting point of the deterministic DEHM/UBM/AirGIS modelling system is an air pollution emission inventory from which the modelling system was built to reflect the physical and chemical processes leading to the air pollution concentration at a specific address. The model takes into account local contributions 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. Because of these detailed input data, the calculated $PM_{2.5}$ concentration at two addresses separated by even a short distance can be very different.

The ability of this study to separate the relative importance of each constituent of $PM_{2.5}$ mass in relation to mortality was challenged by high intercorrelations between some of the $PM_{2.5}$ constituents (appendix Tables E1 and E2), e.g. between SOA and BC/OC ($r_{spearman}$ = 0.89) and between NO_3 and SO_4 ($r_{spearman}$ = 0.85), which makes it difficult to disentangle each of their relative contributions to mortality (Mostofsky et al., 2012). Especially the highly correlated SIA components showed unstable results in two- and three pollutant models. Thus, there is a need for the development of new statistical tools to handle such parametric obstacles. In general, Danish $PM_{2.5}$ concentration levels are much lower compared to for instance southern European countries (Raaschou-Nielsen et al., 2013). Further, the contrast was quite low for SOA and sea salt (cf. Table 1), but nevertheless we showed an association between SOA and mortality, as suggested by Ostro et al. (2015). Sea salt may be less well represented in a cohort as the DCH, which primarily covers the two major cities of Denmark. Future studies at the National level covering also the western coastline may be better suited for investigating possible associations between sea salt and mortality (cf. appendix Fig. A1). Secondly, misclassification is inevitable when applying model-derived exposures due to both input data uncertainties and to the assumption of equating residential front-door exposure to everyday life exposure. An additional challenge is that the specific modelled constituent exposures may differ in their level of uncertainty (Khan et al., 2018), which could trigger that part of a causal effect is transferred from the less precisely modelled constituent to a more adequately modelled constituent (Achilleos et al., 2017; Zeger et al., 2000; Harrison et al., 2018). In both the two- and three-pollutant models of the SIA components, we observed a negative association between NH_4 and all three end-points. It is likely that these estimates result from differences in modelling precision combined with high correlation with other pollutants rather than from a causal protective effect of NH_4. The applied model system is suspected of underestimating some of the PM constituents in the DEHM, e.g. primary organic PM and secondary aerosols, and non-exhaust PM from traffic in the OSPM such as tire wear, road wear, and brake wear (Khan et al., 2018). Also, we were not able to examine road dust, fine fraction sea salt and metal components of $PM_{2.5}$ – the latter are considered to play an important role in overall $PM_{2.5}$ toxicity through mechanisms of oxidative stress and inflammation (Brook et al., 2010). Another point is that the applied version of the modelling system was not able to deliver

Table 5
Two- and three pollutant models of the association between 15-year residential exposure to SIA, SO_4, NH_4, and NO_3 and risk of all-cause, CVD, and respiratory mortality per interquartile range.

Outcome	N cases	Model 3[a] HR (95% CI)		
		Two-pollutant		
		SIA (IQR = 0.26)	**SO_4** (IQR = 0.12)	
All-cause	10,193	1.00 (0.97, 1.04)	1.01 (0.98, 1.04)	
CVD	2319	1.00 (0.93, 1.07)	1.05 (0.99, 1.11)	
Respiratory	870	1.07 (0.94, 1.22)	0.95 (0.85, 1.07)	
		SIA (IQR = 0.26)	**NH_4** (IQR = 0.20)	
All-cause	10,193	1.04 (1.02, 1.07)	0.88 (0.83, 0.94)	
CVD	2319	1.09 (1.05, 1.14)	0.87 (0.78, 0.98)	
Respiratory	870	1.05 (0.97, 1.14)	0.87 (0.69, 1.09)	
		SIA (IQR = 0.26)	**NO_3** (IQR = 0.13)	
All-cause	10,193	0.95 (0.92, 0.98)	1.11 (1.06, 1.17)	
CVD	2319	1.03 (0.97, 1.11)	1.03 (0.93, 1.14)	
Respiratory	870	0.87 (0.76, 0.98)	1.28 (1.07, 1.53)	
		Three-pollutant		
		SO_4 (IQR = 0.12)	**NH_4** (IQR = 0.20)	**NO_3** (IQR = 0.13)
All-cause	10,193	0.99 (0.98, 1.01)	0.88 (0.84, 0.93)	1.09 (1.05, 1.13)
CVD	2319	1.03 (1.00, 1.07)	0.92 (0.83, 1.02)	1.06 (0.99, 1.14)
Respiratory	870	0.95 (0.89, 1.02)	0.85 (0.70, 1.02)	1.19 (1.05, 1.35)

Abbreviations: IQR, interquartile range; SIA, secondary inorganic aerosols; NO_3, nitrate; NH_4, ammonium; SO_4, sulfate; CVD, cardiovascular disease.
[a] Adjusted for age, sex and calendar time, educational level, marital status, occupational status, smoking, alcohol consumption, physical activity, body mass index, waist circumference, environmental tobacco smoke, fruit and vegetable consumption, and neighborhood level SES.

OC at the local scale. Regional OC may vary from local OC, because of uncertainties in the PM emissions from wood stoves in the present emission inventory (e.g. number and location of woodstoves, wood use, emission factors and user behavior) (Plejdrup and Gyldenkærne, 2011). Future results based on newer model versions may therefore deviate from the findings of this paper. Lastly, we cannot rule out residual confounding, as we were only able to account for lifestyle confounding at baseline. Although we expect individuals in the included age ranges (50–64 years at enrolment) to have a relatively stable lifestyle, the occurrence of disease during follow-up may have affected their lifestyle during follow-up.

In conclusion, we observed a relationship between long-term exposure to $PM_{2.5}$, BC/OC, and SOA and all-cause mortality and between $PM_{2.5}$, BC/OC, and SIA and CVD mortality. Future studies based on data sets covering a broader area with higher exposure contrast could impart more knowledge on health effects of the specific $PM_{2.5}$ constituents.

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.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.105268.

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