Environment International 164 (2022) 107241

Contents lists available at ScienceDirect

Environment International

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

Full length article

Long-term exposure to air pollution and mortality in a Danish nationwide administrative cohort study: Beyond mortality from cardiopulmonary disease and lung cancer

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ARTICLE INFO

Handling Editor: Adrian Covaci

Keywords:
Long-term exposure to air pollution
Mortality

ABSTRACT

Background: The association between long-term exposure to air pollution and mortality from cardiorespiratory diseases is well established, yet the evidence for other diseases remains limited.
Objectives: To examine the associations of long-term exposure to air pollution with mortality from diabetes, dementia, psychiatric disorders, chronic kidney disease (CKD), asthma, acute lower respiratory infection (ALRI),

Abbreviations: ALRI, Acute lower respiratory infection; BC, Black carbon; BMI, Body mass index; CanCHEC, Canadian Census Health and Environment Cohort; CI, Confidence interval; COPD, Chronic obstructive pulmonary disease; CVD, Cardiovascular disease; CKD, Chronic kidney disease; DAG, Directed Acyclic Graph; DEHM, Danish Eulerian Hemispheric Model; ELAPSE, Effects of Low-Level Air Pollution: A Study in Europe; ESCAPE, European Study of Cohorts for Air Pollution Effect; HR, Hazard ratio; LUR, Land-use regression; NO_2, Nitrogen dioxide; O_3, Ozone; PM, Particulate matter; $PM_{2.5}$, Particulate matter with a diameter of<2.5 μm; RD, Respiratory disease; SES, Socioeconomic status; SD, Standard deviation; US-EPA NAAQS, US Environmental Protection Agency National Ambient Air Quality Standard; WHO, World Health Organization.

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https://doi.org/10.1016/j.envint.2022.107241
Received 3 January 2022; Received in revised form 4 April 2022; Accepted 9 April 2022
Available online 12 April 2022

Nationwide administrative cohort
Cardiorespiratory disease
Dementia
Psychiatric disorders

as well as mortality from all-natural and cardiorespiratory causes in the Danish nationwide administrative cohort.

Methods: We followed all residents aged ≥ 30 years (3,083,227) in Denmark from 1 January 2000 until 31 December 2017. Annual mean concentrations of fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), black carbon (BC), and ozone (warm season) were estimated using European-wide hybrid land-use regression models (100 m × 100 m) and assigned to baseline residential addresses. We used Cox proportional hazard models to evaluate the association between air pollution and mortality, accounting for demographic and socioeconomic factors. We additionally applied indirect adjustment for smoking and body mass index (BMI).

Results: During 47,023,454 person-years of follow-up, 803,881 people died from natural causes. Long-term exposure to $PM_{2.5}$ (mean: 12.4 μg/m^3), NO_2 (20.3 μg/m^3), and/or BC (1.0×10^{-5}/m) was statistically significantly associated with all studied mortality outcomes except CKD. A 5 μg/m^3 increase in $PM_{2.5}$ was associated with higher mortality from all-natural causes (hazard ratio 1.11; 95% confidence interval 1.09–1.13), cardiovascular disease (1.09; 1.07–1.12), respiratory disease (1.11; 1.07–1.15), lung cancer (1.19; 1.15–1.24), diabetes (1.10; 1.04–1.16), dementia (1.05; 1.00–1.10), psychiatric disorders (1.38; 1.27–1.50), asthma (1.13; 0.94–1.36), and ALRI (1.14; 1.09–1.20). Associations with long-term exposure to ozone (mean: 80.2 μg/m^3) were generally negative but became significantly positive for several endpoints in two-pollutant models. Generally, associations were attenuated but remained significant after indirect adjustment for smoking and BMI.

Conclusion: Long-term exposure to $PM_{2.5}$, NO_2, and/or BC in Denmark were associated with mortality beyond cardiorespiratory diseases, including diabetes, dementia, psychiatric disorders, asthma, and ALRI.

1. . Introduction

The epidemiological evidence supporting the association of long-term exposure to ambient air pollution with mortality from cardiovascular disease (CVD), respiratory disease (RD), and lung cancer is well-established (Chen and Hoek 2020; Health Effects Institute 2020; WHO 2021). In a *meta*-analysis from 2020, used for the development of new World Health Organizations (WHO) Air Quality Guidelines (WHO 2021), Chen and Hoek reported excess risks per 10 μg/m^3 increase in particulate matter (PM) with a diameter of<2.5 μm ($PM_{2.5}$) of 8% for all-cause, 11% for circulatory, 10% for respiratory, and 15% for lung cancer mortality. Recently, there are studies providing additional evidence of the associations from areas with low levels of air pollution, which found similar or even stronger associations between NO_2 and $PM_{2.5}$, and all-cause, CVD, and RD mortality than those reported by Chen and Hoek (Chen and Hoek 2020; Huangfu and Atkinson 2020): two recent analyses from the Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) project (Stafoggia et al. 2022; Strak et al. 2021), a study from New Zealand (Hales et al. 2021), and two studies from the US, both with the Medicare enrollees (Shi et al. 2021; Yazdi et al. 2021).

The Global Exposure Mortality Model estimated that approximately 23 % of deaths attributed to $PM_{2.5}$ globally were due to other causes of deaths than those that have been recognized as related to $PM_{2.5}$, including ischemic heart disease, stroke, chronic obstructive pulmonary disease (COPD), lung cancer, and LRI (Burnett et al. 2018). A recent study by Bowe and colleagues suggested that approximately 17% and 8% of CKD and dementia deaths, respectively, are attributed to $PM_{2.5}$ (Bowe et al. 2019). However, there are only a few epidemiological studies examining the association between long-term air pollution exposures with these mortality outcomes (Brook et al. 2013; Crouse et al. 2015; Klompmaker et al. 2021; Lim et al. 2018; Pope et al. 2015; Ran et al. 2020; So et al. 2020; Zhao et al. 2021), mostly suggesting stronger associations than those with CVD mortality, especially for diabetes. Furthermore, emerging evidence from epidemiological studies also suggested a possible link between long-term exposure to air pollution and the development of psychiatric disorders (or its symptoms), including depression (Borroni et al. 2022; Shen et al. 2021; Wang et al. 2019), anxiety (Zhao et al. 2020), and psychotic experiences (Bakolis et al. 2021), but to our knowledge, no published research exists for the association between air pollution and mortality from these disorders.

The latest State of Global Air analyses stated that there is a comprehensive scientific agreement that long-term exposure to air pollution contributes to increased risks of disease and death from ischemic heart disease, stroke, COPD, lower respiratory infection, lung cancer, type-2 diabetes, and, more recently, adverse birth outcomes; but also that more research is needed on adult-onset asthma, cognitive disorders, and CKD (Health Effects Institute 2020).

In this study, we examined the associations of long-term exposure to air pollution with all-natural cause mortality and cause-specific mortality, including all CVDs, ischemic heart disease, stroke, all RDs, COPD, asthma, acute lower respiratory infections (ALRI), lung cancer, diabetes, CKD, dementia, and psychiatric disorders in a Danish nationwide administrative cohort.

2. Materials and Methods

2.1. Study population

We utilized the framework of the ELAPSE project, in which seven large European administrative cohorts, including one from Denmark, were analyzed to examine the health effects of low-levels of air pollution. Here, we updated the Danish nationwide administrative cohort of 3,323,612 Danish inhabitants by adding two years' longer follow-up than the follow-up time used in the Danish nationwide administrative analyses in the ELAPSE project (Stafoggia et al. 2022). Individuals in the cohort were 30 years or older on 1 January 2000 and were followed up for mortality until 31 December 2017.

The following information was extracted from Statistics Denmark: individual-level covariates (obtained at 1999) including sex, date of birth, household income, occupational status, immigrant status, marital status, highest completed education level; and parish- and regional-level covariates (obtained at 2001) including mean household income and percentage of unemployment. Assignment of the region was determined by individuals' registered and geocoded residential addresses at baseline.

2.2. Definition of mortality outcome

We defined mortality outcomes based on the underlying cause of death from the Danish Register of Cause of Death (Helweg-Larsen 2011) using the following International Classification of Disease 10th revision definitions: all-natural cause mortality (ICD-10: A00-R99), CVD (I10-69), RD (J00-99), lung cancer (C34), diabetes (E10-14), CKD (N18), dementia (F00-F03, G30, G31.8–9), and psychiatric disorders (excluding dementia) (F04-F99). Additionally, we defined more specific subtypes of CVD mortality, including ischemic heart disease (I20-25) and stroke (I60-69), as well as RD mortality, including COPD (J40-44, J47), asthma (J45-46), and ALRIs (J09-J18, J20-22).

2.3. Assessment of air pollution concentration

Annual average exposure to air pollutants [$PM_{2.5}$, nitrogen dioxide (NO_2), black carbon (BC), and ozone (O_3), warm-season (April-September)] for the year 2010 were estimated at the individuals' baseline geocoded residential addresses on 31 December 1999 using 100 × 100 m European-wide hybrid land-use regression (LUR) models. Here, we only used warm-season O_3 because the correlation with annual and winter-season was high, and exposure concentration and variation in concentration are high during the summer (Brunekreef et al. 2021). Methods for developing and evaluating the exposure prediction models have been described in detail elsewhere (De Hoogh et al. 2018). Briefly, the European-wide hybrid LUR models were constructed based on the European Environment Agency AirBase routine monitoring data for 2010 for $PM_{2.5}$, NO_2, and O_3, and the European Study of Cohorts for Air Pollution Effects (ESCAPE) project monitoring data for BC. For O_3, the maximum running 8-hour means for each day were used to calculate the annual warm-season average concentrations of O_3. For BC, annual mean $PM_{2.5}$ absorbance data monitored during 2009 and 2010, based on reflectance measurement of the filters, were used and considered as annual mean concentrations for 2010. The predictor information for the LUR models comprised land use and road data, air pollution data from satellites, and dispersion model estimates. Ordinary kriging was additionally applied to the residuals of $PM_{2.5}$ and O_3. Based on hold-out validation, the explained spatial variations in the measured concentration by the LUR models were 66 % for $PM_{2.5}$, 58 % for NO_2, 51 % for BC, and 60 % for O_3. In the ELAPSE project, 2010 was selected as the year of air pollution assessment modeling because this was the earliest year providing sufficiently broad coverage of $PM_{2.5}$ monitoring data across Europe. For consistency, 2010 was also used for NO_2 and O_3.

For a sensitivity analysis, we also estimated the annual mean levels of $PM_{2.5}$, NO_2, BC, and O_3 every year during follow-up by using a back- and forward-extrapolation method with estimated concentrations from the Danish Eulerian Hemispheric Model (DEHM) (Brandt et al. 2012). The detailed methods were elsewhere (Brunekreef et al. 2021; Stafoggia et al. 2022). Briefly, DEHM provides monthly mean concentration estimates at 26 km × 26 km spatial resolution across Europe back to at least 1990. We used DEHM data because the AirBase data did not continuously measure monitoring data during the study period, and the temporal trends are consistent for these two databases. Within the ELAPSE project, population-weighted annual mean air pollution concentrations (annual warm-season concentration for O_3) at NUTS-1 level (Nomenclature of territorial units for statistics) were calculated (entire Denmark belongs to one NUTS-1 region) and were used for calculating the ratios of exposure levels between each year during the follow-up and 2010. Those ratios were multiplied by the exposure estimates from the LUR model at each residential address.

2.4. Statistical analyses

Our analytical strategy followed the protocol from the ELAPSE project (Brunekreef et al. 2021; Stafoggia et al. 2022). We utilized a Cox proportional hazards regression model with age as the underlying time scale to investigate the association between mortality and air pollution exposure. Exposure to air pollution and other covariates were included in the models as time-invariant variables. The follow-up period began on 1 January 2000 and ended at the date of the event of interest, death from other causes, emigration, loss to follow-up from other reasons, or 31 December 2017, whichever came first.

We modeled the associations between air pollutants and mortality in three steps with increasing adjustment for confounders: Model 1, adjusted for age (underlying time scale) and sex (strata); Model 2, additionally adjusted for individual socioeconomic status (SES) including household income in deciles, occupational status (unemployed, employed, or sick/cash support/student/pension/others), immigrant status (Danish origin, immigrants/descendants from Western country of origin, immigrants/descendants from non-Western country of origin), marital status (unmarried, divorced, widowed, married/registered partnership), and highest completed education level (primary, upper secondary, vocation/qualifying, vocation bachelor/ short-cycle higher education, or more than college level); and Model 3 (main model), additionally adjusted for regional mean household income, regional percentage of unemployment, and the difference of mean household income and percentage of unemployment, between parish and region. All analyses accounted for clustering of the data in the same parish by adjusting the variance of the effect estimates.

We first considered single pollutant models and then two-pollutant models to examine the independent effect of each pollutant after controlling for another. Collinearity tests for exposures in two-pollutant models were performed, and no multi-collinearity was identified [variance inflation factors range from 2.1 to 6.4 (below 10)].

We further fitted the models with a natural spline for the pollutant variable with three degrees of freedom, instead of a linear term, to visualize the shape of the association between exposure to $PM_{2.5}$, NO_2, BC, and O_3 and mortality outcomes.

To examine the effects of air pollutants at levels below the existing limit values, we applied the main model to subsets in which we excluded individuals with exposure to concentrations above a certain value, including 15 and 12 [the US Environmental Protection Agency National Ambient Air Quality Standard (US-EPA NAAQS)] $\mu g/m^3$ for $PM_{2.5}$, 40 (the EU standard), 30, and 20 $\mu g/m^3$ for NO_2, 2, 1.5, 1.0×10^{-5}/m for BC, and 80 $\mu g/m^3$ for O_3. Unlike analyses in the ELAPSE project, we did not restrict the analysis for $PM_{2.5}$ below 25 $\mu g/m^3$ (the EU standard) or below 10 $\mu g/m^3$ (the WHO 2005 guideline) because the maximum concentration for the population was lower than 25 $\mu g/m^3$ (the mean of the top five values: 19.6 $\mu g/m^3$) and less than five percent of the population were exposed to levels below 10 $\mu g/m^3$.

We examined effect modification of the associations between long-term exposure to air pollutants and all-natural cause mortality by introducing an interaction term of each air pollutant and a potential modifier in the model and testing with the Wald test. Potential modifiers include age at baseline (<65 years or ≥ 65 years), sex, household income in quintiles, immigrant status, highest completed education level, and occupational status.

To assess the potential impact of individual-level lifestyle risk factors not measured in our nationwide administrative cohort, we additionally adjusted for age-standardized mortality rate in the baseline year (2000) from lung cancer, COPD, and diabetes at the municipality level as proxies for smoking level and obesity. Furthermore, we adapted an indirect adjustment method proposed by Shin and colleagues to mathematically adjust our hazard ratios (HRs) for lifestyle factors, including smoking status and body mass index (BMI) (Shin et al. 2014). To do this, two pieces of information are needed: 1) the estimated associations between the variables we would indirectly adjust for and exposure to air pollution after adjusting for the covariates included in our main model; 2) risk estimates of the variables we would indirectly adjust for on mortality outcomes. We calculated the first information from the Danish National Health Survey in 2010, which is the closest to the baseline year (2000) of the nationwide administrative cohort, among three cycles (2010, 2013, and 2017) of the survey (Christensen et al. 2020). The Danish National Health Survey was also linked to the information on demographic and SES covariates and exposure to air pollution as those used in our main model. From 177,639 respondents in the Danish National Health Survey, we excluded 24,020 persons younger than 30 years at the survey year (2010) for consistency with the Danish nationwide administrative cohort. Furthermore, we further excluded 6,727 due to missing information on individual SES covariates and 7,676 due to missing information on smoking status and BMI, resulting in 139,183 survey respondents for calculating the first information. We got the second information (risk estimates of BMI and smoking on all studied mortality outcomes) from the pooled European cohorts in the ELAPSE program (Brunekreef et al. 2021; Stafoggia et al. 2022).

We conducted several sensitivity analyses to explore the robustness of the main results. First, we compared HRs using the 2010 exposure estimates with those using back-extrapolated baseline year exposure estimates. Second, we also conducted time-varying analyses with back- and forward-extrapolated exposure estimates from the enrolment to the end of follow-up with 1-year strata of calendar year to consider the effect of temporal variation (decline) in air pollution over time and residential mobility on our estimates. Third, to account for multiple statistical tests, we controlled the False Discovery Rate (FDR) at $q = 0.05$, using the Benjamini & Hochberg method (Benjamini and Hochberg 1995). Fourth, we performed the inverse probability weighting analyses for natural mortality to investigate the possible bias from excluding subjects from the main analyses due to missing information of covariates (Hernán et al. 2004). We estimated probabilities of being included in the main analyses using the most available variables (age, sex, household income, occupational status, education level, immigrant status, marital status; only 244 subjects had missing these variables) as the predictors. We took the inverse of probability and used it as a weight in the cox model. Lastly, we used a Directed Acyclic Graph (DAG) to identify a minimum set of variables for confounding adjustment and estimated the associations of long-term exposure to air pollution and natural cause mortality adjusting for these variables.

We calculated the effects of air pollution exposure as HR with 95% confidence interval (CI) per 5 $\mu g/m^3$ for $PM_{2.5}$, 10 $\mu g/m^3$ for NO_2, 0.5 $\times$ 10^{-5}/m for BC, and 10 $\mu g/m^3$ for O_3. When we compared the effect sizes across exposures, we used the interquartile range of each air pollutant. We did not consider a clustering of the data in the same parish in the analyses with a spline term of an air pollutant and time-varying analyses due to time and computational burden with acknowledging the underestimation of the standard errors.

All statistical tests were two-sided, and p-values of < 0.05 were used for statistical significance. We made all analyses and graphical presentations in R, version 4.1.0, with R scripts developed within the ELAPSE project.

3. Results

3.1. Description of the study population and exposure

From 3,323,612 individuals, we excluded 2,815 due to missing information on parish, 26 due to missing information on individual covariates (2 for occupational status, 24 for immigrant status), and 237,544 due to missing data in geocoding, resulting in a total of 3,083,227 individuals for the final analysis. The excluded participants (N = 240,385) were older, had lower household income and education, were more likely to be men, be unemployed and unmarried, and to die by the end of follow-up compared to individuals included in the analyses (N = 3,083,227) (Table S1 in the supplementary material).

Of the 3,083,227 participants, 803,881 (26.1%) died from natural causes during a mean follow-up time of 15.3 [standard deviation (SD): 5.1] years or 47,023,454 person-years. Among 803,881 natural deaths, 223,553 were from all CVDs [ischemic heart disease (89,914) and stroke (63,492)], 90,028 from all RDs [COPD (53,068), asthma (1,506), and ALRI (27,772)], 58,435 from lung cancer, 20,691 from diabetes, 3,749 from CKD, 41,141 from dementia, and 12,801 from psychiatric disorders. Compared to individuals who were alive at the end of follow-up, those who died were more likely to have lower income and education, be unemployed, divorced/widowed, and be of Danish origin at the cohort baseline in 2000 (Table 1).

The mean air pollution levels were 12.4 (SD: 1.55) $\mu g/m^3$ for $PM_{2.5}$ and 20.3 (SD: 7.94) $\mu g/m^3$ for NO_2 [both well below the current EU standard concentrations for $PM_{2.5}$ (25 $\mu g/m^3$) and NO_2 (40 $\mu g/m^3$)], 1.0 (SD: 0.36) $\times$ 10^{-5}/m for BC, and 80.2 (SD: 4.28) $\mu g/m^3$ for O_3 (Table 2). $PM_{2.5}$ was moderately correlated with NO_2 [Spearman's rank correlation coefficient (ρ) = 0.60] and BC ($\rho = 0.70$), while the correlation between NO_2 and BC was very high ($\rho = 0.89$). O_3 was negatively

Table 1
Descriptive characteristics for 3,083,227 individuals from the Danish nationwide administrative cohort at the cohort baseline (2000) by the status (Alive/emigration/loss to follow-up, or dead) at the end of follow-up.

Characteristics	Total N = 3,083,227	Alive/ emigration/loss to follow-up N = 2,279,346	Dead[a] N = 803,881
Age at baseline (years), mean ± SD	53.0 ± 15.2	47.4 ± 11.4	68.9 ± 12.9
Sex, n (%)			
Man	1,488,951 (48.3)	1,098,199 (48.2)	390,752 (48.6)
Woman	1,594,276 (51.7)	1,181,147 (51.8)	413,129 (51.4)
Household income, mean ± SD	162,308.38 ± 167,475.82	171,080.05 ± 182,695.08	137,436.96 ± 110,002.07
Household income in decile, n (%)			
1st (≤90,138 DKK)	278,007 (9.0)	158,418 (7.0)	119,589 (14.9)
2nd (90,138–103,683.1 DKK)	298,060 (9.7)	135,619 (5.9)	162,441 (20.2)
3rd (103,683.1 – 118,296.3 DKK)	301,294 (9.8)	181,280 (8.0)	120,014 (14.9)
4th (118,296.3 – 132789.9 DKK)	307,172 (10)	218,873 (9.6)	88,299 (11.0)
5th (132,789.9 – 146,860.3 DKK)	311,337 (10.1)	243,353 (10.7)	67,984 (8.5)
6th (146,860.3 – 161567.7 DKK)	314,620 (10.2)	258,539 (11.3)	56,081 (7.0)
7th (161,567.7 – 178,556.8 DKK)	316,455 (10.3)	266,040 (11.7)	50,415 (6.3)
8th (178,556.8 – 200,841.4 DKK)	318,085 (10.3)	271,034 (11.9)	47,051 (5.9)
9th (200,841.4 – 237,928.2 DKK)	319,512 (10.4)	274,102 (12.0)	45,410 (5.6)
10th (>237,928.2 DKK)	318,685 (10.3)	272,088 (11.9)	46,597 (5.8)
Occupational status, n (%)			
Unemployed	78,924 (2.6)	67,925 (3.0)	10,999 (1.4)
Sick/cash support/ pension/student/others	1,162,459 (37.7)	527,380 (23.1)	635,079 (79.0)
Employed	1,841,844 (59.7)	1,684,041 (73.9)	157,803 (19.6)
Immigrant status			
Danish origin	2,907,277 (94.3)	2,129,389 (93.4)	777,888 (96.8)
Immigrants/descendants from western country of origin	78,050 (2.5)	60,314 (2.6)	17,736 (2.2)
Immigrants/descendants from non-western country of origin	97,900 (3.2)	89,643 (3.9)	8,257 (1.0)
Marital status			
Unmarried	521,562 (16.9)	443,627 (19.5)	77,935 (9.7)
Divorced	337,720 (11.0)	238,622 (10.5)	99,098 (12.3)
Widowed	302,741 (9.8)	87,671 (3.8)	215,070 (26.8)
Married/registered partnership	1,921,204 (62.3)	1,509,426 (66.2)	411,778 (51.2)
Highest complete education level			
Primary	1,253,628 (40.7)	732,658 (32.1)	520,970 (64.8)
Upper secondary	105,401 (3.4)	95,904 (4.2)	9,497 (1.2)
Vocation/qualifying	1,073,481 (34.8)	878,150 (38.5)	195,331 (24.3)
Vocation bachelors/ short-cycle higher education	477,180 (15.5)	418,732 (18.4)	58,448 (7.3)
More than college level	173,537 (5.6)	153,902 (6.8)	19,635 (2.4)
Regional mean household income/			

(continued on next page)

Table 1 (*continued*)

Characteristics	Total N = 3,083,227	Alive/ emigration/loss to follow-up N = 2,279,346	Dead[a] N = 803,881
percentage of unemployment			
North Denmark: 155,994.2/2.55	327,210 (10.6)	239,667 (10.5)	87,543 (10.9)
South Denmark: 158,840.3/1.87	682,959 (22.2)	505,450 (22.2)	177,509 (22.1)
Central Denmark: 162,312.0/1.90	675,479 (21.9)	509,879 (22.4)	165,600 (20.6)
Zealand: 166,371.4/1.86	476,038 (15.4)	348,139 (15.3)	127,899 (15.9)
Capital region: 175,561.2/1.90	921,541 (29.9)	676,211 (29.7)	245,330 (30.5)
Parish level mean income in 2001, mean ± SD	165,011.18 ± 27,080.93	165,790.18 ± 27,200.59	162,802.39 ± 26,615.03
Parish level percentage of unemployment, mean ± SD	1.94 ± 0.68	1.93 ± 0.68	1.95 ± 0.68
$PM_{2.5}$, mean ± SD (μg/m^3)	12.40 ± 1.55	12.36 ± 1.55	12.51 ± 1.53
NO_2, mean ± SD (μg/m^3)	20.29 ± 7.94	20.05 ± 7.93	20.94 ± 7.95
BC, mean ± SD (10^{-5}/m)	1.01 ± 0.36	1.00 ± 0.36	1.04 ± 0.37
O_3, mean ± SD (μg/m^3)	80.17 ± 4.28	80.27 ± 4.27	79.89 ± 4.30

Abbreviations: SD – standard deviation; DKK – Danish Krone; $PM_{2.5}$ – Particulate matter aerodynamic diameter < 2.5 μm; NO_2 – Nitrogen dioxide; BC – Black carbon, O_3 – ozone, warm-season (April-September).

[a] Mortality from all-natural causes (see Methods for details).

correlated with all other three pollutants (ρ = -0.50 with $PM_{2.5}$, −0.65 with NO_2, −0.67 with BC). Participants in the upper quantile category of exposure levels at the baseline tended to have died more during the follow-up than those in the lower category (Table S2 in the supplementary material).

3.2. Association between mortality and air pollution exposure

Generally, positive associations of all pollutants (or negative for O_3) in Model 1 attenuated, especially for $PM_{2.5}$, after adjustment for individual SES variables in Model 2 (Table 3). These associations remained statistically significant even after the further adjustment for regional- and neighborhood-level SES variables in Model 3 (except those of diabetes with NO_2, BC, and O_3, and those of dementia with $PM_{2.5}$ and O_3, which became null). The associations for all pollutants with dementia changed from null in Model 1 to statistically significantly positive (except for $PM_{2.5}$ and O_3) in Model 3. That is, in fully adjusted models (Model 3), we found positive associations of all pollutants, except for O_3, with mortality from all-natural causes, all CVDs, all RDs, lung cancer, diabetes (only with $PM_{2.5}$), dementia (with NO_2 and BC), and psychiatric disorders. We identified negative associations of O_3 with all-natural cause mortality and all other cause-specific mortality outcomes except for mortality from diabetes and dementia, which were null.

When we compared the risk estimates for all mortality outcomes, including the subtypes of CVD and RD mortality, across three pollutants [per interquartile range increase for $PM_{2.5}$ (2.0 μg/m^3), NO_2 (10.3 μg/m^3), and BC (0.5 × 10^{-5}/m)], the associations of NO_2 and BC were generally higher in magnitude with mortality from RD, especially from COPD, asthma, and lung cancer than those from CVDs (Figure S1 and Table S3 in supplementary material). The strongest associations were detected with mortality from psychiatric disorders with HRs of 1.13 (95% CI: 1.10, 1.17), 1.24 (95% CI: 1.20, 1.28), and 1.21 (95% CI: 1.17, 1.25) for $PM_{2.5}$, NO_2, and BC, respectively, per interquartile range of each pollutant.

In two-pollutant models for the combination of $PM_{2.5}$ and NO_2 (Table 3), the associations of both pollutants with mortality from all-natural causes and all CVDs were attenuated but remained significantly positive, while those with mortality from all RDs, lung cancer, dementia, and psychiatric disorder were remained positive only for NO_2, and those with diabetes mortality were positive only for $PM_{2.5}$. The association of NO_2 for CKD mortality increased and reached the level of statistical significance after the adjustment of $PM_{2.5}$. The associations of BC generally were weakened after adjusting for $PM_{2.5}$ but remained statistically significant with mortality from all-natural causes, RD, lung cancer, and psychiatric disorders. After adjusting for O_3, the associations of $PM_{2.5}$ and BC remained unchanged, while those of NO_2 were enhanced. Generally, the negative associations with O_3 were closer to unity after adjusting for $PM_{2.5}$ and BC, but changed to significantly positive after adjusting for NO_2 for most mortality outcomes. Interpretations of the two-pollutant models for the combination of NO_2 and BC should be taken with caution due to the high correlations between these pollutants.

The associations of $PM_{2.5}$, NO_2, and BC with all mortality outcomes (except CKD) generally showed a linear or supra-linear shape with no evidence of a threshold below which air pollution is considered safe (Fig. 1 for $PM_{2.5}$; Figure S2 and S3 in Supplementary Material for NO_2 and BC, respectively).

The associations with O_3 showed a flat or inverse shape at the exposure range where most of the participants were exposed to (above the 5th percentile of 70.6 μg/m^3; Figure S4 in supplementary material). Associations with $PM_{2.5}$, NO_2, and BC were stronger below the US-EPA NAAQS of 12 μg/m^3 for $PM_{2.5}$, and 20 μg/m^3 for NO_2, both of which are far below the current EU standard of 25 and 40 μg/m^3 for $PM_{2.5}$ and NO_2, respectively, and below 1 × 10^{-5}/m for BC (except for the association of BC with asthma) (Fig. 2; Table S4 in the Supplementary material). Associations with O_3 below 80 μg/m^3 were close to unity, with the exception for those for mortality from stroke, all RDs, COPD, diabetes, dementia, and psychiatric disorders, which were positive.

We observed significant effect modification of associations between air pollution and all-natural cause mortality by age, sex, and individual SES factors (Table S5 in supplementary table). Associations between $PM_{2.5}$, NO_2, and BC and all-natural cause mortality were higher in magnitude in individuals younger than 65 years, men, those with Danish origin, and the unemployed compared to those older than 65 years, women, immigrants/descendants, and the employed, respectively. Highly educated individuals generally had lower associations with air

Table 2
Descriptive characteristics for air pollutants at individuals' residential addresses of cohort baseline and Spearman's rank correlation coefficients between the air pollutants.

Pollutants	Mean ± SD	Interquartile range	Min.	Percentile					Max.	Spearman's rank correlation coefficients (ρ)		
				5th	25th	50th	75th	95th		$PM_{2.5}$	NO_2	BC
$PM_{2.5}$, μg/m^3	12.4 ± 1.55	2.0	5.8	10.0	11.3	12.3	13.3	15.3	19.6			
NO_2, μg/m^3	20.3 ± 7.94	10.3	3.7	9.4	14.6	18.7	24.9	35.7	72.2	0.60		
BC, 10^{-5}/m	1.0 ± 0.36	0.5	0.1	0.6	0.7	0.9	1.2	1.7	3.7	0.70	0.89	
O_3, μg/m^3	80.2 ± 4.28	4.3	48.8	70.6	78.6	81.2	82.8	85.3	91.9	−0.50	−0.65	−0.67

In Abbreviations: SD – standard deviation; $PM_{2.5}$ – Particulate matter aerodynamic diameter < 2.5 μm; NO_2 – Nitrogen dioxide; BC – Black carbon, O_3 – ozone, warm-season (April-September).
The minimum and maximum values are the mean of the bottom and top five values, respectively, to comply with General Data Protection Regulation.

Table 3
Associations between air pollution (per 5 μg/m^3, 10 μg/m^3, 0.5 × 10^{-5}/m, and 10 μg/m^3 increase in $PM_{2.5}$, NO_2, BC, and O_3, respectively) and all-natural and cause-specific mortality in the Danish administrative cohort study (N = 3,083,227).

Air pollutants	Model1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)	Two-pollutant models: Model 3 further adjusting for the below pollutant			
				$PM_{2.5}$ HR (95 %CI)	NO_2 HR (95 %CI)	BC HR (95 %CI)	O_3 HR (95 %CI)
All-natural causes (n = 803,881)							
$PM_{2.5}$	1.22 (1.18, 1.25)	1.17 (1.15, 1.19)	1.11 (1.09, 1.13)	–	1.04 (1.02, 1.07)	1.07 (1.04, 1.09)	1.10 (1.08, 1.12)
NO_2	1.09 (1.07, 1.10)	1.09 (1.08, 1.10)	1.06 (1.05, 1.07)	1.05 (1.04, 1.06)	–	1.08 (1.06, 1.09)	1.10 (1.08, 1.12)
BC	1.09 (1.08, 1.11)	1.09 (1.08, 1.10)	1.05 (1.04, 1.06)	1.03 (1.02, 1.04)	0.98 (0.97, 1.00)	–	1.06 (1.05, 1.07)
O_3	0.88 (0.86, 0.90)	0.92 (0.91, 0.94)	0.96 (0.95, 0.97)	0.99 (0.98, 1.00)	1.07 (1.04, 1.09)	1.02 (1.00, 1.04)	–
All cardiovascular diseases (n = 223,553)							
$PM_{2.5}$	1.17 (1.13, 1.21)	1.14 (1.11, 1.17)	1.09 (1.07, 1.12)	–	1.06 (1.03, 1.1.0)	1.08 (1.05, 1.12)	1.10 (1.07, 1.13)
NO_2	1.05 (1.03, 1.06)	1.06 (1.05, 1.07)	1.04 (1.03, 1.05)	1.02 (1.01, 1.04)	–	1.06 (1.04, 1.08)	1.07 (1.05, 1.09)
BC	1.05 (1.04, 1.07)	1.06 (1.05, 1.07)	1.03 (1.02, 1.04)	1.01 (0.99, 1.02)	0.98 (0.96, 1.00)	–	1.04 (1.02, 1.06)
O_3	0.91 (0.88, 0.93)	0.95 (0.93, 0.96)	0.98 (0.96, 0.99)	1.01 (0.99, 1.03)	1.05 (1.02, 1.09)	1.02 (0.99, 1.04)	–
All respiratory diseases (n = 90,028)							
$PM_{2.5}$	1.23 (1.18, 1.30)	1.18 (1.14, 1.22)	1.11 (1.07, 1.15)	–	1.00 (0.96, 1.04)	1.04 (1.00, 1.09)	1.08 (1.04, 1.12)
NO_2	1.11 (1.08, 1.13)	1.12 (1.10, 1.13)	1.08 (1.07, 1.10)	1.08 (1.06, 1.11)	–	1.13 (1.09, 1.16)	1.13 (1.11, 1.16)
BC	1.11 (1.08, 1.13)	1.11 (1.09, 1.12)	1.06 (1.05, 1.08)	1.05 (1.03, 1.07)	0.96 (0.93, 0.99)	–	1.07 (1.04, 1.09)
O_3	0.84 (0.81, 0.87)	0.89 (0.87, 0.91)	0.94 (0.92, 0.96)	0.97 (0.94, 0.99)	1.08 (1.05, 1.12)	1.01 (0.98, 1.04)	–
Lung cancer (n = 58,435)							
$PM_{2.5}$	1.29 (1.23, 1.35)	1.28 (1.24, 1.32)	1.19 (1.15, 1.24)	–	1.03 (0.99, 1.08)	1.09 (1.04, 1.14)	1.14 (1.09, 1.19)
NO_2	1.10 (1.08, 1.12)	1.13 (1.12, 1.15)	1.13 (1.11, 1.15)	1.12 (1.09, 1.14)	–	1.17 (1.14, 1.21)	1.17 (1.14, 1.21)
BC	1.11 (1.09, 1.13)	1.13 (1.12, 1.15)	1.10 (1.09, 1.12)	1.08 (1.05, 1.10)	0.95 (0.92, 0.99)	–	1.09 (1.06, 1.12)
O_3	0.83 (0.80, 0.86)	0.85 (0.83, 0.87)	0.89 (0.87, 0.92)	0.94 (0.91, 0.96)	1.07 (1.03, 1.11)	0.98 (0.95, 1.02)	–
Diabetes (n = 20,691)							
$PM_{2.5}$	1.36 (1.27, 1.46)	1.23 (1.17, 1.30)	1.10 (1.04, 1.16)	–	1.11 (1.04, 1.19)	1.16 (1.08, 1.24)	1.16 (1.09, 1.23)
NO_2	1.10 (1.07, 1.13)	1.08 (1.06, 1.10)	1.02 (1.00, 1.05)	0.99 (0.96, 1.02)	–	1.11 (1.05, 1.17)	1.11 (1.06, 1.16)
BC	1.11 (1.08, 1.15)	1.08 (1.06, 1.10)	1.00 (0.97, 1.03)	0.96 (0.93, 0.99)	0.91 (0.86, 0.97)	–	1.03 (0.99, 1.07)
O_3	0.85 (0.81, 0.89)	0.96 (0.93, 1.00)	1.03 (0.99, 1.07)	1.08 (1.04, 1.12)	1.15 (1.08, 1.22)	1.06 (1.01, 1.12)	–
Chronic kidney disease (n = 3,749)							
$PM_{2.5}$	0.99 (0.89, 1.10)	0.96 (0.86, 1.07)	0.95 (0.84, 1.07)	–	0.83 (0.71, 0.97)	0.88 (0.76, 1.03)	0.85 (0.74, 0.97)
NO_2	0.99 (0.95, 1.03)	0.99 (0.95, 1.03)	1.05 (1.00, 1.11)	1.12 (1.04, 1.20)	–	1.18 (1.05, 1.32)	0.98 (0.90, 1.08)
BC	0.99 (0.94, 1.04)	0.99 (0.94, 1.03)	1.02 (0.96, 1.08)	1.06 (0.98, 1.14)	0.88 (0.78, 1.00)	–	0.92 (0.85, 1.01)
O_3	0.88 (0.82, 0.95)	0.91 (0.85, 0.98)	0.90 (0.83, 0.97)	0.85 (0.78, 0.93)	0.88 (0.78, 1.00)	0.83 (0.74, 0.92)	–
Dementia (n = 41,141)							
$PM_{2.5}$	1.05 (1.00, 1.10)	1.03 (0.98, 1.09)	1.05 (1.00, 1.10)	–	0.98 (0.92, 1.04)	1.02 (0.96, 1.08)	1.05 (0.99, 1.11)
NO_2	1.00 (0.99, 1.02)	1.00 (0.98, 1.01)	1.05 (1.03, 1.07)	1.05 (1.03, 1.08)	–	1.11 (1.06, 1.16)	1.11 (1.07, 1.15)
BC	1.01 (0.99, 1.03)	1.00 (0.98, 1.02)	1.03 (1.01, 1.05)	1.02 (1.00, 1.05)	0.94 (0.90, 0.98)	–	1.04 (1.01, 1.08)
O_3	0.99 (0.96, 1.02)	1.00 (0.97, 1.03)	0.99 (0.95, 1.02)	1.00 (0.96, 1.04)	1.11 (1.05, 1.17)	1.03 (0.98, 1.09)	–
Psychiatric disorders (n = 12,801)							
$PM_{2.5}$	2.33 (2.11, 2.57)	1.61 (1.51, 1.73)	1.38 (1.27, 1.50)	–	1.09 (0.98, 1.21)	1.13 (1.02, 1.26)	1.33 (1.21, 1.46)
NO_2	1.44 (1.39, 1.50)	1.25 (1.22, 1.28)	1.23 (1.19, 1.28)	1.20 (1.15, 1.26)	–	1.20 (1.11, 1.30)	1.41 (1.33, 1.50)
BC	1.52 (1.46, 1.59)	1.27 (1.24, 1.31)	1.22 (1.17, 1.26)	1.17 (1.12, 1.23)	1.03 (0.95, 1.12)	–	1.28 (1.21, 1.36)
O_3	0.57 (0.53, 0.60)	0.81 (0.77, 0.84)	0.87 (0.83, 0.91)	0.96 (0.90, 1.01)	1.26 (1.16, 1.37)	1.11 (1.03, 1.19)	–

Abbreviations: HR – hazard ratio; CI – Confidence interval; $PM_{2.5}$ – Particulate matter aerodynamic diameter < 2.5 μm; NO_2 – Nitrogen dioxide; BC – Black carbon, O_3 – ozone, warm-season (April-September).

[a] Model 1 adjusting for age (underlying time scale), sex, and parish level (cluster term).

[b] Model 2 adjusting for household income in decile, occupational status, immigrant status, marital status, and highest completed education level in addition to the covariates in Model 1.

[c] Model 3 (main model) adjusting for regional mean household income, regional percentage of unemployment, and the difference of mean household income and percentage of unemployment, between parish and region in addition to the covariates in Model 2.

pollution than those with lower education.

Analyses to account for missing lifestyle information by adjusting for area-level mortality rate from lung cancer, COPD, and diabetes resulted in no change in HRs (Table S6 in supplementary material). However, applying indirect adjustment for smoking and BMI based on the data from Danish National Health Survey resulted in mild attenuation in HRs for all mortality outcomes except for mortality from RDs, COPD, asthma, lung cancer, and psychiatric disorders, which attenuated more so (Fig. 3; Table S7 in supplementary material). Associations of $PM_{2.5}$, NO_2, and BC with mortality from RDs, lung cancer, and psychiatric disorder remained statistically significant after indirect adjustment for smoking and BMI, while the association of $PM_{2.5}$ with COPD mortality attenuated towards null and the associations of NO_2 and BC with asthma became insignificant. The HRs of CKD mortality with applying the indirect adjustment had very broad CIs because risk estimates of lifestyle risk factors (See Table S8 in supplementary material) were unstable due to the small number of CKD mortality cases in the ELAPSE pooled cohorts. Notably, long-term exposure to air pollution were significantly positively associated with previous, current smoking, overweight, and obese, and negatively with underweight in the Danish National Health Survey (presenting the opposite associations for O_3) (Table S9 in supplementary material).

Associations with $PM_{2.5}$ and NO_2 using the exposure back-extrapolated to the cohort baseline year were slightly weaker in magnitude than those with 2010 exposure estimates and similar for BC and O_3 (Table S10 in supplementary material). Similarly, time-varying exposure analysis resulted in generally smaller or similar HRs for all outcomes, except for null associations of CVD with NO_2 and BC, as well as of ischemic heart disease, stroke, and dementia with all three pollutants ($PM_{2.5}$, NO_2, and BC) (Table S11 in supplementary material). Even after controlling the false positive rate for our main models for 13 mortality outcomes and two-pollutant models in Table 3, most statistically significant findings remain significant, except for two-pollutant models for the association between natural mortality and BC adjusting for NO_2, those for CKD mortality and BC or O_3 adjusting for NO_2 (Table S12 and S13 in supplementary material). The models with inverse

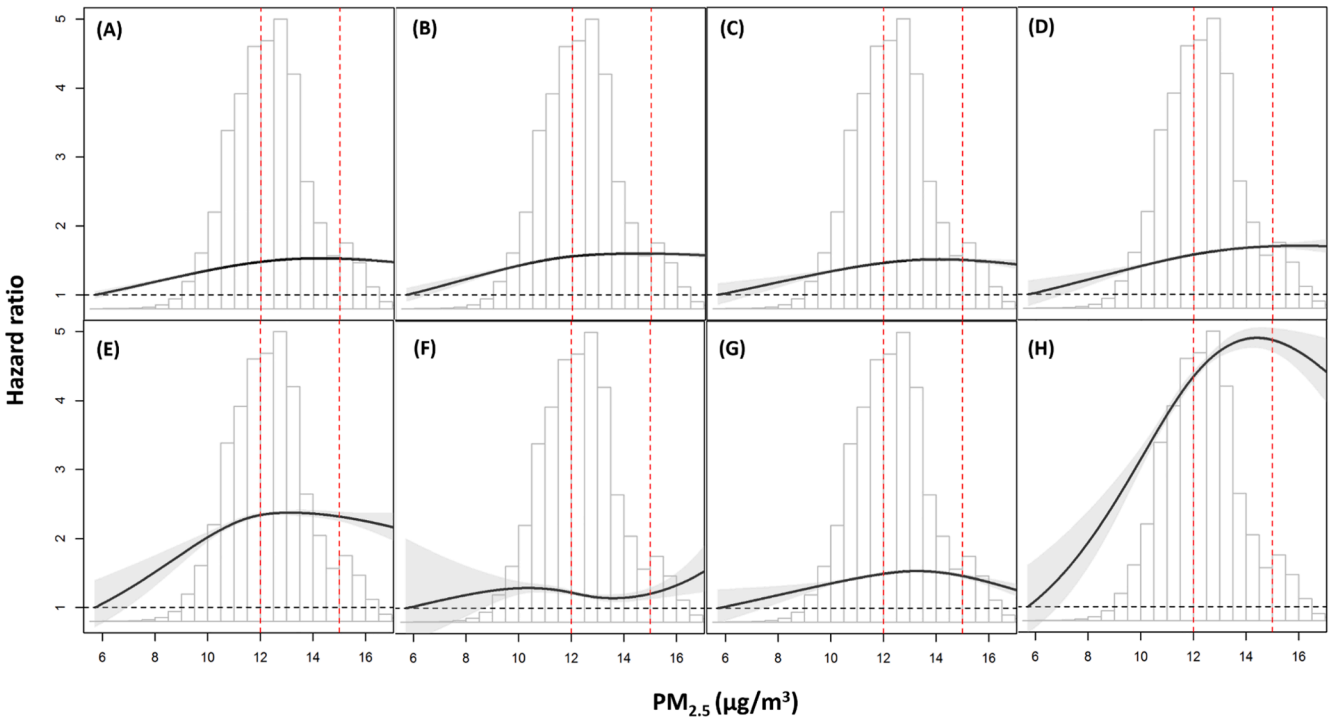

Fig. 1. Exposure-response curve for the association[a] between long-term exposure to $PM_{2.5}$ and mortality from (A) all-natural causes, (B) all cardiovascular diseases, (C) all respiratory diseases, (D) lung cancer, (E) diabetes, (F) chronic kidney disease, (G) dementia, and (H) psychiatric disorders in the Danish administrative cohort (N = 3,083,227).
Abbreviations: $PM_{2.5}$ – Particulate matter aerodynamic diameter < 2.5 μm.
Red vertical dashed lines show values used for subset analyses: 15 and 12 μg/m^3 [the US Environmental Protection Agency National Ambient Air Quality Standard (US-EPA NAAQS)].
The upper limit of the x-axis was truncated at the 99.5 percentile of the distribution of $PM_{2.5}$.
[a]Adjusting for age (underlying time scale), sex (strata), household income in decile, occupational status, immigrant status, marital status, and highest completed education level, regional mean household income, regional percentage of unemployment, and the difference of mean household income and percentage of unemployment, between parish and region.

probability weighting presented almost identical results to those in the main analysis (Table S14 in supplementary material). Additionally, our results for natural-cause mortality were robust to adjusting variables identified by the DAG (all variables in the main model excluding marital status; see Figure S5 for the DAG and Table S15 for the results).

4. Discussion

In the large nationwide analysis of Danish adults, we found that long-term exposure to $PM_{2.5}$, NO_2, and BC were associated with increased risks of all-natural cause mortality. We confirmed the established associations with causes of death, including CVD, RD, lung cancer, as well as diabetes (but only with $PM_{2.5}$), and identified less established associations with mortality from dementia, psychiatric disorders, asthma, and ALRIs for the first time in Denmark. Associations with all three pollutants generally persisted in two-pollutant models for all outcomes, except for those for mortality from RD, lung cancer, dementia, and psychiatric disorders where associations of NO_2 and BC remained and those with $PM_{2.5}$ attenuated toward the null. Negative associations with O_3 were observed for most studied outcomes, which became positive after adjusting for co-pollutants. The impact of the indirect adjustment for BMI and smoking status was mild but not negligible for mortality from respiratory-related diseases and lung cancer.

Our fully adjusted HR for all-natural cause mortality was 1.11 (95% CI: 1.09, 1.13) per 5 μg/m^3 increase in $PM_{2.5}$, which is substantially higher than the HR of 1.04 (95% CI: 1.03–1.05) found in a *meta*-analysis of 25 cohort studies (Chen and Hoek 2020) and the majority of the studies published since the *meta*-analysis (Christidis et al. 2019; Crouse et al. 2019; Fischer et al. 2020; Klompmaker et al. 2021; Lim et al. 2019; Pappin et al. 2019; Pope et al. 2019; Raaschou-Nielsen et al. 2020; So et al. 2020; Stafoggia et al. 2022) [See the Supplementary material, Figure S6 (A)], but weaker in magnitude than those reported in the ELAPSE project with eight pooled European cohorts [HR: 1.13 (95% CI: 1.11–1.15)] (Strak et al. 2021) and the Ontario Health Study [HR:1.20 (95% CI: 1.09–1.32)] (Zhang et al. 2021). The associations of $PM_{2.5}$ with CVD, RD, and lung cancer mortality in our study were also stronger than those presented in the recent *meta*-analysis (Chen and Hoek 2020). However, after the indirect adjustment for smoking and BMI, our associations with RD and lung cancer mortality attenuated, and our association with RD was similar to the results reported in the recent *meta*-analysis (Chen and Hoek 2020), whereas those with CVD remained [See the Supplementary material, Figure S6].

Our association of $PM_{2.5}$ and all-natural cause mortality [HR: 1.11 (95% CI: 1.09, 1.13)] is comparable to the analysis from Danish Diet, Cancer and Health cohort [HR:1.13 (95% CI: 1.05–1.21)] (Hvidtfeldt et al. 2019), and stronger than two other recent Danish studies on $PM_{2.5}$ and all-cause mortality: a nationwide register-based case-control study [Mortality rate ratio: 1.04 (95% CI: 1.02–1.06)] (Raaschou-Nielsen et al. 2020) and the Danish Nurse Cohort [HR: 1.07 (95% CI: 1.02–1.12)] (So et al. 2020) which included only female individuals. Notably, all of these Danish risk estimates at low-level concentrations of air pollutants exposure generally observed stronger associations than those reported in the recent review study (Chen and Hoek 2020), supporting the linear or supra-linear concentration–response relationships suggested by them. Moreover, those results in Danish studies underline the robustness of the findings despite different population and exposure assessment methods across these studies.

Our positive associations of NO_2 and all-natural cause and CVD

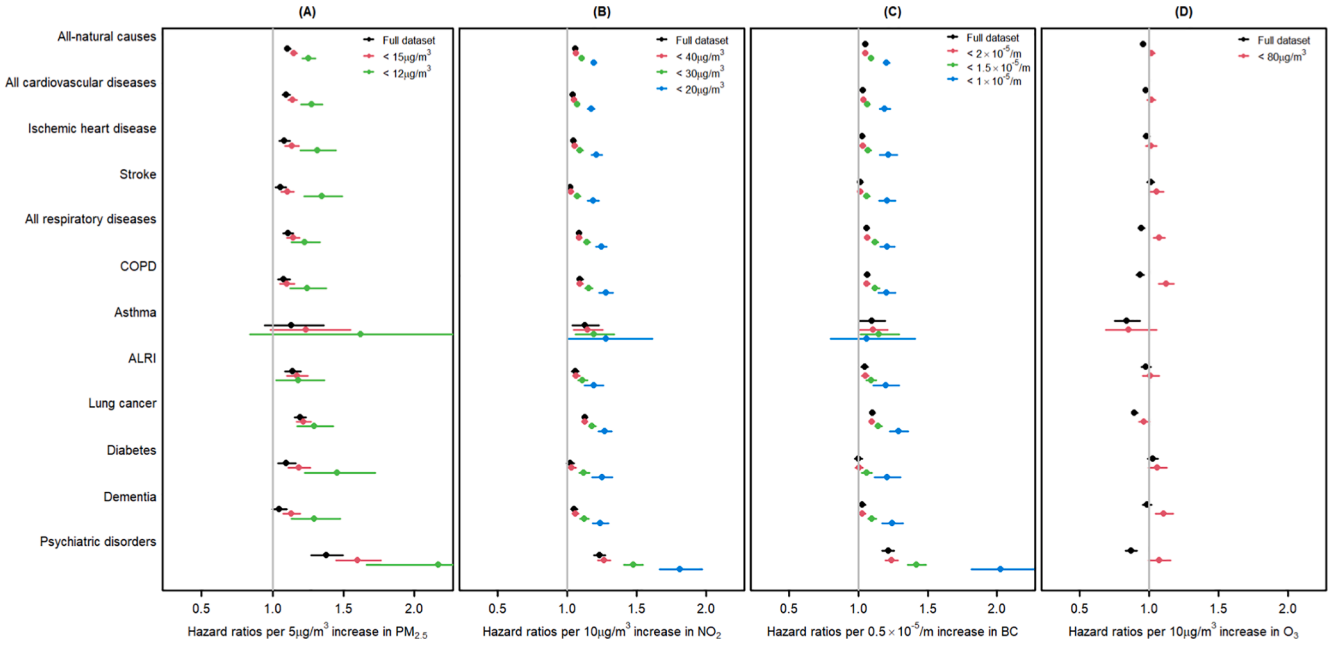

Fig. 2. Association[a] between long-term exposure to air pollutants (per 5 μg/m^3, 10 μg/m^3, 0.5 × 10^{-5}/m, and 10 μg/m^3 increase in $PM_{2.5}$, NO_2, BC, and O_3, respectively) and all-natural cause and cause-specific mortality in main and subset analyses in the Danish administrative cohort study.
Abbreviations: HR – hazard ratio; CI – Confidence interval; $PM_{2.5}$ – Particulate matter aerodynamic diameter < 2.5 μm; NO_2 – Nitrogen dioxide; BC – Black carbon; COPD – Chronic obstructive pulmonary disease; ALRI – Acute lower respiratory infection.
[a]Adjusting for age (underlying time scale), sex (strata), parish level (cluster term), household income in decile, occupational status, immigrant status, marital status, and highest completed education level, regional mean household income, regional percentage of unemployment, and the difference of mean household income and percentage of unemployment, between parish and region.

mortality with a HR of 1.06 (95% CI, 1.05, 1.07) and 1.04 (95% CI: 1.03–1.05), respectively, per 10 μg/m^3 increase were smaller in magnitude than those reported from the pooled cohort analysis within the ELAPSE project (Strak et al. 2021) and the Ontario Health Study (Zhang et al. 2021) but a bit higher than a recent *meta*-analysis (Stieb et al. 2021), a recent study with the US Medicare beneficiaries (Shi et al. 2021), the study from the Netherlands (Klompmaker et al. 2021), and the ELAPSE project with seven administrative cohorts (Stafoggia et al. 2022) (unit increase were converted to 10 μg/m^3 increase for the comparison) [See the Supplementary material, Figure S7 (A) and (B)]. The positive associations of NO_2 with RD and lung cancer mortality in our study were higher than those from the recent *meta*-analysis (Stieb et al. 2021) [See the Supplementary material, Figure S7 (C) and (D)], even after the indirect adjustment. There is another review study on the effect of long-term exposure to NO_2 on mortality (Huang et al. 2021), which reported a similar size of *meta*-estimates for all-cause and respiratory morality with those from Stieb and colleagues (Stieb et al. 2021), except that the *meta*-estimate for CVD mortality presented higher than those from the review study of Stieb and colleagues and our estimate [See the Supplementary material, Figure S7 (B-D)].

Our findings on the association of BC with mortality generally pointed to elevated risks, which is generally in line with existing evidence. In the Danish Diet, Cancer and Health cohort (Hvidtfeldt et al. 2019), Hvidtfledt and colleagues presented positive associations of BC with all-cause and CVD mortality, but not with RD mortality, with a HR of 1.09 (95% CI: 1.04–1.15), 1.16 (95% CI: 1.05–1.27), and 1.00 (95% CI, 0.90–1.12), respectively, per 1 μg/m^3 increase of BC. The ELAPSE study pooled cohorts (Strak et al. 2021) reported HRs of 1.08 (95% CI, 1.07–1.10), 1.09 (95% CI, 1.06–1.12), and 1.08 (95% CI, 1.02–1.15) for all-cause, CVD, and RD mortality, respectively, per 0.5 × 10^{-5}/m, which were a bit higher than the results from our study with HRs of 1.05 (95% CI, 1.04–1.06), 1.03 (95% CI, 1.02–1.04), and 1.06 (95% CI, 1.05–1.08) for all-cause, CVD, and RD mortality, per 0.5 × 10^{-5}/m, respectively. In another Danish nationwide register-based case-control study (Raaschou-Nielsen et al. 2020), Raaschou-Nielsen and colleagues presented positive associations of BC with all-cause, RD, and lung cancer mortality with HRs of 1.05 (95% CI: 1.02–1.08), 1.07 (95% CI: 1.01–1.13), and 1.07 (95% CI: 1.01–1.11) per 1 μg/m^3 increase, but null with CVD mortality.

In line with our results of inverse associations with O_3, the recent ELAPSE pooled cohort study and the *meta*-analysis with seven administrative cohorts found negative associations with all-cause, CVD, RD, and lung cancer mortality (Stafoggia et al. 2022; Strak et al. 2021), while both our study and the subset analysis of the recent ELAPSE pooled cohort (Brunekreef et al. 2021) observed positive associations of O_3 below 80 μg/m^3 for mortality from stroke. Furthermore, our findings of the positive associations of O_3 below 80 μg/m^3 for RD mortality were in line with two review studies reporting the adverse effect of the warm season O_3 on RD mortality (Atkinson et al. 2016; Huangfu and Atkinson 2020). However, we need to be cautious of interpreting our results of O_3. The contrast of O_3 from the ELAPSE land-use regression models was low, possibly indicating that our study is less relevant for investigating the health effect of ozone (Brunekreef et al. 2021; Strak et al. 2021). Furthermore, O_3 was negatively associated with other pollutants (Table 2), so the negative associations of O_3 in the single-pollutant model may reflect this. Furthermore, those two recent ELAPSE studies observed that HRs for O_3 became close to unity and non-significant in two-pollutant models with NO_2 or BC (Stafoggia et al. 2022; Strak et al. 2021), while we observed the reversing to significantly positive associations with O_3 for most mortality outcomes when adjusting for NO_2 in two-pollutant models (Table 3), which may underline the complex interactions between these toxic gases. Previous studies on long-term exposure to O_3 and mortality have presented mixed results. Several studies have reported significant adverse effects of ozone: studies with about 60 million of all US Medicare beneficiaries for all-cause mortality (Di et al. 2017; Shi et al. 2021); a study with the 2011 CanCHEC (Canadian Census Health and Environment Cohort) for all CVDs, ischemic heart disease, and stroke mortality (Pinault et al. 2018); a study with the 1991 CanCHEC for ischemic heart disease mortality (Cakmak et al.

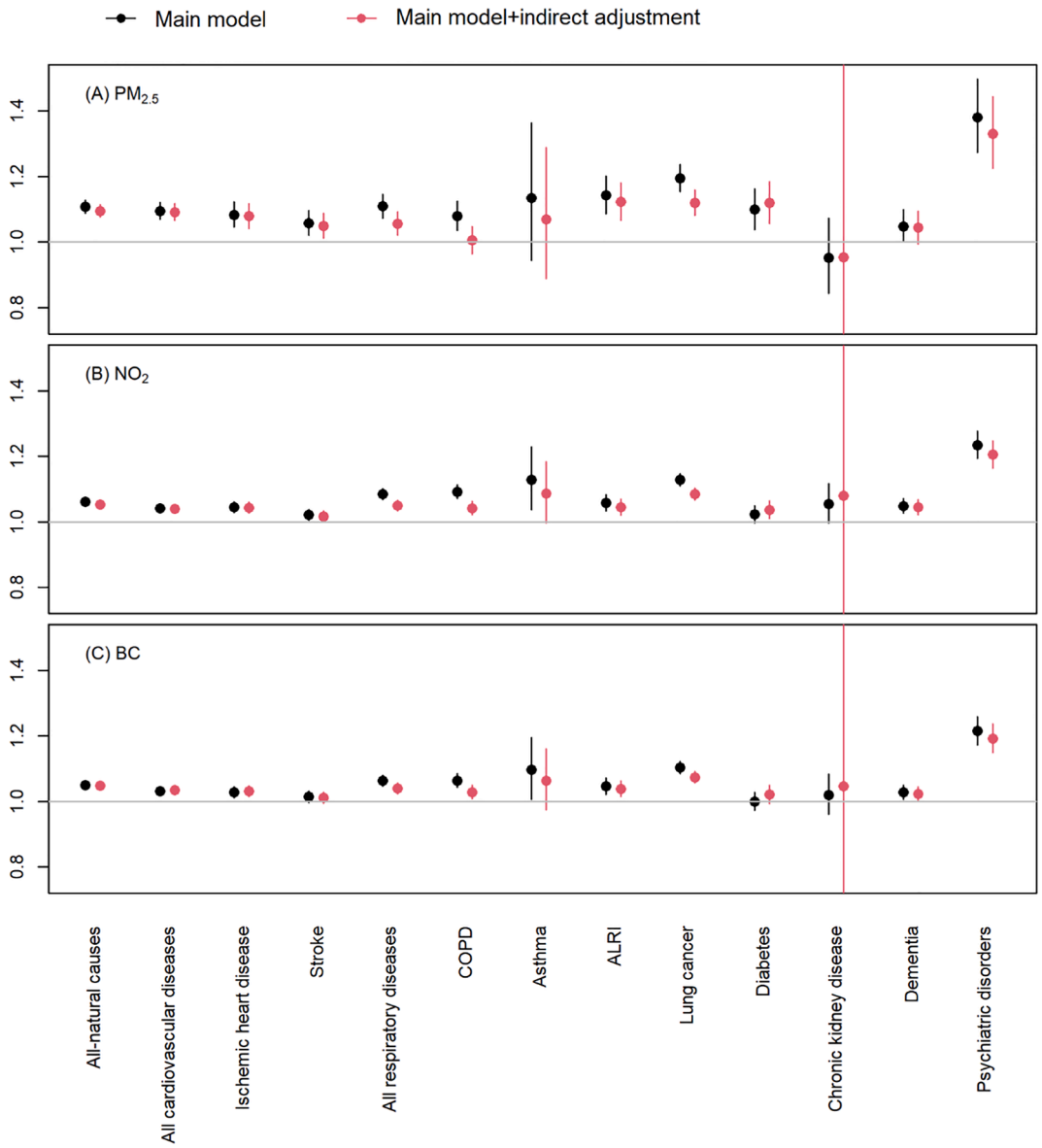

Fig. 3. The comparison of hazard ratios of all-natural causes and cause-specific mortality associated with long-term exposure to air pollutants (per 5 μg/m^3, 10 μg/m^3, and 0.5 10^{-5}/m increase in $PM_{2.5}$, NO_2, and BC, respectively): before and after applying the indirect adjustment for smoking status and body mass index.
Abbreviations: $PM_{2.5}$ – Particulate matter aerodynamic diameter < 2.5 μm; NO_2 – Nitrogen dioxide; BC – Black carbon; COPD – Chronic obstructive pulmonary disease; ALRI – Acute lower respiratory infection.
Main models were adjusted for age (underlying time scale), sex (strata), parish level (cluster term), household income in decile, occupational status, immigrant status, marital status, and highest completed education level, regional mean household income, regional percentage of unemployment, and the difference of mean household income and percentage of unemployment, between parish and region.
The information for applying the indirect adjustment was obtained from the Danish National Health Survey.

2018); and a study with Canadian Community Health Survey cohort for all-cause mortality (Christidis et al. 2019). A study with NIH-AARP Diet and Health Study also reported adverse effects of O_3 on CVD and RD mortality, but not on all-cause mortality (Lim et al. 2019). Another US Medicare beneficiaries study with about 22.2 million participants also found 0.4%, 0.5%, 3%, and 1.5% increased risk in all-cause, CVD, RD, and lung cancer mortality, respectively, per 10 ppb increase in the warm-season average of daily 1 hr maximum of O_3 (Kazemiparkouhi et al. 2020). A study with the Danish Diet, Cancer and Health cohort reported negative associations of long-term O_3 with all-cause and CVD mortality, but null association with RD mortality (Hvidtfeldt et al. 2019), while another Danish nationwide register-based case-control study found positive associations of O_3 with CVD mortality, but negative with all-cause, RD, and lung cancer mortality (Raaschou-Nielsen et al. 2020).

Our finding of the association between $PM_{2.5}$ and diabetes mortality is consistent with recent evidence, all of which also found strong positive and significant associations. The American Cancer Society Cancer Prevention Study II cohort (Pope et al. 2015) and the US NIH-AARP Diet and Health Study (Lim et al. 2018) found a HR of 1.06 (95% CI, 1.01–1.12) and a HR of 1.09 (95% CI, 1.01–1.18), respectively, which are comparable in size with our result [HR: 1.10 (95% CI: 1.04–1.16)] [unit increase were converted to 5 μg/m^3 increase for the comparison]. There are also a few studies reporting even higher associations than our study: the large Canadian cohort study with 2.1 million adults with a HR of 1.22 (95% CI, 1.17–1.27) (Brook et al. 2013); the 2011 CanCHEC with a HR of 1.22 (95% CI: 1.17–1.27) (Pinault et al. 2018); the ELAPSE pooled cohort study with a HR of 1.32 (95% CI: 1.14–1.51) (Strak et al.

2021); the Danish Nurse Cohort (DNC) study with a HR of 1.55 (1.16–2.14) (So et al. 2020) [unit increase were converted to 5 μg/m^3 increase for the comparison]. While our study [HR: 1.02 (95% CI:1.00–1.05) per 10 μg/m^3] and the CanCHEC [HR: 1.03 (95% CI 1.00–1.05) per 10 μg/m^3] (Crouse et al. 2015) found no evidence of the association between NO_2 and mortality due to diabetes, several studies reported positive associations: the US NIH-AARP Diet and Health Study (Lim et al. 2018) with a HR of 1.05 (95% CI: 1.01–1.09); the ELAPSE pooled cohort study (Strak et al. 2021) with a HR of 1.24 (95% CI 1.11 to 1.38); the Diet, Cancer and Health cohort study (Raaschou-Nielsen et al. 2013) with a HR of 1.31 (0.98–1.76); and the DNC study (So et al. 2020) with a HR of 1.21 (0.93, 1.58) [unit increase were converted to 10 μg/m^3 increase for the comparison].

Our lack of association between long-term exposure to air pollutants and mortality from CKD is inconsistent with previous studies: the Elderly Health Service Cohort from Hong Kong suggesting an association between $PM_{2.5}$ and CKD mortality [HR: 1.14 (95% CI 0.96–1.36) per 3.22 μg/m^3 increase in $PM_{2.5}$] (Ran et al. 2020); the US veterans cohort study (Bowe et al. 2019) reporting that $PM_{2.5}$ exposure is contributing to excess burden of death due to CKD mortality; and a recent review of seven studies (Liu et al. 2020) and two additional cohort studies (Bowe et al. 2018; Lin et al. 2020) detecting the associations between air pollution and incident CKD.

In our study, mortality from dementia was positively associated with all three pollutants [HR: 1.05 (95% CI: 1.00–1.10) per 5 μg/m^3 increase in $PM_{2.5}$, HR: 1.05 (95% CI: 1.03–1.07) per 10 μg/m^3 increase in NO_2, and HR: 1.03 (95% CI: 1.01, 1.05) per 0.5 × 10^{-5}/m increase in BC]. However, only a few studies evaluated associations of long-term exposure to air pollution with dementia mortality. In the Dutch national cohort, Klompmaker and colleagues presented the positive associations between air pollutants and dementia mortality with HRs of 1.26 (96% CI, 1.19–1.32) for $PM_{2.5}$, 1.05 (96% CI, 1.03, 1.08) for NO_2, 1.04 (96 % CI, 1.01–1.07) for BC (per same units as our study) (Klompmaker et al. 2021), while in another Dutch database, the national health survey, there was no evidence of these associations (Klompmaker et al. 2020). Furthermore, in the 2001 Canadian Census Health and Environment Cohort, Zhao and colleagues found positive associations of O_3 with dementia [HR: 1.08 (95% CI 1.06–1.10)] while we found no association (Zhao et al. 2021).

We found the strongest associations of all three pollutants with mortality from psychiatric disorders compared to other mortality outcomes [HR: 1.38 (95% CI: 1.27–1.50) per 5 μg/m^3 increase in $PM_{2.5}$, HR: 1.23 (95% CI: 1.19–1.28) per 10 μg/m^3 increase in NO_2, and HR: 1.22 (95% CI: 1.17–1.26) per 0.5 × 10^{-5}/m increase in BC]. Our outcome definition for mortality from psychiatric disorders included all mental and behavioral disorders (ICD 10 code: F) except for dementia (ICD 10 code: F00-03). Based on this definition, about 77.7% of death cases were from mental and behavioral disorders caused by alcohol abuse (ICD 10 code: F10). Only one study examined the associations between long-term exposure to air pollutants and alcohol abuse (Szyszkowicz et al. 2018). Szyszkowicz and colleagues reported the positive associations with emergency visits due to drug and alcohol abuse, and suggested that a plausible explanation of this association could be depression or other psychological outcomes induced by neurochemical or neuropathological changes related to exposure to air pollution. A recent review with 39 studies on the association between exposure to air pollution and depression reported a 7% and 4% increased risk of depression per 10 μg/m^3 increase in $PM_{2.5}$ and NO_2, respectively (Borroni et al. 2022).

We observed that the associations between air pollution and natural mortality differed by age. Several studies found a higher association between long-term exposure to air pollution and all-cause mortality in younger (aged < 65 years at baseline) compared to older (aged above 65) (Bauwelinck et al. 2022; Cesaroni et al. 2013; Wang et al. 2020), others could not find (Kim et al. 2021; Zhang et al. 2021). We do not expect that this was led by selection bias due to the excluded participants (who were older, had lower household income and education, were more likely to be men, be unemployed and unmarried, and to die by the end of follow-up compared to individuals included in the analyses; See Table S1 in supplementary material) since we had similar risk estimates when we applied inverse probability weighting analyses (Table S14 in supplementary material).

The primary strength of our study is the large population size (~3.08 million adults), in which we included all adults of 30 years and older in 2000 from all of Denmark, with a long follow-up of nearly two decades (18 years). Furthermore, we used the estimated annual mean air pollutants at individuals' address level based on 100 × 100 m resolution hybrid LUR models. Several limitations of this study should be noted. We lacked information on exposure to air pollution from work, commuting patterns, or personal outdoor activity. Furthermore, we were not able to account for road-traffic noise when we examined the association between air pollution and mortality, even though there is increasing evidence on the health effects of exposure to road-traffic noise (WHO Regional Office for Europe 2018), including studies on mortality (Halonen et al. 2015; Héritier et al. 2017; Klompmaker et al. 2021) and awareness of the importance of consideration of road-traffic noise for examining the health effect of air pollution (Héritier et al. 2019; Hoek et al. 2013; So et al. 2020; Strak et al. 2021). Moreover, our assessment of the exposure to air pollution was based on the LUR models for the year 2010 and assigned it to the individuals' baseline addresses (the year 2000) due to the lack of monitoring stations for developing the fine-scale models for $PM_{2.5}$ in earlier years, which may introduce exposure misclassification. Furthermore, exposure to air pollution was added in the cox model as a time-invariant variable, so the plausible temporal variation may be neglected in our main model. However, the predictions from the 2010 model were highly correlated with 2000 and 2005 models for NO_2 ($R^2 > 84\%$) and O_3 ($R^2 > 63\%$), and a bit lower with the 2013 model for $PM_{2.5}$ ($R^2 = 49\%$ for $PM_{2.5}$) in Denmark. Furthermore, in sensitivity analyses, we observed lower but generally robust associations either using back-extrapolated baseline year exposures (Table S10 in supplementary material) and time-varying exposures with address history information (Table S11 in supplementary material). Furthermore, other covariates in our main models, such as individual- and area-level SES, were also included as time-invariant variables, so we could not consider the possible variation in SES during the follow-up time (mean of 15 years), which could lead to the residual confounding.

As with many other studies based on administrative records, we lacked individual-level lifestyle risk factors for mortality. We were able to indirectly adjust for some of these unmeasured factors, including smoking status and BMI. Consistently with previous studies of adverse health effects of ambient air pollution using the indirect adjustment method for missing lifestyle factors (Klompmaker et al. 2021; Shin et al. 2019), the associations mildly attenuated or increased (only for diabetes mortality) but remained significant even after adjusting for smoking status and BMI for most cause-specific mortality outcomes. The impact of the indirect adjustment was strongest for respiratory disease-related mortality outcome, including mortality from COPD, asthma, and lung cancer, which implies that future studies on a respiratory-related disease with an administrative cohort should consider the possibility of being biased or overestimated due to missing information on lifestyle.

It is worth noting that the efficacy of the indirect adjustment method largely depends on the extent to which a local ancillary dataset, the Danish National Health Survey in our case, is representative of an administrative cohort (Shin et al. 2014). The Danish Health Survey participants were similar to the Danish nationwide administrative cohort with respect to age, sex, marital status, and immigrant status, but had higher educational and income levels (Table S16 in supplementary material). Therefore, the estimated associations of air pollutants with BMI and smoking status from this survey might be slightly different from the associations in the Danish nationwide administrative cohort if we could calculate it, which could result in a bias of our indirect adjustment results. However, those estimated associations between air pollutants and lifestyle factors (Table S9 in supplementary material) were smaller

in magnitude than the risk estimates of lifestyle factors on mortality outcomes in our study (Table S8 in supplementary material) and other studies using the indirect adjustment method (Klompmaker et al. 2021; Shin et al. 2019). Thus, we expect that the bias due to poor representativeness of the Danish National Health Survey to the Danish nationwide administrative cohort may be modest.

5. Conclusion

In the large nationwide administrative cohort of over three million Danish adult residents, long-term exposure to $PM_{2.5}$, NO_2, and BC was associated with increased risk of mortality from diabetes, dementia, and psychiatric disorders as well as mortality from all-natural causes, CVD, RD, and lung cancer. Associations with these outcomes were even stronger below thresholds of 12 $\mu g/m^3$ for $PM_{2.5}$ and 20 $\mu g/m^3$ for NO_2, which is consistent with the recently revised WHO air quality guidelines where the recommended limits for $PM_{2.5}$ and NO_2 were lowered from 10 to 5 $\mu g/m^3$ and 40 to 10 $\mu g/m^3$, respectively.

CRediT authorship contribution statement

Rina So: Conceptualization, Data curation, Formal analysis, Investigation, Visualization, Writing – original draft. **Zorana J. Andersen:** Conceptualization, Project administration, Supervision, Writing – review & editing. **Jie Chen:** Writing – review & editing. **Massimo Stafoggia:** Methodology, Software, Writing – review & editing. **Kees de Hoogh:** Writing – review & editing. **Klea Katsouyanni:** Writing – review & editing. **Danielle Vienneau:** Writing – review & editing. **Sophia Rodopoulou:** Methodology, Software, Writing – review & editing. **Evangelia Samoli:** Methodology, Software, Writing – review & editing. **Youn-Hee Lim:** Supervision, Writing – review & editing. **Jeanette T. Jørgensen:** Writing – review & editing. **Heresh Amini:** Writing – review & editing. **Tom Cole-Hunter:** Writing – review & editing. **Seyed Mahmood Taghavi Shahri:** Writing – review & editing. **Matija Maric:** Writing – review & editing. **Marie Bergmann:** Writing – review & editing. **Shuo Liu:** Writing – review & editing. **Shadi Azam:** Writing – review & editing. **Steffen Loft:** Writing – review & editing. **Rudi G.J. Westendorp:** Writing – review & editing, Funding acquisition. **Laust H. Mortensen:** Resources, Data curation, Writing – review & editing. **Mariska Bauwelinck:** Writing – review & editing. **Jochem O. Klompmaker:** Writing – review & editing. **Richard Atkinson:** Writing – review & editing. **Nicole A.H. Janssen:** Writing – review & editing. **Bente Oftedal:** Writing – review & editing. **Matteo Renzi:** Writing – review & editing. **Francesco Forastiere:** Writing – review & editing. **Maciek Strak:** Writing – review & editing. **Lau C. Thygesen:** Resources, Data curation, Writing – review & editing. **Bert Brunekreef:** Writing – review & editing, Funding acquisition. **Gerard Hoek:** Writing – review & editing. **Amar J. Mehta:** Conceptualization, Data curation, Supervision, Writing – review & editing.

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.

Acknowledgments

The research described in this article was conducted under contract with the Health Effects Institute (HEI), an organization jointly funded by the United States Environmental Protection Agency (EPA) (Assistance Award No. R-82811201) and certain motor vehicle and engine manufacturers. The contents of this article do not necessarily reflect the views of HEI or its sponsors, nor do they necessarily reflect the views and policies of the EPA or motor vehicle and engine manufacturers.

Funding

This work was supported by funding from HEI Research Agreement (#4954-RFA14-3/16-5-3), jointly funded by the United States Environmental Protection Agency (EPA) (Assistance Award No. R-82811201) and certain motor vehicle and engine manufacturers, and by the Novo Nordisk Foundation Challenge Programme: Harnessing the Power of Big Data to Address the Societal Challenge of Aging (#NNF17OC0027812). The funders had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107241.

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