Research

Source-Specific Air Pollution Including Ultrafine Particles and Risk of Myocardial Infarction: A Nationwide Cohort Study from Denmark

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BACKGROUND: Air pollution is negatively associated with cardiovascular health. Impediments to efficient regulation include lack of knowledge about which sources of air pollution contributes most to health burden and few studies on effects of the potentially more potent ultrafine particles (UFP).

OBJECTIVE: The authors aimed to investigate myocardial infarction (MI) morbidity and specific types and sources of air pollution.

METHODS: We identified all persons living in Denmark in the period 2005–2017, age >50 y and never diagnosed with MI. We quantified 5-y running time-weighted mean concentrations of air pollution at residencies, both total and apportioned to traffic and nontraffic sources. We evaluated particulate matter (PM) with aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$), <0.1 μm (UFP), elemental carbon (EC), and nitrogen dioxide (NO_2). We used Cox proportional hazards models, with adjustment for time-varying exposures, and personal and area-level demographic and socioeconomic covariates from high-quality administrative registers.

RESULTS: In this nationwide cohort of 1,964,702 persons (with 18 million person-years of follow-up and 71,285 cases of MI), UFP and $PM_{2.5}$ were associated with increased risk of MI with hazard ratios (HRs) per interquartile range (IQR) of 1.040 [95% confidence interval (CI): 1.025, 1.055] and 1.053 (95% CI: 1.035, 1.071), respectively. HRs per IQR of UFP and $PM_{2.5}$ from nontraffic sources were similar to the total (1.034 and 1.051), whereas HRs for UFP and $PM_{2.5}$ from traffic sources were smaller (1.011 and 1.011). The HR for EC from traffic sources was 1.013 (95% CI: 1.003, 1.023). NO_2 from nontraffic sources was associated with MI (HR = 1.048; 95% CI: 1.034, 1.062) but not from traffic sources. In general, nontraffic sources contributed more to total air pollution levels than national traffic sources.

CONCLUSIONS: $PM_{2.5}$ and UFP from traffic and nontraffic sources were associated with increased risk of MI, with nontraffic sources being the dominant source of exposure and morbidity. https://doi.org/10.1289/EHP10556

Introduction

A recent review of experimental and clinical studies concluded that air pollution can cause oxidative stress as well as local and systemic inflammation and that it affects vascular tone, fibrinolysis, platelet activity, and plaque formation.[1] Correspondingly, many epidemiological studies have found associations between air pollution and a range of cardiovascular end points with stronger evidence for particulate matter (PM) than gaseous components.[2] With regard to incident myocardial infarction (MI), some studies found higher risk in association with exposure to nitrogen dioxide (NO_2),[3–7] whereas other studies did not.[8–14] For PM with aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$), a recent meta-analysis found a hazard ratio (HR) of 1.08 per 10 μg/m^3 (95% confidence intervals (CI): 0.99, 1.18), with high heterogeneity between studies and concluded that there was suggestive evidence that long-term exposure to $PM_{2.5}$ is associated with MI.[15] Most subsequent studies have reported an elevated risk[14,16–19] with a few exceptions.[8,9]

Ultrafine particles (UFP), PM <0.1 μm, may have health effects disproportionate to their mass contribution to $PM_{2.5}$, because they have a large reactive surface area and may penetrate beyond the respiratory tract.[20–22] Studies of short-term exposure to UFP suggest an association with stroke, blood pressure, systemic inflammation, and autonomic tone.[21–24] Few epidemiological studies have investigated long-term cardiovascular effects of UFP. Two studies found associations between UFP and risk of ischemic heart disease and stroke,[25,26] two studies found associations between UFP and risk of MI,[9,11] and one study found an association between UFP and hypertension.[27] These previous studies all indicate an association between UFP and cardiovascular diseases, but they each have their limitations, e.g., small size, exposure assessed only at single point in time or with at spatial resolution at the kilometer scale, or having only area-level covariates. Several studies have linked air pollution from elemental carbon (EC) or the closely related measures black smoke (BS) and $PM_{2.5}$ absorbance, with higher CVD mortality.[28,29] Two studies showed associations between $PM_{2.5}$ absorbance and coronary heart disease,[30,31] whereas another study found no association between black carbon and ischemic heart disease.[32]

The chemical composition and toxicity of air pollution depends on the emission source, as does the relative contribution to total air pollution exposure.[33] Knowledge about the relative contribution to disease burden of sources such as traffic may therefore facilitate efficient political regulation to improve public health.[34] Most long-term studies have, however, not made such subdivisions, and the few results relating to MI are inconsistent.[10,26]

In a nationwide cohort with extensive data on personal and area-level covariates, we assessed time-varying total and source-specific air pollution at individual residences with a state-of-the-art multiscale air pollution model system and evaluated the association of UFP, $PM_{2.5}$, elemental carbon (EC), and NO_2 with risk of MI.

Methods

The study was conducted in Denmark, where a unique personal identification number has been allocated to all Danish residents

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since 1968. The identification number allows all residents to be traced in and across all health and administrative registers.[35] We identified Danish residents in the Civil Registration System,[36] which also provided complete residential histories (including dates of moving in and out) and information about emigration from Denmark.

We identified all who were born after 1920 (information on education is not available for those born before 1921), who lived in Denmark from birth or 1979 onward, and who were present in Denmark on 1 January 2005, and were 50 y of age or older any time after that date. From this population ($n = 2,048,282$), we excluded 60,967 with prevalent MI at baseline (see below) and 22,613 with missing information about one or more covariates, leaving a final cohort of 1,964,702 persons.

The cohort was followed up from 1 January 2005 to 31 December 2017. Thus, study entry (baseline) of cohort members was 1 January 2005 or the date of turning 50 y of age, whichever came last.

In accordance with Danish law, entirely register-based studies do not require ethical approval.

Outcome

We identified all cases of MI [*International Classification of Diseases, 8th Revision* (ICD8) (ICD8: 410 or ICD10: I21)] recorded as primary diagnosis in the Danish National Patient Register[37] or with the same codes as primary cause of death in the Danish Register of Cause of Death.[38] Individuals registered with an MI in one of those registries, from start of the registration (patient registry: 1977; mortality registry: 1970) and until study entry were excluded as prevalent cases. All other people with a first, incident diagnosis of MI after study entry (age 50 y or 1 January 2005, whichever came last) were counted as cases.

Exposure

We established exact geocodes of all residential addresses in Denmark from the Building and Housing Registry and modeled outdoor air pollution for the period 1995–2017 for these dwellings. We used the fully deterministic Danish DEHM/UBM/AirGIS modeling system,[39] which is based on detailed emission inventories and meteorological data from a weather forecast model and then physical (atmospheric transport and dispersion) and chemical processes in the atmosphere are modeled. The system adds contributions to air pollution concentrations at three scales: *a*) the long-range transported regional background, modeled with the Danish Eulerian Hemispheric Model (DEHM) assessing the contribution from emissions from the entire northern hemisphere[40]; *b*) the local background contribution at a 1-km² resolution calculated from Danish emissions of air pollution[41] (more details below) modeled with the Urban Background Model (UBM)[42]; and *c*) the contribution from the traffic on the address street modeled with the Operational Street Pollution Model (OSPM), with detailed input parameters including traffic load, composition, and emission factors as well as street and building configuration, and meteorology.[39,43] For each address one final estimate was achieved by adding DEHM and UBM, and for addresses with >500 vehicles per day, contribution from local traffic calculated by OSPM was also added. In this coupling of models, it was ensured that emission sources were not counted twice.[39,43,44] For all investigated pollutants hourly, address-level concentrations of air pollutants were then aggregated as monthly means. We modeled $PM_{2.5}$, EC, and NO_2 mass concentration as well as particle number concentration (PNC) as an indicator for UFP (denoted in this article as UFP); further details about the modeling system can be found elsewhere.[45] In brief, we modeled PNC based on an extension of the DEHM/UBM/AirGIS system with the aerosol dynamics module M7.[46] The M7 module represents the aerosol in four size fractions: Nucleation mode (typical size below 10 nm), Aitken mode (10–100 nm), Accumulation Mode (100–1,000 nm) and Coarse Mode (>1,000 nm); and it handles conversion between size modes. The Aitken+Accumulation modes output from the DEHM feed into the UBM and OSPM models without including the particle dynamics. The size range 10–1,000 nm was chosen to facilitate validation against measurement data. We scaled UFP particle number emissions to source-specific $PM_{2.5}$ and EC mass emissions to derive a consistent emission inventory for PNC.

As input data for the modeling system, we used high-resolution emission inventories for Denmark for the period 1990–2020 that are based on registers of high quality and detail,[41] e.g., the National Road and Traffic Database.[47] The emission inventories are subject to an annual review from international experts to ensure that the calculations are done in accordance with best practices and meet the internationally established quality criteria. The inventories are based on the standardized European Selected Nomenclature for Air Pollution (SNAP) code classification of emission categories.[48] The Danish emission estimations are done at the most detailed SNAP level and can be aggregated to the 11 SNAP main categories (Table S1). For large point sources such as power plants or road traffic high-quality estimates are ensured by detailed measurements and detailed information on technology and abatement. This allowed us to model air pollution both with and without the emissions from Danish road traffic (SNAP 07 codes) to the local background (UBM) and the traffic on the address street. Subtracting the two modeling results from each other enabled apportioning of total pollutant levels into national road traffic (denoted as "traffic" in this article) and nontraffic sources, with the latter also including traffic and other sources from surrounding countries. The contribution from road traffic to secondary particles (e.g., nitrate) is therefore not included in the Danish road traffic scenario in this setup. Based on available emission factors, the contribution to $PM_{2.5}$ from national traffic was further divided into contributions from tailpipe (from motorized road transport vehicles) and nontailpipe (resuspended dust, dust from brakes, clutches, tires, road abrasion, and evaporation from vehicles) by running air pollution models with and without these emissions.

Using modeled monthly mean concentrations, we then calculated running mean exposure 1, 5, and 10 y back in time for each cohort member. These calculations were done as monthly updated, running averages of air pollution at the residential address(es) held by each cohort member. These averages took into account the time each person stayed at each address and provided time-weighted averages (TWA). The running 5-y TWA was our *a priori* main exposure metric. The final result of the complete modeling exercise was time-varying estimates of $PM_{2.5}$, UFP, EC, and NO_2 in total and from traffic and nontraffic sources. For $PM_{2.5}$, traffic estimates were further subdivided into tailpipe and nontailpipe emissions. For all 14 estimates, we estimated TWA over 1, 5, and 10 y, with 5 y being the primary averaging period.

Comparisons between modeled and measured air pollution concentrations show generally good performance of the Danish DEHM/UBM/AirGIS modeling system. For total $PM_{2.5}$ and EC, the correlation coefficients were in the range of 0.67–0.85 and 0.77–0.79, respectively, across different locations and measurement periods,[49] and the correlations were similarly high for NO_2.[50] For annual means of UFP, correlations between predictions and measurements were 0.86, 0.87, and 0.95 for validations at the regional, urban, and street scale, respectively.[51] The source apportioning cannot be validated directly against measurements, but as described previously, the input data are of highest

standard, and the model reproduces concentrations in high traffic roads well (Figure S1).[41,52,53]

Covariates

We selected potential confounders *a priori*. Statistics Denmark provided annually updated information about country of origin ("Danish origin" defined as being a Danish citizen or having at least one Danish citizen parent; all other classified as "other country of origin"), civil status (married/cohabiting, other), highest attained education (mandatory, short: vocational training, secondary or <2 y of postsecondary education, medium/long: >2 y of postsecondary education), occupational status (high-level white-collar, low-level white-collar, blue-collar, unemployed, retired), personal income (quintiles), and household per capita income (quintiles). Sex- and calendar year–specific quintiles were used for personal and household income to allow for inflation and sex-specific income disparities. In 2017, the 20th, 40th, 60th, and 80th personal income percentiles in Danish kroner (kr) were 142,926, 198,363, 249,053, and 312,717 kr for women and 147,235, 219,142, 281,097, and 370,134 kr for men. The corresponding percentiles of household income per adult in household were 174,497, 229,476, 286,079, and 365,263 kr for women and 171,817, 232,821, 290,162, and 369,949 kr for men.

To account for potential residual confounding and potential socioenvironmental disparities, we included a comprehensive array of parish-level covariates reflecting aspects of deprivation. In the year 2017, there were 2,160 parishes in Denmark with a mean area of 16.2 km^2 and a median population of 1,032 persons. For socioeconomic area-level covariates, we obtained annually updated information at the parish level about the proportion of inhabitants with a criminal record, living in single-parent households, with only basic education, with manual labor, with income in lowest quartile, living in social housing, and with non-Western background. A Western background was defined as being a citizen of or having at least one parent who is a citizen of a Western country (Denmark and the rest of the EU, the UK, Norway, Iceland, Liechtenstein, Switzerland, Andorra, San Marino, the Vatican, Australia, New Zealand, the United States, and Canada). Persons with missing covariates were excluded.

Statistical Methods

We used Spearman rank correlation coefficient to evaluate correlations between air pollutants and covariates. Cox-proportional hazards models with age as time axis were used to calculate HRs and associated 95% CI for 5-y TWA air pollution and MI.

Cohort members were followed from the age of 50 y or 1 January 2005, whichever came last, until death, MI, more than 14 consecutive days of unknown address, emigration, or 31 December 2017, whichever came first. We evaluated associations linearly per interquartile range (IQR) of exposure to facilitate comparison of risk estimates between pollutants (our primary analyses) and per fixed increment to facilitate comparison with results from other studies. We also performed categorical analysis based on percentiles of exposure (<10 /reference, 10 to <25, 25 to <50, 50 to <75, 75 to <90, 90 to <95, and 95–100) as a graphical illustration of the shape of the exposure–response function. We used Akaike information criteria (AIC) to compare the model fit of linear and categorical representation of pollutants.

We evaluated three models with increasing levels of adjustment. Model 1 was the crude model only adjusted for age, sex, and calendar year (categorical, in 2-y categories). Model 2 was additionally adjusted for personal covariates (country of origin, civil status, educational level, occupational status, personal and household income). Model 3 (our main model) was additionally adjusted

for all eight parish-level factors: proportion of inhabitants with non-Western background, living in single-parent households, with only basic education, with manual labor, with personal income in the lowest quartile, with household income in the lowest quartile, living in social housing, and with a criminal record.

All variables (except sex and country of origin) were time-dependent, and subjects were allowed to change between levels of exposure and covariates over time. Therefore, exposures and covariates changed with time and, at any moment during follow-up, reflected exactly the conditions pertaining to that specific instance.

In sensitivity analyses, we evaluated shorter (1-y) and longer (10-y) TWA periods, and we evaluated effect stratified by age (50–69, 70–80, >80 y) and sex. Because both air pollution and stroke incidence decreased over the study period, we ran three models as sensitivity analyses: *a*) including exact year of entry as strata; *b*) including running calendar year of observation (2-y period) as strata rather than as a covariate; and *c*) analysis restricted to those entering the study in the year 2005.

All statistical analyses were performed in SAS (version 9.4; SAS Institute Inc.).

Results

The final cohort of 1,964,702 persons accrued a total of 18,309,318 person-years of follow-up and 71,285 MI events.

Most (71%) cohort members entered the cohort in 2005 (Figure S2). Table 1 describes the cohort members at entry, where median 5-y average concentrations of air pollutants were: $PM_{2.5} = 11.2\,\mu g/m^3$ (10th–90th percentile: 9.1–12.2), UFP = 11,106 particles/cm^3 (10th–90th percentile: 7,963–15,695), EC = 0.7 $\mu g/m^3$ (10th–90th percentile: 0.5–1.0), and $NO_2 =$ 15.3 $\mu g/m^3$ (10th–90th percentile: 10.5–23.7). High concentrations of UFP or $PM_{2.5}$ were associated with higher age, being retired, being female, not living with a spouse, not being a blue-collar worker, and being of non-Danish origin. Further, higher concentrations at the residence were associated with living in a parish with more social housing and non-Western immigrants (Table S2).

For the vast majority of addresses, national road traffic sources contributed less to air pollution than nontraffic sources, which was most pronounced for UFP and $PM_{2.5}$ (Table 1; Figure S3).

Spearman rank correlations between pollutants ranged from 0.26 to 0.99. Contributions to $PM_{2.5}$ from traffic tailpipes and traffic nontailpipe sources were highly correlated with each other and with their sum ($PM_{2.5}$ from traffic) ($r_s \geq 0.94$) but only moderately correlated with $PM_{2.5}$ from all sources ($r_s = 0.45–0.66$) (Table S3). The correlation between area-level covariates and air pollutants and individual socioeconomic covariates were generally very low to moderate (Table S4). Pollutants averaged over 1, 5, and 10 y were highly correlated ($r_s \geq 0.85$) (Table S5).

Results from our main model (full adjustment) showed HRs per IQR of 1.053 (95% CI: 1.035, 1.071) per 1.85 $\mu g/m^3$ $PM_{2.5}$, 1.040 (95% CI: 1.025, 1.055) per 4,248 particles/cm^3 UFP, 1.027 (95% CI: 1.013, 1.040) per 7.15 $\mu g/m^3$ NO_2, and 1.009 (95% CI: 1.000, 1.019) per 0.28 $\mu g/m^3$ EC (Table 2). Results from the crude model showed HRs below 1.

The HRs per IQR were stronger for the nontraffic contributions than for the traffic contributions to $PM_{2.5}$, UFP, and NO_2. The pattern was opposite for EC, where only the association with the contribution from traffic deviated from the null. The tailpipe and nontailpipe contributions to $PM_{2.5}$ from traffic showed similar associations with MI. Table S6 shows HRs per fixed increase in air pollution.

Results based on categories for $PM_{2.5}$, UFP, and NO_2, indicated increase in risk over the entire exposure range (Figure 1A–D), which was similar for the nontraffic contribution to UFP and NO_2. For $PM_{2.5}$ from nontraffic sources, there was some indication of a

Table 1. Cohort ($N = 1,964,702$) characteristics at baseline (last of: 1 January 2005 and age 50 y), including time-weighted average air pollution concentrations over previous 5 y Denmark, 2005–2017.

Baseline characteristics	Total
Individual level variables	
Women [n (%)]	1,037,088 (53)
Age (y) [median (10%–90%)]	58 (50–76)
Country of origin [n (%)]	
Denmark	1,927,035 (98)
Other	37,667 (2)
Civil status [n (%)]	
Married/cohabiting	1,438,200 (73)
Other	526,502 (27)
Education[a] [n (%)]	
Mandatory	711,579 (36)
Short	888,013 (45)
Medium or long	365,110 (19)
Occupational status[b] [n (%)]	
White-collar, high level	200,884 (10)
White-collar, low level	296,628 (15)
Blue-collar	590,213 (30)
Unemployed	75,957 (4)
Retired	801,020 (41)
Personal income: quintiles[c] [n (%)]	
1st (low)	489,663 (25)
2nd	414,704 (21)
3rd	327,020 (17)
4th	337,208 (17)
5th (high)	396,107 (20)
Household income: quintiles[d] [n (%)]	
1st (low)	406,916 (21)
2nd	355,572 (18)
3rd	328,899 (17)
4th	391,770 (20)
5th (high)	481,544 (25)
Air pollution levels (5-y mean) [median (10%–90%)]	
$PM_{2.5}$ total ($\mu g/m^3$)	11.2 (9.1–12.2)
$PM_{2.5}$ nontraffic ($\mu g/m^3$)	10.9 (8.9–11.6)
$PM_{2.5}$ traffic ($\mu g/m^3$)	0.2 (0.1–0.8)
UFP total (particles/cm^3)	11,106 (7,963–15,695)
UFP nontraffic (particles/cm^3)	9,757 (7,452–12,032)
UFP traffic (particles/cm^3)	1,202 (357–3,649)
EC total ($\mu g/m^3$)	0.7 (0.5–1.0)
EC nontraffic ($\mu g/m^3$)	0.5 (0.4–0.6)
EC traffic ($\mu g/m^3$)	0.1 (0.0–0.4)
NO_2 total ($\mu g/m^3$)	15.3 (10.5–23.7)
NO_2 nontraffic ($\mu g/m^3$)	11.2 (8.5–13.4)
NO_2 traffic ($\mu g/m^3$)	4 (1.4–10.9)
Area level variables [median (10%–90%)]	
% Non-Western background	3 (1–12)
% Only basic education	11 (6–15)
% Manual labor	13 (8–17)
% Unemployed	2 (1–3)
% Low income	4 (2–7)
% Social housing[e]	14 (1–43)
% Sole-providers	6 (4–8)
% with criminal record	0.4 (0.2–0.9)

Note: EC, elemental carbon; UFP, ultrafine particles.
[a]Short: vocational training, secondary education or <2 y of postsecondary education. Medium or long >2 y of postsecondary education.
[b]White-collar, high level: Managers/directors with ≥5 employees and people with employment that requires high-level skills. White-collar, low level: Managers with 0–4 employees and people with employment that requires intermediate level skills. Blue-collar: employment that requires low-level skills.
[c]We applied age and calendar-year specific quintiles to account for inflation and income disparities by sex. In 2017, the 20th, 40th, 60th, and 80th percentile in Danish kroner were 142,926, 198,363, 249,053, and 312,717, respectively, for women and 147,235, 219,142, 281,097, and 370,134 for men.
[d]We applied age and calendar year specific quintiles to account for inflation and income disparities by sex for singles. In 2017, the 20th, 40th, 60th, and 80th percentile per adult in household, in Danish kroner, were 174,497, 229,476, 286,079, and 365,263, respectively, for women and 171,817, 232,821, 290,162, and 369,949, respectively, for men.
[e]Publicly funded nonprofit housing estates, where one-third of the apartments can be used by municipalities for persons in need.

leveling off at higher exposure levels (Figure S4A–D; Table S7). For traffic contributions, categorical analysis indicated a lower threshold for the associations with the traffic contributions. (Figure S5 and S6; Tables S7 and S8). Generally, the linear representation of exposure offered a better or only marginally worse fit of data than the categorical model (ΔAIC: 0.00–1.54). Exceptions included NO_2 traffic, $PM_{2.5}$ tailpipe and $PM_{2.5}$ nontailpipe, and $PM_{2.5}$ nontraffic, where the categorical model was superior (Table S9).

Sensitivity analyses showed that the association between air pollution and MI was stronger in older age groups, with only little evidence of an association before age 70 y (Table 3). Except for $PM_{2.5}$, associations tended to be stronger in males, albeit with widely overlapping CIs. HRs changed little when averaging air pollution over 1 or 10 y (Table S10). Including year of entry or running calendar year as strata produced results identical to those of the main model (Table S11).

Discussion

In this nationwide register-based cohort, with >18 million person-years of follow-up, 71,285 cases, and exposure levels well below EU-regulatory limits (annual mean: $PM_{2.5} = 25 \, \mu g/m^3$, $NO_2 = 40 \, \mu g/m^3$), air pollution was associated with a higher risk of MI. The associations were stronger among older people.

$PM_{2.5}$ and UFP showed the highest HRs per IQR. Contributions to $PM_{2.5}$ and UFP from nontraffic sources showed higher HRs than contributions from national road traffic when expressed per IQR. In general, nontraffic sources contributed more to total air pollution levels than national road traffic sources.

For ease of comparison, risk estimates from other studies have in the following discussion been rescaled to the IQR of the present study by means of this formula: $HR_{new} = HR_{old}^{(Unit_{new}/Unit_{old})}$.

We found $PM_{2.5}$ to be associated with MI with a HR of 1.053 (95% CI: 1.035, 1.071) per IQR ($1.85 \, \mu g/m^3$), which is statistically compatible with the majority of previous studies.,[8–10,18,19,26,54–58] There are, however, also studies suggesting both weaker[3,14,17] and stronger associations.[16,19] The studies with weaker associations generally modeled exposure with lower temporal or spatial resolution than the present study, and two of them found stronger risks after relatively crude adjustment for potential covariates.[14,17] Exposure misclassification and residual confounding may thus have driven results toward the null. Furthermore, the study populations in these studies were much younger than those in the present study, which may have attenuated risk, as our and some other studies suggested a stronger association among older age groups.[17,59] Stronger associations than those of our study were found in a Dutch cross-sectional study, oversampling elderly participants, and showing $PM_{2.5}$ to be associated with self-reported heart attack (OR = 1.16, 95% CI: 1.12, 1.24)[16] and in a Korean cohort dominated by younger people, where $PM_{2.5}$ was associated with higher risk of MI hospitalization (HR = 1.70, 95% CI: 1.38, 2.09).[6] The authors of the Korean study hypothesized that the high risk may be attributable to higher levels of or different composition of air pollution in comparison with air pollution levels or composition in Western cities.

The small size of UFP allows systemic penetration beyond the respiratory tract and provides a large reactive surface area. UFPs may therefore be a more potent risk factor for cardiovascular disease than $PM_{2.5}$, of which they constitute a weight-wise small fraction.[60] The present study showed an association between UFP and higher risk for MI. The few previous studies on long-term exposure to UFP and risk of MI have suggested a positive association with MI,[9,11] which is corroborated by results on self-reported stroke/ischemic heart disease[25] and ischemic heart disease mortality.[26] These results support our UFP and MI findings, although they tended to show weaker associations than those of our study, which

Table 2. Associations between MI (cases = 71,285) and 5-y averages of air pollutants, total and by source. Denmark, 2005–2017, $N = 1,964,702$. Person-years: 18,309,319.

PM$_{2.5}$	IQR	Model 1[a] per IQR HR (95% CI)	Model 2[b]. per IQR HR (95% CI)	Model 3[c] per IQR HR (95% CI)
Total	1.85 µg/m^3	0.983 (0.969, 0.998)	1.019 (1.004, 1.034)	1.053 (1.035, 1.071)
Nontraffic	1.63 µg/m^3	0.989 (0.973, 1.006)	1.032 (1.015, 1.049)	1.051 (1.032, 1.069)
Traffic	0.37 µg/m^3	0.991 (0.985, 0.998)	0.996 (0.990, 1.003)	1.011 (1.003, 1.018)
Tailpipe	0.24 µg/m^3	0.989 (0.982, 0.996)	0.996 (0.989, 1.003)	1.012 (1.004, 1.020)
Nontailpipe	0.12 µg/m^3	0.995 (0.990, 1.000)	0.997 (0.992, 1.002)	1.008 (1.002, 1.014)
UFP				
Total	4,248 particles/cm^3	0.961 (0.950, 0.972)	1.001 (0.990, 1.013)	1.040 (1.025, 1.055)
Nontraffic	2,769 particles/cm^3	0.974 (0.964, 0.985)	1.014 (1.003, 1.024)	1.034 (1.022, 1.046)
Traffic	1,698 particles/cm^3	0.963 (0.953, 0.972)	0.984 (0.974, 0.994)	1.011 (0.999, 1.024)
EC				
Total	0.28 µg/m^3	0.966 (0.957, 0.975)	0.989 (0.981, 0.998)	1.009 (1.000, 1.019)
Nontraffic	0.12 µg/m^3	0.969 (0.960, 0.977)	0.994 (0.987, 1.001)	1.001 (0.996, 1.007)
Traffic	0.17 µg/m^3	0.981 (0.973, 0.989)	0.992 (0.984, 1.000)	1.013 (1.003, 1.023)
NO$_2$				
Total	7.15 µg/m^3	0.969 (0.960, 0.979)	0.994 (0.984, 1.004)	1.027 (1.013, 1.040)
Nontraffic	2.68 µg/m^3	0.984 (0.973, 0.996)	1.025 (1.014, 1.037)	1.048 (1.034, 1.062)
Traffic	5.17 µg/m^3	0.972 (0.963, 0.981)	0.986 (0.977, 0.995)	1.009 (0.998, 1.020)

Note: CI, confidence interval; EC, elemental carbon; HR, hazard ratio; IQR, interquartile range; MI, myocardial infarction; UFP, ultrafine particles.
[a]Adjusted for age, sex, and calendar year (in 2-y categories).
[b]Model 1 with further adjustment for marital status, education, occupational status, ethnicity, and personal and household income.
[c]Model 2 with additional adjustment for area-level percentage of population: living in social housing, being sole providers, of non-Western origin, having low income, being unemployed, having blue-collar work, having only basic education, and having a criminal record.

may reflect differences in age composition, available covariates, or exposure composition and assessment.

The physical, chemical, and toxicological characteristics of PM depend on their sources, which may have implications for development of cost-efficient prevention strategies. Few other studies have investigated source-specific air pollution in relation to MI. A case–control study from Massachusetts, in the United States, found that the strongest risk factor per IQR for acute MI hospitalization was PM$_{2.5}$ from area-level sources,[10] whereas there was only a weak association with local traffic-dominated sources, which corroborates our observation for PM$_{2.5}$. In contrast, in the Californian Teachers Study, PM$_{2.5}$ and UFP from gasoline and diesel combustion were associated with similar HRs per IQR for ischemic heart disease as total PM$_{2.5}$ and UFP.[26] These studies had smaller populations and more crude exposure assessment than the present study. In the present study, nontraffic sources of PM$_{2.5}$ and UFP seemed most important when expressed per IQR. Altogether, PM$_{2.5}$ and UFP from both traffic and nontraffic sources seem associated with risk of MI, with the highest HRs per IQR for nontraffic sources. This finding, combined with nontraffic sources contributing most to exposure, suggests that nontraffic sources may contribute more to the public health burden from MI than national traffic sources. The main nontraffic sources of emissions of PM$_{2.5}$ and UFP air pollution in Denmark are nonindustrial combustion plants (such as wood stoves) and ships (Figure S7; Table S12). Further, the categorical analyses and to some extent the AIC analyses indicated that some of the linear HRs should be treated with caution due to a possible nonlinear shape of the function.

The present study found an association between NO$_2$ and higher risk of MI, which has also been found in several previous studies.[3,5,6,11,14,26] We found associations for NO$_2$ from other sources than traffic but virtually no association with NO$_2$ hailing from traffic sources, indicating that correlated air pollutants rather than NO$_2$ *per se* might have influenced these results for NO$_2$.

We found indicative associations between total EC and traffic EC and risk of MI, but no association with EC from nontraffic sources. One previous study found no association between BC and ischemic heart disease,[32] another study found BC to be associated with coronary heart disease,[31] and a third study found a higher incidence of coronary events in association with PM$_{2.5}$ absorbance

although not statistically significant. Altogether, the literature is inconclusive concerning a possible association between EC and MI.

Strengths and Limitations

The prospective nationwide cohort design was a major strength of our study. Furthermore, we benefited from extensive and continuously updated high-quality public registers providing detailed information on both outcome, residential history, and a wide array of covariates. Similar to two recent state or nationwide studies with millions of participants,[3,14] our study could only discern a positive relationship between air pollution and MI after adjusting for individual- and area-level factors. This phenomenon could be partly due to higher air pollution levels at the residences of individuals of higher socioeconomic position in Denmark,[61] combined with higher risk of MI among individuals of low socioeconomic position.[62] The association of socioeconomic position and risk of MI is likely through lifestyle. We could not adjust our analyses for individual lifestyle factors, such as smoking, diet, and physical activity, which could potentially have confounded our results. In a previous study, we analyzed the consequences of lack of information about such lifestyle factors among 246,766 randomly selected residents in Denmark for whom questionnaire data on lifestyle were also available. We found that when including all individual- and area-level covariates of the present study, information on body mass index, smoking, physical activity, and diet bestowed no additional impact on HRs for air pollution and MI.[63] Even so, we cannot entirely rule out that residual confounding from lifestyle may have affected our results in either direction. Air pollution is a complex mixture of many chemical species that might correlate depending on the source pattern. Thus we cannot exclude the possibility that associations with MI, which was identified with one pollutant, might be (partly) due to exposure to correlated pollutants. Two other qualities of our study was the state-of-the-art, address-level exposure modeling covering an entire country and the ability of the modeling to assess source-specific contributions to air pollution. The validity of separation of the traffic and nontraffic contributions to air pollution depends to a high degree on the quality of the emission inventory for road traffic. The uncertainty of the Danish emission inventory depends on the emission sector and the
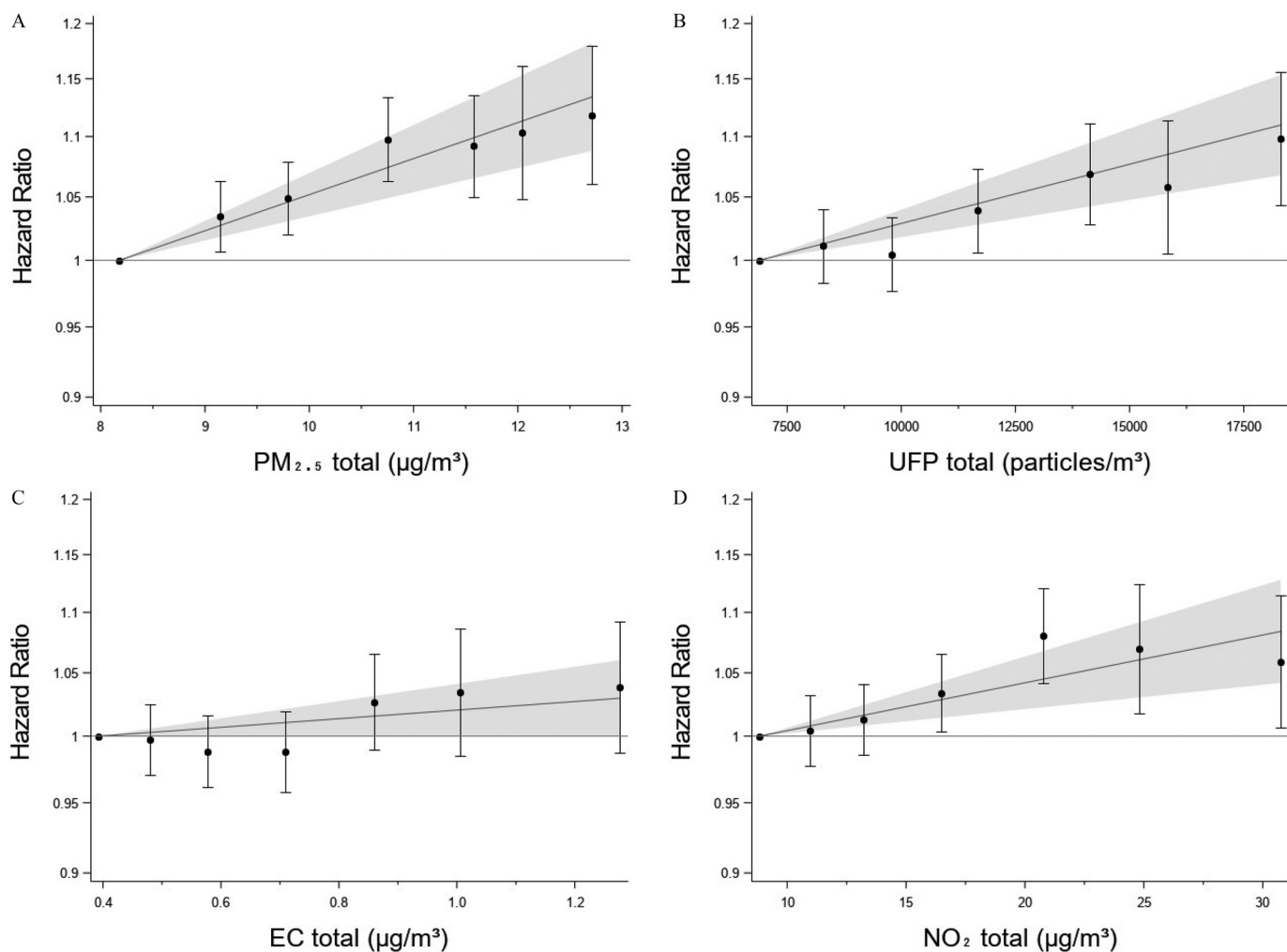
Figure 1. Associations between MI and 5-y time-weighted averages of (A) PM$_{2.5}$, (B) UFP, (C) EC, and (D) NO$_2$ specified both in categories and as linear variables in the fully adjusted model 3. Categories defined from percentile of exposure: <10% (reference), 10%–25%, 25%–50%, 50%–75%, 75%–90%, 90%–95%, and >95%; HRs and 95% CI plotted at the median of each category. The linear estimates from Table 2 with 95% CIs are plotted with the median of the categorical reference category as the null (i.e., = 1). (Table S3 holds the same information in tabulated form). Denmark, 2005–2017, $N = 1,964,702$. Note: CI, confidence interval; EC, elemental carbon; MI, myocardial infarction; UFP, ultrafine particles.

pollutant considered. For some sectors, e.g., large point sources such as power plants and road transport, the data quality is high because a large share of the emission is covered by direct measurements or very detailed information on technology and abatement. For other sectors, such as small-scale combustion, the uncertainty is higher due to a large number of small installations with limited knowledge about technology and abatement measures. Regarding

pollutants, the uncertainty for NO$_x$ is lower than for PM and EC because of a higher data quality of main emitters of NO$_x$ than of PM. Greater uncertainty may also have affected UFP estimates because there are no inventory standards and no mandatory national registration. However, correlations with measurement data were similar to those for other pollutants. Direct validation against measurements was not possible for source-specific

Table 3. Associations[a] between 5-y averages of air pollutants and MI in entire population and stratified by sex and age. Denmark, 2005–2017, $N = 1,964,702$.

	Person-years	Cases	PM$_{2.5}$ per IQR: 1.85 µg/m^3 HR[a] (95% CI)	UFP per IQR: 4,248 particles/cm^3 HR[a] (95% CI)	EC per IQR: 0.28 µg/m^3 HR[a] (95% CI)	NO$_2$ per IQR: 7.15 µg/m^3 HR[a] (95% CI)
Entire study population	18,309,319	71,285	1.053 (1.035, 1.071)	1.040 (1.025, 1.055)	1.009 (1.000, 1.019)	1.027 (1.013, 1.040)
Sex						
Male	8,369,008	43,8s40	1.053 (1.033, 1.073)	1.044 (1.027, 1.061)	1.011 (1.001, 1.022)	1.030 (1.014, 1.045)
Female	9,940,311	27,445	1.052 (1.030, 1.075)	1.033 (1.013, 1.052)	1.005 (0.992, 1.019)	1.022 (1.005, 1.040)
Age (y)						
Age 50–70	11,970,225	28,842	0.993 (0.972, 1.014)	1.007 (0.988, 1.026)	0.992 (0.977, 1.006)	1.016 (0.998, 1.033)
Age 70–80	4,308,188	23,317	1.072 (1.048, 1.097)	1.049 (1.028, 1.070)	1.010 (0.997, 1.025)	1.026 (1.007, 1.045)
Age 80+	2,030,906	19,216	1.123 (1.095, 1.150)	1.078 (1.055, 1.102)	1.028 (1.015, 1.042)	1.043 (1.023, 1.064)

Note: CI, confidence interval; EC, elemental carbon; HR, hazard ratio; IQR, interquartile range; MI, myocardial infarction; UFP, ultrafine particles.
[a]Adjusted for age, sex, calendar year (in 2-y categories), marital status, education, occupational status, ethnicity, personal and household income, and percentage of parish population: living in social housing, being sole providers, of non-Western origin, having low income, being unemployed, having blue-collar work, having only basic education, and having a criminal record.

concentrations. Circumstantial evidence for their quality is, however, provided by our model's ability to predict concentrations also in conditions where traffic is the primary source of air pollution and by the quality of input data inventories.

Our modeling system only allowed separate estimation of primarily emitted national road-traffic pollution, and we can thus not determine to what degree long-distance transported secondary species related to traffic contribute to MI risk. It was a particular strength that our modeling included also UFP, which has not previously been modeled in detail on such a large scale. A limitation of our study is exposure misclassification. First, we did not have information about occupational or other nonresidential exposures. Second, some uncertainty is inevitable when modeling exposure. We would expect the resulting error in the exposure assessment to be a mixture of Berkson and Classical error, which could affect risk estimate in either direction.

We recommend caution when generalizing the results of the present nationwide study to other populations. Potential caveats include differences in the age composition, levels and composition of air pollution, population susceptibility (e.g., due to genetics and comorbidity), and possible differences in correlation between air pollution and sociodemographic characteristics at the individual and area level.

Conclusion

This study adds to the evidence that PM air pollution, including UFP, is associated with higher risk of MI. The association was apparent for PM from both traffic and nontraffic sources, with highest HRs per IQR for nontraffic sources, which also contributed most of the air pollution.

Acknowledgments

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