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Effects of Sociodemographic Characteristics, Comorbidity, and Coexposures on the Association between Air Pollution and Type 2 Diabetes: A Nationwide Cohort Study

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Background: Exposure to air pollution has been associated with a higher risk of type 2 diabetes (T2D), but studies investigating whether deprived groups are more susceptible to the harmful effects of air pollution are inconsistent.

Objectives: We aimed to investigate whether the association between air pollution and T2D differed according to sociodemographic characteristics, comorbidity, and coexposures.

Methods: We estimated residential exposure to $PM_{2.5}$, ultrafine particles (UFP), elemental carbon, and NO_2 for all persons living in Denmark in the period 2005–2017. In total, 1.8 million persons 50–80 y of age were included for main analyses of whom 113,985 developed T2D during follow-up. We conducted additional analyses on 1.3 million persons age 35–50 y. Using Cox proportional hazards model (relative risk) and Aalens additive hazard model (absolute risk), we calculated associations between 5-y time-weighted running means of air pollution and T2D in strata of sociodemographic variables, comorbidity, population density, road traffic noise, and green space proximity.

Results: Air pollution was associated with T2D, especially among people age 50–80 y, with hazard ratios of 1.17 [95% confidence interval (CI): 1.13, 1.21] per 5 $\mu g/m^3$ $PM_{2.5}$ and 1.16 (95% CI: 1.13, 1.19) per 10,000 UFP/cm^3. In the age 50–80 y population, we found higher associations between air pollution and T2D among men in comparison with women, people with lower education vs. individuals with high education, people with medium income vs. those with low or high income, people cohabiting vs. those living alone, and people with comorbidities vs. those without comorbidities. We observed no marked changes according to occupation, population density, road noise, or surrounding greenness. In the age 35–50 y population, similar tendencies were observed, except in relation to sex and occupation, where we observed associations with air pollution only among women and blue-collar workers.

Discussion: We found stronger associations between air pollution and T2D among people with existing comorbidities and weaker associations among people with high socioeconomic status in comparison with those with lower socioeconomic status. https://doi.org/10.1289/EHP11347

Introduction

The prevalence of type 2 diabetes (T2D) has increased markedly in countries of all income levels, from 108 million in 1980 to 422 million in 2014.[1] The main risk factor for T2D is an unhealthy lifestyle, particularly obesity and physical inactivity,[1] but a number of studies have also linked T2D with exposure to ambient air pollution.[2] Proposed mechanistic pathways include air pollution–induced oxidative stress and systemic inflammation, which are both involved in the pathogenesis of T2D.[3,4] Furthermore, epidemiological studies have found air pollution to be associated with early markers of T2D, including decreased glucose tolerance and insulin insensitivity.[5,6] A recent meta-analysis of air pollution and incident T2D found risk estimates of 1.10 [95% confidence interval (CI): 1.04, 1.16] per 10 $\mu g/m^3$ particulate matter (PM) with a diameter <2.5 μm ($PM_{2.5}$) and 1.02 (95% CI: 0.99, 1.05) per 10 $\mu g/m^3$ nitrogen oxide (NO_2).[2] Ultrafine particles (UFP; <0.1 μm in diameter) are potentially more harmful than larger particles,[7,8] and the two studies on UFP and diabetes found long-term exposure to UFP associated with increased risk of diabetes.[9,10]

Previous studies have found socioeconomic inequalities according to air pollution exposure, mainly showing higher exposure among people with low socioeconomic status (SES),[11] although this finding varies across regions/countries if, e.g., living centrally is highly attractive.[12,13] It is unclear whether the harmfulness of air pollution differs in relation to the development of T2D across different socioeconomic groups, because the studies investigating effect modification by sex are inconsistent.[14–16] Systemic inflammation is thought to be a main biological pathway underlying an effect of air pollution on T2D.[17] People with low SES are more likely to have an unhealthy lifestyle, a higher body mass index (BMI), and are at higher risk of, e.g., COPD and cardiovascular disease, which are all habits and conditions characterized by chronic inflammation.[18,19] It is therefore possible that people with low SES are more susceptible to the harmful effects of air pollution on risk of T2D.[14]

Associations between air pollution and T2D may differ between men and women due to socially derived exposure differences according to gender (e.g., in some countries women spend more time at home than men); to physiological differences related to sex (e.g., differences in hormones, lung size, and deposition of particles); or to a combination of these.[20] The studies investigating these associations and exposure differences are inconsistent, because some studies find the highest risk estimates among men,[16,21] some studies find them among women,[14,15] and some studies report no difference in risk according to sex.[9,22]

Road traffic noise has been found to increase the risk of T2D.[23–25] Noise is believed harmful through some of the same

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biological mechanisms as air pollution, including systemic inflammation and oxidative stress.[26] A recent study found that road traffic noise was associated with higher risk of T2D among people exposed to high levels of air pollution in comparison with people exposed to low levels of air pollution, suggesting that high exposure to one of these two traffic pollutants can increase the susceptibility to the other.[24] Surrounding greenness has been found inversely associated with T2D, potentially by promoting physical activity, decreasing psychological stress, or as a result of lower air pollution and traffic noise levels in such areas.[27,28] If surrounding greenness results in a healthier lifestyle, it might protect against the harmful effects of air pollution, but this possible mitigation has not been investigated in relation to T2D.

We aimed to investigate whether the association between long-term exposure to air pollution ($PM_{2.5}$, elemental carbon (EC), UFP, and NO_2) and risk of T2D differed according to sociodemographic characteristics, financial stress, comorbidity, population density, road traffic noise, and green space, based on the entire Danish population.

Methods

Study Population

All persons living in Denmark can be followed across all health and administrative registers based on a unique identification number.[29] Using the Danish Civil Registration System, which contains continuously updated information on exact addresses,[29] we identified address histories for all inhabitants born after 1 January 1921 and living in Denmark from 1979 onward (after 1979, address information is virtually complete). We censored people at the date of missing address information (>14 consecutive days), emigration, death, or 31 December 31 2017. Based on this population, we defined a study base with baseline at 1 January 2005 or age 35 y, whichever came last, such that a person who was below 35 y of age in 2005 was included into the cohort at the time the person turned 35 y ($N = 2{,}757{,}813$).

Outcome

We identified incident diabetes cases based on the National Patient Registry[30] and the National Prescription Registry,[31] using an algorithm developed by the Danish Health Data Agency for the purpose of monitoring diabetes prevalence and incidence in Denmark.[32] This algorithm has been used in various register-based studies based on the Danish population.[33,34]

The Prescription Registry holds information on all dispensed drugs. We defined T2D cases as persons with two contacts with a pharmacy [Anatomical Therapeutic Chemical system (ATC) codes A10B (blood glucose–lowering drugs, excluding insulins), though excluding A10BJ02 (liraglutide: only Saxenda®), as well as A10AE54 (insulin glargine and lixisenatide) and A10AE56 (insulin degludec and liraglutide)] and/or T2D-related hospital contacts (*International Classification of Diseases* (ICD) 8 code 250 or ICD10 code E11). We defined a person as case from the second register record. A diagnosis of type 1 diabetes [ICD-8 code 249 or ICD-10 code E10 and/or at least one dispensed prescription with ATC A10A (insulins and analogs), excluding A10AE54 (insulin glargine and lixisenatide) and A10AE56 (insulin degludec and liraglutide)] resulted in censoring (exclusion if before baseline). All persons with a diagnosis of T2D before baseline (identified as described above for incident cases) were excluded.

Estimation of Air Pollution Exposure

We modeled air pollution concentrations of $PM_{2.5}$, EC, NO_2, and UFP outside the front door of all addresses in Denmark (identified from the Building and Housing Registry) using the Danish Eulerian Hemispheric Model (DEHM) DEHM/ Urban Background Model (UBM) /AirGIS modeling system.[35] This modeling system calculates air pollution contributions from *a*) the regional background, modeled using the DEHM[36]; *b*) the local background, modeled using the UBM[37] covering Denmark in a 1×1 km grid; and *c*) traffic in the address street (modeled for streets with >500 vehicles per day), modeled using the Operational Street Pollution Model (OSPM®), which takes into account emission factors, traffic composition and intensity, meteorology, and street and building configurations.[35,38] We recently implemented modeling of particle number concentration, as an indicator for UFP (in this paper denoted as UFP), into the DEHM/UBM/AirGIS modeling system. In brief, the regional scale model, DEHM, was extended with the M7 aerosol dynamics module[39] to account for number concentrations of particles with a diameter <1 μm.[40] We furthermore developed models for estimating particle number concentrations at the local scale (UBM) and street scale (OSPM).[41] A validation of the model results with long-term UFP measurements in Denmark showed correlations of 0.86, 0.87, and 0.95 between measured and predicted annual averages at, respectively, the regional, urban, and street scale.[41] For $PM_{2.5}$, EC, and NO_2, correlation coefficients between measured and modeled air pollution (using DEHM/UBM/AirGIS) across various measurement periods and locations have been found to be, respectively, 0.67–0.85, 0.77–0.79, and 0.60–0.80.[42,43] Using the DEHM/UBM/AirGIS system, we estimated hourly address-specific concentrations (the modeling system operates at all scales in a 1-h time resolution) of the four air pollutants from 2000 through 2017, which we summarized into monthly averages for each address. We attached the monthly exposures to person-specific address histories and calculated person-specific time-weighted 5-y running means for the four exposures.

Sociodemographic Variables

All SES variables in the present study were collected from the nationwide registers that, based on yearly input from relevant authorities (e.g., the Danish tax authorities for income and all educational institutions for education), accumulate this information. From the registries at Statistics Denmark, we obtained information on a number of individual- and area-level SES variables, selected based on availability and findings of previous papers showing associations between the SES variables and the outcome of interest (T2D) as well as exposure to air pollution (see Directed Acyclic Graph in Figure S1 generated in DAGitty, version 3.0[44]).[45] More specifically, we obtained yearly individual-level information from 2005 to 2017 on highest attained education categorized as short (mandatory), medium (secondary/vocational), and long (e.g., university, nursing, and teaching) education, disposable individual income (calculated as calendar year and sex-specific quintiles based on the income distribution in the Danish population), occupational status (blue-collar, white-collar, unemployed/retired), cohabiting status ["live alone," corresponding to divorced/widowed/never-married persons who do not share address with others (except their children) and "cohabiting," corresponding to married people as well as people sharing address with one or more persons (except children)] and country of birth (Denmark, other). We also obtained yearly information on three neighborhood-level SES indicators: proportion of inhabitants in each parish with only basic education, with a non-Western background (corresponding to being born in a non-Western country), and with a criminal record. Furthermore, we obtained yearly information on population density within each parish (<100, 100 to <2,000, and ≥2,000 persons per square kilometer). In 2017, there were 2,160 Danish parishes with a median of 1,032 inhabitants and a mean size of 16 km^2.

We excluded all persons missing information on one or more of the SES variables described above from the study population.

Financial Stress and Comorbidity

We used the registers of Statistics Denmark to identify people experiencing one or more "financial stress event(s)" defined as family income below the Danish relative poverty limit (time-dependent), personal income drop of 50% or more between 2 consecutive years, family income drop of 50% or more between 2 consecutive years, and/or loss of job. Based on this approach, we created a time-dependent dichotomous variable of one or more financial stressful event(s) in the prior 5 y (yes/no).

Using the National Patient Registry,[30] we calculated a Charlson Comorbidity Index for all cohort members, which is a standard method of categorizing comorbidities of patients based on ICD codes.[46] The index was calculated as a time-dependent variable, summing up a score based on diseases during 5 previous years, calculated with a 1-y lag period (0–1 y; to ensure that the diagnosis of T2D did not impact the index). In analyses, we categorized the comorbidity index score into 0, 1, or ≥2.

Road Traffic Noise

We modeled road traffic noise at all residential addresses at the most exposed facade using the Nordic prediction method[47] for the years 2000, 2005, 2010, and 2015 as previously described.[48] Input variables included address-specific geocodes; height, road type, light/heavy vehicle distributions, travel speed, and annual average daily traffic for all Danish road links[38]; and screening effects from buildings, terrain, and noise barriers. We calculated noise as the equivalent A-weighted sound pressure level for day (0700–1900 hours), evening (1900–2200 hours) and night (2200–0700 hours) and aggregated it as L_{den}. We used linear interpolation between the 5-y exposure calculations to quantify exposure for all years in the period 2000–2017.

Green Space

We used BASEMAP02, which classifies land use in a high-resolution map of Denmark, to calculate area proportions of 36 land-use classes within a 1,000 meter radius around all addresses.[49,50] Green space of high quality was defined as forest, recreational areas, and wet/dry open nature areas.

Statistical Analyses

Correlations between air pollutants were calculated as Spearman's correlation coefficients. We calculated associations between 5-y exposure to air pollution and risk of T2D using two different models: Cox proportional hazard model and Aalen additive hazard model. Based on the Cox model we calculated hazard ratio (HR; relative risk estimate) and based on the Aalen model we calculated the rate difference per 100,000 person-years (absolute risk estimate). In both models, we included age as the underlying time scale (continuous), and air pollution was modeled as 5-y time-weighted running means. In brief, this modeling was done by calculating mean exposure for the 5 y before the T2D diagnosis for all cases, taking all present and historical addresses in this period into account (including exposure before baseline when relevant) and subsequently for each case, and then comparing this exposure with the 5-y exposure for all noncases at the exact same age as the case at the time of diagnosis.

In initial analyses based on the whole study population of people above 35 y of age (using the Aalen model), we observed that all four air pollutants were associated with higher risk of T2D, mainly among people between 50 and 80 y of age (Figure 1). We therefore restricted all main analyses to include only the 1,843,597 persons within this age group. Start of follow-up in all analyses was age 50 y or year 2005 (whichever came last), and people were censored at type 1 diabetes or T2D diagnosis, age 80 y, death, missing address, emigration, or end of follow-up (31 December 2017), whichever came first. Furthermore, we conducted additional analyses using the Cox model on the population age 35–50 y, including 1,300,108 persons, with start of follow-up at age 35 y or year 2005 and censoring at type 1 diabetes or T2D diagnosis, age 50 y, death, missing address, emigration, or end of follow-up (31 December 2017).

We calculated risk estimates for the association between air pollution and T2D adjusted for sex, calendar year (2-y categories), educational level, individual income, cohabiting status, country of birth, and occupation, as well as area-level proportion of inhabitants with only basic education, of non-Western background, and with a criminal record. Estimates were calculated per 5 $\mu g/m^3$ $PM_{2.5}$, 10 $\mu g/m^3$ NO_2, 1 $\mu g/m^3$ EC, and 10,000 particles/cm^3 for UFP. To examine the shape of the exposure–response relationship, we also analyzed associations between the four air pollutants and T2D among people age 50–80 y based on the Cox model in the following categories: <10th (reference group), 10th to <25th, 25th to <50th, 50th to <75th, 75th to <90th, 90th to <95th, and ≥95th percentiles.

For all four air pollutants, we investigated associations between air pollution and T2D in strata of sociodemographic variables (sex, education, income, occupation, and cohabiting status), financial stress (yes, no), comorbidity (Charlson Comorbidity Index; 0, 1, ≥2), population density (<100, 100 to <2,000, ≥2,000 persons/km^2), road traffic noise (<55, 55 to <60, ≥60 dB), and green space within 1,000 m (<9.8%, 9.8% to <17.6%, ≥17.6%).

Descriptive analyses and Cox proportional hazards model analyses were done in SAS 9.4 (SAS Institute Inc.) and Aalen additive hazard model analyses were performed in R (version 3.6.3; R Development Core Team).

Results

From the study base of 2,757,813 people, we excluded 13,535 persons with type 1 diabetes and 88,934 with T2D before baseline. Also, we excluded 23,856 persons missing information on one or more potential confounders. Of the remaining 2,631,488 persons, for the main analyses we excluded 787,891 persons who were below age 50 y at end of follow-up or above 80 y of age at start of follow-up. This approach yielded a study population of 1,843,597 persons with a median follow-up of 9.5 y during which 113,985 developed T2D. Also, we conducted additional analyses on a population of persons between 35–50 y of age, consisting of 1,300,108 persons, of whom 19,662 developed T2D.

We found that people exposed to UFP above the median were more likely to be women, live alone, have high income, have longer education, be of non-Danish origin, be retired/unemployed, and live in neighborhoods with a higher proportion of people with a non-Western background and a criminal record in comparison with people exposed to UFP below the median (Table 1; Table S1). T2D cases were more likely to be men, have a low SES, with low education and income, and working in blue-collar jobs, as well as have comorbidities in comparison with noncases (Table S2). The distributions of 5-y exposure to $PM_{2.5}$, UFP, EC, and NO_2 at baseline are shown in Figure S2, Table 1, and Table S3. UFP, EC, and NO_2 were found skewed to the right. The four air pollutants were correlated with $R_{Spearman}$ coefficients between 0.75 and 0.94 (Table 2).

In the main population of people age 50–80 y, exposure contrasts of 5 $\mu g/m^3$ $PM_{2.5}$, 10,000 UFP per cm^3, 1 $\mu g/m^3$ EC, and 10 $\mu g/m^3$ NO_2 were associated with a higher risk of incident

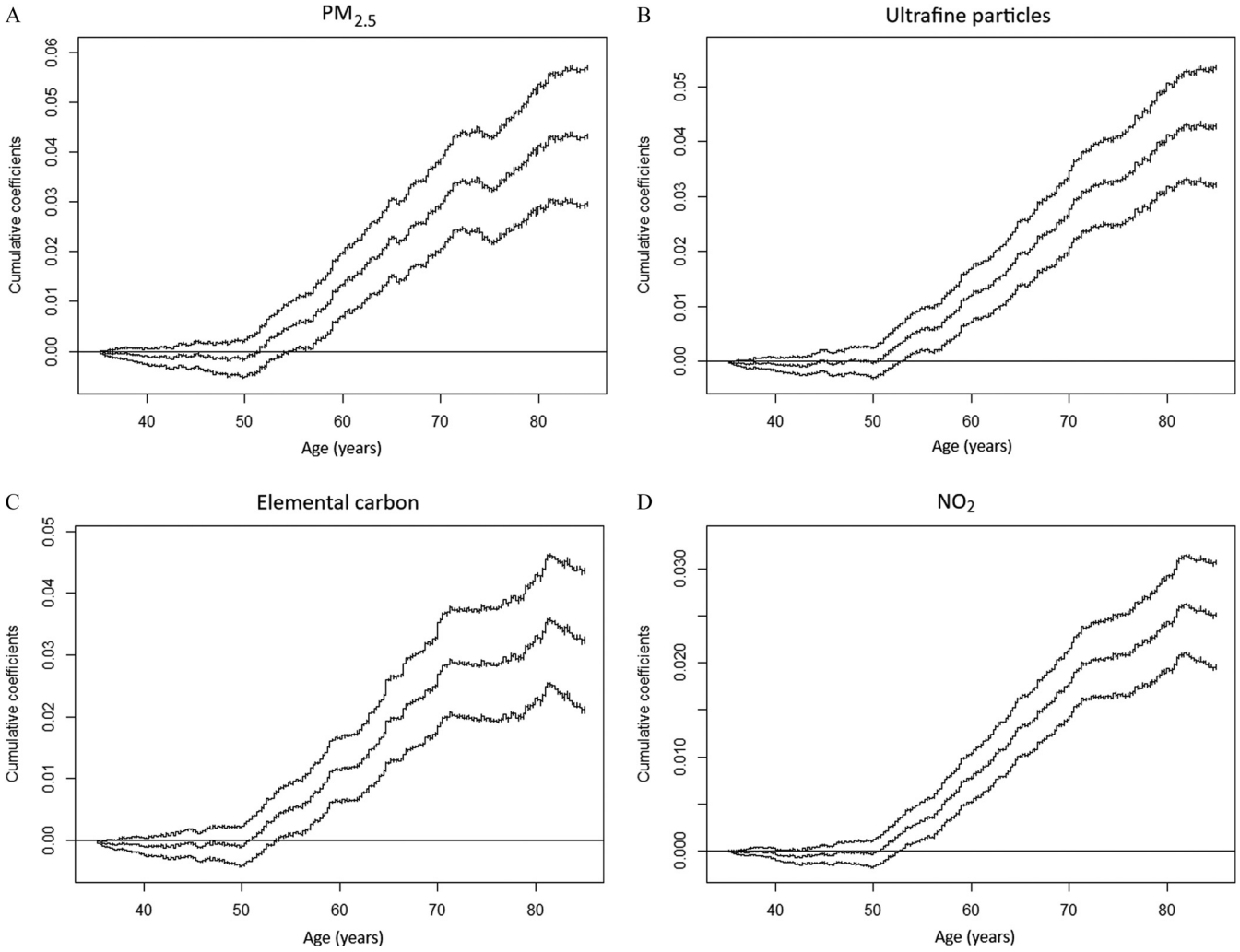

Figure 1. Associations between 5-y exposure to air pollution ($PM_{2.5}$, ultrafine particles, elemental carbon, and NO_2) and risk of type 2 diabetes according to age, expressed as cumulative coefficients (middle curve) with 95% confidence intervals (upper and lower curve).

T2D, with overall HRs 95% CI of 1.17 (95% CI: 1.13, 1.21), 1.16 (95% CI: 1.13, 1.19), 1.10 (95% CI: 1.08, 1.12) and 1.10 (95% CI: 1.08, 1.11), respectively, and overall rate differences of 123 (95% CI: 96, 150), 124 (95% CI: 104, 144), 102 (95% CI: 80, 124), and 73 (95% CI: 62, 85), respectively. Inspection of the exposure–response relationships between the four air pollutants and T2D indicated a linear relationship for EC and NO_2, whereas for $PM_{2.5}$ and UFP there were some indications of a leveling off at high exposures (Figure S3; Table S4). For all four air pollutants, the association with T2D was stronger among men in comparison with women and among people living with a partner in comparison with people living alone (Table 3). Similar trends were observed for relative (HR) and absolute (rate difference) risk estimates. We found lower risk estimates among people with high education in comparison with low/medium education. When comparing people with low vs. medium education, risk estimates were highest among people with medium education. For income, the risk estimates were generally highest in the medium category; one exception was $PM_{2.5}$, where similar size estimates were observed for people with medium and high income. No marked differences were observed between people working in white-collar vs. blue-collar occupations.

People with any financial stress during the last 5 y, such as job loss and an income below the poverty limit, were found to have lower air pollution-T2D risk estimates than people without such events (Table 4). We found stronger associations between air pollution and T2D among people with a comorbidity or comorbidities in comparison with no comorbidity; the association was strongest for people with a comorbidity score of ≥ 2. We found no consistent indications of effect modification by population density, road traffic noise, or surrounding green space across the four air pollutants.

In the population of people age 35–50 y, exposure contrasts of 5 $\mu g/m^3$ $PM_{2.5}$, 10,000 UFP per cm^3, 1 $\mu g/m^3$ EC, and 10 $\mu g/m^3$ NO_2 were associated with overall HRs of 1.05 (95% CI: 0.96, 1.14), 1.05 (95% CI: 0.99, 1.12), 1.05 (95% CI: 0.98, 1.13) and 1.02 (95% CI: 0.99, 1.06), respectively. We observed effect modification trends for the age 35–50 y population to be similar to those for those age 50–80 y [except for sex, where we found stronger association among women in comparison with that of men, and occupation, where we found stronger associations among blue-collar workers in comparison with those of white-collar workers (Tables S5–S6)].

Discussion

In a nationwide study of Denmark, we found that air pollution was associated with higher risk of T2D among people age 50–80 y in comparison with people age 35–50 y. In the population of people

Table 1. Baseline sociodemographic characteristics and exposures among the Danish study population of people age 50–80 y in the period from 2005–2017 according to baseline 5-y exposure to UFP below and above the median.

Baseline Characteristics	Cohort ($N = 1{,}843{,}597$)	UFP <11,064 particles/cm^3 ($n = 921{,}797$)	UFP ≥11,064 particles/cm^3 ($n = 921{,}800$)
Individual level			
Men (%)	47.7	49.4	46.4
Age [y (mean ± SD)]	58.9 ± 9.1	57.6 ± 8.9	60.3 ± 9.1
Cohabiting status (%)			
Cohabiting	74.9	79.0	70.9
Living alone	25.1	21.0	29.1
Individual income (%)			
Low (quintile 1)	23.8	24.0	23.6
Low-medium (quintile 2)	20.5	20.8	20.3
Medium (quintile 3)	17.0	18.3	15.6
Medium-high (quintile 4)	17.8	18.6	16.9
High (quintile 5)	21.0	18.4	23.5
Highest attained education (%)			
Mandatory education	34.8	36.8	32.7
Secondary or vocational education	46.1	46.5	45.7
Medium or long education	19.1	16.7	21.6
Country of birth (%)			
Danish	98.1	99.0	97.3
Other	1.9	1.0	2.7
Occupational status (%)			
Blue-collar	31.4	35.5	27.2
White-collar level	26.6	27.1	26.0
Retired or unemployed	42.1	37.4	46.8
Financial stress (%)			
Yes	17.8	18.9	16.7
No	82.2	81.1	83.4
Charlson Comorbidity Index (%)			
0	86.9	88.6	85.3
1	7.4	6.6	8.3
≥2	5.7	4.8	6.5
Address level			
Road traffic noise [5-y (%)]			
<55 dB	50.6	57.6	43.6
55 to <60 dB	21.6	20.0	23.1
≥60 dB	27.9	22.4	33.4
High-quality green space in 1,000 m (%)			
<9.8 %	34.0	38.2	29.8
9.8 to <17.6 %	33.4	30.0	36.8
≥17.6 %	32.6	31.8	33.5
Air pollution [5-y (mean ± SD)]			
$PM_{2.5}$ (μg/m^3)	10.9 ± 1.3	10.1 ± 1.1	11.6 ± 1.0
UFP (particles/cm^3)	11,578 ± 3,231	9,075 ± 1,316	14,082 ± 2,571
EC (μg/m^3)	0.70 ± 0.29	0.54 ± 0.10	0.87 ± 0.31
NO_2 (μg/m^3)	16.5 ± 5.9	12.5 ± 2.5	20.5 ± 5.6
Area level			
Area-level SES (mean ± SD)			
% with only basic education	10.3 ± 3.4	11.2 ± 3.3	9.5 ± 3.3
% non-Western background	5.2 ± 6.0	3.3 ± 3.9	7.1 ± 7.0
% with criminal record	0.49 ± 0.31	0.40 ± 0.25	0.57 ± 0.34
Population density			
<100/km^2	26.7	47.4	6.0
100 to <2,000/km^2	55.2	48.6	61.8
≥2,000/km^2	18.2	4.1	32.2

Note: EC, elemental carbon; SD, standard deviation; SES, socioeconomic status; UFP, ultrafine particles.

age 50–80 y, we found higher risk estimates among men in comparison with women and a pattern of higher risk estimates among people with low or medium education (highest for medium education) in comparison with high education, among people with medium income vs. low or high income, among people living with a partner vs. living alone, among people with comorbidities vs. without comorbidities, and among people without financial stress vs. people with financial stress. No marked changes in risk estimates were observed according to occupation, population density, road traffic noise, and surrounding green space. We observed similar tendencies among people 35–50 y of age, except in relation to sex and occupation, where we observed associations with air pollution only among women and blue-collar workers. The results showed similar tendencies for relative and absolute risk estimates.

For all four exposures, we observed weaker associations with risk of T2D among people age 35–50 y in comparison with people age 50–80 y. A potential explanation is that a diagnosis of T2D at a young age may have a stronger genetic component than diabetes later in life, and therefore environmental pollutants like air pollution may play a minor role in the development of diabetes in this age group. Also, there could be a higher degree of outcome misclassification among people below 50 y of age, e.g., the general practitioner (GP) may be less likely to test for T2D in younger patients, because the disease is less frequent in this age group.

Table 2. Spearman correlations between 5-y exposure to $PM_{2.5}$, ultrafine particles, elemental carbon, and NO_2 for the main study population (ages 50–80 y) in 2005 ($N = 1{,}252{,}432$).

	$PM_{2.5}$	Ultrafine particles	Elemental carbon	NO_2
$PM_{2.5}$	1	0.75	0.75	0.79
Ultrafine particles	0.75	1	0.90	0.92
Elemental carbon	0.75	0.90	1	0.94
NO_2	0.79	0.92	0.94	1

The previous studies investigating associations between air pollution and metabolic syndrome/T2D according to sex are inconsistent, with some studies reporting the highest risk estimates for men[16,21] and others for women,[14,15] whereas some studies report no difference.[9,22] We found the association between all four air pollutants and T2D to be stronger among men, especially for the absolute risk estimates, where the rate differences were 3–7 times higher in comparison with women. It is unclear whether these differences are caused by socially derived differences in exposure according to gender, by physiological differences related to sex, or a combination of these.[20] Previous studies observing stronger associations between air pollution and T2D among women in comparison with men, suggested that it may be due to less exposure misclassification in women, because they may spend more time at home (where exposure is modeled).[14] However, in Denmark both parents usually work when bringing up their children, and thus fewer differences according to time spend at home are expected in our population. Therefore societal differences across countries may partly explain differences in results across studies. The physiological differences between men and women that could lead to different risk in association with air pollution are numerous, such as differences in lung size, in deposition of particles, and in inflammatory responses.[20,51] Also, men have a higher incidence of T2D and comorbidities, such as cardiovascular disease, than women, partly due to a protective effect of estrogen.[52,53] It is therefore possible that men due to inherent sex-related physiological differences are more susceptible to the hazardous effects of air pollution. An interesting finding was that in the subpopulation of people age 35–50 y, air pollution was associated with higher risk of T2D only among women, whereas no associations were observed among men. These opposite findings in different age groups may partly explain inconsistencies in previous studies with regard to effect modification by sex.

We observed that air pollution was associated with a lower risk of T2D in people with long education in comparison with people with short or medium education, which was most pronounced for the absolute risk estimates. Only a few studies have investigated associations between air pollution and T2D in different strata of education, with one study reporting highest risk estimates among people with high education[16] and two studies observing slightly lower risk estimates among the highly educated.[14,15] Two of these studies investigated only two levels of education, an approach that may be too crude to capture the potentially complex relationship between SES, air pollution, and T2D. Having a short or medium education is associated with a lifestyle that is less healthy than that of people with a long education, e.g., physical inactivity, smoking, and high BMI.[54] These are all risk factors for T2D, which are believed harmful through some of the same mechanistic pathways as air pollution, including oxidative stress and systemic inflammation.[18,19] It is possible that people with an unhealthy lifestyle are more susceptible to the harmful effects of air pollution because their systems are already challenged, which could explain the lower risk found among the highly educated in our study.

We found that air pollution was associated with lower risk of T2D among people with short education in comparison with

Table 3. Association between air pollution and incidence of type 2 diabetes by sociodemographic factors.

		$PM_{2.5}$ (per 5 $\mu g/m^3$)		UFP (per 10,000 particles/cm^3)		Elemental carbon (per 1 $\mu g/m^3$)		NO_2 (per 10 $\mu g/m^3$)	
	n cases	Cox model HR (95% CI)[a]	Aalen model Rate (per 100,000 py) difference (95% CI)[a,b]	Cox model HR (95% CI)[a]	Aalen model Rate (per 100,000 py) difference (95% CI)[a,b]	Cox model HR (95% CI)[a]	Aalen model Rate (per 100,000 py) difference (95% CI)[a,b]	Cox model HR (95% CI)[a]	Aalen model Rate (per 100,000 py) difference (95% CI)[a,b]
All	113,985	1.17 (1.13, 1.21)	123 (96, 150)	1.16 (1.13, 1.19)	124 (104, 144)	1.10 (1.08, 1.12)	102 (80, 124)	1.10 (1.08, 1.11)	73 (62, 85)
Sex									
Men	65,245	1.23 (1.18, 1.28)	198 (165, 232)	1.22 (1.19, 1.26)	210 (183, 279)	1.12 (1.10, 1.15)	183 (147, 220)	1.13 (1.11, 1.15)	119 (104, 134)
Women	48,740	1.09 (1.04, 1.14)	51 (23, 79)	1.07 (1.04, 1.11)	47 (25, 69)	1.03 (1.00, 1.07)	26 (2, 49)	1.06 (1.04, 1.08)	37 (26, 49)
Education									
Short	49,162	1.12 (1.07, 1.17)	96 (58, 133)	1.12 (1.08, 1.16)	121 (90, 152)	1.07 (1.04, 1.10)	101 (66, 136)	1.08 (1.06, 1.10)	75 (57, 92)
Medium	50,992	1.24 (1.19, 1.30)	169 (138, 199)	1.23 (1.19, 1.27)	172 (147, 196)	1.12 (1.10, 1.15)	147 (113, 181)	1.14 (1.12, 1.16)	103 (90, 117)
Long	13,831	1.10 (1.02, 1.19)	48 (12, 84)	1.05 (0.99, 1.11)	16 (−12, 44)	0.98 (0.92, 1.06)	−25 (−58, 8)	1.04 (1.01, 1.07)	14 (−1, 29)
Disposable income									
Quintile 1 (low)	41,633	1.12 (1.07, 1.17)	71 (30, 112)	1.11 (1.07, 1.15)	89 (56, 122)	1.05 (1.02, 1.09)	59 (23, 96)	1.07 (1.05, 1.09)	56 (38, 75)
Quintile 2–4	60,530	1.20 (1.15, 1.25)	140 (111, 170)	1.20 (1.16, 1.23)	147 (122, 171)	1.13 (1.11, 1.16)	141 (109, 173)	1.13 (1.11, 1.15)	90 (77, 103)
Quintile 5 (high)	11,822	1.23 (1.14, 1.33)	141 (103, 179)	1.15 (1.08, 1.22)	93 (63, 122)	1.06 (0.99, 1.13)	54 (18, 88)	1.08 (1.04, 1.11)	51 (35, 67)
Occupation									
White-collar	14,107	1.27 (1.18, 1.36)	194 (157, 231)	1.19 (1.12, 1.25)	138 (109, 167)	1.15 (1.09, 1.21)	141 (106, 175)	1.12 (1.09, 1.15)	78 (62, 94)
Blue-collar	21,423	1.20 (1.13, 1.27)	199 (161, 236)	1.26 (1.21, 1.32)	209 (177, 240)	1.15 (1.11, 1.19)	206 (171, 242)	1.16 (1.14, 1.19)	122 (105, 139)
Cohabiting status									
Cohabiting	78,945	1.22 (1.17, 1.26)	141 (113, 168)	1.20 (1.17, 1.24)	145 (123, 167)	1.11 (1.09, 1.14)	126 (100, 152)	1.14 (1.13, 1.16)	101 (89, 113)
Living alone	35,040	1.08 (1.03, 1.13)	67 (29, 105)	1.07 (1.04, 1.11)	70 (40, 101)	1.03 (0.99, 1.07)	45 (6, 84)	1.04 (1.02, 1.06)	27 (12, 43)

Note: CI, confidence interval; HR, hazard ratio; py, person-years.
[a]Analyses were adjusted for age, sex, calendar year, education, cohabiting status, personal income, country of birth, and area-level percentage of population with only basic education, with non-Western background, and with criminal record.
[b]Risk estimates calculated in Aalen additive hazard model is given as a rate difference per 100,000 py.

Table 4. Association between air pollution and incidence of type 2 diabetes by financial stress, comorbidity, population density, road traffic noise and surrounding green space.

		$PM_{2.5}$ (per 5 μg/m^3)		UFP (per 10,000 particles/cm^3)		Elemental carbon (per 1 μg/m^3)		NO_2 (per 10 μg/m^3)	
	N cases	Cox model HR (95% CI)[a]	Aalen model Rate (per 100,000 py) difference (95% CI)[a,b]	Cox model HR (95% CI)[a]	Aalen model Rate (per 100,000 py) difference (95% CI)[a,b]	Cox model HR (95% CI)[a]	Aalen model Rate (per 100,000 py) difference (95% CI)[a,b]	Cox model HR (95% CI)[a]	Aalen model Rate (per 100,000 py) difference (95% CI)[a,b]
All	113,985	1.17 (1.13, 1.21)	123 (96, 150)	1.16 (1.13, 1.19)	124 (104, 144)	1.10 (1.08, 1.12)	102 (80, 124)	1.10 (1.08, 1.11)	73 (62, 85)
Financial stress[c]									
Yes	19,290	1.05 (0.98, 1.11)	52 (6, 98)	1.08 (1.03, 1.13)	77 (39, 115)	1.03 (0.97, 1.08)	41 (−3, 85)	1.05 (1.02, 1.08)	40 (20, 61)
No	94,695	1.20 (1.15, 1.24)	133 (106, 159)	1.18 (1.15, 1.21)	131 (110, 152)	1.11 (1.08, 1.13)	114 (89, 139)	1.11 (1.09, 1.13)	81 (70, 92)
Charlson Comorbidity Index[d]									
0	77,432	1.04 (1.00, 1.08)	34 (8, 60)	1.09 (1.06, 1.12)	63 (44, 83)	1.07 (1.05, 1.10)	62 (40, 85)	1.08 (1.06, 1.09)	50 (40, 61)
1	18,592	1.28 (1.20, 1.36)	308 (230, 386)	1.19 (1.14, 1.25)	250 (184, 315)	1.08 (1.03, 1.13)	133 (57, 208)	1.07 (1.04, 1.10)	74 (38, 1,109)
≥2	17,961	1.40 (1.31, 1.49)	441 (360, 522)	1.26 (1.20, 1.32)	338 (270, 405)	1.12 (1.08, 1.16)	255 (166, 344)	1.13 (1.10, 1.16)	155 (117, 192)
Population density									
<100/km^2	29,689	1.09 (1.04, 1.16)	74 (35, 113)	1.12 (1.06, 1.18)	103 (56, 150)	1.05 (1.02, 1.09)	56 (12, 101)	1.13 (1.09, 1.18)	97 (65, 129)
100 to <2,000/km^2	63,665	1.16 (1.11, 1.21)	109 (78, 141)	1.15 (1.11, 1.18)	111 (85, 136)	1.10 (1.07, 1.14)	98 (67, 129)	1.13 (1.11, 1.15)	94 (78, 109)
≥2,000/km^2	20,631	1.21 (1.14, 1.28)	144 (101, 188)	1.17 (1.12, 1.23)	127 (93, 162)	1.16 (1.10, 1.22)	122 (82, 162)	1.06 (1.04, 1.09)	50 (34, 66)
Road traffic noise									
<55 dB	55,998	1.12 (1.07, 1.18)	87 (55, 119)	1.14 (1.10, 1.18)	103 (77, 130)	1.11 (1.06, 1.16)	93 (54, 132)	1.13 (1.10, 1.16)	89 (69, 108)
55 to <60 dB	24,918	1.18 (1.11, 1.25)	125 (82, 169)	1.16 (1.11, 1.21)	121 (86, 156)	1.05 (1.01, 1.09)	56 (21, 92)	1.12 (1.08, 1.15)	85 (62, 107)
≥60 dB	33,069	1.15 (1.10, 1.21)	118 (83, 153)	1.15 (1.11, 1.19)	123 (95, 150)	1.09 (1.07, 1.12)	100 (68, 131)	1.08 (1.06, 1.10)	61 (48, 74)
High-quality green space within 1,000 m[e]									
<9.8 %	38,931	1.14 (1.08, 1.20)	104 (69, 139)	1.13 (1.09, 1.17)	106 (78, 134)	1.14 (1.09, 1.20)	111 (74, 148)	1.08 (1.06, 1.10)	59 (44, 74)
9.8 to <17.6 %	38,953	1.16 (1.11, 1.22)	118 (82, 154)	1.14 (1.10, 1.18)	110 (81, 138)	1.16 (1.11, 1.21)	126 (89, 163)	1.09 (1.07, 1.11)	68 (53, 83)
≥17.6 %	36,101	1.18 (1.12, 1.24)	121 (87, 156)	1.19 (1.15, 1.24)	148 (119, 177)	1.08 (1.05, 1.10)	80 (50, 110)	1.13 (1.10, 1.15)	93 (76, 109)

Note: CI, confidence interval; HR, hazard ratio; py, person-years; UFP, ultrafine particles.

[a]Analyses were adjusted for age, sex, calendar year, education, cohabiting status, personal income, country of birth, and area-level percentage of population with only basic education, with non-Western background, and with criminal record.

[b]Risk estimates calculated in Aalen additive hazard model is given as a rate difference per 100,000 py.

[c]Financial stress was defined as ≥1 of the following events during the last 5 years: family income below Danish relative poverty limit, personal income drop of ≥50% between two consecutive years, family income drop of ≥50% between two consecutive years and/or loss of job.

[d]Comorbidity defined as a Charlson Comorbidity Index of 0, 1, or ≥2 during the last 1–6 y with a lag-period of 1 y.

[e]Green space defined as the proportion of recreational areas, forest and wet/dry open nature areas within 1,000 m of the residence.

people with a medium education. A similar pattern was observed for income. Although it seems counterintuitive that the people with the lowest education and income are less susceptible to the harmful effects of air pollution than groups with higher SES, outcome misclassification may be part of the explanation: At least 24% of all T2D cases in Denmark are estimated to be undiagnosed.[55] It is well known that, even in countries like Denmark with free health care for all residents, people with low SES are less likely to visit a GP for regular examinations or act on mild symptoms, such as frequent urination, weight loss, and fatigue, which are early symptoms of T2D.[56–58] Therefore, they will in general be diagnosed later than people with higher SES. If such delay of a diagnosis last for several years, the 5-y exposure time window preceding the diagnosis (or part of it), which we applied in the present study, will also cover exposure after the person should have been censored, and thus result in exposure misclassification, which potentially could drive the risk estimates toward the null. In support, we also observed lower risk estimates between air pollution and T2D among people experiencing one or more "financial stress events," which is a group of people who potentially have reduced "resources" to act on mild symptoms, as well as among people living alone, and therefore with no spouse to encourage seeking health care.[59]

Previous studies investigating comorbidity as a potential modifier of the association between air pollution and T2D are inconsistent, with some studies reporting stronger associations among people without COPD,[9] myocardial infarction,[9,14,15] and/or hypertension,[9,14] whereas others report stronger associations in people with COPD[14,15] and/or hypertension.[15] We found that air pollution was associated with a substantially higher risk of T2D in people with comorbidities (assessed by the Charlson Comorbidity Index) in comparison with people without comorbidity. Furthermore, risk estimates were higher among people with a score of ≥ 2 compared to a score of 1. Part of the explanation is probably that people with, e.g., cardiovascular disease or COPD are automatically tested for T2D when hospitalized. There will, therefore, be fewer persons with undiagnosed T2D among people with comorbidities than among people without comorbidities and thus lower risk of outcome misclassification in this group. However, the difference in risk estimates for $PM_{2.5}$ and UFP exposure among people with and without comorbidities is substantial, and it seems unlikely that outcome misclassification is the only explanation. Another explanation might be that comorbidities like cardiovascular disease, COPD, and asthma are characterized by systemic inflammation and/or oxidative stress, e.g., as a result of an unhealthy lifestyle and high BMI, which could make people with these diseases more vulnerable to the harmful effect of air pollution, because air pollution is believed to be harmful through the same biological pathways.[17]

We have previously found noise to be associated with T2D, with a HR of 1.03 (95% CI: 1.02–1.03) per 10 dB higher road traffic noise based on the entire Danish population (>35 y).[24] However, although previous studies have suggested that noise can be hazardous through similar mechanisms as air pollution,[26] our study does not suggest that noise exposure can modify the association between air pollution and T2D. Also, we found no marked differences in risk estimates according to the level of green space around the home address, suggesting that although previous studies have found greenness to be associated with a lower risk of T2D,[27] it does not protect against the harmful effects of air pollution on risk for T2D.

A strength of the present study is the nationwide design, which minimized the risk of selection bias, and a large number of T2D cases identified using high-quality hospital and prescription registries.[30,31] Furthermore, we obtained information on individual- and area-level SES covariates, comorbidity, financial stress, and residential address history from 2000–2017, using high-quality nationwide registries, and estimated air pollution and road traffic noise using validated models with high spatial resolution and high-quality input data.[35]

Limitations include the large proportion of people with undiagnosed T2D not captured in the present study. A validation study estimated that approximately 24% in Denmark had undiagnosed T2D.[55] However, that study applied a different identification of T2D, including data from the Health Services Register (diabetic foot therapy) and two clinical databases in addition to the Patient and Prescription registries used in the present study. Although results are thus not directly comparable, it is unlikely that the percentage of undiagnosed T2D cases in the present study deviates substantially from the results obtained by Jørgensen et al.[55] Outcome misclassification may be differential because people with low SES more often live with undiagnosed T2D (as described above). Another limitation is the lack of information on lifestyle covariates, especially adiposity. We, however, adjusted for various socioeconomic variables, which are associated with lifestyle. Furthermore, we recently conducted a study on long-term exposure to NO_2 and $PM_{2.5}$ and risk of T2D using a questionnaire-based cohort of 250,000 participants randomly selected across Denmark and with information on lifestyle habits.[13] We found that after adjusting for various register-based individual- and area-level covariates (similar to the present study), further adjustment for lifestyle, resulted in only small changes in HRs, e.g., for $PM_{2.5}$ the HR was 1.27 before and 1.24 after lifestyle adjustment, including smoking status, BMI and physical activity and intake of fruit, vegetables, and red meat. Limitations also include the lack of information on nonresidential exposure to air pollution, e.g., during work. We expect such misclassification to be mainly unrelated to T2D and draw the estimates toward the null. Another limitation is that the indicators of green space, financial stress, and comorbidities used in the present study are based on objective register-based data that may not capture all relevant aspects of these factors. Last, although our study was based on the entire Danish population and we thus believe that our results can be generalized to other Western populations, differences in, e.g., genetics, air pollution sources, and concentrations of air pollution have to be considered when generalizing the results.

In conclusion, we found men and individuals with preexisting comorbidities to be highly susceptible to the harmful effect of air pollution in relation to T2D, whereas people with high SES were less susceptible than people with lower SES. These findings suggest that the health burden of air pollution is not evenly distributed.

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The data that support the findings of this study are available from Statistics Denmark (and only at a secure server at Statistics Denmark). However, restrictions apply to the availability of these

data, which were used under license for the current study, and therefore are not publicly available. Access to data requires permission from Statistics Denmark and the Danish Cancer Society.

The present study is strictly register based, with no contact with the participants. According to Danish legislation, no ethical permission or informed consent is needed for strictly register-based studies.

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