Association of Long-Term Air Pollution with Prevalence and Incidence of Distal Sensorimotor Polyneuropathy: KORA F4/FF4 Study

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BACKGROUND: Air pollution contributes to type 2 diabetes and cardiovascular diseases, but its relevance for other complications of diabetes, in particular distal sensorimotor polyneuropathy (DSPN), is unclear. Recent studies have indicated that DSPN is also increasingly prevalent in obesity.

OBJECTIVES: We aimed to assess associations of air pollutants with prevalent and incident DSPN in a population-based study of older individuals with high rates of type 2 diabetes and obesity.

METHODS: Cross-sectional analyses on prevalent DSPN were based on 1,075 individuals 62–81 years of age from the German Cooperative Health Research in the Region of Augsburg (KORA) F4 survey (2006–2008). Analyses on incident DSPN included 424 individuals without DSPN at baseline (KORA F4), of whom 188 had developed DSPN by the KORA FF4 survey (2013–2014). Associations of annual average air pollutant concentrations at participants’ residences with prevalent and incident DSPN were estimated using Poisson regression models with a robust error variance adjusting for multiple confounders.

RESULTS: Higher particle number concentrations (PNCs) were associated with higher prevalence [risk ratio (RR) per interquartile range (IQR) increase = 1.10 (95% CI: 1.01, 1.20)] and incidence [1.11 (95% CI: 0.99, 1.24)] of DSPN. In subgroup analyses, particulate (PM2.5*, PM10, PM10,ª, and PM2.5,abs) and gaseous (NOx, NO2) pollutants were positively associated with prevalent DSPN in obese participants, whereas corresponding estimates for nonobese participants were close to the null [e.g., for an IQR increase in PM2.5,abs, RR = 1.17 (95% CI: 1.05, 1.31)] vs. 1.06 (95% CI: 0.95, 1.19); Pinteraction = 0.22]. With the exception of PM2.5,abs, corresponding associations with incident DSPN were positive in obese participants but null or inverse for nonobese participants, with Pinteraction ≤ 0.13 [e.g., for PM2.5,abs, RR = 1.28 (95% CI: 1.08, 1.51)] vs. 1.03 (95% CI: 0.90, 1.18); Pinteraction = 0.03].

DISCUSSION: Both particulate and gaseous air pollutants were positively associated with prevalent and incident DSPN in obese individuals. Obesity and air pollution may have synergistic effects on the development of DSPN. https://doi.org/10.1289/EHP7311

Introduction

Multiple studies have indicated that air pollution contributes to the development of type 2 diabetes (Krämer et al. 2010; Wolf et al. 2016; Yang et al. 2020). Exposure to higher levels of air pollutants, such as particulate matter (PM) of various sizes and nitrogen oxides [nitrogen dioxide (NO2), nitrogen oxides (NOx)], is also related to a higher risk of cardiovascular disease (CVD) (Rajagopalan et al. 2018), which represents a common complication of diabetes with high clinical relevance. From a public health perspective, it is noteworthy that these associations of air pollution with cardiometabolic disease or mortality can be observed even below the Air Quality Guidelines of the World Health Organization (WHO), underlining the potential role of this environmental risk factor at both the individual- and the population-
based level (Rajagopalan et al. 2018). However, similar studies on other complications and comorbidities of diabetes are extremely limited.

Distal sensorimotor polyneuropathy (DSPN) is one of the most frequent comorbidities of type 2 diabetes, with a lifetime prevalence of at least 50% in individuals with type 2 diabetes (Pop-Busui et al. 2017). Diabetes is traditionally considered as the main risk factor of DSPN, but aggressive blood glucose lowering has not reduced the incidence of DSPN in large intervention studies (Pop-Busui et al. 2017), pointing toward additional risk factors beyond hyperglycemia. Prediabetes, obesity, and old age have emerged as additional determinants of DSPN, but they fail to explain a substantial part of the risk to develop DSPN (Ziegler et al. 2014; Böhnhof et al. 2019; Andersen et al. 2018; Schlesinger et al. 2019). In particular, there have been neither cross-sectional nor prospective studies on potential environmental toxins that might contribute to the increasing burden of DSPN in patients with diabetes, obesity, and old age.

Inflammatory processes have been proposed as mediators between air pollution and the development of type 2 diabetes or CVD, but other mechanisms, including oxidative stress, endothelial activation, and autonomic imbalance and the activation of the hypothalamic–pituitary axis, may also be involved (Rajagopalan and Brook 2012; Rajagopalan et al. 2018). Because systemic subclinical inflammation contributes to the development of complications of type 2 diabetes, including DSPN (Jha et al. 2018; Donath et al. 2019; Herder et al. 2018; Herder and Hermanns 2019), it can be hypothesized that exposure to air pollution may also be involved.

Of note, several studies have suggested that exposure to air pollution may not have uniform effects but, rather, it affects obese individuals and people with diabetes to a disproportionate extent (Weichenthal et al. 2014; Sacks et al. 2011). Given that obesity and type 2 diabetes are proinflammatory states, it is relevant to investigate to what extent air pollution as an example of an environmental stimulus that is known to fuel inflammation has additive or even synergistic effects on the risk of DSPN when combined with obesity or type 2 diabetes.

Therefore, the aims of this study were a) to assess the cross-sectional association between different air pollutants and prevalent DSPN in a large population-based study, b) to estimate the association between air pollutants and incident DSPN in a prospective design, and c) to test the hypothesis that individuals with obesity or type 2 diabetes are particularly susceptible to the exposure to air pollution regarding the development of DSPN.

Methods

Study Design and Participants

The design of the German Cooperative Health Research in the Region of Augsburg (KORA) studies has been reported in detail (Rathmann et al. 2009; Herder et al. 2017). Briefly, this analysis used data from KORA F4 (2006–2008) and FF4 studies (2013–2014), which are both follow-up examinations of the population-based KORA S4 survey (1999–2001) conducted in the city of Augsburg (Germany) and the two adjacent counties, Augsburg and Aichach-Friedberg.

The KORA S4, F4, and FF4 surveys were carried out in accordance with the Declaration of Helsinki. This included written informed consent from all participants and approval of the surveys by the ethics board of the Bavarian Chamber of Physicians (Munich, Germany).

As shown in Figure S1, of 1,161 participants of the KORA F4 study 62–81 years of age (i.e., the age group in which DSPN was assessed), 28 were excluded due to prevalent type 1 diabetes, diabetes forms other than type 1 or type 2, or unclear glucose tolerance status; 8 because blood samples were taken during a non-fasting state; 41 because of missing baseline values for the outcome variable; and 9 because of missing baseline values for the covariates in the main model [age, sex, years of education, neighborhood socioeconomic status (SES), smoking status, alcohol consumption, physical activity, height, or waist circumference or total cholesterol, hemoglobin A1c (HbA1c), and uric acid levels]. This left 1,075 participants in KORA F4 for the cross-sectional analysis on prevalent DSPN.

In the analysis of incident DSPN, 448 participants were further excluded because of nonparticipation in KORA FF4 (2013–2014) for various reasons (death, moved out of study area, refused, too ill, not interested, too busy to participate, or could not be contacted), leaving 627 individuals who participated in both KORA F4 and FF4. From those, we had to exclude 20 because of missing data for the Michigan Neuropathy Screening Instrument (MNSI) score in KORA FF4 and 183 because of prevalent DSPN (MNSI ≥2) in KORA F4. This left 424 individuals without DSPN in F4, of whom 188 developed incident DSPN while 236 remained DSPN-free. The mean duration of follow-up ± standard deviation (SD) was 6.46 ± 0.21 y.

Assessment of DSPN

DSPN was assessed using the clinical examination part of the MNSI, which included items on the appearance of feet, foot ulceration, ankle reflexes, and vibration perception threshold at the great toes using the Rydel-Seiffer graduated C 64 Hz tuning fork (Feldman et al. 1994). Age-dependent limits were used to classify normal vibration perception thresholds (Martina et al. 1998). The MNSI was extended by bilateral examination of touch/pressure sensation using a 10-g monofilament (Neuropen®) (Boyraz and Saracoglu 2010; Herder et al. 2017), such that the total MNSI score ranged from 0 to 10 points. Prevalent and incident DSPN were defined using a diagnostic cutoff of >2 points as previously suggested (Feldman et al. 1994; Lunetta et al. 1998; Moghtaderi et al. 2006; Herder et al. 2009). This definition meets the diagnostic criteria for possible DSPN according to the Toronto Diabetic Neuropathy Expert Group.

Assessment of Air Pollution

Individual annual average concentrations of air pollutants at residences were estimated by land-use regression (LUR) models within the Environmental Nanoparticles and Health: Exposure, Modeling, and Epidemiology of Nanoparticles and their Composition project (Wolf et al. 2016). We carried out three bi-weekly measurements at 20 locations within the KORA study area between March 2014 and April 2015, covering the warm, cold, and intermediate seasons. Thus, the assessment of air pollution was performed later than the baseline examination for DSPN. However, spatial differences of air pollution are known to remain stable over periods of ≥10 y (Eeftens et al. 2011; Wang et al. 2013), so the risk of exposure misclassification should be low. In order to adjust the discontinuous measurements to the annual average, a reference site was operated continuously throughout the whole measurement period. LUR models were developed based on the adjusted annual average concentrations of air pollutants at monitoring sites and potential predictors of exposure—including digital road network, land use, building and population density, and altitude—gathered from European-wide and local Geographic Information System databases. The following air pollutants were modeled: number concentrations of particles with an aerodynamic diameter ≤100 nm (PNC; an indicator for ultrafine particles) and mass concentrations of PM with an aerodynamic
Assessment of Covariates

The assessment of anthropometric, metabolic, and lifestyle factors has been described previously (Rathmann et al. 2009; Herder et al. 2017). Briefly, anthropometric measurements (height, weight, and waist circumference) were taken after removing shoes and heavy clothing. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters squared). Obesity was defined as a BMI ≥30 kg/m². Waist circumference was measured at the level midway between the lower rib margin and the iliac crest. Abdominal obesity was defined as a waist circumference ≥102 cm for men and ≥88 cm for women.

Smoking status, alcohol consumption, physical activity, and education were assessed in standardized interviews by trained staff. Smoking status was categorized into three categories: current smokers (comprising regular and occasional smokers), past smokers, and never smokers. Alcohol consumption was assessed by asking how much beer, wine, or spirits study participants had consumed on the previous workday and during the previous weekend. This information was used to calculate alcohol intake in grams per day. The physical activity level was estimated using two four-category interview questions about the amount of time per week spent on sports activities during leisure time in the summer and winter (0, <1, 1–2, and >2 h sport/wk); the summer and winter responses were combined into one physical activity variable comprising four categories. For the present analysis, study participants were assigned to the following categories: low (no or almost no physical activity), moderate (physical activity of about 1 h/wk), or high (regular physical activity of ≥2 h/wk in both seasons). Years of education were derived by combining information on the highest level of vocational training and of school graduation.

Glucose tolerance status was assessed with oral glucose tolerance tests (OGTTs) (Rathmann et al. 2009). Glucose levels were measured using the hexokinase method on a Dimension® RxL instrument (Dade Behring). HbA1c levels were measured using cation-exchange high-performance liquid chromatographic, photometric assays on an Adams HA 8,160 Hemoglobin Analysis System (Menarini Diagnostics). Serum lipids were measured in KORA F4 using a Dimension® RxL instrument (Dade Behring). Serum concentrations of uric acid were measured on fresh samples by the uricase method (enzymatic color test, URCA Flex®; Dade Behring). The calculation of the estimated glomerular filtration rate (eGFR) was performed using the chronic kidney disease epidemiology creatinine equation (Inker et al. 2012).

Neighborhood SES was assessed by the percentage of households with a monthly income of <1,250 € in a 500 × 500 m grid cell based on the income score of the AZ Germany Raster calculated by WiGeoGIS GmbH for 2008 (https://www.wigeogis.com/en/market_data_geographical_grid_germany). The AZ Germany Raster is a fixed raster for Germany that is compliant with the Infrastructure for Spatial Information in the European Community directive, and the respective raster values were extracted at the participants’ residences.

History of CVD was defined as the presence of hypertension or a history of myocardial infarction or stroke. Hypertension was defined as a current blood pressure ≥140/90 mmHg or self-reported use of antihypertensive medications given that the participants were aware of having hypertension. Data for the history of myocardial infarction or stroke were based on self-reported physician diagnoses requiring hospital treatment. Neurological conditions that may cause nerve damage comprised mainly herniated vertebral disks but also complications related to previous strokes or sciatica that were self-reported in a standardized interview (Herder et al. 2015).

Data on the use of medications and supplements were collected through a database-supported computer software (Instrument for Databased Assessment of Medication) (Mühlberger et al. 2003). Participants were asked to bring all product packages of ingested medications and supplements to the study center. The inquiry period covered the last 7 d prior to the interview, and data on the participants’ mode of ingestion (regularly or irregularly, i.e., as needed), mode of prescription (prescribed, recommended by physician, self-medication), dosage, and frequency of ingestion were collected for each medication or supplement. The pharmaceutical products were classified according to the Anatomical Therapeutic Chemical Classification System. The use of lipid-lowering medication and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) refer to the regular use of these drugs.

Statistical Analysis

Baseline characteristics of the study participants are given as mean ± SD for continuous variables and as frequency (percent) for categorical variables. p-Values for the difference between subgroups with and without incident DSPN were derived using Kruskal-Wallis rank sum tests for continuous variables and chi-square tests of independence for categorical variables. Correlations between baseline concentrations of air pollutants were estimated using Spearman’s correlation coefficients.

Associations of air pollutants with prevalent and incident DSPN were assessed using Poisson regression models with a robust error variance. We adjusted for different sets of covariates measured in KORA F4 with increasing complexity (Herder et al. 2017, 2018). The minimum model was adjusted for age (continuous; years), sex (male/female), and the year of examination. The main model was adjusted for the covariates in the minimum model plus years of education (continuous; years), neighborhood SES (continuous; percentage), smoking status (current, former, never), alcohol consumption (continuous; grams per day), physical activity (low, medium, high), height (continuous; centimeters) and waist circumference (continuous; centimeters). Adjustment in the main model focused on variables associated with both air pollution and the risk of DSPN but also included additional variables potentially associated with the risk of DSPN in order to be consistent with previous studies (waist circumference, height, alcohol consumption, smoking status, physical activity) (Herder et al. 2017, 2018). The extended model was adjusted for the covariates in the main model plus levels of total cholesterol (continuous; milligrams per deciliter), HbA1c (continuous; percentage), and uric acid (continuous; milligrams per deciliter); history of CVD (yes, no); eGFR (continuous; milliliters per minute per 1.73 m²); neurological conditions that might cause nerve damage (yes, no); use of lipid-lowering medication (yes, no); and use of NSAIDs (yes, no). The rationale of the extended model was to provide a model that contained additional factors associated with risk ofDSPN, although some of these variables may act as...
mediators rather than confounders, so effect estimates from this model are likely overadjusted.

In the incidence analysis, we applied inverse-probability weighting to account for, at least in part, the selection bias introduced by the selection of individuals based on criteria that might be independent of air pollution exposure levels (e.g., individuals who were free of DSPN in KORA F4 and individuals who were alive in KORA FF4). We estimated the weight for each participant in the prevalence analysis (n = 1,075) based on the inverse of the probability of being included in the incidence analysis, aiming to up-weight participants who were underrepresented in the incidence sample. Specifically, we fitted a logistic regression model of being included in the incidence analysis, using the covariates in the main Poisson regression model as predictors.

The results are presented as risk ratios (RRs) of prevalent and incident DSPN for each interquartile range (IQR) increase in air pollutants with corresponding 95% confidence intervals (CIs). The IQRs used in both analyses were based on the prevalence sample.

Effect modification by obesity (BMI ≥30 kg/m²), by abdominal obesity (waist circumference ≥102 cm for men and ≥88 cm for women), by type 2 diabetes, or by prediabetes/type 2 diabetes in KORA F4 was investigated by including an interaction term between the potential effect modifier and the air pollutant in the Poisson regression model. p-Values for interaction (\(p_{\text{interaction}}\)) refer to the p-values for the interaction terms between air pollutants and the potential effect modifiers.

In a first sensitivity analysis, we excluded participants who moved during the study period in order to reduce exposure misclassification. In a second sensitivity analysis, we built two-pollutant models by adding a second pollutant that was not highly correlated with the main pollutant (Spearman correlation coefficient < 0.7) to assess the robustness of the associations.

All statistical analyses were performed with R (version 3.6.2; R Development Core Team) using the mgcv, sandwich, and ipw packages. The significance level was set at a two-sided \(p < 0.05\).

### Results

#### Study Population

Table 1 gives the baseline data of the study participants contributing to the analyses of associations between air pollution and both prevalent and incident DSPN. The prevalence of DSPN in KORA F4 was 35.0%. Individuals with prevalent DSPN were older and taller and had larger BMI values, higher waist circumferences, higher HbA1c and uric acid levels, and more often had neurological conditions that might cause nerve damage compared with individuals without prevalent DSPN. In addition, individuals with prevalent DSPN had lower levels of physical activity, lower total cholesterol levels and eGFRs, and had less favorable glucose tolerance status than individuals without prevalent DSPN (Table 1).

The incidence of DSPN between KORA F4 and FF4 was 68.6 per 1,000 person-years. Individuals who developed CVD during the follow-up were older, had larger BMI values, higher waist circumferences, and more frequently had histories of CVD than individuals who remained DSPN-free, but they did not significantly differ in other anthropometric or clinical variables (Table 1). BMI and waist circumference measurements were highly correlated with the sex-adjusted correlation coefficients of 0.89 and 0.87 for the prevalence and incidence samples, respectively.

#### Air Pollutants

Annual average concentrations of air pollutants based on LUR models in the KORA F4 prevalence analysis are given in

| Table 2. PNC, PM10, PMcoarse, PM2.5, PM2.5abs, NOx, and NO2 showed positive correlations with each other, with correlation coefficients \(r\) ranging from 0.50 to 0.88. Correlations between O3 and the aforementioned pollutants were weaker with \(r\) between −0.18 and 0.11.

In the smaller sample used for the incidence analyses, the positive correlations between PNC, PM10, PMcoarse, PM2.5, PM2.5abs, NOx, and NO2 were slightly stronger (\(r\) between 0.55 and 0.90; Table S1). Correlation coefficients \(r\) for correlations between O3 and the aforementioned pollutants ranged from −0.18 to 0.10 (Table S1).

### Association between Air Pollutants and Prevalent DSPN

Particulate air pollutants were positively associated with prevalent DSPN, with significant associations for PNC: main model RR for an IQR increase = 1.10 (95% CI: 1.01, 1.20); similar but nonsignificant RRs for IQR increases in PM10, PM2.5, and PM2.5abs: and weaker associations for PMcoarse: main model RR = 1.05 (95% CI: 0.93, 1.19) (Table 3). NOx and NO2 were also positively associated with prevalent DSPN [e.g., main model RR for an IQR increase in NOx = 1.09 (95% CI: 0.98, 1.21)], whereas IQR increases in O3 were inversely associated with the outcome [RR = 0.93 (95% CI: 0.84, 1.04)]. Estimates based on the minimum and extended models were similar to main model estimates for all pollutants.

Prevalent DSPN was positively associated with PNC, PM10, PMcoarse, PM2.5, PM2.5abs, NOx, and NO2 among 359 obese participants (BMI ≥30 kg/m²), whereas corresponding associations were closer to the null among 715 nonobese participants (Table 4). The difference was most pronounced for IQR increases in PMcoarse [obese RR = 1.18 (95% CI: 1.00, 1.39) vs. nonobese RR = 0.97 (95% CI: 0.83, 1.12); \(p_{\text{interaction}} = 0.046\)], whereas \(p_{\text{interaction}}\)-values for other pollutants ranged from 0.13 to 0.24.

Patterns were similar for associations with prevalent DSPN stratified by abdominal obesity, with positive associations for all pollutants except O3 among 644 participants with high waist circumferences, and null or inverse associations among 431 participants with normal waist circumferences. The most pronounced difference was estimated for IQR increases in PM2.5 [RR = 1.19 (95% CI: 1.03, 1.38) vs. 0.93 (95% CI: 0.77, 1.12); \(p_{\text{interaction}} = 0.03\)] whereas \(p_{\text{interaction}}\)-values for other pollutants ranged from 0.15 to 0.37 (Table S2). In contrast, there were no clear differences in associations with prevalent DSPN when participants with type 2 diabetes (n = 230) were compared with those who had normal glucose tolerance or prediabetes (n = 845, \(p_{\text{interaction}} = 0.20–0.94\)) (Table S3) or when participants with type 2 diabetes or prediabetes (n = 510) were compared with those who had normal glucose tolerance (n = 565, \(p_{\text{interaction}} = 0.28–0.91\)) (Table S4).

### Association between Air Pollutants and Incident DSPN

In general, associations between air pollutants and incident DSPN were close to the null for the population as a whole, with the exception of PNC: main model RR = 1.11 (95% CI: 0.99, 1.24) (Table 3). In contrast, associations of all pollutants except PM2.5abs and NO2 with incident DSPN were positive among 117 obese participants and null or inverse among 307 nonobese participants (\(p_{\text{interaction}} = 0.01–0.13\); Table 4). The most pronounced difference was observed for PMcoarse: [RR = 1.22 (95% CI: 0.93, 1.61) vs. 0.83 (95% CI: 0.68, 1.01); \(p_{\text{interaction}} = 0.01\)], with corresponding estimates for PNC: [RR = 1.28 (95% CI: 1.08, 1.51) vs. 1.03 (95% CI: 0.90, 1.18); \(p_{\text{interaction}} = 0.03\)]. In contrast, there were no clear differences in associations with incident DSPN.
Abdominal obesity was defined as waist circumference ≥80 cm.

**Table 1. Baseline characteristics [mean ± SD or n (%)] of the study population used in the prevalence and incidence analyses.**

| Characteristic          | Sample for the prevalence analysis (n=1,075) | Prevalent DSPN in F4 | Incident DSPN in F4 |
|-------------------------|---------------------------------------------|----------------------|---------------------|
| Age (y)                 | 69.3 ± 5.1                                  | 71.8 ± 5.4           | <0.001              |
| Sex (male)              | 342 (48.9)                                  | 207 (55.1)           | 0.06                |
| Education (y)           | 11.0 ± 2.4                                  | 11.0 ± 2.5           | 0.60                |
| Low neighborhood SES (%)| 25.5 ± 24.7                                 | 26.9 ± 24.7          | 0.07                |
| Smoking status          |                                            |                      |                     |
| Current smoker          | 80 (7.4)                                    | 32 (7.5)             | 0.12                |
| Former smoker           | 450 (41.9)                                  | 176 (41.5)           | 0.95                |
| Alcohol consumption (g/d)| 14.1 ± 18.4                                 | 14.1 ± 19.0          | 0.23                |
| Physical activity       |                                            |                      |                     |
| Low                     | 421 (39.2)                                  | 122 (28.8)           | 0.001               |
| Moderate                | 424 (39.4)                                  | 186 (43.9)           | 0.001               |
| Height (cm)             | 165.7 ± 9.0                                 | 165.9 ± 9.3          | 0.004               |
| BMI (kg/m²)             | 28.7 ± 4.5                                  | 28.8 ± 5.0           | <0.001              |
| Obesity                 |                                            |                      |                     |
| No                      | 715 (66.6)                                  | 307 (72.4)           | 0.02                |
| Waist circumference (cm)| 98.3 ± 12.2                                 | 102.0 ± 12.7         | <0.001              |
| Abdominal obesity       |                                            |                      |                     |
| Yes                     | 644 (59.9)                                  | 217 (51.2)           | 0.03                |
| No                      | 431 (40.1)                                  | 103 (46.4)           | 0.001               |
| Total cholesterol (mg/dL)| 221.1 ± 40.7                                | 221.7 ± 40.8         | 0.19                |
| HbA1c (%)               | 5.8 ± 0.7                                   | 5.7 ± 0.5            | 0.91                |
| HbA1c (mol/mol)         | 40 ± 8                                      | 39 ± 6               | 0.05                |
| Uric acid (mg/dL)       | 5.6 ± 1.4                                   | 5.8 ± 1.6            | 0.03                |
| eGFR (mL/min/1.73 m²)   | 76.4 ± 15.0                                 | 77.9 ± 14.2          | <0.001              |
| Glucose tolerance status|                                            |                      |                     |
| Normal glucose tolerance| 565 (52.6)                                  | 264 (62.3)           | 0.32                |
| IFG and/or IGT          | 280 (26.0)                                  | 94 (22.2)            | 0.02                |
| Type 2 diabetes         | 230 (21.4)                                  | 66 (15.0)            | 0.04                |
| CVD (yes)               | 691 (64.3)                                  | 258 (60.8)           | 0.06                |
| Neurological condition  |                                            |                      |                     |
| (yes)                   | 174 (16.2)                                  | 106 (25.0)           | 0.01                |
| Lipid-lowering medication (yes) | 270 (25.2)                               | 60 (25.4)            | 0.91                |
| NSAID (yes)             | 44 (4.1)                                    | 5 (1.2)              | 1.00                |

Note: Baseline characteristics were assessed in KORA F4 (2006–2008); prevalent DSPN was assessed in KORA F4 (2006–2008); incident DSPN was assessed in KORA FF4 (2013–2014) for participants who were free of DSPN in KORA F4. Descriptive statistics are given as mean ± SD for continuous variables and as frequency [n (%)] for categorical variables. p-Values for difference between subgroups were derived using Kruskal-Wallis rank sum tests for continuous variables and chi-square tests of independence for categorical variables. Low neighborhood SES was defined based on the percentage of households with income <1,250 € in a 500 x 500 m buffer. Obesity was defined as body mass index ≥30 kg/m². Abdominal obesity was defined as waist circumference ≥102 cm for men and ≥88 cm for women. CVD was defined as presence of hypertension, history of myocardial infarction, or history of stroke. Data were complete for all variables unless otherwise indicated. BMI, body mass index; CVD, cardiovascular disease; DSPN, distal sensomotor polyneuropathy; eGFR, estimated glomerular filtration rate; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; HbA1c, hemoglobin A1c; KORA, Cooperative Health Research in the Region of Augsburg; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; SES, socioeconomic status.

Table 2. Air pollution concentrations (mean ± SD; annual averages for 2014–2015) in the KORA F4 study population in the prevalence analysis (n=1,075) and their mutual correlations.

| Pollutants              | Mean ± SD | IQR | PNC | PM10 | PM2.5 | PM1.0 | PM2.5_sus | NO2 | NO3 |
|-------------------------|-----------|-----|-----|------|-------|-------|------------|-----|-----|
| PNC (10³/cm³)           | 7.3 ± 1.8 | 1.7 | 0.78 |      |       |       |            |     |     |
| PM0.5 (µg/m³)           | 16.6 ± 1.5| 2.0 | 0.75 | 0.77 | 0.50  | 0.55  |            |     |     |
| PM1.0 (µg/m³)           | 5.0 ± 1.0 | 1.3 | 0.63 | 0.50 | 0.81  | 0.59  |            |     |     |
| PM2.5 (µg/m³)           | 11.8 ± 1.0| 1.3 | 0.76 | 0.74 | 0.75  | 0.74  |            |     |     |
| PM2.5_sub≤4 (µg/m³)     | 6.8 ± 0.4 | 0.74 | 0.74 | 0.84 | 0.86  | 0.80  |            |     |     |
| NO2 (µg/m³)             | 22.0 ± 7.2| 8.0 | 0.88 | 0.88 | 0.71  | 0.74  |            |     |     |
| O3 (µg/m³)              | 39.1 ± 2.4| 3.3 | -0.03| 0.11 | 0.16  | 0.00  |            |     |     |

Note: IQR, interquartile range; KORA, Cooperative Health Research in the Region of Augsburg; NO2, nitrogen oxides; NOx, nitrogen dioxide; O3, ozone; PM1.0, particulate matter with an aerodynamic diameter between ≥2.5 µm and 10 µm; PM2.5, particulate matter with an aerodynamic diameter ≤2.5 µm; PM2.5_sub≤4, particulate matter with an aerodynamic diameter ≤4 µm; PM2.5_sub≤4, particulate matter with an aerodynamic diameter ≤4 µm; PNC, particle number concentration; SD, standard deviation.
between participants with vs. without abdominal obesity (n = 217 and 207, respectively; Table S2), type 2 diabetes vs. prediabetes or normal glucose tolerance (n = 66 and 358, respectively; Table S3), or type 2 diabetes/prediabetes vs. normal glucose tolerance (n = 160 and 264, respectively; Table S4).

**Sensitivity Analyses**

In the first sensitivity analysis, we restricted the study sample to participants who did not move during the study period. As shown in Table S5, effect estimates for associations of air pollution with incident DSPN for the whole study sample (398 participants) and subgroups stratified by obesity (290 nonobese participants and 108 obese participants) were similar to those of the study sample that also included people who had moved (Tables 3 and 4). In a second sensitivity analysis, associations between air pollution and both prevalent and incident DSPN were robust in two-pollutant models for the whole study sample (limited to pairs of pollutants with correlation coefficients <0.7; Figure S2).

### Table 3. Risk ratios (RRs) and 95% confidence intervals (95% CIs) for associations of air pollution with prevalent and incident DSPN.

| Outcome          | Pollutant | Minimum model RR (95% CI) | p-Value | Main model RR (95% CI) | p-Value | Extended model RR (95% CI) | p-Value |
|------------------|-----------|---------------------------|---------|------------------------|---------|---------------------------|---------|
| Prevalent DSPN   | PNC       | 1.10 (1.02, 1.18)         | 0.02    | 1.10 (1.01, 1.20)      | 0.02    | 1.11 (1.02, 1.21)         | 0.01    |
|                  | PM10      | 1.11 (1.00, 1.24)         | 0.051   | 1.10 (0.98, 1.24)      | 0.12    | 1.13 (1.00, 1.26)         | 0.04    |
|                  | PMcoarse  | 1.07 (0.96, 1.18)         | 0.23    | 1.05 (0.93, 1.19)      | 0.44    | 1.08 (0.95, 1.21)         | 0.23    |
|                  | PM2.5     | 1.11 (0.99, 1.23)         | 0.07    | 1.09 (0.97, 1.23)      | 0.16    | 1.11 (0.99, 1.25)         | 0.08    |
|                  | PM2.5abs  | 1.14 (1.01, 1.29)         | 0.03    | 1.11 (0.95, 1.29)      | 0.17    | 1.15 (0.99, 1.34)         | 0.06    |
|                  | NO2       | 1.09 (0.99, 1.19)         | 0.07    | 1.09 (0.98, 1.21)      | 0.10    | 1.10 (0.99, 1.22)         | 0.07    |
|                  | NO2       | 1.12 (1.00, 1.27)         | 0.06    | 1.13 (0.96, 1.33)      | 0.15    | 1.16 (0.99, 1.36)         | 0.07    |
|                  | O3        | 0.90 (0.81, 1.00)         | 0.055   | 0.93 (0.84, 1.04)      | 0.20    | 0.92 (0.83, 1.02)         | 0.12    |
| Incident DSPN    | PNC       | 1.04 (0.95, 1.14)         | 0.39    | 1.11 (0.99, 1.24)      | 0.08    | 1.11 (0.99, 1.24)         | 0.07    |
|                  | PM10      | 0.94 (0.81, 1.10)         | 0.44    | 0.97 (0.81, 1.17)      | 0.75    | 0.97 (0.81, 1.17)         | 0.75    |
|                  | PMcoarse  | 0.92 (0.80, 1.06)         | 0.26    | 0.94 (0.78, 1.14)      | 0.54    | 0.94 (0.77, 1.14)         | 0.52    |
|                  | PM2.5     | 0.94 (0.81, 1.09)         | 0.43    | 0.96 (0.81, 1.14)      | 0.65    | 0.95 (0.81, 1.13)         | 0.59    |
|                  | PM2.5abs  | 0.91 (0.77, 1.06)         | 0.22    | 0.90 (0.73, 1.12)      | 0.35    | 0.91 (0.74, 1.13)         | 0.39    |
|                  | NO2       | 1.02 (0.91, 1.14)         | 0.76    | 1.07 (0.93, 1.23)      | 0.33    | 1.07 (0.93, 1.23)         | 0.36    |
|                  | NO2       | 0.93 (0.78, 1.10)         | 0.40    | 0.95 (0.75, 1.21)      | 0.70    | 0.96 (0.76, 1.21)         | 0.70    |
|                  | O3        | 0.97 (0.83, 1.13)         | 0.63    | 0.95 (0.82, 1.10)      | 0.50    | 0.94 (0.81, 1.09)         | 0.41    |

Note: RRs and corresponding 95% CIs were derived from logistic regression models for both prevalence and incidence analyses (inverse-probability weighting was used to account for potential selection bias in the incidence analysis). Effect estimates were given for each IQR increase in residential annual average concentrations of air pollutants calculated based on the prevalence sample for both prevalence and incidence analyses. An IQR was 1.7×10^3/cm^3 for PNC, 2.0 μg/m^3 for PM10, 1.3 μg/m^3 for PMcoarse, 1.3 μg/m^3 for PM2.5, 0.3×10^-3/cm^3 for PM2.5abs, 8.0 μg/m^3 for NO2, 6.8 μg/m^3 for NOx, and 3.3 μg/m^3 for O3. The minimum model was adjusted for age, sex, and year of examination. The main model was adjusted for the covariates in the minimum model plus years of education, neighborhood SES, smoking status, alcohol consumption, physical activity, height, and waist circumference. The extended model was adjusted for covariates in the main model plus levels of total cholesterol, HbA1c, and uric acid and history of cardiovascular disease, estimated glomerular filtration rate, neurological conditions that might cause nerve damage, use of lipid-lowering medication, and use of NSAIDs. DSPN, distal sensorimotor polyneuropathy; HbA1c, hemoglobin A1c; IQR, interquartile range; NO2, nitrogen dioxide; NOx, nitrogen oxides; NSAIDs, nonsteroidal anti-inflammatory drugs; O3, ozone; PMcoarse, particulate matter with an aerodynamic diameter ≤2.5 μm; PM2.5, particulate matter with an aerodynamic diameter ≤10 μm; PM2.5abs, particle number concentration; SES, socioeconomic status.

Numbers of participants included in the extended model were 1,068 and 420 for the prevalence and incidence analyses, respectively.
Discussions

The present study has two key findings. First, none of the air pollutants were significantly associated with DSPN in the study population as a whole, with the exception of PNC and prevalent DSPN. However, nonsignificant positive associations that were similar in magnitude were estimated for prevalent DSPN and PM\textsubscript{10}, PM\textsubscript{2.5}, PM\textsubscript{2.5,abs}, NO\textsubscript{3}, and NO\textsubscript{2} and for incident DSPN and PNC. Second, associations with both particulate and gaseous air pollutants differed between obese and nonobese participants, with positive associations of air pollutants with prevalent and incident DSPN among individuals with obesity, and weak or null associations among the nonobese. Overall associations were robust to adjustment for a range of confounders in general as well as in two-pollutant models (for pairs of pollutants with correlation coefficients <0.7).

**Air Pollution, DSPN, and Nervous System Disorders**

Both short- and long-term exposure to air pollution ranging from low- to high-exposure levels have been related to increased mortality and a higher risk for CVD, respiratory diseases, and type 2 diabetes (Rajagopalan et al. 2018; Yang et al. 2020). Our results are novel, showing associations of long-term exposure levels to different air pollutants with DSPN in obese individuals in the KORA F4/FF4 cohort that were consistent between cross-sectional and prospective analyses. The findings point toward independent adverse health effects of both PM and gaseous compounds in the obese. Importantly, these associations were found for IQR increases at annual average concentrations of PM\textsubscript{2.5} (11.8 µg/m\textsuperscript{3}, IQR 1.3 µg/m\textsuperscript{3}), PM\textsubscript{10} (16.6 µg/m\textsuperscript{3}, IQR 2.0 µg/m\textsuperscript{3}), and NO\textsubscript{2} (14.4 µg/m\textsuperscript{3}, IQR 6.8 µg/m\textsuperscript{3}) that were close to or below those specified by the 2005 global update of the WHO Air Quality Guidelines as levels that should not be exceeded (10, 20, and 40 µg/m\textsuperscript{3} annual mean, respectively; WHO 2006). Of note, some of the most consistent associations with DSPN in our study were found for PNC. This exposure represents an indicator for ultrafine particles (i.e., the smallest fraction that can penetrate much deeper into the alveoli and even across the air–blood barrier) and is currently either not regulated at all or there are no recommendations for regulation. Thus, our study extends the knowledge on health effects of air pollution as representing one of the leading risk factors for global morbidity and mortality.

Although the results of the present study cannot be directly compared with others owing to the lack of data, it is noteworthy that exposure to air pollution has been associated with several neurological disorders and cardiac autonomic dysfunction. In particular, exposure to higher levels of PM\textsubscript{2.5} has been associated with a higher risk of development and progression of dementia, Alzheimer’s disease, and Parkinson’s disease in both short- and long-term studies (Kioumourtzoglou et al. 2016; Fu et al. 2019; Wei et al. 2019). These disorders affect the central, rather than the peripheral, nervous system but may nevertheless be relevant in this context given the proposed contribution of central nervous system disturbances to the pathophysiology of DSPN (Selvarajah et al. 2014). Short-term exposure to both particulate and gaseous air pollutants has also been associated with lower heart rate variability in different study populations (de Hartog et al. 2009; Park et al. 2010; Schneider et al. 2010; Huang et al. 2012).

**Potential Mechanisms Linking Air Pollution, Obesity, and DSPN**

Our results may also be relevant because few risk factors beyond hyperglycemia have been identified that predispose to the incidence and progression of DSPN (Ziegler et al. 2014; Bönhof et al. 2019). In line with this, DSPN is one of the few complications of diabetes without a generally accepted disease-specific treatment. In addition to obesity, prediabetes, and advanced age, environmental factors merit further investigation regarding their role in the development and progression of DSPN to possibly advance our understanding of its pathophysiology.

With respect to the underlying mechanisms linking air pollution and DSPN, a comparison with the mechanisms that have been proposed to mediate effects of air pollution on cardiometabolic diseases is of interest. Studies focusing on cardiovascular outcomes have highlighted oxidative stress and subclinical inflammation as putative mediators. Both might be derived from PM distributed throughout the body or from spillover effects after activation of pulmonary tissue. Additional mediating factors may include endothelial dysfunction, altered hemodynamics, prothrombotic pathways, and autonomic imbalance (Rajagopalan and Brook 2012; Rajagopalan et al. 2018). Most of these factors have also been associated with DSPN (Bönhof et al. 2019) and appear to be plausible mediators between air pollution and DSPN. Increased neuroinflammation and oxidative stress have also been implicated as mechanisms linking air pollution and neurological diseases, with experimental and postmortem studies pointing toward neuronal and glial cell death as consequences of exposure to air pollution (Genc et al. 2012; Zanobetti et al. 2014). However, it is important to note that air pollution consists of a complex mixture of particulate and gaseous constituents with complex chemistry, and exposure measurements in large epidemiological studies are usually not specific enough to disentangle which components affect outcomes of interest such as DSPN by which mechanisms.

Perhaps the most important finding in this study is that exposure to air pollution was associated with prevalent and incident DSPN among obese individuals, whereas corresponding estimates for nonobese participants were weak or null. The evidence for different associations with both prevalent and incident DSPN between the two subgroups was most consistent for PM\textsubscript{10,ox}, PM\textsubscript{2.5}, and NO\textsubscript{2}. In addition, PM\textsubscript{2.5,abs} may also have been more strongly associated with prevalent DSPN in obese individuals, and effect sizes for PNC, PM\textsubscript{10}, and NO\textsubscript{2} appeared to be larger in obese individuals for incident DSPN. Thus, our study indicates that obese people may be particularly susceptible to air pollution. The notion that not all individuals react equally to environmental toxins and that subgroups may exist who are more susceptible than others has been addressed in previous studies (Sacks et al. 2011). Consequently, the Clean Air Act (42 U.S.C. §§ 7401) implemented this concept in the United States by explicitly aiming to protect the health of sensitive subgroups of the population (Rajagopalan et al. 2018). However, analyses involving multiple combinations of exposures and outcomes in different cohorts have identified a range of factors that may influence the susceptibility to air pollution. These factors include age, obesity, preexisting diseases (CVD, respiratory diseases, diabetes), and low SES (Sacks et al. 2011). Of note, one review of cohort and panel studies focusing on cardiovascular health found a consistent pattern of stronger associations between exposure to PM\textsubscript{2.5} and cardiovascular outcomes in people with obesity (Weichenthal et al. 2014). Overweight and obesity have also been identified as effect modifiers in the relationship between air pollution and cardiac autonomic function (de Hartog et al. 2009; Huang et al. 2012). The present study suggests that obesity defined by BMI may be a better indicator of susceptibility to air pollution than abdominal obesity, diabetes, or prediabetes/diabetes when DSPN is assessed as the outcome. However, people with abdominal obesity or diabetes were identified as high-risk subgroups in other studies investigating the effects of air pollution (Sacks et al. 2011), so comparable findings in this study would have been plausible. Here, it is important to note that data for
potential effect modifiers were derived from the baseline examination of this study (KORA F4), so changes in BMI or waist circumference, incidence of prediabetes or type 2 diabetes between KORA F4 and FF4, or the use of glucose-lowering treatment during the follow-up period were not accounted for in the analysis although they might affect the individual susceptibility to air pollutants. Therefore, further studies in other cohorts are necessary to investigate which pathways link BMI and other potential susceptibility factors to the risk of DSPN in people exposed to higher levels of air pollution. Future studies should also address to what extent obesity may represent a mediator between air pollution and risk of DSPN as an alternative explanation as to how these three factors are connected.

Epidemiological studies cannot easily identify the underlying mechanisms why air pollution and obesity may affect health in a synergistic manner. One possible explanation considers obesity and air pollution as major endogenous and exogenous determinants of subclinical inflammation that together may exacerbate local and systemic inflammatory processes. Experimental studies have suggested a direct effect of ambient PM$_{2.5}$ on adipose tissue inflammation in mice, resulting in the development of visceral adiposity, insulin resistance, and systemic immune activation (Sun et al. 2009), all of which represent risk factors for DSPN. There is evidence that adipose tissue inflammation represents an initial step in the development of insulin resistance before the manifestation of systemic subclinical inflammation, suggesting that air pollution may even belong among the modifiable factors initiating the inflammation/insulin resistance syndrome (Roden and Shulman 2019). A second explanation could implicate the structural and functional changes of the lungs that are caused by obesity (Dixon and Peters 2018) and which may increase the susceptibility of obese people to air pollution.

**Strengths and Limitations**

Major strengths of this study include the population-based design of the KORA F4/FF4 cohort, the comprehensive and standardized assessment of residential air pollution, the combination of cross-sectional and prospective analyses and the detailed information on study participants that allowed for adjustment for potential confounders. There are also some limitations of our study. First, our definition of DSPN meets the requirements for possible DSPN, but measurements of nerve conduction as a more sensitive and specific method to assess impairments in large myelinated nerve fibers were not available. Second, exposure misclassification may have occurred due to assessment of residential exposure only. Information on time spent at work addresses for the younger study participants and time spent, for example, at summer homes or traveling was not available. This issue can be solved only with large-scale personal exposure measurements that were not feasible within the KORA cohort. Third, we cannot exclude residual confounding by factors related to both air pollution and risk of DSPN that were not measured in our study. Fourth, data for other air pollutants of interest, such as sulfur dioxide, were not available for our study sample. Fifth, the KORA F4 survey (i.e., baseline of this study) represents a follow-up study of the population-based KORA S4 survey. The response rate in the age group investigated here was 70.2%, and nonparticipants in F4 were older and had a less favorable cardiometabolic risk profile (Klüppelholz et al. 2015). Therefore, we cannot exclude a certain degree of selection bias, which, however, would be expected to have led to an underestimation of effect sizes, not to increased risk ratios. Sixth, sample sizes were a limitation in some of the stratified analyses of incident DSPN. Finally, air pollution levels were relatively low compared with many low- or medium-income countries, so further studies in other areas of the world (e.g., India, China, South America) will be necessary to obtain estimates for the investigated associations at higher levels of air pollution.

**Conclusion**

To our knowledge, this is the first study to assess the relationship between air pollution and DSPN. We identified obese individuals as a susceptible subgroup in which air pollution was associated with both prevalent and incident DSPN. These associations were observed in a cohort with comparatively low levels of air pollution, so our data need to be corroborated in other cohorts of similar and higher exposure. From the clinical perspective, the identification of air pollution as a potential novel determinant of DSPN raises the question to what extent environmental exposures could contribute to this disease. From the public health point of view, these data reinforce the importance of measures to reduce both exposure to air pollution and strategies to prevent obesity in the general population.

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The data are subject to national data protection laws. Therefore, data cannot be made freely available in a public repository. However, data can be requested through an individual project agreement with KORA. To obtain permission to use KORA data under the terms of a project agreement, please use the digital tool KORA.PASSST (https://epi.helmholtz-muenchen.de/).

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