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Environmental risk factors of incident distal sensorimotor polyneuropathy: Results from the prospective population-based KORA F4/FF4 study

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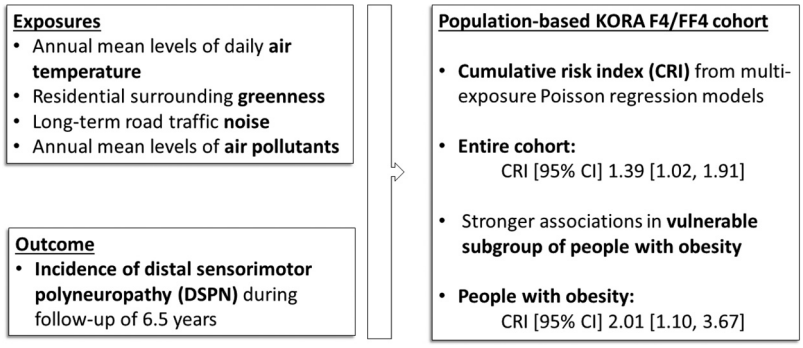
HIGHLIGHTS

- Environmental risk factors for distal sensorimotor polyneuropathy/DSPN are unknown.
- We assessed joint effects of four exposures for DSPN risk in the KORA F4/FF4 cohort.
- Effect sizes of associations were higher in people with obesity.
- The joint-effect model showed a 2-fold increased risk of DSPN in the obese.
- Results were robust to adjustment for multiple confounders.

GRAPHICAL ABSTRACT



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ABSTRACT

Distal sensorimotor polyneuropathy (DSPN) is a common condition in older populations with high prevalence of obesity and type 2 diabetes. We hypothesised that the risk of DSPN is increased by multiple ubiquitous environmental risk factors, particularly in people with obesity. This study was based on 423 individuals aged 62–81 years without DSPN who participated in the population-based Cooperative Health Research in the Region of Augsburg (KORA) F4 survey (2006–2008) in Southern Germany. During 6.5 years of follow-up, 188 participants developed clinical DSPN as assessed by the Michigan Neuropathy Screening Instrument. Environmental exposures, including air temperature,

Abbreviations: BMI, body mass index; CI, confidence interval; CRI, cumulative risk index; CVD, cardiovascular disease; dB(A) Leq, A-weighted decibels; DSPN, distal sensorimotor polyneuropathy; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; IQR, interquartile range; KORA, Cooperative Health Research in the Region of Augsburg; LLIS, Lärm- und Luftschadstoff-Informationssystem; LST, land surface temperature; MNSI, Michigan Neuropathy Screening Instrument; NDVI, normalized difference vegetation index; OGTT, oral glucose tolerance tests; PM, particulate matter; PNC, particle number concentration; RMSE, root mean square error; RR, risk ratio; SD, standard deviation; SE, standard error; SES, socioeconomic status; Ta, air temperature.

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Greenness
Temperature
Population-based cohort

surrounding greenness (assessed with the normalized difference vegetation index [NDVI]), long-term road traffic noise and air pollution, were assessed at participants' residences. The cumulative risk index (CRI) evaluated the joint effects of co-occurring exposures on DSPN risk based on effect estimates from multi-exposure Poisson regression models. The models were adjusted for age, sex, height, waist circumference, smoking, alcohol consumption, physical activity, education and neighbourhood socioeconomic status. In the entire cohort, the co-occurrence of an interquartile range (IQR) decrease in temperature of the warm season and NDVI in a 100-m buffer and of an IQR increase in night-time average traffic noise and in annual average particle number concentration (PNC) was positively associated with incident DSPN (CRI [95 % CI] 1.39 [1.02, 1.91]). Effect estimates for exposure combinations were generally higher in individuals with obesity (CRI 1.34–2.01) than in those without obesity (CRI 0.90–1.33). The four-exposure model showed a twofold increased risk of DSPN among obese (CRI [95 % CI] 2.01 [1.10, 3.67]), but not among non-obese individuals (CRI [95 % CI] 1.18 [0.83, 1.67]). Thus, ubiquitous environmental exposures jointly augment the risk of DSPN in the older population. Lower air temperature in the warm season, less greenness, and higher noise levels and ultrafine particle concentrations identified people with obesity as a particularly vulnerable subgroup.

1. Introduction

Distal sensorimotor polyneuropathy (DSPN) is a common neurological condition in older populations with high prevalence rates of obesity and type 2 diabetes (Ziegler et al., 2014; Callaghan et al., 2016; Hicks et al., 2021; Pop-Busui et al., 2022). Prevalence estimates differ widely based on population characteristics and diagnostic criteria for DSPN with <10 % in elderly people with normal glucose tolerance and a lifetime prevalence exceeding 50 % in people with diabetes (Ziegler et al., 2008; Hanewinckel et al., 2016; Pop-Busui et al., 2022). The presence of obesity increases the risk of DSPN in the general elderly population by 3.5-fold (Schlesinger et al., 2019). DSPN represents a major public health burden as it carries an increased risk not only for foot ulcers and amputations but also for cardiovascular and all-cause mortality (Hicks et al., 2021; Pop-Busui et al., 2022). Although DSPN is generally viewed as a diabetic complication, advanced age, prediabetes and obesity are also relevant contributing factors (Ziegler et al., 2014; Bönhof et al., 2019; Herder et al., 2019; Pop-Busui et al., 2022). There is ample evidence from preclinical, clinical and epidemiological studies suggesting that inflammation and oxidative stress are initiating mechanisms and that endothelial dysfunction and microangiopathy represent effector pathways linking metabolic and aging-related insults with neuropathic damage (Bönhof et al., 2019; Sloan et al., 2021).

Of note, the currently known risk factors explain only a fraction of the risk of DSPN which limits prediction, prevention and treatment (Callaghan et al., 2016; Herder et al., 2019). Given the fact that the aforementioned mechanisms and pathways are also triggered by ubiquitous environmental risk factors (Rajagopalan and Landrigan, 2021; Peters et al., 2021), the paucity of data on environmental exposures as potential determinants of DSPN is surprising. The role of air pollution and noise as triggers of inflammation, oxidative stress and vascular impairments leading to type 2 diabetes, cardiovascular and neurodegenerative diseases has been increasingly recognised (Peters et al., 2021; Münzel et al., 2021; Parra et al., 2022). However, air pollution as a potential risk factor for DSPN has only been addressed by two previous studies (Herder et al., 2020; Li et al., 2022) with the strongest associations found for particle number concentration (PNC), i.e. ultrafine particulate matter (Herder et al., 2020). No data are available for noise in this context. Additionally, both heat and cold stress exacerbate cardiometabolic conditions (Kenny et al., 2016; Ebi et al., 2021), but associations between annual or seasonal average ambient air temperature and DSPN have not been studied. Of note, experimental studies found cold exposure related to sensory neuropathy and decreased nerve conduction velocity (NCV) (Vale et al., 2017; Maetzler et al., 2012). Greenspace exposure and residential greenness have been related to decreased risk of diabetes, cardiovascular and neurodegenerative disease and mortality (Twohig-Bennett and Jones, 2018; Rodriguez-Loureiro et al., 2022), possibly mediated by healthier lifestyle behaviours and attenuated stress-related pathways, but again DSPN has not been considered as a study outcome. Given the existing literature on the aforementioned mechanisms and outcomes, an association between lower greenspace exposure and higher risk of DSPN would appear plausible. Thus, the lack of data linking ubiquitous environmental exposures affecting global health and the risk of DSPN represents a major gap in our knowledge.

Two further aspects need to be considered in studies on the health consequences of the environment. First, environmental risk factors do not act separately, but should be investigated together as delineated in the concept of the exposome (Münzel et al., 2021; Beulens et al., 2022). Air pollution, noise and ambient temperature might influence overlapping pathophysiological mechanisms and have interdependencies, so the assessment of the joint effects of co-occurring exposures can provide a more comprehensive perspective of disease risk. Second, disease risk depends on individual susceptibility. There is increasing evidence that people with obesity or related comorbidities represent a particularly vulnerable subgroup of the population (Sacks et al., 2011; Weichenthal et al., 2014; Yang et al., 2018; Kim et al., 2019; Herder et al., 2020; Kim et al., 2021; Li et al., 2021), suggesting that potential effect modification by obesity might exist.

Therefore, this study had three aims: (i) to comprehensively investigate the associations between ubiquitous environmental long-term exposures (low ambient air temperature, low level of greenness, high traffic road noise and high air pollution; all showing previous associations with cardiometabolic and/or neurological diseases) with incident DSPN in a population-based cohort, (ii) to assess the joint effects of these co-occurring exposures (primary aim of this study), and (iii) to test the hypothesis that the DSPN risk associated with these environmental exposures is higher in people with obesity than in those without obesity.

2. Methods

2.1. Study population

This study was based on data from the population-based Cooperative Health Research in the Region of Augsburg (KORA) F4 (2006–2008) and the KORA FF4 surveys (2013–2014), which are the first and second follow-up examinations of the population-based KORA S4 survey (1999–2001) conducted in Augsburg (Germany) and the adjacent counties Augsburg and Aichach-Friedberg (Holle et al., 2005; Rathmann et al., 2009; Herder et al., 2017). The KORA survey was designed for studies in the fields of epidemiology, health economics, and health care research (Holle et al., 2005). Epidemiological studies have a strong focus on cardiometabolic disease, environmental exposures, psychosocial risk factors and genetic epidemiology. The study sample was drawn based on a two-stage procedure where first Augsburg city and sixteen communities from the adjacent counties were selected by cluster sampling and then stratified random sampling was performed within each community to ensure a population-based design (Holle et al., 2005). The KORA surveys were carried out in line with the Declaration of Helsinki, and participation required written informed consent. The KORA surveys were approved by the ethics board of the Bavarian Chamber of Physicians (Munich, Germany).

This prospective study was restricted to individuals who participated in both the KORA F4 and FF4 surveys and who were aged between 62 and 81 years at F4 (i.e. the subgroup of study participants with a neuropathy

examination module). As described for an almost identical sample (Herder et al., 2020), 1161 individuals in the aforementioned age range participated in the KORA F4 survey. Exclusion of people (i) with missing baseline data for outcome or covariates (n = 50), (ii) with either unclear diabetes status or diabetes types other than type 2 (n = 28) or (iii) with non-fasting blood samples (n = 8) left a study sample of 1075 participants. Of those, we excluded people with non-participation in KORA FF4 (n = 448), people with DSPN at baseline (n = 183) or with missing exposure or follow-up DSPN data (n = 21) which left 423 individuals without DSPN at baseline. Out of those, 188 developed incident DSPN. The follow-up time was 6.46 ± 0.22 years (mean ± SD).

2.2. Assessment of outcome and covariates

DSPN was assessed using identical methods both at study baseline (KORA F4 [2006–2008]) and in the follow-up survey (KORA FF4 [2013–2014]). The clinical examination module included all items of the Michigan Neuropathy Screening Instrument (MNSI), i.e. appearance of feet, foot ulceration, ankle reflexes and vibration perception threshold at the great toes which were assessed with the Rydel-Seiffer graduated C 64 Hz tuning fork (Feldman et al., 1994). Normal vibration perception threshold was based on age-dependent threshold values (Martina et al., 1998). The MNSI score also included the bilateral assessment of touch/pressure sensation using a 10-g monofilament (Neuropen) (Boyraz and Saracoglu, 2010). Thus, the total MNSI score ranged from 0 to 10 points, and DSPN was defined using a cut-off value of >2 points (Feldman et al., 1994; Lunetta et al., 1998; Moghtaderi et al., 2006; Herder et al., 2009) in line with the diagnostic criteria for possible DSPN according to the Toronto Diabetic Neuropathy Expert Group (Tesfaye et al., 2010).

Anthropometric, sociodemographic, metabolic and lifestyle factors were assessed as described before in KORA F4 and KORA FF4 (Rathmann et al., 2009; Herder et al., 2017). Obesity was defined as BMI ≥30 kg/m^2. Waist circumference was measured midway between the lower rib margin and the iliac crest. Information on age, sex, smoking behaviour, alcohol consumption, physical activity and education was obtained in standardised interviews. Neighbourhood socioeconomic status (SES) was defined based on the percentage of households with a monthly income of <1250 € in a 500 × 500 m buffer. Oral glucose tolerance tests (OGTT) were performed to assess glucose tolerance status (Rathmann et al., 2009). Glucose and haemoglobin A1c (HbA1c) were measured using the hexokinase method on a Dimension RxL instrument (Dade Behring, Newark, NJ, USA) and using cation-exchange high-performance liquid chromatographic, photometric assays on an Adams HA 8160 Hemoglobin Analysis System (Menarini Diagnostics, Florence, Italy), respectively. Serum cholesterol was measured using a Dimension RxL instrument (Dade Behring). Uric acid in serum was measured with the uricase method (enzymatic color test, URCA Flex, Dade Behring). Estimated glomerular filtration rate (eGFR) was calculated using the chronic kidney disease epidemiology (CKD-EPI) creatinine equation. Cardiovascular disease was defined as the presence of hypertension or a history of myocardial infarction, angina pectoris, or stroke.

2.3. Exposure measurement

The participants' residential addresses at study baseline (F4; 2006–2008) were used for the assessment of all exposures. Addresses were converted by geocoding into geographic coordinates, which were then linked to the resources detailed below.

2.3.1. Air temperature

Daily mean air temperature (Ta) was estimated in 1 km^2 spatial resolution across Germany using a hybrid regression-based modelling approach (Kloog et al., 2014). The model incorporated satellite-derived land surface temperature (LST) data, ground-based Ta measurements as well as various spatial variables, including elevation, vegetation, urban fabric, arable land, pastures, forests and inland waters. The model consisted of three stages. In the first stage, for grid-day combinations with both Ta and LST data available, Ta measurements were regressed against LST by a linear mixed-effects model with day-specific random intercepts, fixed and random slopes for LST and spatial predictors. In the second stage, the first-stage model was used to predict Ta in grid cells without Ta measurements but with LST data. In the third stage, a generalized additive mixed model with thin-plate splines for spatial smoothing was used. This model was applied to estimate Ta when LST data were not available (due to clouds, snow, or measurement failures) and to obtain fully covered Ta data countrywide, by using the association of second-stage predicted Ta in a certain grid cell with the average Ta values of surrounding measurement stations. The ten-fold cross validation showed excellent model performance with low errors (R^2 = 0.98 and root mean square error [RMSE] = 1.143 °C for 2000–2020). The annual mean Ta and the mean Ta of the warm (May–September) and cold (November–March) seasons for 2006 were assigned to participants based on their residential addresses.

2.3.2. Greenness

We assessed the residential surrounding greenness by the normalized difference vegetation index (NDVI), an indicator of vegetation density, derived from cloud-free satellite images (taken on July 22, 2006) of Landsat 5 Thematic Mapper with a spatial resolution of 30 m × 30 m. The satellite images were gathered from the Global Visualization Viewer from the U.S. Geological Survey (http://earthexplorer.usgs.gov/) (Voss et al., 2021). The NDVI values range from −1 to 1. Values close to one indicate highly vegetated areas and values close to zero correspond to barren areas of rock, sand, or snow. NDVI values below zero were set to missing since they represent mainly water and do not convey information on vegetation (Markevych et al., 2014). The mean NDVI in 100 m, 300 m, 500 m and 1000 m buffers around the residence were assigned to each participant.

2.3.3. Road traffic noise

For the city of Augsburg, long-term noise exposure from traffic was estimated based on the noise and air pollution information system ("Lärm- und Luftschadstoff-Informationssystem"/LLIS, http://www.laermkarten.de/augsburg/), which was developed by the company ACCON GmbH. LLIS provides a digital three-dimensional ground level of Augsburg with information on the road network (width, type, road surface and traffic volume) and building characteristics (ground plan, occupancy, height and reflection). In rural areas, the road network was generated using georeferenced pictures from Google Earth and open-street map data. Additionally, data on speed limits and daily traffic counts were derived from the Bavarian Ministry of the Interior, Building and Transport, the digital street map of Augsburg, several traffic censuses and surveys. ACCON modeled the noise exposure four meters above the ground using predictors collected in 2009 (urban areas) or between 2000 and 2011 if predictors were not available for 2009 (rural areas). Maximum annual A-weighted equivalent continuous sound pressure levels [dB(A) Leq] during the whole day (24 h) and at night (22:00–06:00) were calculated for the residential address of each participant. If the residential address did not correspond to a building available in LLIS, the noise level at the nearest building was assigned.

2.3.4. Air pollution

The annual mean concentrations of air pollutants, including particle number concentration (PNC), PM_{10}, PM_{coarse}, $PM_{2.5}$, $PM_{2.5abs}$, NO_2, NO_x and O_3, were estimated using land-use regression (LUR) models. The modelling approach was detailed before (Wolf et al., 2017). Briefly, the LUR models were built by regressing the annual mean air pollutant concentrations obtained from the measurement campaigns during 2014–2015 against the geographic predictors from the geographic information system at 20 sites in the study area. The adjusted modelexplained variance (R^2) was between 0.68 (PM_{coarse}) and 0.94 (NO_2), and the leave-one-out cross-validation adjusted R^2 was between 0.55 (PM_{coarse}) and 0.89 (NO_2), indicating good model fit. We applied the fitted LUR models to participants' home addresses to estimate their residential air pollution exposure levels.

2.4. Statistical analysis

2.4.1. Descriptive statistics

Descriptive statistics of participant characteristics at baseline are presented as mean ± standard deviation (SD) for continuous variables and frequency [n (%)] for categorical variables in all participants as well as subgroups with or without incident DSPN. We calculated the *P* values for the between-group differences using the Wilcoxon rank-sum tests for continuous variables and chi-square tests of independence for categorical variables. Correlations between environmental exposures were assessed by Spearman's correlation coefficients.

2.4.2. Single-exposure model

We applied a Poisson regression model with a robust error variance to examine the association between individual environmental exposure and incident DSPN in an exploratory approach. We built three models with adjustments for covariates (all measured at baseline KORA F4) that were selected a priori based on our previous publication (Herder et al., 2020). The minimum model was adjusted for age (continuous) and sex (male or female). The main model was additionally adjusted for years of education (continuous), smoking status (current, former or never smoker), alcohol consumption (continuous), physical activity (low, medium or high level), height (continuous), waist circumference (continuous) and the proportion of households with low income in a 500 m buffer (continuous, an indicator of neighbourhood socioeconomic status). The extended model included the covariates in the main model as well as levels of total cholesterol, haemoglobin A1c (HbA1c) and uric acid (all continuous), history of cardiovascular disease (yes or no), estimated glomerular filtration rate (continuous), neurological conditions that might cause nerve damage (yes or no), use of lipid-lowering medication (yes or no) and use of non-steroidal anti-inflammatory drugs (NSAIDs, yes or no). To account for the potential selection bias due to the participant inclusion criteria that might be independent of exposure levels, we incorporated inverse-probability weighting in the model. Specifically, we fitted a logistic regression model of whether being included in the analysis among participants meeting the inclusion criteria (n = 1075). The predictors were identical to the covariates in the main Poisson regression model. The weight of each participant was defined as the inverse of the probability of being included, as predicted by the fitted logistic regression model. This approach up-weighted participants who were underrepresented in the analysed sample. The covariate balance was assessed by standardised mean differences (SMD) before and after inverse-probability weighting. SMDs close to zero indicate a good balance. Exposures were included in the models as a linear term. Single-exposure effects were examined among all participants as well as in subgroups with and without obesity by incorporating an interaction term between exposure and obesity (BMI ≤ 30 vs. BMI > 30 kg/m^2). All effect estimates are presented as the risk ratios (RRs) of developing DSPN per interquartile range (IQR) change in the exposure (an IQR decrease for air temperature and greenness; an IQR increase for traffic noise and air pollution) with 95 % CIs.

2.4.3. Two-exposure model

Two-exposure models were applied to examine whether the effect of one exposure was confounded by other exposures. Given the lack of data on mechanisms linking the four exposures with DSPN, we opted for a systematic and exploratory approach without a priori hypotheses on the mutual relationships between the exposures. Based on the single-exposure analysis results, we first selected a representative for each exposure category (air temperature, greenness, road traffic noise and air pollution), defined as the exposure variable having the most pronounced effects on incident DSPN in all participants, non-obese or obese subgroups. These four representative exposures were then analysed in two-pollutant models. The two-pollutant models were built by adjusting for a second representative exposure that was weakly or moderately correlated (Spearman correlation coefficients $r^2 \leq 0.7$) with the main representative exposure in the main Poisson regression models. Effect modification by obesity was examined by the interaction term between the main representative exposure and obesity.

2.4.4. Cumulative risk index

The assessment of the joint effects of the four exposures investigated here was the main aim of this study so that we consider the single-exposure and two-exposure analyses exploratory and refrained from adjustment for multiple testing. We used the cumulative risk index (CRI) to assess the joint effects of co-occurring exposures (Lippmann et al., 2013; Klompmaker et al., 2019; Voss et al., 2021). Multi-exposure models, which included different combinations of the representative exposures and adjusted for the covariates in the main model as described above, were fitted to derive the effect estimate for each exposure. We assumed additive effects of exposures on incident DSPN and defined the CRI as:

$$CRI = \exp\left(\sum_{p=1}^{P} \widehat{\beta}_p x_p\right) = \exp\left(\widehat{\beta}' x\right) = \prod_{p=1}^{P} JRR_p$$

where $\widehat{\beta}' = \left(\widehat{\beta}_1, \ldots, \widehat{\beta}_p\right)$ denoted the coefficients of the P exposures estimated in the multi-exposure Poisson regression model; $x = (x_1, \ldots, x_p)$ denoted the levels at which the RRs of P exposures were evaluated; $JRR_p = \exp\left(\widehat{\beta}_p x_p\right)$ denoted the joint risk ratio for the pth exposure in the multi-exposure model. It is of note that we used an IQR increase in traffic

Table 1
Baseline characteristics of the study participants.

Characteristic	All (n = 423)	Incident DSPN in FF4		
		No (n = 235)	Yes (n = 188)	*P*
Age (years)	68.2 ± 4.7	67.5 ± 4.4	69.1 ± 4.8	<0.001
Sex (male)	213 (50.4)	110 (46.8)	103 (54.8)	0.13
Education (years)	11.3 ± 2.6	11.3 ± 2.6	11.1 ± 2.5	0.37
Low neighbourhood SES (%)	25.4 ± 24.7	26.7 ± 24.4	23.8 ± 25.0	0.15
Smoking status				0.96
Current smoker	32 (7.6)	17 (7.2)	15 (8.0)	
Former smoker	176 (41.6)	98 (41.7)	78 (41.5)	
Never smoker	215 (50.8)	120 (51.1)	95 (50.5)	
Alcohol consumption (g/day)	14.5 ± 18.6	14.6 ± 19.2	14.5 ± 17.7	0.98
Physical activity				0.24
Low	122 (28.8)	60 (25.5)	62 (33.0)	
Medium	185 (43.7)	108 (46.0)	77 (41.0)	
High	116 (27.4)	67 (28.5)	49 (26.1)	
Height (cm)	165.8 ± 8.7	165.0 ± 8.0	166.9 ± 9.4	0.05
Body mass index (kg/m^2)	27.9 ± 3.8	27.5 ± 3.8	28.4 ± 3.8	0.02
Waist circumference (cm)	95.4 ± 11.3	93.6 ± 11.3	97.8 ± 10.9	<0.001
Obesity (%)	117 (27.7)	58 (24.7)	59 (31.4)	0.16
Total cholesterol (mmol/L)	5.8 ± 1.1	5.9 ± 1.1	5.7 ± 1.1	0.19
HbA1c (mmol/mol)	38.9 ± 5.9	38.8 ± 5.9	39.0 ± 5.9	0.22
Uric acid (mg/dL)	5.5 ± 1.3	5.4 ± 1.3	5.7 ± 1.3	0.05
eGFR	79.1 ± 12.8	79.6 ± 12.8	78.4 ± 12.9	0.29
Glucose tolerance status				0.28
Normal glucose tolerance	264 (62.4)	151 (64.3)	113 (60.1)	
IFG and/or IGT	93 (22.0)	45 (19.1)	48 (25.5)	
Type 2 diabetes	66 (15.6)	39 (16.6)	27 (14.4)	
Cardiovascular disease (yes)	264 (62.4)	135 (57.4)	129 (68.6)	0.02
Neurological condition (yes)	52 (12.4)	26 (11.2)	26 (14.0)	0.47
Lipid-lowering medication (yes)	106 (25.1)	60 (25.5)	46 (24.5)	0.89
NSAID (yes)	5 (1.2)	3 (1.3)	2 (1.1)	0.99

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 Wilcoxon rank sum tests for continuous variables and chi-square tests of independence for categorical variables. Low neighbourhood SES was defined based on the percentage of households with income <1250 € in a 500 × 500 m buffer. Obesity was defined as body mass index ≥30 kg/m^2. Cardiovascular disease was defined as presence of hypertension or history of myocardial infarction, angina pectoris, or stroke. DSPN = distal sensorimotor polyneuropathy, eGFR = estimated glomerular filtration rate, IFG = impaired fasting glucose, IGT = impaired glucose tolerance, HbA1c = haemoglobin A1c, NSAID = nonsteroidal anti-inflammatory drug, SD = standard deviation, SES = socioeconomic status.

Table 2
Distribution of environmental exposures.

	Exposure	Mean ± SD	Range	IQR
Temperature	Annual mean temperature (°C)	9.1 ± 0.4	8.2–10.0	0.67
	Mean temperature of warm season (°C)	16.5 ± 0.5	15.4–17.6	0.75
	Mean temperature of cold season (°C)	1.3 ± 0.4	0.5–2.1	0.58
Greenness	NDVI in 100 m buffer	0.31 ± 0.10	0.05–0.61	0.11
	NDVI in 300 m buffer	0.31 ± 0.08	0.09–0.54	0.11
	NDVI in 500 m buffer	0.31 ± 0.08	0.12–0.52	0.11
	NDVI in 1000 m buffer	0.33 ± 0.08	0.18–0.52	0.11
Noise	Daily average traffic noise (dB(A))	54.6 ± 6.1	39.8–74.5	7.4
	Night-time average traffic noise (dB(A))	45.6 ± 5.9	31.1–64.8	7.2
Air pollutant	PNC (10^3/cm^3)	7.3 ± 1.8	3.3–14.6	2.0
	PM_{10} (μg/m^3)	16.6 ± 1.5	13.9–22.3	2.1
	PM_{coarse} (μg/m^3)	5.0 ± 1.0	2.7–8.3	1.4
	$PM_{2.5}$ (μg/m^3)	11.8 ± 1.0	9.1–14.0	1.5
	$PM_{2.5abs}$ (10^{-5}/m)	1.2 ± 0.2	0.8–1.7	0.3
	NO_2 (μg/m^3)	14.5 ± 4.6	6.9–26.4	6.8
	NO_x (μg/m^3)	22.2 ± 7.5	4.2–50.0	8.6
	O_3 (μg/m^3)	39.2 ± 2.4	32.1–45.8	3.5

Note: Warm season: May–September; cold season: November–March.
IQR = interquartile range, NDVI = Normalized Difference Vegetation Index, NO_2 = nitrogen dioxide, NO_x = nitrogen oxides, O_3 = ozone, PM = particulate matter, PNC = particle number concentration, SD = standard deviation.

noise and air pollution, and an IQR decrease in temperature and greenness as the x_p. The 95 % CI of CRI was defined by

$$exp\left(\hat{\beta}'x \pm 1.96 \times \sqrt{x'Cov\left(\hat{\beta}\right)x}\right)$$

The CRI for the subgroups with and without obesity was estimated by including interaction terms between obesity and each exposure in the multi-exposure levels. The statistical significance of the between-group differences was assessed by $P_{diff} = 2 \times \Phi\left(\frac{-|\widehat{\beta}|}{SE\left(\widehat{\beta}\right)}\right)$, where Φ denoted the cumulative distribution function of a standard normal distribution, $\widehat{\beta}$ denoted the difference in log-CRI between the two sub-groups, $SE\left(\widehat{\beta}\right)$ denoted the standard error (SE) of $\widehat{\beta}$, calculated as $\sqrt{\mathrm{SE}[\ln(\mathrm{CRI}_1)]^2 + \mathrm{SE}[\ln(\mathrm{CRI}_2)]^2}$, where CRI_1 and CRI_2 were the CRI for the obese and non-obese subgroups, respectively.

In addition, we conducted step-wise exposure selection (among the representative exposures) based on Bayesian information criterion. The CRIs of the selected two- and three-exposure combinations, together with that of the four exposures, were compared to assess the effects contributed by additionally included co-exposures.

2.4.5. Sensitivity analyses

We conducted the following sensitivity analyses to examine the robustness of the results of the single-exposure analyses. First, we restricted the analyses to participants who did not move during the study period to reduce the risk of exposure misclassification. Second, we used temperature and NDVI assessed in 2014 (end year of follow-up) to assess the potential effects of the temporal changes in exposures. Since traffic noise and air pollution were estimated only for one year, they were kept unchanged in this sensitivity analysis. The linearity of the exposure-response relationships was examined by including a spline of the exposure variable in the single-exposure Poisson regression model. In addition, we explored the potential interactive effects of exposures by including an interaction term of two continuous exposures in the two-exposure model.

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 $P < 0.05$.

3. Results

3.1. Study population

Table 1 provides an overview of the baseline characteristics of the total study sample and stratified by the incidence of DSPN. This study sample is almost identical to a study population used in a previous analysis focusing on air pollution and DSPN (Herder et al., 2020). Briefly, people who developed DSPN were characterised by older age, higher BMI and waist circumference and a higher proportion of CVD than people who did not develop DSPN. Other characteristics did not differ significantly between both groups.

Table 3
Risk ratios (95 % confidence intervals) of incident DSPN for an IQR change in exposures among all participants.

	Exposure	IQR	Minimum model	Main model	Extended model
Temperature	Annual mean temperature	0.67 °C	1.10 (0.93, 1.31)	1.10 (0.91, 1.34)	1.11 (0.91, 1.35)
	Mean temperature of warm season	0.75 °C	1.11 (0.95, 1.31)	1.12 (0.93, 1.35)	1.13 (0.94, 1.35)
	Mean temperature of cold season	0.58 °C	1.08 (0.90, 1.28)	1.07 (0.88, 1.30)	1.08 (0.89, 1.30)
Greenness	NDVI in 100 m buffer	0.11	1.01 (0.89, 1.14)	1.05 (0.90, 1.21)	1.04 (0.89, 1.20)
	NDVI in 300 m buffer	0.11	0.96 (0.84, 1.10)	0.98 (0.84, 1.15)	0.96 (0.82, 1.13)
	NDVI in 500 m buffer	0.11	0.92 (0.79, 1.07)	0.93 (0.78, 1.12)	0.91 (0.75, 1.09)
	NDVI in 1000 m buffer	0.11	0.88 (0.75, 1.03)	0.88 (0.72, 1.07)	0.85 (0.69, 1.04)
Noise	Daily average traffic noise	7.4 dB(A)	1.00 (0.88, 1.14)	1.04 (0.90, 1.19)	1.05 (0.91, 1.20)
	Night-time average traffic noise	7.2 dB(A)	1.02 (0.89, 1.16)	1.05 (0.92, 1.20)	1.06 (0.93, 1.22)
Air pollutant	PNC	2.0 × 10^3/cm^3	1.05 (0.95, 1.16)	1.13 (1.00, 1.28)†	1.13 (1.00, 1.28)†
	PM_{10}	2.1 μg/m^3	0.96 (0.83, 1.12)	1.00 (0.83, 1.19)	1.00 (0.83, 1.20)
	PM_{coarse}	1.4 μg/m^3	0.94 (0.81, 1.08)	0.97 (0.79, 1.18)	0.96 (0.79, 1.18)
	$PM_{2.5}$	1.5 μg/m^3	0.94 (0.80, 1.10)	0.96 (0.79, 1.17)	0.95 (0.78, 1.15)
	$PM_{2.5abs}$	0.3 × 10^{-5}/m	0.92 (0.79, 1.08)	0.92 (0.73, 1.16)	0.93 (0.74, 1.17)
	NO_2	6.8 μg/m^3	0.94 (0.80, 1.11)	0.98 (0.78, 1.23)	0.98 (0.78, 1.23)
	NO_x	8.6 μg/m^3	1.02 (0.91, 1.14)	1.08 (0.93, 1.26)	1.08 (0.92, 1.26)
	O_3	3.5 μg/m^3	0.98 (0.84, 1.14)	0.97 (0.83, 1.13)	0.95 (0.82, 1.11)

Note: The minimum model was adjusted for age and sex. The main model was adjusted for age, sex, years of education, neighbourhood socioeconomic status, 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, history of cardiovascular disease, estimated glomerular filtration rate, neurological conditions that might cause nerve damage, use of lipid-lowering medication, and use of NSAIDs.
Effects were estimated for an IQR decrease in metrics of air temperature and greenness, and for an IQR increase in metrics of traffic noise and air pollution.
DSPN = distal sensorimotor polyneuropathy, IQR = interquartile range, NDVI = Normalized Difference Vegetation Index, NO_2 = nitrogen dioxide, NO_x = nitrogen oxides, O_3 = ozone, PM = particulate matter, PNC = particle number concentration, SD = standard deviation.
† $P < 0.1$.

3.2. Environmental exposures

Table 2 shows the distributions of the environmental exposures, i.e. different measures of air temperature, greenness, noise and air pollution. Correlations between measures within these four categories were high with r = 0.6 to 1 (Fig. A.1). Moderate to strong positive correlations were also observed between measures of temperature and most air pollutants (r = 0.3 to 0.7), whereas correlations between temperature and noise were less pronounced (r = 0.2 to 0.3). Measures of noise showed positive correlations with all air pollutants (r = 0.3 to 0.5, except O_3). In contrast, NDVI as a measure of greenness was inversely associated with measures of air pollution (r = −0.8 to −0.5, again except O_3), air temperature (r = −0.4 to −0.2) and noise (r = −0.3).

3.3. Environmental exposures and incident DSPN in the total study sample

Associations between environmental exposures and incident DSPN in single-exposure models were strongest for PNC (RR [95 % CI] 1.13 [1.00, 1.28] per IQR in the main model), but not significant for the other exposures (Table 3). Results in two-exposure models were consistent with those from single-exposure models (Fig. 1).

In a step-wise selection of representative exposures for all four categories (IQR decrease in the mean temperature of warm season, IQR decrease in NDVI in a 100 m buffer, IQR increase in night-time average traffic noise, IQR increase in annual average PNC), PNC was selected first, followed by temperature, noise and NDVI (Fig. 2, Table A.2). In the final multi-exposure model, the co-occurrence of all four exposures was associated with a significantly increased risk of DSPN (CRI [95 % CI] 1.39 [1.02, 1.91]) (Fig. 2, Fig. A.2). Table A.1 and Fig. A.2 show the CRI for all combinations of exposure categories for incident DSPN.

3.4. Effect modification by obesity

As shown in Table 4, RR for associations between greenness, noise and air pollutants were generally higher in the obese than in the non-obese subgroup, whereas RR between air temperature and DSPN were lower in the obese subgroup. Evidence for effect modification was found for NDVI in a 100-m buffer (RR [95 % CI] 1.33 [0.99, 1.78] in the obese vs 0.94 [0.80, 1.09] in the non-obese, $P_{interaction}$ = 0.03), night-time traffic noise (RR [95 % CI] 1.23 [1.01, 1.50] in the obese vs 0.94 [0.79, 1.12] in the non-obese, $P_{interaction}$ = 0.05) and PM_{coarse} (RR [95 % CI] 1.24 [0.95, 1.63] in the obese vs 0.85 [0.69, 1.05] in the non-obese, $P_{interaction}$ = 0.01). Within the subgroups, significant associations with incident DSPN were observed for night-time traffic noise (RR [95 % CI] 1.23 [1.01, 1.50]) and PNC (RR [95 % CI] 1.29 [1.08, 1.55]) in the subgroup with obesity (Table 4).

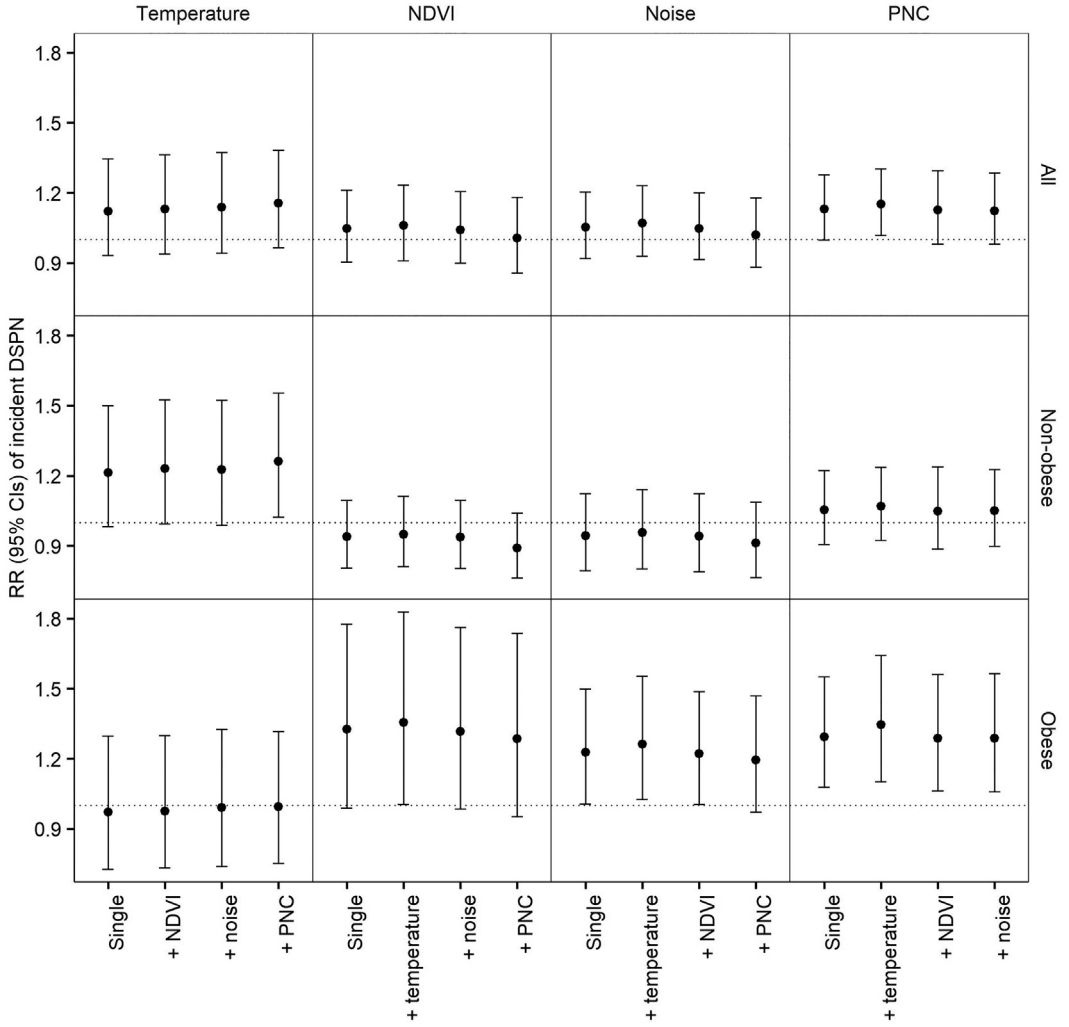

Fig. 1. Risk ratios of incident DSPN associated with mean temperature of warm season, NDVI in a 100 m buffer, night-time average traffic noise, and PNC from single- and two-exposure models among all participants, non-obese participants, and obese participants.
Note: Effects were estimated for an IQR decrease in the mean temperature of warm season and NDVI in a 100 m buffer, and for an IQR increase in night-time average traffic noise and PNC.

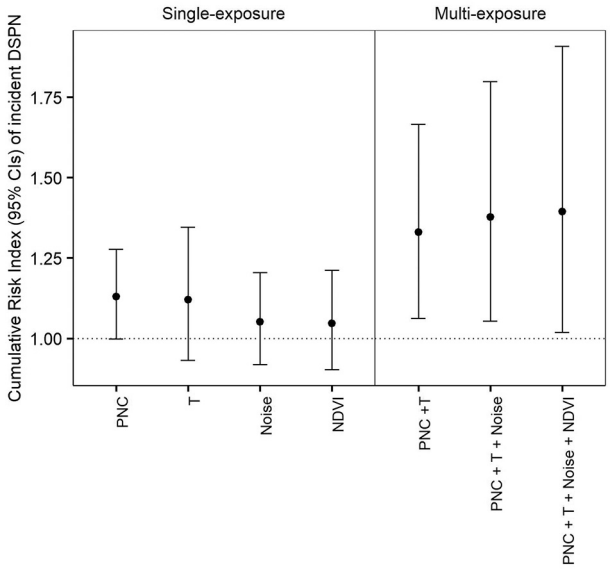

Fig. 2. Cumulative Risk Index of incident DSPN associated with PNC, mean temperature of warm season, night-time average traffic noise, and NDVI in a 100 m buffer from single- and multi-exposure models among all participants.
Note: Presented combinations of multi-exposures were selected based on the Akaike information criterion and Bayesian information criterion. Effects were estimated for an IQR decrease in the mean temperature of warm season and NDVI in a 100 m buffer, and for an IQR increase in night-time average traffic noise and PNC.
NDVI = Normalized Difference Vegetation Index, PNC = particle number concentration, T = temperature.

Again, results were robust in the two-exposure models (Fig. 1) and the extended model with more comprehensive adjustment (Table A.3).

The CRI for exposure combinations were between 0.90 and 1.33 in individuals without obesity, and between 1.34 and 2.01 in individuals with obesity (Table A.1). Significant effect modification was observed for several of these combinations. The same step-wise selection of representative exposures for all four categories was performed with consideration of the interaction between exposures and obesity, NDVI in a 100 m buffer was selected first, followed by PNC, mean temperature of the warm season and night-time traffic noise (Table A.4). In the final multi-exposure model, the co-occurrence of all four exposures was associated with a two-fold increased risk of DSPN among the obese (CRI [95 % CI] 2.01 [1.10, 3.67]), whereas this association was not statistically significant in the non-obese subgroup (CRI [95 % CI] 1.18 [0.83, 1.67], $P_{interaction}$ = 0.13) (Fig. 3, Table A.1). Results from the extended model were almost identical (Table A.5).

3.5. Sensitivity analyses

In sensitivity analyses, effect estimates for the total sample and in the subgroups stratified by obesity were almost unchanged when restricting the analyses to 397 participants who did not move during the study period (Table A.6) or when using air temperature and NDVI as assessed in 2014, i.e. at the end of the follow-up (Table A.7). Including splines of exposures in the regression models showed no deviation from linearity for the exposure-response relationships between representative exposures and incident DSPN (Fig. A.2). We did not find evidence suggesting interactive effects of combined exposures in all, non-obese, or obese participants, with *P* values for the interaction term all above 0.1 (Table A.8).

The inverse-probability weighting approach improved the covariate balance between the participants included in the current analyses (n = 423) and those meeting the inclusion criteria (n = 1075), with mean absolute SMDs decreased from 0.156 to 0.018. The absolute SMDs before and after weighting for each covariate are shown in Table A.9.

4. Discussion

4.1. Key findings

This study has three key findings. First, air pollution, and specifically ultrafine particles, showed the strongest association with incident DSPN, whereas associations between the other exposures were less pronounced or absent in the total study sample. Second, the joint analysis of all exposures demonstrated additive effects with a 1.4-fold increased risk of DSPN based on lower air temperature in the warm season, less greenness close to participants' residences, and higher noise levels and ultrafine particle concentrations. Third, people with obesity appeared more susceptible to

Table 4
Risk ratios (95 % confidence intervals) of incident DSPN for an IQR change in exposures stratified by obesity (main model).

	Exposure	IQR	Non-obese (n = 306)	Obese (n = 117)	$P_{interaction}$
Temperature	Annual mean temperature	0.67 °C	1.20 (0.96, 1.52)	0.95 (0.70, 1.28)	0.19
	Mean temperature of warm season	0.75 °C	1.21 (0.98, 1.50)†	0.97 (0.73, 1.30)	0.19
	Mean temperature of cold season	0.58 °C	1.16 (0.92, 1.47)	0.92 (0.68, 1.23)	0.20
Greenness	NDVI_100 m	0.11	0.94 (0.80, 1.09)	1.33 (0.99, 1.78)†	0.03
	NDVI_300 m	0.11	0.91 (0.76, 1.08)	1.18 (0.91, 1.52)	0.07
	NDVI_500 m	0.11	0.85 (0.69, 1.03)	1.14 (0.85, 1.52)	0.07
	NDVI_1000 m	0.11	0.81 (0.66, 1.00)†	1.02 (0.74, 1.41)	0.17
Noise	Daily average traffic noise	7.4 dB(A)	0.93 (0.78, 1.11)	1.19 (0.98, 1.44)†	0.06
	Night-time average traffic noise	7.2 dB(A)	0.94 (0.79, 1.12)	1.23 (1.01, 1.50)*	0.05
Air pollutant	PNC	$2.0 \times 10^3/cm^3$	1.05 (0.91, 1.22)	1.29 (1.08, 1.55)**	0.07
	PM_{10}	2.1 $\mu g/m^3$	0.90 (0.72, 1.12)	1.16 (0.91, 1.47)	0.10
	PM_{coarse}	1.4 $\mu g/m^3$	0.85 (0.69, 1.05)	1.24 (0.95, 1.63)	0.01
	$PM_{2.5}$	1.5 $\mu g/m^3$	0.89 (0.73, 1.09)	1.13 (0.79, 1.60)	0.21
	$PM_{2.5abs}$	$0.3 \times 10^{-5}/m$	0.88 (0.68, 1.13)	0.99 (0.72, 1.35)	0.48
	NO_2	6.8 $\mu g/m^3$	0.88 (0.68, 1.13)	1.18 (0.87, 1.60)	0.06
	NO_x	8.6 $\mu g/m^3$	1.00 (0.84, 1.18)	1.25 (0.98, 1.59)†	0.10
	O_3	3.5 $\mu g/m^3$	0.92 (0.76, 1.11)	1.06 (0.81, 1.39)	0.40

Note: The model (main model) was adjusted for age, sex, years of education, neighbourhood socioeconomic status, smoking status, alcohol consumption, physical activity, height, and waist circumference.
Effects were estimated for an IQR decrease in metrics of air temperature and greenness, and for an IQR increase in metrics of traffic noise and air pollution.
DSPN = distal sensorimotor polyneuropathy, IQR = interquartile range, NDVI = Normalized Difference Vegetation Index, NO_2 = nitrogen dioxide, NO_x = nitrogen oxides, O_3 = ozone, PM = particulate matter, PNC = particle number concentration, SD = standard deviation.
** $P < 0.01$.
* $P < 0.05$.
† $P < 0.1$.

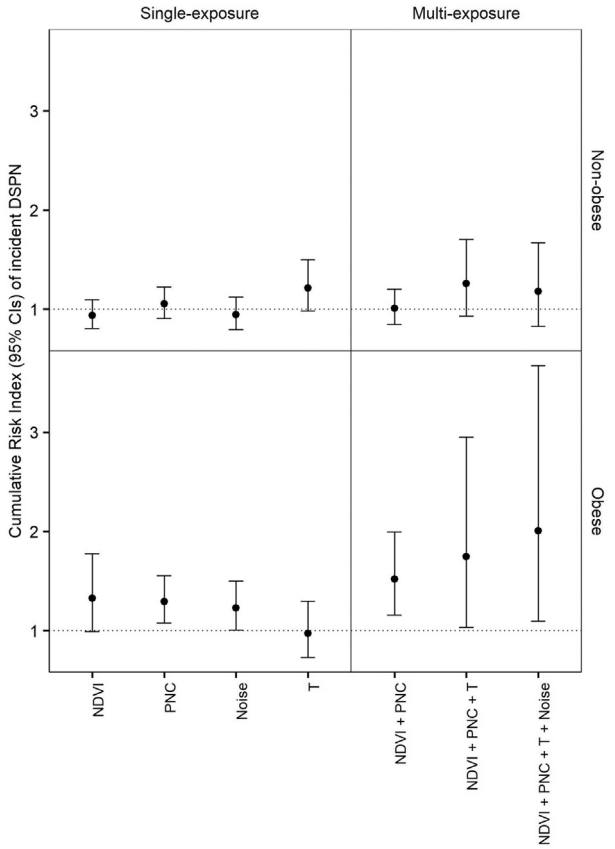

Fig. 3. Cumulative Risk Index of incident DSPN associated with NDVI in a 100 m buffer, PNC, night-time average traffic noise, and mean temperature of warm season from single- and multi-exposure models among non-obese vs. obese participants.
Note: Presented combinations of multi-exposures were selected based on the Akaike information criterion and Bayesian information criterion. Effects were estimated for an IQR decrease in the mean temperature of warm season and NDVI in a 100 m buffer, and for an IQR increase in night-time average traffic noise and PNC.
NDVI = Normalized Difference Vegetation Index, PNC = particle number concentration, T = temperature.

most exposures leading to a 2-fold increased risk for DSPN when the aforementioned risk factors were assessed in a joint model.

4.2. Ambient air temperature, greenness, traffic road noise, air pollution and incident DSPN

These results extend those from our previous study in this cohort that identified novel associations between air pollutants and DSPN (Herder et al., 2020) by providing the first data for ambient air temperature, greenness and traffic road noise in this context. Each exposure group was assessed using several correlated measures. Overall, effect estimates were modest when the total study sample was analysed.

Among the air pollutants, PNC showed the strongest association with incident DSPN as described before (Herder et al., 2020). PNC is an indicator of ultrafine particles which is primarily derived from combustion processes in road traffic (Wolf et al., 2017; Rajagopalan and Landrigan, 2021). Given both their high number concentrations, their ability to penetrate deeply into the lungs and their potential to translocate into the circulation, the detrimental effects of ultrafine particles on multiple cardiovascular, metabolic and neurological diseases are biologically plausible (Stone et al., 2017). The mechanism linking PNC to incident DSPN is not known, but may include neuroinflammation, oxidative stress and endothelial dysfunction (Herder et al., 2020).

Ambient air temperature has not been investigated as a potential risk factor for DSPN. There is evidence that both heat and cold stress may exacerbate cardiometabolic conditions (Kenny et al., 2016; Ebi et al., 2021). Interestingly, non-freezing cold injury has been found related to sensory neuropathy (Vale et al., 2017), whereas short-term exposure to cooled room temperature has been shown to decrease NCV (Maetzler et al., 2012). In line with these observations, our data suggest a higher DSPN risk linked to lower mean temperatures, but effect sizes were small and not significant. One reason for this finding may be that the study area in Southern Germany is located within the cool temperate climate zone, whereas effects might be stronger in warmer or colder climate zones. In future studies it would also be informative to analyse temperature extremes, especially during heat waves, which may have more pronounced effects (Ebi et al., 2021). Heat stress leads to haematological, cardiovascular, neurological and renal dysfunction, and heat waves increase mortality from neurological diseases (Basagaña et al., 2011; Shaposhnikov et al., 2014; Ebi et al., 2021). Given the global rise in mean temperature and temperature extremes due to climate change, temperature effects on peripheral nerve function and the development of DSPN merit further investigations.

We used the NDVI to estimate greenness in the vicinity of participants' residences and found only weak associations with incident DSPN when analysing the whole study sample. Based on the associations between lower residential greenness and higher cardiometabolic and neurodegenerative disease risk (Twohig-Bennett and Jones, 2018; Rodriguez-Loureiro et al., 2022), such an association would also be plausible for DSPN. The neighbourhood and physical environment have only recently been discussed as potential determinants of DSPN, with physical activity, glycaemic control in people with diabetes and overall stress levels being the possible mediators (Hill-Briggs et al., 2020; Pop-Busui et al., 2022). Further studies based on study areas with larger variation in greenness and most likely also larger sample sizes would be important to assess this novel risk factor.

Noise pollution has been investigated in detail primarily in the context of cardiovascular disease (Münzel et al., 2021), and the present study is the first one to assess its assocation with incident DSPN. In the total study sample higher traffic noise levels at day and night tended to be related to higher risk of DSPN but confidence intervals were wide. However, our effect estimates were similar or even larger than those found in a recent meta-analysis on road traffic noise and incident stroke, cardiovascular and all-cause mortality (Hao et al., 2022). Importantly, guidelines for the European region strongly recommend to reduce noise levels from road traffic below 53 dB and night noise exposure to below 45 dB (WHO Europe, 2018) which are close to the mean levels observed in our study area. Given the impact of noise pollution on stress hormone signalling, hypertension, oxidative stress, inflammation and the nervous system (Pitchika et al., 2017; Münzel et al., 2021; Peters et al., 2021) the relationship between noise and risk of DSPN needs to be explored in more detail.

The associations between most environmental risk factors and risk of morbidity or mortality are small or moderate in size but these effects have major public health effects based on the ubiquitous presence of air and noise pollution or other exposures (Rajagopalan and Landrigan, 2021; Münzel et al., 2020). Additionally, the new paradigm of the exposome emphasises the importance of assessing the joint effects of all environmental stressors on disease risk (Münzel et al., 2021; Beulens et al., 2022). The observed effect size for the combined exposures to several environmental risk factors is in the same range as those for established anthropometric and metabolic risk factors of DSPN (Andersen et al., 2018; Schlesinger et al., 2019). This finding underlines the relevance of this novel research area for our understanding of risk factors and the aetiology of DSPN.

4.3. Interaction with obesity

Air pollution represents the environmental exposure that has been investigated most thoroughly with respect to disease risk. Multiple studies in this field, which integrated subgroup analyses in their design, pointed towards a substantial heterogeneity in the susceptibility to air pollutants within populations and indicated that people with obesity represent a particularly vulnerable group (Weichenthal et al., 2014; Yang et al., 2018; Kim

et al., 2019; Kim et al., 2021; Li et al., 2021). Our study is the first to address this issue in the context of DSPN for multiple environmental exposures. We found consistently higher effect estimates for the associations between different exposures in the categories of greenness, noise and air pollution in obese compared to non-obese individuals. This interaction translated to a two-fold increased risk of DSPN in people with obesity in the presence of all four risk factors. Compared with other risk factors of DSPN (Andersen et al., 2018; Schlesinger et al., 2019), this increase in relative risk is remarkable and doubtless also of clinical relevance. Our data extend our previous report on air pollution and DSPN (Herder et al., 2020), and they are in line with other studies showing stronger effects of air pollution in people with obesity on dyslipidaemia (Yang et al., 2018; Kim et al., 2019; Kim et al., 2021), incident type 2 diabetes (Li et al., 2021) and cardiovascular risk (Weichenthal et al., 2014).

Different mechanisms have been suggested for the amplification of the effect of air pollution in obese individuals (Herder et al., 2020). Obesity is associated with endothelial dysfunction, subclinical inflammation and oxidative stress as well as the activation of the hypothalamic-pituitary-adrenal axis and of the autonomic nervous system which affect peripheral nerve function, and these pathways are also stimulated by air pollution and other exposures (Schwartz et al., 2005; O'Brien et al., 2017; Rajagopalan et al., 2018; Herder et al., 2020; Li et al., 2021; Münzel et al., 2021). Thus, it is biologically plausible that obesity might act as effect modifier.

A recent longitudinal study indicated that air pollution may be a direct risk factor for higher fat mass (Wang et al., 2022) in which case obesity could also represent a potential mediator in the association between air pollution, DSPN and other conditions. However, the evidence is certainly not conclusive yet, and such a mediation study would need a larger sample size than ours. If obesity was indeed a partial mediator, one would expect an attenuation of associations when adjusting for waist circumference but this was not the case in our study.

Overall, the public health and policy implications are twofold. First, our study adds DSPN to the growing list of diseases whose incidence is increased by environmental risk factors, in particular by air pollution (Thurston et al., 2017). The environmental risk factors considered here cannot be altered without changing the place of residence and moving into areas with less harmful environmental exposures. This highlights the need for coordinated societal and political interventions to reduce environmental hazards for all and to pursue a more holistic approach for disease prevention by addressing lifestyle, socioeconomic and environmental factors simultaneously (Münzel et al., 2020; Rajagopalan and Landrigan, 2021). Additionally, the Clean Air Act (42 U.S.C. §§ 7401 et seq.) has the explicit aim to protect the health of vulnerable population subgroups so that further support would be required for people with obesity and potentially other subgroups at high risk of DSPN. Second, our data emphasised further the importance of preventing and treating obesity. Of note, obesity is a key modifiable risk factor not only for DSPN but also for complex multimorbidity so that efforts attempting to tackle the obesity epidemic with lifestyle intervention or pharmacological approaches should have profound effects on health outcomes beyond DSPN (Kivimäki et al., 2022).

4.4. Strengths and limitations

Main strengths of this study are the population-based prospective study design, the repeated assessment of DSPN, the comprehensive assessment of multiple environmental exposures, the adjustment for multiple confounders in our analyses, the calculation of joint effects of co-occurring exposures and the consideration of effect modification by obesity, because people with obesity may represent a particularly susceptible fraction of the population with respect to health effects of multiple environmental exposures.

This study also has several limitations. Our definition of DSPN is based on the MNSI, but more objective measurements of nerve conduction velocity were not feasible in this epidemiological setting. As in all studies on environmental hazards, exposure misclassification cannot be ruled out because we could only assess exposures at participants' residences. In addition, we only used the addresses at study baseline rather than a full residential history. However, we performed a sensitivity analysis excluding people who moved during the study period to reduce misclassification and found similar results to that of the main analysis. In this study, we used single-year exposures that reflected the spatial variations but not temporal trends in exposures. This was based on the hypothesis that the spatial variation was more crucial in the assessment of long-term health effects. The sensitivity analysis using temperature and NDVI data from the end year of follow-up suggested that our findings were not substantially affected by potential temporal changes in these two exposures. For air pollution, we only used data from 2014 to 2015 due to the data availability. Nevertheless, there have been studies showing that the spatial contracts in air pollution remained stable over time (Eeftens et al., 2011; Eeftens et al., 2012; de Hoogh et al., 2018; Brunekreef et al., 2021), and using back-extrapolated air pollution data prior to 2014/15 did not change the estimated health effects (Zhang et al., 2021; Wolf et al., 2021). So far, the evidence for the temporal trend in noise and its impacts on the health effect assessment was limited and therefore warrants further investigations. Our sample size was sufficient to detect multiple risk factors and biomarkers of incident DSPN (Herder et al., 2017; Herder et al., 2018; Schlesinger et al., 2019; Herder et al., 2020), but the analysis of environmental hazards in this context may require larger sample sizes for specific exposures. Larger sample sizes would also be necessary for in-depth analyses on confounding and mediating effects between correlated exposures as exemplified by a previous study on similar exposures and the prevalence of cardiometabolic conditions (Klompmaker et al., 2019). The participants of the KORA F4/FF4 studies were mainly of European descent so that data are not generalisable to other ethnicities. We focused on four ubiquitous environmental exposures but future studies should also address light pollution (night-time light) or exposure to e.g. persistent organic pollutants or metals. In addition, it would be important to address environmental determinants of DSPN also in India, China or other parts of the world with higher overall exposure levels. Finally, the observational design of the study precludes any inferences on causality.

5. Conclusion

This study demonstrated that the joint exposure to a ultrafine particles, air temperature during the warm season, residential greenness and night-time average traffic noise was associated with an increased risk of DSPN. Effect estimates were generally higher in individuals with obesity than in those without, and the multi-exposure model resulted in a twofold increased risk of DSPN among people with obesity. Overall, associations between the investigated exposures and DSPN may be of similar effect sizes as those reported for incident diabetes, cardiovascular and neurodegenerative diseases. Our findings emphasise that environmental exposures do not occur in isolation and that multi-exposure approaches are needed to better understand independent and additive effects on the development of DSPN. This study also points towards both obesity prevention and treatment as well as the reduction of environmental hazards as an important public health task.

CRediT authorship contribution statement

Christian Herder: Conceptualization, Methodology, Writing – original draft, Supervision, Project administration. **Siqi Zhang:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization. **Kathrin Wolf:** Conceptualization, Methodology, Writing – review & editing. **Haifa Maalmi:** Writing – review & editing. **Gidon J. Bönhof:** Investigation, Writing – review & editing. **Wolfgang Rathmann:** Investigation, Writing – review & editing. **Lars Schwettmann:** Investigation, Writing – review & editing. **Barbara Thorand:** Investigation, Writing – review & editing. **Michael Roden:** Writing – review & editing, Funding acquisition. **Alexandra Schneider:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision. **Dan Ziegler:** Conceptualization, Methodology, Investigation, Writing – review & editing,

Supervision, Funding acquisition. **Annette Peters:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision, Funding acquisition.

Data availability

Data will be made available on request.

Declaration of competing interest

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

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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.PASST (https://epi.helmholtz-muenchen.de/).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2022.159878.

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