Aus dem
Institut für Epidemiologie
Helmholtz Zentrum München – Deutsches Forschungszentrum für Gesundheit und
Umwelt (GmbH), Neuherberg, Deutschland

Metabolic diseases and related traits: Novel epidemiological approaches and environmental determinants

Dissertation
zum Erwerb des Doktorgrades der Humanbiologie
an der Medizinischen Fakultät
der Ludwig-Maximilians-Universität München

vorgelegt von
Fiona Niedermayer

aus
Füssen

Jahr
2026

Mit Genehmigung der Medizinischen Fakultät der
Ludwig-Maximilians-Universität München

Erstes Gutachten:	Prof. Dr. Annette Peters
Zweites Gutachten:	Prof. Dr. Barbara Hoffmann
Drittes Gutachten:	Prof. Dr. Christine Meisinger

Dekan:	Prof. Dr. med. Thomas Gudermann

Tag der mündlichen Prüfung: 12.01.2026

Für meine Familie

Table of Contents

List of abbreviations

AT	Adipose tissue
BMI	Body mass index
CI	Confidence Interval
CVD	Cardiovascular disease
DAG	Directed acyclic graph
DGEpi	Deutsche Gesellschaft für Epidemiologie
DXA	Dual-energy X-ray absorptiometry
EIONET	European Environment Information and Observation Network
ELAPSE	Effects of Low-Level Air Pollution: A Study in Europe
EUROSTAT	Statistical office of the European Union
FFA	Free fatty acids
HbA1c	Hemoglobin A1c
HOMA-IR	Homeostasis model assessment-estimated insulin resistance
IQR	Interquartile range
ISEE	International Society of Environmental Epidemiology
KORA	Cooperative Health Research of Augsburg (Kooperative Gesundheitsfor-schung in der Region Augsburg)
L_{den}	Day–evening–night noise level
LMU	Ludwig-Maximilians-University
MASLD	Metabolic dysfunction associated steatotic liver disease
MRI	Magnetic resonance imaging
NAKO	German National Cohort (Nationale Kohortenstudie)
NAFLD	Non-alcoholic fatty liver disease
NDVI	Normalized difference vegetation index
NO_2	Nitrogen dioxide
NO_x	Nitrogen oxide
O_3	Ozone
OR	Odds ratio
PM	Particulate matter
$PM_{2.5}$	Particulate matter with an aerodynamic diameter ≤ 2.5 µm
PM_{coarse}	Particulate matter with an aerodynamic diameter between 2.5 µm and 10 µm
PM_{10}	Particulate matter with an aerodynamic diameter ≤ 10 µm
$PM_{2.5}$abs	$PM_{2.5}$ absorbance

SAT	Subcutaneous adipose tissue
SCAAT	Subcutaneous abdominal adipose tissue
SCTAT	Subcutaneous thoracic adipose tissue
SES	Socioeconomic status
TG	Triglyceride
T_{mean}	Mean temperature
VAT	Visceral adipose tissue
WC	Waist circumference
WHO	World Health Organization

Abstract (English)

Background: Metabolic diseases, including diabetes, obesity and metabolic dysfunction associated steatotic liver disease (MASLD), often co-occur and represent a major public health burden. To identify successful prevention strategies, it is necessary to better understand the relationships between different metabolic diseases and their early risk factors. Previous studies have suggested a bidirectional relationship between diabetes and MASLD. However, evidence on the dynamic changes in glycemia and its effect on the accumulation of hepatic fat and iron content, particularly differences in sexes, is scarce. In addition, to aid context-related prevention, it is crucial to understand how environmental factors are associated with metabolic diseases and related traits. There is promising evidence on the association of particulate matter (PM) and road traffic noise with diabetes, but studies on the association of other environmental factors with metabolic traits were inconclusive. Furthermore, previous literature has mainly focused on single environmental factors, neglecting the fact that environmental factors do not occur in isolation. Therefore, the aim of this work was to elucidate the associations of dynamic changes in glycemic traits with hepatic fat and iron and to evaluate individual and joint associations of multiple environmental exposures with metabolic diseases and related traits.

Methods: To assess the interrelationship of glycemia with hepatic fat and iron, we used longitudinal data from the population-based Cooperative Health Research of Augsburg (KORA) cohort with two examination time points. Exposure included glycemia and related traits available at two time points over a seven-year study period, and outcome included hepatic fat and iron content measured by magnetic resonance imaging (MRI) at the second examination. We used a novel statistical two-stage multilevel model adjusted for confounders and stratified by sex. Regarding the impact of environmental factors on metabolic diseases, we used cross-sectional data from KORA Fit (n = 3,047) and baseline data from the multi-center German National Cohort (NAKO) (n = 204,687). As exposures, we considered annual mean levels of air pollutants, air temperature, road traffic noise (NAKO only), and greenness assigned to participants' residential addresses. Outcomes included diabetes (self-report), obesity (body mass index (BMI) ≥ 30 kg/m²), BMI and waist circumference. Single-exposure linear and logistic regression models with covariate adjustment, including an interaction term for sex and urbanization, were applied. In NAKO, we additionally assessed joint associations of multiple environmental exposures with metabolic traits using quantile g-computation. Finally, we used data from the NAKO-MRI subsample with available MRI data between 2014 and 2016 (n = 11,343) to assess the association of long-term exposure to road traffic noise with different MRI-derived adipose tissue depots, including hepatic fat content, and prevalence of MASLD. Estimates derived from linear and logistic regression models quantified the associations of a 10 dB(A) increase in noise exposure with outcomes after controlling for confounders.

Results: We observed a worsening of glycemia and related characteristics over time that was associated with higher hepatic fat content in men and women. In addition, changes from normoglycemia to prediabetes were associated with higher hepatic iron content only in men, suggesting a more complex and sex-specific relationship between diabetes and hepatic iron. In KORA Fit and NAKO, we demonstrated complex sex- and urbanization-specific associations of environmental factors with diabetes, obesity, BMI, and waist circumference. We found consistent associations of annual exposure to $PM_{2.5}$ and road traffic noise with metabolic traits, especially in urban areas. Non-linear associations were found between surrounding greenness and metabolic diseases and their traits, while no clear association was found for annual averages of air temperature. Exposure to a mixture of environmental factors was associated with higher odds of metabolic diseases, higher BMI, and waist circumference, with doubled estimates for joint exposures compared to single-exposure models. In addition, we observed that higher annual levels of road traffic noise were associated with larger fat depots and higher hepatic fat content, even after controlling for air pollution and surrounding greenness.

Conclusion: By using novel epidemiological approaches and methods, this thesis adds important evidence on the interrelationship between metabolic diseases, related traits, and their environmental determinants. Thus, our findings highlight that screening for hepatic steatosis and iron overload in individuals with incipient deterioration of glycemic traits may enable early detection of the development of metabolic comorbidities. We also add to the literature that higher annual levels of $PM_{2.5}$ and road traffic noise were associated with metabolic diseases and related traits in cross-sectional analyses, and that a joint exposure to multiple environmental risk factors showed stronger associations with metabolic diseases and traits. Thus, we provided novel evidence for potential systemic impacts of air pollution and noise on metabolic diseases and related traits. Future studies should focus on longitudinal analyses and combined effects to confirm these findings. More research is needed to fully understand the association of surrounding greenness with metabolic diseases and whether there is a link between average temperature and metabolic diseases in temporal climates. In addition, further research should aim to identify the drivers of metabolic diseases and their traits in rural areas.

Zusammenfassung (Deutsch)

Hintergrund: Stoffwechselerkrankungen wie Diabetes, Adipositas und die metabolisch-assoziierte Lebererkrankung (MASLD) treten häufig gemeinsam auf und stellen eine große Belastung für die öffentliche Gesundheit dar. Um erfolgreiche Präventionsstrategien entwickeln zu können, müssen die Zusammenhänge zwischen den verschiedenen Stoffwechselerkrankungen und deren Risikofaktoren besser verstanden werden. Die derzeitige Studienlage deutet auf eine bidirektionale Beziehung zwischen Diabetes und MASLD hin. Allerdings gibt es bisher nur wenige Studien, die den Verlauf von Diabetesmarkern und deren Einfluss auf die Akkumulation von Leberfett und Lebereisen unter Berücksichtigung geschlechtsspezifischer Unterschiede untersucht haben. Zusätzlich könnte eine Assoziation zwischen Umweltfaktoren und Stoffwechselerkrankungen wichtige Erkenntnisse zu Präventionsmöglichkeiten auf Bevölkerungsebene liefern. Es gibt bereits vielversprechende Hinweise auf einen Zusammenhang zwischen Feinstaub (PM) oder Straßenverkehrslärm und Diabetes, aber Studien zu anderen Umweltfaktoren und deren Assoziation mit Stoffwechselerkrankungen waren nicht schlüssig. Ziel dieser Arbeit war es daher zum einen, die dynamischen Veränderungen von Diabetes-Markern und deren Zusammenhang mit frühen Indikatoren der Lebergesundheit zu bewerten und zum anderen, die individuellen und gemeinsamen Assoziationen zwischen langfristiger Exposition gegenüber Umweltfaktoren und Stoffwechselerkrankungen zu untersuchen.

Methoden: Für die Analyse des Zusammenhangs zwischen Diabetes und Leberfett und Lebereisen untersuchten wir Längsschnittdaten aus der bevölkerungsbasierten „Kooperative Gesundheitsforschung in der Region Augsburg“ (KORA)-Kohorte. Informationen zum Diabetesstatus und zu Blutzuckermarkern wurden an zwei Untersuchungszeitpunkten über einen Zeitraum von sieben Jahren erhoben. Leberfett und Lebereisen wurden mittels Magnetresonanztomographie (MRT) bei der zweiten Untersuchung gemessen. Wir verwendeten ein nach Geschlecht stratifiziertes neues statistisches Mehrebenenmodell, um die Assoziation zwischen Veränderungen der Diabetesmarker und dem Leberfett und Lebereisen zu quantifizieren. Für die Assoziation verschiedener Umweltfaktoren mit metabolischen Erkrankungen und deren Markern wurden Querschnittsdaten aus KORA Fit (n = 3.047) und Basisdaten der Nationalen Kohorte (NAKO) (n = 204.687) analysiert. Als Expositionsindikatoren betrachteten wir Jahresmittelwerte von Luftschadstoffen, Lufttemperatur, Straßenverkehrslärm (nur NAKO) und Grünflächen geschätzt an den Wohnadressen der Teilnehmenden. Als abhängige Variable standen Diabetes (Selbstangabe), Adipositas (Body-Mass-Index (BMI) ≥ 30 kg/m²), BMI und Taillenumfang zur Verfügung. Zur statistischen Auswertung wurden lineare und logistische Regressionsmodelle, zusätzliche Interaktionsanalysen für Geschlecht und Urbanisierung, sowie „Quantile g-computation“ verwendet. Schließlich verwendeten wir Daten aus der NAKO-MRT-

Stichprobe mit verfügbaren MRT-Daten aus den Jahren 2014-2016 (n = 11.343), um die Assoziation zwischen langfristiger Straßenverkehrslärmexposition und verschiedenen MRT-gemessenen Fettdepots und der Prävalenz von MASLD zu untersuchen. Die Assoziationen zwischen einer höheren Lärmbelastung und den Fettdepots wurde mit linearen und logistischen Regressionsmodellen geschätzt und zusätzlich für andere Umweltfaktoren kontrolliert.

Ergebnisse: Wir beobachteten eine Verschlechterung von Diabetes-Markern während des Studienzeitraums, die sowohl bei Männern als auch bei Frauen mit einem erhöhten Leberfettgehalt assoziiert waren. Darüber hinaus fanden wir einen komplexen Zusammenhang zwischen Diabetes und Lebereisen, wobei nur bei Männern eine Verschlechterung zu Prädiabetes mit einem höheren Lebereisengehalt assoziiert war. Die Ergebnisse von KORA Fit und NAKO weisen auf komplexe geschlechts- und urbanisierungsspezifische Assoziationen von Umweltfaktoren mit Diabetes, Adipositas, BMI und Taillenumfang hin. Konsistente Zusammenhänge fanden wir zwischen jährlicher Exposition gegenüber $PM_{2.5}$ und Straßenverkehrslärm mit Stoffwechselerkrankungen und deren Risikofaktoren, insbesondere in städtischen Gebieten. Grünflächen waren nichtlinear mit Stoffwechselerkrankungen assoziiert, während wir keine Assoziation zwischen Lufttemperatur und Stoffwechselerkrankungen beobachteten. Im Vergleich zu einzelnen Umweltfaktoren war die Exposition gegenüber einer Kombination von Umweltfaktoren mit einem doppelt so hohen Risiko für Stoffwechselerkrankungen und deren Markern assoziiert. Darüber hinaus beobachten wird, dass ein Anstieg der Lärmbelastung um 10 dB(A) mit größeren Fettdepots assoziiert war, selbst nach zusätzlicher Adjustierung für Luftschadstoffe und Grünflächen.

Schlussfolgerung: Durch die Nutzung von neuen epidemiologischen Ansätzen und Methoden liefert diese Arbeit wichtige Erkenntnisse über den Zusammenhang zwischen Stoffwechselerkrankungen und deren potenziellen Umweltdeterminanten. Schlussfolgernd könnte ein frühzeitiges Screening auf Leberfett und Lebereisen bei Personen mit beginnender Verschlechterung der Blutzuckerwerte die rechtzeitige Erkennung metabolischer Komorbiditäten ermöglichen. Darüber hinaus zeigt diese Arbeit, dass $PM_{2.5}$ und Straßenverkehrslärm in Querschnittsanalysen mit Stoffwechselerkrankungen und Markern assoziiert war, und dass die gemeinsame Exposition gegenüber mehreren Umweltrisikofaktoren eine stärkere Assoziation mit Stoffwechselerkrankungen zeigte. Dies liefert neue Hinweise auf potenziell systemische Effekte von Luftverschmutzung und Lärm auf Stoffwechselerkrankungen. Zukünftige Studien sollten sich auf Längsschnittanalysen und gemeinsame Effekte von Umweltfaktoren konzentrieren, um diese Ergebnisse zu bestätigen. Weitere Untersuchungen sind erforderlich, um die Zusammenhänge zwischen Grünflächen bzw. Lufttemperatur und Stoffwechselerkrankungen unter derzeitigen Klimabedingungen besser zu verstehen. Zudem ist weitere Forschung zu den Ursachen von Stoffwechselerkrankungen in ländlichen Gebieten notwendig.

1 Introduction and scientific background

1.1 Metabolic diseases: a public health concern

Currently, metabolic diseases pose a severe thread to population health and challenge health systems worldwide. For example, diabetes mellitus, obesity and MASLD are major contributors to the global disease burden with prevalences of approximately 10.5%, 23% and 25% worldwide, respectively (1-5). In addition, 1.4 million, 5 million, and 164,000 deaths are attributed to these diseases, respectively (1, 2). As in scientific literature, the term metabolic diseases is inconsistently used, the following chapter will give a definition of this term in order to clarify the endpoints considered as metabolic diseases throughout this thesis.

1.1.1 Definition of metabolic diseases

The term "metabolic diseases" is commonly used to describe a number of diseases characterized by abnormal metabolic processes (1). In addition to hypertension and hyperlipidemia, metabolic diseases comprise diabetes mellitus, which is characterized by impaired glucose homeostasis and insulin resistance, and obesity, hallmarked by excess adiposity (1, 6, 7) (**Figure 1**). More recently, a further metabolic disease has been added to the list: metabolic dysfunction associated steatotic liver disease (MASLD) (1). The change in nomenclature (formerly non-alcoholic fatty liver disease (NAFLD)) and the revised definition criteria aim to emphasize the abnormal metabolic processes underlying MASLD. These criteria now include the presence of high hepatic fat content (>5.6%) (8) and at least one out of five cardiometabolic conditions: high body mass index (BMI), diagnosis of type 2 diabetes, high blood pressure, high triglyceride levels or low high-density lipoprotein (1, 9).

By referring to obesity as a (metabolic) disease throughout the thesis (6), we follow the call of the World Health Organization (WHO) and several medical societies to recognize obesity as a chronic disease on its own (10-14), although the recognition and a revision of definitional criteria is an ongoing, controversial debate (6). Consequently, we utilized several different measures of body fat in addition to BMI to quantify adiposity in this thesis.

1.1.2 Current and predicted burden of metabolic diseases

As described above, the global burden attributed to diabetes mellitus, obesity and MASLD is already on a high level, but future projections expect a continuous and rapid rise of these three metabolic diseases (1, 5, 15, 16). For example, the number of individuals diagnosed with diabetes is expected to increase from 537 million in 2021 up to 1.3 billion within the next three decades (2, 17). Similarly, the Global Burden of Disease Study predicted an increase from 2 billion in 2021 to 3.8 billion people living with overweight and obesity in 2050 (5). MASLD, the most common liver disease in Western societies (3, 18), represents an early disease stage which can further progress to more severe liver diseases, such as cirrhosis and cancer (19). These dramatic increasing trends in metabolic diseases are driven by the risk factors high fasting plasma glucose and high BMI, which have consistently been among the top ten risk factors in the Global Burden of Disease studies over decades (16, 20). In particular, the increase in diabetes and MASLD is primary due to the ongoing obesity transition worldwide (5, 15). Thereby, the simple anthropometric measure BMI is widely used to define obesity with a cut-off of 30 kg/m² (Asian populations: 27.5 kg/m²) on the population level and in epidemiological analysis (6). However, a shift towards alternative measures is warranted.

1.1.3 BMI and alternative measures

BMI as the sole measure of obesity at the individual level has come under constant criticism as it may be too simplistic and tends to over- or underestimate disease risk in certain subpopulations (6). Consequently, experts advocate the assessment of body fat distribution (6), which is a more specific measure of excess adiposity and may provide more accurate information on individuals' cardiometabolic disease risk (18, 21). Indeed, waist circumference is a simple and feasible anthropometric measure that can serve as a surrogate of visceral adiposity (22). However, non-invasive imaging modalities that assess body composition holistically are considered as gold standard (23). For example, magnetic resonance imaging (MRI) enables to determine and distinguish different volumes of adipose tissue (AT) depots, such as visceral AT (VAT), subcutaneous AT (SAT) or ectopic fat (e.g., intrahepatic, intrapancreatic or pericardial) (18, 21). Although MRI is well established in clinical practice (24), the number of epidemiological studies with longitudinal MRI data is still limited due to cost and time constraints. Therefore, these imaging-derived markers are novel in the epidemiological context and may provide crucial evidence on subclinical disease states and risk prediction (25). In particular, higher VAT has been shown to be associated with increased cardiometabolic disease risk even after controlling for overall obesity defined by BMI (21). In addition to hepatic fat content, on which the definition of hepatic steatosis is based, hepatic iron content is of growing research interest, as it is commonly observed in chronic liver disease and is a marker of potential fibrosis and inflammation (26). In particular, hepatic iron overload, defined as $R2^* > 41\ s^{-1}$ (27, 28), has been identified as a promising key driver and potential risk factor in the degradation to severe liver disease by promoting increased inflammation and damage to hepatocytes (29-31). We addressed the current discussion on the obesity definition by complementing BMI with several clinically relevant metabolic parameters, including waist circumference, and adipose tissue depots. We refer to these different measures as metabolic traits throughout this thesis.

1.1.4 Interrelationship between metabolic diseases and related traits

Metabolic diseases are multifactorial and closely intertwined, specifically obesity, diabetes mellitus and MASLD, as these share common pathways and determinants, making it complex to disentangle and isolate distinct risk factors (**Figure 1**) (18, 21). Obesity, particularly VAT, is a major risk factor for diabetes and MASLD (3, 18, 21, 32). Adipose tissue is known to promote changes in lipid and glucose metabolism through cytokine secretion, causing persistent low-grade inflammation (21). The liver is a crucial organ in lipid and glucose metabolism, as it serves as storage depot for free fatty acids, glucagon and iron (19). Excess adipose tissue is responsible for high levels of free fatty acids due to an increased lipolysis, which elevates lipid uptake by hepatocytes and leads to the accelerated fatty degeneration of the liver (18, 19). In addition, insulin regulates the uptake of fatty acids into the liver, consequently, abnormalities in insulin sensitivity promote excessive lipid storage, which in turn leads to the accumulation of hepatic fat (19). In the same vein, previous studies have shown a more than doubled prevalence of MASLD in diabetes patients compared to the general population (33). On the other hand, a meta-analysis of Mantovani et al. (34) demonstrated that patients with MASLD have also a two-fold higher risk of developing diabetes mellitus, thus, highlighting a bidirectional relationship of diabetes mellitus and MASLD. Moreover, there is a potential link between hepatic iron overload and glucose metabolism, as iron overload may induce oxidative stress related to increased risk for insulin resistance (35). However, evidence on how glucose metabolism markers and prediabetes affect hepatic iron content is scarce. Therefore, more longitudinal studies are needed that provide insights on how changes in glycemia contribute to early markers of liver diseases, such as hepatic fat and iron content.

1.1.5 Sex differences in metabolic diseases

It is an inevitable fact that men and women are affected differently by metabolic diseases and their risk factors (1). For example, men are usually diagnosed with diabetes at younger ages, contributing to the fact that diabetes prevalences are higher in young and middle-aged men compared to women (1, 2, 36). Moreover, men are usually diagnosed with diabetes at lower levels of BMI compared to women (1, 36). Essential differences can also be observed regarding body fat distribution. Women tend to have higher SAT, whereas men tend to accumulate more VAT (21), which is a stronger predictor for cardiometabolic diseases (18). Fat depots in women are marked by the accumulation of adipocytes, called hyperplasia, while fat depots in men are characterized by hypertrophic adipocytes (21). However, most of the existing studies on metabolic diseases neglected these sex differences. Consequently, there is an urgent need to tackle this research gap by investigating and presenting associations with metabolic diseases and their early risk factors separately for men and women.

1.1.6 Prevention of metabolic diseases

Because of the combined burden and the close interrelationship of metabolic diseases highlighted above, prevention of metabolic diseases is key. Early stages of metabolic abnormalities, including impaired insulin sensitivity, MASLD or overweight/obesity, are reversible (3, 4, 7). Furthermore, shared risk factors such as physical inactivity, unhealthy diet, and energy imbalance, are modifiable (3, 4, 32, 37). Moreover, metabolic diseases, especially obesity, are known risk factors for many secondary diseases, including cardiovascular diseases (CVD), depression, and certain cancer types (7, 32, 38). Therefore, optimizing metabolic health may have an immense potential in not only preventing metabolic, but also averting numerous other non-communicable diseases. Nevertheless, the focus on behavioral treatments aiming to reduce these individual modifiable risk factors had only modest success and did not bring the necessary turnaround in the rising trend of metabolic diseases (32). It is also important to consider that prevalences of metabolic diseases vary by socioeconomic status and regions (1, 32, 39). For the latter, the urbanization of areas, which comes along with rises in income, increased expenditure on high-caloric food intake, and lower physical activity levels due to more sedentary jobs in service and administration, were accounted for higher obesity rates in urban areas in the beginning (15, 32). However, latest trends showed that the increase in obesity is predominantly driven by rural areas nowadays (39). According to the WHO definition of health determinants, a holistic approach integrates proximate and distal factors (40, 41). Consequently, preventive approaches that combine individual, environmental and social determinants of metabolic diseases by targeting drivers and determinants at the population level could be effective complementary strategies (32). Therefore, it is essential to understand how environmental factors are linked to the development of metabolic diseases and their early traits.

1.2 Environment as a risk factor for metabolic diseases?

1.2.1 Exposure to environmental factors

Research on the health effects of environmental risk factors, such as air pollution, ambient air temperature, road traffic noise and lack of surrounding greenness, is emerging. In particular, ambient air pollution, e.g., particulate matter (PM), ozone (O_3) or nitrogen dioxide (NO_2), and non-optimal air temperature have been increasingly identified as risk factors for various non-communicable disease and premature deaths in recent Global Burden of Disease studies (16, 20). PM with aerodynamic diameters ≤ 2.5 µm ($PM_{2.5}$) was the leading risk factor in the latest Global Burden of Disease study in 2024, accounting for 8% of the total disability-adjusted life-years (DALYS) (16). There were two explanations discussed for this finding: (I) the increasing proportion of elderly, which are more susceptible towards air pollution health effects (16), and (II) the omnipresence of air pollution in combination with insufficient efforts to reduce ambient air pollution, particularly in middle- and low-income countries (16). Less noted is that the urbanization of the environment adds on to the public health emergency (42). Common sources of environmental exposures concentrate in urban areas, such as industry or road traffic, which leads to high levels of air pollution and noise exposure (42, 43). Moreover, urban areas amplify adverse health effects through the built environment, such as for ambient air temperature through the heat island effect or due to lack of surrounding greenness (42, 43). Consequently, people living in urban areas are exposed to multiple environmental risk factors simultaneously. While there is strong evidence between the exposure-outcome pairs air pollution – mortality/CVD/respiratory disease (16, 44, 45), air temperature – mortality/CVD (44, 46), traffic noise – CVD (47, 48), and surrounding greenness – mental health (49), evidence on how environmental factors contribute to metabolic diseases and their related markers is still little and unclear.

1.2.2 <u>Previous studies on the link between environmental factors and metabolic diseases and potential mechanisms</u>

Based on studies predominantly involving mice, several pathways and mechanisms were already proposed on how environmental factors may contribute to the development of metabolic diseases (50-52). These pathways include the inducement of inflammation and oxidative stress by inhaled air pollutants (53), which interfere with glucose metabolism and adipose tissue processes (51, 52). Higher levels of air pollution and exposure to cold may alter brown adipose tissue, which can be linked to improved insulin sensitivity and energy expenditure (51, 54-56). Exposure to noise and air pollution has shown to alter stress responses via the autonomous nervous system and sympathetic activation, which can lead to elevated levels of stress hormones, glucose-insulin disbalance and endothelial dysfunction (47, 50, 52). While exposure to noise includes interim pathways of sleep disturbances and annoyance (50, 57), mechanistic effects leading to dysregulation of the autonomic nervous system and sympathetic activation have been observed in animal and human studies (52). Surrounding greenness may positively impact metabolic health through improved mental health, stress reduction and an active lifestyle (49, 58). Although these potential pathways were identified and hypothesized, certainty of evidence from epidemiological studies supporting these associations between environmental exposures and metabolic diseases and related traits is still low.

There is emerging evidence on the association between air pollution, specifically $PM_{2.5}$, and diabetes mellitus and BMI (59-61). Latest meta-analyses findings revealed a 1.12-fold higher odds of having diabetes [95%-confidence interval (CI): 1.09; 1.15] and a 0.34 kg/m² [95%-CI: 0.30; 0.38] higher BMI per 10 µg/m³ and 1 µg/m³ increase in $PM_{2.5}$, respectively (60, 61). In line with this, two meta-analyses suggested a 10 dB(A) increase in noise exposure was associated with 0.158 cm higher waist circumference, and 1.08-fold and 1.055-fold increase in the odds of diabetes and central obesity, respectively (62, 63). Although these promising findings suggest a link between noise exposure and metabolic outcomes, evidence is still uncertain due to the latest meta-analysis by Sivakumaran et al. (50). By presenting pooled effect estimates from studies that were heterogeneous in terms of study population, sources of noise exposure and high risk of bias, the authors concluded that there were only tentative positive associations between noise exposure and cortisol, noradrenaline and adrenaline (50). In addition, the association with other air pollutants is discordant (60, 64-66) and evidence on the association of air temperature or surrounding greenness with metabolic diseases is understudied and inconclusive (54, 55, 67, 68).

Besides the limited evidence on associations of environmental exposures with metabolic outcomes in epidemiological studies, there are further limitations that need to be tackled. Previous studies mainly relied on obesity defined by BMI (61, 62, 66), because BMI is commonly used in clinical practice and a simple measurement at the population level (6), but studies on body fat measures are lacking. Hwang et al. (69) and Kim et al. (70) examined imaging-derived adipose tissue measures but did not find any association with increasing air pollutant levels. Altug et al. (71) observed positive associations between PM_{10}, BMI and dual-energy X-ray absorptiometry (DXA)-derived fat mass index in children, but not in adults. Promising results were found in the KORA-MRI study, where higher levels of traffic-related air pollutants were associated with cardiac fat depots, but not with VAT or SAT (72). However, associations with these early body fat markers may give crucial insights into obesity-related health risks and metabolic disease development. In addition, the described research gap regarding sex differences is also present in studies looking into the association of environmental factors with metabolic diseases and traits. Only few studies reported sex-specific associations or examined potential effect modification by sex, but there is no clear evidence on who is more susceptible due to mixed study results (73-77). Therefore, further evidence is needed to conclude about sex-specific associations of environmental factors with metabolic diseases.

Another limitation of previous studies is that most studies examined associations of one exposure group in isolation using single-exposure models, but did not consider potential joint associations of multiple environmental factors. Thereby, potential synergistic, interactive, or confounding effects among environmental exposures were neglected, which may have resulted in inaccurate estimates of the association of metabolic diseases and traits attributed to environmental factors (78-80). Although the number of studies that assessed the potential joint associations is limited (78, 79, 81), they could provide evidence that associations of exposure mixtures with metabolic traits were stronger compared to associations from single-exposure models using different statistical approaches. This emphasizes the importance of considering environmental exposure mixtures and to estimate their joint associations in addition to single associations. This may be especially important in urban areas, where individuals are co-exposed to multiple environmental risk factors (42). In the same vein, urbanization-specific differences exist regarding the prevalence of metabolic diseases (39, 82) and the levels of environmental exposures (82, 83), that need further investigation. However, most previous studies had limited study areas (71, 84-86), and thus, have not been able to examine potential effect modification by degree of urbanization, which represents a critical research gap.

1.3 Objectives of the thesis

To address the research gaps outlined above, the objective of this thesis was to understand the sex-specific interrelationship between metabolic diseases and traits, particularly diabetes mellitus and hepatic fat and iron content, and to evaluate the potential association of long-term exposure to multiple environmental factors with metabolic diseases and related traits in adults. Therefore, this thesis addressed different aims in four manuscripts as follows:

I. To assess how changes in glycemia and its traits are associated with hepatic fat and iron content in men and women. **(Manuscript 1)**

II. To investigate the association between annual exposure to multiple environmental factors and metabolic diseases and related traits in men and women. **(Manuscript 2 & 3)**

    In particular, the manuscript 2 & 3 had specific sub-aims focusing on:

    a. Evaluating a potential effect modification by degree of urbanization in the association of environmental factors with metabolic diseases and related traits.
    b. Estimating joint associations of multiple environmental factors with metabolic diseases and related traits.

III. To quantify the association of annual exposure to road traffic noise with MRI-derived adipose tissue depots and hepatic fat content in men and women. **(Manuscript 4)**

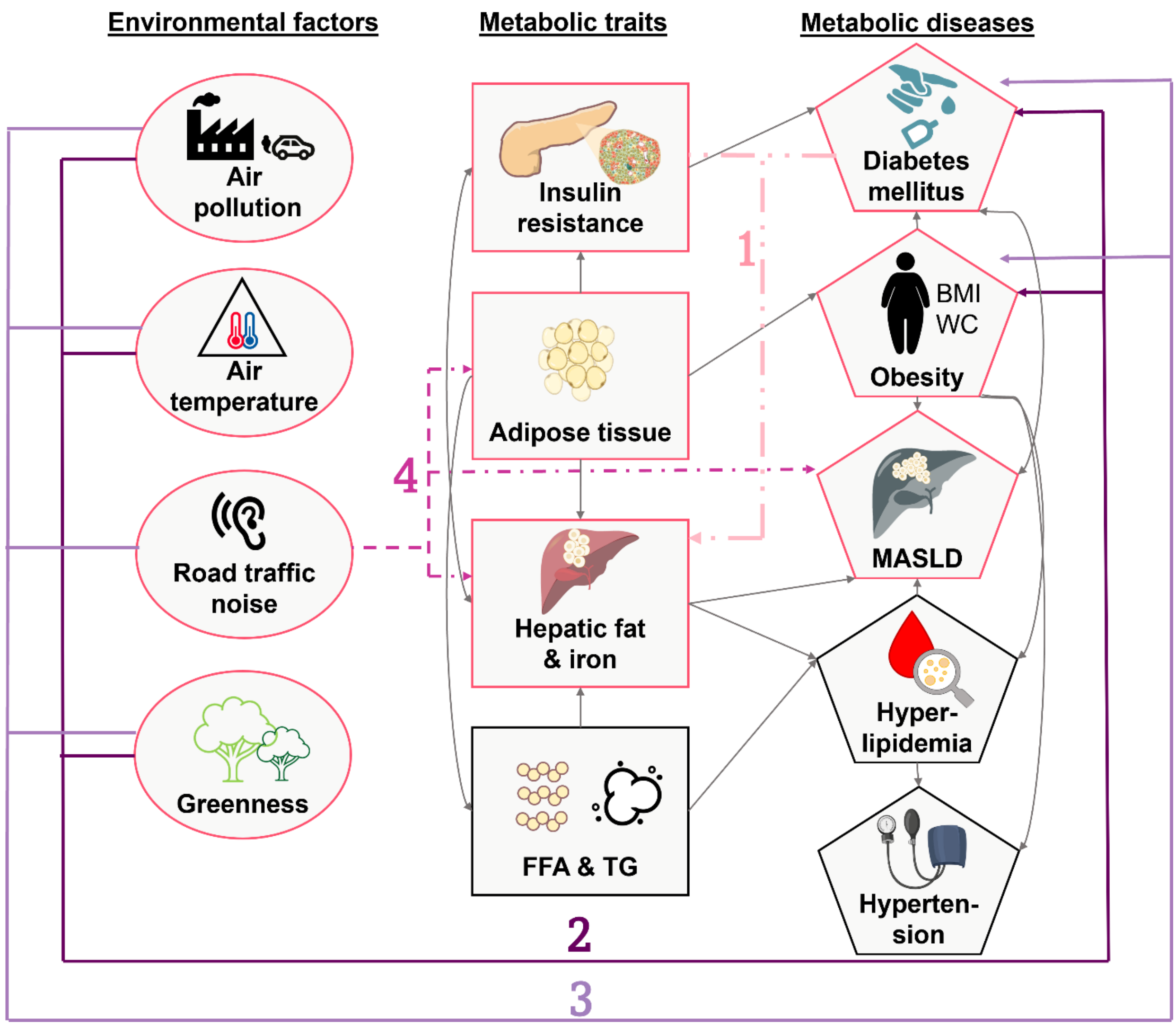


Figure 1: Schematic representation of potential pathways and interrelationships between different metabolic diseases, related traits, and environmental exposures investigated in this thesis. The metabolic disease endpoints (pentagons), related traits (squares) and environmental exposures (ovals) focused on this thesis are highlighted in pink. The colored pathways with numbers 1-4 indicate the exposure→ outcome pairs examined in each manuscript 1-4. *Legend: The grey pathways were strongly simplified and can be more complex and interrelated. Adapted from Chew et al. (1); own illustration. Abbreviations: BMI = body mass index, FFA = free fatty acids, TG = triglycerides, MASLD = metabolic dysfunction associated steatotic liver disease*; *WC = waist circumference*

2 Methods

This thesis comprises four manuscripts, as seen in **Figure 2**, of which two are published. Furthermore, manuscript 3 and 4 have been submitted to peer-reviewed journals, where there are under review at the time of submission of this thesis and therefore, are included in the appendix. To address the thesis' research aims, we analyzed data from two population-based cohorts, the Cooperative Health Research of Augsburg (KORA) and German National Cohort (NAKO). While subsequent chapters briefly summarize the methods of each manuscript, details can be found in the published papers and in the appendix to this thesis.

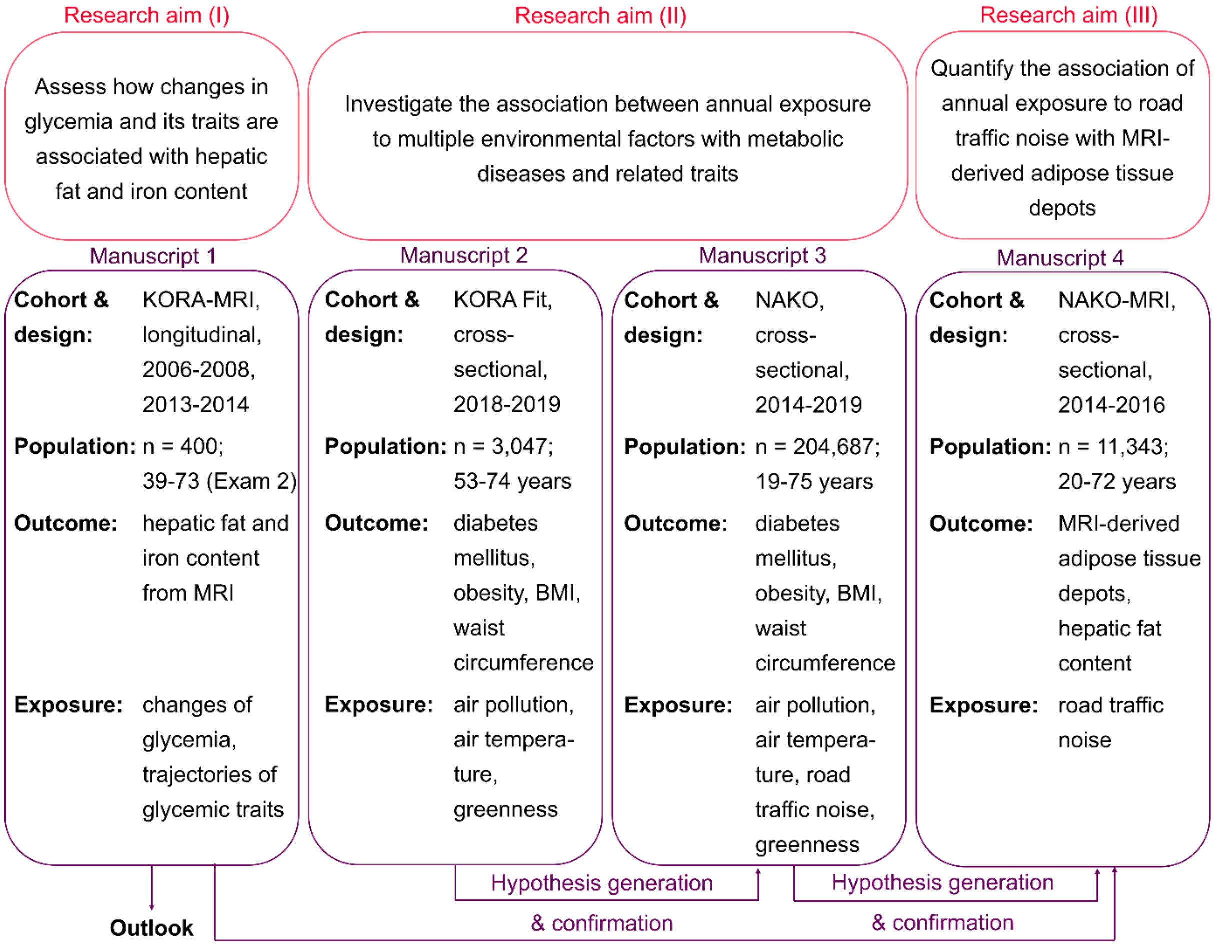


Figure 2: Overview of included manuscripts with details on study cohort and design, outcome, and exposure to address the research aims (I-III) of this thesis. *Legend: Manuscript 1 & 2 are published; manuscript 3 & 4 are submitted and under review in peer-reviewed journals. Own illustration. Abbreviations: BMI = body mass index, KORA = Cooperative Health Research of Augsburg, MRI = magnetic resonance imaging, MASLD = metabolic dysfunction associated steatotic liver disease, NAKO = German National Cohort.*

2.1 Trajectories of glycemic traits with hepatic fat and iron content (Manuscript 1)

2.1.1 Study design and cohort

We used longitudinal data from two examination time points of the prospective KORA study (F4: 2006-2008 and FF4: 2014-2016). The availability of glucose metabolism markers at two examinations spanning seven years of study period allowed us to observe changes in glycemia and related traits (28). In addition, whole-body MRI was conducted in a subsample of 400 participants in KORA FF4 (28), allowing the assessment of the impact of changes in glycemia and related traits on hepatic fat and iron content. Due to the KORA-MRI study objective, the sample was enriched for individuals with prediabetes and diabetes. Therefore, the KORA-MRI study was best suited to address the first research aim (I) of this thesis.

2.1.2 Outcome and exposure assessment

The outcomes of interest were hepatic fat and iron content measured by MRI by two-point Dixon at 3T (28). The mean of the fat fraction (in %) and the mean of the relaxation rate R2* (s^{-1}) in the left and right liver lobes were assessed to determine hepatic fat and iron content, respectively (28). Exposures available at two time points included glycemic state defined as normoglycemia, prediabetes, diabetes, and several serum glucose metabolism markers (Hemoglobin A1c (HbA1c), homeostasis model assessment-estimated insulin resistance (HOMA-IR), fasting insulin and glucose, and 2-hour glucose after an oral glucose tolerance test) (28).

2.1.3 Statistical analysis

We used two different statistical approaches to assess the association between changes of glycemia and its related traits with the outcomes. First, linear regression models stratified by sex with multiple confounder adjustment were used to assess changes of glycemia with hepatic fat and iron content. Second, a novel two-step multi-level model as described by Gadd et al. (87) was implemented to evaluate trajectories of glycemic markers with hepatic fat and iron content. This method allowed to consider individual variations in the changes of markers by modeling trajectories using a linear mixed model with random slopes (28, 87). By entering the standardized coefficients of these models into linear regression models, we modelled the effect of these trajectories on the outcomes in a final second step (28).

2.2 Associations of environmental exposures with metabolic diseases and related traits (Manuscript 2 & 3)

2.2.1 Study design and cohorts

To assess the associations of long-term environmental exposures with metabolic diseases and anthropometric measures, cross-sectional data from the cohorts KORA Fit and the multicentric NAKO were used. KORA Fit included 3,047 middle-aged and older participants with comprehensive medical examinations taking place between 2018 to 2019 (88). NAKO collected health information from 204,687 participants during a five-year baseline examination period starting in 2014 (89).

These two cohorts were excellent for investigating the second research aim (II). Not only are participants characterized and examined in depth with regard to their health (89), but there are also numerous environmental factors available that were linked to participants' residential addresses (83). The study areas of these cohorts comprise urban, suburban, and rural areas. Hence, this allowed us to address the sub-specific research aim, whether the degree of urbanization modifies the associations between environmental factors and metabolic traits (**Figure 3**). Due to 16 different NAKO study regions across Germany (**Figure 3**), a high exposure contrast between and within regions was assured. Moreover, we were able to test and confirm hypotheses and findings generated from the KORA Fit analysis with a larger sample size and increased statistical power.

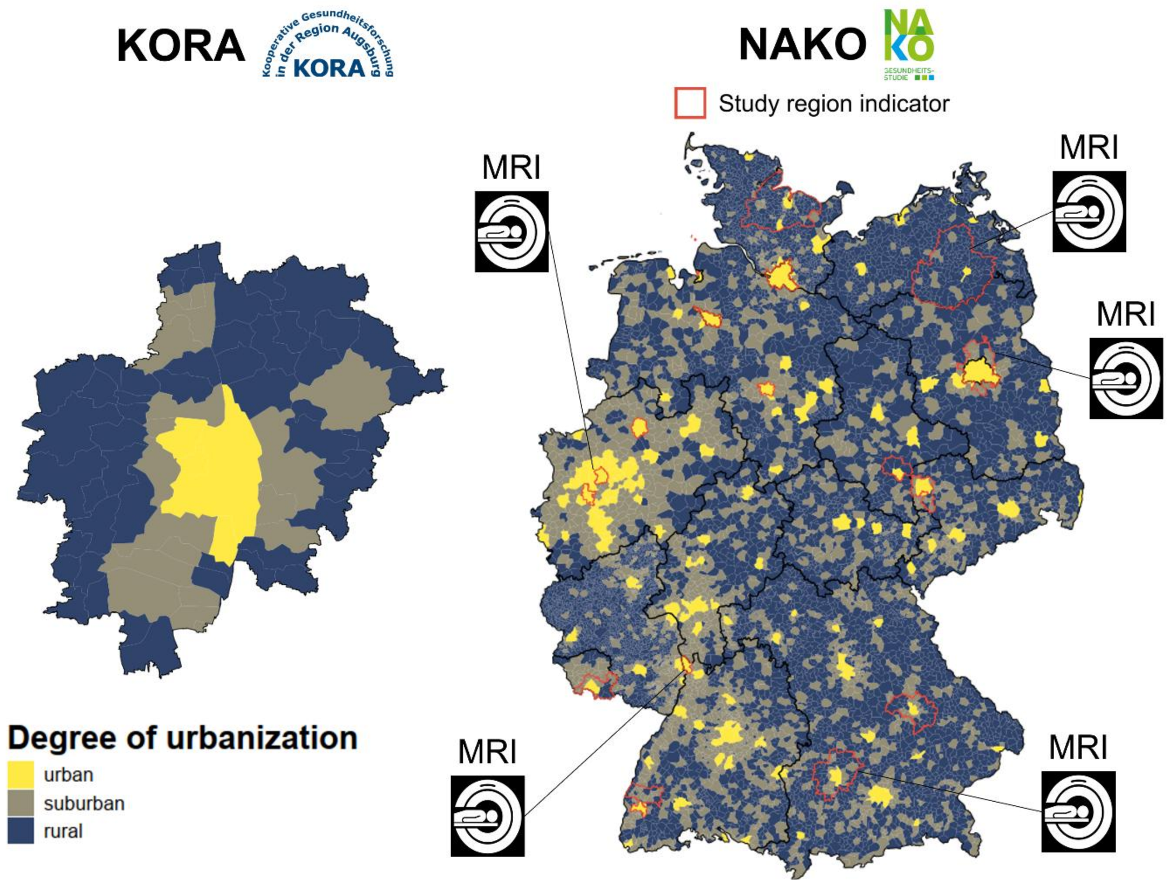


Figure 3*:* Classification of the municipalities within the study regions of KORA and NAKO into urban, suburban, and rural areas based on the EUROSTAT degree of urbanization. *Legend: Figure is adapted from Wolf et al. (83), own illustration. Abbreviations: EUROSTAT = statistical office of the European Union; KORA = Cooperative Health Research of Augsburg, MRI = magnetic resonance imaging, NAKO = German National Cohort*

2.2.2 Outcome and exposure assessment

In KORA Fit and NAKO, outcomes of interest included self-reported diabetes mellitus, a binary indicator for obesity defined as BMI ≥ 30 kg/m², and the measured metabolic traits BMI and waist circumference (88, 90). BMI was calculated from measured height and weight data, dividing weight (kg) by squared height (m²) (88, 90). Trained personnel measured waist circumference according to the WHO recommendation (22, 88).

Annual environmental exposures available from different sources and years were linked to residential address of the participants. In KORA Fit, exposure to several air pollutants were estimated by land use regression modelling (88, 91). These models were based on daily measured concentrations at monitoring stations for the year 2014/2015 and included several spatiotemporal predictors to estimate annual mean levels of NO_2, nitrogen oxide (NO_x), O_3, PM of different sizes (PM with an aerodynamic diameter ≤ 10 µm (PM_{10}), PM with an aerodynamic diameter between 2.5 µm and 10 µm (PM_{coarse}), $PM_{2.5}$) and particle number concentration (88, 91). Air temperature maps for Germany covering several years were compiled by Nikolaou et al. (92) using a multi-stage modeling approach. We analyzed annual and seasonal mean levels (T_{mean}) for winter and summer (88). We obtained normalized difference vegetation index (NDVI) for the year 2018 from satellite-based images taken by Landsat-8 and Sentinel-2 as a measure of surrounding greenness (88).

In NAKO, annual air pollution levels from the ELAPSE *(Effects of Low-Level Air Pollution: A Study in Europe*) project, including NO_2, $PM_{2.5}$ and $PM_{2.5}$absorbance ($PM_{2.5}$abs), were available for the year 2010 (90, 93). Residential air pollution concentrations were estimated by combining daily levels obtained from monitoring stations with spatiotemporal predictors in land-use regression models (83, 93). For air temperature, we considered exposure to the annual and seasonal mean levels derived by Nikolaou et al. (92) for each examination year. Regarding road traffic noise exposure, the European Environment Information and Observation Network (EIONET) repository provides 10 * 10m grid datasets on day-evening-night (L_{den}) levels from 2017 (83, 90, 94, 95). During pre-processing and harmonization, German-wide maps with continuous, area-weighted L_{den} levels within 10 and 100m buffers of residencies were derived (83, 94). Similarly to KORA, we extracted NDVI levels averaged over warm months from MODIS satellite-images to estimate surrounding greenness within 1 km * 1 km grids of the residencies for each examination year (83, 90).

2.2.3 Statistical analysis

In both cohorts, exposure-response functions were determined using generalized additive models with cubic splines (88, 90). Linear and logistic regression models with covariate adjustment were used to assess the association of interquartile range (IQR) increases in each environmental exposure with the respective outcomes. We identified minimum confounder adjustment sets using directed acyclic graphs (DAG) (96). In single-exposure models, effect modification by degree of urbanization in single-exposure models was assessed by including a multiplicative interaction term between exposure and urbanization. Degree of urbanization was given for each municipality based on the population grid of the statistical office of the European Union (EUROSTAT) from 2020 (97). We applied two-exposure models to exclude potential confounding effects between exposures. As results of single-exposure models were contrary to our hypothesis, additional exploratory analyses in KORA Fit and NAKO followed. In KORA Fit, we assessed a potential interaction between air pollution, represented by $PM_{2.5}$abs, and greenness stratified by sex and degree of urbanization (88). In NAKO, we assessed study center specific associations, aiming to identify potential heterogenous findings that point towards structural differences across study regions contributing or explaining differences in the associations of environmental exposures with metabolic diseases (90). In addition, we performed the novel statistical method quantile g-computation (80) using multi-exposure models to assess joint associations of multiple environmental exposures together with metabolic diseases in the NAKO sample (90).

2.3 Associations of road traffic noise with adipose tissue depots (Manuscript 4)

2.3.1 Study design and cohort

Building on the evidence of the previous projects, we focused on the association of road traffic noise with AT depots. By assessing AT depots and hepatic fat content using the gold standard measurement MRI, NAKO provides a detailed phenotyping of more than 30,000 participants for early metabolic diseases markers (24, 89). This made the NAKO-MRI subsample an ideal source of data to answer the third research aim (III) of this thesis. We used cross-sectional data from the NAKO-MRI subsample, which consisted of 11,343 participants with whole-body MRI data obtained from the first half of the baseline examination (2014-2016) in five NAKO-MRI centers (**Figure 3**) (98).

2.3.2 Outcome and exposure assessment

Volumes for the AT depots VAT, subcutaneous abdominal (SCAAT), subcutaneous thoracic (SCTAT) and hepatic fat content were derived from 3T-MRIs with two-point Dixon sequences (98). Images were semi-automatically evaluated by a deep-learning network as described elsewhere (23). A binary variable that indicated the prevalence of MASLD was considered as secondary outcome (98). As described above, we used the area-weighted, continuous L_{den} for the year 2017 obtained from the EIONET grid dataset (83, 95, 98). After harmonization and preprocessing, L_{den} levels ranged from 40 to 75 dB(A) and were available for a 10 and 100m buffer around participants' residential addresses (98).

2.3.3 Statistical analysis

To estimate the percentage change of the mean for each outcome with 10 dB(A) increases in L_{den}, linear and logistic regression models stratified by sex were applied (98). Exposure-response functions were determined using generalized additive models with cubic splines. All models were adjusted for age, lifestyle factors and socioeconomic (SES) status variables derived from DAGs. Two-exposure models additionally adjusting for air pollutants (NO_2 and $PM_{2.5}$) or surrounding greenness were performed to assess the independence of associations between traffic noise and early metabolic traits from co-existing environmental factors. Effect modification by cardiometabolic diseases was considered, as participants with cardiometabolic diseases may represent a stress vulnerable subgroup (98).

3 Main results

In the following sections, the key findings for each manuscript are reported. As in the methods part, the first section belongs to manuscript 1, specifically focusing on the link between glycemia and hepatic fat and iron content, whereas the other sections focus on the association of environmental factors with metabolic diseases and traits (manuscript 2 - 4).

3.1 Trajectories of glycemic traits with hepatic fat and iron content (Manuscript 1)

Over the seven years of the study period, we observed a deterioration of glycemia. For example, 19.8% men and 12.8% women progressed from normoglycemia to prediabetes, and 7.1% men and 4.1% women progressed from prediabetes to diabetes (28). Similarly, levels of multiple glucose metabolism markers increased significantly from baseline to follow-up, particularly in participants with prediabetes and diabetes, indicating a worsening of metabolic health over time. Changes in glycemia and unfavorable trajectories of continuous glucose metabolism markers were consistently associated with increased hepatic fat content in men and women (28). For example, worsening from normoglycemia to prediabetes was associated with increases of 1.03 log(%) [95%-CI: 0.63; 1.43] and 0.37 log(%) [95%-CI: 0.01; 0.73] in hepatic fat content for men and women after adjusting for age, BMI and alcohol consumption, respectively (28). Trajectories of fasting insulin were associated with increases of 0.51 log(%) [95%-CI: 0.29; 0.73] and 0.63 log(%) [95%-CI: 0.36; 0.90] in hepatic fat content for men and women, respectively. In general, our findings provided evidence of sex-specific susceptibilities, as the associations between glycemic trajectories with hepatic fat content were more pronounced in women than in men (28). The relationship with hepatic iron content was less clear, as we only observed changes in glycemia (normoglycemia to prediabetes) and deteriorated trajectories of 2-h glucose to be tentatively associated with increased hepatic iron content in men (e.g., normoglycemia to prediabetes: 2.21 s^{-1} [95%-CI: 0.47; 3.95]; 2-h glucose: 1.27 s^{-1} [95%-CI: 0.12; 2.42]) (28).

With respect to the first research aim (I), we showed that the worsening of glycemia and related markers were associated with increased intrahepatic fat content, whereas the associations with hepatic iron content were more complex.

3.2 Associations of environmental exposures with metabolic diseases and related traits (Manuscript 2 - 3)

In KORA Fit, we observed that sex modified associations of environmental exposures with diabetes, obesity, BMI, and waist circumference in a substantial way (88). Higher levels of air pollutants, air temperature and lower levels of greenness were associated with higher diabetes prevalence only in men (e.g., $PM_{2.5}$: Odds ratio (OR) = 1.41 [95%-CI: 1.08; 1.84]; T_{mean}: OR = 1.48 [95%-CI: 1.15; 1.90]; NDVI: OR = 0.78 [95%-CI: 0.59; 1.01]; per IQR increase) (88). Moreover, the associations with prevalent obesity, BMI and waist circumference were further modified by degree of urbanization. The interaction analysis revealed that higher levels of air pollutants and lower levels of NDVI were associated with increased odds of obesity ($PM_{2.5}$: OR = 1.50 [95%-CI: 1.11; 2.02]; NDVI: OR =0.71 [95%-CI: 0.54; 0.94]), higher BMI ($PM_{2.5}$: 0.59 kg/m² [95%-CI: 0.07; 1.11]; NDVI: -0.71 kg/m² [95%-CI: -1.23; -0.19]), and higher waist circumference ($PM_{2.5}$: 1.94 cm [95%-CI: 0.39; 3.5]; NDVI: -1.43 cm [95%-CI: -2.82; -0.04]; per IQR increase) for men living in urban areas, whereas no or opposite associations were found for women and men living in rural areas (88).

To confirm the findings from the KORA Fit study in a larger cohort, we analyzed cross-sectional NAKO data in regard to sex-specific associations of environmental exposures with diabetes, obesity, BMI, and waist circumference. Controlling for population density substantially changed estimates of air pollutants and surrounding greenness (90). In the models additionally adjusted for population density, we found consistent associations that higher levels of $PM_{2.5}$ and L_{den} were associated with higher odds of metabolic diseases and higher levels of BMI and waist circumference (90). The strongest estimates were found for an IQR increase (8.3 dB(A)) in L_{den}, which was associated with 1.08-fold [95%-CI: 1.03; 1.13] and 1.05-fold [95%-CI: 1.00; 1.10] higher odds of diabetes and 0.11 kg/m² [95%-CI: 0.06; 0.15] and 0.22 kg/m² [95%-CI: 0.16; 0.27] higher BMI in men and women, respectively. Similarly to KORA Fit, we observed that these associations were again more pronounced in urban and suburban areas. For example, associations of $PM_{2.5}$ or L_{den} with BMI steadily attenuated from urban to suburban to rural areas (90).

In both KORA Fit and NAKO analyses we found non-linear associations between NDVI and diabetes, obesity, BMI, and waist circumference (**Figure 4**). In KORA, u-shaped associations were explained by sex, resulting in almost linear but opposite directed associations for men and women, respectively. In contrast, we observed inverse u-shaped functions for men and women in NAKO. This indicated that both a lack of NDVI and NDVI values above the median were associated with lower odds of metabolic diseases and related traits (**Figure 4**). Urbanization-specific associations demonstrated that the inverse u-shaped function was only present in urban areas, whereas we observed negative linear associations in suburban and rural areas (see appendix, manuscript 3 supplement).

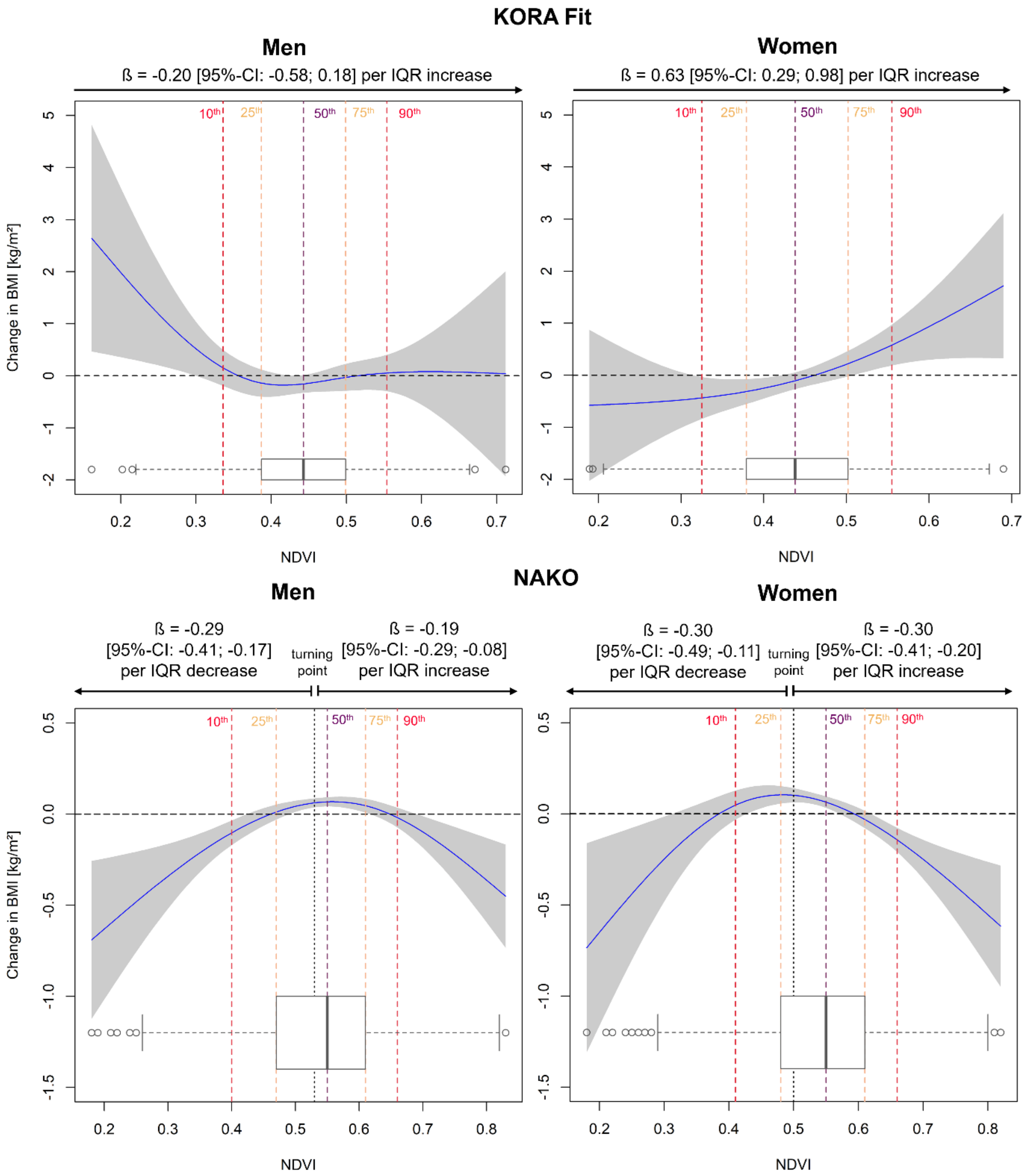


Figure 4: Sex-specific exposure-response functions between NDVI and BMI in KORA Fit (top: n = 1,404 men, n = 1,630 women) and NAKO (bottom: n = 86,710 men, n = 88,245 women). *Legend: Sex-specific estimates and 95%-CI per IQR increase are derived from linear regression models in KORA Fit and piecewise linear regression models (>/≤ below the turning point) in NAKO. Vertical lines indicate percentiles of NDVI. Own illustration. Abbreviations: BMI = body mass index, CI = confidence interval, IQR = interquartile range increase, KORA = Cooperative Health Research of Augsburg, NAKO = German National Cohort, NDVI = normalized difference vegetation index.*

In multi-exposure models, different combinations of air pollutants, air temperature, road traffic noise and greenness showed stronger joint associations with metabolic diseases and related traits using quantile g-computation. For example, exposure mixture combining $PM_{2.5}$, L_{den}, and

NDVI were associated with higher diabetes prevalence (men: OR = 1.28 [95%-CI: 1.12; 1.44]; women: OR = 1.23 [95%-CI: 1.07; 1.42]; IQR increase in all exposures) and higher BMI (men: 0.22 kg/m² [95%-CI: 0.10; 0.35]; women: 0.57 kg/m² [95%-CI: 0.41; 0.72]; IQR increase in all exposures). Estimating associations of exposure mixtures including NO_2, $PM_{2.5}$abs and T_{mean} attenuated joint associations, as higher levels of these factors were tentatively associated with lower BMI, waist circumference and odds of diabetes and obesity (98).

With respect to the second research aim (II), we found mixed findings on the associations of environmental exposures with diabetes, obesity, BMI, and waist circumference. However, we provided evidence for complex sex- and urbanization-specific associations. We found consistent associations of long-term exposure to $PM_{2.5}$ and road traffic noise with metabolic traits, especially in urban areas. Exposure to a mixture of environmental factors was associated with increased odds of metabolic diseases and higher metabolic traits, with doubled estimates for joint exposures derived from multi- versus single-exposure models.

3.3 Associations of road traffic noise with adipose tissue depots (Manuscript 4)

Among 11,101 participants with complete MRI data, we found robust and consistent associations of road traffic noise with higher values of adipose tissue depots and hepatic fat content (98). Strongest %-changes in outcomes per 10 dB(A) increases of L_{den} (10m) were seen for SCAAT and hepatic fat content in men (SCAAT: 2.18 %-change [95%-CI: 0.43; 3.93]; hepatic fat content: 3.57 %-change [95%-CI: 1.41; 5.78]). In women, strongest associations of noise exposure were seen for VAT (2.38 %-change [95%-CI: 0.55; 4.20]) and hepatic fat content (3.08 %-change [95%-CI: 1.00; 5.21]), with larger estimates compared to men. 10 dB(A) higher levels of L_{den} (10m) were also associated with higher odds of MASLD (98). We observed comparable results with the exposure to L_{den} (100m), although 95%-CI were wider and therefore, statistical significance was attenuated. After further adjusting for air pollutants and surrounding greenness, estimates did not change, indicating independent associations of traffic noise exposure on early metabolic traits (98). Interaction analyses with prevalent cardiometabolic disease status were mixed and indicated stronger associations between L_{den} and SCAAT and SCTAT in participants with any metabolic disease. Interestingly, associations of L_{den} with hepatic fat content interacted with the prevalence of hypertension in a sex-specific manner, suggesting stronger associations for hypertensive men but also for non-hypertensive women (98).

With respect to the third research aim of this thesis (III), we showed that higher levels of road traffic noise were associated with higher volumes of adipose tissue depots, even after controlling for air pollution and surrounding greenness.

4 Discussion

This section will briefly discuss the key findings found in this thesis, with strengths and limitations of the conducted studies, future research directions and implications. A more detailed discussion of specific findings can be found in the respective manuscripts.

4.1 Discussion of key points

We observed a strong link between trajectories of diabetes markers and hepatic fat and iron content, which is partly consistent with Wang et al. (99). There is growing evidence on the bidirectional relationship between diabetes and MASLD (100, 101). For example, two longitudinal studies using hepatic fat and iron content as independent and glycemic markers as dependent variables found that hepatic steatosis was associated with glycemic markers and prediabetes (100, 101), but associations with hepatic iron overload alone were less clear (100), which is in good agreement with our study. Specifically, we added evidence on sex-specific associations, suggesting that associations of glycemic trajectories with hepatic fat were stronger in women, whereas tentative associations with liver iron were only present in men (28). It could be hypothesized that the accumulation of hepatic fat in women may explain the excess CVD risk observed in women with type 2 diabetes. However, the association of MASLD and iron overload with CVD is still inconclusive (102, 103). Contributing to this, a recent study showed that the prevalence of hepatic steatosis alone was not significantly associated with increased CVD risk, but a higher CVD risk was observed for hepatic steatosis in combination with obesity and diabetes (104). These findings underpin the interrelationship between metabolic diseases and support the value of the joint assessment of multiple metabolic traits. Given these findings, we considered a broad panel of metabolic traits, including imaging-derived hepatic steatosis, in our further analyses of environmental exposures.

We provided epidemiological evidence on the cross-sectional association of long-term exposure to $PM_{2.5}$ and noise with metabolic diseases and related traits, but could not find clear evidence on the association with other air pollutants and air temperature, which is in line with previous literature (55, 59, 60, 62, 67). Associations were similar between men and women in NAKO, while KORA Fit findings demonstrated that higher annual levels of environmental factors were associated with diabetes prevalence only in men. Due to the older age of KORA Fit participants, this may hint toward a sex-specific susceptibility in elderly. Similarly, Sorensen et al. (77) observed that higher levels of air pollution were associated with increased diabetes risk in men only, particularly in men aged 50 to 80 years. In addition, the doubled ORs for metabolic diseases with environmental exposure mixtures in multi-exposure models are in line with previous studies (78, 79, 81, 105). Three studies in European cohorts showed stronger associations of multiple environmental factors with metabolic syndrome and diabetes using a cumulative risk index (78, 81, 105). Although Zhang et al. (79) reported negative joint associations of multiple environmental exposures with BMI using quantile g-computation, this was mainly driven by neighborhood SES. Excluding this variable resulted in opposite effect estimates, demonstrating a positive joint association of increases in air pollution, air temperature, road traffic noise, residential greenness, and light at night with BMI in two US-based female nurses' cohorts (79). However, joint associations were driven by air pollutants, whereas our findings were mainly attributed to road traffic noise. Two-exposure models indicated robust and independent associations for road traffic noise, but greenness and air pollutants potentially confounded each other (88). As evidence from previous studies has been inconsistent (76, 78, 105-107), more research is needed to fully understand how multiple environmental exposures interact with or confound each other.

We found non-linear associations between greenness and metabolic diseases and related traits, which may explain previous mixed study results (68, 108) and highlights the importance of assessing exposure-response curves. Non-linear associations for NDVI and BMI have already been reported in several studies, although the shape of the curves varied considerably (75, 106, 109-111). Similarly, we observed entirely different exposure-response functions for men and women in KORA Fit and NAKO, for which we have no clear explanation. We speculate that age differences in the two study populations (NAKO: aged 19-75 years; KORA Fit: aged 53-74 years), and stronger contrasts in urbanicity may have contributed to these differences. In good agreement with our NAKO findings, James et al. (78) and Klompmaker et al. (111), reported inverse u-shaped exposure-response curves between NDVI and obesity measures in a US female cohort and a Dutch national health survey, respectively. Possible explanations for these non-linear relationships have been discussed extensively in the literature, mainly pointing to the limitations of NDVI as a measure of greenness (75, 109, 111, 112). NDVI does not provide any information on the accessibility, proximity, subsequent use or vegetation type of the green spaces (109). Residual confounding, particularly in urban areas, may still be present. This is supported by the urbanization-specific exposure-response functions, indicating that inverse u-shaped associations were only seen in urban areas. We hypothesize that the association of lack of NDVI with lower BMI may be confounded by the availability of gyms, indoor sports facilities, or walkability of neighborhoods in central urban areas, whereas the association of high NDVI with lower BMI may be attributed to the outskirts of urban areas. Along with this, physical activity may mediate this relationship (112), however we could not find any changes in estimates after excluding physical activity from the regression models. In addition, vegetation type (e.g., forests, recreational parks, cropland, etc.) may be an important characteristic that varies with the degree of urbanization (109, 111). A direct link between greenness and human health is hypothesized via effects on brain activity (53). For example, studies using electroencephalography measured less arousal, frustration and reduced blood flow in certain brain areas known to control stress responses while participants visited urban green spaces (113-115). Nevertheless, more epidemiological studies are needed that consider different measures of green space, its use and availability, and the assessment of the vegetation type.

Our findings add important evidence on the confounding potential of population density and the effect modification by degree of urbanization, as associations between environmental factors and metabolic diseases were mainly observed in urban areas and attenuated in suburban and rural areas. Contrary to our findings, Liu et al. (82) showed that despite higher obesity rates but lower exposure to air pollution in rural areas, the associations between PM and obesity were stronger in rural areas using data from a Chinese cohort. In contrast, Zhang et al. (79) and Villeneuve et al. (112) did not find any effect modification by degree of urbanization. Based on our findings, population density must be included in adjustment models. Furthermore, due to the increase in metabolic diseases (5, 17), especially the predominance of obesity in rural areas (39), further research is needed to identify the underlying factors that contribute to this urban-rural difference. In previous literature, researchers have hypothesized that this urban-rural difference is due to differences in infrastructure and the "urbanization of rural areas" (39). On the one hand, infrastructure in rural areas may still lack access to and use of public transport, which is associated with increased use of motorized transport (39). In addition, the walkability of neighborhoods and its association with obesity development through altered levels of physical activity needs further research to be fully understood. Similarly, a shift towards more sedentary jobs, even in rural areas, contributes to declining levels of physical activity. Diversity of the food environment and access to gyms in urban areas may encourage healthy behaviors (39). In addition, dietary habits, and socio-economic differences between urban and rural areas, which may contribute to the development of metabolic diseases, need to be addressed in future research.

4.2 Strength and limitations

This thesis has several strengths. First, we have used data from two different well-characterized population-based cohorts that include a wide age range of young, middle-aged, and elderly participants. Both cohorts provided high quality information on a large amount of health outcomes, environmental exposures, and covariates. The large samples gave us adequate statistical power to assess associations in men and women separately and to test for different effect modifications, including urbanicity. Multiple follow-up examinations in KORA allowed us to investigate longitudinal trajectories of glycemia and its traits. In addition, both cohorts provided detailed assessment of adipose tissue measures using gold standard MRI measurements, which are novel imaging approaches in an epidemiological context. This allowed us to not only rely on BMI as measure of obesity, but also to confirm these associations in adipose tissue depots. We used state-of-the-art statistical methods to assess the associations between exposures and outcomes and applied novel techniques and methods to evaluate longitudinal associations of exposures and to assess joint associations of highly correlated environmental factors in multi-exposure models.

However, we need to address certain limitations. First, the associations of environmental exposures with metabolic diseases and related traits were based on cross-sectional analysis, which prevented us from assessing causal effects of environmental exposures. Therefore, there may be residual confounding, particularly of NDVI and air pollutants with metabolic traits, where further studies are warranted. However, we tried to minimize this risk by using DAGs to identify all potential confounders and to adequately control for them in statistical models. Although we assessed changes in glycemia with hepatic iron and fat content in a longitudinal setting, we did not have information on hepatic fat and iron content at baseline, so we could not rule out the possibility that participants who showed a worsening of glycemia during follow-up already had high hepatic fat and iron content at baseline. Therefore, more longitudinal studies that assess hepatic fat and iron content at multiple examinations, such as the ongoing NAKO study, are needed. Second, misclassification of diabetes was likely when we assessed the associations of environmental factors with diabetes because we only had self-reported diabetes diagnosis. In addition, we could not distinguish between type 1 and type 2 diabetes. However, more than 95% of people with diabetes have type 2 diabetes (17), so it is likely that our findings describe the association of environmental factors with type 2 diabetes. Third, we need to address potential measurement errors in environmental exposures, which relate to differences in spatial resolution, different time windows of exposure, high number of missing in noise exposure, particularly rural areas, and the assignment of exposure levels to residential addresses without information on time spent at home. However, studies comparing residential exposure with personalized monitoring showed a high correlation ($R > 0.8$) and almost identical health estimates for these different measurement approaches (116). In addition, several studies have shown the spatial robustness of exposure to air pollution, noise, and greenness over time (93, 117-120). Finally, the generalizability of our studies may be limited. The study regions of KORA and NAKO represent areas with rather low exposure to air pollution and moderate rather than extreme air temperature variability. Particularly because we did not find an association with temperature or gaseous air pollutants, multi-country studies with higher exposure contrasts may shed more light on potential associations of these environmental factors on metabolic diseases and related traits.

4.3 Outlook

The call for longitudinal analyses, improved measures of greenness and research on urban-rural differences was already discussed in the sections above, but further new research opportunities and implications can be drawn from this thesis.

4.3.1 Future research directions

Due to the multifactorial pathways and interrelationship of metabolic diseases, mediation analyses can provide important insights into how much of the associations between environmental factors and metabolic diseases are mediated by fat accumulation. A shift in focus is therefore warranted towards early features of metabolic diseases, such as unfavorable body composition patterns and hepatic iron overload, which may provide additional information on systemic and local effects in the development of metabolic diseases. Further research is needed to establish the incremental clinical value of such imaging-based phenotypes and potential non-imaging surrogate measures. This will also allow the expansion of research into hepatic iron overload and its health consequences, which offers promising research opportunities. To the best of our knowledge, the association between environmental exposures and hepatic iron content, fibrosis and cirrhosis is not yet under investigation. Based on the promising results on the associations of road traffic noise with adipose tissue depots, we aim to extend this by focusing on multiple environmental exposures and their association with adipose tissue depots and hepatic iron overload in the full NAKO-MRI sample (n = 30,000). In addition, the distinction between clinical and preclinical obesity, as advocated by the Group of Obesity Experts and Researchers in early 2025 (6), needs to be applied and implemented in future research. This may add information whether environmental factors have local effects on adipose tissue or if it impacts systemic changes on the multiple pathways leading to more severe, metabolically unhealthy obesity phenotypes, which we could not assess by just defining obesity by BMI. As we have shown doubled estimates for the joint associations of environmental exposures with metabolic diseases (90), more studies that elaborate the antagonistic, synergistic, or confounding effects of environmental factors, especially in urban areas are necessary. In line with this, novel statistical methods that can estimate associations of combined exposures, taking into account multi-collinearity and spatiotemporal exposure distribution, should become state-of-the art in future research.

4.3.2 Clinical and practical implications

Several clinical and practical implications can be drawn from these findings. First, screening for hepatic fat and iron overload in individuals with worsening glycemic traits and early signs of metabolic dysfunction may identify individuals at high risk for MASLD and further progression to more severe liver disease (28). Second, we provide crucial evidence on the association between road traffic noise and early obesity indicators. To address current research limitations, spatially inclusive and comprehensive monitoring of noise exposure is needed to improve health risk assessment attributed to noise (98). The current EIONET database for noise exposure still suffers from a high number of missings, specifically in suburban and rural areas, heterogenous noise mapping that do not allow comparisons between European countries and years, and the high reporting threshold of ≥ 55 dB(A) (95, 98, 121), although studies have shown health consequences at lower noise levels (48). In order to reduce the missing data, we assigned a lower detection limit of 40 dB(A) which likely underestimated the true noise exposure of the population, which probably shifted the associations towards the null (98). Consequently, we anticipate stronger associations with improved noise mapping. There is also a need for the implementation of uniform noise exposure guidelines and limits, which force and allow communities to act and implement mitigation measures, similarly to the WHO and EU air quality guidelines and directives (122, 123). Urban planning holds promising opportunities to create sustainable environments that reduce environmental risk factors such as exposure to air pollution, noise, non-optimal temperatures and lack of surrounding greenness (42). This may promote healthy behaviors and may play a key role in reducing the burden of metabolic diseases at population level. Although more research is needed to confirm our findings, these prevention strategies aimed at reducing risk factors at a population level may be essential to complement current behavioral prevention approaches for metabolic diseases.

5 Conclusion

Using novel epidemiological approaches and methods, this thesis adds important evidence on the interrelationship between metabolic diseases, related traits, and their environmental determinants. Our findings add important evidence on the dynamic relationship between diabetes and hepatic fat and iron content, thus highlighting that early screening for hepatic steatosis and iron overload in individuals with incipient deterioration of glycemic traits may enable early detection of the development of metabolic comorbidities. We also add to the literature that higher levels of $PM_{2.5}$ and road traffic noise were associated with metabolic diseases and related traits in cross-sectional analyses, and that a joint exposure to multiple environmental risk factors showed stronger associations with these outcomes. Thus, we provided novel evidence for potential systemic impacts of air pollution and noise on metabolic diseases and related traits. Moreover, this work indicates that reducing multiple environmental stressors, particularly in urban areas, may have benefits on metabolic diseases, offering a complementary population-level prevention approach to existing strategies targeting individual behaviors. Future studies should focus on longitudinal analyses and joint effects to corroborate these findings. More research is needed to fully understand the association of surrounding greenness with metabolic diseases and whether there is a link between average temperature and metabolic diseases in temporal climates. In addition, further research should aim to identify the drivers of metabolic diseases and their traits in rural areas.

6 Author contributions to each manuscript and additional projects

The present thesis comprises two published manuscripts and two submitted manuscripts (see appendix). The following chapters give a summary of my own contributions to each manuscript and further projects and scientific-related tasks I was involved in during my time as doctoral researcher.

In addition to the program "Dr. rer. biol. hum." at the Ludwig-Maximilians-University (LMU), I participated in the training program *HELENA* offered by Helmholtz Munich. I hold regular annual meetings with my Thesis Advisory Committee where I informed them on the status of my projects, discussed methods and results and agreed on a time plan with next steps. In my third year as doctoral researcher, I did a two-month research stay at the School of Public Health at the Harvard University in Boston, USA.

6.1 **Manuscript 1** – "Trajectories of glycaemic traits exhibit sex-specific associations with hepatic iron and fat content: Results from the KORA-MRI study"

This project aimed to deepen our understanding of the link between diabetes and hepatic metabolism, particularly the excessive accumulation of hepatic fat and iron content. I was involved in the formal analysis and development of the methodology by supporting Yaqi Su, a former master student. As first author, I prepared in conjunction with the corresponding author and the second authors, Susanne Rospleszcz and Yaqi Su, the original draft, and revised the manuscript according to the co-authors' and reviewers' comments. Moreover, I was responsible for the visualization of the results. The manuscript was published in 2023 in the journal *Liver International (28)*.

Liver International has an impact factor of 6.0 and is ranked 20th out of 143 journals in the category "Gastroenterology & Hepatology" according to the 2023 *Journal Citation Reports* of Clarivate. In the same year as published, I introduced this project to the scientific audience via a poster presentation at the 18th Annual Meeting of the DGEpi *(Deutsche Gesellschaft für Epidemiologie)* in Würzburg, Germany.

6.2 **Manuscript 2** – "Sex-specific associations of environmental exposures with prevalent diabetes and obesity - Results from the KORA Fit study"

As first author, I was responsible for the data application to the KORA study board, the data curation and statistical analysis. I drafted the analysis plan, developed, and discussed the conceptualization and methodology of the planned analytical steps with my co-authors. I drafted the manuscript including tables, figures, and supplement, and reviewed and edited it based on the co-author's comments. I was responsible for the submission of the paper to scientific journals, functioned as the corresponding author and revised the manuscript according to the reviewers' comments.

The paper was published in *Environmental Research* in 2024 (88). According to the 2023 *Journal Citation Reports* of Clarivate, *Environmental Research* has an impact factor of 7.7; is ranked as 36th journal out of 358 in the category "Environmental Sciences" and as 16th out of 408 in the category "Public, Environmental & Occupational Health".

I presented this project at two international scientific conferences in person. First, I presented preliminary results in form of a poster presentation at the 34th Annual Conference of the ISEE (*International Society of Environmental Epidemiology*) in 2022 in Athens, Greece. The abstract was published in the conference abstract book in a supplementary issue of the journal *Environmental health perspectives* (doi: https://doi.org/10.1289/isee.2022.P-1068). In addition, I presented the final results in an oral presentation at the 18th Annual Meeting of the DGEpi in 2023 in Würzburg, Germany.

6.3 **Manuscript 3** – "Individual and joint associations of multiple environmental exposures with diabetes and obesity in the population-based German National Cohort (NAKO)"

The manuscript was part of a large data application (NAKO-597) initialized by the NAKO Environmental Data Unit to describe the availability of environmental exposures and their respective health impacts. For this project, I was responsible for the curation of the data set, the development of the methodology and analysis plan and the formal analysis. I further improved and adapted the methodology during my research stay at the School of Public Health in Boston, USA. I drafted the original manuscript, visualized the results, and prepared the corresponding supplement. I also incorporated the co-authors' and reviewers' comments. As corresponding and first author, I was responsible for the submission and correspondence with the journal editors. The manuscript is currently submitted and under review in the *Journal of Hazardous Materials* and therefore, can be found in the appendix of this thesis (90). Additionally, I submitted the abstract for an oral presentation to this year DGEpi 2025 in Münster, Germany.

6.4 **Manuscript 4 –** "Associations of road traffic noise with adipose tissue depots and hepatic fat content – Results from the German National Cohort (NAKO)"

For the last project looking into the association of road traffic noise and highly accurately measured indicators of metabolic and hepatic health, I wrote the data application for the NAKO dataset. As first and corresponding author, I prepared and cleaned the data, developed the methodology and conducted the formal analysis. In addition, I drafted the original manuscript, prepared tables, figures, and the supplementary material and submitted the paper to the journal *Environment International*. I edited the manuscript and incorporated feedback from the co-authors and reviewers after receiving major revisions. The manuscript is currently again under review in *Environment International* after the revision, and is therefore included in the appendix of this thesis (98).

At the 36th annual conference of the ISEE, which took place in 2024 in Santiago, Chile, I gave an online presentation on this project. The abstract was published by *Environmental Health perspectives* in a supplementary issue and can be found here: https://doi.org/10.1289/isee.2024.0577. In addition, I helped drafting a press release on this project, which was initiated by the NAKO press and communication team. This press release will be available online on the NAKO website (https://nako.de/pressemitteilungen/) after publication of the manuscript.

6.5 Additional projects

During my time as doctoral researcher, I was involved in multiple other scientific projects that were related to my research focus on environmental exposures and/or cardiometabolic health.

I drafted the paper titled “Clusters of longitudinal risk profile trajectories are associated with cardiometabolic diseases: Results from the population-based KORA cohort”, which originated from my master thesis. In this study, we identified 3 distinct trajectories of cardiometabolic risk factors which were associated with cardiometabolic events using longitudinal data of the KORA study over a 14-year time period (124). The manuscript was published in *PloS One* in 2024.

Additionally, I am second author on the paper published by Shugaa Addin et al. titled “Association of serum magnesium with metabolic syndrome and the role of chronic kidney disease: A population-based cohort study with Mendelian randomization”, published in *Diabetes, Obesity and Metabolism* (125). The study presented evidence on the association of elevated serum magnesium with prevalent and incident metabolic syndrome and investigated the role of chronic kidney disease (125). I was supporting the development of methodology, mainly on the application of methods on longitudinal data and on testing non-linear exposure response functions. Further I revised the first manuscript draft.

I am co-author on the paper “Environmental exposure assessment in the German National Cohort (NAKO)” (83), where I generated figures and tables together with Marco Dallavalle and Kathrin Wolf. I also revised the first manuscript draft. This paper resulted from the same data application as the manuscript 3 (NAKO-597) and aimed to describe the currently available environmental exposures in the NAKO. Hence, it gives an overview and serves as essential information source for researchers interested in analyzing effects of environmental exposure on health in future NAKO analyses. The paper was published in *Environmental Research* in April 2025.

In addition, I am co-author on two further NAKO-manuscripts, which I edited and reviewed before submission, entitled: “The Association of a Lifestyle Risk Index with Visceral and Subcutaneous Adipose Tissue in the German National Cohort (NAKO)” (first author: Prof. Gertraud Maskarinec) and “Migration and Heart Disease: Comparative Investigation of Prevalence and Risk Factor Profiles in Resettlers from the NAKO Study in Germany” (first author: Glenna Walther). Both manuscripts are intended for publication in peer-reviewed journals.

Since I analyzed several NAKO datasets, a colleague and I initiated and are co-leading a monthly exchange meeting at Helmholtz Munich to discuss issues and problems related to data application, preparation (available on Github: https://github.com/Nikolaos-Nikolaou/EPI-NAKO-data-preparation), analysis, and publication of NAKO projects. Moreover, I have written several NAKO data applications referring to the effects of environmental exposures on cardiovascular mortality and morbidity, mental health as well as Covid-19 related outcomes.

References

1. Chew NWS, Ng CH, Tan DJH, Kong G, Lin C, Chin YH, . . . Muthiah MD. The global burden of metabolic disease: Data from 2000 to 2019. Cell Metab. 2023;35(3):414-28 e3. https://doi.org/10.1016/j.cmet.2023.02.003.

2. IDF (International Diabetes Federation). IDF Diabetes Atlas. 2021. Last access: 05.10.2022. Available from: www.diabetesatlas.org.

3. Brunner KT, Henneberg CJ, Wilechansky RM, Long MT. Nonalcoholic Fatty Liver Disease and Obesity Treatment. Curr Obes Rep. 2019;8(3):220-8. https://doi.org/10.1007/s13679-019-00345-1.

4. WHO (World Health Organization) Regional Office for Europe. WHO European Regional Obesity Report 2022. Report. 2022. Last access: 05.10.2022. Available from: https://www.who.int/europe/publications/i/item/9789289057738.

5. Global Burden of Disease 2021 Adult BMI Collaborators. Global, regional, and national prevalence of adult overweight and obesity, 1990-2021, with forecasts to 2050: a forecasting study for the Global Burden of Disease Study 2021. Lancet. 2025;405(10481):813-38. https://doi.org/10.1016/S0140-6736(25)00355-1.

6. Rubino F, Cummings DE, Eckel RH, Cohen RV, Wilding JPH, Brown WA, . . . Mingrone G. Definition and diagnostic criteria of clinical obesity. Lancet Diabetes Endocrinol. 2025. https://doi.org/10.1016/S2213-8587(24)00316-4.

7. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, Ostolaza H, Martin C. Pathophysiology of Type 2 Diabetes Mellitus. Int J Mol Sci. 2020;21(17). https://doi.org/10.3390/ijms21176275.

8. Schaapman JJ, Tushuizen ME, Coenraad MJ, Lamb HJ. Multiparametric MRI in Patients With Nonalcoholic Fatty Liver Disease. J Magn Reson Imaging. 2021;53(6):1623-31. https://doi.org/10.1002/jmri.27292.

9. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, . . . group NNc. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol. 2023;79(6):1542-56. https://doi.org/10.1016/j.jhep.2023.06.003.

10. Carruba MO, Busetto L, Bryant S, Caretto A, Farpour-Lambert NJ, Fatati G, . . . Nisoli E. The European Association for the Study of Obesity (EASO) Endorses the Milan Charter on Urban Obesity. Obes Facts. 2021;14(1):163-8. https://doi.org/10.1159/000514218.

11. Bray GA, Kim KK, Wilding JPH, World Obesity F. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. Obes Rev. 2017;18(7):715-23. https://doi.org/10.1111/obr.12551.

12. Eisenberg D, Shikora SA, Aarts E, Aminian A, Angrisani L, Cohen RV, . . . Kothari SN. 2022 American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO): Indications for Metabolic and Bariatric Surgery. Surg Obes Relat Dis. 2022;18(12):1345-56. https://doi.org/10.1016/j.soard.2022.08.013.

13. Kim BY, Kang SM, Kang JH, Kang SY, Kim KK, Kim KB, . . . Committee of Clinical Practice Guidelines KSftSoO. 2020 Korean Society for the Study of Obesity Guidelines for the Management of Obesity in Korea. J Obes Metab Syndr. 2021;30(2):81-92. https://doi.org/10.7570/jomes21022.

14. WHO (World Health Organization). Obesity: preventing and managing the global epidemic: report of a WHO consultation. Geneva, Switzerland: WHO; 2000. Last access: 08.02.2025. Available from: https://iris.who.int/handle/10665/42330.

15. Non-Communicable Disease Risk Factor Collaboration. Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. Lancet. 2024;403(10431):1027-50. https://doi.org/10.1016/S0140-6736(23)02750-2.

16. Global Burden of Disease Risk Factors Collaborators. Global burden and strength of evidence for 88 risk factors in 204 countries and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2024;403(10440):2162-203. https://doi.org/10.1016/S0140-6736(24)00933-4.

17. Global Burden of Disease 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2023;402(10397):203-34. https://doi.org/10.1016/S0140-6736(23)01301-6.

18. Khawaja T, Nied M, Wilgor A, Neeland IJ. Impact of Visceral and Hepatic Fat on Cardiometabolic Health. Curr Cardiol Rep. 2024;26(11):1297-307. https://doi.org/10.1007/s11886-024-02127-1.

19. Bechmann LP, Hannivoort RA, Gerken G, Hotamisligil GS, Trauner M, Canbay A. The interaction of hepatic lipid and glucose metabolism in liver diseases. J Hepatol. 2012;56(4):952-64. https://doi.org/10.1016/j.jhep.2011.08.025.

20. Global Burden of Disease Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1223-49. https://doi.org/10.1016/S0140-6736(20)30752-2.

21. Tchernof A, Despres JP. Pathophysiology of human visceral obesity: an update. Physiol Rev. 2013;93(1):359-404. https://doi.org/10.1152/physrev.00033.2011.

22. WHO (World Health Organization). Waist Circumference and Waist–Hip Ratio: Report of a WHO Expert Consultation Geneva, 8–11 December 2008 Geneva: WHO 2008. Last access: 10.02.2025. Available from: http://apps.who.int/iris/bitstream/handle/10665/44583/9789241501491_eng.pdf?sequence=1.

23. Haueise T, Schick F, Stefan N, Schlett CL, Weiss JB, Nattenmuller J, . . . Machann J. Analysis of volume and topography of adipose tissue in the trunk: Results of MRI of 11,141 participants in the German National Cohort. Sci Adv. 2023;9(19):eadd0433. https://doi.org/10.1126/sciadv.add0433.

24. Bamberg F, Schlett CL, Caspers S, Ringhof S, Gunther M, Hirsch JG, . . . Consortium NI. Baseline MRI Examination in the NAKO Health Study-Findings on Feasibility, Participation and Dropout Rates, Comfort, and Image Quality. Dtsch Arztebl Int. 2024;121(18):587-93. https://doi.org/10.3238/arztebl.m2024.0151.

25. Bamberg F, Kauczor HU, Weckbach S, Schlett CL, Forsting M, Ladd SC, . . . German National Cohort MRISI. Whole-Body MR Imaging in the German National Cohort: Rationale, Design, and Technical Background. Radiology. 2015;277(1):206-20. https://doi.org/10.1148/radiol.2015142272.

26. Salomao MA. Pathology of Hepatic Iron Overload. Clin Liver Dis (Hoboken). 2021;17(4):232-7. https://doi.org/10.1002/cld.1051.

27. Kuhn JP, Meffert P, Heske C, Kromrey ML, Schmidt CO, Mensel B, . . . Reeder SB. Prevalence of Fatty Liver Disease and Hepatic Iron Overload in a Northeastern German Population by Using Quantitative MR Imaging. Radiology. 2017;284(3):706-16. https://doi.org/10.1148/radiol.2017161228.

28. Niedermayer F, Su Y, von Kruchten R, Thorand B, Peters A, Rathmann W, . . . Rospleszcz S. Trajectories of glycaemic traits exhibit sex-specific associations with hepatic iron and fat content: Results from the KORA-MRI study. Liver Int. 2023;43(10):2153-66. https://doi.org/10.1111/liv.15635.

29. Imajo K, Kessoku T, Honda Y, Hasegawa S, Tomeno W, Ogawa Y, . . . Nakajima A. MRI-Based Quantitative R2(*) Mapping at 3 Tesla Reflects Hepatic Iron Overload and Pathogenesis in Nonalcoholic Fatty Liver Disease Patients. J Magn Reson Imaging. 2022;55(1):111-25. https://doi.org/10.1002/jmri.27810.

30. Tsurusaki S, Tsuchiya Y, Koumura T, Nakasone M, Sakamoto T, Matsuoka M, . . . Tanaka M. Hepatic ferroptosis plays an important role as the trigger for initiating inflammation in nonalcoholic steatohepatitis. Cell Death Dis. 2019;10(6):449. https://doi.org/10.1038/s41419-019-1678-y.

31. He H, Liao S, Zeng Y, Liang L, Chen J, Tao C. Causal relationships between metabolic-associated fatty liver disease and iron status: Two-sample Mendelian randomization. Liver Int. 2022;42(12):2759-68. https://doi.org/10.1111/liv.15455.

32. Bluher M. Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol. 2019;15(5):288-98. https://doi.org/10.1038/s41574-019-0176-8.

33. Younossi ZM, Golabi P, de Avila L, Paik JM, Srishord M, Fukui N, . . . Nader F. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. J Hepatol. 2019;71(4):793-801. https://doi.org/10.1016/j.jhep.2019.06.021.

34. Mantovani A, Petracca G, Beatrice G, Tilg H, Byrne CD, Targher G. Non-alcoholic fatty liver disease and risk of incident diabetes mellitus: an updated meta-analysis of 501 022 adult individuals. Gut. 2021;70(5):962-9. https://doi.org/10.1136/gutjnl-2020-322572.

35. Orban E, Schwab S, Thorand B, Huth C. Association of iron indices and type 2 diabetes: a meta-analysis of observational studies. Diabetes Metab Res Rev. 2014;30(5):372-94. https://doi.org/10.1002/dmrr.2506.

36. Kautzky-Willer A, Leutner M, Harreiter J. Sex differences in type 2 diabetes. Diabetologia. 2023;66(6):986-1002. https://doi.org/10.1007/s00125-023-05891-x.

37. Bellou V, Belbasis L, Tzoulaki I, Evangelou E. Risk factors for type 2 diabetes mellitus: An exposure-wide umbrella review of meta-analyses. PLoS One. 2018;13(3):e0194127. https://doi.org/10.1371/journal.pone.0194127.

38. Kivimaki M, Strandberg T, Pentti J, Nyberg ST, Frank P, Jokela M, . . . Ferrie JE. Body-mass index and risk of obesity-related complex multimorbidity: an observational multicohort study. Lancet Diabetes Endocrinol. 2022;10(4):253-63. https://doi.org/10.1016/S2213-8587(22)00033-X.

39. Non-Communicable Disease Risk Factor Collaboration. Rising rural body-mass index is the main driver of the global obesity epidemic in adults. Nature. 2019;569(7755):260-4. https://doi.org/10.1038/s41586-019-1171-x.

40. Dahlgren G, Whitehead M. Policies and strategies to promote social equity in health. Background document to WHO—Strategy paper for Europe. Institute for Futures Studies. 1991;Arbetsrapport 2007: 14.

41. Whitehead M, Dahlgren G. Policies and strategies to promote social equity in health. Stockholm: Institute for Future Studies. 1991.

42. Nieuwenhuijsen MJ. Urban and transport planning pathways to carbon neutral, liveable and healthy cities; A review of the current evidence. Environ Int. 2020;140:105661. https://doi.org/10.1016/j.envint.2020.105661.

43. Dyer GMC, Khomenko S, Adlakha D, Anenberg S, Behnisch M, Boeing G, . . . Nieuwenhuijsen M. Exploring the nexus of urban form, transport, environment and health in large-scale urban studies: A state-of-the-art scoping review. Environ Res. 2024;257:119324. https://doi.org/10.1016/j.envres.2024.119324.

44. de Bont J, Jaganathan S, Dahlquist M, Persson A, Stafoggia M, Ljungman P. Ambient air pollution and cardiovascular diseases: An umbrella review of systematic reviews and meta-analyses. J Intern Med. 2022;291(6):779-800. https://doi.org/10.1111/joim.13467.

45. Chen J, Hoek G. Long-term exposure to PM and all-cause and cause-specific mortality: A systematic review and meta-analysis. Environ Int. 2020;143:105974. https://doi.org/10.1016/j.envint.2020.105974.

46. Al-Kindi S, Motairek I, Khraishah H, Rajagopalan S. Cardiovascular disease burden attributable to non-optimal temperature: analysis of the 1990-2019 global burden of disease. Eur J Prev Cardiol. 2023;30(15):1623-31. https://doi.org/10.1093/eurjpc/zwad130.

47. Munzel T, Daiber A, Engelmann N, Roosli M, Kuntic M, Banks JL. Noise causes cardiovascular disease: it's time to act. J Expo Sci Environ Epidemiol. 2024. https://doi.org/10.1038/s41370-024-00732-4.

48. WHO (World Health Organization). Environmental Noise Guidelines for the European Region 2018. Last access: 01.02.2025. Available from: https://www.euro.who.int/__data/assets/pdf_file/0008/383921/noise-guidelines-eng.pdf.

49. Jimenez MP, DeVille NV, Elliott EG, Schiff JE, Wilt GE, Hart JE, James P. Associations between Nature Exposure and Health: A Review of the Evidence. Int J Environ Res Public Health. 2021;18(9). https://doi.org/10.3390/ijerph18094790.

50. Sivakumaran K, Ritonja JA, Waseem H, AlShenaiber L, Morgan E, Ahmadi SA, Denning A, Michaud D, Morgan RL. Impact of Noise Exposure on Risk of Developing Stress-Related Metabolic Effects: A Systematic Review and Meta-Analysis. Noise Health. 2022;24(115):215-30. https://doi.org/10.4103/nah.nah_21_22.

51. Rajagopalan S, Brook RD. Air pollution and type 2 diabetes: mechanistic insights. Diabetes. 2012;61(12):3037-45. https://doi.org/10.2337/db12-0190.

52. Rajagopalan S, Brook RD, Salerno P, Bourges-Sevenier B, Landrigan P, Nieuwenhuijsen MJ, Munzel T, Deo SV, Al-Kindi S. Air pollution exposure and cardiometabolic risk. Lancet Diabetes Endocrinol. 2024;12(3):196-208. https://doi.org/10.1016/S2213-8587(23)00361-3.

53. Peters A, Nawrot TS, Baccarelli AA. Hallmarks of environmental insults. Cell. 2021;184(6):1455-68. https://doi.org/10.1016/j.cell.2021.01.043.

54. Speakman JR, Heidari-Bakavoli S. Type 2 diabetes, but not obesity, prevalence is positively associated with ambient temperature. Sci Rep. 2016;6:30409. https://doi.org/10.1038/srep30409.

55. Valdes S, Maldonado-Araque C, Garcia-Torres F, Goday A, Bosch-Comas A, Bordiu E, . . . Rojo-Martinez G. Ambient temperature and prevalence of obesity in the Spanish population: The Di@bet.es study. Obesity (Silver Spring). 2014;22(11):2328-32. https://doi.org/10.1002/oby.20866.

56. James I, Jain R, Wade G, Stevenson PC, Koulman A, Simcox J, Furse S. Systemic analysis shows that cold exposure modulates triglyceride accumulation and phospholipid distribution in mice. PLoS One. 2024;19(11):e0313205. https://doi.org/10.1371/journal.pone.0313205.

57. Munzel T, Molitor M, Kuntic M, Hahad O, Roosli M, Engelmann N, Basner M, Daiber A, Sorensen M. Transportation Noise Pollution and Cardiovascular Health. Circ Res. 2024;134(9):1113-35. https://doi.org/10.1161/CIRCRESAHA.123.323584.

58. Kondo MC, Jacoby SF, South EC. Does spending time outdoors reduce stress? A review of real-time stress response to outdoor environments. Health Place. 2018;51:136-50. https://doi.org/10.1016/j.healthplace.2018.03.001.

59. He D, Wu S, Zhao H, Qiu H, Fu Y, Li X, He Y. Association between particulate matter 2.5 and diabetes mellitus: A meta-analysis of cohort studies. J Diabetes Investig. 2017;8(5):687-96. https://doi.org/10.1111/jdi.12631.

60. Parasin N, Amnuaylojaroen T, Saokaew S, Sittichai N, Tabkhan N, Dilokthornsakul P. Outdoor air pollution exposure and the risk of type 2 diabetes mellitus: A systematic umbrella review and meta-analysis. Environ Res. 2025;269:120885. https://doi.org/10.1016/j.envres.2025.120885.

61. Huang S, Zhang X, Huang J, Lu X, Liu F, Gu D. Ambient air pollution and body weight status in adults: A systematic review and meta-analysis. Environ Pollut. 2020;265(Pt A):114999. https://doi.org/10.1016/j.envpol.2020.114999.

62. Gui SY, Wu KJ, Sun Y, Chen YN, Liang HR, Liu W, Lu Y, Hu CY. Traffic noise and adiposity: a systematic review and meta-analysis of epidemiological studies. Environ Sci Pollut Res Int. 2022;29(37):55707-27. https://doi.org/10.1007/s11356-022-19056-7.

63. Wang H, Sun D, Wang B, Gao D, Zhou Y, Wang N, Zhu B. Association between noise exposure and diabetes: meta-analysis. Environ Sci Pollut Res Int. 2020;27(29):36085-90. https://doi.org/10.1007/s11356-020-09826-6.

64. Yang BY, Fan S, Thiering E, Seissler J, Nowak D, Dong GH, Heinrich J. Ambient air pollution and diabetes: A systematic review and meta-analysis. Environ Res. 2020;180:108817. https://doi.org/10.1016/j.envres.2019.108817.

65. Yang M, Cheng H, Shen C, Liu J, Zhang H, Cao J, Ding R. Effects of long-term exposure to air pollution on the incidence of type 2 diabetes mellitus: a meta-analysis of cohort studies. Environ Sci Pollut Res Int. 2020;27(1):798-811. https://doi.org/10.1007/s11356-019-06824-1.

66. An R, Ji M, Yan H, Guan C. Impact of ambient air pollution on obesity: a systematic review. Int J Obes (Lond). 2018;42(6):1112-26. https://doi.org/10.1038/s41366-018-0089-y.

67. Valdes S, Doulatram-Gamgaram V, Lago A, Garcia Torres F, Badia-Guillen R, Olveira G, . . . Rojo-Martinez G. Ambient temperature and prevalence of diabetes and insulin resistance in the Spanish population: Di@bet.es study. Eur J Endocrinol. 2019;180(5):273-80. https://doi.org/10.1530/EJE-18-0818.

68. De la Fuente F, Saldias MA, Cubillos C, Mery G, Carvajal D, Bowen M, Bertoglia MP. Green Space Exposure Association with Type 2 Diabetes Mellitus, Physical Activity,

and Obesity: A Systematic Review. Int J Environ Res Public Health. 2020;18(1). https://doi.org/10.3390/ijerph18010097.

69. Hwang SE, Kwon H, Jeong SM, Kim HJ, Park JH. Ambient air pollution exposure and obesity-related traits in Korean adults. Diabetes Metab Syndr Obes. 2019;12:1365-77. https://doi.org/10.2147/DMSO.S208115.

70. Kim JS, Chen Z, Alderete TL, Toledo-Corral C, Lurmann F, Berhane K, Gilliland FD. Associations of air pollution, obesity and cardiometabolic health in young adults: The Meta-AIR study. Environ Int. 2019;133(Pt A):105180. https://doi.org/10.1016/j.envint.2019.105180.

71. Altug H, Ogurtsova K, Breyer-Kohansal R, Schiffers C, Ofenheimer A, Tzivian L, . . . Breyer MK. Associations of long-term exposure to air pollution and noise with body composition in children and adults: Results from the LEAD general population study. Environ Int. 2024;189:108799. https://doi.org/10.1016/j.envint.2024.108799.

72. Woeckel M, Rospleszcz S, Wolf K, Breitner-Busch S, Ingrisch M, Bamberg F, . . . Peters A. Association between Long-Term Exposure to Traffic-Related Air Pollution and Cardio-Metabolic Phenotypes: An MRI Data-Based Analysis. Environ Sci Technol. 2024;58(41):18064-75. https://doi.org/10.1021/acs.est.4c03163.

73. Eze IC, Hemkens LG, Bucher HC, Hoffmann B, Schindler C, Kunzli N, Schikowski T, Probst-Hensch NM. Association between ambient air pollution and diabetes mellitus in Europe and North America: systematic review and meta-analysis. Environ Health Perspect. 2015;123(5):381-9. https://doi.org/10.1289/ehp.1307823.

74. Liu C, Cao G, Li J, Lian S, Zhao K, Zhong Y, . . . Liu T. Effect of long-term exposure to PM(2.5) on the risk of type 2 diabetes and arthritis in type 2 diabetes patients: Evidence from a national cohort in China. Environ Int. 2023;171:107741. https://doi.org/10.1016/j.envint.2023.107741.

75. Persson A, Pyko A, Lind T, Bellander T, Ostenson CG, Pershagen G, Eriksson C, Lohmus M. Urban residential greenness and adiposity: A cohort study in Stockholm County. Environ Int. 2018;121(Pt 1):832-41. https://doi.org/10.1016/j.envint.2018.10.009.

76. Han W, Xu Z, Hu X, Cao R, Wang Y, Jin J, . . . Li G. Air pollution, greenness and risk of overweight among middle-aged and older adults: A cohort study in China. Environ Res. 2023;216(Pt 1):114372. https://doi.org/10.1016/j.envres.2022.114372.

77. Sorensen M, Poulsen AH, Hvidtfeldt UA, Christensen JH, Brandt J, Frohn LM, . . . Raaschou-Nielsen O. Effects of Sociodemographic Characteristics, Comorbidity, and Coexposures on the Association between Air Pollution and Type 2 Diabetes: A Nationwide Cohort Study. Environ Health Perspect. 2023;131(2):27008. https://doi.org/10.1289/EHP11347.

78. Klompmaker JO, Janssen NAH, Bloemsma LD, Gehring U, Wijga AH, van den Brink C, Lebret E, Brunekreef B, Hoek G. Associations of Combined Exposures to Surrounding Green, Air Pollution, and Road Traffic Noise with Cardiometabolic Diseases. Environ Health Perspect. 2019;127(8):87003. https://doi.org/10.1289/EHP3857.

79. Zhang B, Hart JE, Laden F, Bozigar M, James P. Environmental mixtures and body mass index in two prospective US-based cohorts of female nurses. J Hazard Mater. 2024;480:135794. https://doi.org/10.1016/j.jhazmat.2024.135794.

80. Keil AP, Buckley JP, O'Brien KM, Ferguson KK, Zhao S, White AJ. A Quantile-Based g-Computation Approach to Addressing the Effects of Exposure Mixtures. Environ Health Perspect. 2020;128(4):47004. https://doi.org/10.1289/EHP5838.

81. Voss S, Schneider A, Huth C, Wolf K, Markevych I, Schwettmann L, Rathmann W, Peters A, Breitner S. ENVINT-D-20-01309: Long-term exposure to air pollution, road traffic noise, residential greenness, and prevalent and incident metabolic syndrome: Results from the population-based KORA F4/FF4 cohort in Augsburg, Germany. Environ Int. 2021;147:106364. https://doi.org/10.1016/j.envint.2020.106364.

82. Liu M, Tang W, Zhang Y, Wang Y, Baima K, Li Y, . . . China Muti-Ethnic Cohort collaborative g. Urban-rural differences in the association between long-term exposure to ambient air pollution and obesity in China. Environ Res. 2021;201:111597. https://doi.org/10.1016/j.envres.2021.111597.

83. Wolf K, Dallavalle M, Niedermayer F, Bolte G, Lakes T, Schikowski T, . . . Hoffmann B. Environmental exposure assessment in the German National Cohort (NAKO). Environ Res. 2025;273:121259. https://doi.org/10.1016/j.envres.2025.121259.

84. Yang Z, Song Q, Li J, Zhang Y. Air Pollution as a Cause of Obesity: Micro-Level Evidence from Chinese Cities. Int J Environ Res Public Health. 2019;16(21). https://doi.org/10.3390/ijerph16214296.

85. Pyko A, Eriksson C, Lind T, Mitkovskaya N, Wallas A, Ogren M, Ostenson CG, Pershagen G. Long-Term Exposure to Transportation Noise in Relation to Development of Obesity-a Cohort Study. Environ Health Perspect. 2017;125(11):117005. https://doi.org/10.1289/EHP1910.

86. Pyko A, Eriksson C, Oftedal B, Hilding A, Ostenson CG, Krog NH, Julin B, Aasvang GM, Pershagen G. Exposure to traffic noise and markers of obesity. Occup Environ Med. 2015;72(8):594-601. https://doi.org/10.1136/oemed-2014-102516.

87. Gadd SC, Tennant PWG, Heppenstall AJ, Boehnke JR, Gilthorpe MS. Analysing trajectories of a longitudinal exposure: A causal perspective on common methods in lifecourse research. PLoS One. 2019;14(12):e0225217. https://doi.org/10.1371/journal.pone.0225217.

88. Niedermayer F, Wolf K, Zhang S, Dallavalle M, Nikolaou N, Schwettmann L, . . . Peters A. Sex-specific associations of environmental exposures with prevalent diabetes and obesity - Results from the KORA Fit study. Environ Res. 2024;252(Pt 3):118965. https://doi.org/10.1016/j.envres.2024.118965.

89. Peters A, German National Cohort C, Peters A, Greiser KH, Gottlicher S, Ahrens W, . . . Zschocke J. Framework and baseline examination of the German National Cohort (NAKO). Eur J Epidemiol. 2022;37(10):1107-24. https://doi.org/10.1007/s10654-022-00890-5.

90. Niedermayer F, Hoffmann B, Zhang B, Chen J, Hart JE, Laden F, . . . Peters A. Individual and joint associations of multiple environmental exposures with diabetes and obesity in the population-based German National Cohort (NAKO). 2025. Submitted to Journal of Hazardous Material (under review).

91. Wolf K, Cyrys J, Harcinikova T, Gu J, Kusch T, Hampel R, Schneider A, Peters A. Land use regression modeling of ultrafine particles, ozone, nitrogen oxides and markers of particulate matter pollution in Augsburg, Germany. Sci Total Environ. 2017;579:1531-40. https://doi.org/10.1016/j.scitotenv.2016.11.160.

92. Nikolaou N, Dallavalle M, Stafoggia M, Bouwer LM, Peters A, Chen K, Wolf K, Schneider A. High-resolution spatiotemporal modeling of daily near-surface air temperature in Germany over the period 2000-2020. Environ Res. 2023;219:115062. https://doi.org/10.1016/j.envres.2022.115062.

93. de Hoogh K, Chen J, Gulliver J, Hoffmann B, Hertel O, Ketzel M, . . . Hoek G. Spatial PM(2.5), NO(2), O(3) and BC models for Western Europe - Evaluation of

spatiotemporal stability. Environ Int. 2018;120:81-92. https://doi.org/10.1016/j.envint.2018.07.036.

94. Staab J, Schady A, Weigand M, Lakes T, Taubenbock H. Predicting traffic noise using land-use regression-a scalable approach. J Expo Sci Environ Epidemiol. 2022;32(2):232-43. https://doi.org/10.1038/s41370-021-00355-z.

95. Staab J, Droin A, Weigand M, Dallavalle M, Wolf K, Schady A, Lakes T, Wurm M, Taubenböck H. Pixels, chisels and contours - technical variations in European road traffic noise exposure maps. Journal of Environmental Management. 2025;385. https://doi.org/10.1016/j.jenvman.2025.125475.

96. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999;10(1):37-48.

97. European Union. Methodological manual on territorial typologies. Luxembourg: Publications Office of the European Union,; 2018. Report No.: 2315-0815. Last access: 23.12.2022. Available from: https://ec.europa.eu/eurostat/documents/3859598/9507230/KS-GQ-18-008-EN-N.pdf.

98. Niedermayer F, Rospleszcz S, Matthiessen C, Hoffmann B, Stoecklein S, Haueise T, . . . Peters A. Associations of road traffic noise with adipose tissue depots and hepatic fat content – Results from the German National Cohort (NAKO). 2025. Submitted to Environment International (under review).

99. Wang B, Li M, Zhao Z, Wang S, Lu J, Chen Y, . . . Xu Y. Glycemic Measures and Development and Resolution of Nonalcoholic Fatty Liver Disease in Nondiabetic Individuals. J Clin Endocrinol Metab. 2020;105(5). https://doi.org/10.1210/clinem/dgaa112.

100. Naeem M, Schipf S, Bulow R, Werner N, Dorr M, Lerch MM, . . . Volzke H. Association between hepatic iron overload assessed by magnetic resonance imaging and glucose intolerance states in the general population. Nutr Metab Cardiovasc Dis. 2022;32(6):1470-6. https://doi.org/10.1016/j.numecd.2022.02.013.

101. Kim G, Giannini C, Pierpont B, Feldstein AE, Santoro N, Kursawe R, . . . Caprio S. Longitudinal effects of MRI-measured hepatic steatosis on biomarkers of glucose homeostasis and hepatic apoptosis in obese youth. Diabetes Care. 2013;36(1):130-6. https://doi.org/10.2337/dc12-0277.

102. Le MD, Wu Y, Berry JD, Browning JD, de Lemos JA, Neeland IJ, Lingvay I. Associations of liver fat content with cardiometabolic phenotypes and outcomes in a multi-ethnic population: Results from the Dallas Heart Study. Diabetes Obes Metab. 2023;25(2):586-95. https://doi.org/10.1111/dom.14905.

103. Wu S, Wu F, Ding Y, Hou J, Bi J, Zhang Z. Association of non-alcoholic fatty liver disease with major adverse cardiovascular events: A systematic review and meta-analysis. Sci Rep. 2016;6:33386. https://doi.org/10.1038/srep33386.

104. Perdomo CM, Nunez-Cordoba JM, Ezponda A, Mendoza FJ, Ampuero J, Bastarrika G, Fruhbeck G, Escalada J. Cardiometabolic characterization in metabolic dysfunction-associated fatty liver disease. Front Med (Lausanne). 2022;9:1023583. https://doi.org/10.3389/fmed.2022.1023583.

105. Sorensen M, Poulsen AH, Hvidtfeldt UA, Brandt J, Frohn LM, Ketzel M, . . . Raaschou-Nielsen O. Air pollution, road traffic noise and lack of greenness and risk of type 2 diabetes: A multi-exposure prospective study covering Denmark. Environ Int. 2022;170:107570. https://doi.org/10.1016/j.envint.2022.107570.

106. Ye L, Zhou J, Tian Y, Cui J, Chen C, Wang J, . . . Shi X. Associations of residential greenness and ambient air pollution with overweight and obesity in older adults. Obesity (Silver Spring). 2023;31(10):2627-37. https://doi.org/10.1002/oby.23856.

107. Cai M, Li H, Wu Y, Zhang S, Wang X, Zhang Z, Lin H. Ambient Air Pollution Associated with Body Fat Percentages at Different Body Compartments: A Cohort Study of UK Biobank Participants. Environ Health Perspect. 2022;130(6):67702. https://doi.org/10.1289/EHP10920.

108. Luo YN, Huang WZ, Liu XX, Markevych I, Bloom MS, Zhao T, Heinrich J, Yang BY, Dong GH. Greenspace with overweight and obesity: A systematic review and meta-analysis of epidemiological studies up to 2020. Obes Rev. 2020;21(11):e13078. https://doi.org/10.1111/obr.13078.

109. Dempsey S, Lyons S, Nolan A. Urban green space and obesity in older adults: Evidence from Ireland. SSM Popul Health. 2018;4:206-15. https://doi.org/10.1016/j.ssmph.2018.01.002.

110. James P, Kioumourtzoglou MA, Hart JE, Banay RF, Kloog I, Laden F. Interrelationships Between Walkability, Air Pollution, Greenness, and Body Mass Index. Epidemiology. 2017;28(6):780-8. https://doi.org/10.1097/EDE.0000000000000724.

111. Klompmaker JO, Hoek G, Bloemsma LD, Gehring U, Strak M, Wijga AH, . . . Janssen NAH. Green space definition affects associations of green space with overweight and physical activity. Environ Res. 2018;160:531-40. https://doi.org/10.1016/j.envres.2017.10.027.

112. Villeneuve PJ, Jerrett M, Su JG, Weichenthal S, Sandler DP. Association of residential greenness with obesity and physical activity in a US cohort of women. Environ Res. 2018;160:372-84. https://doi.org/10.1016/j.envres.2017.10.005.

113. Nieuwenhuijsen MJ, Khreis H, Triguero-Mas M, Gascon M, Dadvand P. Fifty Shades of Green: Pathway to Healthy Urban Living. Epidemiology. 2017;28(1):63-71. https://doi.org/10.1097/EDE.0000000000000549.

114. Bratman GN, Hamilton JP, Hahn KS, Daily GC, Gross JJ. Nature experience reduces rumination and subgenual prefrontal cortex activation. Proc Natl Acad Sci U S A. 2015;112(28):8567-72. https://doi.org/10.1073/pnas.1510459112.

115. Aspinall P, Mavros P, Coyne R, Roe J. The urban brain: analysing outdoor physical activity with mobile EEG. Br J Sports Med. 2015;49(4):272-6. https://doi.org/10.1136/bjsports-2012-091877.

116. Hoek G, Vienneau D, de Hoogh K. Does residential address-based exposure assessment for outdoor air pollution lead to bias in epidemiological studies? Environ Health. 2024;23(1):75. https://doi.org/10.1186/s12940-024-01111-0.

117. Babisch W, Wolf K, Petz M, Heinrich J, Cyrys J, Peters A. Associations between traffic noise, particulate air pollution, hypertension, and isolated systolic hypertension in adults: the KORA study. Environ Health Perspect. 2014;122(5):492-8. https://doi.org/10.1289/ehp.1306981.

118. Fecht D, Hansell AL, Morley D, Dajnak D, Vienneau D, Beevers S, . . . Gulliver J. Spatial and temporal associations of road traffic noise and air pollution in London: Implications for epidemiological studies. Environ Int. 2016;88:235-42. https://doi.org/10.1016/j.envint.2015.12.001.

119. Chen J, Braun D, Christidis T, Cork M, Rodopoulou S, Samoli E, . . . Brunekreef B. Long-Term Exposure to Low-Level PM2.5 and Mortality: Investigation of

Heterogeneity by Harmonizing Analyses in Large Cohort Studies in Canada, United States, and Europe. Environ Health Perspect. 2023;131(12):127003. https://doi.org/10.1289/EHP12141.

120. Vienneau D, de Hoogh K, Faeh D, Kaufmann M, Wunderli JM, Roosli M, Group SNCS. More than clean air and tranquillity: Residential green is independently associated with decreasing mortality. Environ Int. 2017;108:176-84. https://doi.org/10.1016/j.envint.2017.08.012.

121. European Environment Agency. Environmental noise in Europe — 2020. Copenhagen, Denmark; 2020. Last access: 04.04.2024. Available from: https://www.eea.europa.eu/en/analysis/publications/environmental-noise-in-europe.

122. WHO (World Health Organization). WHO global air quality guidelines: particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. Geneva: World Health Organization; 2021. Last access: 23.01.2025. Available from: https://www.who.int/publications/i/item/9789240034228/.

123. European Parliamentary Research Service. Revision of the EU Ambient Air Quality Directives. 2022. Last access: 10.02.2025. Available from: https://www.europarl.europa.eu/RegData/etudes/BRIE/2022/734679/EPRS_BRI(2022)734679_EN.pdf.

124. Niedermayer F, Schauberger G, Rathmann W, Klug SJ, Thorand B, Peters A, Rospleszcz S. Clusters of longitudinal risk profile trajectories are associated with cardiometabolic diseases: Results from the population-based KORA cohort. PLoS One. 2024;19(3):e0300966. https://doi.org/10.1371/journal.pone.0300966.

125. Shugaa Addin N, Niedermayer F, Thorand B, Linseisen J, Seissler J, Peters A, Rospleszcz S. Association of serum magnesium with metabolic syndrome and the role of chronic kidney disease: A population-based cohort study with Mendelian randomization. Diabetes Obes Metab. 2024;26(5):1808-20. https://doi.org/10.1111/dom.15497.

Manuscript 1

Title:	Trajectories of glycaemic traits exhibit sex-specific associations with hepatic iron and fat content: Results from the KORA-MRI study
Authors:	Niedermayer, Fiona; Su, Yaqi; von Krüchten, Ricarda; Thorand, Barbara; Peters, Annette; Rathmann, Wolfgang; Roden, Michael; Schlett, Christopher L.; Bamberg, Fabian; Nattenmüller, Johanna; Rospleszcz, Susanne
Year:	2023
Status:	Published
Journal:	Liver International
Volume:	43
Issue:	10
Page:	2153-2166
DOI:	https://doi.org/10.1111/liv.15635
2023 Journal Impact Factor:	6.0 (*Journal Citation Reports* (Clarivate, 2023))
Rank by 2023 Journal Impact Factor:	20/143 in the category “Gastroenterology & Hepatology” (*Journal Citation Reports* (Clarivate, 2023))

Received: 20 February 2023 | Revised: 5 May 2023 | Accepted: 25 May 2023

DOI: 10.1111/liv.15635

Liver INTERNATIONAL WILEY

ORIGINAL ARTICLE

Trajectories of glycaemic traits exhibit sex-specific associations with hepatic iron and fat content: Results from the KORA-MRI study

Fiona Niedermayer[1,2] | Yaqi Su[1,2,3] | Ricarda von Krüchten[4] | Barbara Thorand[2,5] | Annette Peters[1,2,5,6] | Wolfgang Rathmann[5,7] | Michael Roden[5,8,9] | Christopher L. Schlett[4] | Fabian Bamberg[4] | Johanna Nattenmüller[4] | Susanne Rospleszcz[1,2,6]

[1]Chair of Epidemiology, Institute for Medical Information Processing, Biometry, and Epidemiology, Faculty of Medicine, LMU München, Munich, Germany

[2]Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany

[3]Pettenkofer School of Public Health, Munich, Germany

[4]Department of Diagnostic and Interventional Radiology, Medical Center, University of Freiburg, Freiburg, Germany

[5]German Center for Diabetes Research (DZD), München-Neuherberg, Germany

[6]German Center for Cardiovascular Disease Research (DZHK), Munich Heart Alliance, Munich, Germany

[7]Institute for Biometrics and Epidemiology, German Diabetes Center (DDZ), Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, Düsseldorf, Germany

[8]Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University, Düsseldorf, Germany

[9]Division of Endocrinology and Diabetology, Medical Faculty, Heinrich Heine University, Düsseldorf, Germany

Correspondence
Susanne Rospleszcz, Ingolstädter Landestraße 1, 85764 Neuherberg, Germany.
Email: susanne.rospleszcz@helmholtz-muenchen.de

Funding information
Centre for Diabetes Research (DZD e.V., Neuherberg, Germany); Deutsche Forschungsgemeinschaft, Grant/Award Number: BA 4233/4-1; Deutsches Forschungszentrum für Gesundheit und Umwelt, Helmholtz Zentrum München; German Centre for Cardiovascular Disease Research (Berlin, Germany), Grant/Award Number: 81X2600209 and 81X2600214; Münchner Zentrum für Gesundheitswissenschaften, Ludwig-Maximilians-Universität München

Handling Editor: Luca Valenti

Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) represents a major disease burden in the population. While the bidirectional association between NAFLD and diabetes is established, little is known about the association of hepatic iron content and glycaemia. Moreover, analyses of sex-specific effects and of dynamic changes in glycaemia are scarce.

Methods: We investigated 7-year sex-specific trajectories of glycaemia and related traits (HbA1c, fasting glucose, fasting insulin, HOMA-IR, 2-h glucose and cross-sectional 2-h insulin) in a sample from a population-based cohort ($N = 365$; 41.1% female). Hepatic iron and fat content were assessed by 3T-Magnetic Resonance Imaging (MRI). Two-step multi-level models adjusted for glucose-lowering medication and confounders were applied.

Results: In women and men, markers of glucose metabolism correlated with hepatic iron and fat content. Deterioration of glycaemia was associated with increased hepatic

Abbreviations: BMI, Body Mass Index; CI, confidence interval; CVD, cardiovascular disease; HbA1c, Haemoglobin A1c; HOMA-IR, homeostasis model of insulin resistance; KORA, Kooperative Gesundheitsforschung in der Region Augsburg; MRI, magnetic resonance imaging; NAFLD, non-alcoholic fatty liver disease; OGTT, oral glucose tolerance test; T2D, type 2 diabetes.

iron content in men (normoglycaemia to prediabetes: beta = 2.21 s^{-1}, 95% CI [0.47, 3.95]). Additionally, deterioration of glycaemia (e.g. prediabetes to diabetes: 1.27 log(%), [0.84, 1.70]) and trajectories of glucose, insulin and HOMA-IR were significantly associated with hepatic fat content in men. Similarly, deterioration of glycaemia as well as trajectories of glucose, insulin and HOMA-IR was significantly associated with increased hepatic fat content in women (e.g. trajectory of fasting insulin: 0.63 log(%), [0.36, 0.90]).

Conclusions: Unfavourable 7-year trajectories of markers of glucose metabolism are associated with increased hepatic fat content, particularly in women, whereas the association with hepatic iron content was less clear. Monitoring changes of glycaemia in the sub-diabetic range might enable early identification of hepatic iron overload and steatosis.

KEYWORDS
diabetes, glucose, HbA1c, hepatic fat, hepatic iron, insulin, NAFLD, sex, trajectories

1 | BACKGROUND

Non-alcoholic fatty liver disease (NAFLD), defined as an excessive build-up of hepatic fat irrespective of alcohol consumption, viral infection, or other causes, is a common and rapidly rising liver disease worldwide. NAFLD can progress to steatohepatitis, fibrosis, cirrhosis and hepatocellular carcinoma, thus representing a precursor state of potentially serious and life-threatening liver outcomes.[1]

NAFLD is tightly connected to insulin resistance, which causes impaired lipolysis and excess fatty acid transport to the hepatocytes, while dysregulated adipose tissue lipolysis in turn promotes insulin resistance. Thus, Type 2 diabetes (T2D) and NAFLD frequently co-exist.[2] Recent meta-analyses estimated that 55.5% of individuals with T2D also had NAFLD[3] and that NAFLD doubles the risk of incident T2D.[4] In addition, Mendelian randomization studies have demonstrated a causal, bi-directional relationship.[5]

Diabetes has also been identified as a risk factor of progression to liver cirrhosis and carcinoma.[6] However, although NAFLD development and progression are known to differ according to biological sex,[7] sex-specific impacts of diabetes on hepatic fat accumulation have not been comprehensively studied. Moreover, since glucose metabolism is dynamic, the development of glycaemia over time might also affect hepatic fat content.

Recently, both animal and human studies have implicated hepatic iron content as a potential factor driving the progression from NAFLD to steatohepatitis via ferroptosis-induced inflammation and necrosis.[8,9] An association between markers of iron metabolism and liver disease has already been established.[10] A recent Mendelian randomization study using data from the UK Biobank showed tentative evidence for a potential causal association of liver iron on fatty liver.[11]

At the same time, oxidative stress induced by iron overload leads to increased insulin resistance, establishing a link between circulating markers of iron metabolism and T2D.[12] Sex-specific associations, with higher T2D risk conferred by elevated ferritin levels in women compared to men, have been reported.[13,14] However, the link between hepatic iron as a major storage site of body iron and glucose metabolism is less clear and again there is a lack of data regarding sex-specific effects.

Quantitative data on hepatic iron and hepatic fat infiltration in population-based studies are scarce. Most non-clinical studies define NAFLD based on ultrasound, which is an established validated technique but cannot estimate hepatic iron content and does not precisely quantify hepatic fat content. However, given the societal burden of NAFLD in the general population, it is crucial to study risk factors and implications in a population-based setting. Magnetic resonance imaging (MRI) is a non-invasive, radiation-free, albeit costly modality to accurately assess hepatic iron and fat content.[15]

With the present analysis, we aim to tackle some of the currently open questions. In a sample from a population-based cohort, we analyse the association of changes in glycaemia over time, as well as the longitudinal trajectories of markers of glucose metabolism, with MRI-derived hepatic iron and hepatic fat content separately for men and women.

Key points

Diabetes mellitus and non-alcoholic fatty liver disease frequently co-exist. We show that not only cross-sectional values but also the deterioration of glycaemic traits over time are associated with higher values of hepatic fat content in a sex-specific fashion. Moreover, our findings demonstrate that trajectories of glucose metabolism are related to hepatic iron content in men.

2 | METHODS

2.1 | Study sample

We used data from two examination time points of a longitudinal, population based cohort study from Southern Germany. Details of the general setup of the Cooperative Health Research in the Region of Augsburg (KORA) studies have been described elsewhere.[16] Our sample is based on $N=400$ individuals that underwent whole-body MRI during the examination in 2013–2014 (KORA-FF4, total $N=2279$, defined as Exam 2 in the present paper). The MRI sub-study aimed to evaluate subclinical cardiometabolic disease burden in individuals with impaired glucose metabolism. Individuals with prevalent cardiovascular disease (stroke, myocardial infarction, revascularization) or any contraindications to MRI were excluded.[17] For these $N=400$ individuals, we used clinical data that was assessed during the examination 7 years prior in 2006–2007 (KORA F4, total $N=3080$, defined as Exam 1 in the present paper).

All KORA studies are approved by the ethics committee of the Bavarian Chamber of Physicians, and the MRI sub-study was additionally approved by the ethics committee of the Ludwig-Maximilians-University Munich. The study complies with the Declaration of Helsinki, including written informed consent from all participants. All participants underwent a standardized face-to-face interview, a blood draw and a comprehensive physical examination conducted by trained examiners at both examination time points.

2.2 | Outcome assessment

Participants underwent whole-body MRI performed on a 3 Tesla MRI scanner (Magnetom Skyra; Siemens AGA, Siemens Healthineers, Erlangen, Germany). Hepatic iron and fat content were obtained in the left and right liver lobes using the high-speed T2-corrected multi-echo sequence (HISTO).[18] Iron was measured as relaxation rate R2* in s^{-1}, and fat content was measured as mean proton density fat fraction in percent.[19] For statistical analysis, we used the arithmetic mean of left and right liver lobe as outcome. Mild hepatic iron overload was defined as $R2^* > 41\,s^{-1}$.[15] Hepatic steatosis was defined as proton density fat fraction >6.4%.[20] Hepatic outcomes were available only at Exam 2.

2.3 | Exposure assessment

Markers of glucose metabolism included diabetes status, Haemoglobin A1c (HbA1c), fasting glucose, fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), 2-h glucose and 2-h insulin. Glycaemia (normoglycaemia, prediabetes, diabetes) was categorized based on prior physician diagnosis, or an Oral Glucose Tolerance Test (OGTT) conducted during the study examination in persons without previous clinically diagnosed diabetes. According to World Health Organization criteria, normoglycaemia was defined as fasting blood glucose concentration below 110 mg/dL and 2-h glucose below 140 mg/dL. Impaired fasting glucose (fasting glucose concentration between 110 and 125 mg/dL) and impaired glucose tolerance (2-h glucose between 140 mg/dL and 200 mg/dL) were subsumed as prediabetes. Diabetes was newly diagnosed when fasting glucose concentrations exceeded 125 mg/dL and/or 2-h glucose concentrations exceeded 200 mg/dL. HbA1c was measured by a turbidimetric inhibition immunoassay at Exam 1 and by a cation-exchange high-performance liquid chromatographic assay at Exam 2. HOMA-IR was calculated as (fasting insulin (mU/L) × fasting glucose (mmol/L))/22.5. Glucose-lowering medication comprised ATC codes A10.

Availability of measurements varied between exams and individuals (Figure 1). Since OGTT was only performed in individuals without prior known diabetes, 2-h glucose and insulin measurements were not available for these participants. Moreover, 2-h insulin was only measured in Exam 2. HOMA-IR was only calculated for individuals who did not use glucose-lowering medication.

2.4 | Risk factors assessment

Body height and weight were measured by Seca's measuring system (Seca GmbH&Co, KG) with accuracy of up to 0.1 cm and 0.1 kg, respectively. Body-Mass-Index (BMI) was calculated as weight divided by squared height (kg/m^2). Waist circumference was measured at the level midway between the lower ribs margin and the iliac crest.

Total cholesterol was measured by enzymatic colorimetric assay.[21]

Blood pressure was measured with an OMRON type HEM-705CP oscillometric device three times (3 min intervals) after participants had rested in a seated position for at least five minutes. The mean of the 2nd and 3rd measurements was used as the final value. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or intake of antihypertensive medication under the awareness of having hypertension.

Medication intake, alcohol consumption and menopausal status were self-reported in the medical interview. Women were categorized into pre- and post-menopausal, as described in Maier et al.[21]

Genotypes for selected SNPs previously reported to be associated with either hepatic fat content or iron markers, including variants in *HFE* and *PNPLA3*, were obtained with Affymetrix Axiom Chip and subsequently imputed with HRC panel 1.1.[21]

2.5 | Statistical analysis

All analyses were stratified by sex. Continuous variables were described as arithmetic mean and standard deviation for each exam. Categorical variables were described as counts and percentages. Changes between exams were quantified by paired *t*-test and Cochran's Q test.

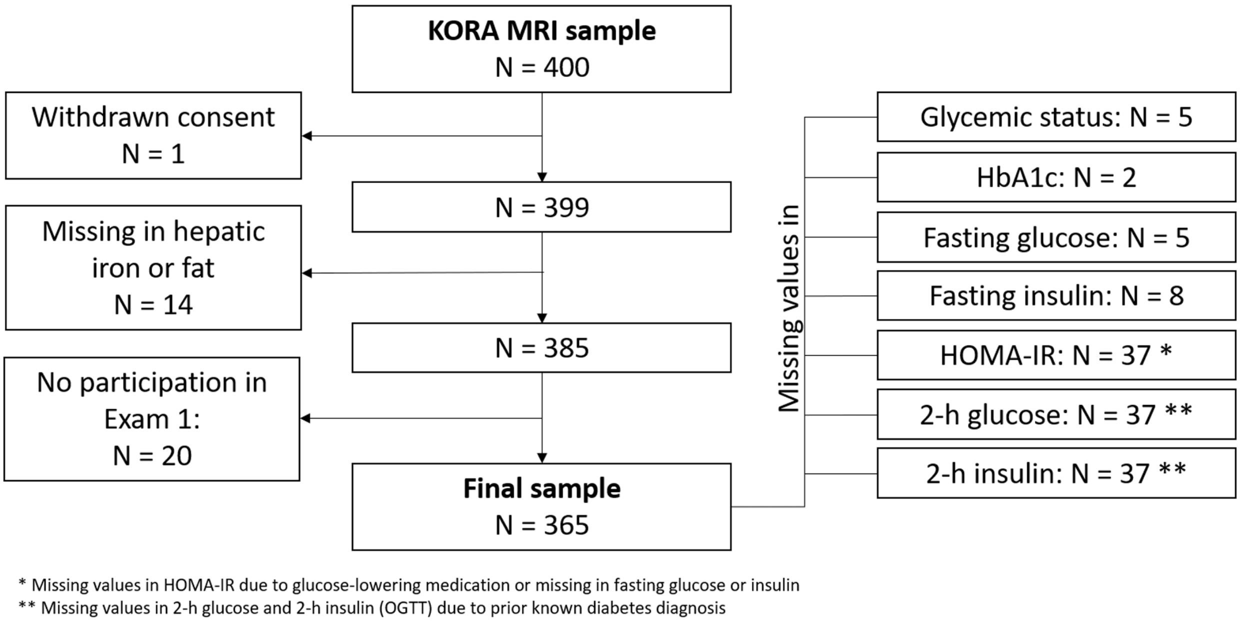


FIGURE 1 Flowchart of the KORA MRI study sample.

Trajectories of markers of glucose metabolism across exams were visualized by line plots. Correlations between markers of glucose metabolism and hepatic iron or fat content were visualized by scatter plots and quantified by Spearman's Rho correlation coefficient and corresponding *p*-value. Distribution of hepatic iron and fat content according to change in diabetes status between both exams were visualized by boxplots and quantified by *t*-test. Variation of hepatic iron and fat content according to genotypes at selected SNPs were visualized by boxplots for the whole sample.

To assess the association of changes in glycaemia between exams with outcomes hepatic iron and fat content, we used a linear regression model adjusted for (1) age at Exam 1, (2) age, BMI and alcohol consumption at Exam 1. Individuals with sustained normoglycaemia served as the reference group. As sensitivity analyses, models were adjusted for WC instead of BMI and for women, models were additionally adjusted for menopausal status. To assess the association of trajectories of glucose metabolism markers between exams with the outcomes, we used a two-step multilevel model.[22] In step one, individual trajectories of every marker were calculated by a linear mixed model with random slope, representing estimated individual variations from the population rate of change for each marker. In this model, also changes in use of glucose-lowering medication were included, where applicable. In step two, the recorded trajectories from step one were standardized and entered into a linear model, with the adjustments outlined above plus the standardized value of the respective marker at Exam 1. For the marker 2-h insulin that was only available at Exam 2, a linear regression model with the adjustments outlined above was used.

For all regression models, the outcome hepatic fat content was log-transformed due to skewness. Results were reported as beta coefficients with corresponding 95% confidence intervals (CI) and *p*-value. *p*-values less than .05 were considered to denote statistical significance.

Statistical analyses were performed using R version 3.6.1.

3 | RESULTS

3.1 | Study sample

Of the original 400 participants of the KORA-MRI study, one individual was excluded because they retroactively withdrew the consent for data usage. Further 14 individuals were excluded because of missing MRI data due to imaging artefacts or insufficient image quality. Further 20 individuals were excluded because they did not participate in Exam 1 (Figure 1). Thus, the final sample consisted of $N=365$ individuals, thereof 215 (58.9%) men and 150 (41.1%) women.

Mean age at Exam 2 was 56.3 years (standard deviation (SD) 9.4 years) for men and 56.6 years (9.1 years) for women (Table 1). Among cardiometabolic risk factors, waist circumference increased significantly between the exams in both sexes, whereas BMI, blood pressure and cholesterol levels did not increase significantly. In men, mean hepatic iron content was 41.8 s^{-1} (4.9 s^{-1}) and mean hepatic fat content 10.7% (8.9%) at Exam 2, while n = 83 (38.6%) had both hepatic iron overload and steatosis. In women, mean iron content was 39.1 s^{-1} (4.0 s^{-1}) and mean fat content was 6.5% (6.3%), while $n=22$ (14.7%) had both iron overload and steatosis, respectively. Hepatic iron and fat content varied according to genotype at selected SNPs (Figures S1 and S2).

TABLE 1 Characteristics of the participants at both exams.

	Men			Women		
	Exam 1	Exam 2	*p*-value	Exam 1	Exam 2	*p*-value
n	215	215		150	150	
Risk factors						
Age [years]	49.3 (9.4)	56.3 (9.4)		49.6 (9.1)	56.6 (9.1)	
BMI [kg/m^2]	27.7 (4.0)	28.4 (4.5)	.086	27.0 (5.0)	27.7 (5.5)	.255
Waist circumference [cm]	98.9 (11.0)	103.4 (12.6)	<.001	87.1 (13.0)	92.0 (14.1)	.002
Total cholesterol [mg/dL]	213.6 (36.3)	217.6 (37.8)	.264	217.2 (38.7)	218.9 (34.4)	.687
HDL cholesterol [mg/dL]	48.7 (11.3)	56.0 (15.1)	<.001	61.2 (13.9)	70.9 (17.5)	<.001
LDL cholesterol [mg/dL]	139.2 (31.6)	142.2 (33.6)	.342	135.5 (36.3)	135.9 (32.0)	.919
Triglycerides [mg/dL]	147.5 (101.2)	152.5 (101.5)	.608	96.9 (55.7)	102.3 (46.7)	.365
Systolic blood pressure [mmHg]	125.6 (15.2)	125.9 (16.2)	.868	114.7 (15.6)	113.6 (14.6)	.539
Diastolic blood pressure [mmHg]	78.4 (9.3)	77.7 (10.5)	.464	73.9 (9.0)	72.3 (8.5)	.11
Hypertension	61 (28.4%)	82 (38.1%)	.041	34 (22.7%)	44 (29.3%)	.236
Alcohol consumption [g/day]	25.4 (27.4)	25.9 (26.9)	.835	8.2 (13.0)	8.5 (14.3)	.839
Postmenopausal				54 (36.0%)	88 (58.7%)	<.001
Medication						
Antihypertensive	29 (13.5%)	51 (23.7%)	.009	26 (17.3%)	42 (28.0%)	.039
Lipid-lowering	19 (8.8%)	21 (9.8%)	.868	7 (4.7%)	17 (11.3%)	.055
Glucose-lowering	7 (3.3%)	18 (8.4%)	.039	4 (2.7%)	12 (8.0%)	.072
Markers of glucose metabolism						
Diabetes			<.001			.246
Normoglycaemia	157 (74.1%)	119 (55.3%)		116 (78.4%)	105 (70.0%)	
Prediabetes	39 (18.4%)	59 (27.4%)		23 (15.5%)	31 (20.7%)	
Diabetes	16 (7.5%)	37 (17.2%)		9 (6.1%)	14 (9.3%)	
HbA1c [%]	5.5 (0.6)	5.6 (0.8)	.209	5.5 (0.5)	5.6 (0.6)	.043
Fasting glucose [mg/dL]	101.1 (19.3)	107.9 (25.4)	.002	93.4 (14.8)	99.7 (18.7)	.002
Fasting insulin [µU/mL]	11.2 (7.1)	12.3 (8.6)	.143	10.0 (6.5)	9.9 (5.8)	.889
HOMA-IR[a]	2.8 (2.0)	3.2 (2.5)	.093	2.4 (1.9)	2.4 (1.6)	.88
2-h glucose [mg/dL][a]	110.3 (33.9)	118.4 (45.5)	.047	106.9 (37.1)	106.5 (35.3)	.916
2-h insulin [µU/mL][a]		72.9 (79.4)			58.1 (48.1)	
MRI derived liver values						
Hepatic iron content [s^{-1}]		41.8 (4.9)			39.1 (4.0)	
Hepatic fat content [%]		10.7 (8.9)			6.5 (6.3)	
No iron overload + no steatosis		52 (24.2%)			85 (56.7%)	
Iron overload (no steatosis)		40 (18.6%)			19 (12.7%)	
Steatosis (no iron overload)		40 (18.6%)			24 (16.0%)	
Iron overload + steatosis		83 (38.6%)			22 (14.7%)	

Note: Continuous variables are described as arithmetic mean and standard deviation. Categorical variables are described as counts and percentages. Changes between exams were quantified by paired *t*-test and Cochran's Q test, respectively.

[a]Only available in participants without established diabetes, for sample sizes see Figure 1.

3.2 | Trajectories of glycaemia and of markers of glucose metabolism

Between exams, 67.4% of men and 78.3% of women maintained their glycaemia state (Table S1). Prevalence of diabetes at Exam 2 was 17.2% in men and 9.3% in women. The majority of men (51.9%) remained normoglycaemic, whereas 19.8% had incident prediabetes and 7.1% progressed from prediabetes to diabetes between exams. In women, the majority remained normoglycaemic (65.5%), whereas 12.8% had incident prediabetes and 4.1% progressed to diabetes (Table S1).

Mean fasting glucose, fasting insulin, HOMA-IR and 2-h glucose increased in men (e.g. fasting glucose: 101.1 mg/dL (19.3 mg/dL) in Exam 1 to 107.9 mg/dL (25.4 mg/dL) in Exam 2), whereas mean trajectories of fasting insulin, HOMA-IR and 2-h glucose remained stable in women (e.g. fasting insulin 10.0 μU/ml (6.5 μU/ml) in Exam 1 to 9.9 μU/ml (5.8 μU/ml) in Exam 2). There were however substantial differences in trajectories according to glycaemia at Exam 2 (Figure 2). In particular, HOMAR-IR and fasting insulin

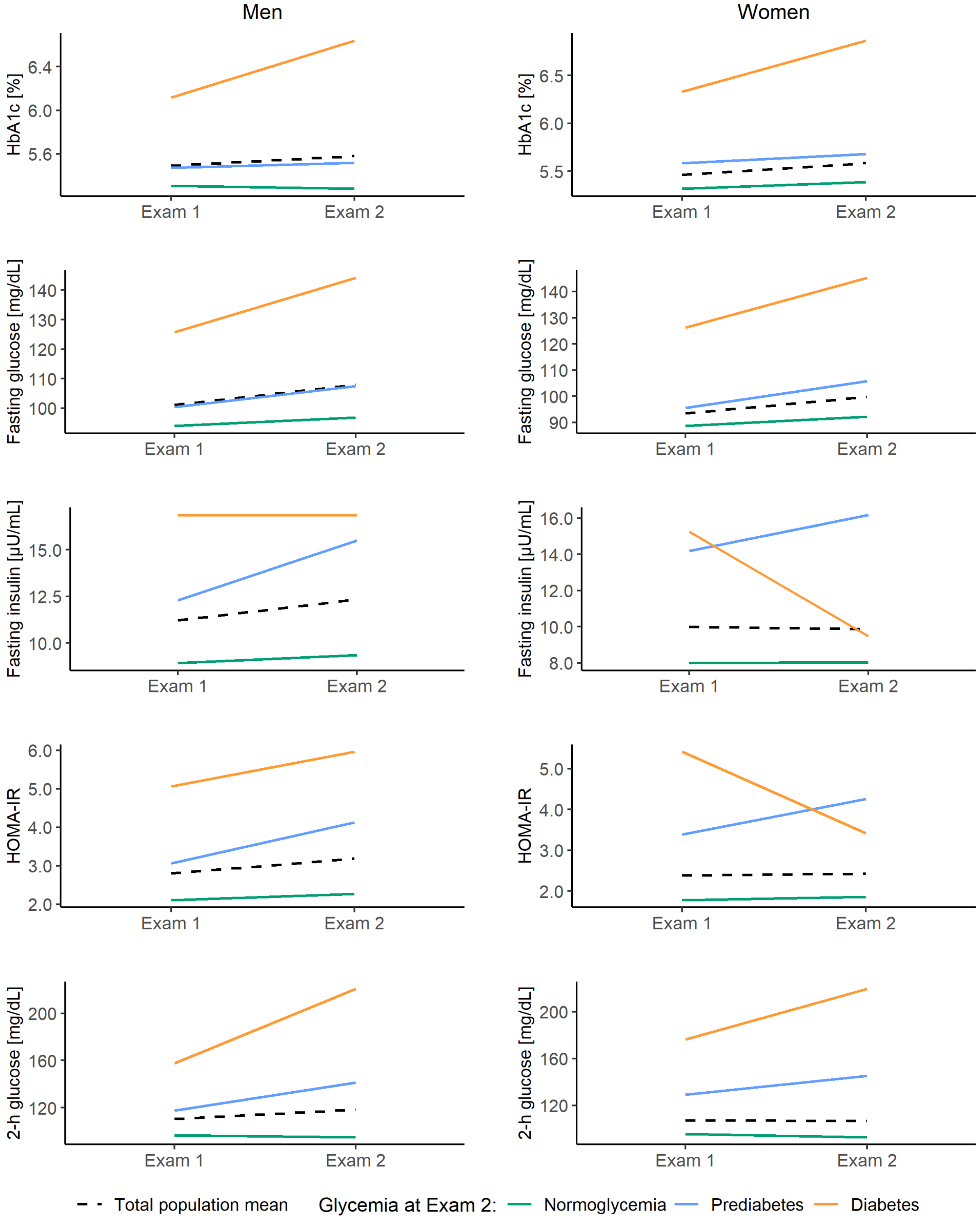


FIGURE 2 Change in mean levels of markers of glucose metabolism from Exam 1 to Exam 2 in the total population and stratified by glycaemia at Exam 2. 2-h insulin was only measured in Exam 2 and is thus not shown.

decreased in women with diabetes, which we did not observe in men.

3.3 | Correlation of glucose metabolism with hepatic iron and fat content

Markers of glucose metabolism were correlated with hepatic iron and fat content to varying degrees (Figures 3 and 4, Table S2). Generally, correlations with hepatic fat content were stronger than correlations with hepatic iron content, and correlations were stronger for glycaemic traits measured at Exam 2 (concurrent to the assessment of iron and fat content) compared to Exam 1. For both iron and fat, correlations were generally stronger in women than in men.

In men, HbA1c values at both exams were negatively correlated with hepatic iron content (R Exam 1 = −0.14, p = .037). Fasting glucose was not significantly correlated with iron, in contrast to 2-h glucose (R Exam 1 = 0.17, p = .016). Fasting and 2-h insulin and HOMA-IR were significantly correlated with hepatic iron content only for the values measured at Exam 2. All markers at both exams were significantly positively correlated with hepatic fat content, with the strongest correlation for HOMA-IR measured at Exam 2 (R Exam 2 = 0.65, p < .001) (Figure 3, Table S2).

In women, HbA1c values at both exams were positively correlated with hepatic iron content (R Exam 1 = 0.20, p = .012). Similarly, fasting glucose, fasting insulin and HOMA-IR, as well as 2-h glucose and 2-h insulin measured at Exam 2, were positively correlated with hepatic iron content. All markers at both exams were significantly positively correlated with hepatic fat content with the strongest correlation for HOMA-IR measured at Exam 2 (R Exam 2 = 0.70, p < .001) (Figure 4, Table S2).

3.4 | Association of changes in glycaemia with hepatic iron and fat content

At Exam 2, hepatic iron content was highest in men with prediabetes: 43.2 s^{-1} (4.4 s^{-1}), compared to men with normoglycaemia (41.2 s^{-1} (4.6 s^{-1})) and diabetes (41.6 s^{-1} (5.8 s^{-1})). Men with incident prediabetes and men with sustained prediabetes had comparable values of hepatic iron content. In contrast, men who progressed from prediabetes to diabetes had higher values compared to men with sustained diabetes (43.0 s^{-1} (7.5 s^{-1}) vs. 40.6 s^{-1} (4.3 s^{-1}), Figure 5). Compared to men with stable normoglycaemia, incident prediabetes was associated with an increase of 2.21 s^{-1} (CI [0.47, 3.95]) in hepatic iron content after adjustment for age, BMI and alcohol consumption (Table 2).

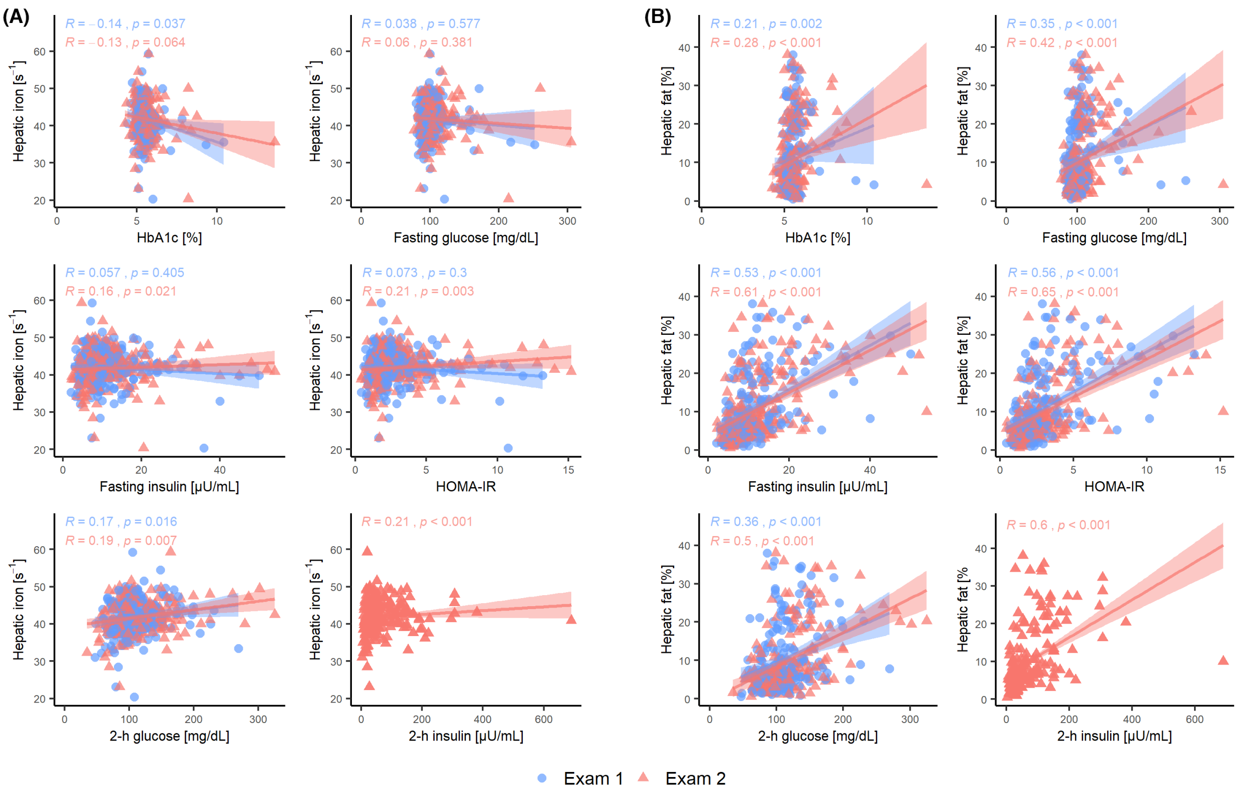


FIGURE 3 Correlation of markers of glucose metabolism with hepatic iron (A) and fat content (B) at Exam 1 and Exam 2 in men. R denotes Spearman's Rho.

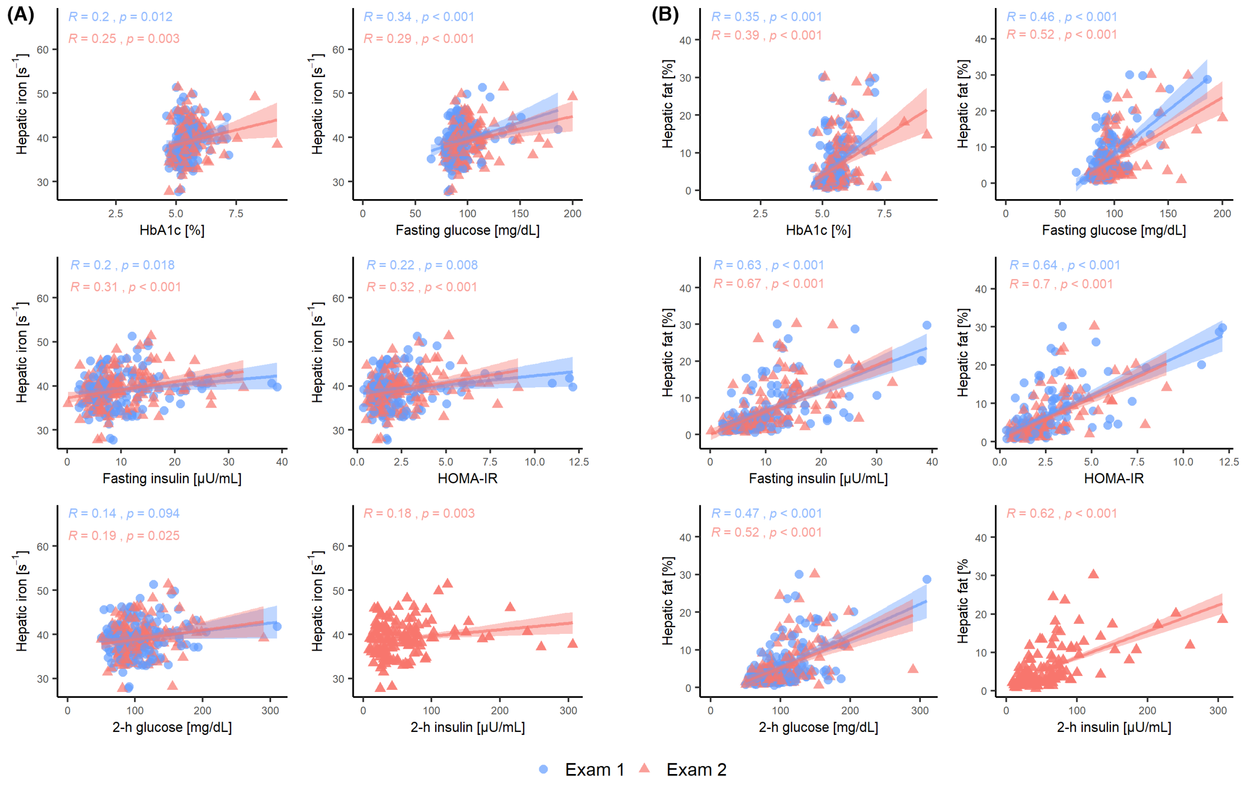


FIGURE 4 Correlation of markers of glucose metabolism with hepatic iron (A) and fat content (B) at Exam 1 and Exam 2 in women. R denotes Spearman's Rho.

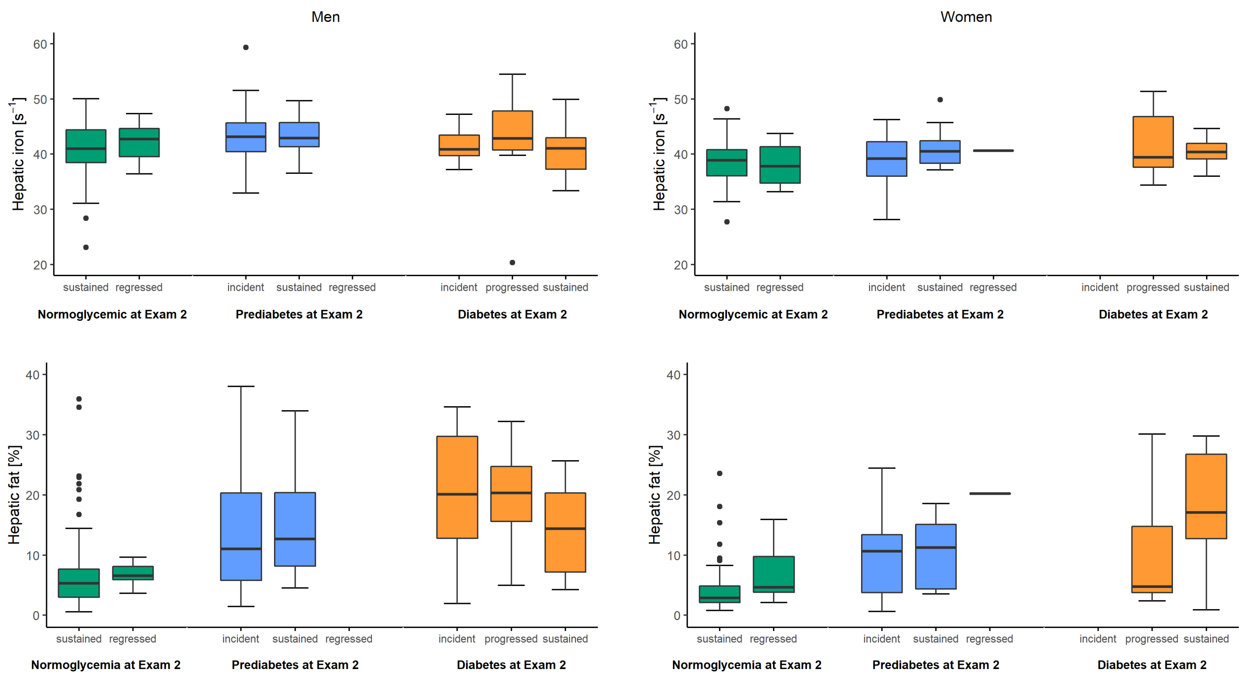


FIGURE 5 Distribution of hepatic iron and fat content according to change in glycaemia between both exams in men and women. 'Sustained': remained glycaemic in Exam 1 and Exam 2, 'Regressed': Regression from prediabetes in Exam 1 to normoglycaemia in Exam 2, or from diabetes in Exam 1 to prediabetes or normoglycaemia in Exam 2, 'Incident': normoglycaemia in Exam 1 and incident prediabetes or diabetes in Exam 2, 'progressed': prediabetes in Exam 1 and diabetes in Exam 2. Sample sizes for the respective groups are given in Table S1.

TABLE 2 Associations of changes of glycaemia with outcomes hepatic iron and fat content.

Glycaemic status (Exam 1 – Exam 2)	Adjustment	Men: Hepatic iron content β (95% CI)	Men: Hepatic iron content p-value	Men: Hepatic fat content β (95% CI)	Men: Hepatic fat content p-value	Women: Hepatic iron content β (95% CI)	Women: Hepatic iron content p-value	Women: Hepatic fat content β (95% CI)	Women: Hepatic fat content p-value
Sustained Normoglycaemia	Age	Reference		Reference		Reference		Reference	
	Age, BMI, alcohol	Reference		Reference		Reference		Reference	
Prediabetes – Normoglycaemia	Age	0.83 (−2.88, 4.54)	.659	0.28 (−0.31, 0.87)	.351	−2.33 (−5.29, 0.64)	.123	0.34 (−0.26, 0.94)	.262
	Age, BMI, alcohol	0.32 (−3.36, 4.01)	.863	0 (−0.54, 0.55)	.996	−1.96 (−4.82, 0.91)	.179	0.38 (−0.17, 0.93)	.17
Diabetes – Normoglycaemia[a]	–	–	–	–	–	–	–	–	–
Normoglycaemia – Prediabetes	Age	**2.07 (0.34, 3.80)**	**.020**	**0.74 (0.46, 1.01)**	**<.001**	−0.14 (−1.88, 1.60)	.873	**0.78 (0.43, 1.13)**	**<.001**
	Age, BMI, alcohol	**2.21 (0.47, 3.95)**	**.013**	**0.59 (0.33, 0.85)**	**<.001**	−1.21 (−3.06, 0.64)	.198	**0.37 (0.01, 0.73)**	**.041**
Sustained Prediabetes	Age	1.74 (−0.80, 4.28)	.178	**0.95 (0.55, 1.36)**	**<.001**	0.49 (−1.80, 2.78)	.672	**0.78 (0.32, 1.25)**	**.001**
	Age, BMI, alcohol	1.66 (−0.88, 4.21)	.199	**0.71 (0.34, 1.09)**	**<.001**	−0.21 (−2.51, 2.09)	.855	**0.45 (0.01, 0.89)**	**.046**
Diabetes – Prediabetes[a]	–	–	–	–	–	–	–	–	–
Normoglycaemia – Diabetes	Age	0.38 (−3.96, 4.73)	.862	**1.03 (0.34, 1.72)**	**.004**	–	–	–	–
	Age, BMI, alcohol	0.73 (−3.63, 5.09)	.742	**0.66 (0.02, 1.31)**	**.044**	–	–	–	–
Prediabetes – Diabetes	Age	1.57 (−1.11, 4.25)	.250	**1.27 (0.84, 1.70)**	**<.001**	1.65 (−1.30, 4.59)	.272	0.58 (−0.02, 1.18)	.056
	Age, BMI, alcohol	2.08 (−0.64, 4.80)	.133	**1.03 (0.63, 1.43)**	**<.001**	0.81 (−2.08, 3.69)	.58	0.47 (−0.08, 1.03)	.094
Sustained Diabetes	Age	−1.03 (−3.73, 1.66)	.450	**0.87 (0.44, 1.30)**	**<.001**	0.43 (−2.15, 3.01)	.742	**1.25 (0.73, 1.77)**	**<.001**
	Age, BMI, alcohol	−0.68 (−3.37, 2.00)	.617	**0.72 (0.32, 1.12)**	**<.001**	−0.2 (−2.80, 2.39)	.876	**0.88 (0.38, 1.38)**	**.001**

Note: Results from a linear regression model with changes in glycaemia as a categorical exposure and hepatic iron and fat content as continuous outcome. Hepatic fat content was log-transformed before analysis.

[a]No calculation possible due to too small sample.

Hepatic fat content was highest in men with diabetes: 17.4% (9.0%) as compared to men with normoglycaemia (7.0% (6.4%)) and prediabetes (14.2% (9.3%)). Men who had incident diabetes, or progressed from prediabetes to diabetes, had higher values compared to men with sustained diabetes (19.8% (8.4%) vs. 13.8% (7.3%), Figure 5). After adjustment, effect estimates were largest for progression from prediabetes to diabetes (1.03 log(%), CI (0.63, 1.43)), compared to those with sustained normoglycaemia (Table 2).

In women, hepatic iron content was highest for those with diabetes: 41.0 s^{-1} (4.7 s^{-1}) compared to women with normoglycaemia (38.7 s^{-1} (3.8 s^{-1})) and prediabetes (39.8 s^{-1} (4.3 s^{-1})). Women who progressed from prediabetes to diabetes had higher hepatic iron content values than those with sustained diabetes (41.8 s^{-1} (6.8 s^{-1}) vs. 40.4 s^{-1} (2.6 s^{-1}), Figure 5). However, after adjustment for age, BMI and alcohol, there were no significant associations of change in glycaemia with hepatic iron content (Table 2).

Hepatic fat content was also highest in women with diabetes: 14.8% (10.8%), compared to women with normoglycaemia 4.2% (3.7%) and prediabetes (10.3% (6.1%)). Women with sustained diabetes had higher values of hepatic fat than those who progressed from prediabetes to diabetes (10.6% (11.2%) vs. 17.9% (10.0%), Figure 5). Sustained diabetes had the largest effect estimate for increased hepatic fat (0.88 log(%), CI [0.38, 1.38], Table 2). Additional adjustment for menopausal status did not substantially affect the results (Table S3).

In sensitivity analyses, adjustment for WC instead of BMI did not alter the associations in men and women (Table S5).

3.5 | Association of trajectories of glucose metabolism with hepatic iron and fat content

For men, trajectories of fasting insulin were tentatively associated with hepatic iron content (beta = 1.48, CI: [−0.02, 2.98]), while trajectories of 2-h glucose were significantly associated with hepatic iron content (beta = 1.27, CI: [0.12, 2.42], Table 3). Trajectories of fasting glucose, fasting insulin, HOMA-IR and 2-h glucose were significantly associated with hepatic fat content (Table 3), with similar effect sizes for fasting insulin, HOMA-IR and 2-h glucose (0.51, 0.51, 0.52 log(%), respectively). Cross-sectional 2-h insulin showed a significant association with hepatic fat content (0.31 log(%), CI: [0.20, 0.42]).

For women, trajectories of fasting glucose were associated with hepatic iron content when adjusted for age only, however, the association attenuated after further adjustment (Table 3). No further marker trajectories were associated with hepatic iron content. Trajectories of fasting glucose, fasting insulin and HOMA-IR were significantly associated with hepatic fat content (Table 3), with the strongest effect sizes for fasting insulin (0.63 log(%), CI: [0.36, 0.90]). Trajectories of 2-h glucose were only associated with hepatic fat content when adjusted for age, but the attenuated after further adjustment (0.21 log(%), CI: [−0.02, 0.44]). Cross-sectional 2-h insulin showed a significant association with hepatic fat content (0.33 log(%), CI: [0.21, 0.46]). Additional adjustment for menopausal status did not substantially affect the results (Table S4).

Results of two-step modelling remained similar after adjusting for WC instead of BMI in men and women (Table S6 and S7).

4 | DISCUSSION

We investigated longitudinal trajectories of a large panel of markers related to glucose metabolism, insulin resistance and diabetes along with MRI-derived parameters of hepatic iron and fat content in a sample from a population-based cohort. Our findings support a sex-specific association between dynamics of glucose metabolism and accumulation of fat and iron in the liver. Our main findings are threefold. First, trajectories of glycaemia were associated with hepatic iron and fat beyond cross-sectional associations. Second, associations between trajectories of markers of glucose metabolism and hepatic outcomes were stronger for hepatic fat than for hepatic iron content. Third, associations of continuous marker trajectories with hepatic fat content were stronger in women than in men.

Our findings are partly in line with a large population-based study on incident NAFLD diagnosed by abdominal ultrasound. Wang et al. found that changes in glycaemic traits conferred a higher risk for incident NAFLD than baseline values of glycaemic measures: For example, the risk ratio for the highest quartile of baseline 2-h glucose was 1.85 (CI: 1.43–2.40), whereas the risk ratio for changes from normal to impaired 2 h-glucose was 2.05 (1.71–2.45), and even higher for changes to the diabetic range.[23] Unfortunately, Wang et al. do not report sex-stratified effect estimates. A potential pathway linking glycaemia to increased hepatic fat content is oxidative stress induced by impaired hepatic mitochondrial capacity.[24] Moreover, in the large population-based SHIP study, Naeem et al. showed associations of MRI-derived hepatic iron content with 2-h glucose levels in participants without established T2D.[25] Our current results corroborate these findings and underscore the importance of taking dynamics of glucose metabolism into account for the risk estimation of excess hepatic fat content and iron.

In our sample, women had on average lower values of hepatic fat, less steatosis and less iron overload, which is in line with current knowledge about sex disparities in NAFLD prevalence.[7] However, we found stronger correlations of glucose markers with iron and fat content for women. Although NAFLD prevalence is lower in women, women are at a higher risk of progression to more severe disease states and advanced fibrosis,[26] which might be due to the loss of oestrogen and its anti-fibrotic effect during menopause. Furthermore, oestrogen promotes a favourable body composition pattern with a mainly gluteal and femoral distribution of adipose tissue. In contrast, the loss of oestrogen induces a shift to the accumulation of visceral adipose tissue, which is the major source of free fatty acids promoting NAFLD progression. We also note that in our analysis, effect estimates attenuated more strongly for women after adjustment for BMI. We have previously shown that hepatic iron content is associated with visceral fat in women but not in men.[21]

TABLE 3 Association of trajectories of markers of glucose metabolism with hepatic iron and fat.

			Men				Women			
			Hepatic iron content		Hepatic fat content		Hepatic iron content		Hepatic fat content	
Marker	Predictor	Adjustment	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
Markers for the full sample										
HbA1c	Trajectory	Age	−0.08 (−1.10, 0.94)	.875	0.12 (−0.07, 0.31)	.202	0.52 (−0.55, 1.58)	.34	0.17 (−0.07, 0.40)	.158
	Value at Exam 1	Age	−0.88 (−1.92, 0.16)	.097	−0.03 (−0.22, 0.16)	.793	−0.51 (−1.51, 0.49)	.317	0.07 (−0.15, 0.30)	.506
HbA1c	Trajectory	Age, BMI, alcohol	0.08 (−0.93, 1.09)	.871	0.13 (−0.04, 0.29)	.131	0.49 (−0.54, 1.52)	.348	0.11 (−0.10, 0.32)	.291
	Value at Exam 1	Age, BMI, alcohol	−1.01 (−2.04, 0.02)	.054	−0.08 (−0.25, 0.09)	.357	−0.54 (−1.51, 0.42)	.269	0.04 (−0.15, 0.24)	.669
Fasting glucose	Trajectory	Age	0.48 (−0.42, 1.38)	.292	0.21 (0.05, 0.37)	.009	1.18 (0.24, 2.13)	**.014**	0.39 (0.20, 0.58)	<.001
	Value at Exam 1	Age	−0.85 (−1.77, 0.07)	.07	0.01 (−0.15, 0.17)	.894	−0.48 (−1.43, 0.46)	.317	0.02 (−0.17, 0.22)	.798
Fasting glucose	Trajectory	Age, BMI, alcohol	0.47 (−0.41, 1.36)	.291	0.17 (0.03, 0.31)	.016	0.8 (−0.17, 1.76)	.106	0.26 (0.08, 0.44)	.006
	Value at Exam 1	Age, BMI, alcohol	−0.94 (−1.85, −0.03)	.043	−0.03 (−0.17, 0.12)	.709	−0.33 (−1.26, 0.60)	.486	0.05 (−0.13, 0.22)	.6
Fasting insulin	Trajectory	Age	1.43 (−0.08, 2.94)	.063	0.54 (0.31, 0.77)	<.001	1.41 (−0.11, 2.93)	.069	0.7 (0.45, 0.96)	<.001
	Value at Exam 1	Age	−1.70 (−3.20, −0.19)	.028	−0.09 (−0.32, 0.14)	.456	−0.92 (−2.42, 0.59)	.231	−0.19 (−0.45, 0.07)	.144
Fasting insulin	Trajectory	Age, BMI, alcohol	1.48 (−0.02, 2.98)	.053	0.51 (0.29, 0.73)	<.001	0.9 (−0.66, 2.46)	.256	0.63 (0.36, 0.90)	<.001
	Value at Exam 1	Age, BMI, alcohol	−1.80 (−3.34, −0.27)	.021	−0.17 (−0.39, 0.06)	.152	−0.68 (−2.17, 0.80)	.366	−0.18 (−0.44, 0.07)	.162
Markers for the sample without previously established diabetes/without glucose-lowering medication										
HOMA-IR	Trajectory	Age	1.12 (−0.23, 2.48)	.104	0.54 (0.33, 0.75)	<.001	1.25 (−0.13, 2.63)	.076	0.69 (0.46, 0.92)	<.001
	Value at Exam 1	Age	−0.83 (−2.18, 0.52)	.226	−0.07 (−0.28, 0.14)	.507	−0.76 (−2.12, 0.61)	.275	−0.22 (−0.44, 0.01)	.058
HOMA-IR	Trajectory	Age, bmi, alcohol	1.16 (−0.19, 2.52)	.091	0.51 (0.31, 0.71)	<.001	0.7 (−0.74, 2.13)	.338	0.60 (0.36, 0.85)	<.001
	Value at Exam 1	Age, BMI, alcohol	−1.12 (−2.49, 0.25)	.11	−0.18 (−0.38, 0.03)	.096	−0.48 (−1.83, 0.87)	.485	−0.22 (−0.45, 0.01)	.06
2-h glucose	Trajectory	Age	1.14 (−0.01, 2.29)	.051	0.58 (0.38, 0.78)	<.001	0.67 (−0.58, 1.92)	.29	0.36 (0.13, 0.59)	.003
	Value at Exam 1	Age	0.04 (−1.12, 1.20)	.945	−0.21 (−0.41, −0.01)	.036	−0.59 (−1.83, 0.66)	.352	0.03 (−0.20, 0.27)	.793
2-h glucose	Trajectory	Age, bmi, alcohol	1.27 (0.12, 2.42)	.03	0.52 (0.35, 0.70)	<.001	0.37 (−0.89, 1.63)	.564	0.21 (−0.02, 0.44)	.074
	Value at Exam 1	Age, BMI, alcohol	−0.22 (−1.37, 0.93)	.708	−0.28 (−0.46, −0.10)	.002	−0.52 (−1.72, 0.67)	.391	0.05 (−0.17, 0.27)	.637
2-h insulin	Value at Exam 2	Age	0.37 (−0.30, 1.04)	.278	0.41 (0.30, 0.52)	<.001	0.15 (−0.47, 0.76)	.642	0.43 (0.32, 0.54)	<.001
2-h insulin	Value at Exam 2	Age, BMI, alcohol	0.29 (−0.41, 0.99)	.412	0.31 (0.20, 0.42)	<.001	−0.13 (−0.83, 0.57)	.713	0.33 (0.21, 0.46)	<.001

Note: Results from two-step multi-level modelling, with trajectories derived from a linear mixed-model with random slopes, adjusted for changes in glucose-lowering medication. The beta coefficient for trajectories thus denotes effects of the standardized individual deviation from population change. Hepatic fat content was log-transformed before analysis.

Data from the current analysis showed a stronger correlation of BMI with liver iron in women ($r=0.25$) than in men ($r=0$), indicating body composition pattern and hepatic iron content are more closely connected in women. Interestingly, we observed that HOMAR-IR and fasting insulin decreased in women with diabetes, which we did not observe in men. This could be explained by the increased number of postmenopausal women and the increased number of glucose-lowering medications.

We found no association of trajectories of HbA1c with hepatic iron or fat content. Hb1Ac is a glycosylated protein stemming from the interaction of glucose and haemoglobin and is a measure of average blood glucose levels in the preceding 2–3 months. Wang et al. reported changes in HbA1c levels to be associated with incident NAFLD,[23] whereas a recent study using cross-sectional NHANES data reported an association of HbA1c measurements with prevalent NALFD in individuals without diabetes only in participants with BMI $\geq 30\,kg/m^2$.[27] This again indicates a possible modulating role of body composition in the association of HbA1c and hepatic phenotypes.

In women, diabetes confers a higher risk for cardiovascular diseases (CVD) and CVD mortality compared to men.[28] This excess risk cannot be explained by underlying traditional confounders[28] and cannot be captured by HbA1c measurements alone.[29] In our analysis, we found a similar pattern in the association of diabetes-related markers and hepatic phenotypes, so one could hypothesize that hepatic steatosis and iron overload might modulate the excess CVD risk in women with diabetes. Excess hepatic lipogenesis leads to secretion of very low-density lipoproteins that induce triglyceride accumulation in other peripheral tissues. Moreover, increased hepatic triglyceride accumulation is accompanied by chronic inflammation, promoting vascular inflammation and vasoconstriction. Current evidence on the independent association of NAFLD with CVD beyond shared risk factors is inconclusive,[30] but a recent study by Pafili et al found a potential mediator role of visceral adipose tissue in the development of NAFLD.[31] In obese patients with NAFLD, mitochondrial respiration in visceral adipose tissue was downregulated compared with obese subjects without NAFLD. In addition, they observed a link of lower insulin sensitivity in adipose tissue and impaired VAT respiration.[31] Further studies are needed that analyse the potentially mediating effect of hepatic phenotypes on the association of diabetes with CVD in women.

The causal, bi-directional, association between diabetes and NAFLD has already been established.[5] Since imaging data was only available at the last examination time point in our study, we cannot derive the temporal sequence of deterioration of glycaemia and accumulation of hepatic iron and fat. We observed substantially higher values of hepatic fat in men who progressed to diabetes compared to those with sustained diabetes, indicating that the dynamics of glucose metabolism might exacerbate existing or induce new accumulation of hepatic adipose tissue. However, it would also be possible that individuals with prevalent diabetes already underwent treatment, counselling, or have implemented lifestyle changes to monitor their risk factors more closely, which would lead to decreased NAFLD risk. Moreover, for men, incident prediabetes was associated with higher hepatic iron content whereas for women, there was no clear association of deteriorating glycaemia with hepatic iron content. There was no significant association of any marker trajectory with hepatic iron content in women. This again underlines that in women factors like body composition and menopausal status might influence the association between diabetes and iron metabolism to a different extent than in men. Regarding causality, there are currently no Mendelian randomization studies on the causal relation between hepatic iron content and glycaemia.

Strengths of our study include the use of a well-characterized sample from a population-based study with a large panel of glucose metabolism markers available. Exposure and outcome data were derived by OGTT and MRI, respectively, which are considered gold standards for these measures. Within the longitudinal setup, the availability of two time points allowed us to investigate incident diabetes and prediabetes as well as marker trajectories. However, our study also has limitations. Most prominently, the MRI-derived outcomes were only available at one time point which prevented us from establishing bi-directional longitudinal associations. Moreover, sample sizes are insufficient for more complex analyses, including further stratification, e.g. according to genotype at relevant SNPs or menopausal status.

5 | CONCLUSION

In conclusion, unfavourable longitudinal trajectories of markers of glucose metabolism are associated with increased hepatic fat content. Associations with hepatic iron content are more complex and deserve further investigation regarding the role of body composition and menopause.

Monitoring trajectories of glycaemia in the sub-diabetic range, particularly in women, might enable the early detection of unfavourable liver phenotypes and vice versa.

AUTHOR CONTRIBUTIONS

Conceptualization: Susanne Rospleszcz; Methodology: Fiona Niedermayer, Susanne Rospleszcz; Formal analysis: Fiona Niedermayer, Yaqi Su, Susanne Rospleszcz; Resources: Ricarda von Krüchten, Barbara Thorand, Annette Peters, Wolfgang Rathmann, Michael Roden, Christopher L. Schlett, Fabian Bamberg, Johanna Nattenmüller; Data Curation: Fiona Niedermayer, Yaqi Su, Ricarda von Krüchten, Barbara Thorand, Annette Peters, Wolfgang Rathmann, Michael Roden, Christopher L. Schlett, Fabian Bamberg, Johanna Nattenmüller, Susanne Rospleszcz; Writing—Original Draft: Fiona Niedermayer, Yaqi Su, Susanne Rospleszcz; Writing—Review & Editing: Fiona Niedermayer, Yaqi Su, Ricarda von Krüchten, Barbara Thorand, Annette Peters, Wolfgang Rathmann, Michael Roden, Christopher L. Schlett, Fabian Bamberg, Johanna Nattenmüller, Susanne Rospleszcz; Visualization: Fiona Niedermayer; Supervision: Susanne Rospleszcz; Funding acquisition: Barbara Thorand, Annette

Peters, Wolfgang Rathmann, Michael Roden, Christopher L. Schlett, Fabian Bamberg.

ACKNOWLEDGEMENTS

We thank all participants for their long-term commitment to the KORA study, the staff for data collection and research data management and the members of the KORA Study Group (https://www.helmholtz-munich.de/en/epi/cohort/kora) who are responsible for the design and conduct of the study. Open Access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

The KORA study was initiated and financed by the Helmholtz Zentrum München–German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research (BMBF) and the state of Bavaria. Data collection in the KORA study is done in cooperation with the University Hospital of Augsburg. Furthermore, KORA research was supported within the Munich Center of Health Sciences (MC-Health), Ludwig-Maximilians-Universität, as part of LMUinnovativ. The KORA MRI sub-study received funding by the German Research Foundation (DFG, Deutsche Forschungsgemeinschaft, BA 4233/4-1), the Centre for Diabetes Research (DZD e.V., Neuherberg, Germany) and the German Centre for Cardiovascular Disease Research (Berlin, Germany, grants 81X2600209 and 81X2600214). The KORA-MRI sub-study was supported by an unrestricted research grant from Siemens Healthcare. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The informed consent given by KORA study participants does not cover data posting in public databases. However, data are available upon request by means of a project agreement. Requests should be sent to kora.passt@helmholtz-muenchen.de and are subject to approval by the KORA Board.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the ethics committee of Ludwig-Maximilians-University Munich (498–12) and the Bavarian Chamber of Physicians (FF4: EC No. 06068) and was performed according to the Declaration of Helsinki.

ORCID

Michael Roden https://orcid.org/0000-0001-8200-6382
Susanne Rospleszcz https://orcid.org/0000-0002-4788-2341

REFERENCES

1. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. *Nat Med*. 2018;24(7):908-922. doi:10.1038/s41591-018-0104-9
2. Roden M, Shulman GI. The integrative biology of type 2 diabetes. *Nature*. 2019;576(7785):51-60. doi:10.1038/s41586-019-1797-8
3. Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. *J Hepatol*. 2019;71(4):793-801. doi:10.1016/j.jhep.2019.06.021
4. Mantovani A, Petracca G, Beatrice G, Tilg H, Byrne CD, Targher G. Non-alcoholic fatty liver disease and risk of incident diabetes mellitus: an updated meta-analysis of 501 022 adult individuals. *Gut*. 2021;70(5):962-969. doi:10.1136/gutjnl-2020-322572
5. Liu Z, Zhang Y, Graham S, et al. Causal relationships between NAFLD, T2D and obesity have implications for disease subphenotyping. *J Hepatol*. 2020;73(2):263-276. doi:10.1016/j.jhep.2020.03.006
6. Alexander M, Loomis AK, van der Lei J, et al. Risks and clinical predictors of cirrhosis and hepatocellular carcinoma diagnoses in adults with diagnosed NAFLD: real-world study of 18 million patients in four European cohorts. *BMC Med*. 2019;17(1):95. doi:10.1186/s12916-019-1321-x
7. Musto J, Spengler EK, German MN. Sexual dimorphisms in non-alcoholic fatty liver disease. *Curr Hepatol Rep*. 2021;20(4):97-107. doi:10.1007/s11901-021-00568-8
8. Imajo K, Kessoku T, Honda Y, et al. MRI-based quantitative R2(*) mapping at 3 tesla reflects hepatic iron overload and pathogenesis in nonalcoholic fatty liver disease patients. *J Magn Reson Imaging*. 2022;55(1):111-125. doi:10.1002/jmri.27810
9. Tsurusaki S, Tsuchiya Y, Koumura T, et al. Hepatic ferroptosis plays an important role as the trigger for initiating inflammation in nonalcoholic steatohepatitis. *Cell Death Dis*. 2019;10(6):449. doi:10.1038/s41419-019-1678-y
10. Czaja AJ. Review article: iron disturbances in chronic liver diseases other than haemochromatosis—pathogenic, prognostic, and therapeutic implications. *Aliment Pharmacol Ther*. 2019;49(6):681-701. doi:10.1111/apt.15173
11. He H, Liao S, Zeng Y, Liang L, Chen J, Tao C. Causal relationships between metabolic-associated fatty liver disease and iron status: two-sample Mendelian randomization. *Liver Int*. 2022;42:2759-2768. doi:10.1111/liv.15455
12. Orban E, Schwab S, Thorand B, Huth C. Association of iron indices and type 2 diabetes: a meta-analysis of observational studies. *Diabetes Metab Res Rev*. 2014;30(5):372-394. doi:10.1002/dmrr.2506
13. Jiang L, Wang K, Lo K, et al. Sex-specific association of circulating ferritin level and risk of type 2 diabetes: a dose-response meta-analysis of prospective studies. *J Clin Endocrinol Metab*. 2019;104(10):4539-4551. doi:10.1210/jc.2019-00495
14. Pitchika A, Kühn JP, Schipf S, et al. Hepatic steatosis and hepatic iron overload modify the association of iron markers with glucose metabolism disorders and metabolic syndrome. *Liver Int*. 2021;41(8):1841-1852. doi:10.1111/liv.14868
15. Kühn JP, Meffert P, Heske C, et al. Prevalence of fatty liver disease and hepatic iron overload in a northeastern German population by using quantitative MR imaging. *Radiology*. 2017;284(3):706-716. doi:10.1148/radiol.2017161228
16. Holle R, Happich M, Lowel H, Wichmann HE, Group MKS. KORA—a research platform for population based health research. *Gesundheitswesen*. 2005;67(Suppl 1):S19-S25. doi:10.1055/s-2005-858235
17. Bamberg F, Hetterich H, Rospleszcz S, et al. Subclinical disease burden as assessed by whole-body MRI in subjects with prediabetes, subjects with diabetes, and normal control subjects from the general population: the KORA-MRI study. *Diabetes*. 2017;66(1):158-169. doi:10.2337/db16-0630
18. Hetterich H, Bayerl C, Peters A, et al. Feasibility of a three-step magnetic resonance imaging approach for the assessment of

hepatic steatosis in an asymptomatic study population. *Eur Radiol*. 2016;26(6):1895-1904. doi:10.1007/s00330-015-3966-y
19. Filler J, von Krüchten R, Wawro N, et al. Association of habitual dietary intake with liver iron-a population-based imaging study. *Nutrients*. 2021;14(1):132. doi:10.3390/nu14010132
20. Tang A, Desai A, Hamilton G, et al. Accuracy of MR imaging-estimated proton density fat fraction for classification of dichotomized histologic steatosis grades in nonalcoholic fatty liver disease. *Radiology*. 2015;274(2):416-425. doi:10.1148/radiol.14140754
21. Maier L, von Krüchten R, Lorbeer R, et al. Distribution and associated factors of hepatic iron—a population-based imaging study. *Metabolites*. 2021;11(12):871. doi:10.3390/metabo11120871
22. Gadd SC, Tennant PWG, Heppenstall AJ, Boehnke JR, Gilthorpe MS. Analysing trajectories of a longitudinal exposure: a causal perspective on common methods in lifecourse research. *PLoS One*. 2019;14(12):e0225217. doi:10.1371/journal.pone.0225217
23. Wang B, Li M, Zhao Z, et al. Glycemic measures and development and resolution of nonalcoholic fatty liver disease in nondiabetic individuals. *J Clin Endocrinol Metab*. 2020;105(5):1416-1426. doi:10.1210/clinem/dgaa112
24. Gancheva S, Kahl S, Pesta D, et al. Impaired hepatic mitochondrial capacity in nonalcoholic steatohepatitis associated with type 2 diabetes. *Diabetes Care*. 2022;45(4):928-937. doi:10.2337/dc21-1758
25. Naeem M, Schipf S, Bulow R, et al. Association between hepatic iron overload assessed by magnetic resonance imaging and glucose intolerance states in the general population. *Nutr Metab Cardiovasc Dis*. 2022;32(6):1470-1476. doi:10.1016/j.numecd.2022.02.013
26. Balakrishnan M, Patel P, Dunn-Valadez S, et al. Women have a lower risk of nonalcoholic fatty liver disease but a higher risk of progression vs men: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2021;19(1):61-71 e15. doi:10.1016/j.cgh.2020.04.067
27. Xie Y, Kong W, Wang X, Wu Z. Association of glycated hemoglobin with non-alcoholic fatty liver disease patients and the severity of liver steatosis and fibrosis measured by transient elastography in adults without diabetes. *BMC Endocr Disord*. 2022;22(1):220. doi:10.1186/s12902-022-01134-z
28. Gnatiuc L, Herrington WG, Halsey J, et al. Sex-specific relevance of diabetes to occlusive vascular and other mortality: a collaborative meta-analysis of individual data from 980 793 adults from 68 prospective studies. *Lancet Diabetes Endocrinol*. 2018;6(7):538-546. doi:10.1016/s2213-8587(18)30079-2
29. de Jong M, Woodward M, Peters SAE. Diabetes, glycated hemoglobin, and the risk of myocardial infarction in women and men: a prospective cohort study of the UK Biobank. *Diabetes Care*. 2020;43(9):2050-2059. doi:10.2337/dc19-2363
30. Wu S, Wu F, Ding Y, Hou J, Bi J, Zhang Z. Association of non-alcoholic fatty liver disease with major adverse cardiovascular events: a systematic review and meta-analysis. *Sci Rep*. 2016;6:33386. doi:10.1038/srep33386
31. Pafili K, Kahl S, Mastrototaro L, et al. Mitochondrial respiration is decreased in visceral but not subcutaneous adipose tissue in obese individuals with fatty liver disease. *J Hepatol*. 2022;77(6):1504-1514. doi:10.1016/j.jhep.2022.08.010

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Niedermayer F, Su Y, von Krüchten R, et al. Trajectories of glycaemic traits exhibit sex-specific associations with hepatic iron and fat content: Results from the KORA-MRI study. *Liver Int*. 2023;43:2153-2166. doi:10.1111/liv.15635

Supplementary Material to

“Trajectories of glycemic traits exhibit sex-specific associations with hepatic iron and fat content: results from the KORA-MRI study”

Niedermayer et al.

Supplementary Table 1: Changes in glycemia between Exam 1 and Exam 2

Glycemia (Exam 1 - Exam 2)	Men		Women	
	N	%	N	%
Sustained Normoglycemia	110	51.9	97	65.5
Prediabetes – Normoglycemia	7	3.3	6	4.1
Diabetes – Normoglycemia	0	0.0	0	0.0
Normoglycemia – Prediabetes	42	19.8	19	12.8
Sustained Prediabetes	17	8.0	11	7.4
Diabetes – Prediabetes	0	0.0	1	0.7
Normoglycemia – Diabetes	5	2.4	0	0.0
Prediabetes – Diabetes	15	7.1	6	4.1
Sustained Diabetes	16	7.5	8	5.4

Supplementary Table 2: Correlation of markers of glucose metabolism with hepatic iron and fat content

Marker	Exam	Men					Women				
			Hepatic iron content		Hepatic fat content			Hepatic iron content		Hepatic fat content	
		n	R	p	R	p	n	R	p	R	p
HbA1c	Exam 1	215	**-0.14**	**0.037**	**0.21**	**0.002**	149	**0.20**	**0.012**	**0.35**	**<0.001**
	Exam 2	215	-0.13	0.064	**0.28**	**<0.001**	149	**0.25**	**0.003**	**0.39**	**<0.001**
Fasting glucose	Exam 1	213	0.04	0.577	**0.35**	**<0.001**	148	**0.34**	**<0.001**	**0.46**	**<0.001**
	Exam 2	215	0.06	0.381	**0.42**	**<0.001**	149	**0.29**	**<0.001**	**0.52**	**<0.001**
Fasting insulin	Exam 1	212	0.06	0.405	**0.53**	**<0.001**	145	**0.20**	**0.018**	**0.63**	**<0.001**
	Exam 2	215	**0.16**	**0.021**	**0.61**	**<0.001**	148	**0.31**	**<0.001**	**0.67**	**<0.001**
HOMA-IR	Exam 1	205	0.07	0.300	**0.56**	**<0.001**	142	**0.22**	**0.008**	**0.64**	**<0.001**
	Exam 2	197	**0.21**	**0.003**	**0.65**	**<0.001**	138	**0.32**	**<0.001**	**0.70**	**<0.001**
2-h glucose	Exam 1	201	**0.17**	**0.016**	**0.36**	**<0.001**	141	0.14	0.094	**0.47**	**<0.001**
	Exam 2	192	**0.19**	**0.007**	**0.50**	**<0.001**	138	**0.19**	**0.025**	**0.52**	**<0.001**
2-h insulin	Exam 2	191	**0.21**	**0.004**	**0.60**	**<0.001**	138	**0.18**	**0.035**	**0.62**	**<0.001**

R denotes Spearman’s Rho correlation coefficient.

Supplementary Table 3: Associations of changes of glycemia with hepatic iron and fat content in women, with adjustment for menopausal status.

Glycemic status (Exam 1 – Exam 2)	Adjustment	Hepatic iron content		Hepatic fat content	
		ß (95%-CI)	p-value	ß (95%-CI)	p-value
Sustained Normoglycemia	age, BMI, alcohol, menopause	Reference		Reference	
Prediabetes – Normoglycemia	age, BMI, alcohol, menopause	-1.91 (-4.74, 0.93)	0.185	0.39 (-0.15, 0.94)	0.156
Normoglycemia – Prediabetes	age, BMI, alcohol, menopause	-1.11 (-2.95, 0.72)	0.233	**0.39 (0.04, 0.74)**	**0.031**
Sustained Prediabetes	age, BMI, alcohol, menopause	-0.19 (-2.46, 2.09)	0.871	**0.46 (0.02, 0.89)**	**0.042**
Diabetes – Prediabetes	age, BMI, alcohol, menopause	-1.05 (-7.80, 5.70)	0.758	1.08 (-0.22, 2.38)	0.102
Prediabetes – Diabetes	age, BMI, alcohol, menopause	0.75 (-2.11, 3.60)	0.606	0.46 (-0.09, 1.01)	0.099
Sustained Diabetes	age, BMI, alcohol, menopause	0.06 (-2.52, 2.65)	0.962	**0.93 (0.43, 1.43)**	**<0.001**

Results from a linear regression model with changes in glycemia as a categorical exposure and hepatic iron and fat content as continuous outcome. Hepatic fat content was log-transformed before analysis.

Supplementary Table 4: Association of trajectories of markers of glucose metabolism with hepatic iron and fat content in women, with adjustment for menopausal status.

Biomarker	predictor	Adjustment	Hepatic iron content		Hepatic fat content	
			ß (95%-CI)	p-value	ß (95%-CI)	p-value
HbA1c	trajectory	age, BMI, alcohol, menopause	0.3 (-0.73, 1.34)	0.563	0.1 (-0.12, 0.31)	0.379
	value at Exam 1	age, BMI, alcohol, menopause	-0.4 (-1.37, 0.57)	0.42	0.06 (-0.14, 0.26)	0.582
Fasting glucose	trajectory	age, BMI, alcohol, menopause	0.64 (-0.34, 1.61)	0.2	**0.24 (0.05, 0.42)**	**0.012**
	value at Exam 1	age, BMI, alcohol, menopause	-0.18 (-1.12, 0.76)	0.703	0.07 (-0.11, 0.24)	0.457
Fasting insulin	trajectory	age, BMI, alcohol, menopause	0.67 (-0.90, 2.23)	0.4	**0.61 (0.34, 0.89)**	**<0.001**
	value at Exam 1	age, BMI, alcohol, menopause	-0.54 (-2.02, 0.94)	0.473	-0.17 (-0.43, 0.09)	0.19
HOMA-IR	trajectory	age, BMI, alcohol, menopause	0.46 (-0.98, 1.91)	0.526	**0.59 (0.34, 0.83)**	**<0.001**
	value at Exam 1	age, BMI, alcohol, menopause	-0.32 (-1.68, 1.03)	0.636	-0.21 (-0.44, 0.02)	0.076
2-h glucose	trajectory	age, BMI, alcohol, menopause	0.23 (-1.02, 1.49)	0.715	0.19 (-0.04, 0.42)	0.106
	value at Exam 1	age, BMI, alcohol, menopause	-0.41 (-1.60, 0.78)	0.501	0.07 (-0.15, 0.29)	0.532
2-h insulin	value at Exam 2	age, BMI, alcohol, menopause	-0.16 (-0.85, 0.53)	0.657	**0.33 (0.21, 0.46)**	**<0.001**

Results from two-step multi-level modelling, with trajectories derived from a linear mixed-model with random slopes, adjusted for changes in glucose-lowering medication. The beta coefficient for trajectories thus denotes effects of the standardized individual deviation from population change. Hepatic fat content was log-transformed before analysis.

Supplementary Table 5: Associations of changes of glycemia with outcomes hepatic iron and fat content, with adjustment for waist circumference (WC)

Glycemic status (Exam 1 – Exam 2)	Adjustment	Men				Women			
		Hepatic iron content		Hepatic fat content		Hepatic iron content		Hepatic fat content	
		ß (95%-CI)	p-value	ß (95%-CI)	p-value	ß (95%-CI)	p-value	ß (95%-CI)	p-value
Sustained Normoglycemia	age, WC, alcohol	Reference		Reference		Reference		Reference	
Prediabetes – Normoglycemia	age, WC, alcohol	0.35 (-3.33, 4.04)	0.851	-0.03 (-0.55, 0.49)	0.908	-1.78 (-4.62, 1.05)	0.216	0.45 (-0.08, 0.98)	0.097
Diabetes – Normoglycemia[a]	-	-	-	-	-	-	-	-	-
Normoglycemia – Prediabetes	age, WC, alcohol	**2.25 (0.50, 4.00)**	**0.012**	**0.54 (0.29, 0.79)**	**<0.001**	-1.36 (-3.18, 0.46)	0.141	**0.33 (-0.01, 0.67)**	**0.056**
Sustained Prediabetes	age, WC, alcohol	1.70 (-0.84, 4.25)	0.188	**0.67 (0.31, 1.03)**	**<0.001**	-0.33 (-2.60, 1.93)	0.773	**0.42 (0.00, 0.85)**	**0.052**
Diabetes – Prediabetes[a]	-	-	-	-	-	-	-	-	-
Normoglycemia – Diabetes	age, WC, alcohol	0.77 (-3.57, 5.11)	0.727	**0.63 (0.01, 1.24)**	**0.045**	-0.75 (-7.46, 5.96)	0.825	1.19 (-0.07, 2.45)	0.063
Prediabetes – Diabetes	age, WC, alcohol	2.18 (-0.57, 4.94)	0.119	**0.90 (0.51, 1.29)**	**<0.001**	0.62 (-2.24, 3.48)	0.669	0.40 (-0.13, 0.94)	0.139
Sustained Diabetes	age, WC, alcohol	-0.59 (-3.30, 2.11)	0.666	**0.61 (0.22, 0.99)**	**0.002**	-0.47 (-3.06, 2.11)	0.717	**0.79 (0.31, 1.28)**	**0.020**

Results from a linear regression model with changes in glycemia as categorical exposure and hepatic iron and fat content as continuous outcome. Hepatic fat content was log-transformed before analysis. [a]No calculation due to too small sample

Supplementary Table 6: Association of trajectories of markers of glucose metabolism with hepatic iron and fat content, with adjustment for waist circumference (WC)

			Men				Women			
Marker	predictor	Adjustment	Hepatic iron content		Hepatic fat content		Hepatic iron content		Hepatic fat content	
			ß (95%-CI)	p-value	ß (95%-CI)	p-value	ß (95%-CI)	p-value	ß (95%-CI)	p-value
Markers for the full sample										
HbA1c	trajectory	age, WC, alcohol	0.08 (-0.93, 1.09)	0.871	0.13 (-0.03, 0.28)	0.110	0.51 (-0.50, 1.52)	0.321	0.13 (-0.07, 0.33)	0.213
	value at Exam 1	age, WC, alcohol	-1.02 (-2.05, 0.01)	0.053	-0.11 (-0.26, 0.05)	0.191	-0.63 (-1.59, 0.32)	0.193	0.00 (-0.19, 0.19)	0.989
Fasting glucose	trajectory	age, WC, alcohol	0.48 (-0.41, 1.36)	0.288	**0.18 (0.05, 0.31)**	**0.008**	0.73 (-0.23, 1.69)	0.134	**0.25 (0.07, 0.43)**	**0.006**
	value at Exam 1	age, WC, alcohol	**-0.94 (-1.85, -0.03)**	**0.043**	-0.06 (-0.20, 0.07)	0.355	-0.37 (-1.29, 0.55)	0.433	0.02 (-0.15, 0.19)	0.797
Fasting insulin	trajectory	age, WC, alcohol	1.49 (-0.02, 2.99)	0.052	**0.48 (0.27, 0.70)**	**<0.001**	0.71 (-0.83, 2.26)	0.365	**0.59 (0.32, 0.85)**	**<0.001**
	value at Exam 1	age, WC, alcohol	**-1.81 (-3.35, -0.26)**	**0.022**	**-0.24 (-0.46, -0.02)**	**0.035**	-0.71 (-2.18, 0.76)	0.340	-0.19 (-0.44, 0.06)	0.141
Markers for the sample without previously established diabetes/without glucose-lowering medication										
HOMA-IR	trajectory	age, WC, alcohol	1.12 (-0.24, 2.48)	0.105	**0.46 (0.26, 0.66)**	**<0.001**	0.5 (-0.92, 1.92)	0.484	**0.57 (0.33, 0.81)**	**<0.001**
	value at Exam 1	age, WC, alcohol	-1.15 (-2.53, 0.22)	0.100	**-0.23 (-0.43, -0.03)**	**0.027**	-0.52 (-1.86, 0.82)	0.445	**-0.23 (-0.45, 0.00)**	**0.049**
2-h glucose	trajectory	age, WC, alcohol	**1.25 (0.09, 2.41)**	**0.035**	**0.47 (0.30, 0.64)**	**<0.001**	0.27 (-0.97, 1.51)	0.664	0.19 (-0.03, 0.41)	0.090
	value at Exam 1	age, WC, alcohol	-0.21 (-1.36, 0.95)	0.725	**-0.25 (-0.42, -0.08)**	**0.004**	-0.52 (-1.70, 0.67)	0.389	0.05 (-0.16, 0.26)	0.629
2-h insulin	value at Exam 2	age, WC, alcohol	0.24 (-0.47, 0.96)	0.505	**0.26 (0.16, 0.37)**	**<0.001**	-0.21 (-0.88, 0.47)	0.546	**0.30 (0.18, 0.42)**	**<0.001**

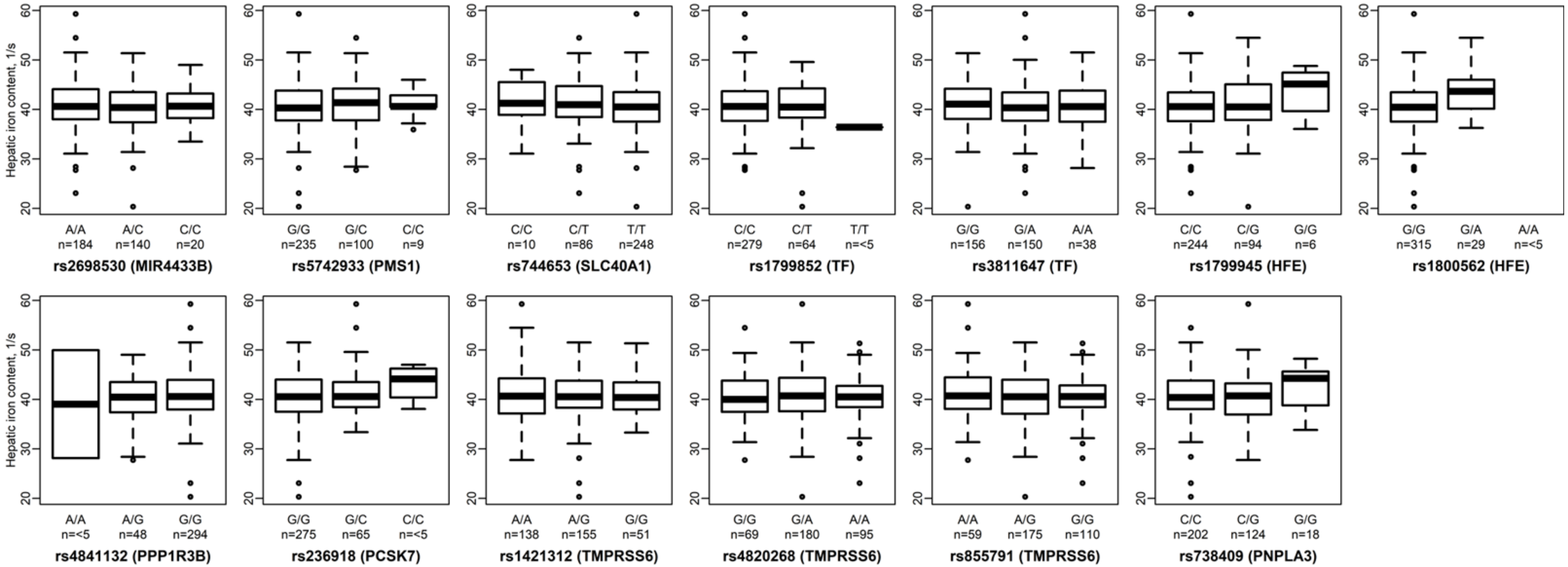
Results from two-step multi-level modelling, with trajectories derived from a linear-mixed model with random slopes, adjusted for changes in glucose-lowering medication. The beta coefficient for trajectories thus denotes effects of the standardized individual deviation from population change. Hepatic fat content was log-transformed before analysis.

Supplementary Table 7: Association of trajectories of markers of glucose metabolism with hepatic iron and fat content in women, with adjustment for menopausal status and waist circumference (WC)

Marker	predictor	Adjustment	Women			
			Hepatic iron content		Hepatic fat content	
			ß (95%-CI)	p-value	ß (95%-CI)	p-value
Markers for the full sample						
HbA1c	trajectory	age, WC, alcohol, menopause	0.30 (-0.72, 1.32)	0.560	0.1 (-0.10, 0.30)	0.332
	value at Exam 1	age, WC, alcohol, menopause	-0.48 (-1.44, 0.48)	0.325	0.02 (-0.17, 0.21)	0.830
Fasting glucose	trajectory	age, WC, alcohol, menopause	0.55 (-0.42, 1.52)	0.262	**0.22 (0.04, 0.40)**	**0.016**
	value at Exam 1	age, WC, alcohol, menopause	-0.21 (-1.14, 0.72)	0.654	0.05 (-0.12, 0.22)	0.593
Fasting insulin	trajectory	age, WC, alcohol, menopause	0.43 (-1.12, 1.98)	0.585	**0.56 (0.29, 0.83)**	**<0.001**
	value at Exam 1	age, WC, alcohol, menopause	-0.56 (-2.01, 0.90)	0.453	-0.18 (-0.43, 0.08)	0.173
HOMA-IR	trajectory	age, WC, alcohol, menopause	0.23 (-1.20, 1.66)	0.751	**0.55 (0.30, 0.79)**	**<0.001**
	value at Exam 1	age, WC, alcohol, menopause	-0.35 (-1.69, 0.98)	0.602	-0.21 (-0.44, 0.01)	0.066
2-h glucose	trajectory	age, WC, alcohol, menopause	0.12 (-1.11, 1.36)	0.844	0.17 (-0.05, 0.39)	0.136
	value at Exam 1	age, WC, alcohol, menopause	-0.39 (-1.57, 0.78)	0.507	0.07 (-0.14, 0.28)	0.508
2-h insulin	value at Exam 2	age, WC, alcohol, menopause	-0.25 (-0.92, 0.42)	0.455	**0.30 (0.18, 0.42)**	**<0.001**

Results from two-step multi-level modelling, with trajectories derived from a linear-mixed model with random slopes, adjusted for changes in glucose-lowering medication. The beta coefficient for trajectories thus denotes effects of the standardized individual deviation from population change. Hepatic fat content was log-transformed before analysis.

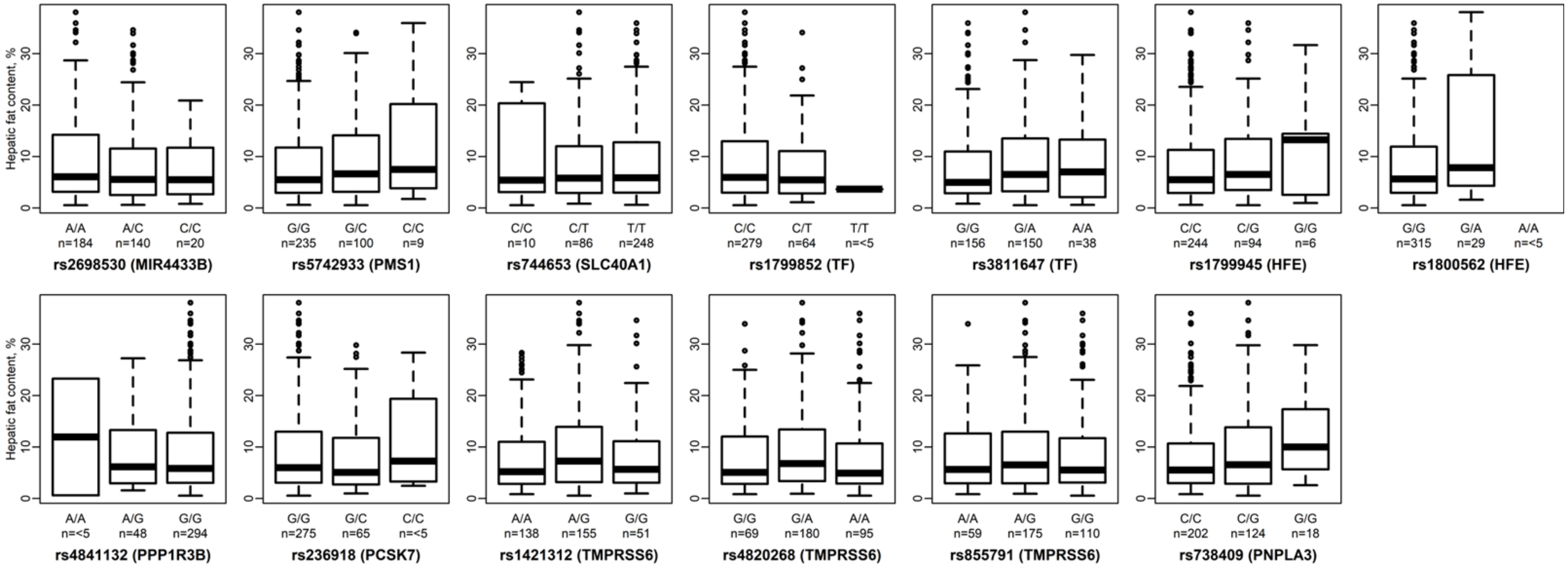
Supplementary Figure 1: Variation of hepatic iron content according to genotype at selected SNPs.



Genotypes were obtained with Affymetrix Axiom Chip and subsequently imputed based on Haplotype Reference Consortium (HRC) imputation panel r1.1. Presented data are based on estimated post-imputation allele dosages. At all SNPs, genotype distributions did not differ significantly between men and women (all p>0.1). Genetic data were available for N=344 participants.

- 7 -

Supplementary Figure 2: Variation of hepatic fat content according to genotype at selected SNPs.



Genotypes were obtained with Affymetrix Axiom Chip and subsequently imputed based on Haplotype Reference Consortium (HRC) imputation panel r1.1. Presented data are based on estimated post-imputation allele dosages. At all SNPs, genotype distributions did not differ significantly between men and women (all p>0.1). Genetic data were available for N=344 participants.

Manuscript 2

Title:	Sex-specific associations of environmental exposures with prevalent diabetes and obesity - Results from the KORA Fit study
Authors:	Niedermayer, Fiona; Wolf, Kathrin; Zhang, Siqi; Dallavalle, Marco; Nikolaou, Nikolaos; Schwettmann, Lars; Selsam, Peter; Hoffmann, Barbara; Schneider, Alexandra; Peters, Annette;
Year:	2024
Status:	Published
Journal:	Environmental research
Volume:	252
Issue:	3
Page:	118965
DOI:	https://doi.org/10.1016/j.envres.2024.118965
2023 Journal Impact Factor:	7.7 (*Journal Citation Reports* (Clarivate, 2023))
Rank by 2023 Journal Impact Factor:	36/358 in the category “Environmental Sciences“ (*Journal Citation Reports* (Clarivate, 2023))
	16/408 in the category “Public, Environmental & Occupational Health” (*Journal Citation Reports* (Clarivate, 2023))

Environmental Research 252 (2024) 118965

Contents lists available at ScienceDirect

Environmental Research

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

Sex-specific associations of environmental exposures with prevalent diabetes and obesity – Results from the KORA Fit study

Fiona Niedermayer [a,b,*], Kathrin Wolf [b], Siqi Zhang [b,h], Marco Dallavalle [a,b], Nikolaos Nikolaou [b], Lars Schwettmann [c,d], Peter Selsam [e], Barbara Hoffmann [f], Alexandra Schneider [b], Annette Peters [a,b,g]

[a] Chair of Epidemiology, IBE, Faculty of Medicine, LMU Munich, Munich, Germany
[b] Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany
[c] Institute of Health Economics and Health Care Management, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany
[d] Department of Health Services Research, School of Medicine and Health Sciences, Carl von Ossietzky Universität Oldenburg, Oldenburg, Germany
[e] Department Monitoring and Exploration Technologies, Helmholtz Centre for Environmental Research GmbH—UFZ, Leipzig, Germany
[f] Institute of Occupational, Social and Environmental Medicine, Centre for Health and Society, Medical Faculty, Heinrich-Heine University Düsseldorf, Düsseldorf, Germany
[g] German Center for Diabetes Research (DZD), München-Neuherberg, Neuherberg, Germany
[h] Department of Environmental Health Sciences, Yale School of Public Health, New Haven, United States

A R T I C L E I N F O

Keywords:
Metabolic diseases
Diabetes
Obesity
Air pollution
Greenness
Urbanization

A B S T R A C T

Promising evidence suggests a link between environmental factors, particularly air pollution, and diabetes and obesity. However, it is still unclear whether men and women are equally susceptible to environmental exposures. Therefore, we aimed to assess sex-specific long-term effects of environmental exposures on metabolic diseases.

We analyzed cross-sectional data from 3,034 participants (53.7% female, aged 53-74 years) from the KORA Fit study (2018/19), a German population-based cohort. Environmental exposures, including annual averages of air pollutants [nitrogen oxides (NO_2, NO_x), ozone, particulate matter of different diameters (PM_{10}, PM_{coarse}, $PM_{2.5}$), $PM_{2.5}$abs, particle number concentration], air temperature and surrounding greenness, were assessed at participants' residences. We evaluated sex-specific associations of environmental exposures with prevalent diabetes, obesity, body-mass-index (BMI) and waist circumference using logistic or linear regression models with an interaction term for sex, adjusted for age, lifestyle factors and education. Further effect modification, in particular by urbanization, was assessed in sex-stratified analyses.

Higher annual averages of air pollution, air temperature and greenness at residence were associated with diabetes prevalence in men (NO_2: Odds Ratio (OR) per interquartile range increase in exposure: 1.49 [95% confidence interval (CI): 1.13, 1.95], air temperature: OR: 1.48 [95%-CI: 1.15, 1.90]; greenness: OR: 0.78 [95%-CI: 0.59, 1.01]) but not in women.

Conversely, higher levels of air pollution, temperature and lack of greenness were associated with lower obesity prevalence and BMI in women. After including an interaction term for urbanization, only higher greenness was associated with higher BMI in rural women, whereas higher air pollution was associated with higher BMI in urban men.

To conclude, we observed sex-specific associations of environmental exposures with metabolic diseases. An additional interaction between environmental exposures and urbanization on obesity suggests a higher susceptibility to air pollution among urban men, and higher susceptibility to greenness among rural women, which needs corroboration in future studies.

1. Introduction

In the last decade, the number of people suffering from metabolic

* Corresponding author. Ingolstädter Landstr. 1, 85764 Neuherberg, Germany.
E-mail address: fiona.niedermayer@helmholtz-munich.de (F. Niedermayer).

https://doi.org/10.1016/j.envres.2024.118965
Received 31 January 2024; Received in revised form 25 March 2024; Accepted 16 April 2024
Available online 18 April 2024

diseases such as diabetes mellitus or obesity has increased worldwide (IDF (International Diabetes Federation), 2021; WHO, 2022). To reverse this trend, prevention is urgently needed, not only because metabolic

Abbreviations

BMI	Body-Mass-Index
CI	Confidence Interval
DAG	Directed acyclic graph
IQR	Interquartile range
KORA	Cooperative Health Research of Augsburg
NDVI	Normalized difference vegetation index
NO	Nitrogen (di)oxide
OR	Odds ratio
PM	Particulate matter
PNC	Particle number concentration
WC	Waist circumference

diseases represent a major global health burden on their own, they are also linked to secondary diseases and constitute risk factors for other diseases (Kivimaki et al., 2022). The risk of metabolic diseases accumulates over a lifetime, resulting in prevalence of metabolic diseases being highest in middle-aged and older adults (WHO, 2022; Diseases and Injuries, 2020). Although it is known that metabolic diseases develop through a complex interplay of biological, social, behavioral and environmental factors (Bluher, 2019), current prevention strategies mainly focus on changing individual behaviors, such as dietary and physical activity habits, without addressing the context in which these changes are supposed to occur (WHO, 2022). However, single interventions alone may not provide effective prevention of these complex diseases on their own (WHO, 2022). To understand the extent to which the environment acts as an obesogenic factor, the positive and negative effects of environmental factors on metabolic diseases need to be further elucidated.

There is increasing evidence that air pollutants play a role in the development of metabolic diseases (He et al., 2017; An et al., 2018). With regard to diabetes, a recent meta-analysis revealed a 25 % higher risk with a 10 $\mu g/m^3$ increase in particulate matter less than 2.5 μm in diameter ($PM_{2.5}$) (He et al., 2017). However, to date, only few studies have addressed the effects of air pollution on obesity (An et al., 2018; De la Fuente et al., 2020). A study in mice suggested that short-term exposure adversely affects adipose tissue through inflammatory processes, whereas long-term exposure induced leptin resistance, leading to higher risk of adiposity (Campolim et al., 2020). A systematic review of human studies by An et al. (2018) observed that 29 (44 %) of the long-term associations between air pollution and obesity were positive, but an equal number of associations showed no association and even 8 (12%) associations were negative. In conclusion, previous studies have focused on assessing the effects of air pollution, mainly particulate matter, on diabetes and obesity, while other air pollutants have so far rarely been studied. In addition, associations regarding obesity were often conflicting, which requires further investigation.

Moreover, only a limited number of studies have focused on the effects of ambient air temperature (Valdes et al., 2014, 2019; Yang et al., 2015). These studies found that increased annual averages of air temperature were associated with higher prevalence of obesity and diabetes and higher levels of glucose metabolism markers (Valdes et al., 2014, 2019). Conversely, higher levels of surrounding greenness can lead to increased physical activity levels (De la Fuente et al., 2020; Fong et al., 2018) and therefore directly mitigate an important risk factor for metabolic diseases. Other potential pathways include improved mental health and well-being due to surrounding greenness (Fong et al., 2018), which may simultaneously have a positive impact on metabolic health. Indeed, a systematic review of greenness confirmed a protective effect of living near green spaces on diabetes, but the association between greenness and obesity was inconclusive (De la Fuente et al., 2020).

Along with the lack of evidence mentioned above, potential sex-specific associations with metabolic diseases are missing or have been inconsistent (Wang et al., 2014; Weinmayr et al., 2015). Nevertheless, research on respiratory outcomes has often shown sex-specific susceptibility to environmental exposures (Clougherty, 2010). Moreover, there are notable sex differences in metabolic health, such as women's reduced tendency to accumulate abdominal fat or a delayed onset of metabolic diseases compared with men (Chang et al., 2018; Kautzky-Willer et al., 2023). In addition to potential sex-specific effects, previous studies have shown that health behaviors and obesity prevalence may differ according to urbanization (NCD Risk Factor Collaboration, 2019; Cohen et al., 2018). However, most of the previous studies were conducted in urban areas and therefore, could not account for different urbanization levels in their study region. Consequently, evidence of associations at different levels of urbanization is lacking.

The present study aimed to evaluate the long-term effects of multiple environmental exposures, including several air pollutants, ambient air temperature and surrounding greenness on prevalent diabetes and obesity in cross-sectional data from a population-based cohort in Augsburg, Germany. We specifically examined sex-specific associations in these middle-aged to older adults, who have often been underrepresented in studies but are at highest risk for metabolic diseases (Schienkiewitz et al., 2022). We further explored these effects by investigating potential differences between urban and rural areas.

2. Methods

2.1. Study population

We used cross-sectional data from the KORA ("Cooperative Health Research in the Region Augsburg") FIT study, a population-based cohort from the city of Augsburg, Southern Germany, and its two adjacent mainly rural counties (Holle et al., 2005). Briefly, the KORA Fit study is a follow-up examination of participants from the four original cohorts S1 (baseline assessment: 1984–1985), S2 (1989–1990), S3 (1994–1995) and S4 (1999–2001) (Rooney et al., 2022). In 2018 and 2019, 3047 participants aged 53–74 years underwent comprehensive standardized physical examination and in-person interviews with a specific focus on cardiometabolic health. All KORA studies adhered to the Declaration of Helsinki. Each participant gave written informed consent and ethical approval was granted by the Ethics Committee of the Bavarian Medical Association and the Bavarian commissioner for data protection and privacy.

2.2. Outcome assessment

Outcomes were prevalent diabetes mellitus and obesity status, as well as continuous body mass index (BMI) and waist circumference (WC) as assessed by standardized anthropometric measurements. Seca's measuring systems (Seca GmbH & Co, KG, Hamburg) were used to measure height and weight, whereupon BMI was calculated as weight in kg divided by squared height in meters (kg/m^2). WC was determined by using an inelastic tape at the level midway between the lower rib margin and the iliac crest (Rospleszcz et al., 2019). Participants were classified as having diabetes mellitus if they reported a physician-based diagnosis of diabetes mellitus diagnosis or intake of glucose-lowering medication during the interview. The latter was verified by checking the medication brought along on the day of the examination. Prevalent obesity was defined by BMI $\geq$30 kg/m^2 and by sex-specific WC cut-offs (men: $\geq$94 cm; women: $\geq$80 cm) (WHO, 2008). In the following paragraphs, unless otherwise noted, the term obesity refers to obesity defined by BMI.

2.3. Exposure assessment

We analyzed the long-term exposure to several environmental factors, including air pollution, air temperature and surrounding greenness, which were linked to participants' geocoded residential addresses.

Air pollution was modeled based on measurements from 20 monitoring stations located within the KORA study area in 2014 and 2015. Land-use regression models were separately developed for each air pollutant and applied to a 50 m × 50 m grid to estimate individual residential annual mean concentrations. Air pollutants included nitrogen oxides (NO_2 and NO_x), ozone (O_3), particulate matter diameter <10 μm in diameter (PM_{10}), 10–2.5 μm (PM_{coarse}), <2.5 μm ($PM_{2.5}$), soot ($PM_{2.5}$abs) and particle number concentration (PNC). $PM_{2.5}$abs can be used as proxy for black carbon, also known as soot, and can be simply measured by the reflectance in the $PM_{2.5}$ filters (Cyrys et al., 2003). More information on the air pollution measurements and predictors used in the modeling has been described elsewhere (Wolf et al., 2017).

Daily mean air temperature was available on a 1 km × 1 km gridded dataset across Germany, derived from a multi-stage regression-based approach. A more detailed description on the air temperature modeling is published elsewhere (Nikolaou et al., 2023). Briefly, several data from multiple sources, including weather station observations and a variety of remote sensing spatiotemporal predictors were incorporated in a modeling procedure which consisted of two linear mixed models and a thin plate spline interpolation technique. The models achieved high accuracy ($R^2 \geq 0.95$) and low errors (Root Mean Square Error (RMSE) ≤ 1.54°C) while validation with a dense and independent monitoring network in Augsburg -the region of the KORA study-confirmed the good performance ($R^2 = 0.99$, RMSE = 1.07°C) (Nikolaou et al., 2023). For the present analysis, we used the annual mean air temperature data from 2018 to match the examination year of most of the participants (69% examined in year 2018). In order to compare exposure effects reflecting more extreme air temperature levels, we additionally analyzed mean air temperature levels of winter and summer by calculating the mean of daily air temperature levels from December to February and from June to August, respectively.

For surrounding greenness, the median normalized difference vegetation index (NDVI) in a Euclidean distance of 300 m, 500 m and 1000 m buffer around participants' residences was available. Briefly, NDVI was extracted and calculated from cloud-free satellite images taken between April and October (Dandolo et al., 2022). Mean values of two different satellites (Landsat 8 and Sentinel-2) were used, which provided images with a resolution of 30 m and 10 m, respectively. Pixels with negative values were excluded prior to assignment (Markevych et al., 2014). Detailed description of the NDVI calculation is given elsewhere (Dandolo et al., 2022; Kabisch et al., 2019). For the present analysis, we used NDVI data from the year 2018, which reflected the main examination year of the KORA Fit sample, and selected the 500 m buffer, which represents a reachable distance within 5–10 min on foot (Smith et al., 2017).

2.4. Study area and degree of urbanization

We used publicly available data on the degree of urbanization in 2020 provided by the EUROSTAT, the statistical office of the European Union (https://ec.europa.eu/eurostat). A basic description of the categorization of municipalities is given elsewhere (European Union, 2018). Briefly, grid cells were defined as high-, moderate- and low-density clusters based on the population density per km (WHO, 2022) and the total number of inhabitants. Municipalities (local administrative units) were then classified as urban, suburban/towns or rural areas based on the proportion of grid cell categories. The KORA study area consists of 77 local administrative units, of which 22 % were classified as urban, 20 % as suburban and 58 % as rural (Supplementary Figure S1).

2.5. Covariate assessment

Participants were asked about sociodemographic characteristics and lifestyle factors in standardized face-to-face interviews. Alcohol consumption was assessed as grams per day derived from participants self-reported consumption of beer, wine and spirits on weekday and weekend. Subjects were classified as never-smokers, ex-smokers or smokers based on their self-reported smoking behavior. Participants' physical activity level was determined by the reported duration of leisure time spent on sport activities. They were classified as active if they spent at least 1 h per week in sports activities during summer and winter, otherwise they were classified as inactive (Conzade et al., 2019). Educational level served as proxy for the individual socioeconomic status. Participants reported their highest level of education attainment, which was categorized based on the International Standard Classification of Education (ISCED) (OECD, 2015). Finally, education was grouped into three categories: low (ISCED levels 0–2), medium (ISCED levels 3–4), and high (ISCED levels 5–8). As an indicator of neighborhood socioeconomic status, the percentage of low-income households (<1250 euro) within a 5 km * 5 km area provided by a private company (WiGeoGIS) for the year 2018 was used.

2.6. Statistical analysis

We performed all analyses with the statistical software R 4.1.2 (R Core Team, 2021). Statistical significance was indicated by two-sided p-values <0.05. Our approach is described in detail in the following sections.

2.6.1. Descriptive

Continuous variables of baseline characteristics and exposure levels are presented as mean and standard deviation (SD), categorical variables are presented as absolute numbers and percentages. For strata differences, we applied two-sample t-tests (or Wilcoxon rank-sum test in case of non-normal distribution) for continuous variables, and Chi (WHO, 2022) test of independence for categorical variables. We performed Spearman's rank correlation to assess correlations between environmental exposures.

2.6.2. Analysis of associations

To estimate sex-specific effects of each environmental exposure on prevalent diabetes and obesity, we applied multivariable logistic regression models with a multiplicative interaction term between exposure and sex. For the continuous obesity measures BMI and WC, we applied multivariable linear regression models including an interaction between exposure and sex. Odds ratios and absolute changes derived from regression models are given for an interquartile range (IQR) increase in environmental exposure with 95% confidence intervals (95% CI). For all linear models, the residuals were normally distributed (data not shown). All models were adjusted for confounders, which we selected a priori using a combined approach of previous studies and knowledge and drawing directed acyclic graphs (DAGs). DAGs help to visualize the interdependence of outcome, exposure, and covariates and help to identify potential bias introduced by confounders and colliders. We used the web-version of the program "DAGitty" (http://www.dagitty.net/), which proposed three minimally sufficient adjustment sets that included only necessary variables to block all backdoor paths (open confounding paths from outcome to exposure), thereby reducing the risk of overadjustment (Pearce and Lawlor, 2016). Our main confounder set consisted of age, lifestyle factors (physical activity, alcohol consumption, smoking), and individual socioeconomic status reflected by educational level (Fig. 1). The other two proposed confounder sets were used in sensitivity analyses.

2.6.3. Effect modification

We split our data by sex to further test for multiple, secondary effect

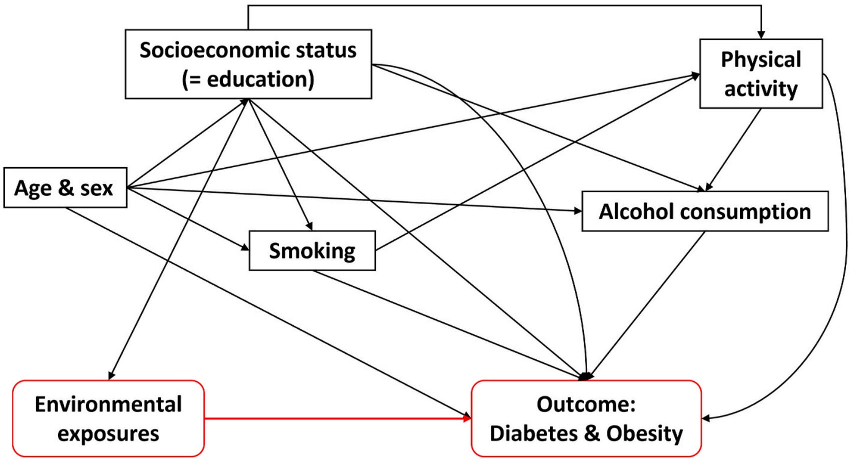


Fig. 1. Directed acyclic graphs presenting hypothesized relationship between exposures, main confounders and the outcomes diabetes and obesity.

modifications found in previous studies by including a multiplicative interaction term with the exposure variable in sex-stratified analyses. We used the following binary effect modifiers: urbanization (urban vs. towns and rural areas), age (≥65 years vs.< 65 years), smoking (never vs. ex- and current smokers), physical activity (yes vs. no), education (low-medium vs. high), and obesity (yes vs. no, only for the outcome diabetes). We only tested for binary effect modifiers in our sex-stratified sample to in order to have enough power in the subgroups. Therefore, for urbanization, we subsumed suburban and rural areas, and for smoking, we subsumed ex-smokers and current smokers together.

2.6.4. *Exploratory analysis*

We determined the exposure-response function between each outcome and environmental exposure visually by plotting the results of generalized additive models with thin plate splines of exposures fitted to our main model. Based on the results of the single-exposure analysis for obesity, we further evaluated potential confounding and interaction of air pollution and greenness on obesity. Therefore, we applied a two-exposure linear and generalized additive model. Because this exploratory analysis was a consequence of the single-exposure models, we describe the methods in more detail in the Results section for a better understanding of the reasoning.

2.6.5. *Sensitivity analysis*

We conducted several sensitivity analyses to check the robustness of our findings: (1) we applied linear and logistic regression models with the other two proposed confounder sets and a third set combining all variables of the different sets (see Supplementary Figure S2). Confounder set 2 included marital status instead of physical activity, which can alternatively be used to block one present backdoor path; confounder set 3 included only neighborhood and socioeconomic status blocking all present backdoor paths. (2) We excluded participants who had moved in the last 10 years to reduce potential misclassification of exposure levels. (3) We adjusted for dietary factors instead of education using the "alternative healthy eating index" (described in detail elsewhere (Wawro et al., 2020)) which was only available in a subsample of 702 participants. (4) We excluded physical activity from the adjustment model of our primary analysis to exclude the possibility that physical activity may act as potential intermediate factor in the association of environmental exposures with metabolic disease.

3. Results

3.1. *Study population*

Our final analytic sample comprised 3034 participants after excluding 13 individuals with missing information on either exposures, outcomes, or covariates (Supplementary Figure S3). Of these, 53.7 % were female (Table 1). The mean age at examination was 63 years and 49.5 % lived in urban and 50.5 % in rural areas at the time of examination. BMI, WC, lifestyle factors, and education level, were significantly different between men and women. Men had on average a higher BMI, WC, and education level, were less physically active and were more often ex-smokers compared to women (Table 1). Men had a higher prevalence of diabetes and obesity based on BMI, whereas women had a higher obesity prevalence defined by WC (diabetes: 9.1 % vs. 7.1 %, obesity (BMI): 31.0 % vs. 29.1 %, obesity (WC): 69.2 % vs. 71.7 %, non-significant).

When we additionally stratified participant characteristics by urbanization, we observed sex and urbanization differences in outcome variables (Supplementary Table S1). For example, the proportion of diabetes was highest in urban men (11.2%) but lowest in urban women (6.9%). BMI-based obesity prevalence was highest in rural women (31.4%) and lowest in urban women (26.8%), whereas it was similar in urban and rural men. In contrast, the distribution of BMI values for men and women did not show a clear urban-rural difference (Supplementary Figure S4).

3.2. *Environmental exposures*

The annual mean concentrations of NO_2 (13.6 μg/m^3), $PM_{2.5}$ (11.6 μg/m^3), and PM_{10} (16.3 μg/m^3) did not exceed the EU limit values (Table 2). Air pollutants were strongly correlated with each other (range: r = 0.55–0.92), except for ozone. Air temperature variables were moderately to strongly correlated with air pollutants (range: r = 0.39–0.76), except for ozone. Greenness was negatively correlated with air pollutants (range: r = −0.84 to −0.73) and temperature (range: r = −0.64 to −0.53) and weakly positively correlated with ozone (r = 0.09). Exposure concentrations differed significantly between urban and rural areas, with higher levels of air pollutants and temperature and lower levels of greenness in urban areas (Supplementary Figure S5 and Table S2). No sex differences in exposure were found except for $PM_{2.5}$abs (Supplementary Table S2).

Table 1
Characteristics of the study participants.

	Total (n = 3034)	Men (n = 1404)	Women (n = 1630)	p-value
Age [years]	63.2 ± 5.5	63.0 ± 5.6	63.4 ± 5.5	0.046
Degree of urbanization				
Urban	1502 (49.5%)	677 (48.2%)	825 (50.6%)	0.201
Rural	1532 (50.5%)	727 (51.8%)	805 (49.4%)	
Lifestyle factors				
Alcohol [g/day]	14.8 ± 19.5	22.1 ± 23.3	8.5 ± 12.3	<0.001
Smoking status				<0.001
Never	1343 (44.3%)	538 (38.3%)	805 (49.4%)	
Ex-smoker	1258 (41.5%)	670 (47.7%)	588 (36.1%)	
Current Smoker	433 (14.3%)	196 (14.0%)	237 (14.5%)	
Physically active	2182 (71.9%)	977 (69.6%)	1205 (73.9%)	0.009
Individual socioeconomic status				
Education				<0.001
low	93 (3.1%)	19 (1.3%)	74 (4.5%)	
medium	2200 (72.5%)	964 (68.7%)	1236 (75.8%)	
high	742 (24.4%)	421 (30.0%)	320 (19.6%)	
Neighborhood socioeconomic status				
Household with low income [%]	25.0 ± 20.1	24.4 ± 19.8	25.5 ± 20.3	0.236
Marital status				
Married	2369 (78.1%)	1194 (85.0%)	1175 (72.1%)	<0.001
Outcome				
Diabetes mellitus	244 (8.0%)	128 (9.1%)	116 (7.1%)	0.051
Obesity				
defined by BMI	909 (30.0%)	435 (31.0%)	474 (29.1%)	0.271
defined by waist circumference	2141 (71.0%)	972 (69.2%)	1169 (71.7%)	0.145
BMI [kg/m^2]	28.2 ± 5.3	28.6 ± 4.6	27.8 ± 5.9	<0.001
Waist circumference [cm]	94.6 ± 14.3	100.7 ± 8.2	89.3 ± 13.8	<0.001

Legend: Continuous variables are given as arithmetic mean and standard deviation. Categorical variables are given as counts and percentages. Differences between sex were quantified by two-sample *t*-test (if not normally distributed: Wilcoxon test) and Chi^2 test, respectively. BMI-based obesity was defined by BMI $\geq$30 kg/m^2; WC-based obesity was defined by WC $\geq$ 94 cm for men and $\geq$80 cm for women.

3.3. Association of environmental exposures with diabetes – interaction sex

In single-exposure models, the associations of NO_2, PM_{10}, $PM_{2.5}$abs and air temperature with diabetes prevalence showed significant interactions with sex (Table 3). In men, we found positive associations between prevalent diabetes and an IQR increase in air pollutants and air temperature (e.g., NO_2: OR: 1.49 [95% CI: 1.13, 1.95], mean temperature: OR: 1.48 [95% CI: 1.15, 1.90], Table 3), and a borderline significant negative association between diabetes and greenness (OR: 0.78, [95% CI: 0.59, 1.01]). Only ozone was not associated with diabetes prevalence in men. In women, we did not observe any association between environmental exposures and prevalent diabetes (Table 3).

The exposure-response functions did not show any clear deviations from linearity (Supplementary Figure S6 and S7). There were no further interactions with urbanization, age, physical activity, BMI, smoking, education (Supplementary Figure S8).

3.4. Association of environmental exposures with obesity – interaction sex

Apart from ozone and winter temperature, all associations of environmental exposures with BMI showed an interaction with sex (Table 4). The effects of environmental exposures on obesity were opposite for men and women. In men, we found no consistent association of any environmental exposure with obesity (Table 4 for the BMI-based and Supplementary Table S3 for the WC-based definition). However, trends showed higher BMI, WC and increased ORs of obesity with higher air pollution and air temperature. In contrast, higher levels of greenness indicated an inverse association with obesity in men (obesity: OR: 0.87 [95% CI: 0.74, 1.03]; BMI: −0.20 kg/m^2 [95% CI: −0.58, 0.18]). In women, IQR increases in NO_2, NO_x, PM_{10}, PM2$_{.5}$abs, and PNC were significantly associated with lower BMI and lower BMI obesity prevalence (BMI: NO_2: −0.60 kg/m^2 [95% CI: −0.96, −0.23], $PM_{2.5}$abs: −0.57 kg/m^2 [95% CI: −0.95, −0.19]; obesity: NO_2: OR: 0.81 [0.68, 0.95]; PM2.5 abs: OR: 0.80 [95% CI: 0.68, 0.95], Table 4). Additionally, we found significant negative associations between annual $PM_{2.5}$, air temperature, and summer temperature and BMI (Table 4). An increase in greenness resulted in significantly higher BMI (0.63 kg/m^2 [95% CI: 0.29, 0.98]) and was associated with higher obesity prevalence (OR: 1.27 [95% CI: 1.09, 1.48]). The results were similar for WC, but we did not observe any associations with obesity defined by WC (Supplementary Table S3).

We observed deviations from linearity for NO_2, PM_{10}, PM_{coarse}, $PM_{2.5}$abs and greenness with almost u-shaped functions in males and females and NOx and temperature in females only (Supplementary Figures S9 and S10). The exposure-response functions were similar for prevalent obesity and WC (data not shown). In addition, our results pointed to an effect modification by age, indicating partly stronger associations for participants younger than 65 years. However, there was no interaction between environmental exposures and physical activity, smoking or education (Supplementary Figure S11).

3.5. Association of environmental exposures with obesity – interaction urbanization

In line with the non-linear exposure-response functions, we found significant interactions between urbanization and NO_2, PM_{10}, PM_{coarse}, $PM_{2.5}$abs, winter temperature, and greenness in men. For women, the effects were similar but did not reach statistical significance (Fig. 2). Except for ozone, we observed significant positive associations between higher levels of air pollutants, lack of greenness and BMI in urban men. None of these associations were significant for urban women. In rural men and rural women, higher levels of NO_2, PM_{10}, $PM_{2.5}$abs, and temperature were suggestive of lower BMI but did not reach significance. Additionally, higher greenness was associated with higher BMI in rural residents and reached significance in rural women (men: 0.24 kg/m^2 [95% CI: −0.31, 0.79]; women: 0.68 kg/m^2 [95% CI: 0.03, 1.34]).

3.6. Exploratory analysis: two-exposure model for BMI

Based on the contradictive associations, particularly of air pollution and greenness with obesity, we explored potential confounding and interaction effects between these exposures on BMI in rural and urban areas. Firstly, to assess confounding effects, we applied a two-exposure model, adding the air pollution and greenness with an interaction term each for urbanization ($PM_{2.5}$abs by urbanization + greenness by urbanization) in our sex-stratified sample. As a representative for air pollution, we chose $PM_{2.5}$abs, for which the interaction effect with urbanization was strongest in men and women. The effect estimates from single- and two-exposure linear regression models can be compared in Fig. 3. In urban males, the adverse effect of $PM_{2.5}$abs did not change after adjusting for greenness (single: 0.99 kg/m^2 [95% CI: 0.41, 1.57], two-exposure: 0.94 kg/m^2 [95% CI: 0.03, 1.85]), whereas the protective effect of greenness disappeared after adjusting for $PM_{2.5}$abs (Fig. 3).

Table 2
Summary statistics of environmental exposures and Spearman's correlation coefficients.

	Mean ± SD	Median (IQR)	Min; Max	NO_2	NO_x	O_3	PM_{10}	PM_{coarse}	$PM_{2.5}$	$PM_{2.5}$abs	PNC	Annual temp.	Winter temp.	Summer temp.
NO_2 [μg/m^3]	13.6 ± 4.2	13.0 (6.3)	6.9; 28.3	–	–	–	–	–	–	–	–	–	–	–
NO_x [μg/m^3]	21.3 ± 7.0	22.0 (8.7)	3.9; 44.0	0.82	–	–	–	–	–	–	–	–	–	–
O_3 [μg/m^3]	39.1 ± 2.3	39.2 (3.5)	31.7; 45.7	−0.21	−0.17	–	–	–	–	–	–	–	–	–
PM_{10} [μg/m^3]	16.3 ± 1.4	16.0 (2.0)	12.9; 22.0	0.72	0.74	0.00	–	–	–	–	–	–	–	–
PM_{coarse} [μg/m^3]	4.8 ± 1.1	4.8 (1.4)	2.5; 8.2	0.81	0.69	0.17	0.80	–	–	–	–	–	–	–
$PM_{2.5}$ [μg/m^3]	11.6 ± 1.03	11.7 (1.4)	7.8; 14.2	0.74	0.81	−0.24	0.58	0.55	–	–	–	–	–	–
$PM_{2.5}$abs [10^{-5}m^{-1}]	1.2 ± 0.2	1.2 (0.3)	0.7; 1.7	0.86	0.73	−0.10	0.77	0.78	0.69	–	–	–	–	–
PNC [n/cm^3]	6960 ± 1692	6088 (1924)	2962; 13,656	0.75	0.92	−0.10	0.81	0.74	0.70	0.74	–	–	–	–
Annual temperature [°C]	10.2 ± 0.4	10.1 (0.6)	9.2; 11.2	0.74	0.47	−0.30	0.50	0.60	0.54	0.66	0.46	–	–	–
Winter temperature [°C]	1.5 ± 0.3	1.4 (0.4)	0.5; 2.2	0.65	0.40	−0.20	0.45	0.57	0.46	0.56	0.39	0.94	–	–
Summer temperature [°C]	19.0 ± 0.6	18.9 (0.8)	17.9; 20.4	0.76	0.50	−0.32	0.52	0.61	0.57	0.68	0.47	0.99	0.87	–
Greenness (NDVI)	0.4 ± 0.1	0.4 (0.1)	0.2; 0.7	−0.84	−0.79	0.09	−0.73	−0.75	−0.75	−0.81	−0.77	−0.62	−0.53	−0.64

Legend: Exposure levels are described as arithmetic mean and standard deviation (SD). Correlation coefficients were calculated using Spearman's rank correlation.
Abbreviations: SD = Standard deviation; PNC = Particle number concentration; NDVI = Normalized difference vegetation index.

Table 3
Associations of air pollution, air temperature and greenness with prevalent diabetes derived from logistic regression models with an interaction term for sex.

	IQR	Men	Women	$p_{interaction}$
		OR (95% CI)	OR (95% CI)	
NO_2 [μg/m^3]	6.3	1.49 (1.13, 1.95)	0.93 (0.70, 1.24)	0.020
NO_x [μg/m^3]	8.7	1.33 (1.05, 1.69)	0.98 (0.77, 1.25)	0.077
O_3 [μg/m^3]	3.5	0.89 (0.66, 1.18)	1.10 (0.82, 1.46)	0.305
PM_{10} [μg/m^3]	2.0	1.42 (1.11, 1.83)	0.96 (0.73, 1.26)	0.037
PM_{coarse} [μg/m^3]	1.5	1.38 (1.06, 1.79)	0.97 (0.74, 1.25)	0.056
$PM_{2.5}$ [μg/m^3]	1.4	1.41 (1.08, 1.84)	1.01 (0.77, 1.33)	0.091
$PM_{2.5}$abs [10^{-5}m^{-1}]	0.3	1.43 (1.08, 1.89)	0.92 (0.69, 1.23)	0.033
PNC [n/cm^3]	1924	1.30 (1.06, 1.61)	0.99 (0.80, 1.23)	0.075
Annual temperature [°C]	0.6	1.48 (1.15, 1.90)	0.96 (0.74, 1.25)	0.019
Winter temperature [°C]	0.4	1.39 (1.10, 1.75)	0.96 (0.75, 1.22)	0.027
Summer temperature [°C]	0.8	1.50 (1.17, 1.92)	0.97 (0.74, 1.26)	0.018
Greenness (NDVI)	0.1	0.78 (0.59, 1.01)	1.05 (0.80, 1.37)	0.118

Legend: Odds Ratios (OR) were calculated by single-exposure logistic regression models with an interaction term for sex.
Models were additionally adjusted for age, physical activity, alcohol, smoking, and education. ORs are given per interquartile range increase in exposure.
$P_{interaction}$ is the p-value derived from the interaction term between the respective exposure and sex.
Abbreviations: OR = Odds Ratio, 95% CI = 95% confidence interval, PNC = Particle number concentration, NDVI = Normalized difference vegetation index.

However, this pattern was not found in urban women or in rural men and women. Second, we further explored a possible interaction between PM2.5 abs and greenness considering non-linear effects. We aimed to evaluate the hypothesis that the association of air pollution or greenness with BMI is stronger with high or low levels of the other exposure, e.g., if the PM2.5 abs-BMI association is stronger with low levels of greenness and vice versa and if this interaction differs in urban and rural areas. Therefore, we applied a generalized additive model in our sex-stratified sample, where we specified a two-way multiplicative interaction ($PM_{2.5}$abs*greenness by urbanization) considering non-linear effects by modeling a thin plate spline. The sex- and urbanization-specific interaction effect between $PM_{2.5}$abs and greenness was visualized by a 3D surface plot (Fig. 4). While the 3D plot shows a complex surface in a 3D space for urban and rural men and rural women, we observed only a 2D surface standing diagonally in space for urban women, suggesting no interaction between exposures. This suggests a complex interaction between traffic-related air pollution and greenness, which appeared to differ between rural and urban areas and between sex.

3.7. Sensitivity analyses

Our results were robust in the different sensitivity analyses. First, adjusting for marital status instead of alcohol consumption, adjusting for education and neighborhood SES only, or adjusting for all proposed confounders did not change our results (Supplementary Table S4). We observed minor effect changes in models including neighborhood SES for obesity, but not for diabetes. Second, excluding participants who had moved in the last 10 years did not change the results (Supplementary Figure S12). Third, in a subsample adjusting for dietary factors instead of education, effect estimates were similar compared to our main model which we used in the final sample (Supplementary Figure S13). Lastly, our results were robust after excluding physical activity from the adjustment set (Supplementary Table S5).

Table 4
Associations of air pollution, air temperature and greenness body mass index (BMI) and BMI-based obesity derived from logistic or linear regression models with an interaction term for sex.

	IQR	BMI			Obesity (BMI)		
		Men	Women	$p_{interaction}$	Men	Women	$p_{interaction}$
		estimate (95% CI)	estimate (95% CI)		OR (95% CI)	OR (95% CI)	
NO_2 [μg/m^3]	6.3	0.21 (−0.20, 0.61)	−0.60 (−0.96, −0.23)	0.004	1.13 (0.95, 1.34)	0.81 (0.68, 0.95)	0.006
NO_x [μg/m^3]	8.7	0.17 (−0.16, 0.51)	−0.39 (−0.7, −0.07)	0.016	1.11 (0.96, 1.28)	0.86 (0.75, 0.99)	0.013
O_3 [μg/m^3]	3.5	0.00 (−0.42, 0.41)	−0.07 (−0.44, 0.31)	0.822	1.03 (0.86, 1.24)	1.01 (0.85, 1.19)	0.823
PM_{10} [μg/m^3]	2.0	0.32 (−0.07, 0.71)	−0.41 (−0.77, −0.06)	0.006	1.21 (1.02, 1.43)	0.82 (0.70, 0.97)	0.001
PM_{coarse} [μg/m^3]	1.5	0.16 (−0.22, 0.54)	−0.42 (−0.76, −0.08)	0.024	1.16 (0.98, 1.36)	0.87 (0.75, 1.01)	0.012
$PM_{2.5}$ [μg/m^3]	1.4	0.19 (−0.18, 0.56)	−0.34 (−0.69, 0.01)	0.039	1.08 (0.92, 1.27)	0.87 (0.75, 1.02)	0.059
$PM_{2.5}$abs [10^{-5}m^{-1}]	0.3	0.30 (−0.11, 0.71)	−0.57 (−0.95, −0.19)	0.002	1.15 (0.96, 1.37)	0.80 (0.68, 0.95)	0.004
PNC [n/cm^3]	1924	0.23 (−0.08, 0.54)	−0.29 (−0.57, 0.00)	0.015	1.15 (1.00, 1.31)	0.86 (0.76, 0.98)	0.003
Annual temperature [°C]	0.6	0.19 (−0.19, 0.56)	−0.43 (−0.78, −0.09)	0.017	1.13 (0.96, 1.33)	0.91 (0.78, 1.06)	0.055
Winter temperature [°C]	0.4	0.11 (−0.24, 0.45)	−0.26 (−0.57, 0.06)	0.123	1.10 (0.94, 1.27)	0.96 (0.84, 1.11)	0.216
Summer temperature [°C]	0.8	0.21 (−0.17, 0.59)	−0.52 (−0.86, −0.17)	0.005	1.13 (0.96, 1.34)	0.88 (0.75, 1.02)	0.025
Greenness (NDVI)	0.1	−0.20 (−0.58, 0.18)	0.63 (0.29, 0.98)	0.001	0.87 (0.74, 1.03)	1.27 (1.09, 1.48)	0.001

Legend: Effect estimates and ORs were calculated by single-exposure linear (BMI) and logistic (obesity) regression models with an interaction term for sex. Models were additionally adjusted for age, physical activity, alcohol, smoking, and education. Estimates and ORs are given per interquartile range increase in exposure. $P_{interaction}$ is the p-value derived from the interaction term between the respective exposure and sex.
Abbreviations: OR = Odds Ratio, 95% CI = 95% confidence interval, PNC = Particle number concentration, NDVI = Normalized difference vegetation index.

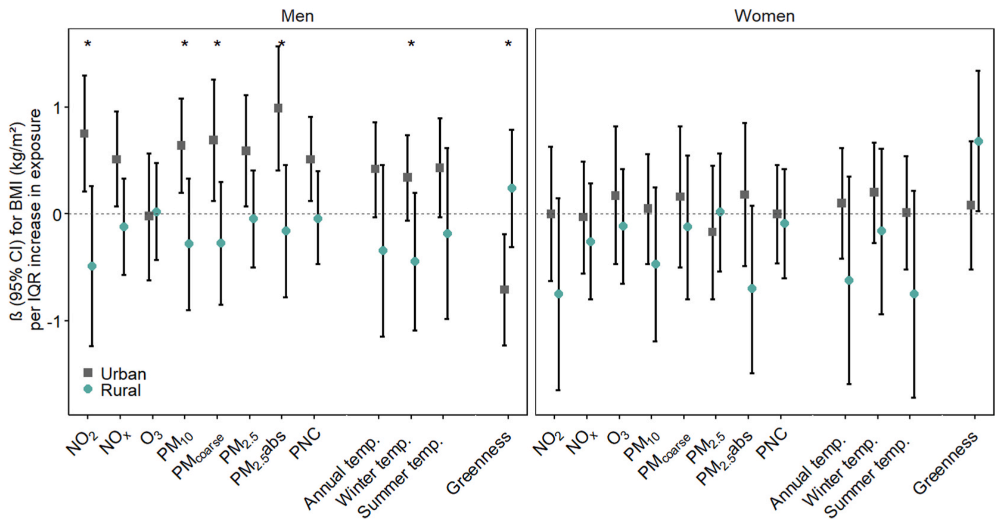


Fig. 2. Associations between BMI and environmental exposures considering effect modification by urbanization in sex-stratified samples. Urbanization-specific effect estimates are given as interquartile range increase in exposure adjusted for age, physical activity, alcohol, smoking, and education. Stars indicate significant interaction with a $p < 0.05$; error bars present 95 % confidence intervals.

4. Discussion

4.1. Summary

The present study analyzed effects of multiple environmental exposures on prevalent diabetes and obesity using cross-sectional data from 3034 middle-aged to older participants from a large population-based cohort. First, we identified higher air pollution and air temperature, and a lack of greenness to be associated with diabetes prevalence in men, but not in women. Second, the associations between environmental exposures and obesity showed a complex interplay with sex and urbanization, suggesting that direction and strength of associations depend on sex and degree of urbanization. Our exploratory analysis suggested a positive association of unfavorable levels of air pollutants and lack of greenness with BMI in urban men, whereas lack of greenness was suggestive of lower BMI in rural women. In addition, we observed a complex interaction between traffic-related pollution and greenness on BMI using a two-exposure model, suggesting that the association of air pollution with obesity may differ with the presence or absence of greenness and vice versa.

4.2. Sex- and urbanization-specific associations of environmental exposures with obesity

We did not expect to see protective effects of higher air pollution, air temperature and lack of greenness on obesity in women, nor did we hypothesize opposite associations of environmental exposures in rural and urban areas. These findings require discussion and further explanation. One explanation for the sex-specific associations could be residual confounding that occurs only in women, such as menopause, for which we could not adjust. Menopause is known to increase visceral fat and central obesity (Chang et al., 2018; Sowers et al., 2007). The age range of our population (53–74 years) reflects predominantly post-menopausal women, supporting the hypothesis that the higher BMI resulted from the transition of pre-to post-menopause.

In addition, we observed differences in obesity prevalence between

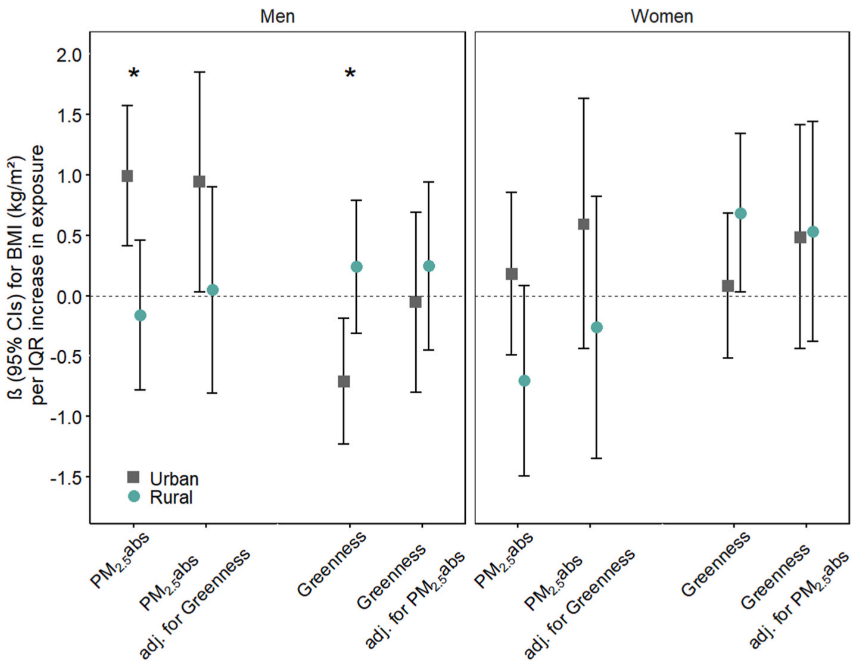


Fig. 3. Associations between BMI and selected environmental exposures from the single-exposure linear model and the two-exposure linear model, including an interaction term between exposures and urbanization. Effects estimates are given as interquartile range increase in exposure for BMI; error bars present 95 % confidence intervals. Abbreviations: adj. = adjusted.

urbanized regions. In our study, rural women were more likely to be obese than urban women, whereas obesity prevalence was similar in urban and rural men. This is consistent with global trends in obesity prevalence, which showed that in high-income countries, obesity prevalence is higher in rural areas than in urban areas; especially among women (NCD Risk Factor Collaboration, 2019). In contrast, environmental exposure concentrations were higher in urban than in rural areas, leading to the suggestive protective effects we observed in rural men and women. Rural areas may have additional factors contributing to obesity risk that we were not able to adjust for in our analyses, thus masking the effect of environmental exposures. For example, rural areas often lack public transportation within walking distance of the residents. This increases the reliance on motorized transport options, such as cars, which are often parked directly in front of homes, reducing walkways and physical activity levels (Wang et al., 2013). Therefore, monitoring the degree of active transportation in future studies could add important evidence on this potential pathway. Moreover, rural populations may have different eating habits including higher meat consumption and more hearty foods (Trivedi et al., 2015). Our results suggest that these obesogenic factors in rural areas may affect men and women unequally, as the suggested protective effects were more pronounced in rural women. This again indicates a complex interdependence of the effects of urbanization and sex on the association between environment and obesity. This is where the concept of sex/gender may come into play, taking into account the different life circumstances and roles of women and men in society, which may differ between urban and rural areas. As the concept of sex/gender is rarely explored in environmental epidemiology (Clougherty, 2010; Bolte et al., 2018, 2019), our findings call for more research in this area to disentangle our conflicting sex-specific associations between environment and obesity.

This complex interaction of both, sex and urbanization were most evident in the association between greenness and BMI. This may be explained by two different reasons. First, green spaces in urban areas are often parks used for recreational purposes. In contrast, high NDVI values occur mainly in rural areas, which are often forests or areas used for pasture or agriculture (Dempsey et al., 2018). Whether this type of greenness has the same positive effects on mental health or physical activity as parks in urban areas needs to be investigated. However, by accounting for urbanization, we may have automatically distinguished between these different vegetation types. This clearly indicates the need for improved measures of greenness to better characterize vegetation types and to be able to disentangle their different health effects. Second, sex-specific effects could also be due to differences in green space usage between men and women. While urban men in our study benefited from higher levels of greenness, this effect was not found for urban women. Recent studies have highlighted sex differences in the use of urban parks, showing that women are less likely to visit parks and to exercise in parks (Derose et al., 2018; Evenson et al., 2019; Lapham et al., 2016). Safety concerns and fear of crime are important factors in park use, and also contribute to sex differences, as women are more likely to have safety concerns (Sowers et al., 2007). Moreover, a study by Astell-Burt et al. (2014) showed that beneficial mental health effects of urban greenness vary over time, indicating an age and sex dependent effect of greenness. While women older than 40 years with moderate degree of greenness benefitted the most, men experienced protective effects in young adulthood (Astell-Burt et al., 2014).

Moreover, we note that the confounding and interaction between traffic-related air pollution and greenness differed by sex and urbanization, further complicating the association between environmental exposures and obesity. The beneficial effect of greenness in urban men seemed to be explained by $PM_{2.5}$abs, while we did not observe any confounding effect in urban women or in rural residents. Based on the interaction analysis in the two-exposure model, we hypothesize that the presence of greenness and air pollution result in different interactions that contribute differently to health risks in urban and rural areas. A possible explanation for these different interactions could be air pollution mitigation by greenness, which depends on vegetation type, tree species, diversity, age and size of the green space (van den Bosch et al., 2024; Nemitz et al., 2020), but to discuss this in detail is beyond the scope of this study. Further studies should explore this interplay of

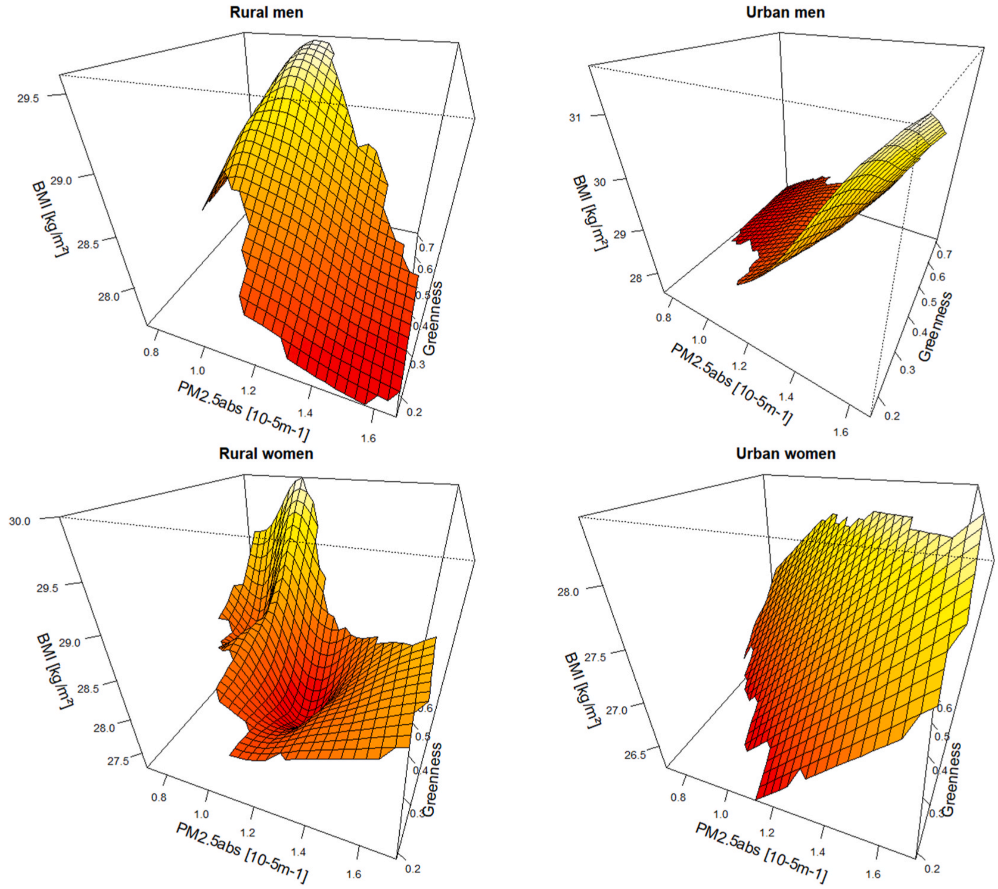


Fig. 4. 3D surface plots of the sex- and urbanization-specific associations between BMI and selected environmental exposures derived from two-exposure model with a thin plate spline and a multiplicative interaction term between $PM_{2.5}$abs and NDVI.

co-occurring environmental factors to corroborate our findings.

4.3. Comparison to previous literature

4.3.1. Air pollution

As summarized in the review by Rajagopalan and Brook (2012), there is strong evidence from animal studies demonstrating effects of air pollution on metabolism. Inhalation of $PM_{2.5}$ over several weeks resulted in increased insulin resistance, accretion of lipids and fatty degeneration of adipose tissue in mice (Rajagopalan and Brook, 2012). In our study, higher air pollution was associated with a higher diabetes prevalence in human males, which is in line with a previous meta-analysis and a systematic review (He et al., 2017; Yang et al., 2020). He et al. (2017) found a clear effect of $PM_{2.5}$ associated with a 1.25-fold higher risk of diabetes after pooling eleven studies. Furthermore, a meta-analysis in 2020 confirmed this association and additionally reported an increased risk of diabetes with increasing NO_2 and PM_{10} levels (Yang et al., 2020). We add evidence that even more air pollutants, such as NO_x, PM_{coarse}, and PNC appear to be associated with diabetes prevalence in men. An analysis of another German cohort study revealed a 10% higher risk for incident diabetes with increasing PM_{10}, which was more pronounced in men than in women and therefore, consistent with our results (Weinmayr et al., 2015). However, the study was also able to show effect modifications with age, education, and BMI, which we did not find. In addition, another meta-analysis reported potentially stronger effects in women, which contradicts to our results (Wang et al., 2014). Further studies are needed to examine sex-specific associations between environmental exposures and diabetes and to investigate possible biological differences in sex-specific susceptibility.

We found mixed results regarding the association of air pollution with obesity, but previous studies of this association have also been inconclusive. For example, Bowe et al. (2021) reported that $PM_{2.5}$ was associated with a higher weight gain and risk for obesity in a cohort of predominantly male participants, whereas we initially failed to show any association between environmental exposure and obesity in men. Only after controlling for urbanization, we observed similar effects in urban male residents. Furthermore, Bowe et al. (2021) found these associations to be non-linear, their exposure-response functions were positive and indicated a steeper slope for lower $PM_{2.5}$ levels, which is quite different from our findings. Hwang et al. (2019) did not observe any association between NO_2 or PM_{10} and obesity and these results were not modified by sex. In contrast, Li et al. (2015) reported significant associations of NO_2, PM_{10} and O_3 with obesity prevalence in Chinese adults, which remained only significant for women after stratification by sex. Results from the UK Biobank are partially consistent with our mixed findings (Furlong and Klimentidis, 2020). While exposure to PM was generally positively associated with BMI, they observed a negative association for NO_2. In fact, none of these studies tested for an effect modification by urbanization. Only Liu et al. (2021) demonstrated urbanization-specific associations of air pollution with obesity in China, with stronger adverse effects of air pollutants in rural areas compared to urban areas. The authors argued that the air pollutant composition may be more toxic in rural areas. However, these results are in contrast to our findings, where the effects appeared to be protective against obesity in rural areas.

4.3.2. Air temperature

We showed a positive association between air temperature exposure and prevalent diabetes in men. This is in line with previous studies that found a positive association of air temperature with glucose metabolism markers and prevalent diabetes (Valdes et al., 2019; Speakman and Heidari-Bakavoli, 2016). It is possible that lower temperature increases brown adipose tissue which is associated with improved glucose homeostasis and higher energy expenditure (Marlatt and Ravussin, 2017).

In contrast, we found a negative association of higher mean summer temperature with obesity in women and no association with obesity in men. This contradicts the findings of Yang et al. (2015) and Valdes et al. (2014), who observed higher odds for higher mean temperatures in a Korean and a Spanish cohort study. However, Speakman and Heidari-Bakavoli (2016) also could not show an association between temperature and obesity prevalence. In addition, a review claimed that the effect of low temperature on energy metabolism via brown adipose tissue stimulation is rather small (Marlatt and Ravussin, 2017). Moreover, these studies often focused on short-term exposure to low air temperature, therefore it is unclear whether long-term air temperature affects brown adipose tissue and if this leads to improved metabolic health (Marlatt and Ravussin, 2017). It is also possible that the temperature range in our study was too small. Compared to the other studies (Valdes et al., 2014, 2019; Yang et al., 2015; Speakman and Heidari-Bakavoli, 2016), the mean air temperature ranged only from a minimum of 9.2 °C to a maximum of 11.2 °C in our comparable small study area.

4.3.3. Greenness

In good agreement with our findings, a systematic review of seven studies on green spaces and diabetes observed that higher levels of green spaces and shorter distances to green spaces had protective effects on diabetes (De la Fuente et al., 2020). However, these studies did not analyze the effects separately for men and women, therefore, our results add sex-specific evidence on the beneficial effects of greenness on diabetes risk. Our results suggest that men benefitted more from higher greenness around their homes. Explanations such as sex-specific park use were already discussed above.

Comparable to our findings on greenness and obesity, Dempsey et al. (2018) found U-shaped exposure-response functions when investigating NDVI with obesity prevalence in an Irish cohort (Dempsey et al., 2018). As the lowest and highest NDVI quintiles were associated with higher odds of obesity, the authors argued that a lack of detailed characterization of greenness might be the reason, as we have discussed earlier. We provided evidence for this hypothesis by examining the effect modification by urbanization, which may have served as a proxy for differences in greenness. On the other hand, a study from Sweden reported lower odds of central obesity and reduced increase in WC with increasing NDVI levels only in women (Persson et al., 2018), which contradicts our results. However, compared to our sample, women were generally younger (aged 35–56) and exclusively from urban areas, so it could be hypothesized that greenness is less important for middle-aged to older adults.

4.4. Strengths and limitations

Our study has several strengths. First, the KORA-Fit study provides several environmental exposures in the year or prior to the year of the participants' examination. Second, the rich data set allowed us to adjust for multiple confounders and to investigate potential effect modifications. Furthermore, the KORA study region covered urban as well as rural areas, which enabled us to examine urbanization-specific effects. Finally, we were able to perform several sensitivity analyses to demonstrate the robustness of our results.

Nevertheless, several limitations must be acknowledged when interpreting the results of our study. First, we were unable to adjust for dietary factors, which are important independent risk factors for obesity and diabetes (Bellou et al., 2018; Schlesinger et al., 2019). However, our sensitivity analyses within a subpopulation that included dietary factors instead of education did not reveal major differences between models. Second, we could not distinguish between different types of diabetes, e.g., gestational diabetes or type 1 diabetes, because we did not have this information. However, only two participants reported an age at diagnosis of less than 20 years. If these were cases of type 1 diabetes, the effect on the associations would be negligible. Third, we must be cautious in interpreting the results of our exploratory analyses, such as secondary effect modifications and the two-exposure model. Regarding the secondary effect modification by urbanization, our sample size may have been underpowered; therefore, our subgroup analysis should be interpreted as an explanatory analysis and was not designed to formally test for significance. Moreover, because of the high correlation between exposures, the effect estimates resulting from the two-exposure models may be biased due to multicollinearity. Moreover, our study region was too small to show variability in air temperature levels and therefore, may not be able to detect associations with metabolic disease which also kept us from including air temperature in the two-exposure model. Larger studies with more exposure contrast are needed to confirm our findings. In addition, not all environmental factors were available in the year of examination and no longer exposure periods than one-year averages were considered. This may increase the risk of misclassification. However, we did not expect changes in spatial contrasts over the years and sensitivity analysis excluding movers within the last 10 years showed robust results. Lastly, due to a large number of missing data, we could not assess the effect of noise on metabolic disease, which is a relevant environmental risk factor, and few studies have been able to demonstrate an association with metabolic health (Gui et al., 2022; Sorensen et al., 2022; Eze et al., 2017).

5. Conclusion

We investigated the effects of air pollutants, air temperature, and surrounding greenness on metabolic outcomes in a population-based cohort of middle-aged to older adults. We showed that adverse environmental exposures were associated with higher diabetes prevalence in men. In addition, our results indicated a complex interaction of sex and urbanization on the association of environmental exposures with obesity. Finally, air pollution and greenness jointly influenced obesity in a complex manner. Therefore, our findings suggest that possible interactions among environmental exposures should be further investigated by taking into account differences between sex and urbanization, especially for study regions comprising urban and rural areas.

Ethics approval and consent to participate

The investigations were carried out in accordance with the Declaration of Helsinki, including written informed consent of all participants. All study methods were approved by the ethics committee of the Bavarian Chamber of Physicians, Munich [EC No. 17040].

Consent for publication

Not applicable, non-identifiable data only included.

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.

Data availability

The authors do not have permission to share data.

Acknowledgements

The KORA study was initiated and financed by the Helmholtz Zentrum München – German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research (BMBF) and by the State of Bavaria. Data collection in the KORA study is done in cooperation with the University Hospital of Augsburg. The project was supported by the European Union's Horizon 2020 research and innovation programme (No 874627). We thank all participants for their long-term commitment to the KORA study, the staff for data collection and research data management and the members of the KORA Study Group (https://www.helmholtz-munich.de/en/epi/cohort/kora) who are responsible for the design and conduct of the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.118965.

References

An, R., Ji, M., Yan, H., Guan, C., 2018. Impact of ambient air pollution on obesity: a systematic review. Int. J. Obes. 42 (6), 1112–1126. https://doi.org/10.1038/s41366-018-0089-y.

Astell-Burt, T., Mitchell, R., Hartig, T., 2014. The association between green space and mental health varies across the lifecourse. A longitudinal study. J. Epidemiol. Community Health 68 (6), 578–583. https://doi.org/10.1136/jech-2013-203767.

Bellou, V., Belbasis, L., Tzoulaki, I., Evangelou, E., 2018. Risk factors for type 2 diabetes mellitus: an exposure-wide umbrella review of meta-analyses. PLoS One 13 (3), e0194127. https://doi.org/10.1371/journal.pone.0194127.

Bluher, M., 2019. Obesity: global epidemiology and pathogenesis. Nat. Rev. Endocrinol. 15 (5), 288–298. https://doi.org/10.1038/s41574-019-0176-8.

Bolte, G., David, M., Debiak, M., Fiedel, L., Hornberg, C., Kolossa-Gehring, M., et al., 2018. [Integration of sex/gender into environmental health research. Results of the interdisciplinary research network Sex/Gender-Environment-Health (GeUmGe-NET)]. Bundesgesundheitsblatt - Gesundheitsforsch. - Gesundheitsschutz 61 (6), 737–746. https://doi.org/10.1007/s00103-018-2745-8.

Bolte, G., Nanninga, S., Dandolo, L., 2019. Sex/gender differences in the association between residential green space and self-rated health-A sex/gender-focused systematic review. Int. J. Environ. Res. Publ. Health 16 (23). https://doi.org/10.3390/ijerph16234818.

Bowe, B., Gibson, A.K., Xie, Y., Yan, Y., Donkelaar, A.V., Martin, R.V., et al., 2021. Ambient fine particulate matter air pollution and risk of weight gain and obesity in United States veterans: an observational cohort study. Environ. Health Perspect. 129 (4), 47003 https://doi.org/10.1289/EHP7944.

Campolim, C.M., Weissmann, L., Ferreira, C.K.O., Zordao, O.P., Dornellas, A.P.S., de Castro, G., et al., 2020. Short-term exposure to air pollution (PM(2.5)) induces hypothalamic inflammation, and long-term leads to leptin resistance and obesity via Tlr4/Ikbke in mice. Sci. Rep. 10 (1), 10160 https://doi.org/10.1038/s41598-020-67040-3.

Chang, E., Varghese, M., Singer, K., 2018. Gender and sex differences in adipose tissue. Curr. Diabetes Rep. 18 (9), 69. https://doi.org/10.1007/s11892-018-1031-3.

Clougherty, J.E., 2010. A growing role for gender analysis in air pollution epidemiology. Environ. Health Perspect. 118 (2), 167–176. https://doi.org/10.1289/ehp.0900994.

Cohen, S.A., Greaney, M.L., Sabik, N.J., 2018. Assessment of dietary patterns, physical activity and obesity from a national survey: rural-urban health disparities in older adults. PLoS One 13 (12), e0208268. https://doi.org/10.1371/journal.pone.0208268.

Conzade, R., Grill, E., Bischoff-Ferrari, H.A., Ferrari, U., Horsch, A., Koenig, W., et al., 2019. Vitamin D in relation to incident sarcopenia and changes in muscle parameters among older adults: the KORA-age study. Calcif. Tissue Int. 105 (2), 173–182. https://doi.org/10.1007/s00223-019-00558-5.

Cyrys, J., Heinrich, J., Hoek, G., Meliefste, K., Lewne, M., Gehring, U., et al., 2003. Comparison between different traffic-related particle indicators: elemental carbon (EC), PM2.5 mass, and absorbance. J. Expo. Anal. Environ. Epidemiol. 13 (2), 134–143. https://doi.org/10.1038/sj.jea.7500262.

Dandolo, L., Hartig, C., Telkmann, K., Horstmann, S., Schwettmann, L., Selsam, P., et al., 2022. Decision tree analyses to explore the relevance of multiple sex/gender dimensions for the exposure to green spaces: results from the KORA INGER study. Int. J. Environ. Res. Publ. Health 19 (12). https://doi.org/10.3390/ijerph19127476.

De la Fuente, F., Saldias, M.A., Cubillos, C., Mery, G., Carvajal, D., Bowen, M., et al., 2020. Green space exposure association with type 2 diabetes mellitus, physical activity, and obesity: a systematic review. Int. J. Environ. Res. Publ. Health 18 (1). https://doi.org/10.3390/ijerph18010097.

Dempsey, S., Lyons, S., Nolan, A., 2018. Urban green space and obesity in older adults: evidence from Ireland. SSM Popul Health 4, 206–215. https://doi.org/10.1016/j.ssmph.2018.01.002.

Derose, K.P., Han, B., Williamson, S., Cohen, D.A., 2018. Gender disparities in park use and physical activity among residents of high-poverty neighborhoods in los angeles. Wom. Health Issues 28 (1), 6–13. https://doi.org/10.1016/j.whi.2017.11.003.

Diseases, G.B.D., Injuries, C., 2020. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 396 (10258), 1204–1222. https://doi.org/10.1016/S0140-6736(20)30925-9.

European Union, 2018. Methodological Manual on Territorial Typologies. Luxembourg. Last access: 19.04.2023.Available from: https://ec.europa.eu/eurostat/web/products-manuals-and-guidelines/-/ks-gq-18-008.

Evenson, K.R., Williamson, S., Han, B., McKenzie, T.L., Cohen, D.A., 2019. United States' neighborhood park use and physical activity over two years: the National Study of Neighborhood Parks. Prev. Med. 123, 117–122. https://doi.org/10.1016/j.ypmed.2019.03.027.

Eze, I.C., Foraster, M., Schaffner, E., Vienneau, D., Heritier, H., Rudzik, F., et al., 2017. Long-term exposure to transportation noise and air pollution in relation to incident diabetes in the SAPALDIA study. Int. J. Epidemiol. 46 (4), 1115–1125. https://doi.org/10.1093/ije/dyx020.

Fong, K.C., Hart, J.E., James, P., 2018. A review of epidemiologic studies on greenness and health: updated literature through 2017. Curr Environ Health Rep 5 (1), 77–87. https://doi.org/10.1007/s40572-018-0179-y.

Furlong, M.A., Klimentidis, Y.C., 2020. Associations of air pollution with obesity and body fat percentage, and modification by polygenic risk score for BMI in the UK Biobank. Environ. Res. 185, 109364 https://doi.org/10.1016/j.envres.2020.109364.

Gui, S.Y., Wu, K.J., Sun, Y., Chen, Y.N., Liang, H.R., Liu, W., et al., 2022. Traffic noise and adiposity: a systematic review and meta-analysis of epidemiological studies. Environ. Sci. Pollut. Res. Int. https://doi.org/10.1007/s11356-022-19056-7.

He, D., Wu, S., Zhao, H., Qiu, H., Fu, Y., Li, X., et al., 2017. Association between particulate matter 2.5 and diabetes mellitus: a meta-analysis of cohort studies. J Diabetes Investig. 8 (5), 687–696. https://doi.org/10.1111/jdi.12631.

Holle, R., Happich, M., Lowel, H., Wichmann, H.E., Group, M.K.S., 2005. KORA–a research platform for population based health research. Gesundheitswesen 67 (Suppl. 1), S19–S25. https://doi.org/10.1055/s-2005-858235.

Hwang, S.E., Kwon, H., Jeong, S.M., Kim, H.J., Park, J.H., 2019. Ambient air pollution exposure and obesity-related traits in Korean adults. Diabetes Metab Syndr Obes 12, 1365–1377. https://doi.org/10.2147/DMSO.S208115.

IDF (International Diabetes Federation), 2021. IDF diabetes atlas. Last access: 19.04.2023.Available from: https://diabetesatlas.org/atlas/tenth-edition/.

Kabisch, N., Selsam, P., Kirsten, T., Lausch, A., Bumberger, J., 2019. A multi-sensor and multi-temporal remote sensing approach to detect land cover change dynamics in heterogeneous urban landscapes. Ecol. Indicat. 99, 273–282. https://doi.org/10.1016/j.ecolind.2018.12.033.

Kautzky-Willer, A., Leutner, M., Harreiter, J., 2023. Sex differences in type 2 diabetes. Diabetologia 66 (6), 986–1002. https://doi.org/10.1007/s00125-023-05891-x.

Kivimaki, M., Strandberg, T., Pentti, J., Nyberg, S.T., Frank, P., Jokela, M., et al., 2022. Body-mass index and risk of obesity-related complex multimorbidity: an observational multicohort study. Lancet Diabetes Endocrinol. 10 (4), 253–263. https://doi.org/10.1016/S2213-8587(22)00033-X.

Lapham, S.C., Cohen, D.A., Williamson, S., Han, B., Evenson, K.R., McKenzie, T.L., et al., 2016. How important is perception of safety to park use? A four-city survey. Urban Stud. 53 (12), 2624–2636. https://doi.org/10.1177/0042098015592822.

Li, M., Qian, Z., Vaughn, M., Boutwell, B., Ward, P., Lu, T., et al., 2015. Sex-specific difference of the association between ambient air pollution and the prevalence of obesity in Chinese adults from a high pollution range area: 33 Communities Chinese Health Study. Atmos. Environ. 117, 227–233. https://doi.org/10.1016/j.atmosenv.2015.07.029.

Liu, M., Tang, W., Zhang, Y., Wang, Y., Baima, K., Li, Y., et al., 2021. Urban-rural differences in the association between long-term exposure to ambient air pollution and obesity in China. Environ. Res. 201, 111597 https://doi.org/10.1016/j.envres.2021.111597.

Markevych, I., Thiering, E., Fuertes, E., Sugiri, D., Berdel, D., Koletzko, S., et al., 2014. A cross-sectional analysis of the effects of residential greenness on blood pressure in 10-year old children: results from the GINIplus and LISAplus studies. BMC Publ. Health 14, 477. https://doi.org/10.1186/1471-2458-14-477.

Marlatt, K.L., Ravussin, E., 2017. Brown adipose tissue: an update on recent findings. Curr Obes Rep 6 (4), 389–396. https://doi.org/10.1007/s13679-017-0283-6.

NCD Risk Factor Collaboration, 2019. Rising rural body-mass index is the main driver of the global obesity epidemic in adults. Nature 569 (7755), 260–264. https://doi.org/10.1038/s41586-019-1171-x.

Nemitz, E., Vieno, M., Carnell, E., Fitch, A., Steadman, C., Cryle, P., et al., 2020. Potential and limitation of air pollution mitigation by vegetation and uncertainties of deposition-based evaluations. Philos Trans A Math Phys Eng Sci 378 (2183), 20190320. https://doi.org/10.1098/rsta.2019.0320.

Nikolaou, N., Dallavalle, M., Stafoggia, M., Bouwer, L.M., Peters, A., Chen, K., et al., 2023. High-resolution spatiotemporal modeling of daily near-surface air temperature in Germany over the period 2000-2020. Environ. Res. 219, 115062 https://doi.org/10.1016/j.envres.2022.115062.

OECD, 2015. Eurostat, Statistics UIf. ISCED 2011 Operational Manual.

Pearce, N., Lawlor, D.A., 2016. Causal inference-so much more than statistics. Int. J. Epidemiol. 45 (6), 1895–1903. https://doi.org/10.1093/ije/dyw328.

Persson, A., Pyko, A., Lind, T., Bellander, T., Ostenson, C.G., Pershagen, G., et al., 2018. Urban residential greenness and adiposity: a cohort study in Stockholm County. Environ. Int. 121 (Pt 1), 832–841. https://doi.org/10.1016/j.envint.2018.10.009.

R Core Team, 2021. A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. Available from: https://www.r-project.org/.

Rajagopalan, S., Brook, R.D., 2012. Air pollution and type 2 diabetes. Diabetes 61 (12), 3037–3045. https://doi.org/10.2337/db12-0190.
Rooney, J.P., Rakete, S., Heier, M., Linkohr, B., Schwettmann, L., Peters, A., 2022. Blood lead levels in 2018/2019 compared to 1987/1988 in the German population-based KORA study. Environ. Res. 215 (Pt 1), 114184 https://doi.org/10.1016/j.envres.2022.114184.
Rospleszcz, S., Lorbeer, R., Storz, C., Schlett, C.L., Meisinger, C., Thorand, B., et al., 2019. Association of longitudinal risk profile trajectory clusters with adipose tissue depots measured by magnetic resonance imaging. Sci. Rep. 9 (1), 16972 https://doi.org/10.1038/s41598-019-53546-y.
Schienkiewitz, A., Kuhnert, R., Blume, M., Mensink, G.B.M., 2022. Overweight and obesity among adults in Germany - results from GEDA 2019/2020-EHIS. J Health Monit 7 (3), 21–28. https://doi.org/10.25646/10293.
Schlesinger, S., Neuenschwander, M., Schwedhelm, C., Hoffmann, G., Bechthold, A., Boeing, H., et al., 2019. Food groups and risk of overweight, obesity, and weight gain: a systematic review and dose-response meta-analysis of prospective studies. Adv. Nutr. 10 (2), 205–218. https://doi.org/10.1093/advances/nmy092.
Smith, G., Cirach, M., Swart, W., Dedele, A., Gidlow, C., van Kempen, E., et al., 2017. Characterisation of the natural environment: quantitative indicators across Europe. Int. J. Health Geogr. 16 (1), 16. https://doi.org/10.1186/s12942-017-0090-z.
Sorensen, M., Poulsen, A.H., Hvidtfeldt, U.A., Brandt, J., Frohn, L.M., Ketzel, M., et al., 2022. Air pollution, road traffic noise and lack of greenness and risk of type 2 diabetes: a multi-exposure prospective study covering Denmark. Environ. Int. 170, 107570 https://doi.org/10.1016/j.envint.2022.107570.
Sowers, M., Zheng, H., Tomey, K., Karvonen-Gutierrez, C., Jannausch, M., Li, X., et al., 2007. Changes in body composition in women over six years at midlife: ovarian and chronological aging. J. Clin. Endocrinol. Metab. 92 (3), 895–901. https://doi.org/10.1210/jc.2006-1393.
Speakman, J.R., Heidari-Bakavoli, S., 2016. Type 2 diabetes, but not obesity, prevalence is positively associated with ambient temperature. Sci. Rep. 6, 30409 https://doi.org/10.1038/srep30409.
Trivedi, T., Liu, J., Probst, J.C., Merchant, A., Jhones, S., Block Martin, A., 2015. Obesity and obesity-related behaviors among rural and urban adults in the USA. Rural Rem. Health 15 (4), 3267. https://doi.org/10.22605/RRH3267.
Valdes, S., Maldonado-Araque, C., Garcia-Torres, F., Goday, A., Bosch-Comas, A., Bordiu, E., et al., 2014. Ambient temperature and prevalence of obesity in the Spanish population: the Di @ bet.es study. Obesity 22 (11), 2328–2332. https://doi.org/10.1002/oby.20866.
Valdes, S., Doulatram-Gamgaram, V., Lago, A., Garcia Torres, F., Badia-Guillen, R., Olveira, G., et al., 2019. Ambient temperature and prevalence of diabetes and insulin resistance in the Spanish population: di@ bet.es study. Eur. J. Endocrinol. 180 (5), 273–280. https://doi.org/10.1530/EJE-18-0818.
van den Bosch, M., Bartolomeu, M.L., Williams, S., Basnou, C., Hamilton, I., Nieuwenhuijsen, M., et al., 2024. A scoping review of human health co-benefits of forest-based climate change mitigation in Europe. Environ. Int. https://doi.org/10.1016/j.envint.2024.108593.
Wang, F., Wen, M., Xu, Y., 2013. Population-adjusted street connectivity, urbanicity and risk of obesity in the U.S. Appl. Geogr. 41, 1–14. https://doi.org/10.1016/j.apgeog.2013.03.006.
Wang, B., Xu, D., Jing, Z., Liu, D., Yan, S., Wang, Y., 2014. Effect of long-term exposure to air pollution on type 2 diabetes mellitus risk: a systemic review and meta-analysis of cohort studies. Eur. J. Endocrinol. 171 (5), R173–R182. https://doi.org/10.1530/EJE-14-0365.
Wawro, N., Pestoni, G., Riedl, A., Breuninger, T.A., Peters, A., Rathmann, W., et al., 2020. Association of dietary patterns and type-2 diabetes mellitus in metabolically homogeneous subgroups in the KORA FF4 study. Nutrients 12 (6). https://doi.org/10.3390/nu12061684.
Weinmayr, G., Hennig, F., Fuks, K., Nonnemacher, M., Jakobs, H., Mohlenkamp, S., et al., 2015. Long-term exposure to fine particulate matter and incidence of type 2 diabetes mellitus in a cohort study: effects of total and traffic-specific air pollution. Environ. Health 14, 53. https://doi.org/10.1186/s12940-015-0031-x.
WiGeoGIS. Gesellschaft für digitale Wirtschaftsgeographie mbH. [Available from: https://www.wigeogis.com/de/impressum].
WHO, 2008. Waist Circumference and Waist–Hip Ratio: Report of a WHO Expert Consultation Geneva. WHO, 8–11 December 2008 Geneva. http://apps.who.int/iris/bitstream/handle/10665/44583/9789241501491_eng.pdf?sequence=1.
WHO, 2022. WHO European Regional Obesity Report 2022. Regional Office for Europe. Last access: 19.04.2023.Available from: https://apps.who.int/iris/bitstream/handle/10665/353747/9789289057738-eng.pdf.
Wolf, K., Cyrys, J., Harcinikova, T., Gu, J., Kusch, T., Hampel, R., et al., 2017. Land use regression modeling of ultrafine particles, ozone, nitrogen oxides and markers of particulate matter pollution in Augsburg, Germany. Sci. Total Environ. 579, 1531–1540. https://doi.org/10.1016/j.scitotenv.2016.11.160.
Yang, H.K., Han, K., Cho, J.H., Yoon, K.H., Cha, B.Y., Lee, S.H., 2015. Ambient temperature and prevalence of obesity: a nationwide population-based study in korea. PLoS One 10 (11), e0141724. https://doi.org/10.1371/journal.pone.0141724.
Yang, B.Y., Fan, S., Thiering, E., Seissler, J., Nowak, D., Dong, G.H., et al., 2020. Ambient air pollution and diabetes: a systematic review and meta-analysis. Environ. Res. 180, 108817 https://doi.org/10.1016/j.envres.2019.108817.

Supplementary Material to

Sex-specific associations of environmental exposures with prevalent diabetes and obesity – results from the KORA Fit study

Fiona Niedermayer[1,2]*, Kathrin Wolf[2], Siqi Zhang[2,8], Marco Dallavalle[1,2], Nikolaos Nikolaou[2], Lars Schwettmann[3,4], Peter Selsam[5], Barbara Hoffmann[6], Alexandra Schneider[2], Annette Peters[1,2,7]

[1] Chair of Epidemiology, IBE, Faculty of Medicine, LMU Munich, Munich, Germany

[2] Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany

[3] Institute of Health Economics and Health Care Management, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany

[4] Department of Health Services Research, School of Medicine and Health Sciences, Carl von Ossietzky Universität Oldenburg, Oldenburg, Germany

[5] Department Monitoring and Exploration Technologies, Helmholtz Centre for Environmental Research GmbH—UFZ, Leipzig, Germany

[6] Institute of Occupational, Social and Environmental Medicine, Centre for Health and Society, Medical Faculty, Heinrich-Heine University Düsseldorf, Düsseldorf, Germany

[7] German Center for Diabetes Research (DZD), München-Neuherberg, Neuherberg, Germany

[8] Department of Environmental Health Sciences, Yale School of Public Health, New Haven, United States

*Corresponding author:

Fiona Niedermayer,

Chair of Epidemiology, IBE, Faculty of Medicine, LMU Munich, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany

Email: fiona.niedermayer@helmholtz-munich.de

Phone: +49 (0)89-3187-49519

ORCID: 0000-0002-6798-2630

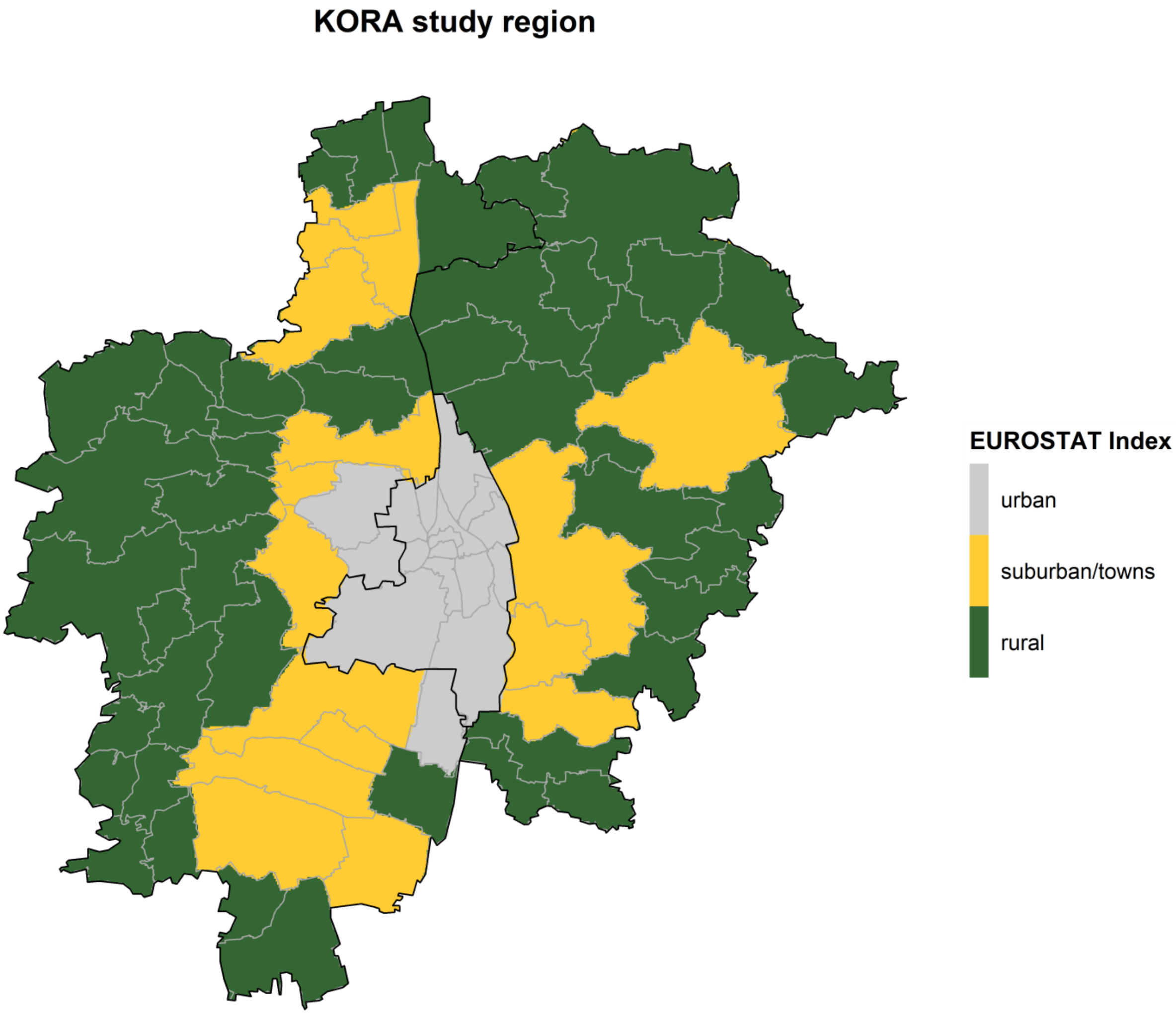


Figure S1. KORA study area with the respective local administrative units (grey lines) and their degree of urbanization based on EUROSTAT. Black borders indicate counties of the study area (*Augsburg Land (left), Augsburg Stadt (center) and Aichach-Friedberg (right)*).

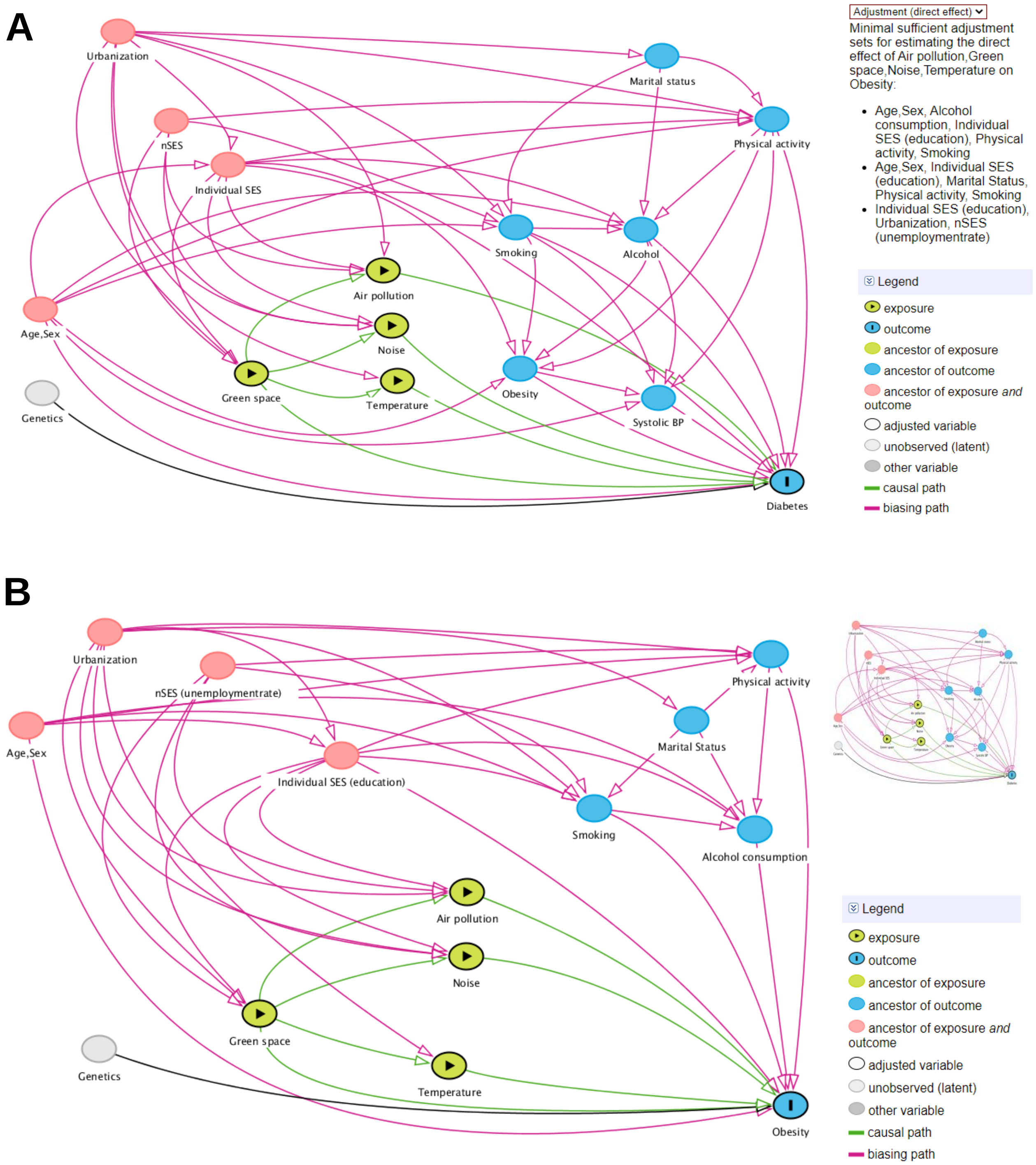


Figure S2. Directed acyclic graphs identifying potential confounders for diabetes (A) and obesity (B).

3

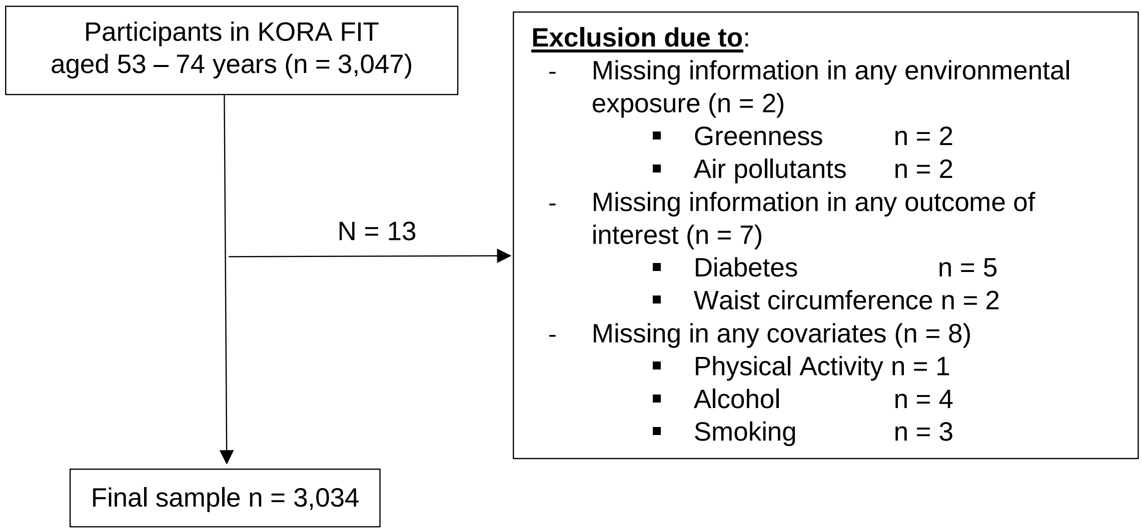


Figure S3. Flowchart of study participant

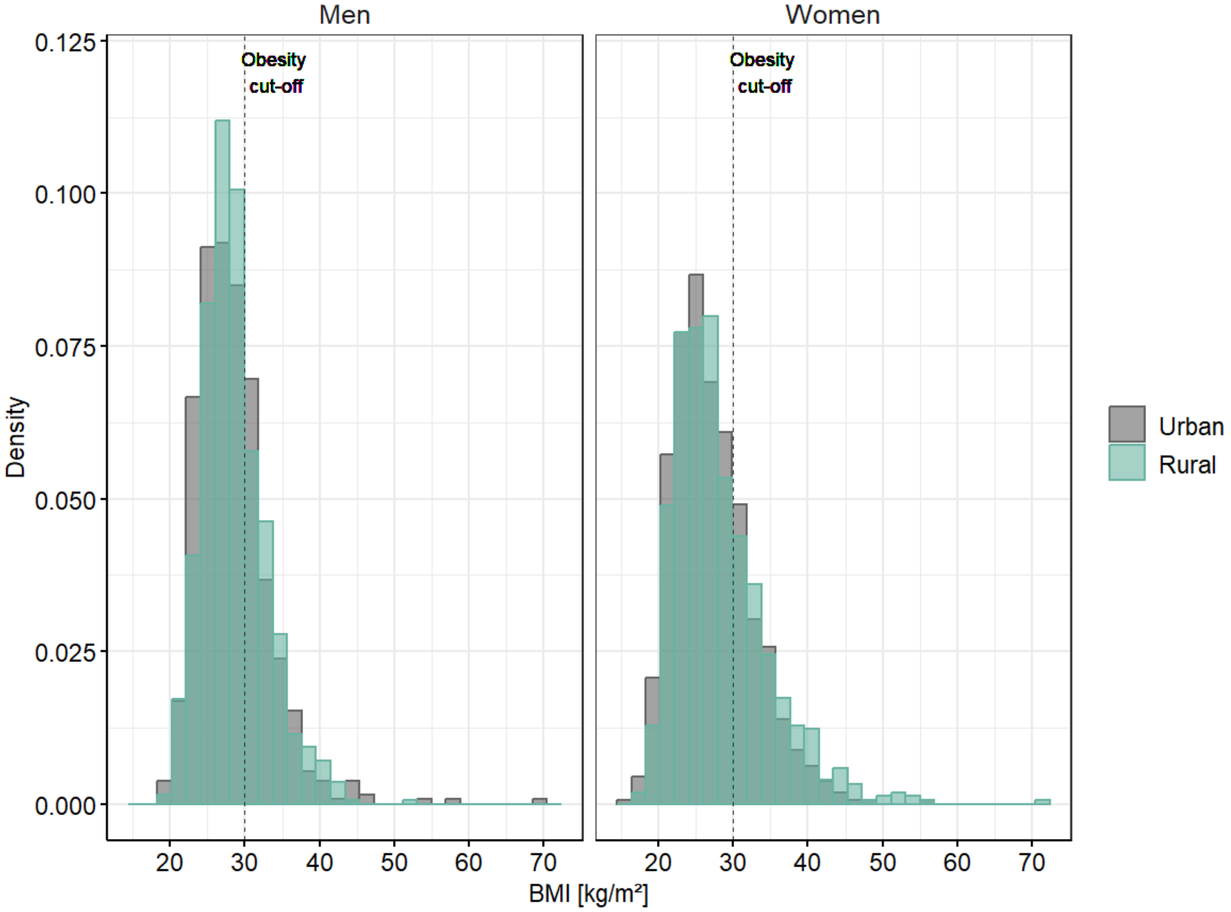


Figure S4. Histogram of BMI stratified by sex and urbanization.

5

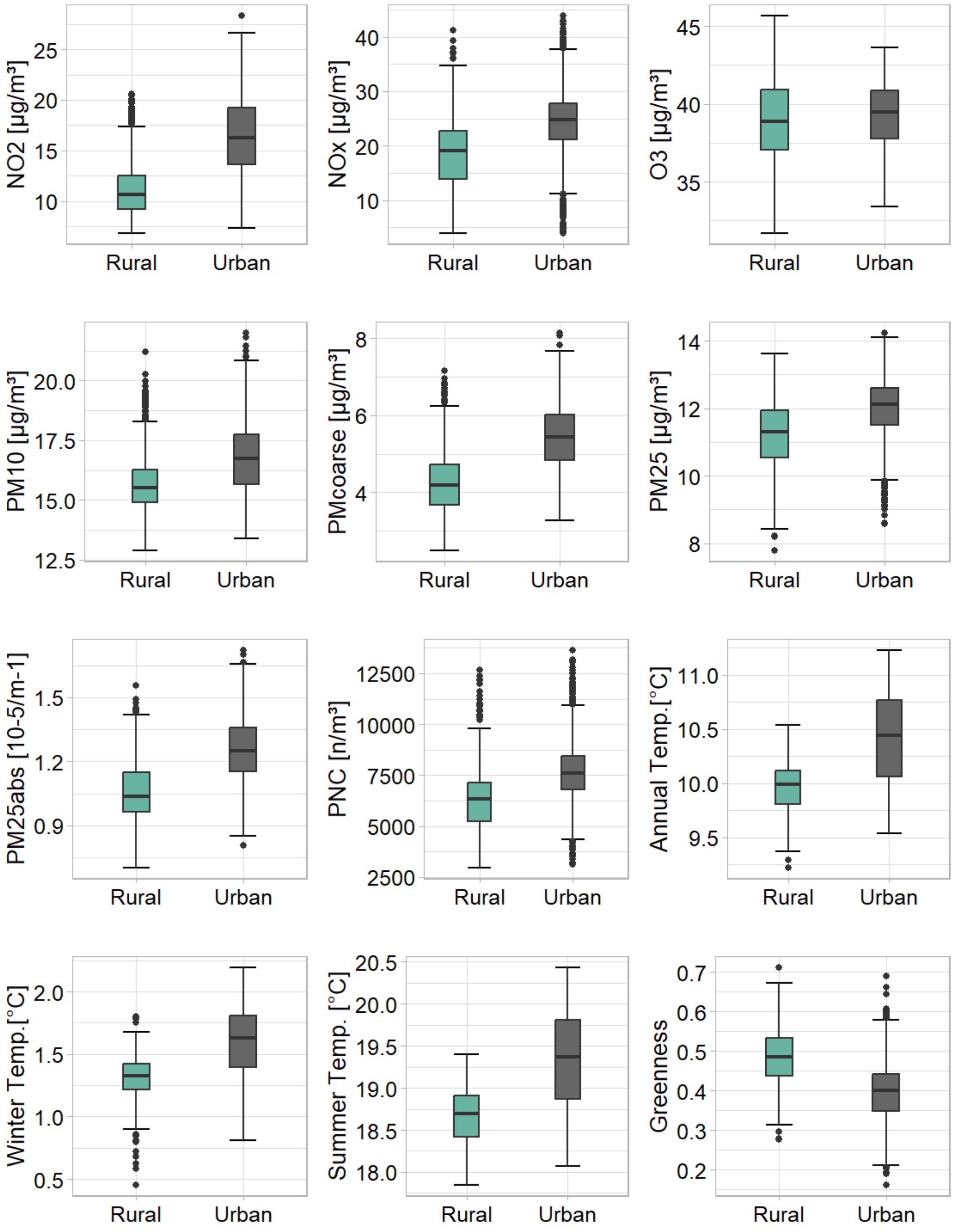


Figure S5. Distribution of environmental exposures by urbanization.

6

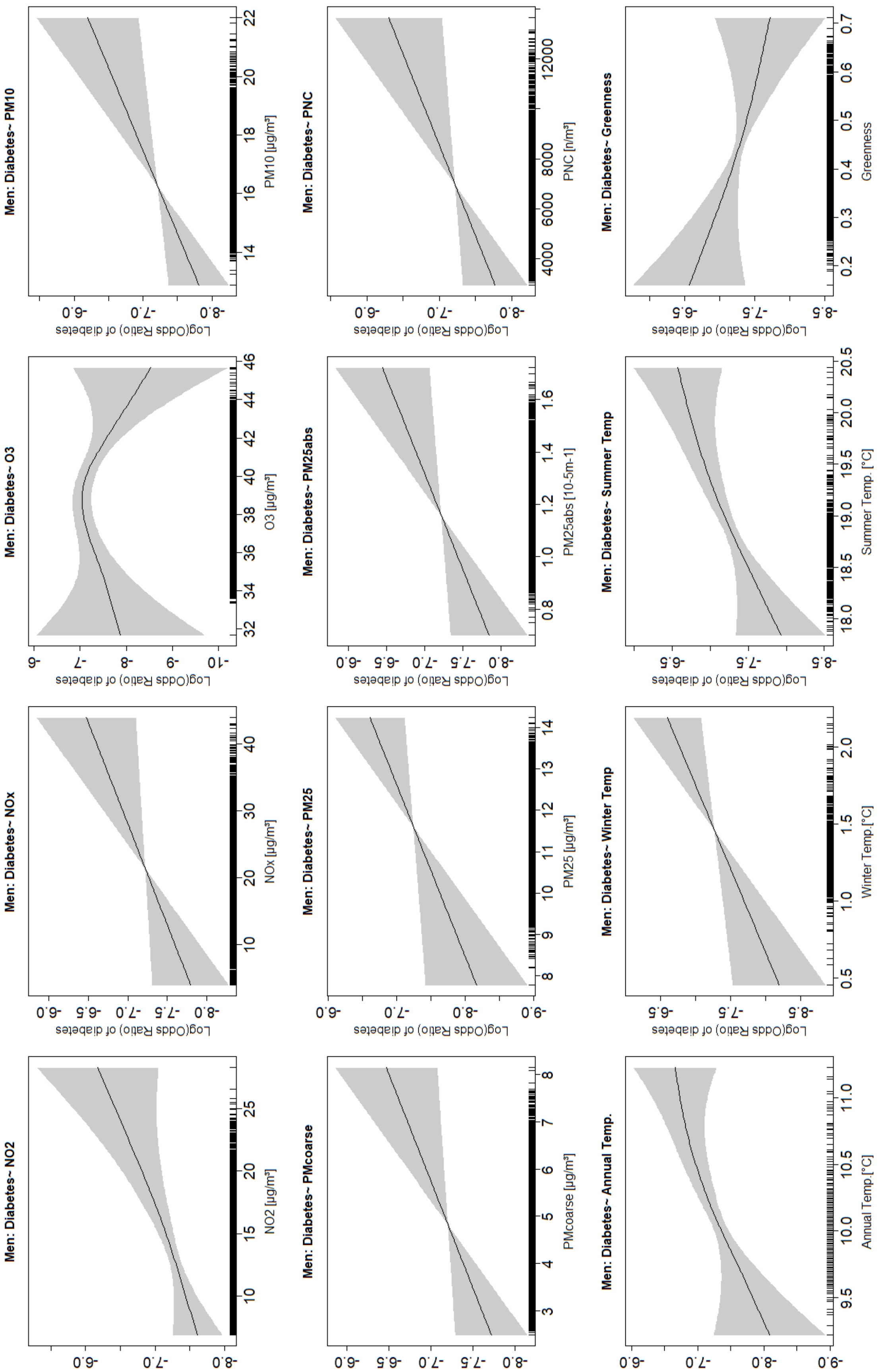


Figure S6. Exposure-response functions for diabetes in men using generalized additive models adjusted for main confounders.

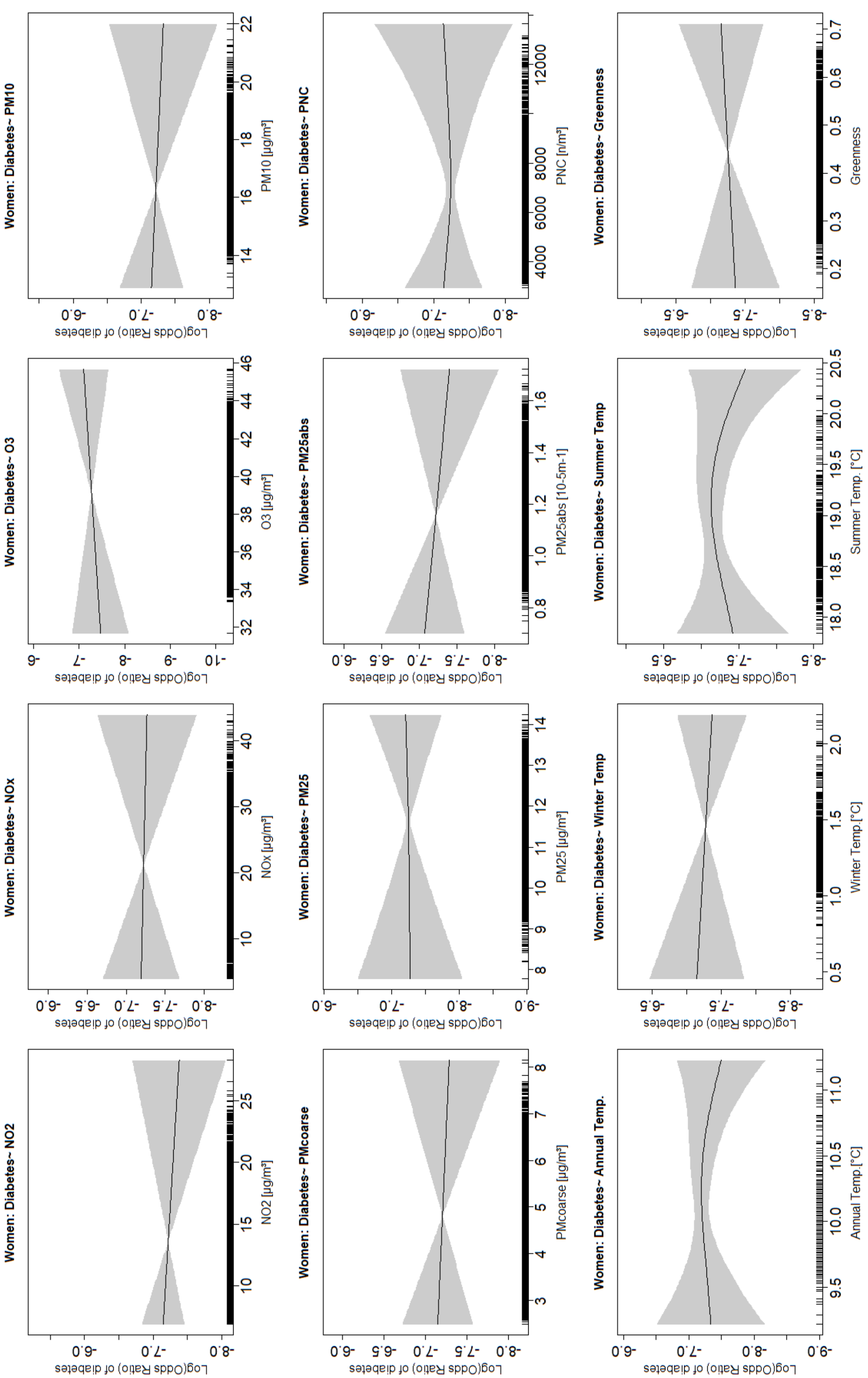


Figure S7. Exposure-response functions for diabetes in women using generalized additive models adjusted for main confounders.

8

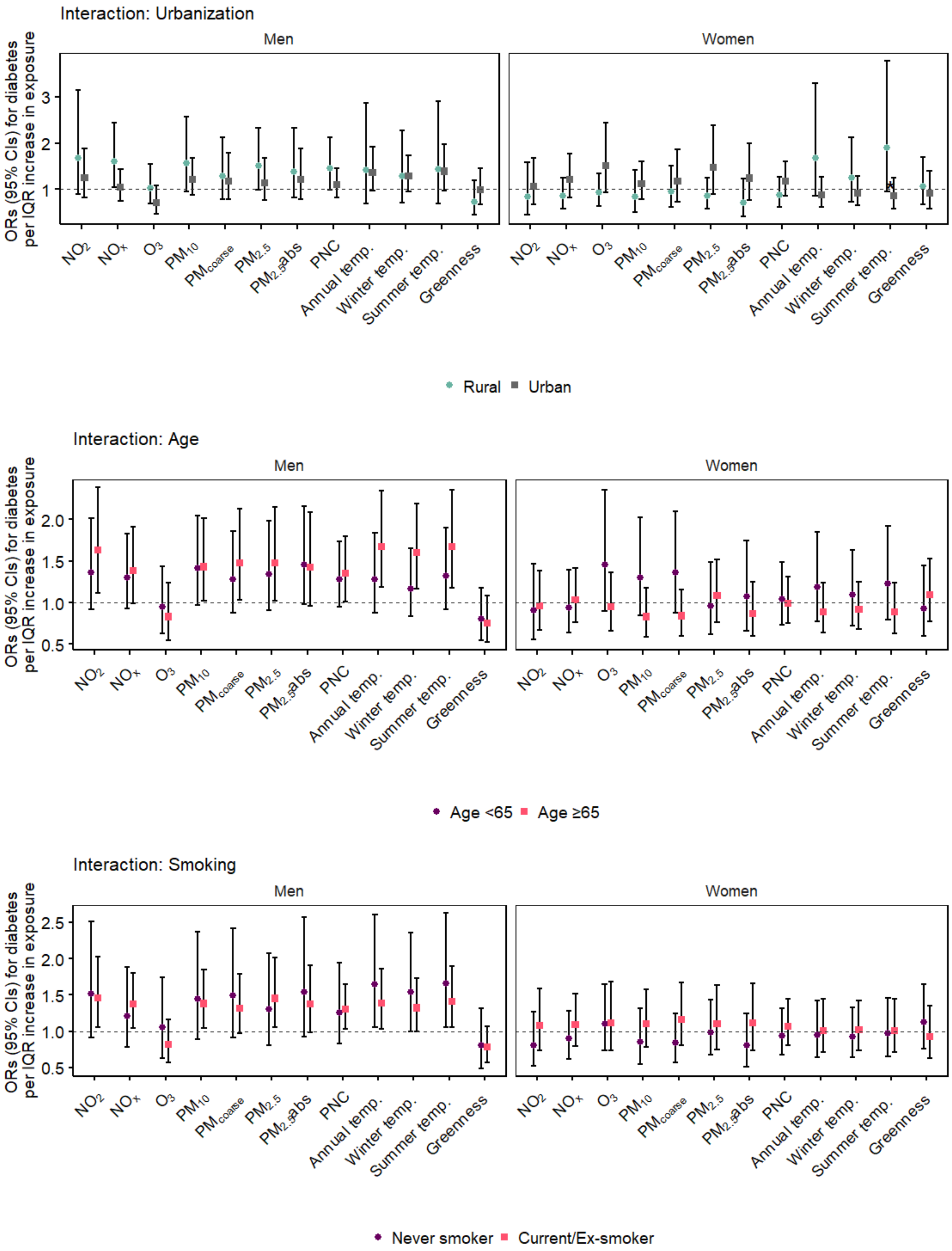


Figure S8. Additional effect modification for diabetes

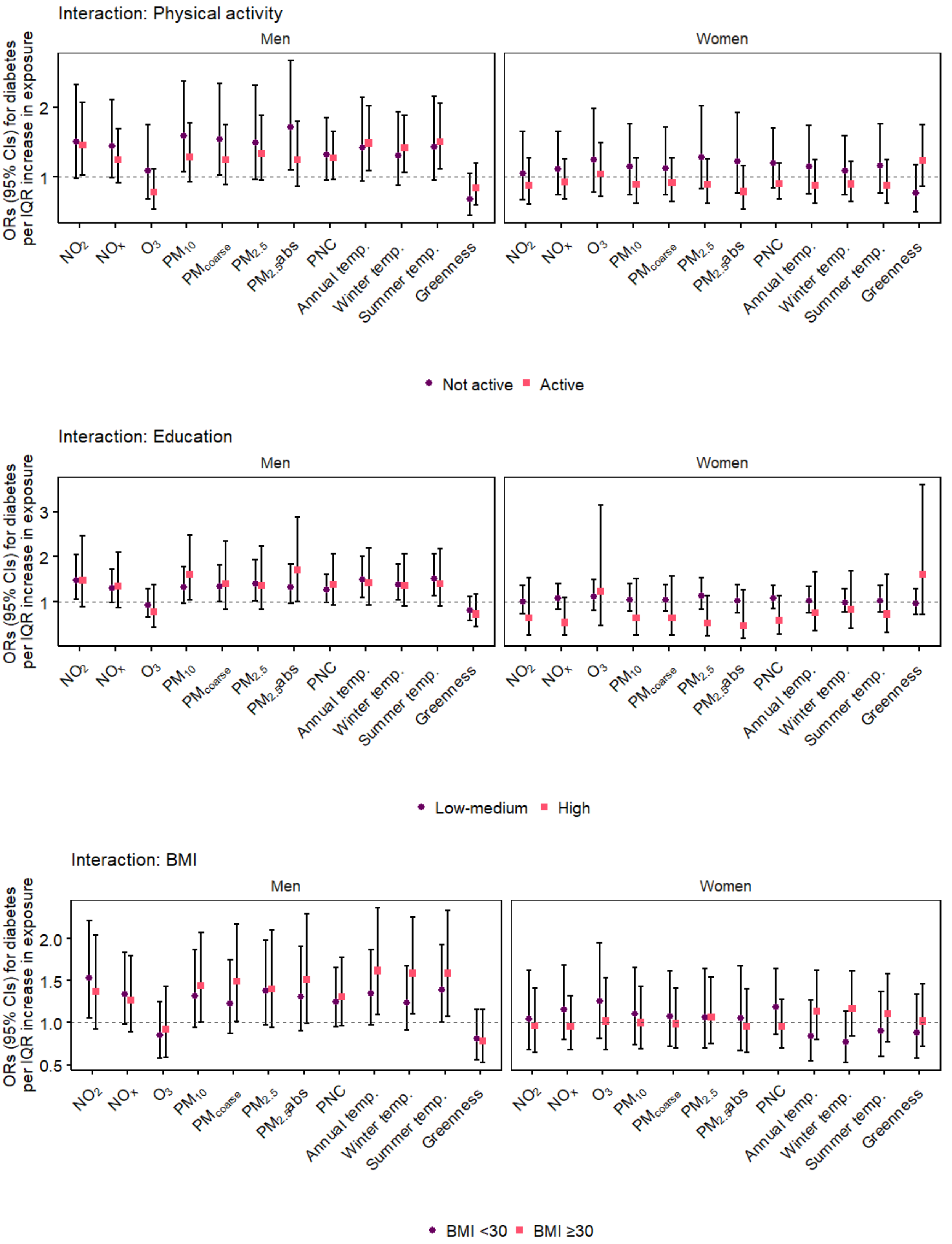


Figure S8. *Continued*

10

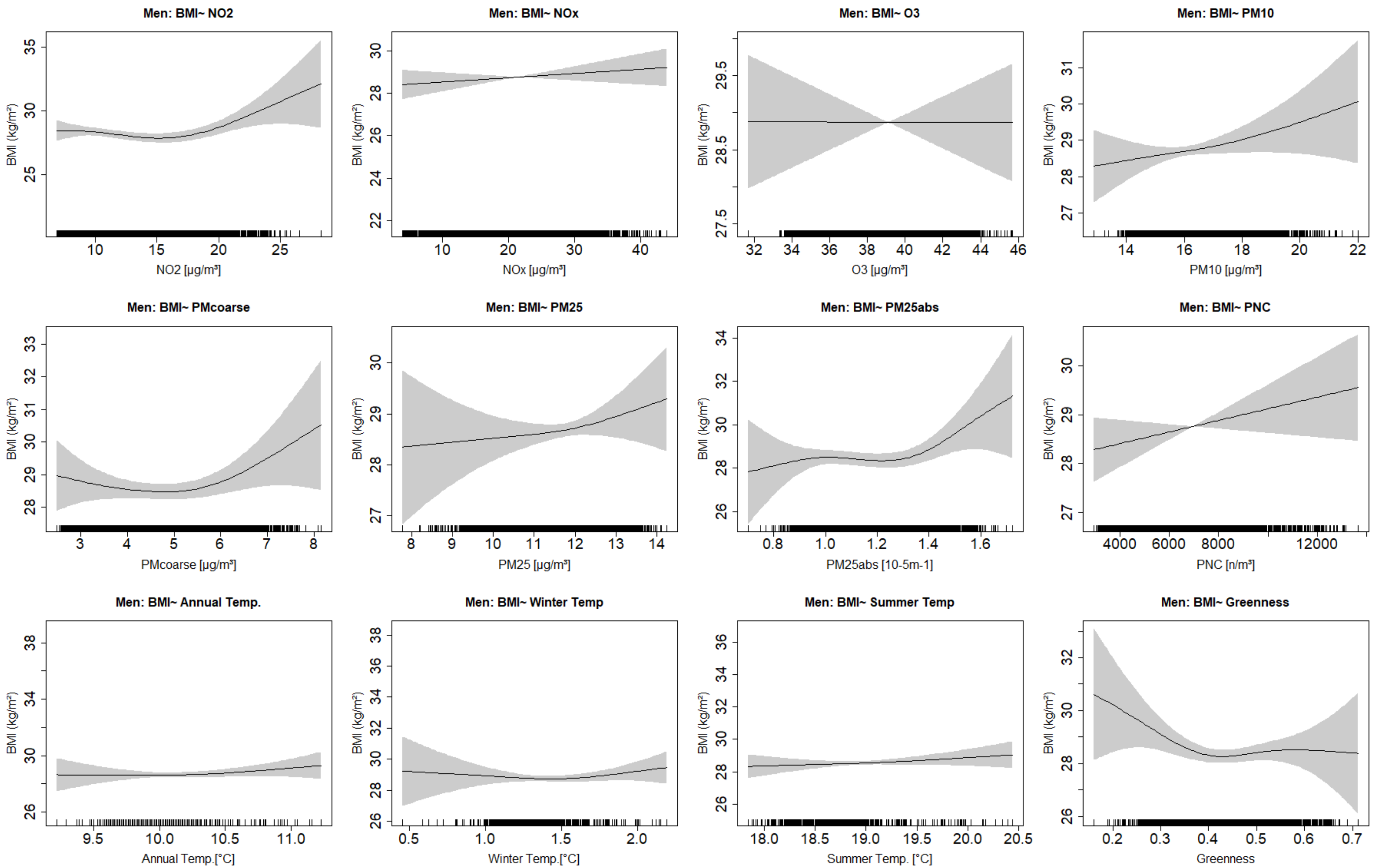


Figure S9. Exposure-response functions between exposures and BMI in men using generalized additive models adjusted for main confounders.

11

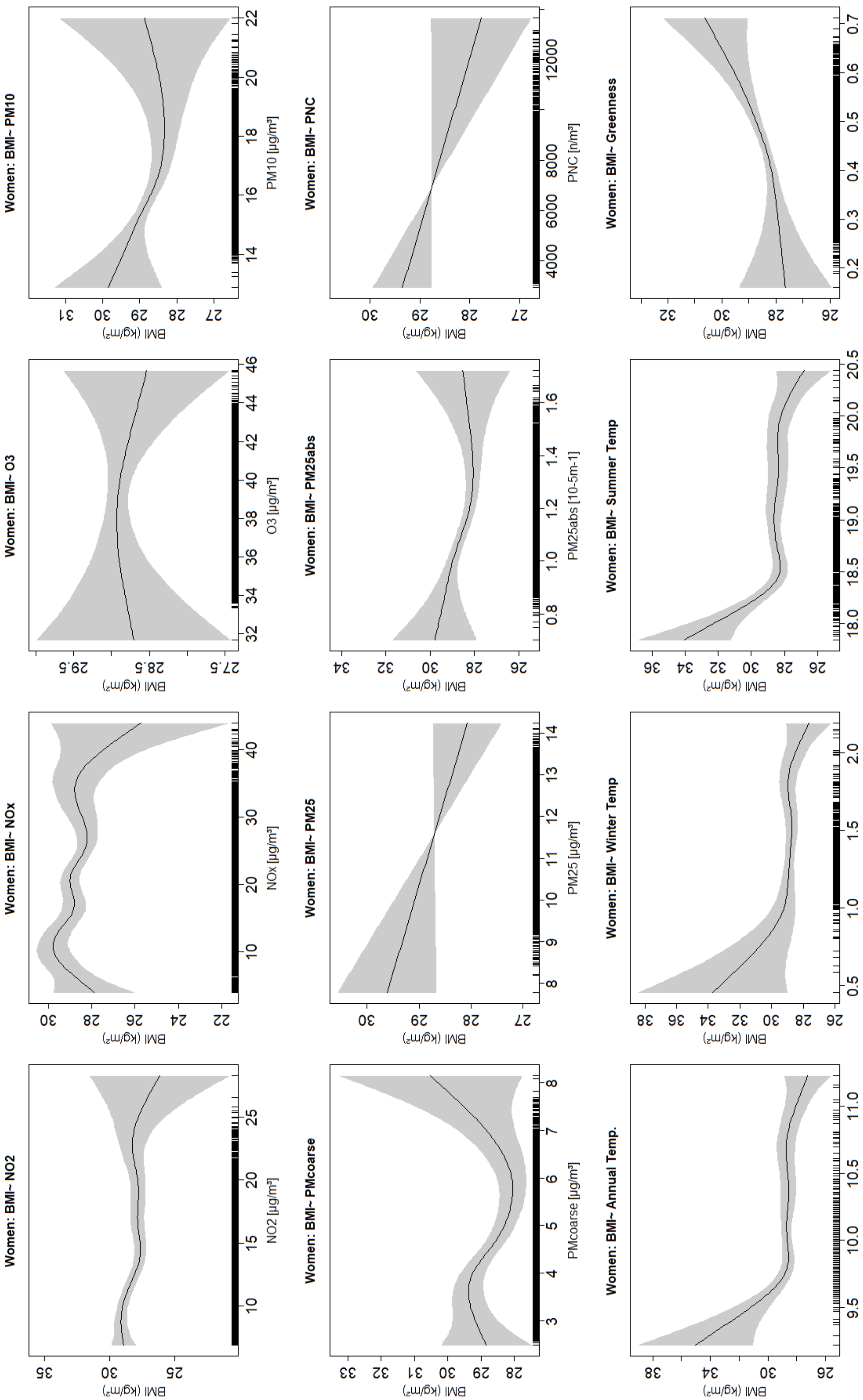


Figure S10. Exposure-response functions between exposures and BMI in women using generalized additive models adjusted for main confounders.

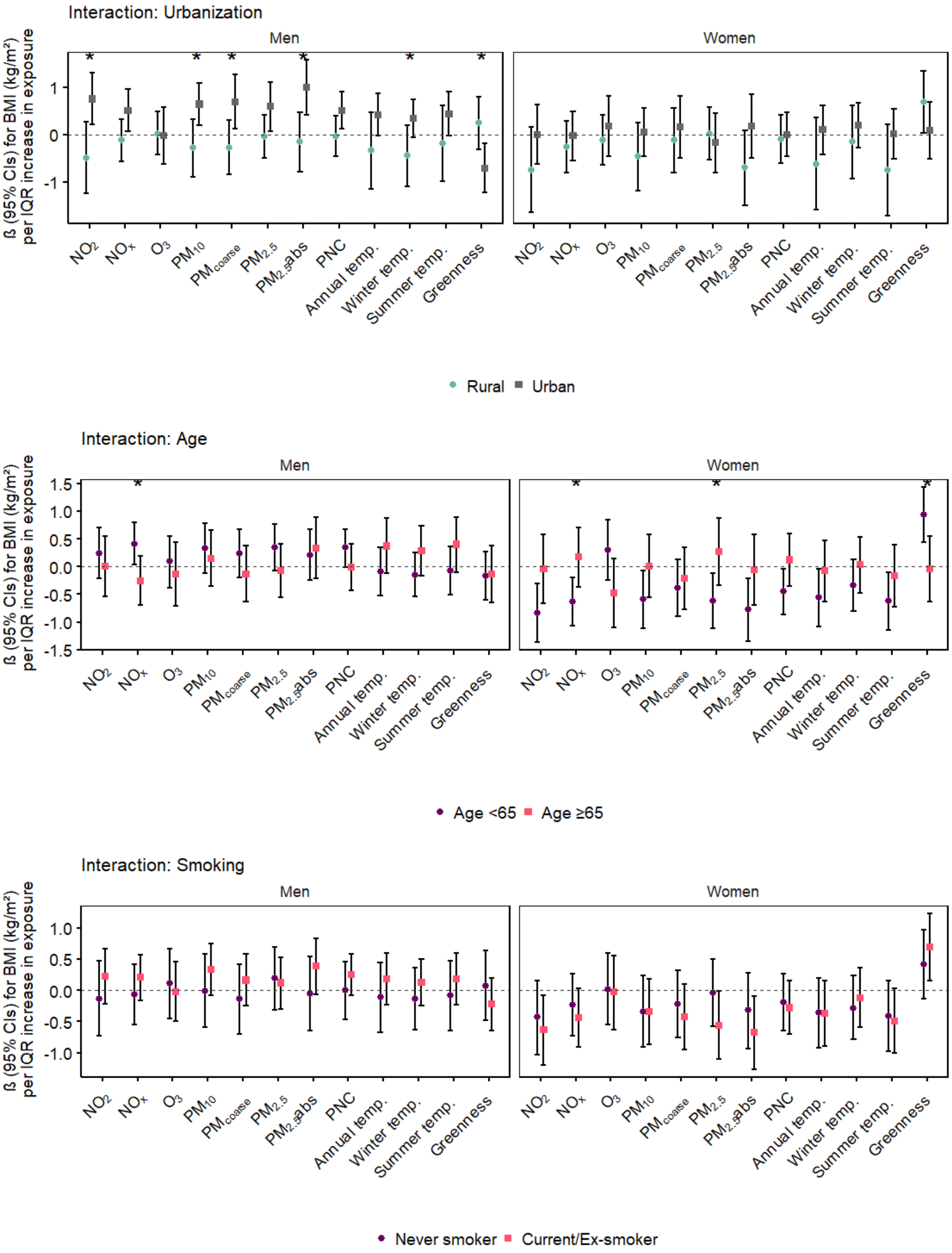
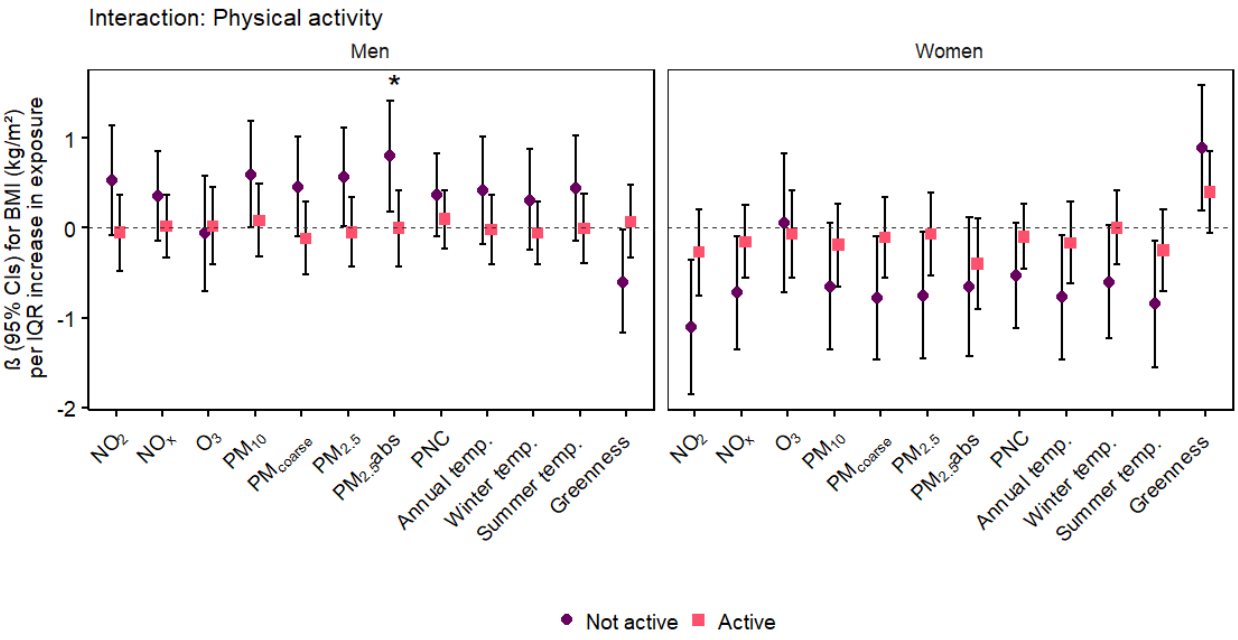


Figure S11. Additional effect modification for outcome BMI.



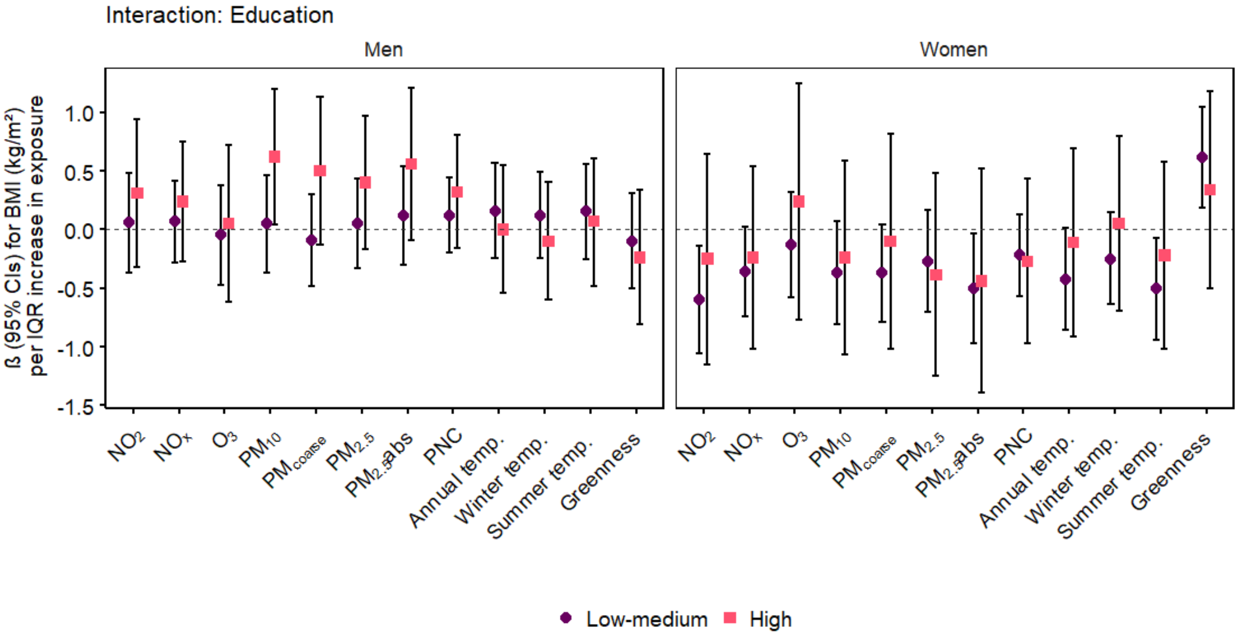


Figure S11. *Continued*

14

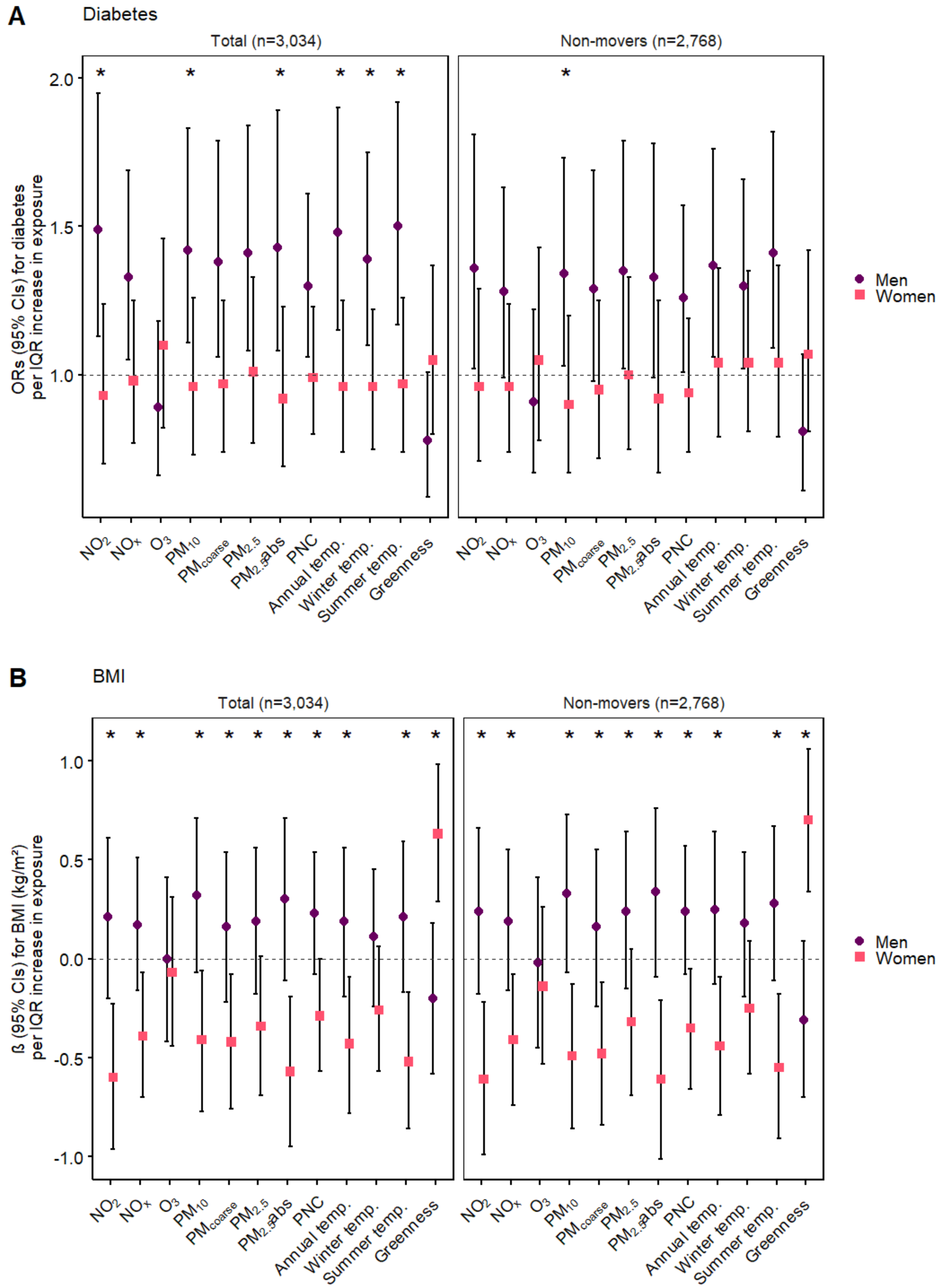
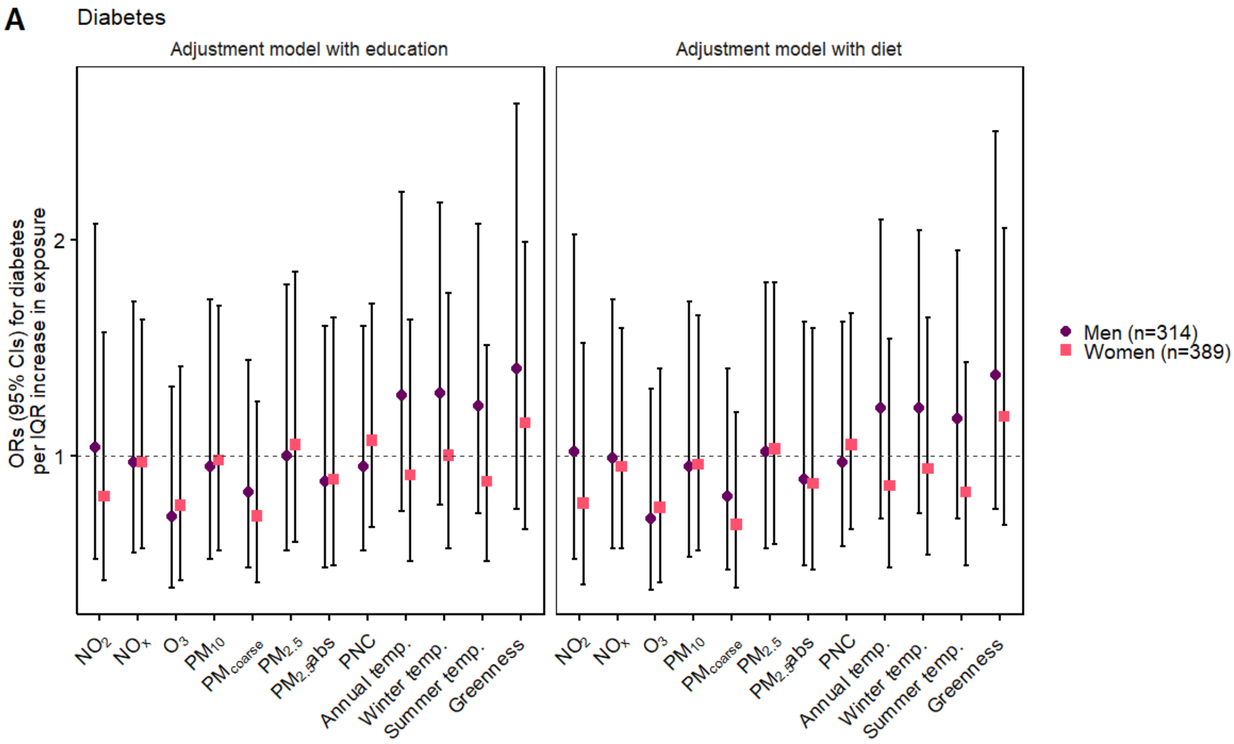


Figure S12. Comparison between total study population and non-movers (excluding movers within the last 10 years).

15



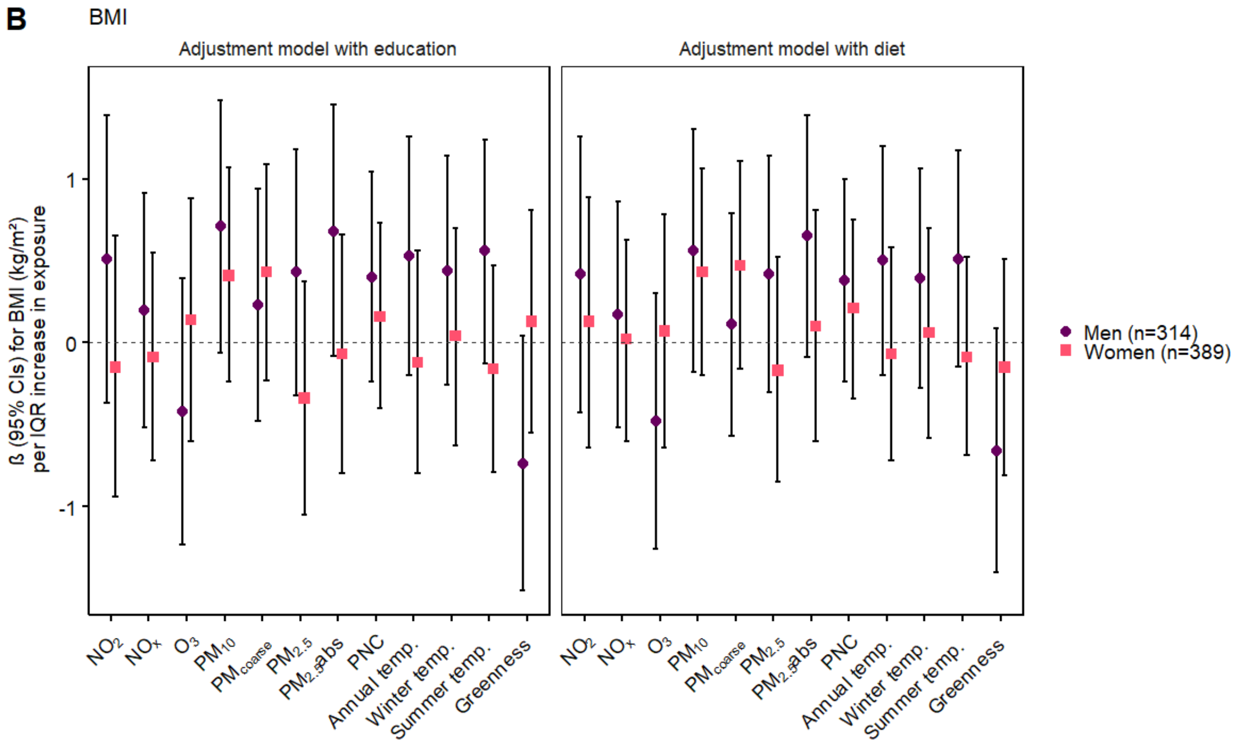


Figure S13. Comparison between two different adjustment models in a subsample (n=702). Adjustment model with education was adjusted with the same model as in the final sample (age, alcohol, physical activity, smoking and education). In the subsample, the “alternative healthy eating index” was used instead of education.

Table S1. Participants' characteristics stratified by sex and degree of urbanization.

	Men			Women		
	Urban (n = 677)	**Rural (n = 727)**	**p value**	**Urban (n = 825)**	**Rural (n = 805)**	**p value**
Age [years]	63.4 ± 5.4	62.6 ± 5.7	0.004	63.8 ± 5.4	63.0 ± 5.5	0.007
Lifestyle factors						
Alcohol [g/day]	22.5 ± 24.1	22.7 ± 22.6	0.067	9.3 ± 13.2	7.6 ± 11.3	0.021
Smoking status			0.010			<0.001
Never	233 (34.4%)	305 (41.9%)		357 (43.3%)	448 (55.6%)	
Ex-smoker	338 (49.9%)	332 (45.7%)		329 (39.9%)	259 (32.2%)	
Current Smoker	106 (15.7%)	90 (12.4%)		139 (16.8%)	98 (12.2%)	
Physically active	486 (71.8%)	491 (67.5%)	0.095	606 (73.5%)	599 (74.4%)	0.702
Individual SES						
Education			<0.001			<0.001
low	7 (1.0%)	12 (1.7%)		25 (3.0%)	49 (6.1%)	
medium	433 (64.0%)	531 (73.0%)		594 (72.0%)	642 (79.7%)	
high	237 (35.0%)	184 (25.3%)		206 (25.0%)	114 (14.2%)	
Neighborhood SES						
Household with low income [%]	39.0 ± 17.9	10.7 ± 8.6	<0.001	39.7 ± 18.3	10.9 ± 8.8	<0.001
Marital status						
Married	545 (80.5%)	649 (89.3%)	<0.001	529 (64.1%)	646 (80.2%)	<0.001
Outcome						
Diabetes mellitus	76 (11.2%)	52 (7.2%)	0.011	57 (6.9%)	59 (7.3%)	0.815
Obesity						
defined by BMI	208 (30.7%)	227 (31.2%)	0.885	221 (26.8%)	253 (31.4%)	0.045
defined by waist circumference	457 (67.5%)	515 (70.8%)	0.195	585 (70.9%)	584 (72.5%)	0.497
BMI [kg/m²]	28.5 ± 4.9	28.7 ± 4.3	0.074	27.3 ± 5.9	28.3 ± 6.3	0.006
Waist circumference [cm]	100.6 ± 12.8	100.7 ± 7.6	0.528	88.4 ± 13.0	90.2 ± 14.5	0.038

Legend: Continuous variables are given as arithmetic mean and standard deviation. Categorical variables are given as counts and percentages. Differences between sex and urbanization were quantified by Wilcoxon test or Chi² test, respectively. BMI-based obesity was defined by BMI ≥ 30 kg/m²; WC-based obesity was defined by WC ≥ 94 cm for men and ≥ 80 cm for women.

Table S2. Mean ± SD of environmental exposures stratified by sex and urbanization**.**

	Sex			Urbanization		
	Men	**Women**	**p value**	**Urban**	**Rural**	**p value**
NO_2 [µg/m³]	13.5 ± 4.2	13.8 ± 4.3	0.073	16.3 ± 3.9	11.0 ± 2.7	<0.001
NO_x [µg/m³]	21.1 ± 7.0	21.4 ± 7.0	0.209	24.3 ± 6.4	18.3 ± 6.2	<0.001
O_3 [µg/m³]	39.2 ± 2.3	39.1 ± 2.3	0.348	39.3 ± 2.1	39.0 ± 2.5	<0.001
PM_{10} [µg/m³]	16.2 ± 1.4	16.3 ± 1.4	0.135	16.8 ± 1.5	15.7 ± 1.1	<0.001
PM_{coarse} [µg/m³]	4.8 ± 1.0	4.9 ± 1.1	0.080	5.5 ± 0.9	4.2 ± 0.8	<0.001
$PM_{2.5}$ [µg/m³]	11.6 ± 1.0	11.6 ± 1.0	0.060	12.0 ± 0.9	11.2 ± 1.0	<0.001
$PM_{2.5}$abs [10^{-5}/m^{-1}]	1.15 ± 0.17	1.16 ± 0.17	0.046	1.26 ± 0.15	1.06 ± 0.13	<0.001
PNC [n/cm³]	6,911 ± 1,674	7,002 ± 1,707	0.075	7,693 ± 1,612	6,241 ± 1,442	<0.001
Annual temperature [°C]	10.2 ± 0.4	10.2 ± 0.4	0.066	10.4 ± 0.4	10.2 ± 0.2	<0.001
Winter temperature [°C]	1.5 ± 0.3	1.5 ± 0.3	0.246	1.6 ± 0.3	1.3 ± 0.2	<0.001
Summer temperature [°C]	19.0 ± 0.6	19.0 ± 0.6	0.062	19.3 ± 0.6	18.7 ± 0.3	<0.001
Greenness (NDVI)	0.4 ± 0.1	0.4 ± 0.1	0.229	0.4 ± 0.1	0.5 ± 0.1	<0.001

Legend: Continuous variables are given as arithmetic mean and standard deviation. Differences between sex and urbanization were quantified by Wilcoxon test.

Table S3. Associations of air pollution, air temperature and greenness with waist circumference (WC) and WC-based obesity.

	IQR	WC			Obesity (WC)		
		Men	Women	$p_{Interaction}$	Men	Women	$p_{Interaction}$
		estimate (95% CI)	estimate (95% CI)		OR (95% CI)	OR (95% CI)	
NO_2	6.3	0.72 (-0.28, 1.72)	-1.19 (-2.10, -0.29)	0.005	1.02 (0.85, 1.22)	0.94 (0.80, 1.10)	0.507
NO_x	8.7	0.52 (-0.31, 1.34)	-0.86 (-1.62, -0.09)	0.016	1.08 (0.93, 1.25)	0.92 (0.80, 1.06)	0.125
O_3	3.5	-0.30 (-1.33, 0.72)	0.00 (-0.92, 0.92)	0.663	0.91 (0.76, 1.09)	1.02 (0.86, 1.20)	0.369
PM_{10}	2.0	0.85 (-0.10, 1.81)	-0.80 (-1.67, 0.06)	0.011	1.07 (0.91, 1.27)	0.93 (0.80, 1.09)	0.215
PM_{coarse}	1.5	0.40 (-0.54, 1.33)	-0.77 (-1.61, 0.07)	0.024	0.98 (0.83, 1.16)	0.97 (0.84, 1.13)	0.951
$PM_{2.5}$	1.4	0.49 (-0.41, 1.40)	-1.03 (-1.89, -0.17)	0.017	1.09 (0.93, 1.28)	0.98 (0.84, 1.14)	0.339
$PM_{2.5}$abs	0.3	0.75 (-0.26, 1.76)	-1.26 (-2.20, -0.32)	0.004	1.06 (0.89, 1.27)	0.91 (0.77, 1.08)	0.214
PNC	1,924	0.62 (-0.14, 1.38)	-0.62 (-1.31, 0.08)	0.018	1.10 (0.96, 1.27)	0.93 (0.82, 1.05)	0.063
Annual temperature	0.6	0.75 (-0.18, 1.68)	-0.92 (-1.77, -0.07)	0.009	1.01 (0.86, 1.19)	0.94 (0.80, 1.09)	0.495
Winter temperature	0.4	0.47 (-0.38, 1.32)	-0.60 (-1.37, 0.18)	0.067	0.96 (0.83, 1.12)	0.97 (0.85, 1.12)	0.939
Summer temperature	0.8	0.83 (-0.10, 1.76)	-1.07 (-1.91, -0.22)	0.003	1.04 (0.88, 1.22)	0.92 (0.79, 1.07)	0.296
Greenness (NDVI)	0.1	-0.50 (-1.44, 0.44)	1.34 (0.49, 2.19)	0.004	0.99 (0.84, 1.17)	1.10 (0.95, 1.29)	0.351

Legend: Effect estimates and ORs were calculated by single-exposure linear (WC) and logistic (obesity) regression models with an interaction term for sex. Models were additionally adjusted for age, physical activity, alcohol, smoking, and education. Estimates and ORs are given per interquartile range increase in exposure. $P_{interaction}$ is the p-value derived from the interaction term between the respective exposure and sex.

Abbreviations: OR = Odds Ratio, 95% CI = 95% confidence interval, PNC = Particle number concentration, NDVI = Normalized difference vegetation index

Table S4. Results of linear and logistic regression models using different adjustment models.

	Adjustment	IQR	Diabetes		Obesity (BMI)		BMI	
			OR (95%-CI)	p-value	OR (95%-CI)	p-value	estimate (95%-CI)	p-value
NO_2	**age, sex, alcohol, smoking, physical activity, education**	6.3	1.18 (0.97, 1.44)	0.094	0.94 (0.83, 1.06)	0.324	-0.24 (-0.51, 0.04)	0.092
	age, sex, smoking, physical activity, education, marital status	6.3	1.15 (0.94, 1.40)	0.163	0.94 (0.83, 1.06)	0.288	-0.24 (-0.52, 0.04)	0.092
	age, sex, alcohol, smoking, physical activity, education, BMI	6.3	1.22 (1.00, 1.48)	0.054	-	-	-	-
	education, urbanization, neighborhood SES	6.3	1.23 (0.89, 1.69)	0.214	1.04 (0.85, 1.26)	0.720	0.20 (-0.27, 0.67)	0.406
	age, sex, alcohol, smoking, physical activity, education, neighborhood SES, marital status, urbanization	6.3	1.22 (0.88, 1.69)	0.234	1.02 (0.83, 1.25)	0.851	0.19 (-0.27, 0.65)	0.419
NO_x	**age, sex, alcohol, smoking, physical activity, education**	8.7	1.15 (0.97, 1.36)	0.106	0.97 (0.88, 1.07)	0.541	-0.13 (-0.36, 0.10)	0.280
	age, sex, smoking, physical activity, education, marital status	8.7	1.13 (0.95, 1.33)	0.164	0.97 (0.87, 1.07)	0.505	-0.13 (-0.36, 0.10)	0.282
	age, sex, alcohol, smoking, physical activity, education, BMI	8.7	1.18 (0.99, 1.40)	0.064	-	-	-	-
	education, urbanization, neighborhood SES	8.7	1.14 (0.94, 1.39)	0.189	1.02 (0.91, 1.15)	0.740	0.08 (-0.20, 0.37)	0.555
	age, sex, alcohol, smoking, physical activity, education, neighborhood SES, marital status, urbanization	8.7	1.12 (0.92, 1.37)	0.252	1.01 (0.9, 1.14)	0.873	0.07 (-0.21, 0.34)	0.632
O_3	**age, sex, alcohol, smoking, physical activity, education**	3.5	0.99 (0.8, 1.21)	0.901	1.02 (0.90, 1.15)	0.763	-0.04 (-0.32, 0.24)	0.784
	age, sex, smoking, physical activity, education, marital status	3.5	1.00 (0.82, 1.23)	0.983	1.02 (0.90, 1.15)	0.754	-0.04 (-0.32, 0.24)	0.787
	age, sex, alcohol, smoking, physical activity, education, BMI	3.5	1.00 (0.81, 1.23)	0.986	-	-	-	-
	education, urbanization, neighborhood SES	3.5	0.99 (0.80, 1.22)	0.919	1.00 (0.88, 1.14)	0.970	-0.06 (-0.36, 0.24)	0.678
	age, sex, alcohol, smoking, physical activity, education, neighborhood SES, marital status, urbanization	3.5	0.99 (0.80, 1.23)	0.951	1.01 (0.89, 1.15)	0.843	-0.05 (-0.34, 0.24)	0.738

PM_{10}	**age, sex, alcohol, smoking, physical activity, education**	2.0	1.18 (0.98, 1.42)	0.080	0.99 (0.88, 1.11)	0.810	-0.08 (-0.35, 0.18)	0.537
	age, sex, smoking, physical activity, education, marital status	2.0	1.14 (0.95, 1.37)	0.155	0.98 (0.88, 1.1)	0.768	-0.08 (-0.35, 0.18)	0.540
	age, sex, alcohol, smoking, physical activity, education, BMI	2.0	1.19 (0.99, 1.43)	0.065	-	-	-	-
	education, urbanization, neighborhood SES	2.0	1.14 (0.92, 1.41)	0.227	1.05 (0.92, 1.19)	0.503	0.13 (-0.18, 0.45)	0.406
	age, sex, alcohol, smoking, physical activity, education, neighborhood SES, marital status, urbanization	2.0	1.15 (0.93, 1.42)	0.203	1.04 (0.91, 1.19)	0.608	0.13 (-0.17, 0.44)	0.396
PM_{coarse}	**age, sex, alcohol, smoking, physical activity, education**	1.5	1.15 (0.96, 1.39)	0.132	0.99 (0.89, 1.11)	0.886	-0.16 (-0.42, 0.10)	0.218
	age, sex, smoking, physical activity, education, marital status	1.5	1.12 (0.93, 1.35)	0.226	0.99 (0.88, 1.11)	0.828	-0.16 (-0.42, 0.10)	0.219
	age, sex, alcohol, smoking, physical activity, education, BMI	1.5	1.18 (0.98, 1.42)	0.080	-	-	-	-
	education, urbanization, neighborhood SES	1.5	1.10 (0.85, 1.42)	0.472	1.08 (0.93, 1.26)	0.308	0.14 (-0.22, 0.51)	0.448
	age, sex, alcohol, smoking, physical activity, education, neighborhood SES, marital status, urbanization	1.5	1.11 (0.86, 1.44)	0.414	1.09 (0.94, 1.28)	0.264	0.19 (-0.17, 0.55)	0.295
$PM_{2.5}$	**age, sex, alcohol, smoking, physical activity, education**	1.4	1.20 (0.99, 1.46)	0.059	0.96 (0.86, 1.08)	0.526	-0.09 (-0.34, 0.17)	0.493
	age, sex, smoking, physical activity, education, marital status	1.4	1.18 (0.98, 1.43)	0.080	0.96 (0.86, 1.08)	0.499	-0.09 (-0.34, 0.17)	0.499
	age, sex, alcohol, smoking, physical activity, education, BMI	1.4	1.23 (1.01, 1.49)	0.038	-	-	-	-
	education, urbanization, neighborhood SES	1.4	1.20 (0.96, 1.49)	0.115	1.01 (0.89, 1.15)	0.878	0.12 (-0.19, 0.42)	0.454
	age, sex, alcohol, smoking, physical activity, education, neighborhood SES, marital status, urbanization	1.4	1.19 (0.96, 1.49)	0.119	1.01 (0.88, 1.15)	0.919	0.12 (-0.18, 0.42)	0.422
$PM_{2.5}$abs	**age, sex, alcohol, smoking, physical activity, education**	0.3	1.16 (0.94, 1.42)	0.160	0.95 (0.84, 1.08)	0.433	-0.16 (-0.44, 0.12)	0.254
	age, sex, smoking, physical activity, education, marital status	0.3	1.13 (0.92, 1.38)	0.247	0.95 (0.84, 1.07)	0.396	-0.16 (-0.45, 0.12)	0.256

21

	age, sex, alcohol, smoking, physical activity, education, BMI	0.3	1.17 (0.96, 1.44)	0.127	-	-	-	-
	education, urbanization, neighborhood SES	0.3	1.12 (0.84, 1.49)	0.451	1.04 (0.88, 1.24)	0.641	0.26 (-0.16, 0.68)	0.220
	age, sex, alcohol, smoking, physical activity, education, neighborhood SES, marital status, urbanization	0.3	1.12 (0.84, 1.5)	0.429	1.03 (0.86, 1.23)	0.752		
PNC	**age, sex, alcohol, smoking, physical activity, education**	1,924	1.14 (0.98, 1.33)	0.084	0.99 (0.9, 1.08)	0.760	-0.05 (-0.26, 0.16)	0.631
	age, sex, smoking, physical activity, education, marital status	1,924	1.12 (0.96, 1.30)	0.137	0.98 (0.9, 1.08)	0.721	-0.05 (-0.26, 0.16)	0.637
	age, sex, alcohol, smoking, physical activity, education, BMI	1,924	1.15 (0.99, 1.34)	0.067	-	-	-	-
	education, urbanization, neighborhood SES	1,924	1.12 (0.95, 1.33)	0.182	1.03 (0.93, 1.15)	0.555	0.14 (-0.11, 0.39)	0.265
	age, sex, alcohol, smoking, physical activity, education, neighborhood SES, marital status, urbanization	1,924	1.12 (0.94, 1.33)	0.209	1.03 (0.92, 1.14)	0.649	0.25 (-0.16, 0.65)	0.231
Annual temperature	**age, sex, alcohol, smoking, physical activity, education**	0.6	1.20 (1.00, 1.44)	0.049	1.00 (0.89, 1.12)	0.978	-0.15 (-0.41, 0.10)	0.241
	age, sex, smoking, physical activity, education, marital status	0.6	1.16 (0.96, 1.39)	0.115	1.00 (0.89, 1.12)	0.970	-0.16 (-0.42, 0.10)	0.238
	age, sex, alcohol, smoking, physical activity, education, BMI	0.6	1.22 (1.02, 1.47)	0.034	-	-	-	-
	education, urbanization, neighborhood SES	0.6	1.22 (0.93, 1.62)	0.152	1.17 (0.99, 1.38)	0.066	0.27 (-0.13, 0.66)	0.187
	age, sex, alcohol, smoking, physical activity, education, neighborhood SES, marital status, urbanization	0.6	1.25 (0.94, 1.66)	0.120	1.14 (0.96, 1.36)	0.122	0.14 (-0.11, 0.38)	0.267
Winter temperature	**age, sex, alcohol, smoking, physical activity, education**	0.4	1.16 (0.98, 1.37)	0.086	1.02 (0.92, 1.13)	0.684	-0.09 (-0.32, 0.14)	0.444
	age, sex, smoking, physical activity, education, marital status	0.4	1.13 (0.95, 1.34)	0.156	1.02 (0.92, 1.13)	0.726	-0.09 (-0.33, 0.14)	0.445
	age, sex, alcohol, smoking, physical activity, education, BMI	0.4	1.22 (1.02, 1.47)	0.034	-	-	-	-
	education, urbanization, neighborhood SES	0.4	1.14 (0.91, 1.43)	0.254	**1.15 (1.00, 1.32)**	**0.044**	0.25 (-0.07, 0.57)	0.128

22

	age, sex, alcohol, smoking, physical activity, education, neighborhood SES, marital status, urbanization	0.4	1.15 (0.91, 1.44)	0.242	1.13 (0.98, 1.30)	0.083	0.24 (-0.15, 0.62)	0.225
Summer temperature	**age, sex, alcohol, smoking, physical activity, education**	0.8	1.21 (1.01, 1.45)	0.038	0.99 (0.88, 1.11)	0.833	-0.19 (-0.45, 0.07)	0.152
	age, sex, smoking, physical activity, education, marital status	0.8	1.17 (0.97, 1.40)	0.098	0.98 (0.88, 1.10)	0.781	-0.19 (-0.45, 0.07)	0.149
	age, sex, alcohol, smoking, physical activity, education, BMI	0.8	1.24 (1.03, 1.49)	0.024	-	-	-	-
	education, urbanization, neighborhood SES	0.8	1.26 (0.94, 1.68)	0.117	1.14 (0.96, 1.36)	0.131	0.20 (-0.21, 0.61)	0.333
	age, sex, alcohol, smoking, physical activity, education, neighborhood SES, marital status, urbanization	0.8	1.30 (0.97, 1.74)	0.082	1.12 (0.94, 1.34)	0.200	0.21 (-0.10, 0.53)	0.179
Greenness (NDVI)	**age, sex, alcohol, smoking, physical activity, education**	0.1	0.90 (0.74, 1.09)	0.282	1.07 (0.95, 1.20)	0.246	0.26 (0.00, 0.52)	0.051
	age, sex, smoking, physical activity, education, marital status	0.1	0.93 (0.77, 1.12)	0.438	1.07 (0.96, 1.20)	0.220	0.26 (0.00, 0.52)	0.050
	age, sex, alcohol, smoking, physical activity, education, BMI	0.1	0.88 (0.72, 1.06)	0.180	-	-	-	-
	education, urbanization, neighborhood SES	0.1	0.96 (0.74, 1.25)	0.772	1.03 (0.88, 1.2)	0.717	0.05 (-0.31, 0.42)	0.782
	age, sex, alcohol, smoking, physical activity, education, neighborhood SES, marital status, urbanization	0.1	0.95 (0.73, 1.24)	0.711	1.02 (0.88, 1.2)	0.757	0.20 (-0.20, 0.60)	0.337

Legend: bold = main model used in final analyses

Table S5. Sensitivity analysis on the associations of air pollution, air temperature and greenness with, diabetes, body mass index (BMI) and BMI-based obesity derived from logistic or linear regression models with an interaction term for sex adjusted for age, alcohol consumption, smoking behavior and education, but not physical activity.

	IQR	Diabetes			BMI			Obesity (BMI)		
		Men	Women	$p_{interaction}$	Men	Women	$p_{interaction}$	Men	Women	$p_{interaction}$
		OR (95% CI)	OR (95% CI)		estimate (95% CI)	estimate (95% CI)		OR (95% CI)	OR (95% CI)	
NO_2 [µg/m³]	6.3	1.50 (1.14; 1.97)	0.94 (0.71; 1.25)	0.020	0.18 (-0.23; 0.6)	-0.55 (-0.92; -0.17)	0.009	1.12 (0.94; 1.33)	0.83 (0.7; 0.97)	0.012
NO_x [µg/m³]	8.7	1.34 (1.05; 1.69)	0.98 (0.77; 1.25)	0.073	0.16 (-0.18; 0.5)	-0.37 (-0.68; -0.05)	0.025	1.10 (0.95; 1.27)	0.87 (0.76; 1.00)	0.019
O_3 [µg/m³]	3.5	0.88 (0.66; 1.18)	1.08 (0.81; 1.44)	0.319	-0.04 (-0.46; 0.39)	-0.11 (-0.50; 0.27)	0.794	1.02 (0.85; 1.22)	0.99 (0.84; 1.16)	0.794
PM_{10} [µg/m³]	2.0	1.43 (1.11; 1.84)	0.96 (0.73; 1.25)	0.030	0.34 (-0.06; 0.73)	-0.40 (-0.76; -0.04)	0.007	1.21 (1.03; 1.43)	0.83 (0.71; 0.97)	0.001
PM_{coarse} [µg/m³]	1.5	1.38 (1.07; 1.8)	0.96 (0.74; 1.24)	0.048	0.13 (-0.26; 0.52)	-0.43 (-0.77; -0.08)	0.034	1.14 (0.97; 1.34)	0.87 (0.75; 1.01)	0.015
$PM_{2.5}$ [µg/m³]	1.4	1.42 (1.08; 1.86)	1.01 (0.77; 1.33)	0.085	0.18 (-0.19; 0.56)	-0.32 (-0.68; 0.03)	0.054	1.07 (0.92; 1.26)	0.88 (0.76; 1.02)	0.075
$PM_{2.5}$abs [$10^{-5}m^{-1}$]	0.3	1.44 (1.09; 1.91)	0.92 (0.69; 1.24)	0.031	0.30 (-0.12; 0.72)	-0.52 (-0.91; -0.14)	0.004	1.15 (0.96; 1.36)	0.82 (0.69; 0.97)	0.006
PNC [n/cm³]	1,924	1.31 (1.06; 1.61)	0.99 (0.79; 1.23)	0.067	0.23 (-0.09; 0.54)	-0.27 (-0.56; 0.01)	0.021	1.14 (1.00; 1.30)	0.87 (0.77; 0.99)	0.003
Annual temperature [°C]	0.6	1.50 (1.17; 1.92)	0.97 (0.75; 1.27)	0.019	0.21 (-0.17; 0.59)	-0.38 (-0.73; -0.03)	0.024	1.13 (0.96; 1.33)	0.93 (0.8; 1.08)	0.073
Winter temperature [°C]	0.4	1.41 (1.12; 1.77)	0.96 (0.76; 1.23)	0.025	0.14 (-0.22; 0.49)	-0.22 (-0.54; 0.1)	0.142	1.10 (0.95; 1.28)	0.98 (0.85; 1.12)	0.247
Summer temperature [°C]	0.8	1.52 (1.18; 1.94)	0.98 (0.75; 1.27)	0.017	0.22 (-0.16; 0.61)	-0.47 (-0.82; -0.12)	0.009	0.90 (0.77; 1.05)	0.89 (0.75; 1.05)	0.036
Greenness (NDVI)	0.1	0.78 (0.59; 1.02)	1.05 (0.8; 1.37)	0.118	-0.16 (-0.55; 0.23)	0.61 (0.26; 0.96)	0.004	0.89 (0.75; 1.05)	1.26 (1.08; 1.46)	0.002

Legend: Effect estimates and ORs were calculated by single-exposure linear (BMI) and logistic (diabetes and obesity) regression models with an interaction term for sex. Models were additionally adjusted for age, alcohol, smoking, and education. Estimates and ORs are given per interquartile range increase in exposure. $P_{interaction}$ is the p-value derived from the interaction term between the respective exposure and sex.
Abbreviations: OR = Odds Ratio, 95% CI = 95% confidence interval, PNC = Particle number concentration, NDVI = Normalized difference vegetation index.

Appendix: Manuscript 3

Title:	Individual and joint associations of multiple environmental exposures with diabetes and obesity in the population-based German National Cohort (NAKO)
Authors:	Niedermayer, Fiona; Hoffmann, Barbara; Zhang, Boya; Chen, Jie; Hart, Jaime E.; Laden, Francine; Bolte, Gabriele; Lakes, Tobia; Schikowski, Tamara; Greiser, Karin Halina; Staab, Jeroen; Nikolaou, Nikolaos; Dallavalle, Marco; Schulze, Matthias B.; Lieb, Wolfgang; Övermöhle, Cara; Tönnies, Thaddäus; Katzke, Verena; Becher, Heiko; Fischer, Beate; Leitzmann, Michael; Berger, Klaus; Mayvaneh, Fatemeh; Keil, Thomas; Krist, Lilian; Klett-Tammen, Carolina J; Heise, Jana-Kristin; Pischon, Tobias; Ilais, Moreno Velásquez; Schmidt, Börge; Nagrani, Rajini; Rach, Stefan; Brenner, Hermann; Holleczek, Bernd; Harth, Volker; Obi, Nadia; Köttgen, Anna; Mikolajczyk, Rafael; Meinke-Franze, Claudia; Hoffmann, Wolfgang; Schneider, Alexandra; Wolf, Kathrin; Peters, Annette
Year:	2026
Status:	Submitted & under review (at the time of thesis evaluation) Published (at the time of thesis publication)
Journal:	Environmental Research
Volume:	297
Issue:	
Page:	124096
DOI:	https://doi.org/10.1016/j.envres.2026.124096
2023 Journal Impact Factor:	7.7 (*Journal Citation Reports* (Clarivate, 2023))
Rank by 2023 Journal Impact Factor:	36/358 in the category “Environmental Sciences“ (*Journal Citation Reports* (Clarivate, 2023))
Note:	The manuscript, including the title, was adapted due to the peer review process. The final publication can be found here: https://doi.org/10.1016/j.envres.2026.124096

Individual and joint associations of multiple environmental exposures with diabetes and obesity in the population-based German National Cohort (NAKO)

Fiona Niedermayer [1, 2]*, Barbara Hoffmann [3], Boya Zhang [4, 5], Jie Chen [4, 5], Jaime E. Hart [4, 5], Francine Laden [4, 5], Gabriele Bolte [6, 7], Tobia Lakes [8, 9], Tamara Schikowski [10, 11], Karin Halina Greiser [11], Jeroen Staab [12], Nikolaos Nikolaou [2], Marco Dallavalle [2], Matthias B. Schulze [13, 14], Wolfgang Lieb [15], Cara Övermöhle [15], Thaddäus Tönnies [16], Verena Katzke [11], Heiko Becher [17], Beate Fischer [18], Michael Leitzmann [18], Klaus Berger [19], Fatemeh Mayvaneh [19], Thomas Keil [20, 21, 22], Lilian Krist [20], Carolina J. Klett-Tammen [23], Jana-Kristin Heise [23], Tobias Pischon [24, 25, 26], Ilais Moreno Velásquez [24], Börge Schmidt [27], Rajini Nagrani [28], Stefan Rach [28], Hermann Brenner [29], Bernd Holleczek [29], Volker Harth [30], Nadia Obi [30], Anna Köttgen [31], Rafael Mikolajczyk [32], Claudia Meinke-Franze [33], Wolfgang Hoffmann [33], Alexandra Schneider [2], Kathrin Wolf [2], Annette Peters [1, 2, 34]

[1] Chair of Epidemiology, IBE, Faculty of Medicine, Ludwig-Maximilians-Universität Munich, Munich, Germany

[2] Institute of Epidemiology, Helmholtz Zentrum München (GmbH) - German Research Center for Environmental Health, Neuherberg, Germany

[3] Institute of Occupational, Social and Environmental Medicine, Medical Faculty and University Hospital, Heinrich Heine University Düsseldorf, Düsseldorf, Germany

[4] Department of Environmental Health, Harvard T. H. Chan School of Public Health, Boston, MA, USA

[5] Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

[6] Department of Social Epidemiology, Institute of Public Health and Nursing Research, University of Bremen, Bremen, Germany

[7] Health Sciences Bremen, University of Bremen, Bremen, Germany

[8] Geography Department, Geoinformation Science Lab, Humboldt Universität zu Berlin, Berlin, Germany

[9] Integrative Research Institute on Transformations of Human Environment Systems (IRI THESys), Berlin, Germany

[10] IUF – Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany

[11] Division of Cancer Epidemiology (C020), German Cancer Research Center (DKFZ), Heidelberg, Germany

[12] German Remote Sensing Data Center, German Aerospace Center (DLR), Weßling, Germany

[13] Department of Molecular Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany

[14] Institute of Nutritional Science, University of Potsdam, Nuthetal, Germany

[15] Institute of Epidemiology, Kiel University, Kiel, Germany

[16] Institute for Biometrics and Epidemiology, German Diabetes Center (DDZ), Leibniz Center for Diabetes Research at Heinrich Heine University, Düsseldorf, Germany

[17] Institute of Global Health, University Hospital Heidelberg, Heidelberg, Germany

[18] Department of Epidemiology and Preventive Medicine, Regensburg, Germany

[19] Institute of Epidemiology and Social Medicine, University of Münster, Germany

[20] Institute of Social Medicine, Epidemiology, and Health Economics, Charité - Universitätsmedizin Berlin, Berlin, Germany

[21] Institute of Clinical Epidemiology and Biometry, University of Würzburg, Würzburg, Germany

[22] State Institute of Health I, Bavarian Health and Food Safety Authority, Erlangen, Germany

[23] Department of Epidemiology, Helmholtz Centre for Infection Research (HZI), Braunschweig, Germany

[24] Max-Delbrück-Center for Molecular Medicine in the Helmholtz Association (MDC), Molecular Epidemiology Research Group, Berlin, Germany

[25] Max-Delbrück-Center for Molecular Medicine in the Helmholtz Association (MDC), Biobank Technology Platform, Berlin, Germany

[26] Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

[27] Institute for Medical Informatics, Biometry and Epidemiology, University Hospital of Essen , University of Duisburg-Essen, Essen, Germany

[28] Department Epidemiological Methods and Etiological Research, Leibniz Institute for Prevention Research and Epidemiology - BIPS, Bremen, Germany

[29] NAKO Study Center Saarbrücken, Saarland Cancer Registry, Saarbrücken, Germany

[30] Institute for Occupational and Maritime Medicine (ZfAM), University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[31] Institute of Genetic Epidemiology, Faculty of Medicine and Medical Center – University of Freiburg, Freiburg, Germany

[32] Institute for Medical Epidemiology, Biometrics, and Informatics, Interdisciplinary Center for Health Sciences, Medical Faculty of the Martin Luther University Halle-Wittenberg, Halle (Saale), Germany

[33] Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany

[34] German Center for Diabetes Research (DZD e.V.), Neuherberg, Germany

*Corresponding author:

Fiona Niedermayer

Ingolstädter Landstr. 1, 85764 Neuherberg, Germany

Email: fiona.niedermayer@helmholtz-munich.de

Phone: +49 (0)89-3187-49519

ORCID: 0000-0002-6798-2630

Word count: 5,671

Number of figures: 3

Number of tables: 3

Abstract

Background: We investigated the individual and joint associations of long-term exposure to multiple environmental factors with diabetes and obesity-related measures.

Methods: We used cross-sectional data from the population-based German National Cohort (NAKO). Outcomes included self-reported diabetes mellitus, body mass index (BMI), obesity (BMI ≥ 30 kg/m²), and waist circumference. Annual mean residential exposures included air pollutants, air temperature, day-evening-night road traffic noise (L_{den}) and surrounding greenness. We used sex-stratified linear and logistic regression models to assess individual associations and quantile g-computation to assess joint associations.

Results: Among 174,955 adult participants (50.4% women), 5.6% reported a diabetes diagnosis and 20.9% were obese. An interquartile range increase in particulate matter ($PM_{2.5}$) and L_{den} was consistently associated with diabetes and obesity-related measures (e.g., $PM_{2.5}$-diabetes for men: odds ratio (OR) [95% confidence interval] = 1.12 [1.02; 1.22]; L_{den}-BMI for women: 0.22kg/m² [0.16; 0.27]). Greenness showed non-linear (inverted U-shaped) with all outcomes. An interquartile range change in multiple exposures simultaneously was associated with two-times greater odds of diabetes and changes in obesity-related measures compared to single-exposure models.

Conclusions: While longitudinal studies need to confirm these findings, the study highlights that reducing multiple adverse environmental exposures may be beneficial in the prevention of diabetes and obesity.

Keywords: metabolic disease; environmental epidemiology; urbanization

Environmental implications

In this study, we used estimated residential annual mean exposure to multiple environmental exposures derived from objective measurement methods and modeling techniques, to represent real-world data. Moreover, in order to capture a realistic exposure scenario, we considered joint associations to multiple environmental exposures simultaneously, e.g., air pollution, air temperature, road traffic noise and surrounding greenness, which often co-exists in urban areas. Given that these harmful environmental exposures can be regulated at the population level, our study emphasizes the potential importance of reducing these adverse factors in the prevention of diabetes and obesity.

Abbreviations

BMI	Body mass index
CI	Confidence Interval
CVD	Cardiovascular disease
DAG	Directed acyclic graph
EIONET	European Environment Information and Observation Network
ELAPSE	Effects of Low-Level Air Pollution: A Study in Europe
END	Environmental Noise Directive
ISCED	International Standard Classification of Education
L_{den}	Day–evening–night road traffic noise level
NAKO	German National Cohort
NDVI	Normalized Difference Vegetation Index
NO_2	Nitrogen dioxide
OR	Odds ratio
PM	Particulate matter
T_{mean}	Mean air temperature
SES	Socioeconomic status
WHO	World Health Organization

Introduction

With over 529 million people diagnosed with diabetes mellitus and 650 million affected by obesity (body mass index (BMI) ≥ 30 kg/m²) in early 2020s,[1, 2] metabolic diseases represent a serious public health challenge worldwide. Moreover, obesity constitutes a risk factor for a wide range of other non-communicable diseases, including cardiovascular disease (CVD), cancer, and type 2 diabetes.[3] The incidence of metabolic diseases continues to rise globally,[1, 4] despite the implementation of behavioral interventions designed to increase physical activity and to improve dietary habits, which are primary strategies in the prevention of metabolic diseases.[3] Low socioeconomic status (SES) has been identified as a crucial risk factor for diabetes and obesity,[5, 6] which often coincides with further socio-economic and environmental disparities due to more disadvantaged living conditions.

Environmental factors such as air pollution, traffic noise, ambient air temperature or lack of surrounding greenness are crucial health determinants.[7, 8] In the latest update of the Global Burden of Disease Study in 2025, air pollution was identified as the most important risk factor attributable to deaths and disability-adjusted life years from diabetes, kidney disease, respiratory disease and CVD.[7, 9] The World Health Organization (WHO) denoted traffic noise as the second most harmful environmental risk factor, evidencing levels above 53 dB(A) to adverse health effects.[10] As environmental risk factors can partly be controlled at the population level, for example by legally binding limit values for air pollution and traffic noise, or by considering re-vegetation of urban areas, these approaches could constitute powerful and essential public health interventions to prevent diabetes and obesity. Therefore, there is an urgent need to elucidate the potential impact of environmental factors on diabetes and obesity-related measures.

Growing evidence links linking high levels of air pollution, especially particulate matter (PM), and road traffic noise to diabetes prevalence and incidence.[11-13] However, the evidence on other air pollutants and environmental factors, including air temperature and greenness, are less clear and presently understudied.[14, 15] Furthermore, evidence on the association of environmental factors with obesity-related measures is inconclusive.[16-19] For example, a meta-analysis from 2018 reported that 56% of the included studies did not find adverse associations of air pollution with obesity markers.[16] High exposure to air pollutants and noise may contribute to diabetes and obesity by causing systemic inflammation, sleep disturbance, and constant release of stress hormones, while beneficial effects on mental health and stress reduction are attributed to higher levels of greenness.[20-23]

In addition, studies have tended to focus on individual exposures, such as air pollution or greenness, rather than examining associations of multiple environmental exposures. This may not adequately capture the true health effects of these environmental factors, as they may confound and interact with each other.[24] It also ignores the fact that these factors co-exist, especially in urban areas.[25] Due to the common traffic source, urban areas are often characterized by adverse levels of air pollution and road traffic noise while surrounding greenness is lacking, exposing urban residents to multiple environmental risk factors at the same time. There are only a few previous studies that looked at joint associations of multiple environmental exposures and metabolic diseases.[24, 26, 27] Although different methods were used, all studies indicated stronger adverse associations when exposures were considered jointly.[24, 26, 27] As study regions in previous studies were often restricted to urban areas,[28-30] there is insufficient evidence on which of these associations can still be observed in more rural and remote areas. Based on our previous analysis using data from another smaller German cohort (KORA-Fit), the associations of air pollutants and greenness with obesity-related measures varied by the degree of urbanization.[31] As the previous study was limited to a smaller sample size (n=3,034), we aimed to confirm these observations in a larger sample.

Therefore, we investigated the associations of various environmental exposures in single-exposure and multi-exposure models taking into account urbanicity. We analyzed cross-sectional data from a multi-center, population-based cohort study and addressed the following research questions:

1. How are higher annual levels of environmental exposures associated with existing diabetes and obesity-related measures in men and women?
2. Are there joint associations of multiple environmental exposures with diabetes and obesity-related measures in men and women?
3. Do these associations vary in urban, suburban and rural areas?

Methods

Study design and population

The German National Cohort (NAKO Gesundheitsstudie) is a nation-wide, population-based, multi-center cohort that aims to investigate a range of chronic diseases, their risk factors, and etiology. A detailed description of the NAKO, including information on study design and participant recruitment, can be found elsewhere.[32, 33] Briefly, between 2014 and 2019, 205,415 participants aged 19-75 years underwent a baseline examination at one of 18 NAKO study centers within Germany. Participants were recruited in 16 different study center regions in Germany from the general population based on a sex and age-stratified designs,[33] that comprised urban and rural living environments. Standardized, comprehensive interviews, medical and physical examinations were carried out by trained staff at the study centers. For the present analyses, we used cross-sectional data from 204,687 eligible participants who attended the baseline examination. The NAKO was approved by the local ethics committees and all participants gave written informed consent before study enrollment.

Outcomes

We used diabetes mellitus, obesity, BMI and waist circumference as outcome variables. The definition of diabetes mellitus was based on self-report. Participants were asked “Have you ever been diagnosed with diabetes mellitus by a physician?” during standardized, computer-assisted interviews at baseline examination.[34] BMI was calculated from standardized measurements of height and weight by dividing weight by the square of height (kg/m²).[35] If height and/or weight measurements were missing (< 1%), values were filled in with self-reported height and weight information. Obesity was defined as BMI ≥ 30 kg/m².[36] Waist circumference was measured according to the WHO guideline using a measuring tape (Seca) placed midway between the lowest rib and the top of the iliac crest.[37]

Exposures

We used the following environmental exposures: annual means of ambient air pollution, ambient air temperature, road traffic noise and greenness (Figure S1). All environmental factors were assigned to the geocoded residential baseline addresses of participants at the time of the baseline examination. Detailed information on the exposure assessment, linkage, harmonization and data sources used can be found in Wolf et al.[38].

Briefly, we used air pollution estimates from the ELAPSE (Effects of Low-Level Air Pollution: A Study in Europe) project, which provides annual levels of nitrogen dioxide (NO_2), particulate matter < 2.5 µm in diameter ($PM_{2.5}$), and $PM_{2.5}$ absorbance ($PM_{2.5}$ abs), a proxy for black carbon, for Western Europe for the year 2010.[38, 39] Land use regression models were developed to predict air pollution concentrations, incorporating measurements from ground-level monitoring stations, satellite observations, estimates from chemistry transport models, and further spatial predictors.[39] These models were then applied to compile country-wide maps with a resolution of 100m*100m.[39]

Data on annual mean, minimum and maximum air temperature were available for the years 2000-2020 with a resolution of 1km*1km. Air temperature measurements from ground-based measurement stations, satellite-derived land surface temperature and spatial factors were combined in a three-stage spatiotemporal model as described by Nikolaou et al.[40]. We assigned each participant the annual mean temperature (T_{mean}) in the examination year.

Road traffic noise data at a scale of 10m*10m for the year 2017 was available from the European Environment Information and Observation Network (EIONET).[41, 42] The maps provide day-evening-night levels (L_{den}) categorized into 5 groups: (55: 55-59 dB(A), 60: 60-64 dB(A), 65: 65-69 dB(A), 70: 70-74 dB(A), 75: ≥75 dB(A)). Participants with missing data or living in urbanized areas not covered by the Environmental Noise Directive (END) obligation

2002/49/EG Article 3 section k[42] were set to 40 dB(A) defining a lower detection limit. We calculated mean values of grid cells within a 100m buffer size around residential addresses to obtain continuous area-weighted noise levels.[38]

Lastly, we used the normalized difference vegetation index (NDVI) as indicator of surrounding greenness. Monthly data on a 1km*1km grid were gathered from the NASA Terra Moderate Resolution Imaging Spectroradiometer (MODIS), available on a 1km*1km grid, for the years 2014 to 2019.[38] Briefly, the NDVI (= reflected radiation in the visible red minus in the near infrared divided by the sum of the two) takes values from -1 to 1. Prior to analysis, water pixels (values < 0) were excluded by masking the data with a mask layer, so values close to 0 indicate grey, less green areas, while values close to 1 indicate dense vegetation.[38] We assigned each participant the annual NDVI of the respective grid cell averaged over the warm months (March to October) of the examination year to reflect the whole vegetation period of this year.

<u>Covariables</u>

Information on sociodemographic, lifestyle factors, and SES were assessed by standardized interviews, questionnaires, and physical examinations at baseline. Alcohol consumption is provided as gram per day. Participants were categorized as never, former and current smoker based on their self-reported smoking behavior. Physical activity was assessed by the Global Physical Activity Questionnaire, evaluated according to the WHO analysis guide.[43] We winsorized implausible values to a maximum of 16 hours a day per week (6,720 min), and categorized into quintiles. We considered educational levels rather than income to reflect individual SES, as there were fewer missing values in this variable. Educational levels were classified by combining information on school and vocational training according to the International Standard Classification of Education (ISCED) 2011[44] and we grouped participants still in education or training into a separate category.

Further geocoded variables assigned to the baseline residential addresses included neighborhood SES, population density and degree of urbanization. Neighborhood SES was represented by the unemployment rate at the district level for 2014 from the Federal Employment Agency.[45] Population density, given as inhabitants per square meters within a 1 km buffer of participants' residencies, was available for the year 2018 from a private company (WiGeoGis GmbH).[46] Information on the degree of urbanization was downloaded from EUROSTAT (statistical office of the European Union) for the year 2020 (population census data 2018), which provides a categorization of German municipalities into urban, suburban, and rural areas based on the proportion of densely populated grid cells in each municipality.[47] We used this information to define the degree of urbanization of participants' municipalities of residence, which we considered as potential effect modifier.

Statistical analysis

We performed Spearman's rank correlation to assess correlations between environmental exposures and population density.

We applied linear and logistic regression models stratified by sex, adjusting for age, study center, lifestyle factors, SES and population density. Our basic model included outcome-related risk factors, such as age, smoking, physical activity, alcohol consumption, which explained some heterogeneity between our participants. We stepwise added the following confounders identified by directed acyclic graphs (DAG) (Figure S2): study center, individual SES, neighborhood SES and population density. First, we examined the shape of the exposure-response functions between each exposure and outcome to identify non-linear associations. We fitted cubic splines for the exposure using the *gam* function of the R package *mgcv*.[48] If there was a visual detection of non-linearity in the main exposure ranges (10^{th} – 90^{th} percentile), we present plots showing the non-linear exposure-response curve. In order to get a proximation of the association between each exposure range and the turning points, we applied piecewise linear and logistic regression models, which is described in detail in the supplement (supplementary methods S1). Odds ratios (OR) and absolute changes derived from the regression models are reported per interquartile range (IQR) increase in environmental exposure with 95% confidence intervals (95% CI).

Furthermore, we exploratory assessed joint associations of an environmental exposure mixture with diabetes and obesity-related measures in multi-exposure models using quantile g-computation. This method has been described by Keil et al.[49] and is suitable for the environmental exposure setting.[27, 50, 51] Briefly, exposures of interest are standardized and categorized into a predefined increment, such as quartiles. In a supervised approach, exposures are ranked according to their importance and contribution to the outcome of interest and a weighted sum index is created. The outcome is regressed on this single index so that the joint association can be interpreted as the change in outcome if all exposures were simultaneously increased by one pre-defined increment, in our case quartiles. In addition, the weights indicate the proportion to which an exposure contributes to the positive or negative joint association. To provide a rough comparison between estimates derived from single-exposure models with multi-exposure models, we multiplied the betas from quantile g-computation by two in order to interpret them as an IQR increase rather than a quartile increase, as described by Stevens et al.[51]. We implemented quantile g-computation using the R package *qgcomp*[49] and ran two scenarios: (1) including exposures that showed significant associations in single-exposure models, (2) including all exposures. The inverse of NDVI was used because it was negatively correlated with air pollution, air temperature and road traffic noise and because we expected negative associations with diabetes and obesity-related measures. We also ran two-exposure models, mutually adjusting each environmental factor for another, to assess the independence of associations. Therefore, we paired exposures with Spearman correlation coefficients < 0.7 to avoid multicollinearity.

We further assessed effect modification by adding an interaction term between exposure and degree of urbanization (urban/suburban/rural). In addition, we analyzed regression models stratified by study center to identify between-center heterogeneity among associations.

We assessed the robustness of our results by performing several sensitivity analyses. Firstly, we used different adjustment sets: (1) we additionally adjusted for income and partnership, (2) we did not adjust for physical activity, as this could be a mediator in the association of

NDVI with diabetes and obesity.[15] Finally, we applied different definitions of diabetes on the associations: (1) we excluded all women who reported a diagnosis of diabetes onset during pregnancy (gestational diabetes) (n = 1,157); (2) we excluded cases with probable type 1 diabetes (defined as age of diagnosis ≤ 30 years according to the DIAB-CORE[52]).

All analyses were done with RStudio Version 4.3.1, and p-values <0.05 indicated statistical significance. All described analyses were performed separately for each outcome.

Results

Sample characteristics

After excluding all individuals with missing data on any outcome, exposure or main covariates, our final analytic sample consisted of 174,955 participants (Figure S3), of whom 50.4% were women, the mean age was 49.5 years, and more than 70% lived in urban areas (Table 1). In the present sample, 6.2% of the men and 5.0% of women reported a diabetes diagnosis, with a mean age at diagnosis of 50 and 45 years, respectively. For men, the mean BMI and waist circumference were 27.2 kg/m² and 96.5 cm, respectively, and 22% were obese. For women, the mean BMI and waist circumference were 26.0 kg/m² and 85.6 cm, respectively, and 19.8%, were obese. Women reported lower alcohol consumption, were less likely to be ex- or current smokers had lower levels of physical activity, were less likely to have a university degree and lived in more densely populated areas compared to men (Table 1).

Environmental exposure levels were similar for men and women but differed according to the study region. Mean levels of NO_2, $PM_{2.5}$ and $PM_{2.5}$ abs were 26.8 µg/m³, 17.3 µg/m³, and 1.6 $10^{-5}m^{-1}$, respectively (Table S1). Mean air temperature was 10.9 °C, and the participants were exposed to a mean road traffic noise level of 44.6 dB(A) and a mean surrounding greenness cover of 0.5. Correlations were positive between air pollution, air temperature, and noise (r = 0.35 to 0.84), NDVI was negatively correlated with all other environmental exposures (r = -0.59 to -0.34) (Table S1). Population density was positively correlated with air pollution, air temperature, and noise (r = 0.42 to 0.72) and negatively with NDVI (r = -0.64).

Single-exposure models

Exposure-response functions showed linear forms in the main exposure ranges (10^{th} – 90^{th} percentile) for air pollution, temperature, and noise (Figures S4-S7) with diabetes and obesity-related measures, therefore we show linear effect estimates (Table 2-3). Estimates changed strongest when population density were included in the model, followed by study center, and education (Table S2-S3).

For men and women, an IQR increase in annual $PM_{2.5}$ was associated with higher odds of diabetes (e.g., men: OR = 1.12 [95% CI: 1.02; 1.22], women: OR = 1.11 [1.01; 1.22]; per 2.9 µg/m³ increase). An association of higher NO_2 and $PM_{2.5}$abs was only found for diabetes in men (OR ranged from 1.08 to 1.10; Table 2). For women only, T_{mean} was associated with higher odds of diabetes, while an increase of 8.3 dB(A) in annual L_{den} was associated with 1.08-fold and 1.05-fold higher odds of diabetes in men and women, respectively. With regard to the obesity-related measures, an IQR increase in annual $PM_{2.5}$ was associated with higher obesity-related measures (Tables 2 and 3). For example, higher annual $PM_{2.5}$ was associated with 0.11 kg/m² and 0.18 kg/m² higher BMI and 0.40 cm and 0.48 cm higher waist circumference in men and women, respectively. Except for T_{mean} and waist circumference, the associations were close to unity for NO_2, $PM_{2.5}$abs and T_{mean} for men and women. Higher annual L_{den} was associated with higher obesity-related measures for both men and women (e.g., men: 0.11 kg/m² [0.06; 0.15], 0.26 cm [0.15; 0.38]; women: 0.22 kg/m² [0.16; 0.27], 0.46 cm [0.34; 0.59]; per 8.3 dB(A) increase).

A deviation from linearity was observed for NDVI with all outcomes, suggesting an inverted U-shaped function and a turning point around the median (0.55) (Figure 1). Thus, indicating that low NDVI (below the median) and high NDVI (above the median) were associated with lower odds of diabetes, obesity, and lower BMI and waist circumference in men and women (Figure 1). The inverted u-shape was independent of the adjustment model (data not shown).

Joint associations of environmental exposure mixtures

For diabetes, we observed positive joint associations for men and women (Table S4). Considering an IQR increase in annual $PM_{2.5}$, L_{den} and an IQR decrease in NDVI simultaneously, these exposures were associated with ORs of 1.28 [1.20; 1.35] and 1.23 [1.15; 1.32] for diabetes in men and women, respectively (Figure 2). For men, the joint association was mainly driven by L_{den} (44% of the positive weight attributed). In women, it was driven by $PM_{2.5}$ (56% of the positive weight attributed) (Figure 2). Compared to the single-exposure models, the ORs from joint associations were two times higher (e.g., ORs in single-exposure models ranged from: 1.08 - 1.12). When all six environmental exposures were considered, the joint association was attenuated but remained because T_{mean}, NO_2 and $PM_{2.5}$abs contributed to the negative side, especially for men (Table S4; Figure S8).

For BMI, an IQR increase in annual $PM_{2.5}$, L_{den} and lack of NDVI was jointly associated with 0.22 kg/m² [0.16; 0.28] and 0.57 kg/m² [0.49; 0.67] higher BMI in men and women, respectively (Figure 2). For men and women, this joint association was mainly driven by L_{den}, which accounted for more than 50% of the total positive association, followed by $PM_{2.5}$. Similarly, ORs of obesity and changes in BMI and waist circumference associated with exposure mixtures were two times higher compared to single-exposure models. When all six environmental exposures were considered, the joint association was attenuated but remained except for BMI in men (Figure S8). Similar results were observed for waist circumference and obesity (Table S4).

Two-exposure models confirmed the main contribution of L_{den}, as additional adjustments for other environmental exposures did not change the associations of L_{den} with diabetes or obesity-related measures (Figure S9). In contrast, associations of air pollutants attenuated after adjustment for L_{den} (Figure S9).

Exploratory analysis

Effect modification by degree of urbanization

For diabetes, interactions between degree of urbanization and exposures were observed for men (Figure S10). In suburban and rural areas, higher annual air pollution was positively associated with diabetes in men. In addition, higher annual L_{den} in urban areas was associated with 1.05-fold and 1.06-fold higher odds of diabetes for men and women, respectively. For obesity-related measures, interactions between degree of urbanization and exposures were observed for men and women (e.g., BMI in Figure 3). In urban and suburban areas, an IQR increase in annual air pollutants and L_{den} were associated with higher BMI, waist circumference and obesity in men and women, respectively. In rural areas, we found no association of environmental factors with obesity-related measures except for NO_2 in women. Non-linear associations between NDVI and obesity-related measures were driven by urban areas (e.g., BMI in Figure S11).

Study center-specific findings

The number of participants per study center can be found in the Supplementary Table S5. Radar plots showed different distribution patterns of environmental factors, BMI and population density across the study centers (Figure S12). Study centers with a higher proportion of rural areas and lower population density had on average higher BMI and NDVI, but lower levels of air pollution, T_{mean} and L_{den} (e.g., Augsburg, Neubrandenburg, Saarbrücken, Regensburg). Study centers with a large proportion of urban areas and high population density were characterized by lower mean BMI and NDVI, but higher air pollution and L_{den} (e.g., Berlin, Düsseldorf, Hannover, Mannheim). We observed a large heterogeneity in the associations when we stratified by study center (Figures S13-14).

Sensitivity analyses

In sensitivity analyses, associations were robust. Using different confounder adjustment sets, consistent associations between adverse $PM_{2.5}$ levels and L_{den} were observed for all outcomes (Table S6-7). The associations with obesity outcomes did not change when we excluded existing diabetes and cancer cases (Table S8). For women, the associations were slightly stronger after excluding those with gestational diabetes (Table S9). For men, the associations slightly attenuated after excluding probable type 1 diabetes cases (Table S9).

Discussion

Summary and key points

In the current analyses, we assessed the associations of multiple environmental exposures with existing diabetes, obesity, BMI, and waist circumference using cross-sectional data from 174,955 participants of the multi-center NAKO study. We found consistent associations linking $PM_{2.5}$ and road traffic noise to diabetes and obesity-related measures, especially in urban and suburban areas. NDVI showed an inverted U-shaped exposure-response with diabetes and obesity-related measures. When we considered a mixture of environmental exposures including all six environmental factors or only $PM_{2.5}$, road traffic noise and lack of greenness, we observed two times greater odds of diabetes, obesity and two times higher changes in BMI and waist circumference compared to single-exposure models. The interaction with degree of urbanization and the study center-specific heterogeneity suggested further variation and unknown factors contributing to diabetes and obesity risk in urban, suburban and rural areas.

Comparison to previous studies

Air pollution

Our findings on the association of adverse levels of $PM_{2.5}$ with metabolic diseases align with previous studies and analyses. Several meta-analyses found an overall association with PM and diabetes and obesity markers, whereas associations with other air pollutants such as NO_2, PM_{10}, or ozone were mixed.[11, 12, 16, 19, 53] In our study, we show that the associations of NO_2 were reversed in two-exposure models, suggesting that $PM_{2.5}$ may have confounded the associations. However, studies with higher levels of NO_2 or other air pollutants have observed positive associations with diabetes and obesity-related measures.[54-56] This suggest that our findings may not be generalizable to highly pollutant areas. Nevertheless, annual mean residential levels of NO_2 and $PM_{2.5}$ exceeded the WHO recommended levels.[57]

Reviews by Rajagopalan et al.[20, 21] gave a summary of the evident mechanistic insights of how air pollutants, in particular PM, affect human metabolism. For example, studies in humans and mice showed a deterioration of endothelial function and insulin sensitivity.[20, 21] Local inflammation in visceral adipose tissue and liver were reported, characterized by increased number of macrophages, oxidative stress, and mitochondrial dysfunction, all linking air pollution to diabetes and obesity.[20, 21]

Air temperature

For annual mean air temperature, our results were mixed and inconclusive, so we could not draw clear conclusions about its effect on diabetes and obesity-related measures. In contrast, two studies using data from the Spanish “Di@bet.es Study” found that an increase from the lowest to the highest quartile of annual air temperature was associated with 1.39 and 1.38 higher odds of diabetes and obesity, respectively.[14, 58] However, Wallwork et al.[59] and Speakman et al.[60] found that increases in air temperature were associated with diabetes prevalence, but not with obesity. These studies reported annual mean air temperature ranges of more than 10°C, which shows a higher variability than in our study (6°C). Previous studies on potential mechanistic pathways have focused on the effects of short-term exposure to air temperature, arguing that exposure to cold may increase activity of brown adipose tissue, which modulates triglyceride accumulation and is associated with improved insulin sensitivity.[58, 61] Furthermore, air temperature may also act via lifestyle changes, as optimal temperatures may increase active transportation and physical activity compared to non-optimal temperatures. However, we assumed that air temperature variability in our study was limited and therefore, would not affect physical activity behavior of participants, as confirmed by our sensitivity analysis. Consequently, multi-country studies which provide more air temperature variability may give important insights into the association of air temperature with metabolic health.

Road traffic noise

We identified robust associations of road traffic noise with diabetes and obesity-related measures, independent of other environmental exposures. Furthermore, noise was the main contributor to the multi-exposure associations. This is in line with previous studies that have found consistent associations between noise exposure and several metabolic-related markers.[13, 18] In a subsample of the NAKO study, we also demonstrated an association of road traffic noise exposure with adipose tissue depots and hepatic fat content measured by whole-body magnetic resonance imaging *(under review)*.[62] There are multiple reviews summarizing the harmful effects of noise exposure on human metabolism.[22, 63] Noise, especially during night, can disrupt sleep and affects its quality.[64, 65] This can result in metabolic abnormalities, characterized by an imbalance in hormones regulating appetite and satiety, which can further lead to an imbalance between energy intake and expenditure.[56] The other pathway involves an overactive hypothalamic-pituitary-adrenal axis and sympathetic nervous system that comes along with increased release of stress hormones such as adrenaline, cortisol or catecholamines, that in turn leads to increased oxidative stress and a constant state of inflammation.[22] We need to note that modeling of road traffic noise exposure is only available at urban areas with > 100,000 inhabitants and along major roads with more than 3 million vehicles per year.[42] However, we were lacking adequate noise exposure assessment in rural and remote areas, nor were we able to take into account other potential sources of noise, such as aircraft or railway, which may have an additional impact on metabolic health.[66]

<u>Greenness</u>

We observed non-linear associations of greenness with diabetes and obesity-related measures, which is comparable to numerous previous studies, although the described shape of the exposure-response function varied between studies.[67-69] Non-linear associations may account for previous mixed evidence on the effect of surrounding greenness on metabolic health.[15, 17] In our study, we observed that these non-linear associations were driven by urban areas, suggesting potential residual confounding. We hypothesize that high NDVI levels in urban areas may be attributed to highly vegetated parks and areas on the outskirts of cities. On the other side, central urban areas may offer more opportunities for indoor physical activity with higher numbers of gyms, which may have resulted in the unexpected association of lower NDVI being related to lower odds of diabetes, obesity and lower BMI and waist circumference. Klompmaker et al.[69] reported that natural greenness is associated with lower odds of overweight and higher physical activity levels, whereas contrary associations were found for urban green. In addition, NDVI as an indicator of greenness has some disadvantages, as it cannot distinguish between different types of greenness, such as parks, grassland, crops, and it does not provide any information on time spent in greenness or accessibility.[67, 70] These aspects have shown to be important determinants of whether greenness positively affect mental health and physical activity behavior.[67, 71, 72]

<u>Joint associations</u>

Recently, the question of how multiple environmental exposures jointly contribute to disease risk has been raised, but only a few studies have investigated metabolic health outcomes.[24, 26, 27, 50, 73] A study by Klompmaker et al.[24] used the cumulative risk index to quantify the cumulative effects of exposures to air pollution, noise and greenness and found a joint odds ratio of 1.13 for diabetes, which was higher than the associations found in single-exposure models. Similarly, a study from Denmark showed a cumulative risk index of 1.12 for diabetes when considering air pollution, greenness and noise together.[26] Applying a quantile-g computation that can handle multi-collinearity, non-additivity and non-linearity,[49] we found joint associations of multiple adverse environmental exposures and diabetes and obesity-related measures. Similarly, Zhang et al.[27] performed a quantile g-computation in two prospective US-based cohorts of female nurses. They observed a negative joint association between their environmental exposures, including air pollution, nighttime noise, greenness, light at night, air temperature, neighborhood SES, and BMI. However, this protective joint association was predominantly driven by neighborhood SES. After dropping the neighborhood SES variable from the models, the environmental exposure mixture was associated with 0.16 kg/m² and 0.06 kg/m² higher BMI in the two cohorts.[27] Partially consistent with our findings, the positive joint associations were mainly driven by the air pollutants NO_2, $PM_{2.5}$ and nighttime noise.[27] In contrast, NO_2 seemed to be confounded in our study in multi-exposure models, which resulted in a contribution of NO_2 to the negative joint association. In addition, we cannot explain why the contribution of weight differed for the joint association between environmental exposures and diabetes in women. Therefore, more research is needed that examines multiple environmental factors together and that investigates potential synergistic and interactive effects.

Degree of urbanization

We observed that adjusting for population density had a strong impact on the associations of air pollution with obesity-related markers. Population density and degree of urbanization may be a proxy for several infrastructure-related variables such as a higher proportion of active travel options, increased walkability and connectivity, a diverse food environment,[74-76] or explain some population characteristics that differed by sex and SES and that may confound the association of some environmental factors with obesity. With regard to the present study, we hypothesized that study center and unemployment rate at the district level may have been too coarse to capture these unmeasured confounders. Contributing to this, the associations of air pollution and road traffic noise were most pronounced in urban areas. Furthermore, study centers with a high proportion of urban areas tended to show expected associations of air pollution with diabetes and obesity-related measures, whereas study centers with regions including a mixture of urban, suburban and rural areas contributed to unexpected protective or null findings. In addition to global trends of higher rates of obesity in rural area,[77-79] these heterogeneous findings indicate that additional factors may contribute to the development of diabetes and obesity in rural areas, which require further investigation.

Strengths and limitations

Our study has several strengths. First, we used data from a large, deeply phenotyped, multi-center cohort study that provided sufficient exposure contrast, included participants from with diverse socio-economic and urbanized environments, and provided several measures of metabolic function. In particular, BMI is critically discussed as measure of obesity,[80] but the

NAKO study allowed us to compare associations across a range of different measures of adiposity. In addition, we used a novel, powerful method to assess the joint associations of environmental exposure mixtures with diabetes and obesity-related measures. Rather than assessing the association of one exposure while the other exposures are kept constant, the quantile g-computation assesses the associations of the mixture by increasing all exposures by the pre-defined increment.[27, 49] As a result, this method may better reflect reality because it takes into account co-existing exposures and deals with multi-collinearity, thus reducing a potential bias of the association of environmental factors with diabetes and obesity.

We note the following limitations of our study. Firstly, misclassification in diabetes cases may be present as we had to rely on self-reported information on diabetes diagnosis. Information on type of diabetes, blood markers, such as hemoglobin A1c, or oral glucose tolerance test results to identify undetected diabetes, was not available at the time of analysis, which would be interesting to investigate in future studies. Secondly, we cannot rule out residual confounding. The proxy of unemployment rate for neighborhood SES was only available at the district level, which was likely too coarse to adequately adjust for potential unmeasured spatial confounders. Thirdly, we did not have information on diet at the time of the study. However, we assumed that dietary factors might have explained some of the heterogeneity of our participants, but our previous findings in the KORA-Fit study did not show relevant confounding by diet.[31] In addition, environmental exposures were available at different resolutions and for different exposure windows, which could introduce exposure measurement errors. In our study, we assume that the spatial and temporal distributions of environmental exposures are relatively stable, as shown in previous studies.[38, 39] Nevertheless, it may have impacted the assessment of joint associations by quantile g-computation, that these methods tend to give more weight to the exposure with the least measurement error.[27, 50] Furthermore, we only had cross-sectional data, which did not allow us to observe a temporal sequence of exposure and outcome. Consequently, we only observed associations and not causal effects, which is specifically true for quantile g-computation which aims to assess causal effects. Therefore, future longitudinal studies investigating the effects of multiple environmental exposures jointly on diabetes and obesity are warranted.

Conclusion

In this large multi-center cohort study, we investigated the associations of six different environmental exposures with diabetes and obesity-related measures. We observed that $PM_{2.5}$ and road traffic noise were consistently associated with diabetes and measures of obesity, particularly in urban areas, using single-exposure models. NDVI showed an inverted U-shaped exposure-response curve with all outcomes. In addition, stronger joint associations were observed when multiple exposures were considered simultaneously, suggesting that targeting multiple environmental exposure together may be beneficial in the prevention of diabetes and obesity. Longitudinal studies are needed to corroborate causal effects of co-existing environmental exposures on diabetes and obesity. Moreover, this study highlights the need to identify socio-economic and environmental drivers that can explain differences in diabetes and obesity-related measures between urban and rural areas in future studies.

Declarations

Conflict of interest

The authors have no conflicts of interest to declare.

Ethics approval and consent to participate

The German National Cohort (NAKO) was approved by the initial vote of the ethics committee of the Bavarian Medical Association (“Bayerische Landesärztekammer” (BLÄK), protocol code 13023), followed by votes from all local on-site institutional review boards, and written informed consent of all participants was obtained at the time of study enrollment. The study was conducted in accordance with the Declaration of Helsinki of 1975 (in the current, revised version).

Acknowledgements / Funding

The NAKO is funded by the Federal Ministry of Education and Research (BMBF) [project funding reference numbers: 01ER1301A/B/C, 01ER1511D, 01ER1801A/B/C/D and 01ER2301A/B/C], the federal states and the Helmholtz Association, with additional financial support by the participating universities and the institutes of the Leibniz Association. The compilation of noise data was funded by the Helmholtz Association's Initiative and Networking Fund (ZT-I-PF-5-42). The manuscript was part of the NAKO data application NAKO-597.We thank all participants who took part in the NAKO and the staff of this research initiative.

Authorship contributions

Fiona Niedermayer: Conceptualization, Methodology, Data Curation, Formal analysis, Visualization, Writing - Original Draft; Writing - Review & Editing; **Barbara Hoffmann**: Supervision, Methodology, Resources, Writing - Review & Editing; **Boya Zhang**: Methodology, Writing - Review & Editing; **Jie Chen**: Methodology, Writing - Review & Editing; **Jaime E. Hart**: Methodology, Writing - Review & Editing; **Francine Laden**: Methodology, Writing - Review & Editing; **Gabriele Bolte**: Resources, Writing - Review & Editing; **Tobia Lakes**: Resources, Writing - Review & Editing; **Tamara Schikowski**: Resources, Writing - Review & Editing; **Karin Halina Greiser**: Resources, Writing - Review & Editing; **Jeroen Staab**: Data curation, Resources, Writing - Review & Editing; **Nikolaos Nikolaou**: Data curation, Resources, Writing - Review & Editing; **Marco Dallavalle**: Data curation, Resources, Writing - Review & Editing; **Matthias B. Schulze**: Resources, Writing - Review & Editing; **Wolfgang Lieb**: Resources, Writing - Review & Editing; **Cara Övermöhle**: Resources, Writing - Review & Editing; **Thaddäus Tönnies**: Resources, Writing - Review & Editing; **Verena Katzke**: Resources, Writing - Review & Editing; **Heiko Becher**: Resources, Writing - Review & Editing; **Beate Fischer**: Resources, Writing - Review & Editing; **Michael Leitzmann**: Resources, Writing - Review & Editing; **Klaus Berger**: Resources, Writing - Review & Editing; **Fatemeh Mayvaneh**: Resources, Writing - Review & Editing; **Thomas Keil**: Resources, Writing - Review & Editing; **Lilian Krist**: Resources, Writing - Review & Editing; **Carolina J. Klett-Tammen**: Resources, Writing - Review & Editing; **Jana-Kristin Heise**: Resources, Writing - Review & Editing; **Tobias Pischon**: Resources, Writing - Review & Editing; **Ilais Moreno Velásquez**: Resources, Writing - Review & Editing; **Börge Schmidt**: Resources, Writing - Review & Editing; **Rajini Nagrani**: Resources, Writing - Review & Editing; **Stefan Rach**: Resources, Writing - Review & Editing; **Hermann Brenner**: Resources, Writing - Review & Editing; **Bernd Holleczek**: Resources, Writing - Review & Editing; **Volker Harth**: Resources, Writing - Review & Editing; **Nadia Obi**: Resources, Writing - Review & Editing; **Anna Köttgen**: Resources, Writing - Review & Editing; **Rafael Mikolajczyk**: Resources, Writing - Review & Editing; **Claudia Meinke-Franze**: Resources, Writing - Review & Editing; **Wolfgang Hoffmann**: Resources, Writing - Review & Editing; **Alexandra Schneider**: Data curation, Resources, Methodology, Writing - Review & Editing; **Kathrin Wolf**: Data curation, Resources, Methodology, Writing - Review & Editing; **Annette Peters**: Conceptualization, Methodology, Supervision, Resources, Writing - Review & Editing, Funding acquisition

Data sharing

The datasets analyzed during the current study are not publicly available. Access to and use of NAKO data and biosamples can be obtained via an electronic application portal (https://transfer.nako.de). Analysis codes are available from the authors upon request.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used DeepL in order to improve the readability and language of this manuscript. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

References

1. Global Burden of Disease 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2023;402(10397):203-34. https://doi.org/10.1016/S0140-6736(23)01301-6.
2. Sorensen TIA, Martinez AR, Jorgensen TSH. Epidemiology of Obesity. Handb Exp Pharmacol. 2022;274:3-27. https://doi.org/10.1007/164_2022_581.
3. Bluher M. Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol. 2019;15(5):288-98. https://doi.org/10.1038/s41574-019-0176-8.
4. Non-Communicable Disease Risk Factor Collaboration. Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. Lancet. 2024;403(10431):1027-50. https://doi.org/10.1016/S0140-6736(23)02750-2.
5. Schienkiewitz A, Kuhnert R, Blume M, Mensink GBM. Overweight and obesity among adults in Germany - Results from GEDA 2019/2020-EHIS. J Health Monit. 2022;7(3):21-8. https://doi.org/10.25646/10293.
6. Hoffmann K, De Gelder R, Hu Y, Bopp M, Vitrai J, Lahelma E, et al. Trends in educational inequalities in obesity in 15 European countries between 1990 and 2010. Int J Behav Nutr Phys Act. 2017;14(1):63. https://doi.org/10.1186/s12966-017-0517-8.
7. Global Burden of Disease Risk Factors Collaborators. Global burden and strength of evidence for 88 risk factors in 204 countries and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2024;403(10440):2162-203. https://doi.org/10.1016/S0140-6736(24)00933-4.
8. Rojas-Rueda D, Morales-Zamora E, Alsufyani WA, Herbst CH, AlBalawi SM, Alsukait R, et al. Environmental Risk Factors and Health: An Umbrella Review of Meta-Analyses. Int J Environ Res Public Health. 2021;18(2). https://doi.org/10.3390/ijerph18020704.
9. Global Burden of Diseases Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of

Disease Study 2019. Lancet. 2020;396(10258):1204-22. https://doi.org/10.1016/S0140-6736(20)30925-9.

10. WHO (World Health Organization). Environmental Noise Guidelines for the European Region 2018. Available from: https://www.euro.who.int/__data/assets/pdf_file/0008/383921/noise-guidelines-eng.pdf.

11. He D, Wu S, Zhao H, Qiu H, Fu Y, Li X, et al. Association between particulate matter 2.5 and diabetes mellitus: A meta-analysis of cohort studies. J Diabetes Investig. 2017;8(5):687-96. https://doi.org/10.1111/jdi.12631.

12. Yang BY, Fan S, Thiering E, Seissler J, Nowak D, Dong GH, et al. Ambient air pollution and diabetes: A systematic review and meta-analysis. Environ Res. 2020;180:108817. https://doi.org/10.1016/j.envres.2019.108817.

13. Wang H, Sun D, Wang B, Gao D, Zhou Y, Wang N, et al. Association between noise exposure and diabetes: meta-analysis. Environ Sci Pollut Res Int. 2020;27(29):36085-90. https://doi.org/10.1007/s11356-020-09826-6.

14. Valdes S, Doulatram-Gamgaram V, Lago A, Garcia Torres F, Badia-Guillen R, Olveira G, et al. Ambient temperature and prevalence of diabetes and insulin resistance in the Spanish population: Di@bet.es study. Eur J Endocrinol. 2019;180(5):273-80. https://doi.org/10.1530/EJE-18-0818.

15. De la Fuente F, Saldias MA, Cubillos C, Mery G, Carvajal D, Bowen M, et al. Green Space Exposure Association with Type 2 Diabetes Mellitus, Physical Activity, and Obesity: A Systematic Review. Int J Environ Res Public Health. 2020;18(1). https://doi.org/10.3390/ijerph18010097.

16. An R, Ji M, Yan H, Guan C. Impact of ambient air pollution on obesity: a systematic review. Int J Obes (Lond). 2018;42(6):1112-26. https://doi.org/10.1038/s41366-018-0089-y.

17. Luo YN, Huang WZ, Liu XX, Markevych I, Bloom MS, Zhao T, et al. Greenspace with overweight and obesity: A systematic review and meta-analysis of epidemiological studies up to 2020. Obes Rev. 2020;21(11):e13078. https://doi.org/10.1111/obr.13078.

18. Gui SY, Wu KJ, Sun Y, Chen YN, Liang HR, Liu W, et al. Traffic noise and adiposity: a systematic review and meta-analysis of epidemiological studies. Environ Sci Pollut Res Int. 2022. https://doi.org/10.1007/s11356-022-19056-7.

19. Huang S, Zhang X, Huang J, Lu X, Liu F, Gu D. Ambient air pollution and body weight status in adults: A systematic review and meta-analysis. Environ Pollut. 2020;265(Pt A):114999. https://doi.org/10.1016/j.envpol.2020.114999.

20. Rajagopalan S, Brook RD. Air Pollution and Type 2 Diabetes. Diabetes. 2012;61(12):3037-45. https://doi.org/10.2337/db12-0190.

21. Rajagopalan S, Brook RD, Salerno P, Bourges-Sevenier B, Landrigan P, Nieuwenhuijsen MJ, et al. Air pollution exposure and cardiometabolic risk. Lancet Diabetes Endocrinol. 2024;12(3):196-208. https://doi.org/10.1016/S2213-8587(23)00361-3.

22. Munzel T, Molitor M, Kuntic M, Hahad O, Roosli M, Engelmann N, et al. Transportation Noise Pollution and Cardiovascular Health. Circ Res. 2024;134(9):1113-35. https://doi.org/10.1161/CIRCRESAHA.123.323584.

23. Fong KC, Hart JE, James P. A Review of Epidemiologic Studies on Greenness and Health: Updated Literature Through 2017. Curr Environ Health Rep. 2018;5(1):77-87. https://doi.org/10.1007/s40572-018-0179-y.

24. Klompmaker JO, Janssen NAH, Bloemsma LD, Gehring U, Wijga AH, van den Brink C, et al. Associations of Combined Exposures to Surrounding Green, Air Pollution, and Road Traffic

Noise with Cardiometabolic Diseases. Environ Health Perspect. 2019;127(8):87003. https://doi.org/10.1289/EHP3857.

25. Nieuwenhuijsen MJ. Urban and transport planning pathways to carbon neutral, liveable and healthy cities; A review of the current evidence. Environ Int. 2020;140:105661. https://doi.org/10.1016/j.envint.2020.105661.

26. Sorensen M, Poulsen AH, Hvidtfeldt UA, Brandt J, Frohn LM, Ketzel M, et al. Air pollution, road traffic noise and lack of greenness and risk of type 2 diabetes: A multi-exposure prospective study covering Denmark. Environ Int. 2022;170:107570. https://doi.org/10.1016/j.envint.2022.107570.

27. Zhang B, Hart JE, Laden F, Bozigar M, James P. Environmental mixtures and body mass index in two prospective US-based cohorts of female nurses. J Hazard Mater. 2024;480:135794. https://doi.org/10.1016/j.jhazmat.2024.135794.

28. Pyko A, Eriksson C, Lind T, Mitkovskaya N, Wallas A, Ogren M, et al. Long-Term Exposure to Transportation Noise in Relation to Development of Obesity-a Cohort Study. Environ Health Perspect. 2017;125(11):117005. https://doi.org/10.1289/EHP1910.

29. Altug H, Ogurtsova K, Breyer-Kohansal R, Schiffers C, Ofenheimer A, Tzivian L, et al. Associations of long-term exposure to air pollution and noise with body composition in children and adults: Results from the LEAD general population study. Environ Int. 2024;189:108799. https://doi.org/10.1016/j.envint.2024.108799.

30. Yang Z, Song Q, Li J, Zhang Y. Air Pollution as a Cause of Obesity: Micro-Level Evidence from Chinese Cities. Int J Environ Res Public Health. 2019;16(21). https://doi.org/10.3390/ijerph16214296.

31. Niedermayer F, Wolf K, Zhang S, Dallavalle M, Nikolaou N, Schwettmann L, et al. Sex-specific associations of environmental exposures with prevalent diabetes and obesity - Results from the KORA Fit study. Environ Res. 2024;252(Pt 3):118965. https://doi.org/10.1016/j.envres.2024.118965.

32. Peters A, German National Cohort C, Peters A, Greiser KH, Gottlicher S, Ahrens W, et al. Framework and baseline examination of the German National Cohort (NAKO). Eur J Epidemiol. 2022. https://doi.org/10.1007/s10654-022-00890-5.

33. Rach S, Sand M, Reineke A, Becher H, Greiser KH, Wolf K, et al. The baseline examinations of the German National Cohort (NAKO): recruitment protocol, response, and weighting. European Journal of Epidemiology [in press]. 2025.

34. Jaeschke L, Steinbrecher A, Greiser KH, Dorr M, Buck T, Linseisen J, et al. [Assessment of self-reported cardiovascular and metabolic diseases in the German National Cohort (GNC, NAKO Gesundheitsstudie): methods and initial results]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2020;63(4):439-51. https://doi.org/10.1007/s00103-020-03108-9.

35. Fischer B, Sedlmeier AM, Hartwig S, Schlett CL, Ahrens W, Bamberg F, et al. Anthropometric measures in the German National Cohort-more than weight and height. Bundesgesundheitsbla. 2020;63(3):290-300. https://doi.org/10.1007/s00103-020-03096-w.

36. WHO (World Health Organization). Obesity : preventing and managing the global epidemic : report of a WHO consultation. Geneva, Switzerland: WHO; 2000. Available from: https://iris.who.int/handle/10665/42330.

37. WHO (World Health Organization). Waist Circumference and Waist–Hip Ratio: Report of a WHO Expert Consultation Geneva, 8–11 December 2008 Geneva: WHO 2008. Available from:

http://apps.who.int/iris/bitstream/handle/10665/44583/9789241501491_eng.pdf?sequence=1.

38. Wolf K, Dallavalle M, Niedermayer F, Bolte G, Tobia Lakes TS, Greiser KH, et al. Environmental exposure assessment in the German National Cohort (NAKO). Environmental Research [in press]. 2025. https://doi.org/10.1016/j.envres.2025.121259.

39. de Hoogh K, Chen J, Gulliver J, Hoffmann B, Hertel O, Ketzel M, et al. Spatial PM2.5, NO2, O3 and BC models for Western Europe - Evaluation of spatiotemporal stability. Environ Int. 2018;120:81-92. https://doi.org/10.1016/j.envint.2018.07.036.

40. Nikolaou N, Dallavalle M, Stafoggia M, Bouwer LM, Peters A, Chen K, et al. High-resolution spatiotemporal modeling of daily near-surface air temperature in Germany over the period 2000-2020. Environ Res. 2023;219:115062. https://doi.org/10.1016/j.envres.2022.115062.

41. Staab J, Droin A, Weigand M, Dallavalle M, Wolf K, Schady A, et al. [Pre-print]. Pixels, Chisels and Contours - Technical Variations in European Road Traffic Noise Exposure Maps. 2024. https://doi.org/10.2139/ssrn.4879933.

42. European Comission. Directive 2002/49/EC of the European parliament and of the council of 25 June 2002 relating to the assessment and management of environmental noise. Official Journal of the European Communities; 2002. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32002L0049.

43. Leitzmann M, Gastell S, Hillreiner A, Herbolsheimer F, Baumeister SE, Bohn B, et al. [Physical activity in the German National Cohort (NAKO): use of multiple assessment tools and initial results]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2020;63(3):301-11. https://doi.org/10.1007/s00103-020-03099-7.

44. UNESCO Institute for Statistics. International Standard Classification of Education ISCED 2011. Montreal, Canada: UNESCO Institute for Statistics 2012. Available from: https://uis.unesco.org/sites/default/files/documents/international-standard-classification-of-education-isced-2011-en.pdf.

45. Bundesagentur für Arbeit [Federal Employment Agency]. Last access: 04.03.2025. Available from: https://www.bmfsfj.de/bmfsfj/service/online-rechner/gleichstellungsatlas?view=.

46. WIGeoGIS Gesellschaft für digitale Wirtschaftsgeographie GmbH. Last access: 04.03.2025. Available from: https://www.wigeogis.com/de/impressum.

47. European Union. Methodological manual on territorial typologies. Luxembourg: Publications Office of the European Union,; 2018. Report No.: 2315-0815.Last access: 23.12.2022. Available from: https://ec.europa.eu/eurostat/documents/3859598/9507230/KS-GQ-18-008-EN-N.pdf.

48. Wood SN. Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. J Roy Stat Soc B. 2011;73:3-36. https://doi.org/10.1111/j.1467-9868.2010.00749.x.

49. Keil AP, Buckley JP, O'Brien KM, Ferguson KK, Zhao S, White AJ. A Quantile-Based g-Computation Approach to Addressing the Effects of Exposure Mixtures. Environ Health Perspect. 2020;128(4):47004. https://doi.org/10.1289/EHP5838.

50. Chen J, Hart JE, Fisher NDL, Yanosky JD, Roscoe C, James P, et al. Multiple Environmental Exposures and the Development of Hypertension in a Prospective US-Based Cohort of Female Nurses: A Mixture Analysis. Environ Sci Technol. 2024;58(32):14146-57. https://doi.org/10.1021/acs.est.4c03722.

51. Stevens DR, Rosen EM, Van Wickle K, McNell EE, Bommarito PA, Calafat AM, et al. Early pregnancy phthalates and replacements in relation to fetal growth: The human placenta and

phthalates study. Environ Res. 2023;229:115975. https://doi.org/10.1016/j.envres.2023.115975.

52. Schunk M, Reitmeir P, Schipf S, Volzke H, Meisinger C, Thorand B, et al. Health-related quality of life in subjects with and without Type 2 diabetes: pooled analysis of five population-based surveys in Germany. Diabet Med. 2012;29(5):646-53. https://doi.org/10.1111/j.1464-5491.2011.03465.x.

53. Yang M, Cheng H, Shen C, Liu J, Zhang H, Cao J, et al. Effects of long-term exposure to air pollution on the incidence of type 2 diabetes mellitus: a meta-analysis of cohort studies. Environ Sci Pollut Res Int. 2020;27(1):798-811. https://doi.org/10.1007/s11356-019-06824-1.

54. Pan W, Wang M, Hu Y, Lian Z, Cheng H, Qin JJ, et al. The association between outdoor air pollution and body mass index, central obesity, and visceral adiposity index among middle-aged and elderly adults: a nationwide study in China. Front Endocrinol (Lausanne). 2023;14:1221325. https://doi.org/10.3389/fendo.2023.1221325.

55. Han W, Xu Z, Hu X, Cao R, Wang Y, Jin J, et al. Air pollution, greenness and risk of overweight among middle-aged and older adults: A cohort study in China. Environ Res. 2023;216(Pt 1):114372. https://doi.org/10.1016/j.envres.2022.114372.

56. Li ZH, Zhong WF, Zhang XR, Chung VC, Song WQ, Chen Q, et al. Association of physical activity and air pollution exposure with the risk of type 2 diabetes: a large population-based prospective cohort study. Environ Health. 2022;21(1):106. https://doi.org/10.1186/s12940-022-00922-3.

57. WHO (World Health Organization). WHO global air quality guidelines: particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. Geneva: World Health Organization; 2021.Last access: 23.01.2025. Available from: https://www.who.int/publications/i/item/9789240034228/.

58. Valdes S, Maldonado-Araque C, Garcia-Torres F, Goday A, Bosch-Comas A, Bordiu E, et al. Ambient temperature and prevalence of obesity in the Spanish population: The Di@bet.es study. Obesity (Silver Spring). 2014;22(11):2328-32. https://doi.org/10.1002/oby.20866.

59. Wallwork RS, Colicino E, Zhong J, Kloog I, Coull BA, Vokonas P, et al. Ambient Fine Particulate Matter, Outdoor Temperature, and Risk of Metabolic Syndrome. Am J Epidemiol. 2017;185(1):30-9. https://doi.org/10.1093/aje/kww157.

60. Speakman JR, Heidari-Bakavoli S. Type 2 diabetes, but not obesity, prevalence is positively associated with ambient temperature. Sci Rep. 2016;6:30409. https://doi.org/10.1038/srep30409.

61. Marlatt KL, Ravussin E. Brown Adipose Tissue: an Update on Recent Findings. Curr Obes Rep. 2017;6(4):389-96. https://doi.org/10.1007/s13679-017-0283-6.

62. Niedermayer F, Rospleszcz S, Matthiessen C, Hoffmann B, Stoecklein S, Haueise T, et al. Associations of road traffic noise with adipose tissue depots and hepatic fat content – Results from the German National Cohort (NAKO). Submitted to Environment International [unpublished work]. 2024.

63. Sivakumaran K, Ritonja JA, Waseem H, AlShenaiber L, Morgan E, Ahmadi SA, et al. Impact of Noise Exposure on Risk of Developing Stress-Related Metabolic Effects: A Systematic Review and Meta-Analysis. Noise Health. 2022;24(115):215-30. https://doi.org/10.4103/nah.nah_21_22.

64. Smith MG, Cordoza M, Basner M. Environmental Noise and Effects on Sleep: An Update to the WHO Systematic Review and Meta-Analysis. Environ Health Perspect. 2022;130(7):76001. https://doi.org/10.1289/EHP10197.

65. Cappuccio FP, Miller MA. Sleep and Cardio-Metabolic Disease. Curr Cardiol Rep. 2017;19(11):110. https://doi.org/10.1007/s11886-017-0916-0.

66. Bozigar M, Laden F, Hart JE, Redline S, Huang T, Whitsel EA, et al. Aircraft noise exposure and body mass index among female participants in two Nurses' Health Study prospective cohorts living around 90 airports in the United States. Environment International. 2024. https://doi.org/10.1016/j.envint.2024.108660.

67. Dempsey S, Lyons S, Nolan A. Urban green space and obesity in older adults: Evidence from Ireland. SSM Popul Health. 2018;4:206-15. https://doi.org/10.1016/j.ssmph.2018.01.002.

68. James P, Kioumourtzoglou MA, Hart JE, Banay RF, Kloog I, Laden F. Interrelationships Between Walkability, Air Pollution, Greenness, and Body Mass Index. Epidemiology. 2017;28(6):780-8. https://doi.org/10.1097/EDE.0000000000000724.

69. Klompmaker JO, Hoek G, Bloemsma LD, Gehring U, Strak M, Wijga AH, et al. Green space definition affects associations of green space with overweight and physical activity. Environ Res. 2018;160:531-40. https://doi.org/10.1016/j.envres.2017.10.027.

70. Evenson KR, Williamson S, Han B, McKenzie TL, Cohen DA. United States' neighborhood park use and physical activity over two years: The National Study of Neighborhood Parks. Prev Med. 2019;123:117-22. https://doi.org/10.1016/j.ypmed.2019.03.027.

71. Villeneuve PJ, Jerrett M, Su JG, Weichenthal S, Sandler DP. Association of residential greenness with obesity and physical activity in a US cohort of women. Environ Res. 2018;160:372-84. https://doi.org/10.1016/j.envres.2017.10.005.

72. Astell-Burt T, Mitchell R, Hartig T. The association between green space and mental health varies across the lifecourse. A longitudinal study. J Epidemiol Community Health. 2014;68(6):578-83. https://doi.org/10.1136/jech-2013-203767.

73. Voss S, Schneider A, Huth C, Wolf K, Markevych I, Schwettmann L, et al. ENVINT-D-20-01309: Long-term exposure to air pollution, road traffic noise, residential greenness, and prevalent and incident metabolic syndrome: Results from the population-based KORA F4/FF4 cohort in Augsburg, Germany. Environ Int. 2021;147:106364. https://doi.org/10.1016/j.envint.2020.106364.

74. Ohanyan H, Portengen L, Huss A, Traini E, Beulens JWJ, Hoek G, et al. Machine learning approaches to characterize the obesogenic urban exposome. Environ Int. 2022;158:107015. https://doi.org/10.1016/j.envint.2021.107015.

75. Sun B, Yao X, Yin C. An N-Shaped Association between Population Density and Abdominal Obesity. Int J Environ Res Public Health. 2022;19(15). https://doi.org/10.3390/ijerph19159577.

76. Sarkar C, Webster C, Gallacher J. Association between adiposity outcomes and residential density: a full-data, cross-sectional analysis of 419 562 UK Biobank adult participants. Lancet Planet Health. 2017;1(7):e277-e88. https://doi.org/10.1016/S2542-5196(17)30119-5.

77. Liu M, Tang W, Zhang Y, Wang Y, Baima K, Li Y, et al. Urban-rural differences in the association between long-term exposure to ambient air pollution and obesity in China. Environ Res. 2021;201:111597. https://doi.org/10.1016/j.envres.2021.111597.

78. Non-Communicable Disease Risk Factor Collaboration. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. Lancet. 2017;390(10113):2627-42. https://doi.org/10.1016/S0140-6736(17)32129-3.

79. Lee GY, Um YJ. Factors Affecting Obesity in Urban and Rural Adolescents: Demographic, Socioeconomic Characteristics, Health Behavior and Health Education. Int J Environ Res Public Health. 2021;18(5). https://doi.org/10.3390/ijerph18052405.

80. Rubino F, Cummings DE, Eckel RH, Cohen RV, Wilding JPH, Brown WA, et al. Definition and diagnostic criteria of clinical obesity. Lancet Diabetes Endocrinol. 2025. https://doi.org/10.1016/S2213-8587(24)00316-4.

Table 1 Participants' characteristics in the final analytical sample of the German National Cohort (NAKO), overall and stratified by sex.

	Overall (n = 174,955)	**Men (n = 86,710)**	**Women (n = 88,245)**
Sex, female n (%)	88,245 (50.4)	-	88,245 (100.0)
Age (years), mean (SD)	49.5 (12.8)	49.6 (12.8)	49.5 (12.7)
Diagnosis of diabetes, yes n (%)	9,747 (5.6)	5,352 (6.2)	4,395 (5.0)
Age at diabetes diagnosis, mean (SD)	47.6 (13.1)	49.9 (12.0)	44.9 (13.8)
Obesity (≥ 30 kg/m²) yes n (%)	36,579 (20.9)	19,096 (22.0)	17,483 (19.8)
Body Mass Index (kg/m²), mean (SD)	26.60 (5.04)	27.19 (4.47)	26.01 (5.48)
Waist circumference (cm), mean (SD)	91.02 (14.31)	96.52 (12.92)	85.62 (13.54)
Physical activity (min/week), mean (SD)	1,440 (1,583)	1,466 (1,621)	1,415 (1,544)
Quintiles of physical activity, n (%)			
Q1	30,679 (17.5)	15,560 (17.9)	15,119 (17.1)
Q2	35,860 (20.5)	17,915 (20.7)	17,945 (20.3)
Q3	36,717 (21.0)	17,790 (20.5)	18,927 (21.4)
Q4	36,009 (20.6)	17,820 (20.6)	18,189 (20.6)
Q5	35,690 (20.4)	17,625 (20.3)	18,065 (20.5)
Alcohol consumption (g/day), mean (SD)	10.58 (16.70)	14.08 (19.39)	7.14 (12.63)
Smoking behavior, n (%)			
Never-smoker	81,151 (46.4)	36,374 (41.9)	44,777 (50.7)
Ex-smoker	56,988 (32.6)	30,547 (35.2)	26,441 (30.0)
Current smoker	36,816 (21.0)	19,789 (22.8)	17,027 (19.3)
Education (ISCED 2011), n (%)			
Primary	687 (0.4)	338 (0.4)	349 (0.4)
Lower secondary	3,527 (2.0)	1,274 (1.5)	2,253 (2.6)
Upper secondary	55,430 (31.7)	25,185 (29.0)	30,245 (34.3)
Post-secondary non-tertiary	15,700 (9.0)	6,426 (7.4)	9,274 (10.5)
Bachelor's	55,324 (31.6)	30,492 (35.2)	24,832 (28.1)
Master's	32,657 (18.7)	16,275 (18.8)	16,382 (18.6)
Doctoral	7,695 (4.4)	4,750 (5.5)	2,945 (3.3)
Still in education or training	3,935 (2.2)	1,970 (2.3)	1,965 (2.2)
Income (Euros), mean (SD)	3,721 (2,493)	3,975 (2,667)	3,466 (2,276)
Partnership, n (%)			
Single	32,807 (18.8)	14,051 (16.2)	18,756 (21.3)
Living with partner	124,039 (71.0)	63,983 (73.9)	60,056 (68.1)
Partner but living separately	17,894 (10.2)	8,576 (9.9)	9,318 (10.6)
Unemployment rate at district level (%), mean (SD)	8.62 (3.21)	8.60 (3.22)	8.63 (3.21)
Population density (n/m²), 1km buffer, mean (SD)	4,652 (4,363)	4,628 (4,350)	4,675 (4,375)
Degree of urbanization at municipality level, n (%)			
Urban	124,979 (71.4)	62,004 (71.5)	62,975 (71.4)
Suburban	27,923 (16.0)	13,771 (15.9)	14,152 (16.0)
Rural	22,045 (12.6)	10,933 (12.6)	11,112 (12.6)

*Q1: ≤ 210 min/wk for men, ≤ 200 min/wk for women, Q2: > 210 - ≤ 540 min/wk for men, > 200 - ≤ 530 min/wk for women, Q3: > 540 - ≤ 1,130 min/wk for men, > 530 - ≤ 1,110 min/wk for women, Q4: > 1,130 - ≤ 2,490 min/wk for men, > 1,110 - ≤ 2,370 min/wk for women, Q5: > 2,490 – 6,720 min/wk for men, > 2,370 – 6,720 for women.
Abbreviations: ISCED = International Standard Classification of Education, N = number, SD = standard deviation,

Table 2. Linear associations of environmental exposures with existing diabetes and obesity from single-exposure logistic regression models in the German National Cohort (NAKO).

		Self-reported diagnosis of diabetes		Obesity (BMI ≥ 30 kg/m²)	
Exposure	**IQR**	**Men (n = 86,710)**	**Women (n = 88,245)**	**Men (n = 86,710)**	**Women (n = 88,245)**
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
NO_2 [µg/m³]	10.6	1.10 (1.02; 1.19)	1.04 (0.96; 1.13)	1.05 (1.01; 1.10)	1.05 (1.01; 1.10)
$PM_{2.5}$ [µg/m³]	2.9	1.12 (1.02; 1.22)	1.11 (1.01; 1.22)	1.07 (1.02; 1.13)	1.10 (1.04; 1.16)
$PM_{2.5}$abs [$10^{-5}m^{-1}$]	0.5	1.08 (1.01; 1.15)	1.03 (0.96; 1.11)	1.01 (0.97; 1.05)	0.98 (0.95; 1.02)
T_{mean} [°C]	1.1	0.96 (0.90; 1.04)	1.10 (1.02; 1.19)	0.98 (0.94; 1.02)	1.00 (0.96; 1.04)
L_{den} (100m) [dB(A)]	8.3	1.08 (1.03; 1.13)	1.05 (1.00; 1.10)	1.07 (1.04; 1.09)	1.08 (1.05; 1.11)

Legend: All models were adjusted for age, study center, physical activity, alcohol consumption, smoking behavior, education, unemployment rate at district level and population density. ORs and confidence intervals are given per IQR increase in exposure. Diabetes was reported in n = 5,352 men and n = 4,395 women, and n = 19,096 men and n = 17,483 women were obese. Abbreviation: BMI = Body Mass Index, CI = confidence interval, IQR = interquartile range; L_{den} = day–evening–night noise level, NO_2= nitrogen dioxide, OR = odds ratio, $PM_{2.5}$ = particulate matter with diameter < 2.5 µm; $PM_{2.5}$abs= $PM_{2.5}$ absorbance, T_{mean} = annual mean temperature.

Table 3. Linear associations of environmental exposures with BMI and waist circumference from single-exposure linear regression models in the German National Cohort (NAKO).

		BMI		Waist circumference	
Exposure	**IQR**	**Men (n = 86,710)**	**Women (n = 88,245)**	**Men (n = 86,710)**	**Women (n = 88,245)**
		ß (95% CI)	ß (95% CI)	ß (95% CI)	ß (95% CI)
NO_2 [µg/m³]	10.6	0.06 (-0.02; 0.13)	0.13 (0.04; 0.22)	0.24 (0.04; 0.44)	0.25 (0.04; 0.47)
$PM_{2.5}$ [µg/m³]	2.9	0.11 (0.02; 0.20)	0.18 (0.07; 0.29)	0.40 (0.16; 0.64)	0.48 (0.21; 0.74)
$PM_{2.5}$abs [$10^{-5}m^{-1}$]	0.5	-0.02 (-0.09; 0.04)	-0.01 (-0.08; 0.07)	0.01 (-0.16; 0.18)	-0.05 (-0.24; 0.14)
T_{mean} [°C]	1.1	-0.06 (-0.12; 0.01)	-0.07 (-0.15; 0.01)	-0.25 (-0.43; -0.07)	-0.28 (-0.48; -0.08)
L_{den} (100m) [dB(A)]	8.3	0.11 (0.06; 0.15)	0.22 (0.16; 0.27)	0.26 (0.15; 0.38)	0.46 (0.34; 0.59)

Legend: All models were adjusted for age, study center, physical activity, alcohol consumption, smoking behavior, education, unemployment rate at district level and population density. Betas and confidence intervals are given as IQR increase in exposure. Abbreviation: BMI = Body Mass Index, CI = confidence interval, IQR = interquartile range, L_{den} = day–evening–night noise level, NO_2= nitrogen dioxide, $PM_{2.5}$ = particulate matter with diameter < 2.5 µm, $PM_{2.5}$abs= $PM_{2.5}$ absorbance, T_{mean} = annual mean temperature.

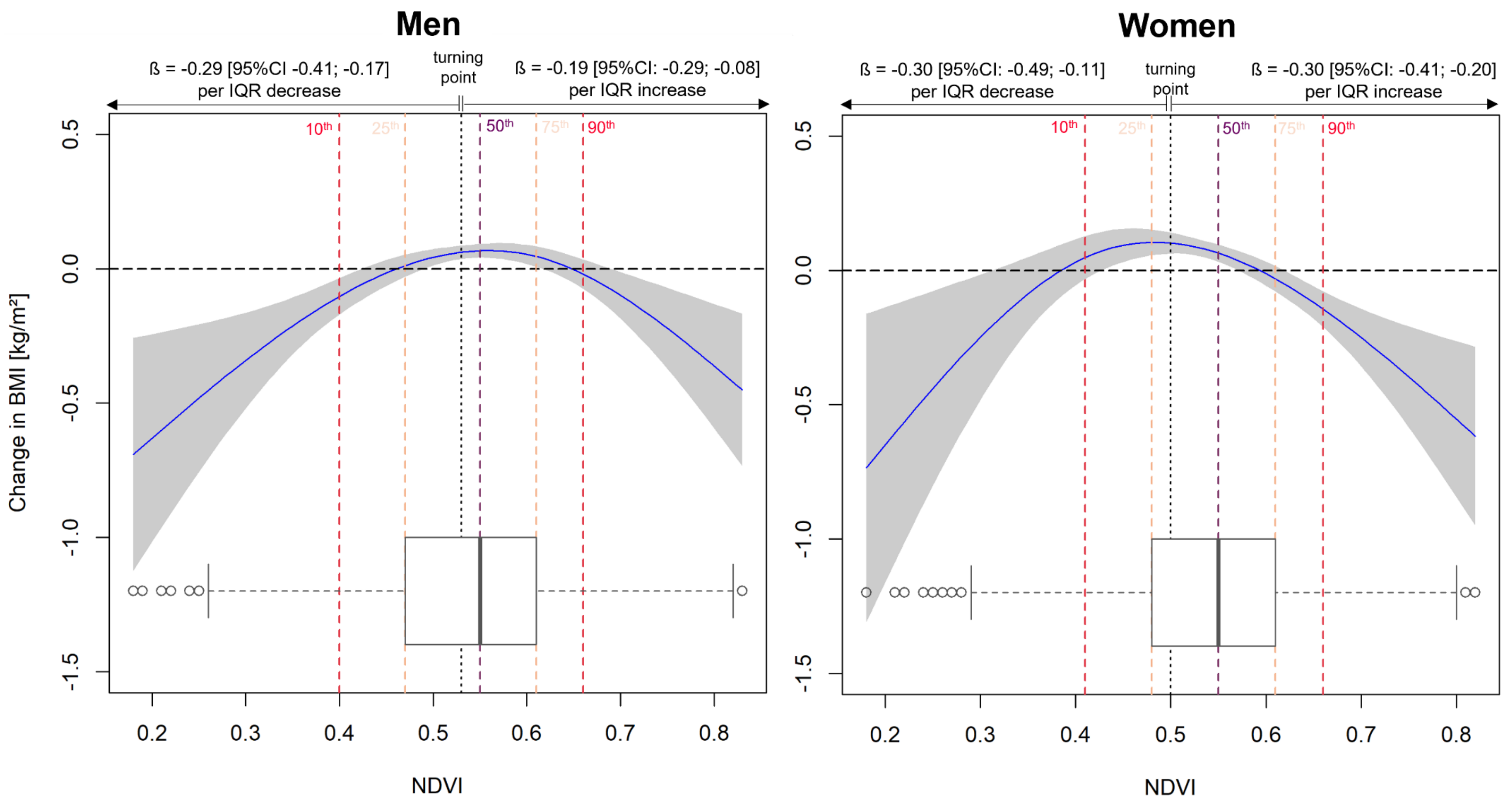


Figure 1. Non-linear associations between NDVI and BMI in n = 86,710 men and n = 88,245 women from the German National Cohort (NAKO).
Legend: Boxplots present distribution of exposure, vertical lines indicate NDVI percentiles (red, yellow, purple) and turning point (black). Models were fitted by cubic splines for the exposure and were additionally adjusted for age, study center, lifestyle factors, education, unemployment rate at district level and population density. The betas and 95%-CI are given per IQR of 0.14 decrease in NDVI below the turning point (≤ 0.53 for men, ≤ 0.50 for women) and per IQR of 0.14 increase in NDVI above the turning point (> 0.53 for men, >0.50 for women) derived from piecewise linear regression models.
Abbreviations: BMI = Body Mass Index, CI = confidence interval, IQR = interquartile range, NDVI = Normalized difference vegetation index.

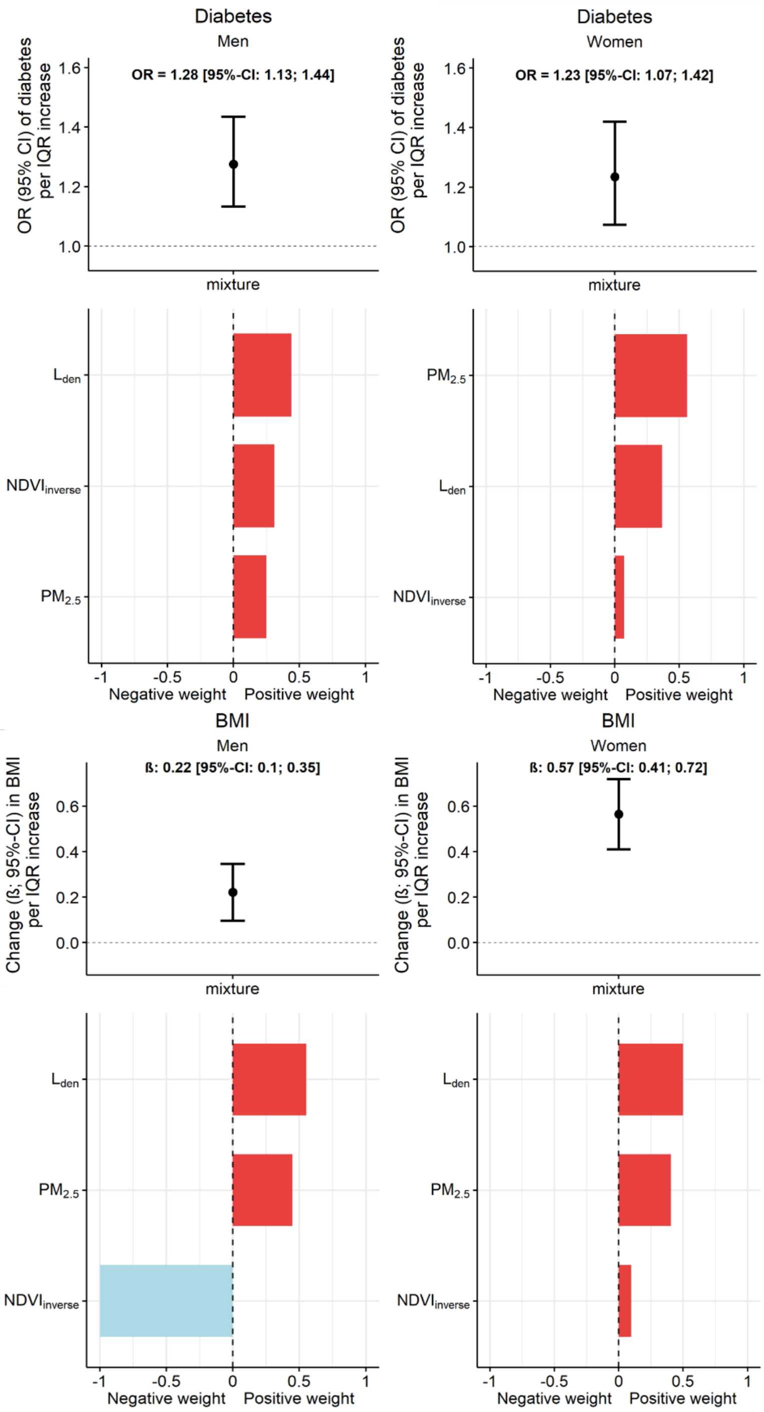


Figure 2. Joint associations of exposure to environmental mixture with diabetes and BMI for n = 86,710 men and n = 88,245 women from the German National Cohort (NAKO). Legend: Joint odds ratios and betas are given per one-IQR increase across all exposures derived from multi-exposure quantile g-computation models. We used the inverse of NDVI; and bars represent exposure weights, indicating the proportion of each exposure contributing to the overall positive and negative association. Models were additionally adjusted for age, study center, lifestyle factors, education, unemployment rate at district level and population density. Abbreviations: BMI = Body Mass Index, CI = confidence interval, L_{den} = day–evening–night noise level, NDVI = normalized difference vegetation index, OR = Odds ratio, $PM_{2.5}$ = particulate matter with diameter < 2.5 µm,

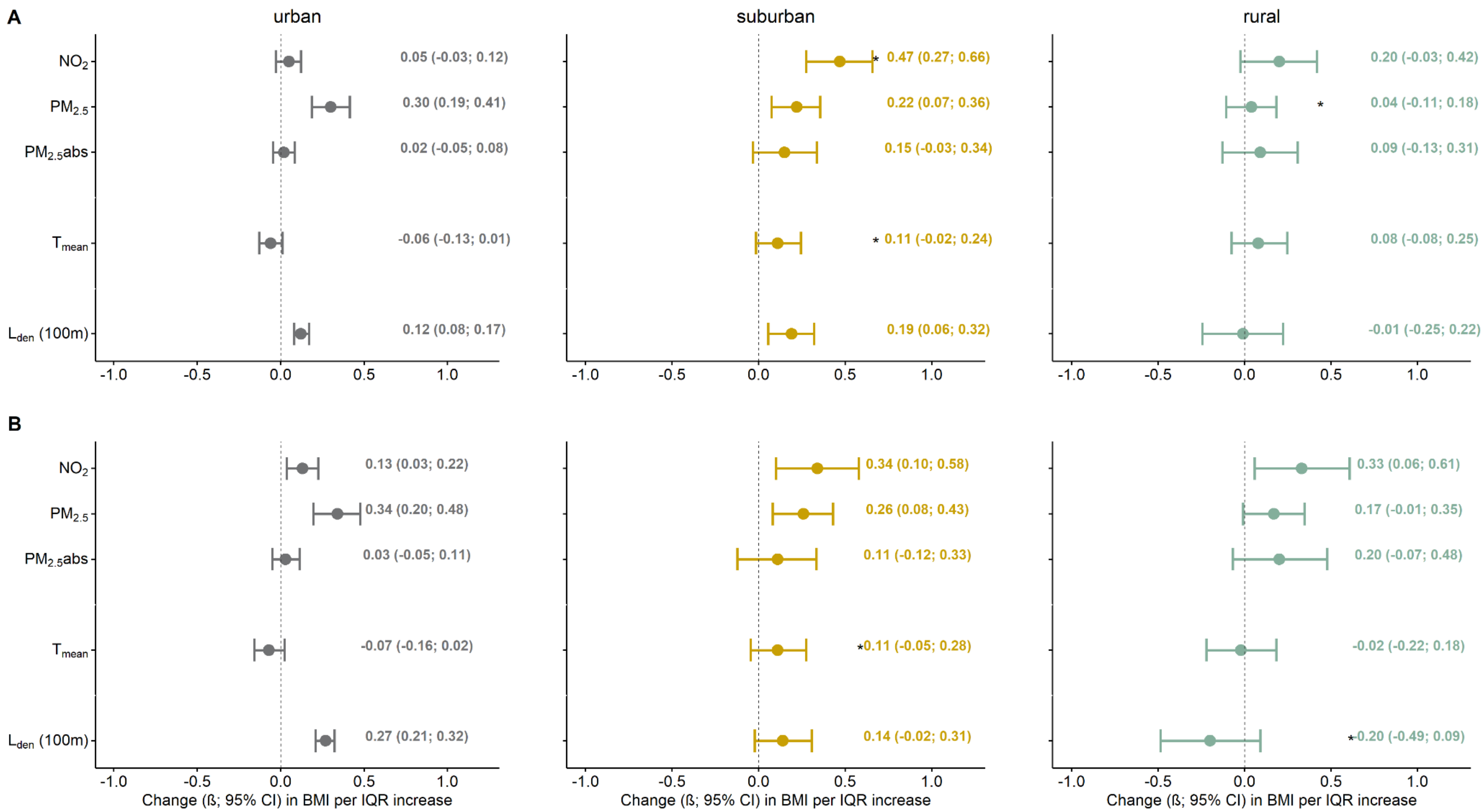


Figure 3. Urbanization-specific linear associations of environmental exposures with diabetes for men (A) and women (B) in the German National Cohort (NAKO). Legend: Betas and 95%-CI were derived from linear regression models including an interaction term between exposure and degree of urbanization from EUROSTAT. Star indicates $p_{interaction} < 0.05$. All models were additionally adjusted for age, study center, lifestyle factors, education, unemployment rate and population density. Urban: n = 62,004 men; n = 62,975 women, suburban: n = 13,771 men, n = 14,152 women, rural: n = 10,933 men, n = 11,112 women. Abbreviation: BMI = Body Mass Index, CI = confidence interval, IQR = interquartile range, L_{den} = day–evening–night noise level, NO_2 = nitrogen dioxide, OR = odds ratio, $PM_{2.5}$ = particulate matter < 2.5 µm, $PM_{2.5}abs$ = $PM_{2.5}$ absorbance, T_{mean} = mean air temperature.

Supplementary material to

Individual and joint associations of multiple environmental exposures with diabetes and obesity in the population-based German National Cohort (NAKO)

Fiona Niedermayer [1, 2]*, Barbara Hoffmann [3], Boya Zhang [4, 5], Jie Chen [4, 5], Jaime E. Hart [4, 5], Francine Laden [4, 5], Gabriele Bolte [6, 7], Tobia Lakes [8, 9], Tamara Schikowski [10, 11], Karin Halina Greiser [11], Jeroen Staab [12], Nikolaos Nikolaou [2], Marco Dallavalle [2], Matthias B. Schulze [13, 14], Wolfgang Lieb [15], Cara Övermöhle [15], Thaddäus Tönnies [16], Verena Katzke [11], Heiko Becher [17], Beate Fischer [18], Michael Leitzmann [18], Klaus Berger [19], Fatemeh Mayvaneh [19], Thomas Keil [20, 21, 22], Lilian Krist [20], Carolina J. Klett-Tammen [23], Jana-Kristin Heise [23], Tobias Pischon [24, 25, 26], Ilais Moreno Velásquez [24], Börge Schmidt [27], Rajini Nagrani [28], Stefan Rach [28], Hermann Brenner [29], Bernd Holleczek [29], Volker Harth [30], Nadia Obi [30], Anna Köttgen [31], Rafael Mikolajczyk [32], Claudia Meinke-Franze [33], Wolfgang Hoffmann [33], Alexandra Schneider [2], Kathrin Wolf [2], Annette Peters [1, 2, 34]

***Corresponding author:**

Fiona Niedermayer

Ingolstädter Landstr. 1, 85764 Neuherberg, Germany

Email: fiona.niedermayer@helmholtz-munich.de

Phone: +49 (0)89-3187-49519

ORCID: 0000-0002-6798-2630

Number of supplementary tables: 9

Number of supplementary figures: 14

Number of supplementary methods: 1

Table S1. Descriptive statistics of environmental exposures and population density and their Spearman correlation coefficients in the German National Cohort (NAKO, n = 174,955).

Exposure	Summary statistics			Correlations					
	Mean (SD)	Median (IQR)	Min; Max	NO_2	$PM_{2.5}$	$PM_{2.5}$abs	T_{mean}	L_{den} (100m)	NDVI
NO_2 [µg/m³]	26.82 (8.11)	26.81 (10.56)	4.76; 76.92	-	-	-	-	-	-
$PM_{2.5}$ [µg/m³]	17.27 (1.98)	17.28 (2.92)	9.32; 23.70	0.56	-	-	-	-	-
$PM_{2.5}$abs [$10^{-5}m^{-1}$]	1.63 (0.38)	1.63 (0.49)	0.73; 4.05	0.84	0.65	-	-	-	-
T_{mean} [°C]	10.87 (0.83)	10.93 (1.11)	7.64; 13.05	0.65	0.48	0.54	-	-	-
L_{den} (100m) [dB(A)]	44.53 (6.03)	40.67 (8.3)	40.00; 72.45	0.61	0.35	0.56	0.40	-	-
NDVI	0.54 (0.10)	0.55 (0.14)	0.18; 0.83	-0.54	-0.39	-0.59	-0.42	-0.34	-
Population density [n/m²]	4,652 (4,363)	3,4450 (13,739)	0; 22,178	0.72	0.48	0.71	0.58	0.42	-0.64

Abbreviation: IQR = interquartile range; L_{den} = day–evening–night noise level, Min = minimum, Max = maximum, NDVI = normalized difference vegetation index, NO_2= nitrogen dioxide, $PM_{2.5}$ = particulate matter < 2.5 µm; $PM_{2.5}$abs= $PM_{2.5}$ absorbance, T_{mean} = mean air temperature.; SD = standard deviation.

Table S2. Linear associations of environmental exposures with diabetes and obesity for n = 86,710 men n = 88,245 women in the German National Cohort (NAKO) adding one confounder at the time to the adjustment model.

Exposure	IQR	Adjustment	Diabetes		Obesity (BMI ≥ 30 kg/m²)	
			Men	Women	Men	Women
			OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
NO_2 [µg/m³]	10.6	Basic	0.97 (0.93; 1.01)	0.95 (0.91; 0.99)	0.86 (0.84; 0.88)	0.90 (0.88; 0.92)
		Basic + study center	1.05 (0.99; 1.11)	1.01 (0.95; 1.08)	0.90 (0.87; 0.93)	0.96 (0.93; 0.99)
		Basic + education	0.99 (0.96; 1.03)	0.96 (0.92; 1.01)	0.90 (0.88; 0.92)	0.94 (0.92; 0.96)
		Basic + unemployment rate	0.96 (0.93; 1.00)	0.94 (0.91; 0.98)	0.86 (0.84; 0.88)	0.89 (0.87; 0.92)
		Basic + population density	1.01 (0.97; 1.06)	0.98 (0.93; 1.04)	0.98 (0.95; 1.00)	0.97 (0.94; 1.00)
		Full model	1.10 (1.02; 1.19)	1.04 (0.96; 1.13)	1.05 (1.01; 1.10)	1.05 (1.01; 1.10)
$PM_{2.5}$ [µg/m³]	2.9	Basic	1.04 (1.00; 1.09)	1.05 (1.00; 1.10)	0.90 (0.87; 0.92)	0.92 (0.90; 0.94)
		Basic + study center	1.12 (1.03; 1.21)	1.11 (1.02; 1.21)	0.98 (0.93; 1.02)	1.05 (1.00; 1.11)
		Basic + education	1.07 (1.02; 1.12)	1.08 (1.03; 1.13)	0.93 (0.91; 0.95)	0.97 (0.94; 0.99)
		Basic + unemployment rate	1.02 (0.97; 1.06)	1.02 (0.97; 1.07)	0.88 (0.86; 0.90)	0.90 (0.88; 0.90)
		Basic + population density	1.10 (1.05; 1.16)	1.11 (1.06; 1.17)	1.00 (0.98; 1.03)	0.99 (0.96; 1.02)
		Full model	1.12 (1.02; 1.22)	1.11 (1.01; 1.22)	1.07 (1.02; 1.13)	1.10 (1.04; 1.16)
$PM_{2.5}$abs [$10^{-5}m^{-1}$]	0.5	Basic	0.98 (0.95; 1.02)	0.97 (0.93; 1.01)	0.85 (0.83; 0.87)	0.88 (0.86; 0.90)
		Basic + study center	1.03 (0.98; 1.09)	0.99 (0.95; 1.07)	0.89 (0.87; 0.92)	0.93 (0.90; 0.96)
		Basic + education	1.01 (0.97; 1.05)	0.99 (0.95; 1.03)	0.89 (0.87; 0.91)	0.92 (0.90; 0.94)
		Basic + unemployment rate	0.98 (0.95; 1.02)	0.97 (0.93; 1.01)	0.85 (0.83; 0.87)	0.88 (0.86; 0.90)
		Basic + population density	1.04 (0.99; 1.09)	1.02 (0.98; 1.08)	0.96 (0.93; 0.98)	0.94 (0.91; 0.96)
		Full model	1.08 (1.01; 1.15)	1.03 (0.96; 1.11)	1.01 (0.97; 1.05)	0.98 (0.95; 1.02)
T_{mean} [°C]	1.1	Basic	0.92 (0.88; 0.95)	0.96 (0.92; 1.00)	0.84 (0.82; 0.85)	0.87 (0.85; 0.89)
		Basic + study center	0.96 (0.90; 1.02)	1.06 (1.00; 1.14)	0.89 (0.85; 0.92)	0.94 (0.90; 0.97)
		Basic + education	0.96 (0.92; 1.00)	1.00 (0.96; 1.04)	0.88 (0.86; 0.90)	0.93 (0.91; 0.96)
		Basic + unemployment rate	0.88 (0.84; 0.91)	0.92 (0.88; 0.97)	0.81 (0.79; 0.83)	0.84 (0.82; 0.86)
		Basic + population density	0.93 (0.89; 0.97)	0.99 (0.95; 1.04)	0.91 (0.89; 0.93)	0.92 (0.89; 0.94)
		Full model	0.96 (0.90; 1.04)	1.10 (1.02; 1.19)	0.98 (0.94; 1.02)	1.00 (0.96; 1.04)
L_{den} (100m) [dB(A)]	8.3	Basic	1.06 (1.02; 1.10)	1.03 (0.98; 1.07)	0.99 (0.97; 1.02)	1.02 (1.00; 1.05)
		Basic + study center	1.09 (1.05; 1.14)	1.06 (1.01; 1.11)	1.05 (1.02; 1.07)	1.08 (1.05; 1.10)
		Basic + education	1.05 (1.01; 1.10)	1.03 (0.99; 1.08)	1.00 (0.98; 1.03)	1.04 (1.01; 1.06)
		Basic + unemployment rate	1.04 (1.00; 1.09)	1.01 (0.97; 1.06)	0.99 (0.97; 1.01)	1.01 (0.99; 1.04)
		Basic + population density	1.08 (1.04; 1.12)	1.05 (1.00; 1.09)	1.06 (1.03; 1.08)	1.07 (1.04; 1.09)
		Full model	1.08 (1.03; 1.13)	1.05 (1.00; 1.10)	1.07 (1.04; 1.09)	1.08 (1.05; 1.11)

Legend: Basic model included age, physical activity, alcohol consumption, smoking behavior. Full model includes the basic model and additionally study center, education, unemployment rate at district level and population density. ORs and confidence intervals are given as IQR increase in exposure derived from logistic regression models. Abbreviation: BMI = Body Mass Index, CI = confidence interval, IQR = interquartile range, L_{den} = day–evening–night noise level, NO_2= nitrogen dioxide, OR = odds ratio, $PM_{2.5}$ = particulate matter < 2.5 µm, $PM_{2.5}$abs= $PM_{2.5}$ absorbance, T_{mean} = mean air temperature.

Table S3. Linear associations of environmental exposures with BMI and waist circumference for n = 86,710 men n = 88,245 women in the German National Cohort (NAKO) adding one confounder at the time to the adjustment model.

Exposure	IQR	Adjustment	BMI Men ß (95% CI)	BMI Women ß (95% CI)	Waist circumference Men ß (95% CI)	Waist circumference Women ß (95% CI)
NO_2 [µg/m³]	10.6	Basic	-0.38 (-0.42; -0.34)	-0.34 (-0.39; -0.30)	-0.73 (-0.83; -0.63)	-0.57 (-0.69; -0.46)
		Basic + study center	-0.30 (-0.36; -0.25)	-0.18 (-0.24; -0.11)	-0.67 (-0.82; -0.52)	-0.35 (-0.51; -0.19)
		Basic + education	-0.26 (-0.30; -0.22)	-0.19 (-0.24; -0.15)	-0.43 (-0.53; -0.33)	-0.25 (-0.36; -0.14)
		Basic + unemployment rate	-0.39 (-0.42; -0.35)	-0.36 (-0.41; -0.31)	-0.78 (-0.88; -0.68)	-0.63 (-0.74; -0.52)
		Basic + population density	-0.08 (-0.13; -0.04)	-0.11 (-0.17; -0.05)	0.01 (-0.12; 0.14)	-0.02 (-0.16; 0.12)
		Full model	0.06 (-0.02; 0.13)	0.13 (0.04; 0.22)	0.24 (0.04; 0.44)	0.25 (0.04; 0.47)
$PM_{2.5}$ [µg/m³]	2.9	Basic	-0.32 (-0.36; -0.27)	-0.28 (-0.33; -0.23)	-0.61 (-0.72; -0.49)	-0.47 (-0.60; -0.35)
		Basic + study center	-0.15 (-0.23; -0.06)	0.03 (-0.07; 0.13)	-0.23 (-0.45; 0.00)	0.17 (-0.08; 0.41)
		Basic + education	-0.23 (-0.27; -0.19)	-0.14 (-0.19; -0.09)	-0.39 (-0.50; -0.27)	-0.17 (-0.29; -0.05)
		Basic + unemployment rate	-0.36 (-0.40; -0.31)	-0.35 (-0.40; -0.29)	-0.81 (-0.93; -0.69)	-0.69 (-0.82; -0.56)
		Basic + population density	-0.04 (-0.09; 0.01)	-0.05 (-0.11; 0.00)	0.04 (-0.10; 0.17)	0.01 (-0.13; 0.15)
		Full model	0.11 (0.02; 0.20)	0.18 (0.07; 0.29)	0.40 (0.16; 0.64)	0.48 (0.21; 0.74)
$PM_{2.5}$abs [$10^{-5}m^{-1}$]	0.5	Basic	-0.42 (-0.46; -0.38)	-0.39 (-0.44; -0.35)	-1.03 (-1.13; -0.93)	-0.79 (-0.90; -0.68)
		Basic + study center	-0.31 (-0.36; -0.27)	-0.23 (-0.29; -0.17)	-0.72 (-0.85; -0.59)	-0.48 (-0.62; -0.34)
		Basic + education	-0.31 (-0.35; -0.27)	-0.26 (-0.30; -0.21)	-0.76 (-0.86; -0.66)	-0.50 (-0.61; -0.39)
		Basic + unemployment rate	-0.42 (-0.46; -0.38)	-0.40 (-0.44; -0.35)	-1.04 (-1.14; -0.94)	-0.81 (-0.92; -0.70)
		Basic + population density	-0.15 (-0.20; -0.10)	-0.19 (-0.25; -0.13)	-0.49 (-0.62; -0.36)	-0.38 (-0.52; -0.23)
		Full model	-0.02 (-0.09; 0.04)	-0.01 (-0.08; 0.07)	0.01 (-0.16; 0.18)	-0.05 (-0.24; 0.14)
T_{mean} [°C]	1.1	Basic	-0.44 (-0.48; -0.41)	-0.44 (-0.49; -0.39)	-0.84 (-0.94; -0.73)	-0.94 (-1.05; -0.82)
		Basic + study center	-0.31 (-0.37; -0.25)	-0.27 (-0.35; -0.20)	-0.84 (-1.00; -0.68)	-0.66 (-0.84; -0.48)
		Basic + education	-0.31 (-0.35; -0.27)	-0.23 (-0.28; -0.19)	-0.50 (-0.60; -0.39)	-0.50 (-0.62; -0.38)
		Basic + unemployment rate	-0.51 (-0.55; -0.47)	-0.53 (-0.58; -0.48)	-1.11(-1.22; -1.00)	-1.22 (-1.34; -1.11)
		Basic + population density	-0.23 (-0.28; -0.19)	-0.28 (-0.33; -0.22)	-0.32 (-0.43; -0.20)	-0.63 (-0.76; -0.50)
		Full model	-0.06 (-0.12; 0.01)	-0.07 (-0.15; 0.01)	-0.25 (-0.43; -0.07)	-0.28 (-0.48; -0.08)
L_{den} (100m) [dB(A)]	8.3	Basic	-0.07 (-0.11; -0.03)	0.04 (-0.01; 0.09)	-0.06 (-0.16; 0.05)	0.16 (0.04; 0.28)
		Basic + study center	0.05 (0.01; 0.09)	0.19 (0.14; 0.24)	0.14 (0.03; 0.26)	0.41 (0.29; 0.53)
		Basic + education	-0.04 (-0.08; 0.00)	0.09 (0.04; 0.14)	0.02 (-0.09; 0.12)	0.27 (0.15; 0.38)
		Basic + unemployment rate	-0.08 (-0.12; -0.04)	0.01 (-0.03; 0.06)	-0.14 (-0.25; -0.03)	0.07 (-0.04; 0.19)
		Basic + population density	0.08 (0.04; 0.12)	0.17 (0.12; 0.22)	0.28 (0.17; 0.39)	0.43 (0.31; 0.55)
		Full model	0.11 (0.06; 0.15)	0.22 (0.16; 0.27)	0.26 (0.15; 0.38)	0.46 (0.34; 0.59)

Legend: Basic model included age, physical activity, alcohol consumption, smoking behavior. Full model = basic model plus study center, education, unemployment rate at district level and population density. Betas and confidence intervals are given as IQR increase in exposure derived from linear regression models.

Abbreviation: BMI = Body Mass Index, CI = confidence Interval, IQR = interquartile range; L_{den} = day–evening–night noise level, NO_2= nitrogen dioxide, $PM_{2.5}$ = particulate matter < 2.5 µm; $PM_{2.5}$abs= $PM_{2.5}$ absorbance, T_{mean} = mean air temperature.

Table S4. Joint associations of two different environmental exposure mixtures with diabetes and obesity-related measures derived from multi-exposure quantile g-computation models in the German National Cohort (n = 86,710 men; n = 88,245 women).

Outcome	**Sex**	**Multi exposure set 1: $PM_{2.5}$, L_{den}, $NDVI_{inverse}$**	**Multi exposure set 2: All exposures**
		OR / ß (95%-CI)	**OR / ß (95%-CI)**
Diabetes	Men	1.28 (1.13; 1.44)	1.19 (1.05; 1.34)
	Women	1.23 (1.07; 1.42)	1.30 (1.11; 1.51)
Obesity	Men	1.10 (1.05; 1.16)	1.07 (1.01; 1.13)
	Women	1.20 (1.14; 1.26)	1.14 (1.08; 1.21)
BMI	Men	0.22 (0.10; 0.35)	0.14 (-0.01; 0.28)
	Women	0.57 (0.41; 0.72)	0.37 (0.19; 0.55)
Waist circumference	Men	0.63 (0.29; 0.97)	0.42 (0.03; 0.81)
	Women	1.22 (0.88; 1.56)	0.86 (0.47; 1.25)

Legend: Multi exposure set 2 included NO_2, $PM_{2.5}$, $PM_{2.5}abs$, T_{mean}, L_{den} and $NDVI_{inverse}$. To compare results to single-exposure models, betas and ORs were multiplied by two to interpret them as one-IQR increase per exposure. Models were further adjusted for age, center, physical activity, alcohol consumption, smoking behavior, education, neighborhood unemployment rate at district level and population density. Abbreviation: BMI = Body Mass Index; CI = confidence interval, IQR = interquartile range, L_{den} = day–evening–night noise level, NDVI = normalized difference vegetation index, NO_2= nitrogen dioxide, OR = odds ratio, $PM_{2.5}$ = particulate matter < 2.5 µm; $PM_{2.5}abs$= $PM_{2.5}$ absorbance, T_{mean} = mean air temperature.

Table S5. Participants distributed across the 16 German National Cohort (NAKO) study centers, total and stratified by sex.

	Overall (n = 174,955)	**Men (n = 86,710)**	**Women (n = 88,245)**
Study center, n (%)			
Augsburg	18,607 (10.6)	9,443 (10.9)	9,164 (10.4)
Berlin	27,555 (15.7)	13,591 (15.7)	13,964 (15.8)
Bremen	9,066 (5.2)	4,481 (5.2)	4,585 (5.2)
Düsseldorf	7,289 (4.2)	3,555 (4.1)	3,734 (4.2)
Essen	9,381 (5.4)	4,680 (5.4)	4,701 (5.3)
Freiburg	9,075 (5.2)	4,563 (5.3)	4,512 (5.1)
Halle	9,042 (5.2)	4,346 (5.0)	4,696 (5.3)
Hamburg	6,640 (3.8)	3,263 (3.8)	3,377 (3.8)
Hannover	8,463 (4.8)	4,139 (4.8)	4,324 (4.9)
Kiel	5,750 (3.3)	2,790 (3.2)	2,960 (3.4)
Leipzig	10,099 (5.8)	5,055 (5.8)	5,044 (5.7)
Mannheim	8,999 (5.1)	4,462 (5.1)	4,537 (5.1)
Münster	8,858 (5.1)	4,414 (5.1)	4,444 (5.0)
Neubrandenburg	18,022 (10.3)	9,009 (10.4)	9,013 (10.2)
Regensburg	9,137 (5.2)	4,579 (5.3)	4,558 (5.2)
Saarbrücken	8,972 (5.1)	4,340 (5.0)	4,632 (5.2)

Table S6. Sensitivity analysis: linear associations of environmental exposures with diabetes and obesity adjusted for different confounder sets in the German National Cohort (NAKO).

Exposure	IQR	Adjustment*	Diabetes		Obesity (BMI ≥ 30 kg/m²)	
			Men	Women	Men	Women
			OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
NO_2 [µg/m³]	10.6	Main model + income & partnership	1.07 (0.99; 1.16)	1.03 (0.94; 1.12)	1.04 (1.00; 1.09)	1.01 (0.97; 1.06)
		Main model without physical activity	1.10 (1.02; 1.18)	1.04 (0.96; 1.13)	1.05 (1.00; 1.09)	1.05 (1.00; 1.09)
$PM_{2.5}$ [µg/m³]	2.9	Main model + income & partnership	1.08 (0.98; 1.18)	1.09 (0.99; 1.20)	1.06 (1.01; 1.12)	1.06 (1.00; 1.12)
		Main model without physical activity	1.11 (1.02; 1.22)	1.11 (1.01; 1.22)	1.07 (1.02; 1.13)	1.09 (1.03; 1.15)
$PM_{2.5}$abs [$10^{-5}m^{-1}$]	0.5	Main model + income & partnership	1.06 (0.99; 1.13)	1.02 (0.95; 1.10)	1.01 (0.97; 1.05)	0.95 (0.92; 0.99)
		Main model without physical activity	0.97 (0.91; 1.04)	1.03 (0.96; 1.10)	1.00 (0.97; 1.04)	0.98 (0.94; 1.02)
T_{mean} [°C]	1.1	Main model + income & partnership	0.97 (0.90; 1.04)	1.11 (1.03; 1.20)	0.98 (0.94; 1.02)	1.00 (0.96; 1.04)
		Main model without physical activity	0.97 (0.91; 1.04)	1.10 (1.02; 1.18)	0.98 (0.94; 1.01)	0.98 (0.93; 1.02)
L_{den} (100m) [dB(A)]	8.3	Main model + income & partnership	1.06 (1.01; 1.10)	1.03 (0.99; 1.09)	1.06 (1.03; 1.09)	1.06 (1.03; 1.09)
		Main model without physical activity	1.08 (1.03; 1.13)	1.05 (1.00; 1.09)	1.06 (1.04; 1.09)	1.08 (1.05; 1.11)

Legend: Main model included age, study center, physical activity, alcohol consumption, smoking behavior, education, unemployment rate at district level and population density. ORs and confidence intervals are given as IQR increase in exposure derived from logistic regression models. Partnership is categorized as: single, living with partner, partner but living separately.

* Main model with income & partnership: men: n = 82,119; women: n = 81,756; model without physical activity: men: n = 86,710; women: n = 88,245

Abbreviation: BMI = Body Mass Index, CI = confidence interval, IQR = interquartile range, L_{den} = day–evening–night noise level, NO_2= nitrogen dioxide, OR = odds ratio, $PM_{2.5}$ = particulate matter < 2.5 µm, $PM_{2.5}$abs= $PM_{2.5}$ absorbance, T_{mean} = mean air temperature.

Table S7. Sensitivity analysis: linear associations of environmental exposures with BMI and waist circumference adjusted for different confounder sets in the German National Cohort (NAKO).

Exposure	IQR	Adjustment*	BMI		Waist circumference	
			Men	**Women**	**Men**	**Women**
			ß (95% CI)	ß (95% CI)	ß (95% CI)	ß (95% CI)
NO_2 [µg/m³]	10.6	Main model + income & partnership	0.05 (-0.02; 0.13)	0.04 (-0.05; 0.14)	0.20 (0.00; 0.40)	0.06 (-0.17; 0.28)
		Main model without physical activity	0.04 (-0.03; 0.11)	0.11 (0.02; 0.20)	0.20 (0.00; 0.40)	0.21 (-0.01; 0.42)
$PM_{2.5}$ [µg/m³]	2.9	Main model + income & partnership	0.10 (0.01; 0.19)	0.10 (-0.02; 0.21)	0.35 (0.10; 0.61)	0.29 (0.02; 0.56)
		Main model without physical activity	0.11 (0.02; 0.20)	0.18 (0.07; 0.29)	0.41 (0.16; 0.65)	0.46 (0.20; 0.72)
$PM_{2.5}$abs [$10^{-5}m^{-1}$]	0.5	Main model + income & partnership	-0.03 (-0.09; 0.04)	-0.06 (-0.14; 0.02)	-0.02 (-0.20; 0.16)	-0.18 (-0.38; 0.01)
		Main model without physical activity	-0.04 (-0.10; 0.03)	-0.02 (-0.10; 0.06)	-0.03 (-0.20; 0.14)	-0.09 (-0.28; 0.10)
T_{mean} [°C]	1.1	Main model + income & partnership	-0.06 (-0.12; 0.01)	-0.06 (-0.14; 0.03)	-0.22 (-0.41; -0.04)	-0.22 (-0.43; -0.02)
		Main model without physical activity	-0.06 (-0.13; 0.00)	-0.08 (-0.16; 0.00)	-0.26 (-0.44; -0.08)	-0.30 (-0.50; -0.10)
L_{den} (100m) [dB(A)]	8.3	Main model + income & partnership	0.10 (0.05; 0.14)	0.19 (0.13; 0.24)	0.23 (0.11; 0.35)	0.38 (0.25; 0.51)
		Main model without physical activity	0.10 (0.06; 0.15)	0.21 (0.16; 0.26)	0.26 (0.14; 0.37)	0.45 (0.33; 0.58)

Legend: Main model included age, study center, physical activity, alcohol consumption, smoking behavior, education, unemployment rate at district level and population density. Betas and confidence intervals are given as IQR increase in exposure derived from linear regression models. Partnership is categorized as: single, living with partner, partner but living separately.

* Main model + income & partnership: men: n = 82,119; women: n = 81,756 due to missings in income and partnership; Main model without physical activity: men: n = 86,710; women: n = 88,245

Abbreviation: BMI = Body Mass Index, CI = Confidence Interval, IQR = interquartile range; L_{den} = day–evening–night noise level, NO_2= nitrogen dioxide, $PM_{2.5}$ = particulate matter < 2.5 µm; $PM_{2.5}$abs= $PM_{2.5}$ absorbance, T_{mean} = mean air temperature.

8

Table S8. Sensitivity analysis: linear associations of environmental exposures with obesity, BMI, and waist circumference in the German National Cohort (NAKO) after excluding prevalent diabetes and cancer cases (in total: n = 9,203).

Exposure	IQR	Obesity (BMI ≥ 30 kg/m²)		BMI		Waist circumference	
		Men (n = 81,671)	**Women (n = 84,081)**	**Men (n = 81,671)**	**Women (n = 84,081)**	**Men (n = 81,671)**	**Women (n = 84,081)**
		OR (95% CI)	OR (95% CI)	ß (95% CI)	ß (95% CI)	ß (95% CI)	ß (95% CI)
NO_2 [µg/m³]	10.6	1.05 (1.00; 1.09)	1.05 (1.00; 1.10)	0.03 (-0.04; 0.1)	0.10 (0.01; 0.18)	0.16 (-0.04; 0.35)	0.20 (-0.01; 0.42)
$PM_{2.5}$ [µg/m³]	2.9	1.07 (1.02; 1.13)	1.09 (1.03; 1.15)	0.10 (0.02; 0.19)	0.16 (0.05; 0.27)	0.39 (0.15; 0.64)	0.42 (0.16; 0.68)
$PM_{2.5}$abs [$10^{-5}m^{-1}$]	0.5	1.00 (0.96; 1.04)	0.98 (0.94; 1.02)	-0.05 (-0.11; 0.01)	-0.02 (-0.10; 0.05)	-0.07 (-0.24; 0.10)	-0.06 (-0.25; 0.12)
T_{mean} [°C]	1.1	0.98 (0.94; 1.02)	1.00 (0.95; 1.04)	-0.06 (-0.12; 0.01)	-0.09 (-0.17; -0.01)	-0.22 (-0.39; -0.04)	-0.31 (-0.50; -0.11)
L_{den} (100m) [dB(A)]	8.3	1.06 (1.03; 1.08)	1.06 (1.03; 1.09)	0.08 (0.04; 0.13)	0.19 (0.14; 0.24)	0.19 (0.08; 0.31)	0.41 (0.29; 0.54)

Legend: All models were adjusted for age, center, physical activity, alcohol consumption, smoking behavior, education, unemployment rate at district level and population density. ORs, betas and confidence intervals are given as IQR increase exposure derived from linear and logistic regression models.

Abbreviation: BMI = Body Mass Index, CI = Confidence Interval, IQR = interquartile range, L_{den} = day–evening–night noise level, NO_2= nitrogen dioxide, OR = Odds ratio, $PM_{2.5}$ = particulate matter < 2.5 µm, $PM_{2.5}$abs= $PM_{2.5}$ absorbance, T_{mean} = mean air temperature.

Table S9. Sensitivity analysis: linear associations of environmental exposures with diabetes by using different definitions in the German National Cohort (NAKO).

Exposure	IQR	Excluding gestational diabetes (n = 1,157)	Excluding Type 1 diabetes likely cases (n = 1,139) *	
		Women (n = 87,019)	**Men (n = 82,088)**	**Women (n = 81,204)**
		OR (95% CI)	OR (95% CI)	OR (95% CI)
NO_2 [µg/m³]	10.6	1.10 (1.00; 1.22)	1.09 (1.01; 1.18)	1.05 (0.96; 1.15)
$PM_{2.5}$ [µg/m³]	2.9	1.19 (1.06; 1.33)	1.10 (1.00; 1.20)	1.14 (1.03; 1.27)
$PM_{2.5}$abs [$10^{-5}m^{-1}$]	0.5	1.10 (1.01; 1.19)	1.07 (1.00; 1.14)	1.04 (0.96; 1.12)
T_{mean} [°C]	1.1	1.08 (0.98; 1.18)	0.97 (0.90; 1.04)	1.11 (1.02; 1.20)
L_{den} (100m) [dB(A)]	8.3	1.07 (1.02; 1.13)	1.07 (1.03; 1.12)	1.04 (0.99; 1.10)

Legend: All models were adjusted for age, center, physical activity, alcohol consumption, smoking behavior, education, unemployment rate at district level and population density. ORs and confidence intervals are given as IQR increase in exposure derived from logistic regression models.

*defined as diagnosis age ≤ 30 years

Abbreviation: CI = Confidence Interval, IQR = interquartile range, L_{den} = day–evening–night noise level, NO_2= nitrogen dioxide, OR = Odds ratio, $PM_{2.5}$ = particulate matter < 2.5 µm, $PM_{2.5}$abs= $PM_{2.5}$ absorbance, T_{mean} = mean air temperature.

10

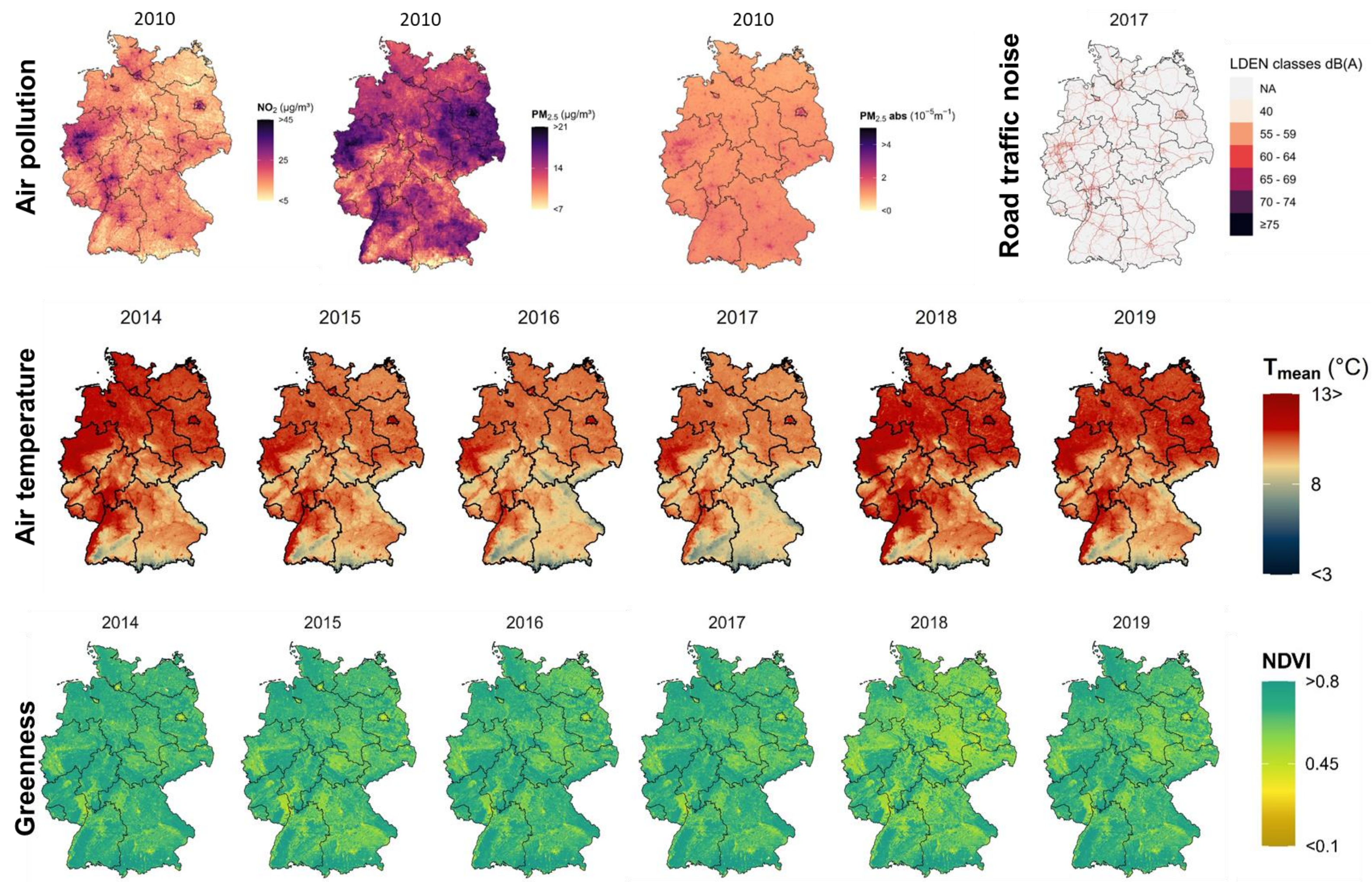


Figure S1: Maps Germany showing environmental exposures (air pollution, road traffic noise, air temperature and greenness) available in the German National Cohort (NAKO). Adapted from Wolf et al.[1]. Abbreviations: L_{den} = day–evening–night noise level, NDVI = normalized difference vegetation index, NO_2= nitrogen dioxide, $PM_{2.5}$ = particulate matter < 2.5 µm, $PM_{2.5}$abs= $PM_{2.5}$ absorbance, T_{mean} = mean air temperature.

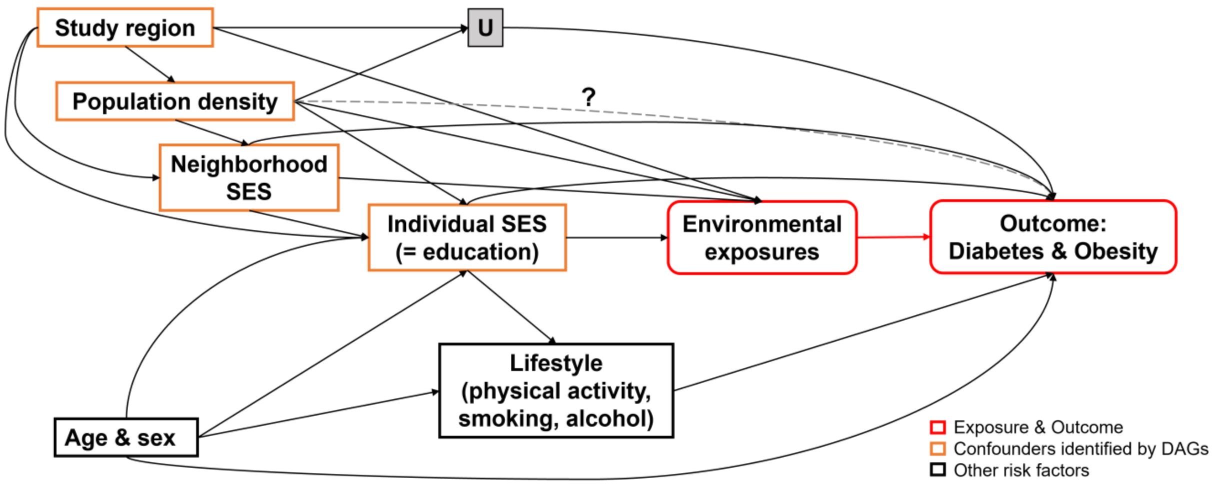


Figure S2. Directed acyclic graphs visualizing links between exposure, outcome, and covariates to identify potential confounders in the associations of environmental exposures with diabetes and obesity-related measures. Legend: U = unmeasured factors related to infrastructure/built environment or other residual confounding. Neighborhood SES is presented by unemployment rate at district level. Abbreviations: SES = socioeconomic status

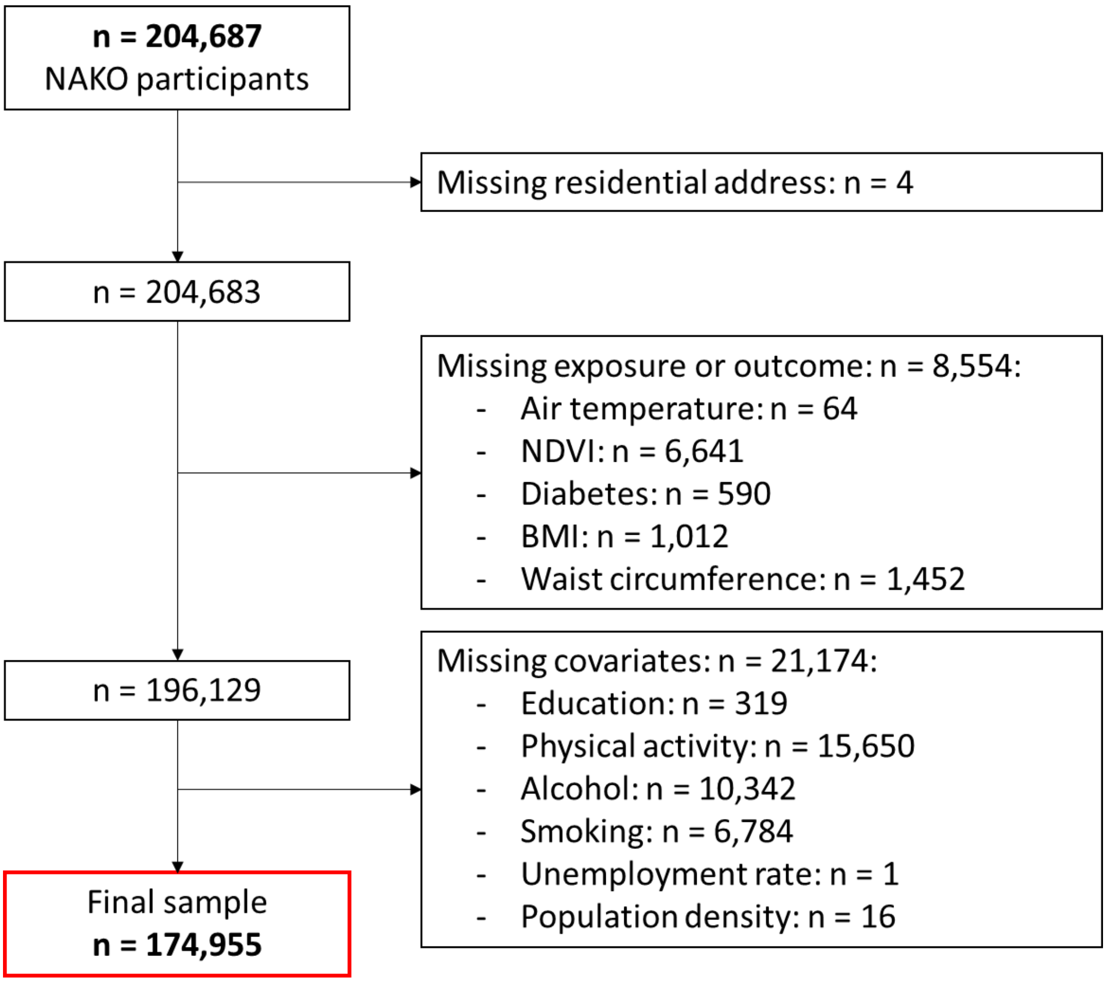


Figure S3. Flowchart presenting number of excluded participants from the German National Cohort (NAKO) and final analytical sample. Abbreviations: BMI = Body Mass Index, NDVI = Normalized difference vegetation index.

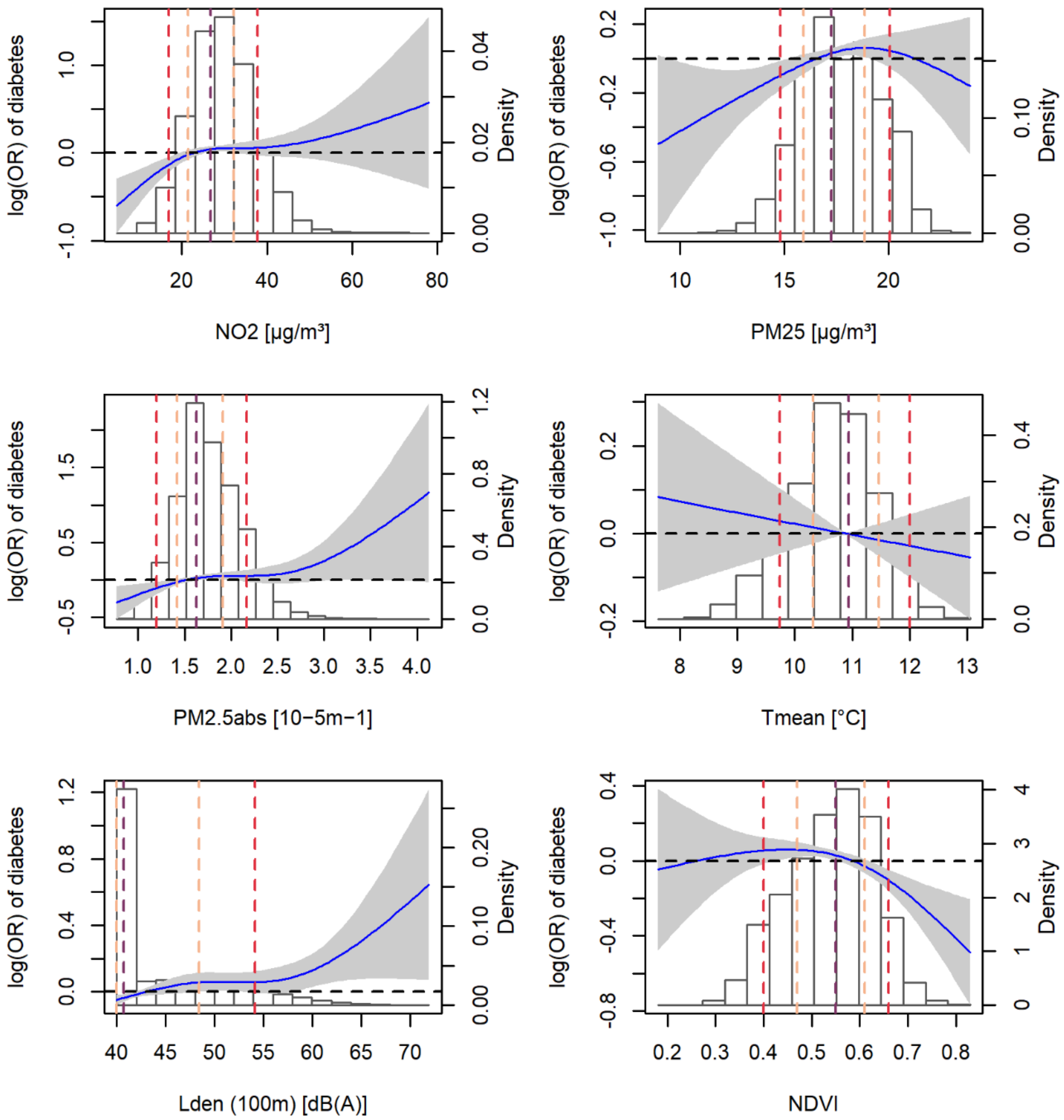


Figure S4. Exposure-response functions between environmental exposures and diabetes for n = 86,710 men in the German National Cohort (NAKO). Legend: Histograms present distribution of exposure (2nd y-axis on the right), vertical lines indicate percentiles of exposures (red: 10th and 90th percentile, yellow: 25th and 75th percentile; purple: 50th percentile). Models were fitted by cubic splines for the exposure and were adjusted for age, study center, lifestyle factors, education, unemployment rate at district level and population density.

Abbreviation: L_{den} = day–evening–night noise level, NDVI = normalized difference vegetation index, NO_2= nitrogen dioxide, log(OR) = log(odds ratio), $PM_{2.5}$ = particulate matter < 2.5 µm, $PM_{2.5}$abs= $PM_{2.5}$ absorbance, T_{mean} = mean air temperature.

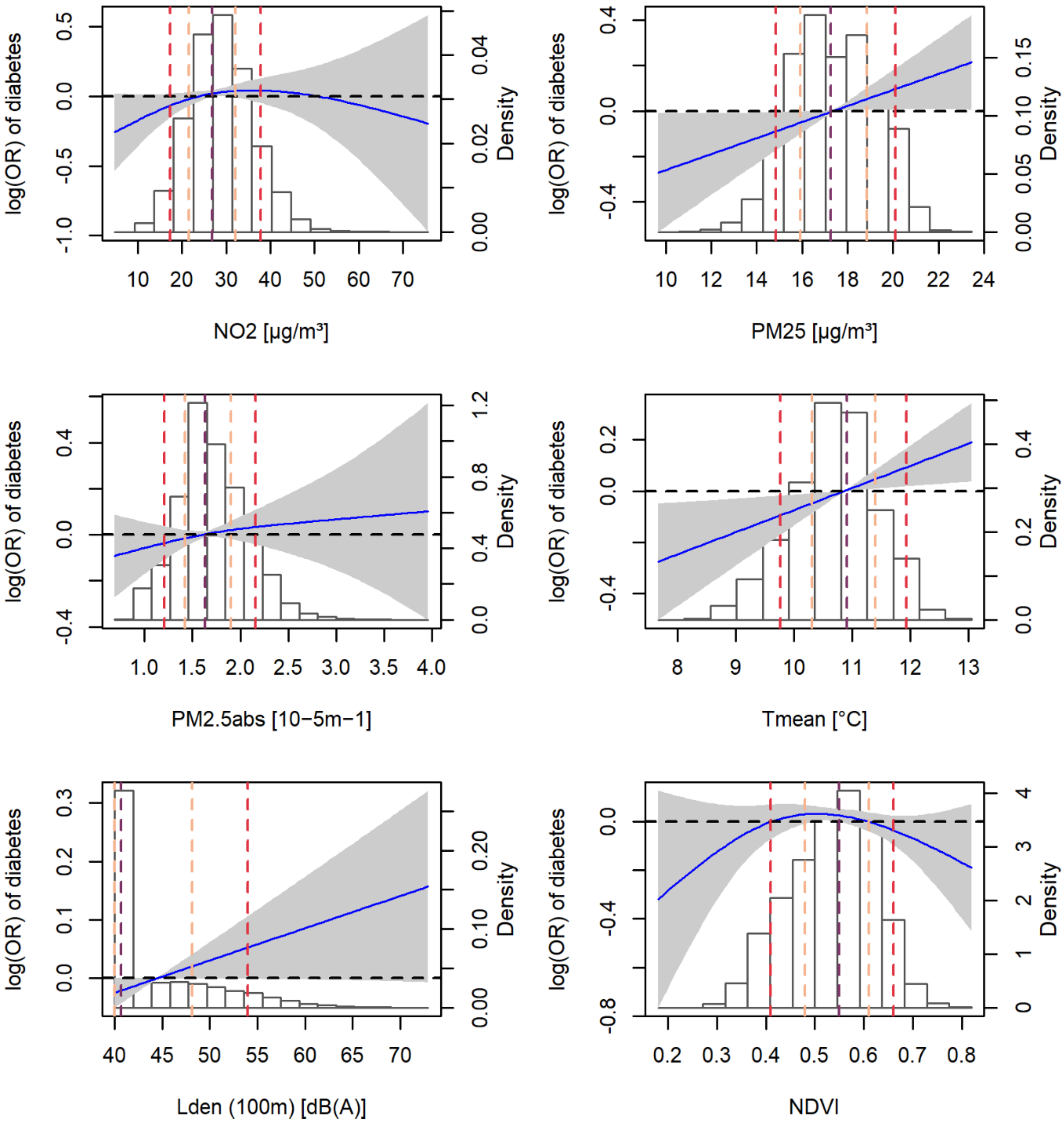


Figure S5. Exposure-response functions between environmental exposures and diabetes for n = 88,245 women in the German National Cohort (NAKO). Legend: Histograms present distribution of exposure (2nd y-axis on the right), vertical lines indicate percentiles of exposures (red: 10th and 90th percentile, yellow: 25th and 75th percentile; purple: 50th percentile). Models were fitted by cubic splines for the exposure and were adjusted for age, study center, lifestyle factors, education, unemployment rate at district level and population density.

Abbreviation: L_{den} = day–evening–night noise level, NDVI = normalized difference vegetation index, NO_2= nitrogen dioxide, log(OR) = log(odds ratio), $PM_{2.5}$ = particulate matter < 2.5 µm, $PM_{2.5}$abs= $PM_{2.5}$ absorbance, T_{mean} = mean air temperature.

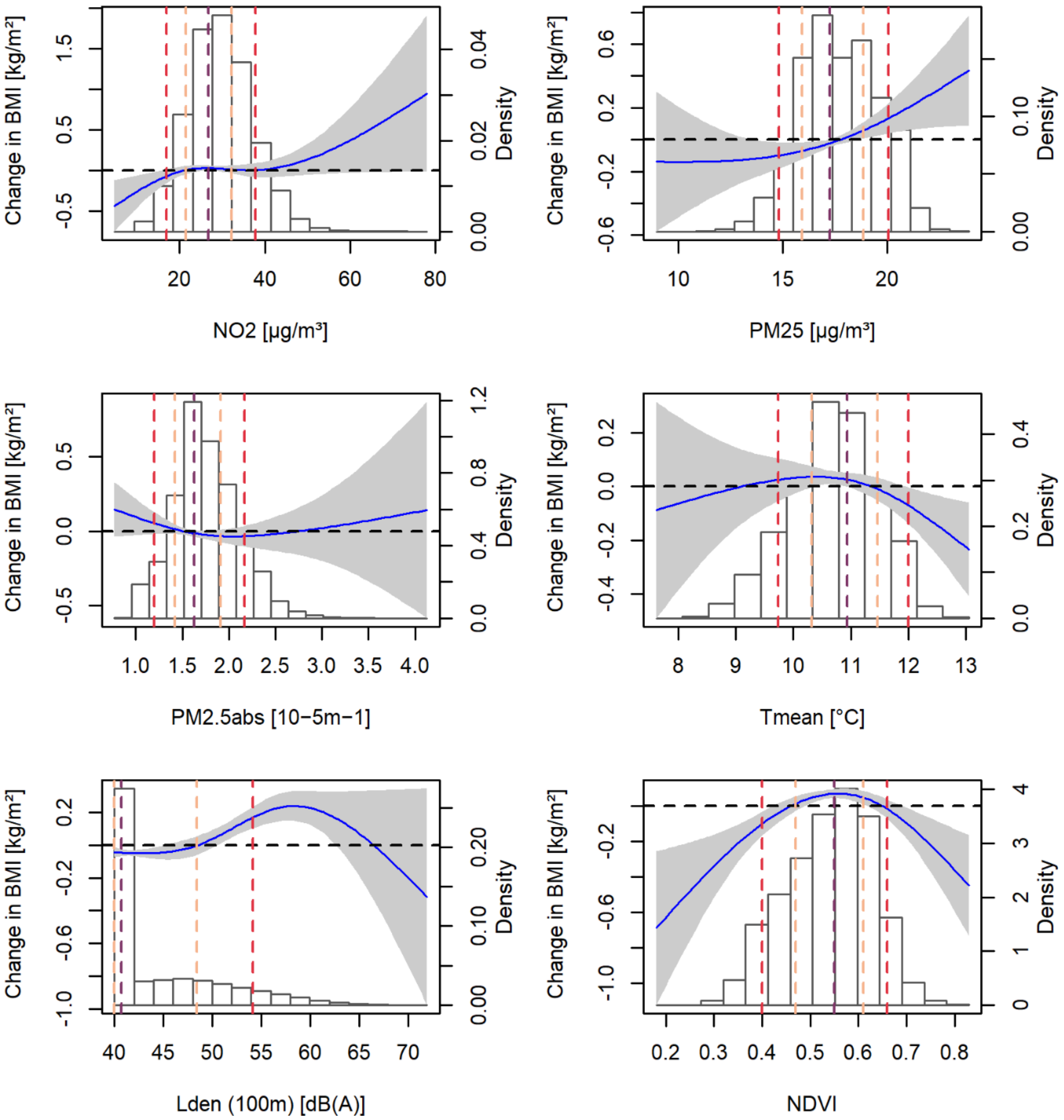


Figure S6. Exposure-response functions between environmental exposures and BMI for n = 86,710 men in the German National Cohort (NAKO). Legend: Histograms present distribution of exposure (2^{nd} y-axis on the right), vertical lines indicate percentiles of exposures (red: 10th and 90th percentile, yellow: 25th and 75th percentile; purple: 50th percentile). Models were fitted by cubic splines for the exposure and were adjusted for age, study center, lifestyle factors, education, unemployment rate at district level and population density.

Abbreviation: BMI = Body Mass Index, L_{den} = day–evening–night noise level, NDVI = normalized difference vegetation index, NO_2= nitrogen dioxide, $PM_{2.5}$ = particulate matter < 2.5 µm, $PM_{2.5}$abs= $PM_{2.5}$ absorbance, T_{mean} = mean air temperature.

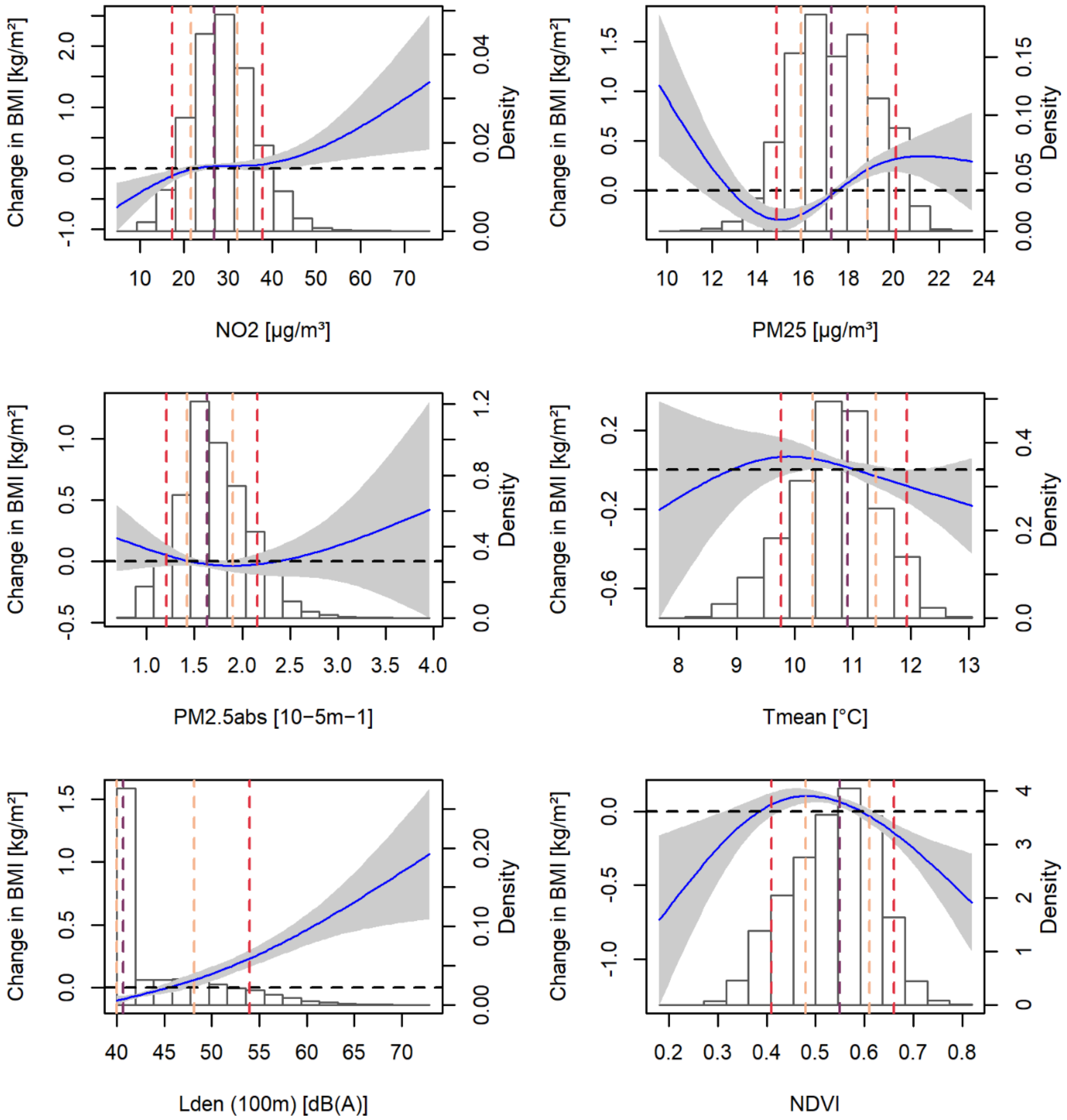


Figure S7. Exposure-response functions between environmental exposures and BMI for n = 88,245 women in the German National Cohort (NAKO). Legend: Histograms present distribution of exposure (2nd y-axis on the right), vertical lines indicate percentiles of exposures (red: 10th and 90th percentile, yellow: 25th and 75th percentile; purple: 50th percentile). Models were fitted by cubic splines for the exposure and were adjusted for age, study center, lifestyle factors, education, unemployment rate at district level and population density.

Abbreviation: BMI = Body Mass Index, L_{den} = day–evening–night noise level, NDVI = normalized difference vegetation index, NO_2= nitrogen dioxide, $PM_{2.5}$ = particulate matter < 2.5 µm, $PM_{2.5}$abs= $PM_{2.5}$ absorbance, T_{mean} = mean air temperature.

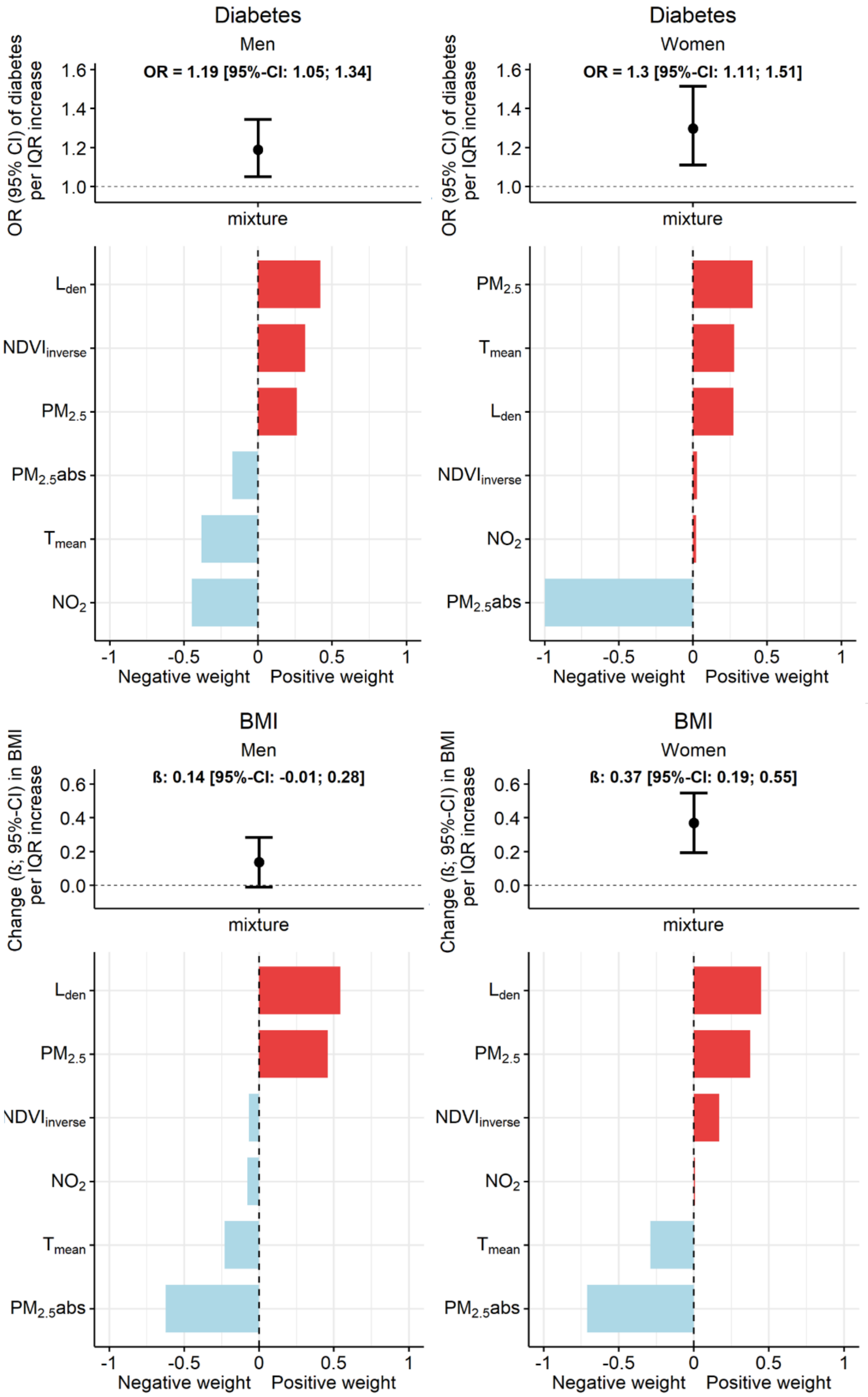


Figure S8. Joint associations of exposure to environmental mixture with diabetes and BMI for n = 86,710 men and n = 88,245 women from the German National Cohort (NAKO).
Legend: Joint odds ratios and betas are given per one-IQR increase across all exposures derived from multi-exposure quantile g-computation models. We used the inverse of NDVI; and bars represent exposure weights, indicating the proportion of each exposure contributing to the overall positive and negative association. Models were additionally adjusted for age, study center, lifestyle factors, education, unemployment rate at district level and population density. Abbreviations: BMI = Body Mass Index, CI = confidence interval, IQR = interquartile range, L_{den} = day–evening–night noise level, NDVI = normalized difference vegetation index, NO_2= nitrogen dioxide, OR = odds ratio, $PM_{2.5}$ = particulate matter < 2.5 µm, $PM_{2.5}$abs= $PM_{2.5}$ absorbance, T_{mean} = mean air temperature.

18

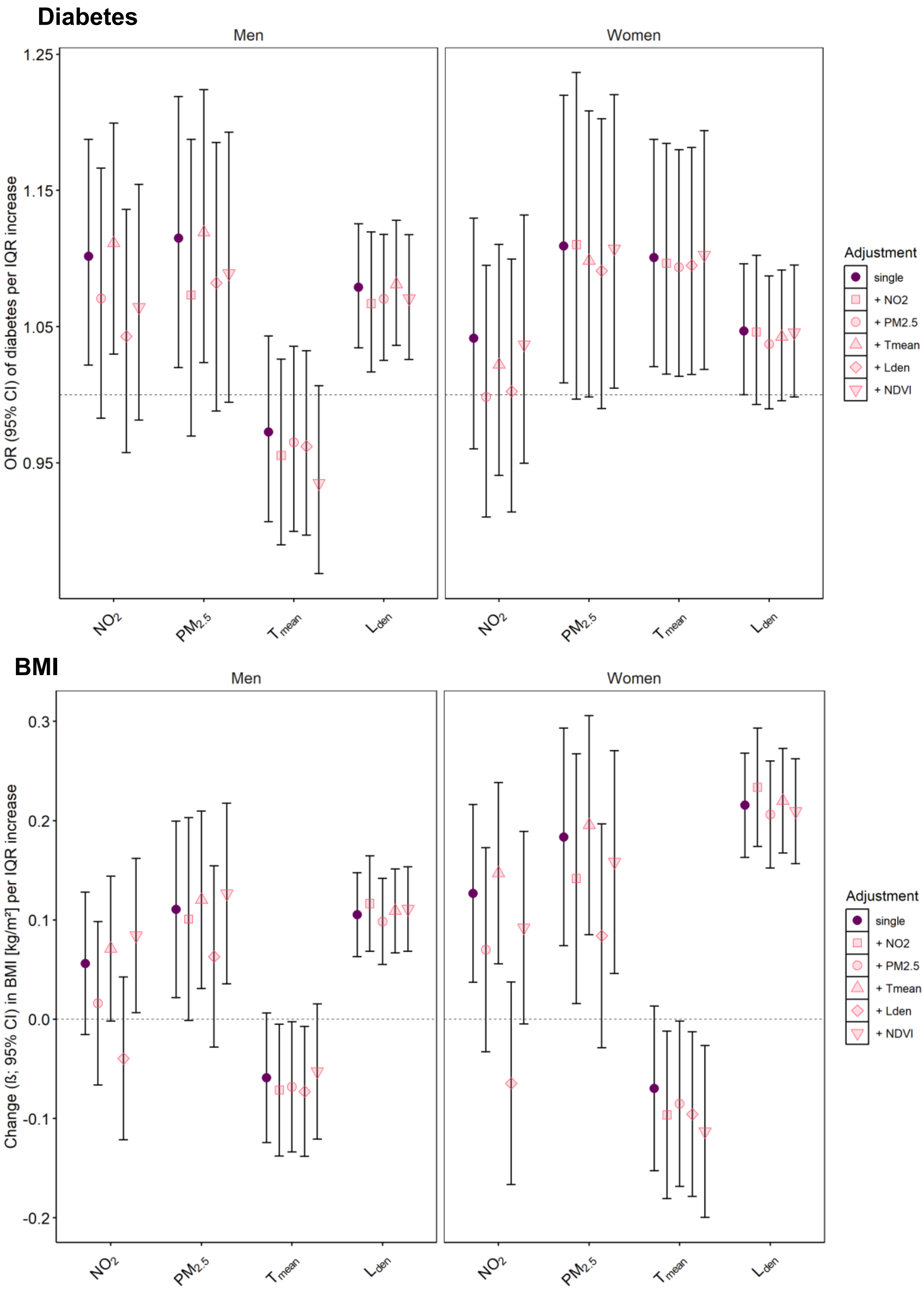


Figure S9: Comparison of single vs. two-exposure models to assess linear associations of environmental exposures with diabetes and BMI for men (n = 86,710) and women (n = 88,245) in the German National Cohort (NAKO). Legend: Linear and logistic regression models were performed and additionally adjusted for age, study center, lifestyle factors, education, unemployment rate at district level and population density. Odds ratios and absolute changes are given per IQR increase in exposure. Abbreviations: BMI = Body Mass Index, CI = confidence interval, IQR = interquartile range, L_{den} = day–evening–night noise level, NDVI = normalized difference vegetation index, NO_2= nitrogen dioxide, OR = odds ratio, $PM_{2.5}$ = particulate matter < 2.5 µm, $PM_{2.5}$abs= $PM_{2.5}$ absorbance, T_{mean} = mean air temperature.

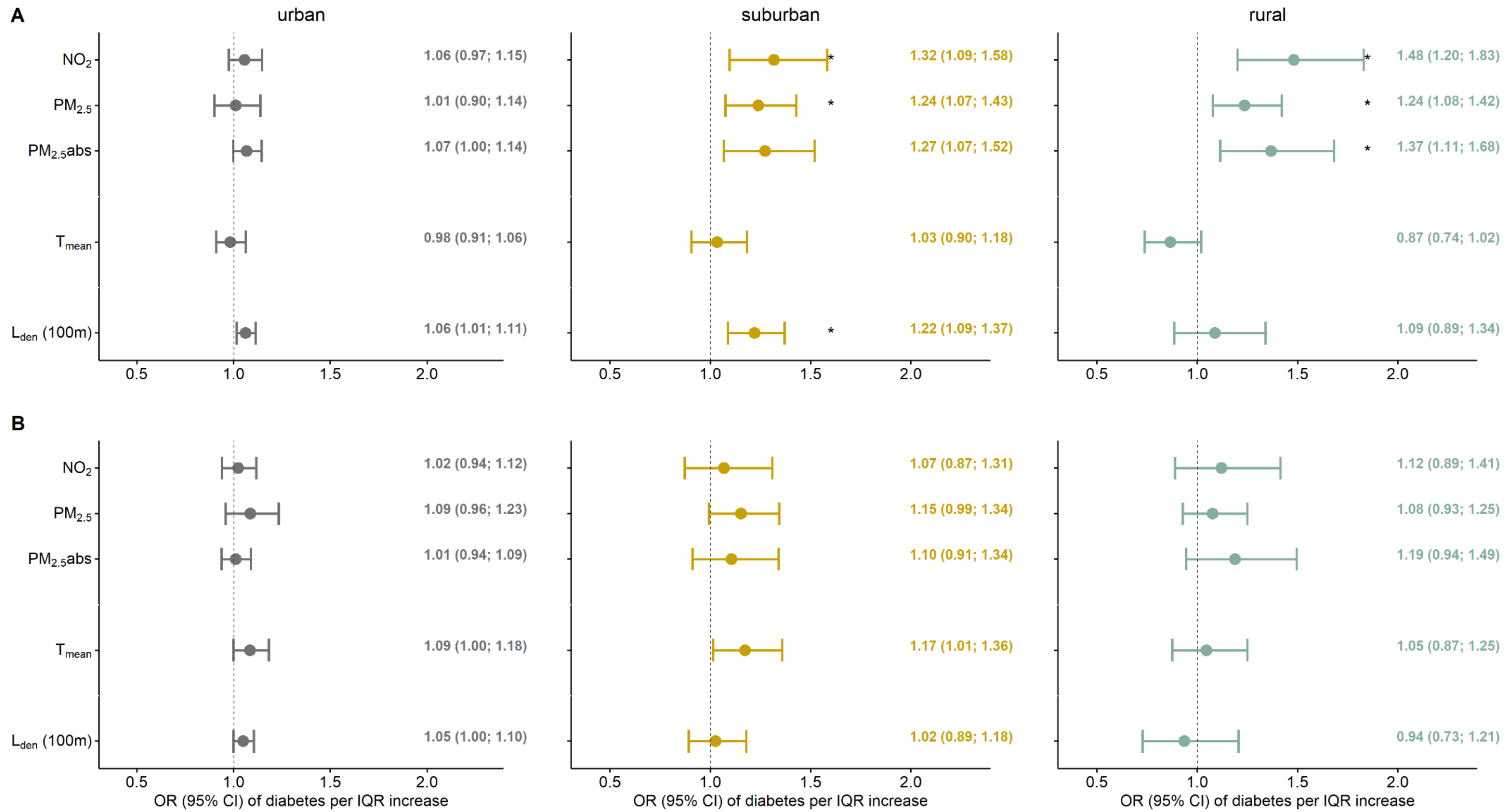


Figure S10. Urbanization-specific linear associations of environmental exposures with diabetes for men (A) and women (B) in the German National Cohort (NAKO). Legend: Odds ratios and 95%-CI were derived from logistic regression models including an interaction term between exposure and degree of urbanization from EUROSTAT. Star indicates $p_{interaction} < 0.05$. All models were additionally adjusted for age, study center, lifestyle factors, education, unemployment rate at district level and population density. Urban: n = 62,004 men; n = 62,975 women, suburban: n = 13,771 men, n = 14,152 women, rural: n = 10,933 men, n = 11,112 women. Abbreviation: CI = confidence interval, IQR = interquartile range, L_{den} = day–evening–night noise level, NO_2= nitrogen dioxide, OR = odds ratio, $PM_{2.5}$ = particulate matter < 2.5 µm, $PM_{2.5}$abs= $PM_{2.5}$ absorbance, T_{mean} = mean air temperature.

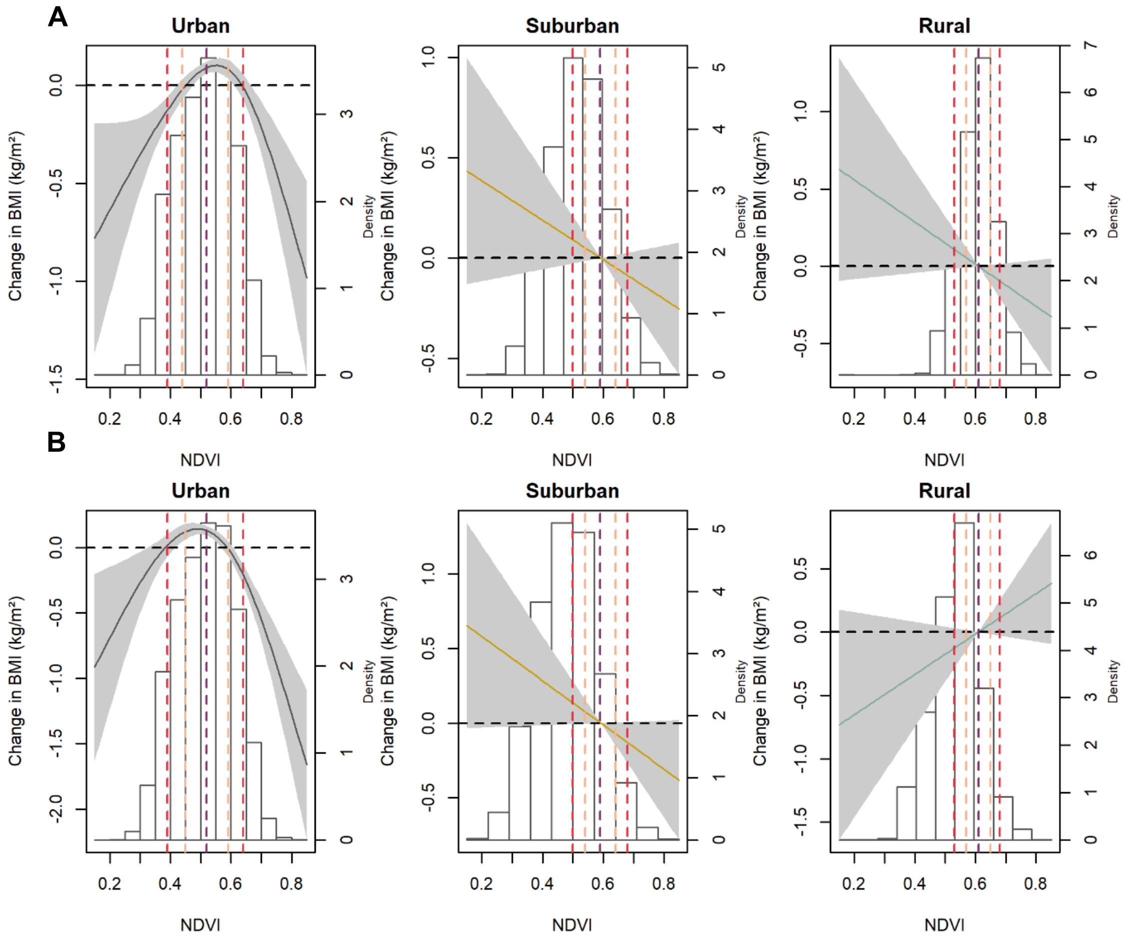


Figure S11. Urbanization-specific exposure-response functions between NDVI and BMI for men (A) and women (B) in the German National Cohort (NAKO). Legend: Histograms present distribution of exposure (2nd y-axis on the right), vertical lines indicate percentiles of exposures (red: 10th and 90th percentile, yellow: 25th and 75th percentile; purple: 50th percentile). Models were fitted by cubic splines for the exposure and were additionally adjusted for age, study center, lifestyle factors, education, unemployment rate at district level and population density. Urban: n = 62,004 men; n = 62,975 women, suburban: n = 13,771 men, n = 14,152 women, rural: n = 10,933 men, n = 11,112 women. Abbreviation: BMI = Body mass index, NDVI = normalized difference vegetation index.

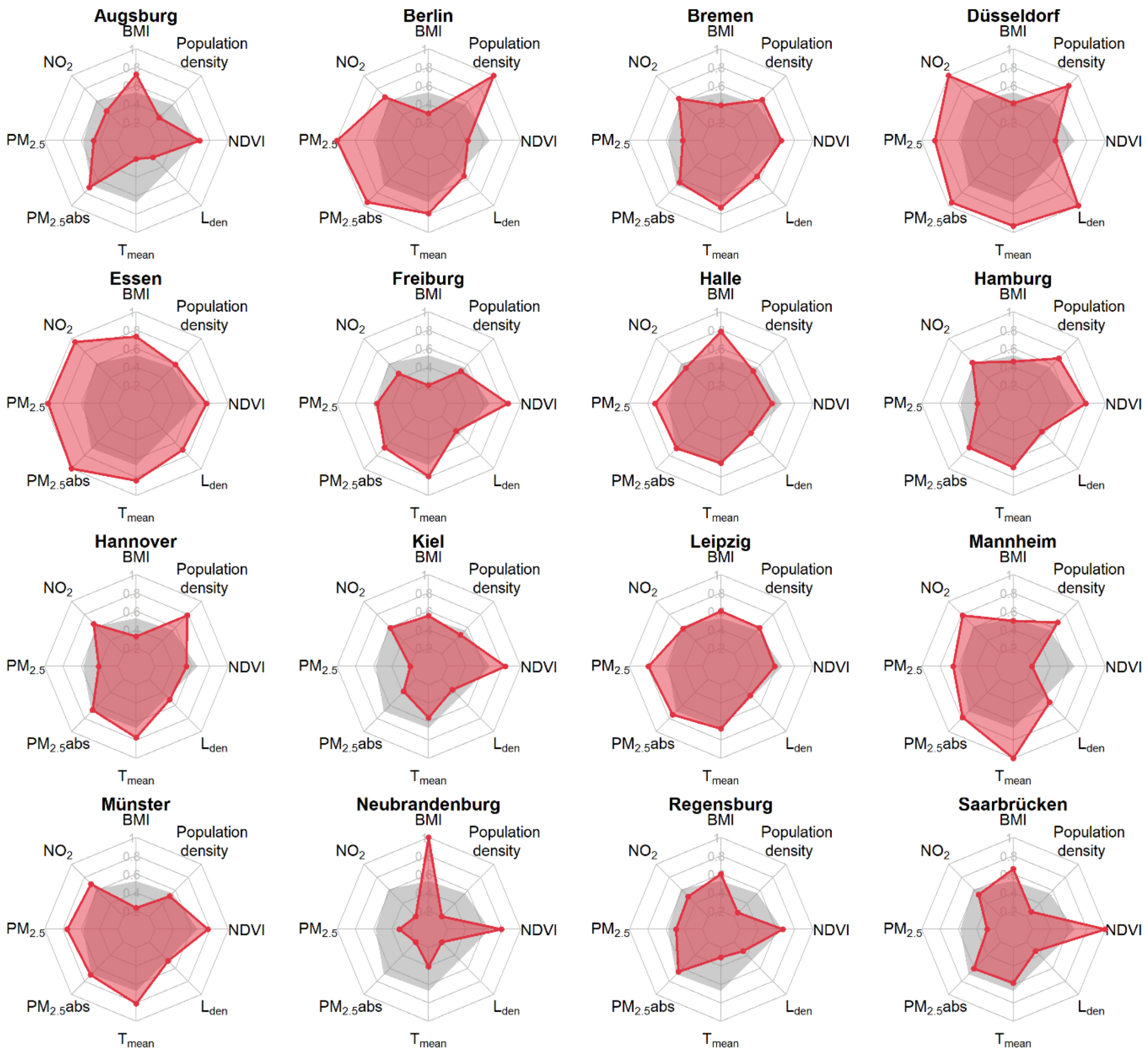


Figure S12. Radar chart presenting standardized means of environmental exposures, population density, and BMI per study center in the German National Cohort (NAKO). Legend: Grey areas indicate mean of the total NAKO sample (n = 174,955), red areas indicate mean of each study centers. Abbreviations: BMI = Body Mass Index, L_{den} = day–evening–night noise level, NDVI = normalized difference vegetation index, NO_2= nitrogen dioxide, $PM_{2.5}$ = particulate matter with diameter < 2.5 µm, $PM_{2.5}abs$= $PM_{2.5}$ absorbance, T_{mean} = annual mean temperature.

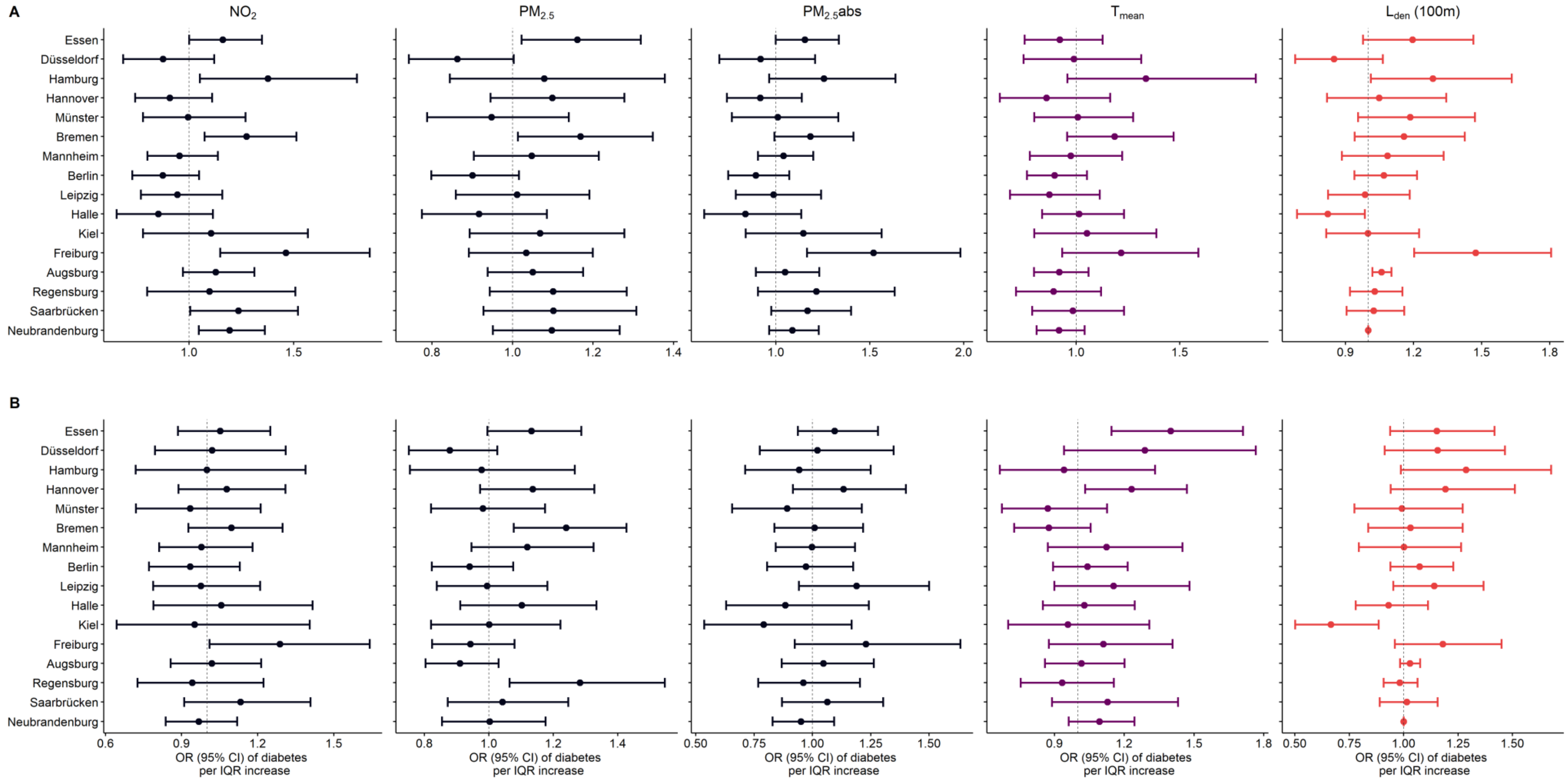


Figure S13. Study center-specific linear associations between environmental exposures and diabetes for men (A) and women (B) in the German National Cohort (NAKO; n = 174,955). Legend: The order of study centers is sorted by decreasing proportion of urban areas from top to bottom. ORs and 95%-CI are given per study center specific IQR increase of exposure derived from logistic regression models and were additionally adjusted for age, lifestyle factors, education, unemployment rate at district level and population density. Abbreviations: CI = confidence interval, IQR = interquartile range, L_{den} = day–evening–night noise level, NO_2= nitrogen dioxide, OR = odds ratio, $PM_{2.5}$ = particulate matter < 2.5 µm, $PM_{2.5}$abs= $PM_{2.5}$ absorbance, T_{mean} = mean air temperature.

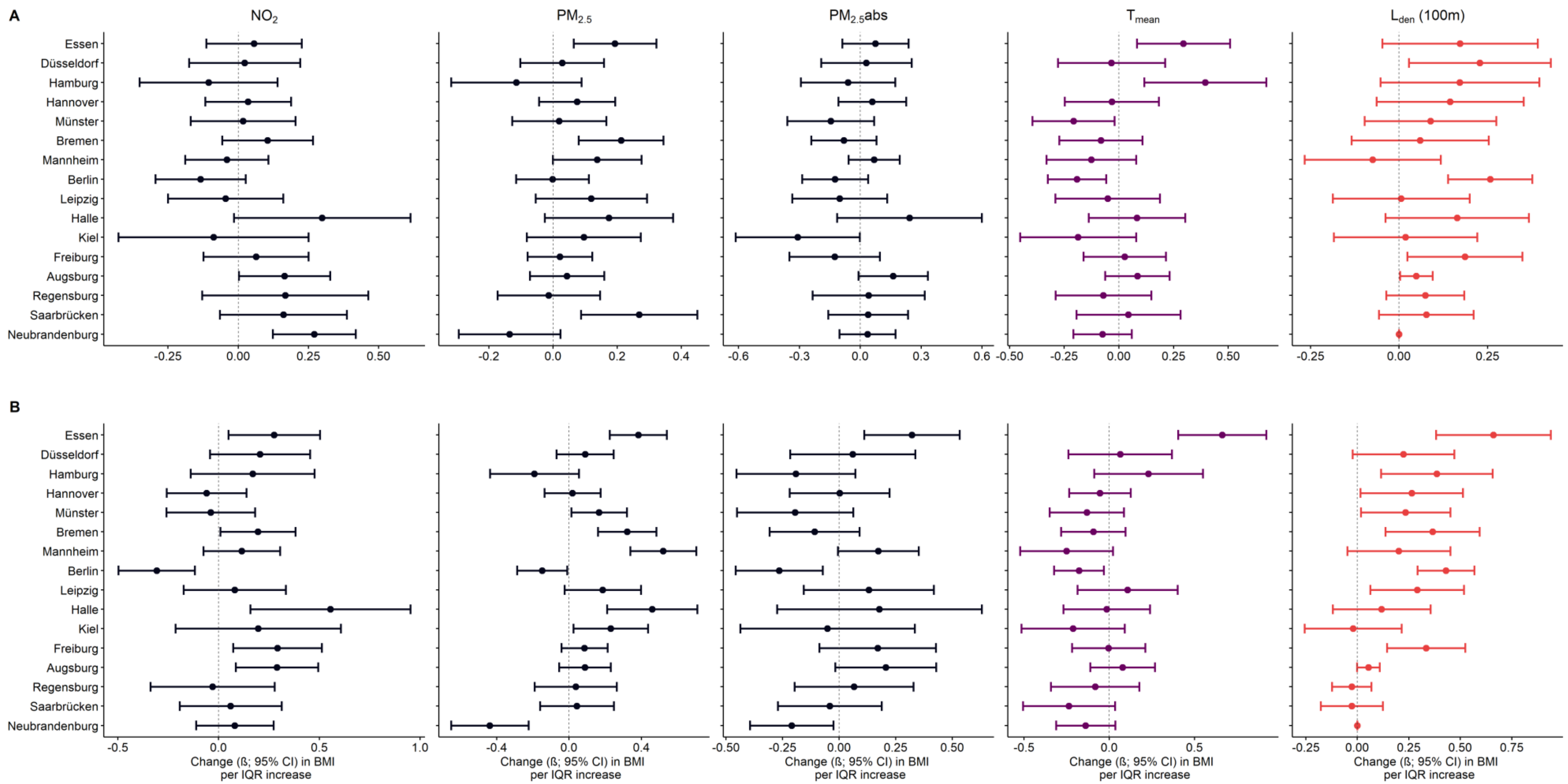


Figure S14. Study center-specific linear associations between environmental exposures and BMI for men (A) and women (B) in the German National Cohort (NAKO). Legend: The order of study centers is sorted by decreasing proportion of urban areas from top to bottom. Betas and 95%-CI are given per study center specific IQR increase of exposure derived from linear regression models and were adjusted for age, lifestyle factors, education, unemployment rate at district level and population density. Abbreviations: BMI = Body Mass Index, CI = confidence interval, IQR = interquartile range, L_{den} = day–evening–night noise level, NO_2= nitrogen dioxide, OR = odds ratio, $PM_{2.5}$ = particulate matter < 2.5 µm, $PM_{2.5}$abs= PM2.5 absorbance, T_{mean} = mean air temperature.

Supplementary Methods

Methods S1: Piecewise linear regression

We detected non-linear associations of NDVI with diabetes, obesity, BMI and waist circumference (Figure S4-S7). The exposure-response curve was inverted u-shaped with a turning point around the median and with two nearly linear associations above and below the turning point. To approximate the association per IQR increase and decrease in NDVI below and above the turning point, we implemented piecewise linear regression models using the *segmented* package in R.[2] From visual inspection of the exposure-response functions, we expected the turning point around the median of NDVI (0.55). To identify the exact turning point for men and women, we compared sex-stratified models with different turning points between 0.50 and 0.55 using R^2 and Akaike information criterion (AIC). The highest R^2 and lowest AIC were obtained using 0.53 and 0.50 as turning point for men and women, respectively.

References

1. Wolf K, Dallavalle M, Niedermayer F, Bolte G, Tobia Lakes TS, Greiser KH, et al. Environmental exposure assessment in the German National Cohort (NAKO). Environmental Research. 2025. https://doi.org/10.1016/j.envres.2025.121259.

2. Muggeo VM. Estimating regression models with unknown break-points. Stat Med. 2003;22(19):3055-71. https://doi.org/10.1002/sim.1545.

Appendix: Manuscript 4

Title:	Associations of road traffic noise with adipose tissue depots and hepatic fat content – Results from the German National Cohort (NAKO)
Authors:	Niedermayer, Fiona; Rospleszcz, Susanne; Matthiessen, Clara; Hoffmann, Barbara; Stoecklein, Sophia; Haueise, Tobias; Norajitra, Tobias; Schlett, Christoph L.; Nattenmüller, Johanna; Bamberg, Fabian; Machann, Jürgen; Günther, Matthias; Hirsch, Jochen; Nagrani, Rajini; Völzke, Henry; Meinke-Franze, Claudia; Hosten, Norbert; Nonnenmacher, Tobias; Budai, Bettina Katalin; Palm, Viktoria; Katzke, Verena; Greiser, Karin Halina; Schulz-Menger, Jeanette; Niendorf, Thoralf; Endemann, Beate; Pischon, Tobias; Staab, Jeroen; Dallavalle, Marco; Schneider, Alexandra; Wolf, Kathrin; Peters, Annette
Year:	2025
Status:	Submitted & under review (at the time of thesis evaluation) Published (at the time of thesis publication)
Journal:	Environment International
Volume:	201
Issue:	
Page:	109566
DOI:	https://doi.org/10.1016/j.envint.2025.109566
2023 Journal Impact Factor:	10.3 (*Journal Citation Reports* (Clarivate, 2023))
Rank by 2023 Journal Impact Factor:	21/35 in the category “Environmental Sciences“ (*Journal Citation Reports* (Clarivate, 2023))

Associations of road traffic noise with adipose tissue depots and hepatic fat content – Results from the German National Cohort (NAKO)

Fiona Niedermayer[1,2]*, Susanne Rospleszcz[2,9], Clara Matthiessen[3], Barbara Hoffmann[3], Sophia Stoecklein[4], Tobias Haueise[5,6], Tobias Norajitra[7,8], Christopher L. Schlett[9], Johanna Nattenmüller[9,10], Fabian Bamberg[9], Jürgen Machann[5,6,11], Matthias Günther[12], Jochen Hirsch[12], Rajini Nagrani[13], Henry Völzke[14], Claudia Meinke-Franze[14], Norbert Hosten[15], Tobias Nonnenmacher[16], Bettina Katalin Budai[16,17], Viktoria Palm[16,17,18], Verena Katzke[19], Karin Halina Greiser[19], Jeanette Schulz-Menger[20,21], Thoralf Niendorf[22], Beate Endemann[23], Tobias Pischon[23,24,25], Jeroen Staab[26], Marco Dallavalle[2], Alexandra Schneider[2], Kathrin Wolf[2], Annette Peters[1,2,6]

[1] Chair of Epidemiology, IBE, Faculty of Medicine, Ludwig-Maximilians-Universität Munich, Munich, Germany

[2] Institute of Epidemiology, Helmholtz Zentrum München (GmbH), German Research Center for Environmental Health, Neuherberg, Germany

[3] Institute of Occupational, Social and Environmental Medicine, Medical Faculty and University Hospital, Heinrich Heine University Düsseldorf, Düsseldorf, Germany

[4] Department of Radiology, University Hospital of Munich, LMU Munich, Munich, Germany

[5] Institute for Diabetes Research and Metabolic Diseases, Helmholtz Munich at the University of Tübingen, Tübingen, Germany

[6] German Center for Diabetes Research (DZD), Neuherberg, Germany

[7] Division of Medical Image Computing, German Cancer Research Center (DKFZ), Heidelberg, Germany

[8] Pattern Analysis and Learning Group, Department of Radiation Oncology, University Hospital Heidelberg, Germany

[9] Department of Diagnostic and Interventional Radiology, Medical Center, University of Freiburg, Freiburg, Germany

[10] Institute for Radiology and Nuclear Medicine Hirslanden Clinic St. Anna, Lucerne, Switzerland

[11] Section on Experimental Radiology, Department for Diagnostic and Interventional Radiology, University Hospital Tübingen, Tübingen, Germany.

[12] Fraunhofer Institute for Digital Medicine MEVIS, Bremen, Germany

[13] Department Epidemiological Methods and Etiological Research, Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany

[14] Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany

[15] Department of Radiology, Universitätsmedizin Greifswald, Greifswald, Germany

[16] Department of Diagnostic and Interventional Radiology, Heidelberg University Hospital, Heidelberg, Germany.

[17] Translational Lung Research Center (TLRC), German Center for Lung Research (DZL), University of Heidelberg, Germany

[18] Diagnostic and Interventional Radiology with Nuclear Medicine, Thoraxklinik Heidelberg, Heidelberg, Germany

[19] Division of Cancer Epidemiology (C020), German Cancer Research Center (DKFZ), Heidelberg, Germany

[20] Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, ECRC Experimental and Clinical Research Center a joint cooperation between Charite and MDC, , Lindenberger Weg 80, 13125 Berlin, Germany

[21] DZHK (German Centre for Cardiovascular Research), partner site Berlin, Berlin, Germany

[22] Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC), Berlin Ultrahigh Field Facility (BUFF), Berlin, Germany

[23] Max-Delbrueck-Center for Molecular Medicine in the Helmholtz Association (MDC), Molecular Epidemiology Research Group, Berlin, Germany

[24] Max-Delbrueck-Center for Molecular Medicine in the Helmholtz Association (MDC), Biobank Technology Platform, Berlin, Germany

[25] Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

[26] German Remote Sensing Data Center, German Aerospace Center, Weßling, Germany

*Corresponding author:

Fiona Niedermayer

Ingolstädter Landstr. 1, 85764 Neuherberg, Germany

Email: fiona.niedermayer@helmholtz-munich.de

Phone: +49 (0)89-3187-49519

ORCID: 0000-0002-6798-2630

Word count: 5,316

Abstract

Little is known about the relation between traffic noise exposure, an established environmental risk factor for cardiovascular disease, and early obesity-related risk markers such as adipose tissue (AT) and hepatic fat. Therefore, we aimed to assess associations of long-term road traffic noise exposure with AT depots measures from whole-body magnetic resonance imaging (MRI). We analyzed cross-sectional data from 11,343 participants from the population-based German National Cohort (NAKO) who underwent MRI examination between 2014 and 2016, considering visceral (VAT), subcutaneous abdominal (SCAAT), subcutaneous thoracic AT (SCTAT) and hepatic fat content as outcomes. Annual road traffic noise (L_{den}) data from the year 2017 (source: central EIONET data repository) was used to calculate weighted mean noise levels on a continuous scale within 10 and 100-meter buffers of participants' residencies. Among 11,101 participants with complete outcome data, 48.7% were women, and the mean age was 51.9 years. Higher annual L_{den} was associated with increased AT depots and hepatic fat content in men (e.g., VAT: 1.72 %-change [95% confidence interval: [0.14%; 3.30%]; SCAAT: 2.18 %-change [0.43%; 3.93%], hepatic fat content: 3.57 %-change [1.41%; 5.78%] per 10 dB(A) increase in L_{den} (10m)) and women (e.g., VAT: 3.13 %-change [1.09%; 5.18 %]; SCAAT: 2.38 %-change [0.55%; 4.20%], hepatic fat content: 3.08 %-change [1.00%; 5.21%] per 10 dB(A) increase in L_{den} (10m)). Associations were robust with all outcomes after adjusting for air pollutants and surrounding greenness, and effect modification by obesity and hypertension was observed for SCAAT, SCTAT and hepatic fat content. Our findings indicate that annual exposure to road traffic noise is associated with increased adipose tissue depots and hepatic fat content, and thus present novel evidence for the cross-sectional association between noise and early MRI-derived metabolic health markers.

Keywords: obesity, hepatic steatosis, metabolic disease, environment

Abbreviations

AT	Adipose tissue
BMI	Body mass index
CI	Confidence Interval
CVD	Cardiovascular disease
DAG	Directed acyclic graph
DXA	Dual-energy x-ray absorptiometry
EIONET	European Environment Information and Observation Network
EEA	European Environment Agency
L_{den}	Day–evening–night noise level
END	Environmental Noise Directive
MASLD	Metabolic-dysfunction associated steatosis liver disease
MRI	Magnetic resonance imaging
NAKO	German National Cohort
NDVI	Normalized Difference Vegetation Index
NO_2	Nitrogen dioxide
OR	Odds ratio
PM	Particulate matter
VAT	Visceral adipose tissue
SCAAT	Subcutaneous abdominal adipose tissue
SCTAT	Subcutaneous thoracic adipose tissue
WHO	World Health Organization

1. Introduction

The continuing rise in cardiometabolic diseases, such as cardiovascular disease (CVD), diabetes mellitus, hypertension, or dyslipidemia, is a severe threat to humans' health.[1-4] Obesity is a major phenotype of cardiometabolic disease; an unfavorable distribution of body adipose tissue (AT) is associated with a clustering of adverse conditions.[5-8] Increased visceral adipose tissue (VAT) is also strongly associated with increased hepatic fat content and hepatic steatosis,[5,8] resulting in metabolic dysfunction-associated steatotic liver disease (MASLD), whereas the role of other AT depots, such as subcutaneous adipose tissue, is less well-defined.

Not only behavioral but also non-behavioral risk factors such as the environment need to be considered in obesity prevention.[9] The WHO (Word Health Organization) has ranked noise exposure as the second most harmful environmental risk factor after air pollution.[10] About one-fifth of the European population is exposed to harmful day-evening-night noise levels (L_{den}) above 55 dB(A), which are associated with various health outcomes including hypertension, CVD, cognitive and hearing impairments, and psychological well-being.[10-13] Numerous studies have suggested direct pathways through which noise exposure affects health.[7,14] In particular, it is suggested that noise-induced chronic stress is associated with the promotion of cardiovascular risk factors, e.g., high blood pressure, and elevated blood glucose and lipids.[14]

Recently, it has also been hypothesized that traffic noise is linked to metabolic disease and obesity.[13,15-17] While previous studies conceptualized obesity by anthropometric measures such as body mass index (BMI) or waist circumference,[15] a differentiation of AT depots and assessment of hepatic fat content is only possible by medical imaging such as dual-energy x-ray absorptiometry (DXA) or magnetic resonance imaging (MRI).[17-19] Contributing to this, defining obesity solely by BMI is currently reconsidered, as BMI may not provide reliable information on an individual disease risk.[20] As advocated by the Lancet Diabetes & Endocrinology commission[20], excess adiposity determined by MRI-derived AT measures may more accurately inform about cardiometabolic disease risk.[5,21,22] Studies using the Framingham Heart study showed that in particular VAT is an independent, strong risk factors for cardiometabolic diseases beyond overall adiposity, particularly in women.[21,22] Consequently, studies of associations between road traffic noise and MRI-derived AT measures are essential to understand the relationship between environmental factors and cardiometabolic disease risk, but are currently lacking.

In addition, other environmental exposures may lead to increased measures of obesity and increased hepatic fat content and may therefore be potential confounders in the association between road traffic noise and obesity.[23-25] In order to assess unbiased associations between noise and health, it is crucial to take into account potential other environmental risk factors, particularly in urban areas, where air pollution and lack of greenness co-occur.[26] Previous studies that adjusted for other environmental exposures indicated predominantly robust associations of noise exposure with various health outcomes, which need further confirmation.[16,27-30]

Previous studies in animals and humans also suggested that individuals with cardiometabolic diseases may be more susceptible to exposure to adverse noise levels,[29,31] which may be attributable to stronger deterioration of endothelial dysfunction.[7,31] Olbrich et al.[32] showed that recurrence of CVD events was higher in patients exposed to higher levels of aircraft noise, with similar but insignificant trends for railway and road traffic noise.[32] Therefore, we hypothesized that the association between noise and AT measures may be stronger in participants with existing cardiometabolic disease, providing important clues to potentially susceptible subgroups of the population.

Therefore, we aimed to assess the sex-specific associations of long-term road traffic noise exposure with AT depots and hepatic fat content measured by MRI in the German National Cohort (NAKO), testing the following hypotheses:

(1) Higher levels of annual road traffic noise are associated with increased AT depots, hepatic fat content, and increased frequency of MASLD.

(2) Adverse associations of long-term road traffic noise are independent of exposures to air pollution, and surrounding greenness.

(3) In participants with prevalent cardiometabolic disease, adverse associations of road traffic noise exposure are more pronounced than in participants without those conditions.

2. Methods

2.1. Study population

NAKO is a German-wide, population-based, multicenter cohort that assesses a range of chronic diseases, their risk factors, and etiology.[33,34] Between 2014 and 2019, 205,415 participants aged 20-74 years underwent a baseline examination across 18 NAKO study centers, where comprehensive medical and physical examinations were performed. A subgroup of 30,868 participants had a complete whole-body MRI using 3T scanners (MAGNETOM Skyra, Siemens Healthineers, Erlangen, Germany) for neurologic, cardiovascular, thoracoabdominal, and musculoskeletal imaging at one of the five imaging sites.[33,35] NAKO was approved by the local ethics committees and all participants gave written informed consent before study enrollment. The current analysis includes 11,343 participants whose imaging data was collected between 2014 and 2016, and for whom image evaluation has been completed at the time of the study.

2.2. Outcome

The main outcome measures were VAT, subcutaneous abdominal AT (SCAAT), subcutaneous thoracic AT (SCTAT)), and hepatic fat content. For the assessment of AT depots and hepatic fat content, a T1-weighted 3D VIBE two-point Dixon technique was performed.[19,36,37] Derivation of MRI-based outcomes used a deep learning approach (3D nnU-Net) that automatically segmented AT depots in the trunk, namely VAT (AT inside the abdominal cavity), SCAAT, SCTAT and the liver on MRI images.[37-39] AT quantification was standardized based on anatomical landmarks: mid-femoral head to cardiac apex for VAT and SCAAT, cardiac apex to mid-humeral head for SCTAT. AT volumes are reported as liters and hepatic content as percentages. Prior to hepatic fat segmentation, fat-water signal swap artifacts were detected and repaired in underlying images by an automatic approach based on nnU-Net. As a secondary outcome, we classified participants as having prevalent MASLD. Therefore, participants with hepatic fat content >5.6% and at least one of the following cardiometabolic conditions: BMI ≥25 kg/m^2, a diagnosis of diabetes, hypercholesterolemia, or hypertension were classified as having MASLD (alcohol consumption: <30 g/day for men, <20 g/day for women) or MetALD (alcohol consumption: ≥30 - <60 g/day for men; ≥20 - <50 g/day for women).[40,41] Participants with high hepatic fat content and excessive alcohol consumption (≥60 g/day (m) and ≥50 g/day (w)), classified as MetALD or with a known hepatitis B and C diagnosis were excluded from the analysis.

2.3. Exposure

Annual road traffic noise exposure data in Germany for the reference year 2017 is provided from the central European Environment Information and Observation Network (EIONET) data repository (https://cdr.eionet.europa.eu/). Separate datasets were available for each urban area (>100,000 inhabitants) or regions along major roads (>3 million vehicle passages annually). According to the Environmental Noise Directive (END) obligation 2002/49/EC Article 3[42], EU member countries are obliged to map harmful noise exposure levels ≥ 55 dB(A) in urban areas or in regions along major roads. Details on how these datasets were processed, harmonized and aggregated into a German-wide map (Figure 1) can be found in Staab et al..[43] Briefly, separate datasets in polygonal shapefile format were available for areas subject to noise mapping under the Directive, with road traffic noise exposure expressed as L_{den} noise classes in five decibel steps (55: 55-59 dB(A), 60: 60-64 dB(A), 65: 65-69 dB(A), 70: 70-74 dB(A), 75: >=75 dB(A)) with a resolution of 10 m × 10 m.[43,44] We assigned the lower road traffic noise values of the 5 dB(A) band (e.g.: 55 dB(A) if 55-59 dB(A)) of the corresponding grid cells to the participants' geocoded addresses. In urban areas covered by the END obligation 2002/49/EC Article 3 section k[42], grid cells with missing values were assigned a value of 40 dB(A) as the lower detection limit (Figure 1), as missing data can be attributed to noise levels below the obligatory reporting thresholds of 55 dB(A). We then calculated mean noise levels in buffers of 10 and 100m around the geocoded address points to derive area-weighted levels on a continuous scale, which we used for our main analysis. Prior to this, grid cells without data (coded NA in Figure 1; not covered by the END obligation as areas are not along major roads or urban areas, 2002/49/EC Article 3 section k and n[42]) were also set to 40 dB(A). In the following sections, we use the term noise for road traffic noise.

2.4. Covariates

Potential covariates were assessed by using standardized touchscreen-based questionnaires, face-to-face interview, or physical examinations conducted by trained staff at examination day. We considered age at examination, study center, various lifestyle factors and individual socioeconomic status. Age in years at examination was available and participants were grouped in eight study center regions (Augsburg, Berlin, Essen, Düsseldorf, Mannheim, Münster, Neubrandenburg, Saarbrücken). Lifestyle factors included physical activity, which was assessed in minutes per week using the standardized Global physical activity questionnaire (GPAQ) questionnaire and evaluated in accordance with the WHO protocol.[45,46]

Alcohol consumption was quantified in drinks per week and subsequently converted to grams per day. Participants were classified as never-smokers, ex-smokers, or current smokers based on their self-reported smoking behavior. Individual socioeconomic status was reflected by income given in euros. Body mass index (BMI) was calculated from measured height and weight by dividing weight by height in square meters (kg/m²). Height and weight were measured using a seca stadiometer 274 and a scale mBCA 515 (seca GmbH & Co. KG, Hamburg, Germany). [47] Information on physician-diagnosed diabetes mellitus and hypercholesterolemia is based on self-report by participants in face-to-face interviews. Hypertension was defined by measured systolic and diastolic blood pressure values (≥140 mmHg and ≥90 mmHg). The blood pressure values were taken with an Omron-Hem-705IT device in the sitting position after a five-minute rest period. Two measurements were conducted two minutes apart and the values of the second measurement were used.[48,49] For diabetes, hypertension and hypercholesterolemia, information on antihypertensive, lipid-lowering or antidiabetic medication intake was not available during the time of the study and therefore, could not be considered. In addition, participants reported the extent to which noise annoys them, with options ranging from 1 = not annoyed at all to 5 = extremely annoyed.[50] A question about the living duration at place of residence was included in the touchscreen questionnaire.

Further spatial geocoded variables at residential addresses were available, including air pollution, surrounding greenness, unemployment rate and population density. A detailed description on the assignment, data preparation, and resources can be found in Wolf et al.[44]. The ELAPSE (Effects of Low-Level Air Pollution: A Study in Europe) project provided high-resolution data on modeled nitrogen dioxide (NO_2) and particulate matter with a diameter below 2.5 µm ($PM_{2.5}$) on a 100m*100m grid for the year 2010.[44,51] Land use regression models were developed to predict air pollution concentrations, incorporating measurements from ground-level monitoring stations, satellite observations, estimates from chemistry transport models, and further spatial predictors.[51] To quantify surrounding greenness, we used the Normalized Difference Vegetation Index (NDVI) on a 1km * 1km grid, extracted from monthly satellite images taken by the NASA Terra Moderate Resolution Imaging Spectroradiometer (MODIS).[44] Briefly, the NDVI (= reflected radiation in the visible red minus in the near infrared divided by the sum of the two) takes values from -1 to 1. Negative NDVI values, reflecting mainly water, were set to missing, while values around 0 reflect areas with no vegetation and 1 reflects areas with intense green vegetation.[44] NDVI data covered the whole baseline period so we assigned each participant the annual NDVI of the respective grid cell averaged over the warm months (March to October) of their examination year. Area-level SES was represented by the unemployment rate at the district level for 2014 from the

Federal Employment Agency.[52] Population density, given as inhabitants per 500 square meters, was available for the year 2018 from a private company (WiGeoGis GmbH).

All covariates were considered in directed acyclic graphs (DAG) to visualize interdependencies and to identify confounders, colliders, and mediators (Supplementary Figure S1).

2.5. Statistical analysis

We performed all analyses with the statistical software RStudio (version 4.3.1)[53] and statistical significance was indicated by two-sided p-values <0.05. Due to the high number of missing values in the covariates (Supplementary Figure S2), which would have resulted in a reduction of the sample size by 15 % using a complete-case approach, we employed a random forest approach to impute the covariates using the function missForest() from the Rpackage missforest.[54] In summary, the process starts with an initial estimation (mean for continuous variables and mode for categorical variables) and then employs a random forest to predict the missing values based on the observed data. These steps are repeated until a stopping criterion is met, or a maximum number of iterations has been reached.[54] The imputation in our analysis achieved a low imputation error, as indicated by a normalized root mean square error (RMSE) of 2.3% for continuous variables and a percentage falsely classified (PFC) of 8.8 % for categorical variables.

To assess the association of noise with our primary outcomes and prevalent MASLD, we performed linear and logistic regression models with covariate adjustment, respectively. We identified the following adjustment set with DAG: age, study region, alcohol consumption, physical activity, smoking behavior, and income (Supplementary Figure S1). As visualized in the DAG (Figure 1), we hypothesized that unmeasured residual confounding would be explained by adjusting for study center region. The area-related variables available at the time of this study were either at a coarse resolution (e.g., district-level unemployment rate) or did not match years of baseline (population density from 2018). However, we extended the adjustment model for these area-level variables in a sensitivity analysis to see if the results changed substantially or if the study center regions captured unmeasured confounding related to contextual differences. We log-transformed hepatic fat content prior to linear regression analysis due to a left-skewed distribution of the regression residuals. All effect estimates are presented as a percentage change of the arithmetic or geometric outcome mean or as an odds ratio (OR) per 10 dB(A) increase in exposure, with the corresponding 95% confidence interval (CI). The percentage change of the arithmetic outcome mean was calculated as follows: $\% - \text{change} = \frac{\text{ß} * \text{increment}}{\text{mean(outcome)}} * 100$, where the increment referred to the 10 dB(A) increase. As hepatic fat content was log-transformed, the calculation was as follows: $\% - \text{change} = (\exp(\text{ß} * \text{increment}) - 1) * 100$, which is interpreted as the percentage change of the geometric outcome mean. We visually inspected the exposure-response functions to detect non-linear associations between noise and outcomes by applying natural cubic splines with three degrees of freedom.

To assess whether the associations of noise were independent of other environmental exposures, we conducted two-exposure models adjusting for other environmental factors associated with exposure and outcome.[55,56] We chose the air pollutants NO_2 and $PM_{2.5}$ because they have common sources with road traffic noise. Moreover, air pollution and noise exposure are more common in urban areas, which are known to have less greenness.[26] To avoid multicollinearity in the two-exposure models, we performed Spearman correlation analysis *a priori* between all environmental exposures with a cut-off of ≤ 0.7. In addition, we calculated the variance inflation factor for the two-exposure models, assuming that if the variance inflation factor for each variable was <5, there was no multicollinearity problem.

We assessed potential effect modification by cardiometabolic disease including a multiplicative interaction term between noise and the following indicators: obesity (BMI ≥/< 30kg/m²), hypercholesterolemia (yes/no), hypertension (yes/no), and “any metabolic disease", indicating either obesity, diabetes, or hypercholesterolemia. Due to the low prevalence of diabetes, a dedicated analysis on diabetes was not sensible. We also tested for potential interactions by age (≥/<65 years), smoking behavior (never smoker/ex and current smokers), and noise annoyance (no-low-moderate/high-extreme).

We conducted several sensitivity analyses to investigate the robustness of our findings.
(1) To account for potential misclassification of the road traffic noise exposure, we performed several sensitivity analyses. Firstly, those individuals who were assigned a value of 40 dB(A) in the continuous road traffic noise variable, but who lived outside the areas covered by the END obligation 2002/49/EC[42] were excluded. Secondly, we examined associations using the categorical road traffic noise classes with the following categories: 40, 55 – 59, 60 – 64, 65 – 70, ≥70. As this categorical variable gives the noise levels extracted at the address points, this sensitivity analysis addressed the potential bias introduced by averaging noise levels across cells in 10m and 100m buffers as used in our main analysis. Thirdly, we assessed the association with a binary road traffic noise variable (</≥ 55 dB(A)) based on categorical L_{den} classes. Finally, a three-category road traffic noise variable was derived based on the continuous variables (40, >40 – <55 and ≥55). For all noise variables included in the sensitivity analysis, participants with missing data in the categorical L_{den} classes were excluded, as these individuals were not subject to the END obligation 2002/49/EG. An overview of the different noise variables used in sensitivity analyses with respective sample sizes can be seen in Table S1.
(2) We conducted a complete-case analysis excluding all cases with missing data in the covariates considered in regression models (age, center, physical activity, alcohol consumption, smoking behavior, income).
(3) We assessed the associations between road traffic noise and the outcome MASLD in combination with metabolic-associated alcoholic liver disease (MetALD).
(4) We adjusted for education as an additional indicator of individual socio-economic status in addition to income. Moreover, we compared models where we dropped income or lifestyle

factors to see whether lifestyle factors explained some SES-related unmeasured confounding not captured by income.

(5) We excluded all with less than five or less than ten years of living duration, hypothesizing that associations tend to be stronger in these subsamples.

3. Results

3.1. Baseline characteristics

After excluding all individuals with missing data in the main outcomes (Supplementary Figure S2), the study sample comprised 11,101 participants (48.7% women, Table 1). The mean age of participants was 51.9 years, and most participants had their MRI scan in 2016 (60%). Furthermore, one-third of the participants lived in the study center Neubrandenburg, followed by Augsburg and Berlin. Mean levels of VAT and hepatic fat content were higher in men than in women (4.8 liter and 8.7% vs. 2.5 liter and 6.4%, respectively). Mean SCAAT and SCTAT were higher in women than in men (Table 1).

The mean L_{den} levels were 43.8 dB(A) and 44.1 dB(A) for the 10m and 100m buffer (Table 1). Based on the categorical noise variable, 43.8% of the participants had missing data, 37.2% were set to 40 dB(A), and the remaining 20% were distributed over the L_{den} classes 55 dB(A) to ≥75 dB(A) (Supplementary Figure S3 and Table S1). However, distributions varied widely between the study centers, with low proportions of missing data in Münster, Essen, Mannheim, and Düsseldorf and high proportions in Neubrandenburg. Noise indicators for sensitivity analysis are described in Supplementary Table S1.

Mean concentrations of NO_2, $PM_{2.5}$, and NDVI were 26.0 µg/m^3, 17.6 µg/m^3, and 0.5, respectively (Supplementary Table S2). Based on the Spearman correlation, NO_2 and $PM_{2.5}$ were positively (range r = 0.4 to 0.6) and NDVI negatively (r = -0.4 to -0.2) correlated with noise (Supplementary Figure S4).

3.2. Associations of noise with outcomes

Increased noise was associated with increased AT depots and hepatic fat content in men and women after adjusting for age, study center, lifestyle factors and income (Table 2). We found the strongest association for hepatic fat content in men and women (men: 3.6%-change (95%-CI: 1.41; 5.78); women: 3.1%-change (95%-CI: 1.00; 5.21) per 10 dB(A) increase in L_{den} (10m)). Accordingly, odds of MASLD were higher with increase of noise (Table 2). L_{den} (10m and 100m) were also associated with a 1.7% to 1.9%-change in VAT for men and a 3.1% to 3.5%-change in VAT for women, respectively. We found a positive association of 1.8%-change in SCTAT and 2.2%-change in SCAAT for men and 2.2%-change in SCAAT and 2.7%-change in SCTAT for women. Adjusting for area-level SES and population density did not alter the results substantially (Supplementary Table S3), although effect estimates tended to be higher, particularly after adjusting for population density.

The exposure-response curves showed some non-linear associations between noise variables and outcomes, in particular for SCAAT and SCTAT and L_{den} (10m) levels above 60 dB(A) (Supplementary Figure S5 and S6). As seen in Figure 2, Supplementary Figure S7 and S8, the effect estimates of noise with all outcomes were robust after adjustment for other environmental exposures. The variance inflation factor was <5 for all two-exposure models, indicating no multicollinearity problem. Results of interaction analysis are presented in Figure 3, S9, and S10. There was no effect modification by cardiometabolic disease on the association of noise with VAT. In men, obesity amplified the association of noise with SCAAT and SCTAT (Figure 3), and hypertension amplified the association of noise with hepatic fat content (Figure 3). In contrast, the association of L_{den} (10m) with hepatic fat content was stronger in women without hypertension (Figure 3). We found no significant interaction between noise and age, noise annoyance, or smoking, except for the association of L_{den} with hepatic fat content in men (Supplementary Figure S9 and S10).

3.3. <u>Sensitivity analysis</u>

After excluding those with missing data (n = 4,864) in the categorical noise variable, the results for continuous variables were slightly stronger (Supplementary Table S4). Noise categories 40 to 54.9 dB(A) and ≥55 dB(A) were positively associated with all outcomes (Supplementary Table S4). We found similar trends for the original categorical noise variable but no clear dose response (Supplementary Table S4). Moreover, we observed robust associations in complete-case analysis (Supplementary Table S5 and S6). We observed similar associations of noise with MASLD and MetALD derived from logistic regression models (Supplementary Table S7). Dropping income or lifestyle factors did not change results substantially, however attenuated or stronger effect estimates could be observed, particularly for women (Supplementary Table S8). Furthermore, the associations were robust after additional adjustment for education (data not shown). The associations were stronger for participants who had the same residential address for at least five or ten years (Supplementary Table S9).

4. Discussion

4.1. Key findings and comparison to current literature

This cross-sectional analysis using data from a German-wide cohort study supports our hypothesis that annual exposure to road traffic noise is associated with increased AT depots and hepatic fat content, as derived by MRI, in adult men and women. Noise associations remained consistent after further adjustment for air pollutants and surrounding greenness, suggesting that long-term exposure to road traffic noise has an independent association with AT measures. Our findings indicated an effect modification by cardiometabolic disease, resulting in higher SCAAT and SCTAT with higher noise exposure in men with obesity and higher hepatic fat content in men with hypertension. All associations remained robust in multiple sensitivity analyses, including different adjustment sets.

Our findings are in line with previous literature on the association of noise with obesity markers. A recent meta-analysis identified 13 epidemiological studies from Europe that analyzed various noise exposures to obesity.[15] Overall, studies showed that the increase in noise exposure is associated with higher waist circumference and higher odds of central obesity. However, waist circumference and BMI do not provide information on AT distribution, which can lead to misclassification of obesity in certain subgroups with low or high lean mass.[57] To date, only a limited number of studies used alternative methods to quantify body fat mass with bioelectrical impedance measurements,[30,58] suggesting a positive association between road traffic noise and total body fat percentage. Findings from the LEAD study in Vienna did not find consistent associations between noise and body composition measures derived by DXA.[17] Our study adds to current evidence by providing findings for metabolically relevant AT depots, including hepatic fat. In addition, our analysis showed that adjusting for population density may capture unmeasured residual confounding related to spatial variation, which may be particularly relevant for multi-center studies with varying urbanization degree. To summarize, our results suggest that noise may play a key role in the pathogenesis of (cardio-)metabolic diseases, as AT are known to be metabolically active, for example by secreting cytokines resulting in low-grade inflammation and altering glucose and lipid metabolism.[5]

Investigating the role of environmental factors is necessary for obesity prevention, especially since visceral obesity and hepatic steatosis are reversible if treated early.[59] We found that higher annual noise exposure was associated with larger MRI-derived AT depots, independent of other environmental exposures including traffic-related air pollutants, which is partly in line with previous studies.[16,28-30] Reducing road traffic and its associated noise may therefore be a promising target to complement behavioral interventions to prevent the development and progression of cardiometabolic disease.

The health impacts of traffic noise may specifically affect susceptible subgroups of the population. Only a few studies investigated potential effect modifications by cardiometabolic disease, showing a stronger effect of noise in individuals with obesity and CVD diagnosis.[29,31,60] This is consistent with our findings although we only observed a stronger effect of noise on SCAAT and SCTAT in men with obesity. Although obesity defined as BMI ≥ 30 kg/m² and MRI-derived AT measures both reflect adiposity, they still capture distinct dimensions. BMI refers to overall adiposity whereas AT measures provide body fat quantification, which is more closely linked to cardiometabolic risk.[5,22] Thus, we aimed to assess whether the strength of the associations between noise and AT measures differed by overall obesity status, as it has been shown by Christensen et al.[60]. In this longitudinal Danish cohort study, associations between higher noise exposure with small increases in BMI and waist circumference were stronger in obese subjects.[60] Moreover, our findings indicated that the effect modification for hypertension was in opposite directions in men and women. We need to note that including cardiometabolic disease status into the model may induced bias from a DAG-point of view, as cardiometabolic disease are descendants of the MRI-derived AT measures. Therefore, the results on these analyses need to be interpreted with caution and future longitudinal analyses with multiple follow-ups, including repeated MRI measurements as provided in NAKO, are needed. This will allow to disentangle the temporal sequence of exposure, disease status and MRI-derived AT measures. In addition, we further noted that the contribution of noise to increased AT depots and hepatic fat content is rather small compared to estimates of cardiometabolic disease such as hypercholesterolemia, diabetes, and hypertension (data not shown).

To date, two main pathways are hypothesized for the effects of noise on human metabolism: sleep disturbance and stress response.[60] There is strong evidence for an association between (nighttime) noise exposure and sleep disturbance.[61] The consequences of poor sleep can be increased energy intake, changes in appetite, and energy-controlling hormones such as leptin and ghrelin, all of which are associated with an increased risk of developing obesity and cardiometabolic disease.[62] Münzel and colleagues[7] summarized how short- and long-term exposure to traffic noise affects endothelial function, hormone levels (e.g., cortisol and adrenaline), and inflammatory markers. These biomarkers are elevated in visceral obesity and are associated with increased cardiometabolic risk.[5,7] For example, chronic overactivation of the sympathetic nervous system via the hypothalamic-pituitary-adrenal axis may lead to increased cortisol release, which in turn may favor the accumulation of ectopic fat.[5] However, a systematic review summarized and rated the evidence of the association between noise exposure and these mechanistic metabolic markers as inconsistent and low.[14] Therefore, studies investigating the underlying mechanisms are needed to understand noise-induced metabolic dysfunction.

4.2. Outlook and implications

Several implications can be drawn from this study. First, road traffic noise reduction may be a promising target to complement behavioral interventions to prevent the development and progression of cardiometabolic disease. In addition, reducing road traffic would have co-beneficial effects by reducing air pollution emissions, another harmful environmental risk factor for humans health.[17,25] To date, WHO has published noise guidelines with exposure limits, e.g. average noise levels from road traffic should not exceed 53 dB(A), which are only recommendations.[10] Uniform, effective guidelines with step-by-step actions to be taken in communities where noise levels exceed these guidelines, similar to the European Union's Ambient Air Quality Directive[63], may be warranted. To justify such guidelines, improvements in the noise mapping are needed as our study also shows the shortcomings of the currently available data on noise exposure. These have been extensively discussed and outlined by Staab et al.[43], including heterogenous mapping and potential biases introduced by the conversion from raster to polygons using different algorithms. At present, the END obligation is still vague, resulting in inconsistent reporting from EU member states which limits comparisons of noise exposure levels between years and countries.[43,64] In addition, as END only requires noise mapping in urban areas and along major roads, we still lack accurate noise exposure levels in rural and suburban areas.[42] Moreover, the reporting threshold of 55 dB(A) may be too high, as the WHO provided evidence that even lower noise levels were associated with various adverse health outcomes.[10] Therefore, a lowering of the current reporting threshold, small-scale assessment of noise levels and a fine-meshed network of monitoring stations combined with modelling techniques, e.g. using land use regressions as in Staab et al.[65], is needed in future studies. This would provide nationwide noise exposure at high resolution and can improve the accuracy of health impact assessments of noise exposure.

4.3. Limitations

We need to address the following limitations. Mean annual noise exposure was only available for 2017, which is later in time than the baseline examination (2014-2016), but based on previous evidence we assumed that noise exposure was relatively stable over the years.[66,67] In particular, substantial changes intra-urban contrasts would require major changes in road construction, engine technology or traffic density, which take several years. Align with this, a comparison of END data from 2012 and 2017 demonstrated a stable number of participants being exposed to harmful noise levels.[64] Therefore, we assume that noise exposure levels from 2017 can be used as a surrogate for long-term exposure prior to the outcome assessment. Furthermore, our exposure is limited to road traffic noise, while exposure to other noise sources, e.g., railway, aircraft or neighborhood, may also contribute to the development of obesity.[68] Only one-fifth of the participants was exposed to noise exposure levels ≥55 dB(A). Additionally, 43.8% of the participants lived in areas not covered by noise exposure mapping. It is therefore likely that misclassification of exposure occurred at the lower levels. However, so far it is reasonable to assume that this would have led to a bias towards the null, with the associations being stronger for more accurate noise exposure measurements. This is confirmed by our sensitivity analysis, where the associations tended to be stronger after excluding participants with missing categorical L_{den} classes. In addition, averaging noise levels within buffers may have introduced bias by altering the spatial scale. Consequently, noise levels within the 100m buffer may reflect not only noise information, but also area-related factors or land use. Nevertheless, we assume that the 10m buffer used in the main analyses was small enough to capture noise levels at buildings. Furthermore, sensitivity analyses using the categorical L_{den} classes, which reflected the exact noise levels at address points, revealed robust associations. A study by Vienneau et al.[69] demonstrated that different noise exposure assessment strategies are important, but changes in spatial scale led to attenuated estimates of the health effects. This further supports our assumption that improved noise exposure assessments would reveal stronger associations. Information on anti-diabetic, lipid-lowering or hypertensive medication was not available, which may have led to misclassification of participants. It is important to note that we used cross-sectional data, so longitudinal studies are needed to confirm our findings by considering the temporal occurrence of exposure and outcome and to conclude causal effects of noise on early obesity markers. Thereby, the NAKO is a unique and excellent database as multiple MRI re-examinations of NAKO participants will be available in the future.[33,35]

5. Conclusion

We observed robust associations of annual mean exposure to road traffic noise with AT depots and hepatic fat content in men and women. Our data suggest that road traffic noise is associated with larger visceral AT depots and higher hepatic fat content, which could potentially mediate the risk of metabolic and cardiovascular diseases. Given that these associations were independent of air pollution, another prominent environmental risk factor in urban areas, preferably longitudinal studies should evaluate potential benefits of traffic noise reduction as an additional route for the prevention of cardiometabolic disease at the population level.

Declarations

Ethics approval and consent to participate

The German National Cohort (NAKO) was approved by the initial vote of the ethics committee of the Bavarian Medical Association ("Bayerische Landesärztekammer" (BLÄK), protocol code 13023), followed by all local on-site institutional review boards in charge of the five imaging sites, and written informed consent of all participants was obtained before study enrollment. The study was conducted in accordance with the Declaration of Helsinki of 1975 (in the current, revised version).

Acknowledgements / Funding

This project was conducted with data from the German National Cohort (NAKO) (www.nako.de). The NAKO is funded by the Federal Ministry of Education and Research (BMBF) [project funding reference numbers: 01ER1301A/B/C, 01ER1511D, 01ER1801A/B/C/D and 01ER2301A/B/C], the federal states and the Helmholtz Association, with additional financial support by the participating universities and the institutes of the Leibniz Association. This project was supported by the Bavarian State Ministry of Health and Care through the research project DigiMed Bayern (www.digimed-bayern.de).

We thank all participants who took part in the NAKO and the staff of this research initiative.

Authorship contributions

All authors contributed substantially to this study. **FN**: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **SR:** Methodology, Supervision, Writing - Review & Editing. **CM:** Resources, Writing - Review & Editing. **BH**: Supervision, Methodology, Resources, Writing – review & editing. **SS:** Methodology, Writing - Review & Editing. **TH:** Data curation, Resources, Writing - Review & Editing. **TNor**: Data curation, Resources, Writing - Review & Editing. **CS:** Data curation, Resources, Writing - Review & Editing. **JN:** Data curation, Resources, Writing - Review & Editing. **FB:** Data curation, Resources, Writing - Review & Editing. **JM:** Data curation, Resources, Writing - Review & Editing. **MG:** Data curation, Resources, Writing - Review & Editing. **JH:** Data curation, Resources, Writing - Review & Editing. **RN:** Resources, Writing - Review & Editing. **HV:** Resources, Writing - Review & Editing; Funding aquisition (NAKO). **CMF:** Resources, Writing - Review & Editing. **NH:** Resources, Writing - Review & Editing. **TNon:** Data curation, Resources, Writing - Review & Editing. **BKB:** Resources, Writing - Review & Editing. **VP:** Resources, Writing - Review & Editing. **VK:** Resources, Writing - Review & Editing. **KHG:** Resources, Writing - Review & Editing. **JSM:** Resources, Writing - Review & Editing. **TNien:** Resources, Writing - Review & Editing. **BE:** Resources, Writing - Review & Editing. **TP:** Resources, Writing - Review & Editing; Funding aquisition (NAKO). **JS:** Data curation, Resources, Writing - Review & Editing **MD:** Data curation, Resources, Writing – review & editing. **AS:** Methodology, Resources, Writing – review & editing. **KW:** Data curation, Methodology, Resources, Writing – review & editing. **AP:** Conceptualization, Methodology, Supervision, Resources, Funding acquisition, Writing - Review & Editing

Data sharing

The datasets analyzed during the current study are not publicly available. Access to and use of NAKO data and biosamples can be obtained via an electronic application portal (https://transfer.nako.de). Analysis codes are available from the authors upon request.

References

1. Roth GA, Mensah GA, Johnson CO, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. *J Am Coll Cardiol*. Dec 22 2020;76(25):2982-3021. doi:10.1016/j.jacc.2020.11.010

2. Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet*. 2020;396(10258):1204-1222. doi:10.1016/s0140-6736(20)30925-9

3. Zhang D, Tang X, Shen P, et al. Multimorbidity of cardiometabolic diseases: prevalence and risk for mortality from one million Chinese adults in a longitudinal cohort study. *BMJ Open*. Mar 3 2019;9(3):e024476. doi:10.1136/bmjopen-2018-024476

4. Cheng X, Ma T, Ouyang F, Zhang G, Bai Y. Trends in the Prevalence of Cardiometabolic Multimorbidity in the United States, 1999-2018. *Int J Environ Res Public Health*. Apr 14 2022;19(8)doi:10.3390/ijerph19084726

5. Tchernof A, Despres JP. Pathophysiology of human visceral obesity: an update. *Physiol Rev*. Jan 2013;93(1):359-404. doi:10.1152/physrev.00033.2011

6. Huang Y, Liu Y, Ma Y, et al. Associations of Visceral Adipose Tissue, Circulating Protein Biomarkers, and Risk of Cardiovascular Diseases: A Mendelian Randomization Analysis. *Front Cell Dev Biol*. 2022;10:840866. doi:10.3389/fcell.2022.840866

7. Munzel T, Molitor M, Kuntic M, et al. Transportation Noise Pollution and Cardiovascular Health. *Circ Res*. Apr 26 2024;134(9):1113-1135. doi:10.1161/CIRCRESAHA.123.323584

8. Bechmann LP, Hannivoort RA, Gerken G, Hotamisligil GS, Trauner M, Canbay A. The interaction of hepatic lipid and glucose metabolism in liver diseases. *J Hepatol*. Apr 2012;56(4):952-64. doi:10.1016/j.jhep.2011.08.025

9. Bluher M. Obesity: global epidemiology and pathogenesis. *Nat Rev Endocrinol*. May 2019;15(5):288-298. doi:10.1038/s41574-019-0176-8

10. WHO (World Health Organization). *Environmental Noise Guidelines for the European Region* 2018. Last access: 10.10.2024. Available from: https://www.euro.who.int/__data/assets/pdf_file/0008/383921/noise-guidelines-eng.pdf

11. Dzhambov AM, Lercher P. Road Traffic Noise Exposure and Depression/Anxiety: An Updated Systematic Review and Meta-Analysis. *Int J Environ Res Public Health*. Oct 27 2019;16(21)doi:10.3390/ijerph16214134

12. Hao G, Zuo L, Weng X, et al. Associations of road traffic noise with cardiovascular diseases and mortality: Longitudinal results from UK Biobank and meta-analysis. *Environ Res*. Sep 2022;212(Pt A):113129. doi:10.1016/j.envres.2022.113129

13. Wang H, Sun D, Wang B, et al. Association between noise exposure and diabetes: meta-analysis. *Environ Sci Pollut Res Int*. Oct 2020;27(29):36085-36090. doi:10.1007/s11356-020-09826-6

14. Sivakumaran K, Ritonja JA, Waseem H, et al. Impact of Noise Exposure on Risk of Developing Stress-Related Metabolic Effects: A Systematic Review and Meta-Analysis. *Noise Health*. Oct-Dec 2022;24(115):215-230. doi:10.4103/nah.nah_21_22

15. Gui SY, Wu KJ, Sun Y, et al. Traffic noise and adiposity: a systematic review and meta-analysis of epidemiological studies. *Environ Sci Pollut Res Int*. Aug 2022;29(37):55707-55727. doi:10.1007/s11356-022-19056-7

16. Thacher JD, Poulsen AH, Hvidtfeldt UA, et al. Long-Term Exposure to Transportation Noise and Risk for Type 2 Diabetes in a Nationwide Cohort Study from Denmark. *Environ Health Perspect*. Dec 2021;129(12):127003. doi:10.1289/EHP9146

17. Altug H, Ogurtsova K, Breyer-Kohansal R, et al. Associations of long-term exposure to air pollution and noise with body composition in children and adults: Results from the LEAD general population study. *Environ Int*. Jul 2024;189:108799. doi:10.1016/j.envint.2024.108799

18. Schaapman JJ, Tushuizen ME, Coenraad MJ, Lamb HJ. Multiparametric MRI in Patients With Nonalcoholic Fatty Liver Disease. *J Magn Reson Imaging*. Jun 2021;53(6):1623-1631. doi:10.1002/jmri.27292

19. Bamberg F, Kauczor HU, Weckbach S, et al. Whole-Body MR Imaging in the German National Cohort: Rationale, Design, and Technical Background. *Radiology*. Oct 2015;277(1):206-20. doi:10.1148/radiol.2015142272

20. Rubino F, Cummings DE, Eckel RH, et al. Definition and diagnostic criteria of clinical obesity. *Lancet Diabetes Endocrinol*. Mar 2025;13(3):221-262. doi:10.1016/S2213-8587(24)00316-4

21. Kammerlander AA, Lyass A, Mahoney TF, et al. Sex Differences in the Associations of Visceral Adipose Tissue and Cardiometabolic and Cardiovascular Disease Risk: The Framingham Heart Study. *J Am Heart Assoc*. Jun 2021;10(11):e019968. doi:10.1161/JAHA.120.019968

22. Abraham TM, Pedley A, Massaro JM, Hoffmann U, Fox CS. Association between visceral and subcutaneous adipose depots and incident cardiovascular disease risk factors. *Circulation*. Oct 27 2015;132(17):1639-47. doi:10.1161/CIRCULATIONAHA.114.015000

23. Matthiessen C, Glaubitz L, Lucht S, et al. Long-term exposure to air pollution and prevalent nonalcoholic fatty liver disease. *Environ Epidemiol*. Oct 2023;7(5):e268. doi:10.1097/EE9.0000000000000268

24. Wang X, Karvonen-Gutierrez CA, Gold EB, et al. Longitudinal Associations of Air Pollution With Body Size and Composition in Midlife Women: The Study of Women's Health Across the Nation. *Diabetes Care*. Sep 9 2022;doi:10.2337/dc22-0963

25. Cai M, Li H, Wu Y, et al. Ambient Air Pollution Associated with Body Fat Percentages at Different Body Compartments: A Cohort Study of UK Biobank Participants. *Environ Health Perspect*. Jun 2022;130(6):67702. doi:10.1289/EHP10920

26. Nieuwenhuijsen MJ. Urban and transport planning pathways to carbon neutral, liveable and healthy cities; A review of the current evidence. *Environ Int*. Jul 2020;140:105661. doi:10.1016/j.envint.2020.105661

27. Vienneau D, Stafoggia M, Rodopoulou S, et al. Association between exposure to multiple air pollutants, transportation noise and cause-specific mortality in adults in Switzerland. *Environ Health*. Mar 27 2023;22(1):29. doi:10.1186/s12940-023-00983-y

28. Sorensen M, Poulsen AH, Hvidtfeldt UA, et al. Air pollution, road traffic noise and lack of greenness and risk of type 2 diabetes: A multi-exposure prospective study covering Denmark. *Environ Int*. Dec 2022;170:107570. doi:10.1016/j.envint.2022.107570

29. Foraster M, Eze IC, Vienneau D, et al. Long-term exposure to transportation noise and its association with adiposity markers and development of obesity. *Environ Int*. Dec 2018;121(Pt 1):879-889. doi:10.1016/j.envint.2018.09.057

30. Cai Y, Zijlema WL, Sorgjerd EP, et al. Impact of road traffic noise on obesity measures: Observational study of three European cohorts. *Environ Res*. Dec 2020;191:110013. doi:10.1016/j.envres.2020.110013

31. Munzel T, Daiber A, Engelmann N, Roosli M, Kuntic M, Banks JL. Noise causes cardiovascular disease: it's time to act. *J Expo Sci Environ Epidemiol*. Jan 2025;35(1):24-33. doi:10.1038/s41370-024-00732-4

32. Olbrich HG, Roosli M, Herrmann E, et al. Aircraft noise exposure and risk for recurrent cardiovascular events after acute coronary syndrome: A prospective patient cohort study. *Environ Res*. Dec 1 2023;238(Pt 1):117108. doi:10.1016/j.envres.2023.117108

33. Peters A, German National Cohort C, Peters A, et al. Framework and baseline examination of the German National Cohort (NAKO). *Eur J Epidemiol*. Oct 2022;37(10):1107-1124. doi:10.1007/s10654-022-00890-5

34. German National Cohort C. The German National Cohort: aims, study design and organization. *Eur J Epidemiol*. May 2014;29(5):371-82. doi:10.1007/s10654-014-9890-7

35. Bamberg F, Schlett CL, Caspers S, et al. Baseline MRI Examination in the NAKO Health Study-Findings on Feasibility, Participation and Dropout Rates, Comfort, and Image Quality. *Dtsch Arztebl Int*. Sep 6 2024;(Forthcoming)doi:10.3238/arztebl.m2024.0151

36. Schlett CL, Hendel T, Weckbach S, et al. Population-Based Imaging and Radiomics: Rationale and Perspective of the German National Cohort MRI Study. *Rofo*. Jul 2016;188(7):652-61. Populationsbasierte Bildgebung und Radiomics: Rationale und Perspektiven der NAKO-Studie. doi:10.1055/s-0042-104510

37. Haueise T, Schick F, Stefan N, et al. Analysis of volume and topography of adipose tissue in the trunk: Results of MRI of 11,141 participants in the German National Cohort. *Sci Adv*. May 12 2023;9(19):eadd0433. doi:10.1126/sciadv.add0433

38. Haueise T, Schick F, Stefan N, Machann J. Comparison of the accuracy of commercial two-point and multi-echo Dixon MRI for quantification of fat in liver, paravertebral muscles, and vertebral bone marrow. *Eur J Radiol*. Mar 2024;172:111359. doi:10.1016/j.ejrad.2024.111359

39. Isensee F, Jaeger PF, Kohl SAA, Petersen J, Maier-Hein KH. nnU-Net: a self-configuring method for deep learning-based biomedical image segmentation. *Nat Methods*. Feb 2021;18(2):203-211. doi:10.1038/s41592-020-01008-z

40. Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol*. Dec 2023;79(6):1542-1556. doi:10.1016/j.jhep.2023.06.003

41. American Association for the Study of Liver Diseases. Electronic address glo, Latin American Association for the Study of the L, European Association for the Study of the L. A call for unity: The path towards a more precise and patient-centric nomenclature for NAFLD. *Ann Hepatol*. Jul-Aug 2023;28(4):101115. doi:10.1016/j.aohep.2023.101115

42. European Comission. *Directive 2002/49/EC of the European parliament and of the council of 25 June 2002 relating to the assessment and management of environmental noise*. Vol. L 189/12. 2002. Available from:

43. Staab J, Droin A, Weigand M, et al. Pixels, chisels and contours - technical variations in European road traffic noise exposure maps. *Journal of Environmental Management*. 2025;385doi:10.1016/j.jenvman.2025.125475

44. Wolf K, Dallavalle M, Niedermayer F, et al. Environmental exposure assessment in the German National Cohort (NAKO). *Environ Res*. May 15 2025;273:121259. doi:10.1016/j.envres.2025.121259

45. Leitzmann M, Gastell S, Hillreiner A, et al. [Physical activity in the German National Cohort (NAKO): use of multiple assessment tools and initial results]. *Bundesgesundheitsblatt*

Gesundheitsforschung Gesundheitsschutz. Mar 2020;63(3):301-311. Korperliche Aktivitat in der NAKO Gesundheitsstudie: erste Ergebnisse des multimodalen Erhebungskonzepts. doi:10.1007/s00103-020-03099-7

46. WHO (World Health Organization). *Global Physical Activity Questionnaire (GPAQ) Analysis Guide*. Last access: 04.08.2024. Available from: https://www.who.int/teams/noncommunicable-diseases/surveillance/systems-tools/physical-activity-surveillance

47. Fischer B, Sedlmeier AM, Hartwig S, et al. [Anthropometric measures in the German National Cohort-more than weight and height]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*. Mar 2020;63(3):290-300. Anthropometrische Messungen in der NAKO Gesundheitsstudie - mehr als nur Grosse und Gewicht. doi:10.1007/s00103-020-03096-w

48. Schikowski T, Wigmann C, Fuks KB, et al. [Blood pressure measurement in the NAKO German National Cohort (GNC) - differences in methods, distribution of blood pressure values, and awareness of hypertension compared to other population-based studies in Germany]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*. Apr 2020;63(4):452-464. Blutdruckmessung in der NAKO - methodische Unterschiede, Blutdruckverteilung und Bekanntheit der Hypertonie im Vergleich zu anderen bevolkerungsbezogenen Studien in Deutschland. doi:10.1007/s00103-020-03109-8

49. Moreno Velasquez I, Peters SAE, Dragano N, et al. Sex Differences in the Relationship of Socioeconomic Position With Cardiovascular Disease, Cardiovascular Risk Factors, and Estimated Cardiovascular Disease Risk: Results of the German National Cohort. *J Am Heart Assoc*. Mar 4 2025;14(5):e038708. doi:10.1161/JAHA.124.038708

50. Wolf K, Kraus U, Dzolan M, et al. [Nighttime transportation noise annoyance in Germany: personal and regional differences in the German National Cohort Study]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*. Mar 2020;63(3):332-343. Nachtliche Verkehrslarmbelastigung in Deutschland: individuelle und regionale Unterschiede in der NAKO Gesundheitsstudie. doi:10.1007/s00103-020-03094-y

51. de Hoogh K, Chen J, Gulliver J, et al. Spatial PM(2.5), NO(2), O(3) and BC models for Western Europe - Evaluation of spatiotemporal stability. *Environ Int*. Nov 2018;120:81-92. doi:10.1016/j.envint.2018.07.036

52. Bundesagentur für Arbeit [Federal Employment Agency]. Last access: 04.03. 2025. Available from: https://www.bmfsfj.de/bmfsfj/service/online-rechner/gleichstellungsatlas?view=

53. *A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2021. https://www.r-project.org/

54. Stekhoven DJ, Buhlmann P. MissForest--non-parametric missing value imputation for mixed-type data. *Bioinformatics*. Jan 1 2012;28(1):112-8. doi:10.1093/bioinformatics/btr597

55. An R, Ji M, Yan H, Guan C. Impact of ambient air pollution on obesity: a systematic review. *Int J Obes (Lond)*. Jun 2018;42(6):1112-1126. doi:10.1038/s41366-018-0089-y

56. Luo YN, Huang WZ, Liu XX, et al. Greenspace with overweight and obesity: A systematic review and meta-analysis of epidemiological studies up to 2020. *Obes Rev*. Nov 2020;21(11):e13078. doi:10.1111/obr.13078

57. Machann J, Horstmann A, Born M, Hesse S, Hirsch FW. Diagnostic imaging in obesity. *Best Pract Res Clin Endocrinol Metab*. Apr 2013;27(2):261-77. doi:10.1016/j.beem.2013.02.003

58. Christensen JS, Raaschou-Nielsen O, Tjonneland A, et al. Road Traffic and Railway Noise Exposures and Adiposity in Adults: A Cross-Sectional Analysis of the Danish Diet, Cancer, and Health Cohort. *Environ Health Perspect*. Mar 2016;124(3):329-35. doi:10.1289/ehp.1409052

59. Brunner KT, Henneberg CJ, Wilechansky RM, Long MT. Nonalcoholic Fatty Liver Disease and Obesity Treatment. *Curr Obes Rep*. Sep 2019;8(3):220-228. doi:10.1007/s13679-019-00345-1

60. Christensen JS, Raaschou-Nielsen O, Tjonneland A, et al. Long-term exposure to residential traffic noise and changes in body weight and waist circumference: A cohort study. *Environ Res*. Nov 2015;143(Pt A):154-61. doi:10.1016/j.envres.2015.10.007

61. Smith MG, Cordoza M, Basner M. Environmental Noise and Effects on Sleep: An Update to the WHO Systematic Review and Meta-Analysis. *Environ Health Perspect*. Jul 2022;130(7):76001. doi:10.1289/EHP10197

62. Cappuccio FP, Miller MA. Sleep and Cardio-Metabolic Disease. *Curr Cardiol Rep*. Sep 19 2017;19(11):110. doi:10.1007/s11886-017-0916-0

63. European Parliamentary Research Service. *Revision of the EU Ambient Air Quality Directives*. 2022. Last access: 10.10.2024. Available from: https://www.europarl.europa.eu/RegData/etudes/BRIE/2022/734679/EPRS_BRI(2022)734679_EN.pdf

64. European Environment Agency. *Environmental noise in Europe — 2020*. 2020. Last access: 04.04.2024. Available from: https://www.eea.europa.eu/en/analysis/publications/environmental-noise-in-europe

65. Staab J, Schady A, Weigand M, Lakes T, Taubenböck H. Predicting traffic noise using land-use regression—a scalable approach. *Journal of Exposure Science & Environmental Epidemiology*. 2021;32(2):232-243. doi:10.1038/s41370-021-00355-z

66. Fecht D, Hansell AL, Morley D, et al. Spatial and temporal associations of road traffic noise and air pollution in London: Implications for epidemiological studies. *Environ Int*. Mar 2016;88:235-242. doi:10.1016/j.envint.2015.12.001

67. Babisch W, Wolf K, Petz M, Heinrich J, Cyrys J, Peters A. Associations between traffic noise, particulate air pollution, hypertension, and isolated systolic hypertension in adults: the KORA study. *Environ Health Perspect*. May 2014;122(5):492-8. doi:10.1289/ehp.1306981

68. Bozigar M, Laden F, Hart JE, et al. Aircraft noise exposure and body mass index among female participants in two Nurses' Health Study prospective cohorts living around 90 airports in the United States. *Environ Int*. May 2024;187:108660. doi:10.1016/j.envint.2024.108660

69. Vienneau D, Heritier H, Foraster M, et al. Facades, floors and maps - Influence of exposure measurement error on the association between transportation noise and myocardial infarction. *Environ Int*. Feb 2019;123:399-406. doi:10.1016/j.envint.2018.12.015

Figures

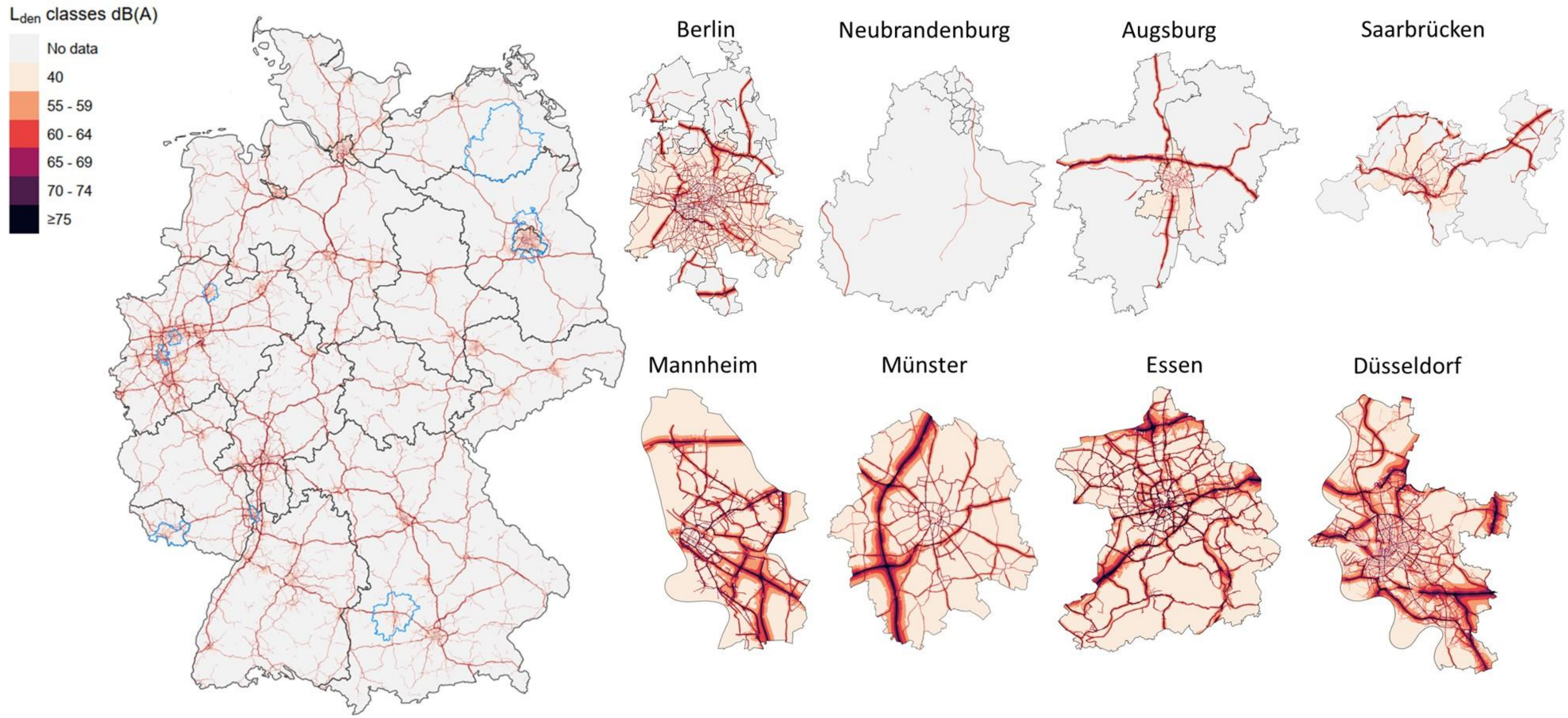


Fig. 1 Map of Germany showing spatial patterns of annual road traffic noise (L_{den}) in 2017. Legend: Zoom on NAKO study centers (in blue). 40 dB(A) is a lower detection limit applied to all grid cells in urban areas covered by Environmental Noise Directive (END) obligation 2002/49/EC Article 3 with levels < 55 dB(A). No data reflect areas where noise mapping is not required according to END. Abbreviations: L_{den} = day–evening–night road traffic noise level. NAKO = German National Cohort

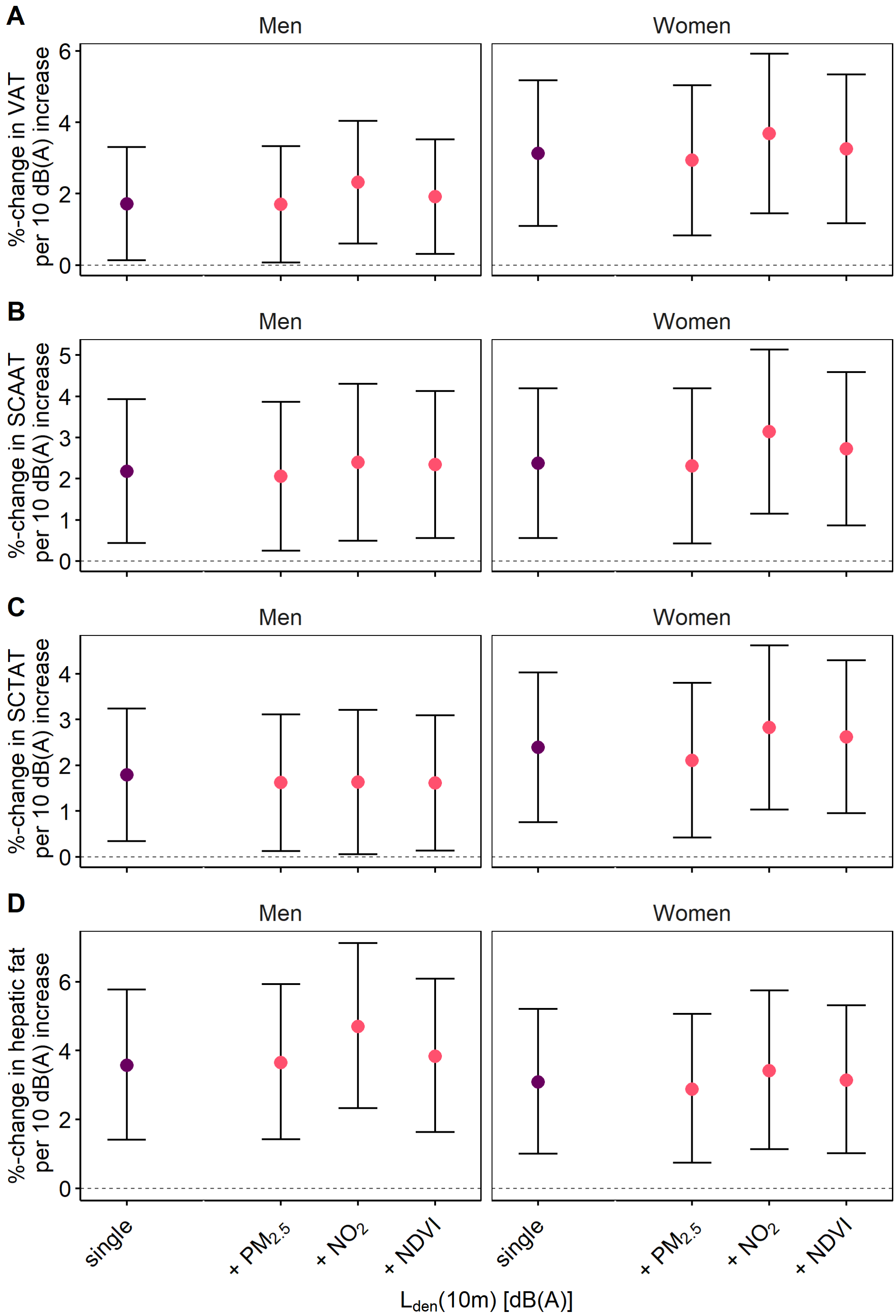


Fig. 2 Comparison of the estimates of road traffic noise (10m buffer) in single and two exposure models adjusting for air pollutants and surrounding greenness in the German National Cohort. Legend: Estimates of single exposure models (purple) and two exposure models (pink) for outcomes (A) VAT, (B) SCAAT, (C) SCTAT, and (D) hepatic fat content. Effect estimates are given as percentage change of the arithmetic (or geometric for hepatic fat content) outcome mean per 10 dB(A) increase in exposure, with 95% confidence intervals derived from linear and logistic regression models stratified by sex and adjusted for study center, age, alcohol consumption, physical activity, smoking behavior, income. Abbreviation: VAT = visceral adipose tissue, SCAAT = subcutaneous abdominal adipose tissue, SCTAT = subcutaneous thoracic adipose tissue, L_{den} = day–evening–night road traffic noise level, NO_2= nitrogen dioxide, $PM_{2.5}$ = particulate matter with diameter < 2.5 µm, NDVI = normalized difference vegetation index

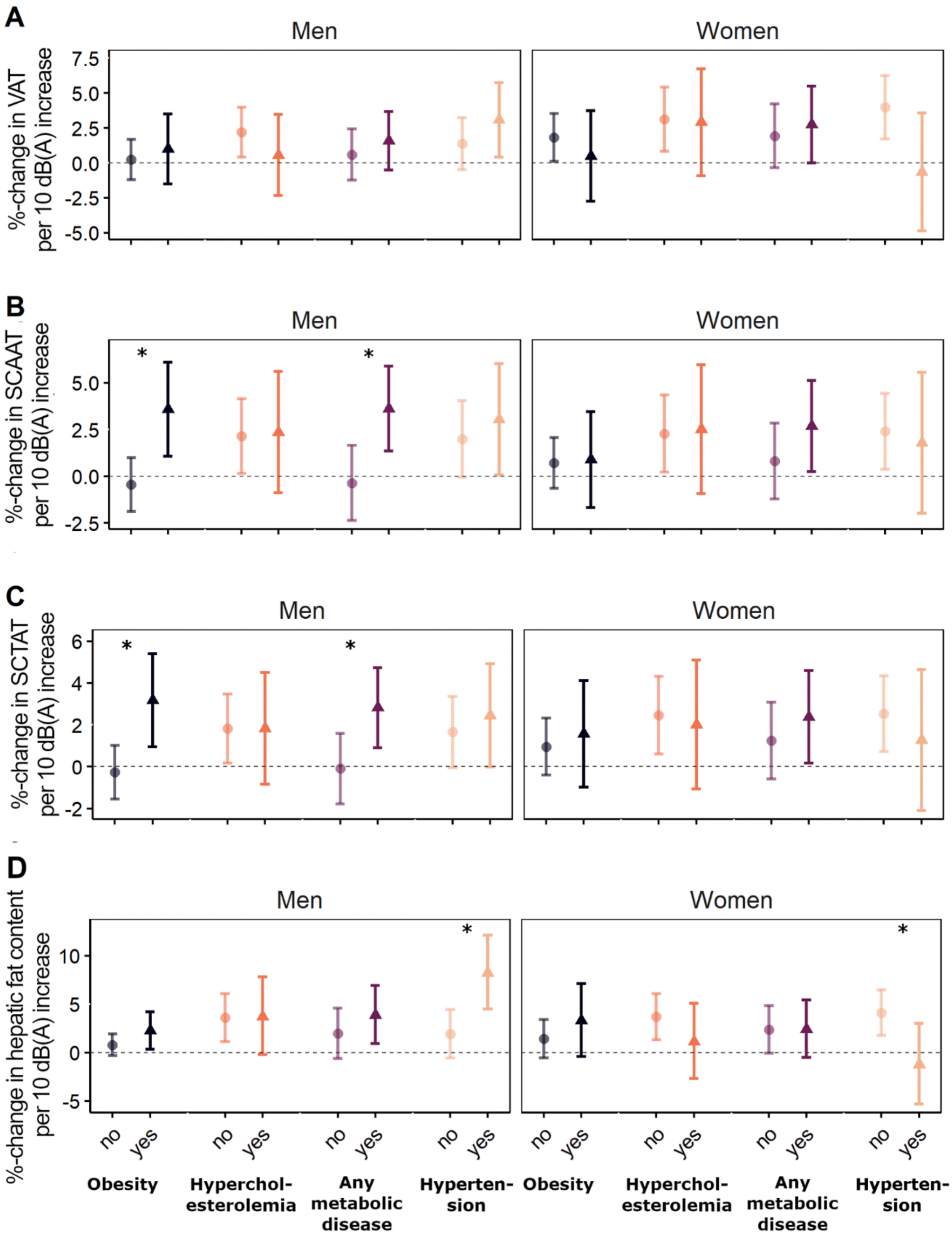


Fig. 3 Cardiometabolic disease-specific associations of L_{den} (10m buffer) with VAT (A), SCAAT (B), SCTAT (C), and hepatic fat content (D) in the German National Cohort. Legend: Associations derived from linear regression models with a multiplicative interaction term between exposure and cardiometabolic disease indicator. Models were adjusted for study center, age, alcohol consumption, physical activity, smoking behavior, income. Effect estimates are given as percentage change of the arithmetic (or geometric for hepatic fat content) outcome mean outcome per 10 dB(A) increase in exposure, with 95% confidence intervals. Asterix indicate significant interaction term with $p < 0.05$. Abbreviation: L_{den} = day–evening–night road traffic noise level, SCAAT = subcutaneous abdominal adipose tissue, SCTAT = subcutaneous thoracic adipose tissue, VAT = visceral adipose tissue

Table 1 Subjects' characteristics of the final analytical German National Cohort sample stratified by sex.

	Overall (n = 11,101)	**Men (n = 5,690)**	**Women (n = 5,411)**
Sex, female n (%)	5,411 (48.7)	-	5,411 (100.0)
Age (years), mean (SD)	51.9 (11.4)	52.07 (11.5)	51.74 (11.3)
VAT (l), mean (SD)	3.7 (2.3)	4.8 (2.4)	2.5 (1.6)
SCAAT (l), mean (SD)	6.9 (3.6)	6.2 (3.1)	7.7 (3.9)
SCTAT (l), mean (SD)	3.3 (1.6)	2.8 (1.2)	3.8 (1.8)
Hepatic fat content (%), mean (SD)	7.6 (6.5)	8.7 (6.9)	6.4 (5.9)
MASLD, yes n (%)	3,639 (35.1)	2,333 (41.0)	1,306 (24.1)
L_{den} (10m) (dB(A)), mean (SD)	43.8 (7.8)	43.8 (7.8)	43.8 (7.7)
L_{den} (100m) (dB(A)), mean (SD)	44.1 (6.2)	44.1 (6.3)	44.0 (6.1)
Study center, n (%)			
Augsburg	2,569 (23.1)	1,410 (24.8)	1,159 (21.4)
Berlin	2,233 (20.1)	1,128 (19.8)	1,105 (20.4)
Düsseldorf	281 (2.5)	155 (2.7)	126 (2.3)
Essen	1,626 (14.6)	815 (14.3)	811 (15.0)
Mannheim	1,196 (10.8)	617 (10.8)	579 (10.7)
Münster	75 (0.7)	43 (0.8)	32 (0.6)
Neubrandenburg	3,023 (27.2)	1,473 (25.9)	1,550 (28.6)
Saarbrücken	98 (0.9)	49 (0.9)	49 (0.9)
Examination year, n (%)			
2014	541 (4.9)	277 (4.9)	264 (4.9)
2015	3,835 (34.5)	1,942 (34.1)	1,893 (35.0)
2016	6,725 (60.6)	3,471 (61.0)	3,254 (60.1)
Degree of urbanization, n (%)			
Urban	7,335 (66.1)	3,707 (65.1)	3,628 (67.0)
Suburban	1,615 (14.5)	884 (15.5)	731 (13.5)
Rural	2,151 (19.4)	1,099 (19.3)	1,052 (19.4)
Physical activity (min/week), mean (SD)	1,424 (1,569)	1,473 (1,622)	1,372 (1,510)
Alcohol consumption (g/day), mean (SD)	11.1 (16.5)	15.02 (19.8)	6.95 (10.8)
Income (Euros), mean (SD)	2,254 (1,426)	2,405 (1,585)	2,096 (1,218)
Smoking behavior, n (%)			
Never smoker	5,085 (45.8)	2,319 (40.8)	2,766 (51.1)
Ex-smoker	3,881 (35.0)	2,219 (39.0)	1,662 (30.7)
Smoker	2,135 (19.2)	1,152 (20.2)	983 (18.2)
Noise annoyance, high-extreme n (%)	1,727 (15.6)	839 (14.7)	888 (16.4)
Living duration (years), mean (SD)	15.6 (11.3)	15.4 (11.5)	15.8 (11.0)
Population density (n/500m²), mean (SD)	1,333 (1,296)	1,332 (1,305)	1,334 (1,287)
Unemployment rate (%) at district level**,** mean (SD)	9.5 (3.7)	9.4 (3.8)	9.7 (3.7)
Body-Mass-Index (kg/m²), mean (SD)	26.8 (4.1)	27.4 (4.1)	26.2 (5.2)
Waist circumference (cm), mean (SD)	91.9 (13.7)	97.4 (12.0)	86.2 (13.0)
Obesity (BMI ≥ 30 kg/m²) , yes n (%)	2,378 (21.4)	1,265 (22.2)	1,113 (20.6)
Hypercholesterolemia, yes n (%)	2,957 (26.6)	1,572 (27.6)	1,385 (25.6)
Diabetes, yes n (%)	658 (5.9)	402 (7.1)	256 (4.7)
Any metabolic disease, yes n (%)	4,646 (41.9)	2,450 (43.1)	2,196 (40.6)
Hypertension, yes n (%)	3,092 (27.9)	1,923 (33.8)	1,169 (21.6)

Legend: Covariate information was imputed as described in Methods S2.

Abbreviations: BMI = Body-Mass-Index, L_{den} = day-evening-night road traffic noise level, MASLD = metabolic dysfunction–associated steatotic liver disease, SCAAT = subcutaneous abdominal adipose, SD = standard deviation, SCTAT = subcutaneous thoracic adipose tissue, VAT = visceral adipose tissue,

Table 2. Associations of road traffic noise with adipose tissue depots, hepatic fat content and MASLD in the German National Cohort.

	Men (n = 5,690)		Women (n = 5,411)	
	%-change (95% CI)	**p**	**%-change (95% CI)**	**p**
VAT [l]				
L_{den} (10m)	1.72 (0.14; 3.30)	0.033	3.13 (1.09; 5.18)	0.003
L_{den} (100m)	1.85 (-0.15; 3.86)	0.070	3.47 (0.84; 6.09)	0.010
SCAAT [l]				
L_{den} (10m)	2.18 (0.43; 3.93)	0.015	2.38 (0.55; 4.20)	0.011
L_{den} (100m)	2.07 (-0.15; 4.29)	0.068	2.22 (-0.12; 4.57)	0.063
SCTAT [l]				
L_{den} (10m)	1.79 (0.34; 3.25)	0.015	2.39 (0.75; 4.03)	0.004
L_{den} (100m)	1.99 (0.15; 3.83)	0.034	2.68 (0.58; 4.79)	0.013
Hepatic fat content [%]				
L_{den} (10m)	3.57 (1.41; 5.78)	0.001	3.08 (1.00; 5.21)	0.004
L_{den} (100m)	3.87 (1.13; 6.69)	0.005	4.03 (1.33; 6.79)	0.003
MASLD[1]	**OR (95% CI)**		**OR (95% CI)**	
L_{den} (10m)	1.10 (1.01; 1.19)	0.022	1.08 (0.99; 1.19)	0.098
L_{den} (100m)	1.08 (0.98; 1.20)	0.135	1.10 (0.98; 1.24)	0.103

Legend: Effect estimates are given as percentage change of the arithmetic (or geometric for hepatic fat content) outcome mean per 10 dB(A) increase in exposure, with 95% confidence intervals derived from linear and logistic regression models stratified by sex and adjusted for study center, age, alcohol consumption, physical activity, smoking behavior, income.

[1]Sample size deviate from full sample (n = 5,147 men and n = 5,258 women) due to MASLD definition.

Abbreviations: CI = confidence interval, L_{den} = day–evening–night road traffic noise level, MASLD = metabolic dysfunction–associated steatotic liver disease, OR = odds ratio, SCAAT = subcutaneous abdominal adipose tissue, SCTAT = subcutaneous thoracic adipose tissue, VAT = visceral adipose tissue

Supplement to

Associations of road traffic noise with adipose tissue depots and hepatic fat content – Results from the German National Cohort (NAKO)

Fiona Niedermayer[1,2]*, Susanne Rospleszcz[2,9], Clara Matthiessen[3], Barbara Hoffmann[3], Sophia Stoecklein[4], Tobias Haueise[5,6], Tobias Norajitra[7,8], Christopher L. Schlett[9], Johanna Nattenmüller[9,10], Fabian Bamberg[9], Jürgen Machann[5,6,11], Matthias Günther[12], Jochen Hirsch[12], Rajini Nagrani[13], Henry Völzke[14], Claudia Meinke-Franze[14], Norbert Hosten[15], Tobias Nonnenmacher[16], Bettina Katalin Budai[16,17], Viktoria Palm[16,17,18], Verena Katzke[19], Karin Halina Greiser[19], Jeanette Schulz-Menger[20,21], Thoralf Niendorf[22], Beate Endemann[22], Tobias Pischon[23,24,25], Jeroen Staab[26], Marco Dallavalle[2], Alexandra Schneider[2], Kathrin Wolf[2], Annette Peters[1,2,6]

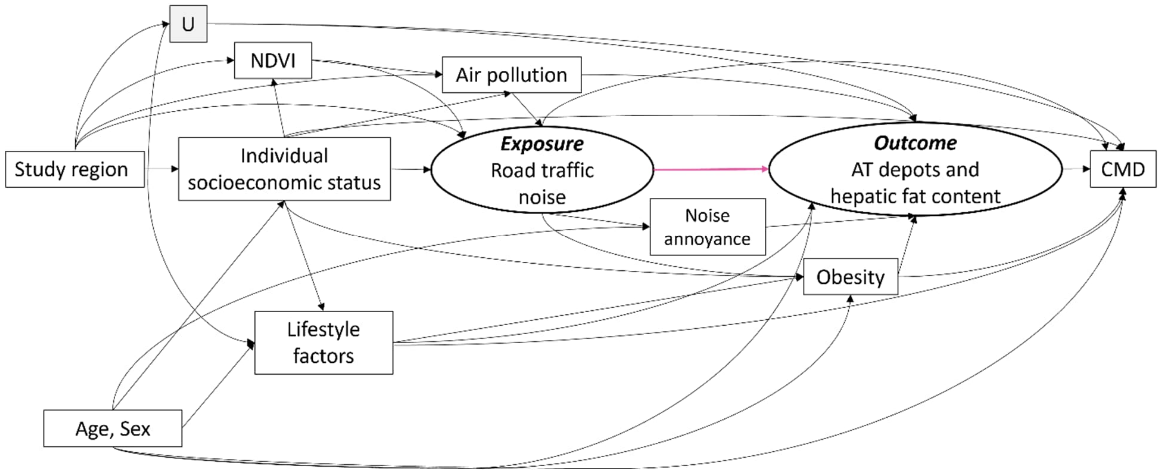


Figure S1. Directed acyclic graph proposing the potential causal relationship between road traffic noise, adipose tissue and hepatic fat content including potential covariates.

Legend: U stands for unmeasured confounders, which would be regional factors such as walkability of the neighborhood, access to public transport, etc.. We assumed that the study center can be used as a proxy for these unmeasured confounders. Abbreviations: AT = adipose tissue, CMD = cardiometabolic disease, NDVI = normalized difference vegetation index, U = unmeasured factor

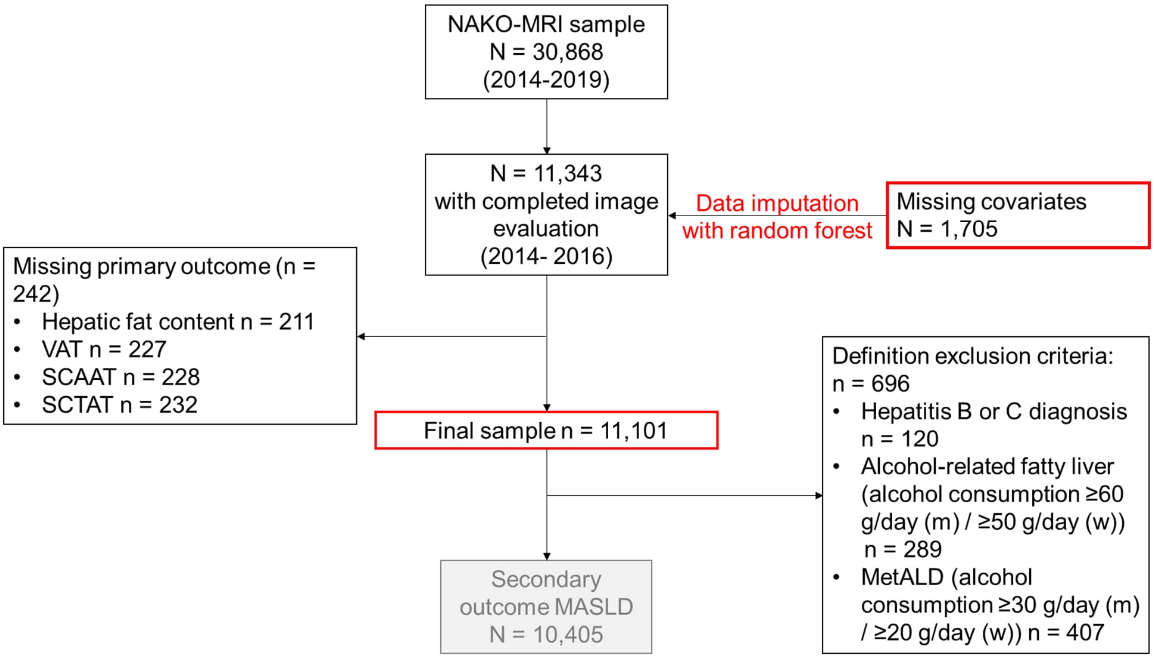
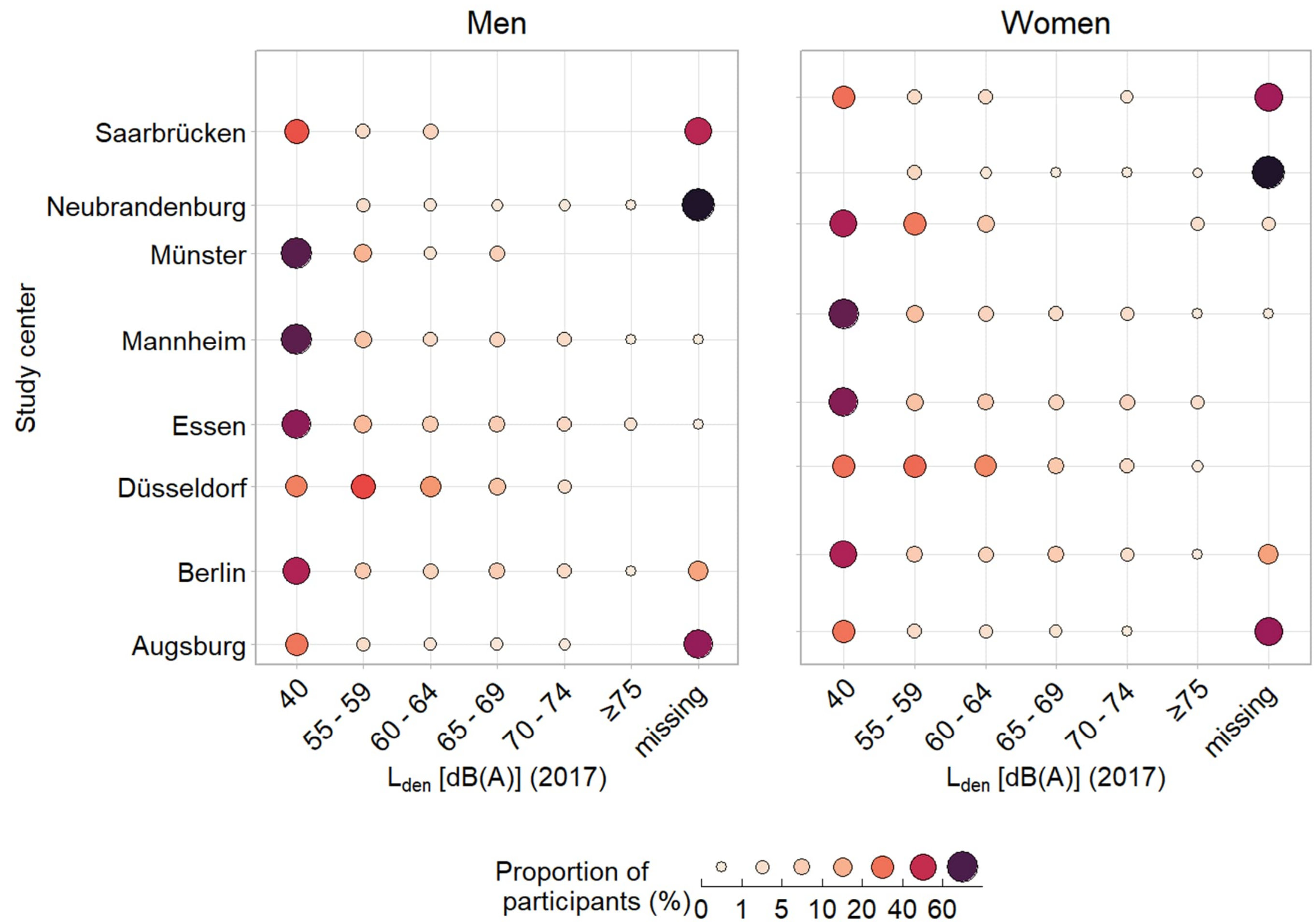


Figure S2 Flowchart of the analytical German National Cohort sample.

Legend: Data imputation is described in Methods S2. Abbreviations: NAKO = German National Cohort, MASLD = metabolic-dysfunction associated steatosis liver disease, SCAAT = subcutaneous abdominal adipose tissue, SCTAT = subcutaneous thoracic adipose tissue, VAT = visceral adipose tissue



L_{den} (10m) Mean ± SD	L_{den} (100m) Mean ± SD
42.0 ± 5.5	42.2 ± 4.8
41.4 ± 4.8	41.6 ± 4.7
45.3 ± 8.0	45.8 ± 6.1
44.8 ± 8.1	45.6 ± 6.1
47.4 ± 10.0	47.4 ± 7.3
53.3 ± 7.8	51.6 ± 5.7
45.5 ± 9.2	45.4 ± 6.7
41.6 ± 4.7	42.1 ± 4.2

Figure S3 Distribution of categorical (L_{den}) and continuous (L_{den} 10m and L_{den} 100m) road traffic noise by study center in the German National Cohort. Legend: missing are participants in areas not covered by the END obligation 2002/49/EG, 40 dB(A) is a lower detection limit assigned to participants covered by the END but with noise levels below the reporting threshold of 55 dB(A). Abbreviation: L_{den} = day–evening–night road traffic noise level;

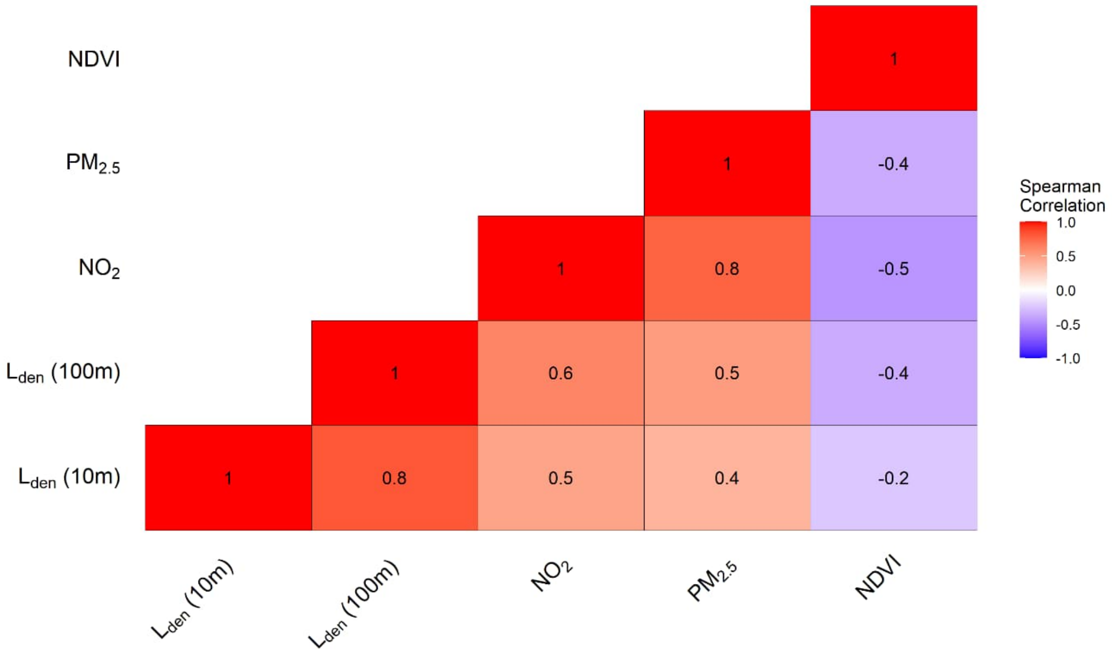


Figure S4 Spearman correlation between road traffic noise and environmental exposures used in two exposure models in the German National Cohort.

Abbreviation: L_{den} = day–evening–night road traffic noise level, NO_2= nitrogen dioxide, $PM_{2.5}$ = particulate matter with diameter < 2.5 µm, NDVI = normalized difference vegetation index

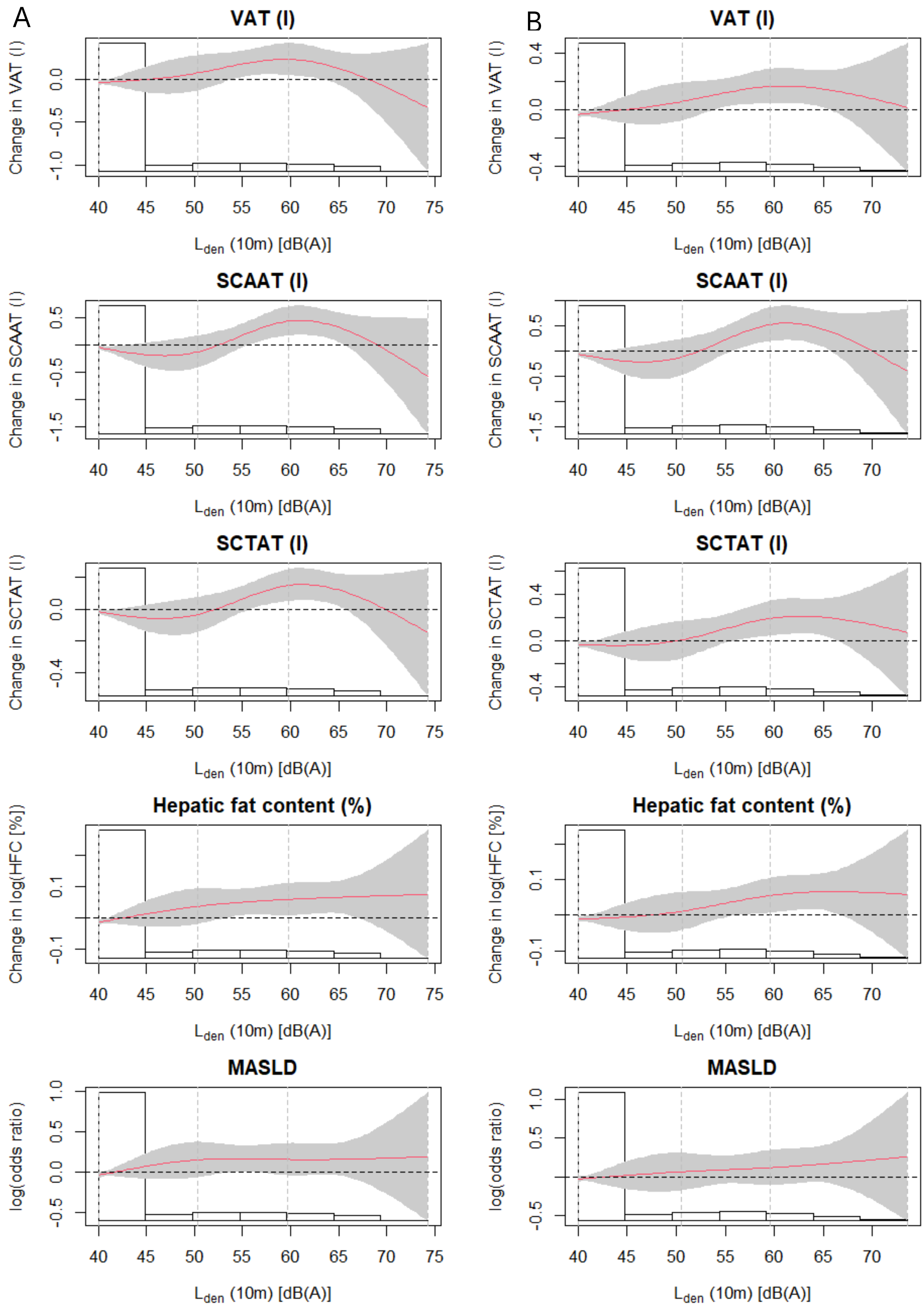


Figure S5 Road traffic noise distribution and exposure-response functions for the association between L$_{den}$ (10m) and outcomes in the German National Cohort. (A) Men; (B) Women. Legend: Exposure response functions are derived from models with natural cubic spline with 3 degrees of freedom adjusted for study center, age, alcohol consumption, physical activity, smoking behavior, income. Vertical lines give placement of the knots. Abbreviation: HFC = hepatic fat content, L$_{den}$ = day–evening–night road traffic noise level, MASLD = MASLD = metabolic-dysfunction associated steatosis liver disease, SCAAT = subcutaneous abdominal adipose tissue, SCTAT = subcutaneous thoracic adipose tissue, VAT = visceral adipose tissue

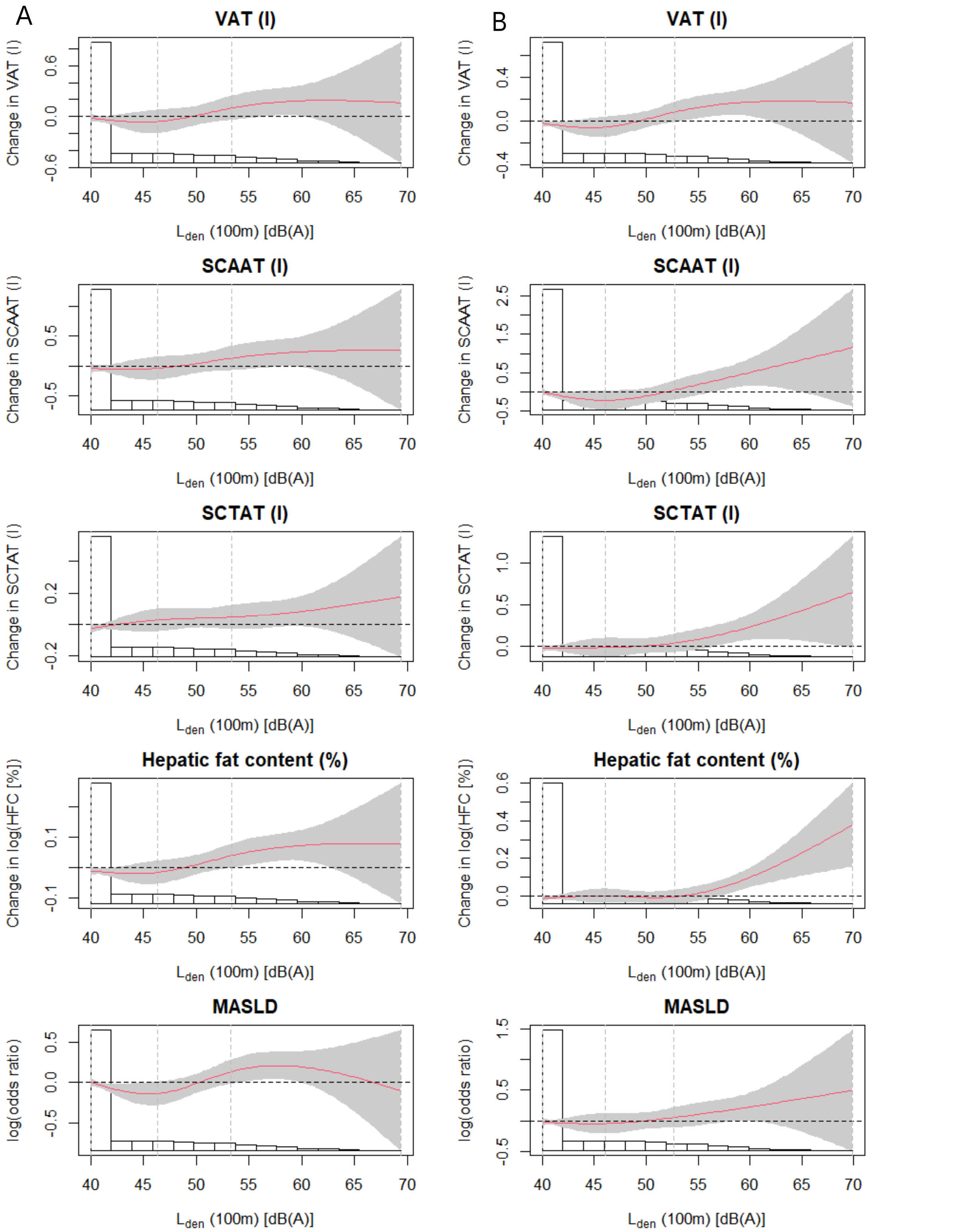


Figure S6 Road traffic noise distribution and exposure-response functions for the association between L_{den} (100m) and outcomes in the German National Cohort. (A) Men; (B) Women. Legend: Exposure response functions are derived from models including natural cubic spline with 3 degrees of freedom adjusted for study center, age, alcohol consumption, physical activity, smoking behavior, income. Vertical lines give placement of the knots. Abbreviation: HFC = hepatic fat content, L_{den} = day–evening–night road traffic noise level, MASLD = metabolic-dysfunction associated steatosis liver disease, SCAAT = subcutaneous abdominal adipose tissue, SCTAT = subcutaneous thoracic adipose tissue, VAT = visceral adipose tissue

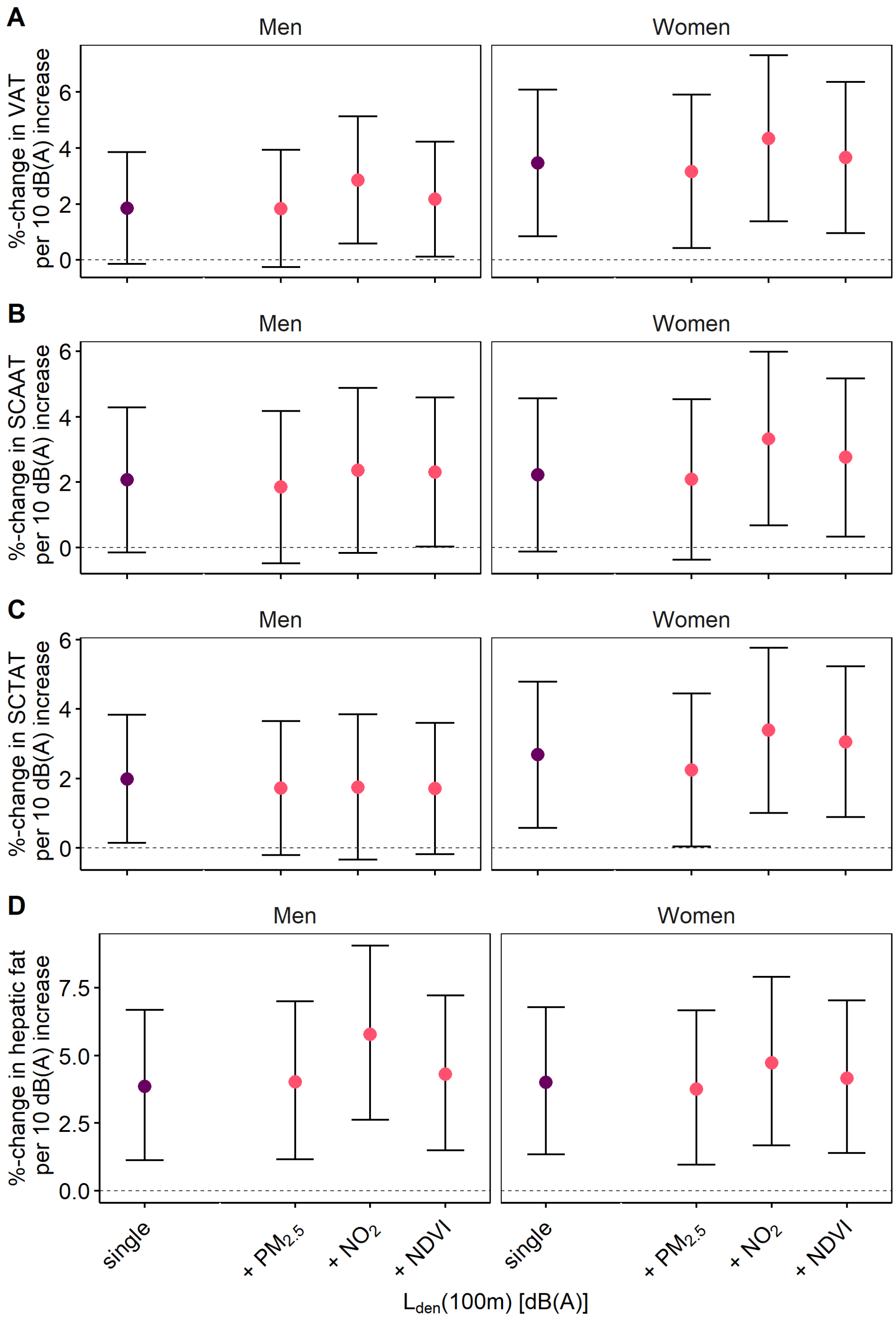


Figure S7 Comparison of the estimates of road traffic noise (100m buffer) in single (purple circles) and two exposure (pink circles) models adjusting for air pollutants ($PM_{2.5}$, NO_2) and surrounding greenness (NDVI) in the German National Cohort. (A) VAT, (B) SCAAT, (C) SCTAT, and (D) hepatic fat content. Legend: Estimates are derived from linear regression models adjusted for study center, age, alcohol consumption, physical activity, smoking behavior, income and are given as percentage change of the arithmetic (geometric for hepatic fat content) outcome mean per 10 dB(A) increase in exposure with 95% confidence intervals. Abbreviation: L_{den} = day–evening–night road traffic noise level, NDVI = normalized difference vegetation index, NO_2= nitrogen dioxide, $PM_{2.5}$ = particulate matter with diameter < 2.5 µm, SCAAT = subcutaneous abdominal adipose tissue, SCTAT = subcutaneous thoracic adipose tissue, VAT = visceral adipose tissue,

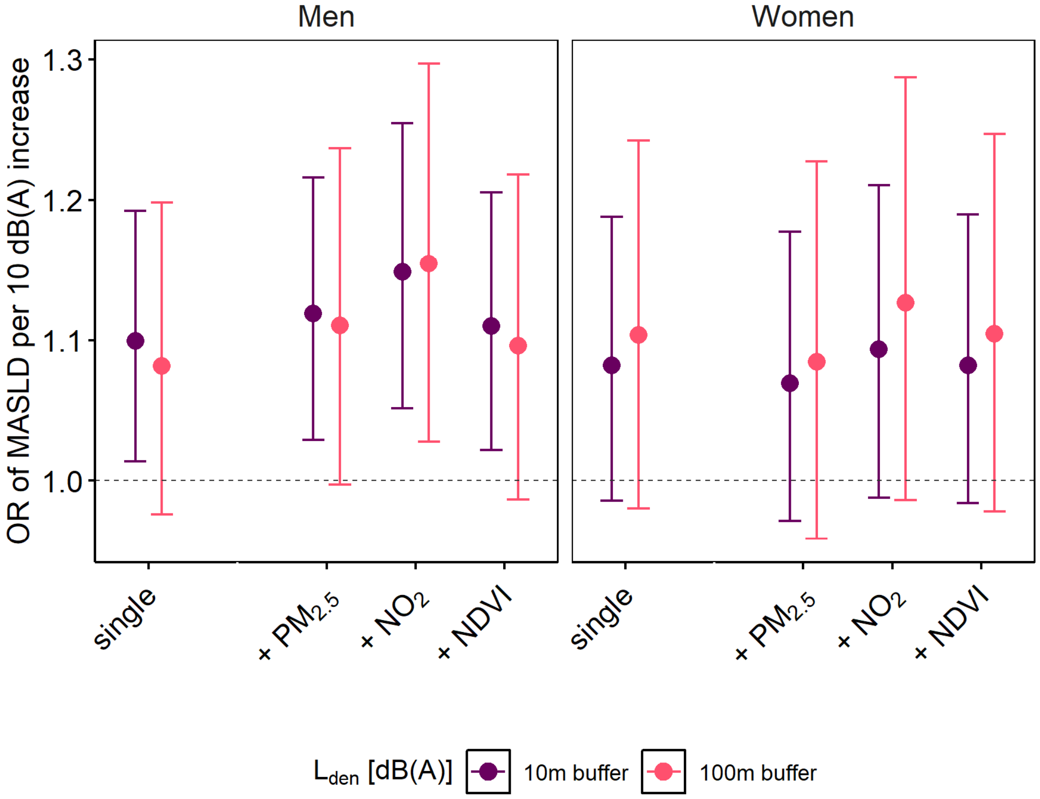


Figure S8 Comparison of the estimates of road traffic noise (10m and 100m buffer) in single and two exposure models adjusting for air pollutants ($PM_{2.5}$, NO_2) and surrounding greenness (NDVI) for the outcome MASLD in the German National Cohort. Legend: Odds ratios are derived from logistic regression models adjusted for study center, age, alcohol consumption, physical activity, smoking behavior, income. Abbreviation: L_{den} = day–evening–night road traffic noise level, MASLD = metabolic-dysfunction associated steatosis liver disease, NDVI = normalized difference vegetation index, NO_2= nitrogen dioxide, OR = odds ratio, $PM_{2.5}$ = particulate matter with diameter < 2.5 µm

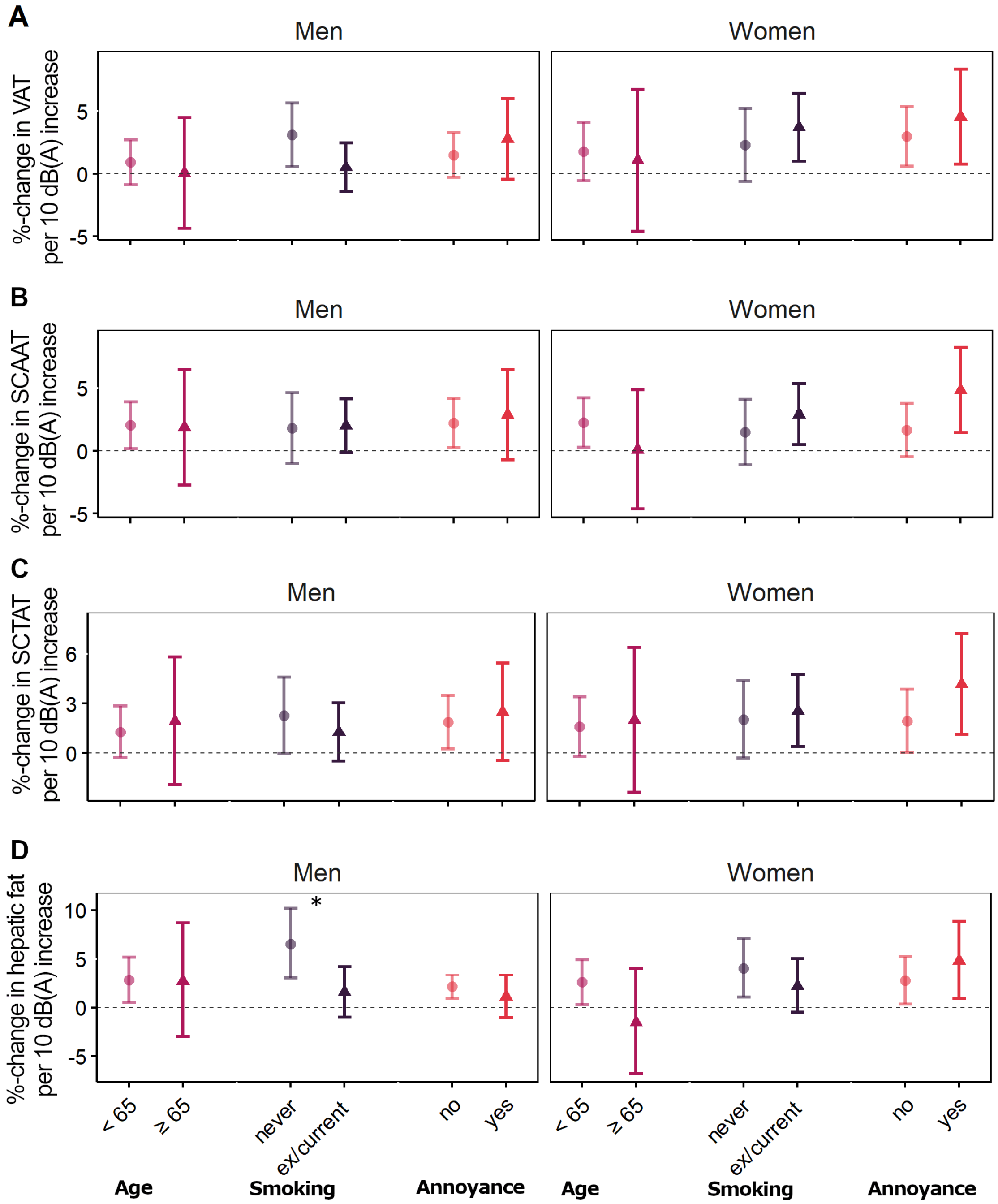


Figure S9 Strata-specific associations of L_{den} (10m buffer) with VAT (A), SCAAT (B), SCTAT (C), and hepatic fat content (D) derived from linear regression with a multiplicative interaction term between exposure and potential effect modifier in the German National Cohort. Legend: Models were adjusted for study center, age, alcohol consumption, physical activity, smoking behavior, income. Effect estimates are given as percentage change of the arithmetic (geometric for hepatic fat content) outcome mean per 10 dB(A) increase in exposure with 95% confidence intervals. Asterix indicate significant interaction term with $p < 0.05$. Abbreviation: L_{den} = day–evening–night road traffic noise level, SCAAT = subcutaneous abdominal adipose tissue, SCTAT = subcutaneous thoracic adipose tissue, VAT = visceral adipose tissue

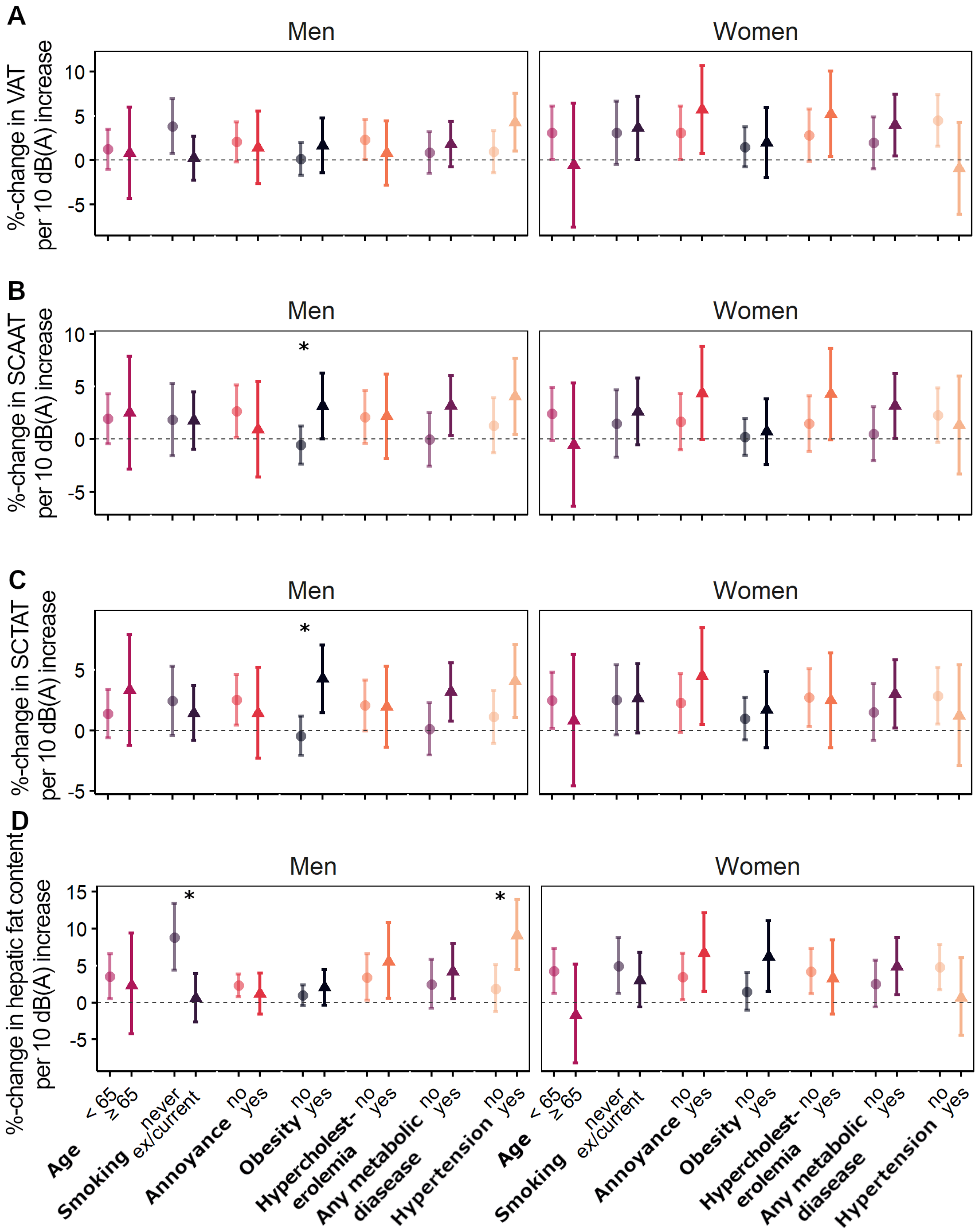


Figure S10 Strata-specific associations of L_{den} (100m buffer) with VAT (A), SCAAT (B), SCTAT (C), and hepatic fat content (D) derived from linear regression with a multiplicative interaction term between exposure and potential effect modifier in the German National Cohort. Legend: Models were adjusted for study center, age, alcohol consumption, physical activity, smoking behavior, income. Effect estimates are given as percentage change of the arithmetic (geometric for hepatic fat content) outcome mean per 10 dB(A) increase in exposure with 95% confidence intervals. Asterix indicate significant interaction term with $p < 0.05$. Abbreviation: L_{den} = day–evening–night road traffic noise level, SCAAT = subcutaneous abdominal adipose tissue, SCTAT = subcutaneous thoracic adipose tissue, VAT = visceral adipose tissue

Table S1 Distribution of different road traffic noise variables used in various sensitivity analyses in the German National Cohort.

	Overall	Men	Women
Categorical	**n = 11,101**	**n = 5,690**	**n = 5,411**
NA	4,864 (43.8)	2,486 (43.7)	2,378 (43.9)
40 dB(A)	4,126 (37.2)	2,121 (37.3)	2,005 (37.1)
55 – 59 dB(A)	844 (7.6)	432 (7.6)	412 (7.6)
60 – 64 dB(A)	508 (4.6)	249 (4.4)	258 (4.8)
65 – 69 dB(A)	437 (3.9)	236 (4.1)	201 (3.7)
70 – 74 dB(A)	260 (2.3)	139 (2.4)	121 (2.2)
≥75 dB(A)	63 (0.6)	27 (0.5)	36 (0.7)
Binary*	**n = 6,237**	**n = 3,204**	**n = 3,033**
< 55 dB(A)	4,126 (66.2)	2,121 (66.2)	2,005 (66.1)
≥ 55 dB(A)	2,111 (33.8)	1,083 (33.8)	1,028 (33.9)
Sensitivity continuous*	**n = 6,237**	**n = 3,204**	**n = 3,033**
L_{den} 10m, [dB(A)]	46.8 (9.3)	46.8 (9.4)	46.7 (9.3)
L_{den} 100m, [dB(A)]	46.8 (6.9)	46.9 (7.0)	46.8 (6.8)
Categorical based on continuous noise 100m buffer variable*	**n = 6,795**	**n = 3,478**	**n = 3,317**
40 dB(A)	1,611 (14.5)	832 (14.6)	779 (14.4)
>40 – 54.9 dB(A)	4,226 (38.1)	2,144 (37.7)	2,082 (38.5)
≥ 55 dB(A)	958 (8.6)	502 (8.8)	456 (8.4)

*Participants with NA in categorical road traffic noise variable were excluded from the regression analysis.
Abbreviations: L_{den} = day–evening–night road traffic noise level

Table S2 Descriptive statistics of exposures used for two-exposure models in the German National Cohort.

	Men (n = 5,690)						Women (n = 5,411)					
	Mean (SD)	**Min**	**25th percentile**	**Median**	**75th percentile**	**Max**	**Mean (SD)**	**Min**	**25th percentile**	**Median**	**75th percentile**	**Max**
L_{den} **10m** (dB(A))	43.86 (7.80)	40	40	40	40.31	74.27	43.84 (7.73)	40	40	40	40.53	73.54
L_{den} **100m** (dB(A))	44.10 (6.27)	40	40	40	47.16	69.4	44.04 (6.12)	40	40	40	47.17	69.86
NO_2 (µg/m^3)	26.03 (9.83)	4.73	18.29	24.71	33.51	74.97	25.79 (9.72)	5.41	18.18	24.52	33.05	74.51
$PM_{2.5}$ (µg/m^3)	17.64 (2.04)	10.13	16.23	17.39	19.48	23.08	17.64 (2.05)	10.94	16.3	17.4	19.49	23.09
NDVI	0.54 (0.09)	0.25	0.48	0.55	0.61	0.82	0.54 (0.09)	0.25	0.48	0.55	0.61	0.79

Abbreviation: L_{den} = day–evening–night road traffic noise level, NO_2= nitrogen dioxide, $PM_{2.5}$ = particulate matter with diameter < 2.5 µm, NDVI = normalized difference vegetation index

Table S3. Sensitivity analysis comparing associations of road traffic noise with adipose tissue depots, hepatic fat content and MASLD in the German National Cohort after additional adjustment for population density and area-level SES.

	Adjustment	Men (n = 5,690)		Women (n = 5,411)	
		%-change (95% CI)	p	%-change (95% CI)	p
VAT [l]					
L_{den} (10m)	Main	1.72 (0.14; 3.30)	0.03	3.13 (1.09; 5.18)	<0.01
	Main + population density	1.93 (0.34; 3.52)	0.02	3.22 (1.16; 5.27)	<0.01
	Main + area level SES	1.78 (0.18; 3.37)	0.03	3.14 (1.08; 5.21)	<0.01
	Main + population density & area level SES	1.90 (0.30; 3.50)	0.02	3.20 (1.13; 5.26)	<0.01
L_{den} (100m)	Main	1.85 (-0.15; 3.86)	0.07	3.47 (0.84; 6.09)	0.01
	Main + population density	2.38 (0.35; 4.40)	0.04	3.77 (1.11; 6.43)	0.01
	Main + area level SES	1.98 (-0.06; 4.02)	0.06	3.50 (0.83; 6.18)	0.01
	Main + population density & area level SES	2.27 (0.22; 4.33)	0.05	3.56 (0.88; 6.24)	0.01
SCAAT [l]					
L_{den} (10m)	Main	2.18 (0.43; 3.93)	0.02	2.38 (0.55; 4.20)	0.01
	Main + population density	2.46 (0.70; 4.22)	0.01	2.57 (0.74; 4.41)	0.01
	Main + area level SES	2.37 (0.60; 4.13)	0.01	2.58 (0.73; 4.42)	0.01
	Main + population density & area level SES	2.51 (0.74; 4.28)	0.01	2.67 (0.82; 4.51)	0.01
L_{den} (100m)	Main	2.07 (-0.15; 4.29)	0.07	2.22 (-0.12; 4.57)	0.06
	Main + population density	2.40 (0.17; 4.64)	0.04	2.50 (0.13; 4.86)	0.04
	Main + area level SES	2.43 (0.17; 4.70)	0.04	2.58 (0.19; 4.97)	0.04
	Main + population density & area level SES	2.54 (0.27; 4.81)	0.03	2.68 (0.29; 5.08)	0.03
SCTAT [l]					
L_{den} (10m)	Main	1.79 (0.34; 3.25)	0.02	2.39 (0.75; 4.03)	<0.01
	Main + population density	1.85 (0.38; 3.31)	0.01	2.55 (0.90; 4.19)	<0.01
	Main + area level SES	1.59 (0.12; 3.05)	0.03	2.30 (0.64; 3.95)	0.01
	Main + population density & area level SES	1.67 (0.20; 3.13)	0.03	2.41 (0.75; 4.07)	<0.01
L_{den} (100m)	Main	1.99 (0.15; 3.83)	0.03	2.68 (0.58; 4.79)	0.01
	Main + population density	2.05 (0.19; 3.90)	0.03	2.90 (0.78; 5.03)	0.01
	Main + area level SES	1.61 (-0.27; 3.49)	0.09	2.53 (0.38; 4.68)	0.02
	Main + population density & area level SES	1.67 (-0.21; 3.55)	0.08	2.67 (0.52; 4.82)	0.02
Hepatic fat content [%]					
L_{den} (10m)	Main	3.57 (1.41; 5.78)	<0.01	3.08 (1.00; 5.21)	<0.01

	Main + population density	4.00 (1.82; 6.23)	<0.01	3.13 (1.03; 5.28)	<0.01
	Main + area level SES	3.57 (1.39; 5.80)	<0.01	3.21 (1.10; 5.36)	<0.01
	Main + population density & area level SES	3.86 (1.67; 6.10)	<0.01	3.22 (1.1; 5.38)	<0.01
L_{den} (100m)	Main	3.87 (1.13; 6.69)	0.01	4.03 (1.33; 6.79)	<0.01
	Main + population density	4.41 (1.63; 7.25)	<0.01	4.11 (1.39; 6.90)	<0.01
	Main + area level SES	3.91 (1.11; 6.78)	0.01	4.30 (1.54; 7.13)	<0.01
	Main + population density & area level SES	4.13 (1.32; 7.01)	<0.01	4.31 (1.55; 7.15)	<0.01
MASLD[1]		**OR (95% CI)**		**OR (95% CI)**	
L_{den} (10m)	Main	1.10 (1.01; 1.19)	0.02	1.08 (0.99; 1.19)	0.1
	Main + population density	1.12 (1.03; 1.21)	0.01	1.09 (0.99; 1.19)	0.08
	Main + area level SES	1.11 (1.02; 1.20)	0.01	1.08 (0.98; 1.18)	0.12
	Main + population density & area level SES	1.12 (1.03; 1.21)	0.01	1.08 (0.98; 1.19)	0.11
L_{den} (100m)	Main	1.08 (0.98; 1.20)	0.14	1.10 (0.98; 1.24)	0.10
	Main + population density	1.10 (0.99; 1.22)	0.07	1.11 (0.99; 1.25)	0.09
	Main + area level SES	1.10 (0.99; 1.22)	0.08	1.10 (0.97; 1.24)	0.13
	Main + population density & area level SES	1.10 (0.99; 1.23)	0.06	1.10 (0.98; 1.24)	0.12

Legend: Effect estimates are given as percentage change of the arithmetic (geometric for hepatic fat content) outcome mean per 10 dB(A) increase in exposure with 95% confidence intervals derived from linear and logistic regression models stratified by sex. Main model adjusted for study center, age, alcohol consumption, physical activity, smoking behavior, income. Area-level SES was represented by unemployment rate at district level, population density was given as inhabitants per 500 m².

[1]Sample size deviate from full sample (n = 5,147 men and n = 5,258 women) due to MASLD definition. Abbreviations: CI = confidence interval, L_{den} = day–evening–night road traffic noise level, MASLD = metabolic dysfunction–associated steatotic liver disease, OR = odds ratio, SCAAT = subcutaneous abdominal adipose tissue, SCTAT = subcutaneous thoracic adipose tissue, SES = socioeconomic status, VAT = visceral adipose tissue

Table S4 Results of sensitivity analysis on the associations of road traffic noise used as continuous, binary, and categorical variable with adipose tissue depots and hepatic fat content in the German National Cohort.

	Men			Women		
	n	**%-change (95% CI)**	**p**	**n**	**%-change (95% CI)**	**p**
VAT [l]						
Continuous						
L_{den} (10m)[1]	3,204	2.28 (0.49; 4.07)	0.03	3,033	3.23 (0.98; 5.48)	<0.01
L_{den} (100m)[1]	3,204	2.98 (0.57; 5.40)	0.01	3,033	4.48 (1.36; 7.59)	<0.01
Categorical						
40 dB(A)	2,121	Ref		2,005	Ref	
55 – 59 dB(A)	432	4.95 (-0.03; 9.93)	0.05	412	6.39 (0.00; 12.78)	0.05
60 – 64 dB(A)	249	3.86 (-2.30; 10.03)	0.22	258	9.94 (2.52; 17.36)	0.01
65 – 69 dB(A)	236	5.33 (-0.89; 11.54)	0.09	201	5.37 (-2.87; 13.6)	0.20
≥ 70[1] dB(A)	166	6.16 (-1.17; 13.49)	0.10	157	7.75 (-1.51; 17.01)	0.10
Binary						
<55 dB(A)	2,121	Ref		2,005	Ref	
≥55 dB(A)	1,083	4.98 (1.40; 8.56)	0.01	1,028	7.31 (2.81; 11.8)	<0.01
Categorical based on L_{den} 100m buffer variable						
40 dB(A)	832	Ref		779	Ref	
>40 – 54.9 dB(A)	2,144	0.77 (-2.95; 4.48)	0.69	2,082	4.17 (-0.55; 8.88)	0.08
≥ 55 dB(A)	502	3.70 (-1.50; 8.91)	0.16	456	12.14 (5.47; 18.81)	<0.01
SCAAT [l]						
Continuous						
L_{den} (10m)[1]	3,204	3.05 (1.08; 5.03)	<0.01	3,033	2.97 (0.99; 4.96)	<0.01
L_{den} (100m)[1]	3,204	3.76 (1.09; 6.42)	<0.01	3,033	4.24 (1.49; 6.98)	<0.01
Categorical						
40 dB(A)	2,121	Ref		2,005	Ref	
55 – 59 dB(A)	432	5.46 (-0.02; 10.95)	0.05	412	2.59 (-3.04; 8.23)	0.37
60 – 64 dB(A)	249	7.64 (0.85; 14.44)	0.03	258	11.34 (4.79; 17.89)	<0.01
65 – 69 dB(A)	236	8.24 (1.38; 15.09)	0.02	201	5.47 (-1.79; 12.74)	0.14
≥ 70[1] dB(A)	166	8.79 (0.71; 16.87)	0.03	157	4.16 (-4.01; 12.33)	0.32
Binary						
<55 dB(A)	2,121	Ref		2,005	Ref	
≥55 dB(A)	1,083	7.12 (3.18; 11.07)	<0.01	1,028	5.71 (1.75; 9.68)	<0.01
Categorical based on L_{den} 100m buffer variable						

40 dB(A)	832	Ref		779	Ref	
>40 – 54.9 dB(A)	2,144	3.05 (-1.03; 7.13)	0.14	2,082	3.65 (-0.51; 7.81)	0.09
≥ 55 dB(A)	502	6.24 (0.52; 11.95)	0.03	456	12.48 (6.6; 18.37)	<0.01
SCTAT [l]						
Continuous						
L_{den} (10m)[1]	3,204	1.94 (0.27; 3.61)	0.02	3,033	2.38 (0.56; 4.20)	0.01
L_{den} (100m)[1]	3,204	2.17 (-0.09; 4.43)	0.06	3,033	3.31 (0.79; 5.82)	0.01
Categorical						
40 dB(A)	2,121	Ref		2,005	Ref	
55 – 59 dB(A)	432	2.80 (-1.85; 7.44)	0.24	412	1.89 (-3.27; 7.05)	0.47
60 – 64 dB(A)	249	6.86 (1.1; 12.61)	0.02	258	7.03 (1.03; 13.02)	0.02
65 – 69dB(A)	236	4.12 (-1.68; 9.92)	0.16	201	3.70 (-2.95; 10.36)	0.28
≥ 70[1] dB(A)	166	6.38 (-0.46; 13.23)	0.07	157	5.98 (-1.51; 13.46)	0.12
Binary						
<55 dB(A)	2,121	Ref		2,005	Ref	
≥55 dB(A)	1,083	4.58 (1.24; 7.93)	0.01	1,028	4.26 (0.63; 7.89)	0.02
Categorical based on L_{den} 100m buffer variable						
40 dB(A)	832	Ref		779	Ref	
>40 – 54.9 dB(A)	2,144	1.05 (-2.40; 4.50)	0.55	2,082	3.38 (-0.43; 7.18)	0.08
≥ 55 dB(A)	502	4.43 (-0.41; 9.26)	0.07	456	10.32 (4.93; 15.7)	0.00
Hepatic fat content [%]						
Continuous						
L_{den} (10m)[1]	3,204	1.94 (0.27; 3.61)	0.02	3,033	2.38 (0.56; 4.20)	0.01
L_{den} (100m)[1]	3,204	2.17 (-0.09; 4.43)	0.06	3,033	3.31 (0.79; 5.82)	0.01
Categorical						
40 dB(A)	2,121	Ref		2,005	Ref	
55 – 59 dB(A)	432	7.70 (1.01; 14.83)	0.02	412	2.84 (-3.33; 9.41)	0.38
60 – 64 dB(A)	249	4.14 (-3.81; 12.74)	0.32	258	8.72 (1.17; 16.83)	0.02
65 – 69 dB(A)	236	8.73 (0.37; 17.8)	0.04	201	4.33 (-3.68; 13.00)	0.30
≥ 70[1] dB(A)	166	13.29 (3.08; 24.51)	0.01	157	8.81 (-0.54; 19.03)	0.07
Binary						
<55 dB(A)	2,121	Ref		2,005	Ref	
≥55 dB(A)	1,083	7.99 (3.12; 13.08)	<0.01	1,028	5.59 (1.09; 10.3)	0.01
Categorical based on L_{den} 100m buffer variable						
40 dB(A)	832	Ref		779	Ref	

>40 – 54.9 dB(A)	2,144	1.52 (-3.25; 6.52)	0.54	2,082	3.86 (-0.81; 8.75)	0.11
≥ 55 dB(A)	502	7.62 (0.61; 15.13)	0.03	456	12.32 (5.24; 19.87)	<0.01
MASLD		**OR (95% CI)**			**OR (95% CI)**	
Continuous						
L_{den} (10m)	2,900	1.10 (1.01; 1.19)	0.01	2,944	1.09 (0.98; 1.21)	0.11
L_{den} (100m)	2,900	1.14 (1.01; 1.29)	0.03	2,944	1.13 (0.98; 1.30)	0.08
Categorical						
40 dB(A)	1,917	Ref		1,950	Ref	
55 – 59 dB(A)	388	1.32 (1.03; 1.69)	0.03	402	1.20 (0.90; 1.59)	0.21
60 – 64 dB(A)	228	1.28 (0.94; 1.74)	0.16	248	1.19 (0.85; 1.67)	0.31
65 – 69 dB(A)	214	1.24 (0.91; 1.69)	0.18	190	0.86 (0.57; 1.28)	0.45
≥ 70[1] dB(A)	153	1.49 (1.04; 2.13)	0.03	154	1.54 (1.03; 2.31)	0.04
Binary						
<55 dB(A)	1,917	Ref		1,950	Ref	
≥55 dB(A)	983	1.32 (1.10; 1.57)	0.01	994	1.17 (0.95; 1.43)	0.13
Categorical based on L_{den} 100m buffer variable						
40 dB(A)	761	Ref		760	Ref	
>40 – 54.9 dB(A)	1,936	0.99 (0.82; 1.19)	0.93	2,021	1.09 (0.88; 1.35)	0.43
≥ 55 dB(A)	456	1.24 (0.96; 1.60)	0.11	442	1.37 (1.02; 1.85)	0.04

Legend: Effect estimates are given as percentage change of the arithmetic (geometric for hepatic fat content) outcome mean per 10 dB(A) increase in exposure with 95% confidence intervals derived from linear and logistic regression models stratified by sex. Models are adjusted for study center, age, alcohol consumption, physical activity, smoking behavior, and income. For all the road traffic exposure variables, participants with missing in the categorical variable were excluded.

[1]Categories 70 – 74 dB(A) and ≥ 75 dB(A) were subsumed due to small sample size. Abbreviations: L_{den} = day–evening–night road traffic noise level, MASLD = metabolic-dysfunction associated steatosis liver disease

Table S5 Participant characteristics for the complete-case German National Cohort sample stratified by sex.

	Overall (n = 9,444)	**Men (n =4,870)**	**Women (n = 4,574)**
Sex, female n (%)	4,574 (48.4)	-	4,574 (100.0)
Age (years), mean (SD)	51.8 (11.3)	51.9 (11.4)	51.6 (11.1)
Study center, n (%)			
Augsburg	2,173 (23.0)	1,211 (24.9)	962 (21.0)
Berlin	1,900 (20.1)	973 (20.0)	927 (20.3)
Düsseldorf	215 (2.3)	120 (2.5)	95 (2.1)
Essen	1,388 (14.7)	695 (14.3)	693 (15.2)
Mannheim	1,025 (10.9)	533 (10.9)	492 (10.8)
Münster	63 (0.7)	37 (0.8)	26 (0.6)
Neubrandenburg	2,599 (27.5)	1,261 (25.9)	1,338 (29.3)
Saarbrücken	81 (0.9)	40 (0.8)	41 (0.9)
Examination year, n (%)			
2014	433 (4.6)	226 (4.6)	207 (4.5)
2015	3,231 (34.2)	1,652 (33.9)	1,579 (34.5)
2016	5,780 (61.2)	2,992 (61.4)	2,788 (61.0)
VAT (l), mean (SD)	3.7 (2.3)	4.8 (2.4)	2.5 (1.5)
SCAAT (l), mean (SD)	6.9 (3.6)	6.2 (3.0)	7.7 (3.9)
SCTAT (l), mean (SD)	3.3 (1.6)	2.81 (1.2)	3.8 (1.8)
Hepatic fat content (%), mean (SD)	7.5 (6.5)	8.7 (6.9)	6.3 (5.9)
MASLD, yes n (%)	2,966 (31.4)	1,922 (39.5)	1,044 (22.8)
L_{den} (10m) (dB(A)), mean (SD)	43.8 (7.7)	43.8 (7.7)	43.8 (7.7)
L_{den} (100m) (dB(A)), mean (SD)	44.0 (6.2)	44.0 (6.2)	44.0 (6.1)
Degree of urbanization, n (%)			
urban	6,238 (66.1)	3,177 (65.2)	3,061 (66.9)
suburban	1,372 (14.5)	755 (15.5)	617 (13.5)
rural	1,834 (19.4)	938 (19.3)	896 (19.6)
Physical activity (min/week), mean (SD)	1,466 (1,614)	1,510 (1,668)	1,420 (1,553)
Alcohol consumption (g/day), mean (SD)	10.9 (16.9)	14.8 (20.4)	6.6 (10.5)
Income (Euros), mean (SD)	2,273 (1,454)	2,420 (1,601)	2,116 (1,261)
Smoking behavior, n (%)			
never smoker	4,474 (47.4)	2,055 (42.2)	2,419 (52.9)
ex-smoker	3,135 (33.2)	1,830 (37.6)	1,305 (28.5)
smoker	1,835 (19.4)	985 (20.2)	850 (18.6)
Noise annoyance, high-extreme n (%)	1,518 (16.1)	730 (15.0)	788 (17.2)
Living duration (years), mean (SD)	15.1 (11.8)	15.1 (12.1)	15.2 (11.6)
Population density (n/500 m²), mean (SD)	1,336 (1,297)	1,325 (1,296)	1,347 (1,299)
Unemployment rate (%) at district level, mean (SD)	9.5 (3.8)	9.3 (3.8)	9.7(3.7)
Body-Mass-Index (kg/m²), mean (SD)	26.8 (4.7)	27.3 (4.1)	26.2 (5.2)
Waist circumference (cm), mean (SD)	91.9 (13.7)	97.3 (12.0)	86.1 (13.0)
Obesity (BMI ≥ 30 kg/m²), yes n (%)	1,984 (21.4)	1,061 (22.3)	923 (20.6)
Hypercholesterolemia, yes n (%)	2,538 (27.0)	1,364 (28.2)	1174 (25.8)
Diabetes, yes n (%)	537 (5.7)	321 (6.6)	216 (4.7)
Any metabolic disease, yes (%)	3,942 (41.7)	2,094 (43.0)	1,848 (40.4)
Hypertension, yes n (%)	2,572 (27.3)	1,606 (33.0)	966 (21.1)

Abbreviations: BMI = Body-Mass-Index, L_{den} = day–evening–night road traffic noise level, MASLD = metabolic-dysfunction associated steatosis liver disease, SCAAT = subcutaneous abdominal adipose tissue, SCTAT = subcutaneous thoracic adipose tissue, VAT = visceral adipose tissue

Table S6 Associations of road traffic noise with adipose tissue depots, hepatic fat content and non-alcoholic fatty liver disease derived from linear and logistic regression models in the complete-case German National Cohort sample (n = 9,444).

	Men (n = 4,870)		Women (n = 4,574)	
	%-change (95% CI)	**p**	**%-change (95% CI)**	**p**
VAT [l]				
L_{den} (10m)	2.39 (0.67; 4.11)	0.01	2.96 (0.72; 5.19)	0.01
L_{den} (100m)	2.82 (0.65; 5.00)	0.01	2.99 (0.10; 5.88)	0.04
SCAAT [l]				
L_{den} (10m)	2.64 (0.75; 4.53)	0.01	2.22 (0.23; 4.20)	0.03
L_{den} (100m)	2.92 (0.53; 5.32)	0.02	1.94 (-0.63; 4.51)	0.14
SCTAT [l]				
L_{den} (10m)	2.19 (0.63; 3.76)	0.01	2.31 (0.53; 4.09)	0.01
L_{den} (100m)	2.84 (0.85; 4.83)	0.01	2.58 (0.28; 4.88)	0.03
Hepatic fat content [%]				
L_{den} (10m)	4.42 (2.07; 6.82)	<0.01	2.94 (0.68; 5.25)	0.01
L_{den} (100m)	4.55 (1.58; 7.62)	<0.01	3.40 (0.47; 6.41)	0.02
MASLD[1]	**OR (95% CI)**		**OR (95% CI)**	
L_{den} (10m)	1.13 (1.03; 1.24)	0.007	1.08 (0.97; 1.20)	0.147
L_{den} (100m)	1.13 (1.01; 1.27)	0.038	1.10 (0.96; 1.25)	0.183

Effect estimates are given as percentage change of the arithmetic (geometric for hepatic fat content) outcome mean per 10 dB(A) increase in exposure with 95% confidence intervals derived from linear and logistic regression models stratified by sex and adjusted for study center, age, alcohol consumption, physical activity, smoking behavior, and income.

[1]Sample size deviate from full sample (n = 4,256 men and n = 4,279 women) due to MASLD definition.

Abbreviations: L_{den} = day–evening–night road traffic noise level, MASLD = metabolic-dysfunction associated steatosis liver disease, SCAAT = subcutaneous abdominal adipose tissue, SCTAT = subcutaneous thoracic adipose tissue, VAT = visceral adipose tissue;

Table S7 Associations between road traffic noise and prevalent MASLD and MetALD derived from logistic regression models in the German National Cohort.

	Men (n = 5,470)		Women (n = 5,342)	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
L_{den} (10m)	1.09 (1.01; 1.17)	0.04	1.11 (1.01; 1.21)	0.03
L_{den} (100m)	1.07 (0.97; 1.18)	0.16	1.13 (1.01; 1.27)	0.03

Effect estimates are given as odds ratio per 10 dB(A) increase in exposure, with 95% confidence intervals derived from logistic regression models stratified by sex and adjusted for study center, age, alcohol consumption, physical activity, smoking behavior, and income.

Abbreviations: CI = Confidence interval, L_{den} = day–evening–night road traffic noise level, MASLD = metabolic-dysfunction associated steatosis liver disease, MetALD = metabolic-associated alcoholic liver disease, OR = odds ratio

Table S8. Sensitivity analysis comparing associations of road traffic noise with adipose tissue depots, hepatic fat content and MASLD in the German National Cohort after different confounder adjustments.

	Adjustment	Men (n = 5,690)		Women (n = 5,411)	
		%-change (95% CI)	p	%-change (95% CI)	p
VAT [l]					
L_{den} (10m)	Main	1.72 (0.14; 3.30)	0.03	3.13 (1.09; 5.18)	<0.01
	Main without income	1.88 (0.30; 3.46)	0.02	3.59 (1.54; 5.65)	<0.01
	Main without lifestyle factors	1.83 (0.24; 3.42)	0.02	3.06 (1.02; 5.10)	<0.01
L_{den} (100m)	Main	1.85 (-0.15; 3.86)	0.07	3.47 (0.84; 6.09)	0.01
	Main without income	2.05 (0.05; 4.06)	0.05	4.07 (1.43; 6.71)	<0.01
	Main without lifestyle factors	2.08 (0.06; 4.10)	0.04	3.34 (0.71; 5.96)	0.01
SCAAT [l]					
L_{den} (10m)	Main	2.18 (0.43; 3.93)	0.02	2.38 (0.55; 4.20)	0.01
	Main without income	2.27 (0.52; 4.02)	0.01	2.64 (0.81; 4.47)	0.01
	Main without lifestyle	2.16 (0.41; 3.92)	0.02	2.24 (0.42; 4.07)	0.02
L_{den} (100m)	Main	2.07 (-0.15; 4.29)	0.07	2.22 (-0.12; 4.57)	0.06
	Main without income	2.18 (-0.04; 4.40)	0.05	2.57 (0.22; 4.92)	0.03
	Main without lifestyle factors	2.11 (-0.11; 4.34)	0.06	2.03 (-0.31; 4.38)	0.09
SCTAT [l]					
L_{den} (10m)	Main	1.79 (0.34; 3.25)	0.02	2.39 (0.75; 4.03)	<0.01
	Main without income	1.88 (0.43; 3.33)	0.01	2.67 (1.03; 4.32)	<0.01
	Main without lifestyle factors	1.91 (0.46; 3.37)	0.01	2.34 (0.70; 3.98)	0.01
L_{den} (100m)	Main	1.99 (0.15; 3.83)	0.03	2.68 (0.58; 4.79)	0.01
	Main without income	2.09 (0.25; 3.93)	0.03	3.05 (0.94; 5.16)	0.01
	Main without lifestyle factors	2.20 (0.36; 4.05)	0.02	2.58 (0.47; 4.68)	0.02
Hepatic fat content [%]					
L_{den} (10m)	Main	3.57 (1.41; 5.78)	<0.01	3.08 (1.00; 5.21)	<0.01
	Main without income	3.81 (1.64; 6.02)	<0.01	3.48 (1.38; 5.62)	<0.01
	Main without lifestyle factors	3.72 (1.55; 5.94)	<0.01	2.99 (0.91; 5.11)	0.01
L_{den} (100m)	Main	3.87 (1.13; 6.69)	0.01	4.03 (1.33; 6.79)	<0.01
	Main without income	4.17 (1.42; 6.99)	<0.01	4.55 (1.83; 7.34)	<0.01
	Main without lifestyle factors	4.15 (1.39; 6.98)	<0.01	3.92 (1.23; 6.69)	<0.01
MASLD[1]		**OR (95% CI)**		**OR (95% CI)**	

22

L_{den} (10m)	Main	1.10 (1.01; 1.19)	0.02	1.08 (0.99; 1.19)	0.1
	Main without income	1.11 (1.03; 1.21)	0.01	1.11 (1.02; 1.22)	0.02
	Main without lifestyle factors	1.09 (1.01; 1.18)	0.03	1.09 (0.99; 1.19)	0.07
L_{den} (100m)	Main	1.08 (0.98; 1.20)	0.14	1.10 (0.98; 1.24)	0.10
	Main without income	1.13 (1.02; 1.25)	0.02	1.16 (1.03; 1.30)	0.01
	Main without lifestyle factors	1.11 (1.01; 1.23)	0.03	1.13 (1.01; 1.27)	0.03

Legend: Effect estimates are given as percentage change of the arithmetic (geometric for hepatic fat content) outcome mean per 10 dB(A) increase in exposure, with 95% confidence intervals derived from linear and logistic regression models stratified by sex. All models are adjusted for study center, age, alcohol consumption, physical activity, smoking behavior, and income.

[1]Sample size deviate from full sample (n = 5,147 men and n = 5,258 women) due to MASLD definition. Abbreviations: CI = confidence interval, L_{den} = day–evening–night road traffic noise level, MASLD = metabolic dysfunction–associated steatotic liver disease, OR = odds ratio, SCAAT = subcutaneous abdominal adipose tissue, SCTAT = subcutaneous thoracic adipose tissue, VAT = visceral adipose tissue

23

Table S9. Sensitivity analysis comparing associations of road traffic noise with adipose tissue depots, hepatic fat content and MASLD in the German National Cohort after excluding those who lived less than five or ten years at the residencies.

	Adjustment	N (men/women)	Men		Women	
			%-change (95% CI)	p	%-change (95% CI)	p
VAT [l]						
L_{den} (10m)	Total sample	5,690/5,411	1.72 (0.14; 3.30)	0.03	3.13 (1.09; 5.18)	<0.01
	Living duration ≥ 5 years	4,623/4,508	1.76 (-0.03; 3.54)	0.05	3.44 (1.18; 5.69)	<0.01
	Living duration ≥ 10 years	3,633/3,598	1.78 (-0.28; 3.84)	0.09	4.94 (2.37; 7.51)	<0.01
L_{den} (100m)	Total sample	5,690/5,411	1.85 (-0.15; 3.86)	0.07	3.47 (0.84; 6.09)	0.01
	Living duration ≥ 5 years	4,623/4,508	2.12 (-0.11; 4.34)	0.06	3.72 (0.87; 6.56)	0.01
	Living duration ≥ 10 years	3,633/3,598	1.95 (-0.58; 4.47)	0.13	4.80 (1.61; 7.98)	<0.01
SCAAT [l]						
L_{den} (10m)	Total sample	5,690/5,411	2.18 (0.43; 3.93)	0.02	2.38 (0.55; 4.20)	0.01
	Living duration ≥ 5 years	4,623/4,508	2.16 (0.20; 4.12)	0.03	2.86 (0.83; 4.89)	0.01
	Living duration ≥ 10 years	3,633/3,598	2.24 (-0.04; 4.51)	0.05	3.64 (1.35; 5.94)	<0.01
L_{den} (100m)	Total sample	5,690/5,411	2.07 (-0.15; 4.29)	0.07	2.22 (-0.12; 4.57)	0.06
	Living duration ≥ 5 years	4,623/4,508	2.26 (-0.19; 4.70)	0.07	2.65 (0.09; 5.21)	0.04
	Living duration ≥ 10 years	3,633/3,598	2.34 (-0.45; 5.13)	0.10	3.16 (0.31; 6.01)	0.03
SCTAT [l]						
L_{den} (10m)	Total sample	5,690/5,411	1.79 (0.34; 3.25)	0.02	2.39 (0.75; 4.03)	<0.01
	Living duration ≥ 5 years	4,623/4,508	1.78 (0.14; 3.42)	0.03	2.85 (1.04; 4.67)	<0.01
	Living duration ≥ 10 years	3,633/3,598	2.10 (0.20; 4.00)	0.03	3.74 (1.68; 5.79)	<0.01
L_{den} (100m)	Total sample	5,690/5,411	1.99 (0.15; 3.83)	0.03	2.68 (0.58; 4.79)	0.01
	Living duration ≥ 5 years	4,623/4,508	2.10 (0.05; 4.14)	0.05	3.29 (1.01; 5.58)	0.01
	Living duration ≥ 10 years	3,633/3,598	2.06 (-0.27; 4.4)	0.08	3.78 (1.23; 6.33)	<0.01
Hepatic fat content [%]						
L_{den} (10m)	Total sample	5,690/5,411	3.57 (1.41; 5.78)	<0.01	3.08 (1.00; 5.21)	<0.01
	Living duration ≥ 5 years	4,623/4,508	3.90 (1.40; 6.46)	<0.01	3.25 (0.83; 5.72)	0.01
	Living duration ≥ 10 years	3,633/3,598	3.75 (0.78; 6.81)	0.01	4.15 (1.28; 7.1)	<0.01
L_{den} (100m)	Total sample	5,690/5,411	3.87 (1.13; 6.69)	0.01	4.03 (1.33; 6.79)	<0.01
	Living duration ≥ 5 years	4,623/4,508	4.39 (1.26; 7.62)	0.01	4.13 (1.07; 7.28)	0.01
	Living duration ≥ 10 years	3,633/3,598	3.46 (-0.16; 7.21)	0.06	4.52 (0.96; 8.20)	0.01
MASLD[1]			**OR (95% CI)**		**OR (95% CI)**	

24

L_{den} (10m)	Total sample	5,147/5,258	1.10 (1.01; 1.19)	0.02	1.08 (0.99; 1.19)	0.10
	Living duration ≥ 5 years	4,143/4,368	1.09 (0.99; 1.19)	0.08	1.08 (0.97; 1.19)	0.17
	Living duration ≥ 10 years	3,223/3,477	1.09 (0.98; 1.22)	0.12	1.10 (0.98; 1.24)	0.10
L_{den} (100m)	Total sample	5,147/5,258	1.08 (0.98; 1.20)	0.14	1.10 (0.98; 1.24)	0.10
	Living duration ≥ 5 years	4,143/4,368	1.07 (0.96; 1.20)	0.24	1.09 (0.96; 1.24)	0.19
	Living duration ≥ 10 years	3,223/3,477	1.08 (0.94; 1.23)	0.27	1.11 (0.97; 1.28)	0.14

Legend: Effect estimates are given as percentage change of the arithmetic (geometric for hepatic fat content) outcome mean per 10 dB(A) increase in exposure, with 95% confidence intervals derived from linear and logistic regression models stratified by sex. All models are adjusted for study center, age, alcohol consumption, physical activity, smoking behavior, and income.

[1]Sample size deviate from full sample due to MASLD definition. Abbreviations: CI = confidence interval, L_{den} = day–evening–night road traffic noise level, MASLD = metabolic dysfunction–associated steatotic liver disease, OR = odds ratio, SCAAT = subcutaneous abdominal adipose tissue, SCTAT = subcutaneous thoracic adipose tissue, VAT = visceral adipose tissue

Acknowledgements

Als erstes möchte ich mich von Herzen bei meiner Betreuerin *Annette Peters* bedanken. Sie hat mir nicht nur die faszinierende Welt der Umweltepidemiologie eröffnet, sondern mit ihrem großen Erfahrungsschatz diese Arbeit überhaupt erst ermöglicht. Durch ihre kontinuierliche Unterstützung und ihr Vertrauen habe ich mir Aufgaben zugetraut, an denen ich persönlich wie fachlich wachsen konnte. Besonders dankbar bin ich ihr für all die Türen, die sie mir geöffnet hat; insbesondere für die Möglichkeit eines Forschungsaufenthalts in Boston. Danke, dass ich all diese wertvollen Erfahrungen sammeln durfte, die mich auf vielen Ebenen bereichert haben.

Ein herzliches Dankschön möchte ich auch meinen TAC-Betreuerinnen *Barbara Hoffmann* und *Sophia Stöcklein* aussprechen, die mich mit ihrer (umwelt-)epidemiologischen und medizinischen Expertise während meiner Promotionszeit begleitet und dabei maßgeblich zu meinen Forschungsarbeiten beigetragen haben.

Ebenfalls danke ich allen Ko-Autor*Innen, mit denen ich über die Jahre zusammenarbeiten durfte. Durch ihre Impulse in statistischen Fragen, der Aufbereitung und Verlinkung von Umweltfaktoren und Auswertung von MRT-Bildern wurden diese Forschungsprojekte überhaupt erst ermöglicht. Aus diesen Kooperationen sind nicht nur spannende Forschungsarbeiten, sondern auch viele neue Ideen für künftige Projekte entstanden. Außerdem danke ich dem Team an der HSPH – *Francine Laden, Jaime Hart, Boya Zhang, Jie Chen* - für ihre wertvolle Unterstützung beim letzten Manuskript.

In den letzten sieben Jahren am Institut für Epidemiologie des Helmholtz Zentrums München durfte ich mit vielen tollen Kolleg*Innen zusammenarbeiten. Angefangen bei der AG *Diabetes & AG KORA (v.a. Cornelia Huth, Birgit Linkohr, Olga Lang, Mainsi Marowsky-Köppl)*, in denen ich als studentische Hilfskraft erste Einblicke in die Forschung erhielt und mir die Bedeutung von Qualitätssicherung in Kohortenstudien nähergebracht wurde, bis hin zu meiner jetzigen Arbeitsgruppe *Exposomics*.

Ein besonderer Dank gilt *Susanne Rospleszcz*, die mich während meiner Masterarbeit und in Teilen der Promotion betreut hat und von der ich unglaublich viel lernen durfte. Sie hat meine Neugier für kardiometabolische Erkrankungen und MRT-Marker geweckt und mich entscheidend darin bestärkt, den Weg der Promotion einzuschlagen.

Ebenso danke ich der AG *EnRi*, die mich als Gast Teil ihrer Arbeitsgruppe werden ließ und mir stets mit Rat und Tat zur Seite gestanden hat – insbesondere *Alexandra Schneider und Kathrin Wolf*. Vielen Dank für all die Möglichkeiten, von euch zu lernen, für eure enorme Unterstützung und Betreuung bei allen umweltspezifischen Projekten.

Diese Promotionszeit wäre jedoch nicht dieselbe gewesen ohne meine wunderbaren PhD-Kolleg*Innen und meinen „Helmholtz-Boulder-Pals“. Durch gemeinsame Mittagspausen und viele schöne Momente abseits des Schreibtischs sind Freundschaften entstanden. Ein besonderer Dank gilt unserer kleinen *„Selbsthilfegruppe“ – Lisa, Sarah und Anne* – mit denen ich gemeinsam gestartet bin, sowie *Max, Nikos und Yueli,* die uns Neulinge mit offenen Armen empfangen haben.

Meinen Freundinnen und Freunden aus München und Füssen verdanke ich so viele wertvolle Auszeiten, die mir neue Energie geschenkt haben und mich immer wieder auf andere Gedanken bringen konnten.

Abschließend möchte ich mich von Herzen bei meiner Familie bedanken - ohne euch wäre all das nicht möglich gewesen. Mein Dank gilt meinem Freund *Felix*, der mich immer unterstützt, zum Lachen bringt und mir den Rücken freihält. Danke, dass du an meiner Seite bist. Ein besonderer Dank geht auch an meine *Schwester Ines* sowie an *meine Eltern, Elke und Udo*, für ihre bedingungslose Unterstützung, Zuversicht und ihr unerschütterliches Vertrauen. Ich selbst hätte nie gedacht, dass ich einmal promovieren würde – aber ihr habt immer an mich geglaubt.

List of publications

Publications included in this cumulative thesis:

Niedermayer F, Su Y, von Kruchten R, Thorand B, Peters A, Rathmann W, . . . Rospleszcz S. Trajectories of glycaemic traits exhibit sex-specific associations with hepatic iron and fat content: Results from the KORA-MRI study. Liver Int. 2023;43(10):2153-66. https://doi.org/10.1111/liv.15635.

Niedermayer F, Wolf K, Zhang S, Dallavalle M, Nikolaou N, Schwettmann L, . . . Peters A. Sex-specific associations of environmental exposures with prevalent diabetes and obesity - Results from the KORA Fit study. Environ Res. 2024;252(Pt 3):118965. https://doi.org/10.1016/j.envres.2024.118965.

Submitted manuscript versions of these publications are included in the appendix of this thesis:

Niedermayer F, Rospleszcz S, Matthiessen C, Hoffmann B, Stoecklein S, Haueise T, . . . Peters A. Associations of road traffic noise with adipose tissue depots and hepatic fat content - Results from the German National Cohort (NAKO). Environ Int. 2025;201:109566. https://doi.org/10.1016/j.envint.2025.109566.

Niedermayer F, Hoffmann B, Zhang B, Chen J, Hart JE, Laden F, . . . Peters A. Sex-specific individual and joint associations of multiple environmental exposures with diabetes and obesity in the population-based German National Cohort (NAKO). Environ Res. 2026;297:124096. https://doi.org/10.1016/j.envres.2026.124096.

Conference presentations (of included manuscripts of this thesis):

Niedermayer F, Wolf K, Zhang S, Dallavalle M, Schneider A, Peters A. Association of multiple environmental risk factors with prevalent diabetes mellitus and obesity - Results from the population-based KORA FIT cohort in Augsburg, Germany. In: ISEE, editor. 34th Annual Conference of The International Society for Environmental Epidemiology; 2022; Athens, Greece: Environmental Health Perspectives; 2022.

Niedermayer F, Wolf K, Zhang S, et al. How associations of environmental exposures with prevalent diabetes and obesity vary in complexity - Results from the KORA Fit study. presented at: 18 Jahrestagung DGEpi: Epidemiologie im Wandel - Innovationen und Herausforderungen 2023; Würzburg, Germany. https://2023.dgepi.de/wp-content/uploads/2023/09/Abstractbook__DGEpi2023_.pdf

Niedermayer F, Su Y, von Kruchten R, et al. Trajectories of glycaemic traits exhibit sex-specific associations with hepatic iron and fat content: Results from the KORA-MRI study. presented at: 18 Jahrestagung DGEpi: Epidemiologie im Wandel - Innovationen und Herausforderungen 2023; Würzburg, Germany. https://2023.dgepi.de/wp-content/uploads/2023/09/Abstractbook__DGEpi2023_.pdf

Niedermayer F, Rospleszcz S, Matthiessen C, Hoffmann B, Stöcklein S, Schlett CL, . . . Peters A. Sex-specific associations of traffic noise with adipose tissue traits and hepatic health 36th Annual Conference of the International Society of Environmental Epidemiology; Santiago de Chile: Environmental Health Perspectives; 2024.

Other publications:

Niedermayer F, Schauberger G, Rathmann W, Klug SJ, Thorand B, Peters A, Rospleszcz S. Clusters of longitudinal risk profile trajectories are associated with cardiometabolic diseases: Results from the population-based KORA cohort. PLoS One. 2024;19(3):e0300966. https://doi.org/10.1371/journal.pone.0300966.

Shugaa Addin N, **Niedermayer F,** Thorand B, Linseisen J, Seissler J, Peters A, Rospleszcz S. Association of serum magnesium with metabolic syndrome and the role of chronic kidney disease: A population-based cohort study with Mendelian randomization. Diabetes Obes Metab. 2024;26(5):1808-20. https://doi.org/10.1111/dom.15497.

Wolf K, Dallavalle M, **Niedermayer F**, Bolte G, Lakes T, Schikowski T, . . . Hoffmann B. Environmental exposure assessment in the German National Cohort (NAKO). Environ Res. 2025;273:121259. https://doi.org/10.1016/j.envres.2025.121259.

Affidavit

LMU | LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN | Dekanat Medizinische Fakultät Promotionsbüro

Eidesstattliche Versicherung

Niedermayer, Fiona

Name, Vorname

Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Thema:

Metabolic diseases and related traits: Novel epidemiological approaches and environmental determinants

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

München, 01.03.2026

Ort, Datum

Fiona Niedermayer

Unterschrift Doktorandin/Doktorand

Confirmation of congruency

LUDWIG-
MAXIMILIANS-
UNIVERSITÄT
MÜNCHEN

Dekanat Medizinische Fakultät
Promotionsbüro

Erklärung zur Übereinstimmung der gebundenen Ausgabe der Dissertation mit der elektronischen Fassung

Niedermayer, Fiona

Name, Vorname

Hiermit erkläre ich, dass die elektronische Version der eingereichten Dissertation mit dem Titel:

Metabolic diseases and related traits: Novel epidemiological approaches and environmental determinants

in Inhalt und Formatierung mit den gedruckten und gebundenen Exemplaren übereinstimmt.

München, 01.03.2026

Ort, Datum

Fiona Niedermayer

Unterschrift Doktorandin/Doktorand