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Long-term Exposure to Environmental Factors and Risk of Metabolic Disorders in Children

vorgelegt von:
Mahnaz Badpa

aus:
Gorgan

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Ludwig-Maximilians-Universität München

Erstes Gutachten von:	Prof. Dr. Annette Peters
Zweites Gutachten von:	Prof. Dr. Dennis Nowak
Drittes Gutachten von:	Prof. Dr. Christa Meisinger
Viertes Gutachtes:	Prof. Dr. Anne Hilgendorff

Dekan: **Prof. Dr. med. Thomas Gudermann**

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*To my **Husband**,*

*To my **Mom** and **Dad**,*

*And to the women in Iran fighting for **#woman_ life_ freedom***

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List of abbreviations

BMI	Body mass index
CI	Confidence interval
CVD	Cardiovascular disease
DiMelli	Diabetes Mellitus Incidence DiMelli cohort study
GAM	Generalized additive model
HR	Hazard ratio
IPCC	Intergovernmental Panel on Climate Change
IQR	Interquartile range
LAN	Light at night
NDVI	Normalized difference vegetation index
NO_x	Nitrogen oxide
NO_2	Nitrogen dioxide
O_3	Ozone
OR	Odds ratio
PM	Particulate matter
PM_{10}	Particulate matter with an aerodynamic diameter ≤ 10 μm
$PM_{2.5}$	Particulate matter with an aerodynamic diameter ≤ 2.5 μm
$PM_{2.5abs}$	$PM_{2.5}$ absorbance
PM_{coarse}	Particulate matter with an aerodynamic diameter > 2.5 μm and ≤ 10 μm
PNC	Particle number concentration
SD	Standard deviation
SES	Socioeconomic status
SO_4	Sulfate
T1D	Type 1 diabetes
T2D	Type 2 diabetes
WHO	World Health Organization

List of publications

This thesis consists of the following publications:

Badpa M, Wolf K, Schneider A, Winkler C, Haupt F, Peters A, Ziegler AG. Association of long-term environmental exposures in pregnancy and early life with islet autoimmunity development in children in Bavaria, Germany. Environmental Research. 2022 Sep 1;212:113503.

Badpa M, Schneider A, Ziegler AG, Winkler C, Haupt F, Wolf K, Peters A. Outdoor light at night and Children's body mass: A cross-sectional analysis in the Fr1da study. Environmental Research. 2023 Jun 3:116325.

Badpa M, Schneider A, Schwettmann L, Thorand B, Wolf K, Peters A. Air pollution, traffic noise, greenness, and temperature and the risk of incident type 2 diabetes: Results from the KORA cohort study. Environmental Epidemiology. 2024 Apr 1;8(2):e302. (Appendix)

Contribution of the Ph.D candidate

The thesis comprises two manuscripts published in Environmental Research, a prestigious international peer-reviewed scientific journal ranked among the top 12% of Environmental Sciences Journals, as per Journal Citations Reports® 2022.

In both publications, I played a central role as the first author, taking responsibility for developing the specific focus and the research question, creating comprehensive statistical analysis plans, preparing and managing the data, creating R scripts, conducting statistical analyses, and interpreting the results, under the supervision of Dr. Alexandra Schneider, Dr. Kathrin Wolf, Prof. Annette Peters, and Prof. Anette-Gabriele Ziegler. I also took the lead in writing the first complete draft of the manuscripts and incorporated the valuable feedback from co-authors to finalize them. As the corresponding author, I managed the submission and publication process, handled all comments from the journal's peer reviewers, revised the manuscripts as required, and ensured a smooth proofreading and post-production process.

Throughout this journey, I presented the research and findings in two Thesis Advisory Committee meetings and thoughtfully considered the feedback provided by the committee members to strengthen the overall quality of the work.

Additionally, this thesis includes (in the appendix) a third manuscript currently under review in the Journal of Environmental Epidemiology, where I am again the first and corresponding author. For this manuscript, I was actively involved in data preparation, developing the statistical analysis plan, creating R scripts and conducting statistical analyses, interpreting the results, and drafting the manuscript. As the corresponding author for this manuscript as well, I effectively managed the entire submission process, ensuring that all aspects were handled.

Summary

Epidemiological studies have yielded evidence that environmental pollution can adversely influence human metabolic health, including conditions such as diabetes and obesity. However, the existing literature has mainly focused on adults or the elderly, leaving a gap in the knowledge about the risks in children. Moreover, potential mechanisms through which early-life exposures may affect children's metabolism require more evidence. To address this gap, the main objective of this research work was to explore associations between exposure to environmental factors and the risk of metabolic disorders during early childhood, using data from a large-scale public health screening of children in Bavaria, Germany.

Long-term exposure estimates of air pollutants, air temperature, greenness, and light at night for each participant's residence were assessed using high-resolution data from reliable sources.

Two important aspects of children's health were studied in this thesis. In the first publication, a novel approach was employed to investigate the associations between prenatal and early life exposure to air pollution, air temperature, and surrounding greenness, and the development of islet autoimmunity (a crucial precursor of type 1 diabetes). This study used high temporal-spatial resolution data to examine different exposure windows in 85,251 children at the zip code level and 52,636 children at the residential level, all aged between 1.75 and 5.99 years. The results showed a higher risk of islet autoimmunity with decreasing air temperature. In the second publication, the effects of outdoor artificial light at night on body mass were investigated among 62,212 children younger than 11 years, and the analyses revealed significant positive associations, with the effects being more pronounced in boys.

In conclusion, this thesis significantly advances our understanding of the adverse health impacts of environmental factors on children's metabolic health. While affirming prior research findings, it also introduces novel evidence and strengthens the existing body of knowledge. This study stands as one of the first to examine the effects of a wide range of environmental factors on children's metabolic health. Nevertheless, further research is needed to gain a deeper understanding of the associations and to explore the underlying mechanisms. Moreover, the impacts of environmental factors on children's health should be further investigated across

different geographic regions with different exposure patterns and with the incorporation of behavioral and lifestyle data.

Zusammenfassung

Epidemiologische Studien haben gezeigt, dass sich Umweltverschmutzung negativ auf die menschliche Stoffwechselgesundheit auswirken kann, einschließlich Erkrankungen wie Diabetes und Adipositas. Die vorhandene Literatur konzentriert sich jedoch hauptsächlich auf Erwachsene oder ältere Menschen, so dass eine Wissenslücke bzgl. der Risiken bei Kindern besteht. Auch die potenziellen Mechanismen, durch die frühkindliche Expositionen den Stoffwechsel von Kindern beeinflssen können, benötigenweiter evidenz. Um diese Lücke zu schließen, bestand das Hauptziel dieser Forschungsarbeit darin, Zusammenhänge zwischen der Exposition gegenüber Umweltfaktoren und dem Risiko von Stoffwechselstörungen in der frühen Kindheit zu untersuchen. Hierzu wurden Daten aus einem groß angelegten Public Health Screening von Kindern in Bayern verwendet wurden.

Anhand von hochauflösenden Daten aus zuverlässigen Quellen wurden für den Wohnort jedes Teilnehmenden Langzeitexpositionsschätzungen für Luftschadstoffe, Lufttemperatur, Grünflächen und Lichtexposition bei Nacht abgeschätzt.

Im Rahmen dieser Forschung wurden zwei wichtige Aspekte der Gesundheit von Kindern untersucht. In der ersten Veröffentlichung wurden ein innovativer Ansatz verfolgt, der die Untersuchung verscgidener Expositionszeitfenster mit hochauflösenden zeitlich-räumlichen Daten einschloss. Dieser ansatz diente dazu, die Zusammenhänge zwischen vorgeburtlicher und frühkindlicher Exposition gegenüber Luftschadstoffen, Lufttemperatur, und Grünheit, und der Autoimmunität der Inselzellen (eine entscheidende Vorstufe von Typ-1-Diabetes) bei 85,251 Kindern auf Postleitzahl- und bei 52,636 Kindern auf Wohngebietsebene im Alter zwischen 1.75 und 5.99 Jahren untersucht. Die Ergebnisse zeigten ein höheres Risiko für Inselzellen-Autoimmunität mit abnehmender Lufttemperatur. In der zweiten Veröffentlichung wurden die Auswirkungen von nächtlichem künstlichem Licht im Freien auf die Körpermasse von 62,212 Kindern im Alter von unter 11 Jahren untersucht. Die Analysen ergaben signifikante positive Zusammenhänge, wobei die Auswirkungen bei Jungen stärker ausgeprägt waren.

Zusammenfassend lässt sich sagen, dass diese Dissertation unser Verständnis für die negativen gesundheitlichen Auswirkungen von Umweltfaktoren auf die meabolische Gesundheit vn Kindern erheblich erweitert. Sie bestätigt frühere forschungsergebnisse und liefert darüer hinaus neue, die

bestehendenErkentnisse Stärkende epidemiologische Evidenz. Diese Studie gehört zu den ersten, die die auswirkunken eines breiten spektrums von umweltfaktoren auf die metabolische Gesundheit von Kindern untersuchen. Dennoch ist weitere Forschung erfordlich, um ein tieferes Verständnis dieser Zusammenhänge zu erlangen und die zugrunde liegenden Mechanismen zu erforschen. Außerdem sollten die Auswirkungen von Umweltfaktoren auf die Gesundheit von Kindern in verschiedenen geografischen Regionen mit unterschiedlichen Expositionsmustern und unter Einbeziehung von Verhaltens- und Lebensstildaten weiter untersucht werden.

I. Introductory Summary

1. General Introduction

The term environmental pollution has been recognized globally for a long time, and its impacts on humanity and the environment have been evident since early human settlements (1,2). Archaeological findings provide evidence of pollution from past human activities. Initially, pollution was not considered a significant problem and its effects were not perceived as harmful (3). However, with rapid population growth and the establishment of permanent settlements, pollution emerged as a major problem affecting both human well-being and the environment (4,5). As human population density rises, so does the intensity of human activities, leading to a concomitant increase in the environmental impact. These impacts extend beyond humans to affect aquatic and terrestrial animals, as well as microorganisms, which, due to their abundance and diversity, play a crucial role in sustaining the ecosystem's biogeochemical functions (6). The Earth is currently facing numerous challenges caused by human activities, triggered mainly by the Industrial Revolution (4). These challenges have led to irreparable damage, including toxic emissions from fossil fuel combustion, disposal of harmful effluents into water bodies, deforestation due to urbanization, and soil productivity decline from plastic waste littering (3). Despite significant recent efforts to address environmental pollution, the problem persists, posing ongoing health risks (7). The importance of environmental factors in determining the health of human populations is becoming increasingly evident. Over the past decades, global concern has grown substantially regarding the public health consequences associated with environmental pollution (8). According to the World Health Organization (WHO), environmental risks were responsible for around 12.6 million deaths in 2012, constituting approximately 22% of the global burden of disease (Figure 1) (9). Furthermore, in 2015, it was estimated that pollution-related ill-health resulted in 9 million premature deaths, surpassing the combined mortality rates of malaria and tuberculosis (10). Undoubtedly, the challenges are most observed in developing regions, where traditional pollution sources significantly impact a large proportion of the population. However, even in developed countries, environmental pollution remains a persistent issue (11).

Figure 1. Worldwide distribution of disease burden attributable to environmental risks in 2012. Reprinted from World Health Organization, Prüss-Ustün, A., Wolf, J., Corvalán, C., Bos, R. & Neira, M. Preventing disease through healthy environments: a global assessment of the burden of disease from environmental risks, copyright (2016).

1.1. Major sources of environmental factors

The sources of environmental exposure include various aspects of pollution. For instance, air pollution, primarily caused by industrial emissions and intensive human activities, introduces harmful particulate matter and gases into the atmosphere, affecting both local and global environments. Depending on their origin, air pollutants can lead to severe health consequences for both humans and other living organisms (12). Water pollution results from both natural processes and human activities, with significant consequences for aquatic life and human health, and can cause health hazards and death of human beings as well as aquatic life (6,13). Urbanization and industrial growth also produce noise pollution, which has a detrimental effect on people's health. Noise pollution is mainly caused by unwanted sounds made by road and rail traffic, airplanes, industrial machinery, and other sources, which can directly and indirectly impact physical human health (14), but also result in psychological problems such as anxiety, and stress (15,16). Additionally, as climate change accelerates, extreme temperature events are becoming more frequent and intense. The observed change in global temperature patterns can increase the risk of heat- and cold-related illnesses (17). According to the Intergovernmental Panel on Climate Change (IPCC), as the global average temperature continues to rise, more heatwaves and heat extremes are expected (18). Finally, urbanization, economic growth,

and new technologies especially in modern societies have led to the widespread use of artificial light, known as light pollution, which affects both natural ecosystems and human health (19,20).

1.2. Impacts on human health

Environment significantly influences human health. Depending on the composition of pollutants, the concentration, and the time of exposure, environmental factors can cause a wide range of acute and chronic diseases (3,21,22). In 2015, air pollution caused 6.4 million deaths around the world, of which 4.2 million were due to exposure to air pollution. During that year, poor-quality air was responsible for 19% of cardiovascular deaths, 21% of strokes, and 23% of lung cancers worldwide (23). Systematic reviews reported an association between high levels of air pollutants, especially fine particulate matter (24), and an increased risk of type 2 diabetes (T2D) and other metabolic disorders. T2D, a chronic condition characterized by insulin resistance and dysfunction of β cells, is a rapidly rising public health concern. Although genetics plays a crucial role, environmental exposures are suggested to have significant impacts on the development of the disease (25). Studies suggest that air pollution may potentially lead to impaired glucose metabolism and insulin resistance (26,27). Exposure to particulate matter (PM), including particles with a median aerodynamic diameter < 10 μm (PM_{10}) and <2.5 μm ($PM_{2.5}$), has also been linked to adverse pulmonary effects such as respiratory symptoms and decreased lung function, cardiovascular diseases (CVD) (28), and cancers (29). Oxidative stress and inflammation are suggested to be key pathways in these associations (30).

Exposure to higher levels of traffic noise is associated with various negative health effects, including myocardial infarction (31), sleep disruption (32), metabolic complications (33), and diabetes (34). According to the European Environment Agency, approximately 22 million individuals experience chronic high annoyance, while 6.5 million suffer from sleep disturbance, both due to long-term exposure to noise pollution (35). A meta-analysis also revealed that traffic noise is among the top four environmental factors with the most significant impacts on human health, resulting in 400-1500 Disability-Adjusted Life Years (DALYs) per million population in Europe (36). Traffic noise exposure acts as an environmental stressor, affecting psychological and physiological processes which may lead to changes in stress hormone levels and increased blood pressure and heart rates (37). However, despite noise levels above recommended guidelines being widely experienced by the general population, it has not been sufficiently addressed in the Global Burden of Disease (GBD) study (38).

The impact of ambient temperature on morbidity and mortality is an important public health concern as there is evidence of a large number of hospitalizations during both heat waves and cold spells (39,40). Temperature extremes are widely evident to increase the risk of mortality and morbidity from cardio-respiratory conditions and diabetes (41,42). According to the literature, urban residents in larger cities are more exposed to temperature changes compared to residents of suburban areas and are at a higher risk of heat-related illnesses (43). Depending on the time scale, ambient temperature may have different health effects. High temperatures have been more commonly associated with immediate impacts, while low temperatures have shown more delayed health effects (44,45). Moreover, ambient temperature plays an important role in air pollution-health associations (46). For example, studies revealed that low temperatures significantly amplified the effect of $PM_{2.5}$, PM_{10}, SO_2, and O_3 levels on chronic obstructive pulmonary disease (COPD) hospitalization rates (47,48).

Green spaces affect human population in multifaceted ways, with evidence indicating its significant impact on health and well-being. Studies have shown that increasing the quantity and quality of natural environments, such as gardens, parks, and open spaces in residential areas can lead to various positive health outcomes (49,50). These effects are supposed to be mediated through several potential effect mechanisms including increased opportunities for physical activity and social interactions (51), mental health recovery (52), relaxation and stress reduction (53,54), and reductions in air and noise pollution (55). Recent studies using satellite imagery to measure neighborhood greenness or vegetative presence have shown associations with lower body mass index (BMI) (56) and a reduced risk of overweight or obesity (57) and CVD (58).

Artificial light at night (LAN) is linked to a range of health problems, with disruption to the biological clock and the suppression of melatonin production being among the most common consequences (59), which could potentially increase the risk of cancers, including breast and prostate cancers, as reported in ecological and observational studies (60–62). Beyond cancer, LAN-induced sleep disturbance might affect metabolism and contribute to several health issues such as heart disease, diabetes, and obesity (63).

1.3. Impacts on Children

The health effects of environmental exposures in children who are believed to be the group with the highest risk level have been widely evident (64–66). It is well evident that environmental factors are linked to the development of a wide range of health conditions in children, from cardiorespiratory diseases to metabolic disorders like diabetes and obesity (67–70). In recent years, researchers have increasingly focused on understanding how environmental factors affect children's health (71). Children, due to their unique physiological and behavioral characteristics, are more vulnerable to the effects of environmental exposures (72). Their organs are still developing and their immune systems are not fully mature, making them more susceptible to potential risks from environmental toxins and pollutants (73,74). Additionally, certain behaviors such as hand-to-mouth activity and increased contact with environmental surfaces may further increase their exposure to harmful substances (64). The significance of early-life exposure cannot be overstated. Research has shown that exposure during critical developmental stages, including prenatal and early childhood periods, can have long-lasting effects on children's health that extend into adulthood (75,76).

1.3.1. Air pollution and air temperature and islet autoimmunity

The increasing prevalence of autoimmune diseases has become a significant global public health concern, affecting millions of individuals worldwide, with children being especially vulnerable (77–79). Islet autoimmunity, characterized by autoantibodies targeting pancreatic islet cells, serves as a precursor to type 1 diabetes (T1D), a chronic and autoimmune disorder triggered by the destruction of insulin-producing cells in the pancreas (80). The epidemiological landscape of T1D has been extensively studied in recent decades, revealing substantial variations in disease incidence among countries and different racial groups (81). Although the causes of these differences have not been fully understood, it is increasingly evident that beyond genetics, environmental factors may significantly contribute to the initiation or modulation of the immune response that leads to islet autoimmunity and T1D (82,83). Ecological studies have reported geographic variations in T1D incident rates in different geographical scales, including global comparisons (81), Europe-wide assessments (84), and within individual countries (85), all indicating the importance of climate as a contributing factor. For instance, distinct differences in rates were observed in Finland (86), Norway (87), Sweden (88), England (89), and Germany (90). In Italy, the incidence rate in certain regions was almost four times higher than on

the mainland (91). Different hypotheses have been put forward to explain the geographical variations in islet autoimmunity and T1D rates, including the potential impact of environmental factors, but our knowledge regarding their connections is still developing.

Limited epidemiological research has been conducted to explore links between air pollution and the onset of childhood T1D. Nonetheless, early findings indicated that both maternal and early-life exposure could contribute to the disease development. For example, in Sweden, a case-control study investigated the impacts of prenatal exposure during gestation and found that mothers of children with T1D mostly resided in regions with higher nitrogen oxide (NO_x) levels in the third trimester or elevated ozone (O_3) levels in the second trimester (92). In the U.S., childhood exposure to O_3 was associated with increased risk of T1D. Also, PM_{10} showed associations with T1D development in children aged 5 and under, and sulfate (SO_4) was linked with diagnosis before the age of 15 (93,94). A prospective birth cohort study in Norway found that higher exposure to ambient nitrogen dioxide (NO_2) in the first year of life was associated with an increased risk of developing islet autoimmunity (95). The exact mechanisms underlying the link between air pollution exposure and the risk of islet autoimmunity are not fully understood. However, existing evidence suggests that air pollution-induced inflammation and oxidative stress play a crucial role in this pathway (96). Exposure to air pollutants like O_3 can generate free oxygen radicals that can lead to damage in β cells or increase the presentation of diabetogenic antigens, thereby increasing the susceptibility to T1D (97).

Air temperature shows significant variations across geographical regions and seasons, playing a crucial role in modulating human physiology and influencing various biological processes. Within Europe, a clear north-south gradient in T1D incidence rates has been identified, with the highest incidence rates observed in northern and north-western regions, characterized by cooler climates, while southern and eastern regions showed the lowest rates (98–100). In Germany, higher incidence rates in the northern regions compared to the southern parts were reported (90). Similarly in Sweden, the north-south pattern in incidence rate was observed. This could potentially be attributed to ambient temperatures, as the mean yearly temperature in Sweden has shown an inverse relationship with latitude (85). Although limited, epidemiological studies have further supported the link between air temperature and the risk of childhood islet autoimmunity. For instance, in Sweden, significant associations between T1D incidence and low mean temperature were observed (101,102). The consistent findings of seasonal patterns in the clinical onset of T1D, with the highest incidence occurring during the colder seasons, in both the northern and southern hemispheres, further strengthen

the evidence for the impact of low temperature on the risk of developing T1D (103–106). The mechanism behind this association is unclear, but it could be due to the impacts of low temperature on immune function and viral infections, which are known to contribute to the pathogenesis of T1D (107,108). Another reason could be the increased demand for insulin production on pancreatic β cells. In low temperatures, both healthy individuals and those at risk of developing islet autoimmunity have shown elevated fasting blood glucose levels and increased insulin levels. This suggests that a cooler environment may put more stress on β cells to maintain glucose homeostasis (109,110).

1.3.2. Light at night exposure and BMI

Childhood overweight and obesity is another health concern with an increasing prevalence worldwide. Even though the trend appears to have slowed down in recent years, the high prevalence rate remains concerning (111). The rise in childhood obesity has serious implications for future health, mainly through metabolic problems and diseases associated with it (112). Traditionally, risk factors for obesity focused on lifestyle behaviors such as unhealthy dietary habits, insufficient physical activities, or sedentary behaviors, all of which result in a chronic imbalance between energy intake and expenditure. However, recent studies suggest that environmental factors such as air pollution and LAN are likely involved as well (20,113,114). LAN has increasingly been recognized as a disruptor of natural light patterns and a new source of environmental pollution (115). The exposure could disrupt the human circadian rhythm by suppressing melatonin secretion (116), even at dim light intensities (117). Investigation of outdoor LAN exposure revealed its contribution to the development of chronobiology-related disorders such as obesity (118), cancers (119,120), and CVD (121). There is only limited research on LAN exposure's impact on children's health. In China, both indoor (70) and outdoor (20) LAN exposures were associated with increased odds of obesity and overweight in children and adolescents. The findings were further supported by studies that reported children living in brighter areas in China (122), Germany (123), and the U.S. (124) had a higher prevalence of sleep disorders, including disruptions in sleep patterns and duration, which are potential contributors to the obesity risk (125,126).

2. Objectives

In light of the evidence highlighting the significant influence of environmental factors on metabolic health, it becomes essential to gain a deeper understanding. While an increasing amount of research is investigating the effects of the environment on health outcomes in adults, there remains a gap in our knowledge concerning children's health. This lack of sufficient evidence poses a barrier to the implementation of effective policies and interventions aiming at promoting metabolic health in this vulnerable group. In addition, given that early life is a critical period for metabolic development, it is necessary to investigate the effects of environmental factors among pediatric populations.

This cumulative thesis aims to bridge this gap by extensively investigating the influence of various exposures on metabolic health outcomes, with the main focus on early-life exposure in children.

The specific objectives of this thesis are:

1. To investigate the effects of long-term exposure to air pollution, ambient air temperature, and the level of nearby greenery throughout pregnancy and the initial years of life with early-onset islet autoimmunity.

2. To explore the long-term effects of nighttime exposure to artificial light on the body mass of children.

Beyond the two main papers, this thesis incorporates a supplementary paper in the appendix with the primary objective being:

1. To examine the long-term effects of air pollutants, traffic noise, ambient air temperature, and surrounding greenness on incident T2D in adults.

3. Methods

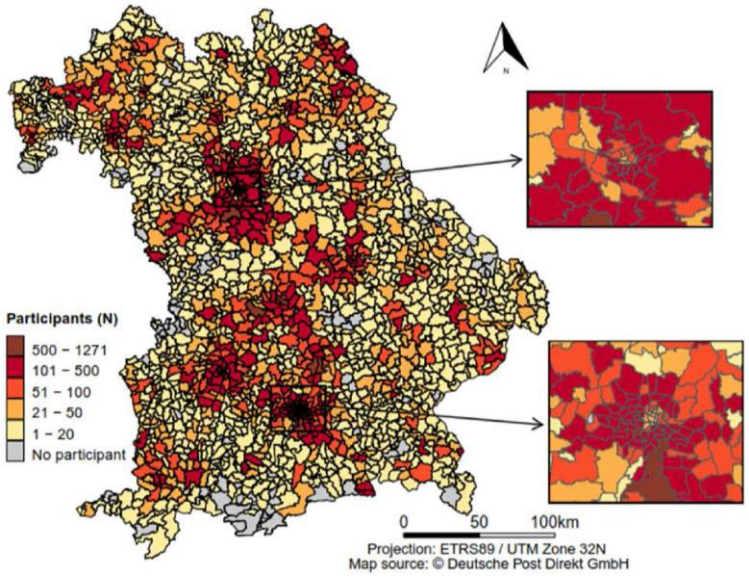
3.1. Study population and design

This cumulative thesis is based on data from the Fr1da cohort study, a large-scale screening program for T1D in Bavaria, Germany. The study was initiated in 2015 and aims to identify children at increased risk for T1D at an early stage, which allows for timely intervention and prevention of complications. The screening process involved the analysis of islet autoantibodies in capillary blood samples taken through a blood spot test. In the context of a well-baby visit, a questionnaire was administered to collect demographic data, including the children's date of birth, sex, weight, height, date of blood collection, residential address, and first-degree family history of T1D. Children with positive autoantibody results were referred for confirmatory diagnostic testing, and those diagnosed with early-stage T1D received early treatment to prevent complications (127). The data used in this thesis were obtained from the Fr1da database and included information on demographic characteristics and screening results for over 90,000 children recruited between 2015 and 2019. The data were collected and managed by the Fr1da study team following strict data protection regulations and were pseudonymized before analysis.

In publication 1, we analyzed data from 85,251 Fr1da participants aged 1.75 to 5.99 years who had valid residential zip code data (Figure 2a). For 52,636 participants, we had access to their full residential address information, which enabled a more precise exposure assessment.

In publication 2, we expanded our analysis to include a larger sample size of Fr1da participants, comprising a total of 62,630 children under the age of 11 who provided complete and accurate residential details (Figure 2b).

a)



b)

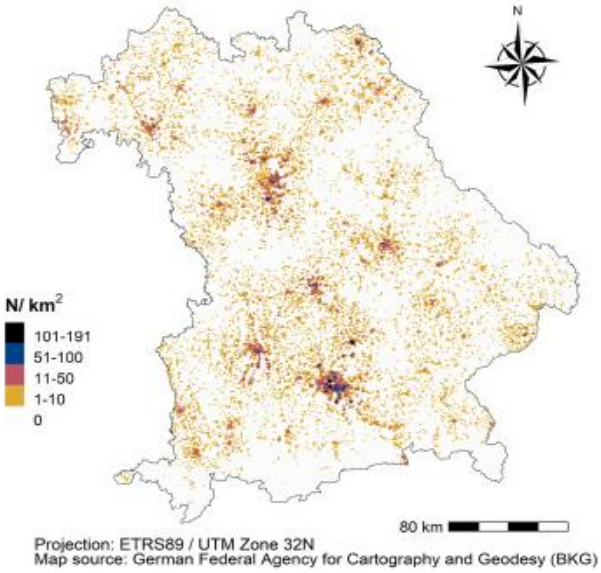


Figure 2. Spatial distribution of study subjects across the Bavarian region in Germany. Panel (a) displays the participant counts per postal code area for the first study and panel (b) presents number of the participants within 1 km × 1 km grid cells for the second study.

3.2. Address geocoding

Residential addresses for more than 100,000 Fr1da participants were geocoded using the 'Adressen-Batch' geocoder application provided by the Federal Agency for Cartography and Geodesy* (128), using the coordinate reference system known as Universal Transverse Mercator (UTM-32) for location determination. Those addresses that did not meet the required match score were manually reviewed and corrected. The final geocodes' positional accuracy was confirmed by cross-referencing a selection of coordinates with Google Maps.

3.3. Outcome definition

Islet autoimmunity was characterized by the identification of minimum of two islet autoantibodies in two sequential blood samples. This definition ensures that the presence of islet autoimmunity is confirmed through repeated testing, reducing the likelihood of false positives and increasing the reliability of the results.

The BMI of each participant was calculated using their height and weight measurements. Subsequently, BMI z-scores specific to age and sex were computed, with reference to the World Health Organization Child Growth Standards (127).

3.4. Exposure assessment and data source

To assess the association between environmental exposures and the risk of islet autoimmunity development, hourly measurements of particulate matter with an aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) were provided by the German Environment Agency† at a spatial resolution of approximately 2 km × 2 km (129). Daily mean air temperature maps were generated through a multi-stage modeling approach at a 1 km × 1 km resolution, incorporating weather station observations, satellite-based land surface temperature, elevation, vegetation, and land use

* *Bundesamt für Kartographie und Geodäsie (BKG)*

† *Umweltbundesamt (UBA)*

predictors (130). Greenness exposure was assessed using monthly average Normalized Difference Vegetation Index (NDVI) data from TERRA MODIS satellite images at a spatial resolution of 1 km × 1 km (131). All exposure data were captured from 2008 to 2019, with a consistent temporal resolution. Exposure values were matched with residential address points and also averaged over zip codes for the epidemiological analyses. We assessed mean exposure during pregnancy, the first year, and the first two years of life for each exposure variable to capture critical developmental periods.

The assessment of artificial light at night (LAN) exposure involved the use of monthly and annual mean raster grids sourced from Visible Infrared Imaging Radiometer Suite (VIIRS) with a spatial resolution of 300 m × 400 m (132,133). The raster grids were matched with participants' residential addresses based on the spatial location, to extract their exposure values. Exposure to LAN was assessed by averaging the raster grids during the reference year of the study (2015) and the12 months preceding the screening month.

3.5. Statistical analysis

Cross-sectional associations between exposure variables and the risk of islet autoimmunity were assessed using generalized additive models in both single-exposure and multi-exposure settings. The models were adjusted for age, sex, family history for T1D, and area-level socioeconomic status (SES) variables.

The associations between LAN and BMI z-scores were examined using generalized additive models without and with adjustment for confounders such as demographic charcteristics (age and sex) and socioeconomic factors (the percentage of low-income households (earning <1200 € per month) at a 1 × 1 km^2 grid resolution, and residential urbanization levels where 1indicated cities with high levels of urbanization, 2 represented towns/suburbs with intermediate levels of urbanization and, 3 indicated rural areas with low levels of urbanization)). In cases where BMI z-scores were missing, a deterministic imputation method was employed using regression predictions. Additionally, we explored effect modification by sex by the inclusion of interaction terms.

In both studies, the reliability and validity of our findings were ensured by analyzing an independent sample as a means of replication. In the first paper, we used data from the Diabetes Mellitus Incidence (DiMelli) cohort study, which monitored T1D incidence in children aged ≤20 in Bavaria from 2009 to 2012 (134). We substituted the cases that tested positive in the Fr1da study with T1D cases from

DiMelli who aged 6 years or under (N = 150) and reanalyzed the data. In the second paper, we replicated the main analyses using data for 39,782 children in the second phase of Fr1da screening, known as Fr1da PLUS, conducted in the same study area from 2019 to 2021, with the recruitment, screening, data collection, consent procedures, and variables measured being identical to the original Fr1da study.

4. Key findings

The first publication addresses the first key objective outlined in this thesis: the investigation of associations between exposure to different environmental factors during pregnancy and early childhood and the oncet of islet autoimmunity.

The results showed that at the level of individual addresses, lower ambient air temperature averages during pregnancy and early life were significantly associated with a higher risk of islet autoimmunity. Specifically, for each interquartile range (IQR) decrease in air temperature, the odds ratios (ORs) for islet autoimmunity were 1.49 (95% confidence interval (CI): 1.21–1.83) during pregnancy, 1.28 (95% CI: 1.06–1.54) in the first year, and 1.25 (95% CI: 1.05–1.49) in the first two years of life. These associations remained stable after accounting for additional environmental variables in multi-exposure models.

At the level of zip codes, a similar inverse association was observed for air temperature exposure during pregnancy (OR: 1.28 (95% CI: 1.04–1.57)). However, the effect estimates for the first year and first two years of life exposures were less pronounced and lacked statistical significance.

The association of air pollutants and greenness did not reach statistical significance; however, the effect estimates remained consistent at both exposure levels.

- **Key finding 1:** Prenatal and early-life exposure to lower air temperature increased the risk of early-onset islet autoimmunity. The associations remained independent of the effects of air pollutants or greenness and were evident at both address- and zipcode-level exposures.

The second publication addresses the second key objective of this thesis: the investigation of associations between LAN exposures and BMI z-score.

The study demonstrated a significant and positive link between LAN exposure and BMI z-scores. The results showed that by each 10 $nW/cm^2/sr$ increase in LAN, BMI z-scores increased by 32.2% (95% CI: 23.6-40.8) at baseline and by 31.1% (95% CI: 22.7-39.5) within one year before screening. The associations remained significant even when accounting for age, sex, percentage of households with low income, and level of urbanization. The study also revealed a significant modification of the associations by sex with stronger effects of LAN in male individuals compared to female individuals.

- **Key finding 2:** Exposure to higher levels of LAN increased age- and sex-adjusted BMI significantly. Sex had a modifying effect with the effect of LAN being more pronounced in male individuals.

5. Discussion

This thesis significantly adds to the existing knowledge in the field of long-term exposure to environmental factors and their effects on children's health. The study extensively investigated the influence of air pollution, air temperature, greenness, and light pollution on metabolic health outcomes in children and yielded two key findings: firstly, a decrease in air temperature significantly raises the odds of early-onset islet autoimmunity, and secondly, an increase in outdoor LAN is linked to increased body mass in children. So far, only a few epidemiological studies have investigated the association between environmental exposures and children's metabolic health. Therefore, this research work substantially bridged the existing gap in the field of environmental risks.

5.1. Plausible biological mechanisms

There are several putative pathways explaining the associations found in this research work.

Temperature and islet autoimmunity Potential mechanisms to explain the increased risk of early-onset islet autoimmunity with low temperatures include:

1. Increased demand on β cells for insulin secretion in low temperatures. This was supported by studies considering seasonality which reported lower glucose values and lower insulin secretion during warmer seasons (109,135).
2. Exposure to viruses during fetal life in low temperatures. Population-based studies have shown increased levels of antibodies to enteroviruses in pregnant mothers whose children later developed T1D (136,137). Laboratory investigations further reported that certain viruses, such as coxsackie, can induce T1D in animals (138,139). Even though the exact mechanism is not yet fully understood, it is hypothesized that direct mimicry of autoantigens or persistent viral infections may lead to chronic inflammation near or within β cells. Inflammatory responses such as cytokine release may contribute to the destruction of β cells (135).
3. Vitamin D deficiency in cooler climates is caused by reduced sunlight exposure and ultraviolet irradiance. According to recent investigations, vitamin D plays a role in modifying the immune-mediated destruction of β cells by interacting with vitamin D receptors and proteins

that bind calcium (140). It also increases insulin secretion by regulating calcium flux and other mechanisms within β cells (141,142).

LAN and BMI Possible pathways connecting night-time light to higher BMI include:

1. Disrupted circadian rhythm. Prolonged or constant exposure to artificial lights can disrupt natural circadian timing which affects the entire physiological state. This includes changes in the rhythmicity of various hormones that may lead to irregulated metabolic function, immune responses, and endocrine balance (121).
2. Insufficient sleep due to sleep-wake cycle disturbance. Meta-analysis of epidemiological studies reported positive associations between sleep duration with higher body mass (125) and negative associations with waist circumference (143). Research suggests that short sleep duration might trigger hormonal responses that increase appetite and calorie intake. Changes in the levels of hormones such as leptin or ghrelin due to insufficient sleep could lead to increased hunger and obesity (144). Moreover, short sleep may activate inflammatory pathways that further contribute to obesity (145).
3. Suppressed nocturnal melatonin secretion. Melatonin is a pineal gland hormone, with higher levels during the night and minimal synthesis during the day. It plays an important role in transmitting timing information to organs and is essential for circadian timing in humans (146). Research findings have reported an inverse link between melatonin and body weight and adiposity. The association is believed to be independent of calorie intake and may be related to its simulation of brown body tissue (147). Studies in animals further revealed the effect of melatonin on improving metabolic parameters and reducing body weight (148).
4. Physiological and stress-related factors. Light exposure can promote oxidative stress, a critical factor in the pathogenesis of various disorders including obesity. Oxidative stress occurs due to an imbalance between free radicals, reactive oxygen species, and antioxidants in the human body (149,150). When organisms are exposed to light, they produce toxic molecules and reactive oxygen species (151). Melatonin and its metabolites play an important role in antioxidant defense and regulate antioxidant enzyme activity (152). Light-induced melatonin suppression could increase oxidative stress and potentially raise the risk of obesity.

5.2. Public health and policy implications

The findings of this thesis provide strong evidence of the adverse impacts of environmental hazards on metabolic health. The results have important public health implications.

Islet autoimmunity is a crucial precursor of T1D, a chronic metabolic condition with potentially serious lifelong effects (80). As global temperature fluctuations are expected to increase due to climate change (17), it becomes necessary for public health officials to acknowledge and address this environmental threat. Raising awareness among parents and healthcare providers regarding the potential effects of air temperature on metabolic health may encourage early detection and timely intervention. Such an approach could result in a substantial improvement in the overall health outcomes of children and prevent potential complications during adolescence and adulthood.

The relationship between light pollution and increased BMI in children was another public health implication of this thesis. Since pediatric obesity remains a major public health challenge, identifying environmental elements that contribute to the disease’s development becomes crucial for creating effective preventive strategies (111). Light pollution is a growing concern in urban areas and has been linked to a range of adverse health outcomes, such as disrupted sleep patterns and higher risks of chronic diseases (115). This study's results highlight that children are also susceptible to the consequences of excessive artificial light exposure. Addressing this issue requires multifaceted strategies that involve public health and legislators, urban planners, and communities. There is a need to develop and enforce regulations and guidelines that prevent or restrict excessive outdoor lighting and promote sustainable and responsible use of artificial illumination in residential areas. Moreover, health education initiatives will inform parents, educators, and the general public about the negative effects of prolonged light exposure during nighttime hours. Encouraging parents to implement healthy sleep practices and create dark environments in bedrooms can further mitigate the impact of light pollution on children's health.

By proactively addressing environmental exposures, we can take substantial steps to preserve children's health and promote a healthier and more sustainable future.

5.3. Methodological considerations

Major strengths of this research work include a large number of participants from a well-known screening study and the wide range of environmental factors being investigated.

The first publication stands as the most extensive assessment to date of the effect of geographical factors, including air pollution, air temperature, and surrounding greenness, on childhood islet autoimmunity. The unique strength is in the comprehensive examination of different exposure windows using high-resolution temporal-spatial data. The comprehensive nature of the study allowed us to investigate multiple exposures while controlling for confounding variables. The analysis approach employed in this study ensured reliable and robust results. Moreover, the publication highlighted the importance of early interventions for the high-risk population to mitigate the risk of developing T1D.

The second publication presents a novel investigation into the effects of artificial light emissions on pre-pubertal weight gain. This unique approach provided valuable insights into potential environmental contributors to obesity. High-resolution satellite data used in this study captured significant variations in LAN across urban areas and strengthened the results.

However, there are several limitations to consider. During the screening, it was presumed that the residential addresses provided were indicative of the relevant exposure locations. Unfortunately, we did not have access to information regarding changes in residence or the duration of time spent outside. This lack of data may have introduced uncertainty into the results due to the possibility of exposure misclassification. Moreover, the Fr1da study lacks comprehensive data on various behavioral and lifestyle variables typically employed as confounding factors or effect modifiers in epidemiological studies.

5.4. Outlook: Future research

In summary, this cumulative thesis indicated that early exposure to certain environmental factors increases the risk of adverse pediatric metabolic outcomes. The complex interplay between environmental factors and metabolic health in children necessitates ongoing research to deepen our understanding and develop effective interventions.

So far, the assessments of exposure-response associations in children were mostly cross-sectional analyses. Conducting longitudinal studies that track children's exposure levels from early ages into adolescence or even adulthood would be beneficial and could offer a more accurate understanding of the long-term effects of these factors as well as their role in shaping the trajectory of metabolic disorders over time.

The studies were based on data collected in Bavaria, Germany, and the results cannot be generalizable to the entire country or globally due to regional variations in both exposure and disease prevalence patterns. To achieve a comprehensive understanding, a comparison of results from investigations in diverse global populations is necessary.

Considering the potential confounding effect of behavioral and lifestyle factors such as physical activity, dietary habits, and sleep patterns is crucial to explore the true exposure-response associations.

6. Conclusion

The consequences of climate change and the rapid urbanization process are expected to result in higher human exposure to environmental pollutants or novel types of pollution. For instance, this could manifest as more temperature fluctuations due to climate change or the expanded use of electronic lighting in urban and industrial areas. Therefore, it is crucial to take action and mitigate these factors to protect human well-being. Findings from this thesis provide strong evidence of the influence of environmental hazards in children's metabolic health by highlighting significant associations between lower temperatures and higher islet autoimmunity as well as higher light pollution and higher body mass.

This research work concludes by emphasizing the need for continued research and collaborative efforts to ensure the harmonious coexistence between humans and environment and safeguard the health of current and future generations. Given the complexity of environmental hazards and intricate links between environmental pollution and human health, addressing their challenges necessitates a multidisciplinary approach involving scientists, policymakers, healthcare professionals, and communities.

II. Publications

Publication 1

Title: Association of long-term environmental exposures in pregnancy and early life with islet autoimmunity development in children in Bavaria, Germany

Authors: Mahnaz Badpa, Kathrin Wolf, Alexandra Schneider, Christiane Winckler, Florian Houpt, Annette Peters, Anette-Gebriele Ziegler

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Association of long-term environmental exposures in pregnancy and early life with islet autoimmunity development in children in Bavaria, Germany

Mahnaz Badpa [a,b,c,*], Kathrin Wolf [a], Alexandra Schneider [a], Christiane Winkler [c,d], Florian Haupt [c,d], Annette Peters [a,c,e,f,1], Anette-Gabriele Ziegler [c,d,g,1,**]

[a] Institute of Epidemiology, Helmholtz Zentrum München, Munich, Germany
[b] Institute for Medical Informatics, Biometrics and Epidemiology, Ludwig-Maximilians-Universität (LMU) Munich, Munich, Germany
[c] German Center for Diabetes Research (DZD), Munich, Germany
[d] Institute for Diabetes Research, Helmholtz Diabetes Center at Helmholtz Zentrum München, Munich, Germany
[e] Chair of Epidemiology, Faculty of Medicine, Ludwig-Maximilians-Universität München, Munich, Germany
[f] Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[g] Forschergruppe Diabetes, Chair of Diabetes and Gestational Diabetes, Faculty of Medicine, Technical University Munich at Klinikum Rechts der Isar, Munich, Germany

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ABSTRACT

Objective: Incidence of early-onset type 1 diabetes (T1D) has been increasing worldwide. Only few studies examined the relationship between geographical environmental variation and T1D incidence or its presymptomatic stage of islet autoimmunity. Our study aimed to investigate the effect of long-term environmental exposures during pregnancy and early life on childhood islet autoimmunity.

Research Design and Methods: We used data from the Fr1da cohort study which screened children aged 1.75–5.99 years for multiple islet autoantibodies in Bavaria, Germany between 2015 and 2019. We included 85,251 children with valid residential information. Daily averages for particulate matter with a diameter <2.5 μm, nitrogen dioxide, ozone, air temperature, and greenness were averaged for each zip-code or directly assigned to the addresses. The exposure windows included pregnancy, the first year and the first two years of life. Generalized additive models adjusting for individual and socioeconomic variables were used to investigate associations between environmental exposures and islet autoimmunity development.

Results: Islet autoimmunity was diagnosed in 272 children. Colder air temperature during pregnancy was associated with developing islet autoimmunity at the address (per 2.2 °C decrease, Odds ratio (OR): 1.49; 95% Confidence interval (CI): 1.21–1.83) and zip-code level (per 2.4 °C decrease, OR: 1.31; 95% CI: 1.08–1.59). Using the addresses, significant associations were also observed during the first years of life.

Conclusion: In this study, children's residential exposure to lower levels of air temperature during pregnancy and early life increased the risk of islet autoimmunity before the age of six.

1. Introduction

Type 1 diabetes (T1D) is one of the prevalent metabolic disorders of childhood (Atkinson et al., 2014; Daneman, 2006). Global epidemiological studies have shown large variations of incidence rates in geographically different regions and an increased incidence of T1D over the past decades (Patterson et al., 2019; Group, 2006) particularly in children <5 years (DiMeglio et al., 2018).

The clinical manifestation of T1D is preceded by a presymptomatic stage of islet autoimmunity marked by the presence of two or more islet autoantibodies. The development of islet autoantibodies has a peak incidence between 1 and 3 years (Ziegler and Bonifacio, 2012; Krischer et al., 2015) and progression to clinical diabetes occurs at a rate of around 10% per year (Bonifacio, 2015). It is generally assumed that, in addition to genetic predisposition, environment plays an important role in the initiation of autoimmunity to pancreatic islet cells and is partially responsible for geographical differences in T1D incidence. Individual environmental exposures such as diet (Ziegler et al., 2003), infections

* Corresponding author . Institute of Epidemiology, Helmholtz Zentrum München, Ingolstädter Landstrasse 1, 85764 Neuherberg, Germany.
** Corresponding author. Institute of Diabetes Research, Helmholtz Zentrum München, Ingolstaedter Landstrasse 1, 85764, MD, Neuherberg, Germany.
E-mail addresses: Mahnaz.badpa@helmholtz-muenchen.de (M. Badpa), Anette-g.ziegler@helmholtz-muenchen.de (A.-G. Ziegler).
[1] Shared last authorship.

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(Lönnrot et al., 2017) and perinatal conditions (Bonifacio et al., 2008) have previously been addressed as potential triggers for T1D. However, the effect of geographic environmental conditions is poorly understood.

In two case-control studies in the US, prediagnosis exposure to ozone (O_3), particulate matter with a diameter <10 μm (PM_{10}), and sulfate (SO_4) were associated with childhood T1D development (Hathout et al., 2002, 2006). In a Swedish case-control study, mothers of offsprings with T1D were more likely to be exposed to higher levels of nitrogen oxides (NO_x) during the third trimester of pregnancy or higher O_3 during the second trimester (Malmqvist et al., 2015). In Israel, exposure to low ambient air temperature during gestation increased the risk of T1D incidence in childhood (Taha-Khalde et al., 2021). In a Swedish study conducted between 1983 and 2008, long-term exposure to low air temperature was associated with the incidence of T1D diagnosis in children (Waernbaum and Dahlquist, 2016). Moreover, one previous study from Bavaria reported associations between environmental exposures and the development of islet autoantibodies (Beyerlein et al., 2015). Nevertheless, no study has yet examined the relationship between geo-environmental variation and islet autoimmunity.

The Fr1da study screens children for islet autoimmunity in a public health setting in Bavaria, Germany, since 2015 and provides an opportunity to investigate geo-environmental exposures in the context of a presymptomatic disease stage on a population-based level. Environmental geo-coding at the address or zip-code level of children's individual residences was used to define long-term exposures to air pollutants, air temperature, and greenness during pregnancy and the first two years of life, with the aim to identify whether there are associations between these exposures and the development of islet autoimmunity in childhood.

2. Method

2.1. Study design and population

The Fr1da study screened children aged 1.75–5.99 years for islet autoimmunity in Bavaria, Germany from February 2015 to March 2019. Participation was voluntary and necessitated having no previous diagnosis for any type of diabetes. The detailed study design has been published (Raab et al., 2016). Islet autoimmunity was defined as having two or more islet autoantibodies in two consecutive blood samples. Children with islet autoimmunity and their families were invited to participate in an educational program and metabolic staging by oral glucose tolerance test, and the child was further monitored at follow-up visits (Raab et al., 2016; Insel et al., 2015).

From a total number of 90,632 Fr1da participants, residential zip-codes of 85,251 children were available. Moreover, we used data of 52,636 participants out of 52,782 with full residential addresses after excluding those for whom geocoding was not possible (N = 146). The spatial distribution of the participants is shown in Fig. 1 (see also Supplemental Figure S1-Figure S2).

Information on participants' residential addresses at the time of screening and individual characteristics (age, sex, body mass index (BMI), and family history for any type of diabetes) were collected with self-administered questionnaires. Fr1da was approved by the institutional review board at Technical University Munich.

2.2. Geocoding

We geocoded the residential addresses using the geocoder application 'Adressen-Batch' provided by the Federal Agency for Cartography and Geodesy (BKG) (Geodesy and G.F.A.f.C.a), using the Universal Transverse Mercator (UTM-32) coordinate reference system. Addresses with a match score <95% with corresponding geocodes (N = 4,958) were reviewed for misspelled information and abbreviation inconsistencies and manually corrected by comparing the address information with Google Maps and Street View. Addresses that could not be

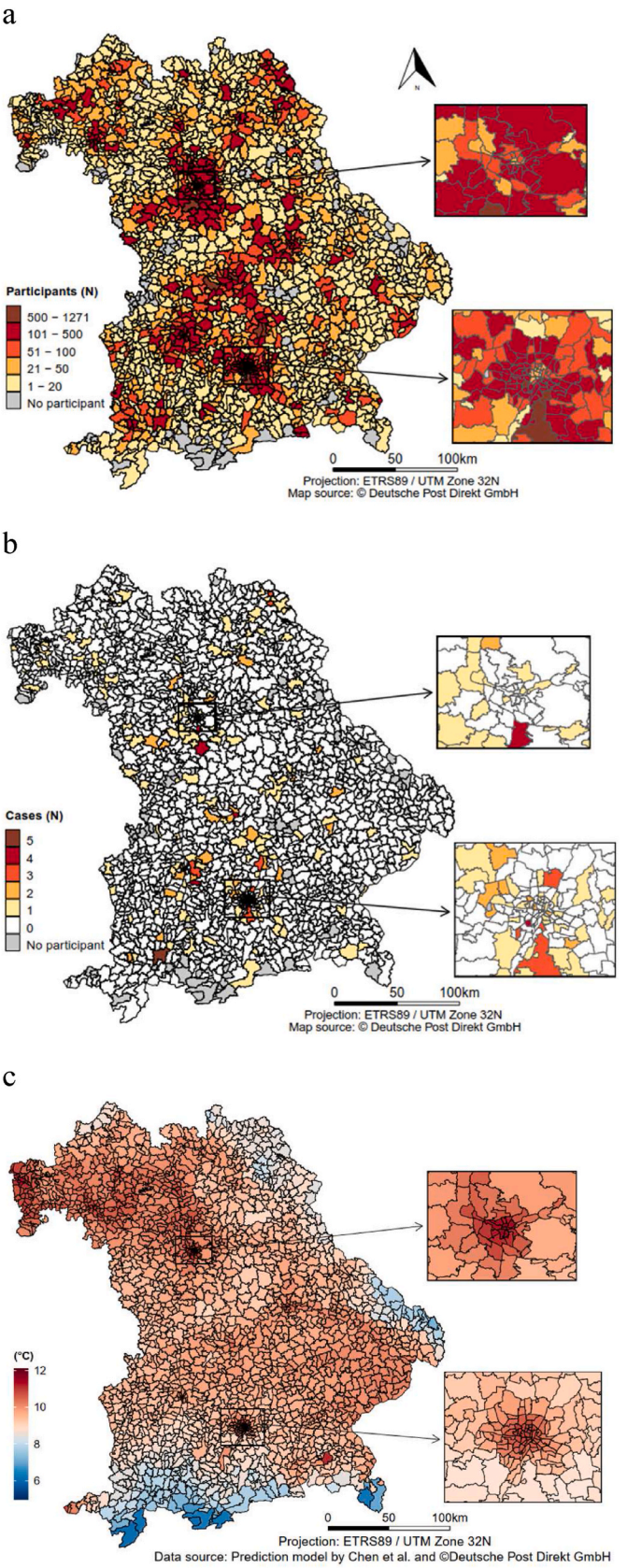

Fig. 1. Fr1da study region and distribution of participants (a), frequency of islet autoimmunity (b) and zip-code mean of annual air temperature (in the year of study entry (2015)) (c) across Bavaria, Germany.

located were further validated with the original questionnaires. The positional accuracy of the final geocodes was checked by matching a sample of ~1% of coordinates (N = 4,800) with addresses on Google Maps.

2.3. Environmental exposures

We selected $PM_{2.5}$, nitrogen dioxide (NO_2), and O_3 to represent ambient air pollution. The daily average concentrations for these pollutants were calculated using hourly measured data provided by the German Environment Agency (UBA) (German Environmental Agency) at approximately 2 × 2 km spatial resolution from 2008 (the year the oldest child was gestated) to 2019 (two years after the youngest child was born). UBA computes air pollution data for entire Germany by combining predicted concentrations from simulations of the chemistry-transport model REM-Calgrid with measurements from up to 250 German monitoring stations by optimal interpolation. Exemplarily for the year 2018, the leave-one-out cross-validation coefficient of determination (R^2) for rural, suburban and urban regions ranged from 0.94 to 0.97 for PM_{10}, 0.71–0.94 for NO_2 and 0.93–0.98 for O_3. The root mean square error (RMSE), reported for four degrees of urbanization (rural, suburban and urban background, traffic), ranged between 6 and 8 μg/m^3 for PM_{10}, 6–23 μg/m^3 for NO_2 and 14–15 μg/m^3 for O_3 (Nordmann et al., 2020).

Daily mean air temperature maps were available from own models for entire Germany with 1 × 1 km resolution from 2008 to 2019. The maps were compiled following previous multi-stage modelling approaches combining historical air temperature measurements with satellite-derived land surface temperature and spatial predictors (land use, Normalized Difference Vegetation Index (NDVI), and elevation). (Rosenfeld et al., 2017; Kloog et al., 2014).

Greenness exposure was assigned using satellite-derived NDVI data from MODerate-resolution Imaging Spectroradiometer (MODIS) satellite images at 1 × 1 km spatial resolution from 2008 to 2019, on a monthly basis. NDVI is derived from the ratio of red and near-infrared sunlight reflectance at the ground level and ranges from −1 (water bodies) through 0 (barren areas) to +1 (completely green areas). (Earth data and N) Following previous studies (Fan et al., 2020) negative values were set to zero.

For each participant, we extracted the exposure values by intersecting the exposure raster grids with the residential address point. For the zip-code-level analyses, we averaged the exposure data over zip-codes by intersecting the exposure raster grids with the German zip-code map provided by BKG (Fig. 1(c), Supplemental Figure S3-Figure S4) and assigned them to the participants' residential zip-code.

For each variable, we considered several long-term exposure windows including mean exposure during 1) pregnancy (defined as 270-day/9-month average before birth), 2) the first year, and 3) the first two years of life (calculated by averaging the daily/monthly mean concentrations from the month of birth to respectively, the 365th day/12th month, and the 730th day/24th month after birth).

2.4. Statistical analysis

Spearman's rank correlation coefficient was calculated between environmental exposures within each exposure window and across multiple windows to investigate correlation patterns of exposure variables.

We investigated the association of environmental exposures during pregnancy and early life with islet autoimmunity using generalized additive models. For each time window, we evaluated environmental variables separately in single-exposure models as well as jointly in a multi-exposure model.

All models were adjusted for potential confounders including age (at the screening time, continuous), sex (female vs. male), family history of type 1 diabetes (yes vs. no), and area-level socioeconomic status (SES) including population density (low/medium density: ≤100 vs. high density: >100 persons/km^2) and percentage of households with low income (continuous) selected based on existing literature (Hathout et al., 2006). SES data were available from a private company (WiGeoGIS) (Gesellschaft für Digitale Wirtschaftsgeographie mbH) at a 1 × 1 km grid for the year 2014 (supplemental Figure S5). Since previous studies suggested BMI could be a mediator and modify the effect of environmental exposures on developing chronic diseases, it was not included in the main analysis (Kim et al., 2019).

Results are presented as odds ratios (OR) with corresponding 95% confidence intervals (CI) per interquartile range (IQR) difference in continuous variables except for age (OR per 1-year increase). Moreover, we assessed the linearity of exposure variables by including them separately as thin-plate splines.

2.5. Sensitivity analysis

To evaluate the robustness of the main findings, we 1) fitted models further adjusting for a) standardized BMI (binary variable, ≤1 vs. >1; BMI standardized using World Health Organization reference values (Ziegler et al., 2020)); b) influenza prevalence in corresponding exposure windows as a potentially precipitating factor in islet autoimmunity onset (Nenna et al., 2011), based on data from Robert Koch Institute (SurvStat@RKI 2.0, 2021); 2) included cold-season (September to February) and warm-season (March to August) average air temperature instead of whole period average.

2.6. Validation analysis

We validated the results by taking advantage of the independent Diabetes Mellitus Incidence (DiMelli) cohort study (Thümer et al., 2010), monitoring incidence of diabetes mellitus in children ≤20 years old in Bavaria, between 2009 and 2012. We replaced the Fr1da antibody-positive children with DiMelli's cases ≤6 years old (N = 150) and repeated our statistical analyses.

All analyses were performed using the software R (version 4.0.2), packages 'mgcv', 'raster', and 'sp'. The level of significance was set at 0.05.

3. Results

Of the 85,251 children included, 272 (0.3%) were in the presymptomatic stage of islet autoimmunity and the mean zip-code-level rate was 0.32 ± 0.90. At the time of screening, the mean age was 3.43 ± 1.22 and there were slightly more males (females: 48.5%). 4.1% of children were obese, the mean standardized BMI was 0.12 ± 1.04 and 3.3% reported a positive family history of diabetes (Table 1).

Mean concentrations of air pollutants varied between the years while mean air temperature and greenness remained relatively stable. Children were exposed to higher levels of $PM_{2.5}$ and NO_2 and lower O_3 during pregnancy compared to the other exposure windows (Table 1). Overall, children with full residential address information showed similar individual characteristics and exposure levels as the whole study population (see supplemental Table S1-Table S2 for details).

Spearman's correlation coefficients indicated the environmental variables were weakly to moderately correlated ($r_{spearman} < 0.7$) at both address and zip-code exposure levels (Table 2). $PM_{2.5}$ and NO_2 were negatively correlated with O_3 and greenness at almost all exposure windows.

The association of environmental exposures with the odds of developing islet autoimmunity is presented in Table 3, after adjustment for age, sex, family history of diabetes, and SES factors. In all models, age and diabetes family history had a significant effect on developing islet autoimmunity.

At the address level, exposure to low ambient air temperature during pregnancy and early life was significantly associated with a higher risk

Table 1
Individual characteristics, socioeconomic factors and environmental exposures of Fr1da participants.

	Address level (N = 52,636)			Zipcode level (N = 85,251)		
	Mean ± SD/N (%)	Min	Max	Mean ± SD/N (%)	Min	Max
Individual Characteristics						
Islet autoimmunity (N cases)	225 (0.43)	..	..	272 (0.32)	..	..
Islet autoimmunity (IR)	..	..	..	0.32 ± 0.90	0.00	50.00
Age [a] (years) (N miss = 141)	3.33 ± 1.21	1.75	5.99	3.43 ± 1.22	1.75	5.99
Sex (female) (N miss = 963)	25,062 (48.3)	..	..	40,891 (48.5)	..	..
Standardized BMI (N miss = 1,979)	0.11 ± 1.01	−4.93	4.97	0.12 ± 1.04	−4.93	4.97
Obese	1,959 (3.8)	..	..	3,440 (4.1)	..	..
Diabetes family history	1,407 (2.7)	..	..	2,825 (3.3)	..	..
Socioeconomic factors						
Population density (persons/km^2)[b]	2,580 ± 3,260	2	21,183	1,673 ± 2,846	7	20,061
Households with low income (<1,250 €) (%)	20.5 ± 22.5	0.0	100.0	13.0 ± 15.8	0.0	88.3
Air pollution						
$PM_{2.5}$ (μg/m^3)						
Pregnancy	11.9 ± 2.1	5.8	19.7	12.0 ± 2.2	5.6	19.5
1st year	11.5 ± 1.8	6.1	18.8	11.6 ± 1.9	6.1	18.6
2 years	11.2 ± 1.6	6.5	18.1	11.3 ± 1.7	6.5	18.4
NO_2 (μg/m^3)						
Pregnancy	16.0 ± 5.7	4.4	37.2	15.9 ± 5.8	4.2	35.6
1st year	15.4 ± 5.4	4.8	36.4	15.2 ± 5.5	4.4	32.2
2 years	14.9 ± 5.2	5.3	35.1	14.8 ± 5.4	4.5	31.2
O_3 (μg/m^3)						
Pregnancy	45.1 ± 5.7	21.8	73.4	45.1 ± 5.7	24.6	74.7
1st year	45.9 ± 5.1	25.4	73.6	45.7 ± 5.0	27.3	70.8
2 years	47.0 ± 5.2	27.0	73.2	46.5 ± 5.1	28.6	69.9
Air temperature & vegetation						
Air temperature (°C)						
Pregnancy	9.0 ± 1.5	2.8	13.3	8.7 ± 1.5	4.3	13.1
1st year	9.1 ± 0.9	4.3	12.3	8.9 ± 0.9	5.1	12.4
2 years	9.1 ± 0.7	5.1	11.8	9.0 ± 0.7	5.5	11.8
Greenness (NDVI)						
Pregnancy	0.62 ± 0.08	0.03	0.84	0.61 ± 0.07	0.27	0.81
1st year	0.62 ± 0.07	0.08	0.83	0.62 ± 0.06	0.29	0.81
2 years	0.63 ± 0.07	0.09	0.82	0.62 ± 0.06	0.30	0.81

SD: Standard deviation; **Min**: Minimum; **Max**: Maximum; **IR**: Incidence rate of islet autoimmunity in zip-code areas; **N miss**: Number of missing observations; **Standardized BMI**: Standardized body mass index, calculated based on height, weight and age through the following formula: [(BMI/M)L − 1]/(L × S) where L = Box-Cox power transformation, M = median and S = variation coefficient. Normal BMI: standardized value < 1, overweight: 1 to 2 and obese: >2 [38]. **$PM_{2.5}$**: Particulate matter with a diameter <2.5 μm; **NO_2**: Nitrogen dioxide; **O_3**: Ozone; **NDVI**: Normalized difference vegetation index; **Pregnancy**: Mean exposure during pregnancy; **1st year**: Mean exposure during the first year of life; **2 years:** Mean exposure during the first two years of life.

[a] Age at screening time.

[b] Density counts were rounded to integer values.

of islet autoimmunity (OR per IQR decrease: 1.49, CI: 1.21–1.83; OR: 1.28, CI: 1.06–1.54 and OR: 1.25, CI: 1.05–1.49 for pregnancy, the first year, and the first two years of life, respectively). The effect estimates remained stable in multi-exposure models at all exposure windows. In the zip-code-level analysis, we observed a similar effect of low air temperature during pregnancy (OR per IQR decrease: 1.28, CI: 1.04–1.57), whereas effect estimates were weaker and not statistically significant for the first year and 2-year exposures (p = 0.19). The associations of other environmental factors remained stable at both exposure levels but did not reach statistical significance. The inspection of the shape of the spline functions indicated linearity for all exposure windows (Figure S6).

In sensitivity analyses, adjustment for standardized BMI and influenza prevalence did not affect the effect estimates at both exposure levels. Also, replacing whole period average air temperature with cold and warm season averages showed stable estimates for almost all exposure windows (Fig. 2, supplemental Table S3-Table S6). The validation analysis also confirmed our results and showed stronger effects of low ambient air temperature at almost all exposure windows (supplemental Table S7).

4. Discussion

In this large children cohort, we found that exposure to low ambient air temperature during pregnancy and early life significantly increased the risk of islet autoimmunity in childhood, after adjusting for age, sex, diabetes family history, and area-level SES factors. The effect estimates remained stable when mutually adjusting for other environmental variables in multi-exposure models. The associations were also pronounced in zip-code-level analyses for exposure during pregnancy. The effects of other environmental factors, namely air pollution and greenness were not statistically significant.

This is the first study reporting an effect of low mean air temperature exposure on islet autoimmunity, supporting the evidence of some studies that have previously detected that cold was associated with increases in T1D incidence. In Sweden, a registry-based study of 5,831 children with T1D onset before the age of 14 found an inverse significant relationship between the incidence rate and low mean air temperature (R^2_{model}: 0.03; $P = 0.005$) (Dahlquist and Mustonen, 1994). An ecological analysis of worldwide incidence of insulin-dependent diabetes mellitus (IDDM) among children <15 years old observed an inverse correlation with average yearly air temperature ($R^2_{correlation} = -0.55$; $P < 0.005$) (Group, 1988). The same study also reported the highest incidence rates in the northern part of the world in the Scandinavian countries and the lowest rates in Japan. A similar geographical variation in risk was also observed within countries such as Sweden (Dahlquist et al., 1985), Finland (Reunanen et al., 1982) and Norway (Joner and Søvik, 1981), highlighting cold environment being a risk determinant for T1D. The hypothesis was additionally supported by epidemiological studies looking at the seasonal variation of T1D incidence rates and reporting lowest rates during the warm season (Dahlquist, 1991). In a recent cohort of 10,681 children including three study regions in Finland, an inverse association between exposure to biodiverse agricultural environment in early life and the risk of islet autoimmunity and T1D was observed in the region Turku which showed the highest annual mean

Table 2
Spearman correlation coefficients of environmental exposures and socioeconomic factors.

Address-level		$PM_{2.5}$			NO_2			O_3			Air temperature			Greenness (NDVI)			Population density	Low-income households
Zip-code-level		Prg	1 yr	2 yrs	Prg	1 yr	2 yrs	Prg	1 yr	2 yrs	Prg	1 yr	2 yrs	Prg	1 yr	2 yrs		
$PM_{2.5}$	**Prg**		0.70	0.74	0.53	0.57	0.60	−0.20	−0.41	−0.48	−0.11	0.18	−0.09	−0.39	−0.31	−0.42	0.54	0.36
	1 yr	0.71		0.99	0.25	0.47	0.37	−0.13	−0.57	−0.62	0.15	0.11	0.03	−0.12	−0.05	0.02	0.57	0.42
	2 yrs	0.78	0.95		0.25	0.47	0.39	−0.07	−0.55	−0.59	0.14	0.16	0.04	−0.14	−0.06	0.00	0.58	0.41
NO_2	**Prg**	0.82	0.59	0.60		0.93	0.92	−0.39	−0.35	−0.36	−0.12	0.11	0.13	−0.33	−0.28	−0.29	0.64	0.46
	1 yr	0.83	0.66	0.68	0.92		0.98	−0.28	−0.43	−0.43	0.07	0.02	0.06	−0.28	−0.31	−0.30	0.63	0.44
	2 yrs	0.83	0.69	0.69	0.91	0.99		−0.31	−0.43	−0.47	0.02	0.06	0.09	−0.31	−0.32	−0.32	0.62	0.42
O_3	**Prg**	−0.57	−0.50	−0.50	−0.47	−0.30	−0.31		0.48	0.54	0.32	−0.20	−0.21	0.18	0.14	0.15	−0.04	−0.05
	1 yr	−0.78	−0.66	−0.47	−0.45	−0.46	−0.47	0.54		0.92	−0.16	−0.03	−0.07	0.23	0.18	0.18	−0.06	−0.05
	2 yrs	−0.81	−0.72	−0.77	−0.44	−0.48	−0.50	0.53	0.92		−0.04	−0.03	−0.06	0.27	0.22	0.21	−0.02	−0.04
Air temperature	**Prg**	−0.46	−0.29	−0.20	−0.24	0.01	0.01	0.47	0.01	0.05		−0.06	0.12	0.17	−0.10	−0.09	0.02	0.02
	1 yr	−0.08	−0.17	−0.09	0.05	0.02	0.02	−0.17	−0.14	−0.02	0.20		0.88	−0.15	−0.04	−0.08	0.05	0.04
	2 yrs	−0.22	−0.23	−0.21	0.08	0.05	0.07	−0.16	−0.21	−0.12	0.26	0.85		−0.12	−0.07	−0.12	0.07	0.04
Greenness (NDVI)	**Prg**	−0.69	−0.43	−0.49	−0.42	−0.32	−0.33	0.28	0.31	0.33	0.35	0.01	−0.01		0.81	0.86	−0.16	−0.09
	1 yr	−0.59	−0.50	−0.53	−0.34	−0.38	−0.37	0.16	0.23	0.29	−0.05	0.06	−0.05	0.73		0.96	−0.15	−0.09
	2 yrs	−0.63	−0.44	−0.50	−0.36	−0.38	−0.38	0.18	0.24	0.27	−0.06	−0.07	−0.10	0.77	0.95		−0.14	−0.08
Population density		0.61	0.26	0.31	0.79	0.81	0.80	−0.15	−0.19	−0.18	0.01	0.08	0.09	−0.19	−0.23	−0.25		0.68
Low-income households		0.62	0.21	0.27	0.63	0.64	0.63	−0.14	−0.18	−0.16	0.01	0.02	0.03	−0.14	−0.17	−0.18	0.77	

$PM_{2.5}$: Particulate matter with a diameter <2.5 μm; **NO_2**: Nitrogen dioxide; **O_3**: Ozone; **NDVI**: Normalized difference vegetation index; **Low-income households**: Households with low monthly income (<1,250 €); **Prg**: Mean exposure during pregnancy; **1 yr:** Mean exposure during the first year of life; **2 yrs:** Mean exposure during the first two years of life.

temperature and the shortest duration of snow cover across the three regions (Nurminen et al., 2021). However, the authors did not investigate the effects of temperature or snow cover itself.

Studies have reported environmental exposures during pregnancy and early childhood influence the risk of immune diseases such as allergy and autoimmunity, as immune development predominantly occurs early in life (Prescott, 2013). Moreover, developing islet autoantibodies mainly happens in the first years of life (Nurminen et al., 2021). Our finding that low air temperature is associated with the emergence of islet autoantibodies indicates that low temperature may already be relevant for disease initiation and not only for the development of clinical T1D.

The biological mechanisms are still unclear. However, there are several possible explanations: The observed effect of low air temperature exposure could be attributed to the increased demand on the β-cell for insulin during the cold months (Dahlquist, 1998). Another reason could be the prevalence of viral infections, rather than influenza that did not affect our results, and its role in human pancreatic β-cell damage (Afoke et al., 1991; Oikarinen et al., 2014). Even though it is unknown how perinatal virus exposure could induce T1D, it is believed that foetal viral exposures might lead to chronic infection within or in the vicinity of the β-cell. It may later cause inflammatory responses such as cytokine release which could initiate β-cell destruction (Mandrup-Poulsen, 1996). Also, the association might be due to lower exposure to sunlight and ultraviolet B (UVB) irradiance in cold environments and therefore, lower levels of vitamin D. Studies have linked vitamin D deficiency with the risk of autoimmunity (Borkar et al., 2010; Ponsonby et al., 2005) and developing pancreatic islets autoantibodies (Group, 1988; Zipitis and Akobeng, 2008).

In this study, we did not observe any significant association between exposure to air pollutants and islet autoimmunity. Mean concentrations for $PM_{2.5}$ and NO_2 were all below half the EU (European Environment Agency, 2019) limits but above the WHO (Organization and W.H., 2021) target values of respectively 5 and 10 μg/m^3. As mentioned above, existing literature mainly investigated the association of environmental determinants and overt clinical disease and not the initial islet autoimmunity stage (Hathout et al., 2002, 2006; Malmqvist et al., 2015; Elten et al., 2020).

Our data did not show any significant effect of surrounding greenness.

5. Strengths and limitations

This study has several strengths: We performed a comprehensive assessment of the impact of environmental exposures on early-stage islet autoimmunity. The study is unique as it represents a public health cohort from a specific region (Bavaria) looking for geo-environmental triggers while the Finnish study (Nurminen et al., 2021) looked at children who were pre-selected by genetic risk. We investigated a large-scale cohort of children with detailed information on participants' characteristics which enabled us to control for potential confounders. We considered a wide range of exposure variables that were investigated separately and jointly as potential determinants of islet autoimmunity precursors. We also conducted the analyses at both address and zip-code levels, a validation analysis and various sensitivity analyses all of which basically showed constant results.

Our study however faced several limitations. First, the residential addresses at the time of screening were assumed to be the addresses of relevant exposure. Changes in residence or differing time periods spent at home were unfortunately not available and added uncertainty to the results through potential exposure misclassification. However, a review from the 1980s–2000s reported that even though 9%–32% of women in the United States and abroad moved during pregnancy, the moves were mainly local and 52.1%–69.1% of mothers stayed in the same general area, e.g. the same county (median distance <10 km) (Bell and Belanger, 2012). The fact that we observed stronger associations when comparing full addresses to zip-code indicates that indeed undifferential exposure

Table 3
Association (Odds Ratio and 95% CI) between islet autoimmunity and individual characteristics, socioeconomic factors and environmental exposures (per IQR difference).

		Address-level analyses (N = 52,636)					Zip-code-level analyses (N = 85,251)				
		IQR	**Single-exposure model**		**Multi-exposure model**		**IQR**	**Single-exposure model**		**Multi-exposure model**	
			OR (95% CI)	**Pvalue**	**OR (95% CI)**	**Pvalue**		**OR (95% CI)**	**Pvalue**	**OR (95% CI)**	**Pvalue**
Age		..	1.41 (1.29–1.54)	0.00	1.35 (1.23–1.49)	0.00	..	1.30 (1.20–1.40)	0.00	1.25 (1.14–1.37)	0.00
Sex (male) (reference: female)		..	1.13 (0.91–1.42)	0.35	1.13 (0.91–1.41)	0.36	..	1.13 (0.92–1.38)	0.32	1.12 (0.92–1.37)	0.31
Diabetes family history (yes) (reference: no)		..	4.55 (3.18–6.51)	0.00	4.57 (3.19–6.54)	0.00	..	3.96 (2.90–5.41)	0.00	3.77 (2.74–5.19)	0.00
Population density (low/med) (reference: high)		..	1.18 (0.83–1.66)	0.29	1.20 (0.84–1.70)	0.41	..	0.91 (0.68–1.22)	0.63	0.94 (0.69–1.28)	0.64
Households with low income (<1,250 €)		31.74	1.00 (0.81–1.23)	0.34	0.94 (0.76–1.16)	0.33	13.06	0.93 (0.82–1.07)	0.20	0.90 (0.78–1.04)	0.22
$PM_{2.5}$	**Pregnancy**	2.71	1.20 (0.99–1.46)	0.06	1.14 (0.88–1.47)	0.33	2.73	1.12 (0.93–1.35)	0.22	1.05 (0.82–1.33)	0.71
	1st year	2.34	1.17 (0.96–1.42)	0.12	1.21 (0.94–1.55)	0.13	2.31	1.07 (0.89–1.29)	0.46	1.05 (0.84–1.32)	0.66
	2 years	2.16	1.19 (0.97–0.46)	0.09	1.26 (0.97–1.63)	0.08	2.14	1.08 (0.89–1.32)	0.43	1.05 (0.83–1.33)	0.67
NO_2	**Pregnancy**	8.61	1.07 (0.85–1.34)	0.57	1.00 (0.74–1.35)	0.99	8.73	1.13 (0.88–1.44)	0.34	1.09 (0.79–1.50)	0.61
	1st year	8.04	1.03 (0.83–1.28)	079	0.96 (0.72–1.27)	0.77	819	1.12 (0.87–1.43)	0.38	1.13 (0.83–1.55)	0.43
	2 years	7.49	1.05 (0.85–1.29)	0.68	0.95 (0.72–1.24)	0.70	7.75	1.14 (0.90–1.44)	0.28	1.16 (0.86–1.56)	0.34
O_3	**Pregnancy**	7.79	1.03 (0.86–1.23)	0.73	1.18 (0.96–1.44)	0.11	7.75	0.96 (0.81–1.13)	0.62	1.03 (0.86–1.25)	0.72
	1st year	6.54	1.06 (0.89–1.27)	0.51	1.09 (0.89–1.32)	0.40	6.32	0.99 (0.84–1.16)	0.86	1.01 (0.84–1.20)	0.95
	2 years	6.74	1.00 (0.82–1.21)	0.97	0.99 (0.80–1.24)	0.96	6.32	0.94 (0.80–1.12)	0.51	0.96 (0.79–1.17)	0.69
Air temperature	**Pregnancy**	2.24	1.49 (1.21–1.83)	0.00	1.51 (1.21–1.88)	0.00	2.36	1.31 (1.08–1.59)	0.01	1.32 (1.07–1.63)	0.01
	1st year	1.25	1.28 (1.06–1.54)	0.01	1.26 (1.04–1.52)	0.02	1.25	1.07 (0.90–1.27)	0.42	1.07 (0.90–1.27)	0.47
	2 years	0.93	1.25 (1.05–1.49)	0.01	1.27 (1.06–1.52)	0.01	0.94	1.05 (0.88–1.24)	0.58	1.05 (0.88–1.25)	0.61
Greenness (NDVI)	**Pregnancy**	0.10	0.93 (0.79–1.11)	0.42	0.99 (0.83–1.20)	0.95	0.09	0.99 (0.84–1.17)	0.93	1.09 (0.91–1.31)	0.34
	1st year	0.10	0.95 (0.80–1.14)	0.60	0.97 (0.81–1.18)	0.78	0.08	1.04 (0.91–1.19)	0.57	1.08 (0.93–1.25)	0.30
	2 years	0.09	0.99 (0.83–1.17)	0.87	0.99 (0.83–1.18)	0.92	0.08	1.01 (0.86–1.18)	0.34	1.14 (0.95–1.36)	0.15

IQR: Interquartile range; **OR:** Odds ratio; **CI**: Confidence interval; **$PM_{2.5}$**: Particulate matter with a diameter <2.5 μm; **NO_2**: Nitrogen dioxide; **O_3**: Ozone; **NDVI**: Normalized difference vegetation index; **Pregnancy**: Exposure during pregnancy; **1st year**: Mean exposure during the first year of life; **2 years:** Mean exposure during the first two years of life.
Note: Models are adjusted for age, sex, diabetes family history and socioeconomic factors. The ORs are based on one IQR decrease in air temperature level and one IQR increase in other continuous variables except for age (OR per 1-year increase).

misclassification may influence the results substantially. In terms of mobility in childhood, studies have found age at diagnosis is correlated with likelihood of residential mobility, meaning that most people move when the child is growing. An Italian study reported that 70% of children lived in the same address from birth to the year prior to diagnosis and 82% among those diagnosed before the age of 5 years did not move. However, several studies indicated a greater likelihood of moving around the time of birth (Vinceti et al., 2012). It is unclear whether the data from other countries applies to Germany. Second, information on human lifestyle such as physical activity, dietary behaviour and exposure to passive smoking were not available which might influence islet autoimmunity (Rytkönen et al., 2003). Finally, accessibility to a pediatrician participating in the Fr1da project being the first step to be recruited into the cohort and regional health policies may affect the composition of the study population which could bias the exposure-disease relationship.

6. Conclusion

In summary, our study provided evidence that exposure to low ambient air temperature during pregnancy and early life might play a critical role in developing islet autoimmunity before 6 years of age, which may lead to T1D later throughout childhood or adult life.

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Authors' contributions

All authors contributed to the study design and conceptualization. The underlying data were verified and analyzed by **MB**, **KW**, and **AS**, and all authors interpreted the findings. The manuscript was drafted by **MB** with support from **KW**, **AS**, and **AGZ**. All authors read and critically

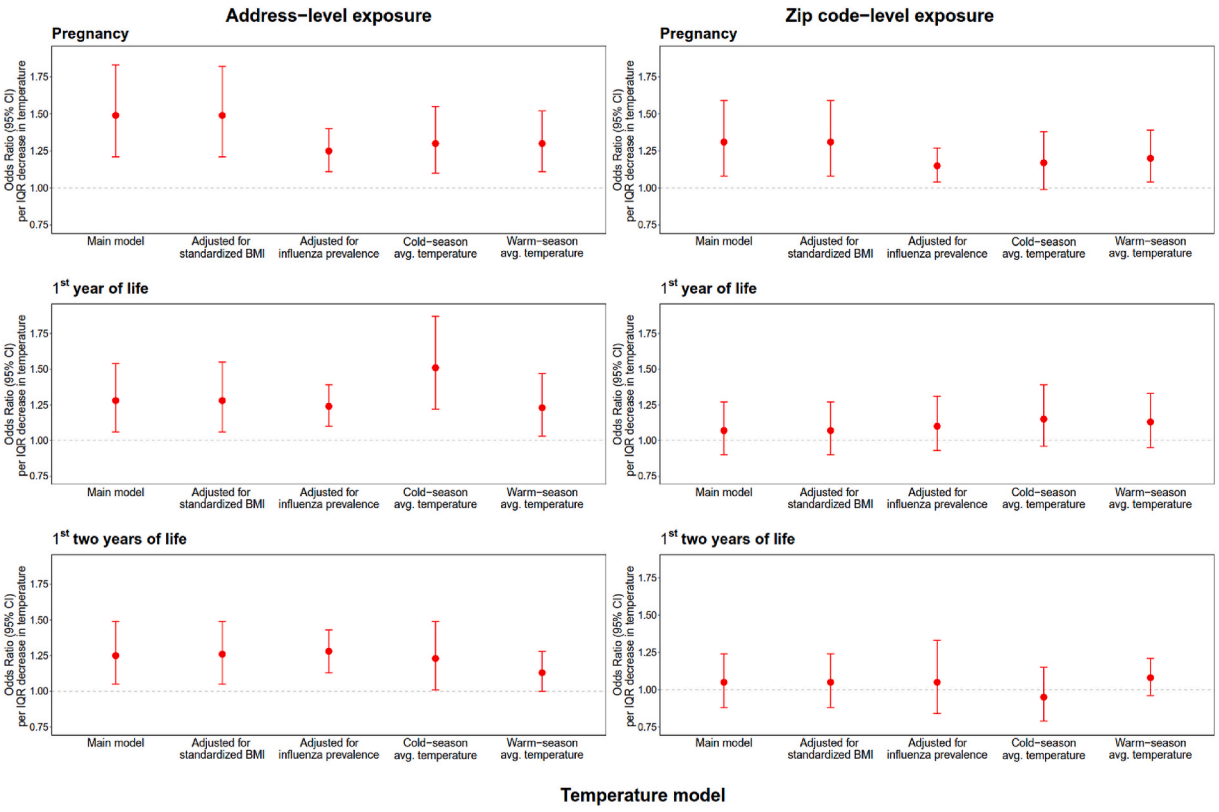

Fig. 2. Association (Odds Ratio and 95% CI) between islet autoimmunity and air temperature (per IQR decrease) at different exposure windows.

revised the manuscript and approved the final version. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. **AGZ** led the project and had final responsibility for the decision to submit for publication.

Role of funding source

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript, and decision to submit the manuscript for publication.

Ethics committee approval

The Fr1da study was approved by the institutional review board at Technical University Munich.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.113503.

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Corrigendum to "Association of long-term environmental exposures in pregnancy and early life with islet autoimmunity development in children in Bavaria, Germany" [Environ. Res. 212 (2022) 113503]

Mahnaz Badpa [a,b,c,*], Kathrin Wolf [a], Alexandra Schneider [a], Christiane Winkler [c,d], Florian Haupt [c,d], Annette Peters [a,c,e,f], Anette-Gabriele Ziegler [c,d,g]

[a] Institute of Epidemiology, Helmholtz Zentrum München, Munich, Germany
[b] Institute for Medical Information Processing, Biometry and Epidemiology (IBE), Faculty of Medicine, Pettenkofer School of Public Health, LMU Munich, Munich, Germany
[c] German Center for Diabetes Research (DZD), Munich, Germany
[d] Institute for Diabetes Research, Helmholtz Diabetes Center at Helmholtz Zentrum München, Munich, Germany
[e] Chair of Epidemiology, Faculty of Medicine, Ludwig-Maximilians-Universität München, Munich, Germany
[f] Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[g] Forschergruppe Diabetes, Chair of Diabetes and Gestational Diabetes, Faculty of Medicine, Technical University Munich at Klinikum Rechts der Isar, Munich, Germany

The authors regret to inform you that an error occurred in the affiliation mentioned in the published version of the paper. In the published version, the authors' affiliation (b) is incorrectly stated as [Institute for Medical Informatics, Biometrics and Epidemiology, Ludwig-Maximilians-Universität (LMU) Munich, Munich, Germany]. The correct affiliation should be [Institute for Medical Information Processing, Biometry and Epidemiology (IBE), Faculty of Medicine, LMU Munich, Pettenkofer School of Public Health, Munich, Germany], which includes the accurate institution name, department, and any other relevant information.

The authors would like to apologise for any inconvenience caused.

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* Corresponding author. Badpa Institute of Epidemiology, Helmholtz Zentrum München, Ingolstädter Landstrasse 1, 85764, Neuherberg, Germany.
E-mail address: Mahnaz.badpa@helmholtz-munich.de (M. Badpa).

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Outdoor Light at Night and Children's Body Mass: A Cross-Sectional Analysis in the Fr1da Study

Mahnaz Badpa [a,b,c,*], Alexandra Schneider [a], Anette-Gabriele Ziegler [c,d,e], Christiane Winkler [c,d], Florian Haupt [c,d], Kathrin Wolf [a,1], Annette Peters [a,c,f,g,1]

[a] Institute of Epidemiology, Helmholtz Zentrum München, Munich, Germany
[b] Institute for Medical Information Processing, Biometry and Epidemiology (IBE), Faculty of Medicine, Pettenkofer School of Public Health, LMU Munich, Munich, Germany
[c] German Center for Diabetes Research (DZD), Munich, Germany
[d] Institute for Diabetes Research, Helmholtz Munich-German Research Center for Environmental Health, Neuherberg, Germany
[e] Chair of Diabetes and Gestational Diabetes, Forschergruppe Diabetes, Faculty of Medicine, Technical University Munich at Klinikum Rechts der Isar, Munich, Germany
[f] Chair of Epidemiology, Faculty of Medicine, LMU Munich, Munich, Germany
[g] Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA

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ABSTRACT

Background: Emerging evidence supports an association between light at night (LAN) exposure with obesity or overweight in adults. However, effects of LAN exposure during childhood have yet to be further investigated.
Objective: In this study, we aimed to determine whether LAN exposure is associated with body mass in young children.
Research design and method: We used data from the Fr1da cohort study which screened children for early-stage islet autoimmunity in Bavaria, Germany from February 2015 to March 2019. A total of 62,212 children aged <11 years with complete residential information was included in the analysis. Self-reported weight and height were used to calculate age- and sex-specific body mass index (BMI) z-scores. LAN exposure was based on remotely sensed images from Visible Infrared Imaging Radiometer Suite and assigned to the children's residencies. We used generalized additive models to estimate the associations between LAN exposure and BMI adjusting for potential confounders.
Results: We observed an increase in BMI z-scores of 34.0% (95% confidence interval (CI): 25.4–42.6) per 10 nW/cm^2/sr increment in LAN exposure at baseline (2015) and of 32.6% (24.3–41.0) for LAN exposure one year prior to screening, both adjusted for age and sex. Similar associations were observed after adjustment for socioeconomic status and urbanization degree.
Conclusion: Our findings suggest that outdoor light exposure may be a risk factor for weight gain during childhood.

1. Introduction

Over the past few decades, the global prevalence of childhood obesity and overweight has increased substantially (Abarca-Gómez, 2017; PARK YS, 2004; WHO, 2015). For example, from 1970 to 2006, the prevalence rates in U.S. children and adolescents more than doubled (Hedley et al., 2004; Ogden et al., 2008). Similar increasing patterns are reported in Australia, China and the United Kingdom (Popkin, 2010). In fact, according to global pooling studies, almost all countries have prevalent obesity/overweight during childhood and adulthood (Boddy, 2020; Collaboration, 2019; Collaboration, 2021). This threatens the health of a generation of children because being overweight or obese during childhood is associated with a variety of negative health consequences in later life, such as cardiovascular diseases, gastrointestinal conditions, cancers, metabolic complications, and diabetes (Bibbins-Domingo et al., 2007; Daniels, 2009; Fourlanos, 2008; Han, 2010).

* Corresponding author. Institute of Epidemiology, Helmholtz Munich-German Research Center for Environmental Health, Ingolstädter Landstraße 1, D-85764 Neuherberg, Germany.
E-mail address: Mahnaz.badpa@campus.lmu.de (M. Badpa).
[1] Shared last authorship.

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Obesity is a multifactorial disorder affected by interacting genetic and non-genetic factors (Han, 2010), with a result of an imbalance between energy intake and expenditure (Bont et al., 2019; Rybnikova, 2016). While a sedentary lifestyle and calorie intake are considered as initial causes, attempts to alleviate their detrimental impacts have not led to significant changes in the prevalence of obesity. It implies the influence of additional factors that may play a role in the etiology of obesity (McFadden, 2014; Pattinson et al., 2016). Artificial light exposure is among the suspected factors.

In modern societies, urbanization and infrastructure development have led to higher exposure to artificial lights, emitted by residential areas, road illumination and economic activities (Amaral, 2006). The widespread use of electrical lighting has beneficial effects on the quality of human life and suits contemporary lifestyles (Doll, 2006; Rybnikova, 2016). However, benefits have been accompanied by adverse health impacts, mainly through disrupting circadian processes driving physiological mechanisms including metabolism (Bass and Takahashi, 2010), sleep-wake cycles (Borbély, 1998), and body mass (Bray and Young, 2007). For example, several epidemiological studies showed a negative association between light at night (LAN) exposure and obesity (Koo et al., 2016; Obayashi et al., 2013, 2016) and diabetes (Knutson, 2007). In China, higher levels of outdoor LAN were associated with larger BMI and higher odds of being overweight and obese in children (Lin, 2022). In the U. S., the increasing trends in LAN exposure paralleled the increase in obesity rates (Fonken, 2014). Night-shift workers with disrupted sleeping and eating phases were more likely to be obese compared with day-shift workers (Antunes, 2010; De Bacquer, 2009). LAN exposure was further associated with the risk of hormone-dependent types of cancer such as breast and prostate cancer in the U.S. (Bauer et al., 2013), Spain (Garcia-Saenz et al., 2018), and worldwide (Kloog et al., 2009).

One potential mechanism that has been suggested is that LAN exposure may lead to disruption of the circadian rhythm, which regulates several physiological processes such as metabolism and sleep-wake cycles. Exposure to LAN may suppress the production of melatonin, a hormone that is involved in regulating circadian rhythms, and change the timing and quality of sleep, which may affect energy balance and lead to weight gain (Bass and Takahashi, 2010; Bray and Young, 2007). Additionally, exposure to LAN may lead to changes in the timing and frequency of meals which can affect energy balance and contribute to weight gain (McFadden, 2014). For example, eating late at night has been linked to weight gain and higher BMI (Baron et al., 2011).

However, although childhood plays a critical role in the establishment of lifelong adiposity trajectories (Campbell et al., 2014), most previous studies focused on adults and only little is known about the LAN impacts on children's health. Therefore, the present study investigated the cross-sectional association between exposure to outdoor LAN with BMI in children in Bavaria, Germany, using data from the Fr1da study, a large cohort of Bavarian children.

2. Methods

2.1. Study population and design

The present study was based on data from the Fr1da cohort in Bavaria, Germany. From February 2015 until March 2019, more than 90,000 children were recruited in this population-based screening for early-stage type 1 diabetes (having ≥2 pancreatic islet autoantibodies). Inclusion criteria were residing in Bavaria and having no previous diagnosis of diabetes. Recruitment was offered by primary care pediatricians during medical check-up visits and written informed consent was obtained from the parents or legal guardians. Information on participants' residential addresses at the screening time and individual characteristics including age, sex, weight, and height were collected with self-administered questionnaires at the visit. The study design is described in detail elsewhere. We included 62,630 Fr1da participants aged <11 years with valid residential information in our analysis. Fig. 1 provides a detailed overview of the exclusion process. Fig. 2(a) presents the distribution of participants across the study area. The study protocol was approved by the institutional review board at Technical University Munich.

2.2. Outcome definition

Height and weight were used to calculate BMI (BMI = weight (kg)/height (m^2)). Age- and sex-specific BMI z-scores were then calculated using the World Health Organization Child Growth Standards (WHO, 2006) through the following formula:

$$\text{BMI z} - \text{score} : [(\text{BMI} / \text{M})\text{L} - 1] / (\text{L} \times \text{S}).$$

where M = median, L = Box-Cox power transformation, and S = coefficient of variation. Missing BMI z-scores (n = 12,574) were imputed using regression predictions for deterministic imputation. Participants with a BMI z-scores >5 or < −5 were excluded (n = 79), following the Fr1da base paper (Ziegler et al., 2020).

2.3. LAN exposure

Population-based studies (Hurley et al., 2014; Kloog et al., 2009, 2010) investigating LAN exposure primarily used data derived from the U.S. Defense Meteorological Satellite Program (DMSP) images. However, the application of the DMSP data in epidemiological research may cause exposure misclassification, mainly due to their poor spatial resolution (~5 km^2 at nadir). In 2011, a new instrument namely Visible Infrared Imaging Radiometer Suite (VIIRS) (Elvidge, 2021; Elvidge et al., 2017) was launched jointly by National Aeronautics and Space

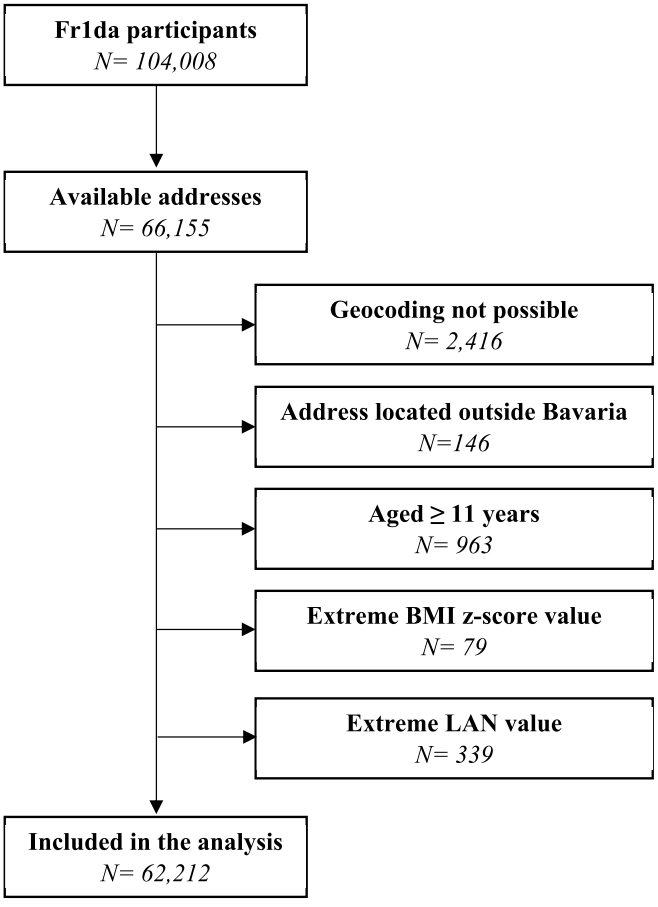

Fig. 1. Flow chart of the exclusion process.

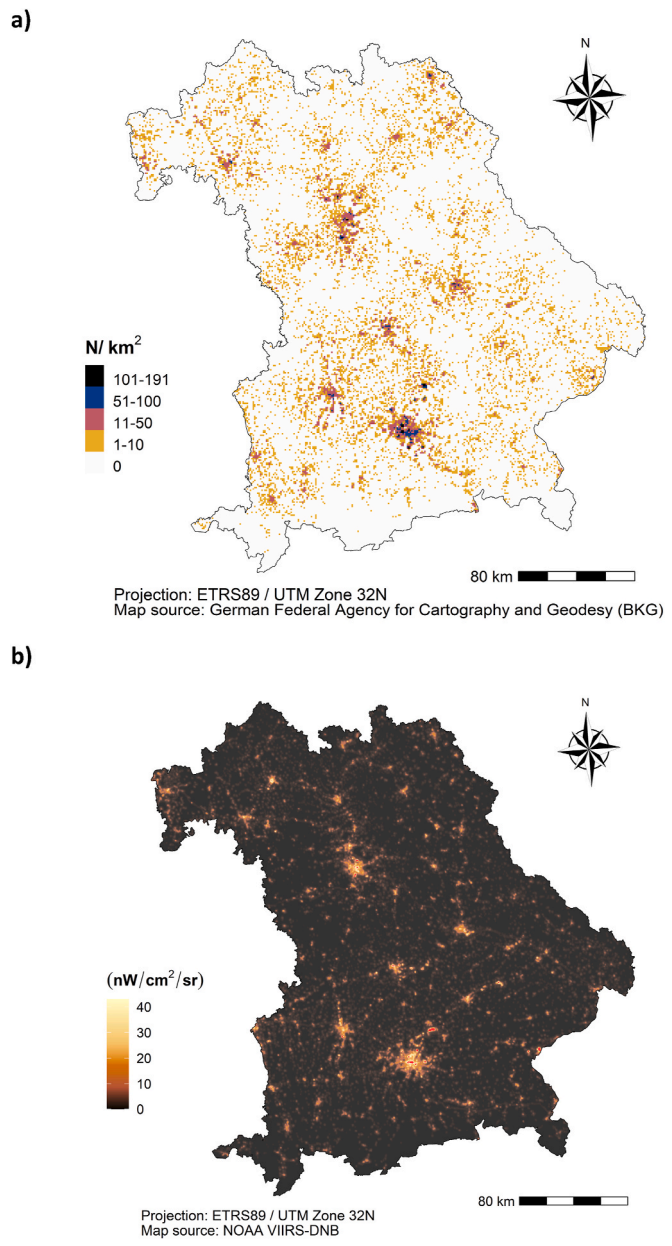

Fig. 2. Spatial distribution of study participants and LAN values in Bavaria, Germany. Maps show a) number of the participants (n = 62,212) in 1 km × 1 km grid cells and b) annual average of LAN (2015) at 300 m × 400 m grid resolution. **LAN**: Light at night; **nW/cm^2/sr**: nanoWatts per square centimeter per steradian. Note: The red grids on the LAN map represent the outliers.

Administration (NASA) and National Oceanic and Atmospheric Administration to collect high-quality radiometric data with worldwide coverage (National Oceanic and Atmospheric Administration (NOAA) National Oceanic and Atmospheric Administration (NOAA)National Oceanic and Atmospheric Administration (NOAA)) The new instrument has several improvements, such as a higher spatial resolution (~750 m^2 at nadir), a finer radiometric quantization (14 bit), a lower light imaging detection limit (~2 × 10^{-11} W cm^{-2} sr^{-1}), a wider dynamic range, radiometric calibration, and having no saturation. Moreover, the VIIRS overpass time is after midnight (around 1:30 a.m.), whereas the DMSP overpass time was early evening (around 7:30 p.m.) (Elvidge, 2013). A recent study in Israel (Rybnikova, 2017) compared DMSP and VIIRS data to investigate the association between light pollution and breast cancer incidence and reported the VIIRS data being a considerably stronger predictor.

We used monthly and yearly average raster grids from 2014 with coverage of 180° W, 75° N, 180° E, and 65° S and a spatial resolution of ~300 m × 400 m and assigned them to the residential address of the study participants. The address geocoding procedure has been described in our previous paper (Badpa et al., 2022). Exposure to LAN was assessed 1) at baseline (annual average for 2015), and 2) within one year prior to screening (by averaging the monthly mean values from the month of screening to the 12th month beforehand). We excluded outliers defined as LAN values more than the 3rd quartile +3*interquartile range (n = 339) (Fig. 2 (b)).

2.4. Confounders

Individual-level covariates included screening age (continuous) and sex (female or male). Percentage of households with low income provided by WiGeoGIS (Gesellschaft für Digitale Wirtschaftsgeographie) maps at 1 × 1 km^2 spatial resolution for 2014 was used as a measure of neighborhood socioeconomic status (SES). Level of urbanization of residence was derived from the Eurostat (EUROSTAT, 2020) maps for 2018 comprising three categories: 1 = cities (highly urbanized areas), 2 = towns and suburbs (intermediate urbanized areas) and, 3 = rural areas (low-urbanized areas).

2.5. Statistical analysis

We used generalized additive models to evaluate the associations between LAN exposure and BMI z-scores. We developed two models including 1) Crude model: with no adjustment; and 2) Main model: adjusting for age, sex, the percentage of low-income households and urbanization degree. Effect estimates are presented as percent change with 95% confidence intervals (CIs) in geometric mean of BMI z-score per 10 nW/cm^2/sr increase in LAN. To examine the exposure-response curve, we included LAN as a thin-plate spline and plotted the respective curves.

As a recent study in China indicated stronger effects of outdoor LAN on BMI z-score and overweight in males (Lin, 2022), we further performed a subgroup analysis stratified by sex. The potential effect modification by sex was investigated by adding an interaction term between LAN and sex (female vs male) into the main model.

In sensitivity analyses we 1) investigated whether the associations were similar in preschool ages by restricting the dataset to children aged 1.75–5.99 years; 2) checked the confounding role of other SES factors by replacing urbanization degree with population density (low/medium density: ≤400 vs. high density: >400 persons/km^2); 3) repeated all analyses using the dataset excluding imputed BMI z-scores; 4) rerun the main model excluding age and sex.

To validate our results we repeated the main analyses using Fr1da PLUS data, the second phase of Fr1da screening additional children between October 2019 and March 2021 in the same area. The recruitment strategy and screening process used in Fr1da PLUS were identical to those used in the original Fr1da study in order to ensure consistency and comparability. Data collection and management for Fr1da PLUS followed the same standards as the original Fr1da study, and all participants provided written informed consent. The variables measured in Fr1da PLUS were the same as those in the original Fr1da sample. For the validation analysis, we examined the data of 39,782 children out of 48,175 available addresses in Fr1da PLUS. Supplemental Figure S1 illustrates the exclusion details and spatial distribution of the validation sample. As the recruitment took place mostly during the Covid-19 pandemic, we generated two pandemic-related variables and further added them to the validation analysis: 1) a binary lockdown variable indicating whether the child was screened during severe lockdown periods (yes vs. no); 2) a monthly time trend starting from the first month of screening and added as a linear term.

All statistical analyses were performed using R 4.0.2 for Windows with the "mgcv" package and spatial analysis tools in the "raster",

"rgdal", and "sp" packages.

3. Results

3.1. Descriptive statistics

A total of 62,212 participants was included in our analyses. The mean age was 3.33 ± 1.28 years, 48.3% were female and the mean BMI z-scores was 0.12 ± 1.03. The mean LAN exposure was 7.93 ± 7.78 nW/cm^2/sr at baseline and slightly higher with 8.31 ± 7.97 nW/cm^2/sr within one year prior to screening (Table 1). On average, participants in the validation sample were older (4.41 ± 2.57) and had higher BMI z-score (0.27 ± 1.15) but similar levels of LAN exposure (Table S1).

3.2. Regression models

Per 10 nW/cm^2/sr increment in LAN, BMI z-scores considerably increased by 32.2% (95% CI: 23.6–40.8) at baseline and by 31.1% (22.7–39.5) within one year before screening (crude model). Similar associations were observed when additionally controlling for age, sex, low-income households, and urbanization degree but in smaller magnitude (baseline exposure, BMI z-score increment: 14.4%, 95% CI: 1.6–27.2; one-year exposure, BMI z-score increment: 12.1%, 95%CI: 0.0–24.8). When stratified by sex, the effect estimates were much more pronounced in males than in females in both the crude and adjusted model (Table 2). In the latter, females showed no considerable associations anymore and effect estimates were small but still positive. We also observed significant effect modification by sex in both the crude and adjusted model ($p_{interaction}<0.05$).

The inclusion of LAN as smooth function indicated linear relationships between both exposure variables and BMI z-scores (Supplemental Figure S2).

In sensitivity analyses, associations remained stable when we restricted the dataset to preschool-aged children. Controlling for population density instead of urbanization degree resulted in slightly higher estimates. Lower estimates were seen after the exclusion of age and sex from the main model (Fig. 3, Supplemental Table S2).

The validation analysis also confirmed positive associations, although the estimates were attenuated. In contrast to our main analysis, the stratification by sex showed no differences for females and males and similar patterns were observed when stratifying by sex, but the interaction term was not significant. Associations remained robust when further adjusting for the pandemic-related variables (Fig. 3, Supplemental Table S3).

Table 1
Descriptive statistics of the study participants.

Study variables	Fr1da (N = 62,212)	Male (N = 31,773)	Female (N = 29,690)	Pvalue
	Mean ± SD/N (%)	Mean ± SD/N (%)	Mean ± SD/ N (%)	
Age (years)	3.33 ± 1.28	3.32 ± 1.28	3.34 ± 1.29	0.63
Sex (female) (n miss = 749)	29,690 (48.3)			
BMI z-score (n miss = 1,034)	0.12 ± 1.03	0.10 ± 1.06	0.15 ± 1.00	<0.00
Households with low income (<1250 €) (%)	20.71 ± 22.31	20.66 ± 20.36	20.77 ± 22.26	0.20
Urbanization degree				0.11
cities	21,130 (34.0)	10,687 (33.6)	10,147 (34.2)	
towns and suburbs	23,547 (37.8)	12,006 (37.8)	11,277 (38.0)	
rural areas	17,533 (28.2)	9079 (28.6)	8265 (27.8)	
LAN (nW/cm^2/sr)				
Baseline exposure	7.93 ± 7.78	7.94 ± 7.83	7.92 ± 7.72	0.43
One-year exposure	8.31 ± 7.97	8.31 ± 8.02	8.31 ± 7.92	0.29

SD: Standard deviation; **Min**: Minimum; **Max**: Maximum; **BMI z-score:** Age- and sex-specific BMI; **N miss**: Number of missing observations; **LAN**: Light at night; **nW/cm^2/sr**: nanoWatts per square centimetre per steradian; **Baseline exposure**: Annual average in the study base year (2015); **One-year exposure**: Average exposure within one year prior to screening.
Pvalues are derived from Kruskal-Wallis rank sum test for continuous variables and Chi-square test for categorical variables, indicating sex differences in study variables.

Table 2
Percent changes (95% CIs) in BMI z-score per 10 nW/cm^2/sr increase in LAN.

LAN (nW/cm^2/sr)	Crude model[a]	Pvalue	Main model[b]	Pvalue
Overall				
Baseline exposure	32.2 (23.6–40.8)	<0.001	14.4 (1.6–27.2)	0.03
One-year exposure	31.1 (22.7–39.5)	<0.001	12.1 (0.0–24.8)	0.04
Female				
Baseline exposure	16.8 (7.0–26.7)	<0.001	3.3 (−11.1 – 17.6)	0.66
One-year exposure	17.7 (8.1–27.3)	<0.001	4.8 (−9.4 – 19.0)	0.51
Male				
Baseline exposure	54.2 (38.8–69.7)	<0.001	31.2 (8.6–53.8)	0.01
One-year exposure	50.3 (35.2–65.3)	<0.001	23.7 (1.3–46.2)	0.04

LAN: Light at night; **nW/cm^2/sr**: nanoWatts per square centimeter per steradian; **Baseline exposure**: Annual average exposure in the study base year (2015); **One-year exposure**: Average exposure within one year prior to screening.
[a] Crude model: with no adjustment.
[b] Main model: adjusted for age, sex, percentage of low-income households, and urbanization degree.

4. Discussion

Despite the growing body of evidence on the adverse effects of light pollution on human health, the planet has been more exposed to LAN over recent years (Hölker, 2010). In this large cross-sectional study of young children, we explored the association of outdoor LAN levels at baseline and within one year prior to screening with BMI z-scores. Our results provided epidemiological evidence that long-term exposure to LAN is associated with higher BMI after controlling for demographic and SES factors. There was also a suggestion of effect modification by sex and the effect estimates were stronger in males than in females.

Despite the limited studies conducted, our findings were consistent with previous studies in children, adults, and animals, meaning that variation in light exposure may affect body mass (Fonken et al., 2013; Pattinson et al., 2016; Reid et al., 2014). In a recent Chinese study among over 47,000 children and adolescents aged 6–18 years, participants exposed to higher outdoor LAN levels had larger BMI z-scores (β = 0.26, 95% CI: 0.18–0.33 per unit increase in LAN) and higher odds of being overweight or obese (the third quartile vs. the lowest quartile: overweight + obesity: OR = 1.40, 95% CI: 1.25–1.56; obesity: OR = 1.46, 95% CI: 1.29–1.65) (Lin, 2022). A Korean cross-sectional study among 10,040 adults found a positive association between outdoor artificial LAN and obesity, after adjustment for various confounders (OR = 1.20; 95% CI = 1.06–1.36) (Koo et al., 2016). A large-scale ecological study looking at data from more than 80 countries around the world reported a positive association between outdoor LAN exposure with overweight and obesity in adult women and men (B = 0.002–0.009, t = 2.739–2.877, P < 0.01 and B = 0.003–0.043, t = 1.972–2.658, P < 0.1, respectively), after adjusting for per capita GDP, level of urbanization, birth rate and regional differences in overweight and obesity prevalence (Rybnikova, 2016). A meta-analysis of 12 studies reported that higher LAN exposure was associated with 13% (summary odds ratio (SOR) = 1.13; 95% CI: 1.10–1.16) and 22% (SOR = 1.22, 95% CI; 1.07–1.38) higher odds of overweight and obesity, respectively (Lai, 2020).

Consistent results were reported for the association of LAN with BMI and the risk of overweight/obesity in shift workers. For example, a meta-

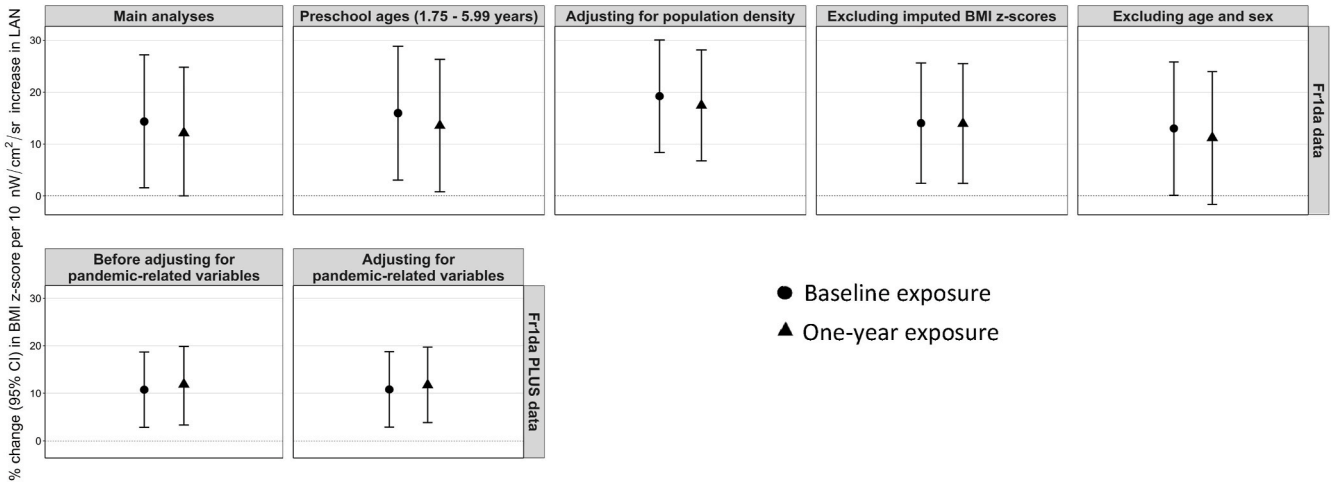

Fig. 3. Associations between exposure to LAN and BMI z-scores in children in Bavaria, Germany: sensitivity and validation analyses. **LAN**: Light at night; **nW/cm^2/sr**: nanoWatts per square centimetre per steradian; **Baseline exposure**: Annual average exposure in the study base year (2015 for Fr1da and 2019 for Fr1da PLUS); **One-year exposure**: Average exposure within one year prior to screening. All estimates were adjusted for age, sex, percentage of low-income households, and urbanization degree if not stated otherwise in the label at the top of the panels. The top row shows the results from the main analysis and sensitivity analyses (using only preschool ages, adjusting for population density instead of urbanization degree, excluding imputed BMI Z-scores, and not adjusting for age and sex). The second row shows the results from the validation analyses using Fr1da PLUS data, including the main model with the same confounders as in the main analysis and the main model after additional adjustment for two pandemic-related variables.

analysis including 28 studies revealed higher odds of obesity/overweight for night shift workers (OR = 1.23; 95% CI = 1.17–1.29) (Sun et al., 2018). However, the results may not be generalized to the general population because the levels of LAN exposure in shift workers are substantially higher than in the general population.

Moreover, our main analysis suggested that exposure to LAN may have a stronger effect on weight gain in males than in females and is thus in line with the findings of the study in China in children (Lin, 2022). Possible explanations for the sex difference might include hormonal differences or susceptibility to environmental exposures. However, in our validation analysis, we could not confirm this pattern and observed similar associations for both females and males. Thus, additional research is needed to explore these mechanisms further.

However, in our validation analysis, we could not confirm this pattern and observed similar associations for both females and males. One possible explanation for not observing the sex difference in the validation analysis could be related to the sample size. The number of participants in the validation analysis was not large enough to detect a difference in effect size between males and females. Thus, additional research is needed to explore these mechanisms further. Even though this is an epidemiological study looking into the links between LAN exposure and BMI and the findings do not directly attribute a causal relationship, the results are in line with results from previous laboratory experiments (Fonken et al., 2010). Fronken et al. (Fonken et al., 2013) reported changes in the circadian clock in mice exposed to dim LAN temporally altered feeding behavior and increased weight gain. Arbel et al. (Arble et al., 2009) showed that after a 6-week period and under similar locomotor activity and calorie intake conditions, mice fed only during the 12-h light phase gained significantly more weight than mice fed only during the 12-h dark phase (32 ± 1.5 g and 26 ± 1.7 g in the case and control groups, respectively; $p < 0.05$).

Several pathways have been suggested through which artificial light pollution could potentially affect human health. For example, it is hypothesized that LAN can alter the circadian rhythm. Circadian cycles regulate almost all organisms to synchronize their physiologic process with daily changes in the environment (Aulsebrook et al., 2018). Disruption of the 24-h light-dark cycle may cause both external and internal desynchrony, impair metabolic functions and result in a variety of disorders such as obesity and diabetes (Moreno, 2011; Navara and Nelson, 2007).

Circadian misalignment induced by LAN exposure can also affect sleep duration. Studies showed short sleep duration was associated with obesity in all age groups (Chen, 2008) and children (Chahal et al., 2013). A review by Cho et al. reported negative health effects of exposure to bright light while sleeping in children and adolescents (Cho et al., 2015). Sleep deprivation and desynchronized sleep-wake cycles may affect metabolism and lead to higher risks of obesity (Lai, 2020). In addition, it can induce behavioural changes such as dietary patterns and physical activity which might be potential mediators in the LAN-obesity relationship (Park et al., 2019). Studies in humans have shown that phase-delayed feeding patterns are associated with altered metabolism and increased BMI (Garaulet and Madrid, 2010).

Another pathway could be through suppression of nocturnal melatonin, a pineal hormone which is primarily known for its critical regulating role in circadian rhythms, sleep onset and the immune system (Karamitri and Jockers, 2019). Melatonin secretion is low during the daytime but high in the dark. Exposure to light during evening and night can delay or suppress normal melatonin secretion which can result in several diseases in humans, including different types of cancer, metabolic syndrome, and weight gain (Tähkämö et al., 2019). An experimental study reported significantly lower melatonin concentrations by exposure to light in both children and adults (Higuchi et al., 2014). The study also showed melatonin suppression by light was particularly pronounced in children, suggesting that melatonin is more sensitive to light during childhood.

4.1. Strengths and limitations

Our study has several strengths. First, to the best of our knowledge, this study is the first epidemiological evidence of the associations between outdoor LAN in pre-pubertal children. Second, This study is based on a large sample size which enabled us to investigate the associations in a statistically precise manner. Third, participants were geographically distributed across the study area which ensured large exposure contrasts. Fourth, we used the VIIRS nighttime light radiance data that have significant improvements in many aspects over the DMPS data which were mainly used in previous epidemiological studies. Fifth, along with the evidence from other cross-sectional and laboratory studies, the association found between outdoor LAN and childhood body mass in our study may help change governmental policy and public health strategies

to reduce outdoor LAN. Finally, we also performed validation and sensitivity analyses and the results were similar to the main results, indicating the robustness of our findings.

Our results may be subjected to several limitations. First, we used satellite data to estimate individual LAN exposure, while outdoor LAN values may not precisely reflect individual LAN exposure as indoor LAN from electronic lamps, television, smartphones and computer screens can also affect individual exposure levels. However, the objective of this study was to investigate outdoor light pollution in order to determine whether it is associated with children's health, especially BMI level, which was found to be considerably associated. In addition, compared to indoor LAN, outdoor LAN exposure is more likely to be reduced by effective government regulations to limit outdoor artificial light pollution. Second, it has previously been shown that the health effects of LAN are related not only to the intensity of light per se, but also to the exposure conditions such as the duration and biological time of the exposure (Cho et al., 2015). These data were not available in our study. The lack of residential history is another limitation. The residential addresses at the screening time were used as a proxy measure for exposure to LAN. Relocation and changes in light pattern might have led to exposure misclassification and biased risk estimates. However, we believe misclassification bias due to mobility changes during childhood to be relatively small because of low mobility rates. A German study reported that 73.3% of the study children lived almost half of their life at the registration address or nearby (Heinrich et al., 1999). Moreover, the BMI variable used in this study was based on self-reported information on children's weight and height, which is prone to misclassification. Finally, because Fr1da was designed to investigate the early stages of pancreatic islet autoimmunity, the collected data are insufficient for an in-depth study. For example, we could not determine potential contributors including indoor lighting and lifestyle-related factors.

5. Conclusion

Our results show that increased exposure to outdoor LAN was associated with higher body mass in children and the associations were stronger in boys. This may draw attention to investigating environmental light as a potential obesogenic factor during human development, suggesting that lowering artificial LAN levels and returning to natural light patterns might be useful interventions for pediatric obesity prevention. Continued research on the impact of indoor and outdoor LAN and their independent and combined effects on human health as well as further interventional studies are needed.

Authors' contributions

All authors contributed to the study design and conceptualization. The underlying data were verified and analyzed by MB, KW, and AS, and all authors interpreted the findings. The manuscript was drafted by MB with support from KW, AS, and AGZ. All authors read and critically revised the manuscript and approved the final version. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. AGZ led the project. MB, KW, and AS had final responsibility for the decision to submit for publication.

Role of funding source

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript, and decision to submit the manuscript for publication.

Ethics committee approval

The Fr1da study was approved by the institutional review board at Technical University Munich.

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 data that has been used is confidential.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2023.116325.

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IV. Appendix

Publication 3: Air Pollution, Traffic Noise, Greenness, and Temperature and the Risk of Incident Type 2 Diabetes

Methods

Study population

The third publication of this thesis was based on data collected in the Cooperative Health Research in the Region of Augsburg (KORA) cohort study. As part of the KORA study, a sequence of four cross-sectional surveys was conducted at five-year intervals (denoted as S1 to S4). Each survey involved selecting a random selection of participants from the urban area of Augsburg, Germany, and the two neighboring rural counties of Augsburg and Aichach-Friedberg. The study population for this analysis comprised a total of 9,116 participants aged between 25 and 74 years old, drawn from the two baseline surveys, S3 (1994-1995), and S4 (1999-2001), with available follow-up information until 2016. Figure A1 presents an overview of the KORA study.

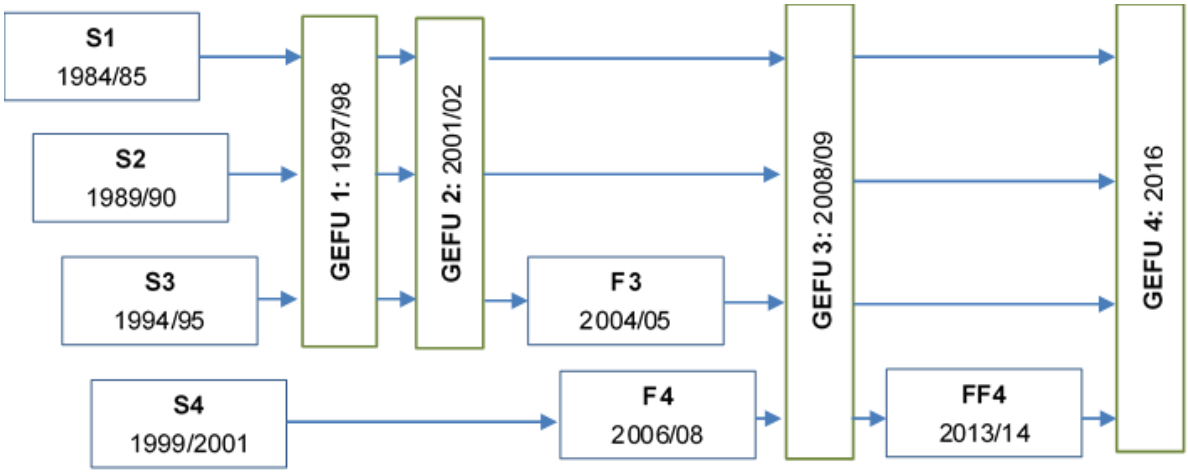

Figure A1. Overview of the KORA study

Outcome definition

The incidence of T2D was determined through written questionnaires administered to all participants during follow-up examinations. To validate the incident T2D status and the date of diagnosis, a questionnaire was sent to the treating physician, or medical chart review was conducted. Participants were considered incident cases of T2D only if the treating physician explicitly reported a T2D diagnosis, if the diagnosis was documented in medical records, or if the participant reported the use of anti-diabetic medication during any follow-up period.

Exposure data assessment

Annual average residential exposure to nitrogen oxides (NO_2, NO_x), ozone (O_3), different PM size classes (PM_{10}, $PM_{2.5}$, PM_{coarse}), $PM_{2.5absorbance}$ (as indicator for soot), and particle number concentration (PNC, an indicator for ultrafine particles) was estimated using land-use regression (LUR) models. These models were based on air pollution measurements recorded at 20 locations in the KORA study area during three two-week periods in 2014-2015, and were developed by statistically regressing the recorded annual average concentrations against spatial predictors derived from geographic information system participants' residential exposure levels were determined based on these models.

The annual average day-evening-night sound level for 2011 was determined using a three-dimensional ground model developed by ACCON GmbH. This comprehensive model considered factors such as breaking edges, bridge constructions, and noise abatement walls, particularly in relation to public roads. Additionally, it took into account characteristics from approximately 87,000 buildings within the study area.

NDVI data derived from Landsat 5 Thematic Mapper satellite images taken in 1994-1995 (S3) and 1999-2001 (S4) at a spatial resolution of 30 meters was used to assess greenness within 300m and 1000m buffers. In this study, all negative values were set to zero.

Annual mean and standard deviation (SD) air temperature data for 2000 were extracted from temperature maps developed through the multi-stage modeling approach involving various data sources for entire Germany at 1 km x 1 km resolution.

Statistical analysis

The longitudinal associations between environmental factors and T2D were examined using Cox Proportional Hazards models, with follow-up time as the underlying timescale and an indicator variable for subcohort (S3/S4). Participants were censored at the earliest occurrence of an event, withdrawal request, death, emigration, loss to follow-up, or the end of the study period. Three predefined models with varying levels of confounder adjustment were employed. Furthermore, effect modification was assessed by introducing interaction terms between each exposure variable and potential effect modifiers, such as sex, age, obesity, educational level, and physical activity.

Key findings

The findings from the third publication revealed that while some positive effect estimates were observed, overall, there were weak or no significant associations between environmental exposures and incident T2D. Furthermore, the inclusion of additional covariates in the models had only minimal impacts on the effect estimates. Interestingly, the effects of NO_x, O_3, PM_{10}, and PNC were found to be modified by sex, with NO_x, PM_{10}, and PNC having more pronounced effects in males, while O_3 showed stronger effects in females, indicating potential sex-specific influences. Additionally, the effect of $PM_{2.5absorbance}$ was modified by educational level, with a more pronounced effect observed in highly educated individuals.

- **Key finding 3:** Exposure to environmental factors showed weak or no significant associations with incident T2D, with some modified effects based on sex (NO_x, O_3, PM_{10}, and PNC) and educational level ($PM_{2.5absorbance}$).

Publication 3

Title: Air Pollution, Traffic Noise, Greenness, and Temperature and the Risk of Incident Type 2 Diabetes: Results from the KORA Cohort Study

Authors: Mahnaz Badpa, Alexandra Schneider, Lars Schwettmann, Barbara Thorand, Kathrin Wolf, Annette Peters

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Original Research Article

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Air pollution, traffic noise, greenness, and temperature and the risk of incident type 2 diabetes

Results from the KORA cohort study

Mahnaz Badpa[a,b,*], Alexandra Schneider[a], Lars Schwettmann[c,d], Barbara Thorand[a,b,e], Kathrin Wolf[a], Annette Peters[a,b,e]

Introduction: Type 2 diabetes (T2D) is a major public health concern, and various environmental factors have been associated with the development of this disease. This study aimed to investigate the longitudinal effects of multiple environmental exposures on the risk of incident T2D in a German population-based cohort.

Methods: We used data from the KORA cohort study (Augsburg, Germany) and assessed exposure to air pollutants, traffic noise, greenness, and temperature at the participants' residencies. Cox proportional hazard models were used to analyze the associations with incident T2D, adjusting for potential confounders.

Results: Of 7736 participants included in the analyses, 10.5% developed T2D during follow-up (mean: 15.0 years). We found weak or no association between environmental factors and the risk of T2D, with sex and education level significantly modifying the effects of air pollutants.

Conclusion: Our study contributes to the growing body of literature investigating the impact of environmental factors on T2D risks and suggests that the impact of environmental factors may be small.

Keywords: Air pollution; Greenness; Traffic noise; Temperature; Type 2 diabetes; Environmental epidemiology; Population-based cohort

[a]Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Munich, Germany; [b]Institute for Medical Information Processing, Biometry and Epidemiology (IBE), Faculty of Medicine, Pettenkofer School of Public Health, LMU Munich, Munich, Germany; [c]Institute of Health Economics and Health Care Management, Helmholtz Zentrum München, Munich, Germany; [d]Department of Health Services Research, School of Medicine and Health Sciences, Carl von Ossietzky University of Oldenburg, Oldenburg, Germany; and [e]German Center for Diabetes Research (DZD), Partner München-Neuherberg, Neuherberg, Germany

Kathrin Wolf and Annette Peters shared last authorship.

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

M.B. did the data analyses and wrote the manuscript. M.B., A.S., L.S., B.T., K.W., and A.P., have verified the underlying data and reviewed the manuscript. A.S., K.W., and A.P. were involved in the study design, results interpretation, and review of the manuscript. A.P. provided oversight on the KORA study design. K.W. was involved in the acquisition of the KORA data, the modeling of air pollution concentrations as well as the assignment of all exposure data. All authors read and approved the final manuscript.

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**Corresponding Author, Address: Institute of Epidemiology, Helmholtz Munich, Ingolstädter Landstrasse 1, 85764 Neuherberg, Germany.*
E-mail: Mahnaz.badpa@campus.lmu.de (M. Badpa).

Introduction

Type 2 diabetes (T2D) is projected to become the 7th highest cause of mortality by 2030.[1,2] Alongside well-known risk factors such as obesity, physical inactivity, and genetic predisposition, several environmental factors have been linked to T2D risk in previous studies.[3,4]

Four reviews[5–8] compiled data from epidemiological studies and suggest a positive association between long-term exposure to particulate matter (PM) and nitrogen dioxide (NO_2), and prevalence and incidence of T2D. Similarly, meta-analyses suggested a positive correlation between exposure to traffic noise, particularly during nighttime, and a higher risk of T2D incidence.[9,10] Moreover, access to green spaces, as measured by either the proportion of greenness or the proximity to green areas, has shown beneficial effects on reducing the likelihood of developing T2D.[11] The association of temperature with T2D risk and fasting plasma glucose levels is, however, complex, with some studies suggesting increased risk with higher temperatures,[12] while others indicated U-shaped relationships involving both high and low temperatures.[13]

Despite these findings, studies assessing multiple environmental exposures are still scarce, and there is a lack of longitudinal investigations examining the link with T2D incidence. In this article, we

What the study adds

This study provides critical insights into the link between environmental exposures and T2D. It emphasizes the significance of exposure to $PM_{2.5}$, highlights the need for cautious interpretation due to uncertainties, and underscores the sex-specific variations in pollutant effects on T2D risk. These findings contribute to our understanding of T2D risk factors.

aimed to investigate the longitudinal effects of various exposures on T2D incidence in a German population-based cohort.

Methods

Study population

We used data from the third (KORA S3, 1994–1995, n = 4856) and fourth (KORA S4, 1999–2001, n = 4260) survey of the KORA (Cooperative Health Research in the Region of Augsburg) study[14] and follow-up information until 2016. For our analysis, we excluded participants who requested data withdrawal (N = 80), with a diabetes diagnosis at baseline (N = 381), lacked follow-up data (N = 521), with unknown residential address (N = 270), or had missing values in the main model's covariates (N = 128) (Figure S1, http://links.lww.com/EE/A267).

Incident T2D assessment

T2D incidence was assessed through self-reported, clinically diagnosed diabetes assessed through follow-up questionnaires that were validated by physicians, medical chart review, or self-reported use of glucose-lowering medication.[15,16] Self-reported dates of diagnosis, were verified through medical records or physician contact. (Text S1, http://links.lww.com/EE/A267).

Exposure assessment

Annual mean concentrations of air pollutants, including nitrogen oxides (NO_2, NO_x), ozone (O_3), PM in different size classes (PM_{10} [≤10 µm], $PM_{2.5}$ [≤2.5 µm], $PM_{2.5absorbance}$ [$PM_{2.5abs}$] as an indicator for soot, PM_{coarse} [2.5–10 µm]), and particle number concentration (PNC) as an indicator for ultrafine particles were estimated using land-use regression models for 2014–2015.[17] Traffic noise exposure was estimated for 2011 using the noise and air pollution information system for Augsburg city and georeferenced pictures for rural areas.[18] Greenness within 300 m and 1000 m buffers was assessed using normalized difference vegetation index (NDVI) from Landsat 5 Thematic Mapper satellite images for 1994–1995 (S3) and 1999–2001 (S4).[19] Annual mean and standard deviation (SD) air temperature were extracted from temperature maps developed within a multi-stage modeling approach for 2000.[20] All exposures were assigned to the participants' residential baseline addresses.

Statistical methods

We used the Cox proportional hazards model to analyze the association between environmental factors and incident T2D, with follow-up time as the underlying timescale and an indicator variable for subcohort (S3/S4). Participants were censored at the time of the event, withdrawal request, death, emigration, loss to follow-up, or the end of the study period, whichever came first.

Three models with varying degrees of confounder adjustment were specified a priori based on previous research[21] and data availability. The minimum model included age, sex, and subcohort indicator, the main model was further adjusted for other baseline characteristics (body mass index [BMI], smoking behavior, alcohol consumption, education level, physical activity, and dietary score[22]), and the extended model additionally included clinical information (cardiovascular diseases (CVD), waist-hip ratio, and cholesterol level) (Text S2, http://links.lww.com/EE/A267).

In premodels, we tested nonlinearity but observed no considerable deviance from linearity. Therefore, exposure variables were included as linear terms (Figure S2, http://links.lww.com/EE/A267).

Effect modification was assessed by including an interaction term between each exposure variable and potential effect modifiers (sex, age, obesity, educational level, and physical activity) (Figure S3, http://links.lww.com/EE/A267). Results are presented as hazard ratios (HRs) per interquartile range (IQR) increase in exposure variables with 95% confidence intervals (CIs).

We used R 3.6.1 with "survival," "mgcv," and "raster" packages for all statistical analyses.

Sensitivity analysis

To evaluate the robustness of our findings, we used an alternative statistical model (Poisson regression) and applied the main model separately for the two subcohorts.

Results

Altogether, 7864 (86.3%) participants out of 9116 participants were included in our study (Figure S1, http://links.lww.com/EE/A267). Of these, 10.5% developed T2D until the end of follow-up (Table 1). At baseline, the mean age was 49.2 years, almost half of the participants were male (49.2%), and the mean BMI was 27.0 kg/m². About a quarter of the participants reported being active smokers, and 47.0% reported being physically active (Table 1).

Annual average concentrations of NO_2, PM_{10}, and $PM_{2.5}$ at participants' residences were below the European air quality standard values but exceeded the current WHO guideline values. The mean levels of traffic noise were above the European-recommended maximum values (Table 2).

Although some of the environmental exposures showed positive effect estimates (e.g. $PM_{2.5}$ showing the strongest effect estimate) confidence limits were large as estimated with the main model (Figure 1). The incorporation of additional covariates in the models had little to moderate impact on the HRs and 95% CIs compared to the minimum adjusted model. Sex modified the effect of NO_x, O_3, PM_{10}, and PNC on T2D incidence, with O_3 being more pronounced in females and the others in males (Figure S3, http://links.lww.com/EE/A267). The effect of $PM_{2.5abs}$ was modified by educational level.

Poisson models provided similar associations (Figure S4, http://links.lww.com/EE/A267) as the main Cox model. Also, stratified analyses by subcohort showed comparable results (Figure S5, http://links.lww.com/EE/A267) to the main pooled model.

Discussion

Our longitudinal analysis showed weak or no associations between the various environmental factors and T2D incidence, after adjusting for confounding factors. These results were consistent across different analytical approaches and stratified analyses of the two subcohorts. Considering the lack of significant associations in the single-exposure models, we refrained from conducting multi-exposure models.

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Table 1.

Baseline characteristics of study participants

Variable	KORA S3 + S4 (n = 7864)[a]		KORA S3 (n = 4042)[a]	KORA S4 (n = 3822)[a]
	Missing n (%)	Mean ± SD/ n (%)	Mean ± SD/ n (%)	Mean ± SD/ n (%)
Incident T2D during follow-up	0 (0.0)	829 (10.5)	486 (12.0)	343 (9.0)
Age (years)	0 (0.0)	49.2 ± 13.8	49.6 ± 13.9	48.8 ± 13.7
Sex (male)	0 (0.0)	3,873 (49.2)	2020 (50.0)	1852 (48.5)
BMI (kg/m²)	71 (0.9)	27.0 ± 4.5	27.0 ± 4.4	27.0 ± 4.6
Waist-hip ratio	55 (0.7)	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1
Education level	8 (0.1)			
Low		1148 (14.6)	676 (16.7)	472 (12.4)
Middle		5671 (72.2)	2895 (71.6)	2776 (72.8)
High		1037 (13.2)	470 (11.6)	567 (14.9)
Smoking status	5 (0.1)			
Current smoker		2012 (25.6)	1013 (25.1)	999 (26.2)
Ex-smoker		2486 (31.6)	1243 (30.8)	1243 (32.6)
Never smoker		3361 (42.8)	1786 (44.2)	1575 (41.3)
Alcohol intake (g/day)	17 (0.2)	16.3 ± 22.1	16.8 ± 22.8	15.9 ± 21.3
Physical activity (active)	18 (0.2)	3687 (47.0)	1784 (44.1)	1903 (50.0)
Dietary score	21 (0.3)	15.3 ± 3.6	15.3 ± 3.6	15.2 ± 3.6
Cardiovascular disease (yes)	17 (0.2)	3057 (39.0)	1674 (41.4)	1383 (36.3)
Total cholesterol (mg/dL)	139 (1.8)	229.2 ± 43.7	230.8 ± 44.0	227.4 ± 43.3

[a]n refers to the sample size before excluding participants with missing confounders used in the main model.

BMI indicates body mass index; KORA, Cooperative Health Research in the Region of Augsburg; S3, Third cross-sectional health survey of the KORA cohort; S4, Fourth cross-sectional health survey of the KORA cohort; SD, standard deviation; T2D, type 2 diabetes.

Table 2.

Descriptive statistics of annual average air pollutant concentrations, traffic noise, NDVI, and air temperature at residences

Variable		KORA S3 + S4 (n = 7864)[a]	KORA S3 (n = 4042)[a]	KORA S4 (n = 3822)[a]
		Mean ± SD	Mean ± SD/ n (%)	Mean ± SD/ n (%)
Air pollutant	NO_2 (μg/m³)	14.2 ± 4.4	14.1 ± 4.3	14.5 ± 4.5
	NO_x (μg/m³)	22.1 ± 7.1	22.0 ± 6.9	22.2 ± 7.4
	O_3 (μg/m³)	38.8 ± 2.4	38.8 ± 2.4	38.9 ± 2.5
	PM_{10} (μg/m³)	16.6 ± 1.5	16.5 ± 1.5	16.7 ± 1.5
	$PM_{2.5}$ (μg/m³)	11.8 ± 1.0	11.8 ± 1.0	11.8 ± 1.0
	$PM_{2.5, abs}$ (10^{-5}/m)	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2
	PM_{coarse} (μg/m³)	4.9 ± 1.0	4.8 ± 1.0	5.0 ± 1.0
	PNC (10^3/cm³)	7.3 ± 1.8	7.2 ± 1.8	7.3 ± 1.8
Noise	Daily average traffic noise (dB)	54.7 ± 6.6	54.6 ± 6.6	54.9 ± 6.6
	Nighttime average traffic noise (dB)	45.7 ± 6.4	45.6 ± 6.3	45.8 ± 6.4
Greenness	NDVI in 300 m buffer	0.5 ± 0.1	0.4 ± 0.1	0.5 ± 0.1
	NDVI in 1000 m buffer	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1
Temperature	Annual mean temperature (°C)	10.6 ± 0.4	10.6 ± 0.4	10.6 ± 0.4
	Annual SD temperature (°C)	6.1 ± 0.2	6.0 ± 0.2	6.1 ± 0.2

The EU air quality standard values are 40 μg/m³ for PM_{10} and NO_2, and 25 μg/m³ for $PM_{2.5}$. The WHO air quality guideline values are 10 μg/m³ for NO_2, 15 μg/m³ for PM_{10}, and 5 μg/m³ for $PM_{2.5}$. The WHO air quality guideline value for O_3 is 60 μg/m³, which is calculated based on the peak season. The EU-recommended maximum value for traffic noise during night is 40 dB in residential areas.

[a]n refers to the sample size before excluding participants with missing confounders used in the main model.

NDVI values below 0 were excluded since they represent water or bare rocks.

KORA indicates Cooperative Health Research in the Region of Augsburg; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; NO_x, nitrogen oxide; O_3, ozone; PM_{10}, particulate matter with an aerodynamic diameter ≤10 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm; $PM_{2.5,abs}$, $PM_{2.5}$ absorbance; PM_{coarse}, particulate matter with an aerodynamic diameter of 2.5–10 μm; PNC, particle number concentration; S3, Third cross-sectional health survey of the KORA cohort; S4, Fourth cross-sectional health survey of the KORA cohort; SD, standard deviation.

Systematic reviews and meta-analyses have reported both positive and null associations between environmental exposures and T2D risk, indicating the complexity of these relationships.[3,11,23] They indicated robust results for T2D prevalence and heterogeneity between studies for incident T2D. A meta-analysis of cohort studies found higher risks of T2D associated with exposure to $PM_{2.5}$ (risk ratio [RR]: 1.39 [1.14–1.68]), PM_{10} (RR: 1.34 [1.22–1.47]), and NO_2 (RR: 1.11 [1.07–1.16]),[5] while another meta-analysis only reported an association for $PM_{2.5}$.[3] Our study found positive but nonsignificant associations for $PM_{2.5}$ (HR: 1.07 [0.97–1.17]) and weak associations for other air pollutants. Air pollution may contribute to insulin resistance and chronic inflammation, which are key mechanisms in the development of T2D.[24]

Similarly, a higher diabetes risk has been associated with higher levels of traffic noise.[9,23] However, this was not confirmed in a meta-analysis of four studies (pooled odds ratio [OR]: 1.49 [0.78–2.82]).[11] In our study, we observed weak and nonsignificant associations for traffic noise during the day (HR: 1.02 [0.93–1.11]) or at night (HR: 1.02 [0.94–1.11]). Noise-induced sleep disturbance and chronic stress may contribute to insulin resistance and an increased risk of diabetes.[25]

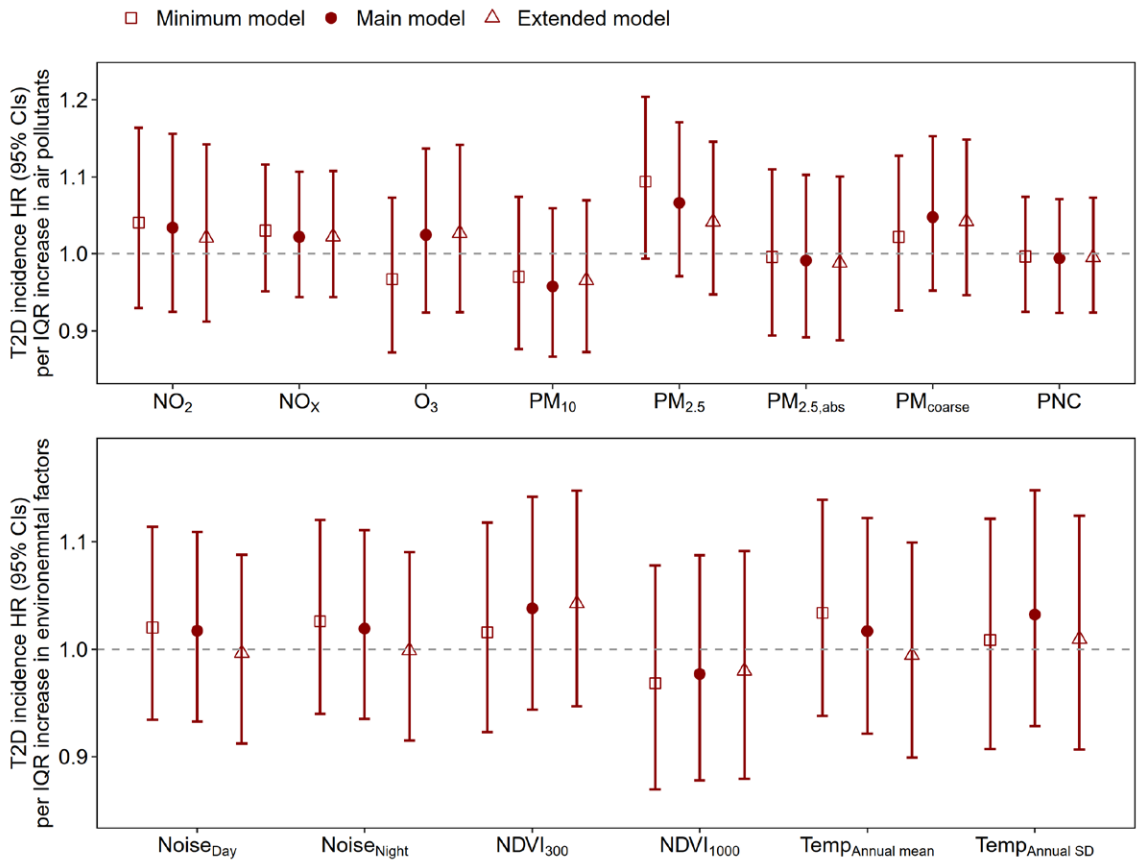

Figure 1. Hazard ratios and 95% CIs for the associations between environmental factors, and the risk of incident T2D. Minimum model included age, sex, and subcohort indicator. Main model was further adjusted for BMI, smoking status, alcohol consumption, education level, physical activity, and dietary score. Extended model additionally included cardiovascular diseases, waist-hip ratio, and total cholesterol level. HRs are expressed per IQR increase for each exposure variable. The IQRs were as follows: NO_2: 7.0 μg/m³, NO_X: 8.1 μg/m³, O_3: 3.6 μg/m³, PM_{10}: 2.2 μg/m³, $PM_{2.5}$: 1.3 μg/m³, $PM_{2.5,abs}$: 0.3 10^{-5}/m, PM_{coarse}: 1.4 μg/m³, PNC: 1.9 10^3/cm³, $Noise_{Day}$: 8.2 dB, $Noise_{Night}$: 7.9 dB, $NDVI_{300}$:0.12, $NDVI_{1000}$: 0.14, $Temp_{annual\ mean}$: 0.6 °C, $Temp_{annual\ SD}$: 0.2 °C. NDVI values below 0 were excluded since they represent water or bare rocks. Note: Minimum and main models were based on data for 7696 participants. In extended models we excluded 141 participants with missing clinical information, resulting in 7555 participants. BMI indicates body mass index; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; NO_x, nitrogen oxide; O_3, ozone; PM_{10}, particulate matter with an aerodynamic diameter ≤10 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm; $PM_{2.5,abs}$, $PM_{2.5}$ absorbance; PM_{coarse}, particulate matter with an aerodynamic diameter of 2.5–10 μm; PNC, particle number concentration; SD, standard deviation; T2D, type 2 diabetes; Temp, temperature.

Systematic reviews reported that green spaces may have a protective effect on T2D.[11,26,27] A meta-analysis provided further evidence that exposure to greenspace is associated with wide-ranging health benefits, including a significant reduction in T2D incidence (pooled OR: 0.72 [0.61–0.85]).[28] However, we observed only weak associations. Green spaces play a crucial role in promoting physical activity and protecting against air and noise pollution, all of which may contribute to mitigating chronic inflammation processes.[29]

Studies on the effect of air temperature on T2D risk are limited. In a study, diabetes incidence increased by 0.31 [0.19–0.43] per 1 °C increase in annual mean temperature.[30] In this study, we observed a weak effect of annual mean air temperature increase (HR: 1.02 [0.92–1.12]). In previous research, both higher temperatures[31] and lower exposure to cold[32] were associated with increased insulin resistance. However, our study found no evidence of this effect.

As previously reported,[33–36] our study found that sex and education level significantly modified air pollutant effects. However, our results showed opposite directions, possibly due to population variations, exposure misclassification, or chance findings. Lifestyle and physiological differences between sexes or education levels may contribute to these variations.[34,37]

Strengths and limitations

Our study's strengths include the use of two datasets from a large and well-characterized population-based prospective cohort, comprehensive exposure assessment, adjustment for important confounders, and application of various analytical approaches. However, limitations such as single-time point exposure assessment, potential exposure misclassification, not accounting for residential mobility from baseline to follow-up, and lack of information on other lifestyle and clinical factors should be acknowledged. Potentially, measurement error may have resulted in underestimation of the underlying associations and insufficient statistical power may be responsible for the wide CI. Our analyses were also restricted to a specific population and geographic region.

Conclusions

Although we observed weaker associations than previous studies indicated, our study contributes to the literature on environmental factors on incident T2D. Future research should continue exploring the role of the environment in T2D development.

Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report

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List of scientific publications to date

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Dean's Office Medical Faculty
Faculty of Medicine

Affidavit

Badpa, Mahnaz

Surname, first name

UKE, Christoph-Probst-Weg 1, 20251 Hamburg

Address

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Hamburg, 21.05.2024

Place, Date

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Dean's Office Medical Faculty
Doctoral Office

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Doctoral candidate: Mahnaz Badpa

Address: UKE, Christoph-Probst-Weg 1, 20251 Hamburg

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