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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

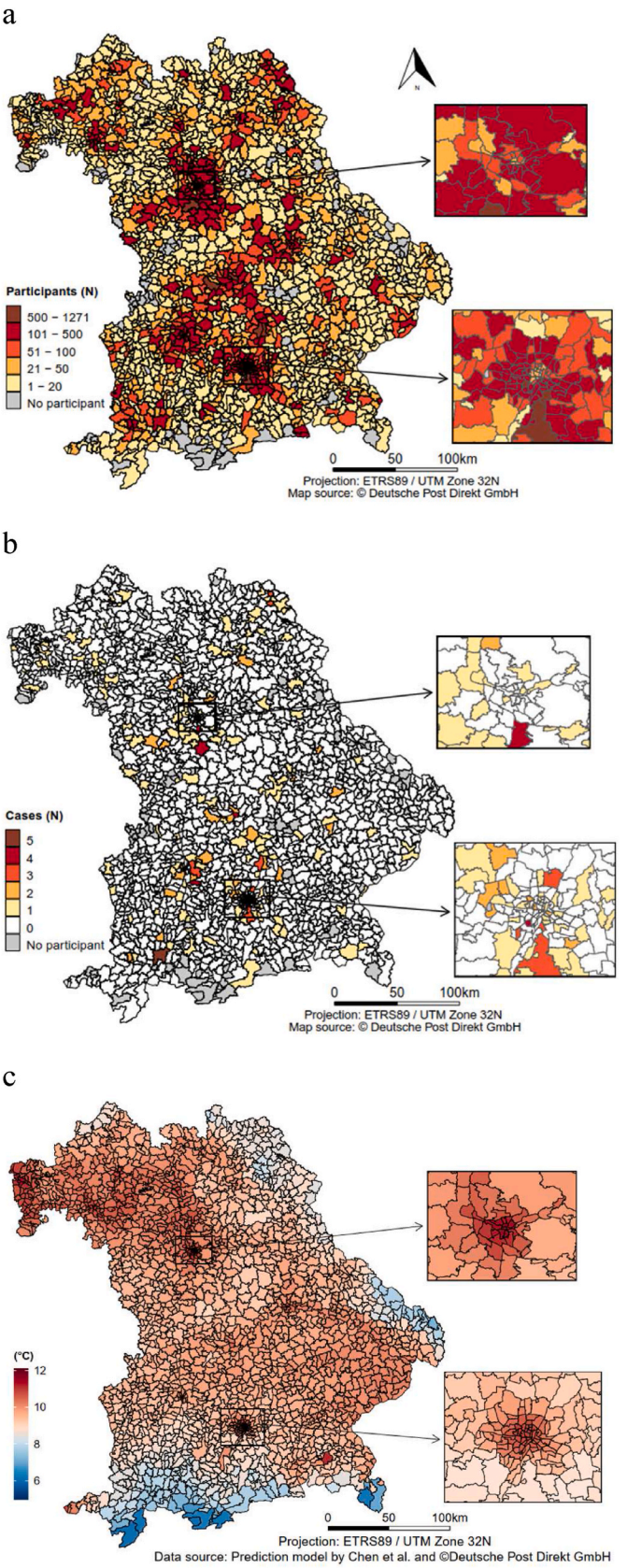

Fig. 1. Fr1da study region and distribution of participants (a), frequency of islet autoimmunity (b) and zip-code mean of annual air temperature (in the year of study entry (2015)) (c) across Bavaria, Germany.

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

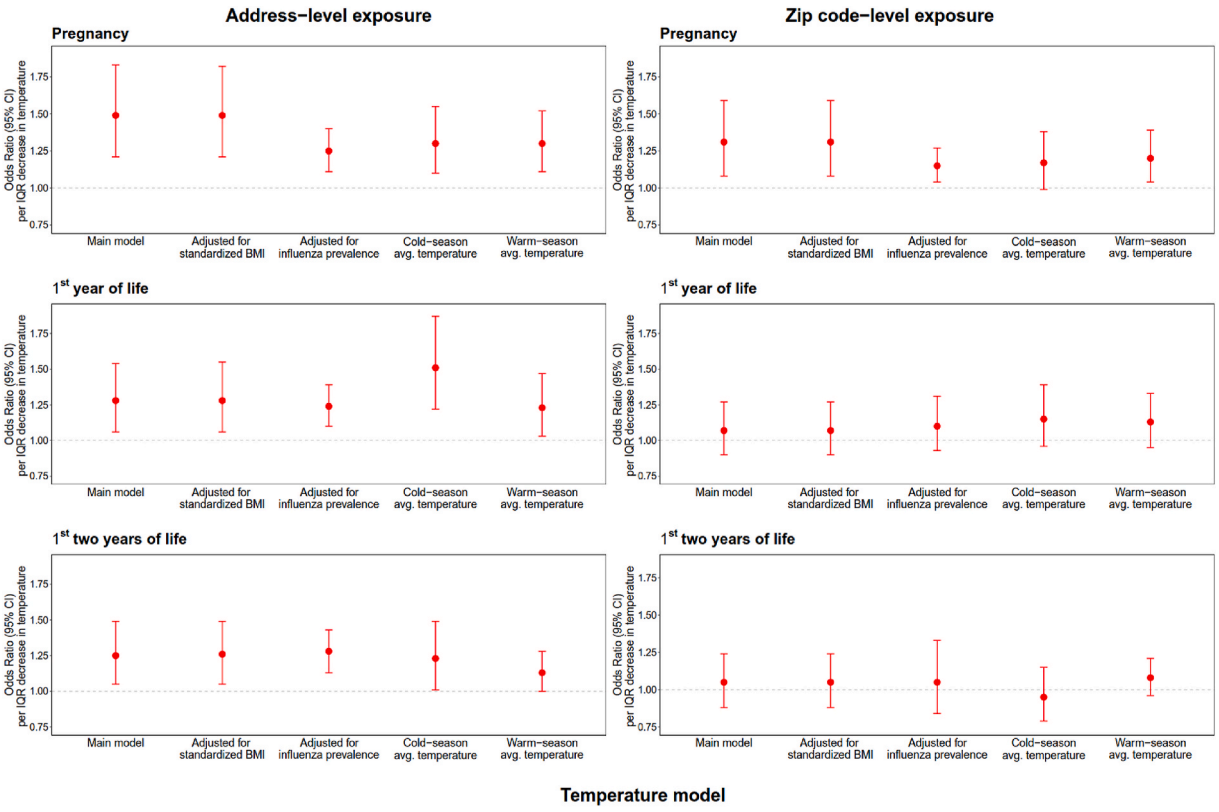

Fig. 2. Association (Odds Ratio and 95% CI) between islet autoimmunity and air temperature (per IQR decrease) at different exposure windows.

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.

References

Afoke, A., et al., 1991. Raised IgG and IgM in" epidemic" IDDM suggest that infections are responsible for the seasonality of type I diabetes. Diabetes Res. 16 (1), 11–17.
Atkinson, M.A., Eisenbarth, G.S., Michels, A.W., 2014. Type 1 diabetes. Lancet 383 (9911), 69–82.
Bell, M.L., Belanger, K., 2012. Review of research on residential mobility during pregnancy: consequences for assessment of prenatal environmental exposures. J. Expo. Sci. Environ. Epidemiol. 22 (5), 429–438.
Beyerlein, A., et al., 2015. Ambient air pollution and early manifestation of type 1 diabetes. Epidemiology 26 (3), e31–e32.
Bonifacio, E., 2015. Predicting type 1 diabetes using biomarkers. Diabetes Care 38 (6), 989–996.
Bonifacio, E., et al., 2008. Maternal type 1 diabetes reduces the risk of islet autoantibodies: relationships with birthweight and maternal HbA 1c. Diabetologia 51 (7), 1245–1252.
Borkar, V.V., et al., 2010. Low levels of vitamin D in North Indian children with newly diagnosed type 1 diabetes. Pediatr. Diabetes 11 (5), 345–350.
Dahlquist, G., 1991. Epidemiological studies of childhood insulin dependent diabetes. Acta Pædiatrica 80, 583–589, 6-7.
Dahlquist, G., 1998. The aetiology of type 1 diabetes: an epidemiological perspective. Acta Paediatr. 87, 5–10.
Dahlquist, G., Mustonen, L., 1994. Childhood onset diabetes—time trends and climatological factors. Int. J. Epidemiol. 23 (6), 1234–1241.
Dahlquist, G., et al., 1985. The epidemiology of diabetes in Swedish children 0-14 years-a six-year prospective study. Diabetologia 28 (11), 802–808.
Daneman, D., 2006. Type 1 diabetes. Lancet 367 (9513), 847–858.
DiMeglio, L.A., Evans-Molina, C., Oram, R.A., 2018. Type 1 diabetes. Lancet 391 (10138), 2449–2462.
Earth data, N. Available from: https://search.earthdata.nasa.gov.
Elten, M., et al., 2020. Ambient air pollution and incidence of early-onset paediatric type 1 diabetes: a retrospective population-based cohort study. Environ. Res. 184, 109291.
European Environment Agency, 2019. In: EEA Report No 10/2019 - Air Quality in Europe 2019. EEA, Copenhagen, Denmark. Available from: https://www.eea.europa.eu/publications/air-quality-in-europe-2019.

Fan, J., et al., 2020. Neighborhood greenness associated with chronic obstructive pulmonary disease: a nationwide cross-sectional study in China. Environ. Int. 144, 106042.
Geodesy, G.F.A.f.C.a. Available from: https://www.bkg.bund.de.
German Environmental Agency. Available from: https://www.umweltbundesamt.de.
Gesellschaft für Digitale Wirtschaftsgeographie mbH. Available from: https://www.wigeogis.com/.
Group, D.E.R.I., 1988. Geographic patterns of childhood insulin-dependent diabetes mellitus. Diabetes 37 (8), 1113–1119.
Group, D.P., 2006. Incidence and trends of childhood Type 1 diabetes worldwide 1990–1999. Diabet. Med. 23 (8), 857–866.
Hathout, E.H., et al., 2002. Role of exposure to air pollutants in the development of type 1 diabetes before and after 5 yr of age. Pediatr. Diabetes 3 (4), 184–188.
Hathout, E.H., et al., 2006. Air pollution and type 1 diabetes in children. Pediatr. Diabetes 7 (2), 81–87.
Insel, R.A., Dunne, J.L., Ziegler, A.-G., 2015. General population screening for type 1 diabetes: has its time come? Curr. Opin. Endocrinol. Diabetes Obes. 22 (4), 270–276.
Joner, G., Søvik, O., 1981. Incidence, age at onset and seasonal variation of diabetes mellitus in Norwegian children, 1973–1977. Acta Pædiatrica 70 (3), 329–335.
Kim, J.S., et al., 2019. Associations of air pollution, obesity and cardiometabolic health in young adults: the Meta-AIR study. Environ. Int. 133, 105180.
Kloog, I., et al., 2014. Predicting spatiotemporal mean air temperature using MODIS satellite surface temperature measurements across the Northeastern USA. Rem. Sens. Environ. 150, 132–139.
Krischer, J.P., et al., 2015. The 6 year incidence of diabetes-associated autoantibodies in genetically at-risk children: the TEDDY study. Diabetologia 58 (5), 980–987.
Lönnrot, M., et al., 2017. Respiratory infections are temporally associated with initiation of type 1 diabetes autoimmunity: the TEDDY study. Diabetologia 60 (10), 1931–1940.
Malmqvist, E., et al., 2015. Maternal exposure to air pollution and type 1 diabetes–accounting for genetic factors. Environ. Res. 140, 268–274.
Mandrup-Poulsen, T., 1996. The role of interleukin-1 in the pathogenesis of IDDM. Diabetologia 39 (9), 1005–1029.
Nenna, R., et al., 2011. Detection of respiratory viruses in the 2009 winter season in Rome: 2009 influenza A (H1N1) complications in children and concomitant type 1 diabetes onset. Int. J. Immunopathol. Pharmacol. 24 (3), 651–659.
Nordmann, S., Mues, A., Feigenspan, S., 2020. Evaluation of area-related air quality data in Germany from chemistry-transport modelling. Gefahrst. Reinhalt. Luft 80 (7–8), 281–290.
Nurminen, N., et al., 2021. Land cover of early life environment modulates the risk of type 1 diabetes. Diabetes Care 44 (7), 1506–1514.
Oikarinen, S., et al., 2014. Virus antibody survey in different European populations indicates risk association between coxsackievirus B1 and type 1 diabetes. Diabetes 63 (2), 655–662.
Organization, W.H., 2021. WHO Global Air Quality Guidelines: Particulate Matter (PM2.5 and PM10), Ozone, Nitrogen Dioxide, Sulfur Dioxide and Carbon Monoxide: Executive Summary.
Patterson, C.C., et al., 2019. Trends and cyclical variation in the incidence of childhood type 1 diabetes in 26 European centres in the 25 year period 1989–2013: a multicentre prospective registration study. Diabetologia 62 (3), 408–417.
Ponsonby, A.L., Lucas, R., van der Mei, I.A., 2005. UVR, vitamin D and three autoimmune diseases—multiple sclerosis, type 1 diabetes, rheumatoid arthritis. Photochem. Photobiol. 81 (6), 1267–1275.
Prescott, S.L., 2013. Early-life environmental determinants of allergic diseases and the wider pandemic of inflammatory noncommunicable diseases. J. Allergy Clin. Immunol. 131 (1), 23–30.
Raab, J., et al., 2016. Capillary blood islet autoantibody screening for identifying pre-type 1 diabetes in the general population: design and initial results of the Fr1da study. BMJ Open 6 (5), e011144.
Reunanen, A., Åkerblom, H.K., Käär, M.L., 1982. Prevalence and ten-year (1970-1979) incidence of insulin-dependent diabetes mellitus in children and adolescents in Finland. Acta Paediatr. 71 (6), 893–899.
Rosenfeld, A., et al., 2017. Estimating daily minimum, maximum, and mean near surface air temperature using hybrid satellite models across Israel. Environ. Res. 159, 297–312.
Rytkönen, M., et al., 2003. The incidence of type 1 diabetes among children in Finland—rural–urban difference. Health Place 9 (4), 315–325.
SurvStat@RKI 2.0, 2021. Available from: https://survstat.rki.de.
Taha-Khalde, A., et al., 2021. Air pollution and meteorological conditions during gestation and type 1 diabetes in offspring. Environ. Int. 154, 106546.
Thümer, L., et al., 2010. German new onset diabetes in the young incident cohort study: DiMelli study design and first-year results. Rev. Diabet. Stud.: Reg. Dev. Stud. 7 (3), 202.
Vinceti, M., et al., 2012. Leukemia risk in children exposed to benzene and PM10 from vehicular traffic: a case–control study in an Italian population. Eur. J. Epidemiol. 27 (10), 781–790.
Waernbaum, I., Dahlquist, G., 2016. Low mean temperature rather than few sunshine hours are associated with an increased incidence of type 1 diabetes in children. Eur. J. Epidemiol. 31 (1), 61–65.
Ziegler, A.-G., Bonifacio, E., 2012. Age-related islet autoantibody incidence in offspring of patients with type 1 diabetes. Diabetologia 55 (7), 1937–1943.
Ziegler, A.-G., et al., 2003. Early infant feeding and risk of developing type 1 diabetes–associated autoantibodies. JAMA 290 (13), 1721–1728.
Ziegler, A.-G., et al., 2020. Yield of a public health screening of children for islet autoantibodies in Bavaria, Germany. JAMA 323 (4), 339–351.
Zipitis, C.S., Akobeng, A.K., 2008. Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis. Arch. Dis. Child. 93 (6), 512–517.