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ARTICLE

Impact of long-term air pollution exposure on metabolic control in children and adolescents with type 1 diabetes: results from the DPV registry

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Abstract

Aims/hypothesis Studies on the association between air pollution and metabolic control in children and adolescents with type 1 diabetes are rare and findings are inconsistent. We examined the relationship between air pollution variables (particulate matter with an aerodynamic diameter <10 μm [PM_{10}], NO_2 and accumulated ozone exposure [O_3-AOT]) and metabolic variables (HbA_{1c} and daily insulin dose [U/kg body weight]) in children and adolescents with type 1 diabetes.

Methods We investigated 37,372 individuals with type 1 diabetes aged <21 years, documented between 2009 and 2014 in 344 German centres of the prospective diabetes follow-up registry (Diabetes-Patienten-Verlaufsdokumentation [DPV]). Long-term air pollution exposure (annual and quinquennial means) data were linked to participants via the five-digit postcode areas of residency. Cross-sectional multivariable regression analysis was used to examine the association between air pollution and metabolic control.

Results After comprehensive adjustment, an interquartile range increase in O_3-AOT was associated with a lower HbA_{1c} (−3.7% [95% CI −4.4, −3.0]). The inverse association between O_3-AOT and HbA_{1c} persisted after additional adjustment for degree of urbanisation or additional adjustment for PM_{10}. Moreover, the inverse association remained stable in further sensitivity analyses. No significant associations between HbA_{1c} and PM_{10} or NO_2 were found. No association was observed between any of the three air pollutants and insulin dose.

Conclusions/interpretation The inverse association between O_3-AOT and HbA_{1c} could not be explained by regional differences in diabetes treatment or by other differences between urban and rural areas. Furthermore, our results remained stable in sensitivity analyses. Further studies on the association between air pollution and HbA_{1c} in children and adolescents with type 1 diabetes are needed to confirm our observed association and to elucidate underlying mechanisms.

Keywords Air pollution · HbA_{1c} · Insulin · Metabolic control · Ozone · Particulate matter · Type 1 diabetes

Stefanie Lanzinger and Joachim Rosenbauer contributed equally to this study.

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Research in context

What is already known about this subject?

- Previous studies have shown an association between air pollution and HbA_{1c} in adults with type 2 diabetes
- Only few studies have focused on the impact of air pollution on children and adolescents with type 1 diabetes

What is the key question?

- Is there an association between long-term exposure to air pollution and metabolic control in children and adolescents with type 1 diabetes?

What are the new findings?

- Results of the prospective diabetes follow-up registry (Diabetes-Patienten-Verlaufsdokumentation [DPV]) showed that lower HbA_{1c} was associated with increased long-term ozone exposure
- The inverse association between HbA_{1c} and ozone remained stable in sensitivity analyses
- No association was observed between particulate matter or NO_2 and HbA_{1c}

How might this impact on clinical practice in the foreseeable future?

- In addition to the factors that can be influenced by an individual with type 1 diabetes, such as treatment compliance, environmental factors that might have an impact on HbA_{1c} need to be considered in diabetes care

Abbreviations

25(OH)D	25-Hydroxyvitamin D
DPV	Diabetes-Patienten-Verlaufsdokumentation
IQR	Interquartile range
KiGGS	German Health Interview and Examination Survey for Children and Adolescents
KORA	Cooperative Health Research in the Region of Augsburg, Germany
O_3-AOT	Accumulated ozone exposure
PM_{10}	Particulate matter with an aerodynamic diameter <10 μm
SDS	Standard deviation score

Introduction

Most epidemiological studies investigating the association between air pollution and diabetes have so far focused on type 2 diabetes mellitus in adults. Studies reported an increased risk of type 2 diabetes with long-term exposure to air pollution [1, 2]. Moreover, individuals with diabetes have been shown to be especially susceptible to the adverse health effects of air pollution [3, 4]. Biological mechanisms explaining the cardiovascular effects in individuals with diabetes in response to air pollution include systemic oxidative stress and inflammation, further leading to changes in the vascular endothelium and changes in metabolism such as impaired insulin sensitivity [2, 5, 6]. The HbA_{1c} level reflects the average plasma glucose concentration over 3 months and is an important marker of metabolic control [7]. Moreover, HbA_{1c} has been shown to be a predictor for diabetes complications [7]. In a previous study, the association between ambient air particulate matter with an aerodynamic diameter <10 μm (PM_{10}) and HbA_{1c} in adults with type 2 diabetes was examined [8]. The authors reported significantly higher HbA_{1c} with higher PM_{10} exposure. Recently, increased HbA_{1c} levels were found to be associated with an increase in the 3 month PM_{10} average (intermediate-term exposure) in individuals with diabetes but no such association was seen for an increase in the 1–7 day PM_{10} exposure (short-term exposure) [9].

Studies on air pollution and type 1 diabetes mellitus in children and adolescents are rare. A recent study investigated the long-term effects of PM_{10}, NO_2 (annual means) and accumulated ozone exposure (O_3-AOT, quinquennial means) on HbA_{1c} in 771 children and adolescents with type 1 diabetes [10]. Individuals with early-onset type 1 diabetes, aged 11–21 years, from a nationwide population-based diabetes registry of the German Diabetes Centre, Düsseldorf (DDZ registry) were included in the study. No adverse effects of PM_{10}, NO_2 or O_3-AOT on HbA_{1c} were found. However, the authors reported an unexpected inverse association between O_3-AOT and HbA_{1c}, showing a decrease in HbA_{1c} (regression estimate −1.5 [95% CI −2.8, −0.2]) in association with an interquartile range (IQR) increase in O_3-AOT. However, the association was not robust in all sensitivity analyses performed. A non-significant inverse association between long-term exposure to O_3 and HbA_{1c} was also reported in a nationwide study of 11,847 adults in China [11].

A previous study emphasised the importance of studying the association between air pollution and metabolic control in children and adolescents with type 1 diabetes in a larger cohort [10]. The aim of our work was to conduct a large-scale study including all children and adolescents with type 1 diabetes documented in German centres of the prospective diabetes follow-up registry (Diabetes-Patienten-Verlaufsdokumentation [DPV]) and to examine the impact of PM_{10}, NO_2 and O_3-AOT on indicators of metabolic control (HbA_{1c} and insulin dose).

Methods

Measurement of air pollutants The German Federal Environmental Agency (Umweltbundesamt [UBA] FG II 4.2) provided air pollution background measures for Germany which were derived by dispersion modelling using the chemical REM-CALGRID model and smoothed by the method of optimal interpolation (as described elsewhere [10]). Concentrations of PM_{10}, NO_2, O_3, and O_3-AOT over a threshold of 80 μg/m^3 were available in 7 km × 8 km raster cells for the whole of Germany. For each air pollutant, an area-weighted mean per five-digit postcode area was calculated by intersection of the 7×8 km^2 raster with the German postcode map using ArcGIS (version 10; Environmental Systems Research Institute [ESRI], Redlands, CA, USA) [10]. The Directive 2008/50/EC of the European Parliament defines limit values for annual means of PM_{10} and NO_2, whereas target values for O_3-AOT are averaged over 5 years [12]. Therefore, annual means for the years 2009–2014 were used for PM_{10} and NO_2 and quinquennial means (2005–2009 to 2010–2014) were used for O_3-AOT in the analyses. To define O_3-AOT, for all values between 08:00 hours and 20:00 hours exceeding a threshold of ≥80 μg/m^3, the difference to this threshold was determined. Therefore, O_3-AOT is defined as the sum of these differences between 1 h means ≥80 μg/m^3 from May to July and averaged over 5 years [13].

Participants and data The DPV registry is a multicentre, prospective survey of routinely collected data for all types of diabetes [14]. DPV registry data are used for quality control and diabetes research. Information is collected during routine examinations and includes demographic and anthropometric characteristics, diabetes therapy, comorbidities and disease outcomes related to diabetes. To date, DPV comprises 454 participating centres predominantly in Germany (412 centres). Of these, 344 centres in Germany provided data for the underlying analysis. Semi-annually, anonymised data were sent to Ulm University for validation and analyses. Data collection and analysis were approved by the ethics committee of Ulm University as well as by the local review boards of the participating centres. Corresponding to the period of air pollutant measurements, individuals with type 1 diabetes documented in German DPV centres between 2009 and 2014 and aged <21 years were selected for the analysis. Participants <6 months of age at diabetes onset were excluded.

Demographic and clinical data extracted from the DPV register were sex, age, diabetes duration, migration background (at least one parent not born in Germany), year of treatment, BMI (kg/m^2), type of insulin treatment (conventional insulin therapy, ≤3 injections per day; intensive insulin therapy, 4–8 injections per day or insulin pump), HbA_{1c} (% or mmol/mol) and daily insulin dose (U/kg body weight). The standard deviation score (SDS) for BMI was calculated based on reference data from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) [15]. SDS values indicate the SD below or above a reference value [15]. Based on BMI, weight status was categorised into underweight/normal weight (BMI ≤ 90th percentile), overweight (BMI > 90th and ≤97th percentile) or obesity (BMI > 97th percentile) using national reference data from KiGGS [15]. The multiple of the mean transformation method was used to standardise HbA_{1c} values to the DCCT reference range of 20.7–42.6 mmol/mol (4.05–6.05%) to account for different laboratory methods [16]. For each participant, demographic and clinical data of the most recent treatment year in the period 2009–2014 were selected and aggregated (median) before analyses. Therefore, the outcomes HbA_{1c} and daily insulin dose were related to PM_{10} and NO_2 annual means for the respective most recent treatment year per participant. For O_3-AOT, the average over the 5 years preceding the most recent treatment year was examined (e.g. if the most recent treatment year was 2012, clinical data from 2012 were aggregated and associated with O_3-AOT exposure data from 2008–2012). Exposure data were linked to participants via the five-digit postcodes of participants' residency. We used the concept of Nielsen areas to account for regional differences, as described elsewhere [10]. The seven German Nielsen areas are presented in the electronic supplementary material (ESM) Methods section.

In a sensitivity analysis, we additionally adjusted for degree of urbanisation. We differentiated three degrees of urbanisation (urban centres, town or suburb and rural areas) based on the population density of local administrative units as provided by Eurostat [17] and as described elsewhere [10].

Statistical analyses Results of descriptive analyses are presented as median (IQR) for continuous variables and proportions for categorical variables. Spearman's rank correlation

coefficient was used to calculate associations between air pollutants. Multivariable linear regression models were used to investigate the association between air pollutants as independent variables and HbA_{1c} or insulin dose as dependent outcomes. PM_{10}, NO_2 and O_3-AOT were included in the model as a continuous variable. Results are presented as per cent changes in outcome means per IQR increase in the respective air pollutant together with 95% CI (per cent change = IQR × regression estimate × 100/outcome mean). Main models were adjusted for sex, age (≤5 years, >5–10 years, >10–15 years, >15–20 years), diabetes duration (<2 years, ≥2 years), migration background, year of treatment, type of insulin treatment and Nielsen area. When analysing the association between air pollutants and insulin dose, we additionally adjusted for weight status.

In additional regression analyses, O_3-AOT was categorised into four quartiles (Q1–Q4: Q1, <10,433 $\mu g/m^3 \times h$; Q2, 10,433 to <12,878 $\mu g/m^3 \times h$; Q3, 12,878 to <15,346 $\mu g/m^3 \times h$; Q4, ≥15,346 $\mu g/m^3 \times h$), with the highest quartile used as reference group. Regression results for air pollution quartiles are presented as adjusted least-square means together with 95% CI estimated from regression models using observed marginal distributions of covariates.

To test the robustness of our results regarding O_3-AOT, we conducted various sensitivity analyses: (1) we fitted models without adjusting for Nielsen areas; (2) Nielsen areas were included as a random intercept into the models using the variance components covariance structure; (3) instead of Nielsen areas, the centre was included as a random intercept; (4) we additionally adjusted for degree of urbanisation; (5) we additionally adjusted for PM_{10} when analysing the association between O_3-AOT and HbA_{1c}; (6) since residuals for HbA_{1c} deviated from normality, we performed sensitivity analyses using log-transformed HbA_{1c}; (7) we investigated the association between annual means of O_3 and HbA_{1c} and insulin dose; and (8) natural cubic regression splines were used to check linearity of the dose–response function. The number of knots was selected by minimising Akaike's information criterion.

Table 1 Characteristics of individuals with type 1 diabetes (n = 37,372) and description of air pollutants

Characteristic	Type 1 diabetes
Age, years	14.7 (6.4)
Age at diabetes onset, years	8.3 (6.9)
Diabetes duration, years	4.8 (6.5)
Weight SDS	0.3 (1.2)
Height SDS	0.1 (1.4)
BMI SDS	0.3 (1.1)
HbA_{1c}, mmol/mol)	61.5 (20.7)
HbA_{1c}, %	7.8 (1.9)
No. of HbA_{1c} measurements/participant	4.0 (2.0)
Daily insulin dose, U/kg	0.8 (0.3)
Number of insulin dose measurements/participant	4.0 (2.0)
Number of glucose self-monitoring measurements per day	5.0 (2.5)
Treatment year	2014 (2)
Male sex	52.8
CT (1–3 injections/day)	3.9
ICT (4–8 injections/day)	54.2
Insulin pump	41.9
Migration background[a]	18.8
Air pollutant[b]	
PM_{10}, $\mu g/m^3$	17.7 (3.5)
NO_2, $\mu g/m^3$	15.0 (7.4)
O_3, $\mu g/m^3$	48.7 (6.9)
O_3-AOT, $\mu g/m^3 \times h$	12,878.1 (4912.5)

Data are presented as median (IQR) or n%

[a] At least one parent not born in Germany

[b] Average exposure for the study population

CT, conventional insulin therapy; ICT, intensive insulin therapy

Table 2 Association between long-term air pollution exposure and HbA_{1c}

Air pollutant and model	IQR	Per cent change[a] (95% CI)	*p* value
PM_{10}			
Main model[b]	3.5	0.1 (−0.3, 0.6)	0.524
Without Nielsen area	3.5	1.4 (1.1, 1.8)	<0.001
Nielsen area as random effect	3.5	0.2 (−0.3, 0.6)	0.432
Centre as random effect	3.5	0.8 (0.3, 1.4)	0.001
Main model+degree of urbanisation	3.5	0.1 (−0.4, 0.5)	0.802
Outcome log-transformed	3.5	0.1 (−0.3, 0.5)	0.484
NO_2			
Main model[b]	7.4	−0.3 (−0.8, 0.1)	0.157
Without Nielsen area	7.4	−0.5 (−0.9, −0.1)	0.025
Nielsen area as random effect	7.4	−0.3 (−0.8, 0.1)	0.155
Centre as random effect	7.4	0.3 (−0.2, 0.8)	0.277
Main model+degree of urbanisation	7.4	−0.7 (−1.3, −0.2)	0.007
Outcome log-transformed	7.4	−0.3 (−0.7, 0.1)	0.112
O_3-AOT			
Main model[b]	4912.5	−3.7 (−4.4, −3.0)	<0.001
Without Nielsen area	4912.5	−2.6 (−3.1, −2.2)	<0.001
Nielsen area as random effect	4912.5	−3.7 (−4.4, −2.9)	<0.001
Centre as random effect	4912.5	−2.1 (−3.0, −1.2)	<0.001
Main model+degree of urbanisation	4912.5	−3.7 (−4.4, −3.0)	<0.001
Main model+PM_{10}	4912.5	−3.8 (−4.5, −3.0)	<0.001
Outcome log-transformed	4912.5	−3.5 (−4.1, −2.8)	<0.001
O_3			
Main model[b]	6.9	−0.8 (−1.3, −0.4)	<0.001
Without Nielsen area	6.9	−1.1 (−1.5, −0.7)	<0.001
Nielsen area as random effect	6.9	−0.8 (−1.3, −0.4)	<0.001
Centre as random effect	6.9	−0.9 (−1.4, −0.4)	<0.001
Main model+degree of urbanisation	6.9	−0.9 (−1.4, −0.4)	<0.001
Main model+PM_{10}	6.9	−1.2 (−1.7, −0.6)	<0.001
Outcome log-transformed	6.9	−0.8 (−1.2, −0.4)	<0.001

[a] Per cent change in HbA_{1c} = IQR × regression estimate × 100/outcome mean

[b] Adjusted for sex, age, diabetes duration, migration background, year of treatment, type of insulin therapy and Nielsen area

Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA). A two-sided *p* value <0.05 was considered as statistically significant.

Results

As of March 2016, 108,052 individuals diagnosed with type 1 diabetes were registered in German DPV centres. Of these individuals, 74,751 were <21 years of age and 42,993 were documented between 2009 and 2014. The study population consisted of 37,372 participants (from 344 German centres) for whom information was available on HbA_{1c}, daily insulin dose, five-digit postcode and air pollution of residence.

The median age of individuals with type 1 diabetes was 14.7 years (53% male sex, Table 1). The median HbA_{1c} was 61.5 mmol/mol (7.8%) and median daily insulin dose was 0.8 U/kg. HbA_{1c} and insulin dose were measured about four times per participant during the most recent treatment year. The median most recent treatment year of the study population was 2014. Most of the participants were treated with intensive insulin therapy (54.2%) followed by insulin pump (41.9%). Around 20% of the study population had a migration background.

A basic description of the distribution of air pollutants and Spearman's rank correlation coefficients are presented in ESM Tables 1 and 2. We observed a decrease in PM_{10}, NO_2 and O_3-

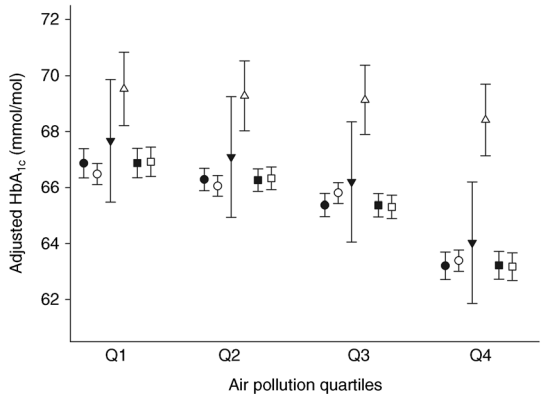

Fig. 1 Adjusted HbA_{1c} (mean and 95% CI) by O_3-AOT quartiles. Black circles, main model adjusted for sex, age, diabetes duration, migration background, year of treatment, type of insulin treatment and Nielsen area; white circles, no adjustment for Nielsen area; black triangles, Nielsen area as random effect; white triangles, centre as random effect; black squares, additional adjustment for degree of urbanisation; white squares, additional adjustment for PM_{10} quartile. Q1, <10,433 μg/m^3 × h; Q2, 10,433 to <12,878 μg/m^3 × h; Q3, 12,878 to <15,346 μg/m^3 × h; Q4, ≥15,346 μg/m^3 × h

AOT averages from 2009 to 2014, with small fluctuations between the years (ESM Table 1). There was a moderate correlation between PM_{10} and NO_2 (Spearman's rank correlation coefficient $r_s = 0.5$ [ESM Table 2]). The correlation between PM_{10} and O_3-AOT and between NO_2 and O_3-AOT was low with $|r_s| \leq 0.1$.

A description of data by Nielsen area is shown in ESM Table 3. The highest HbA_{1c} values were observed in Berlin and the Northeast area and the lowest were seen in the East. Daily insulin dose was comparable across all regions. Berlin showed the highest PM_{10} concentrations compared with the other areas. NO_2 was highest in Berlin and the West. The lowest PM_{10} levels were found in the South and the lowest NO_2 levels were observed in the Northeast. Five-year averages of O_3-AOT were highest in the Southwest and lowest in the North.

Table 2 shows the association between long-term air pollution exposure and HbA_{1c}. We observed a significant inverse association between O_3-AOT and HbA_{1c}. HbA_{1c} decreased by 3.7% (95% CI −4.4, −3.0) with an IQR increase in O_3-AOT (absolute change [IQR × (regression estimate/outcome mean)] in HbA_{1c}: −0.04 [−0.04, −0.03]). The inverse relationship between O_3-AOT and HbA_{1c} was stable in sensitivity analyses. Results for annual means of O_3 were similar, showing that a decrease in HbA_{1c} was associated with an increment in O_3 (Table 2). No robust significant differences in HbA_{1c} in association with PM_{10} or NO_2 were found. We observed no association between any of the air pollutants and insulin dose (data not shown).

Figure 1 shows the association between O_3-AOT quartile and HbA_{1c}. Lower HbA_{1c} levels were associated with higher O_3-AOT quartiles using the main model (Q4, mean HbA_{1c} 63.2 mmol/mol [62.7, 63.7]; Q1, mean HbA_{1c} 66.9 mmol/mol [66.3, 67.4]), confirming the inverse association.

The dose–response functions were only examined for O_3-AOT and HbA_{1c} and for O_3 and HbA_{1c}. We observed no deviation from linearity when O_3-AOT and O_3 were included as a smooth function into the model (ESM Fig. 1).

Discussion

We investigated the association between long-term exposure to PM_{10}, NO_2 and O_3-AOT and indicators of metabolic control in children and adolescents with type 1 diabetes. Our results showed an inverse association between O_3-AOT and HbA_{1c} (HbA_{1c} decrease of 3.7% [95% CI −4.4, −3.0] with an IQR increase in O_3-AOT). The observed association could not be explained by differences with respect to various confounders (e.g. Nielsen area or degree of urbanisation [urban and rural areas]). PM_{10}, NO_2 and O_3-AOT had no impact on insulin dose and PM_{10} and NO_2 had no impact on HbA_{1c}.

Our results showing lower HbA_{1c} with higher O_3-AOT exposure are in line with those of a previous analysis of the long-term effects of air pollution from a population-based registry [10]. However, the association found in that study was not robust to all sensitivity analyses performed by the authors [10]. A non-significant inverse association between long-term exposure to O_3 and HbA_{1c} was also reported in middle-aged and elderly individuals based on a nationwide cohort in China [11]. Some studies have suggested that O_3 has therapeutic effects through a decrease in blood glucose levels, increase in insulin sensitivity and prevention of oxidative stress in individuals with diabetes [18, 19]. Potential mechanisms involved in the response to O_3 have been summarised in a review [19]; especially, animal models support an inverse relationship between O_3 and HbA_{1c}. For example, treatment with either insulin or O_3 was found to significantly reduce HbA_{1c} levels in a rat model of diabetes [20].

In our study, O_3-AOT might have been a surrogate for other individual factors which are not controlled for by adjusting for degree of urbanisation, such as physical activity. For example, previous studies reported lower HbA_{1c} levels in association with increased physical activity in children and adolescents with type 1 diabetes [21, 22]. Another explanation for the inverse association between O_3-AOT and HbA_{1c} might be mild haemolysis of erythrocytes [19]. Moreover, trend analyses showed a general decrease in HbA_{1c} in adults and in children and adolescents with type 1 diabetes [23, 24], therefore, the treatment year might also play an important role. However, we adjusted for year of treatment in our analysis. In addition, O_3-AOT might be a surrogate for sun exposure and therefore higher vitamin D concentrations (measured as 25-hydroxyvitamin D [25(OH)D]) might also play a role. Times spent in sunny regions were associated with higher 25(OH)D

concentrations in participants of the Cooperative Health Research in the Region of Augsburg, Germany (KORA) F4 survey [25]. Moreover, a significant negative association between 25(OH)D levels and HbA_{1c} values was reported [26].

In our analysis, the inverse association between O_3-AOT and HbA_{1c} persisted after additional adjustments for degree of urbanisation and PM_{10}. Hence, the assumption that lower HbA_{1c} with higher O_3 concentration in fact reflects differences in diabetes treatment between urban and rural areas is not supported.

In contrast to our results, authors from Southern Israel observed an increase in HbA_{1c} with an IQR increase in average exposure to PM_{10} over 3 months in individuals with diabetes [9]. However, no association between long-term exposure to PM_{10} and HbA_{1c} has been reported in other studies [10, 27]. German authors observed an association between annual means of PM_{10} and HbA_{1c} in type 2 diabetes [8] but no association in type 1 diabetes [10]. Studies on air pollution and the prevalence and incidence of type 1 diabetes have also produced inconsistent findings [28–30]. Besides other factors, conflicting findings might be due to differences in participant characteristics, individual susceptibility, air pollution sources or exposure misclassification [6]. Methodological differences regarding outcome log-transformation and investigation of linear and non-linear relationships might also play a role. However, in our analysis, results of log-transformed and non-transformed outcomes were similar and we observed no deviation from linearity of the dose–response functions.

The novelty and strength of our study is that we investigated a large-scale, nationwide cohort of children and adolescents with type 1 diabetes whereas previous studies were limited in cohort size or focused on adults with type 2 diabetes. A further strength of our study is the various sensitivity analyses, all showing a robust inverse association between O_3 exposure and HbA_{1c} levels. However, our study is limited by the fact that we did not have information on lifestyle, social factors and dietary habits. Moreover, we did not have information on socioeconomic factors such as educational level or household income. Hence, residual confounding cannot be ruled out. Exposure misclassification should be considered, as five-digit postcodes of place of residence were linked to air pollution data and no information on exposure at school or work was considered. In addition, no information on time spent outdoors was available and background measurements without hotspot stations were used. Air pollution measurements were smoothed using REM-CALGRID model and, therefore, locally higher exposure was not represented.

In conclusion, we observed an inverse association between O_3-AOT and HbA_{1c} which remained stable in sensitivity analyses. In our study, the inverse relationship between O_3-AOT and HbA_{1c} could not be explained by regional differences in diabetes treatment or by other differences between urban and rural areas. Moreover, our results do not suggest an indirect effect of O_3-AOT on HbA_{1c} via an association of PM_{10} and HbA_{1c}. Animal models support our findings. Further studies, especially in other countries, are needed to confirm the association between air pollution and HbA_{1c} in children and adolescents with type 1 diabetes and to elucidate underlying biological mechanisms.

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Data availability The datasets generated during and/or analysed during the current study are not publicly available due to data protection reasons but are available from the corresponding author on reasonable request.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement SL contributed to data management, data analysis and manuscript writing and editing. JR contributed to data analysis and manuscript writing and editing. DS and TS contributed to data analysis and manuscript editing. BT, DK and WR reviewed the manuscript and contributed to interpretation of data and manuscript editing. RWH is the principal investigator of the study and contributed to data analysis and manuscript writing and editing. All co-authors approved the final version to be published. RWH is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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