Long-term #airpollution exposure and the impact on metabolic control in children and adolescents with #type1diabetes – Results from the DPV registry

Long-term air pollution exposure and the impact on metabolic control in children and adolescents with type 1 diabetes – Results from the DPV registry

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Abstract

Aims: 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 particulate matter with an aerodynamic diameter <10 µm (PM_{10}), nitrogen dioxide (NO_2) and accumulated ozone exposure (O_3-AOT) and HbA_{1c} and daily insulin dose (IU/kg body weight) in children and adolescents with type 1 diabetes.

Methods: We investigated 37,372 individuals with type 1 diabetes <21 years documented between 2009 and 2014 in 344 German centres of the diabetes prospective follow-up registry (DPV). Long-term air pollution exposure (annual and quinquennial means) was assigned to 5-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%-confidence interval:-4.4, -3.0]). The inverse association between O_3-AOT and HbA_{1c} persisted after additional adjustment for degree of urbanization 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: The inverse association between O_3-AOT and HbA_{1c} could not be explained by regional differences in diabetes treatment or 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

Research in context

What is already known about this subject?

- Previous studies showed an association between air pollution and HbA_{1c} in adults with type 2 diabetes
- Only few studies 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 DPV registry showed lower HbA_{1c} in association with an increase in 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 nitrogen dioxide and HbA_{1c}

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

- Beside factors that can be influenced by the patient such as compliance, environmental factors need to be considered which might also have an impact on HbA_{1c} in type 1 diabetes

List of Abbreviations

BMI	Body mass index
CT	Conventional insulin therapy
CI	Confidence interval
DCCT	Diabetes Control and Complications Trial
DPV	Prospective diabetes follow-up registry (Diabetes-Patienten-Verlaufsdokumentation)
HbA_{1c}	Haemoglobin A_{1c}
ICT	Intensive insulin therapy
IQR	Interquartile range
IU	Insulin units
KiGGS study	German Health Interview and Examination Survey for Children and Adolescents
KORA	Cooperative Health Research in the Region of Augsburg, Germany
NO_2	Nitrogen dioxide
O_3	Ozone
O_3-AOT	Accumulated ozone exposure over a threshold of 80 $\mu g/m^3$
PM_{10}	Particulate matter with an aerodynamic diameter < 10 µm
SDS	Standard deviation scores
25(OH)D	Vitamin D

Introduction

So far, most epidemiological studies investigating the association between air pollution and diabetes 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]. Haemoglobin A_{1c} (HbA_{1c}) reflects the three-month average plasma glucose concentration 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, increases in HbA_{1c} levels in association with an increase in the three-month PM_{10} average (intermediate-term exposure), but no association with an increase in the one to seven days PM_{10} exposure (short-term exposure) in individuals with diabetes were observed [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}, nitrogen dioxide (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 between 11 and 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 and 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%-confidence interval: -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].

In a previous study the importance to study the association between air pollution and metabolic control in children and adolescents with type 1 diabetes in a larger cohort was emphasized [10]. The aim of our work was to conduct a large-scaled study including all children and adolescents with type 1 diabetes documented in German centers of the prospective diabetes follow-up registry (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 (IU/kg body weight per day).

Methods

Measurements 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 accumulated O_3 exposure over a threshold of 80 µg/m^3 (O_3-AOT) were available in 7 km x 8 km raster cells for whole Germany. For each air pollutant an area-weighted mean per 5-digit postcode area was calculated by intersection of the 7x8 km^2 raster with the German postcode map using ArcGIS (version 10, Environmental Systems Research Institute (ESRI), California, 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 five years [12]. Therefore, for PM_{10} and NO_2 annual means for the years 2009-2014, for O_3-AOT quinquennial means (2005-2009 to 2010-2014) were used in the analyses. In order to define O_3-AOT, for all values between 8 am and 8 pm 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-hour means ≥80 µg/m^3 from May to July and averaged over five years [13].

Participants and data

The DPV registry is a multicentre, prospective survey of routinely collected data for all types of diabetes [14]. Data of the DPV registry are used for quality control and diabetes research. Information is collected during routine examinations and included demographic and anthropometric characteristics, diabetes therapy, comorbidities and disease outcomes related to diabetes. Up to date DPV comprises 454 participating centers predominantly from

Germany (412 centers). Of these 344 centres from Germany provided data for the underlying analysis. Semi-annually, anonymised data are send to Ulm University for data 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 centers. Corresponding to the period of air pollutant measurements, individuals with type 1 diabetes documented in German DPV centers 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, body mass index (BMI, kg/m^2), type of insulin treatment (conventional insulin therapy (CT, ≤3 injections per day), intensive insulin therapy (ICT, 4-8 injections per day) or insulin pump), HbA_{1c} (% or mmol/mol) and daily insulin dose. BMI standard deviation scores (BMI-SDS) were calculated based on reference data of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) study [15]. SDS values indicate the standard deviation below or above a reference value [15]. Based on BMI, weight status was categorized into under-/normal weight (BMI ≤90^{th} percentile), overweight (BMI >90^{th} and ≤97^{th} percentile) or obesity (BMI >97^{th} percentile) using national reference data of the KiGGS study [15]. The multiple of the mean transformation method was used to standardize HbA_{1c} values to the Diabetes Control and Complications Trial (DCCT) reference range of 4.05–6.05% (20.7–42.6 mmol/mol) accounting 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 five-year average preceding the most recent treatment year was examined, for example if the most recent treatment years was

2012, clinical data of 2012 was aggregated and associated with O_3-AOT exposure of 2008-2012. Exposure data were linked to participants via the 5-digit postcodes of participants' residency. We used the concept of Nielsen area to account for regional differences as described elsewhere [10]. The seven German Nielsen areas are presented in the methods section of the electronic supplemental material (ESM methods page 2).

In a sensitivity analysis, we additionally adjusted for degree of urbanization. We differentiated three degrees of urbanization (urban centers, town or suburb, 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 percent changes in outcome means per IQR increase in the respective air pollutant together with 95%-CI (percent change = IQR*regression estimate*100/outcome mean). Main models 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 categorized into four quartile groups (Q1-Q4) with the highest quartile group used as reference group. Regression results for air pollution quartile groups are presented as adjusted least-square means together with 95%-CI estimated

from regression models using observed marginal distributions of covariates.

In order 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 urbanization.

5) We additionally adjusted for PM_{10} groups 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.

8) Natural cubic regression splines were used to check linearity of the dose-response function. The number of knots were selected by minimizing Akaike's Information Criterion.

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

Results

As of March 2016, there were 108,052 individuals diagnosed with type 1 diabetes registered in German DPV centers. Of the individuals with type 1 diabetes, 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 centers with available information on HbA_{1c}, daily insulin dose, 5-digit postcode and air pollution of residence.

The median age of individuals with type 1 diabetes was 14.7 years with 53% males (Table 1). The median HbA_{1c} was 61.5 mmol/mol (7.8%) and median daily insulin dose was 0.8 IU/kg/d. $HbA1_c$ and insulin dose were measured around 4 times per participant during the most recent treatment year. The median most recent treatment year of the study population was 2014. Most of the patients were treated with ICT (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 the ESM. A decrease in the yearly averages of PM_{10} and NO_2 was observed from 2011 to 2014 (ESM Table 1). Whereas, O_3-AOT averages varied between the years. There was a moderate correlation between PM_{10} and NO_2 with Spearman's rank correlation coefficient r_s=0.5 (ESM Table 2). The correlation between PM_{10} and O_3-AOT as well as 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 of the online supplement. Highest HbA_{1c} values were observed in Berlin and the Northeast area with the East showing the lowest HbA_{1c} values. Daily insulin dose was comparable in all regions. Berlin showed the highest PM_{10} concentrations compared to the other Nielsen areas. NO_2 was highest in Berlin and the West. Lowest PM_{10} levels were found in the South, while lowest NO_2 levels were

observed in the Northeast region. 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% [-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 of annual means of O_3 were similar showing a decrease in HbA_{1c} in association with an increment in O_3 (Table 2). No robust significant differences in HbA_{1c} in association with PM_{10} and 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-quartiles and HbA_{1c}. Lower HbA_{1c} levels with higher O_3-AOT-quartile groups (main model: O_3-AOT-Q4: mean HbA_{1c} 63.2 mmol/mol [62.7, 63.7]; O_3-AOT-Q1: mean HbA_{1c} 66.9 mmol/mol [66.3, 67.4]) were found confirming the inverse association.

The dose-response functions were only examined for O_3-AOT and HbA_{1c} as well as 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 Figure 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} (HbA1c decrease by 3.7% [-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, as e.g. Nielsen areas or degree of urbanization (urban and rural areas). No impact of PM_{10}, NO_2 and O_3-AOT on insulin dose as well as of PM_{10} and NO_2 on HbA_{1c} was observed.

Our results showing lower HbA_{1c} with higher O_3-AOT exposure are in line with a previous analysis on the long-term effects of air pollution from a population-based registry [10]. However, the association was not robust to all sensitivity analyses performed in that study [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 suggested therapeutic effects of O_3 amongst others through a decrease in blood glucose levels, increase in insulin sensitivity and prevention of oxidative stress in individuals with diabetes [18, 19]. Potential mechanisms in response to O_3 were summarized in a review and particularly animal models also support an inverse relationship between O_3 and HbA_{1c} [19]. For example, treatment with either insulin or ozone significantly reduced HbA_{1c} levels in a diabetes rat model [20].

In our study, O_3-AOT might be a surrogate for other individual factors which are not controlled for by adjusting for degree of urbanization, 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 both 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 (25(OH)D) concentrations 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 adjustment for degree of urbanization as well as after additional adjustment for 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 the three-month PM_{10}-average in individuals with diabetes [9]. However, no associations between long-term exposure to PM_{10} and HbA_{1c} were also 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 also reported 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 with regard to outcome log-transformation, 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-scaled, nationwide cohort of children and adolescents with type 1 diabetes since previous studies were limited in cohort size or focused on adults with type 2 diabetes. A further strength of our study are 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 as educational level or household income. Hence, residual confounding cannot be ruled out. Exposure misclassification should be considered, as 5-digit postcodes of place of residence were linked to air pollution data and no information on exposure at school or work was considered. Moreover, 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.

Conclusions

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 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, in particular in other countries are needed in order to confirm the association between air pollution and HbA_{1c} in children and adolescent with type 1 diabetes and to elucidate underlying biological mechanisms.

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Sponsors were not involved in data acquisition or analysis.

Duality of Interest

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

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.

Contribution Statement

SL contributed to data management, data analysis, manuscript writing and editing; JR contributed to data analysis, manuscript writing and editing; DS and TS contributed to data analysis and manuscript editing; BT, DK, 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, 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

Tables

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

Characteristics	Median (IQR[a])	Percent
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[b]-SDS	0.3 (1.1)	
HbA_{1c}[c] (mmol/mol)	61.5 (20.7)	
HbA_{1c}[c] (%)	7.8 (1.9)	
Number of HbA_{1c}[c] measurements/participant	4.0 (2.0)	
Daily insulin dose (IU/kg/d)	0.8 (0.3)	
Number of insulin dose measurements/participant	4.0 (2.0)	
Number of glucose self-monitoring per day	5.0 (2.5)	
Treatment year	2014 (2)	
Male sex		52.8
CT[d] (1-3 injections/day)		3.9
ICT[e] (4-8 injections/day)		54.2
Insulin pump		41.9
Migration background[f]		18.8

Air pollutant	
PM_{10}[gk](µg/m^3)	17.7 (3.5)
NO_2[hk] (µg/m^3)	15.0 (7.4)
O_3[ik] (µg/m^3)	48.7 (6.9)
O_3-AOT[jk] (µg/m^3×h)	12878.1 (4912.5)

[a]interquartile range; [b]body mass index; [c]haemoglobin A_{1c}; [d]conventional insulin therapy;

[e]intensive insulin therapy; [f]at least one parent not born in Germany;

[g]particulate matter with an aerodynamic diameter <10 µm; [h]nitrogen dioxide;

[i]ozone; [j]accumulated ozone exposure over a threshold of 80 µg/m^3

[k]average exposure for the study population

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

Air Pollutant	Model	IQR[a]	% Change*	(95%-CI[b])	*p*-value
PM_{10}[c]	main model[g]	3.5	0.1	(-0.3, 0.6)	0.524
	without Nielsen areas	3.5	1.4	(1.1, 1.8)	<0.001
	Nielsen areas 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 urbanization	3.5	0.1	(-0.4, 0.5)	0.802
	outcome lagarithmized	3.5	0.1	(-0.3, 0.5)	0.484
NO_2[d]	main model[g]	7.4	-0.3	(-0.8, 0.1)	0.157
	without Nielsen areas	7.4	-0.5	(-0.9,-0.1)	0.025
	Nielsen areas 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 urbanization	7.4	-0.7	(-1.3; -0.2)	0.007
	outcome lagarithmized	7.4	-0.3	(-0.7, 0.1)	0.112
O_3-AOT[e]	main model[g]	4912.5	-3.7	(-4.4, -3.0)	<0.001
	without Nielsen areas	4912.5	-2.6	(-3.1, -2.2)	<0.001
	Nielsen areas 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 urbanization	4912.5	-3.7	(-4.4, -3.0)	<0.001
	main model+PM10	4912.5	-3.8	(-4.5, -3.0)	<0.001
	outcome lagarithmized	4912.5	-3.5	(-4.1, -2.8)	<0.001
O_3[f]	main model[g]	6.9	-0.8	(-1.3, -0.4)	<0.001
	without Nielsen areas	6.9	-1.1	(-1.5, -0.7)	<0.001

Nielsen areas 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 urbanization	6.9	-0.9	(-1.4, -0.4)	<0.001
main model+PM10	6.9	-1.2	(-1.7, -0.6)	<0.001
outcome lagarithmized	6.9	-0.8	(-1.2, -0.4)	<0.001

[a]interquartile range; [b]confidence interval; [c]particulate matter with an aerodynamic diameter <10 µm;

[d]nitrogen dioxide; [e]accumulated ozone exposure over a threshold of 80 µg/m^3; [f]ozone;

[g]adjusted for sex, age, diabetes duration, migration background, year of treatment,

type of insulin treatment and Nielsen areas

*percent change in HbA1c = (IQR*regression estimate) *100/outcome mean

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Figure Legends

Figure 1. Adjusted HbA_{1c} (mean, 95%-CI) by O_3-AOT-quartile groups.

Black dots: main model adjusted for sex, age, diabetes duration, migration background, year of treatment, type of insulin treatment and Nielsen areas.

White dots: No adjustment for Nielsen areas

Black triangle: Nielsen areas as random effect

White triangle: Centre as random effect

Black square: Additional adjustment for degree of urbanization

White square: Additional adjustment for PM_{10}-quartiles

Q1: <10433 µg/m³×h, Q2: 10433-<12878 µg/m³×h, Q3: 12878-<15346 µg/m³×h,

Q4: ≥15346 µg/m³×h