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Ambient Air Pollution and Early Manifestation of Type 1 Diabetes

Joachim Rosenbauer a,b, Teresa Tamayo a,b, Christina Bächle a,b, Anna Stahl-Pehe a,b, Sandra Landwehr a,c, Dorothee Sugiri d, Ursula Krämer d, Werner Maier e,f, Julia M. Hermann g,h, Reinhard W. Holl g,h, Wolfgang Rathmann a,b

Affiliations:

a Institute for Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, Düsseldorf, Germany,
b German Center for Diabetes Research (DZD), Partner Düsseldorf, Germany
c Institute of Medical Statistics, Heinrich Heine University Düsseldorf, Düsseldorf, Germany
d IUF-Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany
e Helmholtz Zentrum München, Institute of Health Economics and Health Care Management, Neuherberg, Germany
f German Center for Diabetes Research (DZD), Partner Neuherberg, Germany
g Institute for Epidemiology and Medical Biometry, ZIBMT, University of Ulm, Ulm, Germany
h German Center for Diabetes Research (DZD), Associated Partner Ulm, Germany

Corresponding author:
Joachim Rosenbauer, MD
Institute for Biometrics and Epidemiology,
Conflicts of Interest and Source of Funding

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The authors have no conflicts of interest.

Abbreviations: PM$_{10}$ = Particulate matter with an aerodynamic diameter of ≤10 micrometers, NO$_2$ = Nitrogen dioxides, O$_3$ = Ozone, O$_3$-AOT40 = Ozone accumulated over a threshold of 40 parts per billion (ppb), T1D = Type 1 diabetes

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To the Editor:

Animal and epidemiologic studies suggest adverse effects of ambient air pollutants on type 1 diabetes.\textsuperscript{1-4} Increased pre- or postnatal exposure to air pollutants (ozone, particulate matter, sulfate, nitrogen dioxide) was shown to be associated with an increased type 1 diabetes risk, and particulate matter to type 1 diabetes onset before 5 years of age.\textsuperscript{4} However, findings regarding single air pollutants have been inconsistent. A recent study indicated that traffic-related air pollution may accelerate the manifestation of type 1 diabetes in very young children.\textsuperscript{5}

We analyzed the association between air pollutants and age at onset of type 1 diabetes using data from the type 1 diabetes register for North Rhine-Westphalia (NRW, West-Germany), which is part of the EURODIAB initiative.\textsuperscript{2,3} The completeness of registration in the age group 0-19 years was estimated to be 98% in 2002-2014. We obtained data on exposure to particulate matter with an aerodynamic diameter smaller than 10 micrometers (PM\textsubscript{10}), nitrogen dioxides (NO\textsubscript{2}), and accumulated ozone (O\textsubscript{3}-AOT40: excess ozone accumulated over a threshold of 40 ppb) for 2001-2005 from the German Federal Environment Agency (Umweltbundesamt II). Smoothed exposure data are estimated based on an 8x8 squared kilometers grid (see eAppendix: http://links.lww.com/EDE/B50). Average concentrations were calculated for each five-digit postcode area by intersection of the 8x8 squared kilometers grid with the German postcode map. We determined exposure of incident cases to air pollutants by linking exposure data to cases’ residential addresses at type 1 diabetes onset according to 5-digit postcodes. The ethical review board of Düsseldorf University approved the study.

We included 6,807 incident type 1 diabetes patients aged 0 to 19 years at diagnosis (mean age at diagnosis (SD): 9.7 (4.5) years) in 2006-2014 in the principal analyses. To be consistent with a previous study,\textsuperscript{5} we applied simple linear and quantile regression with age at diagnosis and 10\textsuperscript{th}, 30\textsuperscript{th}, 50\textsuperscript{th}, 70\textsuperscript{th} and 90\textsuperscript{th} percentile as dependent and air pollutants as independent variables. Models were adjusted for sex, German vs. Non-German nationality, the German Index of Multiple Deprivation,\textsuperscript{7} family history of type 1 diabetes, level of urbanization of residence (Eurostat definition\textsuperscript{4}), and additionally for patients’ body mass index at diagnosis (available for 5,625 cases). For sensitivity analyses, we performed quantile regressions at a finer grid of percentiles (5\textsuperscript{th} to 95\textsuperscript{th} percentile by 5%) and refitted all models including all incident cases in 2002-2014 from the NRW register (N=9722, mean age at diagnosis (SD): 9.7 (4.5) years) and exposure data for 2001-2009.
Results indicate that exposure to ambient air pollutants or ozone was not associated either with mean age at diagnosis or with any percentile of age at diagnosis, as evident from 95% confidence interval estimates (Figure). All sensitivity analyses confirmed these results (eFigures 1-3).

Our findings indicate that high exposure to traffic-related air pollutants or atmospheric ozone on scale of several kilometers are not related to the age at onset of type 1 diabetes. Thus, our study could not provide further evidence for the recently raised hypothesis that traffic-related air pollution may accelerate the manifestation of type 1 diabetes in very young children.\(^5\)

Compared to the previous study\(^5\), shortcomings of our study that may have biased our findings are the limited spatial resolution of exposure measures (8x8 vs. 1x1 square km), the coarser linkage of exposure data to patients (5-digit postcode area of residence vs. exact residential address), and the lack of individual socio-economic data. We, however, adjusted for community-based German Index of Multiple Deprivation as proxy for individual socio-economic status. Strengths of our study are the high completeness of registered type 1 diabetes cases and the large study cohort.

Given the limited and contradictory evidence, further studies from other regions, ideally prospective studies with improved measures of individual exposure to ambient air pollutants, are warranted to clarify the association of ambient air pollutants with accelerated manifestation and risk of type 1 diabetes.
REFERENCES


Figure legend

**Figure.** Point estimates and 95% confidence intervals for differences in mean and percentiles (10th, 30th, 50th (median), 70th, 90th) of the age at diagnosis of type 1 diabetes per 2 SD increases in PM$_{10}$, NO$_2$, and O$_3$-AOT40 (accumulated ozone) adjusted for sex, German vs. Non-German nationality, German Index of Multiple Deprivation, family history of type 1 diabetes, level of urbanization of residence (upper panel), and additionally for body mass index at onset (lower panel). The dots represent specific quantile regression estimates and are connected by dashes to visualize trends by age quantiles, the whiskers represent 95% CI. The horizontal black lines represent the linear regression coefficients and their respective confidence intervals. The horizontal red line depicts the age difference zero as reference. (Incident cases of 2006 to 2014, exposure data of 2001 to 2005.)
Figure 1.
eAppendix: Exposure assessment

Exposure data of particulate matter with an aerodynamic diameter smaller than 10 micrometers (PM$_{10}$), nitrogen dioxides (NO$_2$), and accumulated ozone (O$_3$-AOT40: Excess ozone accumulated over a threshold of 40 ppb) for the period 2001 to 2005 were obtained from the German Federal Environment Agency (Umweltbundesamt II). In brief, annual (PM$_{10}$, NO$_2$) and quinquennial (O$_3$) average concentrations for the ambient air pollutants are based on measurements of 150 German monitoring stations. These data are then smoothed on a grid with a cell size of eight by eight kilometers using the chemical REM-CALGRID (RCG) model which is continuously fitted with meteorological and air pollution time-series data from Germany and Europe$^{1,2}$. Average concentrations were calculated for each five-digit postcode area by intersection of the eight by eight kilometers grid with the German postcode map. Each postcode area obtained an area-weighted mean of PM$_{10}$, NO$_2$, and O$_3$ of covered raster cells. Intersection was done with ArcGIS (Version 9, Environmental Systems Research Institute (ESRI), California, USA). Further details of measures of air pollutants have been described elsewhere$^3$.


eFigure 1 Point estimates and 95% confidence intervals for differences in mean and percentiles (5th to 95th by 5%) of the age at diagnosis of type 1 diabetes per 2 SD increases in PM$_{10}$, NO$_2$, and O$_3$-AOT40 (accumulated ozone), adjusted for sex, German vs. Non-German nationality, German Index of Multiple Deprivation, family history of T1D, level of urbanization of residence (upper panel), and additionally for body mass index at onset (lower panel). The dots represent specific quantile regression estimates and are connected by dashes to visualize trends by age quantiles, the whiskers represent 95% CI. The horizontal black lines represent the linear regression coefficients and their respective confidence intervals. The horizontal red line depicts the age difference zero as reference. (Incident cases of 2006 to 2014, exposure data of 2001 to 2005.)
eFigure 2 Point estimates and 95% confidence intervals for differences in mean and percentiles (10\(^{th}\), 30\(^{th}\), 50\(^{th}\) (median), 70\(^{th}\), 90\(^{th}\)) of the age at diagnosis of type 1 diabetes per 2 SD increases in PM\(_{10}\), NO\(_2\), and O\(_3\)-AOT40 (accumulated ozone), adjusted for sex, German vs. Non-German nationality, German Index of Multiple Deprivation, family history of T1D, level of urbanization of residence (upper panel), and additionally for body mass index at onset (lower panel). The dots represent specific quantile regression estimates and are connected by dashes to visualize trends by age quantiles, the whiskers represent 95% CI. The horizontal black lines represent the linear regression coefficients and their respective confidence intervals. The horizontal red line depicts the age difference zero as reference. (Incident cases of 2002 to 2014, exposure data of 2001 to 2009.)
**eFigure 3** Point estimates and 95% confidence intervals for differences in mean and percentiles (5th to 95th by 5%) of the age at diagnosis of type 1 diabetes per 2 SD increases in PM$_{10}$, NO$_2$, and O$_3$-AOT40 (accumulated ozone), adjusted for sex, German vs. Non-German nationality, German Index of Multiple Deprivation, family history of T1D, level of urbanization of residence (upper panel), and additionally for body mass index at onset (lower panel). The dots represent specific quantile regression estimates and are connected by dashes to visualize trends by age quantiles, the whiskers represent 95% CI. The horizontal black lines represent the linear regression coefficients and their respective confidence intervals. The horizontal red line depicts the age difference zero as reference. (Incident cases of 2002 to 2014, exposure data of 2001 to 2009.)