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Air pollution and childhood epilepsy diagnosis at a first seizure clinic in The Netherlands: A case-control study

Geertruida Slinger [a,†,*], Sien T. Verbeek [a,†], Eric van Diessen [a,b], Lotte Noorlag [a], Kees P.J. Braun [a], Youchen Shen [c], Willem M. Otte [a,#], George S. Downward [c,d,#]

[a] Department of Neurology and Neurosurgery, University Medical Center Utrecht and Utrecht University, Utrecht, The Netherlands, member of ERN EpiCARE
[b] Department of Pediatrics, Franciscus Gasthuis & Vlietland, Rotterdam, The Netherlands
[c] Institute for Risk Assessment Sciences, Utrecht University, The Netherlands
[d] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht and Utrecht University, Utrecht, The Netherlands

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ABSTRACT

Increasing evidence suggests that exposure to air pollution is linked to neurological disorders, but little is known about the association with epilepsy. This study aimed to quantify the association between exposure to ambient air pollutants and the diagnosis of epilepsy in Dutch children. A population-based case-control study was conducted among children presenting to the first seizure clinic at the Wilhelmina Children's Hospital in Utrecht, the Netherlands, from 1 January 2008 to 31 May 2021. Children were assigned to either cases (i.e., diagnosed with epilepsy, n = 406) or controls (n = 737). Levels of ambient air pollution (nitrogen dioxide [NO_2], ozone [O_3], and particulate matter with aerodynamic diameter < 10 μm [PM_{10}] and < 2.5 μm [$PM_{2.5}$]) exposure were assigned for the year of presentation to the residential addresses of study participants using EU-wide air pollution metrics. Logistic regression models, adjusted for common confounders, were applied to calculate odds ratios (ORs) with 95 % confidence intervals (CIs) for the association between air pollution and epilepsy. Overall, no association between ambient air pollution and an epilepsy diagnosis was observed, including NO_2 (OR: 1.01, 95 % CI: 0.98, 1.03), O_3 (OR: 1.01, 95 % CI: 0.98, 1.03), $PM_{2.5}$ (OR: 0.99, 95 % CI: 0.94, 1.04), and PM_{10} (OR: 0.99, 95 % CI: 0.95, 1.02). Subgroup analysis was suggestive but ultimately underpowered to draw any meaningful conclusions. Additional work, including a longitudinal evaluation of air pollutants, a closer examination of epilepsy etiologies, and a wider, community-based approach, is needed to explore these findings further.

1. Introduction

Epilepsy, characterized by at least two unprovoked seizures occurring more than 24 hours apart, is the most common neurological disorder among children, with a global prevalence of 0.5 to 1 percent (Beghi, 2020; ILAE, 2014). In many children, ongoing seizures are closely associated with the development of comorbidities such as developmental delay and learning disabilities (Binnie et al., 1990; Sillanpää, 2004). Epilepsy etiology is an important guide for treatment and prognosis but remains unknown in many children (Aaberg et al., 2017; Cowan, 2002; Sokka et al., 2017).

Outdoor (ambient) air pollution is a well-known risk factor for multiple adverse health outcomes, including respiratory and cardiovascular diseases (Boogaard et al., 2019). Particulate matter smaller than 2.5 micrometers ($PM_{2.5}$) has a high rate of alveolar deposition, where it can initiate both local and systemic health effects (J. Chen & Hoek, 2020; Downward et al., 2018; Peters, 2005; Pope et al., 2002; Salvi, 2007). There is an increasing, albeit inconsistent, evidence base

Abbreviations: CI, 95 % confidence interval; FSC, first seizure clinic; ILAE, International League Against Epilepsy; NO_2, nitrogen dioxide; OR, odds ratio; O_3, ozone; $PM_{2.5}$, particulate matter with aerodynamic diameter < 2.5 μm; PM_{10}, particulate matter with aerodynamic diameter < 10 μm; SES, socioeconomic status; SES-WOA, socioeconomic status scores.

* Corresponding author at: University Medical Center Utrecht, Department of Pediatric Neurology, KG.01.310.0, P.O. Box 85090, 3508 AB Utrecht, The Netherlands
E-mail address: g.slinger-2@umcutrecht.nl (G. Slinger).
† Shared first author.
# Shared last author.

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suggesting that air pollution can contribute to the development of neurological disorders in adults, such as Parkinson's disease, autism spectrum disorders, and amyotrophic lateral sclerosis (C. Y. Chen et al., 2017; Chun et al., 2020; Loane et al., 2013; Ritz et al., 2016; Seelen et al., 2017; Toro et al., 2019). Previous studies have shown that exposure to certain air pollutants can result in alterations in neural activity and that prenatal exposure can induce irreversible nervous system damage or negatively affect central nervous system development, resulting in neurodevelopmental problems (2008; Xu et al., 2016). In addition, there is mounting evidence from epidemiological and animal toxicological studies that air pollution can change the immune response of the brain and cause neuroinflammation and oxidative stress, leading to neuronal damage and alterations of neurotransmitter expression in both adults and children (Angoa-Pérez et al., 2006; Block & Calderón-Garcidueñas, 2009; Gonzalez-Pina, Escalante-Membrillo, Alfaro-Rodriguez & Gonzalez-Maciel, 2008). These inflammatory processes could further catalyze ongoing damage in the events involved in epileptogenesis, leading to increased hyperexcitability and more seizures (Fernandes et al., 2019; Rana & Musto, 2018). The influence of exposure to air pollution on the risk of developing neurological disorders in children has not yet been extensively investigated. Still, air pollution has been suggested as a potential risk factor for developing epilepsy (Pitkänen et al., 2015).

The goal of the current study is to examine the association between the residential exposure to ambient air pollution (particulate matter with aerodynamic diameter < 10 μm [PM_{10}], < 2.5 μm [$PM_{2.5}$], ozone [O_3] and nitrogen dioxide [NO_2]) at the time of the first seizure and the diagnosis of epilepsy in Dutch children.

2. Methods

2.1. Study design and population

We conducted a retrospective, observational case-control study to investigate the potential association between air pollution and the diagnosis of epilepsy in Dutch children. The study population consisted of children who experienced one or more paroxysmal events suspected of epileptic seizures and visited the first seizure clinic (FSC) of the Wilhelmina Children's Hospital between January 1st, 2008, and May 31st, 2021. The FSC visit includes an in-depth history taking, neurological examination, and routine electroencephalogram. Cases were children (eventually) diagnosed with epilepsy, and controls were children in whom the diagnosis of epilepsy was discarded. Epilepsy diagnoses were made by an experienced child neurologist according to the International League Against Epilepsy (ILAE) definition of epilepsy (Fisher et al., 2014). Children with an unclear diagnosis (i.e., persistent doubt about the origin of the events they presented with) or an unknown or non-Dutch postal code were excluded from this study (see Figure S1 for a schematic overview).

The institutional ethics committee approved the use of anonymized retrospective data for research purposes without informed consent (protocol numbers 09-353/K and 18-354/C).

2.2. Data collection

2.2.1. Demographic and clinical data

All data were obtained via medical record auditing (HiX, version 6.1, ChipSoft B.V., Amsterdam, the Netherlands). Demographic data included sex, age at the FSC visit, and postal code at the moment of the FSC visit. Clinical data included the presence or absence of an epilepsy diagnosis (yes/no) and, for children with epilepsy, information on epilepsy type and epilepsy etiology, classified according to the ILAE guidelines (Scheffer et al., 2017).

2.2.2. Air pollution exposure assessment

We assigned annual average exposure of four pollutants (NO_2, O_3, PM_{10}, and $PM_{2.5}$) at children's residential addresses for the year of presentation.Potential prior residential mobility was not evaluated. We estimated the annual average air pollution levels using Europe-wide land-use regression models developed by geographically-varying linear regression (Shen et al., 2022) from 2000 to 2019, available yearly at every 25m by 25m grid across Europe. In short, routine monitoring observations from the European Environmental Agency were regressed on several spatial predictor variables, such as road variables, satellite-retrieved data, and chemical transport models' estimates. The models explained well the variations of the observed air pollution levels with R^2 values from 5-fold cross-validation ranging from 0.62 to 0.70 for NO_2, 0.43 to 0.66 for O_3, 0.48 to 0.71 for PM_{10} and 0.69 to 0.82 for $PM_{2.5}$. Because no models were available for 2020 and 2021, we used the estimated annual average concentrations of 2019 for those years instead.

2.2.3. Socioeconomic status assessment

Socioeconomic status (SES) is a well-known risk factor for epilepsy (Banerjee et al., 2009; Beghi, 2020; Heaney et al., 2002; Kaiboriboon et al., 2013). For the current study, we leveraged the socioeconomic status scores (SES-WOA) calculated by the Centraal Bureau voor Statistiek (Dutch Bureau of Statistics). The SES-WOA score is calculated based on three different characteristics: financial welfare, education level (determined by the highest education level attained by the household's reference person or partner), and employment history for the last four years (retired, unemployed, partially employed, or fully employed) of households on January 1st of the reporting year. The average score per region (municipality/district/neighborhood) was calculated based on the scores per household, with the total score (SES-WOA) representing the sum of the abovementioned sub-scores. SES-WOA scores were available from 2014 to 2019 and were assigned for the year a child first visited the FSC, or the closest available year. Regardless of the reporting year, the municipality/district/neighborhood classification of 2021 has been applied to all data used in this study.

2.3. Statistical analysis

Demographic and covariate details (age, sex, SES-WOA, and pollutant level) were explored via descriptive statistics. Differences between children with and without epilepsy were first explored by t-tests (Chi-square test for sex). Logistic regression was performed to quantify the association between average exposure to air pollutants and epilepsy diagnosis. Two levels of confounder adjustment were performed, first no adjustment and second following adjustment for age, sex, and SES-WOA. To evaluate whether diagnosis likelihoods differed by epilepsy etiology, analysis was repeated, examining the specific epilepsy etiologies identified for children with epilepsy (genetic, structural, metabolic, or unknown). As SES-WOA scores were only available for 2014-2019, we performed a sensitivity analysis, restricted to only the children who presented during those years. Air pollution exposure is presented at a 1 $\mu g/m^3$ resolution for optimal regression model reporting and all presented odds ratios (ORs) are per 1 $\mu g/m^3$ increase. All analyses were performed with R statistical software (R Core Team, 2022), packages sf (version 1.0-13), sp (version 1.6-1), raster (version 3.6-20), and rgdal (version 1.6-6).The scripts are available via GitHub: https://github.com/trudeslinger/RAPSODE. P-values < 0.05 were considered statistically significant.

3. Results

3.1. Demographics

In total, 1,213 children visited the FSC between January 1, 2008, and May 31, 2021. One of these children was excluded as he came from abroad and had no Dutch postal code and hence no available air

pollution data. Another 69 children were excluded because they had an unclear diagnosis. In total, 1143 children were retained for analysis: 406 cases and 737 controls (Figure S1). The participants were distributed over the Netherlands, with a higher concentration in Utrecht city and Utrecht province (Fig. 1).

Demographic characteristics of the study population are presented in Table 1. There was a higher proportion of boys (55 %) than girls (45 %) among all who presented. The average age at FSC presentation was 6.8 years. Cases were significantly older than controls (7.8 years versus 6.2 years, $p<0.05$). Among cases, the underlying disease etiology was (presumed or established) genetic in 223, structural in 82, metabolic in seven, and unknown in 94.

3.2. Air pollutant concentrations

The cases and controls were sampled from 405 unique postal codes (10.4 % of the total 3,950 postal codes in The Netherlands). The 405 areas have a median of 1,664 inhabitants (1st quantile to 3rd quantile: 945–2,930), a median area of 633,024 squared meters (1st quantile to 3rd quantile: 323,201–1,348,207), and a median diagonal length of 3,805 meters (1st quantile to 3rd quantile: 2,759–5,581).

The mean concentrations of NO_2, O_3, PM_{10}, and $PM_{2.5}$ were 25.8 μg/m^3, 58.0 μg/m^3, 22.6 μg/m^3, and 14.2 μg/m^3, respectively (Table 2). Mean concentrations of the air pollutants did not differ significantly between cases and controls. Boxplots displaying the range of exposures for cases and controls are available in the supplement (Figure S2). $PM_{2.5}$ correlated very strongly with PM_{10} (0.94), whereas the remaining pollutants tended to show weak to moderate positive and negative correlations with each other (Table S1).

Table 1
Mean (SD) or n (%) for demographics of the included children.

	Total	Cases	Controls
Sex: boy	627 (54.9 %)	229 (56.4 %)	398 (54.0 %)
Age*	6.8 (4.7)	7.8 (4.5)	6.2 (4.8)
Socio-economic status	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)

* Significant difference ($p<0.05$ via Wilcoxon-test) between those with and those without epilepsy.

Table 2
Mean (SD) for assigned pollution levels for the included children.

	Total	Cases	Controls
NO_2	25.7 (5.2)	25.8 (5.0)	25.7 (5.3)
O_3	58.0 (4.3)	58.0 (4.2)	57.9 (4.4)
PM_{10}	22.6 (3.2)	22.5 (3.3)	22.6 (3.2)
$PM_{2.5}$	14.2 (2.3)	14.2 (2.3)	14.2(2.3)

NO_2: nitrogen oxide; O_3: ozone; PM_{10}: fine particulate matter <10 μm; $PM_{2.5}$: fine particulate matter <2.5 μm

3.3. Association between air pollution and epilepsy diagnosis

Table 3 shows the unadjusted and adjusted generalized linear model results on the effects of exposure to air pollutants on epilepsy diagnosis.

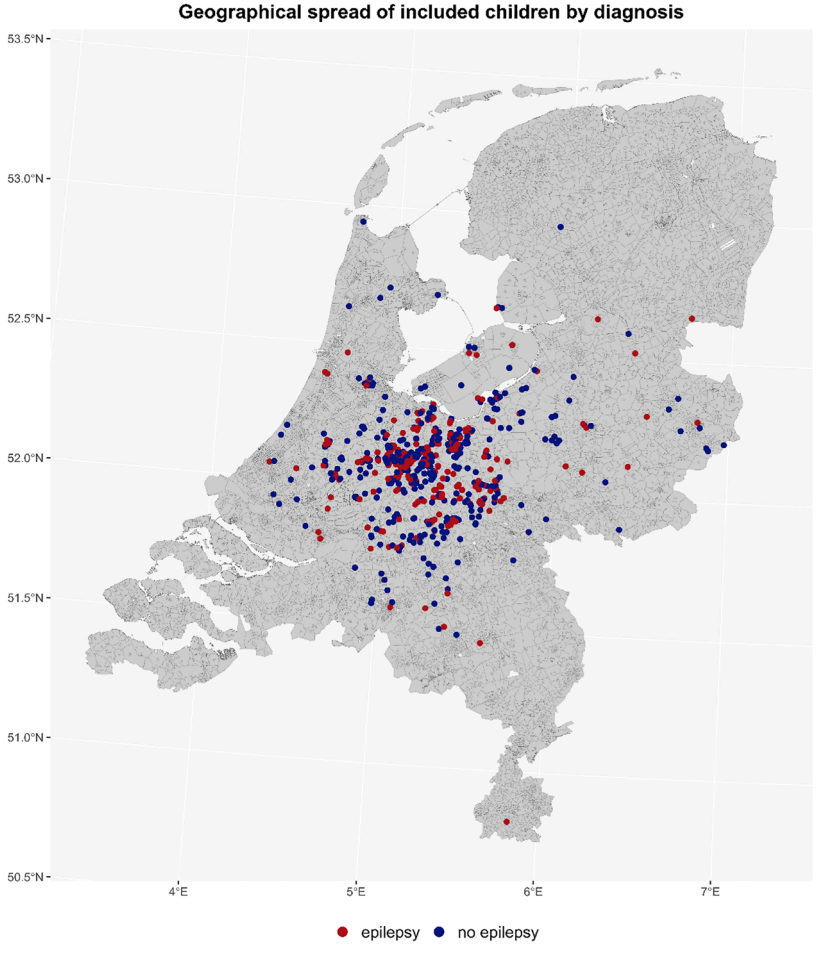

Fig. 1. Distribution of included children's postal codes on the map of the Netherlands based on the European terrestrial reference system 1989 (ETRS). Each dot represents the postal code of one child.

Table 3
Odds Ratios (and 95 % confidence intervals) for exposure to individual air pollutants and diagnosis of epilepsy.

	Unadjusted	Adjusted
NO_2	1.00 (0.98, 1.03)	1.01 (0.98, 1.03)
O_3	1.00 (0.98, 1.03)	1.01 (0.98, 1.03)
PM_{10}	0.99 (0.95, 1.02)	0.99 (0.95, 1.02)
$PM_{2.5}$	1.00 (0.94, 1.05)	1.00 (0.94, 1.05)

Odds ratios are per 1 $\mu g/m^3$ increase. Adjusted models are adjusted for age, sex, and socio-economic status.
NO_2: nitrogen oxide; O_3: ozone; PM_{10}: fine particulate matter <10 μm; $PM_{2.5}$: fine particulate matter <2.5 μm

There was no evidence of an increased likelihood of epilepsy with exposure to any of the air pollutants, with ORs approximating 1 for all examined pollutants and showing no appreciable change after additional adjustment. For example, the OR for an epilepsy diagnosis in relation to a 1 $\mu g/m^3$ increase in NO_2 was 1.01 (95 % confidence interval [CI]: 0.98, 1.03). Similarly, a 1 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with an OR of 0.99 (95 % CI: 0.94, 1.04).

3.3.1. Subgroup analyses

Subgroup analyses were performed to investigate potential differences in exposures and derived ORs between the different etiologies of epilepsy. Exposures to ambient pollutants were similar across epilepsy etiologies (Figure S3).

In regression analysis examining specific etiologies, no statistically significant association was observed between the pollutants or etiology groups (Table 4).

3.3.2. Sensitivity analysis

Restricting the analysis to only participants with the year of first presentation between 2014 and 2019 did not result in substantially different ORs for the pollutants NO_2, O_3, and PM_{10} in both adjusted and unadjusted models (Table S2). For $PM_{2.5}$, the association with the diagnosis of epilepsy became positive but was not statistically significant (adjusted OR 1.10, 95 % CI 0.93-1.30 per 1 $\mu g/m^3$ increase).

Table 4
Odds Ratios (and 95 % confidence intervals) for exposure to individual air pollutants and specific epilepsy etiologies.

Etiology & pollutant	Unadjusted	Adjusted
Genetic (n = 223)		
NO_2	1.01 (0.98, 1.04)	1.01 (0.98, 1.04)
O_3	1.00 (0.96, 1.04)	1.01 (0.96, 1.05)
PM_{10}	0.87 (0.73, 1.01)	0.87 (0.73, 1.01)
$PM_{2.5}$	0.99 (0.95, 1.03)	0.99 (0.95, 1.03)
Structural (n = 82)		
NO_2	0.99 (0.96, 1.03)	0.99 (0.96, 1.03)
O_3	1.03 (0.97, 1.08)	1.03 (0.97, 1.09)
PM_{10}	1.10 (0.92, 1.33)	1.10 (0.92, 1.32)
$PM_{2.5}$	1.01 (0.96, 1.06)	1.01 (0.96, 1.06)
Metabolic (n = 7)		
NO_2	0.99 (0.95, 1.04)	1.00 (0.95, 1.05)
O_3	0.98 (0.91, 1.05)	0.98 (0.91, 1.05)
PM_{10}	0.93 (0.70, 1.18)	0.94 (0.70, 1.18)
$PM_{2.5}$	0.97 (0.91, 1.04)	0.98 (0.91, 1.05)
Unknown (n = 94)		
NO_2	1.01 (0.94, 1.08)	1.01 (0.95, 1.08)
O_3	0.97 (0.88, 1.07)	0.97 (0.88, 1.08)
PM_{10}	1.01 (0.70, 1.37)	1.01 (0.70, 1.37)
$PM_{2.5}$	0.98 (0.90, 1.08)	0.99 (0.90, 1.08)

Odds ratios are per 1 $\mu g/m^3$ increase. Adjusted models are adjusted for age, sex, and socio-economic status.
NO_2: nitrogen oxide; O_3: ozone; PM_{10}: fine particulate matter <10 μm; $PM_{2.5}$: fine particulate matter <2.5 μm

4. Discussion

Recent studies suggested that air pollution contributes to neurological disorders in adults, but less is known about the relationship between air pollution and neurological disorders in children (C. Y. Chen et al., 2017; Ritz et al., 2016; Seelen et al., 2017). This study aimed to investigate the relationship between residential exposure to air pollution and the diagnosis of epilepsy among children in the Netherlands. We did not find statistically significant associations between exposure to different air pollutants and the diagnosis of epilepsy.

Several pathological mechanisms of how air pollution can contribute to neurological disorders have been proposed, including but not limited to alterations in neural activity, neuroinflammation, and production of reactive oxygen species (Block & Calderón-Garcidueñas, 2009; Calderón-Garcidueñas et al., 2008; Campbell et al., 2005; Sun et al., 2005). To date, only a few epidemiological studies have focused on epilepsy. Through a daily time-series analysis, Cakmak et al. demonstrated that air pollution can be a risk factor for epilepsy-related hospitalizations. They found a positive correlation between an increase in the level of various pollutants, including NO_2, O_3, PM_{10}, and $PM_{2.5}$, and an increase in the number of hospitalizations (Cakmak et al., 2010). Two other studies also point to an increased risk of seizure-related hospitalization after short-term exposure to various pollutants, including but not limited to NO2 and particulate matter, in both children (Bao et al., 2019, Cheng et al., 2022) and adults with epilepsy (Bao et al., 2019). Nitrous oxide, on the other hand, was, in another study, found to be negatively associated with hospitalizations for epilepsy (Fluegge & Fluegge, 2017). An Australian panel study by Chen et al. reported no significant associations for NO_2, O_3, PM_{10}, and SO_2. Still, it did report a significant association for carbon monoxide, with an increased seizure risk of 4 % (relative risk: 1.04, 95 % CI: 1.01, 1.07) (Z. Chen et al., 2022). In contrast to all of these studies focusing on seizures in patients already diagnosed with epilepsy, the current study is, to our knowledge, the first to examine the association between air pollutant exposure and the diagnosis of epilepsy in children.

This study has several strengths. First, it uses a well-defined population, representing an extensive multiple-year data collection period with reliable clinical data. All children were extensively examined by experienced pediatric neurologists, and those with unclear diagnoses were excluded from analysis. Additionally, data collection was standardized, thereby reducing data variability, and assigned air pollution values were sourced from well-established modeling approaches applied to various settings.

Despite these strengths, we also have to acknowledge several limitations. First, pollution could only be assigned to the residential address at presentation, meaning that a risk of exposure misclassification arises if a child had prior residential mobility. Owing to privacy requirements, pollution could only be assigned at the post-code level, meaning that changes in pollution at a fine spatial scale may have been misassigned. Furthermore, changes in pollution (or SES) metrics (including cumulative changes) were not evaluated over time, and the temporal resolution of the air pollution is relatively low (yearly). Topographical limitations might have contributed to obfuscating any possible relation between epilepsy and air pollution. The FSC was located in Utrecht, centrally in the Netherlands, meaning that individuals living more peripherally may have sought healthcare elsewhere, illustrated by the higher patient density around the city of Utrecht. Including data from a more peripheral clinical center would, therefore, be of additional value. Another restriction was the limited availability of socioeconomic status data (range 2014-2019). In our sensitivity analysis, however, we observed similar results when restricting the analysis to these years as for our main analysis, except for $PM_{2.5}$, where a positive (but non-significant) relationship with the diagnosis of epilepsy was observed. However, whether this represents a “true” positive change or merely a variation in finding remains unclear. We could not correct for differences in intra-house exposure. Children in the Netherlands spend about 90 % of

their time indoors, on average, and indoor air quality is known to be important for their health (Tsang & De Kleer, 2024). Adjusting for ventilation quality and smoking habits of house members may increase the estimation precision. It is also important to consider that the sample size may have been too limited to detect statistical differences at the etiological subtype level. This is reflected by the small number of seven cases with a metabolic etiology (a rare etiology), which explains why the ORs for this group were the most variable in the subgroup analysis. Finally, the control group is made up of children who presented to a first seizure clinic but ultimately had no diagnosis of epilepsy. While this gives a clear case/control demarcation, how well this group corresponds to the general 'healthy' population is less well known. Any association between air pollution and the underlying reason for presentation among controls may bias findings.

5. Conclusions and further directions

In this study of 406 children with epilepsy and 737 controls, we found no association between ambient air pollution during the year of presentation and a diagnosis of epilepsy in children in the Netherlands. As this is the first population-based study to examine this association, further research, including a larger (topographical) representation of different etiologies and longitudinal exposure metrics, will be required to understand any potential relationships better.

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CRediT authorship contribution statement

Geertruida Slinger: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **Sien T. Verbeek:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft. **Eric van Diessen:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Lotte Noorlag:** Investigation, Writing – review & editing. **Kees P.J. Braun:** Writing – review & editing. **Youchen Shen:** Investigation, Writing – review & editing. **Willem M. Otte:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing – review & editing. **George S. Downward:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

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

Data availability

The authors do not have permission to share data.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.envadv.2024.100541.

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