**Abstract**

**Background:** Attention deficit hyperactivity disorder (ADHD) is a frequently occuring neurodevelopmental disorder, symptoms of which first appear in early childhood. Etiology of ADHD is not well understood. We investigated whether outdoor air pollution and greenspace affect ADHD incidence in children residing in Saxony.

**Methods:** 66,823 children, all beneficiaries of the statutory health insurance company AOK PLUS and born between 2000 and 2004, were followed until 2014. We considered any child with at least one ICD-10-GM F90 diagnosis by a child/adolescent psychiatrist, neuropaediatrician, or psychotherapist an ADHD case. Children’s home addresses were known up to their four-digit postal code area. Population-weighted mean values of particulate matter with diameter of less than 10 µm (PM10), nitrogen dioxide (NO2), and MODIS Normalized Difference Vegetation Index (NDVI) were calculated for 186 postal code areas. Associations with each exposure were assessed by two-level adjusted Poisson regression models.

**Results:** 2,044 children (3.06%) were diagnosed with ADHD within the observation period. An increase of PM10 and NO2 by 10 µg/m³ raised the relative risk of ADHD by a factor of 1.97 [95% CI: 1.35-2.86] and 1.32 [1.10-1.58], respectively. A 0.1-unit increase in NDVI decreased the relative risk of ADHD by a factor of 0.82 [0.68-0.98]. Better access to child/adolescent psychiatrists was the most important confounder that increased ADHD risk across all models.

**Conclusion:** Our results provide some evidence that air pollution might affect ADHD. Future studies with more detailed address information and better control for confounders, in particular socioeconomic status and parental psychopathology, should replicate the observed associations.

**Key words:** air pollution; attention deficit hyperactivity disorder; children; nitrogen dioxide; particulate matter; greenness.

# 1.0. Introduction

# Attention deficit hyperactivity disorder (ADHD) is a frequently occuring neurodevelopmental disorder, symptoms of which first appear in early childhood. High heritability of ADHD is well established but not fully understood (Akutagava-Martins et al., 2016; Nikolas and Burt 2010). The set of risk factors identified as contributing to the prevalence of ADHD in a population is large, ranging from pre- and perinatal (e.g. maternal smoking) to psychosocial (e.g. low family socioeconomic status) to dietary (e.g. zinc nutritional deficiency) and toxicological (e.g. organophosphate pesticides). Their causal role is yet to be confirmed (Thapar et al., 2013).

# Outdoor air pollution has been suggested to affect the incidence of ADHD due to its central nervous system toxicity (Suades-González et al., 2015). Relatively few studies have investigated the association between exposure to air pollution and ADHD (Fluegge and Fluegge 2017; Min and Min 2017; Fuertes et al., 2016; Gong et al., 2014; Newman et al., 2013; Forns et al., 2016), and their findings have been mixed.

# Visual contact with nature might replenish attentional resources, as is grounded by attention restoration theory (ART; Kaplan and Kaplan, 1989) and is at least partially confirmed by experimental research (Ohly et al., 2017). One longitudinal observational study has reported the association between residing at places with higher greenness (ie. vegetation levels) with better scores from attention tests in children (Dadvand et al., 2017). One experimental and one observational study have observed that walking or playing in green spaces decreased symptoms of ADHD, in particular inattention (Taylor and Kuo, 2009; Kuo and Tylor, 2004). Three observational studies have reported inverse correlation between higher residential greenness or nearby green spaces (hereon referred to as “greenspace”) and ADHD at least in a subgroup (Amoly et al., 2014; Markevych et al., 2014; Balseviciene et al., 2014).

# However, only several studies on the associations of air pollution and greenspace with ADHD were based on medical diagnoses of ADHD (Min and Min, 2017, Fluegge and Fluegge, 2017, and Amoly et al., 2014). The rest of these studies relied on symptoms. Moreover, only one study investigated incidence of ADHD (Min and Min, 2017). In our present study, we aimed to further explore whether outdoor air pollution or greenspace affect ADHD. Our analysis was based on incident ADHD cases in a large sample of children residing in Saxony, Germany.

# 2.0. Methods

# 2.1. Study population and ADHD incidence

# We used routine health care claim data from AOK PLUS, a German statutory health insurance company, pertaining to Saxony, a region in eastern Germany with an area of about 18,000 km² and a population of about 4 million. The AOK PLUS Saxony data covers almost half of the local general population and is comparable to the German population as a whole in terms of age and sex (Trautmann et al., 2015). Briefly, we used data on diagnoses as well as individual characteristics of all beneficiaries including their year of birth, sex, and home address as defined by the first four digits (hereafter referred to as PLZ-4; n = 186, area from 4.3 to 408.3 km², population from 1,848 to 100,438 inhabitants, according to the 2011 German census) of the five-digit postal code areas (hereafter referred to as PLZ; n = 386, area from 1.7 to 408.3 km², population from 602 to 41,944 inhabitants). More detailed information on home addresses was unavailable due to protection of individual data.

# For the purpose of this study, we enrolled 66,823 children who were born between 2000 and 2004 and residing in Saxony at least since 2005. We did not include people who were insured by AOK PLUS but residing outside of Saxony in 2005, as well as those who moved into Saxony later and those who lived in Saxony but later changed their insurance company. A child was considered an ADHD incident case if he or she received at least one outpatient ICD-10-GM F90 diagnosis by a child/adolescent psychiatrist, neuropediatrician, or psychotherapist between 2005 and 2014. To receive an ADHD diagnosis according to ICD-10, a child has to show age-inappropriate levels of hyperactivity and inattention. These symptoms have to start early in development, be present for at least six months, occur in two or more settings, and be unexplainable by any other mental disease (Weltgesundheitsorganisation, 2004).

# 2.2. Exposure to air pollution and greenspace

# Annual average (arithmetic mean) concentrations of nitrogen dioxide (NO2) and particulate matter with diameter less than 10 µm (PM10) for the year 2007 were derived from freely available raster images in resolution of 100 m (<http://www.sahsu.org/content/data-download>). These rasters were created for Western Europe by land use regression modelling using air pollution measurements from more than 1,500 AIRBASE monitoring sites, satellite air pollution measurements, and land use characteristics (Vienneau et al., 2013).

# Normalized Difference Vegetation Index (NDVI; Tucker 1979) was used as an indicator of greenspace. NDVI reflects general vegetation degree and is commonly used in epidemiological studies (Markevych et al., 2017). The 10-year average level of NDVI for the years 2005 to 2014 was assessed from freely available MODerate-resolution Imaging Spectroradiometer (MODIS) satellite images in resolution of 250 m (<http://daacmodis.ornl.gov/cgi-bin/MODIS/GLBVIZ_1_Glb/modis_subset_order_global_col5.pl>). The equation of NDVI is based on the difference of surface reflectance over absorbance in two vegetation-informative wavelengths – visible red and near-infrared. NDVI ranges from -1 (water) through 0 (barren areas) to +1 (absolutely vegetated areas).

# Average air pollutant and NDVI values were calculated for each of 386 PLZ areas. To account for the fact that air pollution and greenspace data pertaining to more populated PLZ areas in each PLZ-4 area may serve as a more accurate estimate of exposure, average values were assigned to 186 PLZ-4 areas using numbers of inhabitants from the 2011 German census.

# Geographic data management and calculations were conducted with ArcGIS 10.1 Geographical Information System (ESRI, Redlands, CA, USA).

# 2.3. Statistical analysis

# Due to high correlations between three exposure variables (|Pearson correlation coefficient (ρ)| ≥ 0.80, Table S1) associations were assessed for each exposure separately.

# The semi-individual associations (Künzli and Tager, 1997) were assessed by two-level Poisson models with PLZ-4 area treated as a second level and observation time used as an offset. The results are presented as relative risks (RRs) together with their respective 95% confidence intervals (CIs) (Table 2). Year of birth, sex, proportion of long-term (more than one year) and overall unemployment in PLZ-4 areas, as well as healthcare access were considered as confounders. To calculate healthcare access variables, we had to simplify the standard two-step floating catchment area method (Luo and Wang 2003). We did not have exact addresses for study participants or doctors and therefore assumed that all addresses within a PLZ-4 area were located at the centroid of the most populated constituent PLZ area. As a proxy of access to healthcare, proximity to registered doctors was used. It was defined as the number of doctors divided by the number of people below the age of 18 years in 2011 in a circular buffer normalized to unity through division by the Saxony-wide doctor-over-people ratio. We used arbitrary buffers of 15 km, 30 km, and 40 km to calculate proximity to pediatricians (for the year 2011), child/adolescent psychotherapists (for the years 2008-2014), and child/adolescent psychiatrists and neuropediatricians (for the years 2008-2014), respectively. The PLZ-4 aggregated data on pediatricians, child/adolescent psychotherapists and child/adolescent psychiatrists and neuropediatricians was obtained from the Kassenärztliche Vereinugung Sachsen (KV Sachsen), which is a medical association of medical doctors in Saxony (http://www.kvs-sachsen.de). Briefly, in Germany, all doctors who want to work on statutory insured persons (about 90% of the population) have to license their medical practice by such an association. The associations are obliged by law to control that there is sufficient number of doctors of different specialties in supply areas. The more rare the specialty is, the larger the supply area. To take this into account, we selected different buffer sizes for different doctors. To filter out unassociated variables we selected the model with the lowest Bayesian Information Criterion (BIC) for the regression analyses. As a sensitivity analysis, we excluded 19.4% of children who moved to another PLZ-4 area at least once between 2005 and 2014 to check how this affected the RRs. One of the reasons for this analysis was that access to healthcare for movers changed over time and we could not estimate it adequately.

# Additionally, we plotted predictions of the individual risk of ADHD for different levels of PM10, NO2 and NDVI, separately for boys and girls (Figures S1-S3). These prediction curves are adjusted for all the covariates, according to the Table 2. The prediction intervals represent 50% of all predictions around the median line.

# As a sensitivity analysis, we aggregated ADHD incidence on PLZ-4 level and adjusted them for measurement errors by Bayesian Conditional Autoregressive (CAR) models which take into account first-order spatial dependencies, the shared borders between PLZ-4 areas.

# The associations on aggregated ADHD variable were assessed by Pearson correlations and LOESS regressions (Hastie and Tibshirani 1986). These results are presented as Pearson correlation coefficients (Table S1) and LOESS curves with 95% CIs (Figure S4), respectively. LOESS is an abbreviation for local regression smoother. Here, a polynomial regression was used to estimate each spot, which includes each time 0.75 % of the nearest data points with down weighting (1 - (dist/maxdist)^3)^3) of points by their distant. These estimates were then connected to obtain a line, which follows the pattern of the data. Since for points on the edges of the distribution less information is available, the functional form of LOESS is more uncertain.

# Data management was done in Stata (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). Statistical analyses were conducted using R, version 3.3.2 (Vienna, Austria; R Core Team 2012). Two-level Poisson models were fitted with the R package *lme4*. CAR models were fitted by *BayesX* for R (Umlauf et al., 2015; Brezger, Kneib and Lang 2005).

**3.0. Results**

Out of 66,823 children born between 2000 and 2004 and residing in Saxony in 2005, 2,044 (3,06%) were diagnosed with ADHD up to the year 2014 (Table 1). It agrees well with the most recent meta-analysis on studies that used ICD-10 criterion (Polanczyk et al., 2015). 3.6 times as many males were diagnosed with ADHD than females.

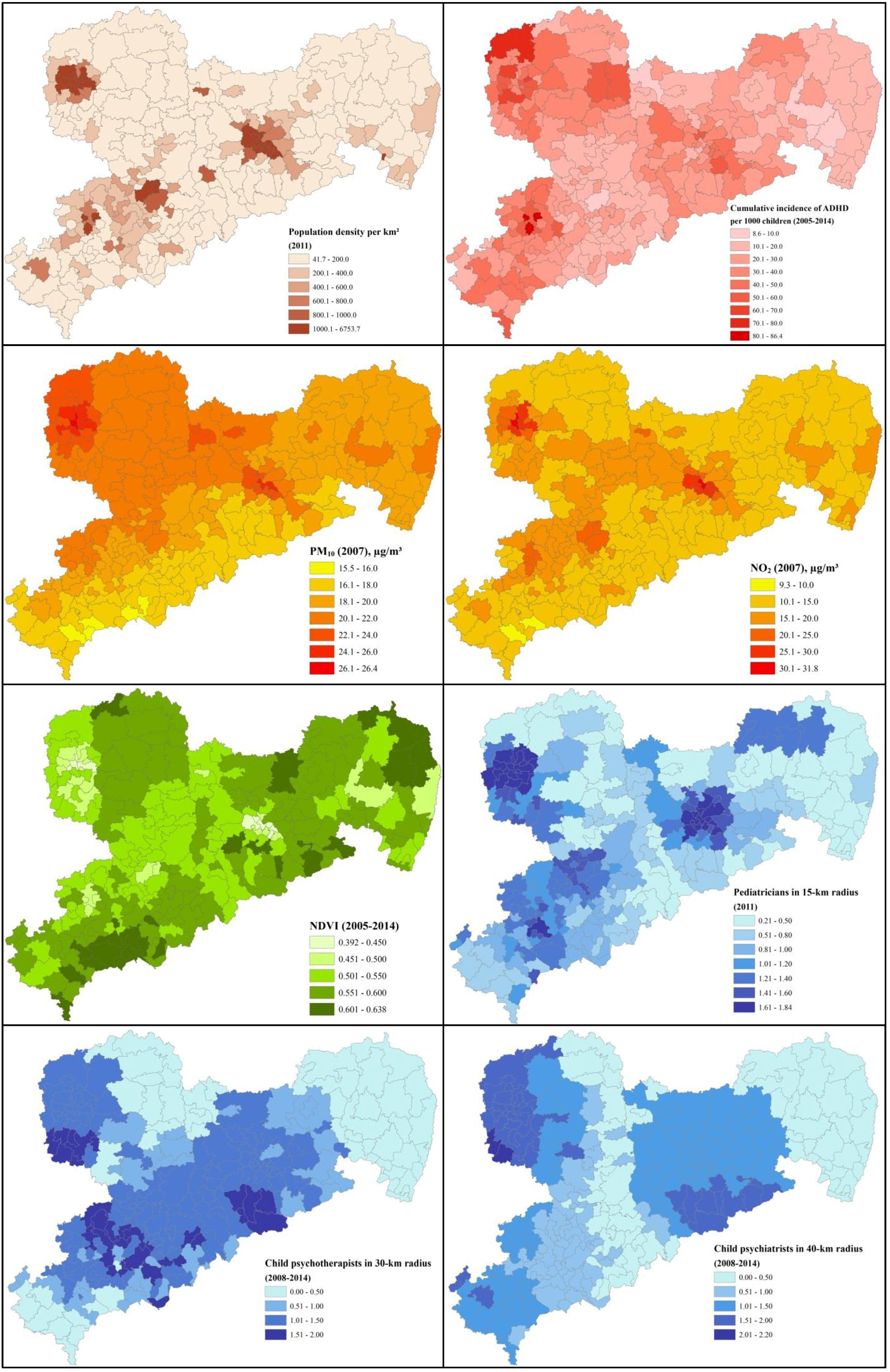
# Table 1. Characteristics of the study population (n (%)).

|  |  |  |
| --- | --- | --- |
| Characteristic | Total study population  (n = 66,823) | ADHD cases  (n = 2,044) |
| Sex  male  female | 34,100 (51.0)  32,723 (49.0) | 1,598 (78.2)  446 (21.8) |
| Birth year  2000  2001  2002  2003  2004 | 13,935 (20.9)  13,217 (19.8)  12,798 (19.1)  12,851 (19.2)  14,022 (21.0) | 466 (22.8)  449 (22.0)  358 (17.5)  390 (19.1)  381 (18.6) |
| Changed place of residence between 2005 and 2014  yes  no | 12,971 (19.4)  53,851 (80.6) | 492 (24.1)  1,552 (75.9) |

ADHD – attention deficit hyperactivity disorder.

Cumulative incidence of ADHD for the period 2005-2014 was very unevenly distributed across the 186 PLZ-4 areas with incidences ranging from 8.6 to 86.4 per 1,000 children (Figure 1). The highest incidence was observed in the city of Zwickau and northwest of the city of Leipzig, in the district of Nordsachsen. Proximity to registered doctors, as defined by three different variables (pediatricians in 15-km radius, child/adolescent psychotherapists in 30-km buffer and child/adolescent psychiatrists and neuropediatricians in 40-km buffer), was the lowest in eastern Saxony, in districts Görlitz and Bautzen, and in the eastern part of Nordsachsen. PM10 was smoothly distributed over space. NO2 levels were the highest in urban areas as opposed to NDVI which was highest in rural areas.

We observed positive correlation between NO2 and ADHD (ρ = 0.43; Table S1), as well as PM10 and ADHD (ρ = 0.37), and negative correlation between ADHD and NDVI (ρ = -0.31). Additionally, ADHD correlated with proximity to doctors, especially with child/adolescent psychiatrists and neuropediatricians (ρ = 0.48). All NO2, PM10 and NDVI were correlated with population density; the strongest correlation was observed with NO2 (ρ = 0.83), followed by NDVI (ρ = -0.67) and PM10 (ρ = 0.61).

****

**Figure 1.** Population density (Source: German population census 2011), ADHD cumulative incidence rates (Source: AOK PLUS), air pollution (Source: SAHSU), greenspace (Source: ORNL DAAC), and healthcare access spatial distribution across 186 PLZ-4 areas in Saxony (Source: KV Sachsen) on a scale 1:800,000.

Higher levels of PM10 and NO2 levels were both observed to be associated with higher incidence of ADHD while NDVI was linked to lower ADHD incidence (Table 2). The strongest effect estimate was observed for PM10: the risk of being diagnosed with ADHD increased by a factor of 1.97 per 10 µg/m³ increase in PM10. Proximity to child/adolescent psychiatrists was the most important confounder that increased ADHD risk across all models. Contrary to that, unemployment variables did not affect the results and were not included in the final models. After children who moved to another PLZ-4 area were excluded the observed associations were similar to those from the main analysis except for the association with NDVI, which was no longer significant (Table S2). The prediction plots (Figures S1-S3) revealed that the change of ADHD risk was the steepest for PM10 compared to the NO2 and NDVI. As the prediction intervals are wide, the area effects are large. The results of the aggregated analyses were in line with results from the semi-individual analyses (Table S1 and Figure S4). Additionally, non-linearity was revealed by LOESS curves (Figure S1).

**Table 2.** Adjusted RRs with 95% CIs of air pollution and greenspace and ADHD estimated by two-level Poisson regression models with observation time as an offset. Fixed part refers to an individual level (level 1) and random part refers to a PLZ-4 level (level 2).

|  |  |
| --- | --- |
| **Models / variables** | **ADHD incidence** |
| **Model 1** |  |
| Fixed part, RR (95% CI) |  |
| PM10 (per 10 µg/m³) | 1.97 (1.35 – 2.86) |
| Child psychiatrists in 40 km-radius | 1.78 (1.50 – 2.11) |
| Sex (ref: female) |  |
| Male | 3.45 (3.11 - 3.83) |
| Year of birth (ref: 2000) |  |
| 2001 | 1.02 (0.90 - 1.16) |
| 2002 | 0.85 (0.74 - 0.97) |
| 2003 | 0.92 (0.80 - 1.05) |
| 2004 | 0.82 (0.71 - 0.93) |
| Fixed part, variance | 0.16 |
| Random part, variance |  |
| Level 2: PLZ-4 area | 0.20 |
|  |  |
| **Model 2** |  |
| Fixed part, RR |  |
| NO2 (per 10 µg/m³) | 1.32 (1.10 – 1.58) |
| Child psychiatrists in 40-km radius | 1.86 (1.57 – 2.20) |
| Sex (ref: female) |  |
| Male | 3.45 (3.11-3.83) |
| Year of birth (ref: 2000) |  |
| 2001 | 1.02 (0.90 - 1.16) |
| 2002 | 0.85 (0.74 - 0.97) |
| 2003 | 0.92 (0.80 - 1.05) |
| 2004 | 0.82 (0.71 - 0.93) |
| Fixed part, variance | 0.16 |
| Random part, variance |  |
| Level 2: PLZ-4 area | 0.20 |
|  |  |
| **Model 3** |  |
| Fixed part, RR (95% CI) |  |
| NDVI (per 0.1 units) | 0.82 (0.68 – 0.98) |
| Child psychiatrists in 40-km radius | 1.92 (1.63 – 2.27) |
| Sex (ref: female) |  |
| Male | 3.45 (3.11 - 3.83) |
| Year of birth (ref: 2000) |  |
| 2001 | 1.02 (0.90 - 1.16) |
| 2002 | 0.85 (0.74 - 0.97) |
| 2003 | 0.92 (0.80 - 1.05) |
| 2004 | 0.82 (0.71 - 0.93) |
| Fixed part, variance | 0.16 |
| Random part, variance |  |
| Level 2: PLZ-4 area | 0.21 |

ADHD – attention deficit hyperactivity disorder; CI – confidence interval; NO2 – nitrogen dioxide; NDVI – Normalized Difference Vegetation Index; PM10 – particulate matter with diameter less than 10 µm; RR – relative risk.

**4.0. Discussion**

The results of our prospective analysis on 10- to 14-year-old children support the notion that higher air pollution is associated with increased risk of ADHD while more greenspace may be associated with lower cumulative incidence of ADHD. These results are in line with a recent study from South Korea (Min and Min 2017) where PM10 and NO2 also increased the risk of ADHD in a much smaller population-based cohort. Increased odds of ADHD symptoms were also related to elemental carbon in one American study (Newman et al., 2013) and to PM2.5 and PM2.5 absorbance in one German study (Fuertes et al., 2016). However, three other studies – from the United States (Fluegge and Fluegge 2017), Spain (Forns et al., 2016), and Sweden (Gong at al. 2014) – did not observe any associations of ADHD diagnoses or symptoms with traffic-related air pollution. Different study settings, methods of air pollution exposure assessment, considered air pollutants and exposure windows, ADHD definition all could have led to these heterogeneous findings. The results of our analysis revealed that the association of ADHD was stronger with PM10 than with NO2. Since PM10 was less correlated with population density than NO2, it makes us more confident that the observed associations with air pollution are not only due to higher urbanicity. As known from animal and postmortem human studies, air pollution might in general cause central nervous system damage via neuroinflammation and oxidative stress (Suades-González et al., 2015) or white matter injury (Babadjouni et al., 2017).

Consistent inverse associations between residential greenness and ADHD symptoms were reported in an observational Spanish study (Amoly et al., 2014). This observation was not replicated, when ADHD DSM-IV diagnosis was considered instead, or when residential proximity to green spaces was used as an exposure. In contrast to that, another observational study from Germany did not observe any association in relation to residential greenness but reported the association with green spaces close by (Markevych et al., 2014). A third observational study has reported the association between proximity to green spaces and ADHD symptoms only in children of mothers with lower educational level (Balseviciene et al., 2014). Our association of higher greenness with lower ADHD incidence generally agrees with observations of Amoly et al. (2014) and disagrees with those of Markevych et al. (2014) and Balseviciene et al. (2014). Due to very high correlation of NDVI with air pollutants in our study, it is impossible to disentangle these associations. It might be that higher greenness simply reflects lower air pollution or residing in a rural area. Nevertheless, correlation with population density was not extremely high. Interestingly, the association with NDVI is not formally statistically significant anymore after the group of children who changed their PLZ-4 of residence were excluded from the analysis. This might be due to reduced power, especially given that there were more movers among ADHD cases than in general population. Among movers, 18.5% moved from one urban area (population density above 500 people/km², according to the German census 2011) to another, 51.5% moved from one rural area to another, 21.6% moved from an urban to a rural area and 8.4% moved from a rural to an urban area. Because the case numbers in the last two subgroups were small, we did not do these subgroup analyses. Although we are not able to test this, observed association with greenness may be also independent from air pollution levels and be explained by improved attention (as inattention is one of the criteria for ADHD diagnosis). As already mentioned in the Introduction, greenspace is hypothesized to alleviate restoration from mental fatigue caused by directed attention needed in everyday tasks (Kaplan and Kaplan, 1989). However, supporting evidence is currently limited to heterogeneous experimental studies (Ohly et al., 2017) and one observational study (Dadvand et al., 2017).

Our analysis was conducted on the routinely collected statutory health insurance claim data. In Germany, about 90% of population hold statutory health insurance and since 1996, are free to select their insurance company. Saxony is the federal state in Germany with the largest share of people insured by one company (about half of the study population) compared to other states. This makes our study population to be unlikely affected by selection bias. Due to the indirect data gathering nonresponse bias and recall bias are not of concern. Huge population size and prospective data collection enabled us for robust assessment of the associations of air pollution and greenspace with ADHD incidence. Unlike many previous studies of environmental impacts on mental health that had to rely on symptoms rather than on doctor-validated diagnoses (Suades-González et al., 2015, Gascon et al., 2015; McCormick, *In press*) we used an ICD-10 ADHD case definition. Nevertheless, definition of ADHD incidence appeared to be a very difficult issue. We included ADHD diagnoses only by specialists to avoid potential overestimation of incidence, which might have been the case if diagnoses of pediatricians are also considered. On the other hand, use of ADHD medication would have underestimated the incidence, as medicament treatment of ADHD is not mandatory in Germany. Therefore, specialty of responsible doctors in psychiatry should serve as a validation criterion. Our definition is in line with one Korean study on similar data (Min and Min, 2017).

Unlike any previous study, we used data on both air pollution and greenspace. Of course, these metrics are not without limitations. While NDVI was possible to average over the entire observation period (2005-2014), PM10 and NO2 estimates were assigned from the rasters for the year 2007 under the explicit assumption that spatial contrasts of air pollution remain relatively stable across several years in the areas without major change in land use pattern (Eeftens at al., 2011; Cesaroni et al., 2012). Moreover, we used NDVI as a greenspace metric, which is not ideal, as our regression estimates based on this dimensionless vegetation index are difficult to communicate to practitioners and general population (Markevych et al., 2017). Proportion of greenspace from land use dataset would have been a better metric, but there are no sufficiently detailed data covering the entire study area.

Nevertheless, our study must be understood in the context of its limitations. Address information was restricted spatially (since available only to the PLZ-4 level) and temporarily (since information on change of the residence was not available prior 2005 und only partially available thereafter). Therefore, the assessed air pollution and greenspace levels did not reflect individual level exposure contrasts. This led to squeezing of the ranges of the exposure estimates. The direction of the bias should not be the problem in this case, since in a large dataset the likelihood to be misclassified to higher, as well as to lower exposure values, should be about the same, and these effects should balance each other. Additionally, the PLZ-4 aggregated exposure estimates could have led to residual confounding by other spatially correlated exposures, in particular, area-level socioeconomic status (SES). We attempted to control for this at least partially by using proportion of long-term and overall unemployment in PLZ-4 areas but such variables had no impact on the results. Unfortunately, more comprehensive area-level SES could not be accounted for. Individual SES data were not available, which likely resulted in an overestimation of the associations of interest. This could have led to wider confidence intervals of unknown magnitude. We also lack data on family psychopathology, the only confirmed causal risk factor for ADHD onset to date (Thapar et al., 2013). Still, we could at least partially account for healthcare access and thus, for potential over-diagnosis of ADHD in some areas compared to others, which is a public concern in Germany. However, proximity to registered doctors, which we used as a proxy of access to healthcare, is not comprehensive enough. Unfortunately, more holistic measures for healthcare access (Gulliford et al., 2002) were not available. One of the most notable observations of our study is the observed huge (ten-fold) difference in cumulative incidence across 186 PLZ-4 areas in Saxony. Genetic variability can be an explanation of these differences only to some extent. Beyond already discussed differences in SES, differences in diagnostic behaviours of specialists practicing in Saxony might be another potential explanation, but we were not able to validate this in the current analysis. Therefore, a potential for residual confounding is our main shortcoming.

In summary, our results provide some evidence that air pollution and greenspace might affect ADHD in Saxony, Germany. Whether this link is causal must be clarified by further studies with more detailed address information and better control for confounders, in particular SES and parental psychopathology.

**Conflict of interests**

Jochen Schmitt reports financial support for IITs from Sanofi, Novartis, ALK, MSD and Pfizer. The rest of the authors state no conflict of interest.

**Acknowledgements**

We thank the Saxony Compulsory Health Insurance AOK PLUS for cooperation in data utilization and for providing technical support.

The project received infrastructure support through the DFG Clusters of Excellence “Inflammation at Interfaces” (grants EXC306 and EXC306/2), and was supported by the German Federal Ministry of Education and Research (BMBF) within the framework of the e:Med research and funding concept (sysINFLAME, grant 01ZX1306A).

We are grateful to Clemens Baumbach for language correction.

**Data statement**

Due to the sensitive nature of the data used in this study, which includes individual-level medical diagnoses, the raw data must remain confidential and cannot be shared.

**References**

Akutagava-Martins, G.C., Rohde, L.A., Hutz, M.H., 2016. Genetics of attention-deficit/hyperactivity disorder: an update. Expert Rev. Neurother. 16(2):145-56, doi: 10.1586/14737175.2016.1130626.

Amoly, E., Dadvand, P., Forns, J., López-Vicente, M., Basagaña, X., Julvez, J., et al., 2014. Green and blue spaces and behavioral development in Barcelona schoolchildren: the BREATHE project. Environ. Health. Perspect. 122(12):1351-8, doi: 10.1289/ehp.1408215.

Babadjouni, R.M., Hodis, D.M., Radwanski, R., Durazo, R., Patel, A., Liu, Q., et al., 2017. Clinical effects of air pollution on the central nervous system; a review. J. Clin. Neurosci. 43:16-24, doi: 10.1016/j.jocn.2017.04.028.

Balseviciene, B., Sinkariova, L., Grazuleviciene, R., Andrusaityte, S., Uzdanaviciute, I., Dedele, A., et al., 2014. Impact of residential greenness on preschool children's emotional and behavioral problems. Int. J. Environ. Res. Public Health 11(7):6757-70, doi: 10.3390/ijerph110706757.

Brezger, A., Kneib, T., Lang, S., 2005. BayesX: Analyzing Bayesian Structural Additive Regression Models. Journal of Statistical Software 14(11), doi: 10.18637/jss.v014.i11.

Cesaroni, G., Porta, D., Badaloni, C., Stafoggia, M., Eeftens, M., Meliefste, K., Forastiere, F., 2012. Nitrogen dioxide levels estimated from land use regression models several years apart and association with mortality in a large cohort study. Environ Health. 11:48. doi: 10.1186/1476-069X-11-48.

Dadvand, P., Tischer, C., Estarlich, M., Llop, S., Dalmau-Bueno, A., López-Vicente, M., 2017. Lifelong residential exposure to green space and attention: a population-based prospective study. Environ Health Perspect. 125(9):097016, doi: 10.1289/EHP694.Eeftens, M., Beelen, R., Fischer, P., Brunekreef, B., Meliefste, K., Hoek, G., 2011. Stability of measured and modelled spatial contrasts in NO(2) over time. Occup Environ Med. 68(10):765-70, doi: 10.1136/oem.2010.061135. Epub 2011 Feb 1.

Fluegge, K., Fluegge, K., 2017 Exposure to ambient PM10 and nitrogen dioxide and ADHD risk: A reply to Min & Min (2017). Environ. Int. 103:109-110, doi: 10.1016/j.envint.2017.02.012.

Forns, J., Dadvand, P., Foraster, M., Alvarez-Pedrerol, M., Rivas, I., López-Vicente, M., et al., 2016. Traffic-related air pollution, noise at school, and behavioral problems in Barcelona schoolchildren: a cross-sectional study. Environ. Health Perspect. 124:529-535, doi: 10.1289/ehp.1409449.

Fuertes, E., Standl, M., Forns, J., Berdel, D., Garcia-Aymerich, J., Markevych, I., et al., 2016. Traffic-related air pollution and hyperactivity/inattention, dyslexia and dyscalculia in adolescents of the German GINIplus and LISAplus birth cohorts. Environ. Int. 97:85-92, doi: 10.1016/j.envint.2016.10.017.

Gascon, M., Triguero-Mas, M., Martínez, D., Dadvand, P., Forns, J., Plasència, A., et al., 2015. Mental health benefits of long-term exposure to residential green and blue spaces: a systematic review. Int. J. Environ. Res. Public Health 12(4):4354-79, doi: 10.3390/ijerph120404354.

Gong, T., Almqvist, C., Bölte, S., Lichtenstein, P., Anckarsäter, H., Lind, T., et al., 2014. Exposure to air pollution from traffic and neurodevelopmental disorders in Swedish twins. Twin Res. Hum. Genet. 17(6):553-62, doi: 10.1017/thg.2014.58.

Gulliford, M., Figueroa-Munoz, J., Morgan, M., Hughes, D., Gibson, B., Beech, R., et al., 2002. What does 'access to health care' mean? J Health Serv. Res. Policy.7(3):186-188.

Hastie, T., Tibshirani, R., 1986. Generalized additive models. Statist. Sci. 1(3):297–318, doi:10.1214/ss/1177013609.

Kaplan, R., Kaplan, S., 1989. The experience of nature: y psychological perspective. New York: Cambridge University Press.

Kuo, F.E., Taylor, A.F., 2004. A potential natural treatment for attention-deficit/hyperactivity disorder: evidence from a national study. Am. J. Public Health 94(9):1580-6.

Künzli. N., Tager, I.B., 1997. The semi-individual study in air pollution epidemiology: a valid design as compared to ecological studies. Environ. Health Perspect. 105(10):1078-1083.

Luo, W., Wang, F., 2003. Measures of spatial accessibility to health care in a GIS environment: synthesis and a case study in the Chicago region. Environment and Planning B: Planning and Design 30:865–884, doi: 10.1068/b29120.Markevych, I., Schoierer, J., Hartig, T., Chudnovsky, A., Hystad, P., Dzhambov, A.M., et al., 2017. Exploring pathways linking greenspace to health: Theoretical and methodological guidance. Environ. Res. 158:301-317, doi: 10.1016/j.envres.2017.06.028.

Markevych, I., Tiesler, C.M., Fuertes, E., Romanos, M., Dadvand, P., Nieuwenhuijsen, M.J., et al., 2014. Access to urban green spaces and behavioural problems in children: Results from the GINIplus and LISAplus studies. Environ. Int. 71:29-35, doi: 10.1016/j.envint.2014.06.002.

McCormick, R. In press. Does access to green space impact the mental well-being of children: a systematic review. J. Pediatr. Nurs., doi: 10.1016/j.pedn.2017.08.027.

Min, J.Y., Min, K.B., 2017. Exposure to ambient PM10 and NO2 and the incidence of attention-deficit hyperactivity disorder in childhood. Environ. Int. 99:221-227, doi: 10.1016/j.envint.2016.11.022.

Newman, N.C., Ryan, P., Lemasters, G., Levin, L., Bernstein, D., Hershey, G.K., et al., 2013. Traffic-related air pollution exposure in the first year of life and behavioral scores at 7 years of age. Environ. Health. Perspect. 121(6):731-6, doi: 10.1289/ehp.1205555.

Nikolas, M.A., Burt, S.A., 2010. Genetic and environmental influences on ADHD symptom dimensions of inattention and hyperactivity: a meta-analysis. J. Abnorm. Psychol. 119(1):1-17, doi: 10.1037/a0018010.

Ohly, H., White, M.P., Wheeler, B.W., Bethel, A., Ukoumunne, O.C., Nikolaou, V., Garside, R., 2016. Attention restoration theory: a systematic review of the attention restoration potential of exposure to natural environments. J. Toxicol. Environ. Health B Crit. Rev. 19(7):305–343.

Polanczyk, G.V., Salum, G.A., Sugaya, L.S. et al., 2015. Annual research review: a meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. J. Child Psychol. Psychiatry. 56:345–365

R Core Team., 2012. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing. Available: http://www.R-project.org/ [accessed 2 November 2017].

Suades-González, E., Gascon, M., Guxens, M., Sunyer, J., 2015. Air pollution and neuropsychological development: a review of the latest evidence. Endocrinology 156(10):3473-82, doi: 10.1210/en.2015-1403.

Taylor, A.F., Kuo, F.E., 2009. Children with attention deficits concentrate better after walk in the park. J. Atten. Disord. 12(5):402-9, doi: 10.1177/1087054708323000.

Thapar, A., Cooper, M., Eyre, O., Langley, K., 2013. Practitioner Review: What have we learnt about the causes of ADHD? J. Child. Psychol. Psychiatry 54(1):3–16, doi: 10.1111/j.1469-7610.2012.02611.x.

Trautmann, F., Schuler, M., Schmitt, J., 2015. Burden of soft-tissue and bone sarcoma in routine care: Estimation of incidence, prevalence and survival for health services research. Cancer Epidemiol. 39(3):440-6, doi: 10.1016/j.canep.2015.03.002.

Tucker, C.J., 1979. Red and photographic infrared linear combinations for monitoring vegetation. Remote Sens. Environ. 8:127–150, doi: 10.1016/0034-4257(79)90013-0.

Umlauf, N., Adler, D., Kneib, T., Lang, S., Zeileis, A., 2015. Structured Additive Regression Models: An R Interface to BayesX. Journal of Statistical Software 63(21);1-46. Available: https://www.jstatsoft.org/article/view/v063i21 [accessed 2 November 2017].

Vienneau, D., de Hoogh, K., Bechle, M.J., Beelen, R., van Donkelaar, A., Martin, R.V., et al., 2013. Western European land use regression incorporating satellite- and ground-based measurements of NO2 and PM10. Environ. Sci. Technol. 47(23):13555-64, doi: 10.1021/es403089q.

Weltgesundheitsorganisation, 2004. Internationale Klassifikation psychischer Störungen: ICD-10 Kapitel V (F) Klinisch-diagnostische Leitlinien (Deutsch).