

**Traffic-related air pollution and hyperactivity/inattention, dyslexia and dyscalculia in adolescents of the German GINIplus and LISApplus birth cohorts**

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## **ABSTRACT**

### *Background*

Few studies have examined the link between air pollution exposure and behavioural problems and learning disorders during late childhood and adolescence.

### *Objectives*

To determine whether traffic-related air pollution exposure is associated with hyperactivity/inattention, dyslexia and dyscalculia up to age 15 years using the German GINIplus and LISApplus birth cohorts (recruitment 1995- 1999).

### *Methods*

Hyperactivity/inattention was assessed using the German parent-completed (10 years) and self-completed (15 years) Strengths and Difficulties Questionnaire. Responses were categorized into normal versus borderline/abnormal. Parent-reported dyslexia and dyscalculia (yes/no) at age 10 and 15 years were defined using parent-completed questionnaires. Individual-level annual average estimates of nitrogen dioxide (NO<sub>2</sub>), particulate matter (PM)<sub>10</sub> mass, PM<sub>2.5</sub> mass and PM<sub>2.5</sub> absorbance concentrations were assigned to each participant's birth, 10 year and 15 year home address. Longitudinal associations between the air pollutants and the neurodevelopmental outcomes were assessed using generalized estimation equations, separately for both study areas, and combined in a random-effects meta-analysis. Odds ratios and 95% confidence intervals are given per interquartile range increase in pollutant concentration.

## *Results*

The prevalence of abnormal/borderline hyperactivity/inattention scores and parental-reported dyslexia and dyscalculia at 15 years of age was 12.9%, 10.5% and 3.4%, respectively, in the combined population (N=4745). In the meta- analysis, hyperactivity/inattention was associated with PM<sub>2.5</sub> mass estimated to the 10 and 15 year addresses (1.12 [1.01, 1.23] and 1.11 [1.01, 1.22]) and PM<sub>2.5</sub> absorbance estimated to the 10 and 15 year addresses (1.14 [1.05, 1.25] and 1.13 [1.04, 1.23], respectively).

## *Conclusions*

We report associations suggesting a potential link between air pollution exposure and hyperactivity/inattention scores, although these findings require replication.

**Keywords:** adolescents, air pollution, hyperactivity, inattention, neurodevelopment

## 1.0 INTRODUCTION

There are numerous studies supporting a link between traffic-related air pollution and several cardio and respiratory health outcomes (Health Effects Institute 2010). In contrast, the strength of the evidence supporting associations between traffic-related air pollution and neurodevelopmental phenotypes is much weaker, and the number of studies fewer. Indeed, recent reviews have concluded that the evidence supporting a causal association is inconsistent/inadequate in most cases and that the existing studies are too heterogeneous to conduct a formal meta-analysis (Clifford et al. 2016; Suades-González et al. 2015).

Nonetheless, recent efforts from around the world continue to build an evidence base, some of which have focused on attention-deficit hyperactivity disorder (ADHD). ADHD was positively associated with PM<sub>10</sub> levels in 969 children (9-17 years) in Delhi, India (Siddique et al. 2010). Elemental carbon attributed to traffic was associated with higher hyperactivity scores in 576 children (7 years) living in the United States (Newman et al. 2013). And most recently, higher levels of traffic-related air pollutants were found to be associated with higher (adverse) scores on the strengths and difficulties questionnaire (SDQ) in 2,876 prospectively followed children (aged 7-10 years) attending schools in Barcelona, Spain (Forns et al. 2016). These studies provide important results, but they all assessed ADHD status and air pollution exposure at a single time point. Additional large prospective studies are required to expand on these findings.

The objective of this study was thus to investigate associations between individual-level long-term annual average concentrations of markers of traffic-related air pollution estimated to the residential home address at three time points in life (birth, 10 and 15 years) and the prevalence of

95 hyperactivity/inattention assessed at 10 and 15 years in two large German birth cohorts.  
96 Associations with dyslexia and dyscalculia at 10 and 15 years were also examined, as these  
97 conditions appear to co-exist with ADHD (Czamara et al. 2013), and no epidemiological studies  
98 have examined their link with traffic-related air pollution exposure.

## 2.0 METHODS

### 2.1 Study populations

Participants of the “German Infant study on the influence of a Nutritional Intervention plus environmental and genetic influences on allergy development” (GINIplus) and “Lifestyle-related factors, Immune System and the development of Allergies in East and West Germany plus the influence of traffic emissions and genetics study” (LISApplus) were used in this analysis.

GINIplus is a German-based prospective birth cohort of 5991 individuals born at full-term and normal weight recruited between 1995 and 1998 in Munich and Wesel. Participants with at least one atopic parent or sibling were allocated to an intervention study arm which investigated the effect of hydrolyzed formulas consumed during the first four months of life on allergy development (N = 2252). All participants whose parents did not give consent for the randomized clinical trial or who did not have a family history of allergic diseases were allocated to the observation study arm (N = 3739). Data from both arms of the study were used in the current analysis. LISApplus is a population-based prospective birth cohort of 3094 individuals born at full-term and normal weight recruited between 1997 and 1999 in Munich, Wesel, Leipzig and Bad Honnef. Detailed descriptions of the cohorts' recruitment and follow-up strategies have been previously published (Heinrich et al. 2002; von Berg et al. 2010; Zutavern et al 2006). Both studies were approved by the local Ethics Committees and informed written consent was obtained from all parents of participants.

The present analysis is restricted to participants living in the city of Munich and adjacent regions of Upper Bavaria and Swabia (a predominantly urban area; hereon referred to as GINI/LISA South) and in the city of Wesel and the adjacent regions of Münster and Düsseldorf (a predominantly rural area; hereon referred to as GINI/LISA North), for which the required air

pollution data were available. The Leipzig and Bad Honnef study areas in LISApplus were excluded as the required air pollution and lung function data were not available. As the GINIplus and LISApplus birth cohorts have similar study designs, especially for the later ages, data were pooled and results are presented per geographical area (GINI/LISA South and GINI/LISA North). This strategy has been frequently used in air pollution studies that included these cohorts (e.g. Fuertes et al. 2015, Gehring et al 2013, Gruzieva et al. 2014), given that separate air pollution land-use regression models were developed for each geographical area.

## *2.2 Outcomes*

Hyperactivity/inattention scores were assessed using the German parent-completed (at age 10 years) and self-completed (at age 15 years) versions of the SDQ (Goodman 1997, Goodman et al. 1998; Woerner et al. 2002, Woerner et al. 2004). Responses at age 10 years were initially categorized into “normal”, “borderline” and “abnormal” groups, according to recommended cut-offs for German populations (Woerner et al. 2004). As no published standards exist for Germans using the self-completed questionnaires (used at the 15 year follow-up), the same cut-off points were employed to allow comparability across ages. For statistical analyses, we created a dichotomous hyperactivity/inattention variable at each age in which the “normal” respondents were compared to “abnormal/borderline” respondents. We chose to create this dichotomous variable as it facilitates interpretation, allows comparisons of the hyperactivity/inattention effect sizes with those for dyslexia and dyscalculia and helps to avoid reporting heterogeneity bias (Lindeboom et al. 2004 and van Doorslaer et al. 2004). In sensitivity analyses, we examined the impact of grouping the “borderline” respondents together with the “normal” respondents (i.e. modelling “normal/borderline” versus “abnormal”), as well as defining hyperactivity/inattention

cases based on the questionnaire information (categorized as “normal” versus “borderline/abnormal”) or a report of hyperactivity/inattention or ADHD medication intake, instead of using only the questionnaire information as was done in the main analyses.

Using parent-completed questionnaires at the 10 and 15 year follow-ups, parents were asked to report whether their child had dyslexia or dyscalculia or had symptoms of these conditions. The structure of the questions used varied slightly by age and cohort. In LISApplus, this information was collected in a single question at age 10 years but using two questions at age 15 years (“symptoms” in one question and “have the condition” in another question). In the GINIplus cohort, one question was used at age 10 for dyscalculia and two questions in all other instances. In the cases that two questions were posed, the responses were merged so that only one answer was analyzed for each outcome at each age (i.e. had the condition or symptoms of the condition). A summary of the questions used to collect the outcome data is provided in the Supplemental Material, Table S1.

### *2.3 Air pollution estimates*

Long-term (annual average) concentrations of nitrogen dioxide (NO<sub>2</sub>), particulate matter (PM)<sub>10</sub> mass, PM<sub>2.5</sub> mass and PM<sub>2.5</sub> absorbance (the latter a proxy for elemental carbon) were estimated to each participant's home address at birth, 10 years and 15 years using land-use regression (LUR) models originally derived as part of the “European Study of Cohorts for Air Pollution Effects” (Beelen et al. 2013; Cyrys et al. 2012; Eeftens et al. 2012a, Eeftens et al. 2012b). Briefly, three two-week air pollution monitoring campaigns were performed at twenty (for PM<sub>10</sub> mass, PM<sub>2.5</sub> mass and PM<sub>2.5</sub> absorbance) and forty (for NO<sub>2</sub>) sites in both study areas between

10.2008 and 11.2009. Site-specific annual averages were calculated using the average of these three measurement periods and were adjusted for temporal variation using data from a centrally located background reference site which operated continuously throughout the measurement year. Area-specific LUR models which relate these site-specific measured annual average concentrations to predictor variables derived from Geographic Information Systems through a supervised stepwise multivariable linear regression were then developed. These area-specific LUR models, which primarily represent traffic-related air pollution sources, were used to estimate air pollution exposures to the birth, 10 and 15-year home addresses of participants. Differences in these estimates come from a change in address, so that individuals who have never moved will have the same estimate for all three home addresses. We chose to focus on these three time points in order to capture early-life effects (birth) and because they coincide with the timing of the collection of the health data (10 and 15-years).

#### *2.4 Analytic strategy*

Longitudinal associations between the annual average of each pollutant and outcome were assessed using generalized estimation equations with a logit link (geeglm function from the geepack package (Halekoh et al. 2006)) separately for the two study areas (GINI/LISA South and North). A combined estimate was subsequently calculated using inverse variance weighted random-effects meta-analysis (metagen function from the meta package (Schwarzer et al. 2016)). Results are presented as odds ratios (ORs) and 95% confidence intervals (CIs) and modelled per interquartile range increase in air pollution concentration. All analyses were conducted with the statistical program R, version 3.2.3.

Models were adjusted for child sex and exact age at follow-up, cohort/intervention group (LISApplus, GINIplus observation, GINIplus intervention), parental education (based on the highest number of years of education reported by either parent; low: <10 years, medium: 10 years, high: >10 years), maternal age at birth (< 30 years, > 30 to < 35 years, >35 years), maternal smoking during pregnancy (yes/no), child secondhand smoke exposure at age 15 years (yes/no), time spent in front of a screen (e.g. computer, television) when child is 15 years old (high ( $\geq 1$  h per day in summer or > 2 h per day in winter) versus low), time spent outside when child is 15 years old (high (> 4 h per day in summer or > 2 h per day in winter) versus low) and single parent status when child is 15 years old (yes/no). These covariates were identified as potentially relevant factors in similar analyses of the GINIplus and LISApplus cohorts with respect to mental and behavioural problems and environmental factors (Markevych et al. 2014; Tiesler et al. 2013). Models were additionally adjusted for parental psychopathology (yes/no), defined as parents with a Global Severity Index score (from the Brief Symptom Inventory 18 (Derogatis 2000) greater than the 90th percentile to ensure a sufficient number of cases, as there are no published reference values for a German population. We used the Global Severity Index score as no subscale specific to hyperactivity/inattention exists. Models were also examined without the inclusion of this covariate. Finally, all covariates assessed when the child was 15 years old were replaced with those assessed when the child was 10 years old to ensure the timing of covariate definition did not affect the results (not possible for parental psychopathology as these data were only collected at 15 years). All these data were collected via parent completed questionnaires.

Effect modification by sex and parental psychopathology was examined by including an interaction term in the model and by stratifying the analysis by these factors. Since 58.7% of

214 participants reported moving, models were also stratified by whether or not the participant had  
215 moved since birth. Further, associations were assessed using the average of the birth, 10 and 15  
216 year air pollution concentrations, which may better reflect a true lifetime exposure for  
217 participants who moved.

218  
219 In a sensitivity analysis, models were further adjusted for distance to urban green spaces  
220 (cemetery, garden, park or plant nursery; assignment for GINI/LISA South described in  
221 Markevych et al 2014; not available for GINI/LISA North) and population density in a 1000 m  
222 buffer, as these factors may confound the investigated associations. Finally, logistic regression  
223 models were used to assess associations between the air pollutants and the outcomes at 10 and 15  
224 years of age separately, as a further method of confirming the longitudinal analysis results.

### 3.0 RESULTS

Information on at least one neurodevelopmental outcome and air pollutant at one time point was available for 4745 participants (characteristics of the combined and area-specific populations presented in Table 1, flowchart of study population depicted in Figure S1). In the combined study population, the prevalence of abnormal/borderline hyperactivity/inattention scores and parental-reported dyslexia and dyscalculia or symptoms of these conditions at 15 years of age was 12.9%, 10.5% and 3.4%, respectively.

Compared to the original participants in the GINI/LISA South and North study areas, adolescents included in the current study were more likely to have parents with high education, as well as a mother who gave birth at an older age and who did not smoke during pregnancy. They were less likely to have moved between birth and 15 years of age.

The distributions of the annual average air pollution concentrations at the birth address are presented in Table 2. Concentrations of NO<sub>2</sub>, PM<sub>10</sub> mass and PM<sub>2.5</sub> mass were higher in GINI/LISA North (23.2 µg/m<sup>3</sup>, 25.2 µg/m<sup>3</sup> and 17.2 µg/m<sup>3</sup>, respectively) whereas the concentration of PM<sub>2.5</sub> absorbance was higher in GINI/LISA South (1.7 10<sup>-5</sup>/m). In the combined data, NO<sub>2</sub> was moderately correlated with PM<sub>10</sub> mass (Pearson's  $r = 0.57$ ) and PM<sub>2.5</sub> mass ( $r = 0.44$ ), and less so with PM<sub>2.5</sub> absorbance ( $r = 0.13$ ), all estimated to the birth addresses. The pollutant concentrations were also correlated across addresses (Spearman correlations  $\geq 0.45$  between air pollutants estimated to the birth and 15-year home addresses among those who moved). The spatial distribution of PM<sub>2.5</sub> mass concentrations at the 15-year home address of participants is provided per study area in the Supplemental Material, Figure S2.

249

250 In the meta-analytic analysis, significant associations were observed between

251 hyperactivity/inattention and PM<sub>2.5</sub> mass estimated to the 10 and 15 year addresses (1.12 [1.01,

252 1.23] and 1.11 [1.01, 1.22]) and PM<sub>2.5</sub> absorbance estimated to the 10 and 15 year addresses (1.14

253 [1.05, 1.25] and 1.13 [1.04, 1.23]). Further, dyscalculia was associated with PM<sub>2.5</sub> mass estimated

254 to the 10 year address (1.29 [1.03, 1.61]). No associations were observed for dyslexia. More

255 basic models containing only adjustments for sex, exact age at follow-up and cohort/intervention

256 yielded similar results (Supplemental Material, Table S2)

257

258 Effect estimates for hyperactivity/inattention were generally larger in the urban GINI/LISA South

259 area than the more rural GINI/LISA North area (Table 3), and among participants who had never

260 moved (Figure 1). The risk estimates obtained using the average of the air pollution

261 concentrations at the three addresses were similar, but only the meta-analytic estimates between

262 hyperactivity/inattention and PM<sub>2.5</sub> mass and PM<sub>2.5</sub> absorbance reached significance (1.13 [1.03,

263 1.24] and 1.14 [1.05, 1.24], respectively).

264

265 Removal of the parental psychopathology covariate from the models led to nearly identical

266 associations. Adjusting the models for secondhand smoke exposure, time spent in front of a

267 screen, time spent outside and single parent status at age 10 years instead of 15 years also did not

268 largely alter the main results. Further adjustment for distance to urban green spaces and

269 population density in a 1000m buffer around the home address in the models for the GINI/LISA

270 South study area, however, led to similar or stronger (especially for NO<sub>2</sub>) associations (Table S3).

271 Adjustment for only population density in GINI/LISA North (urban green space data not

272 available) did not change the null findings for this study area (not shown). Interaction terms

between sex and parental psychopathology and the air pollutants were not significant in the combined meta-analytic models. In-line with this, models stratified by sex did not yield consistent trends (Figure S3) nor did those stratified by parental psychopathology (Figure S4), although this latter result should be interpreted with caution given the small number of cases and large confidence intervals.

When associations were examined at a single time point using logistic regression (outcomes at 10 and 15 years analyzed separately), the effect estimates were relatively stable although statistical significance was not always achieved (Table S4). The associations with hyperactivity/inattention did not differ when cases were defined based on the SDQ results only or either the SDQ results or a report of intake of medication for hyperactivity/inattention or ADHD (14% and 16% at age 10 and 15 years in the combined population, respectively). However, the hyperactivity/inattention results were sensitive to whether individuals classified as “borderline” were grouped with those considered “abnormal” (as presented in the main analyses, Table 3) or as “normal” (Table S5). In the latter case, associations were attenuated.

## 4.0 DISCUSSION

Hyperactivity/inattention by the age of 15 years was associated with  $PM_{2.5}$  mass and  $PM_{2.5}$  absorbance concentrations at the birth (non-movers only), 10-year and 15-year (current) home addresses among German adolescents. Effect estimates appeared stronger in the urban study area compared to the rural study area, and among participants who had not moved since birth.

These results are in line with previous work in India (Siddique et al. 2010), the United States (Newman et al. 2013) and Spain (Forns et al. 2016). Compared to previous efforts, our study has the advantage of prospectively evaluating associations with air pollutants estimated to the home address at three time points in life, thus allowing the examination of early-life versus current exposures. Pregnancy and early-life have been specifically hypothesized and shown to be a likely vulnerable time period for air pollution-related neurodevelopment delays, possibly because of the rapid development of the brain during this time (Grandjean and Landrigan 2014, Perera et al. 2009, Guxens et al. 2012). Given that we observed associations between hyperactivity/inattention with  $PM_{2.5}$  mass and  $PM_{2.5}$  absorbance estimated to all addresses (birth, 10 and 15 years) among non-movers, we are unable to comment on the relative importance of exposure timing for this subset of the study population (ie. we are unable to disentangle the effects of potential susceptibility windows). However, the fact that we detected associations, especially with  $PM_{2.5}$  absorbance, with recent exposures (at the 10 and 15-year addresses) among movers could be interpreted as suggestive evidence that current or cumulative exposures may be important, as has been observed by others (Sunyer et al. 2015).

The apparent stronger effects in the urban GINI/LISA South area may be due to the fact that  $PM_{2.5}$  absorbance levels were higher in this study area. However, the opposite was true for  $PM_{2.5}$  mass, and thus this explanation is unsatisfactory. The larger variance in exposure levels in GINI/LISA South may have rendered it easier to detect associations. Different sources of PM (and consequently the release of PM with different sizes and compositions) could be an additional explanation as, although air pollution levels in both study areas are predominantly attributable to traffic-sources and the LUR models were developed to primarily model traffic-related exposures, industry is an important contributor to air pollution levels in GINI/LISA North given the near proximity of the industrial Ruhr area in Germany (Eeftens et al. 2012b). A fourth possibility may simply be a lack of statistical power in GINI/LISA North as this area had fewer participants. A final explanation may be that the participants living in the more urban study area were exposed to other environmental factors correlated with air pollution that are more prevalent or important in urban centres, such as noise. Unfortunately, we are unable to explore this hypothesis further as noise data are only available for a subset (~30%) of the study population. As past studies have found independent effects of traffic-related air pollution and noise exposure on neurobehavioural outcomes (Forns et al. 2016; van Kempen et al. 2012), future research efforts that consider both of these exposures should be prioritized. When we adjusted the associations in GINI/LISA South for distance to urban green space and population density, other potentially important environmental factors, the associations remained similar or were stronger. The null associations in GINI/LISA North were not affected by adjustment for population density.

Only  $PM_{2.5}$  mass at the 10 year address was positively associated with dyscalculia, and it is challenging to explain why exposures at 10 years (and not at birth or at 15 years) would be most

relevant. This result may represent a chance finding and we recommend interpreting it with caution until it is replicated in future studies, especially as the low number of dyscalculia cases in our sample might have resulted in more unstable models. No associations were seen with dyslexia. We also found no clear evidence that boys may be more susceptible than girls, as has been previously suggested (Clifford et al. 2016; Suades-González E et al. 2015).

The adverse effect of air pollution is believed to be mediated through impaired brain development in children, with heightened inflammation of the central nervous systems, attributable to air pollution induced oxidative stress, believed to be a core underlying mechanism (Sunyer 2008). This hypothesis is supported by experimental animal studies in which biomarkers of inflammation were greater among mice exposed to inhaled PM compared to those not exposed (Campbell et al. 2005). Dogs living in a highly polluted region of Mexico city were also found to have increased brain inflammation compared to animals living in a less polluted area (Calderón-Garcidueñas et al. 2002). This heightened inflammation in the brain may be in part due to particles crossing the blood-brain barrier and/or to an immune response generated due to particles entering the respiratory tract. Given the particularly high pro-inflammatory nature of small PM, both of these mechanisms are supported by the results of this study, in which associations for hyperactivity/inattention were most consistent for PM<sub>2.5</sub> mass and PM<sub>2.5</sub> absorbance.

The fact that all neurodevelopmental data were obtained using only parent and self-completed questionnaires is an important limitation of this study and prevents the exclusion of potential reporting bias. Only the hyperactivity/inattention data were collected using a validated assessment tool, and thus it may have been easier to detect associations for this outcome. The cut-offs employed to define the outcome categories for hyperactivity/inattention at 10 years were

based on published recommendations for a German population (Woerner et al. 2004). The consistency of the effect estimates in the analyses in which the outcomes at 10 and 15 years were modelled separately supports our decision to use the same cut-offs for the 15 year data as well (Table S4), as no published references exist for this age group.

It is also important to note, that although the hyperactivity/inattention results were robust to many sensitivity analyses conducted, they were sensitive to how “borderline” participants were modelled (grouped together with “abnormal” (Table 3) or “normal” (Table S4) respondents). In the latter case, associations were attenuated and not significant. A substantial decrease in the number of cases and consequently statistical power (12.9% and 5.9% of the total population at 15 years of age considered as a case when “borderline” individuals are considered “abnormal” and “normal”, respectively) and outcome misclassification may be possible explanations for the loss of statistical associations. Future studies with longitudinal data are required to confirm these findings.

In this analysis, we were able to adjust for many important covariates, including parental psychopathology, which has been rarely considered in previous analyses. Loss-to-follow up and its associated sampling bias is nonetheless unfortunately common in long-term cohort studies. This may have limited the generalizability of our results and deflated the reported associations if we excluded those most vulnerable. Further, as both the GINIplus and LISApplus cohorts excluded pre-term and low weight babies during study recruitment, we cannot be sure that our results are applicable to these groups. Finally, although we adjusted the models for parental education (as a marker for socioeconomic status), we could not examine associations by parental education strata as only 8.0% of participants were in the “low” category.

This analysis is the largest of its kind to date, participants were older than in previous studies and neurodevelopmental data were collected at two ages (10 and 15 years). Although this repeated outcome assessment is an important strength, it creates the situation that some participants who presented with severe or early symptoms may be taking medication by the age of 15 years. Among those who participated at both follow-ups, only 30% of participants with abnormal/borderline hyperactivity/inattention scores at age 10 years were also in this group at age 15 years (62% and 52% for dyslexia and dyscalculia, respectively). A sensitivity analysis in which taking medication for hyperactivity/inattention or ADHD was considered as a criterion to define a case did not yield differing results. The repeated health outcome data also presents a potential temporal issue for the associations with the air pollutants modelled at the 15-year home address as we are modelling an exposure that potentially occurred after the outcome. However, a series of analyses support the significant associations found between hyperactivity/inattention and PM<sub>2.5</sub> mass and PM<sub>2.5</sub> absorbance estimated to the 15-year home address. Namely, the longitudinal associations for the air pollutants estimated to the 10-year home addresses, the cross-sectional associations (although they did not always reach statistical significance, further emphasizing the strengths of a longitudinal analyses), and the analyses restricted to non-movers all do not suffer from this temporal problem and all yielded similar associations as was observed for the air pollutants estimated to the 15 year home address.

Although we are the first study to examine associations with these outcomes using air pollution concentrations assigned to more than one home addresses during a participant's life, we were not able to model exposures to all years of a participant's life because we lacked residential history information between follow-ups. Thus, our results may still be affected by some bias due to mobility changes (Brokamp et al. 2016). We were also not able to account for *in utero* exposures

as we do not have residential history information during the pregnancy period, although it can be assumed that for a large subset of the population, *in utero* and birth exposures would be the same or correlated. Further, we did not have information on the commuting patterns of the participants nor on the outdoor air pollution levels at the participants' school. These exposures are likely to be increasingly important as participants get older and spend more time away from the home, but are probably less relevant for associations observed with the birth exposures. We also lacked information on indoor air pollution levels at home and in schools. A recent study conducted in 39 schools in Barcelona found that on average, PM<sub>2.5</sub> mass levels were higher in schools compared to outside, possibly because of additional indoor PM<sub>2.5</sub> sources (e.g. chalk, Rivas et al. 2014). The generalizability of these results from Spain to our German study population is unknown. Finally, although we considered several markers of traffic-related air pollution, we did not have information of other potential toxic causal air pollutants.

Finally, the results of this study were not corrected for multiple testing as this could lead to conservative results given that some of the exposures were correlated and may not represent independent associations, especially for the models across different home addresses. Chance findings due to the high number of tests conducted may thus be a concern, but this is unlikely to be an explanation for all associations observed, especially given the consistency of the hyperactivity/inattention results across the different sensitivity analyses, including stratification by moving behaviour.

## 5.0 CONCLUSIONS

Long-term annual average PM<sub>2.5</sub> mass and PM<sub>2.5</sub> absorbance concentrations were consistently positively associated with hyperactivity/inattention in 15-year old German adolescents. This result requires replication in future studies as it was sensitive to how individuals with borderline scores were considered. Given the ubiquitous presence of traffic-related air pollution, there is a continued need to investigate whether it can adversely affect neurodevelopmental phenotypes, especially given the large public health and societal costs of these conditions.

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435    LISApplus study groups.

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**Table 1:** Characteristics of study participants

|                                                      |                       | <b>Combined sample<br/>(N=4745)</b> | <b>GINI/LISA South<br/>(N=2769 )</b> | <b>GINI/LISA North<br/>(N=1976 )</b> |
|------------------------------------------------------|-----------------------|-------------------------------------|--------------------------------------|--------------------------------------|
|                                                      |                       | <b>n (%)</b>                        | <b>n (%)</b>                         | <b>n (%)</b>                         |
| Hyperactivity/inattention<br>(borderline/abnormal)   | 10 yrs                | 559 (13.3)                          | 322 (12.8)                           | 237 (14.0)                           |
|                                                      | 15 yrs                | 457 (12.9)                          | 269 (13.0)                           | 188 (12.7)                           |
| Dyslexia                                             | 10 yrs                | 495 (12.2)                          | 292 (12.2)                           | 203 (12.3)                           |
|                                                      | 15 yrs                | 422 (10.5)                          | 276 (11.8)                           | 146 (8.6)                            |
| Dyscalculia                                          | 10 yrs                | 127 (3.1)                           | 58 (2.4)                             | 69 (4.2)                             |
|                                                      | 15 yrs                | 137 (3.4)                           | 75 (3.2)                             | 62 (3.6)                             |
| Male                                                 |                       | 2423 (51.1)                         | 1414 (51.1)                          | 1009 (51.1)                          |
| Age <sup>a</sup>                                     | 10 yrs                | 10.1 ± 0.2                          | 10.1 ± 0.2                           | 10.1 ± 0.2                           |
|                                                      | 15 yrs                | 15.1 ± 0.3                          | 15.1 ± 0.3                           | 15.1 ± 0.3                           |
| Parental education                                   | < 10 years            | 365 (8.0)                           | 126 (4.8)                            | 239 (12.6)                           |
|                                                      | = 10 years            | 1197 (26.3)                         | 455 (17.2)                           | 742 (39.0)                           |
|                                                      | > 10 years            | 2985 (65.6)                         | 2046 (78.0)                          | 921 (48.4)                           |
| Maternal age at birth                                | ≤ 30 yrs              | 1812 (38.2)                         | 831 (30.0)                           | 981 (49.7)                           |
|                                                      | > 30 & ≤ 35 yrs       | 2090 (44.1)                         | 1303 (47.1)                          | 787 (39.8)                           |
|                                                      | > 35 yrs              | 841 (17.7)                          | 634 (22.9)                           | 207 (10.5)                           |
| Smoking                                              | During pregnancy      | 618 (13.3)                          | 335 (12.4)                           | 283 (14.6)                           |
|                                                      | In home at 15 yrs     | 464 (11.5)                          | 173 (7.4)                            | 291 (17.2)                           |
| Cohort                                               | GINIplus intervention | 1534 (32.3)                         | 866 (31.3)                           | 668 (33.8)                           |
|                                                      | GINIplus observation  | 1993 (42.0)                         | 893 (32.3)                           | 1100 (55.7)                          |
|                                                      | LISAplus              | 1218 (25.7)                         | 1010 (36.5)                          | 208 (10.5)                           |
| Single parent family (15 yrs)                        |                       | 575 (14.6)                          | 358 (15.7)                           | 217 (13.0)                           |
| “High” time in front of screen (15 yrs) <sup>b</sup> |                       | 3403 (83.5)                         | 1901 (80.9)                          | 1502 (87.1)                          |
| “High” time spent outside (15 yrs) <sup>c</sup>      |                       | 1394 (35.3)                         | 585 (25.5)                           | 809 (48.9)                           |
| Parental psychopathology                             |                       | 448 (11.0)                          | 266 (11.4)                           | 182 (10.6)                           |
| Moved between birth and 15 years                     |                       | 2489 (58.7)                         | 1661 (66.5)                          | 828 (47.6)                           |

<sup>a</sup> mean ± standard deviation reported; <sup>b</sup> high defined as ≥1 h per day in summer or > 2 h per day in winter; <sup>c</sup> high defined as > 4 h per day in summer or > 2 h per day in winter

466 **Table 2:** Distribution of the long-term annual average air pollutants at the birth home addresses  
 467

| Air pollutant                                      | Min, Max   | Median | Interquartile range |
|----------------------------------------------------|------------|--------|---------------------|
| NO <sub>2</sub> (µg/m <sup>3</sup> )               |            |        |                     |
| GINI/LISA South                                    | 11.5, 61.1 | 20.6   | 8.1                 |
| GINI/LISA North                                    | 19.7, 62.8 | 23.2   | 3.2                 |
| PM <sub>10</sub> mass (µg/m <sup>3</sup> )         |            |        |                     |
| GINI/LISA South                                    | 14.8, 34.4 | 20.4   | 3.0                 |
| GINI/LISA North                                    | 23.9, 31.6 | 25.2   | 1.5                 |
| PM <sub>2.5</sub> mass (µg/m <sup>3</sup> )        |            |        |                     |
| GINI/LISA South                                    | 10.6, 18.3 | 13.3   | 1.2                 |
| GINI/LISA North                                    | 15.8, 21.4 | 17.2   | 0.9                 |
| PM <sub>2.5</sub> absorbance (10 <sup>-5</sup> /m) |            |        |                     |
| GINI/LISA South                                    | 1.3, 3.6   | 1.7    | 0.2                 |
| GINI/LISA North                                    | 1.0, 3.1   | 1.2    | 0.2                 |

468 **Table 3:** Longitudinal adjusted associations between the annually averaged air pollutants and  
469 health outcomes <sup>a</sup>  
470

|                                                    | Meta-analysis            | Area-specific associations |                                |      |                                |
|----------------------------------------------------|--------------------------|----------------------------|--------------------------------|------|--------------------------------|
|                                                    | OR (95% CI)              | N                          | GINI/LISA South<br>OR (95% CI) | N    | GINI/LISA North<br>OR (95% CI) |
| <b>Hyperactivity/inattention problems</b>          |                          |                            |                                |      |                                |
| Birth exposures                                    |                          |                            |                                |      |                                |
| NO <sub>2</sub> (µg/m <sup>3</sup> )               | 1.03 (0.94, 1.12)        | 1931                       | 0.98 (0.85, 1.14) <sup>f</sup> | 1395 | 1.05 (0.95, 1.16)              |
| PM <sub>10</sub> mass (µg/m <sup>3</sup> )         | 1.07 (0.96, 1.18)        | 1931                       | 1.08 (0.94, 1.24)              | 1395 | 1.05 (0.90, 1.23)              |
| PM <sub>2.5</sub> mass (µg/m <sup>3</sup> )        | 1.06 (0.96, 1.17)        | 1931                       | 1.02 (0.90, 1.16)              | 1395 | 1.12 (0.96, 1.31)              |
| PM <sub>2.5</sub> absorbance (10 <sup>-5</sup> /m) | 1.07 (0.99, 1.16)        | 1931                       | 1.09 (0.98, 1.20)              | 1395 | 1.05 (0.91, 1.20)              |
| 10-year exposures                                  |                          |                            |                                |      |                                |
| NO <sub>2</sub> (µg/m <sup>3</sup> )               | 1.04 (0.93, 1.17)        | 1755                       | 1.01 (0.87, 1.18)              | 1369 | 1.03 (0.93, 1.14)              |
| PM <sub>10</sub> mass (µg/m <sup>3</sup> )         | 1.05 (0.95, 1.17)        | 1755                       | 1.10 (0.94, 1.29)              | 1369 | 1.01 (0.88, 1.17)              |
| PM <sub>2.5</sub> mass (µg/m <sup>3</sup> )        | <b>1.12 (1.01, 1.23)</b> | 1755                       | <b>1.15 (1.01, 1.32)</b>       | 1369 | 1.08 (0.93, 1.24)              |
| PM <sub>2.5</sub> absorbance (10 <sup>-5</sup> /m) | <b>1.14 (1.05, 1.25)</b> | 1755                       | <b>1.19 (1.05, 1.34)</b>       | 1369 | 1.10 (0.98, 1.25)              |
| 15-year exposures                                  |                          |                            |                                |      |                                |
| NO <sub>2</sub> (µg/m <sup>3</sup> )               | 1.02 (0.93, 1.11)        | 1733                       | 1.01 (0.87, 1.17)              | 1363 | 1.02 (0.92, 1.14)              |
| PM <sub>10</sub> mass (µg/m <sup>3</sup> )         | 1.04 (0.94, 1.15)        | 1733                       | 1.09 (0.93, 1.27)              | 1363 | 1.00 (0.87, 1.15)              |
| PM <sub>2.5</sub> mass (µg/m <sup>3</sup> )        | <b>1.11 (1.01, 1.22)</b> | 1733                       | <b>1.16 (1.01, 1.33)</b>       | 1363 | 1.06 (0.93, 1.22)              |
| PM <sub>2.5</sub> absorbance (10 <sup>-5</sup> /m) | <b>1.13 (1.04, 1.23)</b> | 1733                       | <b>1.17 (1.05, 1.29)</b>       | 1363 | 1.08 (0.94, 1.23)              |
| <b>Dyslexia</b>                                    |                          |                            |                                |      |                                |
| Birth exposures                                    |                          |                            |                                |      |                                |
| NO <sub>2</sub> (µg/m <sup>3</sup> )               | 1.04 (0.93, 1.16)        | 1980                       | 1.05 (0.89, 1.25)              | 1454 | 1.03 (0.89, 1.18)              |
| PM <sub>10</sub> mass (µg/m <sup>3</sup> )         | 1.12 (0.98, 1.27)        | 1980                       | 1.07 (0.91, 1.26)              | 1454 | 1.19 (0.97, 1.47)              |
| PM <sub>2.5</sub> mass (µg/m <sup>3</sup> )        | 1.01 (0.82, 1.25)        | 1980                       | 0.92 (0.78, 1.08)              | 1454 | 1.14 (0.92, 1.42)              |
| PM <sub>2.5</sub> absorbance (10 <sup>-5</sup> /m) | 1.08 (0.98, 1.19)        | 1980                       | 1.07 (0.94, 1.21)              | 1454 | 1.09 (0.93, 1.28)              |
| 10-year exposures                                  |                          |                            |                                |      |                                |
| NO <sub>2</sub> (µg/m <sup>3</sup> )               | 1.02 (0.86, 1.22)        | 1802                       | 1.13 (0.94, 1.36)              | 1425 | 0.95 (0.83, 1.09)              |
| PM <sub>10</sub> mass (µg/m <sup>3</sup> )         | 1.05 (0.92, 1.20)        | 1802                       | 1.04 (0.87, 1.25)              | 1425 | 1.06 (0.88, 1.28)              |
| PM <sub>2.5</sub> mass (µg/m <sup>3</sup> )        | 1.08 (0.95, 1.23)        | 1802                       | 1.11 (0.94, 1.31)              | 1425 | 1.04 (0.85, 1.27)              |
| PM <sub>2.5</sub> absorbance (10 <sup>-5</sup> /m) | 1.06 (0.86, 1.31)        | 1802                       | <b>1.18 (1.02, 1.38)</b>       | 1425 | 0.95 (0.82, 1.10)              |
| 15-year exposures                                  |                          |                            |                                |      |                                |
| NO <sub>2</sub> (µg/m <sup>3</sup> )               | 1.00 (0.90, 1.12)        | 1780                       | 1.06 (0.89, 1.26)              | 1418 | 0.97 (0.84, 1.11)              |

|                                                    |                          |      |                          |      |                   |
|----------------------------------------------------|--------------------------|------|--------------------------|------|-------------------|
| PM <sub>10</sub> mass (µg/m <sup>3</sup> )         | 0.98 (0.86, 1.12)        | 1780 | 0.97 (0.81, 1.15)        | 1418 | 1.00 (0.82, 1.22) |
| PM <sub>2.5</sub> mass (µg/m <sup>3</sup> )        | 1.03 (0.90, 1.17)        | 1780 | 1.05 (0.89, 1.24)        | 1418 | 0.99 (0.81, 1.21) |
| PM <sub>2.5</sub> absorbance (10 <sup>-5</sup> /m) | 0.99 (0.90, 1.10)        | 1780 | 1.02 (0.90, 1.16)        | 1418 | 0.95 (0.81, 1.12) |
| <b>Dyscalculia</b>                                 |                          |      |                          |      |                   |
| Birth exposures                                    |                          |      |                          |      |                   |
| NO <sub>2</sub> (µg/m <sup>3</sup> )               | 1.19 (0.79, 1.79)        | 1979 | <b>1.47 (1.12, 1.94)</b> | 1455 | 0.97 (0.76, 1.24) |
| PM <sub>10</sub> mass (µg/m <sup>3</sup> )         | 1.11 (0.89, 1.39)        | 1979 | 1.20 (0.88, 1.64)        | 1455 | 1.02 (0.74, 1.41) |
| PM <sub>2.5</sub> mass (µg/m <sup>3</sup> )        | 1.14 (0.92, 1.41)        | 1979 | 1.21 (0.88, 1.66)        | 1455 | 1.09 (0.82, 1.44) |
| PM <sub>2.5</sub> absorbance (10 <sup>-5</sup> /m) | 1.06 (0.82, 1.38)        | 1979 | 1.20 (0.96, 1.48)        | 1455 | 0.91 (0.70, 1.20) |
| 10-year exposures                                  |                          |      |                          |      |                   |
| NO <sub>2</sub> (µg/m <sup>3</sup> )               | 1.08 (0.91, 1.29)        | 1800 | 1.17 (0.80, 1.72)        | 1426 | 1.06 (0.87, 1.29) |
| PM <sub>10</sub> mass (µg/m <sup>3</sup> )         | 1.05 (0.83, 1.34)        | 1800 | 0.92 (0.66, 1.28)        | 1426 | 1.17 (0.88, 1.58) |
| PM <sub>2.5</sub> mass (µg/m <sup>3</sup> )        | <b>1.29 (1.03, 1.61)</b> | 1800 | 1.36 (0.99, 1.89)        | 1426 | 1.23 (0.91, 1.66) |
| PM <sub>2.5</sub> absorbance (10 <sup>-5</sup> /m) | 1.07 (0.90, 1.28)        | 1800 | 1.15 (0.86, 1.54)        | 1426 | 1.03 (0.83, 1.28) |
| 15-year exposures                                  |                          |      |                          |      |                   |
| NO <sub>2</sub> (µg/m <sup>3</sup> )               | 1.12 (0.94, 1.33)        | 1778 | 1.08 (0.70, 1.65)        | 1419 | 1.13 (0.93, 1.36) |
| PM <sub>10</sub> mass (µg/m <sup>3</sup> )         | 0.97 (0.73, 1.31)        | 1778 | 0.83 (0.61, 1.14)        | 1419 | 1.12 (0.84, 1.50) |
| PM <sub>2.5</sub> mass (µg/m <sup>3</sup> )        | 1.20 (0.97, 1.49)        | 1778 | 1.23 (0.90, 1.68)        | 1419 | 1.18 (0.87, 1.59) |
| PM <sub>2.5</sub> absorbance (10 <sup>-5</sup> /m) | 1.03 (0.84, 1.25)        | 1778 | 0.94 (0.68, 1.29)        | 1419 | 1.08 (0.85, 1.38) |

Bold: p-value <0.05

<sup>a</sup> adjusted for sex, exact age at follow-up, cohort, parental education, maternal age at birth, smoking during pregnancy, as well as secondhand smoke exposure, time spent in front of a screen, time spent outside, single parent status and parental psychopathology all assessed at 15 years of age.

477 **Figure 1:** Meta-analytic longitudinal adjusted associations between the health outcomes and the  
478 annually averaged air pollutants estimated to the birth (stars), 10-year (open circles) and 15-year  
479 (filled triangles) home addresses, stratified by whether or not the child had moved between birth  
480 and 15 years of age. Error bars are 95% confidence intervals. Effect estimates for dyscalculia  
481 among non-movers are not presented due to insufficient sample sizes. Note that for the non-  
482 movers, the effect estimates across addresses are nearly identical as the same exposure is applied  
483 to the birth, 10 and 15 year address. The small differences that do exist are due to missing data at  
484 different ages.

