Impact of commuting exposure to traffic-related air pollution on cognitive development in children walking to school

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16 **Highlights**

- 17 - We estimated air pollution exposure during commuting by foot of 1,234 children
- 18 - PM_{2.5} and BC levels were linked with a diminished growth of superior working memory
- 19 - We observed an impairment in the attention function (not statistically significant)
- 20 - Policies for cleaner walking routes to school should be implemented

21 **Capsule:**

22 Despite the relatively short time spent commuting, the exposure to PM_{2.5} and BC from the home
23 to school commutes by foot of 1,234 schoolchildren was associated with a reduction in the growth
24 of cognitive functions.

25

26 **Keywords:** Commuting, superior working memory, inattentiveness, PM_{2.5}, BC.

Abstract

BACKGROUND: A few studies have reported associations between the exposure to traffic-related air pollution at school and/or home and cognitive development. The impact on cognitive development of the exposure to air pollutants during commuting has not been explored.

OBJECTIVES: We aimed to assess the role of the exposure to traffic-related air pollutants during walking commute to school on cognitive development of schoolchildren.

METHODS: We performed a longitudinal study of children (n=1,234) from 39 schools in Barcelona (Catalonia, Spain) who commuted by foot to school. The children completed four computerized tests during a 12-month follow-up to assess their developmental trajectories in superior working memory (d' of the three-back numbers test) and inattentiveness (hit reaction time standard error of the Attention Network Test). Average particulate matter $\leq 2.5 \mu\text{m}$ (PM_{2.5}), Black Carbon (BC) and NO₂ concentrations were estimated using Land Use Regression for the shortest walking route to school. Differences in cognitive growth were evaluated by linear mixed effects models with age-by-pollutant interaction terms.

RESULTS: An interquartile range increase in PM_{2.5} concentration in commuting routes decreased the annual growth of superior working memory by 5.4 (95% CI [-10.2,-0.6]) points. Similarly, for BC the growth reduction was 4.6 (95% CI [-9.0,-0.1]) points. We also observed an increase in inattentiveness, but the association was not significant. The effects were independent to the exposure at home and at school.

CONCLUSIONS: Exposure to PM_{2.5} and BC from the commutes by foot was associated with a reduction in the growth of superior working memory. Efforts should be made to implement pedestrian school pathways through low traffic streets in order to increase security and minimise children's exposure to air pollutants.

Introduction

Good air quality is required for human health and wellbeing, however more than 80% of people living in urban areas are exposed to air quality levels that are above the World Health Organization (WHO) standards (WHO, 2016). There is increasing evidence of the adverse effects of exposure to air pollution on children's health (WHO, 2005), and air pollution has been recently considered as a suspected cause of developmental neurotoxicity (Block et al., 2012). In previous research within the framework of the BREATHE (Brain Development and Air Pollution Ultrafine Particles in School Children) project (<http://www.creal.cat/projectebreathe>), long-term exposures during school time to traffic-related air pollutants (TRAPs) were associated with a reduction in cognitive development (Basagaña et al., 2016; Sunyer et al., 2015). Studies assessing the impact of air pollution on cognitive function in children are limited and mainly focused on the exposure at home or school (Suades-González et al., 2015). Nonetheless, no studies have assessed the impact on neurodevelopment of the exposure to air pollutants during commuting time.

Children are highly exposed to TRAPs during commuting from home to school which often coincides with traffic pollution peaks (Nieuwenhuijsen et al., 2015). Some studies have found that although time spent during commuting might be short, the commuters receive a high proportion of their daily TRAP dose (De Nazelle et al., 2013; Dons et al., 2012) including children commuting to school (Buonanno et al., 2012; Nieuwenhuijsen et al., 2015; Rivas et al., 2016). In particular, from a BREATHE subpopulation of 45 children, Rivas et al. (2016) showed that while children on average spent 6% of the daytime in commuting, it accounted for about 20% of the daily integrated dose of Black Carbon (BC). Moreover, evidence from toxicological and experimental studies indicates that these short bursts of high pollutant intakes may have disproportionate health impacts (Michaels and Kleinman, 2000) and the health effects are expected to be much more important in children, who inhale a higher normalized dose of airborne particles compared to adults (Buonanno et al., 2011).

The specific health effects from the exposure to air pollutants during commuting remain largely unexplored. Liu et al. (2015) observed associations between the exposure to $PM_{2.5}$ and heart rate variability in young healthy subjects. $PM_{2.5}$ concentrations were dependent on the commuting mode, with the highest concentrations and cardiovascular effects observed in the walking mode.

The time spent in vehicles during commuting (cars, public transportation, motorcycles or bicycles) has also been linked with an increase in the risk of myocardial infarction in adults (Peters et al., 2004).

Some cognitive functions, such as working memory or attention, develop substantially during childhood and adolescence (Tamnes et al., 2013). These capacities are shown to be critical for academic achievement (Shelton et al., 2010). This work aimed to study the effects of long-term exposure to TRAPs during home to school commuting by foot on cognitive development in primary schoolchildren.

Methods

Participants

This study was framed within the ERC-Advanced Grant (FP7) BREATHE Project. All children without special needs (mental, motor or sensory impairment reported by the school) in grades 2 to 4 (7–10 y of age) from 39 schools in Barcelona (Catalonia, Spain) were invited to participate of which 2,897 (59%) children agreed. Participating schools were similar to the remaining schools in Barcelona in terms of the neighborhood socioeconomic vulnerability index (0.46 versus 0.50, Kruskal–Wallis test $p = 0.57$) and NO_2 levels (51.5 versus 50.9 $\mu\text{g}/\text{m}^3$, Kruskal–Wallis test $p = 0.72$). All parents or guardians signed the informed consent form approved by the Clinical Research Ethical Committee (No. 2010/41221/I) of the Institut Hospital del Mar d'Investigacions Mèdiques–Parc de Salut Mar, Barcelona, Spain.

Air pollution exposure during commuting, at school and at home

Data on the main mode of commuting to and from school and time spent during commuting was obtained from parents via questionnaires. Within the BREATHE participants, 1,234 children reported only walking as the main mode of transport. We focused on walkers since mode choice is a determinant of the exposure to air pollutants during commuting (De Nazelle et al., 2012; Kaur and Nieuwenhuijsen, 2009). Estimation of the exposure during commuting other than walking implies several assumptions (e.g. indoor/outdoor ratios for each transport mode) that might lead to differential misclassification. For those BREATHE participants who walked to school, we

identified the shortest walking route to school based on street networks (network distance) by using the network analyst extension from ArcGIS software v10.

We estimated the average concentration of NO₂, particulate matter $\leq 2.5\mu\text{m}$ (PM_{2.5}) and BC (PM_{2.5} absorbance) in each route using the Land Use Regression (LUR) models developed within the European Study of cohorts for Air Pollution Effects (ESCAPE) and described elsewhere (Eeftens et al., 2012b). LUR models are based on simultaneous measurements of vehicle exhaust markers, such as NO₂, taken at many locations throughout an urban area during multiple periods that are temporally corrected to obtain annual concentrations. Various parameters derived from geographic information systems (GIS; e.g. traffic and roadway density, traffic volumes, truck routes, population density) are used to predict the concentration at specific locations (Beelen et al., 2013; Eeftens et al., 2012a).

We estimated the average concentration in the identified shortest route for each individual that reported commute by walking. Only the morning route (home to school) was considered, since these trips are more regular and they take place during the same time of the day across the schoolchildren. Moreover, concentrations of NO₂, PM_{2.5} and BC (PM_{2.5} absorbance) at each participant's home address and at school during the time of the study were also estimated using the ESCAPE LUR models.

Outcomes: Cognitive Development

Cognitive development was assessed through 12-month change in working memory and attention, as these functions grow steadily during pre-adolescence (Anderson, 2002; Rueda et al., 2005) and are strongly related to intelligence and learning (Norman and Shallice, 1986). From January 2012 to March 2013, children were evaluated every three months over four repeated visits, throughout two academic years, using computerized tests that took approximately 40 minutes to complete. We used computerized n-back test for assessing working memory (Anderson, 2002) and the child Attention Network Test (ANT) to characterize inattentiveness (Rueda et al., 2004). Groups of 10–20 children wearing ear protectors were assessed together and supervised by one trained examiner per 3–4 children. For the n-back test, we examined different n-back loads (up to three-back) and stimuli (colors, numbers, letters, and words). For analysis here, we selected the three-back load for number stimuli as it showed a clear age-dependent slope in the four measurements

and had little learning effect (Sunyer et al., 2015). The three-back test predicts general mental abilities as well as superior functions such as fluid intelligence (hereafter called superior working memory) (Shelton et al., 2010). All sets of n-back tests started with colors as a training phase to ensure the participant's understanding. The n-back parameter analyzed was d prime (d'), a measure of detection subtracting the normalized false alarm rate from the hit rate: ($Z_{hit} \text{ rate} - Z_{false \text{ alarm rate}} \text{ rate}) \times 100$. A higher d' indicates more accurate test performance. Among the ANT measures, we chose the hit reaction time standard error (HRT-SE; standard error of reaction time for correct responses), which is a measure of response speed consistency throughout the test (Conners and Multi-Health Systems, 2000). Our choose of HRT-SE among all the ANT measurements was because it showed very little learning effect and the clearest growth during the 12-month study period. A higher HRT-SE indicates highly variable reactions related to inattentiveness.

Contextual and individual covariates

Socio-demographic factors included child age, sex, questionnaire-based parents' responses on parental education (primary or less/secondary/university) and employment (self employed/employed/unemployed), marital status (married/not married), family origin (child and at least one parent born in Spain/two parents or the child born out of Spain), and a neighborhood socioeconomic vulnerability index (based on level of education, unemployment, and occupation at the census tract) according to both the school and home address. Attention deficit hyperactivity disorder (ADHD) symptoms (ADHD/DSM-IV Scales, American Psychiatric Association 2002) were reported by teachers. Parents completed the Strengths and Difficulties Questionnaire (SDQ) on child behavioral problems (Goodman, 2001).

Statistical analysis

A total of 1,234 children with complete data (i.e., repeated outcome at least twice and individual data on maternal education, age and address) and walking as the unique mode of transport to commute to school were included. Because of the multilevel nature of the data (i.e., multiple visits for each child within schools), we used linear mixed effects models with the four repeated cognitive parameters as outcomes (one test at a time), exposure to air pollution during commuting as fixed effect predictor, and child and school as nested random effects. An interaction between age at each visit and the air pollutant concentration (reported as interquartile range (IQR)

increase) was included to capture changes in 12-month progress in cognitive trajectory associated with the exposure to air pollutants during commuting (e.g. a coefficient of -5 in working memory for an IQR increase in NO₂ exposure indicated that those exposed to NO₂ concentrations at the 75th percentile had a mean decrease of 5 point in the 12-month working memory progress, as compared with those exposed to NO₂ concentrations at the 25th percentile). These models were further adjusted for potential confounders identified a priori (age, sex, maternal education (an indicator of individual socioeconomic status (SES)), and residential neighborhood socio-economic status). Moreover, we also carried out models adjusting for commuting time, school and home air pollution, by also including the interaction with age for these variables.

Sensitivity analyses were also conducted to assess effect modification by high-/low-air-pollution school, sex, maternal education, and ADHD to explore the potential residual confounding and susceptibility. We assessed the linearity of the relation between air pollution and cognitive tests stratifying the exposure by tertiles. Statistical significance was set at $p < 0.05$. Stata 12 (StataCorp) statistical package was used to carry out the analyses.

Results

The description of cognitive outcomes, air pollutant's concentration estimates for commuting, school and home, and the time and distance for commuting are described in Table 1. Levels of pollutants during commuting were higher than those at home or school, although for PM_{2.5} the levels were very similar to those at home and slightly higher than at school. Concentrations of TRAPs during commuting were moderately to strongly correlated to mean levels at home (spearman coefficients between 0.61 and 0.69) and school (between 0.60 and 0.83; Table 2).

The study participants (only walkers) had an average age (SD) of 8.5 (0.9) years old and 50% were female (Table 3). The average (SD) distance between home and school was 561 (314) m. Table 3 also shows the characteristics of those children from the BREATHE project that used other modes of transport for commuting different than foot. There were differences in most of the socioeconomic variables as well as in TRAPs levels measured at school between the children who commuted on foot and the rest of the children. Walker's residential areas faced higher

socioeconomic vulnerability and the proportion of parents with lower educational level and unemployed was higher than in the rest of the children.

Table 4 presents the associations between TRAP concentrations during commuting and 12-month change for the two cognitive parameters. All the coefficients were negative for superior working memory and positive for inattentiveness, indicating some impairments, which were statistically significant for the associations between BC and $PM_{2.5}$ and superior working memory. These associations remained statistically significant after further adjustment for the time spent on commuting or levels of pollutants at home or school (Table 4). These results did not change notably after the adjustment was made for pollutant levels at both school and home (data not shown). Therefore children receiving a higher exposure during commuting from home to school had a reduced growth in cognitive parameters during a 1-year follow-up. For example, the annual growth of superior working memory for an IQR increase of $PM_{2.5}$ concentration during commuting had decreased by 5.4 (95% CI [-10.2,-0.6]) points ($p=0.02$; Figure 1). Similarly, an IQR increase of BC concentration implied a reduction in the growth of superior working memory of 4.6 (95% CI [-9.0,-0.1]) points ($p=0.045$). When the exposure was categorized into tertiles (Table S1), a linear trend was observed in all models for superior working memory, being statistically significant for the associations for BC and $PM_{2.5}$ ($p\text{-value}<0.05$). Regarding inattentiveness, we did not observe any statistically significant linear trend, but the estimates for $PM_{2.5}$ and BC on the 3rd tertiles suggested that children exposed to high levels of TRAPS had greater inattentiveness.

In stratified analysis (Table 5), associations of TRAP concentrations and superior working memory were similar in different strata of children in terms of maternal education. The associations were stronger for males (statistically significant for BC and $PM_{2.5}$) than females. Moreover, the negative associations were stronger (although not statistically significant) in children attending schools classified at the design phase as highly polluted for BC, but the contrary was observed for exposures to $PM_{2.5}$ and NO_2 . Regarding ADHD, the stratification did not result in a notable change in our observed associations for superior working memory.

Discussion

We found adverse associations between the exposure to TRAPs during commuting from home to school and superior working memory. We also found an increase in inattentiveness, although the estimates were not statistically significant. Our observed associations appeared to be independent from TRAPs levels at school and at home in the present analysis. However, the collinearity between concentrations at school, home and commuting makes it difficult to disentangle the effect of commuting exposure from the effect of school or home exposure, even though we fitted the different micro-environments in the same model. Thus, we consider we could calculate a fraction of the impact attributed only to commuting.

Until now, most epidemiological studies linking air pollution and children's mental development have been based on levels of air pollutants at home or at the living area (Chiu et al., 2013; Guxens et al., 2012; Harris et al., 2015; van Kempen et al., 2010). In a recent review, Suades-González et al. (2015) identified 17 studies assessing the effect of air pollution on cognitive and psychomotor development in children. Of these, 9 were based on prenatal exposures and 8 on postnatal exposures at home (Calderón-Garcidueñas et al., 2015, 2012; Chiu et al., 2013), at school (Clark et al., 2010; Perera et al., 2012; Sunyer et al., 2015) and at the living area (Abid et al., 2014; Jung et al., 2013). To our knowledge, this is the first study reporting the potential impact of the exposure to air pollution during commuting on neurodevelopment.

Children included in this analysis were participants in the BREATHE study based on which we have recently reported that exposure to air pollution at school was associated with a slower cognitive development (Basagaña et al., 2016; Sunyer et al., 2017, 2015). Moreover, a subsample of 48 BREATHE children filled in a time-activity diary while they were carrying personal BC monitors during 48h. We estimated that while these children spent only 6% of their daily time on commuting, they received 20% of their daily BC dose during commuting (Rivas et al., 2016). Such a relatively large proportion of daily dose receiving during commuting could be attributed to concurrence of commuting to school with road traffic rush hours and the close proximity to the source, especially in urban areas (Rivas et al., 2016). Despite the time spent for commuting being very short, the BC daily dose is comparable to the one received while being at home (35% dose) or at school (37%). Therefore, it is likely to observe an independent effect of the exposure to air

pollutants during commuting from school on neurodevelopment. The relative contribution of time and dose during commuting in BREATHE children is in accordance to those reported in other studies. For instance, in a study of 36 adult volunteers, also in Barcelona, travel activities accounted for 6% of people's time and 24% of their daily inhaled NO₂ dose (De Nazelle et al., 2013). Similarly, Dons et al. (2012) found, when evaluating personal exposure of adults to BC, that while only 6% of participants' time was spent in transport, this corresponded to 21% of their personal exposure and 30% of the total inhaled dose. Other studies using activity-based models or personal monitors also demonstrated that the transport activity can be responsible for quite a large part of integrated personal exposure to pollutants (Dons et al., 2014). Then, although most people spend a relatively small amount of their time traveling, journey-time exposures are disproportionately large in proportion of total personal exposures to air pollution and, consequently, the impact of the journey exposure on health is therefore potentially significant. Exposure during commuting to traffic emissions has already been associated with increased risk of serious adverse health effects such as myocardial infarction (Peters et al., 2004) as well as with an increase in the heart rate variability (Liu et al., 2015). Moreover, the impact is expected to be much more marked in children, who inhale a higher normalized dose of airborne particles compared to adults, due to both their lung capacity and breathing rates (Buonanno et al., 2011).

Recent epidemiological and toxicological studies have shown that ambient air pollution exposure may have neurotoxic effects particularly in children (Block et al., 2012; Grandjean and Landrigan, 2014). Potential biological mechanisms underlying such effects include disruption of the blood-brain barrier, oxidative stress and neuroinflammation. Air pollutants can reach the brain directly via olfactory epithelium or at systemic level via the blood-brain barrier, where microglia, in particular, respond to this toxicants with chronic activation and inducing inflammation and oxidative stress (Block et al., 2012). The findings of the present study were similar to our previous study (Sunyer et al., 2015), where we found an association for superior working memory, which is a good predictor of learning achievement (Shelton et al., 2010). The prefrontal cortex, which is crucial for working memory (Braver et al., 2001), is still immature during childhood (Luna et al., 2001). Therefore working memory is a function susceptible to be affected by the exposure to neurotoxicants during childhood (Boucher et al., 2009). As for inattentiveness, we observed an impairment in the attention function (higher HRT-SE), although the associations were not significant. This might be because, beyond its age-related development, inattentiveness shows

daily fluctuations as it is more dependent on acute exposures, as we previously observed in Sunyer et al. (2017). On the other hand, working memory is more stable over time and therefore it is more robust for assessing the effect of low chronic exposures (Baddeley, 1992; Norman and Shallice, 1986). Children with ADHD symptoms were included in the analysis. The stratified analysis for ADHD (Table 5) did not result in a notable change in our observed associations for superior working memory. In previous research within BREATHE project we found that children with ADHD had a lower working memory at baseline, but a similar cognitive growth trajectories in the numbers variants of the n-back task, as compared to children without ADHD symptoms (López-Vicente et al., 2016). The sensitivity analysis (Table 5) indicated greater difficulties in focusing attention in children with ADHD symptoms (presence of more than 6 symptoms from the Criteria of Diagnostic and Statistical Manual of Mental Disorders list (ADHD-DSM-IV; American Psychiatric Association, 2002). Similar to our previous work (Sunyer et al., 2017), we found that traffic pollution is negatively associated with inattention irrespective of the presence or absence of this syndrome.

In the sex-stratified analyses, the association was restricted only to males who appeared to be much more susceptible to the exposure to PM_{2.5}, BC and NO₂ during commuting. For females, the effect is much lower and always not significant. This higher susceptibility for males was also observed for the exposure to BC (as Elemental Carbon) at school (Sunyer et al., 2015). These findings were consistent with those of animal studies showing that males were more susceptible to airborne metals than females, which might be because of sex-specific altered dopamine function (Curtis et al., 2010) or sex differences in oxidative stress (Cole et al., 2016).

Our study faced some limitations. Our exposure assessment was based on LUR models which have limited capability to capture the transient extreme peaks observed in commuting, especially at road crossings (Moreno et al., 2015). Likewise, the within-day variation is also not taken into account in the LUR models. Commuting very often takes place during traffic rush hours, which results in even higher exposures (De Nazelle et al., 2012; Rivas et al., 2017). Consequently, our exposure estimates for commuting may correspond to an underestimation of the actual concentrations which could have resulted in an underestimation of associations by our analyses. Therefore, our work is being conservative and we would expect even stronger associations if we had used real personal measurements. In order to have an accurate exposure assessment, the

present study was only based on walkers since mode choice is thought to be the most influencing factor of exposure during travel (De Nazelle et al., 2012; Kaur and Nieuwenhuijsen, 2009). In case all children had been included, in-vehicle concentration in each transport mode should have been estimated (Smith et al., 2016). However, these concentrations are often estimated from several assumptions based on literature and probably wrongly extrapolated to all populations and places. Regarding to other factors influencing the exposure during commuting, such as timing of trips (time-of-day, day of the week), or time spent commuting, we selected only morning trips (from home to school). Morning trips are supposed to be more regular and they take place during the same time of the day (morning rush hours). Further adjustment of analyses for the time spent during commuting did not change our findings notably. An additional limitation is the potential residual confounding by socio-economic status (SES), because SES is associated with neurobehavioral outcomes in offspring (Hackman and Farah, 2009) and may also affect residential choice, school and mode of transport and thus determine the estimated exposures to ambient air pollution (Havard et al., 2009). We adjusted our analyses for indicators of SES at both individual (maternal education) and area (SES vulnerability index) levels. The stratified analyses did not reveal a considerable variation in the estimated associations across the strata of maternal education. Moreover, the socioeconomic characteristics appeared to be quite different between children participating in BREATHE according to the mode of transport.

Our findings could be wrongly interpreted as walking being detrimental for health. The benefits of active mobility are well established (Andersen et al., 2000; Council on Sports Medicine and Fitness and Council on School Health, 2006; Martínez-Gómez, 2011), however, it may also increase the exposure to air pollution, leading to negative health consequences. Nonetheless, walking or biking to school is a valuable opportunity for integrating physical activity into everyday life in children and most of the health impact studies conclude that benefits of active travel are significantly larger than the harm caused by increased pollutant inhalation (Mueller et al., 2015). Moreover, although the effects of the exposure in other modes of transport have not been assessed in the current study, it is known that people travelling by car or other passive modes are also highly exposed to air pollution (De Nazelle et al., 2012; Dons et al., 2012; Moreno et al., 2015; Zurbier et al., 2010).

In conclusion, our study demonstrates that a short period of exposure to elevated concentrations

during commuting between home and school is associated with adverse impacts on cognitive development in schoolchildren. Efforts should be made to minimize children's exposures by increasing safer or "well-being" walking routes to school by reducing car use on school routes and thereby creating additional health benefits and safe environments for children (Nieuwenhuijsen and Khreis, 2016).

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Table 1. Air pollutant concentration (estimated by LUR), time spent commuting and cognitive outcomes description (mean (standard deviation)). N=1,234 (only walkers)

Cognitive outcomes	
Baseline (visit 1)	
3-back Numbers, d' (Superior WM)	118 (98)
ANT, HRT-SE, milliseconds (inattentiveness)	271 (91)
Change (visit 4 - visit 1)	
3-back Numbers, d' (Superior WM)	21 (132)
ANT, HRT-SE, milliseconds (inattentiveness)	-37 (88)
Air pollutants	
PM_{2.5}	
Commuting ($\mu\text{g m}^{-3}$)	17.5 (2.7)
Home ($\mu\text{g m}^{-3}$)	17.2 (3.0)
School ($\mu\text{g m}^{-3}$)	16.5 (2.8)
BC	
Commuting ($\mu\text{g m}^{-3}$)	2.99 (0.76)
Home ($\mu\text{g m}^{-3}$)	2.84 (0.84)
School ($\mu\text{g m}^{-3}$)	2.54 (0.66)
NO₂	
Commuting ($\mu\text{g m}^{-3}$)	83.0 (32.3)
Home ($\mu\text{g m}^{-3}$)	57.6 (17.1)
School ($\mu\text{g m}^{-3}$)	53.4 (12.6)
Time commuting (min)	9.25 (4.83)
Distance (m)	561 (314)

d': detectability; WM: Working Memory; ANT: Attention Network Test; NO₂: Nitrogen Dioxide; PM_{2.5}: Particulate matter <2.5 μm ; BC: Black Carbon

Table 2. Spearman correlations of air pollutant concentration (commuting, home and school). All pollutants estimated by LUR.
N=1,234 (only walkers)

	NO ₂ comm	PM _{2.5} comm	BC comm	NO ₂ home	PM _{2.5} home	BC home	NO ₂ school	PM _{2.5} school	BC school	Time comm
NO ₂ comm (LUR)	1.00									
PM _{2.5} comm (LUR)	0.84	1.00								
BC comm (LUR)	0.84	0.94	1.00							
NO ₂ home (LUR)	0.67	0.64	0.64	1.00						
PM _{2.5} home (LUR)	0.66	0.69	0.62	0.81	1.00					
BC home (LUR)	0.64	0.61	0.62	0.94	0.85	1.00				
NO ₂ school (LUR)	0.70	0.75	0.75	0.59	0.54	0.54	1.00			
PM _{2.5} school (LUR)	0.75	0.83	0.78	0.60	0.58	0.56	0.90	1.00		
BC school (LUR)	0.60	0.65	0.68	0.54	0.48	0.49	0.95	0.82	1.00	
Time commuting	0.03	0.08	0.05	0.00	0.00	-0.03	0.01	0.02	-0.01	1.00

NO₂: Nitrogen Dioxide; PM_{2.5}: Particulate matter <2.5 µm; BC: Black Carbon Carbon

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Table 3. Description (percent or mean (standard deviation)) of the population (and school) characteristics by mode of transport used from home to school.

	Foot	Others	p-value [‡]
Number of children	1234	1681	
Socio-economic variables			
Age (y)	8.5 (0.9)	8.5(0.9)	0.400
Girls (%)	50	49	0.755
Foreign origin (% non-Spanish)	18	14	0.002
Siblings, no (%)	22	20	0.279
Adopted child (%)	3	4	0.423
Maternal education, university (%)	53	64	<0.001
Paternal education, university (%)	45	60	<0.001
Maternal occupation, unemployed (%)	21	12	<0.001
Paternal occupation, unemployed (%)	14	5	<0.001
Marital status, married (%)	85	86	0.552
Home SES vulnerability index	0.48 (0.19)	0.42 (0.22)	<0.001
Type of school, public (%)	41	32	<0.001
Health & life style			
ADHD (%)	10	11	0.475
Behavioural Problems (SDQ-TDS)	8.8 (5.2)	8 (5.2)	<0.001
Overweight/obese (%)	30	26	0.017
Computer games weekend, ≥2h (%)	34	29	0.012
Smoking during pregnancy (%)	10	10	0.594
Gestational age, < 37 weeks (%)	7	8	0.265
Birth weight < 2500 (%)	9	10	0.178
Breastfeeding, no (%)	16	20	<0.001
Commuting			
Distance from home to school (m)	561 (314)	3001 (2413)	<0.001
Time (min)	9.2 (4.8)	15.5 (10.7)	<0.001
PM _{2.5} (µg m ⁻³)	17.5 (2.7)	17.4 (2.8)	0.917
BC (µg m ⁻³)	2.99 (0.76)	2.74 (0.67)	<0.001
NO ₂ , (µg m ⁻³)	83.0 (32.3)	76.3 (27.9)	<0.001
School			
PM _{2.5} (µg m ⁻³)	16.5 (2.8)	14.8 (3.6)	<0.001
BC (µg m ⁻³)	2.54 (0.66)	1.82 (0.89)	<0.001
NO ₂ , (µg m ⁻³)	53.4 (12.6)	38.9 (17.8)	<0.001

PM_{2.5}: Particulate matter <2.5 µm; BC: Black Carbon; NO₂: Nitrogen Dioxide; ADHD: Attention Deficit Hyperactivity Disorder based on the DSMIV criteria; SES: socio-economic status based on the neighbourhood vulnerability index ; NDVI index: Normalized Difference Vegetation Index 300 meters around school or home; SDQ - TDS: Strengths and Difficulties Questionnaire (total difficulties score, which can take values from 0 to 40).

[§] Includes: multi modal commuting (2 different modes per week), and commutes by tram. Statistics for those children commuting by 3 or modes of transports per week or commuting by train or underground are not shown.

[‡] Kruskal-Wallis and Chi-square tests

Table 4. Difference (and 95% confidence interval)[‡] in the 12-month change, per commuting air pollution exposure and time spent commuting (interquartile range increase, IQR) in 1.234 children. Air pollution concentrations estimated by LUR.

	Superior Working Memory (3-back Numbers, d')		Inattentiveness (ANT, HRT-SE, milliseconds)	
PM_{2.5} commuting				
Concentration	-5.4*	[-10.2,-0.6]	2.3	[-2.0,6.6]
Concentration, adjusted for time	-5.1*	[-9.9,-0.4]	2.3	[-2.0,6.6]
Concentration, adjusted for time and PM _{2.5} at school	-9.0**	[-15.0,-3.1]	3.2	[-2.1,8.5]
Concentration, adjusted for time and PM _{2.5} at home	-8.2**	[-14.5,-1.8]	3.1	[-2.5,8.8]
BC commuting				
Concentration	-4.6*	[-9.0,-0.1]	2.2	[-1.8,6.1]
Concentration, adjusted for time	-4.6*	[-9.1,-0.2]	2.2	[-1.8,6.1]
Concentration, adjusted for time and BC at school	-7.8**	[-13.3,-2.3]	2.9	[-2.0,7.7]
Concentration, adjusted for time and BC at home	-7.3**	[-12.7,-1.9]	3.5	[-1.3,8.3]
NO₂ commuting				
Concentration	-2.7	[-7.8,2.4]	1.9	[-2.6,6.4]
Concentration, adjusted for time	-2.8	[-7.9,2.3]	1.9	[-2.6,6.4]
Concentration, adjusted for time and NO ₂ at school	-5.4	[-11.7,1.0]	2.6	[-3.0,8.3]
Concentration, adjusted for time and NO ₂ at home	-5.4	[-11.7,1.0]	2.6	[-3.0,8.3]

[‡] Difference in the 12-month change adjusted for age, sex, maternal education and residential neighborhood socio-economic status and other exposure when specified; school and subject as nested random effects.

* p<0.05 **p<0.01 ***p<0.001

ANT: Attention Network Test; HRT-SE: Hit Reaction Time Standard Error; NO₂: Nitrogen Dioxide; PM_{2.5}: Particulate matter <2.5 µm; BC: Black Carbon Carbon

Table 5. Stratified analysis of TRAPs concentration during commuting (only walkers) from home to school (interquartile range increase) on the 12-month change of neurodevelopmental outcomes (superior working memory and inattentiveness). Adjusted models[¶]

	By School Air Pollution (design)		By Maternal Education		By Sex		By ADHD [§]	
	Low (n= 369)	High (n= 834)	Low (n= 566)	High (n= 637)	Male (n=602)	Female (n=601)	No (n=1,099)	Yes (n=120)
Superior Working Memory (3-back Numbers, d')								
PM_{2.5}	-4.4 [-12.8,4.0]	-2.0 [-9.6,5.6]	-6.2 [-12.6,0.2]	-5.1 [-12.3,2.0]	-9.2* [-16.6,-1.8]	-2.1 [-8.3,4.0]	-6.0* [-11.0,-1.0]	-4.9 [-20.2,10.4]
BC	-1.4 [-10.4,7.5]	-2.2 [-9.1,4.8]	-4.5 [-10.6,1.5]	-4.8 [-11.5,1.8]	-9.7** [-16.8,-2.7]	-0.6 [-6.3,5.1]	-5.0* [-9.8,-0.4]	-4.0 [-18.6,10.7]
NO₂	-0.3 [-11.6,12.2]	0.8 [-6.0,7.7]	-3.1 [-10.0,3.7]	-2.7 [-10.3,4.8]	-6.5 [-14.2,1.3]	0.0 [-6.6,6.6]	-2.8 [-8.2,2.5]	-2.6 [-19.1,13.9]
Inattentiveness (ANT, HRT-SE, milliseconds)								
PM_{2.5}	-1.9 [-9.7,5.8]	2.4 [-4.3,9.0]	1.1 [-4.9,7.2]	4.2 [-2.0,10.3]	-0.2 [-6.7,6.2]	4.9 [-0.7,10.6]	2.1 [-2.4,6.6]	5.3 [-8.5,19.1]
BC	-1.1 [-9.2,7.0]	1.3 [-4.8,7.4]	1.2 [-4.5,6.8]	3.5 [-2.1,9.1]	2.8 [-3.4,8.9]	2.1 [-3.1,7.3]	2.2 [-2.0,6.4]	3.7 [-9.5,16.9]
NO₂	1.0 [-9.7,11.7]	-0.4 [-6.4,5.7]	2.6 [-3.8,9.0]	1.3 [-5.1,7.8]	3.2 [-3.6,10.0]	1.6 [-4.4,7.6]	1.8 [-2.9,6.6]	4.7 [-10.1,19.6]

* p<0.05 **p<0.01 ***p<0.001

[¶] Difference in the 12-month change adjusted for age, sex, maternal education, and residential neighborhood socio-economic status; school and subject as nested random effects.

[§]ADHD: children with more than 6 symptoms from the Criteria of Diagnostic and Statistical Manual of Mental Disorders list (ADHD-DSM-IV).

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592 **Figure 1.** Change (95% CI) in cognitive growth per interquartile range increase of PM_{2.5}, BC and NO₂
593 concentrations for children's commuting routes to school (only walkers). Models were adjusted for
594 for age, sex, maternal education and residential neighborhood socio-economic status; school and
595 subject as nested random effects. Superior working memory measured with 3-back numbers, $d' \times$
596 100. Inattentiveness measured with ANT, HRT-SE, ms.

Impact of commuting exposure to traffic-related air pollution on cognitive development in children walking to school

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Highlights

- We estimated air pollution exposure during commuting by foot of 1,234 children
- PM_{2.5} and BC levels were linked with a diminished growth of superior working memory
- We observed an impairment in the attention function (not statistically significant)
- Policies for cleaner walking routes to school should be implemented

Supplementary Material

Impact of commuting-time exposure to traffic-related air pollution on cognitive development in children.

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Table S1: Association between commuting concentration to tertiles of TRAPs (interquartile range increase) during commuting from home to school and neurodevelopmental outcomes. Adjusted models‡.

Table S1. Association between tertiles of TRAPs (interquartile range increase) during commuting from home to school and neurodevelopmental outcomes. Adjusted models‡

	Superior Working Memory (3-back Numbers, d')	Inattentiveness (ANT, HRT-SE, milliseconds)
PM_{2.5}		
2 nd tertile	-5.3 [-13.7,3.0]	-2.9 [-9.3,3.6]
3 rd tertile	-20.1*** [-29.5,-10.8]	5.6 [-2.0,13.3]
BC		
2 nd tertile	-4.1 [-12.6,4.4]	-2.1 [-8.7,4.6]
3 rd tertile	-19.3*** [-28.8,-9.8]	3.8 [-4.0,11.5]
NO₂		
2 nd tertile	-4.3 [-12.8,4.1]	-4.0 [-10.5,2.4]
3 rd tertile	-6.2 [-15.7,3.3]	-0.8 [-8.6,6.9]

* p<0.05 **p<0.01 ***p<0.001

‡ Difference in the 12-month change adjusted for age, sex, maternal education, residential neighborhood socio-economic status and air pollution at school*age; school and subject as nested random effects. ANT: Attention Network Test; HRT-SE: Hit Reaction Time Standard Error; NO₂: Nitrogen Dioxide; PM_{2.5}: Particulate matter <2.5 µm; BC: Black Carbon Carbon

Linear trend P-value<0.05 for BC and PM_{2.5} on superior working memory.

Impact of commuting exposure to traffic-related air pollution on cognitive development in children walking to school

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Highlights

- We estimated air pollution exposure during commuting by foot of 1,234 children.
- PM_{2.5} and BC levels were associated with diminished growth of working memory.
- No significant associations were observed between NO₂ levels and growth of working memory, or between air pollution levels and development of inattentiveness.
- Our findings support policies for cleaner walking routes to school should.

Capsule:

Exposure to PM_{2.5} and BC during commuting between home and school commutes in a sample of 1,234 primary schoolchildren was associated with a reduction in the 12-month growth of cognitive functions.

Keywords: Commuting, working memory, inattentiveness, PM_{2.5}, BC.

Abstract

A few studies have found associations between the exposure to traffic-related air pollution at school and/or home and cognitive development. The impact on cognitive development of the exposure to air pollutants during commuting has not been explored. We aimed to assess the role of the exposure to traffic-related air pollutants during walking commute to school on cognitive development of children. We performed a longitudinal study of children (n=1,234, aged 7-10 y) from 39 schools in Barcelona (Catalonia, Spain) who commuted by foot to school. Children were tested four times during a 12-month follow-up to characterize their developmental trajectories of working memory (d' of the three-back numbers test) and inattentiveness (hit reaction time standard error of the Attention Network Test). Average particulate matter $\leq 2.5 \mu\text{m}$ (PM_{2.5}), Black Carbon (BC) and NO₂ concentrations were estimated using Land Use Regression for the shortest walking route to school. Differences in cognitive growth were evaluated by linear mixed effects models with age-by-pollutant interaction terms. Exposure to PM_{2.5} and BC from the commutes by foot was associated with a reduction in the growth of working memory (an interquartile range increase in PM_{2.5} and BC concentrations decreased the annual growth of working memory by 5.4 (95% CI [-10.2,-0.6]) and 4.6 (95% CI [-9.0,-0.1]) points, respectively). The findings for NO₂ were not conclusive and none of the pollutants were associated with inattentiveness. Efforts should be made to implement pedestrian school pathways through low traffic streets in order to increase security and minimize children's exposure to air pollutants.

Introduction

Good air quality is required for human health and wellbeing, however more than 80% of people residing in urban areas are exposed to air pollutant concentrations that are above the World Health Organization (WHO) standards (WHO, 2016). There is increasing evidence of the adverse effects of exposure to air pollution on children's health (WHO, 2005), and air pollution has been recently considered as a suspected cause of developmental neurotoxicity (Block et al., 2012). In previous research within the framework of the BREATHE (Brain Development and Air Pollution Ultrafine Particles in School Children) project (<http://www.creal.cat/projectebreathe>), long-term exposures during school time to traffic-related air pollutants (TRAPs) were associated with a reduction in cognitive development (Basagaña et al., 2016; Sunyer et al., 2015). Studies evaluating the impact of air pollution on cognitive function in children are limited and mainly focused on the exposure at home or school (Suades-González et al., 2015). Nonetheless, no studies have assessed the impact on cognitive development of the exposure to air pollutants during commuting time.

Children are highly exposed to TRAPs during commuting from home to school which often coincides with traffic pollution peaks (Nieuwenhuijsen et al., 2015). Some studies have found that although time spent during commuting might be short, the commuters receive a high proportion of their daily TRAP dose (De Nazelle et al., 2013; Dons et al., 2012) including children commuting to school (Buonanno et al., 2012; Nieuwenhuijsen et al., 2015; Rivas et al., 2016). In particular, from a BREATHE subpopulation of 45 children, Rivas et al. (2016) showed that while children on average spent 6% of the daytime in commuting, it accounted for about 20% of the daily integrated dose of Black Carbon (BC). Moreover, toxicological and experimental studies have evidenced that these short exposure to extremely high pollutant concentration may have disproportionate health impacts (Michaels and Kleinman, 2000). These health effects are expected to be especially important in children, who breathe in a higher normalized dose of airborne particles than adults (Buonanno et al., 2011).

The specific health effects from the exposure to air pollutants during commuting remain largely unexplored. Liu et al. (2015) observed associations between the exposure to $PM_{2.5}$ and heart rate variability in young healthy subjects. $PM_{2.5}$ concentrations were dependent on the commuting mode, with the highest concentrations and cardiovascular effects observed in the walking mode.

The time spent in vehicles during commuting (cars, public transportation, motorcycles or bicycles) has also been associated with an increase in the risk of myocardial infarction in adults (Peters et al., 2004).

Some cognitive functions, such as working memory or attention, develop substantially during childhood and adolescence (Tamnes et al., 2013). These capacities are shown to be critical for academic achievement (Shelton et al., 2010). This work aimed to study the effects of long-term exposure to TRAPs during home to school commuting by foot on cognitive development in primary schoolchildren.

Methods

Participants

A total of 2,897 children in grades 2 to 4 (7–10 y of age) attending 39 different schools in Barcelona (Catalonia, Spain) agreed to participate in the ERC-Advanced Grant (FP7) BREATHE Project. From the total number of BREATHE participants, we included in this study 1,234 children reporting walking as the unique mode of transport to commute to school and having complete data. All parents or guardians signed the informed consent form approved by the Clinical Research Ethical Committee (No. 2010/41221/I) of the Institut Hospital del Mar d'Investigacions Mèdiques–Parc de Salut Mar, Barcelona, Spain. Further information regarding the BREATHE and schools participating in the BREATHE project can be found elsewhere (Sunyer et al., 2015).

Air pollution exposure during commuting, at school and at home

Information on the main mode of commuting to and from school and time spent during commuting was obtained from parents via questionnaires. Within the BREATHE participants, 1,234 children reported only walking as the main mode of transport. We focused on walkers since mode choice is a determinant of the exposure to air pollutants during commuting (De Nazelle et al., 2012; Kaur and Nieuwenhuijsen, 2009). Estimation of the exposure during commuting other than walking implies several assumptions (e.g. indoor/outdoor ratios for each transport mode) that might lead to differential misclassification. For those BREATHE participants who walked to school, we identified the shortest walking route to school based on street networks (network distance) by using the network analyst extension from ArcGIS software v10.

We estimated the average concentration of NO₂, particulate matter ≤2.5µm (PM_{2.5}) and BC (PM_{2.5} absorbance) in each route using the Land Use Regression (LUR) models developed within the ESCAPE Project and described elsewhere (Eeftens et al., 2012). The validity of the ESCAPE LUR model for PM_{2.5} Absorbance (proxy for BC) was previously evaluated by Nieuwenhuijsen et al. (2015) against personal BC measurements performed in a subsample of 53 BREATHE children with correlation coefficients of 0.59 and 0.68 for home and school, respectively. We did not have enough statistical power to validate the model for the commutes with the BREATHE subsample. We estimated the average concentration in the identified shortest route for each individual that reported commute by walking. Only the morning route (home to school) was considered, since these trips are more regular and they take place during the same time of the day across the schoolchildren. Moreover, concentrations of NO₂, PM_{2.5} and BC (PM_{2.5} absorbance) at every participant's home address and at school during the study period were also estimated using the ESCAPE LUR models. We also calculated the exposure taking into account the commuting duration, as a factor of concentration*time.

Cognitive Development: working memory and inattentiveness

From January 2012 to March 2013, throughout two academic years, we evaluated the children's cognitive development (change in working memory and attention) every three months (resulting in four visits over a year) using computerized tests that took approximately 40 minutes to complete. These functions develop until adulthood. We used the n-back test for assessing working memory (Anderson, 2002) and the child Attention Network Test (ANT) to characterize inattentiveness, including the three attention networks (alerting, orienting, and executive control) (Rueda et al., 2004). We investigated the d prime (d', a measure of detection) from the three-back load for number stimuli. We selected the 3-back since this parameter showed a normal distribution while the 2-back task accuracy was truncated at 100% of correct responses and d' at 3.91 score. The selection of the number stimulus was informed by its evident dependency on age and limited learning effect compared to other stimuli (López-Vicente et al., 2016). The three-back test evaluates general cognitive functioning as well as functions such as fluid intelligence (from now on called working memory) (Shelton et al., 2010). Higher values of d' designate higher accuracy in the execution of the test. From the ANT measures, we evaluated the reaction time (RT) of the three attention networks and the hit reaction time standard error (HRT-SE; standard error

of reaction time for correct responses), which is a measure of response speed consistency throughout the test (Conners and Multi-Health Systems, 2000). A higher HRT-SE means greatly variable reaction related to inattentiveness (Suades-González et al., 2017). These tests have been reported to have acceptable internal consistency, reasonable factorial structure, and good criterion validity and statistical dependencies for use in general population (Forns et al., 2014).

Covariates

Socio-demographic factors included child age, sex, parental education (primary or less/secondary/university) and employment (self employed/employed/unemployed), marital status (married/not married), family origin (child and at least one parent born in Spain/two parents or the child born out of Spain), and a socioeconomic vulnerability index of the neighborhood (derived from the level of education, unemployment, and occupation at the census tract) for both the school and home address. Teachers reported children's Attention deficit hyperactivity disorder (ADHD) symptoms (ADHD/DSM-IV Scales, American Psychiatric Association 2002).

Statistical analysis

Because of the multilevel nature of the data (i.e., children with repeated measures within schools), we used linear mixed effects models with the cognitive parameters from the four repeated visits as outcomes, exposure to air pollution during commuting as a fixed effect predictor, and child and school as nested random effects. We evaluated the interaction between the air pollutant concentration and the children's age at each visit to detect changes in the 12-month cognitive trajectory associated with the exposure to air pollutants during commuting. The exposure was reported as interquartile range (IQR) increase (e.g. a coefficient of -5 in working memory for an IQR increase in NO₂ exposure indicated that those exposed to NO₂ concentrations at the 75th percentile had a mean decrease of 5 point in the 12-month working memory progress, as compared with those exposed to NO₂ concentrations at the 25th percentile). These models were additionally adjusted for age, sex, maternal education (an indicator of individual socioeconomic status (SES)), and residential neighborhood socio-economic status. Moreover, we also carried out models adjusting for commuting time, school and home air pollution, by also including the interaction with age for these variables.

Sensitivity analyses were performed to assess effect modification by school air pollution levels (low/high, according to the classification in the design), sex, maternal education, and ADHD to explore the potential residual confounding and susceptibility. We stratified the exposure by tertiles to assess the linearity of the relationship between the outcomes of the cognitive tests and the air pollution concentrations. Statistical significance was set at $p < 0.05$. We used Stata 12 (StataCorp) to conduct the analyses. Moreover, we repeated the analysis using exposure (concentration*time spent commuting) instead of concentration as fixed effect predictor.

Results

The description of cognitive outcomes, air pollutant's concentration estimates for commuting, school and home, and the time and distance for commuting are described in Table 1. Levels of pollutants during commuting were higher than those at home or school, although for $PM_{2.5}$ the levels were very similar to those at home and slightly higher than at school. Concentrations of TRAPs during commuting were moderately to strongly correlated to mean levels at home (spearman coefficients between 0.61 and 0.69) and school (between 0.60 and 0.83; Table 2).

The study participants (only walkers) had an average age (SD) of 8.5 (0.9) years old and 50% were female (Table 3). The average (SD) distance between home and school was 561 (314) m. Table 3 also shows the characteristics of those children from the BREATHE project that used other modes of transport for commuting different than foot. There were differences in most of the socioeconomic variables as well as in TRAPs levels measured at school between the children who commuted on foot and the rest of the children. Walker's residential areas faced higher socioeconomic vulnerability and the proportion of parents with lower educational level and unemployed was higher than in the rest of the children.

Table 4 presents the associations between TRAPs concentrations during commuting and 12-month change for the two cognitive parameters. We observed inverse associations for working memory and direct associations for inattentiveness, both consistent with cognitive impairment; however, the associations were statistically significant only between BC and $PM_{2.5}$ and working memory. As presented in Table 4, an interquartile range increase in $PM_{2.5}$ and BC concentrations were respectively associated with reduction of -5.4 (95% CI [-10.2,-0.6]) and -4.6 (95% CI [-9.0,-0.1])

points, equivalent to a decrease of 4.6% (95% CI [-8.6%, -0.5%]) and 3.9% (95% CI [-7.6%, -0.1%]) of the 12-month growth in working memory. These associations remained statistically significant after further adjustment for the time spent on commuting or levels of pollutants at home and/or school (Table 4 and Table S1). The coefficients for home and school levels were not statistically significant in the single and multi-pollutant models (Table S1). When the exposure was categorized into tertiles (Table S2), a dose-response trend was observed in all exposures for working memory, being statistically significant for the associations for BC and PM_{2.5} (p-value for trend < 0.05). Regarding inattentiveness, we did not observe any statistically significant linear trend, but the estimates for PM_{2.5} and BC on the 3rd tertiles suggested that children exposed to high levels of TRAPS had greater inattentiveness. We observed similar results for the three attentional networks (data not shown) and general inattentiveness, and therefore we only presented here the results for the HRT-SE.

When the exposure (concentration*time) during commuting was included in the model (Table S3) rather than simply concentration, we also observed an impairment on the working memory which was significant for the three pollutants under study (PM_{2.5}, BC, and NO₂). The effects (i.e. the coefficients) were stronger when considering the exposure than the concentration in the single-pollutant model (not adjusted for concentration at home and/or at school), while they were weaker when comparing the coefficients of the multipollutant models. No significant associations were observed for inattentiveness.

In stratified analysis (Table 5), associations of TRAP concentrations and working memory were similar in different strata of children in terms of maternal education. The associations were stronger for males (the coefficients remaining statistically significant for BC and PM_{2.5} in the group of males) than females. Moreover, the negative associations were stronger (although not statistically significant) in children attending schools classified at the design phase as highly polluted for BC, but the contrary was observed for exposures to PM_{2.5} and NO₂. Regarding ADHD, the stratification did not result in a notable change in the associations for working memory.

Discussion

We found adverse associations between the levels of BC and PM_{2.5} during commuting between home and school and working memory. The findings for NO₂ and working memory, and for all the

pollutants and inattentiveness were not conclusive. Our observed associations appeared to be independent from TRAPs levels at school and at home in the present analysis. However, the potential collinearity between concentrations at school, home and commuting made it difficult to disentangle the effect of commuting exposure from the effect of school or home exposure, although the models fitted with concentrations from the different micro-environments indicate that the contribution to the effect on cognition of the exposure during commuting has an important role. When exposure was considered (concentration*time), instead of concentration alone, an effect on working memory was also observed for NO₂, BC and PM_{2.5}.

Until now, most epidemiological studies linking air pollution and children's mental development have been based on levels of air pollutants at home or at the living area (Chiu et al., 2013; Guxens et al., 2012; Harris et al., 2015; van Kempen et al., 2010). In a recent review, Suades-González et al. (2015) identified 17 studies evaluating the impact of air pollution on cognitive and psychomotor development in children. Of these, 9 were based on prenatal exposures and 8 on postnatal exposures at home (Calderón-Garcidueñas et al., 2015, 2012; Chiu et al., 2013), at school (Clark et al., 2010; Perera et al., 2012; Sunyer et al., 2015) and at the living area (Abid et al., 2014; Jung et al., 2013). To our knowledge, this is the first study reporting the potential impact of the exposure to air pollution during commuting on cognitive development.

Children included in this analysis were participants in the BREATHE study based on which we have recently showed that exposure to air pollution at school was associated with a slower cognitive development (Basagaña et al., 2016; Sunyer et al., 2017, 2015). Moreover, a subsample of 48 BREATHE children completed a diary reporting their activities while they were carrying personal BC monitors for 48h. We estimated that only 6% of children's daily time was spent on commuting. However, during this time they obtained the 20% of their daily BC dose during commuting (Rivas et al., 2016). Such a relatively large proportion of daily dose received during commuting could be attributed to commuting to school coinciding with road traffic peak hours and the closeness to the source, especially in urban areas (Rivas et al., 2016). Despite the time spent for commuting being very short, the BC daily dose is comparable to the one received while being at home (35% dose) or at school (37%). Therefore, it is likely to observe an independent effect of the exposure to air pollutants during commuting from school on cognitive development. The relative contribution of time and dose during commuting in BREATHE children is in accordance to those reported from

personal measurements by De Nazelle et al. (2013) and Dons et al. (2012). Other studies using models based on activity patterns also pointed to transport activity as responsible of a substantial part of integrated personal exposure to pollutants (Dons et al., 2014). Consequently, the impact of the exposure during commuting on health is potentially significant. Peters et al. (2004) found an association between the exposure during commuting to traffic emissions with increased risk of myocardial infarction and Liu et al. (2015) with a decrease in the heart rate variability. The impact is expected to be more important in children because of a smaller lung capacity and higher breathing rates than adults (Buonanno et al., 2011).

Ambient air pollution may have neurotoxic effects, particularly in children (Block et al., 2012; Grandjean and Landrigan, 2014). Potential biological mechanisms underlying such effects include disruption of the blood–brain barrier, oxidative stress and neuroinflammation. Air pollutants can directly reach the brain through the olfactory epithelium or at systemic level via the blood-brain barrier, where microglia, in particular, respond to this toxicants with chronic activation and inducing inflammation and oxidative stress (Block et al., 2012). The findings of the present study were similar to our previous study (Sunyer et al., 2015), where we found an association for working memory, which is a good predictor of learning achievement (Shelton et al., 2010). The prefrontal cortex, which is crucial for working memory (Braver et al., 2001), is still immature during childhood (Luna et al., 2001). Therefore working memory is a function susceptible to be affected by the exposure to neurotoxicants during childhood (Boucher et al., 2009). As for inattentiveness, we observed an impairment in the attention function (higher HRT-SE), although the associations were not significant. This might be because, beyond its age-related development, inattentiveness shows daily fluctuations as it is more dependent on acute exposures, as we previously observed in Sunyer et al. (2017). On the other hand, working memory is more stable over time and therefore it is more robust for assessing the effect of low chronic exposures (Baddeley, 1992; Norman and Shallice, 1986). Children with ADHD symptoms were included in the analysis. The stratified analysis for ADHD (Table 5) did not result in a notable change in our observed associations for working memory. In previous research within BREATHE project we found that children with ADHD had a lower working memory at baseline, but their cognitive growth trajectories in the numbers variants of the n-back task were similar to children without ADHD symptoms (López-Vicente et al., 2016). The sensitivity analysis (Table 5) indicated greater difficulties in focusing attention in children with ADHD symptoms (presence of more than 6 symptoms from the ADHD-DSM-IV;

American Psychiatric Association, 2002). Similar to our previous work (Sunyer et al., 2017), we found that traffic pollution is negatively associated with inattention independently of the presence or absence of this syndrome.

In the sex-stratified analyses, the association was restricted only to males who appeared to be much more susceptible to the exposure to PM_{2.5}, BC and NO₂ during commuting. For females, the effect is much lower and always not significant. This higher susceptibility for males was also observed for the exposure to BC (as Elemental Carbon) at school (Sunyer et al., 2015). These findings were consistent with observations in animal studies showing that males were more susceptible to airborne metals than females, which might be explained by sex-specific altered dopamine function (Curtis et al., 2010) or sex differences in oxidative stress (Cole et al., 2016).

Our study faced some limitations. The exposure assessment was based on LUR models which have limited capability to capture the transient extreme peaks observed in commuting, especially at road crossings (Moreno et al., 2015). Likewise, the within-day variation is also not taken into account in the LUR models since the estimations obtained correspond to an annual mean. Commuting very often takes place during traffic rush hours, which results in even higher exposures (De Nazelle et al., 2012; Rivas et al., 2017, 2016). Consequently, our exposure estimates for commuting may correspond to an underestimation of the actual concentrations which could have resulted in an underestimation of associations by our analyses. In order to have an accurate exposure assessment, the present study was only based on walkers since mode choice is believed to be the most influential determinant of exposure during travel (De Nazelle et al., 2012; Kaur and Nieuwenhuijsen, 2009). In case all children had been included, in-vehicle concentration in each transport mode should have been estimated (Smith et al., 2016). However, these concentrations are often estimated from several assumptions based on literature and probably wrongly extrapolated to all populations and places. Regarding to other factors influencing the exposure during commuting, such as timing of trips (time of the day, day of the week), or time spent commuting, we selected only morning trips (from home to school). Morning trips are supposed to be more regular and they take place during the same time of the day (morning rush hours). Further adjustment of analyses for the time spent during commuting did not change our findings notably. An additional limitation is the potential residual confounding by socio-economic status (SES), because SES is associated with neurobehavioral outcomes in offspring (Hackman and Farah,

2009) and may also affect residential choice, school and mode of transport and thus determine the estimated exposures to ambient air pollution (Havard et al., 2009). The models were adjusted for individual (maternal education) and area (SES vulnerability index) indicators of SES levels. The stratified analyses did not reveal a considerable variation in the estimated associations across the strata of maternal education. Moreover, the socioeconomic characteristics appeared to be quite different between children participating in BREATHE according to the mode of transport. Finally, the possible collinearity between concentrations at school, home and commuting was also a limitation. However, the effects observed for commuting seemed to be independent from school and home levels, since the coefficients for commuting were significant and showed a stronger association both in the single-pollutant and multi-pollutant models, while the coefficients for school and home were not statistically significant in any of the models.

These findings should not be understood as a detrimental effect of walking for health. The benefits of active mobility are well established (Andersen et al., 2000; Council on Sports Medicine and Fitness and Council on School Health, 2006; Martínez-Gómez, 2011), however, it may also increase the exposure to air pollution, leading to negative health consequences. Nonetheless, walking or biking to school is a valuable opportunity for integrating physical activity into everyday life in children and most of the health impact studies conclude that benefits of active travel are significantly larger than the harm caused by increased pollutant inhalation (Mueller et al., 2015). Moreover, although the effects of the exposure in other modes of transport have not been assessed in the current study, it is known that people travelling by car or other passive modes are also highly exposed to air pollution (De Nazelle et al., 2012; Dons et al., 2012; Moreno et al., 2015; Zuurbier et al., 2010).

In conclusion, our study demonstrates that a short period of exposure to elevated concentrations during commuting between home and school is associated with adverse impacts on cognitive development in schoolchildren. Efforts should be made to minimize children's exposures by increasing safer or "well-being" walking routes to school by reducing car use on school routes and thereby creating additional health benefits and safe environments for children (Nieuwenhuijsen and Khreis, 2016).

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Table 1. Air pollutant concentration (estimated by LUR), time spent commuting and cognitive outcomes description (mean (standard deviation)). N=1,234 (only walkers)

Cognitive outcomes

Baseline (visit 1)

3-back Numbers, d' (WM)	118 (98)
ANT, HRT-SE, milliseconds (inattentiveness)	271 (91)

Change (visit 4 - visit 1)

3-back Numbers, d' (WM)	21 (132)
ANT, HRT-SE, milliseconds (inattentiveness)	-37 (88)

Air pollutants

PM_{2.5}

Commuting ($\mu\text{g m}^{-3}$)	17.5 (2.7)
Home ($\mu\text{g m}^{-3}$)	17.2 (3.0)
School ($\mu\text{g m}^{-3}$)	16.5 (2.8)

BC

Commuting ($\mu\text{g m}^{-3}$)	2.99 (0.76)
Home ($\mu\text{g m}^{-3}$)	2.84 (0.84)
School ($\mu\text{g m}^{-3}$)	2.54 (0.66)

NO₂

Commuting ($\mu\text{g m}^{-3}$)	83.0 (32.3)
Home ($\mu\text{g m}^{-3}$)	57.6 (17.1)
School ($\mu\text{g m}^{-3}$)	53.4 (12.6)

Time commuting (min)	9.25 (4.83)
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Distance (m)	561 (314)
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d': detectability; WM: Working Memory; ANT: Attention Network Test; NO₂: Nitrogen Dioxide; PM_{2.5}: Particulate matter <2.5 μm ; BC: Black Carbon

Table 2. Spearman correlations of air pollutant concentration (commuting, home and school). All pollutants estimated by LUR.
N=1,234 (only walkers)

	NO ₂ comm	PM _{2.5} comm	BC comm	NO ₂ home	PM _{2.5} home	BC home	NO ₂ school	PM _{2.5} school	BC school	Time comm
NO ₂ comm	1.00									
PM _{2.5} comm	0.84	1.00								
BC comm	0.84	0.94	1.00							
NO ₂ home	0.67	0.64	0.64	1.00						
PM _{2.5} home	0.66	0.69	0.62	0.81	1.00					
BC home	0.64	0.61	0.62	0.94	0.85	1.00				
NO ₂ school	0.70	0.75	0.75	0.59	0.54	0.54	1.00			
PM _{2.5} school	0.75	0.83	0.78	0.60	0.58	0.56	0.90	1.00		
BC school	0.60	0.65	0.68	0.54	0.48	0.49	0.95	0.82	1.00	
Time commuting	0.03	0.08	0.05	0.00	0.00	-0.03	0.01	0.02	-0.01	1.00

NO₂: Nitrogen Dioxide; PM_{2.5}: Particulate matter <2.5 µm; BC: Black Carbon

All coefficients are statistically significant at p<0.01, except those correlations with time.

Table 3. Description (percent or mean (standard deviation)) of the population (and school) characteristics by mode of transport used from home to school.

	Foot	Others	p-value [‡]
Number of children	1234	1681	
Socio-economic variables			
Age (y)	8.5 (0.9)	8.5(0.9)	0.400
Girls (%)	50	49	0.755
Foreign origin (% non-Spanish)	18	14	0.002
Siblings, no (%)	22	20	0.279
Adopted child (%)	3	4	0.423
Maternal education, university (%)	53	64	<0.001
Paternal education, university (%)	45	60	<0.001
Maternal occupation, unemployed (%)	21	12	<0.001
Paternal occupation, unemployed (%)	14	5	<0.001
Marital status, married (%)	85	86	0.552
Home SES vulnerability index	0.48 (0.19)	0.42 (0.22)	<0.001
Type of school, public (%)	41	32	<0.001
Health & life style			
ADHD [¶] (%)	10	11	0.475
Overweight/obese (%)	30	26	0.017
Computer games weekend, ≥2h (%)	34	29	0.012
Smoking during pregnancy (%)	10	10	0.594
Gestational age, < 37 weeks (%)	7	8	0.265
Birth weight < 2500 (%)	9	10	0.178
Breastfeeding, no (%)	16	20	<0.001
Commuting			
Distance from home to school (m)	561 (314)	3001 (2413)	<0.001
Time (min)	9.2 (4.8)	15.5 (10.7)	<0.001
PM _{2.5} (µg m ⁻³)	17.5 (2.7)	17.4 (2.8)	0.917
BC (µg m ⁻³)	2.99 (0.76)	2.74 (0.67)	<0.001
NO ₂ , (µg m ⁻³)	83.0 (32.3)	76.3 (27.9)	<0.001
School			
PM _{2.5} (µg m ⁻³)	16.5 (2.8)	14.8 (3.6)	<0.001
BC (µg m ⁻³)	2.54 (0.66)	1.82 (0.89)	<0.001
NO ₂ , (µg m ⁻³)	53.4 (12.6)	38.9 (17.8)	<0.001

PM_{2.5}: Particulate matter <2.5 µm; BC: Black Carbon; NO₂: Nitrogen Dioxide; ADHD: Attention Deficit Hyperactivity Disorder based on the DSMIV criteria; SES: socio-economic status based on the neighborhood vulnerability index ;

[§] Includes: multi modal commuting (2 different modes per week), and commutes by tram. Statistics for those children commuting by 3 or modes of transports per week or commuting by train or underground are not shown.

[‡] Kruskal-Wallis and Chi-square tests

[¶] ADHD: children with more than 6 symptoms from the Criteria of Diagnostic and Statistical Manual of Mental Disorders list (ADHD-DSM-IV).

Table 4. Difference (and 95% confidence interval)[‡] in the 12-month change, per commuting air pollution concentration and time spent commuting (interquartile range increase, IQR) in 1.234 children. Air pollution concentrations estimated by LUR.

	Working Memory (3-back Numbers, d')		Inattentiveness (ANT, HRT-SE, milliseconds)	
PM_{2.5} commuting				
Concentration	-5.4*	[-10.2,-0.6]	2.3	[-2.0,6.6]
Concentration, adjusted for time	-5.1*	[-9.9,-0.4]	2.3	[-2.0,6.6]
Concentration, adjusted for time and PM _{2.5} at school	-9.0**	[-15.0,-3.1]	3.2	[-2.1,8.5]
Concentration, adjusted for time and PM _{2.5} at home	-8.2**	[-14.5,-1.8]	3.1	[-2.5,8.8]
Concentration, adjusted for time and PM _{2.5} at home & school	-9.0**	[-15.4,-2.6]	3.3	[-2.4,9.0]
BC commuting				
Concentration	-4.6*	[-9.0,-0.1]	2.2	[-1.8,6.1]
Concentration, adjusted for time	-4.6*	[-9.1,-0.2]	2.2	[-1.8,6.1]
Concentration, adjusted for time and BC at school	-7.8**	[-13.3,-2.3]	2.9	[-2.0,7.7]
Concentration, adjusted for time and BC at home	-7.3**	[-12.7,-1.9]	3.5	[-1.3,8.3]
Concentration, adjusted for time and BC at home & school	-7.8**	[-13.4,-2.3]	3.1	[-1.8,8.0]
NO₂ commuting				
Concentration	-2.7	[-7.8,2.4]	1.9	[-2.6,6.4]
Concentration, adjusted for time	-2.8	[-7.9,2.3]	1.9	[-2.6,6.4]
Concentration, adjusted for time and NO ₂ at school	-5.4	[-11.7,1.0]	2.6	[-3.0,8.3]
Concentration, adjusted for time and NO ₂ at home	-5.4	[-11.7,1.0]	2.6	[-3.0,8.3]
Concentration, adjusted for time and NO ₂ at home & school	-5.4	[-11.7,1.0]	2.6	[-3.0,8.3]

[‡] Difference in the 12-month change adjusted for age, sex, maternal education and residential neighborhood socio-economic status and other exposure when specified; school and subject as nested random effects.

* p<0.05 **p<0.01

ANT: Attention Network Test; HRT-SE: Hit Reaction Time Standard Error; NO₂: Nitrogen Dioxide; PM_{2.5}: Particulate matter <2.5 µm; BC: Black Carbon

Table 5. Stratified analysis of TRAPs concentration during commuting (only walkers) from home to school (interquartile range increase) on the 12-month change of outcomes of cognitive development (working memory and inattentiveness). Adjusted models[¶]

	By School Air Pollution		By Maternal Education		By Sex		By ADHD [§]	
	Low (n= 369)	High (n= 834)	Low (n= 566)	High (n= 637)	Male (n=602)	Female (n=601)	No (n=1,099)	Yes (n=120)
Working Memory (3-back Numbers, d')								
PM_{2.5}	-4.4 [-12.8,4.0]	-2.0 [-9.6,5.6]	-6.2 [-12.6,0.2]	-5.1 [-12.3,2.0]	-9.2* [-16.6,-1.8]	-2.1 [-8.3,4.0]	-6.0* [-11.0,-1.0]	-4.9 [-20.2,10.4]
BC	-1.4 [-10.4,7.5]	-2.2 [-9.1,4.8]	-4.5 [-10.6,1.5]	-4.8 [-11.5,1.8]	-9.7** [-16.8,-2.7]	-0.6 [-6.3,5.1]	-5.0* [-9.8,-0.4]	-4.0 [-18.6,10.7]
NO₂	-0.3 [-11.6,12.2]	0.8 [-6.0,7.7]	-3.1 [-10.0,3.7]	-2.7 [-10.3,4.8]	-6.5 [-14.2,1.3]	0.0 [-6.6,6.6]	-2.8 [-8.2,2.5]	-2.6 [-19.1,13.9]
Inattentiveness (ANT, HRT-SE, milliseconds)								
PM_{2.5}	-1.9 [-9.7,5.8]	2.4 [-4.3,9.0]	1.1 [-4.9,7.2]	4.2 [-2.0,10.3]	-0.2 [-6.7,6.2]	4.9 [-0.7,10.6]	2.1 [-2.4,6.6]	5.3 [-8.5,19.1]
BC	-1.1 [-9.2,7.0]	1.3 [-4.8,7.4]	1.2 [-4.5,6.8]	3.5 [-2.1,9.1]	2.8 [-3.4,8.9]	2.1 [-3.1,7.3]	2.2 [-2.0,6.4]	3.7 [-9.5,16.9]
NO₂	1.0 [-9.7,11.7]	-0.4 [-6.4,5.7]	2.6 [-3.8,9.0]	1.3 [-5.1,7.8]	3.2 [-3.6,10.0]	1.6 [-4.4,7.6]	1.8 [-2.9,6.6]	4.7 [-10.1,19.6]

* p<0.05 **p<0.01

[¶] Difference in the 12-month change adjusted for age, sex, maternal education, and residential neighborhood socio-economic status; school and subject as nested random effects.

[§]ADHD: children with more than 6 symptoms from the Criteria of Diagnostic and Statistical Manual of Mental Disorders list (ADHD-DSM-IV).

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Supplementary Material

Impact of commuting exposure to traffic-related air pollution on cognitive development in children.

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Table S1. Difference (and 95% confidence interval)[‡] in the 12-month change, per commuting air pollution concentration during commuting (interquartile range increase, IQR) in 1.234 children. The estimates are provided for the three different microenvironments (commuting, home, and school) in separated models and all included in a single model. All air pollution concentrations estimated by LUR. Adjusted models[‡].

	Single-pollutant ^a			Multi-pollutant ^b		
	<u>Comm</u>	<u>Home</u>	<u>School</u>	<u>Comm</u>	<u>Home</u>	<u>School</u>
PM2.5	-5.1* [-9.9,-0.4]	-0.5 [-4.4,3.4]	0.2 [-0.6,0.9]	-9.0** [-15.4,-2.6]	0.1 [-7.1,7.3]	0.1 [-0.3,2.2]
BC	-4.6* [-9.1,-0.2]	0.5 [-3.1,4.1]	0.0 [-0.1,0.2]	-7.8** [-13.4,-2.3]	0.0 [-9.8,9.8]	0.2 [-0.2,0.6]
NO2	-2.8 [-7.9,2.7]	0.6 [-2.3,3.6]	0.6 [-2.2,3.3]	-5.4 [-11.7,1.0]	- -	2.3 [-1.1,5.7]

* p<0.05 **p<0.01

‡ Difference in the 12-month change adjusted for age, sex, maternal education, residential neighborhood socio-economic status and time commuting; school and subject as nested random effects.

ANT: Attention Network Test; HRT-SE: Hit Reaction Time Standard Error; NO₂: Nitrogen Dioxide; PM_{2.5}: Particulate matter <2.5 µm; BC: Black Carbon Carbon

^a Each cell corresponds to a single model (including only microenvironment)

^b Each row corresponds to a single model (including the concentrations at the three microenvironments)

Table S2. Association between commuting concentration to tertiles of TRAPs (interquartile range increase) during commuting from home to school and neurodevelopmental outcomes. Adjusted models[‡].

	Working Memory (3-back Numbers, d')	Inattentiveness (ANT, HRT-SE, milliseconds)
PM_{2.5}		
2 nd tertile	-5.3 [-13.7,3.0]	-2.9 [-9.3,3.6]
3 rd tertile	-20.1*** [-29.5,-10.8]	5.6 [-2.0,13.3]
BC		
2 nd tertile	-4.1 [-12.6,4.4]	-2.1 [-8.7,4.6]
3 rd tertile	-19.3*** [-28.8,-9.8]	3.8 [-4.0,11.5]
NO₂		
2 nd tertile	-4.3 [-12.8,4.1]	-4.0 [-10.5,2.4]
3 rd tertile	-6.2 [-15.7,3.3]	-0.8 [-8.6,6.9]

* p<0.05 **p<0.01 ***p<0.001

‡ Difference in the 12-month change adjusted for age, sex, maternal education, residential neighborhood socio-economic status and air pollution during **commuting**; school and subject as nested random effects. ANT: Attention Network Test; HRT-SE: Hit Reaction Time Standard Error; NO₂: Nitrogen Dioxide; PM_{2.5}: Particulate matter <2.5 µm; BC: Black Carbon Carbon

Linear trend P-value<0.05 for BC and PM_{2.5} on superior working memory.

Table S3. Difference (and 95% confidence interval)[‡] in the 12-month change, per commuting air pollution exposure (concentration*time) during commuting (interquartile range increase, IQR) in 1,234 children. Air pollution concentrations estimated by LUR.

	Working Memory (3-back Numbers, d')		Inattentiveness (ANT, HRT-SE, milliseconds)	
PM_{2.5} commuting				
Exposure [§]	-6.8**	[-11.8,-1.7]	0.4	[-4.1,4.9]
Exposure, adjusted for PM _{2.5} at school	-7.0**	[-12.1,-1.9]	0.3	[-4.3,4.8]
Exposure, adjusted for PM _{2.5} at home	-6.8*	[-11.9,-1.6]	0.2	[-4.4,4.8]
Exposure, adjusted for PM _{2.5} at school and home	-6.7*	[-11.9,-1.5]	0.2	[-4.4,4.8]
BC commuting				
Exposure	-7.0**	[-12.2,-1.8]	1.3	[-3.3,5.9]
Exposure, adjusted for PM _{2.5} at school	-7.6**	[-12.9,-2.2]	1.1	[-3.6,5.9]
Exposure, adjusted for PM _{2.5} at home	-7.5**	[-12.8,-2.1]	1.3	[-3.3,6.1]
Exposure, adjusted for PM _{2.5} at school and home	-7.6**	[13.0,-2.2]	1.1	[-3.6,5.9]
NO₂ commuting				
Exposure	-5.2*	[-10.0,-0.3]	1.5	[-2.9,5.8]
Exposure, adjusted for PM _{2.5} at school	-6.0*	[-11.3,-0.8]	1.3	[-3.3,5.9]
Exposure, adjusted for PM _{2.5} at home	-6.0	[-11.3,-0.8]	1.3	[-3.3,5.9]
Exposure, adjusted for PM _{2.5} at school and home				

[‡] Difference in the 12-month change adjusted for age, sex, maternal education and residential neighborhood socioeconomic status and other exposure when specified; school and subject as nested random effects.

[§] Exposure = average concentration during commuting trip * trip time

* p<0.05 **p<0.01

ANT: Attention Network Test; HRT-SE: Hit Reaction Time Standard Error; NO₂: Nitrogen Dioxide; PM_{2.5}: Particulate matter <2.5 µm; BC: Black Carbon Carbon