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Faculty of Medicine and Life Sciences
School for Life Sciences
Master of Biomedical Sciences

Master's thesis

Exposure to traffic-related air pollution impacts neurocognitive performance in children

Nick Giesberts
Thesis presented in fulfillment of the requirements for the degree of Master of Biomedical Sciences, specialization Environmental Health Sciences

SUPERVISOR :
Prof. dr. Tim NAWROT

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Exposure to traffic-related air pollution impacts neurocognitive performance in children

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*Running title: *Traffic-related air pollution impacts cognition*

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ABSTRACT

BACKGROUND: Air pollution is known to adversely impact human health. Black carbon is a toxic air pollutant that is suspected to affect neurocognitive development. During childhood, cognitive development is highly vulnerable to environmental exposures and previous research suggests that black carbon exposure can impede this process. However, no consensus has been reached on the health effects. Here, we examine the association between black carbon exposure and cognitive performance in children.

METHODS: We included 194 children, as part of the CHAIR study and the ENVIR*ON*AGE birth cohort. The exposures were estimated using pollution and road-based data geocoded to residential addresses. The neurocognitive performance was examined using three cognitive tasks. Principal components were generated for sustained attention and short-term memory. Multiple linear regression models were used to study the associations, accounting for relevant covariables and confounders.

RESULTS: In sustained attention tests, interquartile range (IQR) increases in chronic and long-term black carbon exposures were associated with an increased likelihood of answering falsely positive, with an increase of 0.71 (95% CI: 0.21;1.21) and 0.43 (95% CI: 0.06;0.80) in false positive answers.

Further, IQR increases in chronic and long-term black carbon exposures were associated with a decreased reaction time for sustained attention tests, with a decrease of 117.41 milliseconds (95% CI: -173.14;-61.68) for chronic exposure and 50.44 milliseconds (95% CI: -92.58;-8.30) for long-term exposure.

CONCLUSIONS: The results of this study suggest that children exposed to more black carbon show decreased cognitive performance in tests examining sustained attention, with an increase in mindless response behavior.

INTRODUCTION

Air pollution is ranked as a major environmental health threat globally. Exposure to air pollution is linked to many adverse health effects. These effects can vary from an adverse impact on respiratory health (1) and an increased risk of developing cardiovascular events (2) to affecting the development of central nervous system (CNS) diseases (3). Additionally, concerns have been raised about the potential impact on the CNS for humans, especially children, through developmental neurotoxic effects caused by exposure to air pollutants (4,5). Evidence from experimental studies shows a detrimental impact of air pollution exposure on the CNS resulting in both broad and functional effects (6). Common examples among the broad effects are the disruption of the blood-brain barrier, chronic inflammation and microglia activation. However, air pollution exposure can also lead to specific functional effects such as cognitive impairment, caused by an impact on the frontal cortex, striatum, hippocampus and substantia nigra of the brain after exposure (4,7).

Air pollution is a mixture of components with characteristics that vary greatly. Because of this attribute, the composition of air pollution can be different depending on environmental factors and emission sources, which affects the route of exposure. One of the defining characteristics of air pollution behavior is the size of the particulate. Air pollution particles are classified as particulate matter (PM), which is a major constituent of air pollution and can be distinguished based on the aerodynamic diameter. PM_{10} includes PM with an aerodynamic diameter of up to 10 mm, while $PM_{2.5}$ comprises particles up to 2.5 mm. Exposure to these PM groups is known to result in important adverse health effects at the population level (8-10).

The main route of exposure to air pollution is via inhalation. After being inhaled, PM is transported over the respiratory tract towards the lungs. Larger particles are usually not able to reach the lungs and will precipitate in the upper airway, while $PM_{2.5}$ can reach the alveoli in the lungs (3). Upon reaching the alveoli, $PM_{2.5}$ particles can enter the bloodstream and can be transported to other organs, also causing adverse effects in organs that were not directly exposed.

For $PM_{2.5}$, exposure can additionally occur via the olfactory nerves (11). After inhalation in the nose, these particles can be transported over the olfactory nerves of the olfactory bulb. Through transportation over the olfactory nerve, $PM_{2.5}$ can reach the olfactory cortex of the brain, spread to other regions of the brain and affect the development and functioning of these regions (12).

Within Europe, $PM_{2.5}$ has been identified as the most harmful air pollutant in terms of its adverse impact on human health (1). An acknowledged carcinogen and major component of $PM_{2.5}$ is black carbon (BC). This organic compound can originate from different sources, including industry, traffic, households and natural sources (3). Other important sources are oil- or coal-using power stations, residential wood or coal burning, agricultural waste burning and forest fires (13,14). This makes BC an indicator of pollution from a wide distribution of combustion and emission sources (15). When focusing on environmental BC concentrations near roads, between 40-70% of the roadside air pollution mass concentration of $PM_{2.5}$ generally consists of BC (16). This indicates that BC makes up an important part of the mass concentration of $PM_{2.5}$ when estimating exposure near roads.

Exposure to BC could have serious adverse health effects. However, the current European air quality standards for BC are incorporated within the $PM_{2.5}$ regulation. This EU regulation (Directive 2008/50/EU) is based on the association between $PM_{2.5}$ mass concentrations and shown adverse health effects (16). Several sub-standards are included for important components such as ozone, nitrogen dioxide and sulfur dioxide. However, for BC no sub-standard exists, despite the carcinogenic nature and toxic potential of BC.

In recent years multiple studies have investigated the effects of exposure to specific air pollution constituents, because of the realization that not all PM components cause the same health effects or are equally important in this matter.

Since the components that make up $PM_{2.5}$ mixtures can vary greatly, potential adverse health effects caused by BC exposure could be underestimated based on $PM_{2.5}$ exposure measurement as a whole. Mixtures with relatively high BC concentrations could have a greater impact on health outcomes than $PM_{2.5}$ mixtures with lower BC concentrations while having the same $PM_{2.5}$ mass concentrations. After all, combustion-related components are hypothesized to generally cause more serious effects on adverse health, from a wide array of PM components, especially compared to their non-combustion counterparts (17).

An additional reason for studying specific components rather than the mixture is to circumvent intercorrelations issues between particle components, especially those from the same emission source (15).

Considering these insights, BC has been suggested as an additional exposure indicator to reflect the health effects of combustion-related air pollution, to capture specific health effects of primary combustion particles instead of the effects of the mixture (15,16).

Children are an important risk group for air pollution and BC exposure for several reasons.

Firstly, when compared to adults, children undergo a relatively high exposure to BC, due to commuting to school during rush hours for example (5). An additional factor is that children have higher breathing rates than adults and will breathe in higher doses of these pollutants, further contributing to their relatively high exposure (18).

Secondly, an immature brain is more vulnerable to air pollution exposure, because the maturation has to yet be completed. Since the development of the brain is ongoing, this process can be adversely impacted, with severe consequences. Because the neuronal networks are more flexible early in life and change more easily in response to environmental exposures (5,19) and the neocortex of the brain continues to develop until young adolescence (3), childhood represents a window of susceptibility to air pollution exposure. Especially, high executive functions that are essential for academic performance and learning, such as working memory and attention span could be affected as these functions develop greatly between the age of six to ten years as a part of the natural cognitive maturation (4,20).

Thirdly, children lack mature detoxification mechanisms to combat the potential neurotoxic effects of air pollution, further increasing the vulnerability of the brain throughout development to these toxicants (6).

Because of the potential impact of air pollution particles on the development and functioning of different brain regions, multiple studies have investigated the impact of air pollution exposure on cognitive development and performance in different populations, including children. For children, epidemiological evidence suggests that prenatal air pollution exposure and exposure during childhood are related to adverse effects on neurocognitive development (4,21).

Sunyer *et al.* examined the cognitive development of children between the age of seven and nine years old in Barcelonian schools (Spain) in a prospective study (4). The cognitive development was measured four times over a 12-month trajectory using computerized tests. The results indicate that children from schools with high traffic-related air pollution (TRAP) showed smaller improvements in cognitive development.

Porta *et al.* used a comparable design and examined the association between the evolution of IQ scores of children (seven years) from Rome (Italy) and their exposure to TRAP (21). The results from this study show a negative association between the development of verbal cognition and exposure to TRAP, suggesting an adverse impact of air pollution exposure on verbal cognitive development.

Combined these results indicate that exposure to air pollution can impact cognitive development, especially in children.

The effects of BC exposure specifically on cognitive performance and development have been studied as well.

Suglia *et al.* investigated the effect of BC exposure on cognitive performance in nine-year-old children from a prospective birth cohort from Boston, USA (22). In this study, a negative association between BC exposure and cognitive performance has been found. The cognitive performance was negatively impacted, shown by a decline in memory constructs, verbal intelligence and non-verbal intelligence.

Harris *et al.* on the other hand investigated mother-child pairs in a prospective birth cohort study from Massachusetts, at the age of eight years old. Here, childhood exposure to BC has been associated with lower verbal IQ as well. However, this association was attenuated after adjusting for several socioeconomic factors (23).

In a third investigation, Alvarez-Pedrerol *et al.* studied school children between the ages of seven and ten as part of a longitudinal study in Barcelona (Spain). The results of this study indicated that BC exposure during commuting has been associated with a decrease in cognitive development, shown by a decrease in the growth of working memory (5).

Overall, the results of these studies suggest that the effects of BC exposure on cognitive performance are not completely clear, warranting further investigation.

To investigate the effect of BC exposure on cognitive performance in children, we combined children from two different study populations. Children were recruited as part of the cross-sectional study 'The effects of exposure to traffic-related **AIR** pollution on the cardiovascular health and neurocognitive performances in middle school **CH**ildren' (CHAIR). This study is characterized by school children from the capital region of Brussel (Belgium) between the ages of ten and thirteen years. The second study population included children from the second follow-up phase of 'The **ENVIR**onmental influence **ON** early **AGE**ing' (ENVIR*ON*AGE) prospective birth cohort.

We examined the associations between multiple cognitive performance outcomes and BC exposure variables in these children. We included modeled chronic and long-term BC exposure, residential distance to the nearest major road and the length of major roads around the residential address in several buffers as exposure indicators. Residential green space exposure was estimated as well. The cognitive performance was investigated using three cognitive performance tests from the MINDS software package.

This study aimed to investigate the effect of BC exposure on cognitive performance in children between the ages of ten and thirteen. We hypothesize that participants showing higher BC exposure will be associated with lower cognitive performance outcomes.

People are exposed daily to their environment, which can lead to both positive and negative effects on their health. Considering that air pollution and BC are common environmental pollutants and children undergo comparably high exposure, it is important to identify the effects of exposure to these pollutants on their health. There is prior evidence that air pollution could lead to an impact on the neurocognitive development and performance of children, potentially leading to decreased cognitive capabilities later in life. However, the effects of BC exposure are inconclusive. This research further investigates the impact of BC exposure on the cognitive performance in children between the ages of ten and thirteen through the use of different exposure variables. The results of this study will further contribute to scientific knowledge regarding the health effects of BC exposure in children. For air pollution regulation, this study can contribute to the notion that a sub-standard for BC exposure is needed, considering that BC can have more toxic and carcinogenic effects than recognized by current $PM_{2.5}$ thresholds in regulation.

MATERIALS & METHODS

Study area and population – This study combines children from the CHAIR study and the second follow-up phase of the ENVIR*ON*AGE cohort. CHAIR is a cross-sectional study that investigates the effect of air pollution on the cardiovascular health and cognitive performance of Brussels' schoolchildren between the ages of ten and thirteen. ENVIR*ON*AGE is a prospective birth cohort, in which mother-child dyads are recruited after delivery in the East-Limburg Hospital of Genk (Belgium). The participating children and mothers are investigated in two follow-up phases, between the ages of four and six, and ten and twelve.

In this study, 75 children were recruited as part of the CHAIR study and 119 from the second follow-up phase of ENVIR*ON*AGE. From the CHAIR population, 16 children were excluded because any of the cognitive performance tests were incomplete (n=8), any of the tests were not well understood (n=3), they were distracted by external factors during the test (n=3) or the residential information was incomplete (n=2). For the ENVIR*ON*AGE population, 21 children were excluded due to external distraction (n=9), having trouble understanding any test (n=5), missing birth dates (n=2) and incomplete questionnaires (n=5).

For each of the cognitive tasks, the need for exclusion was assessed separately. This resulted in 161, 178 and 169 outcomes for the Continuous Performance Test (CPT), Symbol-Digit Modalities Test (SDMT) and Digit SPAN test (SPAN).

Questionnaires - The participating children completed several questionnaires. At first, they filled out the self-completion version of the Strength and Difficulties Questionnaire (SDQ). This version is suitable and reliable for children and adolescents (24,25). This questionnaire contains 25 statements that provide insight into the child's behavior over the last six months. These statements are attributed to five scales: emotional symptoms, conduct problems, peer relationship problems, hyperactivity and prosocial behavior. Each scale consists of five attributes, which are given a score (0, 1, or 2). Combined, the Total Difficulties Score can be calculated, based on emotional symptoms, conduct problems, hyperactivity and peer relationship problems. For interpretation, the classification is based on British norms.

Secondly, The KIDSCREEN-27 was used, which is a tool that is used in epidemiological studies for people between eight and eighteen years old (26). This questionnaire describes the health-related quality of life in five different dimensions: Psychological Well-being, Physical Well-being, Social Support & Peers, Autonomy & Parent Relation and School Environment. Each dimension has a set number of questions (scored 1-5). Afterward, the raw scale scores are transformed into Rasch person parameter estimates and then into T-values (mean=50, SD=10) (26). Both are further detailed in **Covariables** and **Statistical analysis**.

Several additional questionnaires were completed by the parents, concerning topics such as residential addresses, maternal education, residential heating source(s), parental smoking behavior and the child's exposure to traffic.

Exposure measures – The residential information reported in the parental questionnaires was used to establish the geographical history of the child and corrected for split and previous addresses using a time-weighted average. The addresses were geocoded with Belge Lambert 1972 coordinates using Geopunt and ArcGIS version 10.01.

The BC exposure was estimated using validated air pollution models. The average annual chronic BC exposure (from birth until the end of 2019) was estimated using an interpolation model, called the RIO-IFDM air quality model and air pollution data from the Belgian Interregional Environment Agency (IRCEL – CELINE) to produce BC concentration estimates on a grid of up to a resolution of 25x25m^2. This model is characterized by high spatiotemporal resolution. The average long-term BC exposure (up to a year before the examination) was estimated using daily BC concentrations of lower resolution (4x4 km^2), with the RIO model. Both models are further described elsewhere (27).

In addition, the distance to the nearest major road for the residential address was estimated using the Flemish road register (2018) in ArcGIS. The total length of major roads around the participants' residential addresses was estimated as well, in five buffers (100m, 300m, 500m, 1,000m and 5,000m). European roads (E-road) and National roads (N-road) were considered major roads.

Green space exposure was estimated by calculating the total amount of green area around the residential address in four buffers (100m, 300m, 500m and 1,000m). For participants of ENVIR*ON*AGE the Green Map of Flanders (2012, Geopunt) was used, while for the CHAIR participants the Green Block map (2013, GeoBru) was used. For the Green Map of Flanders, the amount of total green was calculated by combining the coverage of agricultural green, green less than three meters in height (low green) and green more than three meters in height (high green). For the Green Block, the total amount of green was calculated by combining the 'forest' (parts of the Sonian Forest), 'green' (recreational parks) and 'grass' (grass, low green and trees) entities.

Cognitive measures **-** The cognitive performance was measured using software from Testmanager MINDS (28). The CPT, SDMT and SPAN were performed. Before the examination, the child was explained how to perform each task by trained personnel according to a standardized protocol, followed by a training trial.

The CPT was used to measure sustained attention and concentration. A sequence of 300 alphanumerical stimuli (letters) is given over 500 seconds. Upon seeing a specific sequence of two stimuli (targets), a reaction is warranted from the participant. The percentage of correct answers, the mean reaction time and the number of false positive results were included in the statistical analyses.

The manual subtest of the SDMT was used to assess the complex visual scanning and processing speed of the participant. During the three minutes, the participant needs to match the sequence of randomly provided symbols to the corresponding numbers, using a provided key (29,30). Here, the percentage of correct answers was included.

The SPAN provides insight into the short-term memory of the participant. During the forward visual SPAN sequence of numbers is shown on the screen which needs to be reproduced correctly by the participant. When two series of the same length are reproduced correctly, a different and longer sequence will be shown. The reverse visual subtest is used after the forward version, here the participants are required to reproduce the numbers in the reverse sequence (31,32). The number of correct answers for both sequences was included.

Covariables - Covariate data was collected from the questionnaires and measured on the day of examination. The level of maternal education was used as an indicator of socioeconomic status and categorized into three groups: high (university degree or above), middle (high school degree) and low (no diploma or primary school diploma).

For the exposure data, chronic BC exposure weas defined as the exposure from birth until the end of 2019 and long-term exposure as six months and one year before the day of the examination.

The total score from the SDQ was used to create a variable coded as being 'normal' (≤15) or 'raised' (>15). The KIDSCREEN-27 scores were expressed as principal components (PCs).

Statistical analysis **-** For the statistical analyses, R (4.1.2) was used to examine the association between BC exposure and cognitive performance. Three principal component analyses (PCAs) were performed, two for the cognitive outcomes and one for the KIDSCREEN-27 scores. For the cognitive tests, linear combinations were created for outcomes belonging to the same cognitive domain. The outcomes of the CPT were attributed to the domain of sustained attention (attention), and the outcomes of the SDMT and the SPAN to the domain of short-term memory and processing speed (memory) (33). For these PCAs, the number of PCs was chosen so that the cumulative variance explained exceeded 70%.

Multiple linear regression (MLR) models were used for each cognitive outcome as well as for the first two cognitive PCs of the attention and memory domain, with each BC exposure variable separately. These models were adjusted for *a priori* chosen covariables, including sex, BMI, age at follow-up, maternal education (low, middle, high), average hours of sleep, SDQ score (normal, raised) and the first three PCs of the KIDSCREEN. The results are expressed per interquartile range (IQR) increase in the exposure.

Additional effects of green space exposure, distance to the closest major road and the length of major roads were determined via separate multiple linear regression models. These models were corrected for the same *a priori* chosen covariables.

The required assumptions were checked for each regression model and all analyses were performed at a significance level of 0.05, except for the PCAs where 0.025 significance was used due to multiple testing corrections (Bonferroni).

RESULTS

Participant description - In total 75 participants from the CHAIR study in Brussels and 119 participants from the second follow-up phase of the ENVIR*ON*AGE birth cohort were examined, for a total of 194 participants. The characteristics of the study population are presented in Table 1.

The characteristics of both study populations were generally similar and were combined. The mean age of the participants was 10.9 (standard deviation (SD), 0.53). The population was characterized by a higher degree of female participants (54.1%). The average height was 145.8 cm (SD, 7.0), while the children on average weighed 39.4 kg (SD, 8.6). The average BMI of the participants was equal to 18.3 (SD, 2.9). The SDQ score indicated that 13.9% of the children had a higher risk of suffering from mental health problems. The maternal education level was mainly characterized by a middle level of education, with 43.3% having a high school degree. Further, maternal education showed a relatively high number of well-educated mothers with at least a university degree (38.7%).

The T-scores belonging to the five dimensions of the KIDSCREEN-27 of the participating children are summarized in Table 2, expressed as the minimal score (Min), maximum score (Max), the median (p50) and first and third quartile (p25, p75). Higher scores indicate a better state of mental health for each dimension, characterized as having less risk of having mental health problems. The median for all five dimensions is within a score considered normal (mean 50, SD = 10). The first and third quartile for the Autonomy, Peers, Physical and Phycological dimensions are also around the normal. However, the third quartile of the School dimension indicates a relatively high mental state for that dimension.

Table 1 – Characteristics description of the participating mother-child dyads.

Population characteristics	**n = 194**
Characteristics Child	
Age (years)	10.9 ± 0.53
Sex	
Female	54.1%
Height (cm)	145.8 ± 7.0
Weight (kg)	39.4 ± 8.6
BMI	18.3 ± 2.9
Sleep hours	9.5 ± 1.0
Moved	
Never	31.2%
SDQ score	
Raised	13.9%
Characteristics mother	
Education	
Low	15.5%
Middle	43.3%
High	38.7%
Missing	2.6%

The outcomes of the three cognitive tests are summarized in Table 3, with the smallest values (Min), highest values (Max) and three quartiles (p25, p50 and p75) being presented. The median percentage of correct answers in the CPT was 90.0% (86.7 – 93.3), while the median for the number of false positive answers was 2 (1 – 3). In addition, the median reaction time in the CPT was 534.0 milliseconds (464.3 – 656.1). The median percentage correct in the SDMT was 95.0% (91.2 – 100). Regarding the Digit SPAN test, the median of the number of correct answers for the forward SPAN sequence was 5 (4-5), while for the reverse sequence this was equal to 4 (3-5).

The characteristics of BC exposure are described in Table 4. Chronic exposure indicates long-term exposure over the participant's childhood, from birth up to the end of 2019, expressed in $\mu g/m^3$. The average annual chronic BC exposure was equal to

Table 2 – Distribution of the T-score transformed Rasch scores for the five dimensions of the KIDSCREEN-27 questionnaire.

KIDSCREEN -27 scores	Min	p25	p50	p75	Max
Autonomy	31.90	46.53	52.23	59.06	74.39
Peers	31.62	46.93	53.23	57.83	66.34
Physical	30.57	47.08	52.43	57.80	73.20
Psychological	29.42	44.80	51.84	55.96	73.53
School	36.74	51.08	54.40	62.84	70.99

Table 3 – Description of performance in the three cognitive tasks (Continuous Performance Test, Symbol-Digit Modalities Test and Digit SPAN test (SPAN).

Cognitive outcomes	n	Min	p25	p50	p75	Max
CPT	161					
Percentage correct answers		73.3	86.7	90.0	93.3	93.3
Number of false positive answers		0	1	2	3	8
Mean reaction time, milliseconds		351.0	464.3	534.0	656.1	1111.0
SDMT	178					
Percentage correct answers		81.1	91.2	95.0	100.0	100.0
SPAN	169					
Number of correct answers in forward sequence		3	4	5	5	7
Number of correct answers in reverse sequence		2	3	4	5	6

1.53 µg/m^3 (SD, 0.48). The relatively high SD is an indication for emerge of exposure differences due to the type of residential neighborhood, such as metropolitan versus rural. The average long-term BC exposure for one year and six months before the examination was equal to 0.74 µg/m^3 (SD, 0.11) and 0.66 µg/m^3 (SD, 0.08) respectively.

The distributions of the distance to the nearest major road, as well as the length of major roads within five buffers around the residential address (100m to 5,000m) are presented in Table 5. These measures are used to approximate the exposure to traffic-related air pollution. The median distance to the closest major road was equal to 517.11m (236.61 – 1,083.59). Moreover, the length of major roads ranged from 198.11m in a 100m radius, up to78,947.65m in a 5,000m radius.

The distribution of green space coverage in buffers (100m to 1,000m) around the current residential addresses is presented in Table 6. The median green space coverage varied between 6.78% within a 100m radius and 14.30% within a 1,000m radius around the residential address. However, the distribution varies greatly, with some participants having next to no green space around their home (0.00 % to 0.08% for 100m – 1,000m buffer) and others almost exclusively being surrounded by green space coverage (97.06% to 93.1% for the buffers of 100m – 1,000m).

Table 4 – The exposure characteristics for residential black carbon of the included participants. Chronic exposure is defined as the average residential exposure starting from birth until the end of the year 2019. The long-term exposure windows are defined as the average residential exposure during the indicated timeframe, before the day of examination. Results are expressed as the mean ± standard deviation (SD).

Average black carbon exposure (µg/m^3)	Mean ± SD
Chronic exposure	1.53 ± 0.48
1 year before the examination	0.74 ± 0.11
6 months before the examination	0.66 ± 0.08

Table 5 – Distribution of the residential distance to the nearest major road and distribution of the length of major roads within five buffers around the residential address (50m to 5000m).

Distance to major road (m)	Min	p25	p50	p75	Max
	13.24	236.61	517.11	1,083.59	2,826.20
Length of major roads (m)					
100m buffer	11.37	180.65	198.11	1,083.59	2,826.20
300m buffer	24.78	482.49	825.51	1,114.01	1,863.27
500m buffer	0.78	713.04	1,139.37	1,849.12	4,340.71
1,000m buffer	123.32	2,031.57	3,285.48	4,797.47	12,794.08
5,000m buffer	1,428.00	47,952.20	78,947.65	91,948.11	155,348.75

Table 6 – Distribution of the green space coverage (%) around the current residential address.

Green space (%)	Min	p25	p50	p75	Max
100m buffer	0.00	0.00	6.78	55.74	97.06
300m buffer	0.00	0.00	15.32	64.15	96.10
500m buffer	0.00	0.23	15.26	67.64	93.07
1,000m buffer	0.08	2.96	14.30	73.28	93.51

Associations: PCA - The outcomes of the neurocognitive performance tests were used to create PCs, with different linear combinations.

The outcomes of the CPT test (percentage of correct answers, mean reaction time and the number of false positive answers) were combined in PCs representing the neurological domain of sustained attention (attention for short). Here, the first two PCs represented 52.6% and 28.6% of the total variance.

The percentage of correct answers from the SDMT and the number of correctly replicated numbers of the forward and reverse sequence of the SPAN test were combined to form the neurological domain of short-term memory and processing speed (memory for short). The first two memory PCs explained more than 70% of the cumulative variance, with the first PC explaining 48.4% of the variance and the second PC 30.8%.

Additionally, PCAs were performed to combine the five dimensions of the KIDSCREEN-27 questionnaires. Here the first two PCs represent 61.7% and 16.2% of the variance. The characteristics of all PCs used in the different MLR models are shown in the **supplements**.

Associations: Results Attention PCA - While accounting for sex, BMI, age at follow-up, maternal education, average hours of sleep, SDQ status and the first two PCs of the KIDSCREEN-27 questionnaire, an association was observed between the first attention PC and the chronic BC exposure. This PC was characterized by a similar contribution of the percentage of correct answers (loading = -0.53), the mean reaction time (loading = - 0.54) and the number of false positive answers (loading = 0.65) from the CPT. This result reflects a decrease in cognitive performance regarding sustained attention. For the same PC, a similar association was found with the average BC exposure of one year before the day of the examination, as well as for the length of roads within a 5,000m buffer around the participant's residential address. None of the attention PCs was significantly associated with the long-term BC exposure six months before the day of examination.

Additionally, when investigating the effect of green space exposure, the amount of green residential space coverage in the buffers of 100m, 300m, 500m and 1,000m showed an inverse association with the first attention PC. These results indicate an opposite effect of green space exposure compared to BC exposure on sustained attention.

Lastly, the distance to major roads was significantly associated with the second attention PC, which was mainly characterized by the percentage of correct answers (loading = 0.72) and mean reaction time (- 0.69) and only minimally by the number of false positive answers (loading = 0.01).

Associations: Results Memory PCA – While accounting for the same *a priori* chosen covariates, an inverse association was shown between the first memory PC and chronic BC exposure, while the BC exposure over the year before the date of examination showed a borderline significant association. This memory PC was characterized by the number of correct answers from the forward (loading = -0.67) and reverse (loading = -0.63) Digit SPAN tests, with a smaller contribution of the percentage of correct answers from the SDMT (loading = -0.40) These associations suggest an increase in cognitive performance for the Digit

SPAN test with increased exposure. Finally, no significant association was shown between the different memory PCs and the BC exposure period of six months before the examination.

Associations: Results BC exposure – Several MLR models were used to study the associations between the three BC exposure windows (chronic, one year before the examination and six months before the examination) and the different cognitive outcomes of the CPT (percentage correct, number of false positive results and mean reaction), SDMT (percentage correct) and Digit SPAN test (number of correct replications in forward and reverse sequences). These MLR were adjusted for *a priori* chosen covariables, including sex, BMI, age at follow-up, maternal education, average hours of sleep, SDQ score and the first two PCs of the KIDSCREEN. Several significant associations were observed, as visualized in Figure 1 (A-F).

For the CPT, the participant's number of false positive answers was significantly associated with chronic and long-term (one year) BC exposure (Fig.1A). An IQR increase in chronic and one-year BC exposure was associated with an increase in the number of false positive answers of 0.71 (95% CI: 0.21;1.21) and 0.43 (95% CI: 0.06;0.80) respectively. Additionally, the mean reaction time in the CPT showed a significant inverse association with chronic and long-term (one year) exposure (Fig.1B), while the percentage of correct answers was not significant (Fig.1C). An IQR range increase in chronic and one-year BC exposure was associated with a decrease in mean reaction time of 117.41 milliseconds (95% CI: -173.14;-61.68) and 50.44 milliseconds (95% CI: -92.58;-8.30).

In the SDMT, the percentage of correct answers was not found to be significantly associated with any of the BC exposure widows (Fig1.D).

Concerning the forward sequence of the Digit SPAN test, the number of correct forward replications was significantly associated with chronic and one-year (long-term) BC exposure (Fig1.E). Here, an IQR increase in chronic and one-year BC exposure was associated with an increase in correct forward replications of 0.36 (95% CI: 0.06;0.66) and 0.17 (0.01;0.32) respectively. These results were similar in the reverse Digit SPAN test, for chronic BC exposure (Fig1.F), where an IQR increase was associated with an increase in correct reverse replications of 0.49 (95% CI: 0.08;0.90). However, for the BC exposure over one year before the examination, the association was not significant (Fig.1F). For the long term BC exposure over six months before the day of the examination, no associations were shown to be significant.

Associations: Results green space exposure – The effect of residential green space exposure on cognitive performance was studied by several MLR, in different residential buffers (100m, 300m, 500m and 1,000m), while accounting for the same *a priori* chosen covariates.

Regarding the CPT, the number of false positive results was found to be inversely associated with residential green space exposure for several buffers. An IQR increase in the residential green space coverage was significantly associated with a decrease in the number of false positive results of between 0.55 (95% CI: -1.02;-0.08) and 0.54 (95% CI: -1.04;-0.04) in a 100m to 1,000m buffer.

Additionally, the mean reaction time in the CPT was significantly associated with residential green space exposure. Here, an IQR range increase was shown to be associated with a 123.18 millisecond (95% CI: 62.19;184.17) increase for the 100m buffer, and a 102.19 millisecond (95% CI: 43.65;160.76) increase in reaction time for the 1,000m buffer.

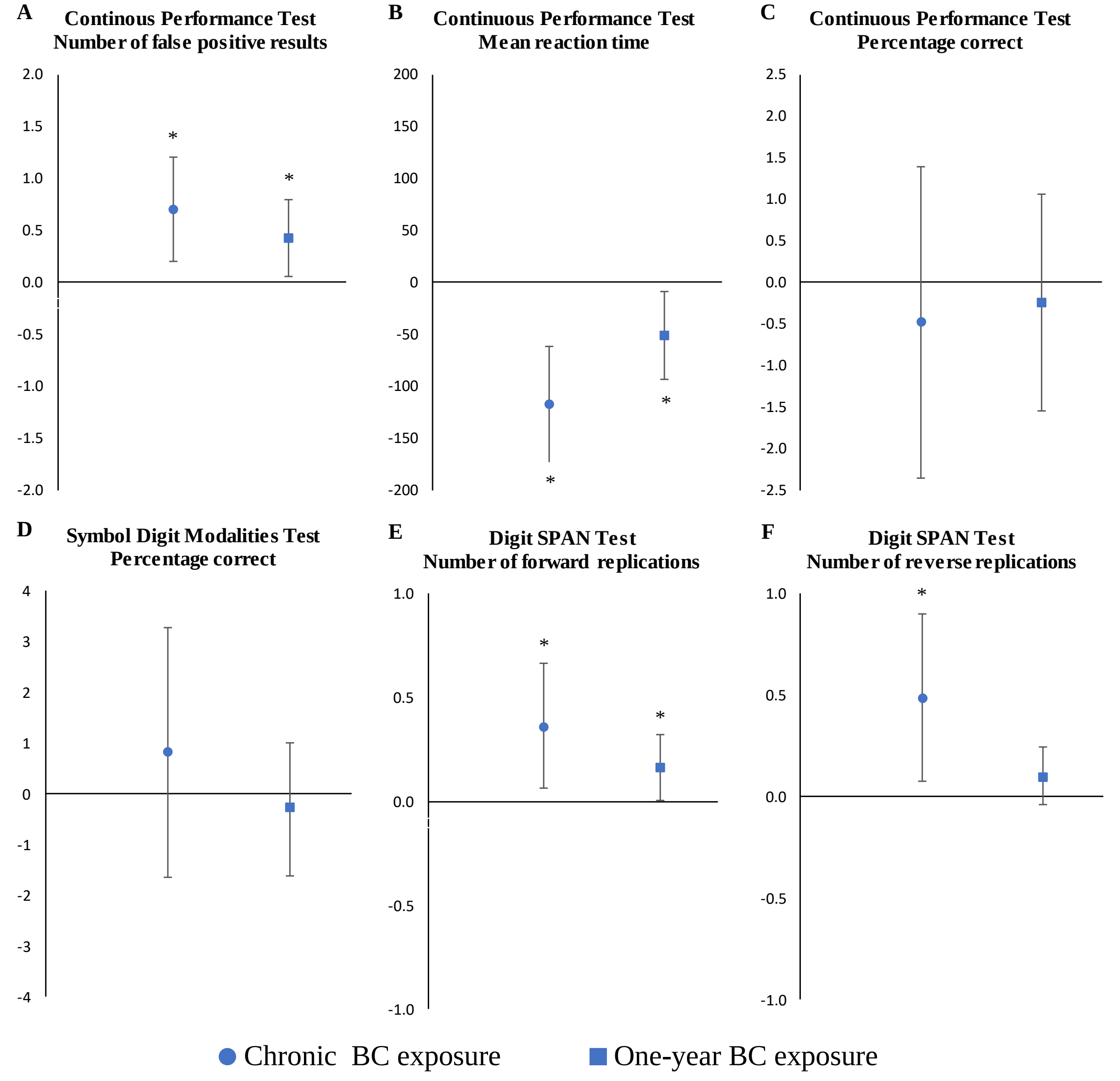

Fig. 1 – Summary of the associations between the cognitive outcomes from the cognitive tests and BC exposure covariables. The BC covariables represent chronic exposure from birth up to the end of 2019 (circle) and long-term exposure over one year before the day of the examination (square). **A-C** Domain of sustained attention, **D-F** Domain of short-term memory and processing speed. **A** Represents the number of false positive answers in the CPT, **B** the mean reaction time in milliseconds during the CPT and **C** the percentage of correct answers in the CPT, all in association with the BC exposure variables. **D** Represents the percentage of correct answers of the SDMT, **E** the number of correct replications in the forward sequence of the Digit SPAN test and **F** the number of correct replications in the reverse sequence of the Digit SPAN test, also all in association with the BC exposure variables. The multiple linear regression models were corrected for BMI, age at follow-up, maternal education, average hours of sleep and the participant's mental health status. Results are expressed as regression coefficients with their 95% confidence interval error bars for an IQR increase in the black carbon exposure variable. Significant associations at 0.05 are indicated by an asterisk.

Sensitivity analyses **-** Several sensitivity analyses were performed to investigate the robustness of the results.

In the first sensitivity analysis, the MLR models for the separate cognitive outcomes were further adjusted with residential green space exposure, expressed as percentage coverage within four buffers around the residential address (100m, 300m, 500m and 1,000m). The results of the largest buffer (1,000 m) are shown in the second group of Figure 2 (A-F). The inclusion of green space exposure changed several associations, with the effect being the greatest for the 1,000m buffer, but not being substantially different from the other buffers. For the CPT, the association between the number of false positive results and one-year BC exposure changed from significant (+0.43, 95% CI: 0.06;0.80) to insignificant (+0.16, 95% CI: -0.25;0.56) upon inclusion of green space exposure. This effect was mimicked for the association between the mean reaction time and one-year BC exposure, with a change from (-50.44, 95% CI: -92.58;-8.30) to (-24.46, 95% CI: -69.52;20.60). Finally, a similar pattern was found for the association between the forward sequence of the Digit SPAN test and chronic BC exposure, corrected for residential green, with (+0.36, 95% CI: 0.06;0.66) becoming insignificant at (+0.30, 95% CI: -0.02;0.61). For the other associations, similar direction and effect estimates were observed compared to the initial models.

In the second through fifth sensitivity analysis, the models were additionally adjusted for the following covariates instead: the average amount of daily screen time, the mode of transport to school (e.g. by foot, by car, by bus, etc.), the child's exposure to parental smoking (expressed as the number of cigarettes smoked indoors) and the residential heating source (e.g. central heating, wood stove, coal stove, etc.). In a sixth sensitivity analysis, the models were adjusted for all these covariates together. The results for the combined adjustment are shown in the third group of Figure 2 (A-F). The effects of the separate adjustments were similar to the combined adjustment, albeit with a smaller effect. The combined inclusion of average daily screen time, parental smoking behavior, mode of commuting to school and residential heating source changed the significance of one of the CPT models compared to the initial models. The mean reaction time in the CPT became insignificant, with the effect size and 95% CI changing from (50.44, 95% CI: -92.58;-8.30) to (-39.80, 95% CI: -83.87;0.51) for the association with one-year BC exposure.

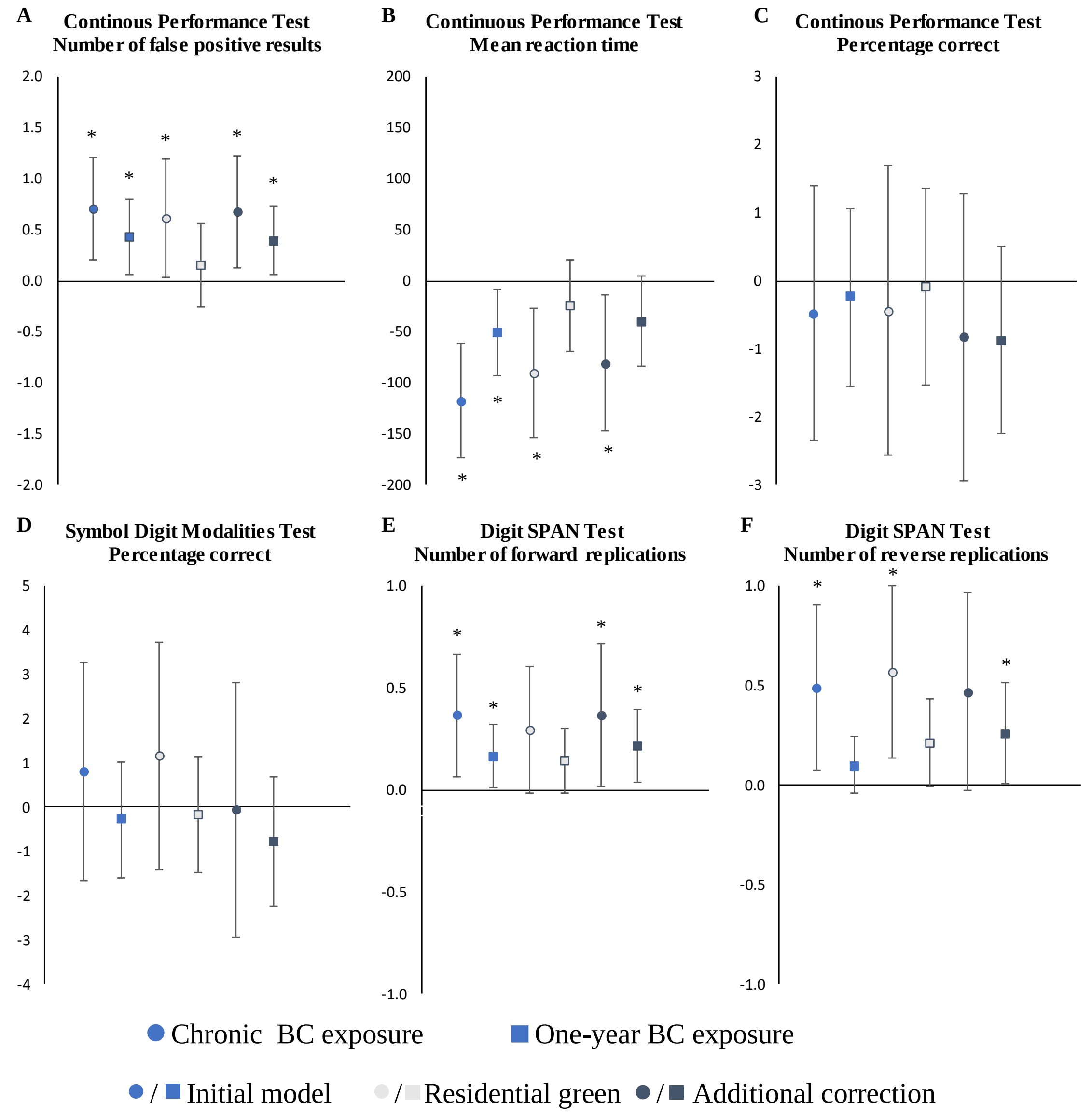

Fig. 2 – Summary of the associations between the cognitive outcomes from the cognitive tests and BC exposure covariables. The BC covariables represent chronic exposure from birth up to the end of 2019 (circle) and long-term exposure over one year before the day of the examination (square). The first group (blue) represents the initial models, while the second group represents the models corrected for residential green space exposure in a 1,000m buffer (grey) and the third group represents the models corrected for the daily average hours of screen time, the mode of commute to school, the exposure to parental smoking and the residential heating source exposure (black). **A-C** Domain of sustained attention, **D-F** Domain of short-term memory and processing speed. **A** Represents the number of false positive answers in the CPT, **B** the mean reaction time in milliseconds during the CPT and **C** the percentage of correct answers in the CPT, all in association with the BC exposure variables. **D** Represents the percentage of correct answers of the SDMT, **E** the number of correct replications in the forward sequence of the Digit SPAN test and **F** the number of correct replications in the reverse sequence of the Digit SPAN test, all in association with the BC exposure variables. The multiple linear regression models were corrected for BMI, age at follow-up, maternal education, average hours of sleep and the participant's mental health status. Results are expressed as regression coefficients with their 95% confidence interval error bars for an IQR increase in the black carbon exposure variable. Significant associations at 0.05 are indicated by an asterisk

DISCUSSION

In this study, we investigated a population created from participants of the CHAIR study and ENVIR*ON*AGE birth cohort. These participants were school-going children between the ages of ten and thirteen. In this investigation, we found that chronic and long-term exposure to black carbon particles in these participants were associated with decreased performance in several cognitive tests. These associations remained significant after adjustment for sex, BMI, age at follow-up, maternal education, average hours of sleep and the participant's mental health status as estimated through the SDQ and KIDSCREEN-27.

Decreases in cognitive performance were seen in the neurocognitive domain of sustained attention related to BC exposure.

We found an increase in the number of false positive answers produced and a decrease in the mean reaction time for answering in the Continuous Performance Test when exposed to higher concentrations of BC over the year before the examination and the chronic exposure from birth until the end of 2019. These results fall under the neurocognitive domain of sustained attention and indicate a decreased performance. This pattern is in line with an increase in spontaneous behavior, resulting in more erroneous answers (34).

Although not all associations between black carbon exposure and the separate cognitive outcomes were significant, the results were consistent as an overall increase in exposure led to reduced cognitive performance for the domain of sustained attention.

For the domain of short-term memory and processing speed, the results were more variable in our study, especially for the percentage of correct answers in the Symbol-Digit Modalities Test. Regarding the results of the Digit SPAN test in both the forward and reverse sequence, several significant associations were found, albeit with opposite results of the expected effect. For example, the number of correct replications in the forward Digit SPAN test was significantly increased in association with chronic and one-year BC exposure, while a decrease would be expected. However, when looking at the actual effect on the cognitive performance for that test, the significant results indicated an increase between 0.17 and 0.37 of correct answers. Regarding these effects, the biological significance can be considered minimal despite the effect being statistically significant in this study due to the small size.

Several sensitivity analyses were conducted to assess the robustness of the models and results. Several significant associations were robust to the additional inclusion of exposure to green space, screen time, mode of commute, exposure to parental smoking and type of residential heating source, as well as to the total correction for the four last factors. However, some exceptions should be noted.

The number of false positive answers for the CPT in association with one-year BC exposure became insignificant after the inclusion of residential green space exposure (100m, 300m, 500m and 1,000m), while the association with chronic BC exposure remained borderline significant. Since green space exposure separately was found to be significantly associated with the same cognitive outcomes, indicating amelioration of the cognitive performance, a reason for the loss in significance here can be the occurrence of multicollinearity. Multicollinearity problems can undermine the significance of the independent variable, here being the number of false positive answers (35).

Secondly, the association between the mean reaction time in the CPT and one-year BC exposure showed to be less robust, becoming insignificant in the models with additional correct for green space exposure and the total correction. Therefore, these results are less reliable, which should be taken into consideration when formulating a conclusion. More research is needed to investigate this specific cognitive outcome for long-term exposure. However, the association with chronic exposure remained robust throughout all sensitivity analyses.

Finally, the associations between the results of the Digit SPAN test and both BC exposures varied in robustness as well. This further contributes to the notion that the significant results for the outcomes of the Digit SPAN test in this study are not biologically relevant.

Overall, our results coincide with several previous studies investigating the effects of BC and traffic-related air pollution exposure on cognition.

In a study investigating a prospective birth cohort of Boston school children between the ages of nine and twelve, BC exposure was associated with decreases in cognitive outcomes regarding attention and memory (22). This study also showed associations between BC exposure and decreased cognitive performance for verbal and nonverbal intelligence, which were not found in our study, together with an effect on memory.

Another study in Boston found an association between BC exposure and decreased mean reaction times in the CPT (36), which was indicated by our results as well.

In a study investigating mother-child pairs from a birth cohort in Massachusetts around the age of eight, childhood BC exposure was associated with decreased verbal IQ, however after adjustment for several socioeconomic factors this association was attenuated (23).

Overall, previous studies show adverse effects of BC exposure on attention, as indicated in our study, which remained significant after adjustment for common covariates and socioeconomic factors.

Several mechanisms could explain the association between exposure to BC particles and decreased cognitive performance.

Firstly, it was shown that ultrafine particles, which include BC particles, can reach the brain through the olfactory nerve, without entering the lungs (11). These particles can cause increased oxidative stress in the brain (37), comparable to the effect in other tissues (38-40). Additionally, BC particles are heterogenous and commonly have several metals adsorbed to their surface, which can further increase the generation of oxidative stress (39) and alter dopamine function (37,41). Additional mechanisms are chronic microglial stimulation (39), increased generation of inflammatory responses (42) and an altered innate immune response (12).

Air pollution exposure in general can also indirectly lead to increased inflammation in the brain, by causing increased pro-inflammatory responses in the respiratory and cardiovascular systems (43,44). These increased responses can lead to increased systemic inflammation, followed by changes in inflammatory responses in the brain (44,45).

The increases in oxidative stress and inflammatory reactions in general, could result in an impact on the development of the nervous system and cognitive abilities as air pollution is considered a developmental neurotoxicant. Children represent an especially vulnerable group because, at that moment in life, the higher executive functions of cognition are particularly vulnerable to environmental exposures (4).

There are a few limitations to our study. For the multiple linear regression analyses, we were not able to include the effect of traffic noise exposure on cognition, due to limitations in data availability.

Previous studies investigated this association and suggest that some form of impact on cognition exists, indicated by a negative impact on attention in 8-year-old children (46). Here, the inattention of the child was based on a questionnaire as part of the Rating Scale for Disruptive Behavior Disorders, filled in by the mother.

In another study, the effects of air pollution exposure remained unchanged for cognitive outcomes belonging to the memory domain while correcting for traffic noise exposure (47). However, when traffic noise was investigated in interaction with air pollution exposure, a significant effect on reaction time for two cognitive tasks was observed.

Cognitive outcomes belonging to the domain of sustained attention were shown to be affected by BC exposure in our study. Further adjustment for traffic noise exposure could lead to different results. However, based on previous literature, we believe that effect to be limited due to the high intercorrelation between traffic-related air pollution and traffic noise.

A second limitation of this study is the limited sample size and the potential for residual confounding. We adjusted the multiple linear regression models for many covariates, however, the associations could still originate from residual or unmeasured confounding. Nonetheless, our models included most of the covariates that are commonly used to correct when investigating cognition.

Another limitation is tied to the response population of both study populations. Regarding the participants, parents and children were recruited based on their own volition and interest, which could lead to biased representativeness of the general population. Therefore, care should be taken in the interpretation of the results towards the population as a whole.

The exposure measures that were used are also subject to limitations. Both the BC exposure variables and green space exposures were based on the participants' residential address. Therefore, exposures for example during commuting, hobbies and at school are not taken into account. However, several covariates that were included in the sensitivity analyses allow partial estimation of this exposure. Screen time was included as a covariate and this factor can be used to investigate the participant's sedentary behavior. Therefore, this factor could partially explain the degree of exposure to outdoor air pollution and green space during hobbies, since people with higher sedentary behavior go less outside. The inclusion of screen time did not alter the interpretation of the significant associations, likely limiting the effect that exposure during performing hobbies would have. To partially take into account the effect of commuting, the mode of transport to school was added as a covariate, which also did not alter the associations significantly.

However, our study also has several strengths.

Firstly, we used computerized and standardized cognitive assessments that are independent of language and are less likely to be affected by subjective answers, as seen in questionnaire-based cognitive assessments.

Secondly, the risk of bias for the associations between BC exposure and cognitive performance was minimized through the statistical approaches used. We performed several PCAs to mitigate collinearity issues and investigate trends in the associations. The interpretation of the PCs was similar to the separate cognitive outcomes, which strengthens the associations found for the separate cognitive outcomes. Additionally, we tested the robustness of our results in several sensitivity analyses, where most of the associations did not change significantly in direction or effect size.

Lastly, we used information on multiple traffic and BC exposure variables to investigate the adverse effects on cognitive performance.

Since the adjustment of type 1 errors through multiple testing correction is based on the assumption of independence of tests, we did not adjust for multiple comparisons in the MLR models for the separate cognitive outcomes, due to the high degree of correlation between the cognitive outcomes as well as the BC exposure variables. However, the MLR for the PCs were corrected for multiple comparison with Bonferroni correction, based on the number of investigated PCs per domain, since the PCs of the two neurocognitive domains are independent.

The BC exposure in this study was estimated with validated spatiotemporal LUR models. However, these models have several weaknesses (48), such as limited temporal resolution and difficulties predicting acute exposures for estimating exposure in highly urbanized areas, due to spatial variability. These drawbacks can lead to underestimation of the exposure and the potential health risks. For further research, it would be important to refine these exposure measurements. By linking the modeled exposure to measurements of internal exposure markers in biological tissues and fluids, such as urine and blood these constraints could be circumvented, which would lead to more accurate assessments of the impact of BC exposure on health.

CONCLUSION

In conclusion, this study provides results that indicate the detrimental effects of BC exposure on neurocognitive performance in children. Here, higher BC exposure was associated with a decreased performance in cognitive tests investigating the neurocognitive domain of sustained attention. The impact on cognitive performance could reflect a decreased cognitive development. Later in life, this could have consequences on the academic achievement of highly exposed individuals, as well as on their learning and behavior.

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SUPPLEMENTARY MATERIAL

Supplemental Table 1 – Characteristics of the first and second principal components for the neurocognitive domain of sustained attention, the neurocognitive domain of short-term memory and processing speed and the five scored domains of the KIDSCREEN-27 questionnaire.

Principal Component	Eigenvalue PC1 (% explained variance)	Eigenvalue PC2 (% explained variance)	Included covariate	Eigenvector PC1	Eigenvector PC2
Sustained attention	52.6	28.6	% correct CPT	-0.53	0.72
			Mean reaction time CPT	-0.54	-0.69
			Number of false positive answers CPT	0.65	0.01
Short-term memory and processing speed	48.4	30.8	% correct SDMT	-0.40	-0.90
			Number of correct answers forward SPAN	-0.67	0.15
			Number of correct answers reverse SPAN	-0.63	0.41
KIDSCREEN-27	61.7	16.2	Autonomy	-0.35	0.75
			Peers	-0.45	-0.41
			Physical	-0.48	0.15
			Psychological	-0.48	0.15
			School	-0.46	-0.48