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Recent *versus* chronic exposure to particulate matter air pollution in association with neurobehavioral performance in a panel study of primary schoolchildren

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ABSTRACT

Children's neuropsychological abilities are in a developmental stage. Recent air pollution exposure and neurobehavioral performance are scarcely studied. In a panel study, we repeatedly administered to each child the following neurobehavioral tests: Stroop Test (selective attention) and Continuous Performance Test (sustained attention), Digit Span Forward and Backward Tests (short-term memory), and Digit-Symbol and Pattern Comparison Tests (visual information processing speed). At school, recent inside classroom particulate matter $\leq$ 2.5 or 10 μm exposure ($PM_{2.5,}$ PM_{10}) was monitored on each examination day. At the child's residence, recent (same day up to 2 days before) and chronic (365 days before examination) exposures to $PM_{2.5}$, PM_{10} and black carbon (BC) were modeled. Repeated neurobehavioral test performances (n=894) of the children (n=310) reflected slower Stroop Test (p=0.05) and Digit-Symbol Test (p=0.01) performances with increasing recent inside classroom $PM_{2.5}$ exposure. An interquartile range (IQR) increment in residential outdoor $PM_{2.5}$ exposure was associated with a total latency of 0.087 seconds (SE: ± 0.034; p=0.01) in the Pattern Comparison Test. Regarding chronic exposure at residence, an IQR increment of $PM_{2.5}$ exposure was associated with slower performances in the Continuous Performance (9.45 ± 3.47 msec; p=0.007) and Stroop Tests (59.9 ± 26.5 msec; p=0.02). Similar results were obtained for PM_{10} exposure. In essence, we showed differential neurobehavioral changes robustly and inversely associated with recent or chronic ambient exposure to PM air pollution at residence, i.e., with recent exposure for visual information processing speed (Pattern Comparison Test) and with chronic exposure for sustained and selective attention.

KEYWORDS

particulate matter; air pollution; neurobehavior; children; repeated measures

ABBREVIATIONS

particulate matter with a diameter ≤ 10 or 2.5 μm (PM_{10}, $PM_{2.5}$); black carbon (BC); interquartile range (IQR); residential proximity to major roads (RPMR); neurobehavioral evaluation system (NES);

1. INTRODUCTION

Polluted air is a complex mixture of water vapor, gases, and solid particles. Evidence is growing that ambient air pollution exposure may be neurotoxic[1]. When small particles (particulate matter with a diameter < 10 µm, PM_{10}) deposit in the lungs, they may trigger the release of inflammatory mediators in the systemic circulation[2,3]. Fine particles (PM < 2.5 µm, $PM_{2.5}$) can also translocate into the circulation leading to increased systemic inflammation[4], which may adversely affect the central nervous system (CNS)[5,6]. Besides the link with systemic inflammation, particles < 0.1 µm might also cause harm to the CNS in a more direct way by crossing the blood-brain-barrier or by retro-axonal translocation via the olfactory nerve[7,8]. Experimental studies in rodents demonstrated a wide range of biological CNS effects of air pollution exposure including a pro-inflammatory cytokine response, glial activation, oxidative stress, changes in gene expression, and perturbations of levels and turnover of neurotransmitters[9-14]. Epidemiological studies in adults showed that long-term exposure to traffic-related air pollution may contribute to neurodegenerative diseases, such as Parkinson's and Alzheimer's disease[15,16]. Studies in children suggested that neurotoxic effects of air pollution may translate into observable deterioration of neurobehavioral performance. In children from Boston of approximately 10 years old, average lifetime residential levels of black carbon (BC) were inversely associated with attention, memory, learning, and intelligence[17,18]. In another prospective cohort study, prenatal air pollution exposure as assessed by personal monitoring of polycyclic aromatic hydrocarbons was inversely associated with neurodevelopmental characteristics (intelligence, behavior) in early childhood[19-21]. Furthermore, cross-sectional studies also reported inverse associations between neurobehavioral performance of children and indicators of chronic air pollution exposure[22,23]. Recently, it has been shown that children exposed to high traffic-related air pollution have a smaller enhancement in neurobehavioral development after one year in comparison to

children exposed to low air pollution[24]. We found that traffic exposure in adolescents, as reflected by a composite factor combining information about traffic density, time spent in traffic, and urinary concentration of *trans,trans*-muconic acid, was negatively associated with sustained attention[25].

Despite these studies are suggestive of a neurobehavioral performance deficit associated with fine particle air pollution, there is still insufficient evidence on the consistency of these associations[26]. Neurobehavioral changes associated with recent air pollution exposure (i.e., exposure on the day and a few days before the neurobehavioral examination) have been scarcely studied. The aim of this study was to investigate with repeated measures whether neurobehavioral performance was differently associated with recent *versus* chronic air pollution exposure in a panel of primary schoolchildren.

2. MATERIALS & METHODS

2.1 Study population

This investigation was part of the COGNAC (COGNition and Air pollution in Children) study. Between 2011 and 2013, we invited children (grades three to six) from three primary schools in Flanders (Belgium) to participate. These schools were located in urban areas with a substantial amount of traffic (Figure 1). Typical particulate matter air pollution ($PM_{2.5}$) in the recruitment area was mainly characterized by the following components: elemental carbon (3%), organic mass (20%), sea salt (5%), ammonium (12%), nitrate (21%), ammonium sulfate (18%) and mineral dust (3%)[27].

The parents of the participants filled out a questionnaire to collect information about the current and previous residential addresses, the socioeconomic status of the family, the smoking behavior of the family members, and they provided informed consent for participation. Socioeconomic status was based on the mother's education (up to high school

diploma; college or university diploma) and the highest rank of occupation of either parents (unemployed or unqualified worker; qualified worker, white collar assistant, or teaching staff; self-employed, specialist or member of management). The out-of-school sport activities were defined as "none" (no out-of-school sport activities), "low" (≤ 3 hours per week), "middle' (> 3 to < 6 hours per week) and "high" (≥ 6 hours per week). The study protocol was approved by the medical ethics commissions of Hasselt University and the East-Limburg Hospital.

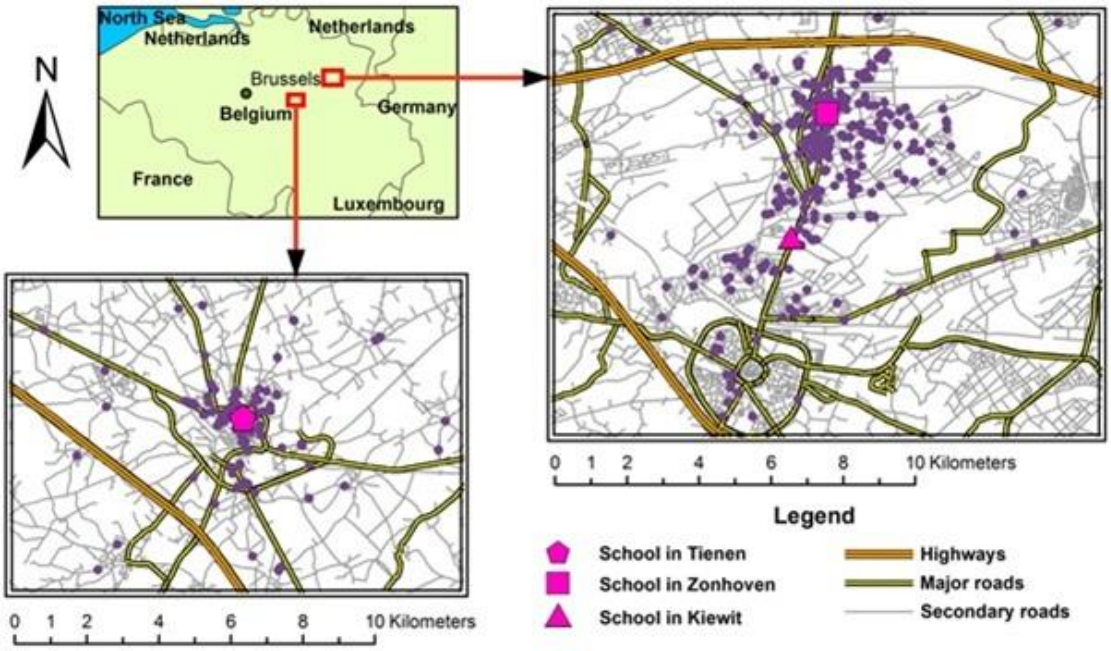

Figure 1. Study area with indication of the school locations in the three municipalities and the road system. Dots represent the residential addresses of the schoolchildren.

In total, 334 children agreed to participate in the study, however 24 had to be removed from the database because of missing data on mother's education and/or occupation of the parents, passive smoking exposure, or residential outdoor exposure. Of the 310 children, 277 (89.3%) were examined three times, 30 (9.7%) two times, and 3 (1%) once, amounting to a total number of 894 examinations. The examinations took place between December 2011 and

February 2014 on Monday, Tuesday, Thursday, and Friday between 9:00 a.m. and 2:00 p.m.. The mean (SD) period of time between two consecutive examinations was 41 (23) days. Each neurobehavioral examination was scheduled for the same time of the day for the same child, but in some cases it was not possible due to school activities. For the same child, the time of the day at which the neurobehavioral examinations took place differed on average (SD) 24 (48) min.

2.2 Assessment of PM air pollution exposure

2.2.1 Air pollution measurements at the schools

At the schools, we used portable devices (AEROCET 531; MetOne Instruments Inc., Grants Pass, OR, USA) to carry out area measurements of particulate matter [PM with a diameter ≤ 2.5 μm ($PM_{2.5}$) and ≤ 10 μm (PM_{10})] inside the classroom on the examination day (Table 1). Continuous air monitoring was carried out from 9 to 12 a.m. as 2 min interval measurements which were averaged and expressed as μg/m³.

2.2.2 Modeled outdoor air pollution and traffic indicators at residence

For the child's residence, we used a spatial temporal interpolation method to model the daily residential exposure levels (μg/m³) of $PM_{2.5}$, PM_{10}, and BC (Table 1). This method takes into account land-cover data obtained from satellite images (CORINE land-cover data set) [28] and pollution data of fixed monitoring stations in combination with a dispersion model [29,30]. The model calculates the daily interpolated exposure concentrations in a high resolution receptor grid based on information from the Belgian telemetric air quality networks, point sources, and line sources. Overall model performance was evaluated by leave-one-out cross-validation and was based on 34 monitoring points for $PM_{2.5}$, 58 for PM_{10}, and 14 for BC. Validation statistics of the interpolation tool gave a spatial temporal explained variance of more than 0.80 for $PM_{2.5}$ [30], 0.70 for PM_{10} [30], and 0.74 for BC [31]. We used this model to estimate the recent

exposure at residence up to 48 hours before the neurobehavioral examination as well as the chronic exposure at residence reflected by the annual mean concentration of the year before the examination. When a child had more than one residential address at the moment of the study, we calculated a weighted average using the proportion of time spent at each location. We calculated also the residential proximity to major roads (RPMR), defined as highways and other national roads, using geographic information system functions (ArcGIS 9.3).

TABLE 1. Overview of the PM air pollution exposure indicator measurements or estimates used for the panel study in schoolchildren.

	$PM_{2.5}$ ($\mu g/m^3$)	**PM_{10}** ($\mu g/m^3$)	**BC** ($\mu g/m^3$)	**RPMR** (m)
Recent exposure:				
At schools on day of examination[a]				
Inside the classroom	×	×		
At residential address[b]				
Lag 0 (day of examination)	×	×	×	
Lag 1 (1 day before examination)	×	×	×	
Lag 2 (2 days before examination)	×	×	×	
Chronic exposure:				
At residential address[b]	×	×	×	×

PM, particulate matter with aerodynamic diameter < 2.5 μm ($PM_{2.5}$) or < 10 μm (PM_{10}); BC, black carbon; RPMR, residential proximity to major road.
[a] Actual air pollution measurements by area sampling in the classrooms.
[b] Estimates of outdoor air pollution by spatial temporal interpolation modeling.

2.3 Assessment of traffic noise

A GIS-based noise model including the Flemish street and railway networks was used to estimate traffic noise levels in 5 dB(A)-intervals according to the European Noise Directive (2002/49/EC)[32]. The modeling of road noise level included road traffic intensity, vehicle-type-specific traffic density, type of street surface, small-scale topography of the area, and the presence or dimensions of buildings and reflecting objects. Railway noise modeling included the amount of passing trains, type of trains, speed, small-scale topography of the area, and the presence or dimensions of buildings and reflecting objects. Weighted equivalent noise levels in dB(A) for traffic over day-time (based on the weighted yearly average noise level between

7 a.m. to 7 p.m., and 7 p.m. to 11 p.m.,) and at night (yearly average noise level between 11 p.m. and 7 a.m) were modeled. Exposure to traffic noise was categorized as ≤ 55 dB, > 55 to ≤ 60 dB, and > 60 dB.

2.4 Neurobehavioral tests

The neurobehavioral examination lasted approximately 20 min. The room where the examinations took place was quiet, appropriately lighted, and ventilated. We administered a computer version of the Stroop Test [33] and the following four tests from the Neurobehavioral Evaluation System 3 (NES3) battery: Continuous Performance, Digit Span, Digit-Symbol, and Pattern Comparison [34,35].

In the Stroop Test (selective attention domain), four buttons are displayed on the screen (yellow, red, blue, and green). During the test, the name of one of these colors appears on the screen printed in a different color than the name. The task is to touch as fast as possible the button that has the same color as the name, ignoring the color of the printed name. Before the test, eight practice trials take place followed by 48 test trials. The mean reaction time is the average time that passed between the appearance of the name and touching the correct button. This performance indicator was only calculated when the total number of test trails with wrong responses was smaller than or equal to 16.

In the Continuous Performance Test (sustained attention domain), silhouettes of animals (e.g., a cat) are displayed on the screen, one at the time and each for approximately 200 msec. The task is to immediately respond to the cat's silhouette in this case by pressing the spacebar, but not the silhouette of another animal. A new silhouette is displayed each 1000 msec.

The Digit Span Test (short-term memory domain) consists of two parts. In the first part, the task is to reproduce a series of digits after an auditory presentation in the order of the presentation. The test starts with a sequence of three digits. In case of a correct answer, a one

digit longer sequence is presented. The test continues until two consecutive incorrect answers are given. In the second part of the test, the task is to reproduce the digits in the reverse order of the presentation.

In the Digit-Symbol Test (visual information processing speed domain), a row of 9 symbols paired with 9 digits is shown at the top of the screen. The same 9 symbols but in a different order are displayed at the bottom of the screen. During the test 27 digits appear consecutively on the screen. When a digit is shown, the task is to indicate as fast as possible the symbol which is paired with this digit in the row of symbols at the bottom of the screen. A new digit appears only after the correct symbol has been indicated.

In the Pattern Comparison Test (visual information processing speed domain), three matrices consisting of 10 × 10 blocks are shown. Two of them are identical. The task is to indicate which pattern is different from the other two patterns. The test includes 25 items.

We used as performance parameters, the mean reaction time in the Continuous Performance Test and the Stroop Test, the maximum span forward and backward in the Digit Span Test, and the total latency or the average latency in the Digit-Symbol Test and Pattern Comparison Test respectively.

2.5 Statistical analysis

We performed recent and chronic PM exposure-response analyses using mixed effects models that included random effects for each participant across the neurobehavioral examinations (SAS, version 9.2; SAS Institute Inc., Cary, NC, USA). This method allows each participant to serve as his/her own control over time and eliminates within-subject confounding by personal characteristics that do not change over time. We express the effect estimates for an interquartile range (IQR) increment in recent ($PM_{2.5}$, PM_{10}) and chronic ($PM_{2.5}$, PM_{10}, BC) exposures or living twice as close to major roads (residential proximity to major roads: RPMR). The effect estimates are presented as change in msec for reaction time of the

Continuous Performance Test and the Stroop Test, change in number of digits for the Digit Span Forward and Backward Tests, and change in seconds for the latency of the Digit-Symbol Test and Pattern Comparison Test. All analyses were adjusted for *a priori* chosen covariates including sex, age (linear and quadratic term), education of the mother, highest rank of occupation of either parents, passive smoking, out-of-school sport activities, traffic noise (weighted noise during day), hours of computer screen time per week, and day of the week. To capture the non-linear effect of age, we included a quadratic term. Furthermore, a time-varying covariate was included for the measurement occasion (relatedness of examination periods) which is an important predictor of neurobehavioral performance due to the learning effect. In the chronic exposure models, we additionally adjusted for the month of examination to account for seasonality. Since differences are possible for between- and within-subject air pollution effects, we fitted explicit models for recent exposure which included terms for between- and within-subject exposure effects. We reported the within effects. Finally, we tested in a sensitivity analysis the robustness of the findings and replaced residential weighted day-time noise levels by weighted night-time levels.

3. RESULTS

3.1 Study population characteristics, neurobehavioral performances, and exposure to PM air pollution

Characteristics and neurobehavioral test performances of the study group are summarized in Table 2. The number of boys and girls for the three schools combined was approximately equal. The mean (SD) age was 10.2 (1.3) years. The majority (60.9%) of the children's mothers had a college or university diploma and 41 participants were exposed to passive smoking. 41.3% of the children participated up to three hours per week in out-of-school sport activities. For residential traffic noise during the day, 78.4% were exposed to $\leq$ 55 dB, 13.2%

to >55 to ≤ 60 dB, and 8.4% to >60 dB. During the night, 96.8% were exposed to ≤ 55dB and 3.2% to > 55 dB residential traffic noise.

Over the examination days, the neurobehavioral test performances averaged ± SD for sustained attention 593 ± 51.2 msec in the Continuous Performance Test and 1417 ± 377 msec for selective attention in the Stroop Test, for short-term memory 5.26 ± 0.94 and 4.03 ± 0.97 digits in the Digit Span Forward and Backward Tests respectively, and for visual information processing speed 123 ± 23.5 sec and 4.18 ± 1.01 sec for total latency and average latency in the Digit-Symbol Test and Pattern Comparison Test respectively.

TABLE 2. Demographic characteristics of the participants.

	N=310
Schools	
Kiewit	69 (22.3%)
Tienen	62 (20.0%)
Zonhoven	179 (57.7%)
Demographic characteristics	
Boys	158 (50.9%)
Age	10.2 ± 1.3
Level of education of the mother	
Up to high school diploma	121 (39.1%)
College or university diploma	189 (60.9%)
Most prestigious category of occupation of either parents,	
Unemployed or not qualified worker	20 (6.4%)
Qualified worker, white-collar assistant, or teaching staff	131 (42.3%)
Self-employed, specialist, or member of management	159 (51.3%)
Passive smoking,	41 (13.2%)
Out-of-school sport activities	
None	36 (11.6%)
≤ 3 hours/week	128 (41.3%)
> 3 to < 6 hours/week	87 (28.1%)
≥ 6 hours/week	59 (19.0%)
Computer screen use, hours per week	4.3 ± 3.8

Values represent number (%) or arithmetic mean ± SD.

The median (interquartile range; IQR) concentrations of PM air pollution inside the classrooms at the schools were, for $PM_{2.5}$ 5.14 (8.85) μg/m^3, and for PM_{10} 33.5 (55.2) μg/m^3 (Table 3). Table 3 also shows the modeled estimates of recent residential ambient air exposure to $PM_{2.5}$, PM_{10}, and BC from Lag 0 to Lag 2. Chronic ambient PM exposure was characterized by the median residential exposure (IQR) over the year before the examination [15.7 (1.16) μg/m^3 for $PM_{2.5}$, 21.3 (1.61) μg/m^3 for PM_{10}, and 1.54 (0.20) μg/m^3 for BC] and median distance (IQR) from residence to major roads [RPMR, 333 (669) m].

TABLE 3. Recent and chronic exposure characteristics (N=310).

	Median	25th percentile	75th percentile	IQR
Recent (at schools)[a]				
$PM_{2.5}$, μg/m^3	5.14	2.80	11.6	8.85
PM_{10}, μg/m^3	33.5	20.9	76.1	55.2
Recent (at residence)[b]				
$PM_{2.5}$, μg/m^3				
Lag 0	16.5	9.10	28.0	18.9
Lag 1	15.2	8.85	27.5	18.7
Lag 2	15.5	8.90	31.8	22.9
PM_{10}, μg/m^3				
Lag 0	21.2	13.0	32.2	19.2
Lag 1	19.5	13.0	30.9	17.9
Lag 2	18.9	13.0	36.2	23.2
BC, μg/m^3				
Lag 0	1.55	1.00	2.25	1.25
Lag 1	1.36	1.03	2.03	1.00
Lag 2	1.52	0.93	2.30	1.37
Chronic (at residence)[b]				
$PM_{2.5}$, μg/m^3	15.7	15.2	16.4	1.16
PM_{10}, μg/m^3	21.3	20.7	22.3	1.61
BC, μg/m^3	1.54	1.43	1.63	0.20
RPMR, m	333	133	832	699

PM, particulate matter with aerodynamic diameter < 2.5 μm ($PM_{2.5}$) or < 10 μm (PM_{10}); BC, black carbon; RPMR, residential proximity to major roads.

[a] Air pollution at school is obtained by area sampling in the classrooms and averaged over the examination days.

[b] Average ambient air pollution at the residential address over different periods before examination is obtained by spatial temporal interpolation modeling.

3.2 Associations between recent PM exposure and neurobehavioral performance

For the sustained attention (Continuous Performance Test) and short-term memory (Digit Span Forward and Backward Tests) domains, the repeated neurobehavioral test performances within the same child were not associated with recent inside classroom exposure ($PM_{2.5}$, PM_{10}) at school on the examination day (Table 4). Similarly, no associations were shown for recent exposure at residence ($PM_{2.5}$, PM_{10}, BC) on the examination day (Lag 0), one day before (Lag 1), and two days (Lag 2) before (Table 5). For selective attention, recent inside classroom $PM_{2.5}$ and PM_{10} exposures were significantly associated with the Stroop Test showing a 42.7 msec longer mean reaction time [95% confidence interval (CI): -0.40 to 85.8, p=0.05] for an IQR increment in $PM_{2.5}$ exposure (Table 4). The corresponding estimate for recent inside PM_{10} exposure was 50.2 msec (95% CI: 8.55 to 91.8, p=0.02).

For the visual information processing speed domain, significant associations were found between the Digit-Symbol Test performance and recent inside classroom $PM_{2.5}$ or PM_{10} exposure (Table 4). An IQR increment in $PM_{2.5}$ exposure showed a total latency increase of 2.05 seconds (95% CI: 0.43 to 3.66; p=0.01). The corresponding result for PM_{10} was 1.9 seconds (p=0.02). The results of the Pattern Comparison Test were adversely associated with recent residential $PM_{2.5}$ and PM_{10} exposure the day of the examination (Lag 0) (Table 5). For an IQR increment of $PM_{2.5}$ exposure, the average latency increased by 0.087 seconds (95% CI: 0.02 to 0.15; p=0.01), while the corresponding estimate for PM_{10} was 0.081 seconds (p=0.01). The days before the examination, i.e., at Lag 1 and Lag 2, an IQR increment of $PM_{2.5}$ exposure also showed an increase in average latency of the Pattern Comparison Test with 0.066 seconds (p=0.04) and 0.079 seconds (p=0.03) respectively. For BC, exposure the day before examination (Lag 1) was also associated with the Pattern Comparison Test (0.051 seconds in average latency, p = 0.04). For the other recent inside classroom and residential

outdoor exposure indicators, no associations were found with the Digit-Symbol or Pattern Comparison Tests (Table 4 and 5).

The associations described above were independent of the covariates sex, age (linear and quadratic), education of the mother, highest rank of occupation of either parents, passive smoking, out-of-school sport activities, traffic noise during day, hours per week spent behind a computer, day of the week, and relatedness of the different examination periods. Additional adjustment for chronic residential exposure as well as replacement of the traffic noise during day by traffic noise during night did not change the results.

TABLE 4. Associations between neurobehavioral test performances and recent inside classroom PM exposures.

Neurobehavioral Test	Recent indoor $PM_{2.5}$			Recent indoor PM_{10}		
	β	95% CI	p-value	β	95% CI	p-value
Attention						
Continuous Performance	-1.29	-5.51 to 2.93	0.55	-2.16	-6.26 to 1.94	0.30
Stroop	42.7	-0.40 to 85.8	0.05	50.2	8.55 to 91.8	0.02
Short-term Memory						
Digit Span Forward	-0.05	-0.16 to 0.05	0.32	-0.002	-0.10 to 0.10	0.97
Digit Span Backward	-0.06	-0.18 to 0.06	0.35	-0.03	-0.15 to 0.08	0.57
Visual Information Processing Speed						
Digit-Symbol	2.05	0.43 to 3.66	0.01	1.9	0.34 to 3.42	0.02
Pattern Comparison	-0.01	-0.11 to 0.09	0.79	-0.03	-0.13 to 0.07	0.54

PM, particulate matter with aerodynamic diameter < 2.5 µm ($PM_{2.5}$) or < 10 µm (PM_{10}); the metric of $PM_{2.5}$ and PM_{10} is µg/m³.
For an interquartile increment in recent indoor exposure to $PM_{2.5}$ (8.85 µg/m³) or PM_{10} (55.2 µg/m³), the effect estimates are represented as msec change for the Continuous Performance Test and the Stroop Test, change in number of digits for the Digit Span Forward and Backward Tests, and change in sec of latency for the Digit-Symbol and Pattern Comparison Tests. All analyses were adjusted for sex, age (linear and quadratic), education of the mother, occupation of the parents, passive smoking, out-of-school physical activity, traffic noise, hours spent after computers, day of the week, and relatedness of the examination periods.

TABLE 5. Associations between neurobehavioral test performances and recent ambient PM exposures at residence.

Attention									
Recent residential exposure	**Continuous performance**					**Stroop**				
	β	95% CI			p-value	β	95% CI			p-value
$PM_{2.5}$, lag 0	-1.57	-4.45	to	1.32	0.29	-16.7	-46.4	to	12.9	0.27
$PM_{2.5}$, lag 1	-0.59	-3.31	to	2.14	0.67	-20.3	-48.3	to	7.66	0.15
$PM_{2.5}$, lag 2	-0.11	-3.11	to	2.89	0.94	-26.0	-56.4	to	4.46	0.09
PM_{10}, lag 0	-1.27	-3.99	to	1.45	0.36	-13.8	-41.8	to	14.1	0.33
PM_{10}, lag 1	-0.47	-2.82	to	1.89	0.70	-12.2	-36.4	to	12.1	0.33
PM_{10}, lag 2	-0.10	-2.94	to	2.74	0.94	-22.4	-51.1	to	6.33	0.13
BC, lag 0	-0.48	-3.17	to	2.20	0.72	-4.48	-32.0	to	23.1	0.75
BC, lag 1	0.27	-1.83	to	2.37	0.80	-3.96	-25.7	to	17.8	0.72
BC, lag 2	0.66	-1.84	to	3.16	0.61	-3.80	-29.6	to	22.0	0.77
Memory										
	Digit Span forward					**Digit Span backward**				
	β	95% CI			p-value	β	95% CI			p-value
$PM_{2.5}$, lag 0	-0.050	-0.124	to	0.024	0.18	0.008	-0.075	to	0.092	0.84
$PM_{2.5}$, lag 1	-0.056	-0.126	to	0.015	0.12	-0.028	-0.11	to	0.051	0.49
$PM_{2.5}$, lag 2	-0.071	-0.149	to	0.007	0.07	0.006	-0.081	to	0.093	0.89
PM_{10}, lag 0	-0.046	-0.116	to	0.024	0.20	-0.0031	-0.082	to	0.075	0.94
PM_{10}, lag 1	-0.045	-0.106	to	0.016	0.15	-0.034	-0.103	to	0.034	0.33
PM_{10}, lag 2	-0.067	-0.140	to	0.006	0.07	0.000	-0.082	to	0.082	0.99
BC, lag 0	-0.065	-0.134	to	0.003	0.06	0.019	-0.059	to	0.096	0.64
BC, lag 1	-0.025	-0.080	to	0.029	0.36	-0.025	-0.086	to	0.036	0.42
BC, lag 2	-0.051	-0.116	to	0.014	0.12	0.013	-0.060	to	0.086	0.72
Visual processing speed										
	Digit Symbol					**Pattern comparison**				
	β	95% CI			p-value	β	95% CI			p-value
$PM_{2.5}$, lag 0	-0.77	-1.88	to	0.33	0.17	0.087	0.020	to	0.15	0.01
$PM_{2.5}$, lag 1	-0.95	-2.00	to	0.10	0.08	0.066	0.004	to	0.13	0.04
$PM_{2.5}$, lag 2	-0.80	-1.95	to	0.35	0.17	0.079	0.010	to	0.15	0.03
PM_{10}, lag 0	-0.50	-1.54	to	0.54	0.35	0.081	0.019	to	0.14	0.01
PM_{10}, lag 1	-0.69	-1.60	to	0.21	0.13	0.046	-0.009	to	0.10	0.10
PM_{10}, lag 2	-0.73	-1.82	to	0.36	0.19	0.057	-0.009	to	0.12	0.09
BC, lag 0	-0.61	-1.64	to	0.42	0.24	0.041	-0.022	to	0.103	0.20
BC, lag 1	-0.78	-1.59	to	0.03	0.06	0.051	0.003	to	0.099	0.04
BC, lag 2	-0.50	-1.47	to	0.47	0.31	0.006	-0.053	to	0.064	0.85

PM, particulate matter with aerodynamic diameter < 2.5 μm ($PM_{2.5}$) or < 10 μm (PM_{10}); BC, Black carbon; the metric of $PM_{2.5}$, PM_{10}, and BC is μg/m³.

For an interquartile increment in recent (Lag 0, 1, and 2) indoor exposure to $PM_{2.5}$ (18.9, 18.7, and 22.9 μg/m³), PM_{10} (19.2, 17.9, and 23.2 μg/m³) or BC (1.25, 1.00, and 1.37 μg/m³), the effect estimates are represented as msec change for the Continuous Performance Test and the Stroop Test, change in number of digits for the Digit Span Forward and Backward Tests, and change in sec of latency for the Digit-Symbol and Pattern Comparison Tests. All analyses were adjusted for sex, age (linear and quadratic), education of the mother, occupation of the parents, passive smoking, out-of-school physical activity, traffic noise, hours of computer screen time per week, day of the week, and relatedness of the examination periods.

3.3 Associations between chronic PM exposure and neurobehavioral performance

In the models studying chronic exposure, we accounted for the following covariates: sex, age (linear and squared term), education of the mother, occupation of the parents, passive smoking, out-of-school sport activities, traffic noise during day , hours per week spent behind a computer, day of the week, month of examination and relatedness of the examination periods. Independent of these covariates, chronic exposure to $PM_{2.5}$ was adversely associated with the attention domain (Continuous Performance and Stroop Tests). For an IQR increment of chronic $PM_{2.5}$ exposure, the reaction time increased by 9.45 msec (95% CI: 2.59 to 16.3; p=0.007) for the Continuous Performance Test and by 59.9 msec (95% CI: 8.1 to 111.6; p=0.02) for the Stroop Test. For PM_{10}, the estimates were in the same direction (Table 6). For BC exposure, we only observed a tendency towards significance for the Continuous Performance Test (5.72 msec; 95% CI: -0.34 to 11.8; p = 0.06) and for residential proximity to major roads (RPMR) no significant associations were found with both attention tests. A sensitivity analysis in which traffic noise during day was replaced by traffic noise during night did not change the main results. For the short-term memory domain, chronic exposures to $PM_{2.5}$, PM_{10}, BC and residential proximity to major roads did not show significant associations with both short-term memory tests (Table 6). For the visual information processing speed domain, none of the chronic exposure indicators ($PM_{2.5}$, PM_{10}, BC, and RPMR) was associated with the performances of the Digit-Symbol and Pattern Comparison Tests (Table 6).

TABLE 6: Associations between neurobehavioral test performances and chronic ambient PM exposures at residence.

	Attention									
Chronic	**Continuous Performance Test**					**Stroop Test**				
exposure	β	95% CI			p-value	β	95% CI			p-value
$PM_{2.5}$	9.45	2.59	to	16.3	0.007	59.9	8.1	to	111.6	0.02
PM_{10}	8.66	2.50	to	14.8	0.006	76.5	29.3	to	123.6	0.002
BC	5.72	-0.34	to	11.8	0.06	6.7	-38.4	to	51.9	0.77
RPMR	1.92	-1.0	to	4.85	0.20	0.90	-20.6	to	22.4	0.93
	Short-term memory									
	Digit Span Forward Test					**Digit Span Backward Test**				
	β	95% CI			p-value	β	95% CI			p-value
$PM_{2.5}$	-0.025	-0.15	to	0.10	0.70	0.057	-0.071	to	0.18	0.38
PM_{10}	-0.063	-0.18	to	0.057	0.30	0.057	-0.064	to	0.18	0.35
BC	0.025	-0.09	to	0.14	0.66	0.10	-0.011	to	0.20	0.08
RPMR	-0.047	-0.10	to	0.005	0.08	-0.043	-0.095	to	0.009	0.11
	Visual information processing speed									
	Digit-Symbol Test					**Pattern Comparison Test**				
	β	95% CI			p-value	β	95% CI			p-value
$PM_{2.5}$	2.1	-0.65	to	4.91	0.13	0.050	-0.089	to	0.19	0.48
PM_{10}	2.09	-0.39	to	4.57	0.10	0.023	-0.103	to	0.15	0.72
BC	0.50	-1.99	to	2.99	0.69	0.065	-0.06	to	0.19	0.30
RPMR	0.39	-0.79	to	1.58	0.51	0.0002	-0.057	to	0.057	1.00

PM, particulate matter with aerodynamic diameter < 2.5 µm ($PM_{2.5}$) or < 10 µm (PM_{10}); BC, black carbon; RPMR, residential proximity to major roads. The metric of $PM_{2.5,}$ $PM_{10,}$ and BC is µg/m³ and residential proximity to major roads (RPMR) is expressed in m.

For an interquartile increment in chronic exposure to $PM_{2.5}$ (1.16 µg/m³), PM_{10} (1.61 µg/m³), and BC (0.20 µg/m³) or for living twice as close to major roads, the effect estimates are represented as msec change for the Continuous Performance Test and the Stroop Test, change in number of digits for the Digit Span Forward and Backward Tests, and change in sec of latency for the Digit-Symbol and Pattern Comparison Tests. All analyses were adjusted for sex, age (linear and quadratic), education of the mother, occupation of the parents, passive smoking, out-of-school physical activity, traffic noise, hours of computer screen time per week, day of the week, and relatedness of the examination periods.

4. DISCUSSION

The CNS of schoolchildren and thus also their neurobehavioral performances are still in a stage of development and may be vulnerable to both recent and chronic PM air pollution. In our panel study of children with repeated measures of neurobehavioral performances, neither recent nor chronic PM exposure did affect short-term memory. However, other findings indicated consistent negative associations of selective attention (Stroop Test) with both recent classroom and chronic ambient residential PM exposure, while decreased sustained attention was associated only with chronic ambient PM exposure at residence. Visual information processing speed seemed to decrease only in conditions of recent PM exposure, either in the classroom (Digit-Symbol Test) or at residence (Pattern Comparison Test). These associations persisted by taking into account the learning effect over the various examination days and by allowing for sex, age, familial socioeconomic position, out-of-school sport activities, and residential traffic noise (day and night). Some of these results highlighted changes in neurobehavioral test performances in association with PM air pollution exposures well below the current EU standards (annual mean $PM_{2.5}$: 25 µg/m³ and PM_{10}: 40 µg/m³) and just above the current US standard ($PM_{2.5}$: 12 µg/m³).

4.1 Recent PM exposure

In contrast to chronic exposure, the neurotoxic potential of recent exposure to PM air pollution in children has not been thoroughly investigated so far. Our panel study of schoolchildren revealed adverse changes in neurobehavioral test performances associated with an IQR increment of recent PM air pollution exposure, i.e., selective attention (Stroop Test) and visual information processing speed (Digit-Symbol and Pattern Comparison Tests).

These findings may be interpreted in the context of experimental studies which emphasized the involvement of inflammatory events on neurobehavioral functioning.

Administration of bacterial lipopolysaccharide showed in rats a rapid induction of systemic inflammation which strongly impaired memory retrieval in a task thought to require hippocampal pattern separation and context-object discrimination, whereas it did not impair mere memory retrieval in hippocampal dependent tasks[36]. This finding supports the contention that acute neuro-inflammation may impair context discrimination memory via disruption of pattern separation processes in the hippocampus. Another experimental study on short-term (4 h) air pollution exposures showed rapid modulation of genes in the vaso-regulatory pathway of the brain[37]. In a randomized cross-over study of humans exposed to diesel motor exhaust (1 h), a significantly lower brain activity (EEG) has been detected in the left frontal cortex as reflected by increased median power frequency within 30 min of exposure, an effect still detectable until 1 h after exposure stopped[38]. Our observational findings are in line with the hypothesis of PM-induced cerebral inflammation and suggest a prompt neurobehavioral response.

4.2 Chronic PM exposure

As to chronic PM exposure, the two tests of the attention domain (Continuous Performance Test and Stroop Test) were adversely associated with an IQR increment of chronic ambient $PM_{2.5}$ and PM_{10} air pollution at residence.

Several recent studies reported an inverse association between chronic air pollution exposure and attention-related outcomes. Recently, we observed in adolescents a negative association between sustained attention, assessed using the Continuous Performance Test, and traffic exposure as reflected by a composite indicator comprising traffic density, time spent in traffic, and urinary *trans,trans* muconic-acid[25]. In a Boston study of 174 children (boys and girls) between 7 and 14 years of age, attention measured by the Continuous Performance Test was negatively associated with residential concentrations of lifetime BC exposure in boys only[18]. Though, their findings did not remain comparing the highest BC exposure quartile

with the lowest quartile. In our study, we found strong associations between PM air pollution and the Continuous Performance Test, and a negative tendency was observed with chronic BC exposure (p=0.06). A possible explanation for the less pronounced effects of BC compared with particulate matter air pollution might be a potential higher exposure misclassification for BC as these models were built using less measuring points (14 for BC compared to 58 for PM_{10}). A Chinese study reported that children whose school was located in an area with low traffic density performed better in the Continuous Performance Test than those from a school with higher traffic-related air pollution[23]. In an Indian study, the prevalence of ADHD was higher in urban children than in controls living in an area with low air pollution[39]. Another study indicated that the average residential elemental carbon concentrations during the first year of life were associated with a higher risk of hyperactivity at 7 years of age as assessed by Parent Rating Scale of the Behavioral Assessment System for Children[40]. A large study in Barcelona including more than 2,700 children showed that those exposed to high traffic-related air pollution levels at school had over a one-year school period a lower development of their working memory[24].

A plausible explanation of our neurotoxic findings with chronic PM exposure may be linked to alterations in several CNS sub-structures, white matter lesions in cortical areas of the left cerebral hemisphere, and vascular changes [41,42]. Calderón-Garcidueñas and colleagues[43] autopsied highly exposed children and young adults who suddenly died in Mexico City (average annual ambient air $PM_{2.5}$: 35.9 $\mu g/m^3$) and compared their findings with those of "control autopsies" of age-matched persons exposed to lower $PM_{2.5}$ concentrations (< 15 $\mu g/m^3$). The authors demonstrated in the highly exposed group an up-regulation of cyclo-oxygenase 2 (COX2), interleukin 1β (IL1β), and CD14 gene expression in the olfactory bulb, frontal cortex, substantia nigra and vagus nerves as well as disruption of the blood-brain-barrier, endothelial activation, and inflammatory cell trafficking. These adverse outcomes

may be directly linked to deposition of ultrafine particles, a sub-fraction of $PM_{2.5}$, in cortical areas or to retro-axonal transport via the olfactory nerve, or alternatively by neuro-inflammation following a systemic inflammatory response to air pollution[7,8].

4.3 Strengths and limitations

Our study has several strengths. First, the risk of bias in the analysis of short-term CNS effects of air pollution was small because of the panel study design and the statistical approach used. More specifically, they allowed to eliminate the risk of reverse causality and confounding of person-related characteristics. Second, recent PM exposure at school was characterized by area sampling in the classroom on the days of the neurobehavioral examinations. Third, recent and chronic ambient exposures to $PM_{2.5}$, PM_{10}, and BC at residence were estimated for each participant using a high-resolution spatial temporal model. This may explain why significant associations were found with attention tests despite the low spatial contrast in chronic $PM_{2.5}$ exposure (IQR difference 1.16 µg/m³). This observation is in line with other studies such as the Worcester Heart Attack Study which showed a link with acute myocardial infarction for an IQR $PM_{2.5}$ exposure contrast of 0.59 µg/m³ [44]. Fourth, we used three estimates for recent ambient exposure at residence to cover the time period of exposure and potential lagged effects up to two days (Lag 0 to 2).

We acknowledge some limitations of the study. First, we cannot exclude residual confounding by other neurotoxic substances, such as lead, if these were strongly associated with the air pollution indexes. However, in a recent study we showed in adolescents that the associations between neurobehavioral performance and traffic-related exposure were independent of blood lead[45]. The present study, based on repeated measures, tested an *a priori* hypothesis involving interrelated neurobehavioral outcomes as well as strongly correlated PM exposures (e.g. correlation coefficients for chronic PM_{10} and $PM_{2.5}$ was r=0.87). Therefore, the neurobehavioral test performances or exposure indicators did not provide a completely

independent opportunity for a type I error. For these reasons we did not perform multiple testing. Nevertheless, it seems unlikely that the consistency of negative phenotype-exposure associations would merely occur by chance as reflected by the significantly diminished performances, not only in the two Attention Tests (chronic ambient exposures to $PM_{2.5}$ and PM_{10} at residence) but also in the Pattern Comparison Test (recent ambient exposures to $PM_{2.5}$, PM_{10}, or BC on Lag 0-2 at residence). Further study is needed to find out why the inverse associations between the Stroop or Digit-Symbol test results and recent inside classroom PM exposure could not be corroborated for recent ambient PM exposure at residence. It is plausible that recent PM exposure characterized by 3-hour monitoring of classroom air displays different features in comparison to modeled recent PM exposure. Furthermore, the robustness and consistency of prompt neurobehavioral responses to recent exposure might be less outspoken than in the case of chronic ambient PM exposure at residence.

5. CONCLUSIONS

This is the first panel study comparing neurobehavioral changes of recent and chronic PM air pollution exposure. The repeated measurement study design in primary schoolchildren showed differential neurobehavioral changes robustly and inversely associated with recent or chronic ambient exposure to PM air pollution at residence, i.e., with recent exposure for visual information processing speed (Pattern Comparison Test) and with chronic exposure for sustained and selective attention. These neurotoxic findings on behavioral performances in schoolchildren associated with PM air pollution as found in Belgium in the years 2012-2014, strongly support the current tendency to bring the EU limits for ambient air PM-exposure as low as the WHO guidelines.

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Competing interests

The authors declare they have no conflict of interest.

References

1. Block ML, Calderon-Garciduenas L. Air pollution: mechanisms of neuroinflammation and CNS disease. *Trends Neurosci* 2009;**32**(9):506-16.
2. Van Eeden SF, Tan WC, Suwa T, Mukae H, Terashima T, Fujii T, Qui D, Vincent R, Hogg JC. Cytokines involved in the systemic inflammatory response induced by exposure to particulate matter air pollutants PM10. *Am J Respir Crit Care Med* 2001;**164**(5):826-30.
3. Sawyer K, Mundandhara S, Ghio AJ, Madden MC. The effects of ambient particulate matter on human alveolar macrophage oxidative and inflammatory responses. *J Toxicol Environ Health A* 2010;**73**(1):41-57.
4. Furuyama A, Kanno S, Kobayashi T, Hirano S. Extrapulmonary translocation of intratracheally instilled fine and ultrafine particles via direct and alveolar macrophage-associated routes. *Arch Toxicol* 2009;**83**(5):429-37.
5. Clark IA, Alleva LM, Vissel B. The roles of TNF in brain dysfunction and disease. *Pharmacol Ther* 2010;**128**(3):519-548.
6. Cunningham C. Microglia and neurodegeneration: the role of systemic inflammation. *Glia* 2013;**61**(1):71-90.
7. Oberdörster G, Sharp Z, Atudorei V, Elder A, Gelein R, Kreyling W, Cox C. Translocation of inhaled ultrafine particles to the brain. *Inhal Toxicol* 2004;**16**(6-7):437-445.
8. Elder A, Gelein R, Silva V, Feikert T, Opanashuk L, Carter J, Potter R, Maynard A, Ito Y, Finkelstein J, Oberdorster G. Translocation of inhaled ultrafine manganese oxide particles to the central nervous system. *Environ Health Perspect* 2006;**114**(8):1172-8.
9. Gerlofs-Nijland ME, Van Berlo D, Cassee FR, Schins RP, Wang K, Campbell A. Effect of prolonged exposure to diesel engine exhaust on proinflammatory markers in different regions of the rat brain. *Part Fibre Toxicol* 2010;**7**:12.
10. Levesque S, Taetzsch T, Lull ME, Kodavanti U, Stadler K, Wagner A, Johnson JA, Duke L, Kodavanti P, Surace MJ, Block ML. Diesel exhaust activates and primes microglia: air pollution, neuroinflammation, and regulation of dopaminergic neurotoxicity. *Environ Health Perspect* 2011;**119**(8):1149-55.
11. MohanKumar SM, Campbell A, Block M, Veronesi B. Particulate matter, oxidative stress and neurotoxicity. *Neurotoxicology* 2008;**29**(3):479-88.
12. Suzuki T, Oshio S, Iwata M, Saburi H, Odagiri T, Udagawa T, Sugawara I, Umezawa M, Takeda K. In utero exposure to a low concentration of diesel exhaust affects spontaneous locomotor activity and monoaminergic system in male mice. *Part Fibre Toxicol* 2010;**7**:7.
13. Tin Tin Win S, Yamamoto S, Ahmed S, Kakeyama M, Kobayashi T, Fujimaki H. Brain cytokine and chemokine mRNA expression in mice induced by intranasal instillation with ultrafine carbon black. *Toxicol Lett* 2006;**163**(2):153-60.
14. Tsukue N, Watanabe M, Kumamoto T, Takano H, Takeda K. Perinatal exposure to diesel exhaust affects gene expression in mouse cerebrum. *Arch Toxicol* 2009;**83**(11):985-1000.
15. Ritz B, Lee PC, Hansen J, Lassen CF, Ketzel M, Sorensen M, Raaschou-Nielsen O. Traffic-related air pollution and Parkinson's disease in Denmark: a case-control study. *Environ Health Perspect* 2016;**124**(3):351-6.
16. Kioumourtzoglou MA, Schwartz JD, Weisskopf MG, Melly SJ, Wang Y, Dominici F, Zanobetti A. Long-term PM2.5 exposure and neurological hospital admissions in the northeastern United States. *Environ Health Perspect* 2016;**124**(1):23-9.
17. Suglia SF, Gryparis A, Wright RO, Schwartz J, Wright RJ. Association of black carbon with cognition among children in a prospective birth cohort study. *Am J Epidemiol* 2008;**167**(3):280-286.

18. Chiu YH, Bellinger DC, Coull BA, Anderson S, Barber R, Wright RO, Wright RJ. Associations between traffic-related black carbon exposure and attention in a prospective birth cohort of urban children. *Environ Health Perspect* 2013;**121**(7):859-64.
19. Edwards SC, Jedrychowski W, Butscher M, Camann D, Kieltyka A, Mroz E, Flak E, Li Z, Wang S, Rauh V, Perera F. Prenatal exposure to airborne polycyclic aromatic hydrocarbons and children's intelligence at 5 years of age in a prospective cohort study in Poland. *Environ Health Perspect* 2010;**118**(9):1326-1331.
20. Perera FP, Rauh V, Whyatt RM, Tsai WY, Tang D, Diaz D, Hoepner L, Barr D, Tu YH, Camann D, Kinney P. Effect of prenatal exposure to airborne polycyclic aromatic hydrocarbons on neurodevelopment in the first 3 years of life among inner-city children. *Environ Health Perspect* 2006;**114**(8):1287-92.
21. Perera FP, Tang D, Wang S, Vishnevetsky J, Zhang B, Diaz D, Camann D, Rauh V. Prenatal polycyclic aromatic hydrocarbon (PAH) exposure and child behavior at age 6-7 years. *Environ Health Perspect* 2012;**120**(6):921-6.
22. Van Kempen E, Fischer P, Janssen N, Houthuijs D, Van Kamp I, Stansfeld S, Cassee F. Neurobehavioral effects of exposure to traffic-related air pollution and transportation noise in primary schoolchildren. *Environ Res* 2012;**115**:18-25.
23. Wang S, Zhang J, Zeng X, Zeng Y, Wang S, Chen S. Association of traffic-related air pollution with children's neurobehavioral functions in Quanzhou, China. *Environ Health Perspect* 2009;**117**(10):1612-1618.
24. Sunyer J, Esnaola M, Alvarez-Pedrerol M, Forns J, Rivas I, Lopez-Vicente M, Suades-Gonzalez E, Foraster M, Garcia-Esteban R, Basagana X, Viana M, Cirach M, Moreno T, Alastuey A, Sebastian-Galles N, Nieuwenhuijsen M, Querol X. Association between traffic-related air pollution in schools and cognitive development in primary school children: a prospective cohort study. *PLoS Med* 2015;**12**(3):e1001792.
25. Kicinski M, Vermeir G, Van Larebeke N, Den Hond E, Schoeters G, Bruckers L, Sioen I, Bijnens E, Roels HA, Baeyens W, Viaene MK, Nawrot TS. Neurobehavioral performance in adolescents is inversely associated with traffic exposure. *Environ Int* 2015;**75**:136-43.
26. Clifford A, Lang L, Chen R, Anstey KJ, Seaton A. Exposure to air pollution and cognitive functioning across the life course - A systematic literature review. *Environ Res* 2016;**147**:383-98.
27. VMM. Chemkar PM10 'hotspots': Chemische karakterisatie van fijn stof in Vlaanderen, 2008-2009. https://www.vmm.be/publicaties/chemkar-pm10-chemische-karakterisatie-van-fijn-stof-in-vlaanderen-2008-2009 Accessed 06-06-2016, 2016.
28. Janssen S, Dumont G, Fierens F, Mensink C. Spatial interpolation of air pollution measurements using CORINE land cover data. *Atmospheric Environment* 2008;**42**(20):4884-4903.
29. Lefebvre W, Degrawe B, Beckx C, Vanhulsel M, Kochan B, Bellemans T, Janssens D, Wets G, Janssen S, de Vlieger I, Int Panis L, Dhondt S. Presentation and evaluation of an integrated model chain to respond to traffic- and health-related policy questions. *Environmental Modelling & Software* 2013;**40**:160-170.
30. Maiheu B, Veldeman B, Viaene P, De Ridder K, Lauwaet D, Smeets N, Deutsch F, S. J. Identifying the best available large-scale concentration maps for air quality in Belgium. http://www.milieurapport.be/Upload/main/0_onderzoeksrapporten/2013/Eindrapport_Concentratiekaarten_29_01_2013_TW.pdf Accessed 26/02/2016, 2016.
31. Lefebvre W, Vercauteren J, Schrooten L, Janssen S, Degraeuwe B, Maenhaut W, de Vlieger I, Vankerkom J, Cosemans G, Mensink C, Veldeman N, Deutsch F, Van Looy S, Peelaerts W, Lefebre F. Validation of the MIMOSA-AURORA-IFDM model chain for policy support: Modeling concentrations of elemental carbon in Flanders. *Atmospheric Environment* 2011;**45**(37):6705-6713.
32. The European Parliament and The Council of The European Union. Directive 2002/49/EC of the European Parliament and of the Council of 25 June 2002 relating to the assessment and

management of environmental noise. http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32002L0049&from=EN Accessed 01-07-2016, 2016.
33. Xavier Educational Software Ltd. Multi Function Stroop Test. http://www.xavier-educational-software.co.uk/multistroop.shtml Accessed 01-10-2011, 2011.
34. Letz R. *NES3 User's Manual*. Atlanta (MA): Neurobehavioral Systems, Inc. Atlanta, 2000.
35. White RF, James KE, Vasterling JJ, Letz R, Marans K, Delaney R, Krengel M, Rose F, Kraemer HC. Neuropsychological screening for cognitive impairment using computer-assisted tasks. *Assessment* 2003;**10**(1):86-101.
36. Czerniawski J, Miyashita T, Lewandowski G, Guzowski JF. Systemic lipopolysaccharide administration impairs retrieval of context-object discrimination, but not spatial, memory: Evidence for selective disruption of specific hippocampus-dependent memory functions during acute neuroinflammation. *Brain Behav Immun* 2015;**44**:159-66.
37. Thomson EM, Kumarathasan P, Calderon-Garciduenas L, Vincent R. Air pollution alters brain and pituitary endothelin-1 and inducible nitric oxide synthase gene expression. *Environ Res* 2007;**105**(2):224-33.
38. Cruts B, van Etten L, Tornqvist H, Blomberg A, Sandstrom T, Mills NL, Borm PJ. Exposure to diesel exhaust induces changes in EEG in human volunteers. *Part Fibre Toxicol* 2008;**5**:4.
39. Siddique S, Banerjee M, Ray MR, Lahiri T. Attention-deficit hyperactivity disorder in children chronically exposed to high level of vehicular pollution. *Eur J Pediatr* 2011;**170**(7):923-9.
40. Newman NC, Ryan P, Lemasters G, Levin L, Bernstein D, Hershey GK, Lockey JE, Villareal M, Reponen T, Grinshpun S, Sucharew H, Dietrich KN. Traffic-related air pollution exposure in the first year of life and behavioral scores at 7 years of age. *Environ Health Perspect* 2013;**121**(6):731-6.
41. Calderon-Garciduenas L, Mora-Tiscareno A, Ontiveros E, Gomez-Garza G, Barragan-Mejia G, Broadway J, Chapman S, Valencia-Salazar G, Jewells V, Maronpot RR, Henriquez-Roldan C, Perez-Guille B, Torres-Jardon R, Herrit L, Brooks D, Osnaya-Brizuela N, Monroy ME, Gonzalez-Maciel A, Reynoso-Robles R, Villarreal-Calderon R, Solt AC, Engle RW. Air pollution, cognitive deficits and brain abnormalities: a pilot study with children and dogs. *Brain Cogn* 2008;**68**(2):117-27.
42. Peterson BS, Rauh VA, Bansal R, Hao X, Toth Z, Nati G, Walsh K, Miller RL, Arias F, Semanek D, Perera F. Effects of prenatal exposure to air pollutants (polycyclic aromatic hydrocarbons) on the development of brain white matter, cognition, and behavior in later childhood. *JAMA Psychiatry* 2015;**72**(6):531-40.
43. Calderon-Garciduenas L, Solt AC, Henriquez-Roldan C, Torres-Jardon R, Nuse B, Herritt L, Villarreal-Calderon R, Osnaya N, Stone I, Garcia R, Brooks DM, Gonzalez-Maciel A, Reynoso-Robles R, Delgado-Chavez R, Reed W. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. *Toxicol Pathol* 2008;**36**(2):289-310.
44. Madrigano J, Kloog I, Goldberg R, Coull BA, Mittleman MA, Schwartz J. Long-term exposure to PM2.5 and incidence of acute myocardial infarction. *Environ Health Perspect* 2013;**121**(2):192-6.
45. Kicinski M, Saenen ND, Viaene MK, Den Hond E, Schoeters G, Plusquin M, Nelen V, Bruckers L, Sioen I, Loots I, Baeyens W, Roels HA, Nawrot TS. Urinary t,t-muconic acid as a proxy-biomarker of car exhaust and neurobehavioral performance in 15-year olds. *Environmental research* 2016 (In press).