2011
2012

GENEESKUNDE

master in de biomedische wetenschappen: milieu en gezondheid

Masterproef

The association between cognitive performance and exposure to particulate air pollution in primary schoolchildren

Promotor :
Prof. dr. Tim NAWROT

Eline Provost

Masterproef voorgedragen tot het bekomen van de graad van master in de biomedische wetenschappen , afstudeerrichting milieu en gezondheid

Maastricht University

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Thank you!

LIST OF ABBREVIATIONS

BMI	Body Mass Index
EU	European Union
ETS	Environmental Tobacco Smoke exposure
GIS	Geographic Information System
IQR	Interquartile Range
NES	Neurobehavioral Evaluation System
NO_x	Nitrogen oxides
O_3	Ozone
PM	Particulate Matter
PM_{10}	Particulate matter with an aerodynamic diameter of ≤ 10 µm
$PM_{2.5}$	Particulate matter with an aerodynamic diameter of ≤ 2.5 µm
$PM_{0.1}$	Particulate matter with an aerodynamic diameter of ≤ 0.1 µm (100 nm)
SO_2	Sulphur dioxide
TSP	Total Suspended Particles
UFP	Ultrafine particles

ABSTRACT

Background - Cardiorespiratory effects and mechanisms of particulate air pollution have been largely investigated and an association with adverse outcomes has been well established. However, little is known regarding neurobehavioral effects. Studies in animals suggest a biological plausibility for a link between ultrafine particles (UFP) and neurological impairment. However, information based on studies in humans is very limited.

Objectives - In a panel of primary schoolchildren, the effect of chronic and acute exposure to fine and ultrafine particulate air pollution on cognitive performance was investigated.

Methods - 70 children, aged 9 to 12 years, were recruited at a primary school in Flanders, Belgium. A series of computerized tests from the Neurobehavioral Evaluation System (NES) battery and the Stroop test were used to evaluate cognitive performance. Acute exposure to particulate matter and UFP was monitored on site. Chronic exposure was estimated based on the proximity between the place of residence and major roads. The change in cognitive test outcome associated with exposure to UFP was estimated using mixed models, taking the clustering of the data into account.

Results - A significant association was found between attention tests and acute as well as chronic exposure to air pollution. An interquartile range increase in indoor UFP was associated with a 5.44% (1.01 to 9.87) delay in response reaction time of the Stroop test. A doubling in the distance to major roads resulted in an estimated reduction in reaction time of -1.34% (-2.30 to -0.38). Indoor UFP was also significantly associated with the outcome of the Continuous Performance test, with an estimated percent change in mean reaction time of 1.00% (0.23 to 1.77), but not with distance to major roads. Similar associations were found with outdoor UFP. None of the other tests from the NES battery showed a significant association with exposure to particulate air pollution and no significant associations were found with other particulate matter fractions (TSP, PM_{10} or $PM_{2.5}$). The reported associations were independent of age, gender, test session number, hour of the day, BMI, maximum outdoor apparent temperature, exposure to environmental tobacco smoke, birth weight, breast feeding and educational level of the mother.

Conclusion - Both acute and chronic exposure to air pollution, as implemented by residential distance to major roads, are associated with an inverse effect on children's attention.

SAMENVATTING

Achtergrond - Cardiorespiratoire gezondheidseffecten en mechanismen van fijn stof zijn reeds uitvoerig bestudeerd, maar er is slechts weinig bekend omtrent de effecten op cognitie. Proefdierstudies tonen een link aan tussen ultrafijne partikels (UFP) en neurologische stoornissen, maar informatie gebaseerd op studies bij mensen is beperkt.

Objectieven - Het effect van chronische en acute blootstelling aan fijn stof op het cognitieve prestatievermogen werd onderzocht bij een groep lagere schoolkinderen.

Methoden - Het cognitieve prestatievermogen van 70 kinderen, tussen 9 en 12 jaar, werd geëvalueerd via testen van de NES (*Neurobehavioral Evaluation System*) batterij en de Stroop test. Acute blootstelling aan fijn stof werd ter plaatse gemeten. Chronische blootstelling werd geschat op basis van de afstand van de woonplaats tot grote wegen. Een verandering in het resultaat van een cognitieve test geassocieerd met een blootstelling aan fijn stof werd geschat aan de hand van *mixed models*, om rekening te houden met de clustering van de data.

Resultaten - Er werd een significante associatie gevonden tussen de resultaten van de aandacht testen en een acute alsook met een chronische blootstelling aan fijn stof. Een interkwartiel stijging van de UFP concentratie binnen het schoolgebouw was geassocieerd met een 5.44% (±4.43) verhoging van de gemiddelde reactietijd van de Stroop test. Een verdubbeling van de afstand tot grote wegen resulteerde in een geschatte daling van de reactietijd met -1.34% (±0.96). UFP in het schoolgebouw was ook significant geassocieerd met het resultaat van de *Continuous Performance* test, met een geschatte verhoging van de gemiddelde reactietijd met 1.00% (±0.77), maar niet met afstand tot grote wegen. Gelijkaardige associaties werden gevonden met UFP concentraties op de speelplaats. Geen enkele andere test van de NES batterij vertoonde significante associaties met blootstelling aan fijn stof en er werden ook geen significante associaties gevonden met andere fijn stof fracties. De aangetoonde associaties waren onafhankelijk van leeftijd, geslacht, test sessie nummer, uur van de dag, BMI, maximum gevoelstemperatuur, blootstelling aan sigarettenrook, geboortegewicht, borstvoeding en opleiding van de moeder.

Conclusie - Zowel acute als chronische blootstelling aan luchtverontreiniging, zoals geïmplementeerd door de residentiele afstand tot grote wegen, is geassocieerd met een invers effect op de aandacht van kinderen.

1. INTRODUCTION

1.1 TRAFFIC-RELATED AIR POLLUTION

Transport is a vital part of modern life. Owing to its flexibility, road transport is a major transport mode [1], but it is also a major source for urban air pollution [2]. Road traffic air pollution originates from the tailpipes of vehicles with internal combustion engines, from other vehicle components (such as brake and clutch linings and pads, tires and fuel tanks), and from road-surface wear and treatment materials [1]. Due to the number of sources, traffic-related air pollution results in a complex mixture that includes both gaseous pollutants such as nitrogen oxides (NO_x), ozone (O_3), and sulphur dioxide (SO_2), and particulate matter pollutants, all of which pose a risk to health [1, 3].

The mixture of air pollution varies in time and space, depending on several characteristics, such as proximity to roads, the composition of the vehicle fleet, traffic patterns and the presence of other pollution sources. Population exposure depends on both pollution levels and time-activity patterns. Both short-term and long-term exposure may lead to adverse effects on health, which may occur either immediately or years later [1].

Epidemiological studies indicate that the most severe health effects from exposure to air pollution are associated with particulate matter [4].

1.1.1 PARTICULATE AIR POLLUTION

Particulate air pollution consists of an air-suspended mixture of solid and liquid particulate matter (PM) particles which vary in mass, number concentration, size, shape, surface area, chemical composition, physical properties, solubility and source [5, 6].

CLASSIFICATION OF PM

For practical reasons, particulate matter is classified by size [7]. The total suspended particles (TSP) can be subdivided into coarse, fine and ultrafine particles, as shown in figure 1 [5, 6].

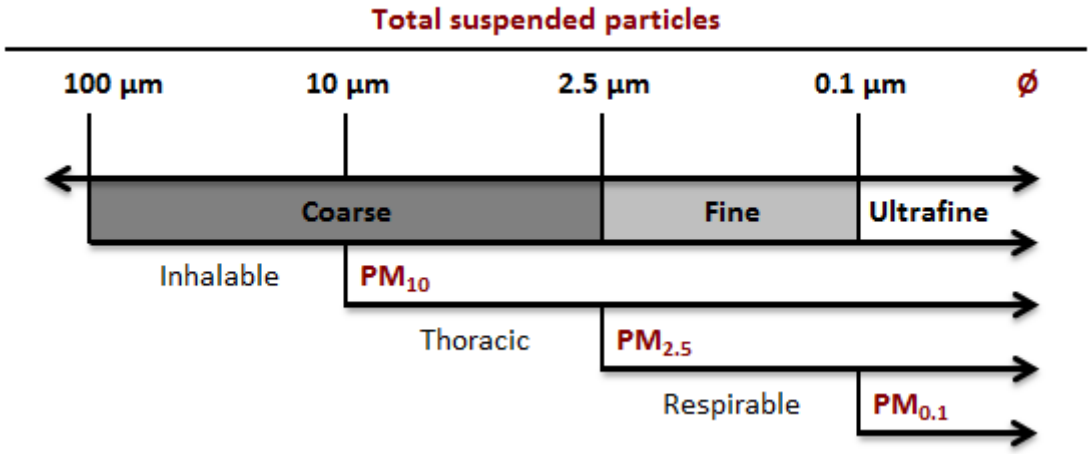

Figure 1. Particulate air pollution: classification of particulate matter (PM).

Under the aspect of emission measurements, the classification of particulate matter is defined by cut-off points in aerodynamic diameter. Accordingly, PM_{10} has an aerodynamic diameter of less than 10 µm, $PM_{2.5}$ less than 2.5 µm and particles with a diameter of less than 0.1 µm (100 nm) are generally defined as ultrafine ($PM_{0.1}$).

Because of their small size, particulate matter particles can be inhaled deeply into the lungs. PM_{10}, also called "thoracic" particles, can penetrate into the lower respiratory system, and $PM_{2.5}$, "respirable" particles, can penetrate into the gas-exchange region of the lung [8].

Sources and composition of PM

Ambient particulate air pollution originates from anthropogenic and natural sources [9]. Both origins have primary and secondary sources. Primary anthropogenic sources of particulate air pollution are: combustion of fossil fuels for energy production and domestic heating, incineration, traffic exhaust, abraded tire and brake dust, and re-suspension of sedimented particles. Man-made reactive and organic gases are emitted to the atmosphere and form particles by coagulation, condensation and chemical reaction, which is a secondary anthropogenic source of particulate air pollution. Primary natural sources are volcanoes, forest fires, oceans, soil erosions, abrasion of stones and plant materials. Secondary natural sources consist of gaseous emissions from natural sources which may form particulate matter [6] in analogue to secondary anthropogenic sources.

As shown in table 1, coarse particles derive primarily from suspension or re-suspension of dust, soil, or other crustal materials from roads, tires, breaks, etc. They also include sea salts, pollen, mold, spores, and other plant parts. Fine particles derive primarily from direct emissions from combustion processes, such as vehicle use of gasoline and diesel, wood burning, coal burning for power generation, and industrial processes [5].

Ultrafine particles (UFP) are found to a large extent in urban air and are the predominant particle size by number in urban PM_{10}, although they contribute only moderately to the mass [10]. Emissions of ultrafine particles result from combustion-related sources, such as vehicle exhaust, and atmospheric photochemical reactions. These primary ultrafine particles, however, have a very short life and rapidly grow (through coagulation and/or condensation) to form larger complex aggregates, but typically remain a part of $PM_{2.5}$ [5].

Traffic intensity is one of the most important determinants of ambient anthropogenic particulate matter concentrations, especially for $PM_{2.5}$ and ultrafine particles [9].

Recently, there has been more interest in fine and ultrafine particles because they can penetrate deeply into the lung and thus are more likely to induce adverse health effects [9].

Table 1. Particulate air pollution: characterization of source and composition according to classification [5, 9].

	Source	Composition
Coarse	Suspension and re-suspension of dust and soil, tire and break wear	Dust, soil, sea salts, pollen, mold, spores, etc.
Fine	Combustion, aggregation of UFP	Combustion particles, organic compounds, metals, etc.
Ultrafine	Combustion and photochemical activity	Combustion particles, organic compounds, metals, etc.

1.1.2 EUROPEAN LEGISLATION CONCERNING PARTICULATE AIR POLLUTION

As established in the European Air Quality Directive 2008/50/EG [11], there are limit values for PM_{10} for short-term (24-hour) and long-term (annual) exposure, while for $PM_{2.5}$ there are only values for long-term (annual) exposure (table 2). The short-term limit value for PM_{10} (i.e. not more than 35 days per year with a daily average concentration exceeding 50 µg/m³) is the limit value most often exceeded in European cities and urban areas [4].

This is evenly true for Belgium, where the limits are also exceeded too often (e.g. in half of the Belgian measuring stations the limits were exceeded more in the first three months of 2011 than in the whole of 2010) and Belgium has even been brought to the EU Court of Justice on this account.

Table 2. Air quality limit and target values for PM_{10} and $PM_{2.5}$ as given in the Air Quality Directive [11].

Size fraction	Averaging period	Value	Comments
PM_{10}, limit value	24-hour average	50 µg/m³	Not to be exceeded on more than 35 years per year. To be met by 1 January 2005.
PM_{10}, limit value	Annual average	40 µg/m³	To be met by 1 January 2005
$PM_{2.5}$, target value	Annual average	25 µg/m³	To be met by 1 January 2010
$PM_{2.5}$, limit value	Annual average	25 µg/m³	To be met by 1 January 2015

As demonstrated above, public health policies have focused primarily on indicators of coarse (PM_{10}) and, more recently, fine ($PM_{2.5}$) particles in terms of establishing guidelines or standards for acceptable levels of particulate air pollution [5]. However, the components of PM_{10} on the whole are not very toxic. Therefore scientific attention has turned to the components that are most likely to have a toxic potential, and the ultrafine particles have been identified as potential mediators [10]. This fact raises the question whether the attention in policy-making should also shift to a nanoparticle air quality standard [12].

1.2 HEALTH EFFECTS OF PARTICULATE AIR POLLUTION

Increases in particulate air pollution levels have been associated with an increase in pulmonary and cardiovascular morbidity and mortality [3, 5, 7, 13]. However, little is known regarding neurological effects.

1.2.1 PARTICULATE AIR POLLUTION AND THE BRAIN

Animal studies have shown that inhaled particles can be translocated from the respiratory system directly to the central nervous system. Oberdorster et al. [14] found ultrafine carbon-13 particles in the olfactory bulb, cerebrum and cerebellum of rats after inhalation exposure. More recently, Elder et al. [15] confirmed that ultrafine particles can reach the brain, either through circulation or by direct translocation to the olfactory nerve from the nose to the brain. The ultrafine particles can cause inflammation [16], potentially damaging the brain.

These findings raise the fact that the brain is a possible new target organ for particulate matter toxicity. However, the few studies that investigated the potentially neurotoxic effects of particulate matter mainly focused on pathologic lesions that are generally associated with neurodegenerative diseases, such as Parkinson's and Alzheimer's disease. Recently, Fonken et al. [17] have associated exposure to particulate air pollution with an impaired cognition in mice, indicating a neurobehavioral effect.

Until now, only four studies have investigated the effect of traffic-related particulate air pollution on cognition in humans, of which just one was in children, yielding only some preliminary results. Chen and Schwartz [18] found an association between PM_{10} exposure and cognitive performance in adults. However, after adjustment for socio-demographic factors, the association was lost. Ranft et al. [19] demonstrated an association between long-term exposure to traffic-related air pollution, indicated by a residential distance to the next busy road, and mild cognitive impairment in the elderly. In accordance, Weuve et al. [20] associated long-term exposure to particulate air pollution with significantly worse cognitive decline in older women. Suglia et al. [21] found an association between intelligence and residential exposure to black carbon, a marker for traffic-related air pollution, in a group of 202 children, though not all associations between black carbon and the cognitive subscales were statistically significant.

1.3 SUSCEPTIBILITY TO PARTICULATE AIR POLLUTION

Numerous characteristics have been shown to influence susceptibility to ambient air pollution such as genetic differences, social factors, age, gender, race, pre-existing respiratory or cardiovascular diseases, diabetes, medication, health care availability, housing characteristics, etc. [5, 6].

1.3.1 CHILDREN

Children exposed to comparable levels of air pollutants are potentially more susceptible than adults [22]. Not only are they exposed during a critical developmental period, children also differ from adults in physiological characteristics and exposure patterns.

The airway epithelium of growing children is more permeable to air pollutants and the lung defenses against particulate and gaseous air pollution are not fully evolved. Children also have a differential ability to metabolize, detoxify and excrete environmental agents. In addition, children perform a greater level of physical activity than adults; hence their intake of air into the lungs is much greater compared to adults. A higher intake of air means that more ambient air pollutants can enter the lungs. Children spend more time outside than adults, particularly in the summer and in the late afternoon. Some of that time is spent in activities that increase breathing rates, which can significantly increase their exposure to ambient air pollutants compared to adults [6, 23, 24].

Young children have a higher resting metabolic rate of oxygen consumption per unit body weight than adults because they have a larger surface per unit body weight and because they are growing rapidly. On the basis of body weight, the volume of air passing through the lungs of a resting child is twice that of a resting adult under the same conditions, and hence twice as much atmospheric pollutant could reach the lungs of a child. In addition, children have narrower airways, thus irritation caused by air pollution that would produce only a slight response in an adult can result in a potentially significant obstruction in the airways of a young child [23, 24].

1.4 AIM OF THE STUDY

Cardiorespiratory effects and mechanisms of particulate air pollution have been largely investigated and an association with adverse outcomes has been well established. However, little is known regarding neurobehavioral effects.

Studies in animals suggest a biological plausibility for a link between ultrafine particles and neurological impairment. However, information based on studies in humans is very limited, with only some preliminary evidence.

Considering the facts that children are more susceptible to particulate air pollution and that ultrafine particles can translocate to the brain, it is the aim of this study to investigate the effects of **chronic and acute** exposure to **fine and ultrafine** particulate air pollution on **cognitive performance** in primary school**children**.

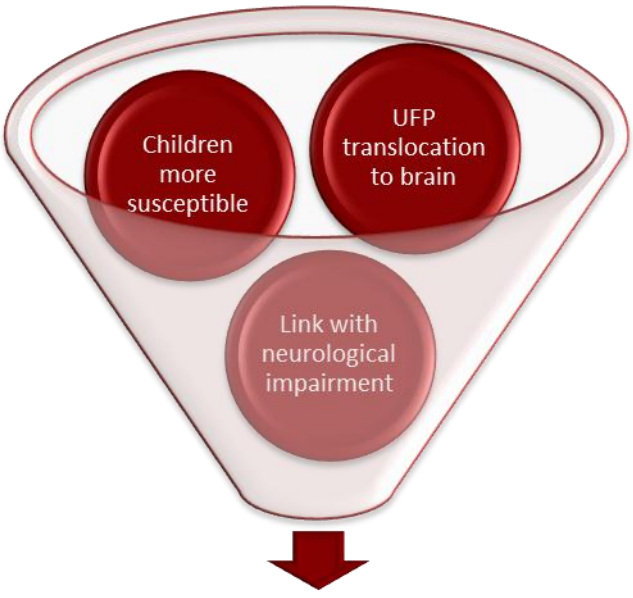

Figure 2. Research question.

2. Materials and Methods

2.1 Study design

In order to investigate the effects of exposure to particulate air pollution on cognitive performance, a repeated measures **panel study design** was applied. In this study design within-subject repeated measures allows each subject to act as its own control.

2.2 Study population

Children aged 9-12 years (3rd to 6th grade) were recruited at a primary school in Flanders, Belgium. Written informed consent was requested from the parents as well as oral consent from the children. The parents were asked to fill out a questionnaire in order to obtain additional information on the child's residence, health, ethnicity, smoking habits of the parents, means of transportation to and from the school, socio-economic status, etc. Of the 210 children invited to the study, 70 children returned the written informed consent and a completed questionnaire. The study was approved by the Medical Ethics Committee of Hasselt University and the East-Limburg Hospital.

2.3 Assessment of cognitive performance

An overall schematic overview of the used cognitive tests is given in figure 3.

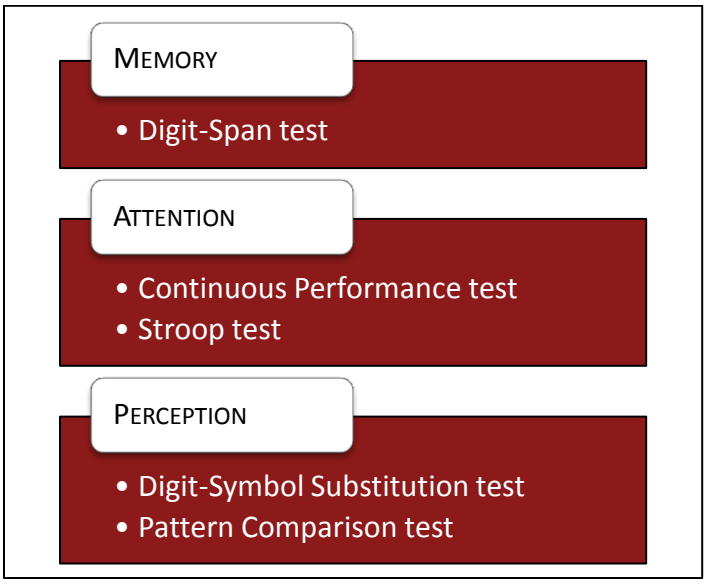

Figure 3. Overall schematic overview of the used cognitive performance tests.

The cognitive performance tests were administered in groups of 4 children with the help of an individual touch-screen laptop with additional hardware (headset/keyboard). The duration of the test was approximately 20 minutes. The test session was repeated three times over the course of the school year.

2.3.1 NEUROBEHAVIORAL EVALUATION SYSTEM (NES)

A series of computerized tests, known as NES (Neurobehavioral Evaluation System) were used to assess cognitive performance. These tests evaluate cognitive functions such as memory, attention, learning and psychomotor performance, and are designed to detect effects of neurotoxicants on the central nervous system. Several studies have provided data supporting the NES' adequate psychometric properties [25, 26]. Evidence that the NES shows an acceptable level of reliability comes from test-retest correlations in the range from 0.6 to 0.9 obtained under both laboratory and field conditions [27]. Furthermore, the testing procedure showed a high level of acceptance by children, teachers and parents [28].

DIGIT-SPAN TEST

In the Digit-Span test, participants had to enter progressively longer series of digits following auditory presentation in order to determine the memory span and capacity of the subject to hold and manipulate information.

The task began with an auditory presentation of two digits and a request that the subject touched the same two numbers on a keypad on the touchscreen, followed by an arrow button in the lower right of the screen (figure 4A). If the subject answered incorrectly, he/she was instructed again and given a second chance with two digits. When a correct response was given a new, one digit longer, sequence was presented. When an error was made, a second trial at that span length was given. When the subjects answered both trials at a span length incorrectly or successfully completed 9 digits forward, the backward condition began. Again starting with two digits, a sequence of digits was presented and the subject was instructed to enter the digits in reverse order. The criteria were the same as in the forward condition. The backward condition ended with two incorrect answers at a span length or successful completion of 8 digits backward. The primary summary measures were the maximum span produced correctly forward and backward.

Digit-Symbol Substitution test

In the Digit-Symbol Substitution test the subject had to find a target digit in a paired digit-symbol array and point to the paired symbol in a second array with a different sequence of symbols in order to assess the subject's visual scanning and information-processing speed.

A row of 9 symbols was paired (vertically) with 9 digits across the top of the screen (figure 4B). A target stimulus was presented in the center. The 9 symbols were presented in a scrambled order near the bottom. The subject had to find the target stimulus number, note the symbol with which it was matched and touch that symbol in the array at the bottom. If answered correctly, the target number in the center of the screen changed. Incorrect responses resulted in an error sound and the target number stayed the same. The primary summary measure was the latency in seconds to complete responses to 27 target digits. If the subject did not complete the 27 items in 180 seconds, the task ended and the subject was assigned a latency of 180 seconds.

Continuous Performance test

In the Continuous Performance test the subject had to respond to a critical stimulus by pressing the spacebar as quickly as possible in order to measure sustained attention.

A pseudorandom sequence of shadow drawings of common animals was presented on the screen, one at a time. A new animal displaced the previous one each 1200 msec. The subject had to press the spacebar as soon as possible after the critical stimulus (figure 4C) appeared, but not for the other four animals. A response within 1200 milliseconds was considered a correct response. 40 critical stimulus trials were administered of which the first four were considered as practice trials. The primary summary measure was the mean reaction time in milliseconds for responding to the critical stimulus.

Pattern Comparison test

In the Pattern Comparison test three matrices consisting of 10 by 10 blocks were presented (figure 4D). Two patterns were identical and the subject had to indicate which of the patterns was different from the other two in order to assess the visuospatial analytic ability.

A practice item was presented and the subject was asked to touch the item that was different from the other two items. If the subject made a mistake on the practice trial, he/she was given a second chance. If he/she still answered incorrectly, the interviewer was called. After the practice trial, the subject was instructed to answer the remaining items as quickly as they could without making any mistakes. The primary summary measure was the average response latency in seconds of the items answered correctly.

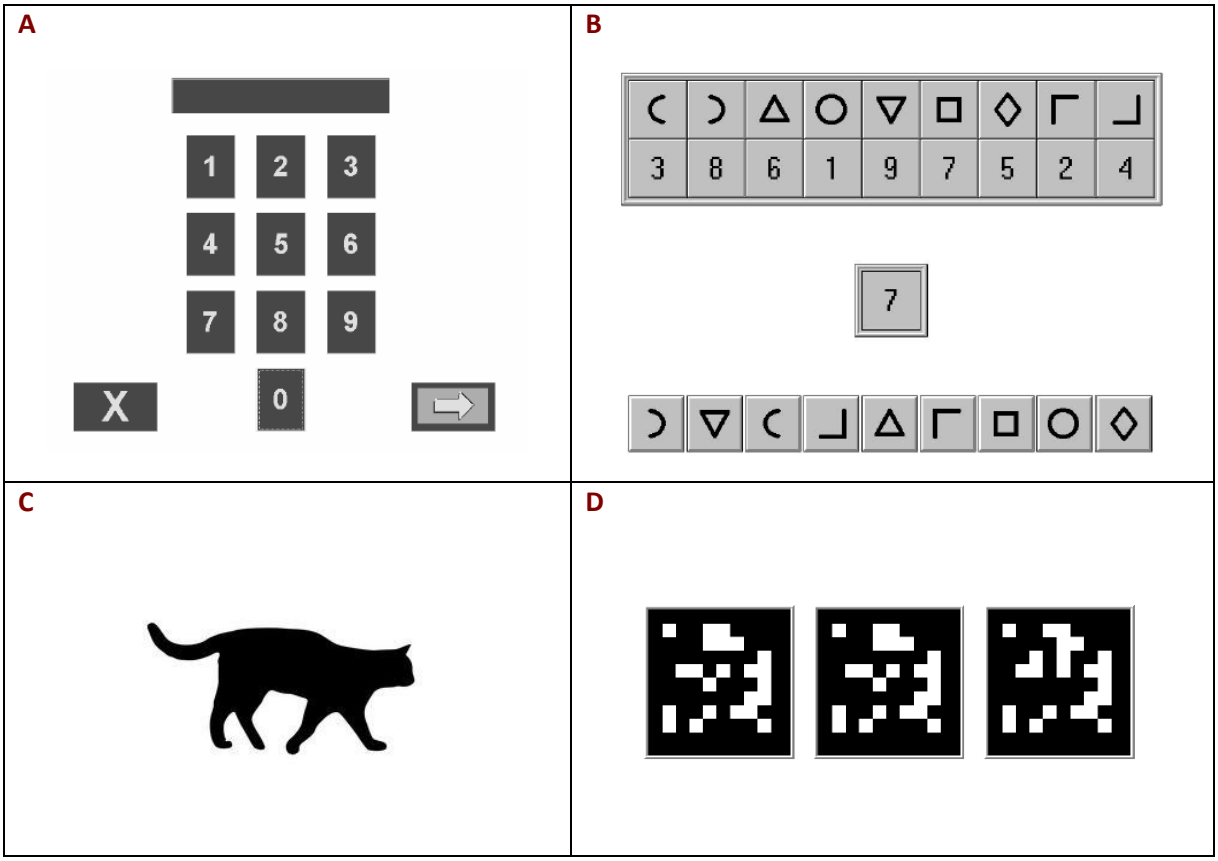

Figure 4. Neurobehavioral Evaluation System (NES) screen lay-out. A: Digit-Span test s; B: Digit-Symbol Substitution test; C: Continuous Performance test with animals; D: Pattern Comparison test.

2.3.2 STROOP TEST

In the Stroop test (Dutch translated version from Xavier Educational Software Ltd, UK) the name of a color (e.g., "blue", "green", "yellow" or "red") was printed in a color not denoted by the name (e.g., the word "red" printed in blue instead of red). The subject was asked to point out the color denoted by the name as fast as possible in order to assess attention.

Eight practice items were presented before the actual task started. The primary summary measure was the mean reaction time in milliseconds for the items answered correctly.

2.4 Assessment of exposure to traffic-related air pollution

Acute exposure to particulate matter pollution was measured at the school. The concentrations of TSP, PM_{10} and $PM_{2.5}$ (in µg/m³) were measured with an Aerocet device (Met One Instruments Inc., US), which also measured temperature (in °C) and relative humidity. Ultrafine particles were measured with the Aerasense NanoTracer (Philips Electronics Ltd, UK). Apart from an UFP concentration (in particles per cm³), this device also provided information on particles size (in nm) and calculated a cumulative exposure estimate. Outside measurements were done before school started and during school breaks. The indoor particulate air pollution levels were measured during the test sessions.

Chronic exposure to particulate air pollution was assessed by calculating the distance (in meters) to major roads (N- or E-roads) based on the children's residence using geocoding. Distance to major roads is considered as a surrogate for traffic-related air pollution [29]. In the statistical analyses, distance to major roads was log-transformed to reduce skewness.

2.5 Sample collection

Apart from the cognitive performance tests, additional samples were collected during the test sessions. Due to time limitations, these samples will be analyzed in the future.

2.5.1 Saliva and buccal swabs

The participants were asked to refrain from eating, drinking, chewing gum or oral hygiene procedures for at least 30 minutes prior to the study and the mouth was rinsed with water three times before the collection of saliva.

An unstimulated saliva sample was collected using an Oragene®-RNA Self-Collecting Kit (DNA Genotek, Canada). In the future, the collected RNA will be used to investigate the transcription of neurological and inflammation related genes in relation to exposure to particulate air pollution and cognitive performance.

DNA for future genotyping was collected using SK-2 Isohelix buccal swabs. The buccal swabs were placed on ice until long-term storage at -20°C.

2.5.2 URINE

Urine samples were collected in designated metal-free sample jars and placed at 4°C until long-term storage at -20°C. With this urine sample, internal heavy metal burden will be determined in the future.

2.6 OTHER STUDY VARIABLES

2.6.1 EMOTIONAL STATE

To assess the emotional state of the participants at the moment of cognitive performance testing, a questionnaire, specifically designed for children by Dr. de Wit, was used. The used questionnaire ("Korte depressie vragenlijst voor kinderen") is added as supplement 1.

2.6.2 BLOOD PRESSURE

Blood pressure was measured repeatedly using the full automatic upper-arm blood-pressure monitor Stabil Graph® (I.E.M., Stolberg, Germany) with a special sized cuff for children. The average of five consecutive measurements was calculated.

2.6.3 VASCULAR STIFFNESS/ELASTICITY

Using CardioTrace (Young at Heart International Ltd, UK) the vascular stiffness/elasticity of the subjects was estimated based on the pulse waveform obtained at the finger (digital volume pulse DVP) with an infra-red sensor.

2.6.4 METEOROLOGICAL VARIABLES

The Belgian Royal Meteorological Institute provided data on daily minimum, mean and maximum temperature and relative humidity, measured at weather station in Uccle, which were used to calculate apparent temperature values.

2.7 STATISTICAL ANALYSIS

For database management and statistical analysis, SAS software (version 9.2, SAS Institute Inc., Cary, NC, USA) was used. In order to investigate the effect of exposure to particulate air pollution on the cognitive performance (operationalized by the NES and Stroop test), analyses were carried out using the MIXED procedure.

Mixed models account for the clustered data within the same person. The participants were entered as random effects. A random intercept model was used and the coefficients (β) and standard errors were estimated under restricted maximum likelihood estimation (REML).

The dependent variables were the outcomes of the cognitive performance tests (the NES and Stroop test). In all models, the main independent variables were the chronic exposure marker, distance to major roads, along with one acute exposure marker (UFP, $PM_{2.5}$, PM_{10} or TSP), included as continuous variables.

Prior to assessing effects of exposure to particulate air pollution on cognitive performance, other possible confounders were examined, which were possibly related both to exposure to particulate air pollution and cognitive performance. Final models included age (years), gender, test session number (time 1, 2 or 3), hour of the day, BMI, maximum outdoor apparent temperature (°C), exposure to environmental tobacco smoke (yes/no), birth weight (g), breast feeding (yes/no) and educational level of the mother (low-middle-high).

The change in each of the cognitive test outcomes associated with each of the particulate matter measures was estimated in separate analyses, using particulate matter concentrations averaged between 09:00 and 10:00 a.m. on the day of the test session. To ensure comparability of the analyses for the different cognitive test outcomes, the same statistical model was used for each.

The results of the analyses are presented as percent change in each cognitive test outcome (and its 95% confidence interval) associated with an interquartile range (IQR) increase in each of the particulate air pollution concentrations and a doubling in distance to major roads.

Residual plots were examined as a check on model assumptions. Statistical significance was defined as $p<0.05$.

3. RESULTS

3.1 STUDY POPULATION CHARACTERISTICS

Table 3 presents the general characteristics of the participating children whose parents completed a questionnaire.

The study population included 70 children (50% girls) aged 9 to 12 years, which were recruited from the third, fourth, fifth and sixth year of primary school. The mean age of the children was 10 years and eight months. The average BMI of the subjects was 17.39. Five participants (7.14%) suffered from a longstanding illness which ranged from chronic otitis media and migraine to epilepsy and kidney disease (only one working kidney), for which the latter two took medication. Of all participants, 14.93% had allergies.

33 participants (47.83%) were exposed to environmental tobacco smoke and 7 (10%) were also exposed during pregnancy. The average birth weight of the participants was 3254 grams. Eight (11.42%) were preterm and 13 (18.54%) had complications during the pregnancy. 61.43% was breastfed. The participants were mainly first (37.68%) and second (39.13%) child.

On average, the participants played sports two times a week, used the computer (PC) three hours a week and watched television (TV) nine hours per week.

91.43% of the participants had parents who were both born in Belgium. 15 participants (21.71%) had divorced parents. 84% of the parents of the participants were home owners, 94.58% of the participants' parents was employed and 57.58% had a high education.

Table 3. Description of the study population.

Number of subjects	70
Anthropometrics	
Age (years)	10.67 ± 1.01
Gender (girls)	35 (50)
BMI	17.39 ± 3.47
School grade	
3rd year	14 (20)
4th year	14 (20)
5th year	26 (37.14)
6th year	16 (22.86)
Health	
Longstanding illness	5 (7.14)
Allergy	10 (14.93)
Lifestyle	
ETS	33 (47.83)
Sport (times per week)	2.33 ± 1.35
PC (hours per week)	3.49 ± 2.65
TV (hours per week)	9.55 ± 5.90
Ethnicity	
Both parents born in Belgium	64 (91.43)
One of the parents born in Belgium	3 (4.29)
None of the parents born in Belgium	3 (4.29)
Divorced parents	15 (21.74)
Pregnancy characteristics	
ETS during pregnancy	7 (10)
Complications during pregnancy	13 (18.57)
Preterm	8 (11.43)
Preterm (weeks)	5.19 ± 2.68
Birthweight (grams)	3253.82 ± 643.40
Breast fed	43 (61.43)
Birth rank	
First	26 (37.68)
Second	27 (39.13)
Third	14 (20.29)
Fourth	2 (2.90)
Socio-economic status	
Home owners	58 (84)
Education parents	
Low	28 (42,42)
High	38 (57.58)
Employment parents	
One of the parents employed	4 (5.71)
Both parents employed	66 (94.29)

Values are number (%) or mean ± SD. BMI: Body Mass Index; ETS: Environmental Tobacco Smoke exposure; PC: personal computer use; TV: use of television.

3.2 EXPOSURE CHARACTERISTICS

Chronic exposure to particulate air pollution is implemented by the use of residential distance to major roads, of which the geometric mean (95% CI) was 39.46 meters (25.81 to 60.33), as shown in table 4. 20% of the participant's residence was located on a major road.

Acute exposure is defined by average exposure to concentrations of ultrafine particles (UFP), $PM_{2.5}$, PM_{10} and total suspended particles (TSP) between 09:00 and 10:00 a.m. Average indoor ultrafine particle concentrations (UFP in) were 18303 ± 7340 particles per cubic centimeter. The outdoor ultrafine particle concentration was on average 33847 ± 12690 particles per cubic centimeter. Indoor $PM_{2.5}$, PM_{10} and TSP concentrations averaged 15.89 ± 7.01 µg/m³, 105.87 ± 43.64µg/m³ and 145.38 ± 61.53 µg/m³ respectively. Table 4 also shows the minimum, maximum, median and interquartile range (IQR) values.

Table 4. Description of the exposure markers.

	Mean ± SD	Median	IQR	Min	Max
Distance (m)	39.46 (25.81 to 60.33)	152.49	7.92	0.10	1093
UFP in (#/cm³)	18303 ± 7340	17493	8113	6879	35449
UFP out (#/cm³)	33847 ± 12690	33848	16322	9059	60330
$PM_{2.5}$ (µg/m³)	15.89 ± 7.01	15.26	9.87	1.58	27.42
PM_{10} (µg/m³)	105.87 ± 43.64	104.35	60.29	20.35	184.10
TSP (µg/m³)	145.38 ± 61.53	140.00	89.64	28.55	244.48

Values are arithmetic mean ± SD, except for distance for which geometric mean (95% CI) is given.

The correlation between the different particulate matter fractions is given in table 5. Indoor UFP concentrations were highly correlated (r=0.95) with outdoor UFP concentrations. The correlation of UFP concentrations with other particulate matter fractions ($PM_{2.5}$, PM_{10} and TSP) decreased with increasing particulate mass, with the lowest correlation coefficient between indoor UFP concentrations and TSP concentrations (r=0.26). PM_{10} concentrations were most highly correlated with TSP concentrations (r=0.99). $PM_{2.5}$ concentrations were correlated with indoor and outdoor UFP concentrations (r=0.67 and r=0.64, respectively) as well as with PM_{10} (r=0.57) and TSP concentrations (r=0.48).

Table 5. Pearson correlation coefficients between the different particulate matter fractions.

	UFP in	UFP out	$PM_{2.5}$	PM_{10}	TSP
UFP in	1	0.95 p<0.0001	0.67 p<0.0001	0.32 p<0.0001	0.26 p=0.0003
UFP out	0.95 p<0.0001	1	0.65 p<0.0001	0.46 p<0.001	0.41 p<0.0001
$PM_{2.5}$	0.67 p<0.0001	0.65 p<0.0001	1	0.57 p<0.0001	0.48 p<0.0001
PM_{10}	0.32 p<0.0001	0.46 p<0.001	0.57 p<0.0001	1	0.99 p<0.0001
TSP	0.26 p=0.0003	0.41 p<0.0001	0.48 p<0.0001	0.99 p<0.0001	1

3.3 COGNITIVE TEST PERFORMANCE OUTCOMES

Table 6 presents the mean scores and standard deviations of the outcomes of the cognitive performance tests, summarized by participants (ID) and test session number (time). Average participant reaction time for the Stroop test (SRT) and Continuous Performance test (CPT) was 1572.99 milliseconds and 598.24 milliseconds respectively. Mean latency for the Digit-Symbol test (DigSym) was 125.18 sec and 4.38 seconds for the Pattern Comparison test (PatCom). On average, the participants could reproduce 5 digits in the forward Digit Span test (DspanF) and 4 digits in the backward Digit Span test (DspanB). Average reaction time and mean response latency of the relevant cognitive performance tests reduced with the number of test session numbers, while the numbers of reproduced digits in the digit span tests increased.

Table 6. Results of the cognitive performance tests averaged by participant (ID) and test session number (time).

	ID	Time 1	Time 2	Time 3
SRT (msec)	1572.99 ± 593.01	1843.32 ± 1734.4	1520.24 ± 480.53	1356.54 ± 273.56
CPT (msec)	598.24 ± 44.92	608 ± 52.41	599.33 ± 45.96	587.45 ± 49.11
DigSym (sec)	125.18 ± 22.15	130 ± 24.56	125.29 ± 24.86	118.58 ± 21.07
DspanF (#)	5.10 ± 0.77	4.97 ± 0.98	5.06 ± 0.95	5.26 ± 0.90
DspanB (#)	4.01 ± 0.73	3.88 ± 0.88	4.07 ± 0.85	4.04 ± 1.06
PatCom (sec)	4.38 ± 0.88	4.57 ± 1.07	4.41 ± 1.14	4.17 ± 0.97

Values are mean ± SD. SRT: mean reaction time Stroop test; CPT: mean reaction time Continuous Performance test; DigSym: latency Digit-Symbol Substitution test; DspanF: forward span length Digit Span test; DspanB: backward span length Digit Span test; PatCom: latency Pattern Comparison test.

3.4 ASSOCIATION BETWEEN TRAFFIC-RELATED AIR POLLUTION AND COGNITIVE PERFORMANCE

Explorative analyses showed that cognitive performance test outcomes were influenced by different predictors. One of the main covariates was the test session number, which implements the 'learning effect' associated with repeated cognitive performance measures. Hour of the day and the maximum outdoor apparent temperature were evenly so associated with differences in the outcome of the cognitive performance tests. Also birth weight and breast feeding influenced cognitive performance. These covariates were included in the adjusted analyses along with age, gender, BMI, exposure to environmental tobacco smoke, a known predictor of cognitive performance and education of the mother, as an indicator of the socioeconomic status. Other study variables, such as emotional state and blood pressure were not significantly associated with the cognitive test performance outcomes.

Figure 5 shows the fully adjusted associations between particulate air pollution and cognitive performance test outcome. The analyses integrated a chronic exposure marker, as implemented by residential distance to major roads, and an acute exposure marker, the indoor UFP concentration.

The Stroop test outcome (SRT) was significantly associated with both the chronic and the acute exposure marker. A doubling in the distance to major roads was significantly associated with the Stroop test outcome, with an estimated percent decrease in the mean reaction time of -1.34% (-2.30 to -0.38; p=0.0073). An interquartile range (IQR) increase in UFP concentrations of 8113 particles per cubic centimeter resulted in an estimated percent change in the mean reaction time of 5.44% (1.01 to 9.87; p=0.017).

Indoor UFP concentrations were also significantly associated with the outcome of the Continuous Performance test (CPT), with an estimated percent increase in the mean reaction time of 1.00% (0.23 to 1.77; p=0.0116). Similar to the Stroop test, acute exposure to higher indoor UFP concentrations resulted in a decrease in the CPT performance. No association was found between the CPT mean reaction time and distance to major roads.

None of the other NES tests, the Digit-Symbol test (DigSym), the Digit Span test (DspanF and DSpanB and the Pattern Comparison test (PatCom), showed any significant association with chronic exposure to particulate air pollution or with acute indoor UFP exposure.

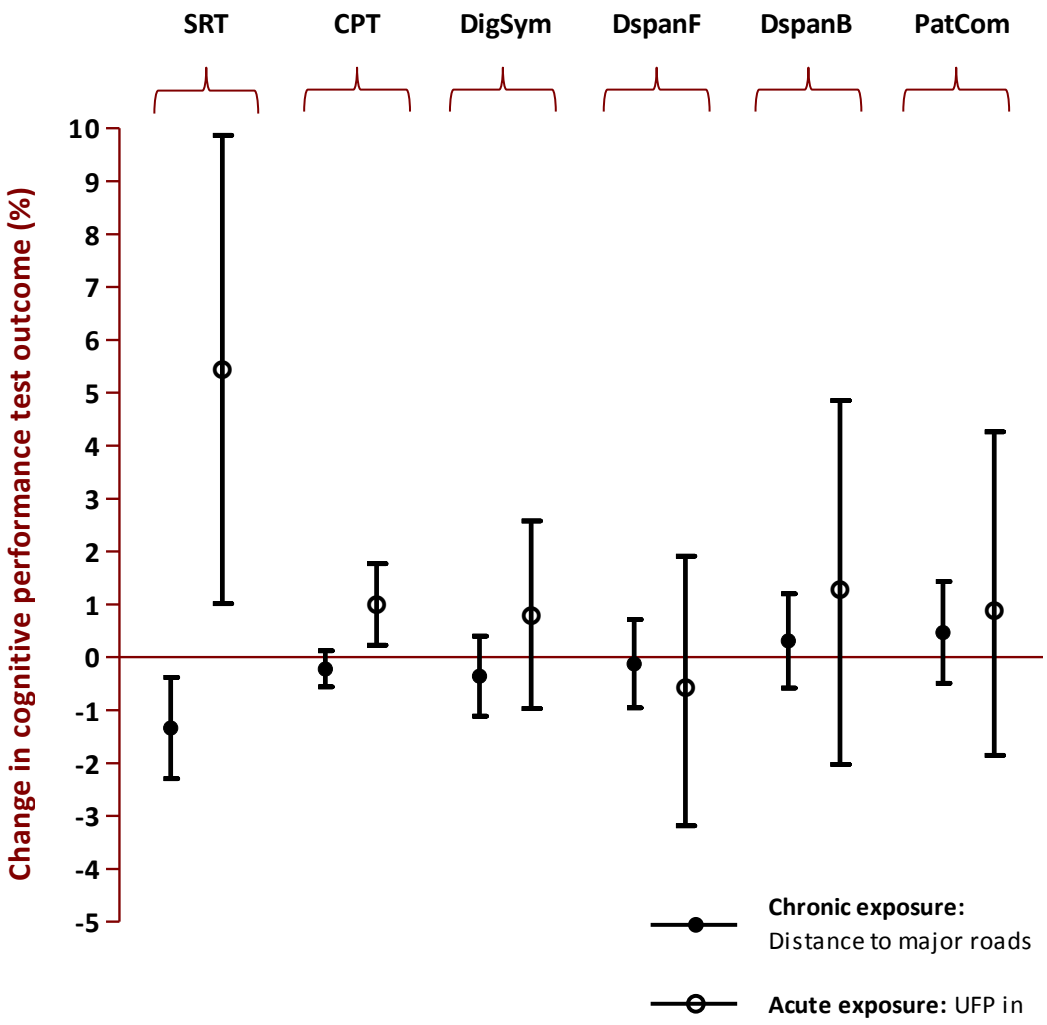

Figure 5. Associations between cognitive performance test outcome and a doubling of the distance to major roads as well as an interquartile range (8113 particles/cm³) increase in **indoor ultrafine particle concentration** (UFP in). Dots represent estimated percent change in cognitive test performance outcome and bars 95% confidence intervals. SRT: mean reaction time Stroop test; CPT: mean reaction time Continuous Performance test; DigSym: latency Digit-Symbol Substitution test; DSpanF: forward span length Digit Span test; DSpanB: backward span length Digit Span test; PatCom: latency Pattern Comparison test. Analyses were adjusted for age, gender, BMI, exposure to environmental tobacco smoke, birth weight, breast feeding, education of the mother, test session number, hour of the day and maximum outdoor apparent temperature.

As shown in figure 6, similar associations were found between cognitive test performance and distance to major roads with outdoor UFP concentrations as acute exposure marker compared to indoor UFP concentrations. A doubling in the distance to major roads was significantly associated with the Stroop test outcome, with an estimated percent change in the mean reaction time of -1.29% (-2.25 to -0.34; p=0.009).

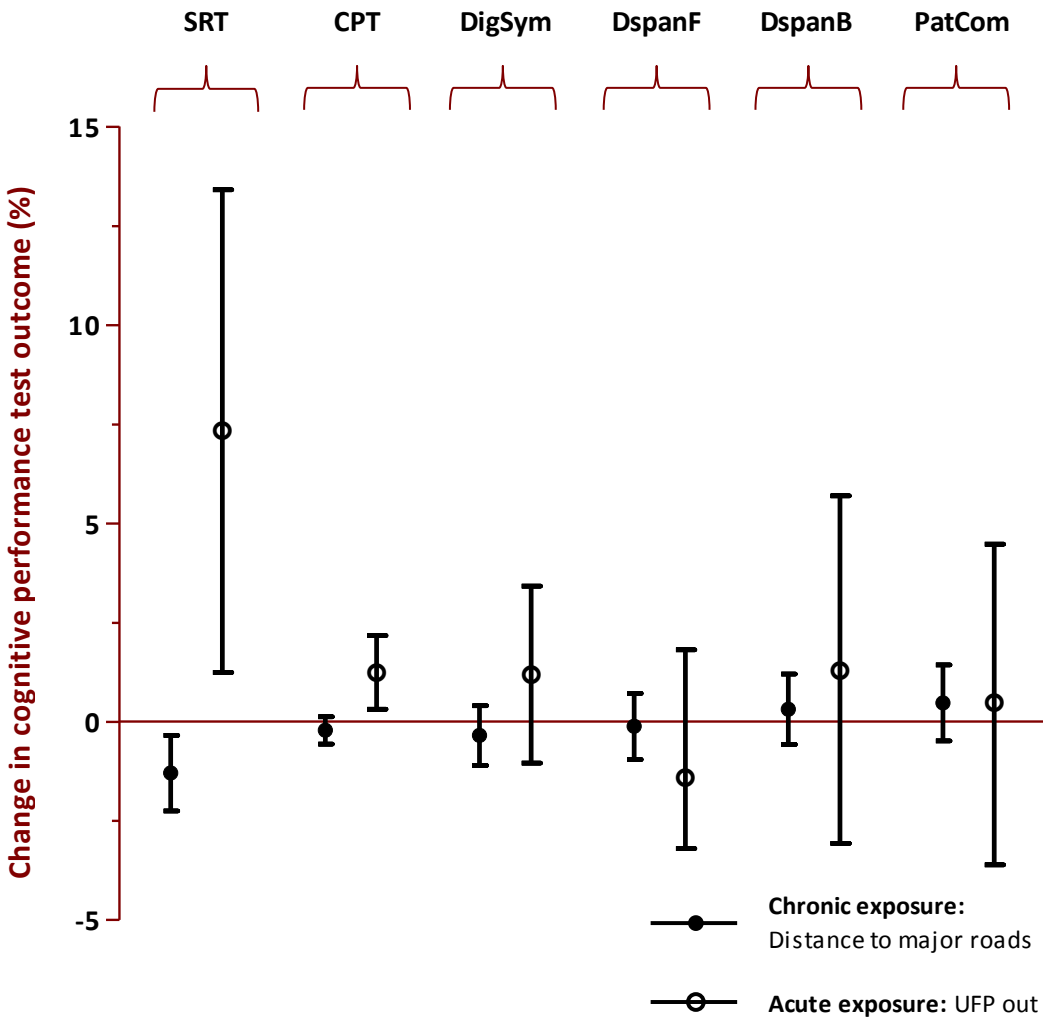

Figure 6. Associations between cognitive performance test outcome and a doubling of the distance to major roads as well as an interquartile range (16322 particles/cm³) increase in **outdoor ultrafine particles concentration** (UFP out). Dots represent estimated percent change in cognitive test performance outcome and bars 95% confidence intervals. SRT: mean reaction time Stroop test; CPT: mean reaction time Continuous Performance test; DigSym: latency Digit-Symbol Substitution test; DSpanF: forward span length Digit Span test; DSpanB: backward span length Digit Span test; PatCom: latency Pattern Comparison test. Analyses were adjusted for age, gender, BMI, exposure to environmental tobacco smoke, birth weight, breast feeding, education of the mother, test session number, hour of the day and maximum outdoor apparent temperature.

An IQR increase in UFP concentrations of 16322 particles per cubic centimeter resulted in an estimated percent change in the mean reaction time of 7.32% (1.24 to 13.41; p=0.0189). Outdoor UFP concentrations were also significantly associated with the CPT, with an estimated percent change in the mean reaction time of 1.24% (0.32 to 2.17; p=0.009).

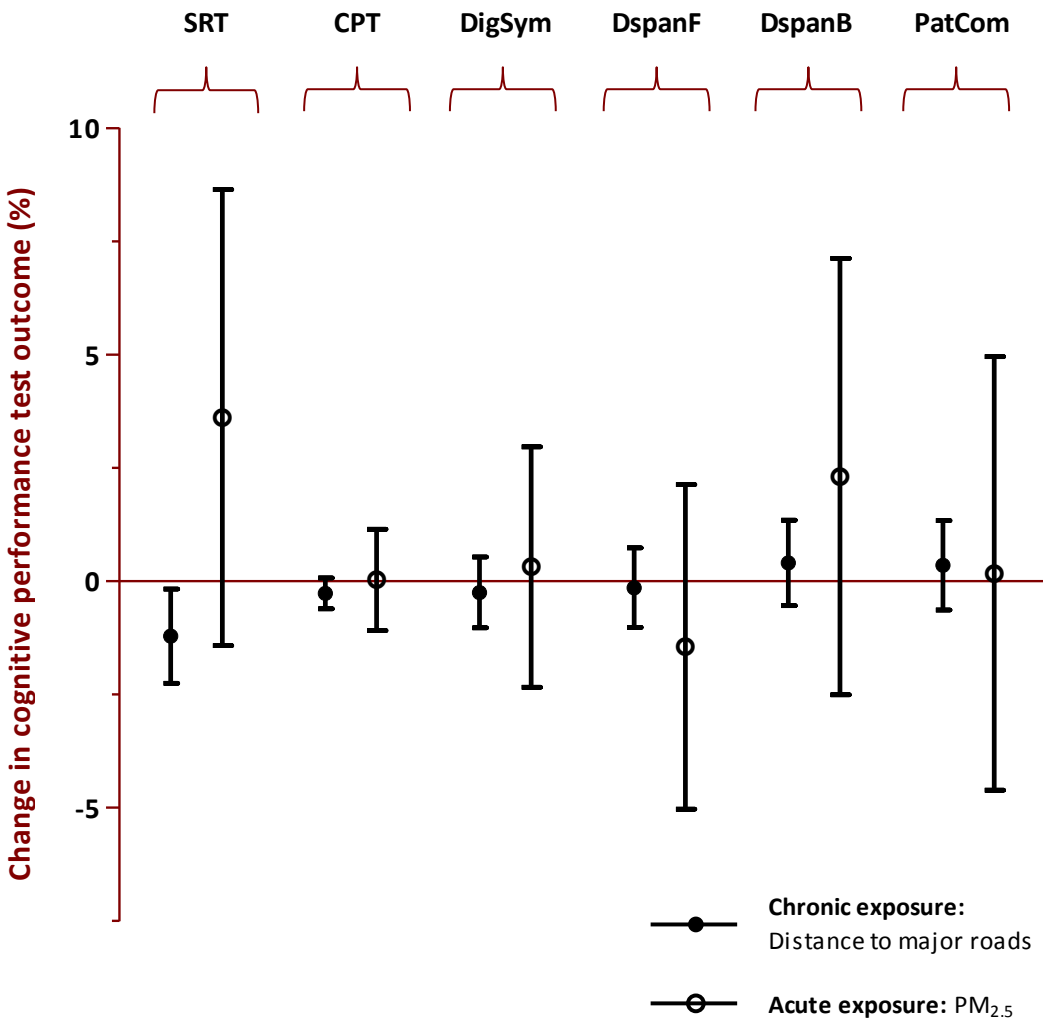

Figure 7. Associations between cognitive performance test outcome and a doubling of the distance to major roads as well as an interquartile range (9.87 µg/m³) increase in **$PM_{2.5}$.** Dots represent estimated percent change in cognitive test performance outcome and bars 95% confidence intervals. SRT: mean reaction time Stroop test; CPT: mean reaction time Continuous Performance test; DigSym: latency Digit-Symbol Substitution test; DSpanF: forward span length Digit Span test; DSpanB: backward span length Digit Span test; PatCom: latency Pattern Comparison test. Analyses were adjusted for age, gender, BMI, exposure to environmental tobacco smoke, birth weight, breast feeding, education of the mother, test session number, hour of the day and maximum outdoor apparent temperature.

Though distance to major roads was consistently and significantly associated with the Stroop test mean reaction time in the adjusted models with the other particulate matter fractions, $PM_{2.5}$ (figure 7), PM_{10} and TSP (data not shown), these fractions showed no significant association with SRT. No associations were found between the outcomes of the NES tests and $PM_{2.5}$ concentrations or distance to major roads.

Results of the adjusted analyses using PM_{10} or TSP were comparable (data not shown). Apart from a significant association between the outcome of the Stroop test and distance to major roads, no associations were found between the outcomes of the NES tests and chronic exposure to particulate air pollution or with PM_{10}/TSP exposure.

Results of the unadjusted analyses (data not shown) were comparable to adjusted analyses.

Effect modification was investigated by including interaction terms in the adjusted models. No significant interaction was found between distance to major roads or UFP and gender, education of the mother, test session number and hour of the day.

4. Discussion

This study investigated the effect of acute and chronic exposure to traffic-related air pollution on cognitive performance in a panel of primary schoolchildren. To date, this is the only study that has explored the association between cognitive performance and markers for both acute as well as chronic exposure.

4.1 Association between traffic-related air pollution and cognitive performance

Acute exposure to ultrafine particles and chronic exposure to particulate air pollution, as implemented by residential distance to major roads, was associated with decreases in cognitive performance test outcome. These associations could not be explained by age, gender, test session number, hour of the day, BMI, maximum outdoor apparent temperature, exposure to environmental tobacco smoke, birth weight, breast feeding or the mother's level of education.

Although observational studies do not establish causation, a number of features strengthen these findings. Decreases were seen consistently in the outcomes of both the attention tests (Stroop and Continuous Performance test) associated with exposure to ultrafine particles inside as well as outside. The association with residential distance to major roads was consistent in the analyses with different particulate matter fractions, though only for the Stroop test.

4.2 Mechanisms by which particulate air pollution affects cognitive performance

Several biological mechanisms have been proposed to explain how particulate air pollution may have an adverse effect on cognitive performance, as presented in figure 8.

First, ultrafine particles can pass through the air–blood barrier of the lung, enter the systemic circulation, and translocate to other body tissues, including the brain [14, 30]. Animal studies have also showed that ultrafine particles can translocate directly to the brain via the olfactory nerve [14, 15]. The presence of such particles in the brain is associated with inflammation and oxidative stress [15, 31].

Second, particulate matter may exert indirect effects on the central nervous function via effects on cardiovascular health. Exposure to PM is associated with a variety of cardiovascular end points [3, 5, 32], including hypertension and atherosclerosis. Several of these factors are also associated with a reduction in cognitive function [33, 34], which likely reflects the link between cognitive impairment and vascular brain pathology [35].

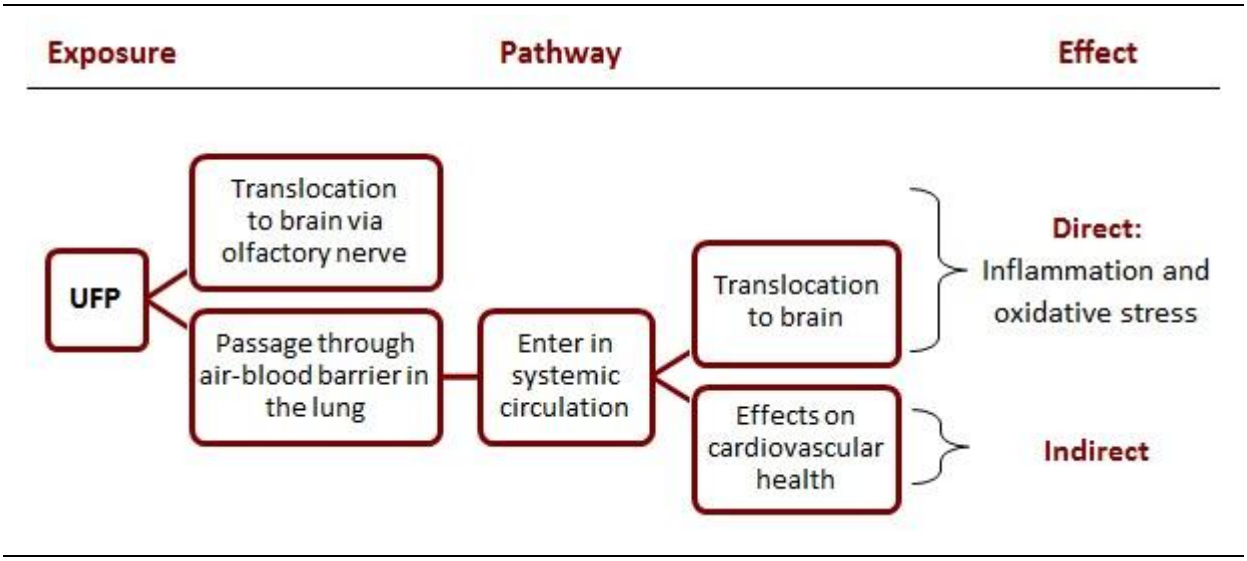

Figure 8. Mechanisms by which ultrafine particles (UFP) can affect cognitive performance.

4.3 COMPARISON WITH LITERATURE

Recently, four studies [18, 19, 21, 36] have reported associations between particulate air pollution exposure and cognitive performance. In the Third National Health and Nutrition Examination Survey (NHANES), the association between NES test outcome and PM_{10} disappeared after adjustment for demographic factors. The NES data included the outcome of the Digit-Symbol Substitution and Digit Span test for 1764 adult participants (aged 37.5 ± 10.9 years). Comparable to this study, the present study did not find an association between particulate air pollution and either of these tests, which reflect perception and memory.

In a prospective birth cohort, Suglia et al. assessed cognition in 202 children, aged 8 to 11 years, and exposure to black carbon as a traffic-related air pollutant. Children who were exposed to higher levels of black carbon showed a decrease in cognitive function across assessments of verbal and nonverbal intelligence and memory constructs.

However, in order to assess cognition Suglia et al. used the Wide Range Assessment of Memory and Learning and the Kaufman Brief Intelligence Test, which did not assess attention. These results are therefore not comparable to the present study.

Ranft et al. associated long-term exposure to particulate air pollution, indicated by distance of the participant's home address to the next busy road, with mild cognitive impairment in 399 elderly women (aged 68-79 years). Consistent with the results of the present study, individuals who lived closer to a busy street performed worse on the Stroop test. Accordingly, Weuve et al. found that long-term exposure to $PM_{2.5-10}$ and $PM_{2.5}$ was associated with significantly worse cognitive decline in older women. These studies however focused on the effect of particulate air pollution exposure on a developed brain in elderly, while the present study addresses the impact on the developing brain in children.

Furthermore, living close to major roads also implies being exposed to high levels of traffic noise [37]. In a cross-sectional study, van Kempen et al. found that chronic exposure to road or aircraft noise has an impact on cognitive performance, more specific in the more difficult parts of the attention tests [26]. It cannot be excluded that the results of the present study are at least partly the consequence of chronic exposure to traffic noise. Conversely, it is also possible that the associations previously found between road or aircraft noise are actually due to air pollutants.

4.4 STUDY LIMITATIONS

The present study has a number of limitations. First, only the characteristics of the 70 subjects that participated in the study were available so no conclusions could be drawn on whether the participants differed from the general primary school population. Also the participation rate was low (33%) and the reason for non-participation was not known.

The use of distance to major roads as a marker for chronic exposure only provides indirect evidence for an effect of traffic-related air pollution exposure since air pollution near streets is a complex mixture where particulate air pollution is one compound among others[19]. In addition, other variables that could influence exposure, such as traffic density, were not taken into account.

While adjustments were made for a number of factors associated with cognitive performance and particulate air pollution, it is still possible that the chronic effects found in the present study could be attributable to unmeasured or residential confounding, perhaps most notably from socioeconomic status. Socioeconomic status has been shown to be a determinant of cognitive ability [38] and can determine whether a family lives in close proximity to roadways [39]. However, as in agreement with studies in the Netherlands, such an association between socioeconomic status and residential proximity to major roads was not found in the present study and analyses were adjusted for educational level of the mother, a known predictor for cognitive function. Another limitation of the present study is the lack of adjustment for special educational needs, such as ADHD and dyslexia.

In contrast with the estimation of chronic effects, confounding due to personal characteristics of the participants is expected to be minimal when estimating the acute effects, due to the repeated measure design. On the other hand, confounding by time dependent variables such as test session number, hour of the day and temperature are more likely. Test sessions were therefore scheduled on a fixed time for each child, consistent over the different test sessions to exclude circadian effects. Further adjustments for maximum outdoor apparent temperature were made.

Due to time limitations there was no data available on the participants' exposure to other environmental pollutants, which are possibly related to cognitive performance, such as lead, which has a known effect on cognitive performance. However, these data will be available in the future since designated samples were collected during the test sessions.

4.5 FUTURE RESEARCH

The present study is still ongoing, with the recruitment of new schools for participation. The number of subjects will be expanded to approximately 200 individuals.

The samples, which were collected in the present study, will be analyzed. With the collected urine samples, internal heavy metal burden will be determined, which can be implemented in the analyses as already discussed in section 4.4.

The collected RNA will be used to investigate the transcription of neurological and inflammation related genes in relation to exposure to particulate air pollution and cognitive performance. The collected DNA will be used for genotyping in order to assess the effect of genotype on the association between cognitive performance and particulate air pollution exposure.

Additional research into the effects of exposure to particulate air pollution on neurological development is desirable, with more emphasis on the effect on attention. Future studies may be designed to distinguish traffic effects due to noise from those due to pollution and should include more variables for the estimation of chronic exposure, such as traffic density but also interpolated data on PM_{10} or $PM_{2.5}$. Furthermore, future molecular research should explore the underlying mechanisms to the associations found in the present study.

5. Conclusion and Synthesis

In summary, the present study investigated the effect of traffic-related air pollution, more specific ultrafine particles, on the cognitive performance in primary schoolchildren.

The key finding is a significant association between acute exposure to ultrafine particles and an increase in the mean reaction time of the Stroop and Continuous Performance test, both designed to assess attention. In addition, a doubling in the residential distance to major roads, a marker for chronic exposure, was associated with a reduction in the mean reaction time of the Stroop test.

To date, this is the first study to implement markers for both acute and chronic exposure.

The present study indicates that **acute exposure to ultrafine particles** and **chronic exposure** to particulate air pollution, as implemented by residential distance to major roads, is **associated** with a **consistent effect** on children's **attention**.

REFERENCES

1. WORLD HEALTH ORGANIZATION. Health effects of traffic-related air pollution. Report 2005.
2. HEALTH EFFECTS INSTITUTE. Traffic-Related Air Pollution: A Critical Review of the Literature on Emissions, Exposure, and Health Effects. Report 2010.
3. NAWROT TS, NEMMAR A, NEMERY B. Air pollution: To the heart of the matter. European heart journal 2006; 27 (19): 2269-71.
4. EUROPEAN ENVIRONMENT AGENCY. Air quality in Europe. Report 2011.
5. POPE CA, 3RD AND DOCKERY DW. Health effects of fine particulate air pollution: lines that connect. J Air Waste Manag Assoc 2006; 56 (6): 709-42.
6. HEINRICH J AND SLAMA R. Fine particles, a major threat to children. International journal of hygiene and environmental health 2007; 210 (5): 617-22.
7. ENGLERT N. Fine particles and human health--a review of epidemiological studies. Toxicology letters 2004; 149 (1-3): 235-42.
8. BRUNEKREEF B AND HOLGATE ST. Air pollution and health. Lancet 2002; 360 (9341): 1233-42.
9. DE KOK TM, DRIECE HA, HOGERVORST JG, BRIEDE JJ. Toxicological assessment of ambient and traffic-related particulate matter: a review of recent studies. Mutation research 2006; 613 (2-3): 103-22.
10. DONALDSON K, STONE V, CLOUTER A, RENWICK L, MACNEE W. Ultrafine particles. Occupational and environmental medicine 2001; 58 (3): 211-6, 199.
11. THE EUROPEAN PARLIAMENT AND COUNCIL. DIRECTIVE 2008/50/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 21 May 2008 on ambient air quality and cleaner air for Europe. Report 11-06-2008.
12. KUNZLI N. From bench to policies: ready for a nanoparticle air quality standard? European heart journal 2011; 32 (21): 2613-5.
13. POPE CA, 3RD. Epidemiology of fine particulate air pollution and human health: biologic mechanisms and who's at risk? Environmental health perspectives 2000; 108 Suppl 4: 713-23.
14. OBERDORSTER G, SHARP Z, ATUDOREI V, ELDER A, GELEIN R, KREYLING W, COX C. Translocation of inhaled ultrafine particles to the brain. Inhalation toxicology 2004; 16 (6-7): 437-45.
15. ELDER A, GELEIN R, SILVA V, FEIKERT T, OPANASHUK L, CARTER J, POTTER R, MAYNARD A, ITO Y, FINKELSTEIN J, OBERDÖRSTER G. Translocation of Inhaled Ultrafine Manganese Oxide Particles to the Central Nervous System. Environmental health perspectives 2006; 114 (8): 1172-8.

16. CAMPBELL A, OLDHAM M, BECARIA A, BONDY SC, MEACHER D, SIOUTAS C, MISRA C, MENDEZ LB, KLEINMAN M. Particulate matter in polluted air may increase biomarkers of inflammation in mouse brain. Neurotoxicology 2005; 26 (1): 133-40.
17. FONKEN LK, XU X, WEIL ZM, CHEN G, SUN Q, RAJAGOPALAN S, NELSON RJ. Air pollution impairs cognition, provokes depressive-like behaviors and alters hippocampal cytokine expression and morphology. Molecular psychiatry 2011; 16 (10): 987-95, 73.
18. CHEN JC AND SCHWARTZ J. Neurobehavioral effects of ambient air pollution on cognitive performance in US adults. Neurotoxicology 2009; 30 (2): 231-9.
19. RANFT U, SCHIKOWSKI T, SUGIRI D, KRUTMANN J, KRAMER U. Long-term exposure to traffic-related particulate matter impairs cognitive function in the elderly. Environmental research 2009; 109 (8): 1004-11.
20. WEUVE J, PUETT RC, SCHWARTZ J, YANOSKY JD, LADEN F, GRODSTEIN F. Exposure to particulate air pollution and cognitive decline in older women. Archives of internal medicine 2012; 172 (3): 219-27.
21. SUGLIA SF, GRYPARIS A, WRIGHT RO, SCHWARTZ J, WRIGHT RJ. Association of black carbon with cognition among children in a prospective birth cohort study. American journal of epidemiology 2008; 167 (3): 280-6.
22. SACKS JD, STANEK LW, LUBEN TJ, JOHNS DO, BUCKLEY BJ, BROWN JS, ROSS M. Particulate matter-induced health effects: who is susceptible? Environmental health perspectives 2011; 119 (4): 446-54.
23. SALVI S. Health effects of ambient air pollution in children. Paediatric respiratory reviews 2007; 8 (4): 275-80.
24. SCHWARTZ J. Air pollution and children's health. Pediatrics 2004; 113 (4 Suppl): 1037-43.
25. LETZ R. Use of computerized test batteries for quantifying neurobehavioral outcomes. Environmental health perspectives 1991; 90: 195-8.
26. VAN KEMPEN E, VAN KAMP I, LEBRET E, LAMMERS J, EMMEN H, STANSFELD S. Neurobehavioral effects of transportation noise in primary schoolchildren: a cross-sectional study. Environmental health : a global access science source 2010; 9: 25.
27. ARCIA E AND OTTO DA. Reliability of selected tests from the neurobehavioral evaluation system. Neurotoxicology and teratology 1992; 14 (2): 103-10.
28. EMMEN HH SB, DEIJEN JB. A feasibility study of the application of neurobehavioral tests for studying the effects of air craf noise on primary schoolchildren living in the vicinity of Schiphol Airport in the Netherlands. Bilthoven: RIVM 1997.

29. HOEK G, BRUNEKREEF B, GOLDBOHM S, FISCHER P, VAN DEN BRANDT PA. Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. Lancet 2002; 360 (9341): 1203-9.
30. PETERS A, VERONESI B, CALDERON-GARCIDUENAS L, GEHR P, CHEN LC, GEISER M, REED W, ROTHEN-RUTISHAUSER B, SCHURCH S, SCHULZ H. Translocation and potential neurological effects of fine and ultrafine particles a critical update. Particle and fibre toxicology 2006; 3: 13.
31. 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 and cognition 2008; 68 (2): 117-27.
32. BROOK RD. Is air pollution a cause of cardiovascular disease? Updated review and controversies. Reviews on environmental health 2007; 22 (2): 115-37.
33. QIU C, WINBLAD B, FRATIGLIONI L. The age-dependent relation of blood pressure to cognitive function and dementia. Lancet neurology 2005; 4 (8): 487-99.
34. KOMULAINEN P, KIVIPELTO M, LAKKA TA, HASSINEN M, HELKALA EL, PATJA K, NISSINEN A, RAURAMAA R. Carotid intima-media thickness and cognitive function in elderly women: a population-based study. Neuroepidemiology 2007; 28 (4): 207-13.
35. POWER MC, WEISSKOPF MG, ALEXEEFF SE, COULL BA, SPIRO A, 3RD, SCHWARTZ J. Traffic-related air pollution and cognitive function in a cohort of older men. Environmental health perspectives 2011; 119 (5): 682-7.
36. TCHETGEN TCHETGEN EJ, GLYMOUR MM, WEUVE J, ROBINS J. Specifying the correlation structure in inverse-probability- weighting estimation for repeated measures. Epidemiology 2012; 23 (4): 644-6.
37. ALLEN RW, DAVIES H, COHEN MA, MALLACH G, KAUFMAN JD, ADAR SD. The spatial relationship between traffic-generated air pollution and noise in 2 US cities. Environmental research 2009; 109 (3): 334-42.
38. NOBLE KG, MCCANDLISS BD, FARAH MJ. Socioeconomic gradients predict individual differences in neurocognitive abilities. Developmental science 2007; 10 (4): 464-80.
39. O'NEILL MS, JERRETT M, KAWACHI I, LEVY JI, COHEN AJ, GOUVEIA N, WILKINSON P, FLETCHER T, CIFUENTES L, SCHWARTZ J. Health, wealth, and air pollution: advancing theory and methods. Environmental health perspectives 2003; 111 (16): 1861-70.

SUPPLEMENTS

SUPPLEMENT 1 – KORTE DEPRESSIEVRAGENLIJST VOOR KINDEREN

Op de achterkant van dit blad staan een aantal vragen die jij moet gaan beantwoorden. Lees elke zin goed door. Het is de bedoeling dat je bij elke zin denkt of die voor jou *waar* is of *niet waar*. Bij elke zin kun je kiezen tussen twee antwoorden, namelijk : 'Dat is waar' en : 'Dat is niet waar'. Bij het antwoord dat je het beste vindt, zet je een kruisje. Denk niet te lang na en probeer je antwoord zo vlug mogelijk te geven.

Je mag bij elke vraag maar één vakje aankruisen.
Sla geen vragen over.

Draai dit blad om.

1. Ik heb de laatste tijd bijna nergens meer zin in
- ☐ Dat is waar
- ☐ Dat is niet waar

2. Ik voel me de laatste tijd niet zo lekker
- ☐ Dat is waar
- ☐ Dat is niet waar

3. Ik slaap de laatste tijd niet zo goed
- ☐ Dat is waar
- ☐ Dat is niet waar

4. Als ik iets ga doen, denk ik vaak dat het toch wel zal mislukken
- ☐ Dat is waar
- ☐ Dat is niet waar

5. Ik denk vaak dat andere kinderen mij niet leuk vinden
- ☐ Dat is waar
- ☐ Dat is niet waar

6. Ik denk de laatste tijd vooral aan vervelende dingen die gaan gebeuren
- ☐ Dat is waar
- ☐ Dat is niet waar

7. Ik denk wel eens dat het later niet goed met mij zal gaan
- ☐ Dat is waar
- ☐ Dat is niet waar

8. Als er iets vervelends gebeurt, denk ik vaak dat het door mij komt
- ☐ Dat is waar
- ☐ Dat is niet waar

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