Outdoor exposure to residential noise, neurodevelopment, and sleep in children and preadolescents

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A la meva família, per donar-me suport en cada decisió que prenc de la meva vida,
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Abstract

Environmental noise pollution has become a major public health concern due to its increase during the last decades as a result of urbanization processes. Environmental noise can be produced by different sources but the most prevalent source in Europe is road traffic. Previous epidemiological and experimental studies have indicated that environmental noise is related to several human health effects. Although children are considered as a vulnerable population to the effects of environmental noise, epidemiological studies that assessed environmental noise exposure and its relationship with neurodevelopment and sleep in children are scarce and inconclusive.

This thesis aimed to better understand the potential association between environmental noise exposure and neurodevelopment and sleep in children by: i) assessing emotional, aggressive, and attention-deficit/hyperactivity disorder (ADHD)-related symptoms, cognitive and motor function, and functional brain connectivity, and ii) assessing sleep using maternal-reported data and physiological sleep measures collected by actigraphy. To this aim, we used existing noise maps from road traffic and multiple (i.e., railway, aircraft, industry, and road traffic) noise, and our study populations consisted of children from two European prospective birth cohorts.

The exposure to outdoor residential road traffic noise was not associated with emotional, aggressive, ADHD-related symptoms, cognitive and motor function, functional brain connectivity, and maternal-reported sleep disturbances in children and preadolescents. However, residential exposure to road traffic noise was related to shorter sleep duration and longer wake after sleep onset in preadolescents. Similar findings were found when multiple noise exposure was assessed. Therefore, sleep may be compromised in preadolescents exposed to higher levels of environmental noise. Although the effect size of the estimates of the physiological sleep measures were small, and may have a small impact at the individual level, it may have a greater effect at population-level, since the majority of the population is exposed to environmental noise, mainly from road traffic.

Resum

La contaminació acústica ambiental s'ha convertit en un problema de salut pública important pel seu augment durant les últimes dècades com a conseqüència dels processos d'urbanització. El soroll ambiental pot ser produït per diferents fonts, però la font més freqüent a Europa és el trànsit rodat. Estudis epidemiològics i experimentals previs han mostrat que el soroll ambiental està relacionat amb diversos efectes sobre la salut humana. Encara que els nens i nenes es consideren una població vulnerable als efectes del soroll ambiental, els estudis epidemiològics que avaluen l'exposició al soroll ambiental i la seva relació amb el neurodesenvolupament i el son són escassos i poc concloents.

Aquesta tesi té com objectiu entendre millor les possibles associacions entre l'exposició al soroll ambiental i el neurodesenvolupament i el son en nens i nenes. Per fer-ho: i) hem avaluat els símptomes emocionals, agressius i relacionats amb el trastorn per dèficit d'atenció/hiperactivitat (TDAH), la funció cognitiva i motora i la connectivitat funcional cerebral, i ii) hem avaluat el son mitjançant dades reportades per les mares i amb mesures del son recollides per actigrafia. Amb aquest objectiu, hem utilitzat mapes de soroll existents del trànsit rodat i soroll múltiple (ferrocarrils, avions, indústria i trànsit rodat). Les nostres poblacions d'estudi consistien en nens i nenes de dues cohorts de naixement prospectives europees.

L'exposició residencial al soroll del trànsit rodat no es va associar amb símptomes emocionals, agressius i relacionats amb el TDAH, la funció cognitiva i motora, la connectivitat funcional cerebral i els trastorns del son reportats per les mares en nens i nenes i preadolescents. Tanmateix, l'exposició residencial al soroll del trànsit es va associar amb una durada del son més curta i una vigília més llarga després de l'inici del son en els preadolescents. Es van trobar resultats similars quan es va avaluar l'exposició al soroll múltiple. Per tant, es pot concloure que el son es pot veure compromès en preadolescents exposats a nivells més alts de soroll ambiental. Tot i que l'efecte de la mida de les estimacions de les mesures fisiològiques del son va ser petit i es pot traduir a un petit impacte a nivell individual, pot tenir un efecte més gran a nivell poblacional, ja que la majoria de la població està exposada al soroll ambiental, principalment del trànsit rodat.

Resumen

La contaminación acústica ambiental se ha convertido en un problema de salud pública importante debido a su aumento durante las últimas décadas como consecuencia de los procesos de urbanización. El ruido ambiental puede provenir de diferentes fuentes, pero la fuente más frecuente en Europa es el tráfico rodado. Estudios epidemiológicos y experimentales previos han indicado que el ruido ambiental está relacionado con varios efectos sobre la salud humana. Aunque los niños y niñas son considerados una población vulnerable a los efectos del ruido ambiental, los estudios epidemiológicos que evaluaron la exposición al ruido ambiental y su relación con el neurodesarrollo y el sueño son escasos y poco concluyentes.

Esta tesis tiene como objetivo comprender mejor las posibles asociaciones entre la exposición al ruido ambiental y el neurodesarrollo y el sueño en niños y niñas mediante: i) la evaluación de los síntomas emocionales, agresivos y relacionados con el trastorno de déficit de atención/hiperactividad (TDAH), la función cognitiva y motora y la conectividad funcional cerebral, y ii) la evaluación del sueño utilizando datos reportados por las madres y medidas fisiológicas del sueño recopiladas mediante actigrafía. Con este objetivo, utilizamos mapas de ruido existentes del tráfico rodado y ruido múltiple (ferrocarril, aviones, industria y tráfico rodado). Nuestras poblaciones de estudio consistieron en niños de dos cohortes de nacimiento prospectivas europeas.

La exposición residencial al tráfico rodado no se asoció con síntomas emocionales, agresivos y relacionados con el TDAH, la función cognitiva y motora, la conectividad funcional cerebral y los trastornos del sueño reportados por las madres en niños y niñas y preadolescentes. Sin embargo, la exposición residencial al ruido del tráfico rodado se relacionó con una menor duración del sueño y una vigilia más prolongada después del inicio del sueño en los preadolescentes. Se encontraron hallazgos similares cuando se evaluó la exposición al ruido múltiple. Por lo tanto, concluimos que el sueño puede verse comprometido en preadolescentes expuestos a niveles más altos de ruido ambiental. Aunque el tamaño del efecto de las estimaciones de las medidas fisiológicas del sueño fue pequeño y puede tener un impacto pequeño a nivel individual, se puede traducir a un efecto mayor a nivel poblacional, ya que la

mayoría de la población está expuesta al ruido ambiental, principalmente del tráfico rodado.

Preface

This PhD thesis was written between 2018 and 2022 at the Barcelona Institute for Global Health (ISGlobal). It was supervised by Dr. Mònica Guxens. This work consists of a compilation of four scientific publications co-authored by the PhD candidate, and complies with the procedures and regulations of the Biomedicine PhD program of the Department of Experimental and Health Sciences of the Universitat Pompeu Fabra. The research presented in this thesis has been funded by the Spanish Institute for Health Carlos III with the *"Radiofrequency electromagnetic fields, noise, and sleep problems in adolescence – INMA-Ado-Sleep Project"*, grant number PI17/01340 and by the Health Effects Institute with *the Air Pollution, Autism spectrum disorders, and brain imaging amongst CHildren in Europe – APACHE* project, grant number R-82811201.

This thesis is focused on the associations between outdoor exposure to residential noise, neurodevelopment, and sleep in children and preadolescents. The book here presented includes an abstract in English, Catalan, and Spanish, a general introduction, objectives, methods, results (four original research articles), a general discussion, and conclusions. The scientific papers included in this thesis are based on noise data from European noise maps created following the European Environmental Noise Directive, on air pollution data from the European Study of Cohorts for Air Pollution Effects (ESCAPE), and data from two European prospective birth cohorts: the INfancia y Medio Ambiente (INMA) Project and the Generation R Study.

The PhD candidate has also contributed in five other research articles, has supervised two master students' final projects, has done epidemiological and statistical courses, has peer-reviewed one scientific article, and has participated in scientific conferences at national and international level as well as in activities address to the general population (see Appendix). As part of the PhD training, the candidate did a research stay at Erasmus University Medical Center (Department of Child and Adolescent Psychiatry/Psychology), under the supervision of Dr. Ryan Muetzel.

Abbreviations

ADHD – Attention-Deficit/Hyperactivity Disorder

BOLD – Blood-oxygen-level-dependent

CBCL – Child behavioural checklist

CPRS – Conners parent rating scale

dB – DeciBels

DSM-IV – Diagnostic and statistical manual of mental disorders 4th edition

HPA – Hypothalamic-pituitary-adrenal axis

L_{DAY} – A-weighted long-term average sound level during the day

L_{DEN} – A-weighted long-term average sound level during the 24-h of the day

L_{NIGHT} – A-weighted long-term average sound level during the night

MRI – Magnetic resonance imaging

NO_x – Nitrogen oxides

NO_2 – Nitrogen dioxide

$PM_{2.5}$ – Particulate matter, aerodynamic diameter <2.5 μm

PM_{10} – Particulate matter, aerodynamic diameter < 10 μm

PM_{coarse} – Particulate matter, difference between PM_{10} and $PM_{2.5}$

$PM_{2.5}$ absorbance – Absorbance of $PM_{2.5}$ filters

rs-fMRI – Resting state functional magnetic resonance imaging

SDQ – Strengths and difficulties questionnaire

SDSC – Sleep disturbance scale for children

WHO – World Health Organization

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1. INTRODUCTION

The past decades have seen an enormous rise in population growth and, consequently, in the urbanization processes. It has been predicted that by 2050, 70% of the population will inhabit in urban areas (United Nations, 2016). Urban design may provide improved sanitation, infrastructures, and access to health services but it could also have detrimental effects on our health and well-being (Wang, 2018). As a result of urbanization, exposure to environmental noise has become impossible to avoid and most of the population is exposed on a daily basis. Transportation noise (i.e., road, railway, and aircraft noise) is a major concern in European cities, being classified as the second most important cause of ill health in Western Europe (European Environment Agency, 2020). Interestingly, previous research, conducted predominantly in adults, has indicated plausible associations for the exposure to environmental noise and high annoyance, high sleep disturbance, premature mortality, and cardiovascular and metabolic effects (European Environment Agency, 2020). However, the health effects of exposure to environmental noise are less studied compared to other environmental factors.

1.1 Environmental noise exposure

The Environmental Noise Directive defines environmental noise as the unwanted or harmful outdoor sound created by human activities, including noise emitted by means of transport - road traffic, railway traffic, aircraft traffic - and from sites of industrial activity (European Environmental Noise Directive, 2002). Therefore, noise in workplaces, noise from domestic and leisure activities, from neighbors, from wind turbines, or noise from military activities is not considered in this definition (European Environmental Noise Directive, 2002).

The Environmental Noise Directive also describes different noise indicators that can be used depending on the outcome, noise source, and time window of interest for the noise effect. These indicators are usually expressed as the equivalent sound pressure level in decibels (dB), determined over all the days of the year, and based on daily annual averages. The daily annual average can be

divided into different time periods of the day, resulting in the following noise indicators:

- L_{DAY}: A-weighted[1] long-term average sound level during the day period.
- $L_{EVENING}$: A-weighted long-term average sound level during the evening period.
- L_{NIGHT}: A-weighted long-term average sound level during the night period.

L_{DEN} represents the A-weighted average sound level over the entire 24-hour day of the three periods described above with an evening (+5 dB) and night (+10 dB) weighting, given the expected greater health impact of these time periods (European Environmental Noise Directive, 2002).

Some guidelines have been published to provide recommended noise exposure levels in order to reduce exposure and improve the health of the population. According to the European Environment Agency, high noise levels are defined as those above 55 dB L_{DEN} and 50 dB L_{NIGHT} (European Environment Agency, 2020). However, the World Health Organization (WHO) established different recommendations based on the individual noise sources (World Health Organization, 2018):

Table 1. Recommendations from the WHO environmental noise guidelines

Noise indicator	Noise threshold levels		
	Road	*Railway*	*Aircraft*
L_{DEN}	53 dB	54 dB	45 dB
L_{NIGHT}	45 dB	44 dB	40 dB

Abbreviations: dB, decibels.

In addition, many countries have put in place national limit values that do not necessary reflect the recommended noise levels mentioned above (EPA Network Interest Group on Noise Abatement (IGNA), 2019). Generally, limit values in European countries are higher, thus less restrictive, than the levels recommended by the WHO. For road and railway noise, around 80

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[1] A frequency-dependent correction that is applied to a measured or calculated sound of moderate intensity to mimic the varying sensitivity of the ear to sound for different frequencies.

to 90% of the countries use higher limit values than the WHO recommendations and for aircraft noise, all countries use higher values than the recommendation (EPA Network Interest Group on Noise Abatement (IGNA), 2019).

Road traffic noise is the most prevalent noise source in Europe, followed by railway, aircraft, and industry noise (European Environment Agency, 2020). The amount of people exposed to L_{DEN} noise levels of 55 dB or higher is estimated to be 113 million for road traffic noise, 22 million for railway noise, 4 million for aircraft, and less than 1 million for industry noise. Road traffic is also the most significant source of environmental noise during the night (European Environment Agency, 2020). These results suggest that at least 20% of the European population is exposed to high levels of noise during the 24 hours of a day and more than 15% during the night.

1.2 Children and preadolescents

Fetuses, children, and preadolescents are most susceptible to the harmful effects of environmental noise, as their neural and immune systems are still in development. The neurodevelopmental period is characterized by numerous crucial processes (e.g. neurulation, cell proliferation and migration, myelination, and synaptic pruning), necessary for proper development (Stiles & Jernigan, 2010). The disruption of any of these processes could lead to irreversible alterations that manifest later in life.

During pregnancy, exposure to environmental noise could act as a stressor that increases the levels of maternal stress hormones and affects the hypothalamic-pituitary-adrenal (HPA) axis, impacting the brain development of the child (Jafari et al., 2017; Lautarescu et al., 2020). In children, it could also be a stressor that alters the HPA axis as well as the size and neural architecture of some brain areas (Smith & Pollak, 2020). In addition, children have less developed coping strategies than adults to deal with environmental noise and less control over the noise to which they are exposed (S. A. Stansfeld & Matheson, 2003).

1.3 Environmental noise exposure and neurodevelopment

It is widely recognized that children exposed to adverse events early in life are at increased risk for atypical neurodevelopment which can impact on individual's attention, conduct, language, memory, motor skills or other neurological functions (Nelson & Gabard-Durnam, 2020). Although the symptoms and behaviors of neurodevelopmental disabilities often evolve as a child gets older, some of them are likely to be long-lasting. Epidemiological studies investigating the possible association between exposure to environmental noise and neurodevelopment in children are emerging. In the present thesis, emotional, aggressive, and attention-deficit/hyperactivity disorder (ADHD)-related symptoms, cognitive and motor function, and functional brain connectivity are contemplated to assess child's neurodevelopment.

Related to emotional, aggressive, and ADHD-related symptoms, there is previous evidence that examined its relationship with environmental noise exposure, mainly from road traffic, in children (Clark et al., 2020; Clark & Paunovic, 2018a, 2018b; S. Stansfeld & Clark, 2015; Zijlema et al., 2021). However, they often show heterogeneous results. During pregnancy, no evidence was found of an association between residential road traffic noise and emotional and aggressive symptoms (Hjortebjerg et al., 2016) or ADHD-related symptoms (Hjortebjerg et al., 2016; K. V. Weyde et al., 2017). Similarly, with relation to residential road traffic noise exposure throughout childhood, no associations with emotional and aggressive symptoms were found in previous studies (Forns et al., 2016; Hjortebjerg et al., 2016). However, two studies reported that road traffic noise exposure at schools was related with less aggressive symptoms in children at 9-10 years of age (Crombie et al., 2011; S. A. Stansfeld et al., 2009). Regarding ADHD-related symptoms, most of the studies showed an association of higher road traffic noise exposure at home or at school with higher hyperactivity or inattention problems in children at 7-11 years of age (Forns et al., 2016; Hjortebjerg et al., 2016; Tiesler et al., 2013; K. V. Weyde et al., 2017). In contrast, one study found no association between road traffic noise exposure at school and ADHD-related symptoms in children at 10-12 years of age (Zijlema et al., 2021).

Recent years have also seen an increase of the evidence linking environmental noise exposure and cognitive development in children, but this is still limited and inconclusive (Clark & Paunovic, 2018a). Some previous studies found no evidence of the association between residential or school road traffic noise exposure and deficits in non-verbal and language/verbal intelligence in children aged 6-11 years (Clark et al., 2006; Julvez et al., 2021; S. A. Stansfeld et al., 2005). However, a previous study showed that higher noise levels at schools, mainly from road traffic, was related to lower non-verbal intelligence in children aged 10-12 years (Bhang et al., 2018). In addition, reading deficits were observed in children exposed to higher levels of residential noise from multiple sources (Cohen et al., 1973) as well as to higher levels of road traffic noise at schools (Ljung et al., 2009). Further, it has been reported that road traffic noise exposure is not related with working memory (Clark et al., 2012; Julvez et al., 2021; Matheson et al., 2010; S. A. Stansfeld et al., 2005; van Kempen et al., 2010, 2012). In contrast, a recent study found that outdoor exposure to road traffic at schools, but not at home, was associated with lower development in working memory (Foraster et al., 2022). Findings from studies that explored the association between road traffic noise exposure and children's short and long term memory (Clark et al., 2012; Héroux et al., 2015; Lercher et al., 2016; Matheson et al., 2010; S. A. Stansfeld et al., 2005; van Kempen et al., 2010, 2012) or attentional function (Cohen et al., 1973; Foraster et al., 2022; Julvez et al., 2021; Lercher et al., 2016; Sanz et al., 1993; van Kempen et al., 2010, 2012; Wass et al., 2019) were not consistent between studies. Differences in results across studies might be due to methodological differences, such as cognitive outcome assessed, exposure assessment approach, cognitive test used, or the age of assessment of the outcome of interest. The relationship between environmental noise exposure and motor function was assessed in a single study in children between 3 and 6 years old in which no association was found (Raess et al., 2022).

During the last years, magnetic resonance imaging (MRI) has been increasingly used to assess neurodevelopment in epidemiological studies. MRI is a non-invasive method using magnetic fields to study the brain in vivo. Neuroimaging can be divided into two main categories, namely structural imaging and functional imaging. In this thesis only functional imaging

techniques are considered. Functional MRI relies on a blood oxygenation level depend (BOLD) signal and can be a result of unregulated processes in the resting brain, i.e., not induced by an external stimulus (Glover, 2011). The BOLD signal measures inhomogeneities in the magnetic field due to changes in the level of oxygen in the blood. The increase of oxygenated haemoglobin leads to an increase of the BOLD signal and consequently of the magnetic resonance signal. To the best of our knowledge, no studies have assessed noise in relation to brain MRI. Nevertheless, some studies have shown that noise exposure could act as a stressor that affects the HPA axis (Jafari et al., 2017; Lautarescu et al., 2020), leading to increased levels of stress hormones, and such early life stress could be related to disturbances in functional brain connectivity (De Asis-Cruz et al., 2020; Hermans et al., 2011) .

1.4 Environmental noise exposure and sleep

Sleep is an essential biological process that serves several vital functions. Sufficient sleep is important for optimal daily functioning since it impacts alertness and attention, cognitive performance, and motor skill development, among others (Paavonen et al., 2010). The exposure to environmental noise is considered as a possible explanation of sleep disturbances as well as to a lower amount and quality of sleep in adults (Basner et al., 2014). However, there have been few studies on environmental noise and sleep in children (S. Stansfeld & Clark, 2015). Previous literature reported an association of higher exposure to levels of outdoor nocturnal road traffic noise and self- and parental-reported sleep disturbances in children at 7-14 years of age (Öhrström et al., 2006; Skrzypek et al., 2017; Tiesler et al., 2013; K. Weyde et al., 2017). In contrast, in other studies, this association was not found in children of similar ages exposed to average levels of outdoor daily road traffic noise (Lee et al., 2021) nor in infants exposed to outdoor nocturnal transportation noise (Blume et al., 2022). Additionally, only two studies used actigraphy methodology to assess physiological sleep measures in children. However, no associations were found in relation to nocturnal exposure to road traffic noise (Öhrström et al., 2006) or to transportation noise (Blume et al., 2022).

1.5 Scientific gaps

The number of studies looking into the relationship between exposure to environmental noise, neurodevelopment, and sleep in children and preadolescents has increased recently. However, there are still several unanswered questions remaining. First, both pregnancy and childhood periods might be susceptible windows of exposure when assessing associations between environmental noise and neurodevelopment. However, most of the existing studies mainly focused on exposure during pregnancy or during childhood but not on both. Second, the assessment of exposure to noise from multiple sources including road traffic, railway, aircraft, and industry is scarce. Studies usually assessed each noise source separately, although most studies only included aircraft noise. An individual can be exposed to more than one source, and therefore the effect of the overall environmental noise exposure could be greater and should be investigated. Third, the association between environmental noise exposure with neurodevelopment throughout the different lifetime periods of the children is under investigated, given that previous studies were mainly cross-sectional. Longitudinal designs would allow exploring the long-term effects of environmental noise exposure on children's neurodevelopment. Fourth, the use of magnetic resonance imaging in addition to neuropsychological tests to study how environmental noise exposure might affect brain development has not been studied before. Neuropsychological tests are very useful for detection but cannot explain the possible biological mechanisms that underlie the association between environmental noise exposure and neurodevelopment. Fifth, the use of actigraphy is needed to replicate the observed associations between environmental noise exposure and sleep disturbances in previous studies. Most of the studies on the association between environmental noise exposure and sleep have used parental- or self-reported data. However, actigraphy data could provide more accurate and consistent information about sleep patterns and has been scarcely used previously.

2. OBJECTIVES

The overall aim of this thesis is to assess the relationship between outdoor exposure to residential noise during pregnancy and childhood, and neurodevelopment and sleep in children and preadolescents. This is addressed through the following specific objectives:

1. To assess the association between prenatal and childhood outdoor exposure to residential road traffic and multiple (i.e., road, railway, aircraft, and industry) noise with emotional, aggressive, and ADHD-related symptoms in children from two European birth cohorts **(Study I)**.

2. To assess the association between prenatal and childhood outdoor exposure to residential road traffic noise with cognitive and motor function in children from two European birth cohorts **(Study II)**.

3. To assess the association between outdoor exposure to residential traffic-related air pollution and noise during pregnancy and childhood, and functional brain connectivity in preadolescents **(Study III)**.

4. To assess the association between outdoor exposure to residential road traffic and multiple noise with sleep using both maternal-reported and wrist-actigraphy data in preadolescents from two European birth cohorts **(Study IV)**.

3. METHODS

This section briefly summarizes the design and study population, the noise and air pollution assessment, and the neurodevelopment and sleep assessments. A more detailed explanation of the methodology is described in each of the different studies included in the results section.

3.1 Design and study population

This thesis is based on data from two population-based birth cohorts: the INfancia y Medio Ambiente (INMA) Project from Spain (Guxens et al., 2012) and the Generation R Study from the Netherlands (Kooijman et al., 2016). The INMA Project is a network of population-based birth cohorts from several regions of Spain. However, in the present thesis, only the sub-cohort from Sabadell city was included due to noise data availability. Both cohorts were included as they had exhaustive information on noise exposure and neurodevelopment, and sleep assessments. In the INMA-Sabadell cohort, the period of recruitment in which mothers were invited to participate was between July 2004 and July 2006 whereas in the Generation R Study was between April 2002 and January 2006. Children were followed until 13-16 years old in both cohorts although follow-up periods were different between them. In Study **I**, **II** and **IV** we used data from both cohorts and in Study **III,** we used data only from the Generation R Study since MRI data was not available in the INMA project.

3.2 Exposure assessment

i) Noise exposure assessment

In Study **I**, **II**, **III**, and **IV**, we used noise maps created for the municipalities of Sabadell in Spain and of Rotterdam, Maassluis, Rozenburg, Schiedam, and Vlaardingen in the Netherlands to estimate the outdoor exposure to residential average noise levels. These maps met the requirements of the European Environmental Noise Directive (European Environmental Noise Directive, 2002). Briefly, environmental noise exposure from both cohorts was

estimated at each participant's residential address where they lived at during the periods of interest according to the study. In cases where the child had lived in more than one address, we considered the amount of time spent at each address to determine the average noise levels of each participant. For both cohorts, we calculated noise levels from road traffic source in all of the studies included in this thesis. Additionally, in Study **I** and **IV** we calculated exposure to multiple noise in which railway, aircraft and industry noise sources were additionally considered, but only in the Generation R Study. For both road traffic and multiple noise sources, the L_{DEN} indicator has been calculated in all the studies.

ii) Air pollution assessment

In Study **III**, air pollution levels were estimated using land use regression models based on monitor campaigns carried out between 2009 and 2010 in the Netherlands and Belgium (Beelen et al., 2013; Eeftens et al., 2012). The measurements were performed three times during two-week periods in a year for several pollutants including nitrogen oxides (NO_x), nitrogen dioxide (NO_2), particulate matter (PM) with aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), less than 10 μm (PM_{10}), between 2.5 μm and 10 μm (PM coarse), and the absorbance of $PM_{2.5}$ ($PM_{2.5}$ absorbance) from the filters of $PM_{2.5}$ measurements. For each pollutant, the levels of the three two-week measurements were averaged resulting in a single annual mean concentration. Land use regression models were applied to each geocoded address where the participants had lived at during the period of interest to estimate the levels of each air pollutant at each of the participant's addresses. Similar to noise estimates, if more than one address was collected during the period of interest, we took into account the amount of time that the participant had lived at each address to weight the levels of air pollution accordingly.

3.3 Outcome assessment

i) Neurodevelopment

Emotional, aggressive, and ADHD-related symptoms

In Study **I**, emotional, aggressive, and ADHD-related symptoms were assessed using validated questionnaires completed by mothers or teachers, which were different between the INMA-Sabadell cohort and the Generation R Study. In the INMA-Sabadell cohort, emotional and aggressive symptoms were assessed using the Strength and Difficulties Questionnaire (SDQ) (Goodman et al., 2009) and the Child Behavioral Checklist 6–18 (CBCL 6–18) (Achenbach & Rescorla, 2001a). ADHD-related symptoms were assessed using the ADHD Criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association, 2000) and the Conner's Parent Rating Scale-Revised (CPRS) (Conners, 1997a). In the Generation R Study, emotional, aggressive, and ADHD-related symptoms were reported using the CBCL 1.5-5 and the CBCL 6-18 (Achenbach & Rescorla, 2001a).

Cognitive and motor function

In Study **II**, cognitive and motor function were measured as non-verbal intelligence, language/verbal intelligence, memory, processing speed, attentional function, visual attention, working memory, cognitive flexibility, risky decision-making, and fine and gross motor function using a battery of validated neurocognitive tests in both cohorts and explained in detail in the methods section of this study.

Functional brain connectivity

In Study **III**, participants from the Generation R Study were invited to receive a resting-state functional MRI (rs-fMRI) scan to assess functional brain connectivity. The rs-fMRI data was preprocessed and parcellated using the Human Connectome Project multimodal parcellation (Glasser et al., 2016) resulting in 382 brain areas. Under resting state conditions, brain regions that are functionally

connected show high correlation coefficients in their BOLD time series. Therefore, we computed pair-wise correlation coefficients of time series amongst the 382 brain areas in the parcellation. This coefficient indicated the strength and the direction of the functional connectivity between the different brain areas. We grouped the brain areas into 31 brain regions based on location and common properties and those regions into five brain functional networks and a sixth group that comprised subcortical structures and the cerebellum.

ii) Sleep

Sleep disturbances and physiological sleep measures were assessed in Study **IV** using validated questionnaires and wrist-actigraphy, respectively. Children's sleep disturbances were reported by mothers through the Sleep Disturbance Scale for Children (SDSC) (Bruni et al., 1996) in both cohorts. We used the following SDSC subscales in this study: problems with initiating and maintaining sleep, excessive problems, and arousal problems (i.e., partial awakening from deep sleep in which the subjects are partially or totally unconscious). Sleep was also measured using accelerometers placed on the non-dominant wrist of the participants during seven consecutive days. Physiological sleep measures obtained were total sleep time, sleep efficiency, sleep onset latency, and wake after sleep onset.

4. RESULTS

In this section, the following four scientific studies are presented:

Study I: Environmental noise exposure and emotional, aggressive, and attention-deficit/hyperactivity disorder-related symptoms in children from two European birth cohorts.

Study II: Association between outdoor exposure to residential noise and cognitive and motor function in children and preadolescents.

Study III: Exposure to traffic-related air pollution and noise during pregnancy and childhood, and functional brain connectivity in preadolescents.

Study IV: Outdoor residential noise exposure and sleep in preadolescents from two European birth cohorts.

Study I

Environmental noise exposure and emotional, aggressive, and attention-deficit/hyperactivity disorder-related symptoms in children from two European birth cohorts

Esmée Essers, Laura Pérez-Crespo, Maria Foraster, Albert Ambrós, Henning Tiemeier, Mònica Guxens

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Environmental noise exposure and emotional, aggressive, and attention-deficit/hyperactivity disorder-related symptoms in children from two European birth cohorts

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ABSTRACT

Background: Environmental noise exposure is increasing but limited research has been done on the association with emotional, aggressive, and attention-deficit/hyperactivity disorder (ADHD)-related symptoms in children.
Objective: To analyze the association between prenatal and childhood environmental noise exposure and emotional, aggressive, and ADHD-related symptoms in children from two European birth cohorts.
Methods: We included 534 children from the Spanish INMA-Sabadell Project and 7424 from the Dutch Generation R Study. Average 24 h noise exposure at the participants' home address during pregnancy and childhood periods were estimated using EU maps from road traffic noise and total noise (road, aircraft, railway, and industry). Symptom outcomes were assessed using validated questionnaires: Strengths and Difficulties Questionnaire, Child Behavioral Checklist, ADHD Criteria of Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition List, and Conner's Parent Rating Scale-Revised at 4, 7 and 9 years (INMA-Sabadell cohort) and 18 months, 3, 5, and 9 years (Generation R Study). Adjusted linear mixed models of prenatal and repeated childhood noise exposure with repeated symptom outcomes were run separately by cohort and overall estimates were combined with random-effects meta-analysis.
Results: Average prenatal and childhood road traffic noise exposure levels were 61.3 (SD 6.1) and 61.7 (SD 5.8) for INMA-Sabadell and 54.6 (SD 7.9) and 51.6 (SD 7.1) for Generation R, respectively. Prenatal and childhood road traffic noise exposure were not associated with emotional, aggressive, or ADHD-related symptoms. No heterogeneity was observed between cohorts and results were comparable for total noise exposure.
Conclusions: No association was observed between prenatal or childhood road traffic or total noise exposure and symptom outcomes in children. Future studies should include a more comprehensive noise exposure assessment considering noise sensitivity and noise exposure at different settings such as work for pregnant women and school for children.

1. Introduction

The continuously growing world population is accompanied by a rapid increase in urbanization, with a projected growth of 55% to 70% living in urban areas by 2050 (The World Bank, 2019; United Nations: Department of Economic and Social Affairs, 2019). Within our urbanized world, exposure to noise has become unavoidable due to a growing demand of transport (Erickson and Newman, 2017; European Environmental Agency, 2020). Transportation noise exposure from road traffic, railway, and aircraft is considered the second most significant

environmental cause of ill-health in Western Europe (European Environmental Agency, 2020). Evidence of increased risk in negative physiological and psychological health due to prolonged exposure to environmental noise is the driving force behind the guidelines and recommendations that the World Health Organization sets in an attempt to limit the levels of noise exposure and protect human health (World Health Organization, 2018).

Children specifically are more vulnerable and susceptible to the potential harmful effects of environmental noise exposure (Erickson and Newman, 2017; Gupta et al., 2018). A suggested biological mechanism highlights how environmental noise exposure during pregnancy can increase the levels of maternal stress hormones and influence the hypothalamic–pituitary adrenal axis, ultimately impacting the brain development of the child (Beijers et al., 2014; Gitau et al., 1998; Graignic-Philippe et al., 2014; Jafari et al., 2017; Lautarescu et al., 2020). Children also have less developed coping strategies than adults and less control over the levels of noise they are exposed to (Evans et al., 1991; Gupta et al., 2018; Stansfeld and Matheson, 2003). Studies investigating the association between environmental noise exposure, mainly residential road traffic and aircraft noise, and emotional, aggressive, and attention-deficit/hyperactivity disorder (ADHD)-related symptoms in children often show heterogenous results (Clark et al., 2020; Clark and Paunovic, 2018a, 2018b; Stansfeld and Clark, 2015; Zijlema et al., 2021). Studies mainly assessed ADHD-related symptoms and very few include emotional and aggressive symptoms. Further, most studies focused primarily on the exposure during childhood, while pregnancy exposure could also be a relevant window since the developmental processes of the fetus might be influenced by noise exposure-induced maternal stress. Also, studies usually assessed the transportation noise sources separately, while an individual can be exposed to more than one source, and thus the overall effect of exposure to multiple noise sources should also be investigated.

Therefore, this study aims to evaluate the association between prenatal and childhood exposure to road traffic and overall transportation noise with emotional, aggressive, and ADHD-related symptoms in children from two European birth cohorts.

2. Methods

2.1. Population and study design

This study was embedded in two population-based prospective cohort studies: the Spanish INMA Project (Guxens et al., 2012) and the Dutch Generation R Study (Hofman et al., 2004; Kooijman et al., 2016). The INMA Project is a network of birth cohorts set up in several regions of Spain following a common protocol, and for this analysis we only included the INMA-Sabadell cohort due to availability on noise exposure data. The cohort includes 778 pregnant women and their children resident in the city of Sabadell (Catalonia, Spain) who visited the public health center of Sabadell between July 2004 and July 2006 for an ultrasound in the first trimester. Inclusion criteria were 16 years or older, singleton pregnancy, no assisted reproduction program, intention to deliver in the reference hospital, and no communication problems. The Generation R Study is a cohort study that recruited 9749 pregnant women living in the city of Rotterdam, the Netherlands, with an expected delivery date between April 2002 and January 2006. Inclusion criterium was being resident in Rotterdam when the child was born. In our study, we included children with at least one noise exposure value and one symptom outcome measurement (n = 534 for INMA-Sabadell and 7424 for Generation R, Fig. S1). Ethical approval was obtained prior to recruitment from the Clinical Research Ethical Committee of the Municipal Institute of Healthcare (CEIC-IMAS) for the INMA-Sabadell cohort and from the Medical Ethical Committee of Erasmus MC, University Medical Centre Rotterdam, in accordance with Dutch law for the Generation R Study. Informed consent was obtained from parents in both studies.

2.2. Noise exposure

Existing noise maps developed in 2012 for Rotterdam and 2006 and 2012 for Sabadell were used to assess the annual levels of outdoor noise exposure at each participant's home address. We did not use an earlier noise map for Rotterdam (i.e., the one of 2007) because the methodology used to develop that earlier map differed to the one of 2012, making the estimations incomparable. The noise maps meet the requirements of the European Environmental Noise Directive (European Environmental Noise Directive, 2002). The noise maps for Sabadell were based on a model at street level that covered the entire municipal surface and the noise map for Rotterdam was solely based on residential buildings. Accuracy of the noise models was assured because they were developed to assess exposure at the residential addresses. Noise maps were available for exposure levels of residential road traffic, railway, aircraft, and industry noise. However, in the INMA-Sabadell cohort, children were not exposed to railway, aircraft, or industry noise, so data solely from residential road traffic was used. Noise exposure levels for the Generation R Study consisted of data from residential road traffic, railway, aircraft, and industry.

For each noise exposure source, the day-evening-night noise indicator (L_{DEN}) was calculated as the A-weighted average sound levels over the entire 24 h of a day with penalties for the evening (+5 decibel (dB)) and night (+10 dB) (European Environmental Noise Directive, 2002). The L_{DAY}, $L_{EVENING}$ and L_{NIGHT} indicators were respectively the A-weighted average sound levels assessed during the day (12 h for Generation R, 07:00–19:00 and 14 h for INMA-Sabadell, 07:00–21:00), the evening (4 h for Generation R, 19:00–23:00 and 2 h for INMA-Sabadell, 21:00–23:00), and the night (8 h for both cohorts, 23:00–07:00), and were calculated using the formulas detailed in Methods S1 (European Environmental Noise Directive, 2002). Total noise exposure levels for the Generation R Study were calculated using the formula detailed in Methods S1. The levels of L_{DEN} of each noise exposure source were applied to each geocoded participant's address during the period of interest. In one address where L_{DEN} was below the threshold of 40 dB, considered as the minimum reliable value, we changed the value of that address to 40 dB. Considering the number of days that the participant spent at each address and weighting the noise levels accordingly, we calculated the mean levels of L_{DEN} for each participant for the pregnancy period (from conception until birth), and for different periods during childhood, depending on the assessment of the outcomes. For the INMA-Sabadell cohort these periods were: from birth to 4 years old, from 4 to 7 years old, and from 7 to 9 years old, and for the Generation R Study: from birth to 18 months old, from 18 months to 3 years old, from 3 to 5 years old, and from 5 to 9 years old. In both cohorts, we considered the mean level of L_{DEN} during a period of interest as missing if the child had lived outside of the study area for more than 50% of the time. A subject was included in the analysis if they had at least one noise exposure measurement (Fig. S1).

2.3. Emotional, aggressive, and ADHD-related symptom assessment

Validated questionnaires were used throughout childhood to assess emotional, aggressive, and ADHD-related symptoms in both cohorts (Methods S2). The questionnaires used varied between cohorts and measurement time points (Fig. S2). In the INMA-Sabadell cohort, emotional and aggressive symptoms were assessed using the Strength and Difficulties Questionnaire (SDQ) (Goodman et al., 2003) at 7 years of age and the Child Behavioral Checklist 6–18 (CBCL 6–18) (Achenbach and Rescorla, 2001) at 9 years of age. ADHD-related symptoms were reported using the ADHD Criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (ADHD-DSM-IV) list at 4 years of age (American Psychiatric Association, 2000) and the Conner's Parent Rating Scale-Revised (CPRS) at 7 and 9 years of age (Conners, 1997). In the Generation R Study, emotional, aggressive, and ADHD-related symptoms were reported at 18 months, 3, and 5 years of age using the CBCL

1.5–5 questionnaire and at 9 years of age using the CBCL 6–18 questionnaire (Achenbach and Rescorla, 2001). All questionnaires were completed by the mother, except for the ADHD-DSM-IV list, which was done by the teacher. To make the results from the questionnaires comparable across cohorts, sum scores of the symptom categories were square root transformed to reach normal distribution and then standardized by calculating the Z-score of the raw scores. A higher score indicates more symptoms.

2.4. Potential confounding variables

Potential confounding variables for both cohorts were defined a priori based on previous scientific literature, available data, and using a direct acyclic graph (Hernán et al., 2002). Information for both cohorts on parental age at enrollment (in years), parental ethnicity (Spanish or Others for the INMA-Sabadell cohort, and Dutch, Surinamese, Turkish, Moroccan or Others for the Generation R Study), parental education level (low: no education, unfinished primary or primary; medium: secondary; high: university degree), parental social class based on occupation (low: unskilled or (partly) skilled manual workers; medium: financial management, administrative and other support staff, other self-employed professionals, supervisors of manual workers, and skilled non-manual workers; high: managers of companies, and intermediate or higher level professionals), family status (dual or single parent), maternal parity (nulliparous, one child, two or more children), maternal smoking during pregnancy (yes or no), maternal alcohol use during pregnancy (yes or no) and monthly household income (only for the Generation R Study, (<€900, €900–1600, €1600–2220 or >€2200) was collected by questionnaires during pregnancy. Parental psychological distress was measured during pregnancy using the Brief Symptom Inventory for the Generation R Study and at child's 14 months using the General Health Questionnaire for the INMA-Sabadell cohort (Derogatis, 1993; Goldberg et al., 1997). Child sex was obtained from hospital records, and parental height (cm) and weight (kg) was measured or self-reported in the 1st trimester of pregnancy and subsequently used to calculate the pre-pregnancy body mass index (in kg/m^2) for both cohorts. Traffic-related air pollution was not explored as co-exposure because we did not find associations between air pollution and our symptom outcomes in either cohort (Forns et al., 2018; Jorcano et al., 2019).

2.5. Statistical analyses

To increase validity of results and limit attrition bias, missing values of the potential confounding variables were 25 times imputed for all subjects using standard procedures for multiple imputation (Table S1) (Spratt et al., 2010; Sterne et al., 2009). The percentage of missing values for the confounding variables was low, except for paternal characteristics in the Generation R Study which were between 30.4% and 48.5%. Distributions in imputed datasets were similar to those in observed datasets (Table S2).

Children included in the analysis (534 for INMA-Sabadell cohort and 7424 for Generation R Study, Fig. S1) were more likely to have parents with a national origin from the cohort site (Spanish or Dutch), have a higher education level and social class, and have mothers that are older, nulliparous, and did not smoke during pregnancy than those not included (Table S3). Thus, inverse probability weighting was used to correct for selection bias (Weisskopf et al., 2015; Weuve et al., 2012). In brief, we used information available for all participants at recruitment to predict the probability of participation in the current study and used the inverse of those probabilities as weights in the analyses so that results would be representative for the initial population. The variables used to create the weights can be found in Table S4.

First, linear mixed models (LMM) were run separately per cohort to examine the association between average prenatal noise exposure in relation to the repeated measures of emotional, aggressive, and ADHD-

related symptoms at 4, 7, and 9 years old for INMA-Sabadell and at 18 months, 3, 5 and 9 years for Generation R (Fig. S2). Overall estimates of each cohort were then combined using random effects meta-analysis and the heterogeneity of the estimates was assessed using Cochran Q test and the I^2 statistic.

Second, LMM were run separately per cohort to examine the association between the repeated estimates of noise exposure during childhood in relation to the repeated measures of emotional, aggressive, and ADHD-related symptoms. Thus, for INMA-Sabadell, LMM for emotional and aggressive symptoms included noise exposure estimations between birth and 7 years and between 7 and 9 years, and symptom outcome data at 7 and 9 years. LMM for ADHD-related symptoms included noise exposure estimations between birth and 4 years, between 4 and 7 years, and between 7 and 9 years, and symptom outcome data at 4, 7, and 9 years. For Generation R, all LMM included noise exposure estimations between birth and 18 months, between 18 months and 3 years, between 3 and 5 years, and between 5 and 9 years, and symptom outcome data at 18 months, 3, 5, and 9 years. Each LMM resulted in one overall childhood effect estimate. Overall estimates of each cohort were then combined using random effects meta-analysis and the heterogeneity of the estimates was assessed using Cochran Q test and the I^2 statistic.

Third, to examine the association between each lifetime period of childhood noise exposure and the repeated emotional, aggressive, and ADHD-related symptoms at each time point, LMM detailed in the previous paragraph were re-run including an interaction term between noise exposure and the age at the assessment of the symptom outcome. These models could not be combined into random effects meta-analysis because each cohort assessed the outcomes at different ages. Thus, effect estimates at each age of the assessment of the symptom outcome are presented separately per cohort.

All LMM included a random intercept to account for the non-independence due to repeated measures of exposure and outcome per subject. All models were first unadjusted, and then adjusted for all potential confounding variables described above. We conducted a sensitivity analysis where we performed all LMM with only the children that had complete childhood noise exposure measurements. Statistical analyses were carried out using STATA (version 14.0; StataCorporation, College Station, TX) and R (version 4.0.0; R Core Team (2020)).

3. Results

Participant characteristics of the study population from both cohorts are shown in Table 1. The average age of mothers was 31.8 and 30.7 years in the INMA-Sabadell cohort and Generation R Study, respectively. In the INMA-Sabadell cohort, most mothers were Spanish (90.5%), had a medium education (43.8%), and were from a low social class (44.5%). In the Generation R Study, the household income was mostly high (59.9%), and most mothers were Dutch (56.2%), had a high education (48.9%), and were from a high social class (63.9%).

Average prenatal road traffic noise exposure levels were 61.3 (standard deviation (SD) 6.1) and 54.6 (SD 7.9), whereas average childhood road traffic noise exposure levels were 61.7 (SD 5.8) and 51.6 (SD 7.1) in the INMA-Sabadell cohort and the Generation R Study, respectively. Average total noise exposure levels in the Generation R Study were 55.8 (SD 7.1) during pregnancy and 52.8 (SD 6.8) during childhood. Distribution of the noise exposure levels can be found in Table S5 and Fig. S3. Road traffic noise exposure levels throughout the different lifetime periods were moderately to strongly correlated (between 0.69 and 0.94 in the INMA-Sabadell cohort and between 0.48 and 0.91 in the Generation R Study, respectively). In the Generation R Study, total noise exposure during pregnancy and childhood was moderately to strongly correlated (between 0.49 and 0.91) and traffic and total noise exposure were strongly correlated (between 0.95 and 0.97, Table S6).

Prenatal road traffic noise exposure was not associated with emotional, aggressive, or ADHD-related symptoms in the unadjusted and adjusted models for the INMA-Sabadell cohort and Generation R

Table 1
Population characteristics of the INMA-Sabadell cohort and Generation R Study.

Characteristics		INMA-Sabadell (n = 534)	Generation R (n = 7,424)
Noise Exposure (decibels)			
Road	Prenatal	61.3 (6.1)	54.6 (7.9)
	Childhood	61.6 (6.1)	53.7 (7.5)
Total	Prenatal	–	55.8 (7.1)
	Childhood	–	55.2 (6.7)
Maternal Characteristics			
Age at enrolment (years)		31.8 (4.2)	30.7 (5.0)
Pre-pregnancy body mass index (kg/m²)		22.7 (21.1; 25.4)	22.6 (20.8; 25.2)
Ethnicity			
Spanish		90.5	–
Dutch		–	56.2
Surinamese		–	7.3
Turkish		–	8.1
Moroccan		–	5.1
Others		9.5	23.3
Education during pregnancy			
Low		24.1	8.3
Medium		43.8	42.8
High		32.1	48.9
Social Class during pregnancy			
Low		44.5	3.9
Medium		32.4	32.2
High		23.1	63.9
Psychological distress[1]		9.0 (7.0; 12.0)	0.2 (0.1; 0.3)
Parity			
0		56.1	56.7
1		37.3	30.5
2+		6.6	12.8
Smoking during pregnancy (no vs. yes)		73.2	84.0
Alcohol during pregnancy (no vs. yes)		77.9	59.2
Paternal Characteristics			
Age at enrolment (years)		33.6 (4.8)	33.2 (5.5)
Body mass index during pregnancy (kg/m²)		25.4 (23.5; 27.7)	24.9 (22.9; 27.2)
Ethnicity			
Spanish		89.8	–
Dutch		–	64.8
Surinamese		–	5.6
Turkish		–	5.6
Moroccan		–	3.2
Others		10.2	20.8
Education during pregnancy			
Low		36.7	6.7
Medium		42.0	39.4
High		21.2	53.9
Social Class during pregnancy			
Low		57.4	8.5
Medium		18.7	22.7
High		23.9	68.8
Psychological distress[1]		9.0 (7.0; 11.0)	0.1 (0.0; 0.2)
Household Characteristics			
Family status (dual vs. single parent)		98.8	89.0
Monthly income during pregnancy			
<900€		–	9.0
900–1600€		–	15.7
1600–2200€		–	15.4
>2200€		–	59.9

Values are percentages for categorical, mean (standard deviation) for continuous variables, and median (25th; 75th percentile) for body mass index and psychopathological distress.

[1] Score range 0–36 for the INMA-Sabadell cohort (assessed at child's 14 months) and 0–4 for the Generation R Study (assessed during pregnancy).

Study, separately or combined in the meta-analysis (Fig. 1A, Table S7). Similarly, overall childhood road traffic noise exposure showed no association with emotional, aggressive, or ADHD-related symptoms (Fig. 1B, Table S7). When analyzing the associations per childhood lifetime period, there were no associations between road traffic noise exposure and emotional, aggressive, or ADHD-related symptoms at 4, 7 or 9 years of age for the INMA-Sabadell cohort (Fig. 2A, Table S8). In the Generation R Study, higher road traffic noise exposure was not associated with any symptoms at 18 months, 3 years, or 5 years. However, higher road traffic noise exposure was associated with lower emotional, but not aggressive or ADHD-related, symptoms at 9 years (Fig. 2B, Table S8). Effect estimates were materially unchanged when looking at

prenatal and childhood total noise exposure in the Generation R Study (Fig. S4 and Tables S7-S8). Effect estimates were also unchanged in children with complete childhood noise exposure levels or in children with no missing values for potential confounding variables (Tables S9 and S10).

4. Discussion

In this study, we found no evidence of an association of residential road traffic noise exposure during pregnancy or childhood with emotional, aggressive, and ADHD-related symptoms in children from two European birth cohorts. Associations were also absent for total noise
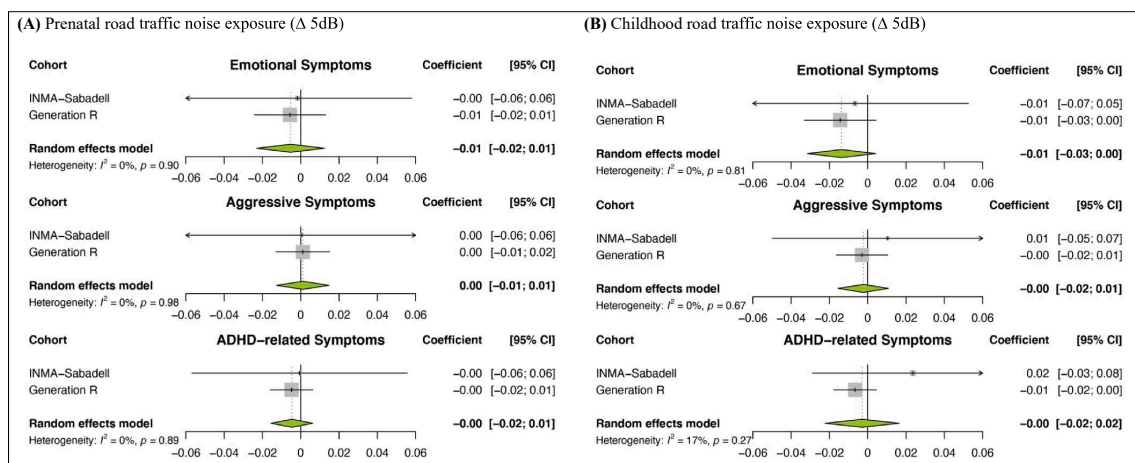
Fig. 1. Fully adjusted associations of a 5 dB increase in prenatal (A) or childhood (B) road traffic noise exposure and standardized emotional, aggressive, or attention-deficit/hyperactivity disorder (ADHD)-related symptom scores in the INMA-Sabadell cohort and Generation R Study. Abbreviations: ADHD, attention-deficit/ hyperactivity disorder; CI, confidence interval; dB, decibels; I², percentage of the total variability due to between-cohort heterogeneity; p; p-value of heterogeneity using the Cochran's Q test. Coefficients and 95% confidence intervals were obtained by random-effects meta-analysis. Within each cohort, linear mixed models were adjusted for child sex, parental age, body mass index, ethnicity, education, social class and psychological distress, parity, smoking and alcohol during pregnancy, and family status. Generation R Study models were additionally adjusted for monthly household income.
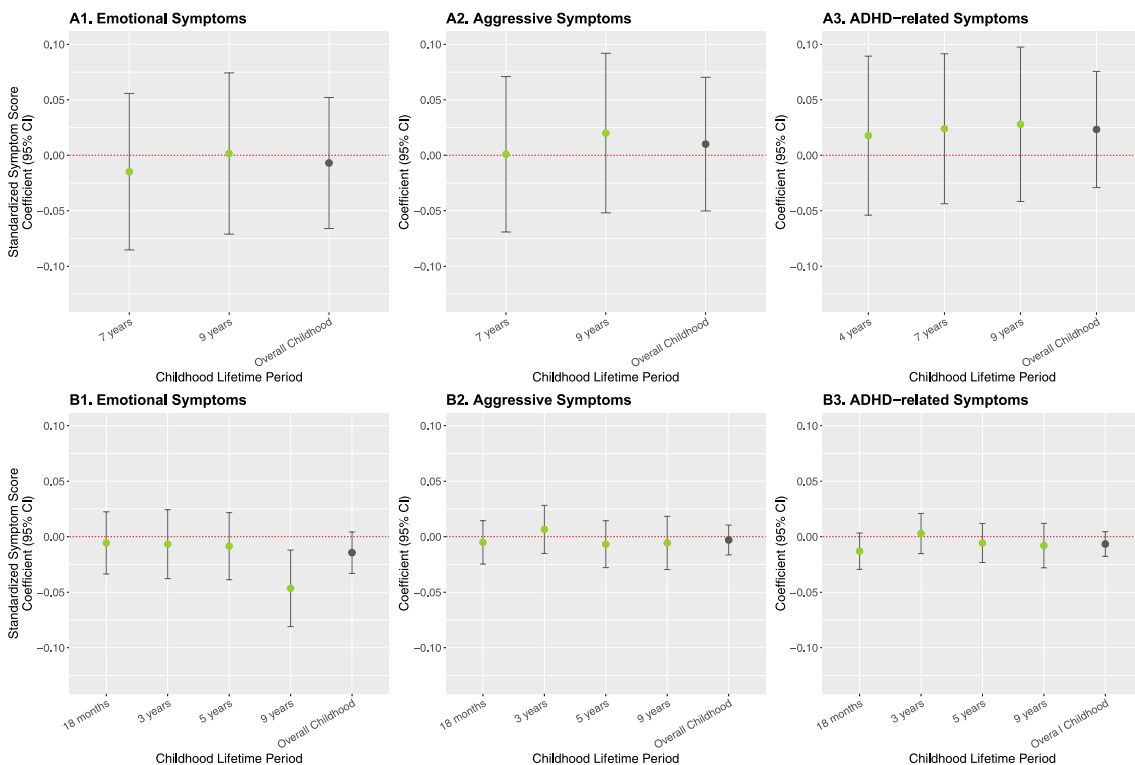
Fig. 2. Fully adjusted associations of a 5 dB increase in road traffic noise exposure in the INMA-Sabadell cohort (A) and the Generation R Study (B) during childhood lifetime periods and overall childhood, and standardized emotional, aggressive, or attention-deficit/hyperactivity disorder (ADHD)-related symptom scores. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; dB, decibels. Coefficients and 95% confidence intervals were obtained by linear mixed models. Linear mixed models were adjusted for child sex, parental age, body mass index, ethnicity, education, social class and psychological distress, parity, smoking and alcohol during pregnancy, and family status. Generation R Study models were additionally adjusted for monthly household income.

exposure in which railway, aircraft, and industry noise exposure were additionally assessed.

Regarding emotional and aggressive symptoms, the absence of associations with environmental noise exposure during pregnancy is consistent with a study looking at these relationships. They found no indication of an association between prenatal road traffic noise and emotional or aggressive symptoms (Hjortebjerg et al., 2016). Similarly, no associations between childhood road traffic noise exposure and emotional and aggressive symptoms were found, which is in line with results from a few studies (Crombie et al., 2011; Forns et al., 2016; Hjortebjerg et al., 2016; Stansfeld et al., 2009). However, two studies observed that road traffic noise exposure at schools in the Netherlands, Spain, and United Kingdom were related to less aggressive symptoms in children aged 9–10 years (Crombie et al., 2011; Stansfeld et al., 2009). They attributed their counterintuitive findings to chance, difficulties experienced in accurately measuring road traffic noise exposure, or to exposure misclassification (Crombie et al., 2011; Stansfeld et al., 2009). In our study, we also found an unexpected protective association between road traffic and total noise exposure and emotional symptoms at 9 years in children from the Generation R Study. Of our population at 18 months, around 26% had missing noise exposure levels at 9 years, because they moved outside Rotterdam and noise exposure could not be estimated. These children had parents with a higher socio-economic status and reported less emotional symptoms at younger ages and more symptoms at 9 years old compared to those children who continued living in Rotterdam. Thus, our unexpected results were most probably due to selection bias. With limited literature available on the association between environmental noise exposure and emotional and aggressive symptoms, it is important that future studies include these outcomes to better understand the possible impact on children, especially at older ages.

The relationship between environmental noise exposure and ADHD-related symptoms has been studied more intensively. No associations were found between prenatal environmental noise exposure and ADHD-related symptoms in previous literature (Hjortebjerg et al., 2016; Weyde et al., 2017). However, with relation to environmental noise exposure throughout childhood, two cross-sectional and two longitudinal studies in different European cities showed an association of higher road traffic noise exposure at home or at school with higher hyperactivity or inattention problems in children aged 7–11 years (Forns et al., 2016; Hjortebjerg et al., 2016; Tiesler et al., 2013; Weyde et al., 2017). Further, three other cross-sectional studies found that higher aircraft noise exposure at school was associated with higher hyperactivity or inattention problems in children from the Netherlands, United Kingdom, and Spain aged 8–11 years (Crombie et al., 2011; Haines et al., 2001; Stansfeld et al., 2009). In contrast, Zijlema et al. also found no association between residential and school road traffic noise exposure and ADHD-related symptoms in Dutch children aged 10–12 years, rather, they observed a protective association with ADHD clinical diagnosis (Zijlema et al., 2021). Most previous studies focused on noise exposure at school instead of at the residential address, which could explain the discrepancies between their results and ours (Crombie et al., 2011; Forns et al., 2016; Haines et al., 2001; Stansfeld et al., 2009; Zijlema et al., 2021). Noise exposure at school might become especially relevant during the older lifetime periods of our study (compulsory age to attend school in the Netherlands is 5 years and in Spain is 6 years), since they spend more time at school when overall road traffic flow is higher. In line with this idea, mothers likely spend a large portion of their pregnancy at their place of work, thus noise exposure at work can be relevant to include for the estimations during the pregnancy period. Having information on noise exposure at school, work, and residential address would give a more accurate and comprehensive estimation of the noise levels that children are exposed to. Lastly, noise sensitivity has been shown to be associated with more behavioral problems and ADHD-related symptoms (Lim et al., 2018; Zijlema et al., 2021). It is defined as lower tolerance to everyday environmental sounds, and an increased

sensitivity is normal in younger children, while they become more desensitized as the auditory system matures (NHS Foundation Trust, 2021; Potgieter et al., 2020). It can contribute to how children cope with negative effects of noise, potentially moderating the association between noise exposure and symptom outcomes (Eze et al., 2020; Lim et al., 2018; Zijlema et al., 2021). Evaluating noise sensitivity as a possible effect modifier of the association between environmental noise exposure and symptom outcomes can also help to give a more comprehensive idea of the potential impact of noise exposure.

The main strength of our study is the inclusion of two population-based birth cohorts from two different areas in Europe, and the prospective nature of these studies. Also, noise exposure estimations accounted for the time a child spent at each address. We also used multiple imputation and inverse probability weighting to account for selection bias, which increases the validity of our results (Sterne et al., 2009). We included the symptom outcome scores as continuous scales, allowing us to examine whether an association was present on a wide spectrum, improving the statistical power of the study and reducing outcome misclassification. Furthermore, the assessment of repeated exposure and outcome measurements using a LMM approach is another strength of our study. Using this approach increased the statistical power of the analysis, allowed for a correct modelling of the non-independence in the longitudinal data, and ensured the proper handling of missing data (Harrison et al., 2018).

Our study also has some limitations that merit discussion. The first is the possibility of information bias. Non-uniformity could be present in the data, since we used different questionnaires to assess symptoms outcomes at different ages completed by different reporters. However, we standardized the symptoms scales and results were similar across questionnaires and reporters. Also, even though multiple imputation was performed, some potential confounding variables had high percentage of missingness (30.4 – 48.5%). To ensure validity of the results based on the imputed datasets, in the multiple imputation procedure we applied models that used predictor variables that were moderately to strongly correlated with the missing potential confounding variables and explored the plausibility of the imputation data. Further, effect estimates were unchanged in children with no missing values for potential confounding variables. The possibility of non-differential exposure misclassification should be addressed. Measurement error in the noise estimations and including children that lived at least 50% of the time in the study area may have resulted in incorrect assignment of the noise exposure levels of some participants. Thus, our effect estimates may be biased towards the null and lead to incorrect estimations of the true association. However, we aimed to improve the noise estimations as much as possible by assessing them as a continuous exposure variable and accounting for the changes in residential address. Also, we used the L_{DEN} indicator instead of the L_{NIGHT} indicator because it includes the noise exposure during the evening (i.e., between 19:00 and 23:00) which is also a relevant exposure time for children and the exposure during both the evening and the night has a greater weight than the exposure during the day. Nevertheless, L_{DEN} and L_{NIGHT} were highly correlated (rho = 0.90). Further, we could not investigate whether our results were influenced by two potential effect modifiers such as noise sensitivity and location of the child's bedroom. Having information on the location of the child's bedroom (e.g., if the bedroom has windows facing the street where the noise exposure is estimated or the floor where the bedroom is located) would have reduced the measurement error on the noise estimation and could have provided more valid effect estimates of the association (Eze et al., 2020; Grelat et al., 2016; Hjortebjerg et al., 2016; Pujol et al., 2012). Even though we were able to assess multiple noise sources (road traffic, aircraft, railway, and industry) for the Generation R Study, there were too few children exposed to the separate noise sources to conduct source-specific analyses. Future studies should include populations where the prevalence of these exposure sources is higher, include a more exhaustive noise exposure assessment, and determine the overall effect on symptom outcomes.

5. Conclusion

In conclusion, in this study no association was observed between prenatal and childhood environmental noise exposure and emotional, aggressive, and ADHD-related symptoms in children in two European birth cohorts. Our analyses using longitudinal data and information from multiple noise sources showed absence of associations in line with previous research that found no association with emotional or aggressive symptoms, but not with research that more consistently showed associations with higher ADHD-related symptoms. Further longitudinal studies including a more comprehensive noise exposure assessment considering noise sensitivity, exposure at work for pregnant women or at school for children are warranted to fully understand how environmental noise exposure can affect children's health.

CRediT authorship contribution statement

Esmée Essers: Conceptualization, Formal analysis, Methodology, Writing – original draft, Visualization. **Laura Pérez-Crespo:** Conceptualization, Formal analysis, Methodology, Writing – review & editing, Visualization, Supervision. **Maria Foraster:** Methodology, Writing – review & editing. **Albert Ambrós:** Methodology, Writing – review & editing. **Henning Tiemeier:** Writing – review & editing, Funding acquisition. **Mònica Guxens:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.

org/10.1016/j.envint.2021.106946.
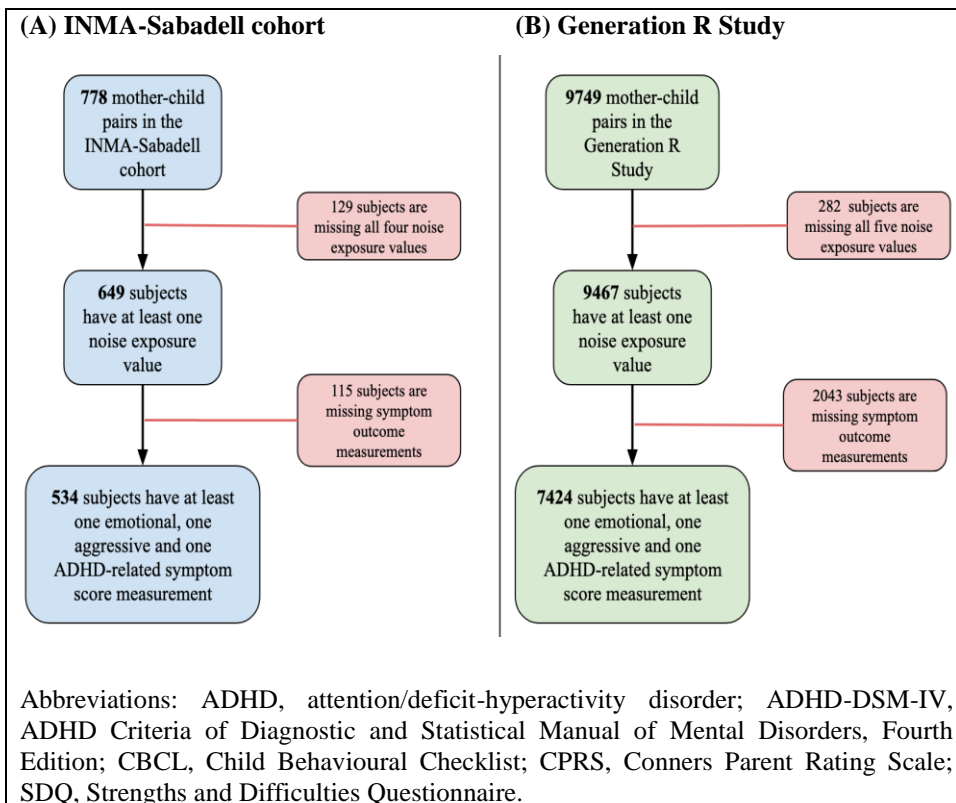
References

Achenbach, T.M., Rescorla, L.A., 2001. Manual for the ASEBA school-age forms and profiles. J. Child Neurol. https://doi.org/10.1016/S1474-4422(03)00585-4.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, fourth ed., Text Revision (DSM-IV-TR).

Beijers, R., Buitelaar, J.K., de Weerth, C., 2014. Mechanisms underlying the effects of prenatal psychosocial stress on child outcomes: beyond the HPA axis. Eur. Child Adolesc. Psychiatry 23 (10), 943–956. https://doi.org/10.1007/s00787-014-0566-3.

Clark, C., Crumpler, C., Notley, H., 2020. Evidence for environmental noise effects on health for the United Kingdom policy context: a systematic review of the effects of environmental noise on mental health, wellbeing, quality of life, cancer, dementia, birth, reproductive outcomes, and cognition. Int. J. Environ. Res. Public Health 17 (2), 393. https://doi.org/10.3390/ijerph17020393.

Clark, C., Paunovic, K., 2018a. WHO environmental noise guidelines for the European region: a systematic review on environmental noise and quality of life, wellbeing and mental health. Int. J. Environ. Res. Public Health 15 (11), 2400. https://doi.org/10.3390/ijerph15112400.

Clark, C., Paunovic, K., 2018b. WHO environmental noise guidelines for the European region: a systematic review on environmental noise and cognition. Int. J. Environ. Res. Public Health. 15 (2), 285. https://doi.org/10.3390/ijerph15020285.

Conners, C.K., 1997. Conners' Rating Scales-Revised Technical Manual. Multi-Health Syst.

Crombie, R., Clark, C., Stansfeld, S.A., 2011. Environmental noise exposure, early biological risk and mental health in nine to ten year old children: a cross-sectional field study. Environ. Heal. A Glob. Access Sci. Source. https://doi.org/10.1186/1476-069X-10-39.

Derogatis, L.R., 1993. BSI Brief Symptom Inventory: Administration, Scoring, and Procedure Manual, Minneapolis MN: National Computer Systems. https://doi.org/10.1037/t00789-000.

Erickson, L.C., Newman, R.S., 2017. Influences of background noise on infants and children. Curr. Dir. Psychol. Sci. https://doi.org/10.1177/0963721417709087.

European Environmental Agency, 2020. Environmental Noise in Europe – 2020. Luxemburg. https://doi.org/10.2800/686249.

European Environmental Noise Directive, 2002. Directive 2002/49/EC.

Evans, G.W., Kliewer, W., Martin, J., 1991. The role of the physical environment in the health and well-being of children. In: New Directions in Health Psychology Assessment.

Eze, I.C., Foraster, M., Schaffner, E., Vienneau, D., Pieren, R., Imboden, M., Wunderli, J.-M., Cajochen, C., Brink, M., Röösli, M., Probst-Hensch, N., 2020. Incidence of depression in relation to transportation noise exposure and noise annoyance in the SAPALDIA study. Environ. Int. 144, 106014. https://doi.org/10.1016/j.envint.2020.106014.

Forns, J., Dadvand, P., Foraster, M., Alvarez-Pedrerol, M., Rivas, I., López-Vicente, M., Suades-Gonzalez, E., Garcia-Esteban, R., Esnaola, M., Cirach, M., Grellier, J., Basagaña, X., Querol, X., Guxens, M., Nieuwenhuijsen, M.J., Sunyer, J., 2016. Traffic-related air pollution, noise at school, and behavioral problems in Barcelona schoolchildren: a cross-sectional study. Environ. Health Perspect. 124 (4), 529–535. https://doi.org/10.1289/ehp.1409449.

Forns, J., Sunyer, J., Garcia-Esteban, R., Porta, D., Ghassabian, A., Giorgis-Allemand, L., Gong, T., Gehring, U., Sørensen, M., Standl, M., Sugiri, D., Almqvist, C., Andiarena, A., Badaloní, C., Beelen, R., Berdel, D., Cesaroni, G., Charles, M.-A., Eriksen, K.T., Estarlich, M., Fernandez, M.F., Forhan, A., Jaddoe, V.W.V., Korek, M., Lichtenstein, P., Lertxundi, A., Lopez-Espinosa, M.-J., Markevych, I., de Nazelle, A., Raaschou-Nielsen, O., Nieuwenhuijsen, M., Pérez-Lobato, R., Philippat, C., Slama, R., Tiesler, C.M.T., Verhulst, F.C., von Berg, A., Vrijkotte, T., Nybo Andersen, A.-M., Heude, B., Krämer, U., Heinrich, J., Tiemeier, H., Forastiere, F., Pershagen, G., Brunekreef, B., Guxens, M., 2018. Air pollution exposure during pregnancy and symptoms of attention deficit and hyperactivity disorder in children in Europe. Epidemiology 29 (5), 618–626. https://doi.org/10.1097/EDE.0000000000000874.

Gitau, R., Cameron, A., Fisk, N.M., Glover, V., 1998. Fetal exposure to maternal cortisol. Lancet 352 (9129), 707–708. https://doi.org/10.1016/S0140-6736(05)60824-0.

Goldberg, D.P., Gater, R., Sartorius, N., Ustun, T.B., Piccinelli, M., Gureje, O., Rutter, C., 1997. The validity of two versions of the GHQ in the WHO study of mental illness in general health care. Psychol. Med. 27 (1), 191–197. https://doi.org/10.1017/S0033291796004242.

Goodman, R., Ford, T., Simmons, H., Gatward, R., Meltzer, H., 2003. Using the Strength and Difficulties Questionnaire (SDQ) to screen for child psychiatric disorders in a community sample. Int. Rev. Psychiatry 15, 166–172.

Graignic-Philippe, R., Dayan, J., Chokron, S., Jacquet, A.-Y., Tordjman, S., 2014. Effects of prenatal stress on fetal and child development: a critical literature review. Neurosci. Biobehav. Rev. 43, 137–162. https://doi.org/10.1016/j.neubiorev.2014.03.022.

Grelat, N., Houot, H., Pujol, S., Levain, J.P., Defrance, J., Mariet, A.S., Mauny, F., 2016. Noise annoyance in urban children: a cross-sectional population-based study. Int. J. Environ. Res. Publ. Health 13, 1056. https://doi.org/10.3390/ijerph13111056.

Gupta, A., Gupta, A., Jain, K., Gupta, S., 2018. Noise pollution and impact on children health. Indian J. Pediatr. https://doi.org/10.1007/s12098-017-2579-7.

Guxens, M., Ballester, F., Espada, M., Fernández, M.F., Grimalt, J.O., Ibarluzea, J., Olea, N., Rebagliato, M., Tardón, A., Torrent, M., Vioque, J., Vrijheid, M., Sunyer, J., 2012. Cohort profile: the INMA-INfancia y medio ambiente-(environment and childhood) project. Int. J. Epidemiol. https://doi.org/10.1093/ije/dyr054.

Haines, M.M., Stansfeld, S.A., Soames Job, R.F., Berglund, B., Head, J., 2001. A follow-up study of effects of chronic aircraft noise exposure on child stress responses and cognition. Int. J. Epidemiol. https://doi.org/10.1093/ije/30.4.839.

Harrison, X.A., Donaldson, L., Correa-Cano, M.E., Evans, J., Fisher, D.N., Goodwin, C.E. D., Robinson, B.S., Hodgson, D.J., Inger, R., 2018. A brief introduction to mixed effects modelling and multi-model inference in ecology. PeerJ. https://doi.org/10.7717/peerj.4794.

Hernán, M.A., Hernández-Diaz, S., Werler, M.M., Mitchell, A.A., 2002. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. Am. J. Epidemiol. https://doi.org/10.1093/aje/155.2.176.

Hjortebjerg, D., Andersen, A.M.N., Christensen, J.S., Ketzel, M., Raaschou-Nielsen, O., Sunyer, J., Julvez, J., Forns, J., Sørensen, M., 2016. Exposure to road traffic noise and behavioral problems in 7-year-old children: a cohort study. Environ. Health Perspect. 124 (2), 228–234. https://doi.org/10.1289/ehp.1409430.

Hofman, A., Jaddoe, V.W.V., Mackenbach, J.P., Moll, H.A., Snijders, R.F.M., Steegers, E. A.P., Verhulst, F.C., Witteman, J.C.M., Buller, H.A., 2004. Growth, development and health from early fetal life until young adulthood: the generation R study. Paediatr. Perinat. Epidemiol. 18, 61–72. https://doi.org/10.1111/j.1365-3016.2003.00521.x.

Jafari, Z., Mehla, J., Kolb, B.E., Mohajerani, M.H., 2017. Prenatal noise stress impairs HPA axis and cognitive performance in mice. Sci. Rep. 7 (1) https://doi.org/10.1038/s41598-017-09799-6.

Jorcano, A., Lubczyńska, M.J., Pierotti, L., Altug, H., Ballester, F., Cesaroni, G., El Marroun, H., Fernández-Somoano, A., Freire, C., Hanke, W., Hoek, G., Ibarluzea, J., Iñiguez, C., Jansen, P.W., Lepeule, J., Markevych, I., Polańska, K., Porta, D., Schikowski, T., Slama, R., Standl, M., Tardon, A., Vrijkotte, T.G.M., von Berg, A., Tiemeier, H., Sunyer, J., Guxens, M., 2019. Prenatal and postnatal exposure to air pollution and emotional and aggressive symptoms in children from 8 European birth cohorts. Environ. Int. 131, 104927. https://doi.org/10.1016/j.envint.2019.104927.

Kooijman, M.N., Kruithof, C.J., van Duijn, C.M., Duijts, L., Franco, O.H., van IJzendoorn, M.H., de Jongste, J.C., Klaver, C.C.W., van der Lugt, A., Mackenbach, J. P., Moll, H.A., Peeters, R.P., Raat, H., Rings, E.H.H.M., Rivadeneira, F., van der Schroeff, M.P., Steegers, E.A.P., Tiemeier, H., Uitterlinden, A.G., Verhulst, F.C., Wolvius, E., Felix, J.F., Jaddoe, V.W.V., 2016. The Generation R study: design and cohort update 2017. Eur. J. Epidemiol. 31 (12), 1243–1264. https://doi.org/10.1007/s10654-016-0224-9.

Lautarescu, A., Craig, M.C., Glover, V., 2020. Prenatal stress: effects on fetal and child brain development. Int. Rev. Neurobiol. https://doi.org/10.1016/bs.irn.2019.11.002.

Lim, J., Kweon, K., Kim, H.W., Cho, S.W., Park, J., Sim, C.S., 2018. Negative impact of noise and noise sensitivity on mental health in childhood. Noise Heal. https://doi.org/10.4103/nah.NAH_9_18.

NHS Foundation Trust, 2021. Sound sensitivity in children.

Potgieter, I., Fackrell, K., Kennedy, V., Crunkhorn, R., Hoare, D.J., 2020. Hyperacusis in children: a scoping review. BMC Pediatr. 20 (1) https://doi.org/10.1186/s12887-020-02223-5.

Pujol, S., Berthillier, M., Defrance, J., Lardiès, J., Petit, R., Houot, H., Levain, J.-P., Masselot, C., Mauny, F., 2012. Urban ambient outdoor and indoor noise exposure at home: a population-based study on schoolchildren. Appl. Acoust. 73 (8), 741–750. https://doi.org/10.1016/j.apacoust.2012.02.007.

Spratt, M., Carpenter, J., Sterne, J.A.C., Carlin, J.B., Heron, J., Henderson, J., Tilling, K., 2010. Strategies for multiple imputation in longitudinal studies. Am. J. Epidemiol. 172 (4), 478–487. https://doi.org/10.1093/aje/kwq137.

Stansfeld, S., Clark, C., 2015. Health effects of noise exposure in children. Curr. Environ. Heal. Rep. https://doi.org/10.1007/s40572-015-0044-1.

Stansfeld, S.A., Clark, C., Cameron, R.M., Alfred, T., Head, J., Haines, M.M., van Kamp, I., van Kempen, E., Lopez-Barrio, I., 2009. Aircraft and road traffic noise exposure and children's mental health. J. Environ. Psychol. 29 (2), 203–207. https://doi.org/10.1016/j.jenvp.2009.01.002.

Stansfeld, S.A., Matheson, M.P., 2003. Noise pollution: non-auditory effects on health. Br. Med. Bull. https://doi.org/10.1093/bmb/ldg033.

Sterne, J.A.C., White, I.R., Carlin, J.B., Spratt, M., Royston, P., Kenward, M.G., Wood, A. M., Carpenter, J.R., 2009. Multiple imputation for missing data in epidemiological and clinical research: Potential and pitfalls. BMJ. https://doi.org/10.1136/bmj.b2393.

The World Bank, 2019. Urban Development [WWW Document]. URL https://www.worldbank.org/en/topic/urbandevelopment/overview (accessed 3.31.20).

Tiesler, C.M.T., Birk, M., Thiering, E., Kohlböck, G., Koletzko, S., Bauer, C.P., Berdel, D., Von Berg, A., Babisch, W., Heinrich, J., Wichmann, H.E., Schoet-zau, A., Mosetter, M., Schindler, J., Höhnke, A., Franke, K., Laubereau, B., Gehring, U., Sausenthaler, S., Thaqi, A., Zirngibl, A., Zutavern, A., Schnappinger, M., Chen, C.M., Berdel, D., VonBerg, A., Filipiak-Pittroff, B., Albrecht, B., Baumgart, A., Beckmann, C., Büttner, S., Diekamp, S., Groß, I., Jakob, T., Klemke, K., Kurpiun, S., Möllemann, M., Varhelyi, A., Koletzko, S., Reinhardt, D., Weigand, H., Antonie, I., Bäumler-Merl, B., Tasch, C., Göhlert, R., Mühlbauer, D., Sönnichsen, C., Sauerwald, T., Kindermann, A., Waag, M., Koch, M., Bauer, C.P., Grübl, A., Bartels, P., Brockow, I., Fischer, A., Hoffmann, U., Lötzbeyer, F., Mayrl, R., Negele, K., Schill, E.M., Wolf, B., Paschke, M., Krämer, U., Link, E., Ranft, U., Schins, R., Sugiri, D., Cramer, C., Behrendt, H., Grosch, J., Martin, F., Heinrich, J., Wichmann, H.E., Sausenthaler, S., Chen, C.M., Schnappinger, M., Borte, M., Diez, U., VonBerg, A., Beckmann, C., Groß, I., Schaaf, B., Lehmann, I., Bauer, M., Gräbsch, C., Röder, S., Schilde, M., Her-barth, O., Dick, C., Magnus, J., Krämer, U., Link, E., Cramer, C., Bauer, C.P., Hoffmann, U., Behrendt, H., Grosch, J., Martin, F., 2013. Exposure to road traffic noise and children's behavioural problems and sleep disturbance: results from the GINIplus and LISAplus studies. Environ. Res. https://doi.org/10.1016/j.envres.2013.01.009.

United Nations: Department of Economic and Social Affairs, 2019. Revision of World Urbanization Prospects. New York.

Weisskopf, M.G., Sparrow, D., Hu, H., Power, M.C., 2015. Biased exposure-health effect estimates from selection in cohort studies: are environmental studies at particular risk? Environ. Health Perspect. 123 (11), 1113–1122. https://doi.org/10.1289/ehp.1408888.

Weuve, J., Tchetgen Tchetgen, E.J., Glymour, M.M., Beck, T.L., Aggarwal, N.T., Wilson, R.S., Evans, D.A., Mendes De Leon, C.F., 2012. Accounting for bias due to selective attrition: the example of smoking and cognitive decline. Epidemiology 23, 119–128. https://doi.org/10.1097/EDE.0b013e318230e861.

Weyde, K., Krog, N.H., Oftedal, B., Aasvang, G.M., Magnus, P., Overland, S., Stansfeld, S., Nieuwenhuijsen, M.J., Vrijheid, M., De Castro Pascual, P., 2017. Road traffic noise and children's inattention. Environ. Heal. A Glob. Access Sci. Source. https://doi.org/10.1186/s12940-017-0337-y.

World Health Organization, 2018. Environmental Noise Guidelines for the European Region. Copenhagen.

Zijlema, W.L., De Kluizenaar, Y., Van Kamp, I., Hartman, C.A., 2020. Associations between road traffic noise exposure at home and school and ADHD in school-aged children: the TRAILS study. Eur. Child Adolescent Psychiatry. https://doi.org/10.1007/s00787-020-01521-8.

Supplementary Material

FIGURE S1: Flowchart of study participants in the INMA-Sabadell (A) and Generation R (B) cohorts.

Abbreviations: ADHD, attention/deficit-hyperactivity disorder; ADHD-DSM-IV, ADHD Criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; CBCL, Child Behavioural Checklist; CPRS, Conners Parent Rating Scale; SDQ, Strengths and Difficulties Questionnaire.

Methods S1. Formulas used to calculate total noise exposure in Generation R and the L_{DEN} value in the INMA-Sabadell and Generation R cohorts.

Formula for total noise exposure levels in the Generation R Study:

$$Total\ noise = 10\lg\left(10^{\frac{road}{10}} + 10^{\frac{railway}{10}} + 10^{\frac{aircraft}{10}} + 10^{\frac{industry}{10}}\right)$$

Formula for the day-evening-night noise indicator (L_{DEN}) in the Generation R Study:

$$L_{DEN} = 10\lg\frac{1}{24}\left(\left(12 \cdot 10^{\frac{L_{DAY}}{10}}\right) + \left(4 \cdot 10^{\frac{L_{EVENING}\ +5}{10}}\right) + \left(8 \cdot 10^{\frac{L_{NIGHT}\ +10}{10}}\right)\right)$$

Formula for the day-evening-night noise indicator (L_{DEN}) in the INMA-Sabadell cohort:

$$L_{DEN} = 10\lg\frac{1}{24}\left(\left(14 \cdot 10^{\frac{L_{DAY}}{10}}\right) + \left(2 \cdot 10^{\frac{L_{EVENING}\ +5}{10}}\right) + \left(8 \cdot 10^{\frac{L_{NIGHT}\ +10}{10}}\right)\right)$$

Methods S2. Description of the measurement instruments used to determine emotional, aggressive, and attention-deficit/hyperactivity disorder (ADHD)-related symptoms.

The Strength and Difficulties Questionnaire

The SDQ is a parental-reported questionnaire about the child consisting of five scales related to emotional symptoms, conduct problems, hyperactivity-inattention, peer problems and pro-social behavior (Goodman, 1997). Each scale consists of five items, and we used the 'Emotional Problems' scale to measure emotional symptoms, and the 'Conduct Problems' scale to measure aggressive symptoms. Symptom scores were calculated based on a 3-point Linkert scale (0 = not true, 1 = somewhat true and 2 = certainly true), generating the emotional and aggressive symptom scores from 0 to 10 points (Goodman, 1997; Goodman et al., 2003).

Child Behavioral Checklist 1½-5 and 6-18

The CBCL 1½-5 and 6-18 are questionnaires that measure behavioral and emotional problems of a child as reported by the parents (Achenbach & Rescorla, 2001b). The CBCL 1½-5 consists of 99 items and uses a 3-point Linkert severity scale (0 = not true, 1 = somewhat or sometimes true and 2 = very true or often true) based on the previous 2 months. To assess emotional symptoms, summed raw scores from the syndrome scales 'Anxious/Depressed' (8 items) and 'Withdrawn' (8 items) were used, generating an emotional symptom score ranging from 0 to 32 points. For aggressive symptoms, the raw score from the syndrome scale 'Aggressive Behavior' (19 items) was used, generating an aggressive symptom score ranging from 0 to 38 points. To assess ADHD-related symptoms, the raw score from the syndrome scale 'Attention Problems' (5 items) was used, generating an ADHD-related symptom score ranging from 0 to 10 points. The CBCL 6-18 questionnaire consists of 112 items and uses the same 3-point Linkert scale but based on the preceding 6 months. To assess emotional symptoms, summed raw scores from the syndrome scales 'Anxious/Depressed' (13 items) and 'Withdrawn/Depressed' (8 items) were used. To assess aggressive symptoms, summed raw scores from the syndrome scales 'Rule-Breaking Behavior' (17 items) and 'Aggressive Behavior' (18 items) were used. This

generated an emotional symptom score ranging from 0 to 42 points and an aggressive symptom score from 0 to 70 points. The syndrome scale 'Attention Problems' (10 items) was used to calculate the ADHD-related symptom score, ranging from 0 to 20 points.

ADHD Criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

The ADHD-DSM-IV list consists of 18 items and is categorized into two groups with nine symptoms each: 'inattention' and 'hyperactivity/impulsivity'. The ADHD-related symptom score was calculated based on a 4-point Linkert severity scale (0 = never or rarely, 1 = sometimes, 2 = often, and 3 = very often). This generated the ADHD-related symptom score ranging from 0 to 54 points (American Psychiatric Association, 2000).

Conner's Parent Rating Scale-Revised

The CPRS consists of three scales (oppositional, cognitive problems/inattention and hyperactivity), each having 9 items and the questionnaire having 27 items in total. The CPRS uses a 4-point Linkert severity scale (0 = not true at all, 1 = just a little true, 2 = pretty much true and 3 = very much true) based on the preceding month. The questionnaire also calculates a separate ADHD index score ranging from 0 to 36 points, which was used as the ADHD-related symptom scale (Conners, 1997b).

FIGURE S2: Symptom outcome assessment time points and measuring instruments used in the INMA-Sabadell and Generation R cohorts.
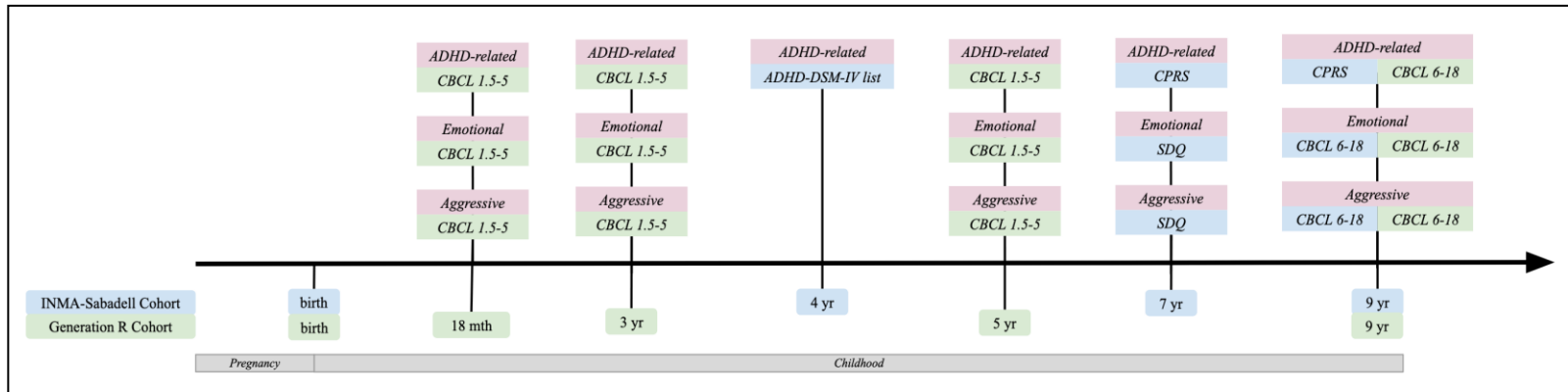
Abbreviations: ADHD, attention/deficit-hyperactivity disorder; ADHD-DSM-IV, ADHD Criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; CBCL, Child Behavioural Checklist; CPRS, Conners Parent Rating Scale; SDQ, Strengths and Difficulties Questionnaire.

TABLE S1. Details of the imputation modelling.

Software used and key setting: R (version 4.0.0; R Core Team (2020)) – mice package (with 25 iterations) and Stata Statistical Software: Release 14. College Station, TX: StataCorp LP (with 25 iterations)
Number of imputed datasets created: 25
Variables included in the imputation procedure for the INMA-Sabadell cohort: Noise exposure during pregnancy; emotional symptoms at 7 and 9 years; behavioural symptoms at 7 and 9 years; attention symptoms at 4, 7 and 9 years; maternal height, maternal pre-pregnancy body mass index, paternal height, paternal pre-pregnancy body mass index, family status, maternal education level, paternal education level, maternal parity, maternal smoking during pregnancy, maternal alcohol use during pregnancy, maternal social class, paternal social class, maternal country of birth, paternal country of birth, maternal age, paternal age, sex of new-born, maternal pathological distress, paternal pathological distress. **Variables included in the imputation procedure for the Generation R cohort:** noise exposure during pregnancy, noise exposure during childhood, emotional symptoms at 18 months, 3, 5, and 9 years, behavioural symptoms at 18 months, 3, 5, and 9 years, attention symptoms at 18 months, 3, 5, and 9 years, maternal country of birth, paternal country of birth, maternal education level, paternal education level, family status, income, maternal parity, maternal smoking during pregnancy, maternal alcohol use during pregnancy, sex of new-born, maternal age, paternal age, maternal pre-pregnancy body mass index, paternal pre-pregnancy body mass index, maternal social class, paternal social class, maternal pathological distress, paternal pathological distress
Treatment of non-normally distributed variables: sqrt-transformed
Treatment of binary/categorical variables: logistic and multinomial models
Statistical interactions included in imputation models: none

TABLE S2: Population characteristics in observed and imputed datasets of the INMA-Sabadell cohort and Generation R Study.

Characteristics	INMA-Sabadell (n = 534)			Generation R (n =7,424)		
	Observed	Imputed	% Imputed	Observed	Imputed	% Imputed
Child Characteristics						
Sex (male vs. female)	51.5	51.5	0.0	50.5	50.5	0
Maternal Characteristics						
Age at enrolment (years)	31.8 (4.2)	31.8 (4.2)	0.2	30.7 (5.0)	30.7 (5.0)	0
Pre-pregnancy body mass index (kg/m^2)	22.7 (21.1; 25.4)	22.7 (21.0; 25.4)	2.1	22.6 (20.8; 25.2)	22.6 (20.8; 25.3)	25.0
Ethnicity			1.5			1.8
Spanish	90.5	90.3		-	-	
Dutch	-	-		56.2	56.0	
Surinamese	-	-		7.3	7.3	
Turkish	-	-		8.1	8.2	
Moroccan	-	-		5.1	5.2	
Others	9.5	9.7		23.3	23.3	
Education during pregnancy			2.1			7.9
Low	24.1	24.3		8.3	8.9	
Medium	43.8	43.8		42.8	43.2	
High	32.1	31.8		48.9	47.9	
Social Class during pregnancy			9.1			36.5
Low	44.5	45.6		3.9	7.9	
Medium	32.4	31.8		32.2	36.7	
High	23.1	22.6		63.9	55.4	
Pathological distress[1]	9.0 (7.0; 12.0)	9.0 (7.0; 12.0)	5.8	0.2 (0.1; 0.3)	0.2 (0.1; 0.3)	25.7
Parity			1.1			3.4
0	56.1	56.2		56.7	56.5	
1	37.3	37.2		30.5	30.6	
2+	6.6	6.6		12.8	12.9	
Smoking during pregnancy (no vs. yes)	72.2	73.2	1.5	84.0	83.9	12.2
Alcohol during pregnancy (no vs. yes)	77.9	77.8	10.3	59.2	58.8	19.9

Abbreviations: p25, 25th percentile; p75, 75th percentile. Values are percentages for categorical, mean (standard deviation) for continuous variables, and median (p25; p75) for body mass index and pathological distress. [1] Chi-square tests for categorical variables, two-sample t-test for normally distributed and Wilcoxon Rank Sum test for non-normally distributed continuous variables. [2] Score range 0 – 36 for the INMA-Sabadell cohort (assessed at child's 14 months) and 0 – 4 for the Generation R Study (assessed during

TABLE S2, continued: Population characteristics in observed and imputed datasets of the INMA-Sabadell cohort and Generation R Study.

Characteristics	INMA-Sabadell (n = 534)			Generation R (n =7,424)		
	Observed	Imputed	% Imputed	Observed	Imputed	% Imputed
Paternal Characteristics						
Age at enrolment (years)	33.6 (4.8)	33.6 (4.8)	1.1	33.2 (5.5)	33.2 (5.7)	30.4
Body mass index during pregnancy (kg/m^2)	25.4 (23.5; 27.7)	25.4 (23.5; 27.7)	10.4	24.9 (22.9; 27.2)	25.0 (23.0; 27.2)	30.6
Ethnicity			0.7			30.8
Spanish	89.8	89.8		-	-	
Dutch	-	-		64.8	60.0	
Surinamese	-	-		5.6	6.5	
Turkish	-	-		5.6	6.9	
Moroccan	-	-		3.2	3.9	
Others	10.2	10.2		20.8	22.7	
Education during pregnancy			1.1			38.5
Low	36.7	36.9		6.7	9.8	
Medium	42.0	42.0		39.4	42.2	
High	21.2	21.1		53.9	48.0	
Social Class during pregnancy			13.8			48.5
Low	57.4	58.6		8.5	11.5	
Medium	18.7	18.5		22.7	26.3	
High	23.9	22.9		68.8	62.2	
Pathological distress[1]	9.0 (7.0; 11.0)	9.0 (7.0; 11.0)	9.5	0.1 (0.0; 0.2)	0.1 (0.0; 0.2)	41.2
Household Characteristics						
Family status (dual vs. single parent)	98.8	98.0	9.3	89.0	88.7	7.8
Monthly income during pregnancy (€)			-			22.9
< 900	-	-		9.0	10.3	
900 - 1600	-	-		15.7	17.3	
1600 - 2200	-	-		15.4	15.8	
> 2200	-	-		59.9	56.6	

Abbreviations: p25, 25th percentile; p75, 75th percentile. Values are percentages for categorical, mean (standard deviation) for continuous variables, and median (p25; p75) for body mass index and pathological distress. [1] Chi-square tests for categorical variables, two-sample t-test for normally distributed and Wilcoxon Rank Sum test for non-normally distributed continuous variables. [2] Score range 0 – 36 for the INMA-Sabadell cohort (assessed at child's 14 months) and 0 – 4 for the Generation R Study (assessed during

TABLE S3: Population characteristics of the subjects included and not included in the analyses of the INMA-Sabadell cohort and Generation R Study.

Characteristics	INMA-Sabadell (n = 778)			Generation R (n = 9749)		
	Included (n = 534)	Not Included (n = 244)	p-value[1]	Included (n = 7,424)	Not Included (n = 2,325)	p-value[1]
Child Characteristics						
Sex (male vs. female)	51.5	49.3	0.645	50.5	51.2	0.576
Maternal Characteristics						
Age at enrolment (years)	31.8 (4.2)	30.2 (4.9)	< 0.001	30.7 (5.0)	27.4 (5.7)	< 0.001
Pre-pregnancy body mass index (kg/m^2)	22.7 (21.1; 25.4)	22.5 (20.8; 25.6)	0.735	22.6 (20.8; 25.2)	22.8 (20.7; 26.2)	0.015
Ethnicity			< 0.001			< 0.001
Spanish	90.5	77.1		-	-	
Dutch	-	-		56.2	25.8	
Surinamese	-	-		7.3	14.9	
Turkish	-	-		8.1	11.5	
Moroccan	-	-		5.1	13.0	
Others	9.5	22.9		23.3	33.8	
Education during pregnancy			< 0.001			< 0.001
Low	24.1	39.5		8.3	22.4	
Medium	43.8	41.6		42.8	58.7	
High	32.1	18.9		48.9	18.9	
Social Class during pregnancy			< 0.001			< 0.001
Low	44.5	67.4		3.9	9.8	
Medium	32.4	24.4		32.2	53.0	
High	23.1	8.2		63.9	37.2	
Pathological distress[2]	9.0 (7.0; 12.0)	9.0 (7.0; 12.0)	0.982	0.2 (0.1; 0.3)	0.3 (0.1; 0.6)	< 0.001
Parity			< 0.001			< 0.001
0	56.1	50.0		56.7	49.7	
1	37.3	34.6		30.5	29.4	
2+	6.6	15.4		12.8	20.9	
Smoking during pregnancy (no vs. yes)	73.2	64.2	0.025	84.0	74.1	< 0.001
Alcohol during pregnancy (no vs. yes)	77.9	71.8	0.168	59.2	77.9	< 0.001

Abbreviations: p25, 25th percentile; p75, 75th percentile. Values are percentages for categorical, mean (standard deviation) for continuous variables, and median (p25; p75) for body mass index and pathological distress. [1] Chi-square tests for categorical variables, two-sample t-test for normally distributed and Wilcoxon Rank Sum test for non-normally distributed continuous variables. [2] Score range 0 – 36 for the INMA-Sabadell cohort (assessed at child's 14 months) and 0 – 4 for the Generation R Study (assessed during pregnancy).

TABLE S3, continued: Population characteristics of the subjects included and not included in the analyses of the INMA-Sabadell cohort and Generation R Study.

Characteristics	INMA-Sabadell (n = 778)			Generation R (n = 9749)		
	Included (n = 534)	Not Included (n = 244)	p-value[1]	Included (n = 7,424)	Not Included (n = 2,325)	p-value[1]
Paternal Characteristics						
Age at enrolment (years)	33.6 (4.8)	32.8 (6.1)	0.107	33.2 (5.5)	30.8 (6.3)	< 0.001
Body mass index during pregnancy(kg/m^2)	25.4 (23.5; 27.7)	25.3 (23.7; 27.8)	0.478	24.9 (22.9; 27.2)	25.2 (22.8; 27.8)	0.171
Ethnicity			0.002			< 0.001
Spanish	89.8	81.4		-	-	
Dutch	-	-		64.8	33.5	
Surinamese	-	-		5.6	11.1	
Turkish	-	-		5.6	11.5	
Moroccan	-	-		3.2	8.4	
Others	10.2	18.6		20.8	35.5	
Education during pregnancy			< 0.001			< 0.001
Low	36.7	53.7		6.7	18.7	
Medium	42.0	34.5		39.4	52.5	
High	21.2	11.8		53.9	28.8	
Social Class during pregnancy			0.020			< 0.001
Low	57.4	69.8		8.5	18.1	
Medium	18.7	14.5		22.7	42.1	
High	23.9	15.7		68.8	39.8	
Pathological distress[2]	9.0 (7.0; 11.0)	9.0 (7.0; 11.0)	0.808	0.1 (0.0; 0.2)	0.1 (0.0; 0.3)	< 0.001
Household Characteristics						
Family status (dual vs. single parent)	98.8	97.7	0.519	89.0	72.6	< 0.001
Monthly income (€)			-			< 0.001
< 900	-	-		9.0	30.8	
900 - 1600	-	-		15.7	31.6	
1600 - 2200	-	-		15.4	12.9	
> 2200	-	-		59.9	24.6	

Abbreviations: p25, 25th percentile; p75, 75th percentile. Values are percentages for categorical, mean (standard deviation) for continuous variables, and median (p25; p75) for body mass index and pathological distress. [1] Chi-square tests for categorical variables, two-sample t-test for normally distributed and Wilcoxon Rank Sum test for non-normally distributed continuous variables. [2] Score range 0 – 36 for the INMA-Sabadell cohort (assessed at child's 14 months) and 0 – 4 for the Generation R Study (assessed during pregnancy).

TABLE S4. Variables used in logistic regression model to calculate inverse probability of attrition weights in the INMA-Sabadell cohort and Generation R Study.

Variables	INMA-Sabadell Cohort		Generation R Study	
	Explored	*Included*	*Explored*	*Included*
Sex new-born	x		x	
Maternal pre-pregnancy weight	x		x	
Maternal height	x		x	
Maternal pre-pregnancy BMI	x		x	x
Paternal weight	x		x	
Paternal height	x		x	
Paternal BMI	x		x	
Family status	x		x	x
Maternal education	x		x	x
Paternal education	x	x	x	
Parity	x	x	x	x
Smoking during pregnancy	x	x	x	x
Maternal social class	x	x	x	
Paternal social class	x		x	x
Maternal ethnicity	x	x	x	x
Paternal ethnicity	x		x	x
Alcohol during pregnancy	x		x	x
Maternal age	x	x	x	x
Paternal age	x		x	x
Maternal pathological distress	x		x	
Paternal pathological distress	x		x	
Monthly household income			x	

TABLE S5. Descriptive statistics of the noise exposure levels in the INMA-Sabadell and Generation R cohorts.

	Mean	p25; p75	Min.	Max.	N
INMA-Sabadell (N = 534)					
Road traffic noise exposure (dB)					
Pregnancy	61.3	57.4; 65.0	43.0	77.4	519
Birth – 4 years	61.3	58.4; 65.0	45.0	77.4	484
4 – 7 years	61.6	58.0; 66.0	45.0	76.0	486
7 – 9 years	61.8	58.0; 66.0	45.0	76.0	480
Generation R (N = 7,424)					
Road traffic noise exposure (dB)					
Pregnancy	54.6	48.0; 61.0	40.0	73.0	7054
Birth – 18 months	54.4	48.0; 60.0	40.0	73.0	7136
18 months – 3 years	53.9	48.0; 60.0	40.0	73.0	6479
3 – 5 years	53.4	47.8; 59.0	40.0	73.0	5816
5 – 9 years	53.2	47.1; 58.0	40.0	73.0	5474
Total noise exposure (dB)					
Pregnancy	55.8	50.1; 61.4	40.1	73.0	7054
Birth – 18 months	55.7	50.1; 60.9	40.1	73.0	7136
18 months – 3 years	55.3	49.9; 60.2	40.1	73.0	6479
3 – 5 years	54.9	49.8; 59.5	40.1	73.0	5816
5 – 9 years	54.7	49.8; 59.2	40.0	73.0	5474

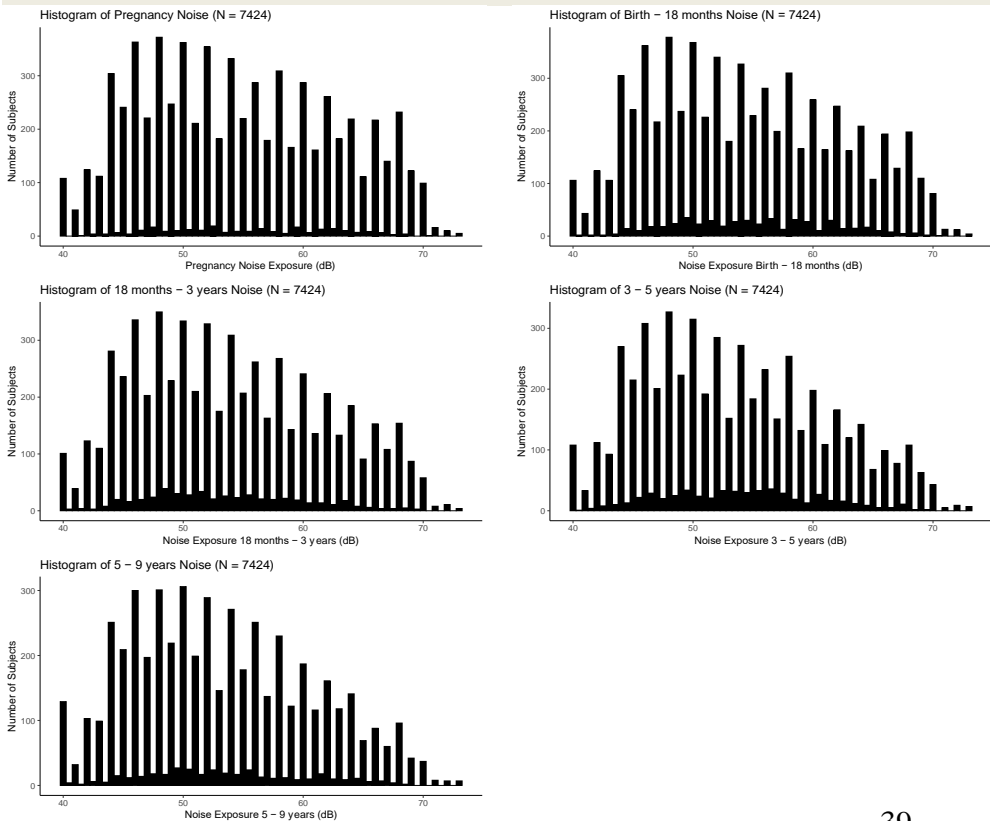Abbreviations: dB, decibels; p25, 25th percentile; p75, 75th percentile

FIGURE S3: Road traffic noise exposure distribution for the pregnancy period and the childhood periods in the INMA-Sabadell (A) and Generation R (B) analysis cohorts.

(A) INMA-Sabadell cohort
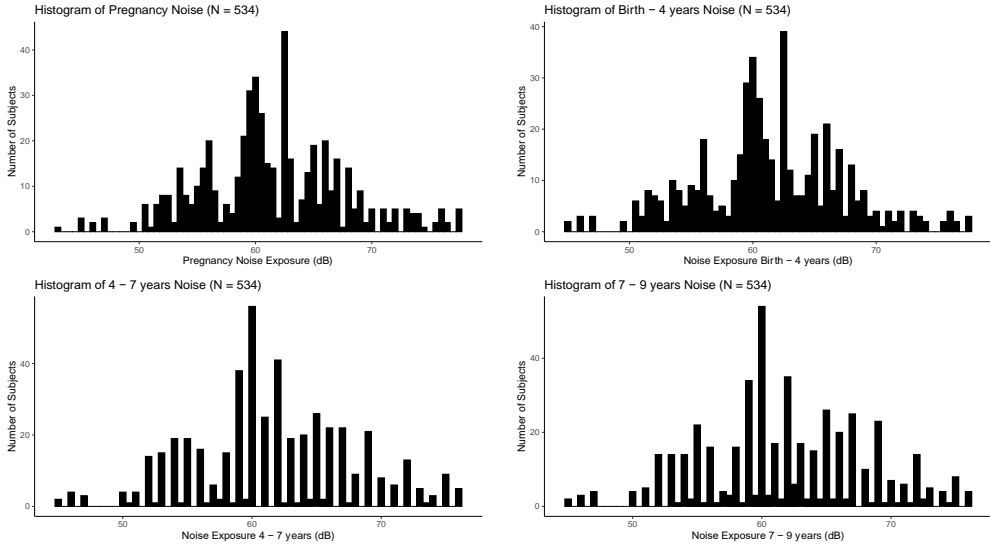
(B) Generation R Study

TABLE S6. Pearson correlations between the road traffic noise exposure values during different lifetime periods of the child for the INMA-Sabadell cohort (n = 534) (A), the road traffic noise exposure values (B1) and total noise exposure values (B2), and between the road traffic and total noise exposure values (C) for the Generation R Study (n = 7424).

(A) road traffic	Pregnancy	Birth - 4 years	4 - 7 years	7 - 9 years
Pregnancy	1			
Birth - 4 years	0.85	1		
4 - 7 years	0.69	0.84	1	
7 - 9 years	0.69	0.77	0.94	1

(B1) road traffic	Pregnancy	Birth – 18 months	18 months – 3 years	3 - 5 years	5 - 9 years
Pregnancy	1				
Birth - 18 months	0.91	1			
18 months - 3 years	0.75	0.88	1		
3 - 5 years	0.60	0.71	0.88	1	
5 - 9 years	0.48	0.58	0.72	0.89	1

(B2) total	Pregnancy	Birth – 18 months	18 months – 3 years	3 - 5 years	5 - 9 years
Pregnancy	1				
Birth - 18 months	0.91	1			
18 months - 3 years	0.75	0.89	1		
3 - 5 years	0.60	0.72	0.88	1	
5 - 9 years	0.49	0.58	0.73	0.89	1

(C) road traffic and total	
Pregnancy	0.97
Birth - 18 months	0.97
18 months - 3 years	0.96
3 - 5 years	0.95
5 - 9 years	0.95

TABLE S7: Unadjusted and fully adjusted associations of a 5 decibel (dB) increase in prenatal or childhood road traffic noise exposure for the INMA-Sabadell cohort, and road traffic or total noise exposure for the Generation R Study and standardized emotional, aggressive or attention-deficit/hyperactivity disorder (ADHD)-related symptom scores.

	Emotional Symptoms				Aggressive Symptoms				ADHD-related Symptoms			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	B	95% CI	B	95% CI	B	95% CI	B	95% CI	B	95% CI	B	95% CI
INMA-Sabadell Cohort – Road Traffic Noise Exposure (n = 534)												
Prenatal	-0.02	-0.08 to 0.04	-0.00	-0.06 to 0.06	-0.02	-0.09 to 0.04	0.00	-0.06 to 0.06	-0.03	-0.09 to 0.03	-0.00	-0.06 to 0.05
Childhood	-0.03	-0.09 to 0.03	-0.01	-0.07 to 0.05	-0.02	-0.08 to 0.04	0.01	-0.05 to 0.07	0.00	-0.05 to 0.06	0.02	-0.03 to 0.08
Generation R Study – Road Traffic Noise Exposure (n = 7,424)												
Prenatal	-0.00	-0.02 to 0.02	-0.01	-0.02 to 0.01	0.00	-0.01 to 0.02	0.00	-0.01 to 0.02	0.00	-0.01 to 0.01	-0.00	-0.02 to 0.01
Childhood	0.00	-0.02 to 0.02	-0.01	-0.03 to 0.00	0.00	-0.01 to 0.02	-0.00	-0.02 to 0.01	0.00	-0.01 to 0.01	-0.01	-0.02 to 0.00
Generation R Study – Total Noise Exposure (n = 7,424)												
Prenatal	-0.00	-0.02 to 0.02	-0.01	-0.03 to 0.01	0.00	-0.01 to 0.02	-0.01	-0.03 to 0.01	-0.00	-0.01 to 0.01	-0.01	-0.02 to 0.00
Childhood	0.00	-0.02 to 0.02	-0.02	-0.04 to 0.00	0.00	-0.01 to 0.02	-0.00	-0.02 to 0.01	0.00	-0.01 to 0.02	-0.01	-0.02 to 0.00

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; B; coefficient of the linear mixed model; CI, confidence interval; dB, decibels. Coefficients and 95% confidence intervals by cohort were obtained by linear mixed models. Within each cohort, linear mixed models were adjusted for child sex, parental age, height, weight, body mass index, ethnicity, education, social class and pathological distress, parity, smoking and alcohol during pregnancy, and family status. Generation R Study models were additionally adjusted for monthly household income.
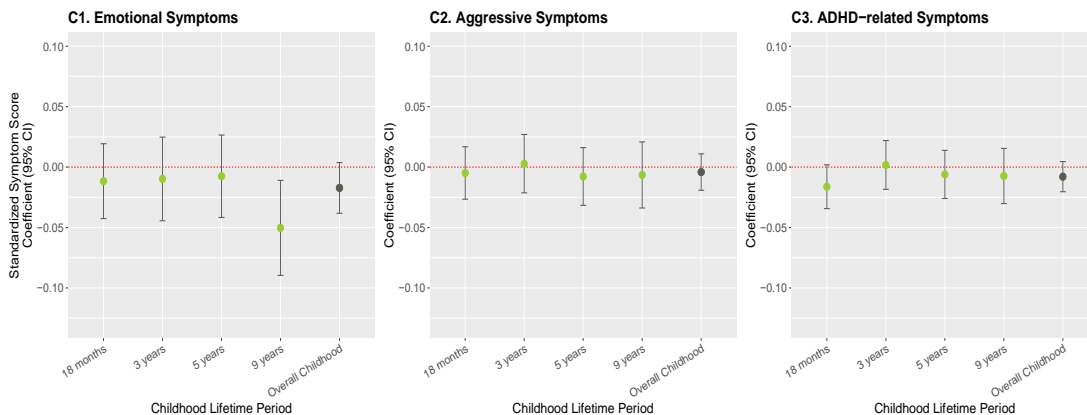
TABLE S8: Unadjusted and fully adjusted associations of a 5 decibel (dB) increase in road traffic noise exposure for the INMA-Sabadell cohort, and road traffic or total noise exposure for the Generation R Study during childhood lifetime periods and standardized emotional, attention-deficit/hyperactivity disorder (ADHD)-related symptom scores.

	Emotional Symptoms				Aggressive Symptoms				ADHD-related Symptoms			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	B	95% CI	B	95% CI	B	95% CI	B	95% CI	B	95% CI	B	95% CI
INMA-Sabadell Cohort – Road Traffic Noise Exposure (n = 534)												
Birth to 4 years	---		---		---		---		0.00	-0.07 to 0.07	0.02	-0.05 to 0.09
4 to 7 years	-0.04	-0.11 to 0.04	-0.01	-0.08 to 0.06	-0.03	-0.10 to 0.04	0.00	-0.07 to 0.07	0.00	-0.07 to 0.07	0.02	-0.04 to 0.09
7 to 9 years	-0.02	-0.09 to 0.06	0.00	-0.07 to 0.07	-0.01	-0.09 to 0.06	0.02	-0.05 to 0.09	0.01	-0.06 to 0.08	0.03	-0.04 to 0.10
Generation R Study – Road Traffic Noise Exposure (n = 7,424)												
Birth to 18 months	0.01	-0.02 to 0.03	-0.01	-0.03 to 0.02	0.00	-0.02 to 0.02	-0.01	-0.02 to 0.01	-0.00	-0.02 to 0.01	-0.01	-0.03 to 0.00
18 months to 3 years	0.01	-0.02 to 0.04	-0.01	-0.04 to 0.02	0.01	-0.01 to 0.03	0.01	-0.02 to 0.03	0.01	-0.01 to 0.03	0.00	-0.02 to 0.02
3 to 5 years	0.01	-0.02 to 0.04	-0.01	-0.04 to 0.02	0.00	-0.02 to 0.02	-0.01	-0.03 to 0.01	0.00	-0.01 to 0.02	-0.01	-0.02 to 0.01
5 to 9 years	-0.03	-0.06 to 0.00	-0.05*	-0.08 to -0.01	-0.00	-0.02 to 0.02	-0.01	-0.02 to 0.01	-0.00	-0.02 to 0.01	-0.01	-0.03 to 0.01
Generation R Study – Total Noise Exposure (n = 7,424)												
Birth to 18 months	0.00	-0.03 to 0.03	-0.01	-0.04 to 0.02	0.00	-0.02 to 0.02	-0.01	-0.03 to 0.02	-0.01	-0.02 to 0.01	-0.02	-0.03 to 0.00
18 months to 3 years	0.01	-0.02 to 0.04	-0.01	-0.04 to 0.02	0.01	-0.01 to 0.04	0.00	-0.02 to 0.03	0.01	-0.01 to 0.03	0.00	-0.02 to 0.02
3 to 5 years	0.02	-0.02 to 0.05	-0.01	-0.04 to 0.03	0.00	-0.02 to 0.03	-0.01	-0.03 to 0.02	0.01	-0.01 to 0.03	-0.01	-0.03 to 0.01
5 to 9 years	-0.03	-0.07 to 0.01	-0.05*	-0.09 to -0.01	0.00	-0.03 to 0.03	-0.00	-0.02 to 0.01	0.00	-0.02 to 0.03	-0.01	-0.02 to 0.00

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; B, coefficient of the linear mixed model; CI, confidence interval; dB, decibels. Coefficients and 95% confidence intervals by cohort and lifetime period were obtained by linear mixed models. Within each cohort, linear mixed models were adjusted for child sex, parental age, height, weight, body mass index, ethnicity, education, social class and pathological distress, parity, smoking and alcohol during pregnancy, and family status. Generation R Study models were additionally adjusted for monthly household income.
* Statistically significant at the 0.05 level.

FIGURE S4: Fully adjusted associations of a 5 decibel (dB) increase in total noise exposure in the Generation R Study during childhood lifetime periods and overall childhood, and standardized emotional (C1), aggressive (C2) or attention-deficit/hyperactivity disorder (ADHD)-related (C3) symptom scores.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; dB, decibels. Coefficients and 95% confidence intervals by cohort, noise exposure source and lifetime period were obtained by linear mixed models. Linear mixed models were adjusted for child sex, parental age, height, weight, body mass index, ethnicity, education, social class and pathological distress, parity, smoking and alcohol during pregnancy, family status, and monthly household income.

TABLE S9: Unadjusted and fully adjusted associations of a 5 decibel (dB) increase in prenatal or childhood road traffic noise exposure, and childhood lifetime periods for the INMA-Sabadell cohort, and road traffic or total noise exposure for the Generation R Study and standardized emotional, aggressive, or attention-deficit/hyperactivity disorder (ADHD)-related symptom scores in the children with complete childhood noise exposure assessments.

	Emotional Symptoms				Aggressive Symptoms				ADHD-related Symptoms			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	B	95% CI	B	95% CI	B	95% CI	B	95% CI	B	95% CI	B	95% CI
INMA-Sabadell Cohort – Road Traffic Noise Exposure (n = 462)												
Prenatal	-0.01	-0.08 to 0.05	0.01	-0.06 to 0.07	-0.02	-0.09 to 0.04	0.01	-0.06 to 0.07	-0.02	-0.08 to 0.04	0.01	-0.05 to 0.07
Childhood	-0.02	-0.08 to 0.05	-0.00	-0.06 to 0.06	-0.02	-0.08 to 0.04	0.01	-0.05 to 0.07	0.00	-0.05 to 0.06	0.02	-0.03 to 0.08
Generation R Study – Road Traffic Noise Exposure (n = 5,364)												
Prenatal	0.00	-0.02 to 0.03	-0.01	-0.03 to 0.01	0.00	-0.01 to 0.02	-0.00	-0.02 to 0.01	-0.00	-0.01 to 0.01	-0.01	-0.02 to 0.01
Childhood	0.00	-0.02 to 0.02	-0.02	-0.04 to 0.00	0.00	-0.01 to 0.02	-0.00	-0.02 to 0.01	0.00	-0.01 to 0.01	-0.01	-0.02 to 0.01
Generation R Study – Total Noise Exposure (n = 5,364)												
Prenatal	-0.00	-0.03 to 0.02	-0.02	-0.04 to 0.01	-0.00	-0.02 to 0.02	-0.02	-0.04 to 0.01	-0.00	-0.02 to 0.01	-0.01	-0.03 to 0.00
Childhood	0.00	-0.02 to 0.03	-0.02	-0.05 to 0.00	0.00	-0.01 to 0.02	-0.00	-0.02 to 0.01	0.00	-0.01 to 0.02	-0.01	-0.02 to 0.01

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; B; coefficient of the linear mixed model; CI, confidence interval; dB, decibels. Coefficients and 95% confidence intervals by cohort were obtained by linear mixed models. Within each cohort, linear mixed models were adjusted for child sex, parental age, height, weight, body mass index, ethnicity, education, social class and pathological distress, parity, smoking and alcohol during pregnancy, and family status. Generation R Study models were additionally adjusted for monthly household income.

TABLE S9, continued: Unadjusted and fully adjusted associations of a 5 decibel (dB) increase in prenatal or childhood road traffic noise exposure, and childhood lifetime periods for the INMA-Sabadell cohort, and road traffic or total noise exposure for the Generation R Study and standardized emotional, aggressive, or attention-deficit/hyperactivity disorder (ADHD)-related symptom scores in the children with complete childhood noise exposure assessments.

	Emotional Symptoms				Aggressive Symptoms				ADHD-related Symptoms			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	B	95% CI	B	95% CI	B	95% CI	B	95% CI	B	95% CI	B	95% CI
INMA-Sabadell Cohort – Road Traffic Noise Exposure (n = 462)												
Birth to 4 years		---		---		---		---	0.01	-0.07 to 0.08	0.02	-0.05 to 0.09
4 to 7 years	-0.02	-0.10 to 0.04	-0.01	-0.08 to 0.07	-0.02	-0.10 to 0.05	0.00	-0.07 to 0.08	0.00	-0.07 to 0.07	0.02	-0.05 to 0.09
7 to 9 years	-0.01	-0.09 to 0.06	0.00	-0.07 to 0.08	-0.01	-0.09 to 0.06	0.02	-0.06 to 0.09	0.00	-0.07 to 0.08	0.03	-0.05 to 0.10
Generation R Study – Road Traffic Noise Exposure (n = 5,364)												
Birth to 18 months	0.01	-0.02 to 0.04	-0.01	-0.04 to 0.02	-0.00	-0.02 to 0.02	-0.01	-0.03 to 0.01	-0.00	-0.02 to 0.01	-0.01	-0.03 to 0.00
18 months to 3 years	0.01	-0.02 to 0.05	-0.01	-0.04 to 0.02	0.01	-0.01 to 0.04	0.01	-0.02 to 0.03	0.01	-0.01 to 0.03	0.00	-0.01 to 0.02
3 to 5 years	0.01	-0.02 to 0.04	-0.01	-0.04 to 0.03	0.00	-0.02 to 0.02	-0.00	-0.03 to 0.02	0.01	-0.01 to 0.02	-0.00	-0.02 to 0.01
5 to 9 years	-0.03	-0.07 to 0.00	-0.05*	-0.09 to -0.02	-0.00	-0.03 to 0.02	-0.01	-0.03 to 0.02	-0.00	-0.02 to 0.02	-0.01	-0.03 to 0.01
Generation R Study – Total Noise Exposure (n = 5,364)												
Birth to 18 months	0.00	-0.03 to 0.04	-0.02	-0.05 to 0.02	0.00	-0.03 to 0.03	-0.01	-0.03 to 0.02	-0.00	-0.03 to 0.02	-0.02	-0.04 to 0.00
18 months to 3 years	0.01	-0.03 to 0.05	-0.01	-0.05 to 0.03	0.01	-0.01 to 0.04	0.00	-0.02 to 0.03	0.01	-0.01 to 0.04	0.00	-0.02 to 0.03
3 to 5 years	0.02	-0.02 to 0.05	-0.01	-0.05 to 0.03	0.00	-0.02 to 0.03	-0.01	-0.03 to 0.02	0.01	-0.01 to 0.03	-0.00	-0.02 to 0.02
5 to 9 years	-0.03	-0.08 to 0.01	-0.06*	-0.10 to -0.02	-0.00	-0.03 to 0.03	-0.01	-0.04 to 0.02	0.00	-0.02 to 0.03	-0.01	-0.02 to 0.01

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; B, coefficient of the linear mixed model; CI, confidence interval; dB, decibels. Coefficients and 95% confidence intervals by cohort and lifetime period were obtained by linear mixed models. Within each cohort, linear mixed models were adjusted for child sex, parental age, height, weight, body mass index, ethnicity, education, social class and pathological distress, parity, smoking and alcohol during pregnancy, and family status. Generation R Study models were additionally adjusted for monthly household income. * Statistically significant at the 0.05 level.

TABLE S10: Unadjusted and fully adjusted associations of a 5 decibel (dB) increase in prenatal or childhood road traffic noise exposure, and childhood lifetime periods for the INMA-Sabadell cohort, and road traffic or total noise exposure for the Generation R Study and standardized emotional, aggressive, or attention-deficit/hyperactivity disorder (ADHD)-related symptom scores in the children with no missing values for any potential confounding variables.

	Emotional Symptoms				Aggressive Symptoms				ADHD-related Symptoms			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	B	95% CI	B	95% CI	B	95% CI	B	95% CI	B	95% CI	B	95% CI
INMA-Sabadell Cohort – Road Traffic Noise Exposure (n = 396)												
Prenatal	-0.05	-0.12 to 0.02	-0.04	-0.10 to 0.03	-0.01	-0.08 to 0.06	0.01	-0.05 to 0.08	-0.32	-0.09 to 0.04	-0.01	-0.08 to 0.05
Childhood	-0.05	-0.12 to 0.02	-0.04	-0.11 to 0.02	-0.01	-0.08 to 0.06	0.00	-0.07 to 0.07	0.01	-0.05 to 0.07	0.01	-0.05 to 0.07
Generation R Study – Road Traffic Noise Exposure (n = 2,397)												
Prenatal	0.01	-0.01 to 0.03	-0.00	-0.02 to 0.02	0.01	-0.01 to 0.03	0.01	-0.01 to 0.03	0.00	-0.01 to 0.02	0.00	-0.02 to 0.02
Childhood	0.01	-0.01 to 0.03	0.00	-0.01 to 0.02	0.01	-0.00 to 0.03	0.01	-0.01 to 0.03	-0.00	-0.02 to 0.02	-0.00	-0.02 to 0.02
Generation R Study – Total Noise Exposure (n = 2,397)												
Prenatal	0.00	-0.02 to 0.03	-0.00	-0.03 to 0.02	0.01	-0.01 to 0.04	0.00	-0.02 to 0.03	0.01	-0.02 to 0.03	0.00	-0.02 to 0.02
Childhood	0.01	-0.01 to 0.03	0.00	-0.02 to 0.02	0.01	-0.01 to 0.04	0.01	-0.01 to 0.03	-0.00	-0.02 to 0.02	-0.00	-0.02 to 0.02

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; B; coefficient of the linear mixed model; CI, confidence interval; dB, decibels. Coefficients and 95% confidence intervals by cohort were obtained by linear mixed models. Within each cohort, linear mixed models were adjusted for child sex, parental age, height, weight, body mass index, ethnicity, education, social class and pathological distress, parity, smoking and alcohol during pregnancy, and family status. Generation R Study models were additionally adjusted for monthly household income.

TABLE S10, continued: Unadjusted and fully adjusted associations of a 5 decibel (dB) increase in prenatal or childhood road traffic noise exposure, and childhood lifetime periods for the INMA-Sabadell cohort, and road traffic or total noise exposure for the Generation R Study and standardized emotional, aggressive, or attention-deficit/hyperactivity disorder (ADHD)-related symptom scores in the children with no missing values for any potential confounding variables.

	Emotional Symptoms				Aggressive Symptoms				ADHD-related Symptoms			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	B	95% CI	B	95% CI	B	95% CI	B	95% CI	B	95% CI	B	95% CI
INMA-Sabadell Cohort – Road Traffic Noise Exposure (n = 462)												
Birth to 4 years		---		---		---		---	0.01	-0.07 to 0.09	0.00	-0.08 to 0.08
4 to 7 years	-0.06	-0.15 to 0.02	-0.06	-0.14 to 0.02	-0.01	-0.09 to 0.07	0.00	-0.07 to 0.08	-0.00	-0.08 to 0.08	-0.00	-0.08 to 0.08
7 to 9 years	-0.03	-0.12 to 0.05	-0.03	-0.11 to 0.05	-0.02	-0.10 to 0.07	-0.00	-0.08 to 0.08	0.04	-0.04 to 0.12	0.03	-0.04 to 0.11
Generation R Study – Road Traffic Noise Exposure (n = 2,397)												
Birth to 18 months	0.02	-0.01 to 0.04	0.01	-0.02 to 0.04	0.01	-0.02 to 0.03	-0.00	-0.03 to 0.02	-0.01	-0.04 to 0.01	-0.02	-0.04 to 0.01
18 months to 3 years	0.02	-0.01 to 0.05	0.01	-0.02 to 0.04	0.03*	0.00 to 0.06	0.03*	0.00 to 0.06	0.03	-0.00 to 0.06	0.02	-0.01 to 0.06
3 to 5 years	0.01	-0.02 to 0.05	0.01	-0.02 to 0.04	0.02	-0.01 to 0.05	0.02	-0.01 to 0.05	-0.01	-0.04 to 0.02	-0.01	-0.04 to 0.02
5 to 9 years	-0.02	-0.05 to 0.02	-0.02	-0.06 to 0.01	-0.00	-0.04 to 0.03	-0.00	-0.04 to 0.03	0.00	-0.03 to 0.03	0.00	-0.03 to 0.04
Generation R Study – Total Noise Exposure (n = 2,397)												
Birth to 18 months	0.01	-0.02 to 0.04	0.00	-0.03 to 0.03	0.01	-0.02 to 0.04	-0.00	-0.03 to 0.03	-0.02	-0.05 to 0.01	-0.02	-0.05 to 0.01
18 months to 3 years	0.02	-0.01 to 0.06	0.01	-0.03 to 0.04	0.03*	0.00 to 0.07	0.03	-0.00 to 0.06	0.03	-0.01 to 0.06	0.03	-0.01 to 0.06
3 to 5 years	0.02	-0.01 to 0.06	0.01	-0.02 to 0.05	0.03	-0.01 to 0.06	0.02	-0.01 to 0.06	-0.00	-0.04 to 0.03	-0.01	-0.04 to 0.03
5 to 9 years	-0.02	-0.06 to 0.02	-0.03	-0.07 to 0.01	-0.00	-0.04 to 0.03	-0.01	-0.05 to 0.03	0.01	-0.03 to 0.05	0.01	-0.03 to 0.05

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; B, coefficient of the linear mixed model; CI, confidence interval; dB, decibels. Coefficients and 95% confidence intervals by cohort and lifetime period were obtained by linear mixed models. Within each cohort, linear mixed models were adjusted for child sex, parental age, height, weight, body mass index, ethnicity, education, social class and pathological distress, parity, smoking and alcohol during pregnancy, and family status. Generation R Study models were additionally adjusted for monthly household income. * Statistically significant at the 0.05 level.

Study II

Association between outdoor exposure to residential noise and cognitive and motor function in children and preadolescents

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Abstract

Background: Exposure to environmental noise is increasing in recent years but limited research has been conducted to assess the relationship with cognitive and motor function in children and preadolescents.

Objective: To investigate the association between outdoor exposure to residential noise from road traffic during pregnancy and childhood with cognitive and motor function in children and preadolescents from two European birth cohorts.

Methods: We used data of 619 participants from the INMA-Sabadell cohort and 7,115 from the Generation R Study. We used noise maps to assess the average outdoor road traffic noise levels (day-evening-night noise indicator LDEN) at each participants' home address during pregnancy and childhood periods. We assessed non-verbal and language/verbal intelligence, memory, processing speed, attentional function, visual attention, working memory, cognitive flexibility, risky decision-making, and fine and gross motor function using a battery of validated neurocognitive tests throughout childhood in both cohorts. Adjusted linear models, linear mixed models, and negative binomial models were run depending on the exposure and outcome measures separately by cohort. Additionally, overall estimates were combined with random-effects meta-analysis. Results were corrected for multiple testing.

Results: Average road traffic noise exposure levels during pregnancy and childhood were 61.3 (SD 6.0) and 61.5 (SD 5.4) dB for the INMA-Sabadell cohort and 54.6 (SD 7.9) and 53.5 (SD 6.5) dB for the Generation R Study, respectively. Outdoor exposure to residential road traffic noise during pregnancy and childhood was not associated with any of the cognitive and motor function outcomes explored in this study (e.g. -0.92 (95% CI -2.08; 0.24) in overall estimates of memory per an increase of 10 dB in road traffic noise during childhood).

Conclusions: These findings suggest that outdoor exposure to noise from road traffic at residences has no long-term effects on child's cognition. However, more studies evaluating this association at both school and home settings are needed to provide recommendations and implement environmental noise policies for protecting child's health. Also, future studies should include longitudinal designs to

explore the long-term effects as well as noise fluctuations measures instead of average noise levels.

Introduction

Urbanization processes that have been occurring during the past decades may have negative impacts in human well-being and health (Wang, 2018). Exposure to environmental noise has increased as a consequence of this urbanization growth and most of the population is exposed to it on a daily basis. In Europe, environmental noise remains a major health concern and it occurs from different sources, mainly: road traffic, railway, aircraft, and industry (European Environment Agency, 2020). Road traffic noise is the principal environmental noise source affecting human health and it has been estimated that at least 20% of the European population is exposed to noise levels exceeding the recommended thresholds of 55 decibels (dB) (European Environment Agency, 2020).

Previous epidemiological and experimental research has indicated that environmental noise exposure is related to diverse health effects (Héroux et al., 2015). Children are often considered as a vulnerable population to the effects of environmental noise because fetal life and childhood are periods of rapid growth and brain maturation (S. Stansfeld & Clark, 2015). In addition, children have less developed coping strategies and less control than adults to deal with environmental noise (S. Stansfeld & Clark, 2015). The evidence for the association between exposure to road traffic noise and cognitive development in children is still limited (Clark & Paunovic, 2018). No evidence was found of the association between road traffic noise exposure both at home (Julvez et al., 2021; van Kempen et al., 2010) and at school (Clark et al., 2012; Julvez et al., 2021; Matheson et al., 2010; S. A. Stansfeld et al., 2005; van Kempen et al., 2010, 2012) and working memory in children at 6-11 years old except in one study where outdoor exposure to road traffic noise at schools, but not at home, was associated with lower development of working memory from 7 to 10 years old (Foraster et al., 2022). Also, findings from studies assessing the association between road traffic noise exposure at school, at home, or at both settings and children's memory (Clark et al., 2012; Lercher et al., 2016; Matheson et al., 2010; S. A. Stansfeld et al., 2005; van Kempen et al., 2010, 2012), attentional function (Cohen et al., 1973; Foraster et al., 2022; Julvez et al., 2021; Lercher et al., 2016; Sanz et al., 1993; S. A. Stansfeld et al., 2005; van Kempen et al., 2010, 2012) or language/verbal and non-verbal intelligence (Bhang et al.,

2018; Clark et al., 2006; Cohen et al., 1973; Julvez et al., 2021; Ljung et al., 2009; S. A. Stansfeld et al., 2005) at 6-12 years old were not consistent. Lastly, the relationship between environmental noise exposure at home and motor function has only been investigated previously in a single study in children aged 3 and 6 years but no association was found (Raess et al., 2022).

Overall, research on the association between road traffic noise and cognitive and motor functions is still inconclusive. Additionally, most studies evaluated school-outdoor road traffic noise levels and were predominantly cross-sectional. Therefore, our study aims to investigate the association between outdoor exposure to residential noise from road traffic during pregnancy and childhood with cognitive and motor function in children and preadolescents from two European birth cohorts, the Dutch Generation R Study and the Spanish INMA Project.

Methods

Population and Study Design

This cross-sectional study used data from two population-based birth cohort studies: the Spanish INfancia y Medio Ambiente (INMA) Project (Guxens et al., 2012) and the Dutch Generation R Study (Kooijman et al., 2016). The INMA Project is a network of birth cohorts set up in several regions of Spain following a common protocol. For the present study, we included the INMA-Sabadell cohort due to data availability of the noise exposure maps. The cohort includes 775 pregnant women and their children resident in the city of Sabadell (Catalonia, Spain) who visited the public health centre of Sabadell for an ultrasound in the first trimester between July 2004 and July 2006. Mothers were eligible for the study if they were 16 years or older, had a singleton pregnancy, and had intention to deliver in the reference hospital. Exclusion criteria were having assisted to a reproduction programme or having communication problems. The Generation R Study is a prospective population-based cohort from fetal life onwards in Rotterdam, the Netherlands. This study contains a multi-ethnic population birth cohort including 9,610 pregnancies (Kooijman et al., 2016). Mothers were eligible for the study if they had an expected delivery date from April 2002 until January 2006 and were living in the study area of Rotterdam. We included a total of 7,734 children from both cohorts, 619 from INMA-Sabadell and 7,115 from the Generation R Study, with at least one noise exposure value and one cognitive or motor function measurement (Supplementary Material Figure S1). Ethical approval was obtained prior to recruitment from the Clinical Research Ethical Committee of the Municipal Institute of Healthcare (CIEC-IMAS) for the INMA-Sabadell cohort and from the Medical Ethical Committee of Erasmus MC, University Medical Centre Rotterdam, in accordance with Dutch law for the Generation R Study. We obtained written informed consent from parents in both cohorts.

Noise exposure assessment

Existing noise maps developed in 2006 and 2012 for Sabadell in Spain and in 2012 and 2017 for the municipalities of Rotterdam, Maassluis, Rozenburg, Schiedam, and Vlaardingen in the Netherlands were used to estimate the outdoor annual average

levels of environmental noise exposure at each participant's geocoded residential address. We selected these maps because they were the available ones matching which the period from conception until the last outcome assessment in each cohort, except for Generation R Study where we would need to include a map from 2007. However, we did not include it because the methodology used to develop it was different from the one used in the 2012 and 2017 maps, making the noise estimations not comparable. These maps met the requirements of the European Environmental Noise Directive (European Environmental Noise Directive, 2002). For the INMA-Sabadell cohort, noise was measured using a street categorization method taking into account the different types of street and land uses. Additionally, street geometry, presence of activities, type of traffic, and traffic flow were also considered to determine the noise level. For the Generation R Study, noise was modelled using the standardized Dutch calculation methods ('Standaard Rekenmethoden', SRM), including surfaces polygon, buildings, barriers, slope, crossings, roundabouts as well as the corresponding emission sources for each of the specific models. The maps from both countries were developed to estimate the noise levels at a height of 4 meters at the most exposed façade of the residential addresses. Noise maps were available for exposure levels of residential road traffic, railway, aircraft, and industry noise. However, in both cohorts, there were few children exposed to railway, aircraft, or industry noise, and only data from road traffic noise was used in the present study.

To estimate road traffic noise exposure, we calculated the day-evening-night EU noise indicator (L_{DEN}) using the formulas detailed in Supplementary Material Methods S1. L_{DEN} represents the A-weighted average sound level over the entire 24-hour day with penalties for the evening (+5 dB) and the night (+10 dB), as suggested by the Environmental Noise Directive to account for the expected greater health impact of the evening and night-time periods. The L_{DAY}, $L_{EVENING}$, and L_{NIGHT} indicators were defined as the A-weighted average sound levels assessed during the day (07:00 to 21:00 for INMA-Sabadell and 07:00 to 19:00 for Generation R), the evening (21:00 to 23:00 for INMA-Sabadell and 19:00 to 23:00 for Generation R), and the night (23:00 to 07:00 for both cohorts), respectively (European Environmental Noise Directive, 2002). The levels of L_{DEN} for both cohorts were calculated at each geocoded address that the participants have lived at during the period of

interest. We calculated the noise of the street closest to the geocode at a distance of 50 meters in the INMA-Sabadell cohort. However, in the Generation R Study, we performed an intersection of the buildings noise data obtained from the maps with the geocodes. In case that the geocode was outside the noise building, but in less than 50 meters, it was assigned to the closest building. If more than one address were available, the number of days that the participant spent at each address was considered to derive the average noise levels for each participant for the pregnancy period (from conception until birth), and for different periods during childhood, depending on the outcome assessments and the cohort. For the INMA-Sabadell cohort these periods were: from birth to 4 years old, from 4 to 7 years old, from 7 to 9 years old, and from 9 to 11 years old, and for the Generation R Study: from birth to 6 years old, from 6 to 9 years old, and from 9 to 13 years old.

Cognitive and motor function

Cognitive and motor function were measured as non-verbal intelligence, language/verbal intelligence, memory, processing speed, attentional function, visual attention, working memory, cognitive flexibility, risky decision-making, and fine and gross motor function using a battery of validated neurocognitive tests throughout childhood in both cohorts. Details of the tests used, outcomes calculated, and their interpretation are detailed in Table 1 and Figure 1.

Potential confounding variables

The potential confounding variables were a priori defined with a direct acyclic graph (Hernán et al., 2002) according to the existing literature and based on data availability in each cohort. In both cohorts, these variables were collected by questionnaires and instruments completed by the parents. We included information for both cohorts on parental ages at enrollment (in years), parental countries of birth (country of the cohort vs. others), parental education level (low: no education, unfinished primary or primary; medium: secondary; high: university degree or higher), parental social class based on occupation (low: semi-skilled/unskilled; medium: skilled manual and non-manual; high: managers/technicians), family status (dual or single parent),

maternal parity (nulliparous vs. multiparous)), maternal smoking during pregnancy (yes or no), and maternal alcohol use during pregnancy (yes or no). Child sex was obtained from hospital records and included as a covariate. Parental height (in cm) and weight (in kg) were measured or self-reported in the first trimester of pregnancy and body mass index (in kg/m^2) was calculated based on the collected weight and height data.

Statistical analyses

After checking that all the assumptions of the models (i.e., linearity between exposure and outcomes, independence, homoscedasticity, normality of the residuals) were fulfilled, we used linear regression models to assess the associations between outdoor exposure to residential road traffic noise and memory, processing speed, visual attention, and fine and gross motor function in both cohorts. We also performed linear regression models to assess the association of outdoor exposure to residential road traffic noise with cognitive flexibility and risky decision-making in the INMA-Sabadell cohort, and with working memory in the Generation R Study. In those outcomes with repeated measurements throughout childhood, we performed linear mixed models with subject as random intercept to account for the non-independence due to repeated measures of exposure and outcome. Therefore, we ran linear mixed models to assess the associations between outdoor exposure to residential road traffic noise and repeated language/verbal and non-verbal intelligence in both cohorts, and repeated working memory in the INMA-Sabadell cohort. Finally, we used negative binomial regression models to assess the association between outdoor exposure to residential road traffic noise and omission and commission errors in both cohorts. All models were adjusted for potential confounding variables specified in the previous section. All models were first run separately per cohort and overall estimates of those outcomes that were assessed in both cohorts were combined using random effects meta-analysis. The heterogeneity of the estimates was assessed using Cochran Q test and the I2 statistic. Analyses were corrected for multiple testing using the Bonferroni correction to a total of 74 tests (Abdi, 2007). After the correction, we obtained a new critical p-value for each association.

Multiple imputation of missing values of potential confounding variables for each cohort was performed using chained equations where 25 complete datasets were generated and analyzed (Spratt et al., 2010) (Supplementary Material Table S1). The percentage of missing values for the confounding variables was below 30% except for paternal education and social class in the Generation R Study which were between 30.94% and 52.48%. The distributions of the imputed datasets were similar to the non-imputed datasets (data not shown). Of the mother-child pairs recruited initially in the Spanish and Dutch cohorts, children included in this analysis (619 for INMA-Sabadell cohort and 7,115 for Generation R Study) were more likely to have parents that were older, from the country of the cohort, and with high level of education and social class than those not included (156 for INMA-Sabadell cohort and 2,495 for Generation R Study), and had mothers that consumed less alcohol during pregnancy (Supplementary Material Table S2). In addition, Dutch children included in this analysis (n= 7,115) had mothers that had smoked less during pregnancy, were nulliparous, and had a dual family status compared to children from the Dutch cohort not included (n=2,495). Thus, we used inverse probability weighting to correct for the losses to follow-up in both cohorts and account for potential selection bias when including only participants with available data as compared to the full initial cohort recruited at pregnancy.

All analyses were performed using Stata version 14 (StataCorporation, College Station, TX) and R (version 3.6.0 R Core Team (2019)).

Results

Participant characteristics of the study population from both cohorts are shown in Table 2. The average age of mothers was 31.7 and 30.5 years old in the INMA-Sabadell cohort and the Generation R Study, respectively. In the INMA-Sabadell cohort, almost all mothers were Spanish (89.3%), had a medium education (42.9%), and were from a high social class (47.4%). In the Generation R Study, most mothers were Dutch (54.1%), had a high education (47.0%), and were from a high social class (62.6%).

Average road traffic noise levels during pregnancy were 61.3 (standard deviation (SD) 6.0) and 54.6 (SD 7.9) deciBels (dB), whereas average road traffic noise levels during childhood were 61.5 (SD 5.4) and 53.5 (SD 6.5) dB in the INMA-Sabadell cohort and the Generation R Study, respectively (Table 2). Distribution of descriptive statistics of the noise exposure levels for the different periods of interest for both cohorts can be found in Supplementary Material Table S3. In addition, correlations between road traffic noise levels throughout the different time periods of study were moderate to strong (between 0.43 and 0.97), depending on the time period and the study cohort (Supplementary Material Table S4). Distributions of descriptive statistics of cognitive and motor outcomes for both cohorts are shown in Supplementary Table S5.

Outdoor exposure to residential road traffic noise during pregnancy or childhood was not associated with non-verbal intelligence, language/verbal intelligence, memory or processing speed in the unadjusted and adjusted models for the INMA-Sabadell cohort and Generation R Study, separately or combined in the meta-analysis (e.g. -0.92 (95% confidence interval (CI) -2.08; 0.24) in overall estimates of memory per an increase of 10 dB in road traffic noise during childhood) (Table 3).

Regarding attentional function, higher exposure to residential road traffic noise during pregnancy was associated with less commission errors and more omissions errors in the INMA-Sabadell cohort (Incidence Risk Ratio (IRR) 0.88 (95% CI 0.81; 0.96) and 1.13 (95% CI 1.01; 1.28), respectively, per an increase of 10 dB in road traffic noise levels) (Table 4). Also, we found an association between higher exposure to outdoor residential road

traffic noise during childhood and less commissions errors in the INMA-Sabadell cohort (IRR 0.85 (95% CI 0.78; 0.93) per an increase of 10 dB in road traffic noise levels) (Table 4). However, none of these associations survived correction for multiple testing.

We found no association between outdoor exposure to residential road traffic noise during pregnancy and childhood and visual attention (Table 4), fine and gross motor function (Table 5), and working memory (Supplementary Material Table S6) for any of the study cohorts (e.g. -0.34 (95% CI -0.95; 0.27) fine motor function in the right hand per an increase of 10 dB in road traffic noise levels). In INMA-Sabadell, we further assessed cognitive flexibility and risky decision-making with no associations observed related to outdoor noise exposure from road traffic at participants' home addresses (Supplementary Material Table S7 and S8).

TABLE 1. Details of cognitive and motor development assessment.

Cognitive and motor function domain	Test and subtest	Outcome of interest	Interpretation	Cohort	References
Non-verbal intelligence	MSCA: Perceptive-performance scale	Raw score	↓score; lower non-verbal intelligence	INMA-Sabadell	(MacCarthy & Cordero Pando, 2006)
	Raven	Number of correct items	↓number of correct items; lower non-verbal intelligence		(Raven, 2003)
	SON-R: Mosaics and Categories subtests	Age-standardized score	↓score; lower non-verbal intelligence	Generation R	(Laros & Tellegen, 1991)
	WISC-V: Matrix reasoning subtest	T score	↓score; lower non-verbal intelligence		(Kaufman et al., 2015)
Verbal intelligence	MSCA: Verbal scale	Raw score	↓score; lower verbal intelligence	INMA-Sabadell	(MacCarthy & Cordero Pando, 2006)
	Semantic Verbal Fluency	Number of words of animals that do not repeat	↓number of words; lower verbal intelligence		(Sauzéon et al., 2004)
	TVK: Receptive subtest	Percentage correct score: total correct answers divided by the total number of items answered	↓percentage correct score; lower verbal intelligence	Generation R	(Van Bon & Hoekstra, 1982)
	WISC-V: Vocabulary subtest	T score	↓score; lower verbal intelligence		(Kaufman et al., 2015)

Abbreviations: ANT, Attention Network Task; FTT, Finger Tapping Test; K-CPT, Conners' Kiddie Continuous Performance Test; MSCA, McCharty Scales of Children's Ability; NEPSY-II, Developmental NEuroPSYchological Assessment Second Edition; SON-R, Snijders-Oomen Niet-verbale intelligentie Test – Revisie; TMTA, Trail Making Test Part A; TMTB, Trail Making Test Part A; TVK, Talltest voor Kinderen; WISC-IV,4th edition of Wechsler Intelligence Scale for Children-IV ; WISC V, 5th edition of Wechsler Intelligence Scale for Children.

TABLE 1, continued. Details of cognitive and motor development assessment.

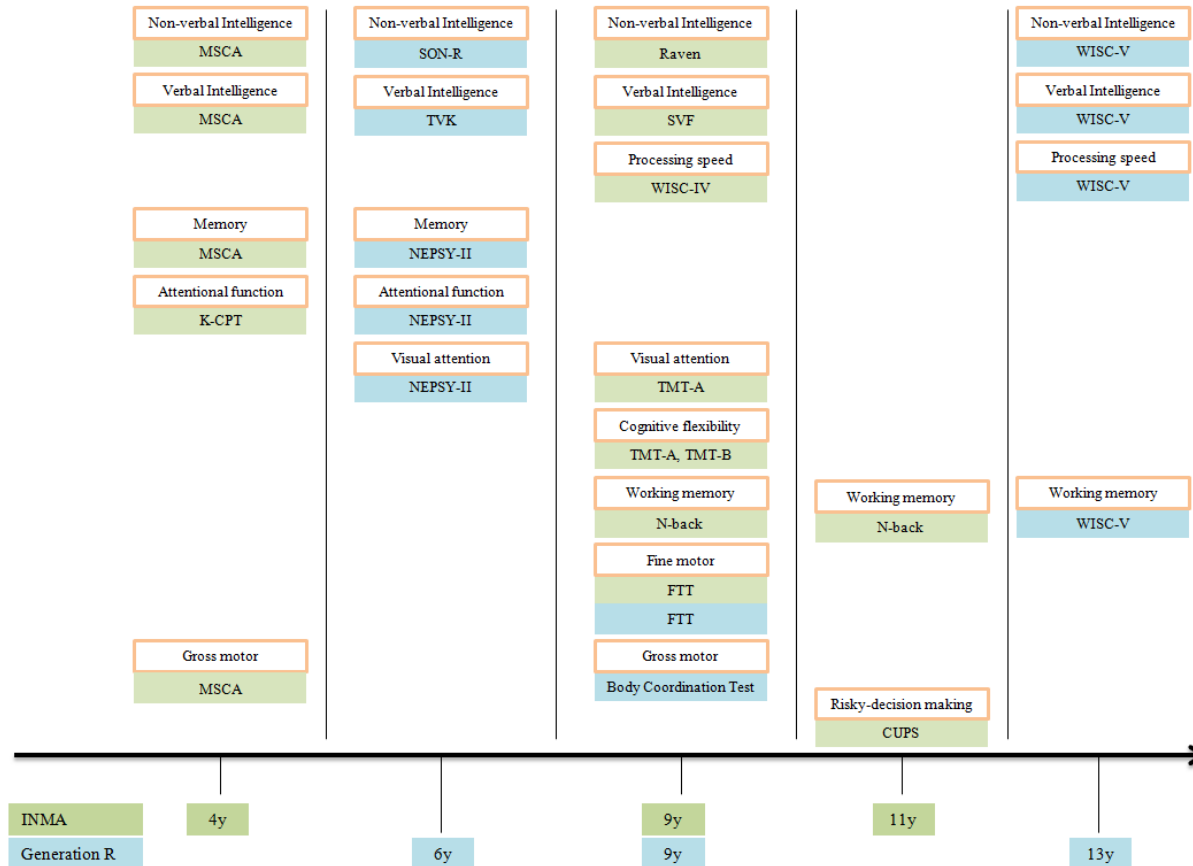| Cognitive and motor function domain	Test and subtest	Outcome of interest	Interpretation	Cohort	References
Memory	MSCA: Memory scale	Raw score	↓score; lower memory	INMA-Sabadell	(MacCarthy & Cordero Pando, 2006)
	NEPSY-II: Memory for faces, memory for faces delayed and memory, narrative memory	Scaled score		Generation R	(Brooks et al., 2009)
Processing speed	WISC-IV: Coding and Symbol search subtests	Raw score	↓score; lower speed of information processing	INMA-Sabadell	(Kaufman et al., 2006)
	WISC-V: Coding subtest	T score		Generation R	(Kaufman et al., 2015)
Attentional function	K-CPT	-Omission errors: Number of times the individual did not respond to a stimuli	↑omission errors ↑commissions errors; higher inattention	INMA-Sabadell	(Conners, 2006)
	NEPSY-II: Auditory attention subtest	-Commission errors: Number of times that the individual respond wrongly		Generation R	(Brooks et al., 2009)
Visual attention	TMT-A	Time to complete the task (ms)	↑time; lower visual attention	INMA-Sabadell	(Tombaugh, 2004)
	NEPSY-II: Visuomotor precision subtest	Scaled score	↓score; lower visual attention	Generation R	(Brooks et al., 2009)

Abbreviations: ANT, Attention Network Task; FTT, Finger Tapping Test; K-CPT, Conners' Kiddie Continuous Performance Test; MSCA, McCharty Scales of Children's Ability; NEPSY-II, Developmental NEuroPSYchological Assessment Second Edition; SON-R, Snijders-Oomen Niet-verbale intelligentie Test – Revisie; TMTA, Trail Making Test Part A; TMTB, Trail Making Test Part A; TVK, Talltest voor Kinderen; WISC-IV,4th edition of Wechsler Intelligence Scale for Children-IV ; WISC V, 5th edition of Wechsler Intelligence Scale for Children.

TABLE 1, continued. Details of cognitive and motor development assessment.

Cognitive and motor function domain	Test	Outcome of interest	Interpretation	Cohort	References
Working memory	N-back: 3-back subtest	-Hit Reaction Time (HRT): Mean response time for all correct answers (ms) -d': z (hit rate) – z (false alarm rate)	↑HRT ↓d'; lower working memory	INMA-Sabadell	(Pelegrina et al., 2015)
	WISC-V: Digit Span subtest	T score	↓score; lower working memory	Generation R	(Kaufman et al., 2015)
Cognitive flexibility	TMT-B	Task switching score: Time to complete the task (ms)	↑time; lower task switching capacity	INMA-Sabadell	(Tombaugh, 2004)
	TMT-A and TMT-B	Task shifting score: (Time to complete the TMT-B (ms) – Time to complete the TMT-A (ms)) / Time to complete the TMT-A (ms))	↑score; lower task shifting capacity		
Risky decision-making	CUPS	Total number of risky choices made in the gain condition	↓number of risky choices; higher risky decision-making	INMA-Sabadell	(Levin et al., 2007)
		total number of risky choices in the loss condition			

Abbreviations: ANT, Attention Network Task; FTT, Finger Tapping Test; K-CPT, Conners' Kiddie Continuous Performance Test; MSCA, McCharty Scales of Children's Ability; NEPSY-II, Developmental NEuroPSYchological Assessment Second Edition; SON-R, Snijders-Oomen Niet-verbale intelligentie Test – Revisie; TMTA, Trail Making Test Part A; TMTB, Trail Making Test Part A; TVK, Talltest voor Kinderen; WISC-IV,4th edition of Wechsler Intelligence Scale for Children-IV ; WISC V, 5th edition of Wechsler Intelligence Scale for Children.

TABLE 1, continued. Details of cognitive and motor development assessment.

Cognitive and motor function domain	Test	Outcome of interest	Interpretation	Cohort	References
Risky decision-making	CUPS	sensitivity to expected value in the gain condition (i.e., number of risk-advantageous choices minus number of risk-disadvantageous choices).	↓score; higher risky decision-making	INMA-Sabadell	(Levin et al., 2007)
		sensitivity to expected value in the loss condition (i.e., number of risk-advantageous choices minus number of risk-disadvantageous choices).			
Gross motor function	MSCA: Gross motor scale	Standard score	↓score; lower gross motor function	INMA-Sabadell	(MacCarthy & Cordero Pando, 2006)
	Body Coordination Test: Walking backwards subtest	number of steps the participant can take on each beam	↓number of steps; lower gross motor function	Generation	(Kiphard, 2007)
Fine motor function	FTT	Number of taps the participant made during the measurement with the left and right hand	↓number of taps; lower fine motor function	INMA-Sabadell and Generation R	(Lezak, 1995)

Abbreviations: ANT, Attention Network Task; FTT, Finger Tapping Test; K-CPT, Conners' Kiddie Continuous Performance Test; MSCA, McCharty Scales of Children's Ability; NEPSY-II, Developmental NEuroPSYchological Assessment Second Edition; SON-R, Snijders-Oomen Niet-verbale intelligentie Test – Revisie; TMTA, Trail Making Test Part A; TMTB, Trail Making Test Part A; TVK, Talltest voor Kinderen; WISC-IV,4th edition of Wechsler Intelligence Scale for Children-IV ; WISC V, 5th edition of Wechsler Intelligence Scale for Children.

FIGURE 1: Cognitive and motor outcome assessment time points and measuring instruments used in the INMA-Sabadell cohort and the Generation R Study.

TABLE 2. Participant characteristics of the INMA-Sabadell cohort and Generation R Study.

Characteristics	INMA-Sabadell (n = 618)	Generation R (n = 7,115)
Maternal characteristics		
Age at enrolment (years)	31.7 (4.3)	30.5 (5.1)
Pre-pregnancy body mass index (kg/m^2)	23.7 (21.0; 25.3)	23.6 (20.8; 25.4)
Country of birth (country of cohort vs. others)	89.3	54.1
Education level during pregnancy		
Low	26.1	9.4
Medium	42.9	43.6
High	31.0	47.0
Social class during pregnancy		
Low	21.2	4.3
Medium	31.4	33.1
High	47.4	62.6
Parity (nulliparous vs. multiparous)	57.0	56.0
Smoking use during pregnancy (no vs. yes)	85.3	83.4
Alcohol consumption during pregnancy (no vs. yes)	78.0	59.9
Paternal characteristics		
Age at enrolment (years)	33.6 (5.0)	33.4 (5.9)
Pre-pregnancy body mass index (kg/m^2)	25.8 (23.5; 27.8)	25.3 (22.9; 27.2)
Country of birth (country of cohort vs. others)	88.9	56.7
Education level during pregnancy		
Low	34.4	7.0
Medium	42.5	40.4
High	23.1	52.6
Social class during pregnancy		
Low	22.9	8.8
Medium	18.6	23.7
High	58.5	67.5
Household characteristics		
Family status (dual vs. single parent)	98.6	87.7
Child characteristics		
Sex (male vs. female)	51.5	50.0
Noise exposure (decibels)		
Road traffic noise (L$_{DEN}$)[1] (dB)		
Prenatal	61.3 (6.0)	54.6 (7.9)
Childhood	61.5 (5.4)	53.5 (6.5)

Values are percentages for categorical variables, mean (standard deviation) for continuous variables, and median (25th; 75th percentile) for body mass index.

Abbreviations: dB, decibels.

[1] Residential outdoor annual average noise levels for the 24h of the day from road traffic.

TABLE 3. Fully adjusted associations of a 10 decibel increase in prenatal and childhood outdoor exposure to residential road traffic noise and standardized non-verbal and verbal intelligence, memory, and processing speed outcomes for the INMA-Sabadell cohort and the Generation R Study.

	Non-verbal intelligence		Language/verbal intelligence		Memory		Processing speed	
	Coef.	(95% CI)	Coef.	(95% CI)	Coef.	(95% CI)	Coef.	(95% CI)
Prenatal exposure								
INMA	0.15	-1.68; 1.98	-0.81	-2.59; 0.96	-1.08	-3.23; 1.07	0.16	-2.31; 2.63
Generation R	0.18	-0.24; 0.59	0.38	-0.05; 0.81	0.18	-1.03; 1.39	0.29	0.32; 0.89
Overall	0.18	-0.22; 0.58	0.11	-0.86; 1.09	-0.13	-1.20; 0.93	0.28	-0.31; 0.87
Childhood exposure								
INMA	-0.18	-1.98; 1.62	-0.95	-2.70; 0.80	-1.18	-3.39; 1.03	0.09	-2.59; 2.76
Generation R	0.01	0.44; 0.47	0.08	-0.39; 0.54	-0.82	-2.20; 0.55	0.48	-0.24; 1.19
Overall	-0.00	-0.44; 0.44	-0.08	-0.81; 0.65	-0.92	-2.08; 0.24	0.45	-0.22; 1.14

Abbreviations: Coef; coefficient; CI, confidence interval.
Coefficients and 95% confidence intervals by cohort were obtained by linear regression mixed models for non-verbal and verbal IQ and linear regression models for memory and processing speed outcomes. Models were adjusted for child sex, parental age, height, weight, body mass index, country of birth, education, social class, parity, smoking and alcohol during pregnancy, and family status. Overall coefficients and 95% confidence intervals were obtained by random-effects meta-analysis.

TABLE 4. Fully adjusted associations of a 10 decibel increase in prenatal and childhood outdoor exposure to residential road traffic noise and standardized attentional function and visual attention outcomes for the INMA-Sabadell cohort and the Generation R Study.

	Attentional function – Commission errors		Attentional function – Omission errors		Visual attention	
	IRR	(95% CI)	IRR	(95% CI)	Coef.	(95% CI)
Prenatal exposure						
INMA	**0.88**	**0.81; 0.96**	**1.13**	**1.01; 1.28**	0.86	-1.57; 3.29
Generation R	0.96	0.77; 1.21	0.98	0.88; 1.08	1.01	-0.16; 2.18
Overall	NA	NA	NA	NA	0.98	-0.08; 2.04
Childhood exposure						
INMA	**0.85**	**0.78; 0.93**	1.13	0.99; 1.27	1.02	-1.60; 3.65
Generation R	0.95	0.75; 1.21	0.98	0.87; 1.10	0.17	-1.18; 1.51
Overall	NA	NA	NA	NA	0.35	-0.84; 1.54

Abbreviations Coef; coefficient; CI, confidence interval; IRR, incidence risk ratio; NA, Not Applicable.

Coefficients and 95% confidence intervals by cohort were obtained by negative binomial models for the attentional function and linear regression models for the visual attention outcome. Models were adjusted for child sex, parental age, height, weight, body mass index, country of birth, education, social class, parity, smoking and alcohol during pregnancy, and family status. Overall coefficients and 95% confidence intervals were obtained by random-effects meta-analysis.

In bold, associations p<0.05.

TABLE 5. Fully adjusted associations of a 10 decibel increase in prenatal and childhood outdoor exposure to residential road traffic noise and motor function for the INMA-Sabadell cohort and the Generation R Study.

	Fine motor function– Right hand		Fine motor function – Left hand		Gross motor function	
	Coef.	(95% CI)	Coef.	(95% CI)	Coef.	(95% CI)
Prenatal exposure						
INMA	-0.31	-2.78; 2.17	0.56	-1.90; 3.06	0.28	-1.98; 2.53
Generation R	-0.34	-0.98; 0.30	-0.08	-0.71; 0.55	-0.09	-0.47; 0.29
Overall	-0.34	-0.95; 0.27	-0.04	-0.65; 0.57	-0.07	-0.64; 0.50
Childhood exposure						
INMA	-1.57	-4.19; 1.05	-0.39	-3.03; 2.24	0.26	-2.06; 2.56
Generation R	0.50	-0.23; 1.22	0.33	-0.39; 1.04	0.04	-0.38; 0.47
Overall	-0.14	-2.02; 1.74	0.28	-0.40; 0.96	0.05	-0.38; 0.47

Abbreviations Coef; coefficient; CI, confidence interval
Coefficients and 95% confidence intervals by cohort were obtained by linear regression models. Models were adjusted for child sex, parental age, height, weight, body mass index, country of birth, education, social class, parity, smoking and alcohol during pregnancy, and family status. Overall coefficients and 95% confidence intervals were obtained by random-effects meta-analysis.

Discussion

The present study investigated the association of outdoor exposure to residential noise from road traffic during pregnancy or childhood with a large number of cognitive and motor function outcomes, some of them assessed repeatedly from preschool age until preadolescence in two European birth cohorts. We found no evidence of an association between outdoor exposure to residential noise from road traffic and any of the outcomes.

To date, only few studies have looked into the association between road traffic noise and cognitive function in children (Clark & Paunovic, 2018; Foraster et al., 2022; Thompson et al., 2022). Regarding non-verbal and language/verbal intelligence, some previous epidemiological studies did not find a relationship with residential or school road traffic noise exposure in children aged 6 to 11 years (Clark et al., 2006; Julvez et al., 2021; S. A. Stansfeld et al., 2005), similarly to our findings. In contrast, a study carried out in children aged 10-12 years found that those exposed to higher noise levels at schools, mainly from road traffic, had lower non-verbal intelligence scores than those exposed to lower noise levels (Bhang et al., 2018). Also, it was observed reading deficits in children exposed to higher levels of residential noise from several sources (Cohen et al., 1973) or to higher road traffic noise at schools (Ljung et al., 2009). Of note, noise levels reported in our study were lower than those reported in these previous studies (Bhang et al., 2018; Cohen et al., 1973; Ljung et al., 2009). The overall mixed findings on the association between noise exposure and non-verbal and language/verbal intelligence suggest that more research is needed, in particular assessing noise exposure at school settings together with residential noise exposure to have a more comprehensive exposure assessment.

Our results on the absence of association between road traffic noise exposure and memory or working memory in children were consistent with some previous studies (Clark et al., 2012; Julvez et al., 2021; van Kempen et al., 2010, 2012) but not with some others (Foraster et al., 2022; Lercher et al., 2016; Matheson et al., 2010; S. A. Stansfeld et al., 2005). Lercher et al. reported that higher exposure to residential road traffic and railway noise was related with worse memory in children around 9 years old (Lercher et al., 2016). In contrast, Matheson et al. and Stansfeld et al. found an unexpected association between exposure to road traffic noise at schools and better memory (Matheson et al., 2010; S. A. Stansfeld et al., 2005) in children aged 9-10 years. A recent study found that school outdoor exposure to road traffic was related to slower

development in working memory in children aged 7-10 years (Foraster et al., 2022). But this association was not found for exposure to road traffic noise at participants' residential addresses. In addition, this study measured noise fluctuations at schools defined as the average number of noise peaks during the measurement period. They observed that exposure to higher number of noise peaks in the classrooms were associated with slower working memory, while this association was not found in relation to indoor annual average noise levels in the classrooms. This novel finding can support the hypothesis that noise fluctuation might be more disruptive for children's neurodevelopment than average noise levels (Foraster et al., 2022). Unfortunately, individual exposure assessment to investigate noise fluctuation could not be carried out in our study. Further research is needed to assess noise fluctuation measures to investigate whether this type of exposure may have a higher impact on child's cognitive development than average noise levels.

Also, our null results between road traffic noise exposure and attentional function in children were consistent with the majority of the previous literature (Cohen et al., 1973; Julvez et al., 2021; Lercher et al., 2016; S. A. Stansfeld et al., 2005). However, two studies found that children attending schools with higher road traffic noise levels made more errors in the most difficult parts of the attention tests (van Kempen et al., 2010, 2012). Also, Foraster et al. reported that both outdoor and indoor exposure to road traffic noise at school was associated with greater inattentiveness in children aged 7-10 years whereas home-outdoor noise exposure was not associated with attentional function (Foraster et al., 2022). Children and preadolescents spend most of the time at schools when road traffic noise levels are increased. Therefore, it could be possible that exposure to noise at school, instead of at home, may have more negative effects on concentration and learning processes.

The main strength of our study is the availability of data in children and preadolescents from two population-based birth cohorts from two different European countries and the longitudinal nature of these cohort studies. Also, the assessment of noise exposure that accounted for the time that child spent at each address during the entire follow-up and the assessment of cognitive function using a battery of validated neurocognitive tests at different ages. We have also used multiple imputation and inverse probability weighting to reduce the potential selection bias (Spratt et al., 2010; Weuve et al., 2012). Furthermore, the assessment of repeated exposure and outcome measurements for some of the cognitive outcomes using linear mixed models increased the statistical power of the analysis, allowing the correct modeling of the non-

independence in the longitudinal data and accounting for the missing data (Harrison et al., 2018).

However, our study has some limitations that merit to be discussed. The main limitation of the study is that the noise levels corresponded to outdoor residential noise rather than indoor noise levels in the child's bedroom. Also, we were not able to include noise assessment at schools due to data availability. Thus, misclassification due to underestimation or overestimation of accurate noise exposure cannot be excluded in the present study. Furthermore, we considered modeled average noise levels that did not account for noise fluctuations, while these fluctuations could be more disruptive for children's cognition than average noise levels (Foraster et al., 2022). Another limitation is the possibility of the introduction of measurement error due to the lack of information on noise sensitivity (i.e., the physiological and psychological individual perception and the degree of reactivity to noise) or on the location and floor's level of the child's bedroom. Related to the outcome assessment, information bias might be introduced since we used different validated neurological tests to assess cognitive outcomes at different ages and also between cohorts. However, we standardized all the cognitive scales to make them comparable between ages and study cohorts, and results were quite consistent across ages and study cohorts.

Conclusions

In conclusion, this study indicates that outdoor exposure to residential road traffic noise during pregnancy and childhood was not associated with several cognitive and motor function outcomes in children. Future research including indoor noise measurements both at school and home environments should be contemplated to further explore the association. Furthermore, noise fluctuations as well as populations with higher prevalence of people exposed to other noise sources (i.e., railway, aircraft, or industry) should be considered in future studies in order to include a more comprehensive noise exposure assessment and explore the overall effect on the cognitive and motor development during childhood and preadolescence periods.

Funding and acknowledgements:

Supplementary Material

FIGURE S1: Flowchart of study participants of INMA-Sabadell cohort (A) and Generation R Study (B).

(A) INMA-Sabadell cohort

(B) Generation R Study
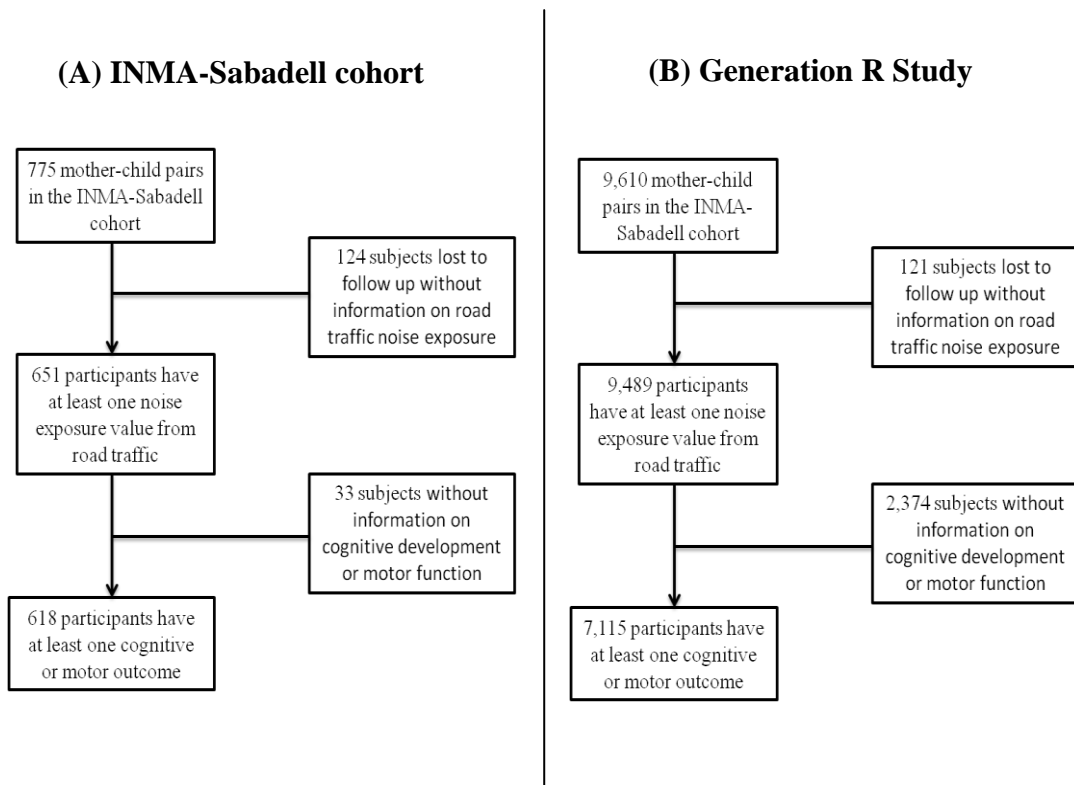
METHODS S1: Formulas used to calculate the road traffic L$_{DEN}$ values of noise exposure in the INMA-Sabadell cohort and the Generation R Study.

Formula for the day-evening-night noise indicator (L$_{DEN}$) in the INMA-Sabadell cohort:

$$L_{DEN} = 10\lg\frac{1}{24}(\,(14 \cdot 10^{\frac{L_{DAY}}{10}}) + (2 \cdot 10^{\frac{L_{EVENING} + 5}{10}}) + (8 \cdot 10^{\frac{L_{NIGHT} + 10}{10}})\,)$$

Formula for the day-evening-night noise indicator (L$_{DEN}$) in the Generation R Study:

$$L_{DEN} = 10\lg\frac{1}{24}(\,(12 \cdot 10^{\frac{L_{DAY}}{10}}) + (4 \cdot 10^{\frac{L_{EVENING} + 5}{10}}) + (8 \cdot 10^{\frac{L_{NIGHT} + 10}{10}})\,)$$

TABLE S1. Details of the imputation modelling.

Software used and key setting: Stata Statistical Software: Release 14.2 (Stata Corporation, College Station, Texas) – Ice command (with 10 cycles)
Number of imputed datasets created: 25
Variables included in the imputation procedure for both cohorts: Road traffic noise exposure, non-verbal intelligence, verbal intelligence, memory, processing speed, attentional function, visual attention, working memory, cognitive flexibility, risky decision-making, gross motor, fine motor, maternal age at enrolment, maternal height, maternal weight, maternal pre-pregnancy body mass index, maternal country of birth, maternal education level, maternal social class, maternal parity, maternal smoking use during pregnancy, maternal alcohol consumption during pregnancy, paternal age at enrolment, paternal height, paternal weight, paternal pre-pregnancy body mass index, paternal country of birth, paternal education level, paternal social class, family status, child age, and child sex.
Treatment of binary/categorical variables: logistic and multinomial models
Statistical interactions included in imputation models: none

TABLE S2: Population characteristics of the subjects included and not included in the analyses of the INMA-Sabadell cohort and the Generation R Study.

Characteristics	INMA-Sabadell (n = 775)			Generation R (n =9,610)		
	Included (n = 619)	Not Included (n = 156)	p-value[1]	Included (n = 7,115)	Not Included (n = 2,495)	p-value[1]
Maternal characteristics						
Age at enrolment (years)	31.7 (4.3)	29.9 (5.0)	<0.001	30.5 (5.1)	28.4 (5.6)	<0.001
Pre-pregnancy body mass index (kg/m^2)	23.7 (21.0; 25.3)	24.0 (20.8; 26.3)	0.408	23.6 (20.8; 25.4)	23.8 (20.7; 25.7)	0.154
Country of birth (country of the cohort vs. others)	89.3	74.5	0.000	54.1	38.7	<0.001
Education level during pregnancy			0.001			<0.001
Low	26.1	40.2		9.4	16.3	
Medium	42.9	44.9		43.6	52.7	
High	31.0	14.9		47.0	31.0	
Social Class during pregnancy			<0.001			<0.001
Low	21.2	6.7		4.3	6.2	
Medium	31.4	23.3		33.1	41.2	
High	47.4	70.0		62.6	52.6	
Parity (nulliparous vs. multiparous)	57.0	48.9	0.153	56.0	52.3	0.002
Smoking use during pregnancy (no vs. yes)	85.3	82.9	0.506	83.4	77.7	<0.001
Alcohol consumption during pregnancy (no vs. yes)	78.0	69.3	0.026	59.9	72.9	<0.001

Values are percentages for categorical, mean (standard deviation) for continuous variables, and median (25th percentile; 75th percentile) for body mass index and preadolescents' age at sleep questionnaire assessment for Generation R Study.
[1] Chi-square tests for categorical variables, two-sample t-test for normally distributed and Wilcoxon Rank Sum test for non-normally distributed continuous variables.

TABLE S2, continued: Population characteristics of the subjects included and not included in the analyses of the INMA-Sabadell cohort and the Generation R Study.

Characteristics	INMA-Sabadell (n = 775)			Generation R (n =9,610)		
	Included (n = 619)	Not Included (n = 156)	p-value[1]	Included (n = 7,115)	Not Included (n = 2,495)	p-value[1]
Paternal characteristics						
Age at enrolment (years)	33.6 (5.0)	32.5 (6.3)	0.036	33.4 (5.9)	31.6 (6.3)	<0.001
Pre-pregnancy body mass index (kg/m^2)	25.8 (23.5; 27.8)	25.8 (23.7; 27.8)	0.748	25.3 (22.9; 27.2)	25.4 (22.9; 27.5)	0.211
Country of birth (country of the cohort vs. others)	88.9	80.3	0.004	56.7	41.8	<0.001
Education level during pregnancy			0.032			<0.001
Low	34.4	45.3		7.0	13.7	
Medium	42.5	38.5		40.4	43.1	
High	23.1	16.2		52.6	43.2	
Social Class during pregnancy			0.023			<0.001
Low	22.9	14.6		8.8	13.5	
Medium	18.6	11.0		23.7	31.1	
High	58.5	74.4		67.5	55.4	
Household characteristics						
Family status (dual vs. single parent)	98.6	97.8	0.551	87.7	79.5	<0.001
Preadolescents' characteristics						
Sex (male vs. female)	51.5	47.9	0.477	50.0	52.6	0.024

Values are percentages for categorical, mean (standard deviation) for continuous variables, and median (25th percentile; 75th percentile) for body mass index and preadolescents' age at sleep questionnaire assessment for Generation R Study.

[1] Chi-square tests for categorical variables, two-sample t-test for normally distributed and Wilcoxon Rank Sum test for non-normally distributed continuous variables.

TABLE S3. Descriptive statistics of the noise exposure levels in the INMA-Sabadell cohort and the Generation R Study.

	Mean	SD	p25; p75	Min.	Max.	N
Road traffic noise exposure (dB)						
INMA-Sabadell (N = 619)						
Pregnancy	61.3	6.0	58.0; 65.0	43.0	77.4	633
Birth – 4 years	61.4	5.8	58.4; 65.0	45.0	77.4	601
4 – 7 years	61.5	6.1	58.3; 65.6	45.0	76.0	592
7 – 9 years	61.7	6.1	58.0; 66.0	45.0	76.0	587
9 – 11 years	61.8	5.7	59.0; 65.0	46.0	76.0	567
Generation R (N = 7,115)						
Pregnancy	54.6	7.9	48.0; 61.0	40.0	73.0	7058
Birth – 6 years	53.8	7.0	48.0; 58.9	40.0	73.0	5982
Birth – 9 years	53.5	6.8	48.0; 58.9	40.0	73.0	5704
6 – 13 years	53.3	6.5	47.9; 58.1	40.0	73.0	5315

Abbreviations: dB, decibels; p25, 25th percentile; p75, 75th percentile; SD, standard deviation.

TABLE S4. Pearson correlations between the road traffic noise exposure values during different lifetime periods of the child for the INMA-Sabadell cohort (n = 619) (A) and for the Generation R Study (n= 7,115) (B).

(A) road traffic	Pregnancy	Birth – 4 years	4 – 7 years	7 – 9 years	9 – 11 years
Pregnancy	1				
Birth - 4 years	0.85	1			
4 - 7 years	0.71	0.82	1		
7 - 9 years	0.69	0.79	0.97	1	
9 – 11 years	0.61	0.69	0.71	0.87	1

(B) road traffic	Pregnancy	Birth – 6 years	Birth – 9 years	6 – 13 years
Pregnancy	1			
Birth – 6 years	0.75	1		
Birth - 9 years	0.67	0.97	1	
6 – 13 years	0.43	0.76	0.87	1

TABLE S5. Descriptive statistics of the cognitive and motor outcomes in the INMA-Sabadell cohort and the Generation R Study.

	INMA-Sabadell			Generation R		
	Mean	**SD**	**p25; p75**	**Mean**	**SD**	**p25; p75**
Non-verbal intelligence						
4 years	100	15	88.42; 112.15	-	-	-
6 years	-	-	-	100.72	15.19	91; 111
9 years	100	15	91.35; 112.76	-	-	-
13 years	-	-	-	100	15	98.9; 110
Verbal intelligence						
4 years	100	15	90.65; 110.24	-	-	-
6 years	-	-	-	99.99	14.99	90.44; 109.99
9 years	100	15	88.13; 109.78	-	-	-
13 years	-	-	-	99.97	14.97	86.81; 111.89
Memory	100	15	91.28; 109.78	100	15	90.86; 110.53
Processing speed	100	15	90.84; 108.64	100	15	87.7; 109.95
Attentional function – Commission errors						
4 years	22.83	10.85	15; 31	-	-	-
6 years	-	-	-	1.82	7.62	0; 1
Attentional function – Omission errors						
4 years	27.28	17.28	13; 37	-	-	-
6 years	-	-	-	2.29	3.21	0; 3
Visual attention	100	15	90.18; 106.91	100	15	92.25; 109.82

Abbreviations: d, detectability; HRT, Hit Reaction Time; ms, milliseconds; p25, 25th percentile; p75, 75th percentile; SD, standard deviation.

TABLE S5, continued: Descriptive statistics of the cognitive and motor outcomes in the INMA-Sabadell cohort and the Generation R Study.

	INMA-Sabadell			Generation R		
	Mean	**SD**	**p25; p75**	**Mean**	**SD**	**p25; p75**
Working memory – Digit Span	-	-	-	100	15	91.9; 108.1
Working memory – HRT (ms)						
9 years	799.24	237.81	637.67; 947.33	-	-	-
11 years	550.56	138.97	449.00; 651.00	-	-	-
Working memory – d'						
9 years	1.49	1.05	0.78; 2.21	-	-	-
11 years	1.89	0.81	1.39; 2.80	-	-	-
Cognitive flexibility – Task switching (ms)	67500.09	26187.00	50341.29; 75940.93	-	-	-
Cognitive flexibility – Task shifting	0.11	0.37	-0.12; 0.25	-	-	-
Risky decision-making – Number of risky choices in the gain condition	3.62	2.45	2; 6	-	-	-
Risky decision-making - Number of risky choices in the loss condition	2.97	2.60	1;5	-	-	-
Risky decision-making - Sensitivity to expected value in the gain condition	14.30	5.72	10; 18	-	-	-
Risky decision-making - Sensitivity to expected value in the loss condition	15.42	5.86	12; 20	-	-	-
Gross motor function						
4 years	100	15	91.36; 109.76	-	-	-
9 years	-	-	-	26.23	8.55	20; 32
Fine motor function – right hand	100	15	91; 109.98	99.98	15	89.94; 110.55
Fine motor function – left hand	100	15	89.87; 111.13	100	15	89.36; 110

Abbreviations: d, detectability; HRT, Hit Reaction Time; ms, milliseconds; p25, 25th percentile; p75, 75th percentile; SD, standard deviation.

TABLE S6. Fully adjusted associations of a 10 decibel increase in prenatal and childhood outdoor exposure to residential road traffic noise and standardized working memory outcomes for the INMA-Sabadell cohort and the Generation R Study.

	Working memory - Digit Span score		Working memory - N-back test – HRT (ms)		Working memory – N-back test – d'	
	Coef.	(95% CI)	Coef.	(95% CI)	Coef.	(95% CI)
Prenatal exposure						
INMA	NA	NA	-0.83	-21.60; 19.94	-0.06	-0.16; 0.04
Generation R	0.20	-0.41; 0.81	NA	NA	NA	NA
Childhood exposure						
INMA	NA	NA	-3.37	-25.15; 18.41	-0.03	-0.13; 0.07
Generation R	-0.08	-0.80; 0.64	NA	NA	NA	NA

Abbreviations Coef., coefficient; CI, confidence interval; d', detectability; HRT, Hit Reaction Time (in milliseconds (ms)); NA, Not Applicable.

Coefficients and 95% confidence intervals by cohort were obtained by linear regression models and linear mixed models for the Generation R Study and the INMA-Sabadell cohort, respectively. Models were adjusted for child sex, parental age, height, weight, body mass index, country of birth, education, social class, parity, smoking and alcohol during pregnancy, and family status.

TABLE S7. Fully adjusted associations of a 10 decibel increase in prenatal and childhood outdoor exposure to residential road traffic noise and cognitive flexibility for the INMA-Sabadell cohort.

	Cognitive flexibility – Task switching (ms)		Cognitive flexibility – Task shifting	
	Coef.	**(95% CI)**	**Coef.**	**(95% CI)**
Prenatal exposure				
INMA	1128.78	-2908.34; 5165.89	0.00	-0.06; 0.06
Childhood exposure				
INMA	1060.26	-3304.70; 5425.22	-0.01	-0.07; 0.06

Abbreviations Coef., coefficient; CI, confidence interval; ms, milliseconds. Coefficients and 95% confidence intervals were obtained by linear regression models. Models were adjusted for child sex, parental age, height, weight, body mass index, country of birth, education, social class, parity, smoking and alcohol during pregnancy, and family status.

TABLE S8. Fully adjusted associations of a 10 decibel increase in prenatal and childhood outdoor exposure to residential road traffic noise and risky decision-making for the INMA-Sabadell cohort.

	Risky decision-making – Number of risky choices in the gain condition		Risky decision-making – Number of risky choices in the loss condition		Risky decision-making - Sensitivity to expected value in the gain condition		Risky decision-making – Sensitivity to expected value in the loss condition	
	Coef.	(95% CI)	Coef.	(95% CI)	Coef.	(95% CI)	Coef.	(95% CI)
Prenatal exposure								
INMA	-0.25	-0.64; 0.15	-0.39	-0.82; 0.36	0.06	-0.92; 1.03	-0.34	-1.39; 0.70
Childhood exposure								
INMA	-0.20	-0.65; 0.24	-0.47	-0.95; 0.01	0.59	-0.50; 1.68	0.28	-1.45; 0.89

Abbreviations Coef., coefficient; CI, confidence interval
Coefficients and 95% confidence intervals were obtained by linear regression models. Models were adjusted for child sex, parental age, height, weight, body mass index, country of birth, education, social class, parity, smoking and alcohol during pregnancy, and family status.

References

Abdi, H. (2007). Bonferroni and Šidák corrections for multiple comparisons. *Encyclopedia of Measurement and Statistics*, *3*, 103–107.

Bhang, S. Y., Yoon, J., Sung, J., Yoo, C., Sim, C., Lee, C., Lee, J., & Lee, J. (2018). Comparing Attention and Cognitive Function in School Children across Noise Conditions: A Quasi-Experimental Study. *Psychiatry Investigation*, *15*(6), 620–627. https://doi.org/10.30773/PI.2018.01.15

Brooks, B. L., Sherman, E. M. S., & Strauss, E. (2009). NEPSY-II: A Developmental Neuropsychological Assessment, Second Edition. *Https://Doi.Org/10.1080/09297040903146966*, *16*(1), 80–101. https://doi.org/10.1080/09297040903146966

Clark, C., Crombie, R., Head, J., Van Kamp, I., Van Kempen, E., & Stansfeld, S. A. (2012). *Does Traffic-related Air Pollution Explain Associations of Aircraft and Road Traffic Noise Exposure on Children's Health and Cognition? A Secondary Analysis of the United Kingdom Sample From the RANCH Project*. https://doi.org/10.1093/aje/kws012

Clark, C., Martin, R., Van Kempen, E., Alfred, T., Head, J., Davies, H. W., Haines, M. M., Barrio, I. L., Matheson, M., & Stansfeld, S. A. (2006). Exposure-effect relations between aircraft and road traffic noise exposure at school and reading comprehension: the RANCH project. *American Journal of Epidemiology*, *163*(1), 27–37. https://doi.org/10.1093/AJE/KWJ001

Clark, C., & Paunovic, K. (2018). WHO Environmental Noise Guidelines for the European Region: A Systematic Review on Environmental Noise and Cognition. *International Journal of Environmental Research and Public Health 2018, Vol. 15, Page 285*, *15*(2), 285. https://doi.org/10.3390/IJERPH15020285

Cohen, S., Glass, D. C., & Singer, J. E. (1973). Apartment noise, auditory discrimination, and reading ability in children. *Journal of Experimental Social Psychology*, *9*(5), 407–422. https://doi.org/10.1016/S0022-1031(73)80005-8

Conners, C. K. (2006). Conners' kiddie continuous performance test. *Multi-Health Systems Incorporated.*

European Environment Agency. (2020). *Environmental noise in Europe, 2020 - Publications Office of the EU*.

https://op.europa.eu/en/publication-detail/-
/publication/ed51a8c9-6d7e-11ea-b735-
01aa75ed71a1/language-en

European Environmental Noise Directive. (2002). *Directive 2002/49/EC*. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32002L0049&from=en

Foraster, M., Esnaola, M., López-Vicente, M., Rivas, I., Álvarez-Pedrerol, M., Persavento, C., Sebastian-Galles, N., Pujol, J., Dadvand, P., & Sunyer, J. (2022). Exposure to road traffic noise and cognitive development in schoolchildren in Barcelona, Spain: A population-based cohort study. *PLOS Medicine*, *19*(6), e1004001. https://doi.org/10.1371/journal.pmed.1004001

Guxens, M., Ballester, F., Espada, M., Fernández, M. F., Grimalt, J. O., Ibarluzea, J., Olea, N., Rebagliato, M., Tardón, A., Torrent, M., Vioque, J., Vrijheid, M., & Sunyer, J. (2012). Cohort Profile: The INMA—INfancia y Medio Ambiente—(Environment and Childhood) Project. *International Journal of Epidemiology*, *41*(4), 930–940. https://doi.org/10.1093/ije/dyr054

Harrison, X. A., Donaldson, L., Correa-Cano, M. E., Evans, J., Fisher, D. N., Goodwin, C. E. D., Robinson, B. S., Hodgson, D. J., & Inger, R. (2018). A brief introduction to mixed effects modelling and multi-model inference in ecology. *PeerJ*, *2018*(5), e4794. https://doi.org/10.7717/PEERJ.4794/FIG-3

Hernán, M. A., Hernández-Diaz, S., Werler, M. M., & Mitchell, A. A. (2002). Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. *American Journal of Epidemiology*, *155*(2), 176–184. https://doi.org/10.1093/AJE/155.2.176

Héroux, M. E., Babisch, W., Belojevic, G., Brink, M., Janssen, S., Lercher, P., Paviotti, M., Pershagen, G., Waye, K. P., Preis, A., Stansfeld, S., van den Berg, M., & Verbeek, J. (2015). WHO environmental noise guidelines for the European Region. *Euronoise 2015*, 2589–2593.

Julvez, J., López-Vicente, M., Warembourg, C., Maitre, L., Philippat, C., Gützkow, K. B., Guxens, M., Evandt, J., Andrusaityte, S., Burgaleta, M., Casas, M., Chatzi, L., de Castro, M., Donaire-González, D., Gražulevičienė, R., Hernandez-Ferrer, C., Heude, B., Mceachan, R., Mon-Williams, M., … Vrijheid, M. (2021). Early life multiple

exposures and child cognitive function: A multi-centric birth cohort study in six European countries. *Environmental Pollution*, *284*, 117404. https://doi.org/10.1016/J.ENVPOL.2021.117404

Kaufman, A. S., Flanagan, D. P., Alfonso, V. C., & Mascolo, J. T. (2006). Test Review: Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV). *Journal of Psychoeducational Assessment*, *24*(3), 278–295. https://doi.org/10.1177/0734282906288389/ASSET/07342829 06288389.FP.PNG_V03

Kaufman, A. S., Raiford, S. E., & Coalson, D. L. (2015). *Intelligent testing with the WISC-V*. 814.

Kiphard, E. (2007). *Körperkoordinationstest für Kinder : KTK ; Manual*. Beltz Test.

Kooijman, M. N., Kruithof, C. J., van Duijn, C. M., Duijts, L., Franco, O. H., van IJzendoorn, M. H., de Jongste, J. C., Klaver, C. C. W., van der Lugt, A., Mackenbach, J. P., Moll, H. A., Peeters, R. P., Raat, H., Rings, E. H. H. M., Rivadeneira, F., van der Schroeff, M. P., Steegers, E. A. P., Tiemeier, H., Uitterlinden, A. G., … Jaddoe, V. W. V. (2016). The Generation R Study: design and cohort update 2017. *European Journal of Epidemiology*, *31*(12), 1243–1264. https://doi.org/10.1007/s10654-016-0224-9

Laros, J. A., & Tellegen, P. J. (1991). *Construction and validation of the SON-R 5 1/2-17, the Snijders-Oomen non-verbal intelligence test*. 168.

Lercher, P., Evans, G. W., & Meis, M. (2016). Ambient Noise and Cognitive Processes among Primary Schoolchildren: *Http://Dx.Doi.Org/10.1177/0013916503256260*, *35*(6), 725–735. https://doi.org/10.1177/0013916503256260

Levin, I. P., Weller, J. A., Pederson, A. A., & Harshman, L. A. (2007). Age-related differences in adaptive decision making: Sensitivity to expected value in risky choice. *Judgment and Decision Making*, *2*(4), 225–233.

Lezak, M. D. (1995). Neuropsychological assessment 3r edition. *Oxford University Press*, 1026.

Ljung, R., Sörqvist, P., & Hygge, S. (2009). Effects of road traffic noise and irrelevant speech on children's reading and mathematical performance. *Noise and Health*, *11*(45), 198. https://doi.org/10.4103/1463-1741.56212

MacCarthy, D., & Cordero Pando, A. (2006). *MSCA : escalas*

McCarthy de aptitudes y psicomotricidad para niños. TEA Ediciones.

Matheson, M., Clark, C., Martin, R., Van Kempen, E., Haines, M., Barrio, I. L., Hygge, S., & Stansfeld, S. (2010). The effects of road traffic and aircraft noise exposure on children's episodic memory: the RANCH project. *Noise & Health*, *12*(49), 244–254. https://doi.org/10.4103/1463-1741.70503

Pelegrina, S., Lechuga, M. T., García-Madruga, J. A., Elosúa, M. R., Macizo, P., Carreiras, M., Fuentes, L. J., & Bajo, M. T. (2015). Normative data on the n-back task for children and young adolescents. *Frontiers in Psychology*, *6*(OCT), 1544. https://doi.org/10.3389/FPSYG.2015.01544/BIBTEX

Raess, M., Valeria Maria Brentani, A., Flückiger, B., Ledebur de Antas de Campos, B., Fink, G., & Röösli, M. (2022). Association between community noise and children's cognitive and behavioral development: A prospective cohort study. *Environment International*, *158*. https://doi.org/10.1016/J.ENVINT.2021.106961

Raven, J. J. (2003). Raven Progressive Matrices. *Handbook of Nonverbal Assessment*, 223–237. https://doi.org/10.1007/978-1-4615-0153-4_11

Sanz, S. A., García, A. M., & García, A. (1993). Road traffic noise around schools: a risk for pupil's performance? *International Archives of Occupational and Environmental Health*, *65*(3), 205–207. https://doi.org/10.1007/BF00381157

Sauzéon, H., Lestage, P., Raboutet, C., N'Kaoua, B., & Claverie, B. (2004). Verbal fluency output in children aged 7–16 as a function of the production criterion: Qualitative analysis of clustering, switching processes, and semantic network exploitation. *Brain and Language*, *89*(1), 192–202. https://doi.org/10.1016/S0093-934X(03)00367-5

Spratt, M., Carpenter, J., Sterne, J. A. C., Carlin, J. B., Heron, J., Henderson, J., & Tilling, K. (2010). Strategies for Multiple Imputation in Longitudinal Studies. *American Journal of Epidemiology*, *172*(4), 478–487. https://doi.org/10.1093/aje/kwq137

Stansfeld, S. A., Berglund, B., Clark, C., Lopez-Barrio, I., Fischer, P., Öhrström, E., Haines, M. M., Head, J., Hygge, S., Van Kamp, I., & Berry, B. F. (2005). Aircraft and road traffic noise and children's cognition and health: a cross-national study. *The Lancet*, *365*(9475), 1942–1949. https://doi.org/10.1016/S0140-

6736(05)66660-3

Stansfeld, S., & Clark, C. (2015). Health Effects of Noise Exposure in Children. *Current Environmental Health Reports*, *2*(2), 171–178. https://doi.org/10.1007/S40572-015-0044-1

Thompson, R., Smith, R. B., Bou Karim, Y., Shen, C., Drummond, K., Teng, C., & Toledano, M. B. (2022). Noise pollution and human cognition: An updated systematic review and meta-analysis of recent evidence. *Environment International*, *158*, 106905. https://doi.org/10.1016/J.ENVINT.2021.106905

Tombaugh, T. N. (2004). Trail Making Test A and B: Normative data stratified by age and education. *Archives of Clinical Neuropsychology*, *19*(2), 203–214. https://doi.org/10.1016/S0887-6177(03)00039-8

Van Bon, W. H. J., & Hoekstra, J. G. (1982). Taaltests voor kinderen. *Lisse: Swets & Zeitlinger*.

van Kempen, E., Fischer, P., Janssen, N., Houthuijs, D., van Kamp, I., Stansfeld, S., & Cassee, F. (2012). Neurobehavioral effects of exposure to traffic-related air pollution and transportation noise in primary schoolchildren. *Environmental Research*, *115*, 18–25. https://doi.org/10.1016/J.ENVRES.2012.03.002

van Kempen, E., van Kamp, I., Lebret, E., Lammers, J., Emmen, H., & Stansfeld, S. (2010). *Neurobehavioral effects of transportation noise in primary schoolchildren: a cross-sectional study*. http://www.ehjournal.net/content/9/1/25

Wang, Q. (2018). Urbanization and Global Health: The Role of Air Pollution. *Iran J Public Health*, *47*(11), 1644–1652. http://ijph.tums.ac.ir

Weuve, J., Tchetgen Tchetgen, E. J., Glymour, M. M., Beck, T. L., Aggarwal, N. T., Wilson, R. S., Evans, D. A., & Mendes de Leon, C. F. (2012). Accounting for Bias Due to Selective Attrition: The Example of Smoking and Cognitive Decline. *Epidemiology*, *23*(1), 119–128. https://doi.org/10.1097/EDE.0b013e318230e861

Study III

Exposure to traffic-related air pollution and noise during pregnancy and childhood, and functional brain connectivity in preadolescents

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Full length article

Exposure to traffic-related air pollution and noise during pregnancy and childhood, and functional brain connectivity in preadolescents

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ARTICLE INFO

ABSTRACT

Background: The amount of people affected by traffic-related air pollution and noise is continuously increasing, but limited research has been conducted on the association between these environmental exposures and functional brain connectivity in children.
Objective: This exploratory study aimed to analyze the associations between the exposure to traffic-related air pollution and noise during pregnancy and childhood, and functional brain connectivity amongst a wide-swath of brain areas in preadolescents from 9 to 12 years of age.
Methods: We used data of 2,197 children from the Generation R Study. Land use regression models were applied to estimate nitrogen oxides and particulate matter levels at participant's homes for several time periods: pregnancy, birth to 3 years, 3 to 6 years, and 6 years of age to the age at magnetic resonance imaging (MRI) assessment. Existing noise maps were used to estimate road traffic noise exposure at participant's homes for the same time periods. Resting-state functional MRI was obtained at 9–12 years of age. Pair-wise correlation coefficients of the blood-oxygen-level-dependent signals between 380 brain areas were calculated. Linear regressions were run and corrected for multiple testing.
Results: Preadolescents exposed to higher levels of NO_2, NO_x, and $PM_{2.5}$ absorbance, from birth to 3 years, and from 3 to 6 years of age showed higher correlation coefficients among several brain regions (e.g. from 0.16 to 0.19 higher correlation coefficient related to $PM_{2.5}$ absorbance exposure, depending on the brain connection). Overall, most identified associations were between brain regions of the task positive and task negative networks, and were mainly inter-network (20 of 26). Slightly more than half of the connections were intra-hemispheric (14 of 26), predominantly in the right hemisphere. Road traffic noise was not associated with functional brain connectivity.
Conclusions: This exploratory study found that exposure to traffic-related air pollution during the first years of life was related to higher functional brain connectivity predominantly in brain areas located in the task positive and task negative networks, in preadolescents from 9 to 12 years of age. These results could be an indicator of differential functional connectivity in children exposed to higher levels of air pollution.

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1. Introduction

The world's population is continuously growing and urbanization is rapidly increasing. Although urbanization is related to improved human health and wellbeing, it could also worsen air and noise quality (Wang, 2018). In urban areas, traffic is the most important source of both air pollution and noise. The health effects of air pollution have been widely investigated, and the central nervous system has been demonstrated as a target organ negatively affected by air pollutants (Block et al., 2012). Air pollution exposure has been linked to neuronal death, synaptic toxicity, and altered gene expression in the brain (Thomson, 2019; U.S. EPA, 2019). Also, the exposure to both noise and air pollution could be a stressor affecting the hypothalamic–pituitary-adrenal (HPA) axis, increasing the levels of stress hormones, affecting the brain (Jafari et al., 2017; Thomson, 2019). Air pollution and noise can affect the brain at any age, but the developing brain is particularly vulnerable because of its immature metabolic system and because many crucial neurodevelopmental processes take place during fetal life and childhood (Stiles & Jernigan, 2010).

Previous epidemiological studies have suggested that exposure to air pollution and noise may be related to impaired cognitive function and neurodevelopmental disorders, although evidence is still inconsistent across studies (Clark & Paunovic, 2018; Costa et al., 2020; Stansfeld & Matheson, 2003; Stansfeld & Clark, 2015; Volk et al., 2021). During the last years, magnetic resonance imaging (MRI) has opened up new possibilities in epidemiological research for investigating the structure and the functioning of the brain. Blood oxygenation level dependent (BOLD) imaging is the standard technique to generate images in functional MRI studies and measures inhomogeneities in the magnetic field due to the difference in magnetic properties between oxygenated and deoxygenated blood (Gauthier & Fan, 2019). BOLD signals can result from spontaneous processes, i.e. not induced by an external stimulus and conscious mentation (Glover, 2011). Spontaneous brain activity is organized in resting state networks defined by their spatiotemporal configuration and functional roles (Biswal et al., 1995; Fox & Raichle, 2007). Biswal et al. were the first to show that this spontaneous brain activity was consistent in regions belonging to the somato/sensory motor network (Biswal et al., 1995). Their results were confirmed later and extended to other networks such as the visual, auditory, and language processing networks (Hampson et al., 2002; van de Ven et al., 2004). Task negative (also known as Default Mode Network) and task positive networks are the strongest anticorrelated resting state networks in the brain (i.e. when one is active, the other one is in its inactive state) (Fox et al., 2005). Additionally, functional connectivity studies have reported a number of other neural networks that are strongly functionally connected during rest (Thomas Yeo et al., 2011).

Only a limited number of studies have used brain MRI to assess its association with air pollution exposure in children, most of them investigating the brain structure (Burnor et al., 2021; Calderón-Garcidueñas et al., 2008, 2011; Cserbik et al., 2020; Guxens et al., 2018; Lubczyńska et al., 2020, 2021; Mortamais et al., 2017, 2019; Peterson et al., 2015; Pujol et al., 2016a; Pujol et al., 2016b), and only one investigating functional brain connectivity (Pujol et al., 2016b). Regarding air pollution exposure and brain functional connectivity, Pujol et al. found that exposure at school was associated with lower functional integration and segregation in key brain networks relevant to both inner mental processes and stimulus-driven responses in children from 8 to 12 years of age. They used a focused seed-voxel based approach instead of exploring connectivity across all functional networks. The best of our knowledge, no studies have assessed noise in relation to brain MRI.

Using the Generation R Study, previous studies found an association between traffic-related air pollution and several brain structure alterations, including altered brain volumes, reduced cortical thickness, increased surface area, and lower fractional anisotropy and higher mean diffusivity in white matter microstructure (Guxens et al., 2018; Lubczyńska et al., 2020, 2021). Thus we hypothesized that higher exposure to air pollution could also be associated with altered functional brain connectivity in resting-state networks. Furthermore, previous evidence indicated that environmental noise exposure is related to impairment in cognitive functions in children, but there is no evidence of brain alterations that underlie this association. Also, the single study on functional brain connectivity of Pujol et al. explored the exposure in childhood, not being able to identify specific windows of susceptibility. The pregnancy period and first years of life would be critical to the optimal foundation and assembling of large-scale brain functional networks, and we hypothesized that they could be especially more affected by the exposure of traffic-related air pollution and noise compared to other exposure periods. Therefore, the aim of this exploratory study was to investigate the association between the exposure to traffic-related air pollution and noise during different specific windows of susceptibility in pregnancy and childhood periods, and functional brain connectivity in pre-adolescents from 9 to 12 years of age. We used a multimodal atlas to explore the functional connectivity amongst a wide-swath of brain areas.

2. Methods

2.1. Population and study design

This study was embedded in the Generation R Study, a population-based birth cohort from fetal life onwards in the city of Rotterdam, the Netherlands (Kooijman et al., 2016). Pregnant women with an expected delivery date between April 2002 and January 2006 were eligible for participation in the study. We included only singleton pregnancies, resulting in 9,610 pregnant women recruited for the study. Children still enrolled in the study at the age of 9 to 12 years, were invited to participate in an MRI scanning session. The written informed consent was obtained from 3,992 mothers and their children, of which 3,439 received a rs-fMRI scan (White et al., 2018). From this total, 2,197 children had good quality imaging scans as well as data on traffic-related air pollution and noise, and hence were included in this analysis. Ethical approval was obtained from the Medical Ethical Committee of Erasmus MC, University Medical Centre Rotterdam, in accordance with Dutch law.

2.2. Traffic-related air pollution exposure

Air pollution exposure levels were estimated at all reported home addresses of each participant from conception until children's age at MRI assessment, following a standard procedure that is detailed in previous literature (Beelen et al., 2013; Eeftens et al., 2012a). In brief, within the ESCAPE (European Study of Cohorts for Air Pollution Effects) project, air pollution monitoring campaigns were performed in the Netherlands and Belgium in the warm, cold, and intermediate seasons between February 2009 and February 2010 (Cyrys et al., 2012; Eeftens et al., 2012b). Nitrogen oxides (NO_x) and nitrogen dioxide (NO_2) were measured in three two-week periods within one year in 80 sites (Cyrys et al., 2012). In addition, measurements of particulate matter (PM) with aerodynamic diameter of less than 10 μm (PM_{10}) and of less than 2.5 μm ($PM_{2.5}$) were also carried out three times during two-week periods in 40 sites (Eeftens et al., 2012b). From the $PM_{2.5}$ measurements, we used the filters to measure the absorbance of $PM_{2.5}$ ($PM_{2.5}$ absorbance), as a marker for black carbon. For each pollutant, the levels of the three two-week measurements were averaged, resulting in one annual mean concentration for each pollutant.

Next, land use regression models were developed for each pollutant

based on the measurements of the monitoring campaigns, and on a variety of potential land use predictors (e.g. proximity to the nearest road, traffic intensity on the nearest road, and population density) (Beelen et al., 2013; Eeftens et al., 2012a). To estimate the levels of each air pollutant at each of the participant addresses, these models were applied to each geocoded address where the participants had lived at during the period of interest (i.e. since conception until the date of MRI assessment). If more than one address was collected during the period of interest, we took into account the number of days that the participant had lived at each address and weighted the air pollution levels accordingly (8.9% of children had moved during pregnancy, 44.6% from birth to 3 years, 24.5% from 3 to 6 years, and 19.7% from 6 years of age to the MRI assessment). To back- and forward- extrapolate the concentrations during each period of interest, daily data from seven available routine background monitoring network sites were used where data was collected on daily basis covering the entire period of interest of each participant, i.e. from conception until the age at MRI assessment (Supplementary Material Methods S1) (Brunekreef, 2012). This resulted in a single, time-adjusted mean concentration of each pollutant for each participant for several time periods: i) for the pregnancy period, ii) from birth until 3 years old, iii) from the day after 3 years until 6 years old (hereafter from 3 years until 6 years old), and iv) from the day after 6 years old until the age at MRI assessment (hereafter from 6 years old until the age at MRI assessment). These study periods are based on the prenatal development, infancy and toddlerhood, early childhood, and middle childhood developmental periods (Centers for Disease Control and Prevention, 2022).

2.3. Road traffic noise exposure

To estimate the annual average exposure to noise at all reported home addresses of each participant during pregnancy and childhood, we used existing EU noise maps developed in 2012 for the municipalities of Rotterdam (including Maassluis, Rozenburg, Schiedam, and Vlaardingen) (European Environmental Noise Directive, 2002). Noise maps are created every 5 years. However, we did not use the noise maps created in 2007 because the methodology was different and the estimations not comparable. The maps used in the present study were developed following the requirements of the European Environmental Noise Directive, and for different noise sources including residential road traffic, railway, aircraft, and industry noise. However, for this study, only noise levels from residential road traffic were included, since only a smaller proportion of children had levels above 40 deciBels (dB), considered as the minimum reliable value, for the other noise sources (52.6% for railway noise, 19.2% for aircraft noise, and 19.6% for industry noise).

We used the day-evening-night level noise indicator (L_{den}). It was the A-weighted average sound level over 24-hours, with a penalty of 10 dB for night time noise (L_{night}) and an additional penalty of 5 dB for evening noise ($L_{evening}$) due to higher nuisance perception and greater health impacts during those hours (World Health Organization, 2018). L_{den} was constructed by the following formula:

$$Lden = 10lg\frac{1}{24}\left(12 \times 10\frac{Lday}{10} + 4 \times 10\frac{Levening + 5}{10} + 8 \times 10\frac{Lnight + 10}{10}\right)$$

L_{day}, $L_{evening}$, and L_{night} were the A-weighted equivalent continuous sound pressure level when the reference time interval is the day (from 7:00 to 19:00), the evening (from 19:00 to 23:00), and the night (from 23:00 to 7:00), respectively (European Environmental Noise Directive, 2002). Levels of L_{den} were assigned to each geocoded home address where the participants had lived during the study period. If more than one address was collected during the period of interest, we took into

account the number of days that the participant spent at each address and weighted the noise levels accordingly (percentages detailed in the Traffic-related air pollution exposure section). We calculated the mean levels of L_{den} for each participant for the same time periods as above: i) for the pregnancy period, ii) from birth until 3 years old, iii) from 3 until 6 years old), and iv) from 6 years old until the age at MRI assessment. When a child spent 50% of the time or more living outside of the municipality of Rotterdam for a study time period, we considered the noise exposure of that time period as missing (4.6% in pregnancy, 8.9% in birth to 3 years, 22.3% in 3 to 6 years, and 25.2% in 6 years of age to the MRI assessment).

2.4. Resting-state functional MRI acquisition

Prior to the MRI scanning session, all children were first familiarized with the MRI scanning environment during a 30-minute mock scanning session to reduce the possibility of failure to complete the scanning session (White et al., 2018). During the rs-fMRI session, children were instructed to stay awake and with their eyes closed. MRI imaging data were acquired on a study-dedicated 3 Tesla GE Discovery MR750w MRI System (General Electric, Milwaukee, WI, USA) scanner using a standard 8-channel head coil. Structural T1-weighted images were obtained using a 3D coronal inversion recovery fast spoiled gradient recalled (IR-FSPGR, BRAVO) sequence using ARC acceleration (TR = 8.77 ms, TE = 3.4 ms, TI = 600 ms, flip angle = 10°, matrix = 220 × 220, field of view (FOV) = 220 × 220 mm, slice thickness = 1 mm). A total of 200 volumes of rs-fMRI data were obtained using an interleaved axial gradient recalled echo planar imaging sequence sensitive to BOLD contrast. The scan parameters for functional imaging data were as follows: repetition time = 1760 msec, echo time = 30 msec, flip angle = 85°, acquisition matrix = 64 × 64, field of view = 230 × 230 mm, number of slices = 36, slice thickness = 4 mm, in-plane resolution = 3.4 · 3.4 mm. The total duration of the scan was 5 min and 52 s (White et al., 2018). Imaging scans with excessive motion were defined based on whether they had at least one of the following motion parameters criteria: maximum absolute motion higher than 3 mm, mean relative translation higher than 0.5 mm, and root mean square relative motion higher than 0.5 mm. Scans were also visually inspected and screened for major artifacts (e.g. from dental retainers) as well as whole-brain coverage (e.g. missing from field of view). Children with scans considered as being of poor quality following the above criteria were excluded for the analyses. Participants with air pollution data and high quality scans included in the present study had similar characteristics compared with those of children with air pollution data but with poor quality scans not included in these analyses (Supplementary Material Table S1). The rs-fMRI data was subsequently preprocessed using the standardized fMRIPrep software (Esteban et al., 2019). After pre-processing the data, de-spiking was applied, and the cerebrospinal fluid, white matter and global signals, as well as motion parameters (and their quadratic terms and temporal derivatives) were regressed out of the data (Satterthwaite et al., 2013). Next, the Human Connectome Project (HCP) multimodal parcellation was applied to the data for functional connectivity analysis in grayordinate space (Glasser et al., 2016) as well as the FreeSurfer subcortical segmentation included in fMRIPrep software (Esteban et al., 2019). It has been reported that in subjects under resting state conditions, time series of voxels within functionally connected regions of the brain have high cross-correlation coefficients (Cordes et al., 2001). Pair-wise correlation coefficients of residualized time series amongst the 382 brain areas in the parcellation were computed and subsequently transformed using Fisher transformation to Z scores to reach a normal distribution. Given overlap issues with the HCP parcellation and FreeSurfer regions of interest (ROIs), two of the brain areas in the parcellation related to the

Table 1

Population characteristics of the subjects included and not included in the analyses of the study.

Participant characteristics	Distribution		
	Included (n = 2,197)	Non-included (n = 7,413)	p-value[1]
Maternal education level			<0.001
Low	5.9	13.0	
Medium	39.7	48.1	
High	54.4	38.9	
Paternal education level			<0.001
Low	5.2	9.4	
Medium	37.2	42.7	
High	57.6	47.9	
Monthly household income during pregnancy (€)			<0.001
< 900	6.7	14.6	
900–1600	13.1	20.1	
1600–2200	14.4	15.2	
> 2200	65.8	50.1	
Maternal Country of birth			<0.001
Dutch	59.1	47.2	
Other Western	9.1	8.3	
Non-western	31.8	44.5	
Paternal Country of birth			<0.001
Dutch	69.8	58.4	
Other Western	6.2	7.1	
Non-western	24.0	34.5	
Family status			<0.001
Married	52.3	49.1	
Living together	37.5	35.2	
No partner	10.2	15.7	
Maternal parity (nulli vs. multiparous)	56.4	54.8	0.001
Maternal smoking use during pregnancy			<0.001
Never	78.8	71.8	
Smoking use until pregnancy known	9.2	8.2	
Continued smoking use during pregnancy	12.0	20.0	
Maternal alcohol consumption during pregnancy			<0.001
Never	41.0	52.5	
Alcohol consumption until pregnancy known	14.5	13.2	
Continued alcohol consumption during pregnancy	44.5	34.3	
Maternal age at intake (years)	31.3 (4.8)	29.5 (5.5)	<0.001
Paternal age at intake (years)	33.6 (5.4)	32.4 (5.8)	<0.001
Maternal height (cm)	168.2 (7.4)	166.8 (7.4)	<0.001
Paternal height (cm)	182.8 (7.6)	181.2 (8.0)	<0.001
Pre-pregnancy maternal body mass index (kg/m^2)	23.4 (20.8; 25.1)	23.7 (20.7; 25.6)	0.212
Pre-pregnancy paternal body mass index (kg/m^2)	25.2 (22.9; 27.2)	25.3 (22.9; 27.4)	0.291
Maternal psychological distress during pregnancy[2]	0.2 (0.1; 0.3)	0.3 (0.1; 0.4)	<0.001
Paternal psychological distress during pregnancy[2]	0.1 (0.0; 0.2)	0.2 (0.0; 0.2)	0.005
Maternal intelligence quotient score	98.4 (90.0; 107.0)	94.4 (84.0; 107.0)	<0.001
Child's sex (boy vs. girl)	51.0	48.9	0.086
Child's age at scanning session (years)	10.2 (0.6)	10.1 (0.6)	<0.001

Values are percentages for categorical, mean (standard deviation) for continuous variables, and median (25th percentile; 75th percentile) for body mass index and psychopathological distress. [1] Chi-square tests for categorical variables, two-sample *t*-test for normally distributed and Wilcoxon Rank Sum test for non-normally distributed continuous variables. [2] Score range from 0 to 4.

HCP hippocampus complex were excluded in these analyses. Therefore, the included pair-wise correlation coefficients amongst 380 brain areas resulted in a correlation matrix with 144,400 connectivity scores that indicated the strength and the direction of the functional connectivity amongst the different brain areas, resulting in a total of 71,820 unique connectivity scores between brain areas. We grouped the brain areas into 31 regions based on location and common properties (e.g. architecture, task-fMRI profiles, or functional connectivity) (Glasser et al., 2016) (Supplementary Material Table S2). Next, we grouped those 31 regions into 5 different brain functional networks: auditory, somatosensory/motor, visual, task positive, and task negative (Glasser et al., 2016), and a 6th group comprising subcortical structures and the cerebellum (Supplementary Material Table S2).

2.5. Covariates

Covariates were defined a priori using a direct acyclic graph (Hernan, 2002) based on up-to-date knowledge of the scientific literature, and on data availability within the Generation R cohort. We

included the following characteristics variables collected by questionnaires during pregnancy: parental ages at enrollment in the cohort (in years), parental education levels (low: primary education or lower, medium: secondary education, high: university degree or higher), parental countries of birth (Dutch, other Western, or non-Western), maternal smoking during pregnancy (never, smoking use until pregnancy known, continued smoking use during pregnancy), maternal alcohol consumption during pregnancy (never, alcohol consumption until pregnancy known, continued alcohol consumption during pregnancy), maternal parity (nulliparous, one child, two or more children), marital status (married, living together, no partner), and monthly household income (< €900, €900 – 1600, €1600 – 2220 or > €2200). Since previous studies showed an association between prenatal parental psychological distress and child brain functional connectivity, as well as between air pollution exposure and parental psychological distress (Sass et al., 2017), we also included parental psychological distress assessed with the Brief Symptom Inventory (Derogatis, 2011) as a covariate. We also included the parental weights and heights (in kilograms and centimeters, respectively) measured or self-reported at the first trimester of

pregnancy and thereafter used to calculate the pre-pregnancy body mass index (in kg/m²). Maternal intelligence was also assessed using the Ravens Advanced Progressive Matrices Test, set I (Raven, 1962). Child's sex (boy or girl) was obtained from hospital records at birth, and child's age (in years) at the scanning session was also collected. Additionally, as motion has been shown to be a major concern in rs-fMRI research (Power et al., 2012), we have extracted framewise displacement values from the fMRIPrep output.

2.6. Statistical analyses

The study population was limited to children with available data on traffic-related air pollution and noise exposure and good quality resting state imaging scans (n = 2,197). We first performed multiple imputation of missing values of potential confounding variables using chained equations to generate 25 complete datasets (Spratt et al., 2010) (Supplementary Material Table S3). The percentage of missing values for the confounding variables was below 30%, except for paternal education level and paternal psychological distress during pregnancy, which were 34.7% and 37.4%, respectively. Distributions in imputed datasets were very similar to those observed (Supplementary Material Table S4).

Children included in the analysis (n = 2,197) were more likely to have Dutch parents, with a higher education level, and from a higher household income compared with children who were not included (n = 7,413) (Table 1). To correct for the losses to follow-up we used the inverse probability weighting. This technique allows accounting for selection bias that potentially arises when only participants with available exposure and outcome data are included as compared to a full initial cohort recruited at pregnancy (Weuve et al., 2012). The variables used to create the weights can be found summarized in Supplementary Material Table S5.

After confirming that the assumptions of the linear regression models (i.e. normality of the residuals, linearity between exposure and outcomes, homoscedasticity, no collinearity between covariates) were fulfilled, we performed linear regression models to assess the association between the exposure to each traffic-related air pollutant and noise exposure variable and each brain area pair correlation, adjusting for all potential confounding variables described previously (Supplementary Material Methods S2). Models were performed separately for each air pollutant and the road traffic noise variable. Models were also performed for each exposure period separately. Several sensitivity analyses were performed: i) we evaluated the association between air pollution and functional brain connectivity excluding those children with exposure estimates above or below of 4 standard deviations of the mean, ii) we evaluated the potential effect modification of sex by adding a product interaction between each air pollutant and the road traffic noise variable separately and sex. In the case of interaction terms statistically significant (p < 0.05), we would quantify the potential differences by performing stratified analysis by sex. Due to the high correlation between the air pollutants that were associated with functional brain connectivity, multi-pollutant analyses were not carried out.

All analysis were corrected for multiple testing using false discovery rate at p < 0.05 level (Benjamini & Hochberg, 1995). Statistical analyses were carried out using STATA (version 14.0; Stata Corporation, College Station, TX) and R (version 3.4.2; R Core Team (2017)).

3. Results

3.1. Descriptive results

Participant characteristics of the study population are shown in Table 1. Mean NO₂ and PM₂.₅ exposure levels during pregnancy were 39.7 μg/m³, ranging from 24.2 μg/m³ and 90.8 μg/m³, and 19.5 μg/m³, ranging from 15.4 μg/m³ and 31.0 μg/m³, respectively (Fig. 1 and Supplementary Material Table S6). Mean road traffic noise exposure levels during pregnancy were 54.7 dB, ranging from 40 dB and 73 dB

(Fig. 1 and Supplementary Material Table S6). The individual traffic-related air pollutants and noise exposure levels between the different time periods were low to highly correlated, ranging from 0.26 for NO₂ between pregnancy and childhood period from 6 years to the age at MRI assessment, to 0.90 for road traffic noise between the childhood periods from 3 to 6 years and from 6 years of age to the age at MRI assessment (Supplementary Material Table S7). Correlations between the concentrations of traffic-related air pollutants also varied depending on the pollutant and the period of interest (e.g. correlations between NOₓ and PM₂.₅ during pregnancy and between NO₂ and PM₂.₅ absorbance during pregnancy were 0.39 and 0.86, respectively) (Supplementary Material Figure S1). Noise exposure levels were low to moderately correlated with the concentrations of traffic-related air pollutants (e.g. correlation between road traffic noise and PM₁₀ was 0.17 during pregnancy (Supplementary Material Fig. S1). The mean of the correlations between brain areas was 0.12, ranging from −0.49 to 1.68 after Fisher transformation, and 24.1% of the correlations were negative (data not shown).

3.2. Air pollution exposure and functional brain connectivity

Higher exposures to NO₂ and PM₂.₅ absorbance from birth to 3 years of age, and to NOₓ from 3 to 6 years of age were associated with higher functional brain connectivity (Fig. 2 and Supplementary Material Table S8). In contrast, exposure to PM₁₀ and PM₂.₅ were not associated with functional brain connectivity.

#### 3.2.1. NO₂ exposure and functional brain connectivity

Higher exposure to NO₂ from birth to 3 years of age was associated with 2 higher correlation coefficients between brain areas (Fig. 2 and Supplementary Material Table S8). For these associations, we observed 0.11 higher correlation coefficient per 10 μg/m³ increase in NO₂ (Supplementary Material Table S8). The mean values of these correlation coefficients were positive, therefore, the exposure to NO₂ increased the positive correlation. Both connections were inter-network: regions belonging to the visual and auditory networks were connected with regions belonging to the task positive network, respectively (Fig. 2 and Supplementary Material Table S8). Additionally, one of the connections was inter-hemispheric while the other was intra-hemispheric (Supplementary Material Fig. 2 and Table S8). No associations were found between higher exposure to NO₂ during pregnancy, from 3 to 6 years, and 6 years of age to the age at MRI assessment, and any correlation coefficients between brain areas.

3.2.2. Noₓ exposure and functional brain connectivity

Higher exposure to NOₓ from 3 to 6 years of age was associated with 2 higher correlation coefficients between brain areas (Fig. 2 and Supplementary Material Table S8). For these associations, we observed 0.07 higher correlation coefficient per 20 μg/m³ increase in NOₓ (Supplementary Material Table S8). The pattern on how the functional connectivity increased was similar to that of NO₂, as the mean values of these correlation coefficients were positive, which means that exposure to NOₓ increased the positive correlation. Both connections were inter-network (visual with task positive network) and intra-hemispheric (Supplementary Material Fig. 2 and Table S8). No associations were found between exposure to NOₓ during pregnancy, from birth to 3 years, and from 6 years of age to the age at MRI assessment, and any correlation coefficients between brain areas.

#### 3.2.3. PM₂.₅ absorbance exposure and functional brain connectivity

Higher exposure to PM₂.₅ absorbance from birth to 3 years of age was related to 22 higher correlation coefficients between brain areas (Fig. 2 and Supplementary Material Table S8). For these associations, we observed between 0.16 and 0.19 higher correlation coefficients per 10⁻⁵m⁻¹ increase of PM₂.₅ absorbance (Supplementary Material Table S8). Almost all the mean values of these correlation coefficients were
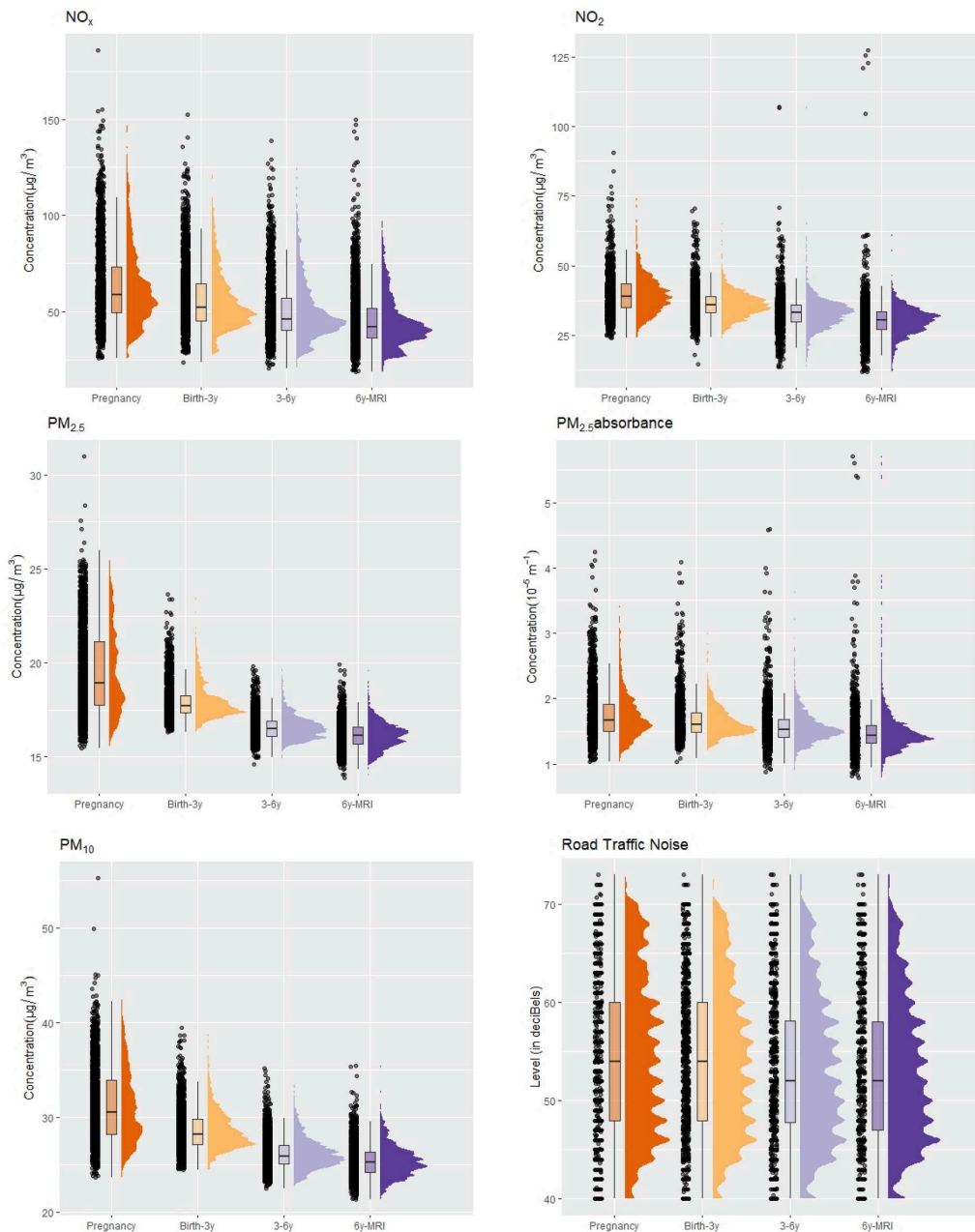
Fig. 1. Traffic-related air pollution and road traffic noise exposure levels during pregnancy and childhood periods from birth to 3 years, from 3 to 6 years, and from 6 years to the age at MRI assessment. Abbreviations: NO_2, nitrogen dioxide in $\mu g/m^3$; NO_x, nitrogen oxides in $\mu g/m^3$; PM, particulate matter with different aerodynamic diameters: <10 μm (PM_{10}) in $\mu g/m^3$; <2.5 μm ($PM_{2.5}$) in $\mu g/m^3$; absorbance of $PM_{2.5}$ filters ($PM_{2.5}$absorbance) in $10^{-5} m^{-1}$.

positive, meaning more exposure to $PM_{2.5}$ absorbance was related to stronger positive correlations between regions, except for three connections which had negative mean correlation coefficients (right lateral occipital (area 1) with left lateral intraparietal dorsal area, left parieto-occipital sulcus (area 2) with the right superior parietal cortex (area 7PC), and right frontal opercular cortex (area 4) with the right lateral

temporal cortex (TE1 posterior area)), and thus connectivity shifted from negative to positive with increasing $PM_{2.5}$ absorbance. The brain areas of these three connections belong to regions of the visual, task positive, and task negative networks. Most of the connections related with the exposure to $PM_{2.5}$ absorbance were inter-network (16 of 22) between brain regions predominantly belonging to the task positive and

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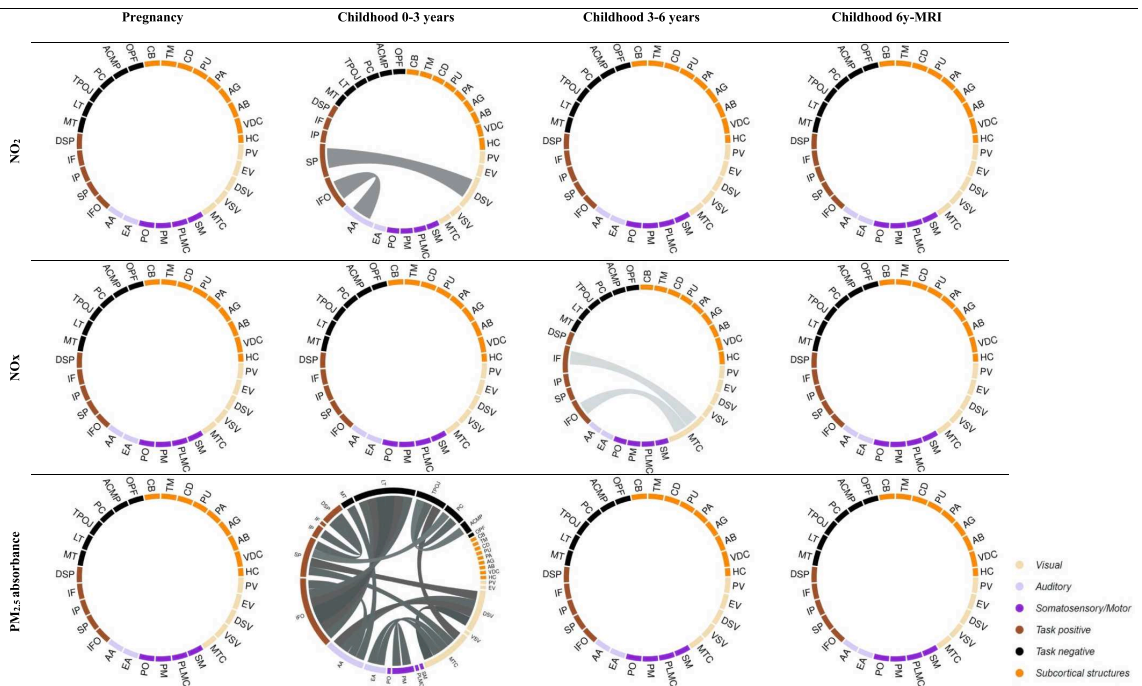
Fig. 2. Adjusted associations between exposure to air pollution at each time period and functional brain connectivity in preadolescents. Brain areas were grouped into 31 brain regions (described below) and into 5 different brain functional networks: visual, auditory, somatosensory/motor, task positive, task negative (also known as Default Mode Network (DMN)), and a 6th group with the subcortical structures and the cerebellum: AA, Auditory Association Cortex; AB, Nucleaus Accumbens; ACMP, Anterior Cingulate and Medial Prefrontal Cortex; AG, Amygdala; CB, Cerebellum; CD, Caudate; DSP, DorsoLateral Prefrontal Cortex; DSV, Dorsal Stream Visual Cortex; EA, Early Auditory Cortex; EV, Early Visual Cortex; HC, Hippocampus; IF, Inferior Frontal Cortex; IFO, Insular and Frontal Opercular Cortex; IP, Inferior Parietal Cortex; LT, Lateral Temporal Cortex; MT, Medial Temporal Cortex; MTC, MT + Complex and Neighboring Visual Areas; NOx, nitrogen oxides; NO2, nitrogen dioxide; OPF, Orbital and Polar Frontal Cortex; PA, Pallidum; PC, Posterior Cingulate Cortex; PLMC, Paracentral Lobular and Mid Cingulate Cortex; PM, Premotor Cortex; PM2.5absorbance, absorbance of PM2.5 filters; PO, Posterior Opercular Cortex; PU, Putamen; PV, Primary Visual Cortex; SM, Somatosensory and Motor Cortex; SP, Superior Parietal Cortex; TPOJ, Temporo-Parieto-Occipital Junction; TM, Thalamus; VDC, Ventral Diencephalon; VSV, Ventral Stream Visual Cortex. Associations from linear regression models adjusted for maternal and paternal education, ethnicity, age, body mass index, and psychological distress during pregnancy, maternal smoking and alcohol use during pregnancy, parity, and intelligence quotient, family status, household income, child's gender and age at the scanning session, and mean framewise displacement that survived correction for multiple testing using false discovery rating. All associations showed positive coefficients and the color of the connection represents the strengths of the association (the darkness of the color indicates a larger beta coefficient). Linear regression models were performed separately for each air pollutant.

task negative networks, and half of them were inter-hemispheric (Supplementary Material Fig. 2 and Table S8). No associations were found between higher exposure to PM2.5 absorbance during pregnancy, from 3 to 6 years, and from 6 years of age to the age at MRI assessment, and any correlation coefficients between brain areas.

3.3. Road traffic noise and functional brain connectivity

Exposure to road traffic noise was not associated with functional brain connectivity (Supplementary Material Table S9).

3.4. Sensitivity analyses

Excluding children with air pollution exposure estimates above or below of 4 standard deviations of the mean showed similar results (data not shown). Sensitivity analyses assessing the interaction of each air pollutant and road traffic noise separately with sex yielded to non-significant results (data not shown).

4. Discussion

In this study, we found that higher exposures to NO2 and PM2.5 absorbance from birth to 3 years, and to NOx from 3 to 6 years of age were associated with higher functional brain connectivity among several brain regions in preadolescents from 9 to 12 years of age. PM2.5 absorbance showed a higher number of associations with functional brain connectivity. Also, the childhood period from birth to 3 years was the period with the highest susceptibility to air pollution. Most associations were found with functional brain connections between brain regions that are part of the task positive and the task negative networks. Also, slightly more than half of the identified connections were intra-hemispheric. We found no evidence of associations between PM10, PM2.5, or road traffic noise during pregnancy or childhood, and brain functional connectivity.

To our knowledge, this is the first study exploring the associations of the exposures to traffic-related air pollution and noise during pregnancy and childhood, and whole-brain functional connectivity. Previous evidence of such associations is limited to a single study (Pujol et al.,

2016b) where higher exposure to NO$_2$ and elemental carbon at schools in children from 8 to 12 years of age were associated with lower integration and segregation in key brain networks. Our findings indicated that most of the functional connections associated with exposure to air pollution were between brain regions belonging to different networks (20 of 26), which would suggest an indicator of lower segregation.

In our study, we investigated functional connectivity during resting conditions. Under these conditions, the brain is engaged in spontaneous, intrinsic activity (i.e. not attributable to specific inputs or intended to generate specific outputs) (Hausman et al., 2020). Brain areas with higher connectivity in relation to exposure to air pollution were located in most of the networks explored but mainly in brain regions that are part of the task negative and task positive networks. Increased connectivity within the task negative network during rest could be interpreted as a sign of increased self-referential thoughts, and less activity in cognitive-control networks such as attention and inhibitory control (Whitfield-Gabrieli & Ford, 2012). Consistent with these findings, some previous studies also found an association of exposure to air pollution with impaired attentional function and inhibitory control, measured using neuropsychological tests (Basagaña et al., 2016; Chiu et al., 2013; Guxens et al., 2018; Pujol et al., 2016a; Sentís et al., 2017; Sunyer et al., 2015, 2017). Additionally, previous evidence found an association between the exposure to air pollution and thinner cortex as well as alterations in cortical surface in regions belonging to the task negative network (Cserbik et al., 2020; Guxens et al., 2018; Lubczyńska et al., 2021). While Guxens et al. reported that children exposed to higher levels of air pollution during pregnancy had thinner cortex in several regions of both hemispheres, Cserbik et al. reported hemispheric-specific differences in the associations between air pollution exposure during childhood and cortical thickness and surface area. We also found higher functional connectivity in brain areas belonging to the task positive network during resting conditions. For optimal cognitive processing, the task positive and task negative networks should have an opposite relationship, i.e., the activation of one network would inhibit the other, to avoid the other's interference in the coordination of a neural process (Cheng et al., 2020). Task negative tend to be activated during resting conditions while task positive tend to be activated during attention-demanding tasks and includes our conscious attention towards the external environment. Therefore, increased connectivity of the task positive network during resting conditions, in addition to the activation of both networks at the same time, could be an indicator of functional brain connectivity impairment. Previous evidence also described thinner cortex and a decrease in cortical surface in regions that are part of the task positive network in relation to the exposure to air pollution (Guxens et al., 2018; Lubczyńska et al., 2021).

The specific windows of exposure of air pollution on functional brain connectivity have not been previously explored. We have identified the first years of life as sensitive periods of exposure. Consistent findings of both fetal and neonatal rs-fMRI studies have hypothesized that the foundations of resting-state networks are already laid before 37 weeks of gestation, with rapid neural growth in the last trimester of pregnancy (Doria et al., 2010). However, some networks appear to be more developed than others (e.g., visual and auditory networks). Additionally, changes in network size, represented by a percentage of brain volume, have been observed during first years of life, and several resting state networks also showed a significant increase in functional connectivity during first years of life (Lin et al., 2008). The development of connectivity networks during first years of life could be the explanation of why the exposure to air pollution from birth to 3 years of age was related to more changes in brain functional connectivity than the exposure to air pollution during the other periods of interest in our study. From the age of 2 years onwards, neurodevelopment is characterized by a gain in higher-order cognitive abilities, such as attention and memory (de Bie et al., 2012), and functional networks continue in development between childhood and adulthood. It has been described that the structure of these functional networks differed between children

and adults, shifting from a local anatomical architecture in children (i.e., correlations between brain regions close in space) to a more distributed architecture in adults (i.e., correlations between brain regions more distant in space) (Fair et al., 2009). In addition, synaptic pruning and myelination take place until late the second decade of life (Williamson & Lyons, 2018). During synaptic pruning, the brain eliminates extra connections that are no longer needed. Both neurodevelopmental events result in an increased signal propagation that allows for a more efficient communication between distant regions, allowing for a more effective response to any processing demand. Finally, functional neuroimaging investigations have shown that inter-hemispheric connectivity appears at birth and slowly shifts during development to a predominant intra-hemispheric connectivity in the adult, as a result of the process of brain's lateralization (Tzourio-Mazoyer, 2016). In the results of this study, we found that half of the connections associated with air pollution in the exposure period from birth to 3 years of age were intra-hemispheric while the connections we found in the exposure period from 3 to 6 years of age were all intra-hemispheric, although these last results should be interpreted with caution due to the small number of connections identified.

In the present study, we identified NO$_2$, NO$_x$, and PM$_{2.5}$ absorbance as the traffic-related pollutants associated with functional brain connectivity. The same pollutants were identified in the previous study on air pollution exposure at school and functional brain connectivity (Pujol et al., 2016b). In Europe, NO$_x$ and NO$_2$ gasses in the air are predominantly produced by an incomplete combustion of hydrocarbons, mainly originating from diesel fuel (European Environment Agency, 2019). The absorbance of PM$_{2.5}$ is considered as a measure of exposure to black carbon particles. Black carbon refers to the sooty black material emitted during incomplete combustion. Diesel-powered vehicles intensively used in urban areas are an important source, though not the unique source (European Environment Agency, 2019).

Regarding the association between exposure to road traffic noise and functional brain connectivity, we did not find any association in preadolescents exposed to higher road traffic noise during pregnancy or childhood in our study. Nevertheless, some studies have shown that noise exposure could act as a stressor that affects the HPA axis leading to an increased level of stress hormones (Jafari et al., 2017; Lautarescu et al., 2020). During pregnancy, these hormones could cross the fetal-placental barrier and influence brain development (Lautarescu et al., 2020), while in children, they could alter the size and neuronal architecture of some brain areas (Smith & Pollak, 2020). Such early life stress could be also related to disturbances in functional brain connectivity (De Asis-Cruz et al., 2020; Hermans et al., 2011; van Marle et al., 2010). Additionally, it has been demonstrated that noise exposure might have negative effects on children's cognition, mainly on memory and reading outcomes (Clark & Paunovic, 2018; S. Stansfeld & Clark, 2015). However, the evidence on the effect of noise exposure on children's cognition remains inconsistent and further studies are warranted. There is no previous evidence evaluating the effect of the exposure to road traffic noise in brain's structure and function. Our null results could be due to the fact that we evaluated long-term exposure to noise instead of acute exposure. Previous studies found an association between the acute exposure to noise generated by MRI and altered functional brain connectivity (Andoh et al., 2017; Pellegrino et al., 2022).

Our study has several strengths: i) the large sample size of study participants with resting state functional imaging data; ii) the longitudinal exposure assessment and prospective nature of the study; iii) the use of multiple imputation and inverse probability weighting to reduce the selection bias in the study; iv) the availability for a large number of socioeconomic and lifestyle factors to control for confounding; v) the standardized and validated traffic-related air pollution and road traffic noise measurement assessments across different time periods to assess sensitive windows of exposure. However, some limitations should also be considered. One of our main limitations related to the exposure assessment is the possibility of measurement error in the air pollution

estimates. Air pollution monitor campaigns were performed between 2009 and 2010 and we used back- and forward- extrapolated concentration levels for the periods of interest of our study, which have been shown to remain spatially stable over time for periods up to 8 or 18 years (Eeftens et al., 2011; Gulliver et al., 2013), however, we cannot discard the introduction of measurement error. Exposure to air pollution and road traffic noise was assessed at the residential home addresses of the study participants, while pregnant women could have spent a large amount of time at work, and children older than 6 years also possibly spent many hours in school settings in the hours that road traffic was higher. This fact could have introduced measurement error on the exposure estimations, and lead to non-differential misclassification, which in turn could have led to underestimation of the effect estimates. Misclassification could also occur if participants changed home addresses and this change was not documented. We used air pollution and noise average levels for the entire pregnancy and for different periods during childhood. Although it has been reported that some neurodevelopmental outcomes are related to a specific exposure window, we did not use statistical methods with higher temporal resolution due to computational reasons. Therefore, the effects could be underestimated. Another limitation that should be addressed is that although we used multiple imputation for missing data, some variables have more than 30% of participants with missing data (e.g. paternal education level and paternal psychological distress during pregnancy). However, the distributions in the imputed datasets were very similar to those observed. Furthermore, we cannot discard the possibility of residual confounding due to the unavailability of other, potentially relevant, confounding variables such as parental social class or genetic and family factors related to both air pollution and brain development. Also, information on some effect modifiers, such as noise sensitivity, location of the child's bedroom, and other noise sources should be included to more accurately estimate the effects of noise exposure and reduce the measurement error in the noise pollution estimates.

5. Conclusions

In conclusion, we observed associations of exposure to NO_2, NO_x, and $PM_{2.5}$ absorbance from birth to 3 years, and from 3 to 6 years of age, with higher functional brain connectivity in preadolescents from 9 to 12 years of age. NO_x and NO_2 gasses as well as the absorbance of $PM_{2.5}$ are mainly produced by diesel-powered vehicles in urban areas. $PM_{2.5}$ absorbance was the traffic-related air pollutant most frequently associated with functional brain connectivity, and the period from birth to 3 years of age was the time window most susceptible to the effects of air pollution. The associations found in our study are in brain areas predominantly located in the task positive and task negative networks. An increased connectivity in these networks during resting conditions could be an indicator of differential functional connectivity in children exposed to higher levels of air pollution. No association was observed between exposure to road traffic noise and brain functional connectivity. Future longitudinal studies with repeated brain functional connectivity measures, and including multipollutant approaches, are warranted to better understand the associations found in this study.

CRediT authorship contribution statement

Laura Pérez-Crespo: Conceptualization, Formal analysis, Methodology, Writing – original draft, Visualization. **Michelle S.W. Kusters:** Formal analysis, Writing – review & editing. **Mónica López-Vicente:** Methodology, Writing – review & editing. **Małgorzata J. Lubczyńska:** Writing – review & editing. **Maria Foraster:** Writing – review & editing. **Tonya White:** Conceptualization, Writing – review & editing. **Gerard Hoek:** Writing – review & editing. **Henning Tiemeier:** Conceptualization, Writing – review & editing, Funding acquisition. **Ryan L. Muetzel:** Conceptualization, Methodology, Writing – review & editing. **Mònica Guxens:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107275.

References

Andoh, J., Ferreira, M., Leppert, I.R., Matsushita, R., Pike, B., Zatorre, R.J., 2017. How restful is it with all that noise? Comparison of Interleaved silent steady state (ISSS) and conventional imaging in resting-state fMRI. NeuroImage 147, 726–735. https://doi.org/10.1016/j.neuroimage.2016.11.065.

Basagaña, X., Esnaola, M., Rivas, I., Amato, F., Alvarez-Pedrerol, M., Forns, J., López-Vicente, M., Pujol, J., Nieuwenhuijsen, M., Querol, X., Sunyer, J., 2016. Neurodevelopmental deceleration by urban fine particles from different emission sources: a longitudinal observational study. Environ. Health Perspect. 124 (10), 1630–1636. https://doi.org/10.1289/EHP209.

Beelen, R., Hoek, G., Vienneau, D., Eeftens, M., Dimakopoulou, K., Pedeli, X., Tsai, M.-Y., Künzli, N., Schikowski, T., Marcon, A., Eriksen, K.T., Raaschou-Nielsen, O., Stephanou, E., Patelarou, E., Lanki, T., Yli-Tuomi, T., Declercq, C., Falq, G., Stempfelet, M., Birk, M., Cyrys, J., von Klot, S., Nádor, G., Varró, M.J., Dėdelė, A., Gražulevičienė, R., Mölter, A., Lindley, S., Madsen, C., Cesaroni, G., Ranzi, A., Badaloni, C., Hoffmann, B., Nonnemacher, M., Krämer, U., Kuhlbusch, T., Cirach, M., de Nazelle, A., Nieuwenhuijsen, M., Bellander, T., Korek, M., Olsson, D., Strömgren, M., Dons, E., Jerrett, M., Fischer, P., Wang, M., Brunekreef, B., de Hoogh, K., 2013. Development of NO2 and NOx land use regression models for estimating air pollution exposure in 36 study areas in Europe – the ESCAPE project. Atmos. Environ. 72, 10–23. https://doi.org/10.1016/j.atmosenv.2013.02.037.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. Roy. Stat. Soc.: Ser. B (Methodol.) 57 (1), 289–300. https://doi.org/10.1111/j.2517-6161.1995.tb02031.x.

Biswal, B., Zerrin Yetkin, F., Haughton, V.M., Hyde, J.S., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar mri. Magn. Reson. Med. 34 (4), 537–541. https://doi.org/10.1002/mrm.1910340409.

Block, M.L., Elder, A., Auten, R.L., Bilbo, S.D., Chen, H., Chen, J.-C., Cory-Slechta, D.A., Costa, D., Diaz-Sanchez, D., Dorman, D.C., Gold, D.R., Gray, K., Jeng, H.A., Kaufman, J.D., Kleinman, M.T., Kirshner, A., Lawler, C., Miller, D.S., Nadadur, S.S., Ritz, B., Semmens, E.O., Tonelli, L.H., Veronesi, B., Wright, R.O., Wright, R.J., 2012. The outdoor air pollution and brain health workshop. NeuroToxicology 33 (5), 972–984. https://doi.org/10.1016/j.neuro.2012.08.014.

Brunekreef, B., 2012. ESCAPE Procedure for Extrapolation Back in Time. Available from: <http://www.escapeproject.eu/manuals/Procedure_for_extrapolation_back_in_time.pdf>.

Burnor, E., Cserbik, D., Cotter, D.L., Palmer, C.E., Ahmadi, H., Eckel, S.P., Berhane, K., McConnell, R., Chen, J.-C., Schwartz, J., Jackson, R., Herting, M.M., 2021. Association of outdoor ambient fine particulate matter with intracellular white matter microstructural properties among children. JAMA Network Open 4 (12), e2138300. https://doi.org/10.1001/jamanetworkopen.2021.38300.

Calderón-Garcidueñas, L., Mora-Tiscareño, A., Ontiveros, E., Gómez-Garza, G., Barragán-Mejía, G., Broadway, J., Chapman, S., Valencia-Salazar, G., Jewells, V., Maronpot, R. R., Henríquez-Roldán, C., Pérez-Guillé, B., Torres-Jardón, R., Herrit, L., Brooks, D., Osnaya-Brizuela, N., Monroy, M.E., González-Maciel, A., Reynoso-Robles, R., Villarreal-Calderon, R., Solt, A.C., Engle, R.W., 2008. Air pollution, cognitive deficits and brain abnormalities: a pilot study with children and dogs. Brain Cogn. 68 (2), 117–127. https://doi.org/10.1016/j.bandc.2008.04.008.

Calderón-Garcidueñas, L., Engle, R., Mora-Tiscareño, A., Styner, M., Gómez-Garza, G., Zhu, H., Jewells, V., Torres-Jardón, R., Romero, L., Monroy-Acosta, M.E., Bryant, C., González-Gonzalez, L.O., Medina-Cortina, H., D'Angiulli, A., 2011. Exposure to severe urban air pollution influences cognitive outcomes, brain volume and systemic inflammation in clinically healthy children. Brain Cogn. 77 (3), 345–355. https://doi.org/10.1016/j.bandc.2011.09.006.

Centers for Disease Control and Prevention, 2022, enero 31. Child Development. Available from: <https://www.cdc.gov/ncbddd/childdevelopment/positiveparenting/index.html>.

Cheng, X., Yuan, Y., Wang, Y., Wang, R., 2020. Neural antagonistic mechanism between default-mode and task-positive networks. Neurocomputing 417, 74–85. https://doi.org/10.1016/j.neucom.2020.07.079.

Chiu, Y.-H.-M., Bellinger, D.C., Coull, B.A., Anderson, S., Barber, R., Wright, R.O., Wright, R.J., 2013. Associations between traffic-related black carbon exposure and attention in a prospective birth cohort of urban children. Environ. Health Perspect. 121 (7), 859–864. https://doi.org/10.1289/ehp.1205940.

Clark, C., Paunovic, K., 2018. WHO environmental noise guidelines for the European region: a systematic review on environmental noise and cognition. Int. J. Environ. Res. Public Health 15 (2), 285. https://doi.org/10.3390/ijerph15020285.

Cordes, D., Haughton, V.M., Arfanakis, K., Carew, J.D., Turski, P.A., Moritz, C.H., Quigley, M.A., Meyerand, M.E., 2001. Frequencies contributing to functional connectivity in the cerebral cortex in «resting-state» data. AJNR Am. J. Neuroradiol. 22 (7), 1326–1333.

Costa, L.G., Cole, T.B., Dao, K., Chang, Y.-C., Coburn, J., Garrick, J.M., 2020. Effects of air pollution on the nervous system and its possible role in neurodevelopmental and neurodegenerative disorders. Pharmacol. Ther. 210, 107523. https://doi.org/10.1016/j.pharmthera.2020.107523.

Cserbik, D., Chen, J.-C., McConnell, R., Berhane, K., Sowell, E.R., Schwartz, J., Hackman, D.A., Kan, E., Fan, C.C., Herting, M.M., 2020. Fine particulate matter exposure during childhood relates to hemispheric-specific differences in brain structure. Environ. Int. 143, 105933. https://doi.org/10.1016/j.envint.2020.105933.

Cyrys, J., Eeftens, M., Heinrich, J., Ampe, C., Armengaud, A., Beelen, R., Bellander, T., Beregszaszi, T., Birk, M., Cesaroni, G., Cirach, M., de Hoogh, K., De Nazelle, A., de Vocht, F., Declercq, C., Dėdelė, A., Dimakopoulou, K., Eriksen, K., Galassi, C., Graŭlevičienė, R., Grivas, G., Gruzieva, O., Gustafsson, A.H., Hoffmann, B., Iakovides, M., Ineichen, A., Krämer, U., Lanki, T., Lozano, P., Madsen, C.,

Meliefste, K., Modig, L., Mölter, A., Mosler, G., Nieuwenhuijsen, M., Nonnemacher, M., Oldenwening, M., Peters, A., Pontet, S., Probst-Hensch, N., Quass, U., Raaschou-Nielsen, O., Ranzi, A., Sugiri, D., Stephanou, E.G., Taimisto, P., Tsai, M.-Y., Vaskövi, É., Villani, S., Wang, M., Brunekreef, B., Hoek, G., 2012. Variation of NO2 and NOx concentrations between and within 36 European study areas: results from the ESCAPE study. Atmos. Environ. 62, 374–390. https://doi.org/10.1016/j.atmosenv.2012.07.080.

De Asis-Cruz, J., Krishnamurthy, D., Zhao, Li., Kapse, K., Vezina, G., Andescavage, N., Quistorff, J., Lopez, C., Limperopoulos, C., 2020. Association of prenatal maternal anxiety with fetal regional brain connectivity. JAMA Network Open 3 (12), e2022349. https://doi.org/10.1001/jamanetworkopen.2020.22349.

de Bie, H.M.A., Boersma, M., Adriaanse, S., Veltman, D.J., Wink, A.M., Roosendaal, S.D., Barkhof, F., Stam, C.J., Oostrom, K.J., Delemarre-van de Waal, H.A., Sanz-Arigita, E. J., 2012. Resting-state networks in awake five- to eight-year old children. Hum. Brain Mapp. 33 (5), 1189–1201. https://doi.org/10.1002/hbm.21280.

Derogatis, L.R., 2011. Brief Symptom Inventory [Data set]. American Psychological Association. doi: 10.1037/t00789-000.

European Environmental Noise Directive, 2002. Directive 2002/49/EC. Available from: <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32002L0049&from=en>.

Doria, V., Beckmann, C.F., Arichi, T., Merchant, N., Groppo, M., Turkheimer, F.E., Counsell, S.J., Murgasova, M., Aljabar, P., Nunes, R.G., Larkman, D.J., Rees, G., Edwards, A.D., 2010. Emergence of resting state networks in the preterm human brain. Proc. Natl. Acad. Sci. 107 (46), 20015–20020. https://doi.org/10.1073/pnas.1007921107.

Eeftens, M., Beelen, R., Fischer, P., Brunekreef, B., Meliefste, K., Hoek, G., 2011. Stability of measured and modelled spatial contrasts in NO2 over time. Occup. Environ. Med. 68 (10), 765–770. https://doi.org/10.1136/oem.2010.061135.

Eeftens, M., Beelen, R., de Hoogh, K., Bellander, T., Cesaroni, G., Cirach, M., Declercq, C., Dėdelė, A., Dons, E., de Nazelle, A., Dimakopoulou, K., Eriksen, K., Falq, G., Fischer, P., Galassi, C., Gražulevičienė, R., Heinrich, J., Hoffmann, B., Jerrett, M., Keidel, D., Korek, M., Lanki, T., Lindley, S., Madsen, C., Mölter, A., Nádor, G., Nieuwenhuijsen, M., Nonnemacher, M., Pedeli, X., Raaschou-Nielsen, O., Patelarou, E., Quass, U., Ranzi, A., Schindler, C., Stempfelet, M., Stephanou, E., Sugiri, D., Tsai, M.-Y., Yli-Tuomi, T., Varró, M.J., Vienneau, D., Klot, S.V., Wolf, K., Brunekreef, B., Hoek, G., 2012a. Development of land use regression models for PM 2.5, PM 2.5 absorbance, PM 10 and PM coarse in 20 European Study Areas; results of the ESCAPE Project. Environ. Sci. Technol. 46 (20), 11195–11205. https://doi.org/10.1021/es301948k.

Eeftens, M., Tsai, M.-Y., Ampe, C., Anwander, B., Beelen, R., Bellander, T., Cesaroni, G., Cirach, M., Cyrys, J., de Hoogh, K., De Nazelle, A., de Vocht, F., Declercq, C., Dėdelė, A., Eriksen, K., Galassi, C., Gražulevičienė, R., Grivas, G., Heinrich, J., Hoffmann, B., Iakovides, M., Ineichen, A., Katsouyanni, K., Korek, M., Krämer, U., Kuhlbusch, T., Lanki, T., Madsen, C., Meliefste, K., Mölter, A., Mosler, G., Nieuwenhuijsen, M., Oldenwening, M., Pennanen, A., Probst-Hensch, N., Quass, U., Raaschou-Nielsen, O., Ranzi, A., Stephanou, E., Sugiri, D., Udvardy, O., Vaskövi, É., Weinmayr, G., Brunekreef, B., Hoek, G., 2012b. Spatial variation of PM2.5, PM10, PM2.5 absorbance and PMcoarse concentrations between and within 20 European study areas and the relationship with NO2 – Results of the ESCAPE project. Atmos. Environ. 62, 303–317. https://doi.org/10.1016/j.atmosenv.2012.08.038.

Esteban, O., Markiewicz, C.J., Blair, R.W., Moodie, C.A., Isik, A.I., Erramuzpe, A., Kent, J. D., Goncalves, M., DuPre, E., Snyder, M., Oya, H., Ghosh, S.S., Wright, J., Durnez, J., Poldrack, R.A., Gorgolewski, K.J., 2019. fMRIPrep: a robust preprocessing pipeline for functional MRI. Nat. Methods 16 (1), 111–116. https://doi.org/10.1038/s41592-018-0235-4.

European Environment Agency, 2019. Air quality in Europe: 2019 report. Publications Office. doi: 10.2800/822355.

Fair, D.A., Cohen, A.L., Power, J.D., Dosenbach, N.U.F., Church, J.A., Miezin, F.M., Schlaggar, B.L., Petersen, S.E., Sporns, O., 2009. Functional brain networks develop from a "Local to Distributed" organization. PLoS Comput. Biol. 5 (5), e1000381. https://doi.org/10.1371/journal.pcbi.1000381.

Fox, M.D., Raichle, M.E., 2007. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat. Rev. Neurosci. 8 (9), 700–711. https://doi.org/10.1038/nrn2201.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., Raichle, M.E., 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc. Natl. Acad. Sci. 102 (27), 9673–9678. https://doi.org/10.1073/pnas.0504136102.

Gauthier, C.J., Fan, A.P., 2019. BOLD signal physiology: models and applications. NeuroImage 187, 116–127. https://doi.org/10.1016/j.neuroimage.2018.03.018.

Glasser, M.F., Coalson, T.S., Robinson, E.C., Hacker, C.D., Harwell, J., Yacoub, E., Ugurbil, K., Andersson, J., Beckmann, C.F., Jenkinson, M., Smith, S.M., Van Essen, D. C., 2016. A multi-modal parcellation of human cerebral cortex. Nature 536 (7615), 171–178. https://doi.org/10.1038/nature18933.

Glover, G.H., 2011. Overview of functional magnetic resonance imaging. Neurosurg. Clin. N. Am. 22 (2), 133–139. https://doi.org/10.1016/j.nec.2010.11.001.

Gulliver, J., de Hoogh, K., Hansell, A., Vienneau, D., 2013. Development and back-extrapolation of NO 2 land use regression models for historic exposure assessment in Great Britain. Environ. Sci. Technol. 47 (14), 7804–7811. https://doi.org/10.1021/es4008849.

Guxens, M., Lubczyńska, M.J., Muetzel, R.L., Dalmau-Bueno, A., Jaddoe, V.W.V., Hoek, G., van der Lugt, A., Verhulst, F.C., White, T., Brunekreef, B., Tiemeier, H., El Marroun, H., 2018. Air pollution exposure during fetal life, brain morphology, and cognitive function in school-age children. Biol. Psychiatry 84 (4), 295–303. https://doi.org/10.1016/j.biopsych.2018.01.016.

Hampson, M., Peterson, B.S., Skudlarski, P., Gatenby, J.C., Gore, J.C., 2002. Detection of functional connectivity using temporal correlations in MR images. Hum. Brain Mapp. 15 (4), 247–262. https://doi.org/10.1002/hbm.10022.

Hausman, H.K., O'Shea, A., Kraft, J.N., Boutzoukas, E.M., Evangelista, N.D., Van Etten, E.J., Bharadwaj, P.K., Smith, S.G., Porges, E., Hishaw, G.A., Wu, S., DeKosky, S., Alexander, G.E., Marsiske, M., Cohen, R., Woods, A.J., 2020. The role of resting-state network functional connectivity in cognitive aging. Front. Aging Neurosci. 12, 177. https://doi.org/10.3389/fnagi.2020.00177.

Hermans, E.J., van Marle, H.J.F., Ossewaarde, L., Henckens, M.J.A.G., Qin, S., van Kesteren, M.T.R., Schoots, V.C., Cousijn, H., Rijpkema, M., Oostenveld, R., Fernandez, G., 2011. Stress-related noradrenergic activity prompts large-scale neural network reconfiguration. Science 334 (6059), 1151–1153. https://doi.org/10.1126/science.1209603.

Hernan, M.A., 2002. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. Am. J. Epidemiol. 155 (2), 176–184. https://doi.org/10.1093/aje/155.2.176.

Jafari, Z., Mehla, J., Kolb, B.E., Mohajerani, M.H., 2017. Prenatal noise stress impairs HPA axis and cognitive performance in mice. Sci. Rep. 7 (1), 10560. https://doi.org/10.1038/s41598-017-09799-6.

Kooijman, M.N., Kruithof, C.J., van Duijn, C.M., Duijts, L., Franco, O.H., van IJzendoorn, M.H., de Jongste, J.C., Klaver, C.C.W., van der Lugt, A., Mackenbach, J. P., Moll, H.A., Peeters, R.P., Raat, H., Rings, E.H.H.M., Rivadeneira, F., van der Schroeff, M.P., Steegers, E.A.P., Tiemeier, H., Uitterlinden, A.G., Verhulst, F.C., Wolvius, E., Felix, J.F., Jaddoe, V.W.V., 2016. The generation R study: design and cohort update 2017. Eur. J. Epidemiol. 31 (12), 1243–1264. https://doi.org/10.1007/s10654-016-0224-9.

Lautarescu, A., Craig, M.C., Glover, V., 2020. Prenatal stress: effects on fetal and child brain development. In: International Review of Neurobiology, vol. 150. Elsevier, pp. 17–40. doi: 10.1016/bs.irn.2019.11.002.

Lin, W., Zhu, Q., Gao, W., Chen, Y., Toh, C.-H., Styner, M., Gerig, G., Smith, J.K., Biswal, B., Gilmore, J.H., 2008. Functional connectivity MR imaging reveals cortical functional connectivity in the developing brain. Am. J. Neuroradiol. 29 (10), 1883–1889. https://doi.org/10.3174/ajnr.A1256.

Lubczyńska, M.J., Muetzel, R.L., El Marroun, H., Basagaña, X., Strak, M., Denault, W., Jaddoe, V.W.V., Hillegers, M., Vernooij, M.W., Hoek, G., White, T., Brunekreef, B., Tiemeier, H., Guxens, M., 2020. Exposure to air pollution during pregnancy and childhood, and white matter microstructure in preadolescents. Environ. Health Perspect. 128 (2), 027005. https://doi.org/10.1289/EHP4709.

Lubczyńska, M.J., Muetzel, R.L., El Marroun, H., Hoek, G., Kooter, I.M., Thomson, E.M., Hillegers, M., Vernooij, M.W., White, T., Tiemeier, H., Guxens, M., 2021. Air pollution exposure during pregnancy and childhood and brain morphology in preadolescents. Environ. Res. 198, 110446. https://doi.org/10.1016/j.envres.2020.110446.

Mortamais, M., Pujol, J., van Drooge, B.L., Macià, D., Martínez-Vilavella, G., Reynes, C., Sabatier, R., Rivas, I., Grimalt, J., Forns, J., Alvarez-Pedrerol, M., Querol, X., Sunyer, J., 2017. Effect of exposure to polycyclic aromatic hydrocarbons on basal ganglia and attention-deficit hyperactivity disorder symptoms in primary school children. Environ. Int. 105, 12–19. https://doi.org/10.1016/j.envint.2017.04.011.

Mortamais, M., Pujol, J., Martínez-Vilavella, G., Fenoll, R., Reynes, C., Sabatier, R., Rivas, I., Forns, J., Vilor-Tejedor, N., Alemany, S., Cirach, M., Alvarez-Pedrerol, M., Nieuwenhuijsen, M., Sunyer, J., 2019. Effects of prenatal exposure to particulate matter air pollution on corpus callosum and behavioral problems in children. Environ. Res. 178, 108734. https://doi.org/10.1016/j.envres.2019.108734.

Pellegrino, G., Schuler, A.-L., Arcara, G., Di Pino, G., Piccione, F., Kobayashi, E., 2022. Resting state network connectivity is attenuated by fMRI acoustic noise. NeuroImage 247, 118791. https://doi.org/10.1016/j.neuroimage.2021.118791.

Peterson, B.S., Rauh, V.A., Bansal, R., Hao, X., Toth, Z., Nati, G., Walsh, K., Miller, R.L., Arias, F., Semanek, D., Perera, F., 2015. 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 72 (6), 531. https://doi.org/10.1001/jamapsychiatry.2015.57.

Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. NeuroImage 59 (3), 2142–2154. https://doi.org/10.1016/j.neuroimage.2011.10.018.

Pujol, J., Fenoll, R., Macià, D., Martínez-Vilavella, G., Alvarez-Pedrerol, M., Rivas, I., Forns, J., Deus, J., Blanco-Hinojo, L., Querol, X., Sunyer, J., 2016a. Airborne copper exposure in school environments associated with poorer motor performance and altered basal ganglia. Brain and Behavior 6 (6), e00467. https://doi.org/10.1002/brb3.467.

Pujol, J., Martínez-Vilavella, G., Macià, D., Fenoll, R., Alvarez-Pedrerol, M., Rivas, I., Forns, J., Blanco-Hinojo, L., Capellades, J., Querol, X., Deus, J., Sunyer, J., 2016b. Traffic pollution exposure is associated with altered brain connectivity in school children. NeuroImage 129, 175–184. https://doi.org/10.1016/j.neuroimage.2016.01.036.

Raven, 1962. Advanced Progressive Matrices: Sets I and II. H.K. Lewis, London.

Sass, V., Kravitz-Wirtz, N., Karceski, S.M., Hajat, A., Crowder, K., Takeuchi, D., 2017. The effects of air pollution on individual psychological distress. Health Place 48, 72–79. https://doi.org/10.1016/j.healthplace.2017.09.006.

Satterthwaite, T.D., Elliott, M.A., Gerraty, R.T., Ruparel, K., Loughead, J., Calkins, M.E., Eickhoff, S.B., Hakonarson, H., Gur, R.C., Gur, R.E., Wolf, D.H., 2013. An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. NeuroImage 64 (1), 240–256. https://doi.org/10.1016/j.neuroimage.2012.08.052.

Sentís, A., Sunyer, J., Dalmau-Bueno, A., Andiarena, A., Ballester, F., Cirach, M., Estarlich, M., Fernández-Somoano, A., Ibarluzea, J., Íñiguez, C., Lertxundi, A., Tardón, A., Nieuwenhuijsen, M., Vrijheid, M., Guxens, M., 2017. Prenatal and postnatal exposure to NO 2 and child attentional function at 4–5 years of age. Environ. Int. 106, 170–177. https://doi.org/10.1016/j.envint.2017.05.021.

Smith, K.E., Pollak, S.D., 2020. Early life stress and development: potential mechanisms for adverse outcomes. J. Neurodevelop. Disord. 12 (1), 34. https://doi.org/10.1186/s11689-020-09337-y.

Spratt, M., Carpenter, J., Sterne, J.A.C., Carlin, J.B., Heron, J., Henderson, J., Tilling, K., 2010. Strategies for multiple imputation in longitudinal studies. Am. J. Epidemiol. 172 (4), 478–487. https://doi.org/10.1093/aje/kwq137.

Stansfeld, S., Clark, C., 2015. Health effects of noise exposure in children. Curr. Environ. Health Rep. 2 (2), 171–178. https://doi.org/10.1007/s40572-015-0044-1.

Stansfeld, S.A., Matheson, M.P., 2003. Noise pollution: non-auditory effects on health. Br. Med. Bull. 68 (1), 243–257. https://doi.org/10.1093/bmb/ldg033.

Stiles, J., Jernigan, T.L., 2010. The basics of brain development. Neuropsychol. Rev. 20 (4), 327–348. https://doi.org/10.1007/s11065-010-9148-4.

Sunyer, J., Esnaola, M., Alvarez-Pedrerol, M., Forns, J., Rivas, I., López-Vicente, M., Suades-González, E., Foraster, M., Garcia-Esteban, R., Basagaña, X., Viana, M., Cirach, M., Moreno, T., Alastuey, A., Sebastian-Galles, N., Nieuwenhuijsen, M., Querol, X., Lanphear, B.P., 2015. Association between traffic-related air pollution in schools and cognitive development in primary school children: a prospective cohort study. PLoS Med. 12 (3), e1001792. https://doi.org/10.1371/journal.pmed.1001792.

Sunyer, J., Suades-González, E., García-Esteban, R., Rivas, I., Pujol, J., Alvarez-Pedrerol, M., Forns, J., Querol, X., Basagaña, X., 2017. Traffic-related air pollution and attention in primary school children: short-term association. Epidemiology 28 (2), 181–189. https://doi.org/10.1097/EDE.0000000000000603.

Thomas Yeo, B.T., Krienen, F.M., Sepulcre, J., Sabuncu, M.R., Lashkari, D., Hollinshead, M., Roffman, J.L., Smoller, J.W., Zöllei, L., Polimeni, J.R., Fischl, B., Liu, H., Buckner, R.L., 2011. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J. Neurophysiol. 106 (3), 1125–1165. https://doi.org/10.1152/jn.00338.2011.

Thomson, E.M., 2019. Air pollution, stress, and allostatic load: linking systemic and central nervous system impacts. J. Alzheimer's Dis. 69 (3), 597–614. https://doi.org/10.3233/JAD-190015

Tzourio-Mazoyer, N., 2016. Intra- and Inter-hemispheric Connectivity Supporting Hemispheric Specialization. In: Kennedy, H., Van Essen, D.C., Christen, Y. (Eds.), Micro-, Meso- and Macro-Connectomics of the Brain. Springer International Publishing, pp. 129–146. doi: 10.1007/978-3-319-27777-6_9.

U.S. EPA, 2019. Integrated Science Assessment (ISA) for Particulate Matter (Final Report, Dec 2019).

van de Ven, V.G., Formisano, E., Prvulovic, D., Roeder, C.H., Linden, D.E.J., 2004. Functional connectivity as revealed by spatial independent component analysis of fMRI measurements during rest. Hum. Brain Mapp. 22 (3), 165–178. https://doi.org/10.1002/hbm.20022.

van Marle, H.J.F., Hermans, E.J., Qin, S., Fernández, G., 2010. Enhanced resting-state connectivity of amygdala in the immediate aftermath of acute psychological stress. NeuroImage 53 (1), 348–354. https://doi.org/10.1016/j.neuroimage.2010.05.070.

Volk, H.E., Perera, F., Braun, J.M., Kingsley, S.L., Gray, K., Buckley, J., Clougherty, J.E., Croen, L.A., Eskenazi, B., Herting, M., Just, A.C., Kloog, I., Margolis, A., McClure, L. A., Miller, R., Levine, S., Wright, R., 2021. Prenatal air pollution exposure and neurodevelopment: a review and blueprint for a harmonized approach within ECHO. Environ. Res. 196, 110320. https://doi.org/10.1016/j.envres.2020.110320.

Wang, C., 2018. Urbanization and Global Health: The Role of Air Pollution. 47, 1644–1652.

Weuve, J., Tchetgen Tchetgen, E.J., Glymour, M.M., Beck, T.L., Aggarwal, N.T., Wilson, R.S., Evans, D.A., Mendes de Leon, C.F., 2012. Accounting for bias due to selective attrition: the example of smoking and cognitive decline. Epidemiology 23 (1), 119–128. https://doi.org/10.1097/EDE.0b013e318230e861.

White, T., Muetzel, R.L., El Marroun, H., Blanken, L.M.E., Jansen, P., Bolhuis, K., Kocevska, D., Mous, S.E., Mulder, R., Jaddoe, V.W.V., van der Lugt, A., Verhulst, F. C., Tiemeier, H., 2018. Paediatric population neuroimaging and the Generation R Study: the second wave. Eur. J. Epidemiol. 33 (1), 99–125. https://doi.org/10.1007/s10654-017-0319-y.

Whitfield-Gabrieli, S., Ford, J.M., 2012. Default mode network activity and connectivity in psychopathology. Ann. Rev. Clin. Psychol. 8 (1), 49–76. https://doi.org/10.1146/annurev-clinpsy-032511-143049.

Williamson, J.M., Lyons, D.A., 2018. Myelin dynamics throughout life: an ever-changing landscape? Front. Cell. Neurosci. 12, 424. https://doi.org/10.3389/fncel.2018.00424.

World Health Organization, 2018. Environmental noise guidelines for the European Region. Available from: <http://www.euro.who.int/en/publications/abstracts/environmental-noise-guidelines-for-the-european-region-2018>.

Supplementary Material

METHODS S1. Details of the back- and forward-extrapolation method in air pollution exposure assessment.

To back- and forward- extrapolate the concentrations during each period of interest, we used daily data from seven available routine background monitoring network sites. The procedure for back- and forward- extrapolate was performed in the following steps:

1. Collect daily air pollution data for routing monitoring sites covering both the period of interest of our study and the period that ESCAPE measurements were conducted.

2. Calculate the yearly concentration for the routine monitoring sites covering the measurement period of the ESCAPE ($C_{routine-ESCAPE}$).

3. Calculate for the routine monitoring sites for each day the ratio between the daily concentration (C_{daily}) and the yearly average covering the ESCAPE measurement period:
   $Ratio_{routine}$: $C_{daily}/ C_{routine-ESCAPE}$.

4. Calculate for each day the back- or forward-extrapolated concentration by multiplying the ratio with the modelled ESCAPE yearly mean concentration (LUR models) for each subject (C_{ESCAPE}): $C_{extrapolated} = C_{ESCAPE} * Ratio_{routine}$.

5. For each subject the back- and forward- extrapolated concentration for each study period was calculated using the daily back-extrapolated concentrations.

TABLE S1. Population characteristics of the subjects with high quality scans included in the analyses and with poor quality scans not included in the analyses of the study.

Participant characteristics	Distribution		p-value[1]
	High quality scans (n=2,197)	Poor quality scans (n=478)	
Maternal education level			0.511
Low	5.9	7.0	
Medium	39.7	41.1	
High	54.4	51.9	
Paternal education level			0.856
Low	5.2	4.4	
Medium	37.2	38.0	
High	57.6	57.6	
Monthly household income during pregnancy (€)			0.152
< 900	6.7	7.0	
900 – 1600	13.1	17.1	
1600 – 2200	14.4	11.5	
> 2200	65.8	64.4	
Maternal Country of birth			0.089
Dutch	59.1	60.6	
Other Western	9.1	6.0	
Non-western	31.8	33.4	
Paternal Country of birth			0.513
Dutch	69.8	69.7	
Other Western	6.2	4.6	
Non-western	24.0	25.7	
Family status			0.352
Married	52.3	53.0	
Living together	37.5	34.8	
No partner	10.2	12.2	
Maternal parity (nulli vs. multiparous)	56.4	60.0	0.363
Maternal smoking use during pregnancy			0.297
Never	78.8	77.8	
Smoking use until pregnancy known	9.2	7.8	
Continued smoking use during pregnancy	12.0	14.4	
Maternal alcohol consumption during pregnancy			0.693
Never	41.0	42.9	
Alcohol consumption until pregnancy known	14.5	45.0	
Continued alcohol consumption during pregnancy	44.5	42.1	

Abbreviations: p25, 25th percentile; p75, 75th percentile. Values are percentages for categorical, mean (standard deviation) for continuous variables, and median (p25; p75) for body mass index and psychopathological distress. [1] Chi-square tests for categorical variables, two-sample t-test for normally distributed and Wilcoxon Rank Sum test for non-normally distributed continuous variables.
[2] Score range from 0 to 4.

TABLE S1, continued. Population characteristics of the subjects with high quality scans included in the analyses and with poor quality scans not included in the analyses of the study.

Participant characteristics	Distribution		
	High quality scans (n=2,197)	Poor quality scans (n=478)	p-value[1]
Maternal age at intake (years)	31.2 (4.8)	31.2 (4.9)	0.769
Paternal age at intake (years)	33.6 (5.4)	33.2 (4.9)	0.211
Maternal height (cm)	168.2 (7.4)	167.9 (7.2)	0.377
Paternal height (cm)	182.8 (7.6)	182.4 (8.0)	0.478
Pre-pregnancy maternal body mass index (kg/m^2)	23.4 (20.8; 25.1)	23.4 (20.5; 24.8)	0.483
Pre-pregnancy paternal body mass index (kg/m^2)	25.2 (22.9; 27.2)	25.3 (23.0; 27.5)	0.672
Maternal psychological distress during pregnancy[2]	0.2 (0.1; 0.3)	0.3 (0.1; 0.3)	0.411
Paternal psychological distress during pregnancy[2]	0.1 (0.0; 0.2)	0.1 (0.0; 0.2)	0.340
Maternal intelligence quotient score	98.4 (90.0; 107.0)	96.8 (90.0; 107.0)	0.031
Child's sex (boy vs. girl)	51.0	45.8	0.041
Child's age at scanning session (years)	10.2 (0.6)	10.1 (0.6)	0.002

Abbreviations: p25, 25th percentile; p75, 75th percentile. Values are percentages for categorical, mean (standard deviation) for continuous variables, and median (p25; p75) for body mass index and psychopathological distress. [1] Chi-square tests for categorical variables, two-sample t-test for normally distributed and Wilcoxon Rank Sum test for non-normally distributed continuous variables.
[2] Score range from 0 to 4.

TABLE S2. List of the brain areas obtained after Human Connectome Project multimodal parcellation grouped into brain regions and into functional brain networks.

Visual network

Primary Visual Cortex

> *Primary Visual Cortex*

Early Visual Cortex

> *Second Visual Area*
>
> *Third Visual Area*
>
> *Fourth Visual Area*

Dorsal Stream Visual Cortex

> *Sixth Visual Area*
>
> *Area V3A*
>
> *Seventh Visual Area*
>
> *IntraParietal Sulcus Area 1*
>
> *Area V3B*
>
> *Area V6A*

Ventral Stream Visual Cortex

> *Eight Visual Area*
>
> *Fusiform Face Complex*
>
> *Posterior InferoTemporal Complex*
>
> *VentroMedial Visual Area 1*
>
> *VentroMedial Visual Area 2*
>
> *VentroMedial Visual Area 3*
>
> *Ventral Visual Cortex*

MT + Complex and Neighboring Visual Areas

> *Medial Superior Temporal Area*
>
> *Area Lateral Occipital 1*
>
> *Area Lateral Occipital 2*
>
> *Area Lateral Occipital 3*
>
> *Middle Temporal Area*
>
> *Area PH*
>
> *Area V4t*
>
> *Area FST*
>
> *Area V3CD*

TABLE S2, continued. List of the brain areas obtained after Human Connectome Project multimodal parcellation grouped into brain regions and into functional brain networks.

Somatosensory/Motor network

Primary Motor Cortex

Primary Sensory Cortex

Area 1

Area 2

Area 3a

Paracentral Lobular and Mid Cingulate Cortex

Area 5m

Area 5m ventral

Area 23c

Area 5L

Dorsal Area 24d

Ventral Area 24d

Supplementary and Cingulate Eye Field

Area 6m anterior

Area 6mp

Premotor Cortex

Frontal Eye Fields

Premotor Eye Field

Area 55b

Dorsal area 6

Ventral area 6

Rostral Area 6

Area 6 anterior

Posterior Opercular Cortex

Area 43

Area OP4/PV

Area OP1/SII

Area OP2-3/VS

Frontal Opercular Area 1

TABLE S2, continued. List of the brain areas obtained after Human Connectome Project multimodal parcellation grouped into brain regions and into functional brain networks.

Auditory network

Early Auditory Cortex

      Primary Auditory Cortex

      Area 52

      RetronInsular Cortex

      Area PFcm

      ParaBelt Complex

      Lateral Belt Complex

      Medial Belt Complex

      Area STSd anterior

      Area STSd posterior

      Area STSv anterior

      Area STSv posterior

Task positive network

Insular and Frontal Opercular Cortex

      Posterior Insular Area 2

      Middle Insular Area

      Pirform Cortex

      Anterior Ventral Insular Area

      Anterior Agranular Insula Complex

      Frontal Opercular Area 2

      Frontal Opercular Area 3

      Frontal Opercular Area 4

      Area Posterior Insular 1

      Insular Granular Complex

      Area Frontal Opercular 5

      Para-Insular Area

TABLE S2, continued. List of the brain areas obtained after Human Connectome Project multimodal parcellation grouped into brain regions and into functional brain networks.

Task positive network

Superior Parietal Cortex

       Medial Area 7P

       Lateral Area 7P

       Lateral Area 7A

       Medial Area 7A

       Area 7PC

       Area Lateral IntraParietal ventral

       Ventral IntraParietal Complex

       Medial IntraParietal Area

       Area Lateral IntraParietal dorsal

       Anterior IntraParietal Area

Inferior Parietal Cortex

       Area PFt

       Area PGp

       Area Intraparietal 0

       Area Intraparietal 1

       Area Intraparietal 2

       Area PF opercular

       Area PF Complex

       Area PFm Complex

       Area PGi

       Area PGs

Inferior Frontal Cortex

       Area 44

       Area 45

       Area 47l

       Area anterior 47r

       Area posterior 47r

       Area IFJa

       Area IFJp

       Area IFSp

       Area IFSa

TABLE S2, continued. List of the brain areas obtained after Human Connectome Project multimodal parcellation grouped into brain regions and into functional brain networks.

Task positive network

Dorsolateral Prefrontal Cortex

Superior Frontal Language Area

Area 8Av

Area 8Ad

Area 8B Lateral

Area 9 Posterior

Area 8C

Area posterior 9-46v

Area anterior 9-46v

Area 46

Area 9-46d

Area 9 anterior

Interior 6-8 Transitional Area

Superior 6-8 Transitional Area

Task negative network

Medial Temporal Cortex

Entorhinal Cortex

PreSubiculum

Perirhinal Ectorhinal Cortex

ParaHippocampal Area 1

ParaHippocampal Area 2

ParaHippocampal Area 3

Area TF

Lateral Temporal Cortex

Area TG dorsal

Area TE1 anterior

Area TE1 posterior

Area TE1 Middle

Area TE2 anterior

Area TE2 posterior

Area PHT

Area TG Ventral

TABLE S2, continued. List of the brain areas obtained after Human Connectome Project multimodal parcellation grouped into brain regions and into functional brain networks.

Task negative network

Temporo-Parieto-Occipital Junction

      PeriSylvian Language Area

      Superior Temporal Visual Area

      Area TemporoParietoOccipital Junction 1

      Area TemporoParietoOccipital Junction 2

      Area TemporoParietoOccipital Junction 3

Posterior Cingulate Cortex

      RetroSplenial Complex

      Parieto-Occipital Sulcus Area 2

      PreCuneus Visual Area

      Area 7m

      Parieto-Occipital Sulcus Area 1

      Area 23d

      Area ventral 23 a+b

      Area dorsal 23 a+b

      Area 31p ventral

      ProStriate Area

      Dorsal Transitional Visual Area

      Area 31pd

      Area 31a

      Area anterior 32 prime

      Area posterior 24

Orbital and Polar Frontal Cortex

      Area 47m

      Area 10d

      Area anterior 10p

      Polar 10p

      Area 11l

      Area 13l

      Orbital Frontal Complex

      Area 47s

      Area posterior 10p

TABLE S2, continued. List of the brain areas obtained after Human Connectome Project multimodal parcellation grouped into brain regions and into functional brain networks.

Subcortical structures and cerebellum
Cerebellum
Thalamus
Caudate
Putamen
Pallidum
Amygdala
Accumbens
Ventral Dienchepalon
Hippocampus

Functional brain networks are written in bold format; Brain regions are written in regular format; Brain areas are written in italic format.
Brain areas described above were explored for both hemispheres.

TABLE S3. Details of the imputation modelling.

Software used and key setting: Stata Statistical Software: Release 14.2 (Stata Corporation, College Station, Texas) – Ice command (with 10 cycles)
Number of imputed datasets created: 25
Variables included in the imputation procedure: Traffic-related air pollution during pregnancy ($PM_{2.5}$, $PM_{2.5}$ absorbance, PM_{10}, PMcoarse, NO_x, NO_2), noise exposure during pregnancy, maternal age, paternal age, maternal education level, paternal education level, maternal country of birth, paternal country of birth, maternal smoking during pregnancy, maternal alcohol consumption during pregnancy, maternal parity, family status, monthly household income, maternal pathological distress, paternal pathological distress, maternal weight, paternal weight, maternal height, paternal height, maternal pre-pregnancy body mass index, paternal pre-pregnancy body mass index, maternal IQ, child's sex, child's age at the scanning session.
Treatment of binary/categorical variables: logistic and multinomial models
Statistical interactions included in imputation models: none

TABLE S4. Population characteristics in observed and imputed datasets of the population study.

Participant characteristics	Distribution		% Imputed
	Observed (N=2,197)	Imputed (N=54,925)	
Maternal education level			7.5
Low	5.9	6.7	
Medium	39.7	40.5	
High	54.4	52.8	
Paternal education level			34.7
Low	5.2	7.4	
Medium	37.2	40.2	
High	57.6	52.4	
Monthly household income during pregnancy (€)			21.0
< 900	6.7	8.2	
900 – 1600	13.1	14.5	
1600 – 2200	14.4	14.7	
> 2200	65.8	62.6	
Maternal Country of birth			1.7
Dutch	59.1	58.7	
Other Western	9.1	9.2	
Non-western	31.8	32.3	
Paternal Country of birth			28.4
Dutch	69.8	61.6	
Other Western	6.2	6.3	
Non-western	24.0	32.1	
Family status			7.7
Married	52.3	52.3	
Living together	37.5	37.5	
No partner	10.2	10.2	
Maternal parity (nulli vs. multiparous)	56.4	56.1	3.2

Abbreviations: p25; 25th percentile; p75, 75th percentile. Values are percentages for categorical, mean (standard deviation) for continuous variables, and median (p25; p75) for body mass index and psychopathological distress.[1] Score range from 0 to 4.

TABLE S4, continued. Population characteristics in observed and imputed datasets of the population study.

Participant characteristics	Distribution		% Imputed
	Observed (N=2,197)	Imputed (N=54,925)	
Maternal smoking use during pregnancy			
Never	78.8	78.7	12.2
Smoking use until pregnancy known	9.2	9.1	
Continued smoking use during pregnancy	12.0	12.2	
Maternal alcohol consumption during pregnancy			
Never	41.0	41.4	19.4
Alcohol consumption until pregnancy known	14.5	14.2	
Continued alcohol consumption during pregnancy	44.5	44.4	
Maternal age at intake (years)	31.2 (4.8)	31.3 (4.8)	0.0
Paternal age at intake (years)	33.6 (5.4)	33.8 (5.7)	11.5
Maternal height (cm)	168.2 (7.4)	168.2 (7.4)	10.0
Paternal height (cm)	182.8 (7.6)	182.6 (8.6)	27.6
Pre-pregnancy maternal body mass index (kg/m^2)	23.4 (20.8; 25.1)	23.4 (20.6; 24.9)	24.5
Pre-pregnancy paternal body mass index (kg/m^2)	25.2 (22.9; 27.2)	25.1 (22.8; 27.0)	27.7
Maternal psychological distress during pregnancy[1]	0.2 (0.1; 0.3)	0.3 (0.1; 0.3)	23.3
Paternal psychological distress during pregnancy[1]	0.1 (0.0; 0.2)	0.1 (0.0; 0.2)	37.4
Maternal intelligence quotient score	98.4 (90.0; 107.0)	98.0 (90.0; 107.0)	8.9
Child's sex (boy vs. girl)	51.0	51.0	0.0
Child's age at scanning session (years)	10.2 (0.6)	10.2 (0.6)	0.0

Abbreviations: p25; 25th percentile; p75, 75th percentile. Values are percentages for categorical, mean (standard deviation) for continuous variables, and median (p25; p75) for body mass index and psychopathological distress. [1] Score range from 0 to 4.

TABLE S5. Variables used in logistic regression model to calculate inverse probability of attrition weights in the study.

Variables	Explored	Included
Maternal education level	x	x
Paternal education level	x	
Monthly household income during pregnancy	x	x
Maternal Country of birth	x	
Paternal Country of birth	x	x
Family status	x	
Maternal parity	x	x
Maternal smoking use during pregnancy	x	x
Maternal alcohol consumption during pregnancy	x	x
Maternal age at intake	x	x
Paternal age at intake	x	
Maternal height	x	
Paternal height	x	
Maternal weight	x	
Paternal weight	x	
Pre-pregnancy maternal body mass index	x	
Pre-pregnancy paternal body mass index	x	
Maternal psychological distress during pregnancy	x	x
Paternal psychological distress during pregnancy	x	
Maternal intelligence quotient score	x	x
Child's sex	x	x
Child's age at scanning session	x	

METHODS S2. Formulas of the regression models used to analyse the associations between traffic-related air pollution and noise and functional brain connectivity in preadolescents.

The dependent variable in the present study is a correlation matrix with pair-wise correlation coefficients amongst 380 brain areas, where Y_{nm} is each pair-wise correlation coefficient between 2 different brain areas:

$$\mathbf{Y} = \begin{bmatrix} Y_{11} & Y_{12} & \cdots & Y_{1m} \\ Y_{21} & Y_{22} & \cdots & Y_{2m} \\ \vdots & \vdots & \ddots & \vdots \\ Y_{n1} & Y_{n2} & \cdots & Y_{nm} \end{bmatrix}$$

We performed a linear regression model for each correlation coefficient of the matrix (Y_{nm}):

$$Y_{nm} = [\beta_0 + \beta_1 X_{nm} + \beta_2 X_{nm} + \ldots + \beta_p X_{nm}] + \varepsilon_{nm}$$

where β_0 is the intercept, β_p the slope coefficients for each independent variable, X_{nm} the independent variables (exposure and covariates), and ε_{nm} the model's error term.

For example, for NO_2 exposure during pregnancy, and the correlation coefficient Y11, we set up this model:

$Y_{11} = \beta 0 + \beta_1 NO_{211} + \beta_2 Maternal\_education_{11} +$

$\beta_3 Paternal\_education_{11} + \beta_4 Maternal\_Ethnicity_{11} +$

$\beta_5 Paternal\_Ethnicity_{11} + \beta_6 Maternal\_age_{11} + \beta_7 Paternal\_age_{11} +$

$\beta_8 Maternal\_bodymassindex_{11} + \beta_9 Paternal\_bodymassindex_{11} +$

$\beta_{10} Maternal\_psychologicaldistress_{11} +$

$\beta_{11} Paternal\_psychologicaldistress_{11} + \beta_{12} Maternal\_smoking_{11} +$

$\beta_{13} Maternal\_alcohol_{11} + \beta_{14} Maternal\_parity_{11} +$

$\beta_{15} Maternal\_intelligencequotient_{11} + \beta_{16} Familystatus_{11} +$

$\beta_{17} Householdincome_{11} + \beta_{18} Child\_age_{11} + \beta_{19} Child\_sex_{11} +$

$\beta_{20} MeanFramewiseDisplacement_{11} + \varepsilon_{11}$

We set up these models successively for all the correlation pair-wise coefficients of the correlation matrix.

Linear regression models were performed separately for each air pollutant and study period. Road traffic noise was also assessed separately from traffic-related air pollutants in a single model for each study period.

TABLE S6: Air pollution and road traffic noise exposure levels during pregnancy and childhood periods from: birth to 3 years, from 3 to 6 years, and from 6 years of age to the age at MRI assessment.

Pollutant	Pregnancy				Childhood 0-3 years				Childhood 3-6 years				Childhood 6 years- MRI assessment			
	Mean	p25	p50	p75	Mean	p25	p50	p75	Mean	p25	p50	p75	Mean	p25	p50	p75
NO_X	63.5	49.4	59.0	73.5	54.9	44.3	50.5	61.4	49.5	39.5	45.3	56.4	43.8	34.9	40.0	49.5
NO_2	39.7	35.0	38.9	43.5	35.3	32.1	35.0	37.8	32.8	29.3	32.9	35.8	29.4	26.1	29.3	32.2
PM_{10}	31.2	28.2	30.5	34.0	28.1	26.8	27.8	29.1	25.7	24.7	25.5	26.6	23.7	22.6	23.5	24.6
$PM_{2.5}$	19.5	17.8	18.9	21.2	17.7	17.1	17.5	18.1	16.3	15.9	16.2	16.6	15.1	14.6	15.1	15.5
$PM_{2.5}$absorbance	1.7	1.5	1.7	1.9	1.6	1.5	1.6	1.7	1.6	1.4	1.5	1.7	1.4	1.2	1.3	1.5
Road traffic noise	54.7	48.0	54.0	60.0	54.2	48.0	54.0	60.0	53.4	47.8	52.0	58.1	53.1	47.0	52.0	58.0

Abbreviations: NO_2, nitrogen dioxide in $\mu g/m^3$; NO_X, nitrogen oxides in $\mu g/m^3$; PM, particulate matter with different aerodynamic diameters: <10µm (PM_{10}) in $\mu g/m^3$; <2.5µm ($PM_{2.5}$) in $\mu g/m^3$; absorbance of $PM_{2.5}$ filters ($PM_{2.5}$absorbance) in $10^{-5}m^{-1}$; p25, 25th percentile; p50, 50th percentile, p75, 75th percentile. Road traffic noise measured in decibels (dB).

TABLE S7. Pearson's correlations of the levels of the pollutants and road traffic noise between time periods (pregnancy, childhood from birth to 3 years, from 3 to 6 years, and from 6 years of age to the age at MRI assessment).

NO_2	Pregnancy	Birth – 3 years	3 - 6 years	6 years – MRI assessment
Pregnancy	1			
Birth – 3 years	0.69	1		
3 years- 6 years	0.26	0.60	1	
6 years- MRI assessment	0.26	0.48	0.90	1

NO_X	Pregnancy	Birth – 3 years	3 - 6 years	6 years – MRI assessment
Pregnancy	1			
Birth – 3 years	0.78	1		
3 years- 6 years	0.43	0.72	1	
6 years- MRI assessment	0.38	0.59	0.90	1

$PM_{2.5}$	Pregnancy	Birth – 3 years	3 - 6 years	6 years – MRI assessment
Pregnancy	1			
Birth – 3 years	0.58	1		
3 years- 6 years	0.15	0.47	1	
6 years- MRI assessment	0.60	0.61	0.38	1

PM_{10}	Pregnancy	Birth – 3 years	3 - 6 years	6 years – MRI assessment
Pregnancy	1			
Birth – 3 years	0.61	1		
3 years- 6 years	0.23	0.61	1	
6 years- MRI assessment	0.46	0.58	0.68	1

Abbreviations: MRI, magnetic resonance imaging; NO_2, nitrogen dioxide; NO_X, nitrogen oxides; PM, particulate matter with different aerodynamic diameters: <10μm (PM_{10}); <2.5μm ($PM_{2.5}$); absorbance of $PM_{2.5}$ filters ($PM_{2.5}$absorbance).

TABLE S7, continued. Pearson's correlations of the levels of the pollutants and road traffic noise between time periods (pregnancy, childhood from birth to 3 years, from 3 to 6 years, and from 6 years of age to the age at MRI assessment).
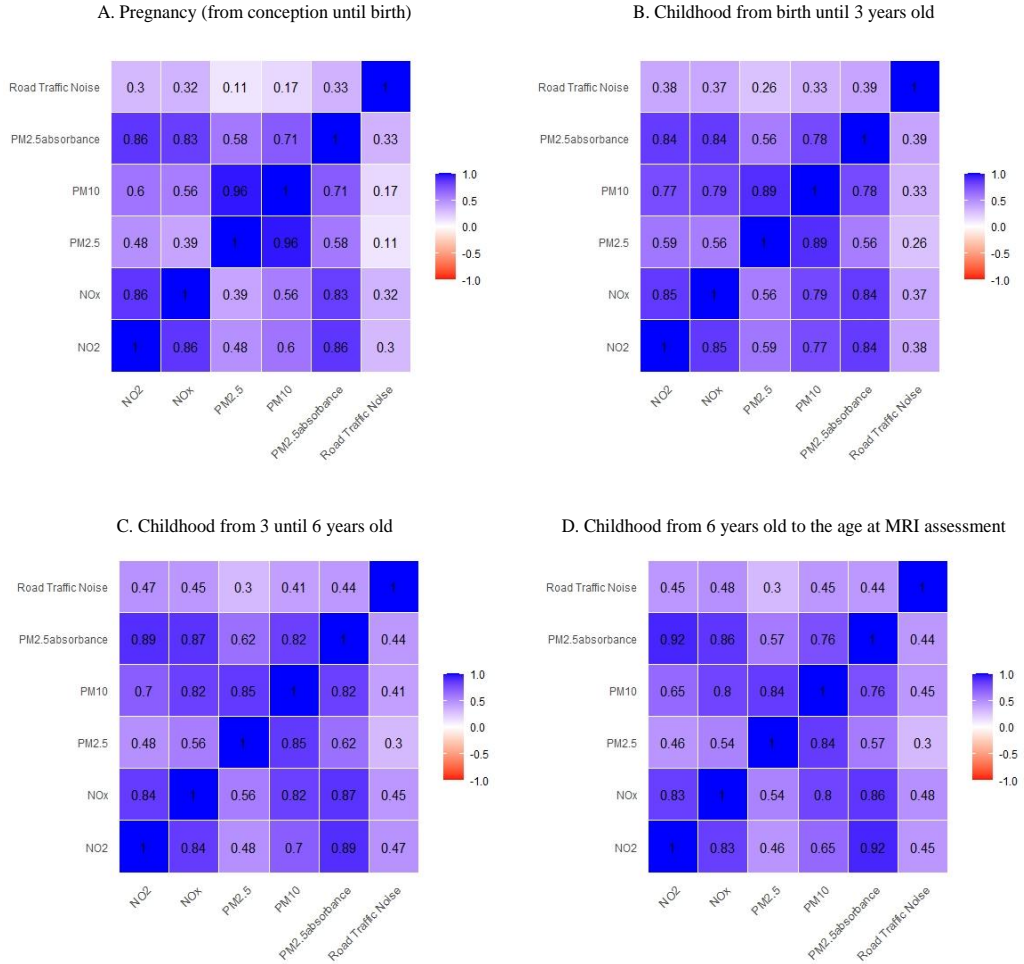
$PM_{2.5}$ absorbance	Pregnancy	Birth – 3 years	3 - 6 years	6 years – MRI assessment
Pregnancy	1			
Birth – 3 years	0.72	1		
3 years- 6 years	0.33	0.66	1	
6 years- MRI assessment	0.30	0.49	0.88	1

Road traffic noise	Pregnancy	Birth – 3 years	3 - 6 years	6 years – MRI assessment
Pregnancy	1			
Birth – 3 years	0.86	1		
3 years- 6 years	0.60	0.83	1	
6 years- MRI assessment	0.50	0.70	0.90	1

Abbreviations: MRI, magnetic resonance imaging; NO_2, nitrogen dioxide; NO_X, nitrogen oxides; PM, particulate matter with different aerodynamic diameters: <10μm (PM_{10}); <2.5μm ($PM_{2.5}$); absorbance of $PM_{2.5}$ filters ($PM_{2.5}$absorbance).

FIGURE S1. Pearson's correlations between the different traffic-related air pollutants and noise during pregnancy, childhood from birth to 3 years, from 3 to 6 years, and from 6 years of age to the age at MRI assessment.

A. Pregnancy (from conception until birth)

B. Childhood from birth until 3 years old

C. Childhood from 3 until 6 years old

D. Childhood from 6 years old to the age at MRI assessment

Abbreviations: NO_2, nitrogen dioxide; NO_X, nitrogen oxides; PM, particulate matter with different aerodynamic diameters: <10μm (PM_{10}); <2.5μm ($PM_{2.5}$); absorbance of $PM_{2.5}$ filters ($PM_{2.5}$absorbance).

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TABLE S8. Fully adjusted associations between exposure to air pollutants and road traffic noise during pregnancy, childhood from birth to 3 years old, from 3 to 6 years old, and from 6 years old to MRI assessment and brain functional connectivity in preadolescents that survived correction for multiple testing using false discovery rating.

Air pollutant – Brain connection	Childhood 0-3y exposure		Childhood 3-6y exposure		Adjusted R-squared	Correlation coefficient
	Coef	(95% CI)	Coef	(95% CI)		
NO₂ (Δ 10 µg/m³)						
Visual – Task positive						
Dorsal Stream Visual Cortex – Superior Parietal Cortex						
Left V3A area - Right ventral intraparietal complex area	0.11	(0.07; 0.15)	---	---	0.063	0.149
Auditory – Task positive						
Auditory association cortex - Insular and Frontal Opercular Cortex						
Left TA2 area – Left Insular granular complex area	0.11	(0.07; 0.15)	---	---	0.122	0.725
NOₓ (Δ 20 µg/m³)						
Visual – Task positive						
MT+ Complex and Neighboring Visual Areas - Inferior Frontal Cortex						
Right Lateral Occipital 3 Area - Right Area IFJp	---	---	0.07	(0.04; 0.10)	0.053	0.161
MT+ Complex and Neighboring Visual Areas - Insular and Frontal Opercular Cortex						
Right Lateral Occipital 3 Area - Right Area Frontal Opercular 5	---	---	0.07	(0.04; 0.10)	0.127	0.132
PM₂.₅absorbance (Δ 10⁻⁵m⁻¹)						
Visual – Visual						
Dorsal Stream Visual Cortex – MT+ Complex and Neighboring Visual Areas						
Left V3A area - Right Area Lateral Occipital 3	0.19	(0.12; 0.27)	---	---	0.064	0.597
Visual – Auditory						
Dorsal Stream Visual Cortex – Auditory Association Cortex						
Left Area V6 - Right Area STGa	0.17	(0.10; 0.25)	---	---	0.057	0.108
Right Area V6A - Right Area STGa	0.19	(0.11; 0.26)	---	---	0.132	0.048
MT+ Complex and Neighboring Visual Areas - Early Auditory Cortex						
Left Area Lateral Occipital 3 -Right RetroInsular Cortex	0.17	(0.10; 0.25)	---	---	0.129	0.157
Left Area Lateral Occipital 3 -Right Primary Auditory Cortex	0.18	(0.10; 0.25)	---	---	0.116	0.104

Associations from linear regression models adjusted for maternal and paternal education, ethnicity, age, body mass index, and psychological distress during pregnancy, maternal smoking and alcohol use during pregnancy, parity, and intelligence quotient, family status, household income, and child's gender and age at the scanning session, and mean framewise displacement. Linear regression models were performed separately for each air pollutant.

TABLE S8, continued. Fully adjusted associations between exposure to air pollutants and road traffic noise during pregnancy, childhood from birth to 3 years old, from 3 to 6 years old, and from 6 years old to MRI assessment and brain functional connectivity in preadolescents that survived correction for multiple testing using false discovery rating.

Air pollutant – Brain connection	Childhood 0-3y exposure		Childhood 3-6y exposure		Adjusted R-squared	Correlation coefficient
	Coef	(95% CI)	Coef	(95% CI)		
PM$_{2.5}$absorbance (Δ 10^{-5}m^{-1})						
Visual – Task positive						
Dorsal Stream Visual Cortex – Superior Parietal Cortex						
Left Area V3A – Right Ventral IntraParietal Complex	0.18	(0.11; 0.26)	---	---	0.061	0.150
MT + Complex and Neighboring Visual Areas - Superior Parietal Cortex						
Right Area Lateral Occipital 1 – Left Area Lateral IntraParietal dorsal	0.17	(0.10; 0.25)	---	---	0.091	-0.011
Visual – Task Negative						
MT + Complex and Neighboring Visual Areas - Temporo-Parieto-Occipital Junction						
Left Area Lateral Occipital 1 – Right TemporoParietoOccipital Junction 3 area	0.18	(0.10; 0.26)	---	---	0.067	0.163
Auditory – Task positive						
Auditory Association Cortex – Insular and Frontal Opercular Cortex						
Left Area TA2 - Left Insular granular complex area	0.17	(0.09; 0.25)	---	---	0.118	0.725
Auditory – Task Negative						
Auditory Association Cortex – Medial Temporal Cortex						
Right Area STGa - Right PreSubiculum -	0.17	(0.10; 0.24)	---	---	0.047	0.130
SomatoSensory/Motor – SomatoSensory/Motor						
Premotor Cortex - Premotor Cortex						
Right Premotor Eye Field - Right Ventral Area 6	0.17	(0.10; 0.24)	---	---	0.079	0.430
Task positive – Task positive						
DorsoLateral Prefrontal Cortex - Superior Parietal Cortex						
Right Area anterior 9-46v - Right Anterior Area IntraParietal	0.17	(0.09; 0.24)	---	---	0.137	0.148
DorsoLateral Prefrontal Cortex – Inferior Parietal Cortex						
Right Area anterior 9-46v - Right Area IntraParietal 2	0.17	(0.10; 0.25)	---	---	0.115	0.487

Associations from linear regression models adjusted for maternal and paternal education, ethnicity, age, body mass index, and psychological distress during pregnancy, maternal smoking and alcohol use during pregnancy, parity, and intelligence quotient, family status, household income, and child's gender and age at the scanning session, and mean framewise displacement. Linear regression models were performed separately for each air pollutant.
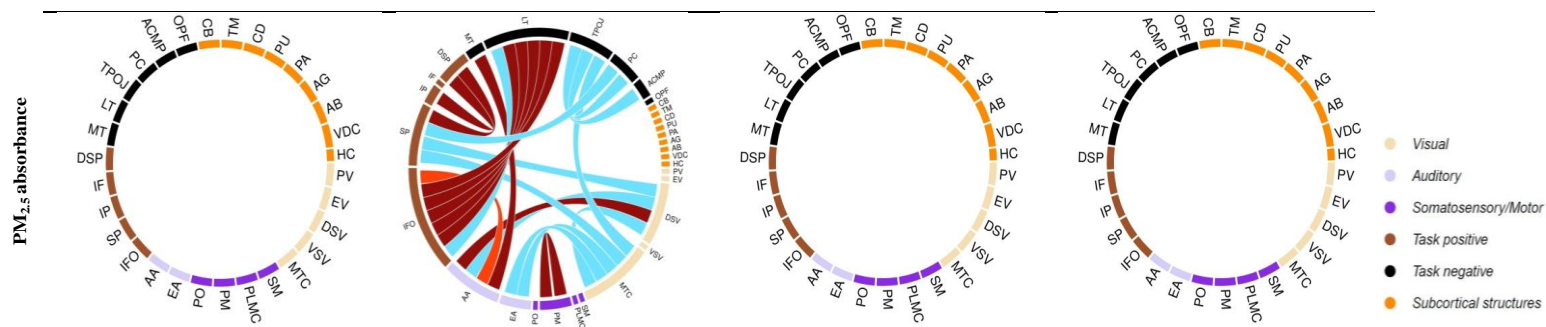
TABLE S8, continued. Fully adjusted associations between exposure to air pollutants and road traffic noise during pregnancy, childhood from birth to 3 years old, from 3 to 6 years old, and from 6 years old to MRI assessment and brain functional connectivity in preadolescents that survived correction for multiple testing using false discovery rating.

Air pollutant – Brain connection	Childhood 0-3y exposure		Childhood 3-6y exposure		Adjusted R-squared	Correlation coefficient
	Coef	(95% CI)	Coef	(95% CI)		
PM$_{2.5}$absorbance (Δ 10^{-5}m^{-1})						
Task positive – Task Negative						
Posterior Cingulate Cortex - Superior Parietal Cortex						
Left Parieto-Occipital Sulcus Area 2 - Right Area 7PC	0.16	(0.09; 0.23)	---	---	0.051	-0.124
Insular and Frontal Opercular Cortex - Lateral Temporal Cortex						
Left Middle Insular Area – Right Area PHT	0.17	(0.10; 0.25)	---	---	0.043	0.144
Right Area Frontal Opercular 5 - Right Area PHT	0.18	(0.10; 0.26)	---	---	0.043	0.156
Right Posterior Insular Area 2 - Right Area PHT	0.19	(0.11; 0.26)	---	---	0.043	0.202
Right Frontal Opercular Area 4 - Right Area PHT	0.19	(0.12; 0.27)	---	---	0.048	0.154
Right Middle Insular Area – Right Area PHT	0.17	(0.10; 0.26)	---	---	0.050	0.160
Right Frontal OPercular Area 4 - Right Area TE1 posterior	0.17	(0.10; 0.25)	---	---	0.072	-0.143
Task Negative – Task Negative						
Temporo-Parieto-Occipital Junction - Posterior Cingulate Cortex						
Left TemporoParietoOccipital Junction 1 area - Right Area 31pd	0.17	(0.09; 0.25)	---	---	0.135	0.073
Temporo-Parieto-Occipital Junction - Anterior Cingulate and Medial Prefrontal Cortex						
Right Superior Temporal Visual Area - Left Area 25	0.17	(0.09; 0.24)	---	---	0.117	0.020

Associations from linear regression models adjusted for maternal and paternal education, ethnicity, age, body mass index, and psychological distress during pregnancy, maternal smoking and alcohol use during pregnancy, parity, and intelligence quotient, family status, household income, and child's gender and age at the scanning session, and mean framewise displacement. Linear regression models were performed separately for each air pollutant.

FIGURE S2. Hemispheric differences of the brain connections associated with exposure to air pollutants during pregnancy, childhood from birth to 3 years, from 3 to 6 years, and from 6 years of age to the age at MRI assessment.

FIGURE S2, continued. Hemispheric differences of the brain connections associated with exposure to air pollutants during pregnancy, childhood from birth to 3 years, from 3 to 6 years, and from 6 years of age to the age at MRI assessment.

Brain areas were grouped into 31 brain regions (described below) and into 5 different brain functional networks: visual, auditory, somatosensory/motor, task positive, task negative (also known as Default Mode Network (DMN)), and a 6th group with the subcortical structures and the cerebellum:

AA, Auditory Association Cortex; AB, Nucleaus Accumbens; ACMP, Anterior Cingulate and Medial Prefrontal Cortex; AG, Amygdala; CB, Cerebellum; CD, Caudate; DSP, DorsoLateral Prefrontal Cortex; DSV, Dorsal Stream Visual Cortex; EA, Early Auditory Cortex; EV, Early Visual Cortex; HC, Hippocampus; IF, Inferior Frontal Cortex; IFO, Insular and Frontal Opercular Cortex; IP, Inferior Parietal Cortex; LT, Lateral Temporal Cortex; MT, Medial Temporal Cortex; MTC, MT+ Complex and Neighboring Visual Areas; NOx, nitrogen oxides; NO2, nitrogen dioxide; OPF, Orbital and Polar Frontal Cortex; PA, Pallidum; PC, Posterior Cingulate Cortex; PLMC, Paracentral Lobular and Mid Cingulate Cortex; PM, Premotor Cortex; PM2.5absorbance, absorbance of PM2.5 filters; PO, Posterior Opercular Cortex; PU, Putamen; PV, Primary Visual Cortex; SM, Somatosensory and Motor Cortex; SP, Superior Parietal Cortex; TPOJ, Temporo-Parieto-Occipital Junction; TM, Thalamus; VDC, Ventral Diencephalon; VSV, Ventral Stream Visual Cortex.

Associations from linear regression models adjusted for maternal and paternal education, ethnicity, age, body mass index, and psychological distress during pregnancy, maternal smoking and alcohol use during pregnancy, parity, and intelligence quotient, family status, household income, child's gender and age at the scanning session, and mean framewise displacement that survived correction for multiple testing using false discovery rating. The color of the connection represents if the connection was intra-hemispheric (light red indicates connections of the left hemisphere and dark red of the right hemisphere) or inter-hemispheric (in blue). Linear regression models were performed separately for each air pollutant.

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TABLE S9. Range of coefficient estimates and p-values of the fully adjusted associations between exposure to road traffic noise during pregnancy, childhood from birth to 3 years old, from 3 to 6 years old, and from 6 years old to MRI assessment and brain functional connectivity in preadolescents after correction for multiple testing using false discovery rating.

	Coefficient		P-value	
	Min.	**Max.**	**Min.**	**Max.**
Pregnancy	-0.04 ; 0.06		0.06 ; 0.99	
Childhood 0-3 years	-0.05 ; 0.06		0.18 ; 0.99	
Childhood 3-6 years	-0.04 ; 0.09		0.09 ; 0.99	
Childhood 6y- MRI	-0.05 ; 0.10		0.16 ; 0.99	

Abbreviations: Min., minimum; Max. maximum.

Study IV

Outdoor residential noise exposure and sleep in preadolescents from two European birth cohorts

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Abstract

Objective: To examine whether outdoor residential exposure to annual average road traffic and multiple (i.e., road traffic, railway, aircraft, industry) noise levels is related with preadolescents' sleep using maternal-reported and wrist-actigraphy data in two European birth cohorts.

Methods: This cross-sectional study used data of 1,245 preadolescents from the Dutch Generation R Study and 232 from the Spanish INMA-Sabadell cohort with a mean age of 12.3 years old. We used noise maps to assess average outdoor road traffic and multiple noise levels (day-evening-night noise indicator, L_{DEN}) at each child's residential address for the year before the sleep assessment. Sleep disturbances were reported by mothers through the Sleep Disturbance Scale for Children and objectively recorded using GeneActiv wrist-actigraphy during seven subsequent days. Linear and Poisson regression models adjusted for several potential confounding variables were performed.

Results: The mean (SD) exposure to road traffic noise was 53.2 dB (7.3) in the Generation R Study and 61.3 dB (5.9) in the INMA-Sabadell cohort. Exposure to road traffic was related with reduced total sleep time and longer wake after sleep onset (e.g. -3.62 minutes (95%CI -6.87; -0.37) and 6.88 minutes (95%CI 1.15; 12.61) per an increase of 10 dB in road traffic noise, respectively) collected by wrist-actigraphy. We observed no association between road traffic exposure and maternal-reported sleep disturbances. Results were similar for multiple noise exposure.

Conclusions: These findings indicate that sleep may be compromised for preadolescents living in areas highly exposed to outdoor residential noise. Future studies using longitudinal designs to further explore these associations during the different stages of sleep development across childhood and adolescence are warranted. Also, wrist-actigraphy measurements which provide more accurate information and may be complementary to the parental- and self-reported data should be considered.

1. Introduction

In recent decades, the increase in population growth rates has resulted in nearly half of the current world population living in urbanized environments (United Nations, 2016). In urban areas, exposure to environmental noise, especially road traffic noise, is an important and growing public health problem (Salter et al., 2015). It has been estimated that more than 100 million European citizens are exposed to an average daily noise level (day-evening-night noise indicator, L_{DEN}) from road traffic of at least 55 decibels (dB) (European Environment Agency, 2020). Other prevalent sources of environmental noise in Europe are railway, aircraft, and industry noise (European Environment Agency, 2020). The World Health Organization (WHO) established different noise recommendations based on the individual noise sources and the noise indicators. For example, WHO recommends reducing noise levels to 53 dB for L_{DEN} noise exposure and to 45 dB for night exposure (night-time noise indicator, L_{NIGHT}) for road traffic noise (World Health Organization, 2018).

Sleep is an essential biological process that serves several vital functions, including promotion of neuroplasticity and neural development (Meerlo et al., 2015). Since these neural processes occur from early life through adolescence, sleep may be particularly important during these life stages (Rice & Barone, 2000). Sleep disruption has been related with numerous short- and long-term health consequences (Medic et al., 2017). Short-term consequences include increased stress responsivity, somatic problems, cognitive, memory, and performance deficits as well as emotional and behavioral problems. Long-term consequences of sleep disruption include hypertension, dyslipidemia, cardiovascular diseases, weight related health issues, metabolic syndrome, and diabetes mellitus type 2. Several studies have linked environmental noise exposure to higher sleep disturbance as well as shorter sleep time and quality of sleep in adults (Basner & McGuire, 2018; Evandt et al., 2017; Janson et al., 2020). However, the relationship between environmental noise and its influence on children's sleep is less well-known (Kamp et al., 2015). Some previous studies reported that children aged 7-14 exposed to higher levels of outdoor nocturnal road traffic noise levels showed more self- and parental-reported sleep disturbances (Öhrström et al., 2006; Skrzypek et al., 2017; Tiesler et al., 2013; Weyde et al., 2017). However, there are existing studies that found no association in children of similar ages

exposed to outdoor daily average noise levels from road traffic (Lee et al., 2021) or in infants during their first year of life exposed to outdoor nocturnal transportation noise (i.e., road, railway, and aircraft) (Blume et al., 2022). To the best of our knowledge, only two prior studies using actigraphy to evaluate physiological sleep measures in children have found no associations with exposure to road traffic (Öhrström et al., 2006) or transportation noise (Blume et al., 2022).

Overall, research examining whether environmental noise from road traffic is related to sleep disturbances in children is inconclusive. Wrist-actigraphy, which can provide valuable and complementary information alongside parental- or self-reports, has been scarcely used. Also, previous literature has mostly ignored other noise sources such as railway, aircraft, or industry, which could play a different role in sleep patterns. It has been suggested that aircraft and railway noise exposure are more disturbing than road traffic noise, and may last longer than road traffic noise events, which may be too short to be perceived by the individuals and fail to wake them up (Basner et al., 2011). Additionally, the majority of the population is exposed to more than one noise source, and, while individual source limit values may not be exceeded, the overall noise exposure may be greater due to the cumulative effects of exposure to multiple noise sources. Thus, this study aims to investigate the association between road traffic and multiple noise exposure (i.e. road, railway, aircraft, and industry) and sleep, using maternal-reported and wrist-actigraphy data in preadolescents from two birth cohorts in Europe.

2. Methods

2.1 Population and Study Design

For this cross-sectional study, data from the Dutch Generation R Study (Kooijman et al., 2016) and the Spanish INfancia y Medio Ambiente (INMA) Project (Guxens et al., 2012) were used. The Generation R Study includes a multi-ethnic population birth cohort of 9,610 pregnancies (Kooijman et al., 2016). Mothers were included in the study if they had an expected date of delivery between April 2002 and January 2006 and lived in the study area of Rotterdam, the Netherlands. The INMA Project is a network of population-based birth cohorts established in several regions of Spain following a common protocol. In the present study, we included the INMA-Sabadell cohort because noise maps were available only in this cohort. The cohort includes 775 pregnant women and their children residing in the city of Sabadell (Catalonia, Spain) who visited the public health centre of Sabadell for a first trimester ultrasound examination between July 2004 and July 2006. Mothers were included in the study if they were 16 years or older, had a singleton pregnancy, and intended to deliver at the reference hospital. Exclusion criteria were participation in a reproduction programme or having communication problems. We included a total of 1,477 children from both cohorts, 1,245 from Generation R and 232 from INMA-Sabadell, with information on environmental noise exposure and sleep disturbances or physiological sleep measures at mean age of 12.3 years old (Supplementary Material Figure S1). Ethical approval was obtained before recruitment from the Medical Ethical Committee of Erasmus MC, University Medical Centre Rotterdam, in accordance with Dutch law for the Generation R Study and from the Clinical Research Ethical Committee of the Municipal Institute of Healthcare (CIEC-IMAS) for the INMA-Sabadell cohort. We obtained written informed consent from parents in both cohorts and from all the participants in the Generation R Study.

2.2 Noise exposure assessment

We used noise maps created in 2012 for the municipalities of Rotterdam, Maassluis, Rozenburg, Schiedam, and Vlaardingen in the Netherlands and of Sabadell in Spain to estimate the outdoor exposure to residential annual average levels of environmental

noise. These maps met the requirements of the European Environmental Noise Directive (European Environmental Noise Directive, 2002). For the Generation R Study, noise was modelled using the standardized Dutch calculation methods ('Standaard Rekenmethoden', SRM), including surfaces polygon, buildings, barriers, slope, crossings, roundabouts as well as the corresponding emission sources for each of the specific models. Briefly, in the SRM method, the noise level at the geocoded point is determined by the noise emission of the source and other factors that denote the attenuation from source to receiver due to geometric spreading, air absorption, ground impedance, noise barriers as well as wind directions and temperature gradients (Supplementary Methods S1). For the INMA-Sabadell cohort, noise was measured using a street categorization method taking into account the different types of street and land uses. Additionally, street geometry, presence of activities, type of traffic, and traffic flow were also considered to calculate the noise level. Both maps were developed to estimate the noise levels at a height of 4 meters at the most exposed façade of the residential addresses. Environmental noise exposure for both cohorts was calculated at each participant's geocoded address where they lived at during the year prior to the sleep assessment. If more than one address was available, the amount of days that the participant spent at each address was considered to derive the average noise levels for each participant of the year prior the sleep assessment. For the Generation R Study, we performed an intersection of the buildings noise data from the maps with the geocodes. In cases where the geocode was outside the noise building, but within 50 meters, it was assigned to the closest building. For the INMA-Sabadell cohort, we calculated the noise level of the street closest to the geocode at a distance of 50 meters. Using the residential noise levels, we calculated exposure to road traffic for both cohorts. In the Generation R Study, exposure to multiple noise in which railway, aircraft, and industry noise sources was additionally considered by adding up the four different noise sources in the sound pressure scale as indicated in the formulas detailed in Supplementary Material Methods S2. For both cohorts, noise maps have integer resolution for road traffic noise and for the other noise sources in the Generation R Study. However, noise maps for multiple noise have decimal resolution in the Generation R Study. Additionally, in both study areas, noise was subtracted from the maps in categories of 1 dB. For both road traffic and multiple noise, we calculated the day-evening-night EU noise indicator

(L_{DEN}) using the formulas described in Supplementary Material Methods S2. L_{DEN} represents the A-weighted average sound level over the entire 24-hour day with penalties for the evening (+5dB) and the night (+10dB), as suggested by the Environmental Noise Directive to account for the expected greater health effects of the evening and night-time periods. The indicators L_{DAY}, $L_{EVENING}$, and L_{NIGHT} were defined as the A-weighted mean sound levels obtained during the day (07:00 to 19:00 for Generation R and 07:00 to 21:00 for INMA-Sabadell), the evening (19:00 to 23:00 for Generation R and 21:00 to 23:00 for INMA-Sabadell), and the night (23:00 to 07:00 for both cohorts), respectively (European Environmental Noise Directive, 2002). We used the L_{DEN} indicator instead of L_{NIGHT} since children generally go to bed earlier in the evening, when road traffic noise levels are usually higher than during the night (Skinner & Grimwood, 2000). From now on, we will refer to road traffic L_{DEN} and multiple L_{DEN} as road traffic noise exposure and multiple noise exposure.

2.3 Sleep disturbances

Children's sleep disturbances were reported by mothers through the Sleep Disturbance Scale for Children (SDSC) in both cohorts (Bruni et al., 1996). SDSC is a 26-item scale validated questionnaire that provides a standardized measure of sleep disturbances in children and adolescents for the previous six months. The items were grouped into six components which evaluated the most common sleep disturbances during childhood and adolescence. In this study, we used the following SDSC components: i) problems with initiating and maintaining sleep, ii) excessive somnolence, and iii) arousal problems (i.e. partial awakening from deep to light sleep, or from sleep to a state of being awake in which the subjects are partially or totally unconscious). We treated the first two components (problems with initiating and maintaining sleep (range = 0 - 35) and excessive somnolence (range = 0 - 25)) as continuous variables in which a higher rating indicates more sleep disturbances. Arousal problems were categorized due to its skewed distribution in our study population (presence of arousal problems (yes) vs. no arousal problems (no)).

2.4 Physiological sleep measures

Sleep was objectively measured with a GeneActiv tri-axial wrist accelerometer placed on the non-dominant wrist during seven consecutive days in both cohorts (Cabré-Riera et al., 2021; Koopman-Verhoeff et al., 2019; Koopman-Verhoeff et al., 2019). The accelerometers recorded raw data of sleep/wake measurements, that were processed using the R-package GGIR (van Hees et al., 2015). Using this method, the following physiological sleep measures were obtained for each day: total sleep time (in hours), sleep efficiency (in %), sleep onset latency (in minutes), and wake after sleep onset (in minutes). Total sleep time refers to the total amount of time asleep during the night, extracting the time scored as awake in between. Sleep efficiency is defined as the ratio of total sleep time to the total time in bed. Sleep onset latency is the time a child needs to fall asleep, indicating the time from being fully awake to falling asleep. Wake after sleep onset is the amount of time a child spends awake, starting from the time they fall asleep until the time they fully awake and without trying to fall asleep again. Finally, we calculated the mean of each of the preceding physiological sleep measures over the seven days.

2.5 Potential confounding variables

Potential confounding variables were defined a priori using a direct acyclic graph (Hernán et al., 2002) based on updated knowledge of the scientific literature and data availability in each cohort (Supplementary Material Figure S2). In both cohorts, these variables were collected via questionnaires and instruments completed by the parents. We included information on preadolescent's sex (male or female) and age (in years), parental ages at enrollment (in years), country of birth (country of the cohort vs. others), education level (low: no education, unfinished primary or primary; medium: secondary; high: university degree or higher), social class based on occupation (low: semi-skilled/unskilled; medium: skilled manual and non-manual; high: managers/technicians) and family status (dual or single parent), maternal parity (nulliparous vs. multiparous)), smoking during pregnancy (yes or no), and alcohol use during pregnancy (yes or no) for both cohorts.

2.6 Statistical analyses

We applied a square root transformation to best approximate the normality of the residuals for the following variables: problems with initiating and maintaining sleep, excessive somnolence, and sleep onset latency. After ensuring that assumptions of the linear regressions models (i.e., normality residual, linearity between exposure and outcomes, homoscedasticity, no collinearity) were met, we applied linear regression models to assess the association of road traffic noise exposure with problems with initiating and maintaining sleep, excessive somnolence, total sleep time, sleep efficiency, sleep onset latency, and wake after sleep onset. We performed Poisson regression models with robust variance to avoid overdispersion to assess the relationship between road traffic noise exposure with problems of arousal. We calculated prevalence ratios (PR) rather than odds ratios (OR), because OR can overestimate PR, especially when the prevalence of the outcome is moderate or high (prevalence rates above 10%) in cross-sectional studies (Espelt et al., 2016). Associations were analyzed performing pooled analysis that combined data from both cohorts when we assessed the exposure to road traffic noise. We adjusted the statistical models for cohort and all potential confounding variables described in the previous section.

As sensitivity analyses, we assessed i) the association between road traffic noise exposure and each of the sleep outcomes restricted to children living in the basement, ground, or first floor to reduce the measurement error of noise exposure; ii) the associations between road traffic noise exposure and each of the sleep outcomes stratified by cohort; and iii) the association between multiple noise exposure with all the sleep outcomes in the Generation R Study.

To increase the validity of the results and limit attrition bias, we performed multiple imputation of missing values of potential confounding variables by using chained equations to generate 25 complete datasets for each subset of the analysis and separately for each cohort (Spratt et al., 2010) (Supplementary Material Table S1). The percentage of missing data was less than 30% for all the confounding variables, except for paternal social class in the Generation R Study which was approximately 33%. The imputed datasets showed similar distributions to the observed datasets (data not shown). Preadolescents from the Generation R Study (n=1,245) included in the analysis were more likely to have older parents, parents from the Netherlands, and with higher education and social

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class than children who were not included in the analysis (n=8,365). Preadolescents from the INMA-Sabadell cohort (n=232) included in the analysis had similar characteristics to those who were not included (n=543), with the exception of parental country of birth and paternal age (Supplementary Material Table S2). Inverse probability weighting was also used to correct for the losses to follow-up in both cohorts, i.e. to account for potential selection bias when including only participants with available data compared with the full cohort recruited at pregnancy (Weisskopf et al., 2015; Weuve et al., 2012). The variables used to generate the weights can be found in Supplementary Material Table S3.

We used Stata version 14 (StataCorporation, College Station, TX) to perform the statistical analyses.

3. Results

3.1 Descriptive analysis

In the INMA-Sabadell cohort, 32.2% of preadolescents reported arousal problems compared to 20.4% in the Generation R Study (Table 1). Total sleep time was an average of between 7.2-7.5 hours and sleep efficiency was around 85% in both cohorts. Sleep onset latency and wake after sleep onset were weakly and positively correlated with disorders of initiating and maintaining sleep (r=0.16 and 0.10, respectively) (Supplementary Material Table S4). Average road traffic noise exposure levels were 53.2 dB (standard deviation (SD) 7.3) in the Generation R Study and 61.3 dB (SD 5.9) in the INMA-Sabadell cohort. Multiple noise exposure levels were 54.4 dB (SD 6.7) in the Generation R Study (Table 2). Correlation between road traffic and multiple noise exposure was 0.94 in the Generation R Study (data not shown). Additional descriptive statistics of the noise exposure levels for both cohorts are shown in Table 2 and Supplementary Material Figure S3. Descriptive participant characteristics of the study population can be found in Table 1. The average age of preadolescents in the Generation R Study was 12.7 years, ranging from 10.3 to 15.6 years old. In the INMA-Sabadell cohort, the mean age was 11.1 years, ranging from 9.8 to 12.7 years old. Most parents in these cohorts were from the country of the cohort (Dutch or Spanish), had a high social class (e.g., 71.3% and 44.5% of the mothers in Generation R Study and INMA-Sabadell cohort, respectively), and most of the mothers did not smoke during pregnancy (87.1% and 85.6% in Generation R Study and INMA-Sabadell cohort, respectively). However, the education level of both parents differed between the cohorts, with most of the parents having a high education level in the Generation R Study (e.g., 61.9% of the mothers) and a medium education level in the INMA-Sabadell cohort (e.g., 40.6% of the mothers).

3.2 Association between road traffic and multiple noise exposure, sleep disturbances, and physiological sleep measures

Road traffic noise exposure was not associated with problems of initiating and maintaining sleep, excessive somnolence, and arousal problems (0.02 points (95% confidence interval (CI) -0.03; 0.08), -0.04 points (95% CI -0.10; 0.02), and prevalence ratio (PR) 1.03

(95% CI 0.89; 1.18) per 10 dB increase in road traffic noise, respectively) (Table 3).

When we assessed the physiological sleep measures, we found that greater road traffic noise exposure was associated with reduced total sleep time (-3.62 minutes (95% CI -6.87; -0.37) per 10 dB increase in road traffic noise) (Table 4). However, road traffic noise exposure was not associated with the rest of physiological sleep measures: sleep efficiency, sleep onset latency, and wake after sleep onset (-0.12% (95% CI -0.53; 0.28), 0.09 minutes (95% CI -0.09; 0.27), and 1.42 minutes (-1.60; 4.44) per 10 dB increase in road traffic noise, respectively).

3.3 Sensitivity analysis

Analyses restricted to preadolescents who were living in the basement, ground, or first floor did not show relevant differences with the main analysis of the analysis study population when sleep disturbances were explored (Table 3). However, we found that road traffic was more strongly associated with shorter total sleep time (-5.63 minutes (95% CI -10.98; -0.29) per 10 dB increase in road traffic noise). Additionally, road traffic noise exposure was associated with longer wake after sleep onset (6.88 minutes (95% CI 1.15; 12.61) per 10 dB increase in road traffic noise) when analysis were restricted to those preadolescents (Table 4 and Supplementary Table S6).

When these associations were stratified by cohorts, most associations remained (Supplementary Material Tables S5 and S6). However, we found that road traffic exposure for preadolescents who were living in the basement, ground, or first floor were associated with reduced sleep efficiency in the INMA-Sabadell cohort (e.g. -2.02% (95% CI -3.87; -0.18) per 10 dB increase in road traffic noise) and with longer wake after sleep onset in the Generation R Study (e.g. 9.15 minutes (95% CI 2.69; 15.60) per 10 dB increase in road traffic noise) (Supplementary Material Tables S5 and S6).

Effect estimates of the associations between multiple noise exposure and all the sleep outcomes in the Generation R Study were similar than those of the associations with road traffic noise exposure (Supplementary Table S5 and S6).

TABLE 1. Participant characteristics of the INMA-Sabadell cohort and Generation R Study.

Characteristics	INMA-Sabadell (n = 232)	Generation R (n = 1,245)
Sleep disturbances		
Disorders of initiating and maintaining sleep[1]	2.5 (2.4)	5.5 (3.3)
Disorders of excessive somnolence[2]	2.0 (2.2)	3.2 (2.4)
Disorders of arousal (yes vs. no)	32.2	20.4
Physiological sleep measures		
Total sleep time (hours)	7.2 (0.6)	7.5 (0.8)
Sleep efficiency (%)	85.0 (4.4)	84.6 (5.8)
Sleep onset latency (minutes)	7.7 (12.4)	41.5 (35.7)
Wake after sleep onset (minutes)	40.3 (22.4)	79.0 (42.5)
Preadolescents' characteristics		
Sex (male vs. female)	51.7	48.0
Age at sleep questionnaire assessment (years)	11.1 (0.6)	12.7 (1.5)
Maternal characteristics		
Age at enrolment (years)	31.8 (4.3)	32.2 (4.2)
Country of birth (country of cohort vs. others)	92.0	81.1
Education level during pregnancy		
Low	25.5	2.7
Medium	40.6	35.4
High	33.9	61.9
Social class during pregnancy		
Low	23.3	1.3
Medium	32.2	27.4
High	44.5	71.3
Parity (nulliparous vs. multiparous)	55.5	56.7
Smoking use during pregnancy (no vs. yes)	85.6	87.1
Alcohol consumption during pregnancy (no vs. yes)	76.6	44.8
Paternal characteristics		
Age at enrolment (years)	34.0 (5.3)	34.6 (5.1)
Country of birth (country of cohort vs. others)	91.2	83.5
Education level during pregnancy		
Low	34.8	3.6
Medium	43.2	35.6
High	22.0	60.8
Social class during pregnancy		
Low	20.1	5.7
Medium	18.0	17.1
High	61.9	77.2
Household characteristics		
Family status (dual vs. single parent)	98.5	94.4

Values are percentages for categorical variables and mean (standard deviation) for continuous variables. [1]Higher scores indicate more sleep disturbances. Score range: 0 – 35. [2]Higher scores indicate more sleep disturbances. Score range: 0 – 25.

TABLE 2. Descriptive statistics of the noise exposure levels in the INMA-Sabadell cohort and Generation R Study.

	Mean	SD	p25; p75	Min.	Max.
INMA-Sabadell (N = 232)					
Road traffic noise (L_{DEN})[1] (dB)	61.3	5.9	58.0; 65.0	46.0	76.0
Generation R (N = 1,245)					
Road traffic noise (L_{DEN})[1] (dB)	53.2	7.3	48.0; 58.0	40.0	72.0
Multiple noise (L_{DEN})[2] (dB)	54.4	6.7	49.5; 58.8	40.0	72.0

Abbreviations: dB, decibels; Min., minimum; Max., maximum; p25, 25th percentile; p75, 75th percentile; SD, standard deviation.
[1] Residential outdoor annual average noise levels for the 24h of the day from road traffic.
[2] Residential outdoor annual average noise levels for the 24h of the day in which road traffic, railway, aircraft, and industry sources are considered.

TABLE 3. Fully adjusted cross-sectional associations between a 10 dB increase in road traffic noise exposure and sleep disturbances score in preadolescents.

	N	Disorders of initiating and maintaining sleep[1] Coefficient (95% CI)	Disorders of excessive somnolence[1] Coefficient (95% CI)	Disorders of arousal (yes vs. no) PR (95% CI)
Road traffic noise (L$_{DEN}$)[2]				
Overall	1,432	0.02 (-0.03; 0.08)	-0.04 (-0.10; 0.02)	1.03 (0.89; 1.18)
Living in the basement, ground, or first floor	460	0.08 (-0.02; 0.18)	-0.01 (-0.12; 0.10)	0.96 (0.74; 1.24)

Coefficients and 95% confidence intervals (CI) were obtained by linear and prevalence ratio and 95% CI by Poisson with robust variance regression models. All models were adjusted for cohort, preadolescent sex and age at sleep questionnaire assessment, parental age, country of birth, education, social class, parity, smoking and alcohol during pregnancy, and family status.
Abbreviations: CI, confidence interval; dB, decibels; PR, prevalence ratio.
[1] Values were square root transformed.
[2] Residential outdoor annual average noise levels for the 24h of the day from road traffic.

TABLE 4. Fully adjusted cross-sectional associations between a 10 dB increase in road traffic exposure and physiological sleep measures in preadolescents.

	N	Total sleep time (minutes)	Sleep efficiency (%)	Sleep onset latency[1] (minutes)	Wake after sleep onset (minutes)
		Coefficient (95% CI)	*Coefficient (95% CI)*	*Coefficient (95% CI)*	*Coefficient (95% CI)*
Road traffic noise (L$_{DEN}$)[2]					
Overall	1,367	**-3.62 (-6.87; -0.37)**	-0.12 (-0.53; 0.28)	0.09 (-0.09; 0.27)	1.42 (-1.60; 4.44)
Living in the basement, ground, or first floor	432	**-5.63 (-10.98; -0.29)**	-0.22 (-0.83; 0.38)	0.21 (-0.12; 0.55)	**6.88 (1.15; 12.61)**

Coefficients and 95% confidence intervals were obtained by linear regression models adjusted for cohort, preadolescent sex and age at sleep questionnaire assessment, parental age , country of birth, education, social class, parity, smoking and alcohol during pregnancy, and family status.

Statistically significant associations in bold (p-value <0.05).

Abbreviations: CI, confidence interval; dB, decibels.

[1] Values are square root transformed.

[2] Residential outdoor annual average noise levels for the 24h of the day from road traffic.

4. Discussion

The present study examined the association between outdoor residential L$_{DEN}$ road traffic and multiple noise exposure, and maternal-reported sleep disturbances as well as physiological sleep measures in preadolescents from two birth cohorts set up in Europe. No associations were found between road traffic and multiple noise exposure and sleep disturbances reported by mothers. In contrast, actigraphy data showed that greater road traffic was related to shorter sleep duration. In addition, road traffic and multiple noise exposure were associated with longer wake after sleep onset in children who were living in the basement, ground, or first floor. Our findings were mainly driven by the Generation R Study due to the large sample size. However, road traffic noise levels were higher in the INMA-Sabadell cohort and effect estimates for some sleep outcomes were also higher when we stratified the analyses by cohort. Therefore, we could expect stronger associations if the sample size in the INMA-Sabadell cohort would have been larger.

   To date, few studies have looked into the association between environmental noise and sleep in children (Blume et al., 2022; Lee et al., 2021; Öhrström et al., 2006; Skrzypek et al., 2017; Tiesler et al., 2013; Weyde et al., 2017). The results of our study were not fully consistent with previous research. Four studies found associations between outdoor residential nocturnal road traffic noise exposure and some sleep outcomes reported by the parents such as poorer sleep quality and excessive sleepiness during the day (Öhrström et al., 2006), more sleep disorders (Skrzypek et al., 2017; Tiesler et al., 2013), greater difficulty falling asleep (Tiesler et al., 2013), and shorter sleep duration, but only in girls (Weyde et al., 2017). In contrast, two studies found no evidence for a relationship between exposure to nocturnal road traffic in children aged 9-12 years (Öhrström et al., 2006) or transportation noise (i.e., road, railway, and aircraft) in infants during their first year of life (Blume et al., 2022) and sleep measured by actigraphy. In our study, we found that road traffic noise exposure was associated with total sleep time using wrist-actigraphy data, in line with one of the previous studies that found an association only when the analysis was restricted to infants without siblings (Blume et al., 2022). Overall, there is little agreement among studies, but some studies suggest a possible relationship between road traffic noise exposure and sleep in children and preadolescents.

There are some potential explanations for the differing results observed between previous studies. First, children seem to be 10-15 dB less sensitive to noise as compared to adults and therefore they may be less likely to awaken due to noise events than adults (Eberhardt, 1983). However, children are considered to be at particular risk due to the neural processes that occur in this stage of life, and also because they tend to have earlier bedtimes and longer periods of sleep than adults, which may coincide with periods of heavy road traffic (Gau & Merikangas, 2004). Second, some individual habituation to noise may occur. This happens when neurons adapt to repetitive auditory stimuli, but respond to stimuli with different physical properties and therefore process them differently (Pérez-González & Malmierca, 2014). Interestingly, Tiesler et. al reported an association between nocturnal road traffic noise at the least exposed façade and maternal-reported sleeping problems in children, and this association was stronger when models were adjusted for sleeping alone in a room (Tiesler et al., 2013). It has also been shown that infants without siblings who are therefore accustomed to lower levels of noise, may be more susceptible to nocturnal transportation noise and consequently to its adverse effects (Blume et al., 2022). Unfortunately, we did not have information if the child had slept alone or not. Third, the degree of misclassification between outdoor and indoor noise in the bedroom as well as differences in the exposure and outcomes measures used may affect the comparability of the studies (Basner et al., 2011). Finally, there is evidence of an association between socioeconomic status (SES) and sleep, showing that low-SES children reported shorter sleep duration and self-reported subjective sleep disturbances (e.g. difficulty falling asleep or maintaining sleep), compared with high-SES children (Bagley et al., 2015). Parental education has also been linked to preadolescent's sleep, with earlier sleep times, shorter sleep latencies, and more regular sleep routines for their children (McDowall et al., 2017). Families with lower socioeconomic resources may have more difficulty providing an optimal sleep environment for their children. They are also more likely to live in noisy neighborhoods and in smaller and crowded dwellings. In our study, we adjusted the main analysis for several SES indicators, including parental education, parental social class, country of birth, and maternal smoking during pregnancy among others. Nevertheless, residual confounding cannot be completely discarded.

Strengths of the present study include a relatively large sample size, especially for physiological sleep measures, using two population-based birth cohorts from two different European countries, the assessment of noise exposure considering the amount of time the child lived at each geocoded address, and the availability of sleep measures using both maternal-reported and wrist-actigraphy data. We have also included information about the floor of the bedroom that could have led to more accurate noise estimations to reduce the measurement error in assessing noise exposure. Adjustments were made for many confounding variables that may be related to environmental noise exposure and sleep in preadolescents. Additionally, multiple imputation and inverse probability weighting were used in order to reduce the potential selection bias (Spratt et al., 2010; Weuve et al., 2012). Finally, we treated most of the sleep outcomes as continuous variables, to avoid outcome misclassification bias.

However, our study also has some limitations that need to be discussed. The main limitation of the study was its cross-sectional design. Longitudinal studies may be necessary to further explore whether environmental noise exposure is associated with sleep during the different stages of sleep pattern development across childhood and adolescence periods. Although reverse causality cannot be completely discarded, we do not expect that families with more sleep problems had moved to areas with higher environmental noise exposure. A further limitation is that the noise levels corresponded to estimated outdoor noise levels instead of noise levels in the bedroom. Unfortunately, as all other large epidemiological studies, we did not have this data, nor did we have information on noise insulation characteristics, if windows were left open or closed during the night, and noise from neighbors, restaurants, or cafés. Therefore, we cannot exclude the possibility of misclassification due to under- or overestimation of true noise exposure levels. Nevertheless, one of the most important sources of misclassification for long-term noise exposure is the effect of shielding due to the orientation of the bedroom towards the noise source (here mainly the street). Future studies should include data related to the child's bedroom (i.e., location of the bedroom, orientation of the windows, floor's level, etc.) in order to reduce the measurement error and provide more accurate effect estimates of the association. Only two previous studies considered bedroom window orientation in their analyses (Öhrström et al., 2006; Tiesler

et al., 2013). In one study, an approximation of the road traffic noise levels at night was done by subtracting 10 dB when the window of the bedroom was facing a courtyard instead of the most exposed façade (Öhrström et al., 2006). They found an association between higher noise exposure at night and increased awakenings and reduced sleep quality was found. In the other study, Tiesler et al. also found that nocturnal road traffic noise at the least exposed façade, but not at the most exposed façade, was associated with more sleeping problems, especially with problems falling asleep, after adjustment for the orientation of the child's room window (Tiesler et al., 2013). However, these findings seems counterintuitive because bedrooms facing a quieter façade of the dwellings were exposed to lower levels of rad traffic noise. Furthermore, in our study we assessed sleep disturbances reported by mothers together with physiological sleep measures. Actigraphy consistently reports more accurate data than parental questionnaires, but it cannot provide information about bedtime routines that can influence the child's sleep, which can be collected by questionnaires. A limitation of actigraphy is that since sleep parameter estimation is based on monitoring activity, absence of movement that may occur during quiet activities could be registered as sleep periods and on the other hand movements during restless sleep episodes (typical in young children) could be interpreted as sleepwalkings, biasing the sleep estimations. Another limitation is that actigraphy only reflected the sleep of a one-week period in our study. However, questionnaires also introduce limitations since they are susceptible to recall bias and parents are sometimes unaware of their children's behaviors. Therefore, parental reports and actigraphy data provide differing, but complementary information about a child's sleep habits (Holley et al., 2010). Additionally, information on children's self-reported sleep habits as well as sleep medication use were not collected and could not be included in the present study. Another limitation is that we were not able to conduct separate source analyses in the Generation R Study because the population exposed to railway, aircraft, and industry noise sources was too small to perform them. These analyses would have been interesting to further explore the effect of each noise source on children's sleep. For example, road traffic noise tends to be constant and children can habituate to it. Although constant noise exposure can alter sleep structure and continuity, habituated children will less likely consciously perceive noise events. In contrast, aircraft and

railway sources are characterized by intermittent noise with higher peak noise levels and less predictability, being scored as more disturbing than road traffic noise (Basner et al., 2011). Finally, the study did not consider individual noise sensitivity which could influence the results (Potgieter et al., 2020).

5. Conclusions

In conclusion, this study indicates that long-term outdoor exposure to residential road traffic noise, the most prevalence noise source in Europe, was associated with reduced total sleep time and longer wake after sleep onset collected by wrist-actigraphy in preadolescents. Results were similar for multiple noise exposure, although most of the association was attributable to road traffic noise as it is the most predominant noise source. Road traffic or multiple noise exposures were not associated with sleep disturbances reported by mothers. Although the observed estimates were relatively small, these results might be more meaningful at the population-level due to the high prevalence of exposure to environmental noise. In future studies, efforts should be made to measure sleep longitudinally using wrist-actigraphy data, which provides more accurate and consistent information about sleep patterns of children.

Funding and acknowledgements:

Supplementary Material

FIGURE S1: Flowchart of the participants in the study.

Mothers enrolled during pregnancy, n=10,385

Generation R, n=9,610

764 lost to follow up or without information on noise exposure

Generation R, n= 400
INMA-Sabadell, n= 364

Preadolescents with information on noise exposure during the year before sleep assessment, n= 9,912

Generation R, n=9,501
INMA-Sabadell, n=411

8,435 without information on sleep disturbances or sleep physiological measures

Generation R, n= 8,256

Preadolescents with information on noise exposure and at least one sleep disturbance (subscale of the SDSC) or one sleep physiological measure, n= 1,477

Generation R, n=1,245

Main analyses

Preadolescents with information on noise exposure and at least one sleep disturbance measured by SDSC questionnaire (dims, does or da subscale), **n= 1,432**

Generation R, n= **1,226**
INMA-Sabadell. n= **206**

Preadolescents with information on noise exposure and at least one mean physiological sleep measure (total sleep time, sleep efficiency, sleep onset latency or wake after sleep onset), **n= 1,367**

Generation R, n= **1,191**
INMA-Sabadell. n= **176**

METHODS S1: Formula used in the standardized Dutch calculation SRM methods.

$$L_{DEN,i} = L_{E,i} - A_{Geo,i} - A_{Air,i} - A_{Ground,i} - A_{Barrier,i} - C_{Meteo} - 58.6$$

in which L_{DEN} is the noise level at the observation point. L_E is the noise emission of the source and "A" terms denote the attenuation from source to receiver due to geometric spreading (A_{Geo}), air absorption (A_{air}), ground impedance (A_{ground}), and Noise Barriers. C_{Meteo} is a frequency independent meteorological correction accounting for varying wind directions and temperature gradients. The constant of 58.6 dB is a correction for dimension changes.

METHODS S2: Formulas used to calculate the L_{DEN} road traffic noise values in the INMA-Sabadell cohort and Generation R Study and L_{DEN} multiple noise values in the Generation R Study.

Formula for the day-evening-night noise indicator (L_{DEN}) in the INMA-Sabadell cohort:

$$L_{DEN} = 10 \lg \frac{1}{24} \left((14 \cdot 10^{\frac{L_{DAY}}{10}}) + (2 \cdot 10^{\frac{L_{EVENING} + 5}{10}}) + (8 \cdot 10^{\frac{L_{NIGHT} + 10}{10}}) \right)$$

Formula for the day-evening-night noise indicator (L_{DEN}) in the Generation R Study:

$$L_{DEN} = 10 \lg \frac{1}{24} \left((12 \cdot 10^{\frac{L_{DAY}}{10}}) + (4 \cdot 10^{\frac{L_{EVENING} + 5}{10}}) + (8 \cdot 10^{\frac{L_{NIGHT} + 10}{10}}) \right)$$

Formula for multiple noise exposure levels in the INMA-Sabadell cohort and Generation R Study:

$$Multiple\ noise = 10 \lg \left(10^{\frac{road}{10}} + 10^{\frac{railway}{10}} + 10^{\frac{aircraft}{10}} + 10^{\frac{industry}{10}} \right)$$

FIGURE S2: Direct acyclic graph for the hypothesized causal association between noise exposure and sleep.
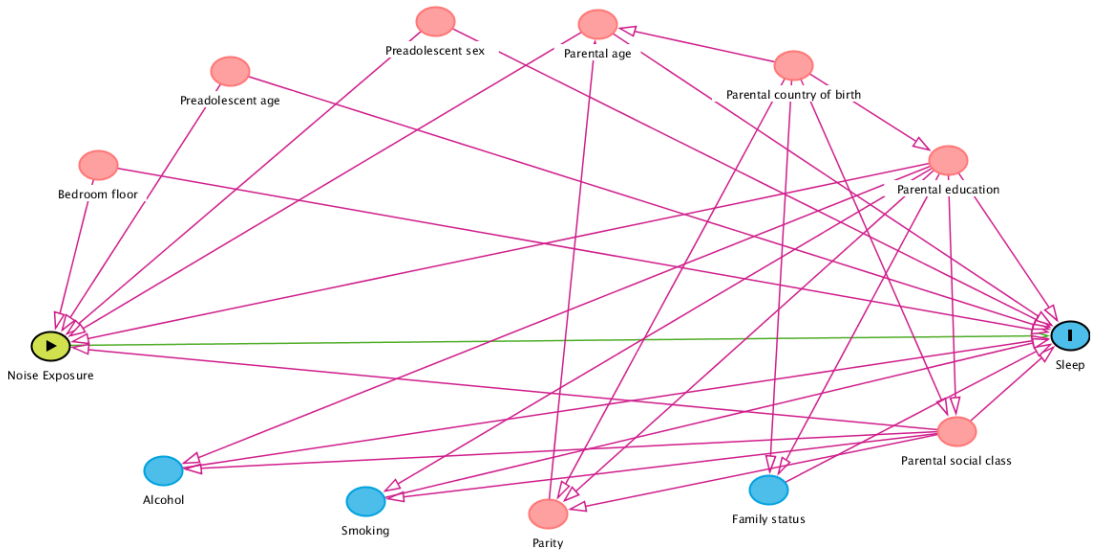
The green node represents the exposure variable and the blue node with I indicates the outcome variable. The green pathway between them indicates the causal path. Other blue nodes are ancestors of the outcome and pink nodes are ancestors of both the exposure and outcome. Pink pathways indicate a biasing path.

TABLE S1. Details of the imputation modelling.

Software used and key setting: Stata Statistical Software: Release 14 (Stata Corporation, College Station, Texas) – Ice command (with 10 cycles)
Number of imputed datasets created: 25
Variables included in the imputation procedure for both cohorts: Road traffic noise exposure, disorders of initiating and maintaining sleep, disorders of excessive somnolence, disorders of arousal, total sleep time, sleep efficiency, sleep onset latency, wake after sleep onset, maternal age at enrolment, maternal country of birth, maternal education level, maternal social class, maternal parity, maternal smoking use during pregnancy, maternal alcohol consumption during pregnancy, paternal age at enrolment, paternal country of birth, paternal education level, paternal social class, family status, preadolescent age, and preadolescent sex.
Treatment of non-normally distributed variables: sqrt-transformed
Treatment of binary/categorical variables: logistic and multinomial models
Statistical interactions included in imputation models: none

TABLE S2: Population characteristics of the subjects included and not included in the analyses of the INMA-Sabadell cohort and Generation R Study.

Characteristics	INMA-Sabadell (n = 775)			Generation R (n =9,610)		
	Included (n = 232)	Not Included (n = 543)	p-value[1]	Included (n = 1,245)	Not Included (n = 8,365)	p-value[1]
Maternal characteristics						
Age at enrolment (years)	31.8 (4.3)	31.2 (4.5)	0.053	32.2 (4.2)	29.6 (5.4)	<0.001
Country of birth (country of the cohort vs. others)	92.0	84.0	0.003	81.1	54.6	<0.001
Education level during pregnancy			0.100			<0.001
Low	25.5	29.5		2.7	12.5	
Medium	40.6	44.4		35.4	47.7	
High	33.9	26.2		61.9	39.8	
Social Class during pregnancy			0.084			<0.001
Low	23.3	17.4		1.3	5.4	
Medium	32.2	29.5		27.4	36.3	
High	44.5	53.2		71.3	58.3	
Parity (nulliparous vs. multiparous)	55.5	56.1	0.877	56.7	54.8	0.201
Smoking use during pregnancy (no vs. yes)	85.6	84.7	0.746	87.1	81.2	<0.001
Alcohol consumption during pregnancy (no vs. yes)	76.6	76.1	0.880	44.8	66.3	<0.001

Values are percentages for categorical, mean (standard deviation) for continuous variables, and median (25th percentile; 75th percentile) for preadolescents' age at sleep questionnaire assessment for Generation R Study.

[1] Chi-square tests for categorical variables, two-sample t-test for normally distributed and Wilcoxon Rank Sum test for non-normally distributed continuous variables.

TABLE S2, continued: Population characteristics of the subjects included and not included in the analyses of the INMA-Sabadell cohort and Generation R Study.

Characteristics	INMA-Sabadell (n = 775)			Generation R (n =9,610)		
	Included (n = 232)	Not Included (n = 543)	p-value[1]	Included (n = 1,245)	Not Included (n = 8,365)	p-value[1]
Paternal characteristics						
Age at enrolment (years)	34.0 (5.3)	33.1 (5.1)	0.031	34.6 (5.1)	32.7 (6.1)	<0.001
Country of birth (country of the cohort vs. others)	91.2	85.5	0.030	83.5	48.2	<0.001
Education level during pregnancy			0.799			<0.001
Low	34.8	37.3		3.6	9.4	
Medium	43.2	41.1		35.6	42.2	
High	22.0	21.7		60.8	48.4	
Social Class during pregnancy			0.793			<0.001
Low	20.1	22.6		5.7	10.6	
Medium	18.0	17.4		17.1	27.0	
High	61.9	60.0		77.2	62.4	
Household characteristics						
Family status (dual vs. single parent)	98.5	98.5	0.962	94.4	84.2	<0.001
Preadolescents' characteristics						
Sex (male vs. female)	51.7	50.5	0.757	48.0	51.1	0.041
Age at sleep questionnaire assessment (years)	11.1 (0.6)	10.9 (0.6)	<0.001	11.6 (10.3;11.8)	11.7 (10.6;11.9)	0.209

Values are percentages for categorical, mean (standard deviation) for continuous variables, and median (25th percentile; 75th percentile) for preadolescents' age at sleep questionnaire assessment for Generation R Study.

[1] Chi-square tests for categorical variables, two-sample t-test for normally distributed and Wilcoxon Rank Sum test for non-normally distributed continuous variables.

TABLE S3. Variables used in logistic regression model to calculate inverse probability of attrition weights in the INMA-Sabadell cohort and Generation R Study.

Variables	Explored	INMA-Sabadell Cohort — Sleep disturbances analysis (Included)	INMA-Sabadell Cohort — Physiological sleep measures analysis (Included)	Generation R Study — Sleep disturbances analysis (Included)	Generation R Study — Physiological sleep measures analysis (Included)
Maternal age	x			x	x
Maternal height	x				
Maternal weight	x	x			
Maternal country of birth	x		x	x	x
Maternal education level during pregnancy	x			x	x
Maternal social class during pregnancy	x	x			
Maternal parity	x			x	x
Maternal smoking use during pregnancy	x			x	x
Maternal alcohol consumption during pregnancy	x			x	x
Paternal age	x		x		
Paternal height	x	x	x		
Paternal weight	x	x	x		
Paternal country of birth	x	x		x	x
Paternal education level during pregnancy	x			x	
Paternal social class during pregnancy	x			x	
Family status	x			x	x
Preadolescent sex	x				x
Preadolescent age at sleep questionnaire assessment	x	x	x	x	x

FIGURE S3. Road traffic noise exposure distribution in the INMA-Sabadell cohort (A) and Generation R Study (B).

(A) INMA-Sabadell cohort

Road traffic noise

(B) Generation R Study

Road traffic noise

Multiple noise
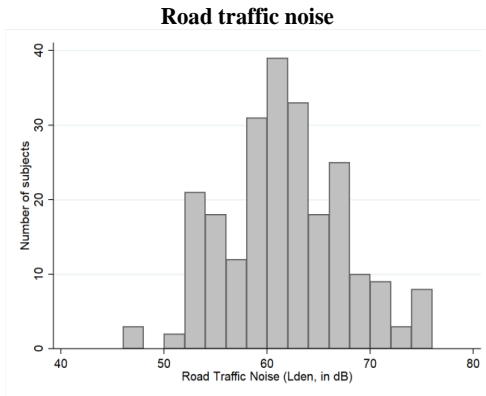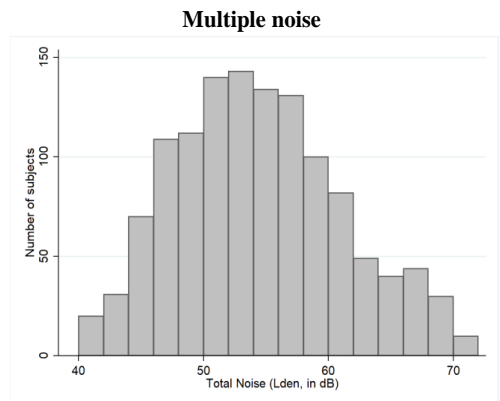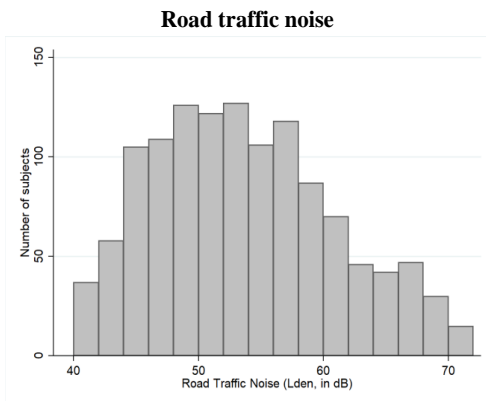
TABLE S4. Spearman correlations between sleep disturbances and physiological sleep measures in the study population from both cohorts (n=1,477).

	(1)	(2)	(3)	(4)	(5)	(6)
Problems with initiating and maintaining sleep (1)	1.00					
Excessive somnolence (2)	**0.41**	1.00				
Total sleep time (hours) (3)	**-0.08**	**-0.07**	1.00			
Sleep efficiency (%) (4)	-0.03	-0.01	**0.42**	1.00		
Sleep onset latency (minutes) (5)	**0.16**	0.02	**-0.10**	**-0.17**	1.00	
Wake After Sleep Onset (minutes) (6)	**0.10**	0.03	**-0.07**	**-0.79**	**0.29**	1.00

Values are rho coefficients from spearman correlations.
Statistically significant associations in bold (p-value <0.05).
Abbreviations: min, minutes.

TABLE S5. Fully adjusted cross-sectional associations between a 10 dB increase in road traffic and multiple noise exposure and sleep disturbances score in preadolescents by cohorts.

	N	Disorders of initiating and maintaining sleep[1] Coefficient (95% CI)	Disorders of excessive somnolence[1] Coefficient (95% CI)	Disorders of arousal (yes vs. no) PR (95% CI)
Road traffic noise (L$_{DEN}$)[2]				
INMA-Sabadell				
Overall	206	-0.25 (-0.23; 0.18)	0.16 (-0.38; 0.06)	0.90 (0.63; 1.31)
Living in the basement, ground, or first floor	71	0.16 (-0.22; 0.55)	-0.24 (-0.63; 0.15)	0.39 (0.15; 0.99)
Generation R				
Overall	1,226	0.02 (-0.04; 0.08)	-0.03 (-0.09; 0.03)	1.05 (0.90; 1.23)
Living in the basement, ground, or first floor	389	0.07 (-0.04; 0.17)	-0.01 (-0.12; 0.10)	0.99 (0.75; 1.31)
Multiple noise (L$_{DEN}$)[3]				
Generation R				
Overall	1,226	0.02 (-0.04; 0.09)	-0.02 (-0.09; 0.04)	1.09 (0.92; 1.29)
Living in the basement, ground, or first floor	389	0.08 (-0.04; 0.19)	0.03 (-0.09; 0.15)	1.07 (0.80; 1.44)

Coefficients and 95% confidence intervals (CI) were obtained by linear and prevalence ratio and 95% CI by Poisson with robust variance regression models. All models were adjusted for cohort, preadolescent sex and age at sleep questionnaire assessment, parental age, country of birth, education, social class, parity, smoking and alcohol during pregnancy, and family status.

Abbreviations: CI, confidence interval; dB, decibels; PR, prevalence ratio.

[1] Values were square root transformed.

[2] Residential outdoor annual average noise levels for the 24h of the day from road traffic.

[3] Residential outdoor annual average noise levels for the 24h of the day in which road traffic, railway, aircraft, and industry sources are considered.

TABLE S6. Fully adjusted cross-sectional associations between a 10 dB increase in road traffic and multiple noise exposure and physiological sleep measures in preadolescents stratified by cohorts.

	N	Total sleep time (min) Coefficient (95% CI)	Sleep efficiency (%) Coefficient (95% CI)	Sleep onset latency[1] (min) Coefficient (95% CI)	Wake after sleep onset (min) Coefficient (95% CI)
Road traffic noise (L$_{DEN}$)[2]					
INMA-Sabadell					
Overall	176	-6.54 (-17.11; 4.02)	-0.95 (-2.17; 0.26)	-0.19 (-0.78; 0.40)	1.87 (-4.25; 7.99)
Living in the basement, ground, or first floor	62	-13.67 (-31.15; 3.81)	**-2.02 (-3.87; -0.18)**	0.58 (-0.72; 1.88)	-5.55 (-15.25; 4.15)
Generation R					
Overall	1,191	-3.42 (-6.89; 0.07)	-0.12 (-0.56; 0.31)	0.12 (-0.08; 0.31)	1.87 (-1.47; 5.22)
Living in the basement, ground, or first floor	370	-4.54 (-10.36; 1.29)	-0.15 (-0.81; 0.50)	0.18 (-0.19; 0.55)	**9.15 (2.69; 15.60)**
Multiple noise (L$_{DEN}$)[3]					
Generation R					
Overall	1,191	-2.87 (-6.70; 0.95)	-0.18 (-0.66; 0.30)	0.14 (-0.07; 0.36)	2.60 (-1.07; 6.27)
Living in the basement, ground, or first floor	370	-5.44 (-12.01; 1.13)	-0.23 (-0.97; 0.51)	0.27 (-0.14; 0.68)	**11.28 (4.04; 18.53)**

Coefficients and 95% confidence intervals were obtained by linear regression models adjusted for cohort, preadolescent sex and age at sleep questionnaire assessment, parental age, country of birth, education, social class, parity, smoking and alcohol during pregnancy, and family status.

Statistically significant associations in bold (p-value <0.05).

Abbreviations: CI, confidence interval; dB, decibels.

[1] Values are square root transformed.

[2] Residential outdoor annual average noise levels for the 24h of the day from road traffic.

[3] Residential outdoor annual average noise levels for the 24h of the day in which road traffic, railway, aircraft, and industry sources are considered.

References

Bagley, E. J., Kelly, R. J., Buckhalt, J. A., & El-Sheikh, M. (2015). What keeps low-SES children from sleeping well: the role of presleep worries and sleep environment. *Sleep Medicine*, *16*(4), 496–502. https://doi.org/10.1016/j.sleep.2014.10.008

Basner, M., & McGuire, S. (2018). WHO Environmental Noise Guidelines for the European Region: A Systematic Review on Environmental Noise and Effects on Sleep. *International Journal of Environmental Research and Public Health*, *15*(3). https://doi.org/10.3390/IJERPH15030519

Basner, M., Müller, U., & Elmenhorst, E. M. (2011). Single and combined effects of air, road, and rail traffic noise on sleep and recuperation. *Sleep*, *34*(1), 11–23. https://doi.org/10.1093/SLEEP/34.1.11

Blume, C., Schoch, S. F., Vienneau, D., Röösli, M., Kohler, M., Moeller, A., Kurth, S., & Usemann, J. (2022). Association of transportation noise with sleep during the first year of life: A longitudinal study. *Environmental Research*, *203*. https://doi.org/10.1016/J.ENVRES.2021.111776

Bruni, O., Ottaviano, S., Guidetti, V., Romoli, M., Innocenzi, M., Cortesi, F., & Giannotti, F. (1996). The Sleep Disturbance Scale for Children (SDSC) Construct ion and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. *Journal of Sleep Research*, *5*(4), 251–261. https://doi.org/10.1111/j.1365-2869.1996.00251.x

Cabré-Riera, A., van Wel, L., Liorni, I., Koopman-Verhoeff, M. E., Imaz, L., Ibarluzea, J., Huss, A., Wiart, J., Vermeulen, R., Joseph, W., Capstick, M., Vrijheid, M., Cardis, E., Röösli, M., Eeftens, M., Thielens, A., Tiemeier, H., & Guxens, M. (2021). Estimated all-day and evening whole-brain radiofrequency electromagnetic fields doses, and sleep in preadolescents. *Environmental Research*, 112291. https://doi.org/10.1016/j.envres.2021.112291

Eberhardt, J. (1983). *The disturbance by road traffic noise of the sleep of prepubertal children as studied in the home. Proceedings of the Fourth International Congress on Noise as a Public Health Problem : Turin, Italy, June 21-25, 1983*. Centro Ricerche e Studi Amplifon, Milan y 1983.

Espelt, A., Marí-Dell'olmo, M., Penelo, E., & Bosque-Prous, M. (2016). Estimación de la Razón de Prevalencia con distintos

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modelos de Regresión: Ejemplo de un estudio internacional en investigación de las adicciones. *Adicciones*, *29*(2), 105–112. https://doi.org/10.20882/ADICCIONES.823

European Environment Agency. (2020). *Environmental noise in Europe, 2020 - Publications Office of the EU*. https://op.europa.eu/en/publication-detail/-/publication/ed51a8c9-6d7e-11ea-b735-01aa75ed71a1/language-en

European Environmental Noise Directive. (2002). *Directive 2002/49/EC*. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32002L0049&from=en

Evandt, J., Oftedal, B., Hjertager Krog, N., Nafstad, P., Schwarze, P. E., & Marit Aasvang, G. (2017). A Population-Based Study on Nighttime Road Traffic Noise and Insomnia. *Sleep*, *40*(2). https://doi.org/10.1093/sleep/zsw055

Gau, S. S. F., & Merikangas, K. R. (2004). Similarities and Differences in Sleep-Wake Patterns Among Adults and Their Children. *Sleep*, *27*(2), 299–304. https://doi.org/10.1093/SLEEP/27.2.299

Guxens, M., Ballester, F., Espada, M., Fernández, M. F., Grimalt, J. O., Ibarluzea, J., Olea, N., Rebagliato, M., Tardón, A., Torrent, M., Vioque, J., Vrijheid, M., & Sunyer, J. (2012). Cohort Profile: The INMA—INfancia y Medio Ambiente—(Environment and Childhood) Project. *International Journal of Epidemiology*, *41*(4), 930–940. https://doi.org/10.1093/ije/dyr054

Hernán, M. A., Hernández-Diaz, S., Werler, M. M., & Mitchell, A. A. (2002). Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. *American Journal of Epidemiology*, *155*(2), 176–184. https://doi.org/10.1093/AJE/155.2.176

Holley, S., Hill, C. M., & Stevenson, J. (2010). A Comparison of Actigraphy and Parental Report of Sleep Habits in Typically Developing Children Aged 6 to 11 Years. *Behavioral Sleep Medicine*, *8*(1), 16–27. https://doi.org/10.1080/15402000903425462

Janson, E., Johannessen, A., Holm, M., Franklin, K., Holst, G. J., Gislason, T., Jögi, R., Lindberg, E., Svartengren, M., & Janson, C. (2020). Insomnia associated with traffic noise and proximity to traffic—a cross-sectional study of the Respiratory Health in Northern Europe III population. *Journal of Clinical*

Sleep Medicine, *16*(4), 545–552. https://doi.org/10.5664/jcsm.8274

Kamp, I. van, Waye, K. P., & Gidlöf-Gunnarsson, A. (2015). The Effects of Noise Disturbed Sleep in Children on Cognitive Development and Long Term Health. *Journal of Child and Adolescent Behaviour*, *03*(01). https://doi.org/10.4172/2375-4494.1000179

Kooijman, M. N., Kruithof, C. J., van Duijn, C. M., Duijts, L., Franco, O. H., van IJzendoorn, M. H., de Jongste, J. C., Klaver, C. C. W., van der Lugt, A., Mackenbach, J. P., Moll, H. A., Peeters, R. P., Raat, H., Rings, E. H. H. M., Rivadeneira, F., van der Schroeff, M. P., Steegers, E. A. P., Tiemeier, H., Uitterlinden, A. G., … Jaddoe, V. W. V. (2016). The Generation R Study: design and cohort update 2017. *European Journal of Epidemiology*, *31*(12), 1243–1264. https://doi.org/10.1007/s10654-016-0224-9

Koopman-Verhoeff, M. E., Serdarevic, F., Kocevska, D., Bodrij, F. F., Mileva-Seitz, V. R., Reiss, I., Hillegers, M. H. J., Tiemeier, H., Cecil, C. A. M., Verhulst, F. C., & Luijk, M. P. C. M. (2019). Preschool family irregularity and the development of sleep problems in childhood: a longitudinal study. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *60*(8), 857–865. https://doi.org/10.1111/JCPP.13060

Koopman-Verhoeff, M. E., Bolhuis, K., Cecil, C. A. M., Kocevska, D., Hudziak, J. J., Hillegers, M. H. J., Mileva-Seitz, V. R., Reiss, I. K., Duijts, L., Verhulst, F., Luijk, M. P. C. M., & Tiemeier, H. (2019). During day and night: Childhood psychotic experiences and objective and subjective sleep problems. *Schizophrenia Research*, *206*, 127–134. https://doi.org/10.1016/j.schres.2018.12.002

Lee, J., Park, J., Lee, J., Ahn, J.-H., Sim, C. S., Kweon, K., & Kim, H.-W. (2021). Effect of Noise on Sleep and Autonomic Activity in Children according to Source. *Journal of Korean Medical Science*, *36*(37), e234. https://doi.org/10.3346/jkms.2021.36.e234

McDowall, P. S., Galland, B. C., Campbell, A. J., & Elder, D. E. (2017). Parent knowledge of children's sleep: A systematic review. *Sleep Medicine Reviews*, *31*, 39–47. https://doi.org/10.1016/j.smrv.2016.01.002

Medic, G., Wille, M., & Hemels, M. E. (2017). *Nature and Science of Sleep Short-and long-term health consequences of sleep*

disruption. https://doi.org/10.2147/NSS.S134864

Meerlo, P., Benca, R. M., & Abel, T. (2015). Sleep, Neuronal Plasticity and Brain Function. In *Current Topics in Behavioral Neurosciences* (Vol. 25). Springer Berlin Heidelberg. http://link.springer.com/10.1007/978-3-662-46878-4

Öhrström, E., Hadzibajramovic, E., Holmes, M., & Svensson, H. (2006). Effects of road traffic noise on sleep: Studies on children and adults. *Journal of Environmental Psychology*, *26*(2), 116–126. https://doi.org/10.1016/j.jenvp.2006.06.004

Pérez-González, D., & Malmierca, M. S. (2014). Adaptation in the auditory system: an overview. *Frontiers in Integrative Neuroscience*, *8*. https://doi.org/10.3389/fnint.2014.00019

Potgieter, I., Fackrell, K., Kennedy, V., Crunkhorn, R., & Hoare, D. J. (2020). Hyperacusis in children: a scoping review. *BMC Pediatrics*, *20*(1), 319. https://doi.org/10.1186/s12887-020-02223-5

Rice, D., & Barone, S. (2000). Critical periods of vulnerability for the developing nervous system: Evidence from humans and animal models. *Environmental Health Perspectives*, *108*(SUPPL. 3), 511–533. https://doi.org/10.1289/ehp.00108s3511

Salter, C. M., Ahn, R., Yasin, F., Hines, R., Kornfield, L., Salter, E. C., & Burke, T. F. (2015). Community noise, urbanization, and global health: Problems and solutions. *Innovating for Healthy Urbanization*, 165–192. https://doi.org/10.1007/978-1-4899-7597-3_8/COVER

Skinner, C. J., & Grimwood, C. J. (2000). *The UK National Noise Incidence Study 2000/2001*.

Skrzypek, M., Kowalska, M., Czech, E., Niewiadomska, E., & Zejda, J. E. (2017). Impact of road traffic noise on sleep disturbances and attention disorders amongst school children living in Upper Silesian Industrial Zone, Poland. *International Journal of Occupational Medicine and Environmental Health*. https://doi.org/10.13075/ijomeh.1896.00823

Spratt, M., Carpenter, J., Sterne, J. A. C., Carlin, J. B., Heron, J., Henderson, J., & Tilling, K. (2010). Strategies for Multiple Imputation in Longitudinal Studies. *American Journal of Epidemiology*, *172*(4), 478–487. https://doi.org/10.1093/aje/kwq137

Tiesler, C. M. T., Birk, M., Thiering, E., Kohlböck, G., Koletzko, S., Bauer, C. P., Berdel, D., Von Berg, A., Babisch, W.,

Heinrich, J., Wichmann, H. E., Schoet-zau, A., Mosetter, M., Schindler, J., Höhnke, A., FrankeK., Laubereau, B., Gehring, U., Sausenthaler, S., … Martin, F. (2013). Exposure to road traffic noise and children's behavioural problems and sleep disturbance: results from the GINIplus and LISAplus studies. *Environmental Research*, *123*, 1–8. https://doi.org/10.1016/J.ENVRES.2013.01.009

United Nations. (2016). *The world's cities in 2016: data booklet / United Nations, Department of Economic and Social Affairs, Population Division*. United Nations.

van Hees, V. T., Sabia, S., Anderson, K. N., Denton, S. J., Oliver, J., Catt, M., Abell, J. G., Kivimäki, M., Trenell, M. I., & Singh-Manoux, A. (2015). A Novel, Open Access Method to Assess Sleep Duration Using a Wrist-Worn Accelerometer. *PLOS ONE*, *10*(11), e0142533. https://doi.org/10.1371/journal.pone.0142533

Weisskopf, M. G., Sparrow, D., Hu, H., & Power, M. C. (2015). Biased exposure-health effect estimates from selection in cohort studies: Are environmental studies at particular risk? *Environmental Health Perspectives*, *123*(11), 1113–1122. https://doi.org/10.1289/EHP.1408888

Weuve, J., Tchetgen Tchetgen, E. J., Glymour, M. M., Beck, T. L., Aggarwal, N. T., Wilson, R. S., Evans, D. A., & Mendes de Leon, C. F. (2012). Accounting for Bias Due to Selective Attrition: The Example of Smoking and Cognitive Decline. *Epidemiology*, *23*(1), 119–128. https://doi.org/10.1097/EDE.0b013e318230e861

Weyde, K., Krog, N., Oftedal, B., Evandt, J., Magnus, P., Øverland, S., Clark, C., Stansfeld, S., & Aasvang, G. (2017). Nocturnal Road Traffic Noise Exposure and Children's Sleep Duration and Sleep Problems. *International Journal of Environmental Research and Public Health*, *14*(5), 491. https://doi.org/10.3390/ijerph14050491

World Health Organization. (2018). *Environmental noise guidelines for the European Region*. http://www.euro.who.int/__data/assets/pdf_file/0008/383921/noise-guidelines-eng.pdf?ua=1

5. DISCUSSION

The results obtained of the different studies included in the present thesis have been already presented and discussed individually in more detail in the previous section *(see Section 4, Results).* In this section, I will summarize and interpret the main findings and provide a general discussion about the methodological issues of the different studies. The implications of the research for public health and policy making as well as ideas and recommendations for future research directions will be also considered in this section.

Table 2. Main study findings of this doctoral thesis

Study	What is known	What this study adds	Main results	Main conclusions
Study I. Environmental noise exposure and emotional, aggressive, and attention-deficit/hyperactivity disorder-related symptoms in children from two European birth cohorts	▪ Emotional, aggressive and ADHD-related symptoms are not related with environmental noise exposure during pregnancy ▪ Exposure to road traffic and aircraft noise during childhood are associated with higher hyperactivity or inattention problems in children	▪ Inclusion of two relevant exposure periods: pregnancy and childhood ▪ Assessment of the overall effect of exposure to multiple noise sources instead of transportation noise sources separately ▪ Longitudinal design	▪ Road traffic noise exposure during pregnancy or childhood was not associated with emotional, aggressive, and ADHD-related symptoms in children ▪ Associations were also absent for multiple noise exposure in which railway, aircraft and industry noise exposure are also assessed	The absence of associations found in this study are in line with previous research that found no association with emotional or aggressive symptoms, but not with research that showed associations with higher ADHD-related symptoms
Study II. Association between outdoor exposure to residential noise and cognitive and motor function in children and preadolescents	▪ Previous studies assessing the relationship between road traffic noise exposure and non-verbal and language/verbal intelligence, memory and attentional function showed inconsistent findings ▪ Exposure to road traffic noise is not associated with working memory except in one of the existing studies	▪ Comprehensive assessment of cognition and motor function using a large battery of tests to assess many cognitive domains ▪ Assessment of the road traffic noise exposure at participant's residences instead of schools ▪ Longitudinal design	▪ Outdoor exposure to residential road traffic noise was not associated with any of the cognitive and motor function outcomes	Outdoor exposure to residential road traffic noise during pregnancy and childhood does not seem to be associated with a large number of cognitive and motor functions in different ages from early childhood to preadolescence

Table 2, continued: Main study findings of this doctoral thesis

Study	What is known	What this study adds	Main results	Main conclusions
Study III. Exposure to traffic-related air pollution and noise during pregnancy and childhood, and functional brain connectivity in preadolescents	▪ Traffic-related air pollution exposure is related to several brain structure alterations in children. It is also associated with altered brain connectivity in children, although this is limited to a single previous study ▪ Noise could act as stressor affecting the HPA axis. Early life stress is related to disturbances in functional brain connectivity	▪ Exposure assessment during pregnancy and first years of life, which is a critical period to the optimal foundation and assembling of brain functional networks ▪ Use of multimodal atlas to explore the whole functional brain connectivity instead of seed-voxel based approaches ▪ Assessment of the association between road traffic noise and functional brain connectivity	▪ Exposure to NO_2, NO_x and $PM_{2.5}$ absorbance during first years of life showed higher functional brain connectivity among several brain regions ▪ Most of the identified associations were between brain regions of the task positive and task negative networks, mainly inter-network, and half of them intra-hemispheric ▪ Exposure to road traffic noise was not related with functional brain connectivity	An increased connectivity in brain areas predominantly located in the task positive and task negative networks could be an indicator of differential functional brain connectivity in preadolescents exposed to higher levels of air pollution Road traffic noise exposure did not affect functional brain connectivity in preadolescents
Study IV. Outdoor residential noise exposure and sleep in preadolescents from two European birth cohorts	▪ Sleep disruption is related to many short- and long-term health effects ▪ Exposure to outdoor nocturnal road traffic is associated with some reported sleep disturbances in children	▪ Assessment of sleep including physiological sleep measures measured by wrist-actigraphy, along with maternal-reported sleep disturbances ▪ Assessment of the overall effect of exposure to multiple noise sources	▪ Exposure to road traffic and multiple noise was related with reduced total sleep time and longer wake after sleep onset collected by actigraphy ▪ Exposure to road traffic and multiple noise was not associated with maternal-reported sleep disturbances	Sleep may be compromised for preadolescents living in areas highly exposed to outdoor residential noise

Note: HPA, hypothalamic–pituitary–adrenal axis; L_{DEN}, day-evening-night noise indicator; L_{NIGHT}, night-time noise indicator; MRI, magnetic resonance image; NO_2, nitrogen dioxide; NO_X, nitrogen oxides; $PM_{2.5}$ absorbance, absorbance from filters of particulate matter with aerodynamic diameter < 2.5μm.

5.1. Main findings and interpretation

The main findings originated in the studies presented in this thesis indicate that: i) outdoor exposure to residential noise is not associated with neurodevelopment including emotional and behavioural symptoms, cognitive and motor function, and functional brain connectivity, and ii) outdoor exposure to residential noise is related with physiological sleep measures, but not with maternal-reported sleep disturbances.

i) Outdoor exposure to residential noise is not associated with neurodevelopment

In this thesis, we explored emotional, aggressive, and ADHD-related symptoms, cognitive and motor function, and functional brain connectivity as outcomes of neurodevelopment in children and preadolescents, divided into three studies:

In Study **I**, we assessed the association between prenatal and childhood outdoor exposure from road traffic and multiple noise with emotional, aggressive, and ADHD-related symptoms. We found that prenatal and childhood exposure to residential road traffic was not associated with emotional, aggressive, and ADHD-related symptoms for the INMA-Sabadell cohort and Generation R Study when we considered the entire exposure periods of pregnancy and childhood. Also, results did not show heterogeneity between cohorts. However, when we analyzed the associations per lifetime period of childhood, we found that higher road traffic noise exposure was associated with lower emotional, but not aggressive or ADHD-related symptoms, at 9 years old in children from the Generation R Study. No associations were found for the rest of the lifetime periods in this cohort or in the INMA-Sabadell cohort. Furthermore, effect estimates were similar when we looked at prenatal and childhood exposure to residential multiple noise in the Generation R Study. The unexpected protective result between higher road traffic and multiple noise exposure and lower emotional symptoms at 9 years in the Generation R Study could be due to selection bias. The sample of children that have moved out of the noise maps of the municipalities of Rotterdam, Maassluis, Rozenburg, Schiedam, and Vlaardingen, who therefore have more

missing noise values, increases with age (around 4% of the population had missing noise levels at 18 months compared to around 26% at 9 years). Those children have less emotional symptoms at younger ages (18 months and 3 years) and more emotional symptoms at 9 years than children who did not move outside of the noise map areas. Therefore, we are missing information on these children that have increased emotional symptoms, which could provide an explanation for the protective association.

In general, our null findings are in line with the previous literature that assessed the exposure to residential road traffic noise during pregnancy (Hjortebjerg et al., 2016) and childhood (Forns et al., 2016; Hjortebjerg et al., 2016) and emotional and aggressive symptoms in children aged 7-11 years. In contrast, two previous studies showed that road traffic noise exposure at schools in children aged 9-10 years was associated with less emotional symptoms (Crombie et al., 2011; S. A. Stansfeld et al., 2009). However, these findings were attributed to chance, inaccurate measures of road traffic noise exposure, or exposure misclassification. The relationship between road traffic noise exposure and ADHD-related symptoms has been more comprehensively studied. In that case, our null findings were consistent with studies that assess this relationship at home during pregnancy (Hjortebjerg et al., 2016; K. V. Weyde et al., 2017), but not with studies looking to road traffic noise exposure throughout childhood, which showed an association of higher road traffic noise at home or at school with higher hyperactivity or inattention problems in children aged 7-11 years (Forns et al., 2016; Hjortebjerg et al., 2016; Tiesler et al., 2013; K. V. Weyde et al., 2017).

In Study **II**, we assessed the association between prenatal and childhood outdoor exposure from road traffic noise with cognitive and motor function. No associations were found with any of the cognitive and motor function outcomes evaluated in this study. In INMA-Sabadell cohort, higher exposure to residential road traffic noise was related with more omission errors (i.e., number of times that the participant did not respond to the stimuli) during pregnancy and less commission errors (i.e., number of times that the participant responds incorrectly) during pregnancy and childhood

periods. However, these associations disappeared after correction for multiple testing.

The findings of our study related to language/verbal and non-verbal intelligence are in line with some of the existing studies that found no relationship in children aged 6 to 11 years exposed to higher levels of road traffic noise (Clark et al., 2006; Julvez et al., 2021; S. A. Stansfeld et al., 2005). In contrast, a study carried out at schools in children with similar ages found that children exposed to higher levels of noise, mainly from road traffic, had lower non-verbal intelligence compared to children exposed to lower noise levels (Bhang et al., 2018). Reading deficits have also been observed in relation to residential multiple noise exposure (Cohen et al., 1973) as well as to road traffic noise exposure at schools (Ljung et al., 2009). However, these previous studies reported greater noise levels compared to our study (Bhang et al., 2018; Cohen et al., 1973; Ljung et al., 2009). Consistency between studies that assessed road traffic noise exposure and memory in children was limited. Our null findings were aligned with some previous studies (Clark et al., 2012; van Kempen et al., 2010, 2012) but not with others (Lercher et al., 2016; Matheson et al., 2010; S. A. Stansfeld et al., 2005). While one of the studies found worsened memory in children exposed to higher residential levels of road and rail traffic noise (Lercher et al., 2016), two other studies found an unexpected association related to improved memory in children exposed to higher school levels of road traffic noise. Both studies included children around 9 years old (Matheson et al., 2010; S. A. Stansfeld et al., 2005). Related to working memory capacity, the majority of the previous studies found no evidence for the association between exposure to road traffic noise and poorer working memory capacity in children aged 6-11 years (Cohen et al., 1973; Julvez et al., 2021; Lercher et al., 2016; S. A. Stansfeld et al., 2005), similar to our findings. Only one recent study found that higher outdoor levels of road traffic noise at schools was related to slower development in working memory in children between 7 and 10 years old (Foraster et al., 2022). Also, our results on the association between road traffic noise exposure and attentional function in children were consistent with some prior studies (Cohen et al., 1973; Julvez et al., 2021; Lercher et al., 2016; S. A. Stansfeld et al., 2005), in which no evidence of this association was found. Nevertheless, it has been reported that higher levels of road traffic noise at schools was related to worsened results in attention tests

(van Kempen et al., 2010, 2012) as well as greater inattentiveness (Foraster et al., 2022).

The Study **III** was the first epidemiological study exploring the association between the residential exposure to traffic-related air pollution and noise, and whole-brain functional connectivity during pregnancy and childhood in preadolescents.

Regarding exposure to traffic-related air pollution, we found that higher exposure to NO_2 and $PM_{2.5}$ absorbance from birth to 3 years of age, and to NO_x from 3 to 6 years of age was associated with increased functional brain connectivity. No associations were found between exposure to $PM_{2.5}$ and PM_{10} and functional brain connectivity for any of the study periods. The relationship between traffic-related air pollution exposure and functional brain connectivity has been explored previously in a single study (Pujol et al., 2016). However, they used a focused seed-voxel based approach to evaluate the functional connectivity of the brain, which does not allow for examining the connectivity between all brain areas. In this study, they found that exposure to NO_2 at schools was associated with lower integration (i.e., interactions between networks) and segregation (i.e., interactions inside the same network) in key brain networks in children aged 8-12 years. Graph theoretical analyses are the best approach to explore brain integration and segregation. Although these approaches were not implemented in our study, our findings suggested lower segregation given that most of the functional connections associated with air pollution were between brain regions belonging to different brain networks. Furthermore, most of the associations related to air pollution exposure were between brain regions of the task positive and task negative networks. These networks have an opposite relationship; the activation of one network would inhibit the other. Therefore, the increased connectivity of both networks at the same time could be an indicator of functional connectivity impairment. Additionally, the task positive network tends to be activated during attention-demanding tasks, and greater connectivity during resting conditions could also indicate differential brain connectivity in those children exposed to higher air pollution levels. Previous literature has also shown structural brain alterations in regions belonging to the task negative and task positive networks (Cserbik et al., 2020; Guxens et al., 2018; Lubczyńska et al., 2021).

Regarding exposure to road traffic noise, we found no evidence related to functional brain connectivity in preadolescents. To the best of our knowledge, no prior studies have assessed exposure to environmental noise in relation to brain using MRI techniques. Noise could act as a stressor affecting the HPA axis and increasing stress hormones (Jafari et al., 2017; Lautarescu et al., 2020). These hormones could influence proper brain development with alterations in size and neuronal architecture of some brain areas (Smith & Pollak, 2020). Also, early life stress has been related to disturbances in functional brain connectivity (De Asis-Cruz et al., 2020; Hermans et al., 2011). Therefore, we hypothesized that exposure to road traffic noise, which could act as a stressor, could have an impact in functional brain connectivity in preadolescents. However, we evaluated long-term exposure to road traffic noise instead of acute exposure, which could explain our null findings. Indeed, some previous studies found that acute exposure to noise from MRI machines during the scans is related to altered functional brain connectivity (Andoh et al., 2017; Pellegrino et al., 2022).

ii) Outdoor exposure to residential noise is related with physiological sleep measures

The relationship between outdoor exposure to residential road traffic and multiple noise and sleep in preadolescents was assessed in Study **IV**. In this study, we used maternal-reported data to assess sleep disturbances and wrist-actigraphy to assess physiological sleep measures.

We found that outdoor residential road traffic and multiple noise exposure were not related with sleep disturbances reported by mothers. We used L_{DEN} instead of L_{NIGHT}, because children tend to go to bed earlier in the evening. A study that also used road traffic L_{DEN} noise observed no association between sleep and road traffic noise exposure (Lee et al., 2021), similar to our findings. However, some previous studies that used L_{NIGHT} found a relationship between outdoor exposure to residential road traffic noise exposure and poorer sleep quality and excessive somnolence during the day (Öhrström et al., 2006), more sleep disorders (Skrzypek et al., 2017; Tiesler et al., 2013), greater difficulty to fall asleep (Tiesler et al., 2013), and shorter sleep duration (K. Weyde et al., 2017).

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Although parental questionnaires could provide information about bedtime routines, actigraphy generally reports more accurate data based on monitoring activity. This study indicated that outdoor exposure to residential road traffic noise was associated with reduced total sleep time and longer wake after sleep onset in preadolescents. Results were similar when we assessed multiple noise exposure in the Generation R Study. A limited number of studies previously used actigraphy to assess this association (Blume et al., 2022; Öhrström et al., 2006). In general, these two studies found no evidence for a relationship between exposure to L_{NIGHT} road traffic noise and sleep in children aged 9-12 years (Öhrström et al., 2006) and to L_{NIGHT} transportation (i.e., road, railway, and aircraft) noise and sleep in infants during their first year of life (Blume et al., 2022). However, when analyses were restricted to infants without siblings, an association between L_{NIGHT} exposure to transportation noise and reduced total sleep time was observed, consistent with our findings (Blume et al., 2022).

5.2. Methodological considerations

All the studies included in this thesis were based on two prospective population-based birth cohorts with a follow-up from fetal life onwards. They followed similar protocols to assess environmental noise exposure, neurodevelopment, and sleep. We relied on relative large sample sizes including individuals from both cohorts set up in different countries with different characteristics, which increases the external validity and the generalizability of the results. Additionally, we were the first in assessing the relationship of exposure to traffic-related air pollution and noise with functional brain connectivity amongst all brain areas in preadolescents. However, imaging data was only available in one of the cohorts. The prospective design of the cohorts allowed for an extensive assessment of the association between exposures from early life with long-term health effects. Also, we corrected the results for multiple testing since the inclusion of multiple tests increases the likelihood of type error I, which means that increases the possibility to obtain significant results that can be attributable to chance. However, being too strict with the correction might increase the likelihood of type error II, meaning that actual true effects are being rejected as not significant based on the correction, which reduces the potentiality of the findings.

Nevertheless, the studies presented in this thesis have also several limitations, mainly related to the study design and exposure and outcome assessments. These limitations will be discussed separately in the following sections:

i) Study design

Confounding

As a result of their prospective nature, birth cohorts provide a rich source of potential confounding variables, including child and parental socioeconomic and lifestyle variables, which enables statistical models to be adjusted accordingly. However, in order to increase the comparability when analyzing more than one cohort, potential confounding variables were selected based on data availability in both cohorts. Despite the comprehensive control for various potential confounding variables in this thesis, we cannot

discard residual confounding. It is possible that other potential confounding variables were not considered or that we considered them, but were unable to include due to poor measurements or lack of measurement, for example for information on parental social class or genetic and family factors in Paper **III** or sleep medication in Paper **IV**. Therefore, residual confounding could introduce bias leading to inaccurate estimates of the main associations.

Selection bias

The prospective nature of birth cohorts allows for the enrollment of subjects who have not yet developed the health outcomes of interest. Therefore, selection bias due to enrollment procedures is not usual. In addition, in our studies, we applied inverse probability weighting to correct for the losses to follow-up and account for potential selection bias when including only participants with available data compared to the full initial cohort at the recruitment in the studies. Even so, we cannot completely avoid selection bias as we have observed in Study **I** in which children who have moved outside the noise maps presented more emotional symptoms at 9 years old. In that case, selection bias could have led to unexpected findings between higher residential exposure to road traffic noise and less emotional symptoms in children at age of 9 years old.

Changes in the outcome over time

Having repeated measurements of outcome data allows analyzing long-term effects and changes in the outcome over time in relation to the exposure. Repeated measurements of the outcome data were only available in Study **I** and **II**. However, in these studies we looked at the overall association of the noise exposure on the outcomes but including the measurements at the different time points in the model without exploring the potential developmental changes of the outcomes over time. Future studies should collect repeated measurements and consider this approach to explore the changes in neurodevelopment and sleep related to the exposure to environmental noise.

ii) Exposure assessment

Exposure misclassification

Epidemiological studies need accurate data on exposure to correctly assess the relationship between the exposure and the health outcome of interest. Nevertheless, in most studies addressing noise-related health problems, exposure levels are often modeled to estimate individual levels for each participant. Personal noise measurements would be a more precise method to assess individual levels of exposure. However, in cohort studies with large number of participants, the use of personal measurements are time-consuming and very expensive. Additionally, personal noise measurements are often carried out for a short period of time and therefore do not reflect the long-term exposure as compared to noise models. Although exposure misclassification is inherent to any study, modeled exposure is more likely to be prone to misclassification. In this thesis, noise exposure was modeled to estimate the individual noise levels at participants' home addresses using existing noise maps. One source of misclassification is that noise estimates corresponded to outdoor noise levels instead of indoor noise levels when indoor noise may be more relevant because individuals spend approximately 90% of their time indoors (Schweizer et al., 2006). Indoors, people are exposed to noise from both outdoor and indoor sources being a complex mixture of noise migrating from outdoor sources such as transportation noise, together with noise generated by indoor sources such as children and equipment including television and musical instruments. However, indoor noise measurements are more lenghtly and costly than outdoor modeled noise. In our studies, we considered the residential mobility taking into account the amount of time a child spent at each address during the study period. However, exposure could be misclassified if participants changed addresses and this change was not documented and therefore not accounted for in our analyses. Another source of misclassification could emerge if the exposure to noise of a participant during the entire day would be different from the residential exposure. For example, children spend most of their time at schools and if these were located in noisy areas, the children therefore being exposed to high levels of noise, their assigned modeled noise exposure levels might not represent their true levels. This could under- or overestimate noise

exposure, which can modify the strength of the association. Also, most of the previous studies used average noise levels to estimate individual noise exposure. However, noise fluctuations defined as the average number of noise peaks during the measurement period might be more disruptive than average noise levels and thus exposure could be misclassified. Finally, in studies assessing the relationship between environmental noise exposure and sleep, L_{DEN} or L_{NIGHT} are the most used noise indicators. However, a better indicator for residential noise exposure would be the combination of $L_{EVENING}$ and L_{NIGHT}, since children and preadolescents spend most of the evening at home and often go to bed earlier than adults.

Measurement error

Another limitation related to the exposure assessment is the possibility of introduction of measurement error. There is increasing uncertainty about the extent of exposure measurement error in studies addressing noise-related health problems. For noise exposure assessment based on measurements or models, the measurement error is more likely to be non-differential and thus not related to the outcome. Error in exposure assessment is a mixture of classical-like and Berkson-like errors. Classical-like error tends to attenuate the risk estimates (i.e., biased toward the null) whereas Berkson-like error causes little to no bias in the measurements although confidence intervals are inflated (Vienneau et al., 2019). In this thesis, errors may be related to uncertainty in the exposure proxy since we were not able to account for isolation characteristics, location of the bedroom, window orientation, or individual noise sensitivity. Residential floor level was only considered in Study **IV** but indicated that linkage by floor could be crucial for reducing measurement error.

iii) Outcome assessment

Heterogeneity in neuropsychological tests

The inclusion of various cohorts increases the sample size, the statistical power, and the representativeness of the study population to the general population. However, one of the limitations that could emerge related to such an approach is the heterogeneity in methodological issues in each cohort. Each cohort was conducted

independently and followed its own protocols. Although protocols were similar between cohorts, there could be discrepancies between assessments, collected data, and timelines. In this thesis, the main discrepancy was related to the outcome data, especially in the neuropsychological tests used. In Study **I** and **II**, we tried to mitigate this heterogeneity by selecting those tests, or subtests, that represent similar neuropsychological domains in both cohorts in order to increase the comparability between them. We have also aimed to increase the comparability by standardizing some test scores to mean of 1 and standard deviation of 0 in Study **I** and to a mean of 100 and standard deviation of 15 in Study **II**. However, we should contemplate the influence of this heterogeneity in the final estimates.

Sleep assessment

In Study **IV** preadolescents' sleep was assessed using maternal-reported questionnaires and wrist-actigraphy to have a more comprehensive assessment of preadolescents' sleep. Nowadays, the only widely accepted method for clinically monitoring sleep is the polysomnography (De Zambotti et al., 2019). Even so, it is an expensive and intrusive method, disrupts natural sleep patterns, and is not commonly used in epidemiological studies. An alternative method to objectively measure sleep is actigraphy, which is less invasive and can be used over multiple nights in the child's natural environment (Werner et al., 2008). However, it has some limitations since sleep parameter estimation is based on monitoring activity. Therefore, absence of movement that may occur during quiet activities can be registered as sleep periods or movements during restless sleep episodes (typical in young children) can be interpreted as sleepwalkings, impacting the sleep estimations. Nevertheless, actigraphy consistently reports more accurate data than subjective methods such as parental questionnaires. Parental questionnaires are widely used because they are simple and economically preferred and can give information about bedtime routines that can influence the child's sleep and cannot be measured with polysomnography or actigraphy (Werner et al., 2008). However, they are susceptible to recall bias and parents sometimes are not aware of their children's behaviors. Therefore, parental questionnaires and actigraphy data provide differing but complementary information about a child's sleep habits, and the

usage of only one of them is insufficient to perform a comprehensive assessment of sleep.

5.3. Implications for public health and policymaking

In general, the findings of the studies presented in this thesis, suggest that exposure to higher levels of environmental noise during pregnancy and childhood is not associated with various neurodevelopmental conditions. Nevertheless, inadequate sleep is related to environmental noise exposure. In turn, sleep disruption has been related with diverse short-term and long-term health consequences including increased stress responsivity, somatic problems, cognitive, memory, and performance deficits, hypertension, cardiovascular diseases, and weight related health issues, among others (Medic et al., 2017). Although the effect size of the estimates of the physiological sleep measures were small, and may have a small impact at the individual level, it may have a greater effect at population-level, since the majority of the population is exposed to environmental noise, mainly from road traffic. Therefore, if the association is causal, noise abatement policies that target the entire population would contribute to sleep improvement which could benefit millions of people.

There should be specific noise policies at the population level that aim to ensure correct noise management and reduce noise pollution. Considering that road traffic is the main source of noise in cities, policies may seek for a reduction of the vehicles' noise emission levels by incentives for electric vehicles or low emission zones, along with other noise policies. For example, noise barriers also prevent propagation between noise sources and receivers. Therefore, another strategy to reduce road traffic noise is to promote noise barriers alongside major roads combined with replacement of traditional asphalt with more efficient options such as porous and rubber asphalt pavements (Ling et al., 2021). Furthermore, besides the growing evidence that vegetation itself affects noise perception positively (Gascon et al., 2015), it has been observed that natural elements, such as plants and trees, could absorb noise (Lacasta et al., 2016) and therefore should be considered in combating noise pollution in urban environments. The mitigation of the negative effects of noise pollution can also be carried out through designing buildings in a manner that minimizes the exposure to noise, and making use of acoustic insulation (e.g., stone wool structure or double-glazed windows). Insulation

changes to buildings can also significantly reduce heating and cooling bills, and help protect the environment by reducing carbon emissions into the atmosphere. Although noise exposure is of involuntary nature, individual choices can have an impact on personal exposure, such as avoid very noisy leisure activities or opting for alternative means of transport such as public or active transportation instead of cars.

Our findings should be confirm and the risks associated with environmental noise should be quantified so that they can be used for prevention. As a result, it would be possible to determine how much morbidity can be attributed to environmental noise, as well as which health benefits would result from reducing environmental noise exposure.

5.4. Future research directions

The evidence exploring the potential effects of environmental noise exposure to child's neurodevelopment and sleep is still limited and inconclusive. However, since levels of noise are increasing in the recent decades as a result of urbanization processes, it is important to understand its effects in our health. Several uncertainties remain that suggest recommendations for future research studies on environmental noise exposure, neurodevelopment, and sleep:

Related to the exposure:
- To assess environmental noise exposure both at homes and schools since children spend most of their time in these settings, which would allow for a comprehensive exposure assessment.
- To perform noise models that estimate indoor noise levels, taking insulation into account, and therefore provide more precise values of exposure.
- To assess the effects of the exposure to other noise sources including the cumulative noise resulting from the exposure to multiple noise sources.
- To assess noise fluctuation measures to investigate whether this type of exposure is more disruptive and has more impact on child's neurodevelopment and sleep than average noise levels.

Related to the outcome:
- To additionally assess sleep using physiological sleep measures by actigraphy to complement parental-reported and self-reported data.
- To use MRI techniques to assess brain alterations related to noise in addition to neuropsychological tests.

Related to the study design:
- To replicate existing findings and our results in other population-based studies worldwide to increase the consistency of evidence. Larger sample sizes are recommended.

- To collect repeated measures on neurodevelopment and sleep outcomes in order to perform longitudinal studies to investigate the changes in the outcome over time.

6. CONCLUSIONS

The main conclusions of this thesis are:

- Outdoor exposure to residential road traffic and multiple noise during pregnancy and childhood was not associated with emotional, aggressive, and ADHD-related symptoms in children.

- Outdoor exposure to residential road traffic noise during pregnancy and childhood was not related with cognitive and motor function in children and preadolescents.

- Outdoor exposure to residential road traffic noise exposure was not associated with functional brain connectivity in preadolescents.

- Outdoor exposure to residential road traffic and multiple noise was not associated with any maternal-reported sleep disturbances in preadolescents.

- Preadolescents exposed to higher levels of residential road traffic noise showed reduced sleep duration.

- Preadolescents exposed to higher levels of residentital road traffic and multiple noise showed higher wake after sleep onset.

7. REFERENCES

Achenbach, T. M., & Rescorla, L. A. (2001a). Manual for the ASEBA school-age forms & profiles : an integrated system of multi-informant assessment. *An Integrated System of Multi-Informant Assessment*, 238.

Achenbach, T. M., & Rescorla, L. A. (2001b). Manual for the ASEBA School-Age Forms and Profiles. *Journal of Child Neurology*. https://doi.org/10.1016/S1474-4422(03)00585-4

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR)*.

Andoh, J., Ferreira, M., Leppert, I. R., Matsushita, R., Pike, B., & Zatorre, R. J. (2017). How restful is it with all that noise? Comparison of Interleaved silent steady state (ISSS) and conventional imaging in resting-state fMRI. *NeuroImage*, *147*, 726–735. https://doi.org/10.1016/J.NEUROIMAGE.2016.11.065

Basner, M., Babisch, W., Davis, A., Brink, M., Clark, C., Janssen, S., & Stansfeld, S. (2014). Auditory and non-auditory effects of noise on health. *The Lancet*, *383*(9925), 1325–1332. https://doi.org/10.1016/S0140-6736(13)61613-X

Beelen, R., Hoek, G., Vienneau, D., Eeftens, M., Dimakopoulou, K., Pedeli, X., Tsai, M. Y., Künzli, N., Schikowski, T., Marcon, A., Eriksen, K. T., Raaschou-Nielsen, O., Stephanou, E., Patelarou, E., Lanki, T., Yli-Tuomi, T., Declercq, C., Falq, G., Stempfelet, M., … de Hoogh, K. (2013). Development of NO2 and NOx land use regression models for estimating air pollution exposure in 36 study areas in Europe – The ESCAPE project. *Atmospheric Environment*, *72*, 10–23. https://doi.org/10.1016/J.ATMOSENV.2013.02.037

Bhang, S. Y., Yoon, J., Sung, J., Yoo, C., Sim, C., Lee, C., Lee, J., & Lee, J. (2018). Comparing Attention and Cognitive Function in School Children across Noise Conditions: A Quasi-Experimental Study. *Psychiatry Investigation*, *15*(6), 620–627. https://doi.org/10.30773/PI.2018.01.15

Blume, C., Schoch, S. F., Vienneau, D., Röösli, M., Kohler, M., Moeller, A., Kurth, S., & Usemann, J. (2022). Association of transportation noise with sleep during the first year of life: A longitudinal study. *Environmental Research*, *203*. https://doi.org/10.1016/J.ENVRES.2021.111776

Brooks, B. L., Sherman, E. M. S., & Strauss, E. (2009). NEPSY-II: A Developmental Neuropsychological Assessment, Second Edition. *Https://Doi.Org/10.1080/09297040903146966*, *16*(1), 80–101. https://doi.org/10.1080/09297040903146966

Bruni, O., Ottaviano, S., Guidetti, V., Romoli, M., Innocenzi, M., Cortesi, F., & Giannotti, F. (1996). The Sleep Disturbance Scale for Children (SDSC) Construct ion and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. *Journal of Sleep Research*, *5*(4), 251–261. https://doi.org/10.1111/j.1365-2869.1996.00251.x

Clark, C., Crombie, R., Head, J., Van Kamp, I., Van Kempen, E., & Stansfeld, S. A. (2012). *Does Traffic-related Air Pollution Explain Associations of Aircraft and Road Traffic Noise Exposure on Children's Health and Cognition? A Secondary Analysis of the United Kingdom Sample From the RANCH Project*. https://doi.org/10.1093/aje/kws012

Clark, C., Crumpler, C., & Notley, H. (2020). Evidence for Environmental Noise Effects on Health for the United Kingdom Policy Context: A Systematic Review of the Effects of Environmental Noise on Mental Health, Wellbeing, Quality of Life, Cancer, Dementia, Birth, Reproductive Outcomes, and Cognition. *International Journal of Environmental Research and Public Health 2020, Vol. 17, Page 393*, *17*(2), 393. https://doi.org/10.3390/IJERPH17020393

Clark, C., Martin, R., Van Kempen, E., Alfred, T., Head, J., Davies, H. W., Haines, M. M., Barrio, I. L., Matheson, M., & Stansfeld, S. A. (2006). Exposure-effect relations between aircraft and road traffic noise exposure at school and reading comprehension: the RANCH project. *American Journal of Epidemiology*, *163*(1), 27–37. https://doi.org/10.1093/AJE/KWJ001

Clark, C., & Paunovic, K. (2018a). WHO Environmental Noise Guidelines for the European Region: A Systematic Review on Environmental Noise and Cognition. *International Journal of Environmental Research and Public Health 2018, Vol. 15, Page 285*, *15*(2), 285. https://doi.org/10.3390/IJERPH15020285

Clark, C., & Paunovic, K. (2018b). WHO Environmental Noise Guidelines for the European Region: A Systematic Review on Environmental Noise and Quality of Life, Wellbeing and Mental Health. *International Journal of Environmental*

Research and Public Health 2018, Vol. 15, Page 2400, *15*(11), 2400. https://doi.org/10.3390/IJERPH15112400

Cohen, S., Glass, D. C., & Singer, J. E. (1973). Apartment noise, auditory discrimination, and reading ability in children. *Journal of Experimental Social Psychology*, *9*(5), 407–422. https://doi.org/10.1016/S0022-1031(73)80005-8

Conners, C. K. (1997a). Conner's Rating Scales—Revised Technical Manual. *Multi-Health Systems*.

Conners, C. K. (1997b). Conners' Rating Scales-Revised Technical Manual. *Multi-Health Systems*.

Conners, C. K. (2006). Conners' kiddie continuous performance test. *Multi-Health Systems Incorporated.*

Crombie, R., Clark, C., & Stansfeld, S. A. (2011). Environmental noise exposure, early biological risk and mental health in nine to ten year old children: A cross-sectional field study. *Environmental Health: A Global Access Science Source*, *10*(1), 1–8. https://doi.org/10.1186/1476-069X-10-39/TABLES/3

Cserbik, D., Chen, J. C., McConnell, R., Berhane, K., Sowell, E. R., Schwartz, J., Hackman, D. A., Kan, E., Fan, C. C., & Herting, M. M. (2020). Fine particulate matter exposure during childhood relates to hemispheric-specific differences in brain structure. *Environment International*, *143*. https://doi.org/10.1016/J.ENVINT.2020.105933

De Asis-Cruz, J., Krishnamurthy, D., Zhao, L., Kapse, K., Vezina, G., Andescavage, N., Quistorff, J., Lopez, C., & Limperopoulos, C. (2020). Association of Prenatal Maternal Anxiety With Fetal Regional Brain Connectivity. *JAMA Network Open*, *3*(12), e2022349–e2022349. https://doi.org/10.1001/JAMANETWORKOPEN.2020.22349

De Zambotti, M., Cellini, N., Goldstone, A., Colrain, I. M., & Baker, F. C. (2019). Wearable Sleep Technology in Clinical and ResearchSettings. *Medicine and Science in Sports and Exercise*, *51*(7), 1538. https://doi.org/10.1249/MSS.0000000000001947

Eeftens, M., Beelen, R., De Hoogh, K., Bellander, T., Cesaroni, G., Cirach, M., Declercq, C., Dedele, A., Dons, E., De Nazelle, A., Dimakopoulou, K., Eriksen, K., Falq, G., Fischer, P., Galassi, C., Gražulevičiene, R., Heinrich, J., Hoffmann, B., Jerrett, M., … Hoek, G. (2012). Development of land use regression models for PM2.5, PM 2.5 absorbance, PM10 and PMcoarse in 20 European study areas; Results of the ESCAPE project.

Environmental Science and Technology, *46*(20), 11195–11205. https://doi.org/10.1021/ES301948K/SUPPL_FILE/ES301948K_SI_001.PDF

EPA Network Interest Group on Noise Abatement (IGNA). (2019). *Overview of critical noise values in the European Region European Network of the Heads of Environment Protection Agencies (EPA Network) Interest Group on Noise Abatement*. www.mplusp.eu

European Environment Agency. (2020). *Environmental noise in Europe, 2020 - Publications Office of the EU*. https://op.europa.eu/en/publication-detail/-/publication/ed51a8c9-6d7e-11ea-b735-01aa75ed71a1/language-en

European Environmental Noise Directive. (2002). *Directive 2002/49/EC*. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32002L0049&from=en

Foraster, M., Esnaola, M., López-Vicente, M., Rivas, I., Álvarez-Pedrerol, M., Persavento, C., Sebastian-Galles, N., Pujol, J., Dadvand, P., & Sunyer, J. (2022). Exposure to road traffic noise and cognitive development in schoolchildren in Barcelona, Spain: A population-based cohort study. *PLOS Medicine*, *19*(6), e1004001. https://doi.org/10.1371/journal.pmed.1004001

Forns, J., Dadvand, P., Foraster, M., Alvarez-Pedrerol, M., Rivas, I., López-Vicente, M., Suades-Gonzalez, E., Garcia-Esteban, R., Esnaola, M., Cirach, M., Grellier, J., Basagaña, X., Querol, X., Guxens, M., Nieuwenhuijsen, M. J., & Sunyer, J. (2016). Traffic-Related air pollution, noise at school, and behavioral problems in barcelona schoolchildren: A cross-sectional study. *Environmental Health Perspectives*, *124*(4), 529–535. https://doi.org/10.1289/EHP.1409449

Gascon, M., Mas, M. T., Martínez, D., Dadvand, P., Forns, J., Plasència, A., & Nieuwenhuijsen, M. J. (2015). Mental Health Benefits of Long-Term Exposure to Residential Green and Blue Spaces: A Systematic Review. *International Journal of Environmental Research and Public Health 2015, Vol. 12, Pages 4354-4379*, *12*(4), 4354–4379. https://doi.org/10.3390/IJERPH120404354

Glasser, M. F., Coalson, T. S., Robinson, E. C., Hacker, C. D., Harwell, J., Yacoub, E., Ugurbil, K., Andersson, J., Beckmann, C. F., Jenkinson, M., Smith, S. M., & Van Essen, D. C. (2016).

A multi-modal parcellation of human cerebral cortex. *Nature 2016 536:7615*, *536*(7615), 171–178. https://doi.org/10.1038/nature18933

Glover, G. H. (2011). Overview of Functional Magnetic Resonance Imaging. *Neurosurgery Clinics of North America*, *22*(2), 133–139. https://doi.org/10.1016/J.NEC.2010.11.001

Goodman, R. (1997). The Strength and Difficulties Questionnaire: A Research Note. *Journal of Child Psychology and Psychiatry*, *38*, 581–586.

Goodman, R., Ford, T., Simmons, H., Gatward, R., & Meltzer, H. (2003). Using the Strength and Difficulties Questionnaire (SDQ) to Screen for Child Psychiatric Disorders in a Community Sample. *International Review of Psychiatry*, *15*, 166–172.

Goodman, R., Ford, T., Simmons, H., Gatward, R., & Meltzer, H. (2009). Using the Strengths and Difficulties Questionnaire (SDQ) to screen for child psychiatric disorders in a community sample. *Http://Dx.Doi.Org/10.1080/0954026021000046128*, *15*(1–2), 166–172. https://doi.org/10.1080/0954026021000046128

Guxens, M., Ballester, F., Espada, M., Fernández, M. F., Grimalt, J. O., Ibarluzea, J., Olea, N., Rebagliato, M., Tardón, A., Torrent, M., Vioque, J., Vrijheid, M., & Sunyer, J. (2012). Cohort Profile: The INMA—INfancia y Medio Ambiente—(Environment and Childhood) Project. *International Journal of Epidemiology*, *41*(4), 930–940. https://doi.org/10.1093/ije/dyr054

Guxens, M., Lubczyńska, M. J., Muetzel, R. L., Dalmau-Bueno, A., Jaddoe, V. W. V., Hoek, G., van der Lugt, A., Verhulst, F. C., White, T., Brunekreef, B., Tiemeier, H., & El Marroun, H. (2018). Air Pollution Exposure During Fetal Life, Brain Morphology, and Cognitive Function in School-Age Children. *Biological Psychiatry*, *84*(4), 295–303. https://doi.org/10.1016/j.biopsych.2018.01.016

Hermans, E. J., Van Marle, H. J. F., Ossewaarde, L., Henckens, M. J. A. G., Qin, S., Van Kesteren, M. T. R., Schoots, V. C., Cousijn, H., Rijpkema, M., Oostenveld, R., & Fernández, G. (2011). Stress-related noradrenergic activity prompts large-scale neural network reconfiguration. *Science*, *334*(6059), 1151–1153.

https://doi.org/10.1126/SCIENCE.1209603/SUPPL_FILE/HE

RMANS.SOM.PDF

Héroux, M. E., Babisch, W., Belojevic, G., Brink, M., Janssen, S., Lercher, P., Paviotti, M., Pershagen, G., Waye, K. P., Preis, A., Stansfeld, S., van den Berg, M., & Verbeek, J. (2015). WHO environmental noise guidelines for the European Region. *Euronoise 2015*, 2589–2593.

Hjortebjerg, D., Andersen, A. M. N., Christensen, J. S., Ketzel, M., Raaschou-Nielsen, O., Sunyer, J., Julvez, J., Forns, J., & Sørensen, M. (2016). Exposure to road traffic noise and behavioral problems in 7-year-old children: A cohort study. *Environmental Health Perspectives*, *124*(2), 228–234. https://doi.org/10.1289/EHP.1409430

Jafari, Z., Mehla, J., Kolb, B. E., & Mohajerani, M. H. (2017). Prenatal noise stress impairs HPA axis and cognitive performance in mice. *Scientific Reports*, *7*(1). https://doi.org/10.1038/S41598-017-09799-6

Julvez, J., López-Vicente, M., Warembourg, C., Maitre, L., Philippat, C., Gützkow, K. B., Guxens, M., Evandt, J., Andrusaityte, S., Burgaleta, M., Casas, M., Chatzi, L., de Castro, M., Donaire-González, D., Gražulevičienė, R., Hernandez-Ferrer, C., Heude, B., Mceachan, R., Mon-Williams, M., … Vrijheid, M. (2021). Early life multiple exposures and child cognitive function: A multi-centric birth cohort study in six European countries. *Environmental Pollution*, *284*, 117404. https://doi.org/10.1016/J.ENVPOL.2021.117404

Kaufman, A. S., Flanagan, D. P., Alfonso, V. C., & Mascolo, J. T. (2006). Test Review: Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV). *Journal of Psychoeducational Assessment*, *24*(3), 278–295. https://doi.org/10.1177/0734282906288389/ASSET/07342829 06288389.FP.PNG_V03

Kaufman, A. S., Raiford, S. E., & Coalson, D. L. (2015). *Intelligent testing with the WISC-V*. 814.

Kiphard, E. (2007). *Körperkoordinationstest für Kinder : KTK ; Manual*. Beltz Test.

Kooijman, M. N., Kruithof, C. J., van Duijn, C. M., Duijts, L., Franco, O. H., van IJzendoorn, M. H., de Jongste, J. C., Klaver, C. C. W., van der Lugt, A., Mackenbach, J. P., Moll, H. A., Peeters, R. P., Raat, H., Rings, E. H. H. M., Rivadeneira, F., van der Schroeff, M. P., Steegers, E. A. P.,

Tiemeier, H., Uitterlinden, A. G., … Jaddoe, V. W. V. (2016). The Generation R Study: design and cohort update 2017. *European Journal of Epidemiology*, *31*(12), 1243–1264. https://doi.org/10.1007/s10654-016-0224-9

Lacasta, A. M., Penaranda, A., Cantalapiedra, I. R., Auguet, C., Bures, S., & Urrestarazu, M. (2016). Acoustic evaluation of modular greenery noise barriers. *Urban Forestry & Urban Greening*, *20*, 172–179. https://doi.org/10.1016/J.UFUG.2016.08.010

Laros, J. A., & Tellegen, P. J. (1991). *Construction and validation of the SON-R 5 1/2-17, the Snijders-Oomen non-verbal intelligence test*. 168.

Lautarescu, A., Craig, M. C., & Glover, V. (2020). Prenatal stress: Effects on fetal and child brain development. *International Review of Neurobiology*, *150*, 17–40. https://doi.org/10.1016/BS.IRN.2019.11.002

Lee, J., Park, J., Lee, J., Ahn, J.-H., Sim, C. S., Kweon, K., & Kim, H.-W. (2021). Effect of Noise on Sleep and Autonomic Activity in Children according to Source. *Journal of Korean Medical Science*, *36*(37), e234. https://doi.org/10.3346/jkms.2021.36.e234

Lercher, P., Evans, G. W., & Meis, M. (2016). Ambient Noise and Cognitive Processes among Primary Schoolchildren: *Http://Dx.Doi.Org/10.1177/0013916503256260*, *35*(6), 725–735. https://doi.org/10.1177/0013916503256260

Levin, I. P., Weller, J. A., Pederson, A. A., & Harshman, L. A. (2007). Age-related differences in adaptive decision making: Sensitivity to expected value in risky choice. *Judgment and Decision Making*, *2*(4), 225–233.

Lezak, M. D. (1995). Neuropsychological assessment 3r edition. *Oxford University Press*, 1026.

Ling, S., Yu, F., Sun, D., Sun, G., & Xu, L. (2021). A comprehensive review of tire-pavement noise: Generation mechanism, measurement methods, and quiet asphalt pavement. *Journal of Cleaner Production*, *287*. https://doi.org/10.1016/J.JCLEPRO.2020.125056

Ljung, R., Sörqvist, P., & Hygge, S. (2009). Effects of road traffic noise and irrelevant speech on children's reading and mathematical performance. *Noise and Health*, *11*(45), 198. https://doi.org/10.4103/1463-1741.56212

Lubczyńska, M. J., Muetzel, R. L., El Marroun, H., Hoek, G.,

Kooter, I. M., Thomson, E. M., Hillegers, M., Vernooij, M. W., White, T., Tiemeier, H., & Guxens, M. (2021). Air pollution exposure during pregnancy and childhood and brain morphology in preadolescents. *Environmental Research*, *198*, 110446. https://doi.org/10.1016/J.ENVRES.2020.110446

MacCarthy, D., & Cordero Pando, A. (2006). *MSCA : escalas McCarthy de aptitudes y psicomotricidad para niños*. TEA Ediciones.

Matheson, M., Clark, C., Martin, R., Van Kempen, E., Haines, M., Barrio, I. L., Hygge, S., & Stansfeld, S. (2010). The effects of road traffic and aircraft noise exposure on children's episodic memory: the RANCH project. *Noise & Health*, *12*(49), 244–254. https://doi.org/10.4103/1463-1741.70503

Medic, G., Wille, M., & Hemels, M. E. (2017). *Nature and Science of Sleep Short-and long-term health consequences of sleep disruption*. https://doi.org/10.2147/NSS.S134864

Nelson, C. A., & Gabard-Durnam, L. J. (2020). Early Adversity and Critical Periods: Neurodevelopmental Consequences of Violating the Expectable Environment. *Trends in Neurosciences*, *43*(3), 133. https://doi.org/10.1016/J.TINS.2020.01.002

Öhrström, E., Hadzibajramovic, E., Holmes, M., & Svensson, H. (2006). Effects of road traffic noise on sleep: Studies on children and adults. *Journal of Environmental Psychology*, *26*(2), 116–126. https://doi.org/10.1016/j.jenvp.2006.06.004

Paavonen, E. J., Räikkönen, K., Pesonen, A.-K., Lahti, J., Komsi, N., Heinonen, K., Järvenpää, A.-L., Strandberg, T., Kajantie, E., & Porkka-Heiskanen, T. (2010). Sleep quality and cognitive performance in 8-year-old children. *Sleep Medicine*, *11*(4), 386–392. https://doi.org/10.1016/j.sleep.2009.09.009

Pelegrina, S., Lechuga, M. T., García-Madruga, J. A., Elosúa, M. R., Macizo, P., Carreiras, M., Fuentes, L. J., & Bajo, M. T. (2015). Normative data on the n-back task for children and young adolescents. *Frontiers in Psychology*, *6*(OCT), 1544. https://doi.org/10.3389/FPSYG.2015.01544/BIBTEX

Pellegrino, G., Schuler, A. L., Arcara, G., Di Pino, G., Piccione, F., & Kobayashi, E. (2022). Resting state network connectivity is attenuated by fMRI acoustic noise. *NeuroImage*, *247*, 118791. https://doi.org/10.1016/J.NEUROIMAGE.2021.118791

Pujol, J., Martínez-Vilavella, G., Macià, D., Fenoll, R., Alvarez-Pedrerol, M., Rivas, I., Forns, J., Blanco-Hinojo, L.,

Capellades, J., Querol, X., Deus, J., & Sunyer, J. (2016). Traffic pollution exposure is associated with altered brain connectivity in school children. *NeuroImage*, *129*, 175–184. https://doi.org/10.1016/J.NEUROIMAGE.2016.01.036

Raess, M., Valeria Maria Brentani, A., Flückiger, B., Ledebur de Antas de Campos, B., Fink, G., & Röösli, M. (2022). Association between community noise and children's cognitive and behavioral development: A prospective cohort study. *Environment International*, *158*. https://doi.org/10.1016/J.ENVINT.2021.106961

Raven, J. J. (2003). Raven Progressive Matrices. *Handbook of Nonverbal Assessment*, 223–237. https://doi.org/10.1007/978-1-4615-0153-4_11

Sanz, S. A., García, A. M., & García, A. (1993). Road traffic noise around schools: a risk for pupil's performance? *International Archives of Occupational and Environmental Health*, *65*(3), 205–207. https://doi.org/10.1007/BF00381157

Sauzéon, H., Lestage, P., Raboutet, C., N'Kaoua, B., & Claverie, B. (2004). Verbal fluency output in children aged 7–16 as a function of the production criterion: Qualitative analysis of clustering, switching processes, and semantic network exploitation. *Brain and Language*, *89*(1), 192–202. https://doi.org/10.1016/S0093-934X(03)00367-5

Schweizer, C., Edwards, R. D., Bayer-Oglesby, L., Gauderman, W. J., Ilacqua, V., Juhani Jantunen, M., Lai, H. K., Nieuwenhuijsen, M., & Künzli, N. (2006). Indoor time–microenvironment–activity patterns in seven regions of Europe. *Journal of Exposure Science & Environmental Epidemiology 2007 17:2*, *17*(2), 170–181. https://doi.org/10.1038/sj.jes.7500490

Skrzypek, M., Kowalska, M., Czech, E., Niewiadomska, E., & Zejda, J. E. (2017). Impact of road traffic noise on sleep disturbances and attention disorders amongst school children living in Upper Silesian Industrial Zone, Poland. *International Journal of Occupational Medicine and Environmental Health*. https://doi.org/10.13075/ijomeh.1896.00823

Smith, K. E., & Pollak, S. D. (2020). Early life stress and development: potential mechanisms for adverse outcomes. *Journal of Neurodevelopmental Disorders 2020 12:1*, *12*(1), 1–15. https://doi.org/10.1186/S11689-020-09337-Y

Stansfeld, S. A., Berglund, B., Clark, C., Lopez-Barrio, I., Fischer,

P., Öhrström, E., Haines, M. M., Head, J., Hygge, S., Van Kamp, I., & Berry, B. F. (2005). Aircraft and road traffic noise and children's cognition and health: a cross-national study. *The Lancet*, *365*(9475), 1942–1949. https://doi.org/10.1016/S0140-6736(05)66660-3

Stansfeld, S. A., Clark, C., Cameron, R. M., Alfred, T., Head, J., Haines, M. M., van Kamp, I., van Kempen, E., & Lopez-Barrio, I. (2009). Aircraft and road traffic noise exposure and children's mental health. *Journal of Environmental Psychology*, *29*(2), 203–207. https://doi.org/10.1016/J.JENVP.2009.01.002

Stansfeld, S. A., & Matheson, M. P. (2003). Noise pollution: non-auditory effects on health. *British Medical Bulletin*, *68*, 243–257. https://doi.org/10.1093/bmb/ldg033

Stansfeld, S., & Clark, C. (2015). Health Effects of Noise Exposure in Children. *Current Environmental Health Reports*, *2*(2), 171–178. https://doi.org/10.1007/S40572-015-0044-1

Stiles, J., & Jernigan, T. L. (2010). The Basics of Brain Development. *Neuropsychology Review*, *20*(4), 327. https://doi.org/10.1007/S11065-010-9148-4

Tiesler, C. M. T., Birk, M., Thiering, E., Kohlböck, G., Koletzko, S., Bauer, C. P., Berdel, D., Von Berg, A., Babisch, W., Heinrich, J., Wichmann, H. E., Schoet-zau, A., Mosetter, M., Schindler, J., Höhnke, A., FrankeK., Laubereau, B., Gehring, U., Sausenthaler, S., … Martin, F. (2013). Exposure to road traffic noise and children's behavioural problems and sleep disturbance: results from the GINIplus and LISAplus studies. *Environmental Research*, *123*, 1–8. https://doi.org/10.1016/J.ENVRES.2013.01.009

Tombaugh, T. N. (2004). Trail Making Test A and B: Normative data stratified by age and education. *Archives of Clinical Neuropsychology*, *19*(2), 203–214. https://doi.org/10.1016/S0887-6177(03)00039-8

United Nations. (2016). *The world's cities in 2016: data booklet / United Nations, Department of Economic and Social Affairs, Population Division*. United Nations.

Van Bon, W. H. J., & Hoekstra, J. G. (1982). Taaltests voor kinderen. *Lisse: Swets & Zeitlinger*.

van Kempen, E., Fischer, P., Janssen, N., Houthuijs, D., van Kamp, I., Stansfeld, S., & Cassee, F. (2012). Neurobehavioral effects of exposure to traffic-related air pollution and transportation

noise in primary schoolchildren. *Environmental Research*, *115*, 18–25. https://doi.org/10.1016/J.ENVRES.2012.03.002

van Kempen, E., van Kamp, I., Lebret, E., Lammers, J., Emmen, H., & Stansfeld, S. (2010). *Neurobehavioral effects of transportation noise in primary schoolchildren: a cross-sectional study*. http://www.ehjournal.net/content/9/1/25

Vienneau, D., Héritier, H., Foraster, M., Eze, I. C., Schaffner, E., Thiesse, L., Rudzik, F., Habermacher, M., Köpfli, M., Pieren, R., Brink, M., Cajochen, C., Wunderli, J. M., Probst-Hensch, N., & Röösli, M. (2019). Façades, floors and maps – Influence of exposure measurement error on the association between transportation noise and myocardial infarction. *Environment International*, *123*, 399–406. https://doi.org/10.1016/J.ENVINT.2018.12.015

Wang, Q. (2018). Urbanization and Global Health: The Role of Air Pollution. *Iran J Public Health*, *47*(11), 1644–1652. http://ijph.tums.ac.ir

Wass, S. V., Smith, C. G., Daubney, K. R., Suata, Z. M., Clackson, K., Begum, A., & Mirza, F. U. (2019). Influences of environmental stressors on autonomic function in 12-month-old infants: understanding early common pathways to atypical emotion regulation and cognitive performance. *Journal of Child Psychology and Psychiatry*, *60*(12), 1323–1333. https://doi.org/10.1111/JCPP.13084

Werner, H., Molinari, L., Guyer, C., & Jenni, O. G. (2008). Agreement rates between actigraphy, diary, and questionnaire for children's sleep patterns. *Archives of Pediatrics & Adolescent Medicine*, *162*(4), 350–358. https://doi.org/10.1001/ARCHPEDI.162.4.350

Weyde, K., Krog, N., Oftedal, B., Evandt, J., Magnus, P., Øverland, S., Clark, C., Stansfeld, S., & Aasvang, G. (2017). Nocturnal Road Traffic Noise Exposure and Children's Sleep Duration and Sleep Problems. *International Journal of Environmental Research and Public Health*, *14*(5), 491. https://doi.org/10.3390/ijerph14050491

Weyde, K. V., Krog, N. H., Oftedal, B., Magnus, P., Øverland, S., Stansfeld, S., Nieuwenhuijsen, M. J., Vrijheid, M., De Castro Pascual, M., & Aasvang, G. M. (2017). Road traffic noise and children's inattention. *Environmental Health*, *16*(1). https://doi.org/10.1186/S12940-017-0337-Y

World Health Organization. (2018). *Environmental noise guidelines*

for the European Region. http://www.euro.who.int/__data/assets/pdf_file/0008/383921/noise-guidelines-eng.pdf?ua=1

Zijlema, W. L., de Kluizenaar, Y., van Kamp, I., & Hartman, C. A. (2021). Associations between road traffic noise exposure at home and school and ADHD in school-aged children: the TRAILS study. *European Child and Adolescent Psychiatry*, *30*(1), 155–167. https://doi.org/10.1007/S00787-020-01521-8/TABLES/8

8. APPENDIX

Courses	Year
• International Programme of Advanced Epidemiology and Statistics - Causal Inference with Directed Graphs. Llatzaret de Maó, Spain.	2017
• International Programme of Advanced Epidemiology and Statistics - Causal Mediation and Interaction Analysis. Llatzaret de Maó, Spain.	2017
• International Programme of Advanced Epidemiology and Statistics - Methods to deal with attrition and missing data. Llatzaret de Maó, Spain.	2017
• FSL Course: functional and structural brain image analysis. Split, Croatia.	2019
• PRBB Intervals Programme: Say it so it stays: oral presentation skills for scientists.	2020
• PRBB Intervals Programme: Time management in science: how to get the best out of your day.	2020
• PRBB Intervals Programme: Becoming a scientific writer: Putting the "Why" before the "How".	2021
• Harvard EdX course by Miguel Hernán on Causal Diagrams.	2021
• Workshop on Causal Mediation Analysis by Tyler J. VanderWeele.	2021
Conferences – oral presentations	**Year**
• XXXVII Reunión Científica Anual de la Sociedad Española de Epidemiología. Oviedo, Spain. *Temporal trends and geographical variability of the prevalence and incidence of attention deficit/hyperactivity disorder among children in Catalonia.*	2019
• ISEE-Young – online. *Residential Road Traffic Noise Exposure and Emotional, Aggressive and ADHD Symptoms in Children from Two European Birth Cohorts.*	2021
• ISEE-Young – online. *Residential traffic noise and air pollution exposure and functional brain connectivity in preadolescents aged 9 to 12 years.*	2021
• 13th ICBEN Congress on Noise as a Public Health Problem - online. *Association between environmental noise exposure and sleep problems in children.*	2021

• XXXIX Reunión Científica de la SEE. León, Spain. *Traffic-related air pollution and noise exposure and functional brain connectivity in preadolescents aged 9 to 12 years.*	2021
• XXXIX Reunión Científica de la SEE. León, Spain. *Association between environmental noise exposure and sleep problems in children*	2021
• XXXIX Reunión Científica de la SEE. León, Spain. *Environmental Noise Exposure and Emotional, Aggressive, and ADHD-related Symptoms in Children from Two European Birth Cohorts.*	2021

Conferences – poster presentations	Year
• XXXVI Reunión Científica Anual de la Sociedad Española de Epidemiología. Lisboa, Portugal. *Prevalence and incidence of autism spectrum disorders in Catalonia, Spain*	2018
• ISEE, Utrecht. *Attention deficit/hyperactivity disorder in Catalonia, Spain: a new Population-Based Case-Control Study to Investigate Environmental Factors*	2019
• ISEE, Utrecht. *Estimated whole-brain and lobe-specific RF-EMF doses and brain volumes in preadolescents.*	2019

Conferences – attendance	Year
• INSAR Annual Meeting. Rotterdam, The Netherlands	2018
• 15ª Jornadas Científicas INMA, Donostia	2018
• RespiraMI. L'inquinamento atmosferico e la nostra salute. Milan, Italy	2019

Others	Year
• Interview about the health effects of air pollution for a student of Audiovisual Media Degree.	2018
• Participate in the Nit de Recerca Europea with a talk about the health effects of air pollution in a secondary school of Barcelona	2018
• Supervise the master thesis of two students from Maastricht University	2019 2020
• Contribute as a peer-reviewer to the Environmental Pollution journal	2019
• Award for the best video of the PhD ISGlobal Symposium	2019
• Radio interview on Radio Mar del Plata. Argentina	2022

Other publications

- Iglesias-Vázquez L, Binter AC, Canals J, Hernández-Martínez C, Voltas N, Ambròs A, Fernández-Barrés S, **Pérez-Crespo L**, Guxens M, Arija V. Maternal exposure to air pollution during pregnancy and child's cognitive, language, and motor function: ECLIPSES study. Environ Res. 2022 Sep;212(Pt D):113501. doi: 10.1016/j.envres.2022.113501. Epub 2022 May 28. PMID: 35640710.

- López-Vicente, M., Agcaoglu, O., **Pérez-Crespo, L.**, Estévez-López, F., Heredia-Genestar, J. M., Mulder, R. H., Flournoy, J. C., van Duijvenvoorde, A. C. K., Güroğlu, B., White, T., Calhoun, V., Tiemeier, H., & Muetzel, R. L. (2021). Developmental Changes in Dynamic Functional Connectivity From Childhood Into Adolescence. Frontiers in Systems Neuroscience, 15, 724805. https://doi.org/10.3389/fnsys.2021.724805.

- Kusters MSW, **Pérez-Crespo L**, Canals J, Guxens M. Lifetime prevalence and temporal trends of incidence of child's mental disorder diagnoses in Catalonia, Spain. Rev Psiquiatr Salud Ment (Engl Ed). 2021 Mar 9:S1888-9891(21)00031-8. English, Spanish. doi: 10.1016/j.rpsm.2021.02.005.

- **Pérez-Crespo L**, Canals-Sans J, Suades-González E, Guxens M. Temporal trends and geographical variability of the prevalence and incidence of attention deficit/hyperactivity disorder diagnoses among children in Catalonia, Spain. Sci Rep. 2020 Apr 14;10(1):6397. doi: 10.1038/s41598-020-63342-8.

- **Pérez-Crespo L**, Prats-Uribe A, Tobias A, Duran-Tauleria E, Coronado R, Hervás A, Guxens M. Temporal and Geographical Variability of Prevalence and Incidence of Autism Spectrum Disorder Diagnoses in Children in Catalonia, Spain. Autism Res. 2019 Nov;12(11):1693-1705. doi: 10.1002/aur.2172.

About the author

Laura Pérez-Crespo was born on 15th of August 1992 in Girona, Spain. She received her bachelor in Human Biology and her Master degree in Public Health at the Pompeu Fabra University, Barcelona. During her bachelor degree, she worked in the Department of microbiology at Hospital Moisès Broggi in Sant Joan Despí. Also, during her master degree, she did an internship at Center for epidemiological studies on STIs and HIV/AIDS in Catalunya (CEEISCAT) with the aim to know the information systems for monitoring and the evaluation of epidemics of HIV and other sexual transmitted infections. She started as a PhD student in 2018 at the Barcelona Institute for Global Health (ISGlobal) under the supervision of Dr. Mònica Guxens. She started working in the APACHE project but most of her studies were embedded within the INMA-Ado-Sleep project with the goal of exploring potential associations between environmental noise exposure, and neurodeveliopment, and sleep problems in childhood and adolescence. She is currently working as epidemiologist at the Agency for health quality and evaluation of Catalunya (AQuAS).