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Maternal exposure to air pollution during pregnancy and child's cognitive, language, and motor function: ECLIPSES study

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ABSTRACT

Prenatal exposure to air pollution, even at low levels, has been associated with negative effects on a child's neuropsychological functioning. The present work aimed to investigate the associations between prenatal exposure to air pollution on a child's cognitive, language, and motor function at 40 days of age in a highly exposed area of Spain. From the ECLIPSES study population, the present work counted 473 mother-child pairs. Traffic-related air pollution levels at home addresses during the whole pregnancy were estimated including particulate matter (PM) with an aerodynamic diameter <2.5 μm ($PM_{2.5}$), <10 μm (PM_{10}) and 2.5–10 μm (PM_{coarse}), $PM_{2.5}$absorbance, nitrogen dioxide (NO_2), other nitrogen oxides (NO_x), and ozone (O_3) using land-use regression models developed within ESCAPE and ELAPSE projects. Children's cognitive, language, and motor functions were assessed using the Bayley Scales of Infant Development 3rd edition (BSID-III) at around 40 days of age. Linear regression models were adjusted for maternal biological, sociodemographic and lifestyle characteristics, area deprivation index, and amount of greenness around the home's address. All air pollutants assessed, except $PM_{2.5}$ absorbance, were associated with lower motor function in children, while no association was observed between prenatal exposure to air pollution and cognitive and language functions. This finding highlights the need to continue raising awareness of the population-level impact that maternal exposure to air pollution even at low levels can have on the neuropsychological functions of children.

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Ethics approval

The study was designed in agreement with the Declaration of Helsinki/Tokyo. All procedures involving human subjects were approved by the Clinical Research Ethics Committee of the Jordi Gol University Institute for Primary Care Research [Institut d' Investigació en Atenció Primària; IDIAP], the Pere Virgili Health Research Institute [Institut d'Investigació Sanitària Pere Virgili; IISPV] and of the Spanish Agency for Medicines and Medical Devices [Agencia Española del Medicamento y Productos Sanitarios; AEMPS]. Signed informed consent was obtained from all women participating in the study.

1. Introduction

Air quality is a global public health concern nowadays. Motor vehicles, industrial activity, and burning of terrestrial waste are the main sources of air pollutants in developed countries, mainly including particulate matter (PM), nitrogen oxides and a wide variety of heavy metals (Nadal et al., 2011; Costa et al., 2020; Grandjean and Landrigan, 2006; Iqubal et al., 2020). Air pollutants, especially those related to traffic or industrial activity, have potential neurotoxic effects (Costa et al., 2020; Iqubal et al., 2020; Kim et al., 2014). Despite the exposure to air pollution has been linked to many health problems at any age (Dominski et al., 2021; Manisalidis et al., 2020), the foetal period constitutes a window of great susceptibility, especially regarding brain function (Forns et al., 2012; Grandjean and Landrigan, 2014; Rice and Barone, 2000). Although the exact physiological mechanisms underlying the negative association between air pollutants and child neuropsychological function are still unknown, the studies on pollutant-induced neurological disorders involve oxidative stress, inflammation, glial and hypothalamic-pituitary-adrenal (HPA) axis activation, and altered gene expression in the brain (Costa et al., 2020; Iqubal et al., 2020; Kim et al., 2014; Thomson, 2019).

Increasing evidence in the last decade is showing the short- and long-term effects of prenatal exposure to air pollution, even at low levels, on a child's neuropsychological functioning. Prenatal exposure to NO_2 has been repeatedly found associated with lower motor function in children aging between 6 months and 6 years (Kim et al., 2014; Guxens et al., 2014; Lertxundi et al., 2015; Binter et al., 2022). Prenatal exposure to higher levels of particulate matter of different sizes ($PM_{2.5}$ and PM_{10}) has been found associated with lower motor function in childhood around the world (Kim et al., 2014; Guxens et al., 2014; Lertxundi et al., 2015; Binter et al., 2022; Tozzi et al., 2019; Zou et al., 2021; Wang et al., 2021; Li et al., 2021; Ha et al., 2019). Similarly, exposure to high levels of NO_2 and $PM_{2.5}$ during foetal life has also been related to lower cognitive function in children of 5–8 years of age in some cases (Sent í s et al., 2017; Chiu et al., 2016; Rivas et al., 2019). Moreover, exposure to $PM_{2.5}$ during foetal life has also been associated with delayed language development from 6 to 24 months of age (Hurtado- D í az et al., 2021). However, controversial results exist regarding cognitive and language functions since some authors did not find associations with air pollution (Guxens et al., 2014). Finally, recent studies on prenatal exposure to ozone (Zou et al., 2021; Ha et al., 2019) found that it was associated with child's developmental delays in fine motor, language, and personal-social functioning.

The province of Tarragona (Catalonia, Spain) houses one of the largest petrochemical industry poles in southern Europe, a waste incinerator and an important industrial harbour (Nadal et al., 2011; Rovira et al., 2020). Additionally, an important seasonal activity takes place in this region, largely increasing the population and traffic density, especially during summer (Nadal et al., 2011). Despite the presence of such important sources of air pollutants, to our knowledge, there are no studies evaluating how foetal exposure to them is related to cognitive and motor function in early postnatal life in this geographic region. The aim of the present work was, therefore, to investigate the associations between prenatal exposure to air pollution on a child's cognitive, language, and motor function at 40 days of age in this highly exposed area of Spain.

2. Materials and methods

2.1. Population and study design

The present analyses were based on a subsample of the ECLIPSES study, a community-based study carried out on pregnant women from the province of Tarragona (Catalonia, Spain) between 2013 and 2017 (Arija et al., 2014). Participants were contacted in their primary care centres during the first routine visit with midwives and were included in the trial according to the following inclusion criteria: women had to be over 18 years of age, before 12 weeks of gestation, have no indication of anaemia (haemoglobin ≥110 g/L on week 12), and be able to understand the official State languages (Spanish or Catalan) and the characteristics of the study. Out of all women initially recruited (n = 791), we assessed the child's neuropsychological function in 503 cases. Losses to follow-up were mainly due to voluntary abandonment (moving or change to other obstetrical services), the emergence of exclusion criteria during pregnancy (appearance of health or pregnancy complications both for mother and foetus during the gestational period), and miscarriage. Furthermore, assessment of maternal exposure to air pollution was not possible in 30 cases, so 473 mother-child pairs with available data on both prenatal exposure and child cognitive, language, and motor function were finally considered in the present analyses (Fig. 1).

2.1.1. Air pollution exposure

Traffic-related air pollution levels at home addresses were estimated. As the estimates were very similar among the trimesters, the values for the entire pregnancy were used. Within the ESCAPE (European Study of Cohorts for Air Pollution Effects) project, three two-week measurements of nitrogen oxides (NO_X, NO_2) were performed in various seasons between January 2009 and January 2010 at 80 sites spread in Catalonia (Cyrys et al., 2012). Additionally, at 40 of those sites, particulate matter (PM) measurements were carried out (Eeftens et al., 2012a). Specifically, PM with an aerodynamic diameter of less than 10 μm (PM_{10}), less than 2.5 μm ($PM_{2.5}$) and absorbance of $PM_{2.5}$ fraction ($PM_{2.5}$absorbance) were measured. PM mass between 10 μm and 2.5 μm (PM_{coarse}) was calculated by subtracting $PM_{2.5}$ from PM_{10}. For each pollutant, the results of all measurements were averaged to obtain one annual mean concentration after correction for temporal variability, by calculating the difference between the concentration for a specific sampling period and the annual average at a continuous reference monitoring site, and then subtracting that difference from each measurement. Land use regression (LUR) models were developed using a variety of land use predictors (Eeftens et al., 2012b; Beelen et al., 2013), and we applied these models to predict air pollution levels at each address where participants lived during pregnancy. The LUR models yielded R^2 values of 62%, 76%, 76%, 75%, 71%, and 69% for $PM_{2.5}$, PM_{10}, PM_{coarse}, $PM_{2.5}$absorbance, NO_2, and NOx, respectively, in Catalonia.

Within the ELAPSE (Effects of Low-Level Air Pollution: A Study in Europe) project, warm-season O_3 concentration (from April to September inclusive) was centrally modelled for western Europe for the year 2010 using LUR models (R^2 69.6%) (de Hoogh et al., 2018). Briefly, routine monitoring data of O_3 from the AirBase network of the European Environmental Agency were regressed on satellite observations, chemical transport model estimates, land use, and road data. Models were then applied to 100 m grids to produce concentration surfaces and assigned the respective exposures of the grids corresponding to each address where participants lived during pregnancy.

Using daily data from a routine background monitoring site in the study area, we extrapolated the air pollution levels of all pollutants to the exact period of residency at each address, resulting in daily air pollution data for each participant for the entire pregnancy. We then averaged the daily levels of each pollutant for the entire pregnancy.

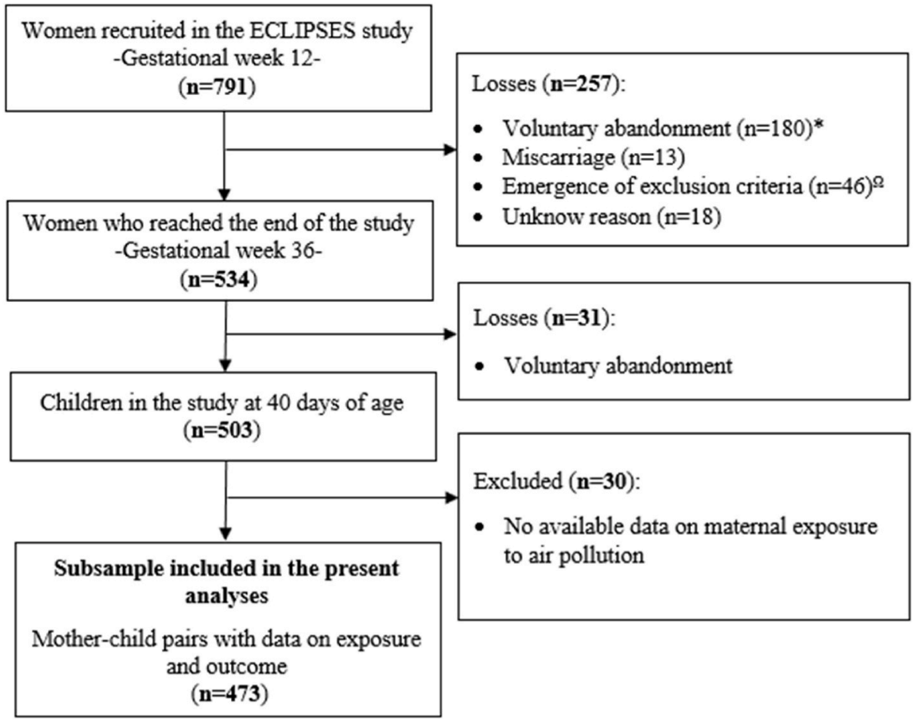

Figure 1. Flowchart of the study.
*Voluntary abandonment included the following reasons: moving and change to other obstetrical services.
ΩEmergence of exclusion criteria referred to the appearance of health or pregnancy complications in the mother or foetus during the gestational period.

2.1.1.1. Cognitive, language, and motor function. Children's cognitive, language, and motor functions were assessed by two trained psychologists (CH-M and NV) using the Bayley Scales of Infant Development 3rd edition (BSID-III) (Bayley, 2006) at around 40 days of age. The BSID-III evaluates the current developmental functioning of infants from 0 to 42 months old. Three general scales (cognitive scale, language scale, and motor scale) and four subscales (expressive language, receptive language, fine motor, and gross motor) of the BSID-III were used, with higher scores representing better functioning. In the present analyses, only the general scales were used after being homogenized by standardizing all raw scores to a mean of 100 and a standard deviation of 15.

2.1.1.2. Other maternal and child variables. Baseline maternal characteristics were collected by questionnaires during a face-to-face interview at the recruitment. They included maternal age (years), maternal ethnicity (Caucasian, Latin American, Arab, other minorities), parity (none, 1, ≥2 previous children), pregnancy planning (yes, no), maternal smoking (yes, no), and alcohol consumption (yes, no). Maternal weight and height were self-reported also at inclusion and body mass index (BMI, kg/m^2) was calculated. Familiar socioeconomic status (SES) (low, middle, high) was calculated using information on the educational level (unfinished primary school, primary school, secondary school, and higher education including university and vocational studies) and occupational status (student, employed, and unemployed). Women's occupation was classified following the Catalan classification of occupations (CCO-2011) (de Estad í stica de Catalu ñ a, 2012). Maternal psychological distress was assessed in the first and third trimester of pregnancy using the State-Trait Anxiety Inventory questionnaire (Spielberger et al., 1997) and, given their similarity, the scores were averaged for the whole gestation (Fig. 2).

Area deprivation index –a multidimensional evaluation of a region's socioeconomic conditions– (Messer et al., 2006) (less deprived, middle deprived, most deprived) and amount of greenness were calculated based on home's address and included as covariates. To measure the surrounding greenness, we applied the Normalized Difference Vegetation Index (NDVI) (Weier and Herring, 2020) within 300 m around each home's address. Based on that vegetation absorb red light, satellites detect the amount of greenness in a specific region. NDVI values range from −1 to +1, with higher numbers indicating more greenness.

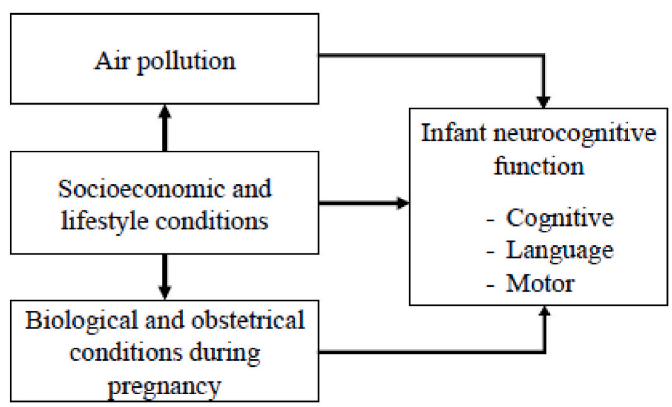

Fig. 2. Conceptual framework of analysis.

2.2. Statistical analyses

Complete case analyses were performed in this study. Single-exposure models were performed using multivariate linear regressions to quantify the association between each exposure independently and each outcome. All statistical models were adjusted for all the covariates previously described, based on prior literature as follows: NDVI in 300 m buffer, deprivation index, maternal age, BMI at recruitment, ethnicity, smoking at the recruitment, alcohol use at the recruitment, parity, pregnancy planning, familiar SES, and maternal psychological distress during pregnancy.

To allow comparability with previous studies, we used standard increases of each exposure as follows: 20 μg/m^3 for NO_X; 10 μg/m^3 for NO_2, PM_{10}, and O_3; 5 μg/m^3 for PM_{coarse} and $PM_{2.5}$; and $10^{-5}m^{-1}$ for $PM_{2.5}$absorbance.

The analyses were performed with SPSS (version 27, SPSS Inc, Chicago, IL, USA) and R statistical software (version 3.3.1; R Function Core Team), using the function *ggplot 2* for drawing plots. The GIS analyses were done within PostgreSQL (copyright © 1996–2017 The PostgreSQL Global Development Group) and PostGIS (Creative Commons Attribution-Share Alike 3.0 License).

3. Results

Maternal and child characteristics are described in Table 1. Mothers were 31 ± 7 years old at recruitment, they were at 11 ± 0.8 gestational week, most of them were Caucasian (76.1%) followed by Latin Americans (15.4%), 25.6% were overweight and 14% were obese in the first trimester of pregnancy, almost 14% reported to have smoked at recruitment, and more than 80% had middle or low SES. More than 80% of participants had a planned pregnancy and almost 10% of them had ≥2 previous children. The descriptive for NDVI-300 m (mean = 0.28, SD = 0.10) indicated a moderate amount of greenness around the participants' homes. Children (49.9% girls) aged 47 ± 13 days at the assessment and all the scores for BSID-III fitted normal ranges. There were no statistically significant differences between participants whose data were included or not included in the present analyses (Supplementary Table 1).

Table 1
Maternal and child characteristics (n = 473).

Mother		Child	
Age at recruitment (years)	31 ± 7	Age at assessment (days)	47 ± 13
Gestational age at recruitment (weeks)	11 ± 0.8	Gestational age (weeks)	39.73 (1.40)
BMI at recruitment		Sex (girl)	49,9
Normal weight	60,5	Head circumference at birth (cm)	34.51 (1.53)
Overweight	25,6	Apgar test score (mean)	9.59 (0.42)
Obesity	14,0	Neurocognitive assessment	
Pregnancy planning (yes)	81,8	Cognitive function	101,73 (8,70)
Parity		Language function	96,38 (8,25)
No child	54,5	Motor function	107,54 (11,14)
1 child	35,9		
≥2 child	9,5		
Smoking at recruitment			
Yes	13,7		
No	86,3		
Alcohol use at recruitment			
Yes	0,6		
No	99,4		
Familiar SES			
High	19,9		
Middle	67,0		
Low	13,1		
Deprivation index at area-level			
Less deprived	33,2		
Middle deprived	45,7		
Most deprived	21,1		
Ethnicity			
Caucasian	76,1		
Latin American	15,4		
Arab	6,3		
Other	2,1		
Anxiety Trait assessment[a]	17,23 (7,69)		
Greenness (NDVI-300 m)	0,28 (0,10)		

[a] Measured by STAI questionnaire. The score ranges from 0 to 60 points.

Descriptive statistics and Spearman correlation coefficients for air pollutants estimated during pregnancy can be found in Table 2. PM_{10} was found strong correlated with $PM_{2.5}$ (r = 0.71) and PM_{coarse} (r = 0.86). Very strong correlations (r > 0.90) were observed between $PM_{2.5}$absorbance, NO_2 and NO_x. Additionally, moderate correlations (r = 0.31 to 0.53) were found between PM of different sizes, NO_2 and NO_x. About O_3, it was negative and moderately correlated with $PM_{2.5}$ absorbance, NO_2 and NO_x. Also, a negative correlation was found between greenness in 300 m buffer and the levels of all the air pollutants assessed (r = −0.22 to −0.54), except for O_3 (data not shown).

All air pollutants assessed, except $PM_{2.5}$absorbance, were associated with lower motor function in children aged 40 days (Fig. 2). For example, an increase of each 10 μg/m^3 in PM_{10} concentration was related to −6.18 points (95%CI: 8.70, −3.66) in motor function. Similarly, a 5-units increase in $PM_{2.5}$ and PM_{coarse} levels was associated with −4.92 points (95%CI: 8.24, −1.60) and −3.76 points (95%CI: 5.25, −2.28), respectively, in motor function (**Supplementary Table 2**). No association was observed between prenatal exposure to air pollution and cognitive and language functions (Fig. 3, Supplementary Table 2).

4. Discussion

In this study, we observed an association between prenatal exposure to air pollution and motor function at the age of 40 days. To our knowledge, this is the first study reporting that prenatal exposure to air pollution affects a child's motor function already at birth. Contrary to what was expected, a trend toward a positive association between prenatal exposure to air pollution and language function was found in this study. On the contrary, no association was found with cognitive function at 40 days of age.

Epidemiological research on air pollution has experienced a notable increase in the last decade, valuable contributing to a better understanding of how exposure to low air quality during foetal life affects a child's neurodevelopment. The wide range of air pollutants that we assessed included $PM_{2.5}$, PM_{10}, PM_{coarse}, $PM_{2.5}$absorbance, NO_2, NO_x, and O_3. The association with motor function of children was found with all of them, except for $PM_{2.5}$absorbance. Most of the studies have been mainly focused on NO_2 and PM, obtaining highly consistent results in regard to a child's motor function. Thus, prenatal exposure to NO_2 has been repeatedly associated with lower motor function in children from 6 months to 6 years of age around the world (Kim et al., 2014; Guxens et al., 2014; Binter et al., 2022; Lertxundi et al., 2019). Likewise, exposure to $PM_{2.5}$ and PM_{10} during foetal life has also been associated with a reduction in motor function in children in several large epidemiological studies (Kim et al., 2014; Guxens et al., 2014; Lertxundi et al., 2015, 2019; Binter et al., 2022; Tozzi et al., 2019; Zou et al., 2021; Wang et al., 2021; Li et al., 2021; Ha et al., 2019). In some cases, however, the negative associations found between air pollutants and child motor function were stronger in children under 2 years of age compared with older ones (Kim et al., 2014; Lertxundi et al., 2015, 2019; Zou et al., 2021), suggesting that environmental and social factors in postnatal life might affect children's neurodevelopment (Kim et al., 2014). More recently, an increased risk of motor developmental delays in children whose mother had been prenatally exposed to high O_3 levels has also been brought to light in a couple of studies (Zou et al., 2021; Ha et al., 2019). Contrary to the wide evidence about the damage that exposure to air pollution during the gestational period can cause to a child's motor function, only one study from Mexico found no association with prenatal exposure to $PM_{2.5}$ (Hurtado- Díaz et al., 2021). Overall, the body of knowledge supports our finding regarding the adverse effects of air pollution during pregnancy on motor function in childhood, although all previous studies have assessed that outcome at ages older than that of children in our study.

It is worth mentioning that, among all the pollutants, only mean NO_2 levels (52.32 μg/m^3) exceeded the EU standards from 2008 (40 μg/m^3 annual mean) (European Environmental Agency, 2021). However,

Table 2
Description and Spearman correlation coefficients of air pollution concentrations estimated at home's address during pregnancy.

	Limit values														
	EU 2008	WHO 2005	WHO 2021	Min	Median	Mean (SD)	IQR	Max	$PM_{2.5}$	PM_{10}	PM_{coarse}	$PM_{2.5}$abs	NO_2	NO_x	O_3
$PM_{2.5}$, μg/m^3	25	10	5	5,40	10,11	10,33 (1,67)	1,85	16,07	1						
PM_{10}, μg/m^3	40	20	15	11,76	23,09	23,14 (4,23)	5,45	41,48	**0,71**	1					
PM_{coarse}, μg/m^3				6,13	13,31	13,26 (3,54)	5,04	26,85	**0,45**	**0,86**	1				
$PM_{2.5}$abs, 10^{-5}m^{-1}				1,12	2,81	2,85 (0,69)	0,98	5,22	**0,31**	**0,47**	**0,47**	1			
NO_2, μg/m^3	40	40	10	2,71	53,28	52,32 (19,91)	29,28	93,24	**0,31**	**0,53**	**0,52**	**0,96**	1		
NO_x, μg/m^3				2,20	88,61	87,71 (34,48)	50,59	157,68	**0,32**	**0,53**	**0,53**	**0,97**	**0,99**	1	
O_3, μg/m^3	120	100	100	65,96	81,83	82,01 (6,53)	8,81	104,46	**0,30**	**0,25**	**0,14**	**−0,47**	**−0,44**	**−0,43**	1

Statistically significant Spearman correlations are highlighted in bold.
IQR, interquartile range; $PM_{2.5}$, particulate matter with an aerodynamic diameter <2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter <10 μm; PM_{coarse}, particulate matter with an aerodynamic diameter between 2.5 and 10 μm; $PM_{2.5}$abs, absorbance of particulate matter with an aerodynamic diameter <2.5 μm; NO_2, nitrogen dioxide; NO_x, other nitrogen oxides; O_3, ozone.

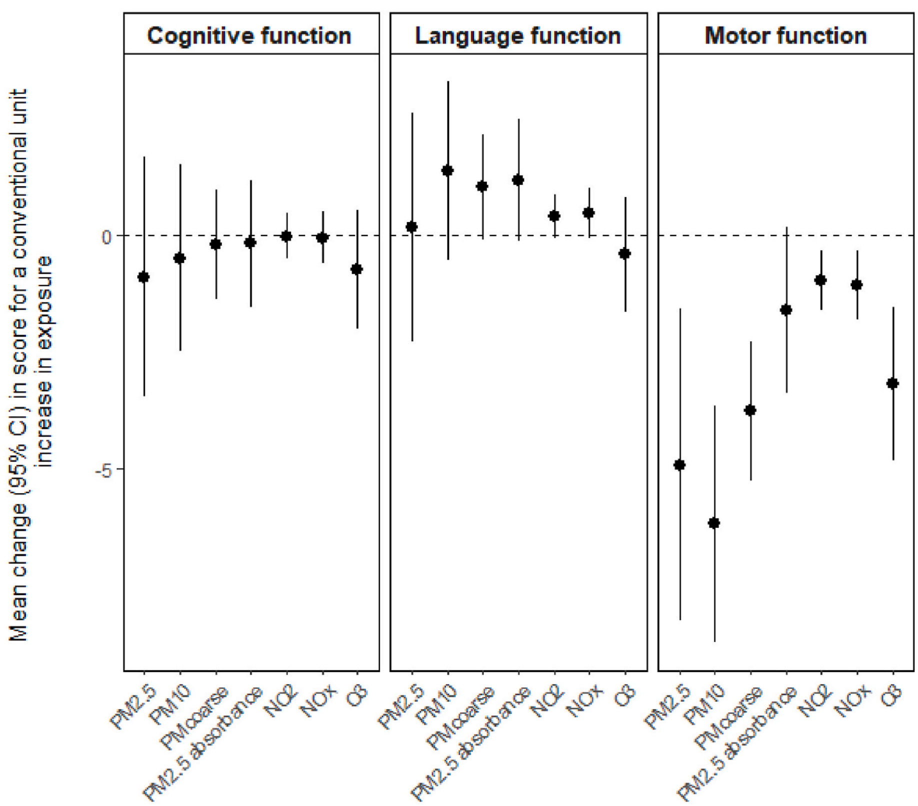

Fig. 3. Association between prenatal exposure to air pollutants on cognitive, language, and motor function of children at around 40 days of age (n = 468). Conventional units: 20 μg/m^3 for NO_X; 10 μg/m^3 for NO_2, PM_{10}, and O_3; 5 μg/m^3 for PM_{coarse} and $PM_{2.5}$; and 10^{-5} m^{-1} for $PM_{2.5}$absorbance. Model adjusted for: NDVI in 300 m buffer, deprivation index, maternal age, BMI at recruitment, ethnicity, smoking at the recruitment, alcohol use at the recruitment, parity, pregnancy planning, familiar SES, and maternal psychological distress during pregnancy.

based on the WHO limits, both NO_2 and PM_{10} (23.14 μg/m^3) overcame those from 2005 (40 and 20 μg/m^3, respectively) (World Health Organization, 2006). Beyond, if we compare the air pollution levels detected in our study with the WHO air quality standards updated in 2021, which have become more restrictive over the years, the concentrations of NO_2, PM_{10} and $PM_{2.5}$ (10.33 μg/m^3) exceeded the current international recommendations (10, 15, and 5 μg/m^3, respectively) (World Health Organization, 2021). This reinforces the need to reduce air pollution levels because, while it is known that even low levels of air pollution exposure during pregnancy can affect children's motor development, when pregnant women are exposed to air pollution above the recommended limits, the hazardous effects on a child's motor function are greater. Nonetheless, certain protective measures against air pollution should also be recommended for pregnant women; some examples would be the use of face masks in highly polluted places (e.g., areas with high traffic density or close to industrial activities), and the frequent practice of recreational activities in green places with good air quality, to offset the exposure to air pollution to which they are subjected in the places where they live or work.

As for the physiological and cellular mechanisms traditionally proposed as responsible for the adverse association between prenatal exposure to air pollution on a child's motor development, they involve neuroinflammation both indirectly by maternal inflammation during pregnancy or directly by air pollutants reaching the foetal central nervous system (Boda et al., 2020; Block et al., 2012). Brain inflammation goes hand in hand with processes such as oxidative stress, glial activation, and white matter injury during the developmental period, which can also delay the motor function later in childhood (Boda et al., 2020; Block et al., 2012; Davis et al., 2018). Furthermore, recent experimental evidence has shown that some air pollutants, specifically particulate matter and ozone, can activate the HPA axis and trigger the release of stress hormones, affecting cognition and mental health. Inhalation of pollutants has also been shown to modify gene expression, which could underlie biochemical and structural brain changes that can occur when the pollution-induced stress response becomes chronic (Thomson, 2019; Thomson et al., 2013). Some in vitro and animal studies have also revealed a link between air pollution and a dysregulation of the dopaminergic system in specific brain areas (Suzuki et al., 2010; Yokota et al., 2009; Levesque et al., 2011, 2013). Dopamine is a neurotransmitter that plays an important role in neuromodulation and synaptic plasticity (Klein et al., 2019). Among other physiological processes, dopamine controls motor function and the learning of new motor skills. For this reason, any imbalance in dopamine levels in the brain, specifically during the highly sensitive period of foetal development, can lead to later motor impairments (Suzuki et al., 2010; Klein et al., 2019).

We did not find an association between prenatal exposure to traffic-related air pollution and a child's cognitive function at around 40 days of age. In addition, contrary to the expectations, a non-significant trend towards a positive association was observed between exposure to some air pollutants during pregnancy and a child's language function. Conflicting results have been obtained so far concerning prenatal air pollution and cognitive and language skills in children. Several epidemiological studies reported a strong negative association between maternal exposure to air pollution and child's cognitive function. Specifically, prenatal exposure to high concentrations of NO_2 and PM of different sizes has been found linked to lower mental development in children of a wide range of ages, from 6 months to 6 years (Kim et al., 2014; Lertxundi et al., 2015; Tozzi et al., 2019; Li et al., 2021; Hurtado-D í az et al., 2021; Lertxundi et al., 2019), although the observed associations were attenuated during the follow-up in some cases (Kim et al., 2014; Hurtado- D í az et al., 2021). Otherwise, coinciding with our findings, some results from the INMA project (Guxens et al., 2012) and the Six European Birth Cohorts study (Guxens et al., 2014) did not allow the authors to conclude that an association existed between prenatal exposure to air pollution and cognitive function at ages around 2 years. The authors argue the lack of relationship between air pollution and cognitive function in these studies could have been because most of the children evaluated were under 2 years of age, an early stage of development when measurement can yield greater variability. We propose the same hypothesis in our study, given that the evaluation of cognitive domain at 40 days postpartum is very brief, including only visual-perceptual functions, and still not very specific. As for the language function, our results are contrary to most of the previous findings. Some studies have reported an adverse association with prenatal exposure mostly to $PM_{2.5}$, but also to NO_2 and O_3, and language development delay both at young ages (2, 6 and 24 months) (Zou et al., 2021; Wang et al., 2021; Hurtado- D í az et al., 2021) and at older ones (3–6 years) (Ha et al., 2019; Lertxundi et al., 2019). However, a recent large study involving four European birth cohorts (Binter et al., 2022) found no association between maternal exposure to NO_2 and $PM_{2.5}$ during pregnancy and the verbal and non-verbal abilities at 5 years of age. While the motor function is modulated by cortical activity from early foetal age (Hadders-Algra, 2018), language development is related to a greater extent to individual factors (genetics) and postnatal environment (sociodemographic factors, cognitive and sensory stimulation) (Ford et al., 2020), which may partly explain the large variability in the results obtained in different studies. In sum, there is only moderate evidence so far about the harmful effect of prenatal exposure to air pollution on child's cognitive and language function. In addition, there are no previous studies involving children at very young ages so further research is warranted to replicate and better understand our findings.

The main strengths of this study include i) the variety of traffic-related air pollutants assessed at the individual level during the complete pregnancy period, ii) the outcome assessment at a very young age, which allowed us to affirm that the observed effect on motor function was due to prenatal exposures since there had been no time for postnatal exposure to intervening, and iii) the availability of a wide range of socioeconomic and lifestyle factors known to be associated with both air pollution exposure and brain development.

However, some limitations should be noted. First, air pollution was measured based on the home addresses of participants but no information from work address or commuting routes were considered. The lack of this information could have led us to an underestimation of the total outdoor air pollution exposure and the observed associations (Pollack et al., 2013). Certain misclassification is unavoidable when researching outdoor air pollution because of possible uncertainties in some environmental covariates and because the modelled exposure at the residential address is not equivalent to personal exposure (Evangelopoulos et al., 2020). Second, women who moved during pregnancy ($n = 24$) reported only the municipality for the former address instead of the complete address. This prevented us from geocoding the previous address, so only air pollution estimates for the current address were considered in these cases. Third, we were unable to include some air pollutants (e.g., polycyclic aromatic hydrocarbons, which have long been associated with vehicular exhaust emissions) due to poor prediction performances in the LUR models of Catalonia (Jedynska et al., 2014). Finally, even after adjustment for known risk factors, residual confounding due to unmeasured or unknown risk factors may occur.

5. Conclusions

Our study has shown for the first time that exposure to traffic-related air pollution during foetal life is adversely associated with motor function in very young children. Even if, all children obtained BSID-III scores in the normal range, so this negative effect did not seem to have clinical implications at the individual level. However, this finding highlights the need to continue raising awareness of the population-level impact that maternal exposure to air pollution can have on the neuropsychological functions of children.

Entities and participants in the ECLIPSES study

Research Group in Nutrition and Mental Health (NUTRISAM), Universitat Rovira i Virgili, Reus, Spain (Victoria Arija, Josefa Canals, Lucía Iglesias-Vázquez, Cristina Jardí, Cristina Bedmar, Carmen Hernández-Martínez, Núria Voltas, Meritxell Rojo-Marticella).

Sexual and Reproductive Health Care Services (ASSIR) of Tarragona, Spain (Francesc Fargas, Francisca Ruiz, Gemma March, Susana Abajo) and the team of midwives who recruited the study participants (Susana Abajo, Irene Aguilar, Sònia Aguiles, Rosa Alzúria, Judit Bertrán, Carmen Burgos, Elisabet Bru, Montserrat Carreras, Beatriz Fernández, Carme Fonollosa, María Leiva, Gemma March, Demetria Patricio, Teresa Pinto, María Ramírez, Eusebia Romano, Inés Sombreo).

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Author contributions

Lucía Iglesias-Vázquez: Formal analysis, Investigation, Writing-original draft preparation, Writing – review & editing. **Anne-Claire Binter**: Formal analysis, Writing – review & editing. **Josefa Canals**: Conceptualization, Investigation, Project administration, Supervision. Carmen **Hernández-Martínez**: Investigation, Writing – review & editing. **Núria Voltas**: Investigation, Writing – review & editing. **Albert**

Ambròs: Software, Writing – review & editing. **Laura Pérez-Crespo**: Investigation, Writing – review & editing. **Mònica Guxens**: Conceptualization, Investigation, Supervision, Writing – review & editing. **Victoria Arija**: Data curation, Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Writing – review & editing, Supervision.

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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.113501.

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