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Association of environmental noise exposure with cortisol levels in children from eight European birth cohorts

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ABSTRACT

Environmental noise is a major environmental risk factor for public health. According to the noise reaction model the release of stress hormones like cortisol in response to noise exposure, plays a key role in the development of noise-induced health effects. We aimed to study the association between environmental noise with both acute (UCC) and cumulative (HCC) cortisol levels in children 5–12 years of age. To do so, we analysed data from the HELIX cohort –with spot UCC data- and from the Generation R and INMA cohorts (Gipuzkoa and Sabadell) –with HCC data. The analytical sample involved: 750 HELIX children (mean age = 7.75), 1326 Generation R children (mean age = 6.06), 111 INMA-Sabadell children (mean age = 8.75) and 288 INMA-Gipuzkoa children (mean age = 7.85). Day-evening-night equivalent (L_{den}) environmental noise exposure during the year of the follow-up was

Abbreviations: BM, Body Mass Index; CBCL, Child Behaviour Checklist; DAG, Directed acyclic graph; HCC, hair cortisol concentration; HPA, hypothalamic-pituitary-adrenal; LC-MS/MS, liquid chromatography-tandem mass spectrometry; L_{den}, day-evening-night noise indicator; NDVI, Normalized Difference Vegetation Index; RIA, radioimmunoassay; UCC, urine cortisol concentration.

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estimated in the addresses of participants, using existing noise maps. Directed acyclic graphs (DAGs) were used to identify appropriate covariates and reduce the chance for biased estimation. We used mixed-effects modelling and linear modelling to examine the association between L_{den} and cortisol concentration using complete case analyses. None of the models reached the statistical significance. We observed no correlation between HCC and UCC in INMA-Sabadell participants, for whom both urinary and hair cortisol data were available. Future research should prioritize investigating the effects of environmental noise on HCC, as it may serve as a more reliable indicator for assessing associations with chronic exposures. Additionally, future studies on noise-induced health effects in children should incorporate other biomarkers of stress and chronic inflammation to provide a more comprehensive understanding of these associations.

1. Introduction

Environmental noise is a ubiquitous urban exposure and it is considered a major environmental risk factor for public health (European Environment Agency, 2020), and contributes to a wide range of adverse health effects such as noise annoyance, sleep disturbances, cardiovascular and metabolic diseases, and cognitive impairment as shown in previous literature (Clark and Paunovic, 2018; Guski et al., 2017; Smith et al., 2022; van Kempen et al., 2018; Vienneau et al., 2019). The knowledge of the mechanistic pathway underlying noise-induced health effects has been considerably strengthened the last decade (Sørensen et al., 2024). Exposure to noise triggers a primary stress reaction: the activation of hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (Daiber et al., 2019). The HPA axis is one of the main biological systems that manages the stress response, and its activation causes the release of stress hormones, such as cortisol. Hence, cortisol has been frequently used as a biomarker of stress, as it participates in the response to acute and chronic bio-psychosocial stressors (Adam et al., 2017). In an acute stress reaction, the increased production of cortisol by the adrenal glands provides immediate energy to muscles, the brain and other vital organs to respond to the stressor (van der Valk et al., 2018). These elevated cortisol levels also serve as a negative feedback mechanism, restoring basal levels of stress hormones (Herman et al., 2016). However, in cases of chronic stress, dysfunction in the HPA axis occurs, and buffering mechanisms become insufficient to return to baseline conditions. This physiological phenomenon is known as allostatic load and has been associated with several detrimental health outcomes, such as increased risk of cardiovascular diseases and diabetes, cognitive impairment and mental health problems (Guidi et al., 2021; Mc Ewen, 1998). Several factors may act as a stressor activating HPA axis and simultaneous interrelationship between multiple variables may affect levels of stress hormones: the physical environmental surrounding such as noise exposure, green spaces or air pollution such as noise exposure, green spaces or air pollution, social and familial relationships, early life stressful conditions and individual characteristics (Arregi et al., 2024).

Although numerous studies point out the negative effect that psychosocial stressors have on the physical and mental health of children (Carlsson et al., 2014), the scientific literature on the effects of noise on children is scarce. Cortisol levels have been studied as indicator of acute stress responses to environmental noise. In that vein, most of the studies have measured cortisol in saliva or urine samples (Hellhammer et al., 2009). Nevertheless, this approach informs about short-term cortisol levels, while hair cortisol concentration (HCC) has been proposed as a valid method to assess chronic stress and HPA axis activity (Kirschbaum et al., 2009; Stalder et al., 2017) and it is considered a viable tool for studying the relation between environmental noise exposure and cumulative stress (Dopico et al., 2023; Michaud et al., 2022). To the best of our knowledge, only two studies have focused on the relation between environmental noise and HCC. One of these, found no association between residential exposure to traffic noise and HCC in 14–15-year-old adolescents (Verheyen et al., 2021). The other study with children aged 11 years, higher exposure to environmental noise was associated with lower HCC. Moreover sex-stratification revealed that this relation was only found in boys (Arregi et al., 2024).

Regarding short-term cortisol levels, many studies have found environmental noise to impact on cortisol levels, measured in urine or saliva. Some studies with adults showed elevated salivary cortisol levels in those living near airports (Baudin et al., 2019; Lefèvre et al., 2017; Selander et al., 2009). Nonetheless, a sleep laboratory study found no significant influence of aircraft noise on urinary cortisol (Maass and Basner, 2006). In addition, a systematic review concluded that road traffic noise was related to higher urinary or salivary cortisol levels (Hohmann et al., 2013). Studies regarding the effect of environmental noise on acute cortisol levels in children, however, showed inconsistent results. Some of them showed higher cortisol levels in children living in noisier areas (Evans et al., 2001; Ising and Ising, 2002; Ising, 2003) while others observed no association (Bloemsma et al., 2021; Evans et al., 1998; Haines et al., 2001; Wallas et al., 2018).

Given the discrepancies in previous literature on the association of environmental noise exposure and cortisol levels in children, the main objective was to study the association between environmental noise exposure and stress response in children, as indicated by both short-term (urinary cortisol concentration, UCC) as well as cumulative (HCC) cortisol. We hypothesized that noise exposure as an environmental stressor may increase both acute and chronic cortisol levels in children.

2. Methods

2.1. Participants

This study is based on the Advancing Tools for human Early Life-course Exposome Research and Translation (ATHLETE) project (Vrijheid et al., 2021). Specifically, we included data from those cohorts with available cortisol concentration data during childhood. We used data from the Generation R cohort (Jaddoe et al., 2006), the Gipuzkoa and Sabadell INfancia y Medio Ambiente cohort (Guxens et al., 2012) (INMA), Born in Bradford (McEachan et al., 2024) (BiB), Étude des Déterminants pré et postnatals précoces du développement et de la santé de l'ENfant (Heude et al., 2016) (EDEN) the Kaunas birth cohort (Grazuleviciene et al., 2015) (KANC) The Norwegian Mother, Father and Child Cohort Study (Magnus et al., 2016) (MoBa) and the Rhea mother-child cohort (Chatzi et al., 2017). The later six cohorts (INMA-Sabadell, BiB, EDEN, KANC, MoBa and Rhea) are participants from the Human Early-Life Exposome (HELIX) subcohort. The HELIX subcohort is based on six birth cohort studies throughout Europe and implemented a common follow-up visit when children were 6–11 years old. Further details regarding the selection and characteristics of the HELIX subcohort can be found in Maitre et al. (2018).

We requested data from the HELIX subcohort follow-up, the 5-year-old follow-up from the Generation R study, and the 8-year-old follow-up from the INMA-Gipuzkoa study. For the analyses presented in this manuscript, we included only participants with complete data for the study variables (see Fig. 1). Approval was obtained from the ethics committees in every site and all participating mothers provided informed written consent.

2.2. Environmental noise exposure

The noise exposure assessment was based on existing noise maps developed under the framework of the European Noise Directive, END (Directive 2002/49/EC, 2002) in cases there were available. Outdoor annual traffic noise level noise maps were available for all cases but INMA-Gipuzkoa, and Rhea. For the rest of the cohorts (Generation R, INMA-Sabadell, BiB, EDEN, KANC and MoBa), existing maps were utilized. A new noise map for Rhea was developed by ISGlobal, following same methodology specified in the END and using data from a traffic monitoring campaign conducted as part of the EXPOsOMICS project (de Castro et al., 2021). Environmental noise exposure for these cohorts was calculated at each participant's geocoded address during the year prior to the follow-up. The noise levels were determined based on the type of available noise map. If noise layer type was "line", the closest street was used to assess noise values, like the approach taken for INMA Sabadell and Rhea cohorts. In the other cases, where the layer type was polygon or raster, an intersection between noise maps and geocodes was performed to estimate noise levels at each participant's residential address at the time of the follow-up (Essers et al., 2022; Pérez-Crespo et al., 2024; Robinson et al., 2018).

In the case of INMA-Gipuzkoa, the study area is less urbanized, consisting of small towns with populations below 15,000 inhabitants. However, in the Basque Country, the region where the INMA-Gipuzkoa cohort is set, regional regulations require that all local councils with a population exceeding 10,000 must create a noise map (Decree 213/2012, 2012). Moreover, as part of the INMA project, noise maps for municipalities with between 6000 and 10,000 inhabitants were compiled using the same methodology. Data from 2019 was used to obtain the total environmental noise exposure, where traffic noise, railway noise and industry was considered. These maps illustrate the levels of sound immissions on building façades: calculation points are positioned at a height of 4 m. The procedure involves calculating the noise level that reaches a specific receptor from noise sources mentioned above. Geocoded residential addresses were utilized to estimate the environmental noise exposure for each participant.

In all the cases, we calculated the day-evening-night noise indicator (L_{den}). L_{den} represents the A-weighted average sound level over a 24-h period, incorporating penalties for the evening (+5 dB) and night (+10 dB) periods. This approach, recommended by the Environmental Noise Directive, aims to account for the health impacts related to noise exposure during the evening and nighttime hours. Noise exposure was calculated from L_{den} 55 dB and in 5 dB categories. Even if L_{night} was also available, L_{den} was only used in this study, as both variables were strongly associated in all cases, as indicated by the Chi-square tests ($p < 0.001$, Cramér's V = 0.74–0.84)

2.3. Cortisol

Among the eight cohorts with available cortisol concentration data, some measured cortisol in urine, while others collected it from hair samples. Hair cortisol concentration (HCC) was available for Generation R and INMA cohorts, both Gipuzkoa and Sabadell centres. Urinary cortisol concentration (UCC) was available in the case of the HELIX cohorts (BiB, EDEN, INMA Sabadell, KANC, MoBa, and Rhea). Both samples were collected during the follow-up period. It is noteworthy that both sets of data were available only for participants from INMA-Sabadell.

2.3.1. Hair cortisol concentration (HCC)

Trained staff collected hair samples from the posterior vertex area of the participants' heads following the guidelines of the Society of Hair Testing (Cooper et al., 2012), and then stored at room temperature until analysis. The initial 3 cm of hair growth was examined for cortisol concentration, which serves as an indicator of average HPA axis activity over the past weeks or months (Colding-Jørgensen et al., 2023). For the INMA-Gipuzkoa cohort, analysis was conducted at the Clinical Chemistry Laboratory of the University of Linköping in Sweden using a competitive radioimmunoassay (RIA) on methanol extracts. Further explanation on this methodology can be found elsewhere (Karlén et al.,

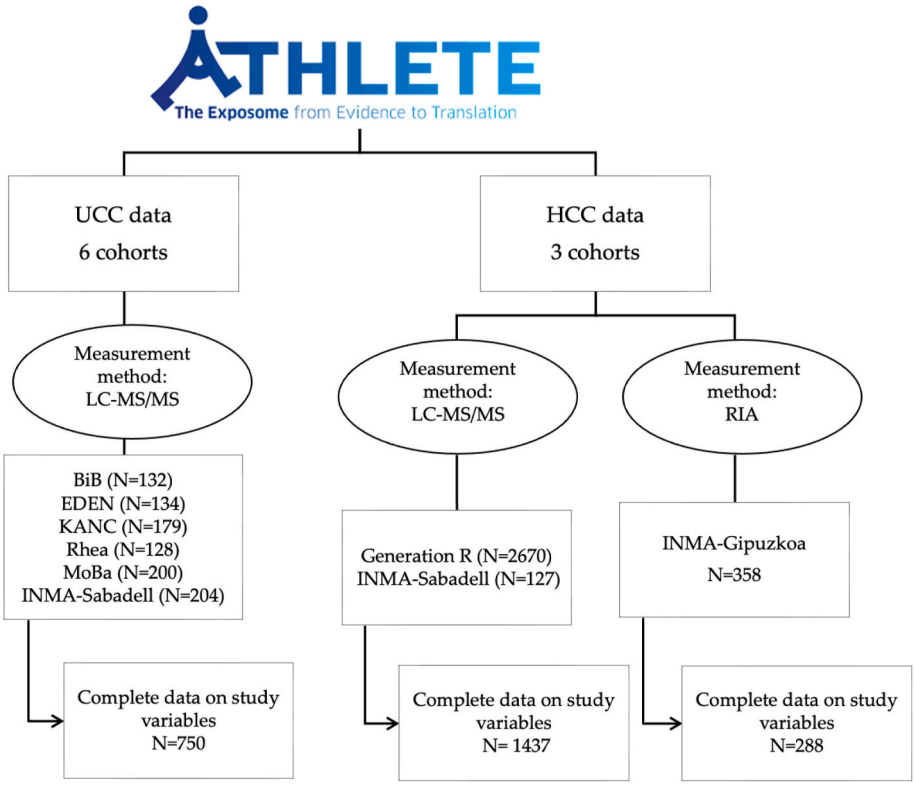

Fig. 1. Flowchart depicting the cohorts included in the study and cortisol measurement in each case.

2013). In the INMA-Sabadell cohort hair cortisol analysis were performed at the Hospital del Mar Research Institute using liquid chromatography-tandem mass spectrometry (LC-MS/MS) as explained by Gomez-Gomez and Pozo (2020). LC-MS/MS was also used for hair sample analysis in the Generation R cohort, as explained by Noppe et al. (2015). It is worth noting that RIA analysis produces 2–3 times higher cortisol levels that LC-MS/MS analysis, as explained by Russell et al. (2015) in the interlaboratory analysis.

2.3.2. Urinary cortisol concentration (UCC)

Cortisol and related metabolites were measured in urine samples. One urine sample was collected during the last void before bedtime on the night preceding the clinical visit to minimise the influence of diurnal variation. These samples were analysed in the Hospital del Mar Research Institute following the protocol described in Marcos et al. (2014), by liquid chromatography-tandem mass spectrometry (LC-MS/MS)Briefly, after addition of isotopic labelled internal standard, an enzymatic hydrolysis was performed to release the conjugated metabolites. Released steroids were then extracted by liquid-liquid extraction and determined by LC-MS/MS using a selected reaction monitoring method. Furthermore, the overall cortisol production was assessed by adding several cortisol metabolites, which were normalized based on creatinine values (divided by the creatinine values within each sample): Cortisol, 20α-dihydrocortisol, 20β-dihydrocortisol, 5β-dihydrocortisol, 5α-tetrahydrocortisol, 5β-tetrahydrocortisol, 6β-hydroxycortisol, 5α,20α-cortol, 5α,20β-cortol, 5β,20α–cortol and 5β,20β–cortol. The overall cortisol concentration represents the total cortisol production and it is preferred for use in analysis over cortisol alone (Levine et al., 2007)

2.4. Other assessed variables

Based on the literature, a set of environmental, social and individual covariates were selected because of their potential relationships with exposure to noise and/or cortisol concentrations. Regarding environmental factors, neighbourhood greenness and air pollution were included. *Neighbourhood greenness* was assessed using Normalized Difference Vegetation Index (NDVI; Tucker, 1979) derived from the Landsat 4–5 Thematic Mapper (TM), Landsat 7 Enhanced Thematic Mapper Plus (ETM+), and Landsat 8 Operational Land Imager (OLI)/-Thermal Infrared Sensor (TIRS) with 30 m × 30 m resolution at 30 m × 30 m resolution. NDVI, an indicator of greenness, measures the difference between visible (red) and near-infrared light reflected by vegetation. Its values fall within the range of −1 to 1, where higher values indicate increased greenness. Surrounding greenness was abstracted as the average of NDVI in 300 m buffer around each geocoded residential address over the last year when the follow-up phase was conducted. Two or more images were selected for each cohort to cover the time points of interest.

Traffic related air pollution was estimated by nitrogen dioxide (NO_2) exposure. Individual NO_2 exposure at each participant's geocoded residential address during the past year of the follow-up phase was estimated using a land use regression (LUR) models. In the case of HELIX cohorts, exposure assessment is based on LUR modelling approach developed in the European Study of Cohorts for Air Pollution Effects (ESCAPE) framework (Beelen et al., 2013). In case of Gipuzkoa and Generation R, exposure estimation at each participant's geocoded residential address was estimated within the framework of the LifeCycle project (Jaddoe et al., 2020). Briefly, to estimate exposure levels for the relevant period temporal adjustment was applied, by combining LUR-based spatial estimates with a temporal adjustment factor from routine monitoring stations, following ESCAPE guidelines (Hoek et al., 2008).

Regarding social factors *neighbourhood SES* was described using country specific deprivation indexes and harmonized following Lyfecycle protocol (de Castro et al., 2021). Specifically, for the Generation R cohort Status scores were used, for INMA cohorts Urban vulnerability index, for BiB we used the Index of Multiple Deprivation, French European deprivation index score for EDEN. In the case of KANC and Rhea deprivation index was calculated based on educational level and for MoBa it was measured based on income. Between one and four layers were selected for each country to cover the entire study period and were assigned to correspond with the follow-up period. Finally it was categorized them into tertiles, where 1 means less deprived and 3 more deprived.

Several individual factors were also selected. *Body Mass Index* (BMI) was determined by dividing children's weight in kilograms by the square of their height in meters (kg/m^2) at the time of the follow-up. In the present study, z-scores proposed by the World Health Organisation were used (WHO, 2006).

Externalizing problems and *sleep disturbances* were evaluated using the Child Behaviour Checklist (CBCL (Achenbach and Rescorla, 2001). The CBCL is a widely validated and reliable instrument for assessing emotional and behavioural problems (Achenbach and Ruffle, 2000). At the time of the follow up, the primary caregiver rated on a three-point scale (Not True, Somewhat True, Very/Often True) 113 items to assess behavioural problems in children during the last two months. This total score can be subdivided into several subscales: we used externalizing behaviour score, which is the combination of the rule-breaking behaviour and aggressive behaviour scales. Total raw score in these scales was used, higher scores indicating more externalizing problems (lowest score: 0, highest score: 38). Further, we also employed the items from the CBCL referring to sleep problems: 47, nightmares; 54, overtired without good reason; 76, sleeps less than most kids; 77, sleeps more than most kids during day and/or night; 92, talks or walks in sleep; 100, trouble sleeping and 108, wets the bed. These items were added to obtain total sleeping problems with higher scores indicating greater sleep problems (range 0–8). Previous studies employed these items to estimate sleeping problems in children (González-Safont et al., 2023; Gregory et al., 2008) they showed remarkable convergent validity, as their scores highly correlated with existing sleep scales (Mancini and Pearcy, 2021) and objective measurements (Gregory et al., 2011).

Finally, parent-reported information on *physical activity* was gathered through a questionnaire filled out by the main caregiver. For HELIX and INMA-Gipuzkoa participants a validated questionnaire designed to assess physical activity in children aged 6–12 years was utilized (Prieto-Botella et al., 2022). In this questionnaire, parents specified their children's type of physical activity and the duration during the week. Specifically, they were asked about the activities that their child engaged in both at school and outside of school hours during a typical week in the past year. These activities were classified as light (playing, sitting on swings, going to the theatre, etc.), moderate (walking, cycling, rollerblading, skating, etc.), or vigorous (swimming, baseball, football, basketball, etc.), based on metabolic equivalent of task value assigned to every activity. For Generation R participants, parents completed an ad-hoc questionnaire on their children's physical activity. The questionnaire included frequency and duration of physical education on school, outdoor play, swimming and in other sports (tennis, hockey, dancing, basketball, athletics, etc). Following previous studies, the time spent on each activity was calculated as hours per day x days per week and total physical activity by adding hours in each activity (Rodriguez-Ayllon et al., 2020, 2023). In both cases we focused on the total minutes per day of moderate to vigorous physical activity, calculated by combining the duration of moderate and vigorous activities.

2.5. Data analysis

Data were analysed using R software v.4.0.3 (R Core Team, 2022). After computing descriptive statistics, we followed a three-step process to determine the covariates for inclusion in the regression models. All the analyses were independently applied to UCC and HCC analyses. In the latter case, we also separated the analysis for HCC measured by RIA and LC-MS/MS. First, we proposed a Direct Acyclic Graph (DAG)

adapted from a previous study based on the hair cortisol determinants in children (Arregi et al., 2024) (see Fig. 2). Second, the validity of the DAG was assessed following the procedure described elsewhere (Ankan et al., 2021; Subiza-Pérez et al., 2023): we used R package dagitty (Textor, 2020; Textor et al., 2016) and lavaan (Rosseel, 2012). Testable implications refer to the pairwise marginal and conditional independencies inferred from a DAG. Conditional independencies were assessed using the most appropriate statistical test for each specific case. When the p-values for the independence tests were lower than 0.05, and the *r*-scores were larger than 0.20, testable implications were considered unmet, thereby suggesting missing relationships that were subsequently included in the DAG. After validating the DAG, we proceeded with the last step: the identification of the minimum and sufficient set of variables to estimate the effects of the exposure variable on the outcomes of interest (Perković et al., 2015; Van Der Zander et al., 2014). Covariate adjustment sets were obtained using the function adjustmentSets () of the R package dagitty.

All the analyses were performed with the complete cases (analytical sample from now on). There were substantial missing variables in the environmental variables, so we conducted a series of chi-square tests and Welch's *t*-test to determine if the analytical sample differed from the initial sample (described in Supplementary Tables S1–S2). Statistically significant differences were observed between the initial sample and the analytical sample averages for the following variables: physical activity, neighbourhood greenness and air pollution. However, we concluded the analytical sample was representative of the initial sample as mean differences between the final and initial samples were not substantial.

Finally, we estimated the total and direct effects of L_{den} on outcomes (in this case, UCC and HCC). For this purpose, L_{den} was treated as a continuous variable to obtain more interpretable results. For HCC measured by LC-MS/MS analysis and we applied mixed-effects modelling with the function lme () of the R package nlme (Pinheiro et al., 2022) with <cohort> as a random factor and the identified sets of covariates as adjustment sets. For the sample with HCC measured by RIA (INMA-Gipuzkoa cohort), linear modelling was applied.

3. Results

3.1. Sample description and DAG validation

Table 1 contains descriptive statistics of the study variables in the analytical sample with hair cortisol concentration (HCC), separated by cohort. The INMA-Gipuzkoa analytical sample consisted of 288 children: 53.8 % were female and age average was 7.87 years (SD = 0.11). Regarding the analytical sample with HCC measured by LC-MS/MS, it included 1326 children from Generation R (49.2 % Female, mean age = 6.06, SD = 0.51) and 111 children from INMA Sabadell (51.4 % Female, mean age = 8.75, SD = 0.53).

In the INMA-Gipuzkoa cohort, 61.1 % of the children were exposed to noise levels exceeding 55 dB L_{den}. Within the analytical sample where HCC was measured using LC-MS/MS, 44.7 % of the participants were exposed to noise levels above 55 dB at their residential address. No significant differences were observed in sleep disturbances [F (5, 282) = 0.223, p = 0.952] or total scores on externalizing problems [F (5, 282) = 0.322, p = 0.9] across different environmental noise exposure groups. Participants from the INMA-Sabadell cohort were exposed to higher noise levels compared to children in the Generation R study. Similar to the INMA-Gipuzkoa sample, there were no significant differences in sleep disturbances [F (5, 1431) = 0.613, p = 0.69] or total scores on externalizing problems [F (5, 1431) = 0.435, p = 0.824] among children in different environmental noise exposure groups.

HCC levels were higher when measured by RIA (median = 8.75 pg/mg) compared to LC-MS/MS (median = 1.55 pg/mg). No differences in HCC were observed between girls and boys, either in the INMA-Gipuzkoa subsample (female median: 8.20 pg/mg, male median: 8.23 pg/mg) or in the subsample analysed using LC-MS/MS (female median: 1.46 pg/mg, male median: 1.62 pg/mg).

All descriptive statistics for the studied variables in the analytical sample with urine cortisol concentration (UCC) are presented in Table 2, stratified by cohort. This analytical sample was comprised of 125 BiB children (42.4 % Female, mean age = 6.60, SD = 0.24), 27 EDEN

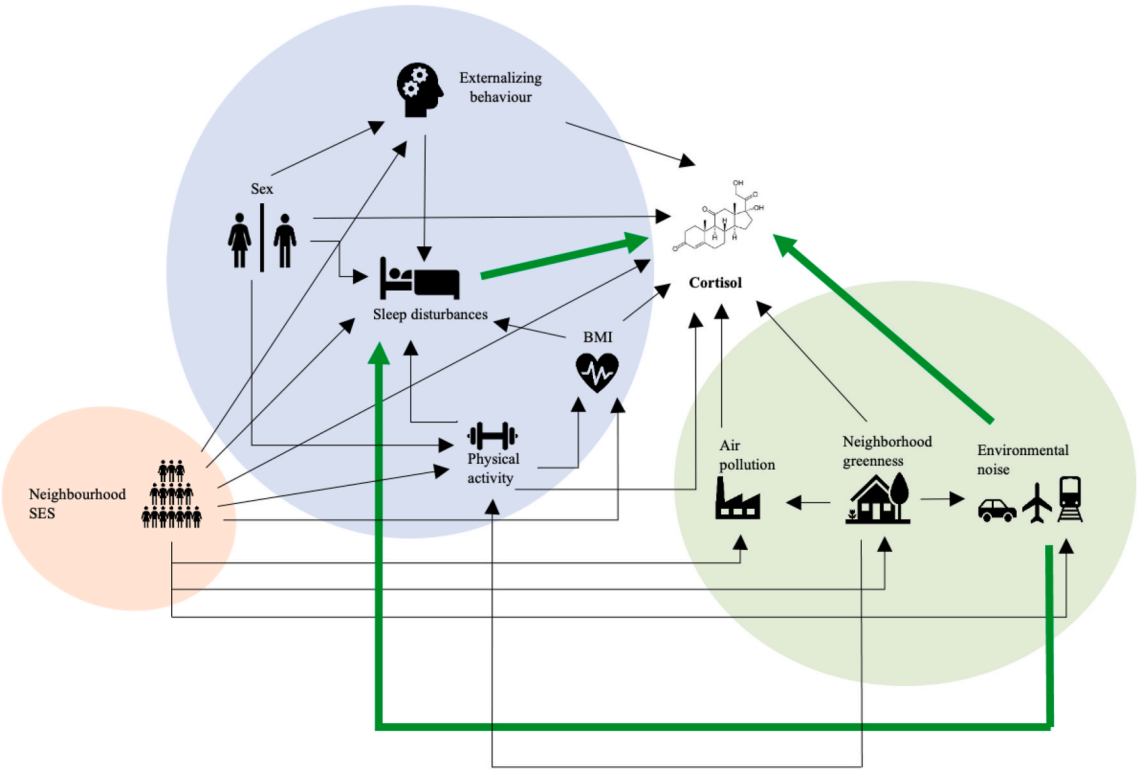

Figure 2. DAG explaining the relationship between exposure to environmental noise and cortisol. All the relationships were defined based on previous literature.

Table 1
Descriptive statistics of the study variables in the sample with HCC (analytical sample). Mean (SD) is shown in the numeric variables and frequency (%) in the categorical ones.

Variable name		INMA-Gipuzkoa N = 288	Generation R N = 1326	INMA-Sabadell N = 111
		Mean (SD)/Feq (%)	Mean (SD)/Feq (%)	Mean (SD)/Feq (%)
Age		7.87 (0.11)	6.06 (0.51)	8.75 (0.53)
Sex	*Female*	155 (53.8)	674 (50.8)	57 (51.4)
	Male	133 (46.2)	652 (49.2)	54 (48.6)
Area-level SES	*Low deprivation*	240 (83.3)	346 (26.1)	49 (44.1)
	Medium deprivation	48 (16.7)	231 (17.4)	43 (38.7)
	High deprivation	0 (0.0)	749 (56.5)	19 (17.1)
Externalizing problems		5.69 (5.62)	7.02 (6.21)	6.33 (6.47)
Sleep Disturbances		0.99 (1.19)	0.76 (1.2)	0.99 (1.44)
BMI		17.4 (2.3)	16.14 (0.17)	18.0 (3.0)
BMI (adjusted for sex and age)		0.8 (1.05)	0.43 (0.97)	0.71 (1.14)
Physical Activity (min per day)		63.5 (46.34)	127.6 (71.04)	49.94 (35.19)
NDVI (300 m)		0.42 (0.09)	0.42 (0.1)	0.25 (0.07)
Traffic-related Air Pollution (NO2)		14.32 (1.69)	33.39 (6.65)	36.48 (10.82)
L_{den}	<55 dB	112 (38.9)	785 (59.2)	10 (9.0)
	[55–60)dB	93 (32.3)	258 (19.5)	21 (18.9)
	[60–65)dB	59 (20.5)	178 (13.4)	36 (32.4)
	[65–70)dB	20 (6.9)	89 (6.7)	26 (23.4)
	[70–75)dB	2 (0.7)	16 (1.2)	11 (9.9)
	>75 dB	2 (0.7)	0 (0.0)	7 (6.3)
L_{night}	<50 dB	208 (72.2)	1018 (76.8)	28 (25.2)
	[50–55)dB	54 (18.8)	184 (13.9)	38 (34.2)
	[55–60)dB	22 (7.69	92 (6.9)	23 (20.7)
	[60–65)dB	3 (1.0)	32 (2.4)	13 (11.7)
	[65–70)dB	1 (0.3)	0 (0.0)	9 (8.1)
Hair Cortisol (pg/mg)		11.10 (7.83)	4.85 (15.91)	1.65 (3.74)
Urine Total Cortisol (μg/μmol creatinine)		–	–	0.23 (0.14)

Note: No statistically significant differences in the variables present in the model were found between the analytical sample composed by only complete cases and the initial sample, except for physical activity ($W = 843163$, $p < 0.001$), neighbourhood greenness (t-student (1501.9) = 3.46, $p < 0.001$) and air pollution (t-student (1591.3) = −6.278, $p < 0.001$). However, mean differences between the analytical and initial samples were not substantial and therefore, we determined the analytical sample composed by only complete cases was a representative sample of the initial data. Descriptive statistics of the initial sample are shown in Table S1.

children (33.3 % Female, mean age = 10.73, SD = 0.52), 160 KANC children (45.0 % Female, mean age = 6.45, SD = 0.48), 57 Rhea children (47.4 % Female, mean age = 6.55, SD = 0.30) 198 MoBa children (46.5 % Female, mean age = 8.50, SD = 0.49) and 183 INMA-Sabadell children (42.6 % Female, mean age = 8.78, SD = 0.55).

52.1 % of the children were exposed to higher noise levels than 55 dB L_{den}, with statistically significant differences between cohorts. There were no significant differences in sleep disturbances [F (5, 744) = 0.565, p = 0.727] or total scores on externalizing problems [F (5, 744) = 1.797, p = 0.111] among children in different environmental noise exposure groups.

A Pearson correlation analysis showed no significant relationship between UCC and HCC (n = 104), $r = 0.04$, $p = 0.707$. The ANOVA showed significant differences between cohorts on UCC levels, [F (5, 744) = 107, $p = <0.01$]. We did not observe differences in UCC between girls (mean = 0.40 μg/μmol creatinine; SD = 0.33) and boys (mean = 0.40 μg/μmol creatinine; SD = 0.37). All the descriptive statistics for the studied variables in the analytical sample with hair cortisol concentration (HCC), are shown in Table 2, separated by cohort.

In the case of the sample with HCC measured by RIA and the one with UCC, none of the testable implications derived from the initial DAG obtained r-coefficients above 0.2 and p-values below 0.05 (see Appendix I). In the case of the sample with HCC measured by LC-MS/MS, the testable implication "AirPol ⊥ EnvNoi | NeiGre, SES" was not met, thereby suggesting the existence of a relationship between traffic-related air pollution and environmental noise (once controlled for neighbourhood greenness and SES). We updated the DAG with this relationship (see Supplementary Fig. 1) and identified the minimum adjustment set of covariates to estimate the total and effect of environmental noise on cortisol levels. For the total effects, the adjustment set included neighbourhood socioeconomic status and neighbourhood greenness. Traffic related air pollution was also included in the case of the analysis with HCC measured by LC-MS/MS. For the direct effects, the three variables mentioned above plus externalizing problems, physical activity, sleep disturbances and sex were included.

3.2. Effect estimation

Table 3 shows results of the total and direct effects of L_{den} on hair cortisol concentration (HCC). Regarding the effect on the cortisol measured by LC-MS, both the total and direct effect were non-significant (β-estimate = -0.002). In the case of the total and direct effect of noise on HCC measured by RIA, the β-estimate for each 5 dB increase in L_{den} was about 0.05, but none of the models revealed statistically significant effects. Hence, we did not observe any statistically significant association between environmental noise exposure and HCC, nor in the case of hair cortisol measured by RIA neither in the case of LC-MS/MS analysis.

Results regarding the total and direct effect of L_{den} on urine cortisol concentration (UCC) are also shown in Table 3. The β-estimate for the total and direct effect of noise exposure on UCC was - 0.025 in both cases. None of the effects showed statistically significant association.

4. Discussion

In this study, our objective was to investigate the association between environmental noise exposure and both acute and cumulative cortisol levels in children from eight European birth cohorts. The β-estimates for the effect of L_{den} on hair cortisol concentration (HCC) measured by LC-MS/MS and RIA were −0.002 and 0.05 respectively, even if none of the models reached statistical significance. Similarly, no significant association was found for urine cortisol concentration (UCC; β-estimate = −0.025).

Regarding chronic cortisol levels, as indicated by hair cortisol concentration (HCC), as far as we know, only two studies focused on HCC

Table 2
Descriptive statistics of the study variables in the sample with UCC (analytical sample). Mean (SD) is shown in the numeric variables and frequency (%) in the categorical ones.

Variable name		BiB N = 125	EDEN N = 27	KANC N = 160	Rhea N = 57	MoBa N = 198	INMA-Sabadell N = 183
		Mean (SD)/Feq (%)	Mean (SD)/Feq (%)	Mean (SD)/Feq (%)	Mean (SD)/Feq (%)	Mean (SD)/Feq (%)	Mean (SD)/Feq (%)
Age		6.60 (0.24)	10.73 (0.52)	6.45 (0.48)	6.55 (0.30)	8.50 (0.49)	8.78 (0.55)
Sex	*Female*	53 (42.4)	9 (33.3)	72 (45.0)	27 (47.4)	92 (46.5)	78 (42.6)
	Male	72 (57.6)	18 (66.7)	88 (55.0)	31 (52.6)	106 (53.5)	105 (57.4)
Area-level SES	*Low deprivation*	16 (10.8)	12 (44.4)	47 (29.4)	34 (59.6)	81 (40.9)	83 (45.4)
	Medium deprivation	55 (44)	6 (22.2)	84 (52.5)	12 (21.1)	83 (41.9)	67 (36.6)
	High deprivation	54 (43.2)	9 (33.3)	29 (18.1)	11 (19.3)	34 (17.2)	33 (18.0)
BMI		16.10 (2.2)	16.80 (2.6)	16.37 (2.2)	16.64 (2.4)	16.39 (1.94)	17.97 (3.04)
BMI (adjusted for age and sex)		0.30 (1.17)	′-0.25 (1.04)	0.47 (1.20)	0.61 (1.28)	0.14 (0.91)	0.75 (1.23)
Externalizing Behaviour		5.5 (6.2)	8.74 (7.50)	8.61 (6.27)	8.58 (6.08)	3.14 (4.43)	7.01 (6.95)
Sleep Disturbances		1.13 (1.59)	1.19 (1.42)	1.54 (1.70)	0.93 (1.22)	0.89 (1.1)	1.09 (1.43)
Physical Activity (min per day)		57.76 (43.9)	27.01 (24.66)	66.00 (53.67)	26.42 (20.57)	69.71 (41.09)	48.65 (33.14)
NDVI (300 m)		0.46 (0.09)	0.53 (0.09)	0.51 (0.08)	0.29 (0.12)	0.60 (0.09)	0.27 (0.09)
Traffic-related Air Pollution (NO2)		31.59 (3.91)	13.59 (3.25)	14.17 (2.61)	12.45 (4.29)	27.35 (5.40)	34.52 (12.36)
L_{den}	<55 dB	69 (55.2)	20 (74.1)	118 (73.8)	0 (0.0)	129 (65.2)	23 (12.6)
	[55–60)dB	37 (29.6)	3 (11.1)	30 (18.8)	4 (7.0)	38 (19.2)	39 (21.3)
	[60–65)dB	14 (11.2)	2 (7.4)	9 (5.6)	41 (73.7)	21 (10.6)	61 (33.3)
	[65–70)dB	5 (4.0)	1 (3.7)	3 (1.9)	9 (15.8)	8 (4.0)	35 (19.1)
	[70–75)dB	0 (0.0)	1 (3.7)	0 (0.0)	2 (3.5)	0 (0.0)	16 (8.7)
	>75 dB	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	9 (4.9)
L_{night}	<50 dB	99 (79.2)	22 (9.2)	–	–	0 (0.0)	58 (31.7)
	[50–55)dB	20 (16.0)	3 (11.2)	–	–	183 (92.4)	63 (34.4)
	[55–60)dB	5 (4.0)	1 (3.7)	–	–	10 (5.1)	29 (15.8)
	[60–65)dB	1 (0.8)	1 (3.7)	–	–	4 (2.0)	22 (12.0)
	[65–70)dB	0 (0.0)	0 (0.0)	–	–	1 (0.5)	11 (6.0)
Urine Total Cortisol (μg/μmol creatinine)		0.79 (0.35)	0.20 (0.14)	0.38 (0.29)	0.77 (0.55)	0.26 (0.15)	0.22 (0.12)

Note: No statistically significant differences in the variables present in the model were found between the analytical sample composed by only complete cases and the initial sample, except for physical activity ($W = 843163$, $p < 0.001$), neighbourhood greenness (t-student $(1501.9) = 3.46$, $p < 0.001$) and air pollution (t-student $(1591.3) = -6.278$, $p < 0.001$). However, mean differences between the analytical and initial samples were not substantial and therefore, we determined the analytical sample composed by only complete cases was a representative sample of the initial data. Descriptive statistics of the initial sample are shown in Table S1.

Table 3
Results of the linear regression models showing total and direct effects of environmental noise on cortisol levels.

Exposure	Outcome	Cortisol measurement method	N	Model	Covariate adjustment	*β*-estimates	%95 CI	t-value	p-value
L_{den}	HCC	LC-MS/MS	1437	Total Effect	Neighbourhood greenness, neighbourhood SES, traffic-related air pollution	−0.002	(-0.06; 0.06)	−0.05	0.96
				Direct effect	Neighbourhood greenness, neighbourhood SES, traffic-related air pollution, emotional and behavioural problems, physical activity, maternal stress, sex and sleep disturbances	−0.002	(-0.06; 0.06)	−0.08	0.93
L_{den}	HCC	RIA	288	Total Effect	Neighbourhood greenness, neighbourhood SES	0.048	(-0.03-0.12)	1.29	0.20
				Direct effect	Neighbourhood greenness, neighbourhood SES, traffic-related air pollution, emotional and behavioural problems, physical activity, maternal stress, sex and sleep disturbances	0.046	(-0.03-0.12)	1.25	0.21
L_{den}	UCC	LC-MS/MS	750	Total Effect	Neighbourhood greenness, neighbourhood SES	−0.026	(-0.07; 0.19)	−1.133	0.258
				Direct effect	Neighbourhood greenness, neighbourhood SES, traffic-related air pollution, emotional and behavioural problems, physical activity, maternal stress, sex and sleep disturbances	−0.024	(-0.07; 0.21)	−1.046	0.296

when studying the relation between environmental noise exposure and chronic cortisol levels. Like our results, Verheyen and colleagues (2021) reported that residential exposure to traffic noise, as characterized by day-evening-night equivalent noise levels, were not associated with HCC measured using LC-MS/MS in boys nor girls aged 14–15. However, in another study with 11-year-old INMA-Gipuzkoa participants, higher total environmental noise exposure (rail, road and industry) in the participants building was related to lower hair cortisol concentrations in boys (Arregi et al., 2024) Importantly, this result was not replicated in the present study using data from the INMA-Gipuzkoa 8-year follow-up, despite the fact that most participants were similar across both studies. To further explore these findings, we examined the correlation between HCC measured at 8 and 11 years, and found no significant correlation between cortisol levels across the different follow-up periods. Therefore, we suggest that sex and age could be relevant factors when studying the relation between these variables and future studies should consider them.

More literature is available with regards to the association with urinary cortisol concentration (UCC). Some studies showed higher UCC in children living under higher traffic noise exposure (Evans et al., 2001;

Ising and Ising, 2002). However, Evans et al. (1998) found no statistically significant differences in UCC between children living near to an airport and children residing in nearby communities outside the noise-affected area of the airport. Other studies also did not find a relation between salivary cortisol and traffic noise (Bloemsma et al., 2021; Haines et al., 2001; Wallas et al., 2018) or aircraft noise (Haines et al., 2001). Therefore, results regarding acute cortisol levels in children and environmental noise exposure are not conclusive and more research is needed.

Previous studies regarding the association between environmental noise and cortisol levels have measured cortisol in a single biological matrix, with the majority assessing cortisol in urine or saliva samples. As aforementioned, both urinary and hair cortisol data were available only for INMA-Sabadell participants. We observed no correlation between HCC and UCC. Our results align with previous studies reporting low correlation (van Ockenburg et al., 2016) or even null correlations between hair and urinary cortisol (Chen et al., 2019; Short et al., 2016). Short et al. (2016) determined that out of the studied short-term cortisol measures, HCC was most strongly associated with the prior 30-day integrated cortisol production based on average salivary cortisol area under the curve. It is likely that cortisol measured in different samples provides different information regarding HPA axis productivity; UCC provides a measure of short-term cortisol levels while HCC reflects long-term levels. Multiple urinary cortisol measures may be necessary to investigate long-term stress responses (van Ockenburg et al., 2016) and therefore, overnight UCC can be difficult to interpret in relation to chronic environmental noise exposure. Because hair cortisol concentration reflects cortisol levels over several weeks (Staufenbiel et al., 2013) or months it may be a better indicator when examining associations with chronic exposures (Michaud et al., 2022). In the current study, we did not observe an association between environmental noise and cortisol levels, as measured in both urine and hair samples. The total environmental noise exposure may have been misclassified by considering only residential noise, as noise exposure was estimated solely at the subject's building façade. Consequently, noise exposure at the participant's residential address may not encompass all relevant sources of noise, particularly exposure in other contexts, such as at school. Nevertheless, numerous studies have identified associations between outdoor residential L_{den} and L_{night} and various health outcomes. In this study, L_{den} was categorized into 5 dB intervals, and information on noise levels below 55 dB was not available. This limitation may have influenced our results, as treating noise levels as a continuous variable could provide more precise information regarding exposure. However, such data were not available for all cohorts included in this study.

In addition, individual noise perception could also be an important factor in the association between environmental noise exposure and cortisol levels, as subjective perceptions of noise may mediate association between noise exposure and cortisol levels (Subiza-Pérez et al., 2024; Tao et al., 2020). Previous studies have also shown that individual noise sensitivity and perception can influence cortisol levels even more than the level of exposure itself. Wallas et al. (2018) found that noise annoyance tended to increase salivary cortisol levels, while road traffic noise exposure was not associated with cortisol. Similar results were reported in another study, where they observed that individual noise sensitivity was related to cortisol measured in blood, while the association was non-significant in the case of L_{den} (Kim et al., 2017). In this study, no differences were observed in individual factors, such as sleep disturbances or externalizing problems, between environmental noise exposure groups in the bivariate analyses. Had such differences been found, they could have supported the notion that individual noise sensitivity plays a crucial role in studying the relationship between noise exposure and cortisol levels Nevertheless, future research should include noise perception as a moderator variable.

Hence, it is important to highlight the complexity of the relationship between noise exposure and cortisol levels, which may depend on different situations. Factors such as individual susceptibility – previously discussed-as well as the duration and source of noise exposure, can influence this association. Previous research suggests that noise characteristics—such as loudness, frequency, and pattern—may influence its effects (Münzel et al., 2017), and consequently, the stress response may also be affected by the noise source. In our study, road traffic noise was estimated in all cases except for the INMA-Gipuzkoa cohort, where total environmental noise exposure—including traffic, railway, and industrial noise—was considered. Additionally, the duration of noise exposure may also play a role in the stress response. As previously mentioned, HCC may serve as a better indicator of chronic noise exposure, while UCC might be more reflective of acute exposure.

This study makes a meaningful contribution to the field for several reasons. First, taking into account the small number of studies in children, the inconclusive results among them and the fact that this population is considered particularly vulnerable to the effects of environmental noise, it is of vital importance to add evidence focusing on this population. Second, we used data from eight European prospective birth cohorts, which provides us with extensive information on several environmental, social, and individual stressors and a large sample size. Third, we used a DAG and the d-separation criterion to identify the set of adjustment variables. Even if the use of DAGs is becoming popular in epidemiological studies in the last years, testable implications are rarely checked (Ankan et al., 2021). Therefore, we reduced the risk of bias by residual confounding on our estimates.

Nevertheless, there are some limitations that must be considered when extracting conclusions from our study. First, cortisol was measured in urine samples in some cohorts and in hair samples in other ones. Both types of samples were only available for INMA-Sabadell participants. Having cortisol measured in both matrices would provide the opportunity to compare the two measures and determine which is more appropriate for studying the relationship between environmental noise exposure and cortisol levels. Nevertheless, we believe that future research should prioritize investigating the effects of environmental noise on HCC, as it may serve as a more reliable indicator for assessing associations with chronic exposures. Furthermore, hair cortisol was also measured with different methods: LC-MS/MS analysis in the INMA-Sabadell and Generation R, and RIA analysis in the case of INMA-Gipuzkoa. As aforementioned RIA analysis produces higher cortisol levels than LC-MS/MS analysis (Russell et al., 2015) and therefore, we had to conduct separate analysis, reducing sample size and statistical power. The lack of statistical power could be the reason for not detecting a significant effect.

Secondly, the assessment of noise exposure focused on outdoor residential noise, which was categorized into 5 dB intervals starting at 55 dB. This approach may not accurately reflect actual noise exposure. As previously mentioned, treating noise levels as a continuous variable could yield more accurate information regarding exposure. Additionally, estimating noise exposure solely at the building façade may not encompass overall exposure, as noise levels in other contexts, such as schools or recreational areas, were not considered. Therefore, the lack of significant findings may be attributed to potential inaccuracies in estimating environmental noise exposure. Future studies should incorporate additional contexts to provide a more comprehensive assessment.

Third, even though considerable effort has been made to construct a comprehensive DAG that attempts to capture the complexity of the relationship between environmental noise and cortisol levels, the model we have developed is influenced by data availability across all cohorts. For instance, a standardized, validated questionnaire on sleep disturbances was not available for all cohorts. Consequently, items from the CBCL related to sleep problems were used as a proxy for sleep disturbances. Finally, data on perceived noise and noise sensitivity –or annoyance-was not available, which seems to be an important factor when studying the relation between environmental noise and cortisol levels (Kim et al., 2017; Wallas et al., 2018). Hence, future studies of the issue should consider this variable too.

5. Conclusion

This study aimed to provide additional evidence regarding the association between environmental noise exposure and cortisol levels in children. Our findings indicate no significant relationship between these variables among children from eight European birth cohorts. Negative results do not necessarily indicate the absence of an association between the studied variables. Instead, the limitations of the study may account for the lack of observed relationship between environmental noise and cortisol levels. Therefore, further research is necessary to explore how environmental noise exposure may influence chronic stress biomarkers in children, and we propose that HCC may serve as a valid tool for investigating the relationship between environmental stressors and cumulative cortisol levels. Focusing on stress biomarkers could deepen our understanding of the mechanistic pathways underlying health effects associated with noise exposure. In this regard, future research should incorporate additional biomarkers of stress and chronic inflammation, such as other stress hormones or immune markers. The use of a comprehensive chronic stress indicator, such as the allostatic load score—which encompasses neuroendocrine, immune, metabolic, and cardiovascular biomarkers—could also provide valuable insights.

CRediT authorship contribution statement

Ane Arregi: Writing – original draft, Formal analysis, Conceptualization. **Oliver Robinson:** Writing – review & editing, Supervision, Funding acquisition. **Gunn Marit Aasvang:** Writing – review & editing, Conceptualization. **Sandra Andrusaityte:** Writing – review & editing, Project administration. **Audrius Dedele:** Writing – review & editing. **Jorunn Evandt:** Writing – review & editing, Validation. **Gonzalo Garcia-Baquero:** Methodology, Formal analysis, Conceptualization. **Norun Hjertager Krog:** Writing – review & editing. **Mònica Guxens:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Vincent W.V. Jaddoe:** Writing – review & editing, Project administration, Funding acquisition. **Marianna Karachaliou:** Writing – review & editing. **Aitana Lertxundi:** Writing – review & editing, Validation, Supervision, Funding acquisition. **Katerina Margetaki:** Writing – review & editing. **Rosemary McEachan:** Writing – review & editing, Funding acquisition. **Mark Nieuwenhuijsen:** Writing – review & editing, Funding acquisition. **Claire Philippat:** Writing – review & editing. **Oscar J. Pozo:** Writing – review & editing, Resources, Investigation. **Remy Slama:** Writing – review & editing. **Mikel Subiza-Pérez:** Writing – review & editing, Formal analysis, Conceptualization. **Elisabeth F.C. van Rossum:** Writing – review & editing. **Martine Vrijheid:** Writing – review & editing, Project administration, Funding acquisition. **John Wright:** Writing – review & editing. **Tiffany C. Yang:** Writing – review & editing, Validation. **Oscar Vegas:** Writing – review & editing, Validation, Supervision, Conceptualization. **Nerea Lertxundi:** Writing – review & editing, Validation, Supervision, Conceptualization.

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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.2025.121541.

Data availability

The authors do not have permission to share data.

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