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Hair cortisol determinants in 11-year-old children: Environmental, social and individual factors

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ABSTRACT

Introduction: Children's exposure to chronic stress is associated with several health problems. Measuring hair cortisol concentration is particularly useful for studying chronic stress but much is unknown about hair cortisol determinants in children and adolescents, and previous research has often not considered the simultaneous exposure of multiple variables. This research is focused on investigating the relationship between environmental, social and individual factors with hair cortisol concentration in children.

Methods: The data used in this study are from the INMA prospective epidemiological cohort study. The assessment of chronic stress was made on the basis of hair samples taken at the age of 11 years in the INMA-Gipuzkoa cohort ($n = 346$). A metamodel summarizing the hypothesized relationships among environmental, social and individual factors and hair cortisol concentration was constructed based on previous literature. Structural Equation Modelling was performed to examine the relationships among the variables.

Results: In the general model higher behavioural problems were associated with higher cortisol levels and an inverse relationship between environmental noise and cortisol levels was observed, explaining 5 % of the variance in HCC. Once stratified by sex these associations were only hold in boys, while no significant effect of any of the study variables was related with cortisol levels in girls. Importantly, maternal stress was positively related to behavioural difficulties in children. Finally, higher traffic-related air pollution and lower exposure to neighborhood greenness were related to higher environmental noise.

Discussion: This study highlights that simultaneous exposure to different environmental, social and individual characteristics may determine the concentration of hair cortisol. More research is needed and future studies should include this complex view to better understanding of hair cortisol determinants in children.

1. Introduction

Exposure to chronic stress can lead to physiological dysregulation and brain alterations, which are associated with several health outcomes such as metabolic, cardiovascular, and respiratory problems (Guidi et al., 2021; Juster et al., 2010). Exposure to chronic stress can be

Abbreviations: BMI, Body Mass Index; CFI, comparative fit index; HCC, hair cortisol concentration; HPA, Hypothalamic-Pituitary-Adrenal; INMA, INfancia y Medio Ambiente; L_{den}, Day-evening-night noise level; L_{night}, Night noise level; NDVI, Normalized Difference Vegetation Index; OBVQ, Olweus Bully Victim Questionnaire; PSS, Perceived Stress Scale; RMSEA, root-mean-square error of approximation; SDSC, Sleep Disturbance Scale for Children; SDQ, Strengths and Difficulties; SEM, Structural Equation Modeling; SES, socioeconomic status.

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especially damaging to children, as childhood is a critical and sensitive stage of development (Condon, 2018). The hypothalamic-pituitary-adrenal (HPA) axis may play a key role in the stress-disease pathway (Guidi et al., 2021). Several environmental, social and individual factors may act as a stressor activating HPA axis. Activation of the HPA axis causes secretion of glucocorticoids, such as cortisol. This glucocorticoid has been identified as a valuable biomarker of stress through HPA function and it has been investigated in relation to numerous indicators of individual and social stressors (Bryson et al., 2021; Law and Clow, 2020).Under normal conditions, the body has several mechanisms to restore basal state (Sterling and Eyer, 1988). However, in cases of chronic stress, dysfunction in the HPA axis occurs, and buffering mechanisms may prove insufficient to return to baseline conditions (Mc Ewen, 1998). While acute stress reaction is vital for facing daily challenging situations, chronic stress has been linked to various diseases (Guidi et al., 2021).

Most research examining cortisol response has focused on blood, saliva, and urine samples (Hellhammer et al., 2009; El Mlili et al., 2021), which are reliable methods for measuring acute cortisol levels (Wright et al., 2015). In contrast, hair cortisol analysis provides information on HPA activity over several months as the average hair growth is 1 cm per month (Stalder et al., 2017). Therefore, this innovative and minimally invasive technique is particularly useful for studying chronic stress (Kirschbaum et al., 2009), which is associated with a higher risk of metabolic, cardiovascular, and neurological diseases (Iob and Steptoe, 2019; Meng et al., 2021; Saeedi and Rashidy-Pour, 2021; Xiong and Zhang, 2013). Several factors have been found to influence hair cortisol concentration (HCC) in adults such as, age, sex, anthropometric measures, demographic factors, neighborhood characteristics or physical and mental health status (Abell et al., 2016; Koumantarou Malisiova et al., 2021; El Mlili et al., 2021; Stalder et al., 2017). Therefore, the physical environmental surrounding, social and familial relationships, early life stressful conditions and individual characteristics may all be associated with HCC in children, but much remains unknown about the determinants of HCC in children and adolescents (Gray et al., 2018; Li et al., 2023). Moreover, previous research has usually analysed effect of these variables independently and often has not considered the simultaneous interrelationship between multiple variables that may explain hair cortisol levels in children. Understanding factors that can affect hair cortisol levels in children is vital for a healthy young population. Several individual factors and the exposome, which encompasses all environmental exposures, affect children's stress and health (Siroux et al., 2016). Both the physical and social environment are included in the exposome.

1.1. Physical environment

The environmental surroundings in which children live, including urbanization level, presence and access to green or blue spaces, and air pollution, may have an impact on their cortisol levels (Bloemsma et al., 2021). Exposure to nature has been shown to have a positive effect on reducing physiological stress (Shuda et al., 2020), and increased exposure to green spaces has been associated with decreased salivary cortisol levels (Twohig-Bennett and Jones, 2018). Green spaces may reduce stress by providing opportunities to escape from physical and social stressors or by acting as a buffer against other environmental stressors such as air pollution, heat stress, artificial night light, or environmental noise (Bloemsma et al., 2021; Markevych et al., 2017). A study focusing on chronic cortisol levels measured in hair, found no association between HCC and residential greenness (Van Aart et al., 2018).

Continuing with environmental-related factors, both air pollution and environmental noise can act as stressors, causing activation of the HPA axis and subsequent release of stress hormones (Babisch, 2003; Daiber et al., 2019; Munzel et al., 2014; Thomson, 2019). Exposure to air pollution activates the HPA axis and stimulates the liberation of cortisol (Miller et al., 2016; Verheyen et al., 2021a; Wing et al., 2018). Nevertheless, one study found no association between hair cortisol and residential air pollution in school-aged children (Van Aart et al., 2018). An important limitation of the study is the high limit of detection of the cortisol analysis (1.6 pg/mg). Regarding environmental noise, studies on adults have shown a positive association between noise exposure and acute cortisol levels (Baudin et al., 2019; Lefèvre et al., 2017; Selander et al., 2009; Wagner et al., 2010). However, studies on children showed inconsistent results: three cross-sectional studies showed higher urinary or salivary cortisol levels in children living in noisier areas (Evans et al., 2001; Ising et al., 2004; Ising, 2003), whereas others have shown no statistically significant increase in urinary or salivary cortisol levels (Bloemsma et al., 2021; Evans et al., 1998; Haines et al., 2001; Wallas et al., 2018). Although measuring hair cortisol is considered a viable tool for assessing the association between environmental noise exposure and chronic stress (Michaud et al., 2022), to the best of our knowledge, only one study has measured hair cortisol and found no association between residential exposure to traffic noise and hair cortisol concentration in 14–15-year-old adolescents (Verheyen et al., 2021a).

1.2. Social environment

Besides the physical environment, few studies have considered the impact of social environment on HCC in children (Fuchs et al., 2018). Family context may have a significant influence on the regulation of the HPA axis in children, and research has shown that children's cortisol response can be altered by the quality of caregiving, relationships with parents, and family structure (DeCaro and Worthman, 2008; O'Neal et al., 2010). Evidence suggests that family environment, presence of traumatic events and parental stress are associated with children's hair cortisol concentration, and maternal factors have been found to be highly correlated (Anand et al., 2020; Erickson et al., 2022; Karlén et al., 2013a, 2013b; Simmons et al., 2016). According to a systematic review, HCC levels are higher in children who experience persistent forms of stress such as maternal distress (Bates et al., 2017). Additionally, Bates et al. (2017) found that several socioeconomic status (SES) factors, including parental education and neighborhood SES, were negatively associated with childhood HCC, thus HCC was elevated in those with low socioeconomic status.

In addition to family environment, school environment plays a crucial role during childhood and adolescence development. School-related stress has been found to have a negative impact on health outcomes. In the school context young individuals build social connections with their peers and encounter a multitude of stressful situations (García-Moya et al., 2013). Previous research on this topic has relied on saliva samples to measure cortisol levels, and it has been observed that unsupportive school environments and difficulties in relationships with teachers and peers are linked to flattened cortisol slopes (Ahnert et al., 2012; Bai et al., 2017). Regarding chronic cortisol levels, a recent review found limited and inconsistent evidence on the association between social adversity and hair cortisol levels in children (Bryson et al., 2021). Bullying is one of the most significant stressors during this period, and numerous studies have investigated the association between bullying and salivary cortisol levels, yielding inconsistent results (Kliewer et al., 2019). Prior studies exploring the link between bullying and HCC found higher cortisol levels in children involved as bullies/victims, although the relation was only marginally significant (Babarro et al., 2022) and higher HCC levels in boys who experienced high victimization (Ouellet-Morin et al., 2021) .

1.3. Individual factors

HPA axis activity may also be affected by other individual characteristics and lifestyle factors (De Nys et al., 2022; Jia et al., 2022; Nollet et al., 2020). Higher hair cortisol has been found to be associated with various lifestyle factors, such as sleep disturbances, doing less physical activity in adults (Gerber et al., 2013; El Mlili et al., 2021). Nevertheless, a recent study observed that objective measures of sleep and physical activity were not associated with chronic stress as measured by hair cortisol levels among normal-weight children aged 2–6 years (Eythorsdottir et al., 2020). Puberty, age, sex, and body mass index (BMI) are known to contribute to hair cortisol concentration in healthy children (Genitsaridi et al., 2020; Ursache et al., 2017; Wagner et al., 2020). Besides, HCC in children has been associated with behavioural problems (Fuchs et al., 2018) and self-reported quality of life (Buchan et al., 2021).

Given that several factors are thought to affect stress state and HPA axis activity in children, our main objective is to investigate the interaction between physical and social environment, experienced stressful events and individual characteristics affecting hair cortisol concentration in children, considered as a physiological biomarker of stress.

We hypothesize that childhood HCC may be determined by a complex pathway resulting from the interaction of environmental, social, and individual factors.

2. Materials and methods

2.1. Participants

The research focused on participants from the INMA-Gipuzkoa cohort situated in the Basque Country, northern Spain. The INMA study (www.proyectoinma.org; INfancia y Medio Ambiente), a prospective cohort study emcompassing seven different areas, aims to investigate the association between exposure to environmental factors and their impact on children's health as well as their physical and neuropsychological development (Guxens et al., 2012). This particular study exclusively involved individuals from the Gipuzkoa cohort. During the first trimester of pregnancy mothers were informed and recruited at public health centers or hospitals. Prior to enrollment, all participants provided written informed consent, and the study protocol received approval from the Ethics Committee of Donostia Hospital in Gipuzkoa. The study started with 638 women recruited during the first trimester of pregnancy, between 2006 and 2008, and 612 of them were monitored at birth. Subsequently, data were gathered through multiple follow-up phases. From the 377 who participated in the 11-year old follow-up the present study included 346 participants from which we had hair samples . 57 % of the participants were girls and mean age was 10.8 years (SD = 0.23).

2.2. Hair cortisol concentration

A nurse visited the participants' school and followed the guidelines outlined by the Society of Hair Testing (Cooper et al., 2012) to cut strands of hair from the posterior vertex area of their heads. The collected hair samples were then stored at room temperature until analysis, which took place at the Clinical Chemistry Laboratory of the University of Linköping in Sweden. The first 3 cm of hair outgrowth was examined using a competitive radioimmunoassay in methanol extracts. This specific hair segment offers an estimate of systemic cortisol levels over the preceding three months, considering that hair grows at an average rate of approximately 1 cm per month (Cooper et al., 2012). The limit of detection of the radioimmunoassay analysis was 0.1 nmol/L. Thus, when the cortisol concentration from a hair sample was lower analysis was repeated. In addition, hair samples were required to keep a total inter-assay coefficient of variation below 8 %. When the inter-assay coefficient was higher, analysis was repeated too. In both cases, when the result was repeated in the second analysis too, that sample was excluded from analysis, considering out of range. Detailed information about this method can be found elsewhere (Karlén et al., 2013a, 2013b). To ensure the accuracy of the results, certain external factors like sun exposure, frequent shampooing, and the use of hair bleaching products, which could influence cortisol levels, were taken into consideration. To minimize these effects, participants were instructed not to wash their hair for 24 h before sampling. Additionally, individuals with dyed hair were excluded from the analysis.

2.3. Environmental stressors

Traffic-related air pollution: Nitrogen dioxide (NO_2) exposure was assessed through passive samples distributed across the study area. The estimation of NO2 exposure at each participant's geocoded residential address was calculated within the LifeCycle project framework using a land use regression (LUR) modelling approach (Jaddoe et al., 2020). Altitude, valley factor, distance to the nearest road, urban land cover and industrial land cover has been included in the LUR models to predict NO_2 levels. The Coefficient of determination of the model was 0.51 (Estarlich et al., 2011). To determine the annual averages of individual NO_2exposure, the average of measurements taken during three different periods was used. These values were then adjusted for temporal variation by considering the average over a one-year period.

Neighborhood greenness: The measurement of greenspace around residential areas utilized the Normalized Difference Vegetation Index (NDVI) derived from Landsat Thematic Mapper TM at a resolution of 30 m × 30 m. NDVI measures greenspace based on the difference between visible (red) and near-infrared light reflected by vegetation. Its values vary from −1 to 1, with higher values signifying greater greenery. To assess residential greenspace for each participant, the average NDVI values were calculated within a 300 m buffer around their geocoded residential address over the past year.

Environmental Noise: To evaluate the annual outdoor noise exposure levels at participants' homes, noise maps specifically developed for Gipuzkoa were utilized. These maps were created in accordance with the measurement methods recommended by the European Environmental Noise Directive (Directive 2002/49/EC, 2002) and regional regulations requires to generate noise maps to all local councils with populations exceeding 10,000 (Decree 213/2012, 2012). Additionally, we created noise maps for municipalities with populations ranging from 6000 to 10,000 inhabitants following the same methodology. Finally, information on environmental noise for 87 % of the INMA-Gipuzkoa participants in the 11-year follow-up stage was obtained. Equivalent noise levels during the night (L_{night}) and day-evening-night noise level (L_{den}) on the façade of the residential address were estimated, as explained elsewhere (Arregi et al., 2022).

2.4. Social stressors

Maternal stress: At the 11-year follow-up, mothers were requested to complete a brief version of The Perceived Stress Scale (PSS-4) comprising four items. s a commonly employed self-report questionnaire crafted to assess an individual's perception of stress in their life situations (Cohen et al., 1983). The Spanish version of PSS-4 has demonstrated satisfactory psychometric properties (Ruisoto et al., 2020). In this study, the total score was used (ranging from 0 to 16), where higher scores denoted elevated perceived stress levels.

Neighborhood SES: For each participant, the area level socioeconomic status (SES) was determined using a census deprivation index recorded in 2021. This index took into account various factors such as the percentage of manual workers, unemployment rate, prevalence of temporary workers, and insufficient education (Duque et al., 2021; Felícitas Domínguez-Berjón et al., 2008). A five-level variable was established based on this index, spanning from 1 (indicating very low deprivation) to 5 (representing very high deprivation). A higher deprivation index corresponds to a lower socioeconomic status within the neighborhood.

Number of stressful events: Data regarding the number of stressful life events occurring since the child's birth were gathered. This information was obtained through an adapted version of the Children's Life Events Inventory (Monaghan et al., 1979), focusing on events like changes in residence or school, parental separation, and the death or hospitalization of a relative. A binary variable was established; participants reporting at least one stressful event were categorized as having experienced such events.

Bullying involvement: Participants' propensity to be involved in bullying was estimated using a 16 item version of the Olweus Bully Victim Questionnaire, where children were asked to recount their experiences over the preceding two months (OBVQ; Gothwal et al., 2013). Responses were rated on a 5-point Likert scale, ranging from 0 ("it hasn't happened to me in the past couple of months") to 4 ("it happens several times a week"). A binary variable was established (Solberg and Olweus, 2003): participants reporting encountering any form of bullying 2–3 times a month or more frequently were categorized as being involved in bullying. The OBVQ, a widely utilized self-report instrument, demonstrates well-established psychometric properties (Kyriakides et al., 2006).

2.5. Individual factors

Health related quality of life: The health-related quality of life was evaluated using the Kidscreen-27 questionnaire (Ravens-Sieberer et al., 2007). This self-report questionnaire consists of 27 items categorized into five subscales: Physical Well-Being (five items), Psychological Well-Being (seven items), Autonomy & Parents (seven items), Peer and Social Support (four items), and School Environment (four items). Respondents rated each item on a 5-point Likert scale: (1 = "not at all," 2 = "a little," 3 = "moderately",4 = "much" and 5 = "very much"). The Spanish version of the questionnaire has been validated and demonstrated satisfactory psychometric properties (Vélez et al., 2012). To calculate the total score (ranging from 27 to 135), all item responses were added, accounting for negatively worded questions. Higher scores indicate a better overall health-related quality of life.

Physical activity: Parents provided subjective information about their children's physical activity levels through a validated questionnaire (Prieto-Botella et al., 2022). The questionnaire included a list of 31 physical activities commonly undertaken by children throughout a typical week, both in and out of school. Parents were queried about the duration of time their children spent on each activity on both weekdays and weekends. These activities were categorized as light (e.g., playing, sitting on swings, going to the theatre), moderate (e.g., walking, cycling, scootering, rollerblading, skating), or vigorous (e.g., swimming, baseball, football, basketball), based on the associated calorie consumption. To quantify total physical activity, the minutes spent in moderate and vigorous activities were added together.

Sleep Disturbances: Children's sleep disturbances were measured by the Sleep Disturbance Scale for Children (SDSC; Bruni et al., 1996) reported by mothers. The SDSC contains 26 items divided into six subscales: problems with initiating and maintaining sleep, sleep breathing disorders, disorders of arousal, sleep-wake transition problems, excessive somnolence, and sleep hyperhidrosis. The Spanish version of the questionnaire showed adequate psychometric properties (Pagerols et al., 2023) and provides a standardized measure of sleep disturbances in children and adolescents over the previous six months. In this study, total score was used (range: 26–130), in which a higher rating indicates more sleep disturbances.

Behavioural problems: Parents completed the Spanish validated version of the Strengths and Difficulties Questionnaire (SDQ; García et al., 2000; Goodman, 1997) to evaluate children's internalizing and externalizing problems. The SDQ comprises 25 items distributed across five subscales: emotional symptoms, conduct problems, hyperactivity-inattention, peer relationship problems, and prosocial behaviour. Responses are rated on a 3-point Likert scale (0 = "not true"–2 "certainly true"). To calculate the total difficulty score, scores from all scales, excluding the prosocial scale, were summed, resulting in a range from 0 to 40. A higher total score indicates a higher level of behavioural difficulties.

Body mass index: Anthropometric measurements were measured at the children's schools by a nurse. BMI was calculated by dividing children's weight in kilograms by their height in meters squared (kg/m^2).

2.6. Data analysis

R software version 4.0.3 (R Core Team, 2022) was used to conduct all the analyses. Initially, we examined the descriptive statistics, and we conducted a bivariate analysis.

Structural Equation Modelling (SEM) was performed to examine the relationships between the variables illustrated in Fig. 1. SEM presupposes linearity in the relationships between variables; therefore, as aforementioned, we analysed the symmetry of each relevant variable and transformed the data as needed (Tukey, 1977). Moderate to vigorous physical activity, behavioural problemsand sleep disturbance variables were square root-transformed, and the HCC variable was log-transformed to ensure linearity of relationships and appropriateness of the global estimation method. The sem() function of the lavaan package was used to test the model, which was modified iteratively using meaningful suggestions from modindices() until no further modifications were proposed. The final models were accepted when the following conditions were met: chi-square test p-value >0.05, the CFI > 0.95, and RMSEA p-value <0.05. Once we fitted the general model, we proceeded to re-estimate the path coefficients for boys ($n_M = 126$) and girls ($n_F = 174$) separately. This was done to explore potential differences between boys and girls. Same procedure was performed using both environmental noise indicators L_{den} and L_{night}.

Additionally, robust causal inference techniques were applied. Thus, we used DAGitty software (Textor et al., 2016) to identify a sufficient adjustment set for each of the subsequent regression models. We then used ordinary least squares estimation to fit linear regression models aiming at estimating 1. Direct effect of neighborhood greenness on traffic-related air pollution; 2. Direct effect of deprivation index on neighborhood greenness; and 3. Both total and direct effect of deprivation index on traffic-relatedair pollution.

3. Results

3.1. Descriptive statistics and bivariate findings

The present study included 346 mother-child pairs for which we had hair samples from 11-year-old children. No hair sample was collected from the remaining ones because their hair was too short or because

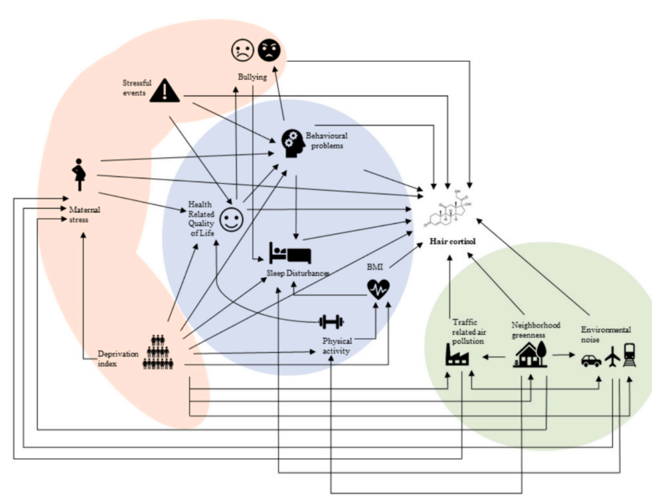

Fig. 1. Metamodel summarizing hypothesized relationships among environmental (green background), social (orange background) and individual factors (blue background) and hair cortisol concentration. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

their hair was dyed. Due to missing data, 46 out of the 346 participants initially considered were excluded, as SEM requires complete data (Fig. S1). Most of the excluded participants (41 out of 46) were due to the lack environmental noise information, as noise maps for municipalities under 6000 inhabitants are not available. Nonetheless, globally, the final sample used did not differ significantly from the initial sample, as no statistically significant differences in the SEM variables were found between the final sample composed of only complete cases ($N_{fs} = 300$) and the initial sample ($N_{is} = 346$), except for neighborhood greenness and air pollution (Table S1). A description of the study variables is provided in Table 1. The mean of HCC was 11.13 pg/mg hair (SD = 13.11) and our results did not show statistically significant differences by sex in hair cortisol. Girls' hair cortisol concentration was 11.52 pg/mg (SD = 15.33), while boys mean of HCC was 10.64 pg/mg (SD = 9.52).

Bivariate analyses showed that HCC was significantly and positively correlated with behavioural problems and negatively correlated with environmental noise, both L_{den} and L_{night}. Table S2 presents the correlations between the study variables and HCC. The hair cortisol concentration also differed from that of subjects who experienced at least one stressful event (mean = 12.00 pg/mg; SD = 15.1), and no stressful event was reported (mean = 10.40 pg/mg; SD = 11.1).

3.2. Structural equation model

The fitted SEM (Fig. 2, Table 2) showed a satisfactory goodness of fit [($\chi^2(43) = 37.874$, with p-value = 0.693, comparative fit index (CFI) = 1, and root-mean-square error of approximation (RMSEA) $\leq$ 0.001).]. The results indicated that environmental noise behavioural problems were associated with HCC, explaining 5 % of the variance (Fig. 2). Specifically, higher behavioural problems were associated with higher cortisol concentrations ($b = 0.16$; $p = 0.005$), and higher L_{den} was associated with lower cortisol concentrations ($b = -0.15$; $p = 0.007$). When using L_{night} results were similar, higher L_{night} was associated with lower cortisol concentrations ($b = -0.12$; $p = 0.038$; data not shown).

It should be pointed out that higher maternal stress was related with higher behavioural problems, explaining the 4 % of the variance ($b = 0.20$, $p < 0.001$). Similarly, higher neighborhood greenness was related to lower noise exposure ($b = -0.27$, $p < 0.001$) and lower traffic-related air pollution ($b = -0.55$, $p < 0.001$), and finally, traffic-related air pollution and noise were positively associated with each other, although marginally ($b = 0.11$, $p = 0.059$). Moreover, higher deprivation index (lower neighborhood SES) was related to higher neighborhood greenness ($b = 0.30$, $p < 0.001$) and higher traffic-relatedair pollution ($b = 0.24$, $p < 0.001$).

Additionally, we observed that health-related quality of life was negatively associated with bullying ($b = -0.19$; $p = 0.001$), and behavioural problems ($b = 0.12$; $p = 0.030$) and environmental noise ($b = 0.12$; $p = 0.033$) were positively associated with bullying. Together, these three variables explain 7 % of the variance in bullying. Higher traffic-related air pollution was also associated with a lower health-related quality of life ($b = -0.13$, $p = 0.026$), and physical activity was positively associated ($b = 0.17$; $p = 0.003$) with quality of life. 4 % of the variance in the health-related quality of life was explained. Maternal stress ($b = 0.13$; $p = 0.019$) and behavioural problems ($b = 0.27$; $p < 0.001$) showed a significant association with sleep disturbances, explaining the 11 % of the variance. Finally, the existence of stressful events ($b = -0.19$; $p = 0.001$) was negatively associated with physical activity, and being involved in bullying was related to more sleep problems ($b = 0.15$; $p = 0.008$).

Finally, we re-estimated the path coefficients separately for females ($n_F = 174$) and males ($n_M = 126$) (Fig. 3; Table 3). Both models showed a satisfactory goodness of fit: in case of models just for girls [($\chi^2(35) = 27.105$ with p-value = 0.828, CFI = 1.00 and RMSEA $\leq$0.001)] and in the case of boys [($\chi^2(39) = 45.305$ with p-value = 0.226, CFI = 0.952 and RMSEA = 0.026)]. When stratifying by sex, only associations between physical environment remained stable between two models: the association between neighborhood greenness with traffic-related air pollution and noise. Relations with hair cortisol, however, were only observed in boys: higher behavioural problems and lower environmental noise exposure were related with higher HCC. In addition, the presence of stressful events ($b = 0.27$, $p = 0.002$) was also related to cortisol. These three variables together explain the 16 % of boys HCC variability. However, none of the variables was associated with HCC in girls. In addition, the fitted model suggests that the relation between maternal stress and behavioural problems might be sex-dependant: this relation was only significant in boys.

3.3. Robust causal inference

In order to double-check and further confirm the SEM unexpected results about the relationships among deprivation index, traffic-related air pollution and neighborhood greenness, we also applied techniques for robust causal inference (Pearl, 2009), thereby estimating the relevant effects by ordinary least square estimation. The results we obtained are shown in Table 4, in which regression coefficients are presented in their standardized form, so that the comparison of these coefficients to

Table 1
Descriptive statistics of the considered variables. Mean (SD) Min (= minimum), Median and Max (= maximum) are shown for numerical variables and percentage for categorical variables.

	Variable name		N	Mean (SD) / %	Min	Median	Max
Outcome variable	Hair cortisol (pg/mg)		346	11.13 (13.11)	1.25	8.62	160.69
Environmental factors	Traffic-related air pollution (NO_2 levels; μg/m^3)		346	11.03 (1.72)	6.63	11.40	16.38
	Neighborhood greenness		346	0.48 (0.11)	0.23	0.46	0.81
	Day-evening-night environmental noise (L_{den},dB)		305	56.73 (5.92)	31.48	56.18	77.36
	Nocturnal environmental noise (L_{night}, dB)		305	46.76 (5.95)	22.28	46.61	67.40
Social Factors	Maternal stress		344	4.93 (2.42)	0.00	5.00	11.00
	Deprivation Index	*Very low*	29	6.90			
		Low	131	37.90			
		Medium	112	32.40			
		High	64	18.50			
		Very High	15	4.30			
	Bullying	*Not involved*	301	86.99			
		Involved	45	13.01			
	Stressful events	*0*	188	54.33			
		1 or more	158	45.66			
Individual factors	Health-related quality of life		346	117.50 (10.26)	82.00	118.00	135.00
	Physical activity		344	112.42 (66.42)	8.57	98.57	462.86
	Sleep disturbances		342	10.51 (7.46)	0.00	9.00	11.00
	Behavioural problems		342	13.23 (3.95)	6.00	13.00	27
	BMI (Kg/m^2)		345	18.86 (2.90)	10.66	18.40	30.41

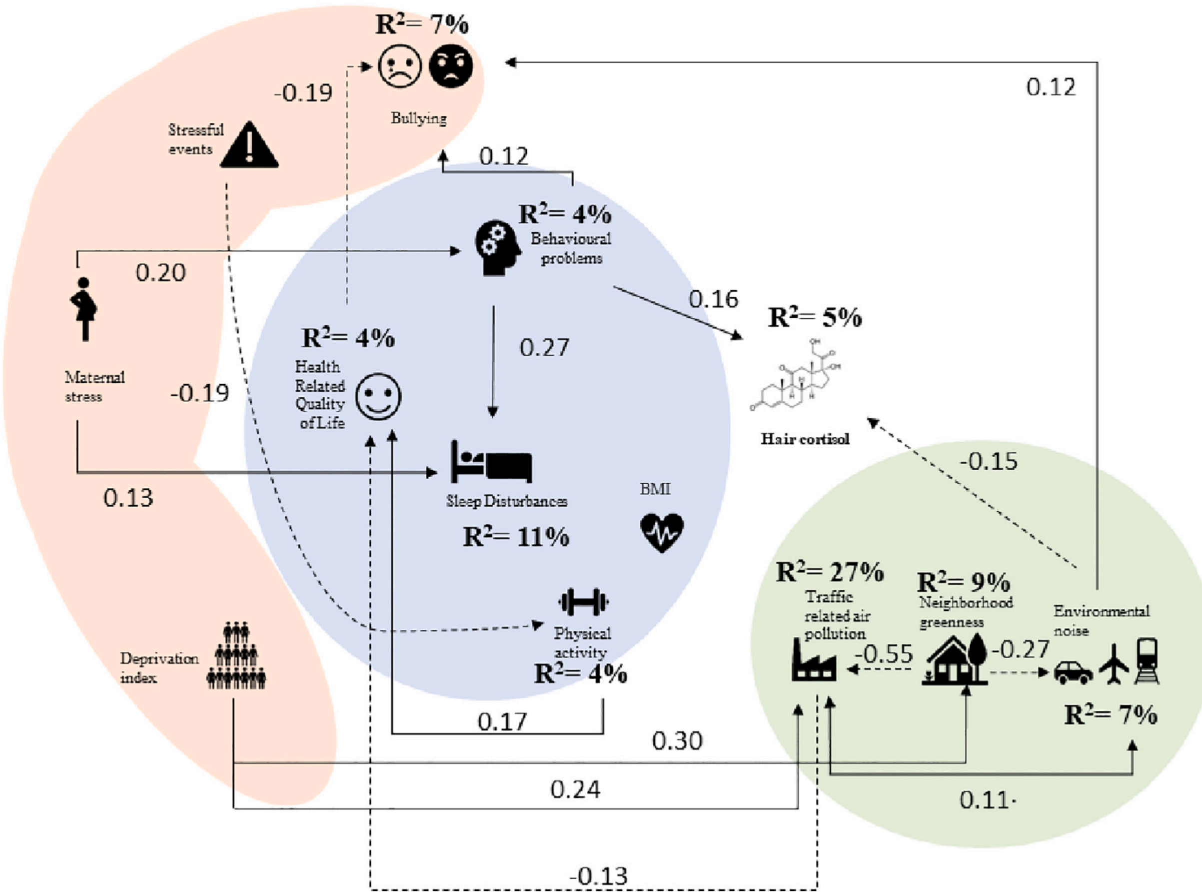

Fig. 2. Final structural equation model where standardized coefficients estimates are showed. Continuous arrows mean positive associations, while discontinuous negative ones. · means marginally significant relationship.

Table 2
Non-standardized effect sizes, together with standard errors, *z*-values and *p*-values for the structural equation model depicted in Fig. 2 (where standardized coefficients are provided); the reported R^2 correspond to the joint contribution of all predictors for each variable.

Variable	Predictor	Estimate	St.Err.	*z*-value	*p*-value	R^2(%)
Hair cortisol						4.80
	Environmental noise	−0.01	0.01	−2.71	0.007	
	Behavioural problems	0.15	0.05	2.80	0.005	
Behavioural problems						3.90
	Maternal stress	0.04	0.01	3.50	<0.001	
Environmental noise						7.20
	Neighborhood greenness	−18.53	3.83	−4.83	<0.001	
	Traffic-related air pollution	0.73	0.40	1.90	0.059	
Traffic-related air pollution						27.30
	Neighborhood greenness	−8.59	0.82	−10.52	<0.001	
	Deprivation index	0.28	0.82	10.52	<0.001	
Neighborhood greenness						8.70
	Deprivation index	0.02	0.01	5.36	<0.001	
Bullying						6.70
	Health-related quality of life	−0.01	0.01	−3.46	0.001	
	Environmental noise	0.01	0.01	2.13	0.033	
	Behavioural problems	0.08	0.04	2.18	0.03	
Health-related quality of life						4.30
	Traffic-related air pollution	−0.96	0.43	−2.23	0.026	
	Physical activity	0.62	0.21	2.94	0.003	
Physical activity						3.70
	Stressful events	−1.08	0.32	−3.40	0.001	
Sleep disturbances						11.40
	Maternal Stress	0.06	0.03	2.34	0.019	
	Behavioural problems	0.61	0.12	4.95	<0.001	

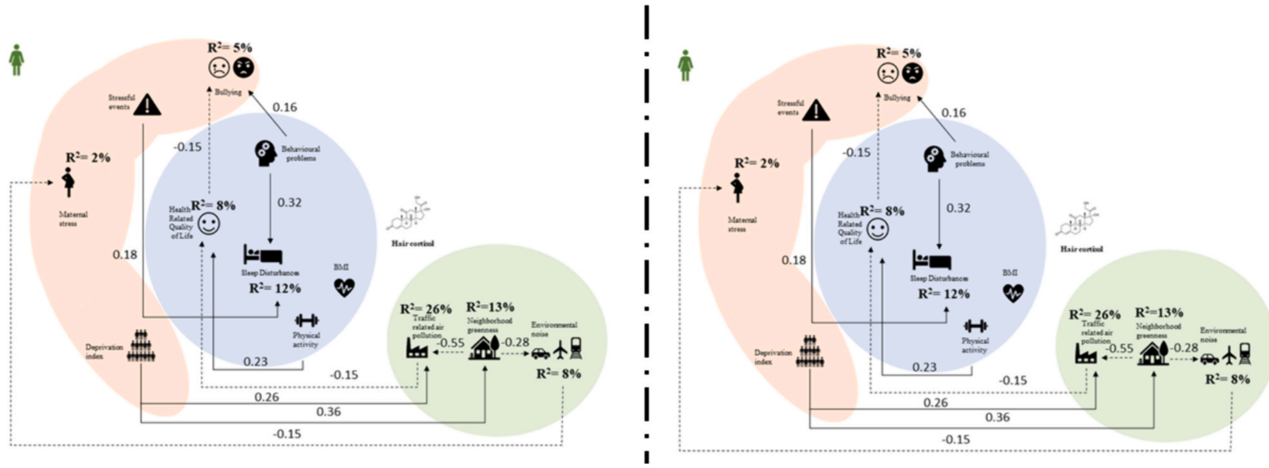

Fig. 3. Final structural equation model separated by sex. Left panel presents final model in boys, while fitted model in girls is shown in the right panel. Standardized coefficients estimates are showed. Continuous arrows mean positive associations, while discontinuous negative ones.

Table 3
Non-standardized effect sizes, together with standard errors, *z*-values and *p*-values for the structural equation model depicted in Fig. 3 (where standardized coefficients are provided); the reported R^2 correspond to the joint contribution of all predictors for each variable.

Female

Variable	Predictor	Estimate	St. Err.	z-value	p-value	R^2(%)
Environmental Noise						7.70
	Neighborhood greenness	−20.45	5.37	−3.81	<0.001	
Neighborhood greenness						13.20
Deprivation index						
Traffic-related air pollution		0.03	0.01	5.16	<0.001	26.20
	Neighborhood greenness	−9.24	1.18	−7.81	<0.001	
	Deprivation index	0.32	0.08	3.78	<0.001	26.20
Sleep disturbances						12.20
Behavioural problems		0.68	0.15	4.49	<0.001	
	Stressful Events	−0.40	0.16	2.46	0.014	
Health-related quality of life						7.80
	Physical activity	1.00	0.32	3.20	0.001	
	Traffic-related air pollution	−1.23	0.58	−2.11	0.035	
Bullying						4.90
	Health-related quality of life	−0.01	0.01	−2.05	0.041	
	Behavioural problems	0.09	0.05	2.19	0.028	
Maternal Stress						2.30
	Environmental Noise	−0.06	0.03	−2.05	0.041	

Male

Variable	Predictor	Estimate	St. Err.	z-value	p-value	R^2(%)
Environmental noise						7.80
	Neighborhood greenness	−17.76	5.43	−3.27	0.001	
Neighborhood greenness						4.30
	Deprivation index	0.01	0.01	2.37	0.018	
Traffic-related air pollution						29.50
	Neighborhood greenness	−8.22	1.12	−7.19	<0.001	
	Deprivation index	0.24	0.08	2.93	0.004	
Physical activity						5.00
	Stressful events	−1.36	0.50	−2.73	0.006	
Health-related quality of life						5.30
	Stressful events	−4.46	1.67	−2.67	0.008	
Behavioural problems						7.10
	Maternal stress	0.06	0.02	3.11	0.002	
Bullying						13.00
	Health-related quality of life	−0.01	0.01	−2.91	0.004	
	Environmental Noise	0.15	0.01	3.32	0.001	
Sleep Disturbances						11.50
	Behavioural problems	0.65	0.20	3.32	0.001	
Hair cortisol						16.30
	Behavioural problems	0.13	0.07	2.00	0.04	
	Environmental noise	−0.02	0.01	−3.51	<0.001	
	Stressful events	0.21	0.07	2.87	0.004	

SEM estimates (Fig. 2) is direct and simple. Thus, we see that the different methods of estimations lead to similar results, both in terms of sign and magnitude, for 1. direct effect of neighborhood greenness on traffic-relatedair pollution; 2. direct effect of deprivation index on neighborhood greenness; and 3. direct and indirect effects of deprivation index on traffic-relatedair pollution. It has to be noted that there is not a

Table 4

Linear total and direct effects models of neighborhood greenness on traffic-related air pollution and effects of deprivation index on those two variables. The standardized estimates shown in this table are of similar size and have the same direction (sign) than those obtained via SEM (Fig. 2). Thus, SEM estimates and ordinary least squares estimates are consistent.

Predictor (Exposure)	Outcome	Model	Sufficient adjustment set	Standardized Estimate	Std. Error	t-value	p-value
Neighborhood greenness	Traffic related air pollution	Total/Direct Effect	Deprivation index	**−0.531**	**0.052**	**−10.135**	**< 0.001**
Deprivation index	Neighborhood greenness	Total/Direct Effect	No adjustment is necessary	**0.304**	**0.055**	**5.517**	**< 0.001**
Deprivation index	Traffic related air pollution	Total Effect	No adjustment is necessary	0.077	0.058	1.328	0.185
Deprivation index	Traffic related air pollution	Direct Effect	Neighborhood greenness	**0.238**	**0.052**	**4.55**	**< 0.001**

Note: Statistically significant effects are presented in bold. In the first two relationships, the direct effect and the total effect are equal, since there is no indirect effect. Regarding the effect of deprivation index on air pollution, however, the total effect can be roughly understood as the addition of the direct and the indirect (via neighborhood greenness) effects. The total effect of deprivation index on air pollution is not significant because the magnitude of the direct and indirect effects is similar, while the sign is opposite (the direct effect has a positive sign, whereas the indirect effect has a negative sign because it occurs through neighborhood greenness).

statistically significant total effect of deprivation index in traffic-related air pollution.

4. Discussion

In this study, SEM modelling was used to assess the factors that affect hair cortisol concentration in 11-year-old from the INMA Gipuzkoa cohort. We hypothesized that a complex pathway compiled by the simultaneous relationships among several environmental, social, and individual factors may explain hair cortisol levels. Our hypothesis is reflected in a metamodel that included environmental (environmental noise, traffic-related air pollution, and neighborhood greenness), social (neighborhood socioeconomic status, maternal stress, presence of stressful events, and bullying involvement) and individual factors (sex, health-related quality of life, behavioural problems, sleep disturbances, physical activity, and BMI) that may be related to stress response, as well as the relationship between them. As mentioned above, in our general model two variables were related to hair cortisol concentration.

In the final SEM model, we observed that behavioural problems and environmental noise, estimated in children's residence, were related to children's hair cortisol concentration, explaining the 5 % of the variance in the total sample. When the analysis was stratified by sex, these associations were only observed in the model for boys, explaining the 16 % of the HCC variance together with the presence of stressful events. We did not observe sex differences in HCC. Some previous showed differences in hair cortisol concentration in males and females (Gerber et al., 2017; Gray et al., 2018; Stalder et al., 2017), while others found no significant differences (Karlén et al., 2013a, 2013b; Ursache et al., 2017; White et al., 2017). Sex differences may appear not only in cortisol levels but also in cortisol release following a stressor, as both testosterone and estrogen modulate stress physiology and cortisol levels (Oyola and Handa, 2017). Some studies found sex differences in the relation between physical environment and HCC (Verheyen et al., 2021a, 2021b) However, a recent systematic review could not conclude the modifying effect of sex in the relationship between chronic stress and hair cortisol concentration due to the limited number of available studies. It's worth noting that chronic stress was mostly attributed to stressful life events (Li et al., 2023). In this sense, this study provides evidence regarding sex differences in children's cumulative cortisol exposure, with boys showing alterations in hair cortisol concentration depending on their personal and social surrounding.

Regarding relation between behavioural problems assessed by SDQ and HCC, we observed that the higher the problems, the higher the HCC. This is in line with previous studies, which showed higher hair cortisol concentration in children with teacher-reported behavioural problems (Fuchs et al., 2018). Methodological issues could explain the lack of significant associations in the relation between other children's individual characteristics and HCC, and not the missing relation per se; previous research failed to find a significant association between parent-reported children outcomes and HCC, and found an association between HCC and child self-reported factors (Fuchs et al., 2018; Gerber et al., 2013; Simmons et al., 2016). Further research is needed regarding the relationship between children's individual characteristics and HCC.

Importantly, higher maternal perceived stress was also related to higher behavioural problems, and therefore, higher maternal stress could also explain higher HCC in children via behavioural difficulties. This study highlights the importance of the maternal stress state in children's development, as it could lead to higher behavioural problems and higher cortisol concentrations in children, which are also related to lower health outcomes (Vanaelst et al., 2012). Previous research has also pointed out the relevance of maternal stress in children's behaviour and stress responses (Agapaki et al., 2022). The relationship between maternal stress and children's stress, mediated by children's behavioural difficulties, could be explained by the fact that mothers with higher stress are less able to help their children cope with stressful situations. The fact that this relation was only observed in boys, could be explained as follows: previous literature has pointed out sex differences in associations between childhood adversity and behaviour, observing that hat early adversity influences particularly boys behaviour problems (Coe et al., 2020).

In the other hand, higher exposure to residential environmental noise had a significant negative effect on HCC. Thus, contrary to our hypothesis, higher environmental noise exposure is related to lower cortisol levels in children. The estimates from the total and direct effects were also similar, suggesting that noise directly affects hair cortisol concentration. Previous studies regarding the effects of environmental noise on children's cortisol levels showed higher cortisol levels in children living in noisier areas (Evans et al., 2001; Ising et al., 2004; Ising, 2003) or no statistically significant effect (Bloemsma et al., 2021; Evans et al., 1998; Haines et al., 2001; Wallas et al., 2018). It is important to note that most of the research on this issue has focused on acute cortisol levels measured in saliva or urine. To the best of our knowledge, the only study assessing the effect of environmental noise on hair cortisol concentration found no association among 14–15-year-old adolescents (Verheyen et al., 2021a).

The noise reaction model states that noise causes activation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system. This results in a cascade of reactions, including the release of stress hormones such as cortisol, adrenaline, and noradrenaline, or a delayed increase in circulating cytokines, including IL-6 and IL-1β (Daiber et al., 2019), causing a state of chronic stress when high noise exposure is recurrent. However, we observed that higher noise exposure was associated with lower HCC. A hypothesis to explain this phenomenon could be that long-term stress exposure could lead to lowering hair cortisol concentration, as previous research also observed lower hair cortisol levels in adults living in a stressful economic situation (Faresjö et al., 2013) and adults experiencing childhood trauma (Hinkelmann et al., 2013). Another explanation could be that hair cortisol could be a metric of the basal level rather than a stress response (Sugaya et al., 2020); therefore, lower levels of hair cortisol concentration may reflect a lack of HPA axis reactivity in those exposed to long-term high environmental noise.

Misestimation of environmental noise exposure could also explain the inverse association between environmental noise and hair cortisol concentration. Noise exposure was estimated in the subject's building façade. Outdoor noise levels may not reflect indoor noise exposure and noise exposure in other contexts was not considered neither. More research is needed regarding the effect of environmental stressors on children's hair cortisol concentration, as most of our knowledge relies on studies on salivary and urine cortisol levels.

The results of our study underline the importance of the neighborhood environment affecting cortisol levels. Importantly, higher neighborhood greenness, estimated by NDVI average values within a 300 m buffer around the geocoded residential address, was related to lower environmental noise and lower traffic-related air pollution as measured by NO_2 levels. Moreover, traffic-related air pollution and environmental noise were positively related to each other; traffic density could explain these relations, as higher traffic density could cause both higher noise and traffic-related air pollution (Foraster et al., 2011; Nieuwenhuijsen, 2016). Therefore, one of the mechanisms by which green spaces may affect stress state, is by acting as a buffer against other environmental stressors such as air pollution and noise (Bloemsma et al., 2021; Markevych et al., 2017). Hence, considering the effect of physical environment on children's hair cortisol concentration, this study highlights the importance of effective urban planning, reducing environmental stressors, and facilitating access to green spaces.

We observed, neighborhood SES was related to neighborhood greenness and traffic-related air pollution. In the last years, research has focused on the idea of environmental injustice: the unequal distribution of environmental exposures that disproportionately affect certain population groups (Murray et al., 2022). Most of the research agrees with the idea of people with higher socioeconomic status having higher access to green spaces in cities (European Environment Agency, 2022; Murray et al., 2022). Our study observed also differences in the distribution of exposures to green spaces by SES levels, but not in the expected direction: children living in deprived areas had higher green spaces according to NDVI scores. Previous studies also reported similar results in our study area (Robinson et al., 2018). It is a fact that urban residents from higher socioeconomic status consider work opportunities, proximity to educational and medical resources or transportation when choosing their living location and therefore, they live in urban centres (Jiao et al., 2018). Meanwhile, people from lower status remain in suburbs, far from gray city centres and closer to the natural environment, and therefore they have higher neighborhood greenness. The results showed a positive direct effect of deprivation index on NO_2 exposure. Thus, people with a lower socioeconomic status are exposed to higher levels of air pollution. Notably, the total effect of deprivation index on traffic-related air pollution was not significant. Hence, the indirect effect of the deprivation index on traffic-related air pollution via neighborhood greenness voids the direct effect. This result suggests that higher residential green exposure mitigates the association between SES and traffic-related air pollution. Research addressing unequal exposure of air pollutants in Europe showed mixed results (Hajat et al., 2015; Subiza-Pérez et al., 2023). In conclusion, these results are consistent with the finding that social distribution of environmental exposures are diverse in Europe and not always agrees with environmental injustice hypothesis (European Environment Agency, 2022; Robinson et al., 2018). These results suggest that location specific studies should be carried out, in order to identify most vulnerable groups and to create specific interventions and public policies. It is important to highlight that in the present study we used the neighborhood socioeconomic status instead of the family socioeconomic status. It is important to note that in the present study the socioeconomic level was determined from the socioeconomic status of the neighborhood and not from the occupation of the parents, as in other studies.

In addition, we observed some relationships between predictor variables. First 7 % of the variability in bullying involvement was explained by lower health related quality of life, more behavioural problems and higher environmental noise exposure and higher behavioural problems. Higher aggressiveness due to annoyance caused by noise may explain the unexpected relationship between environmental noise and bullying. It should be noted that the three roles are aggregated into just one variable when using bullying involvement: bully, victim, and bully/victim roles. We believe that this association could be exclusive to the bully and bully victim roles. Exposure to noise has been associated with aggressive behaviour in both humans and rats (Alimohammadi et al., 2018; Molina et al., 2022); thus, children living in noisier areas could have more aggressive behaviours mediated by noise-induced annoyance, and therefore, a involvement in bullying as bullies or bully/victims. However, more research is needed regarding the relation between environmental noise and bullying.

Moreover, lower residential traffic-related air pollution, and higher physical activity, were related to higher health-related quality of life, which is in line with previous research (Boudier et al., 2022; Mansour et al., 2003; Olson et al., 2004; Wu et al., 2019). As reported by previous literature, higher maternal stress and behavioural difficulties were related to sleeping problems (Caldwell and Redeker, 2015; Quach et al., 2017). Finally, having stressful events was related to doing less physical activity, in line with previous research (Malinauskas et al., 2018).

This study, however is not without limitations. First, the cross-sectional nature of our study does not allow us to assume the causality of the observed relationships. However, when studying hair cortisol concentration it is important to measure stressors at the same time, in this case, the last three months. Previous stressors in time might not be related with hair cortisol concentration (Li et al., 2023). Moreover, we are probably misestimating exposure to physical environment, as we only considered residential exposures and the children spend a lot of time in other contexts. Regarding environmental noise exposure estimation, this misestimation could explain the inverse association between environmental noise and hair cortisol concentration. As stated before, noise levels were estimated outdoors by calculating the mean of all projected points on the subject's building façade and it may not reflect noise exposure indoor. Noise exposure in other spaces was not considered neither. Furthermore, environmental noise exposure information was available for 87 % of the INMA-Gipuzkoa participants on the 11-year follow-up stage. Information for those living in smaller municipalities than 6000 inhabitants was not available, since these municipalities do not have noise maps. It is possible that these participants are exposed to lower noise levels. A more precise noise exposure estimation should give us more information regarding the inverse relationship between environmental noise and hair cortisol. Moreover, estimation of NO_2 exposure was not completely accurate. However, it has to be noted that the study area is an urban industrial zone, and therefore NO_2 levels are generally lower than in big cities.

Another limitation is that we only have parent-reported information for most of the variables. Previous studies have reported differences between actigraph-based and parent-reported sleep measures (Mazza et al., 2020) and found no relationship between parent-reported child outcomes and HCC, although these associations were significant with teacher- or child-self-reported outcomes (Fuchs et al., 2018; Gerber et al., 2017; Simmons et al., 2016). In addition, census-based indicators are used instead of familial indicators to assess socioeconomic status, as the deprivation index was used. Despite this, the deprivation index is thought to be more accurate and representative than the family socioeconomic status, which may be outdated. Therefore, methodological limitations could explain the lack of relationships observed in these studies. Finally, although we added large number hair cortisol determinants, some of them were not included in the model. Future studies should also include other potential determinants, such as, atopic disease, use of corticosteroids, or other environmental stressors like light pollution or exposure to chemicals.

Despite these limitations, this study had some strengths that are worth highlighting. First of all the large sample size considering information comes from a prospective study. Moreover, the study population;

given the scarce amount of evidence that currently exists regarding hair cortisol determinants in 11-year-old children, exploring factors that may affect HPA axis is crucial. In addition, as mentioned before, most studies on changes in cortisol levels have been performed in salivary, urinary, or blood samples, which are methods for measuring acute cortisol levels (Wright et al., 2015). Hair cortisol measurement is an innovative and minimally invasive method for studying chronic cortisol levels. Finally, the methodology employed to analyze the determinants of HCC often does not consider multiple variables; in this study, simultaneous interrelationships between several environmental, social, and individual factors were studied. This allowed us to obtain a more complex image of how all these factors result in hair cortisol concentrations in children.

5. Conclusion

We observed that internalizing and externalizing and environmental noise were related to hair cortisol levels in 11 year old children. This study highlights the relevance of including a more complex view when studying hair cortisol determinants in children and adolescents, as simultaneous exposure to different environmental, social and individual characteristics can determine the concentration of hair cortisol. We believe, hair cortisol could be a viable tool for assessing the effect of environmental exposures on chronic stress. However, more research is needed because a better understanding of hair cortisol determinants in vulnerable groups could help on the implementation of effective pubic policies.

CRediT authorship contribution statement

Ane Arregi: Writing – original draft, Formal analysis, Data curation. **Oscar Vegas:** Writing – review & editing, Supervision, Conceptualization. **Aitana Lertxundi:** Supervision, Methodology, Conceptualization. **Gonzalo García-Baquero:** Methodology, Formal analysis, Data curation. **Jesus Ibarluzea:** Funding acquisition, Conceptualization. **Ainara Andiarena:** Writing – review & editing, Validation. **Izaro Babarro:** Writing – review & editing, Validation. **Mikel Subiza-Pérez:** Writing – review & editing, Validation. **Nerea Lertxundi:** Writing – review & editing, Supervision, Conceptualization.

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.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yhbeh.2024.105575.

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