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The impact of prenatal mercury on neurobehavioral functioning longitudinally assessed from a young age to pre-adolescence in a Spanish birth cohort

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ABSTRACT

The objective is to investigate the relation between cord blood mercury concentrations and child neurobehavioural functioning assessed longitudinally during childhood until pre-adolescence.
Methods: The study involves mothers and their offspring engaged in the Spanish INMA birth cohort (n = 1147). Total mercury (THg) was determined in cord blood. Behavioural problems were assessed several times during childhood using the ADHD-DSM-IV at age 4, SDQ at ages 7 and 11, CPRS-R:S and the CBCL at ages 7, 9 and 11. Covariates were obtained through questionnaires during the whole period. Multivariate generalised negative binomial (MGNB) models or mixed-effects MGNB (for those tests with information at one or more time points, respectively) were used to investigate the relation between cord blood THg and the children's punctuations. Models were adjusted for prenatal fish intake. Effect modification by sex, prenatal and postnatal fish intake, prenatal fruit and vegetable intake, and maternal polychlorinated biphenyl concentrations (PCBs) was assessed by interaction terms.
Results: The geometric mean ± standard deviation of cord blood THg was 8.22 ± 2.19 μg/L. Despite adjusting for fish consumption, our results did not show any statistically significant relationship between prenatal Hg and the children's performance on behavioural tests conducted between the ages of 4 and 11. Upon assessing the impact of various factors, we observed no statistically significant interaction.

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Conclusion: Despite elevated prenatal THg exposure, no association was found with children's behavioural functioning assessed from early childhood to pre-adolescence. The nutrients in fish could offset the potential neurotoxic impact of Hg. Further birth cohort studies with longitudinal data are warranted.

1. Introduction

Methylmercury (MeHg) is a widespread environmental pollutant identified as a neurotoxin, particularly impactful during brain development (Grandjean and Landrigan, 2006; Pan et al., 2022). The primary route of human exposure is through the ingestion of fish and marine mammals, with predatory blue fish having the highest MeHg concentrations (Marti-Cid et al., 2008). The majority of consumed MeHg is absorbed and can cross the placental and blood-brain barriers (Clarkson et al., 2007; World Health Organization (WHO), 2007). The nervous system undergoes an extended developmental phase from embryonic stages through adolescence. Consequently, exposure to toxins in early stages could result in developmental neurotoxicity (Debes et al., 2006; Rice and Barone S Jr, 2000). Additionally, the impact of MeHg neurotoxicity may appear in the long term (Landrigan et al., 2005).

Previous research unveiled elevated prenatal Hg exposure within the INMA birth cohort (Ramon et al., 2011), much higher than concentrations found in other European countries, such as Croatia (median = 3.74 μg/L)(Sekovanić et al., 2020), Italy (median = 3.97 μg/L) (Valent et al., 2013), or Austria (median = 1.1 μg/L) (Gundacker et al., 2010). However, no association was recorded with the mental or psychomotor development examined during infancy. Nonetheless, sex-specific findings indicated a potential negative impact of prenatal Hg exposure and psychomotor development in girls (Llop et al., 2012). At 5 years of age, the association between cord blood Hg and neuropsychological development in children did not show a clear pattern, but a strong influence of the maternal diet was observed (Llop et al., 2017). In fact, children born to mothers with an intake of fish below three servings/week during pregnancy obtained worse punctuations in the cognitive test.

So far, the relation between prenatal exposure to this toxicant and behavioural disorders in INMA participants has not been investigated. The existing literature regarding this subject is insufficient and heterogeneous, making it challenging to formulate definitive conclusions (Ealo Tapia et al., 2023). While findings from a few birth cohort studies have shown a significant association between prenatal Hg concentrations and behavioural problems during childhood (Boucher et al., 2012; Debes et al., 2006; Suzuki et al., 2010), other investigations have reported a lack of significant relationship (Myers et al., 2000; Patel et al., 2019; Plusquellec et al., 2010). Results derived from a recent meta-analysis (Dimitrov et al., 2023) showed that exposure to certain chemicals prenatally and during early childhood increased the risk for attention-deficit/hyperactivity disorder (ADHD). In the case of Hg, despite the authors found some significant correlations, the high heterogeneity observed justifies further research on this topic.

These previous results suggest the existence of some uncertainties, such as the shape of the relationship, the existence of threshold values, and the influence of confounders and effect modifiers. Among the factors that could influence Hg neurotoxicity, fish consumption may be the most important. Apart from Hg, fish contains nutrients beneficial for neurodevelopment, such as fatty acids, which could counteract the deleterious effect of Hg (Julvez et al., 2016). In addition, fish could also contain other toxicants, such as polychlorinated biphenyls (PCBs), which have been reported to be developmental neurotoxicants (Boucher et al., 2014; Song et al., 2023). Furthermore, although evidence is still limited, the antioxidant and anti-inflammatory characteristics of dietary fruits and vegetables could act as a protective factor against Hg neurotoxicity, as has been observed for other effects related to early Hg exposure, such as on respiratory health (Carrasco et al., 2021; Razi et al., 2011).

The objective is to investigate the relation between cord blood Hg concentrations and child neurobehavioural functioning assessed longitudinally during childhood until pre-adolescence, and to study the influence of certain factors, such as sex, pre- and postnatal fish consumption, PCB concentrations, and maternal fruit and vegetable intake.

2. Methods

2.1. Study participants

The study involves mothers and their offspring engaged in the Spanish INMA (Child and Environment) Project (http://www.proyectoinma.org) (Guxens et al., 2012). The initial population included 2644 pregnant women recruited at the beginning of pregnancy (2003–2008) in four of the INMA sub-cohorts (Valencia, Sabadell, Gipuzkoa and Asturias). We monitored 2506 (95.0%) women until their deliveries. Their offspring were enrolled in the study upon birth and their neurobehavioral functioning was evaluated across four different appointments: at 4, 7, 9 and 11 years of age (Fig. S1). The study population consisted of 1147 children (45.6%) with available cord blood THg concentrations, neurobehavioural functioning data up to age 11, and covariate information. Mothers provided written informed consent for the prenatal phase, while one parent or legal representative provided consent for each postnatal phase. The Ethics Committee of the Public Health Research Centre in Valencia (CSISP), the Ethics Committee of the University Hospital La Fe (Valencia), Parc de Salut MAR (Sabadell), University Central Hospital of Asturias (Asturias) and the Donostia Hospital (Gipuzkoa) approved the study protocol.

2.2. Mercury exposure

Whole cord blood samples were obtained by venepuncture of the umbilical cord vessels before delivery of the placenta. The samples were processed, separated into 1 ml aliquots, and then frozen at −80 °C until analysis. Cord blood THg concentrations were determined by thermal decomposition, amalgamation and atomic absorption spectrometry using a single-purpose AMA-254 advanced Hg analyser (LECO Corporation, St. Joseph, Michigan, USA). The total analytical imprecision for this analysis was estimated to be 9.9%, 4.2%, and 3.1% at mercury concentrations of 3.8, 12, and 37 μg/L, respectively. The analysis was carried out in the.

Public Health Laboratory in Alava (LSPPV), Basque Country, Spain. The limit of quantification (LOQ) of the procedure was 2.0 μg/L. For quality control, the reference material 'Seronorm Trace Elements in Whole Blood' was used to check the accuracy of the results (LOT 0503109 and 201605). The average recovery was 93% (range: 85%–104%). Since 2009, LSPPV has participated (three times per year) in inter-laboratory comparisons organized by the New York State Department of Health in the Wadsworth Center, with satisfactory results.

2.3. Assessment of children's behaviour

Different tests validated in Spanish population were employed to evaluate the behavioural problems of the children at different stages of development: at age 4 (mean ± SD = 4.89 ± 0.70 years) using the Attention-Deficit/Hyperactivity Disorder Criteria of the Diagnostic and Statistical Manual of Mental Disorders (ADHD-DSM-IV); at ages 9 (mean ± SD = 9.10 ± 0.50 years) and 11 (mean ± SD = 10.92 ± 0.43 years) using the Strengths and Difficulties Questionnaire (SDQ); and at ages 7 (mean ± SD = 7.54 ± 0.61 years), 9 and 11 using the Child Behaviour Checklist (CBCL) and the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S). Increased punctuations across all the scales denote heightened behavioural problems. The ADHD-SDM-IV is a teacher-report instrument and the other tests were filled out by the mother. Not all the tests were administered in all sub-cohorts at the same ages (see Fig. S1). More information about the tests can be found in Appendix S2.

2.4. Other variables

Two questionnaires were administered to the women during their pregnancy—one during the first trimester and the other during the third trimester. These questionnaires were centred on gathering information about sociodemographic, environmental, and lifestyle aspects during pregnancy, and they were carried out by trained interviewers. In particular, the parental covariates used were: season of delivery (spring, summer, autumn, winter), maternal age (years), maternal country of birth (Spain, other), educational level (up to primary education, secondary, university), body mass index before pregnancy (maternal and paternal BMI, kg/m^2), maternal working status (employed, unemployed), maternal alcohol and tobacco consumption (yes, no), and parity (0, 1, $\geq$2). Parental social class was classified using the Spanish adaptation of the ISCO88 as I + II (managerial jobs, senior technical staff, and commercial managers); III (skilled non-manual workers); and IV + V (manual and unskilled workers). Gestational age and sex of the children were obtained from patient records. Data regarding the employment status of both parents (employed or unemployed) and maternal smoking habits (smoker or non-smoker) were collected during an interview conducted concurrently with the last neuropsychological assessment (age 11). The Similarities Subtest of the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) was used for the maternal verbal intelligence quotient (IQ).

Maternal fish consumption was collected using a semi-quantitative food frequency questionnaire (FFQ) previously validated in the same population and administered during the first and third trimesters of pregnancy (Vioque et al., 2013). Covering the period from the initial stages of pregnancy to the third trimester, the questionnaires inquired about the average dietary intake. The FFQ provided nine response categories to indicate how often different food groups were consumed and included eleven questions on the intake of different types of seafood: mixed fried fish, large oily fish, canned tuna, lean fish, small oily fish, canned sardines or mackerel, cephalopods, crustaceans, shellfish, processed fish, and dried or smoked fish. The average intake calculated from both FFQs was utilized, and seafood items were categorised into the following groups: lean fish, large oily fish, canned tuna, other oily fish, and other seafood. We also calculated the weekly intake of total seafood (expressed in servings). From the same FFQ, we also used the variable intake of fruit and vegetables (weekly servings) in this analysis. Information on total fish consumption in children at ages 4 and 7 was obtained using an adapted and validated version of the FFQ (Vioque et al., 2016, 2019). Energy intake adjustments for all food groups were made employing the residual method. This method involved calculating residuals from a linear regression model where the natural logarithm of the food group served as the dependent variable, while the natural logarithm of the total energy intake served as the independent variable.

Levels of four individual PCB congeners (IUPAC numbers: 118, 138, 153 and 180) were determined in blood samples collected during the first trimester of pregnancy. Detailed information about the laboratory procedures for analysis and quality control can be found in another source (Llop et al., 2010). Total cholesterol and triglycerides were determined by enzymatic methods. The sum of the four PCBs corrected for lipids was used for analysis.

We categorised the variables of total fish intake during pregnancy and childhood (at ages 4 and 7) into quartiles. For prenatal total fish intake, the values were: (i) $\leq$4.93, (ii) (4.93–6.48], (iii) (6.48–8.33], and (iv) > 8.33 weekly servings. For postnatal total fish intake at 4 and 7 years old, the values were: (i) $\leq$3.55, $\leq$3.75 (ii) (3.55–4.58], (3.75–5.10], (iii) (4.58–5.72], (5.10–6.77], and (iv) > 5.72, >6.77 weekly servings, respectively. Tertiles of PCBs and consumption of fruits and vegetables were also calculated and factorised on two levels (low: tertiles 1 and 2, and high: tertile 3). The corresponding values were: (i) low: [6.96, 91.11], [43.75, 440.28]; (ii) high: (91.11, 145.34], (440.28, 604.13] for PCBs (expressed in ng/g of lipids) and consumption of fruits and vegetables (expressed in daily grams), respectively.

2.5. Statistical analysis

First, we described the study population and behavioural test scores by percentages and mean±standard deviations (SD). For THg, the geometric mean (GM) and geometric standard deviation (GSD) were calculated. In addition, Spearman's correlation tests were performed between behavioural test scores and cord blood THg at the follow-up visit. Furthermore, Wilcoxon paired tests were carried out to investigate differences within the tests between visits. THg concentrations and fish variables were log2 transformed for additional analysis.

Multivariate generalised negative binomial (MGNB) models were used to investigate the relation between child neurobehavioural functioning and THg concentrations at birth, given the nature and the skewed distribution of our response variables. Methodology used for model building can be found in Appendix S2.

Effect modification by maternal and child total fish intake, sex, maternal PCBs and fruit/vegetable intake was also assessed by including them as interaction terms in Model 2 and calculating interaction p-values (LRT). To do this, tertiles (for maternal PCBs and fruit/vegetable intake) and quantiles (for fish intake) were calculated.

Residual analyses and collinearity diagnoses did not show any influential observations or extreme outliers. Finally, sensitivity analyses were carried out by excluding preterm children (<37 weeks of gestation, n = 62), as this condition has been previously related to an increase of behaviour problems during childhood (Arpi and Ferrari, 2013).

Models 1,2 and 3 were also implemented using inverse probability censoring weights (IPW) to try to assess the impact of selection bias (Carry et al., 2021).

All analyses were performed separately using R software, version 4.2.2. All results are expressed as incidence rate ratios (IRR) and their 95% confidence intervals (95% CI), which indicate whether the exposure to Hg increases (IRR>1) or decreases (IRR<1) the rate of a particular incidence. Associations at $p < 0.05$ were noted as statistically significant and associations at $p < 0.10$ as marginally significant.

3. Results

The mean ± SD of maternal age was 31.58 ± 3.89 years and Spain was the birthplace of 97% of the women. Near 45% and 26% of the mothers and fathers, respectively, had a university education. In addition, 82.3% of the women were employed during pregnancy, 13.3% of them smoked during pregnancy and 9.9% reported alcohol consumption during pregnancy. The geometric mean ± geometric standard deviation (GM ± GSD) of cord blood THg concentrations was 8.22 ± 2.19 μg/L. Women reported an intake of 7.09 ± 2.94 weekly servings of total fish during pregnancy (Table 1).

Differences in characteristics between included (n = 1156) and excluded children (the latter being those without available information on behavioural functioning at age 11 years, n = 1350) are shown in Supplementary Table S1. Statistically significant differences were observed in the following variables: country of birth, parental social class, maternal age, maternal pre-pregnancy body mass index (BMI), maternal/paternal education, maternal working status, season of birth, THg cord concentrations, and prenatal fish variables except lean fish. The children included in the study came from families with older, more educated parents and a higher social standing than those in the excluded population. Prenatal fish intake was higher among the included population, as well as cord blood THg concentrations.

Descriptives for the behavioural test scores are presented in Table S2. Marginally significant differences were found in the different scores

Table 1
Characteristics of the study population. The INMA Project, 2004–2015 (Spain).

Variables	Study sample (n = 1156)
Maternal age (years)[a]	31.58 ± 3.89
Maternal place of birth (Spain)	1120(97.0%)
Maternal university education (yes)	515(44.9%)
Paternal university education (yes)	297(25.9%)
Maternal working status (employed)[a]	953(82.3%)
Parental social class (high)[a]	452(39.4%)
Maternal smoking habit (yes)[a]	152(13.3%)
Maternal alcohol intake (yes) [a]	114(9.9%)
Maternal BMI (kg/m^2)[b]	23.22 ± 3.98
Paternal BMI (kg/m^2) [a]	26.02 ± 3.38
Number of previous deliveries (primiparous)[1]	688 (59.2%)
Child variables	
Child's sex (female)	549(47.9%)
Mercury in cord blood (μg/L)[c]	8.22 ± 2.19
Fish variables (prenatal)[a,d]	
Total fish	7.09 ± 2.94
Large oily fish	0.96 ± 0.88
Other oily fish	0.22 ± 0.36
Canned tuna	1.69 ± 1.25
Lean fish	1.43 ± 0.98
Other seafood	2.73 ± 1.53

Sample size and percentage, n(%), are presented for categorical variables and mean ± standard deviation for continuous variables. Cord blood mercury expressed as GM ± GSD. High social class refers to classes I + II. BMI: Body mass index.
[a] Information obtained during pregnancy.
[b] Before pregnancy.
[c] Geometric mean ± geometric standard deviation.
[d] Expressed in weekly servings.

obtained for CBCL by visit. In particular, scores on the total problems scale were lower at 7–8 years compared to scores obtained at 9 and 11 years old. Spearman correlations between the test scores obtained at each age and cord blood THg are shown in Table S3. The higher coefficients were observed for the cognitive and oppositional scales of the CPRS-R:S test at age 9, but none of the coefficients were statistically significant.

Spearman's correlations between prenatal fish variables were assessed and the results are shown in Supplementary Fig. S2. Overall, low correlations were found ($\rho < 0.15$), with only a slightly higher statistically significant correlation between large oily and lean fish ($\rho = 0.4$).

Table 2 shows the IRR (95% CI) of the Models 1 to 3. In all cases, no statistically significant associations were found. Inclusion of the fish intake variables yielded similar results within the models. Furthermore, when examining the effect modification by the previously presented variables (Figs. 1–4), none of the interaction p-values yielded statistically significant results (data not shown). Only for CBCL and CPRS-R:S there was an indication of effect modification by prenatal total fish. Specifically, a negative association (better behaviour) was found between cord blood THg and the scores recorded in both CBCL internalizing and total problem scales for those children whose mothers ingested ≤4.93 fish per week during pregnancy (IRR = 0.91[0.82, 1.02], interaction p-value = 0.098 and 0.92[0.83, 1.02], interaction p-value = 0.099, respectively) (Fig. 1). Conversely, we also found suggestive evidence of effect modification for CPRS-R:S-ADHD by prenatal total fish intake, in that the association between THg and the scores was positive (worse behaviour) for those whose mothers consumed ≤4.93 weekly servings of fish (IRR = 1.20[0.98, 1.48], interaction p-value = 0.080).

Results for the transversal analyses are shown in Figs. S3–S5. We found statistically significant associations for CPRS-R:S-Hyperactivity in Model 2 at age 11 (0.91[0.83, 0.99], p-value = 0.030) as well as marginally significant associations for Models 1 and 3 at age 11 (0.92 [0.85, 1.00], p-value = 0.063; and 0.91[0.84, 1.00], p-value = 0.057).

The coefficients of the association between Hg and the different behavioural scales obtained after running the same models utilizing inverse probability censoring weights (IPW) can be found in Supplemental Fig. S6. The results remained virtually the same, except for the Hyperactivity and Inattention scales of the ADHD-DSM-IV test, where the coefficients obtained using the IPW followed the same direction but became statistically significant in some cases.

GAM models with one degree of freedom are plotted in Fig. 5. In all cases, the best model was the linear one (in terms of AIC); however, some suggestive evidence of a non-linear relationship was found for some of the scales (see Table S5 for the AIC values obtained). Finally, after excluding preterm birth from the models, all coefficients remained nearly unchanged in the sensitivity analyses (data not shown).

4. Discussion

Our focus was on investigating the relationship between prenatal THg concentrations and behaviour assessed longitudinally from early childhood to pre-adolescence in a Spanish birth cohort with elevated fish consumption. Although prenatal Hg concentrations were elevated in this study population, we observed no statistically significant association with children's scores on the various behavioural tests assessed throughout childhood. Additionally, we evaluated the possible influence of several maternal and child factors, such as sex, prenatal fish intake,

Table 2
Association between prenatal mercury concentrations and behavioural functioning for each of the proposed models. The INMA Project, 2004–2015 (Spain).

ADHD-DSM-IV	Model 1		Model 2		Model 3	
	IRR[95%CI]	p-value	IRR[95%CI]	p-value	IRR[95%CI]	p-value
ADHD	1.01[0.94,1.08]	0.857	0.99[0.92,1.06]	0.778	1.00[0.93,1.07]	0.927
Inattention	0.99[0.92,1.07]	0.797	0.98[0.91,1.06]	0.582	0.99[0.91,1.07]	0.724
Hyperactivity	1.02[0.94,1.10]	0.686	0.99[0.91,1.08]	0.846	1.00[0.92,1.09]	0.985
SDQ						
Total problems score	0.98[0.95,1.01]	0.204	0.98[0.95,1.02]	0.311	0.98[0.95,1.02]	0.333
CPRS-R:S						
ADHD	1.01[0.96,1.06]	0.845	1.02[0.96,1.07]	0.592	1.02[0.97,1.08]	0.482
Hyperactivity	0.99[0.90,1.08]	0.763	0.97[0.89,1.07]	0.582	0.99[0.90,1.09]	0.791
Cognitive	1.00[0.95,1.07]	0.898	1.02[0.96,1.09]	0.516	1.03[0.97,1.10]	0.362
Oppositional	1.02[0.97,1.07]	0.488	1.02[0.97,1.08]	0.478	1.01[0.96,1.07]	0.630
CBCL						
Internalizing problems	0.99[0.94,1.04]	0.627	0.98[0.93,1.04]	0.510	0.98[0.94,1.04]	0.647
Externalizing problems	1.00[0.95,1.07]	0.911	0.99[0.93,1.06]	0.812	0.99[0.93,1.05]	0.716
Total problems	0.99[0.94,1.03]	0.593	0.98[0.93,1.03]	0.407	0.98[0.93,1.03]	0.478

Variables included in each model are presented in Table S4.
ADHD-DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition); CBCL: Child Behaviour Checklist; CI: Confidence Interval; CPRS-R:S: Conners' Parent Rating Scale-Revised; IRR: Incidence Rate Ratio; SDQ: Strengths and Difficulties Questionnaire; Model 1: core models plus cord blood mercury; Model 2: core models plus cord blood mercury and prenatal total fish; Model 3: Core models plus cord blood mercury and the five prenatal fish variables.

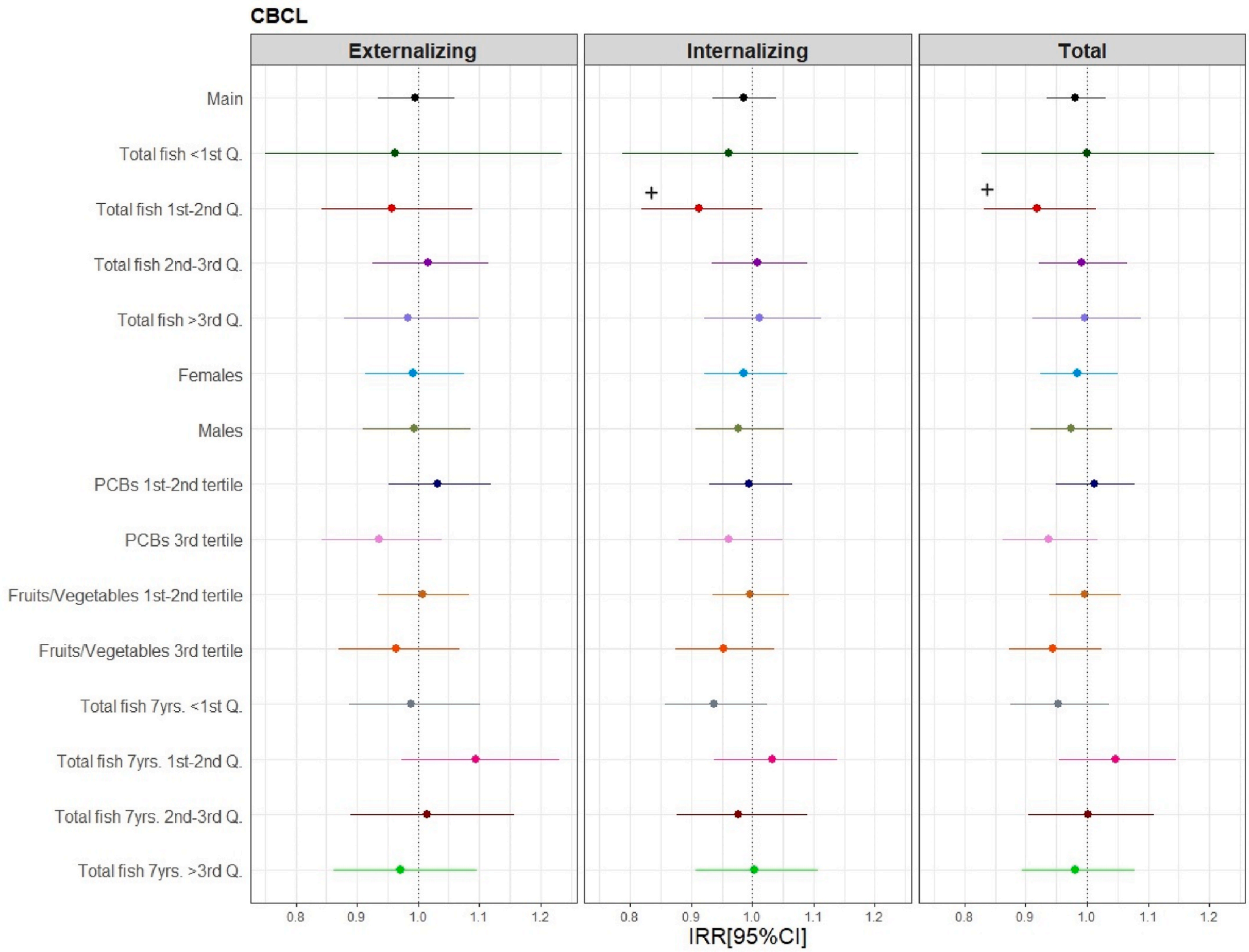

Fig. 1. Effect modification of the association between cord blood mercury concentrations and behavioural functioning measured at ages 7, 9 and 11 by the CBCL test (IRR±95%CI). Table S4 CBCL: Child Behaviour Checklist; CI: Confidence Interval; IRR: Incidence Rate Ratio; Q: quartile. Prenatal total fish (total fish) and total fish at age 7 (total fish 7yrs.) expressed in weekly servings and quartiles. PCB concentrations expressed in ng/g of lipids and categorised into tertiles. Fruit/vegetable intake expressed in daily grams and tertiles. IRRs of marginally significant interactions are expressed by +. Effect modification performed with Model 2: adjusted for prenatal total fish intake (except coefficients of effect modification by prenatal fish).Effect modification was assessed by including the interaction term between mercury and the considered variables. Variables included in each model are presented in Table S4.

postnatal fish intake, maternal blood PCB concentrations and prenatal fruit and vegetable intake, and we found no statistically significant interaction. Only a marginal effect modification by prenatal fish consumption was observed but with inconsistent results for the CBCL and CPRS-R:S tests.

Previous research has also explored the link between foetal Hg exposure and behavioural outcomes in children but with heterogeneous results. For example, in the Tohoku birth cohort from Japan, maternal hair Hg at birth (median = 1.96 μg/g) was negatively associated with the motor cluster of the Neonatal Behavioural Assessment Scale at three days after birth (Suzuki et al., 2010). In a recent study conducted in Poland, maternal hair Hg concentration (median = 0.18 μg/g) was associated with hyperactivity and inattention as assessed at 7 years of age using the SDQ test (Garí et al., 2022). In a research involving children from Arctic Quebec, the concentration of Hg in cord blood (with a median of 16.6 μg/L) showed no association with behavioural deficits at the age of 5, as evaluated using the Infant Behaviour Rating Scale (Plusquellec et al., 2010); however, this prenatal exposure was associated with increasing ADHD symptoms at age 11 by the CBCL and the Disruptive Behaviour Disorders Rating Scale (Boucher et al., 2012). In the New Bedford cohort from Massachusetts (USA), the association between maternal hair Hg (median 0.45 μg/g) and obtaining worse scores on the CRS-T DSM-IV test assessed at 8 years of age showed a non-linear pattern (Sagiv et al., 2012). The authors observed an apparent threshold of 1 μg/g of Hg for some of the outcomes and a protective effect of maternal fish consumption (>2 servings/week) during pregnancy. In the Faroe birth cohort, which comprises a population exposed to high levels of mercury during prenatal stages (cord blood GM = 22.5 μg/L), there was a relation between prenatal exposure and attention deficits observed at age 14, evaluated through the Neuropsychological Examination System (NES2) and the Continuous Performance Test (CPT) (Debes et al., 2006). Other investigations have explored the relationship between early exposure to Hg and different dimensions of child behaviour, but none have yielded statistically significant findings. For instance, the Seychelles Study found no association between Hg concentrations measured in maternal hair (mean = 6.8 μg/g), a population known for its high fish intake, and children's behaviour at the age of 5 assessed by the CBCL scales (Myers et al., 2000). Similar results were observed at age 7 in the same cohort (Strain et al., 2021). Results from the HOME cohort in Ohio (USA) showed no significant relationship

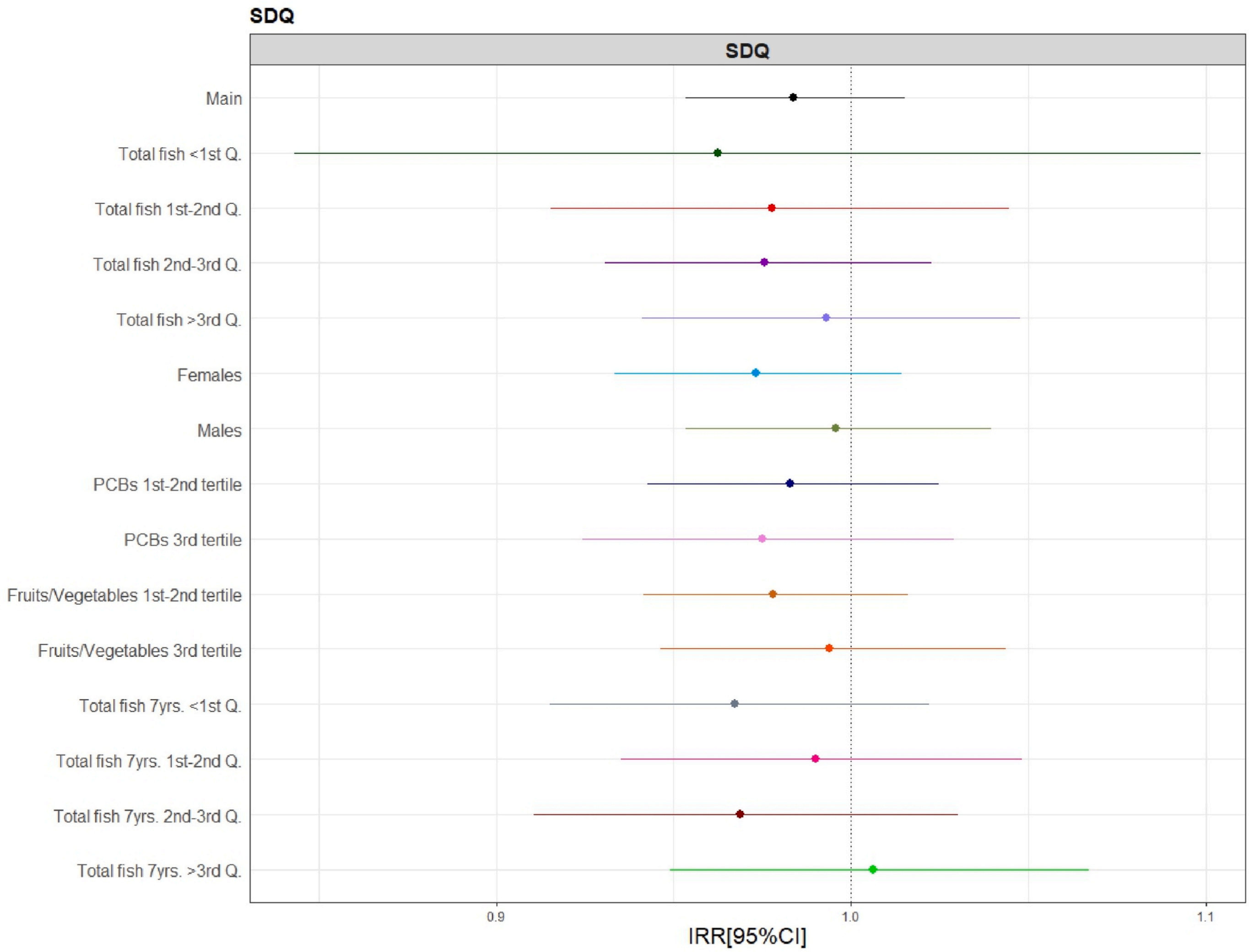

Fig. 2. Effect modification of the association between cord blood mercury and behavioural functioning measured at ages 7 and 11 by the SDQ test (IRR±95%CI). . Table S4.CI: Confidence Interval; IRR: Incidence Rate Ratio; Q: Quartile; SDQ: Strengths and Difficulties Questionnaire; Prenatal total fish (total fish) and total fish at age 7 (total fish 7yrs.) expressed in weekly servings and quartiles. PCB concentrations expressed in ng/g of lipids and tertiles. Fruit/vegetable intake expressed in daily grams and tertiles. Effect modification performed with Model 2: adjusted for prenatal total fish intake (except coefficients of effect modification by prenatal fish). Effect modification was assessed by including the interaction term between mercury and the considered variables. Variables included in each model are presented in Table S4.

between prenatal Hg (median in cord blood = 0.70 μg/L) and children's behaviour as assessed by the Behavioural Assessment System for Children (BASC-2) at various times from 2 to 8 years of age (Patel et al., 2019). Nevertheless, upon incorporating maternal fish intake into the models the association became statistically significant but negative (better behaviour) for some of the scales, such as aggression and externalizing problems. In addition, prenatal Hg exposure was related to increasing child anxiety scores at age 8 on the self-reported Spence Children's Anxiety Scale (SCAS). In a Norwegian birth cohort, maternal blood Hg (median = 1.02 μg/L) was not associated with children's emotional behaviour as assessed by the CBCL at age 5. Nonetheless, the rise in estimated MeHg intake through diet (median 0.15 μg/kg body weight/week) showed a significant association with reduced internalizing and externalizing child behaviours (Vejrup et al., 2022). Finally, increasing gestational Hg was associated with a lowered risk of both ASD and ADHD in 3-year-old children living in Norway (geometric mean = 1.38 μg/L in controls and 1.17 μg/L in ADHD cases) (Skogheim et al., 2021).

Despite the evidence for the developmental neurotoxicity of Hg (Grandjean, 2007; Grandjean and Landrigan, 2006), results from studies of the potential neurobehavioural effects of early exposure may turn out to be controversial. In addition, heterogeneity in the methodology used, such as differences in the biomarkers used to assess Hg exposure, and the ages and tests used to evaluate behaviour, adds to the difficulty of comparing them. Different matrices have been used to assess prenatal exposure between studies (maternal hair and blood at different trimesters or cord blood). Even these biomarkers of exposure seem to be correlated (Lukina et al., 2021), a decreasing trend in hair Hg concentrations through pregnancy has been reported, as well as higher Hg levels in cord blood than in maternal blood in the third trimester (Lukina et al., 2021; Morrissette et al., 2004; Sakamoto et al., 2007). Cord blood Hg is considered the most accurate biomarker of prenatal exposure and a good predictor of neurobehavioural deficits during childhood (Choi et al., 2008). If an imprecise biomarker is used to measure Hg exposure, it might result in an underestimation of the true effect of the exposure and potentially bias the dose-response relationship toward null (Grandjean and Budtz-Jørgensen, 2010).

Another source of heterogeneity between studies is the adjustment for fish. Some of the studies described above included a variable for fish intake in their multivariate models (Debes et al., 2006; Sagiv et al.,

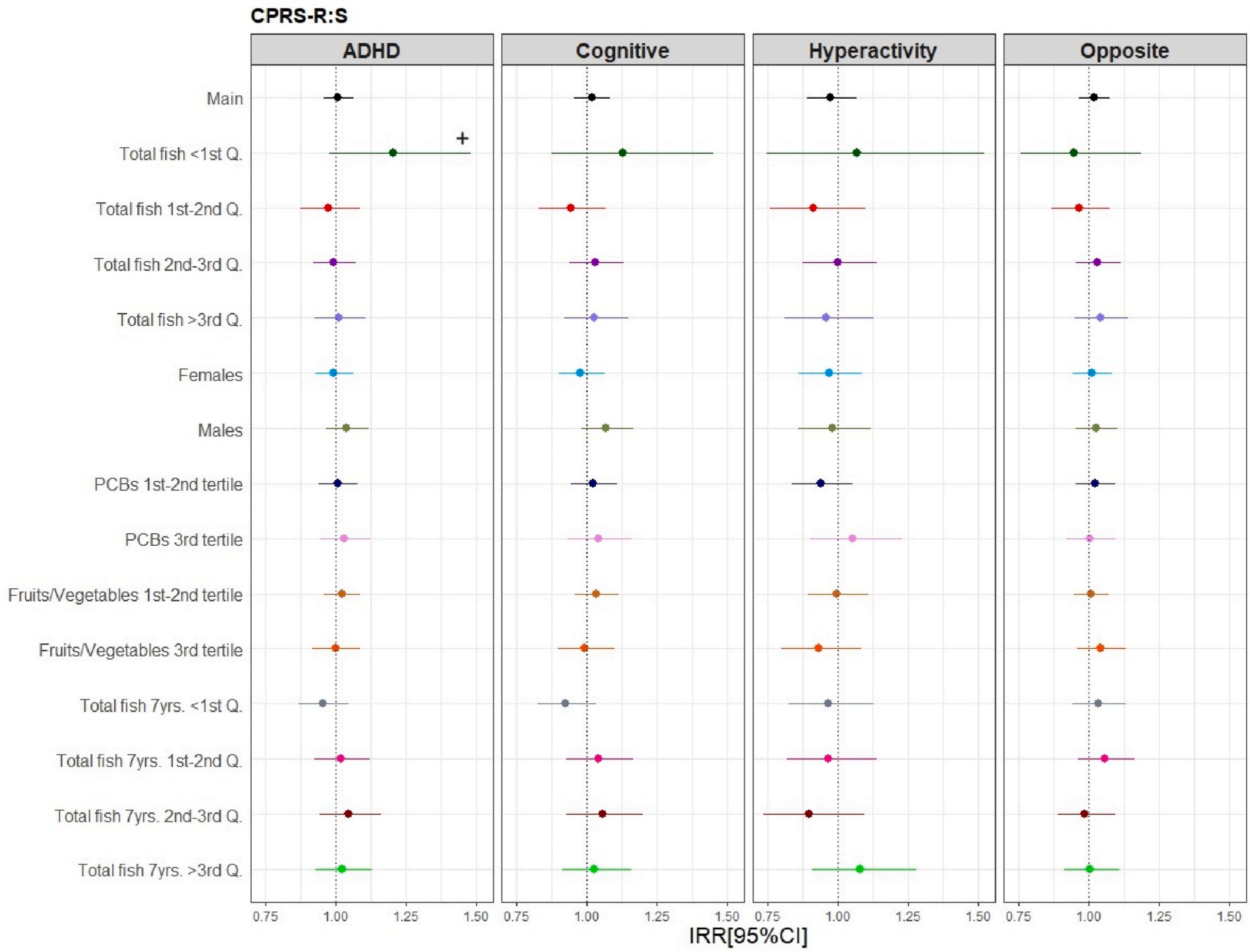

Fig. 3. Effect modification of the association between cord blood mercury and behavioural functioning measured at ages 7, 9 and 11 by the CPRS-R:S test (IRR±95% CI). . Table S4ADHD: Attention Deficit Hyperactivity Disorder; CPRS-R:S: Conners' Parent Rating Scale-Revised; CI: Confidence Interval; IRR: Incidence Rate Ratio; Q: Quartile. Prenatal total fish (total fish) and total fish at age 7 (total fish 7yrs.) expressed in weekly servings and quartiles. PCB concentrations expressed in ng/g of lipids and tertiles. Fruit/vegetable intake expressed in daily grams and tertiles. IRRs of marginally significant interactions are expressed by +. Effect modification performed with Model 2: adjusted for prenatal total fish intake (except coefficients of effect modification by prenatal fish). Effect modification was assessed by including the interaction term between mercury and the considered variables. Variables included in each model are presented in Table S4.

2012; Skogheim et al., 2021; Suzuki et al., 2010):however, most of them did not (Boucher et al., 2012; Garí et al., 2022; Myers et al., 2000; Vejrup et al., 2022). Because fish contains nutrients beneficial for neurodevelopment, such as fatty acids or selenium, alongside Hg and other pollutants, it has the potential to act as a confounding variable in the association between Hg exposure and neurodevelopment. Not accounting for this confounding factor might result in an underestimated impact of Hg, but inaccuracies in measuring confounders can also affect exposure variable estimates.(Budtz-Jorgensen et al., 2007). In our models, we used two different approaches for maternal fish consumption adjustment: in Model 2 we included maternal total fish intake and in Model 3 we included intake of four different fish species, but we did not find any change in the Hg coefficients. The FFQ is considered a reliable instrument for the assessment and classification of mothers and children according to their diet (Vioque et al., 2013, 2016); however, it is susceptible to measurement errors stemming from the complexity involved in appraising food intake, including issues like memory bias or difficulties in estimation portion sizes. This imprecision in the measurement of confounding variables could lead to an underestimation of their effect and bias the effect estimates of the exposure. However, the bias's trend will depend on how the exposure and the confounder are linked, along with the direction of the confounder's impact. From our prior research, we noted positive coefficients (better cognitive development) for the association between prenatal Hg exposure and the MSCA scores of children at the age of 5 (Llop et al., 2020); however, this association weakened when we included children's fish intake variables in the models or when we contemplated theoretical situations of low precision in measuring fish intake and Hg.

We also examined pre- and postnatal fish intake variables as possible effect modifiers, but no pattern or statistically significant interaction was found. In previous studies, we observed that prenatal Hg exposure was negatively associated with children's MSCA scores when their mothers consumed less than three weekly servings of fish and the coefficients turned positive as maternal fish intake increased (Llop et al., 2017). In the present study, we also evaluated other possible effect modifiers, such as maternal PCB concentrations, sex and fruit/vegetable intake during pregnancy; however, none of these variables significantly modified the Hg coefficients in the multivariate models. As PCBs accumulate in fish, there may be concurrent exposure to PCBs and Hg in fish-eating populations (Adamou et al., 2020; Grandjean et al., 2001).

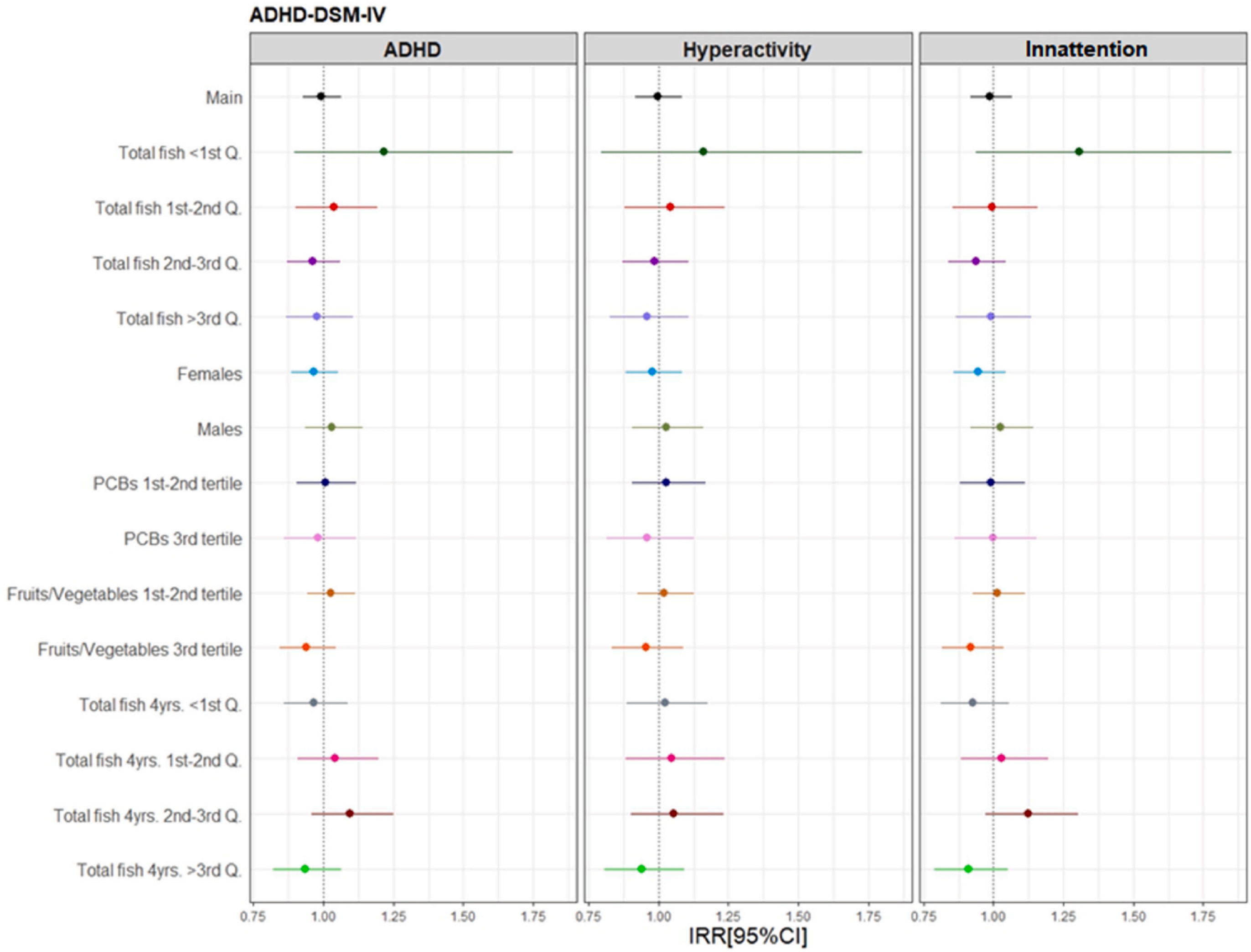

Fig. 4. Effect modification of the association between cord blood mercury and behavioural functioning measured at age 4 by the ADHD-DSM-IV test (IRR±95%CI) Table S4.ADHD-DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition); CI: Confidence Interval; IRR: Incidence Rate Ratio; Q: Quartile. Prenatal total fish (total fish) and total fish at age 4 (total fish 4yrs.) expressed in weekly servings and quartiles. PCB concentrations expressed in ng/g of lipids and tertiles. Fruit/vegetable intake expressed in daily grams and tertiles. Model 2: adjusted for prenatal total fish intake. Effect modification was assessed by including the interaction term between mercury and the considered variables. Variables included in each model are presented in Table S4.

Adverse effects on neuropsychological development have been documented for both compounds, especially in highly exposed populations such as Inuit children (Bastien et al., 2022; Boucher et al., 2014), and an interactive effect has been shown in experimental studies (Fischer et al., 2008); however, the results of the effect of co-exposure to PCBs and Hg in other populations highly exposed to MeHg, such as Faroese children, are inconclusive (Grandjean et al., 2012).

There are some weaknesses in our study; first, the attrition observed in our cohort may cause selection bias and change the extendibility of the findings. An analysis of the sociodemographic characteristics between the included and excluded populations revealed that mothers with children included in this study tended to have higher education levels, were of advanced age, and belonged to a more elevated social class. Furthermore, these women ingested more fish throughout their pregnancy, resulting in their children having elevated cord blood THg concentrations. The inclusion of these participants may undermine the sample's representativeness in contrast to the reference population, potentially affecting the evaluation of relationships between exposure and outcomes. Despite these socioeconomic differences between the two populations—the included and the excluded—the social class variable was not found to be significant in the multivariable models; nonetheless, we cannot exclude the potential for residual confounding. In order to mitigate this limitation, we ran again all the models utilizing inverse probability censoring weights to try to assess the impact of selection bias. The results obtained remained quite similar, except for some scales in the ADHD-DSM-IV test. Another limitation could arise due to potential misclassification within the fish intake variable obtained through the FFQ; nevertheless, for this study we employed a validated questionnaire, noting a moderate to high correlation between maternal fish consumption and THg concentrations in cord blood (Pearson correlation = 0.36) (Ramon et al., 2011). Nevertheless, a biomarker of omega-3 fatty acids would have been a more accurate measure of the nutrients that could counteract the neurotoxicity of Hg.

Notwithstanding its weaknesses, we cannot ignore the strengths of the present study. Few birth cohort studies have gathered such a substantial volume of longitudinal information from the outset of pregnancy through to the age of 11. In addition, we used different validated tests at different ages in order to assess children's behavioural functioning. Furthermore, due to the ongoing nature of the INMA cohort study, we will have the opportunity to explore potential adverse effects of prenatal Hg exposure in later ages. In fact, internalizing symptoms are typically present in adolescence and so the manifestations of early-life

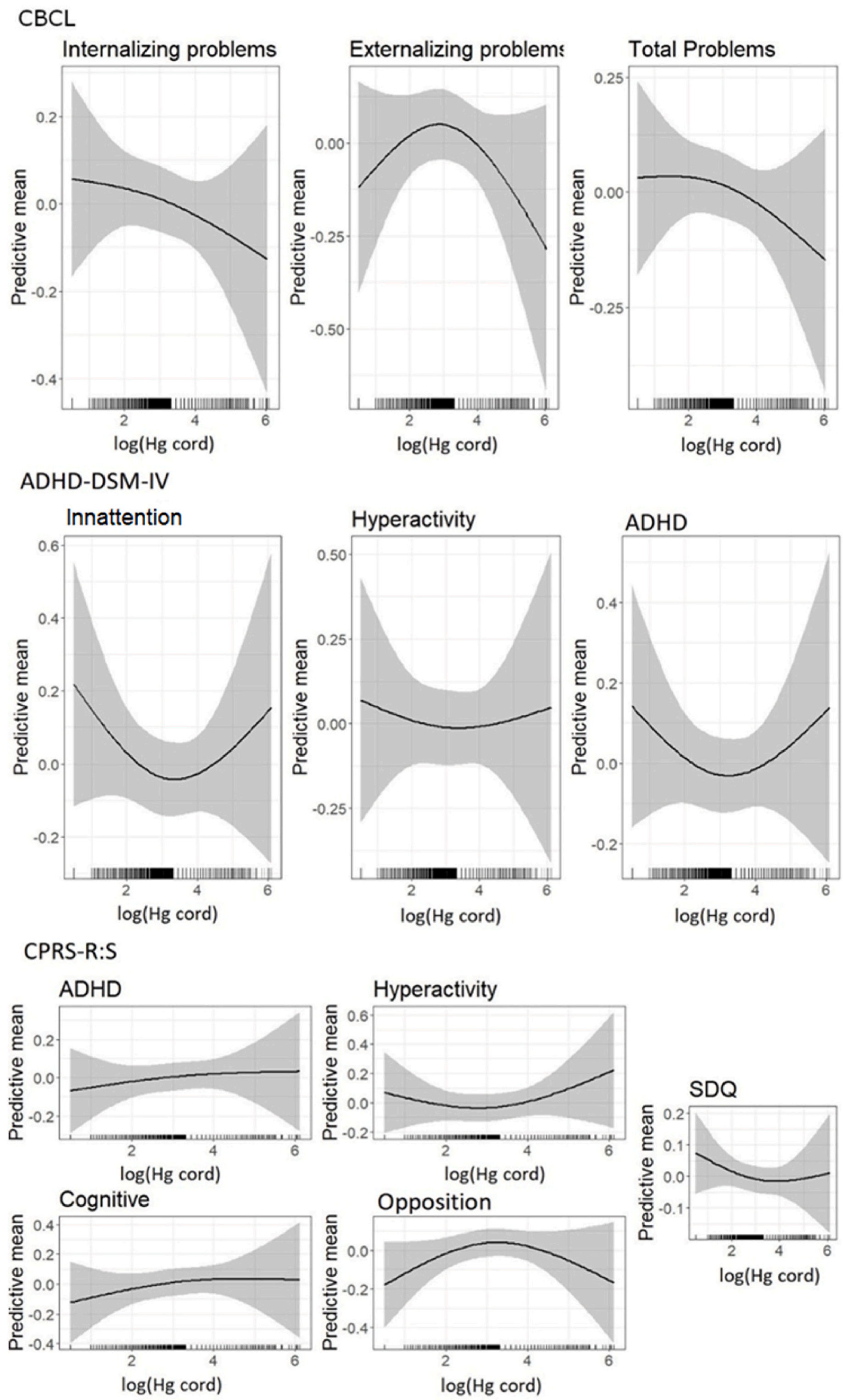

Fig. 5. Generalised additive models of the association between cord blood mercury concentrations and behavioural functioning (Model 2) Variables included in each model are presented in Table S4. ADHD: Attention Deficit Hyperactivity Disorder; CBCL: Child Behaviour Checklist; CPRS-R:S: Conners' Parent Rating Scale-Revised; DSMIV: Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition); SDQ: Strengths and Difficulties Questionnaire; Model 2: adjusted for prenatal total fish intake.

neurotoxicants may not become apparent until this life stage. Moreover, we can assess the influence of other variables, such as genetics or gut microbiota.

In conclusion, within this Spanish birth cohort study, we detected elevated prenatal exposure to Hg, but no detrimental impact on the neurobehavioral function of the children was observed from early childhood to pre-adolescence. Nor did we observe any influence of the factors studied, such as sex, maternal and child fish consumption, maternal fruit/vegetable intake, or prenatal exposure to PCBs. The advantageous nutrients present in fish might be mitigating the potential neurotoxic impact of Hg. Currently, there is not enough evidence regarding the neurotoxic impacts of Hg at lower to moderate dosages, specifically concerning behavioural function. More birth cohort studies with data on Hg exposure during vulnerable periods and longitudinal assessment of children's behavioural functioning would be warranted.

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Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the University Hospital La Fe (Valencia), the Ethics Committee of the Public Health Research Centre in Valencia (CSISP), Donostia Hospital (Gipuzkoa), Parc de Salut MAR (Sabadell), and University Central Hospital of Asturias (Asturias).

Consent to participate

Written informed consent was obtained from the mother for the prenatal period and from one of the parents or a legal representative for each phase of the postnatal period.

CRediT authorship contribution statement

Blanca Sarzo: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Ferran Ballester:** Writing – review & editing, Project administration, Funding acquisition. **Raquel Soler-Blasco:** Writing – review & editing. **Jordi Sunyer:** Writing – review & editing, Project administration, Funding acquisition. **Maria-Jose Lopez-Espinosa:** Writing – review & editing, Funding acquisition. **Jesus Ibarluzea:** Writing – review & editing, Project administration, Funding acquisition. **Manuel Lozano:** Writing – review & editing. **Jordi Julvez:** Writing – review & editing, Project administration, Funding acquisition. **Gorka Iriarte:** Writing – review & editing, Data curation. **Mikel Subiza-Perez:** Writing – review & editing. **Llúcia González-Safont:** Writing – review & editing. **Ana Fernández-Somoano:** Writing – review & editing, Project administration, Funding acquisition. **Jorge Vallejo-Ortega:** Writing – review & editing, Data curation. **Mònica Guxens:** Project administration, Funding acquisition. **Ulises-Alfredo López-González:** Writing – review & editing. **Isolina Riaño-Galán:** Project administration, Funding acquisition. **Gabriel Riutort-Mayol:** Writing – review & editing, Data curation. **Mario Murcia:** Data curation. **Sabrina Llop:** Writing – original draft, Project administration, Funding acquisition, Formal analysis, 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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.118954.

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