



# Postnatal exposure to mercury and neuropsychological development among preschooler children

Sabrina Llop<sup>1,2</sup> · Mario Murcia<sup>1,2</sup> · Rubén Amorós<sup>3</sup> · Jordi Julvez<sup>4,2,5,6,7</sup> · Loreto Santa-Marina<sup>2,8,9</sup> · Raquel Soler-Blasco<sup>1</sup> · Marisa Rebagliato<sup>1,2,10</sup> · Carmen Iñiguez<sup>1,2</sup> · Xabier Aguinagalde<sup>11</sup> · Gorka Iriarte<sup>11</sup> · Maria-Jose Lopez-Espinosa<sup>1,2,12</sup> · Ainara Andiaarena<sup>9,13</sup> · Lúcia Gonzalez<sup>1,2</sup> · Jesús Vioque<sup>2,14</sup> · Jordi Sunyer<sup>2,5,6,7</sup> · Ferran Ballester<sup>1,2,12</sup>

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## Abstract

The objective of this study was to describe the postnatal exposure to Hg and to evaluate its association with neuropsychological development among preschool children. The study population are 4–5 years old children (n = 1252) participant in the Spanish INMA Project. Total Hg was measured in cord blood and in hair samples taken at 4 years of age (2008–2012). Neuropsychological development was assessed using the McCarthy Scales of Children's Abilities (MSCA). Information on covariates and possible confounders was obtained by questionnaires during pregnancy and childhood. Generalized additive and linear regression models were built in order to assess the relationship between MSCA scores and Hg exposure. We also evaluated the magnitude of the possible bias generated from measurement error in seafood intake estimate from questionnaire and Hg determination. The geometric mean of hair Hg was 0.98 µg/g [95% confidence interval (CI) 0.94, 1.03]. In the regression analysis, the association between Hg and the MSCA scores was positive for all the scales and statistically significant for the verbal ( $\beta = 0.89$ ; 95%CI 0.38, 1.39), memory ( $\beta = 0.42$ ; 95%CI 0.09, 0.76) and general cognitive scales ( $\beta = 1.35$ ; 95%CI 0.45, 2.25). However, these associations were clearly attenuated when we adjusted by the children's fish intake variables or when took into account theoretical scenarios of low precision in fish intake and Hg measurements. Hg levels in this Spanish population were high in comparison with other European countries; however, we did not observe adverse effects on child neuropsychological development associated with this postnatal exposure to Hg.

**Keywords** Methylmercury · Cognitive · Development · Postnatal · Fish

## Introduction

Methylmercury (MeHg) is an environmental pollutant known to be neurotoxic to humans, being the major windows of vulnerability the *in utero* and early infancy periods [1]. The nervous system has a long development time that extends from the embryonic period to adolescence. Although most neurons have been formed by the time of birth, growth of glial cells and myelination of axons continues for several years [2]. In addition, the susceptibility of

infants and children to environmental toxicants is further enhanced by their increased absorption rates and diminished ability to detoxify compared to that of adults [3]. Exposure to environmental pollutants both prenatally and early during postnatal life may cause alterations in the development of the brain that give rise to learning and behavioural disorders affecting the development of school-aged children [4].

The main source of human exposure to MeHg is through eating seafood; being predatory fish such as swordfish, shark and fresh tuna those with the highest concentrations [5, 6]. Indeed, a positive association between fish intake and mercury (Hg) concentrations has been shown in different populations [7–12]. Given that fish contains important components of a healthy diet, such as omega-3 polyunsaturated fatty acids (PUFAs), iodine, selenium and vitamins, there is concern that exposure to MeHg at concentrations reached

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✉ Sabrina Llop  
llop\_sab@gva.es

Extended author information available on the last page of the article

by children with regular fish consumption may impair child development despite these beneficial nutrients [13].

In previous studies, we reported relatively high levels of prenatal exposure to Hg (measured as cord blood total Hg [THg]) in the Spanish INMA (Environment and Childhood) birth cohort [10]. In fact, we observed that the 64% of the newborns had cord blood THg above the equivalent to the US Environmental Protection Agency reference dose (5.8 µg/L of MeHg in whole blood), and the 25% of them have levels above the equivalent to the WHO Provisional Tolerable Weekly Intake (1.6 µg/kg of body weight per week). We also described a decreasing temporal trend in Hg concentrations from birth to 4 years old in one of the INMA cohorts located in Valencia [14]. Despite these elevated concentrations, prenatal exposure to Hg did not associate with a delay in child neuropsychological development evaluated at 14 months [15] and at 4–5 years [16] of age.

The brain susceptibility to Hg exposure starts during the prenatal period but it continues through the postnatal life; thus, the aim of this study was to explore the trend in Hg exposure between birth and age four in three of the INMA cohorts, as well as to evaluate the association between this postnatal exposure to Hg and child neuropsychological development evaluated at 4–5 years old.

## Methods

### Study population

Study subjects were participants in the INMA Project—a multicentre birth cohort study that aims to investigate the effects of environmental exposures and diet during pregnancy and childhood on foetal and child development in different areas of Spain (<http://www.proyectoinma.org>).

Our study was based on data from three INMA project cohorts (Gipuzkoa, Sabadell, and Valencia), which had followed the same protocol since the beginning of pregnancy [17]. Pregnant women ( $n=2150$ ) were recruited at their first routine specialised prenatal care visit in their reference primary health care centre or public hospital. The inclusion criteria were: at least 16 years of age, 10–13 weeks of gestation, singleton pregnancy, intention of undergoing follow-up and delivery in the corresponding centre of reference, and no impediment for communication. Excluding the women who withdrew from the study, were lost to follow-up and had induced or spontaneous abortions or foetal deaths, we followed up a total sample of 2021 (94%) women until delivery. Their children were enrolled at birth and were monitored until they were 4–5 years of age ( $n=1554$ , 72%). The final study sample was made up of 1252 mother–child pairs in whom both hair Hg concentrations and neuropsychological test scores were available.

Informed consent was obtained from all participants in each phase, and the study was approved by the hospital ethics committees in the participating regions.

### Mercury exposure

Whole blood samples were collected from cord vessels using venipuncture before the placenta was delivered and then kept frozen at  $-80\text{ }^{\circ}\text{C}$  until analysis. Hair samples were collected from the occipital scalp when children were 4 years old, placed in a plastic bag and stored at room temperature until analysis. The analyses of THg were carried out in the Public Health Laboratory of Araba (Basque Country, Spain). Both sample types were analysed in two different single-purpose Hg analysers (AMA 254 Leco Corporation and DMA-80 Milestone). Blood samples were weighed in a boat and directly analysed in the AMA 254 equipment by catalytic combustion, gold amalgamation, thermal desorption, and atomic absorption spectrometry. Hair samples were rinsed with 10 ml of Triton X-100 at 1% (Panreac) before performing the same procedure used with blood samples (in this case, AMA 254 and DMA-80 analysers were used). In both cases, replicate analyses were performed for each sample. The limits of quantification of the method (LOQ) were 2.0 µg/L for blood samples and 0.01 µg/g for hair samples. For measurements in cord blood below the LOQ (<5%) we used the  $\text{LOQ}/\sqrt{2}$  approach. No measurements of Hg in hair were below the LOQ.

Whole blood sample batches were internally controlled with Seronorm (Levels 2 and 3; SERO AS, Billingstad, Norway) reference materials. Hair sample batches were controlled with IAEA-086 (International Atomic Energy Agency, Austria) and NCS ZC 81002b (NCS Institute, Beijing, China) reference materials. Additionally, the accuracy of the method was also externally verified by participation in different inter-laboratory exercises organised by the New York State Department of Health in the Wadsworth Centre (Trace elements in whole blood PT programme) and the Centre de toxicologie du Québec (Quebec Multi-element External Quality Assessment Scheme, QMEQAS programme). In all cases satisfactory results were obtained.

### Neuropsychological evaluation

The neuropsychological development of the children was assessed at 4–5 years of age (range 4.1–6.4 years) by using a standardised version of the McCarthy Scales of Children's Abilities (MSCA) adapted to the Spanish population [18]. The MSCA comprises 18 subtests that yield standardised test scores for six conventional domains. The verbal scale refers to cognitive tasks related to the processing of verbal information; numerical abilities; the perceptive-manipulative scale refers to cognitive tasks related to perceptual

information processing, including manual performance; the memory scale considers short-term retention of information (verbal, visual or numerical); and the motor scale refers to fine (fingers and hands movements) and gross (limb movements and coordination such as walking) abilities. The sum of the first three scales provides a general cognitive scale.

Testing was conducted by four trained psychologists using a strict protocol. For a small number of children, evaluations were performed by several neuropsychologists with results reached by consensus (the inter-observer variability was < 5%). Raw scores were used for the analysis and the variables psychologist and children's age were included in the multivariate models.

### Other variables

The women completed two questionnaires during their pregnancy, one at the first trimester [mean  $\pm$  standard deviation (SD) =  $12 \pm 1.7$  weeks of gestation] and the other at the third trimester ( $32.7 \pm 2.2$  weeks of gestation). The questionnaires were administered by trained interviewers and focused on socio-demographic, environmental and lifestyle information during pregnancy. The parental covariates and potential confounders collected were: maternal and paternal age (years), maternal and paternal educational level (up to primary studies, secondary, university), maternal country of birth (Spain, other), parity (0, 1, > 1), body mass index (BMI, kg/m<sup>2</sup>) before pregnancy [low weight (< 18.5), healthy (18.5, < 25), overweight (25, < 30), obesity ( $\geq 30$ )], working status during pregnancy (non-worker, worker) and season of birth. Parental social class was defined from the maternal or paternal occupation during pregnancy with the highest social class, according to a widely used Spanish adaptation of the International Standard Classification of Occupations approved in 1988 (ISCO88) (Class I+II: managerial jobs, senior technical staff and commercial managers; class III: skilled non-manual workers; and class IV + V: manual and unskilled workers).

Information on fish intake during pregnancy was collected by using a validated semi-quantitative food frequency questionnaire (FFQ) administered at the first and third trimesters of pregnancy [19]. Both questionnaires covered average intakes from the last menstrual period until the third trimester of pregnancy. In the present study, we used the average of the intakes from the two FFQs for each seafood item. We calculated the weekly intake (expressed in servings) of total seafood (sum of lean fish, large oily fish, canned tuna, small oily fish, shellfish, cephalopods and other seafood) and adjusted it for energy intake.

Information on the children's gestational age and sex was obtained from clinical records. Information about maternal and paternal working status (non-worker, worker), maternal and paternal smoking habit (smoker, non-smoker) and main

care provider (mother, mother and others, other combinations without mother) was obtained in an interview at the same time point as the neuropsychological evaluation. A proxy of the maternal verbal intelligence quotient (IQ) was assessed using the Similarities Subtest of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) simultaneously to the MSCA.

In addition, a validated semi-quantitative FFQ of 105 food items was administered at age 4 in order to assess the usual daily intake for main foods and nutrients among children [20]. This FFQ was a modified version of the previous one which we used for the pregnant women but adapted for children. Nutritionists collected dietary information by asking mothers or caregivers of children how often, on average, their children had consumed each specific food and serving size during the year prior to the interview. We considered separately 5 seafood groups: lean fish (two items), swordfish, canned fish (tuna, sardine, and mackerel), other large oily fish (tuna, bonito, salmon), and other seafood (5 items). We also calculated the weekly intake (expressed in servings and adjusted for energy intake) of total seafood as the sum of all the seafood groups.

### Statistical analysis

First, a descriptive analysis of the study population and THg concentrations was performed. The association between children's intake of each seafood group and hair THg concentrations was evaluated using a multivariate linear regression model. This model was built with those covariates associated to the THg concentrations in a bivariate analysis using the likelihood ratio test. In this multivariate model we introduced all fish intake variables and the change (%) in hair Hg concentrations caused by each fish intake variable was calculated. Although fish intake variables were mutually correlated, we found no collinearity problems among them according to the variance inflation factor (VIF < 2).

In order to study the Hg concentrations trend from birth to age 4, we applied the factor proposed by the WHO Expert Committee (hair:blood ratio of 250) to the cord blood THg concentrations and obtained the equivalent hair sample THg concentrations [21]. The difference between the two variables was calculated and a Kernel density diagram was plotted including both exposure variables for the three cohorts.

The association between hair THg concentrations and the scores for the six MSCA scales was evaluated by multivariate linear regression models in a pooled analysis. These models were built in a two-step procedure. First, a core model was built for each of the scales using all the related covariates in the univariate analysis ( $p < 0.10$ ). Following a backward elimination procedure, all the covariates associated with the scores ( $p < 0.10$ ) in the likelihood ratio test were retained in the models. The log<sub>2</sub> transformed hair

THg variable was introduced into these adjusted models. In all these models, additional potential confounders were included if they changed the magnitude of the main effects by more than 10% (Model 1). Children's fish intake was forced in the models because of its association with both the outcome and the exposure variables (Model 2). Cord blood THg concentrations and maternal fish intake during pregnancy were also included in the models (Model 3). In the last model, we replaced the variable children's total fish intake by the different fish categories (lean fish, swordfish, canned fish, other large oily fish and other seafood) (Model 4).

General additive models (GAMs) using cubic smoothing splines with two to four degrees of freedom were performed on the multivariate models (Model 4) in order to study the shape of the relationship between neurodevelopment test scores and hair THg concentrations. We compared linear and non-linear models with the aid of graphical examination and the likelihood ratio (LR) test ( $p < 0.05$ ).

A meta-analysis was also performed to obtain combined estimates of the association between postnatal Hg exposure and infant neurodevelopment by cohort in order to explore if there was heterogeneity among cohorts. The estimates of association were obtained through weighted regression in which the weights were the inverse of the local variances, that is, the "fixed-effect model." Heterogeneity was quantified with the I-squared measure ( $I^2$ ) under the fixed-effect hypothesis and, if heterogeneity was detected ( $I^2 > 50\%$ ), the "random effect model" was applied.

Finally, we evaluated the magnitude of the possible bias generated from measurement error in seafood intake estimate from questionnaire through sensitivity analysis. We considered separately 5 the seafood groups to allow for different patterns of association with both exposure and outcome variables. Fish intake variables and THg concentrations were log-transformed in all analysis. We assumed fish intake groups as having an additive random measurement error component with variances varying in a realistic range of imprecision levels:

$$\text{Measured fish}(i) = \text{Latent fish}(i) + U,$$

with  $U$  = random measurement error

$$\text{Reliability} = (\text{Var}(\text{Measured fish}(i)) - \text{Var}(U)) / \text{Var}(\text{Measured fish}(i))$$

We simulated reliability varying in {100%, 68%, 56%, and 43%} [22]. Maternal fish intake during pregnancy was also adjusted and, for simplicity, assumed to have a measurement error of the same magnitude as child's intake. For a more realistic scenario, additional sensitivity analysis included also a measurement error term in Hg determination. According to the estimations obtained in the Faeroe birth cohort study [23, 24], we assumed a reliability of 79% for Hg determination in hair samples and 88% in cord blood samples.

Models were fitted with the aid of structural equation models (SEM) that allow explicit measurement error specifications in study variables. The general path diagram for the SEM is shown in Online Resource 3. The lavaan package of R [25] was used for SEM adjustment. Confidence intervals were estimated on the basis of robust Huber–White standard errors.

In order to ratify the previous results, error in variables regression models, modeled with the eivtools package of R were also fitted and compared with the previous ones, given that the measurement component of the SEM is only intended to reflect the measurement error of the explanatory variables.

The analyses were carried out using Stata, version 13 (StataCorp LP, College Station, Texas) and R (v 3.5.1).

## Results

The geometric mean (95%CI) of hair Hg concentrations was 0.98 (0.94, 1.03)  $\mu\text{g/g}$ , with an inter-quartile range of 1.02 and a mean and standard deviation (mean  $\pm$  SD) of 1.38  $\pm$  1.42  $\mu\text{g/g}$ . Fifty per cent of the children had hair Hg concentrations above 1  $\mu\text{g/g}$  (equivalent for the reference dose proposed by the US EPA [26, 27] and 11% had Hg concentrations above the equivalent for the provisional tolerable weekly intake (PTWI) proposed by the WHO (i.e. 2.5  $\mu\text{g/g}$ ) [28].

Hair Hg concentrations according to parental and child characteristics are shown in Table 1. We observed statistically significant differences according to the cohort, children from the Valencia cohort being the ones who presented the highest concentrations. The total intake of fish was higher in the Sabadell cohort (0.98  $\pm$  0.46 weekly servings vs. 0.89  $\pm$  0.43 in Gipuzkoa and 0.74  $\pm$  0.43 in Valencia), although the intake of swordfish was higher in Valencia (0.37  $\pm$  0.54 weekly servings vs. 0.02  $\pm$  0.11 in Gipuzkoa and 0.14  $\pm$  0.34 in Sabadell). Hair Hg concentrations were higher among children whose parents were between 31 and 35 years old, had finished university studies, belonged to the highest social class and were employed. Hair Hg concentrations increased with the children's fish consumption at 4 years old. The Pearson correlation coefficient between cord blood Hg and 4-year-olds' hair Hg concentrations, both log<sub>2</sub> transformed, was 0.308 ( $p < 0.001$ ).

There was a decrease of 27.2  $\pm$  105.1% in Hg concentrations from birth to the age of 4, after applying the factor proposed by the WHO Expert Committee (hair: blood ratio of 250). The highest reduction was observed in Gipuzkoa (35.3  $\pm$  52.4%), followed by Valencia (24.4  $\pm$  144.1%) and Sabadell (23.7  $\pm$  85.0%). The reduction in Hg concentrations between birth and the age of 4 was also evident in the Kernel diagram (Fig. 1), where the mode and the larger amount of

**Table 1** Hair mercury concentrations at age 4 (µg/g) according to the socio-demographic, life style and dietary characteristics of the study population. INMA Project, Spain

	N	%	GM	95%CI		<i>p</i> value
All children	1251		0.98	0.94	1.03	
<b>Cohort</b>						
Gipuzkoa	309	25	0.99	0.91	1.06	<0.001
Sabadell	441	35	0.83	0.78	0.89	
Valencia	502	40	1.13	1.04	1.22	
<b>Maternal age (years)<sup>a</sup></b>						
<25	70	6	0.77	0.63	0.93	<0.001
25–29	411	33	0.98	0.90	1.06	
30–34	544	43	1.03	0.96	1.10	
≥35	226	18	0.96	0.86	1.08	
<b>Paternal age (years)<sup>a</sup></b>						
<26	57	5	0.75	0.60	0.94	0.009
26–30	355	28	0.96	0.88	1.05	
31–35	522	42	1.03	0.96	1.11	
≥36	315	25	0.98	0.89	1.07	
<b>Maternal educational level</b>						
Up to primary	281	22	0.79	0.72	0.88	0.002
Secondary	519	42	0.96	0.89	1.03	
University	449	36	1.16	1.08	1.24	
<b>Paternal educational level</b>						
Up to primary	436	35	0.87	0.80	0.94	<0.001
Secondary	534	43	1.01	0.94	1.08	
University	273	22	1.14	1.04	1.24	
<b>Body mass index before pregnancy (kg/m<sup>2</sup>)</b>						
<18.5	55	4	0.77	0.61	0.97	0.002
18.5–25	884	71	1.03	0.98	1.09	
>25–30	221	18	0.92	0.83	1.03	
>30	92	7	0.80	0.66	0.97	
<b>Parity</b>						
0	714	57	1.07	1.01	1.13	<0.001
1	453	36	0.88	0.82	0.95	
>1	83	7	0.84	0.70	1.01	
<b>Maternal country of birth</b>						
Spain	1163	93	1.00	0.95	1.05	0.001
Other	86	7	0.75	0.65	0.87	
<b>Social class</b>						
I+II	441	35	1.17	1.09	1.26	<0.001
III	334	27	0.98	0.90	1.07	
IV+V	477	38	0.83	0.77	0.90	
<b>Sex</b>						
Female	658	53	1.00	0.94	1.07	0.532
Male	594	47	0.96	0.89	1.03	
<b>Maternal smoking<sup>b</sup></b>						
Yes	339	28	0.86	0.79	0.94	0.002
No	886	72	1.02	0.97	1.08	
<b>Paternal smoking<sup>b</sup></b>						
Yes	414	34	0.94	0.87	1.02	0.122
No	797	66	1.01	0.95	1.07	
<b>Maternal working situation<sup>b</sup></b>						
Employed	913	75	1.03	0.98	1.08	0.007
Not employed	307	25	0.86	0.78	0.95	

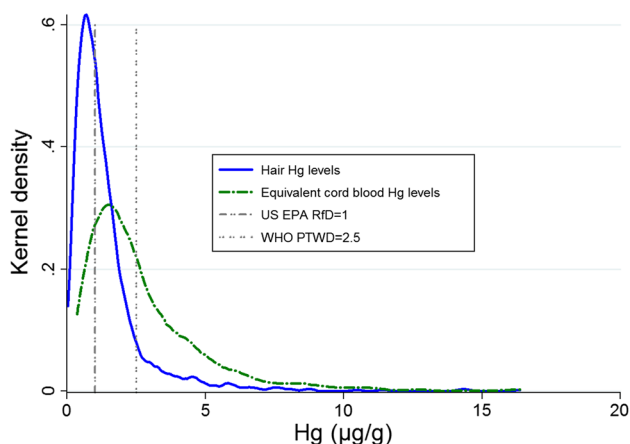
**Table 1** (continued)

	N	%	GM	95%CI		<i>p</i> value
Paternal working situation <sup>b</sup>						
Employed	1090	90	1.01	0.96	1.06	0.031
Not employed	116	10	0.84	0.72	1.00	
Total fish intake at 4 years (quartiles of weekly servings)						
≤ 3.5	301	25	0.68	0.62	0.76	<0.001
> 3.5–4.5	301	25	0.94	0.86	1.02	
> 4.5–5.7	295	25	1.10	1.02	1.19	
> 5.7	305	25	1.31	1.19	1.43	

<sup>a</sup>At the beginning of pregnancy

<sup>b</sup>At neuropsychological assessment

*p* value from the Mann-Whitney or Kruskal Wallis tests



**Fig. 1** Kernel diagram with hair mercury concentrations at age 4 and the equivalent cord blood mercury concentrations after applying the factor proposed by the WHO Expert Committee (hair: blood ratio of 250). INMA Project, Spain

density for Hg concentrations was found in higher values at birth than at the age of 4. This diagram was similar among the three cohorts (Online Resource 1).

The intake of swordfish, lean fish and canned fish were the clearest types related to hair Hg concentrations (Table 2). A doubling of the consumption of swordfish, lean fish and canned fish was associated with an increase in Hg concentrations of 24.3% (95%CI 19.6, 29.2), 18.3% (95%CI 13.4, 23.4) and 15.6% (95%CI 10.0, 21.3), respectively.

Online Resource 2 shows that hair THg was strongly and positively correlated with seafood intake, especially with swordfish ( $r = 0.35$ ) and lean fish intake ( $r = 0.34$ ), while it was essentially unrelated to the ‘other seafood’ group. The correlation between the general cognitive score and seafood intake was also direct but weaker: higher positive correlations were found for lean fish and swordfish, while they were almost zero or even negative with the rest of items. The general cognitive score was also correlated with THg both in hair ( $r = 0.17$ ) and in cord blood

**Table 2** Percentage of change in hair total mercury concentrations (95% CI) associated with a doubling of the consumption of each fish subtype. INMA Project, Spain

	% change	95%	
Lean fish	18.3	13.4	23.4
Swordfish	24.3	19.6	29.2
Other large blue fish	6.9	3.2	10.7
Canned fish	15.6	10.0	21.4
Other fish	1.4	-4.5	7.8

The linear regression model was adjusted for social class, parity, paternal working situation and cord blood total mercury concentrations

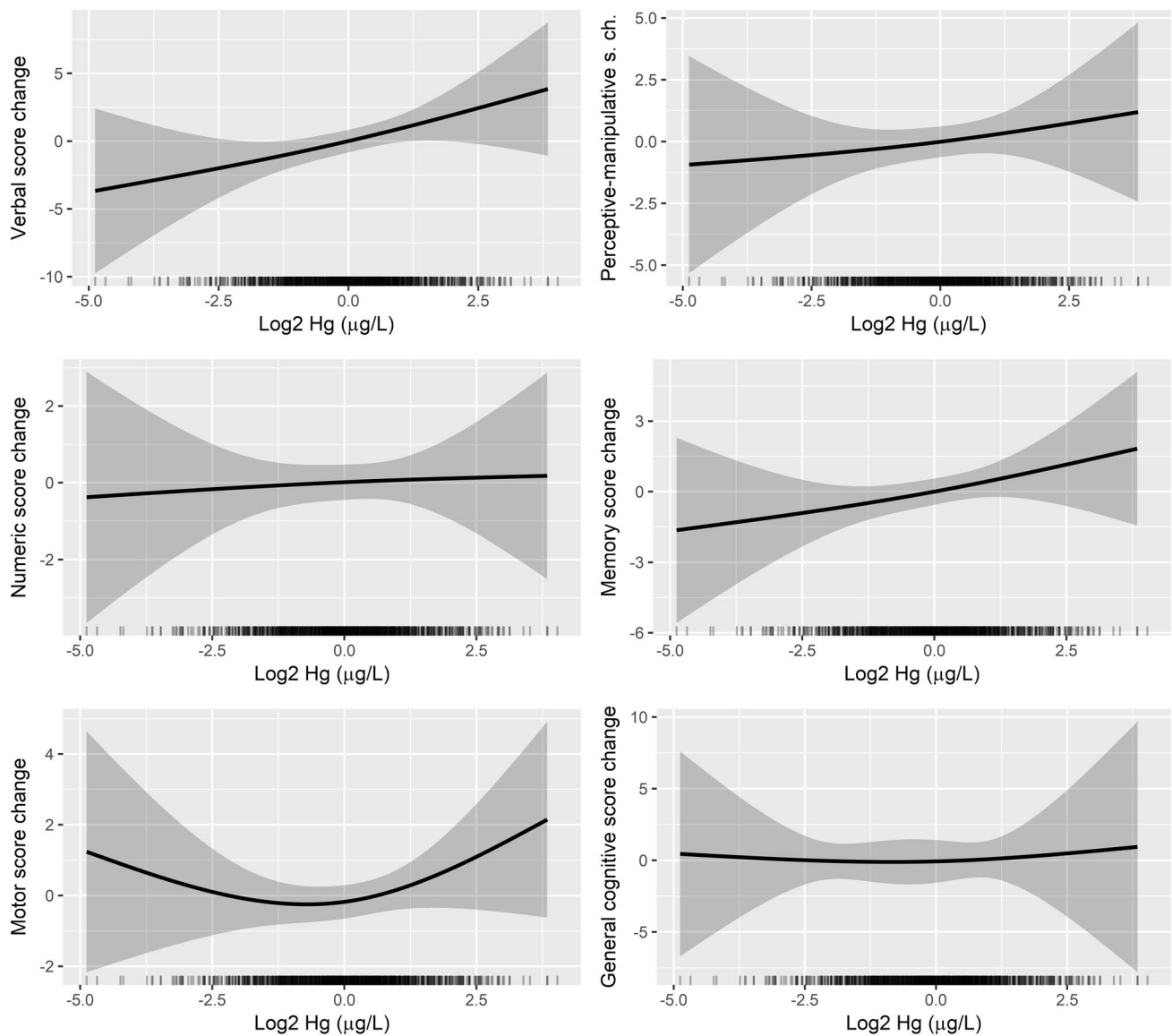
The response variable was T-Hg log<sub>2</sub>-transformed and was simultaneously adjusted for all the fish groups (log<sub>2</sub>-transformed)

( $r = 0.13$ ). Subsequently, models were adjusted separately for the seafood items to account for these different patterns of association with exposure and outcome variables.

The shape of the relationship between Hg and the test scores was explored by GAM. Linear and positive patterns were observed for all the scales (Fig. 2).

The association between postnatal exposure to Hg and the scores obtained by the children in the MSCA test was positive for all the scales and statistically significant for the verbal, memory and general cognitive scales (Table 3, Model 1). When the variable total fish intake at 4 years was included in the models (Model 2), the coefficients remained virtually the same. Subsequently, cord blood Hg and maternal fish intake during pregnancy were also included in the models (Model 3), and we obtained similar results. When we replaced the children’s total fish intake variable by the different fish categories all the beta coefficients were attenuated and the only scale that remained statistically significant was the verbal one (Model 4).

No heterogeneity was found in the association between hair Hg concentrations and children’s neuropsychological



**Fig. 2** Generalised additive models of the hair mercury concentrations and child neuropsychological development assessed by the McCarthy test scores at age 4–5 years. INMA Project, Spain. Models adjusted for the same variables as in Table 3 (model 4)

development according to the cohort, except for the memory scale (Fig. 3). However, an overall pattern of more positive coefficients for the Mediterranean cohorts was observed.

Figure 4 shows how the imprecision in seafood and THg measurement could bias the effect estimates for THg. The sensitivity of the coefficients to measurement error depended, not only on the reliability of the variables, but also on the complexity of the model: the coefficients were clearly attenuated while reliability decreased in the models adjusted for seafood groups separately, while they were virtually unaffected when models were adjusted for total

seafood. As expected, the standard error of the estimates increased with imprecision in all cases, especially when we assumed also measurement error for Hg determination. No significant association was retained when models were adjusted for fish groups in a scenario of 68% reliability in seafood intake estimates, irrespectively of the presence of measurement error in Hg. Estimates were similar for both methodologies (SEM versus error in variables regression), with a mildly higher confidence intervals in the second case, especially as reliability diminishes.

**Table 3** Association between hair mercury concentrations at age 4 and child neuropsychological development assessed by the McCarthy test scores (INMA Project, Spain)

	Model 1			Model 2			Model 3			Model 4						
	$\beta$	95%CI	<i>p</i>	B	95%CI	<i>p</i>	B	95%CI	<i>P</i>	B	95%CI	<i>p</i>				
Verbal	0.89	0.38	1.39	0.001	0.87	0.32	1.42	0.002	0.94	0.29	1.58	0.004	0.87	0.18	1.56	0.013
Perceptive-manipulative	0.34	-0.02	0.71	0.066	0.36	-0.04	0.76	0.076	0.32	-0.14	0.80	0.168	0.25	-0.25	0.75	0.329
Numeric	0.21	-0.07	0.48	0.140	0.23	-0.07	0.54	0.133	0.13	-0.22	0.49	0.456	0.11	-0.27	0.49	0.566
Memory	0.42	0.09	0.76	0.012	0.37	0.01	0.74	0.047	0.49	0.06	0.92	0.025	0.43	-0.03	0.89	0.066
Motor	0.16	-0.13	0.45	0.274	0.22	-0.10	0.54	0.171	0.21	-0.15	0.58	0.252	0.20	-0.19	0.59	0.312
General cognitive	1.35	0.45	2.25	0.003	1.37	0.38	2.35	0.007	1.29	0.14	2.43	0.028	1.07	-0.16	2.30	0.089

Hair and cord blood mercury concentrations were log<sub>2</sub> transformed

Model 1: all models adjusted for children’s age at evaluation, psychologist and season at birth

Verbal model adjusted for social class, maternal country of birth, maternal age, parental educational level, maternal working situation during pregnancy, body mass index before pregnancy and sex

Perceptive-manipulative model adjusted for social class, parental educational level, sex, maternal employment at evaluation and maternal intelligence

Numeric model adjusted for social class, parental educational level, maternal country of birth, maternal employment at evaluation and maternal intelligence

Memory model adjusted for social class, parental educational level, maternal country of birth, maternal employment during pregnancy, sex, parental smoking and maternal intelligence

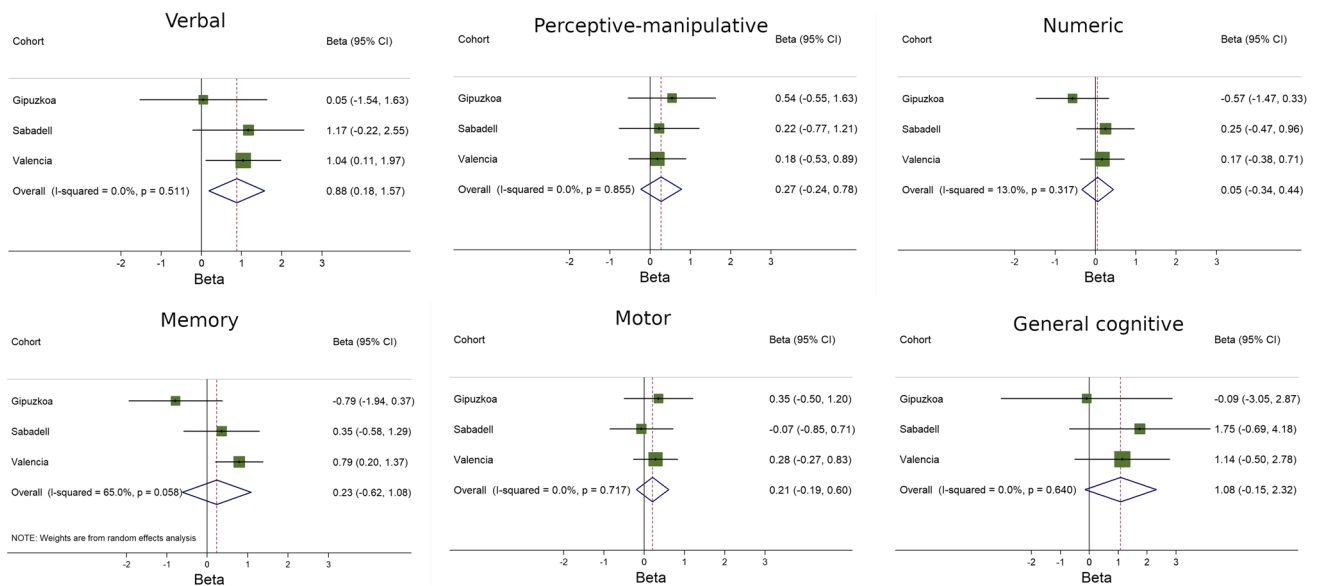
Motor model adjusted maternal educational level, sex, parity and parental employment

General cognitive scale adjusted for social class, maternal country of birth, maternal age, parental educational level, parity, sex, maternal employment and maternal intelligence

Model 2: model 1 + children’s total fish consumption

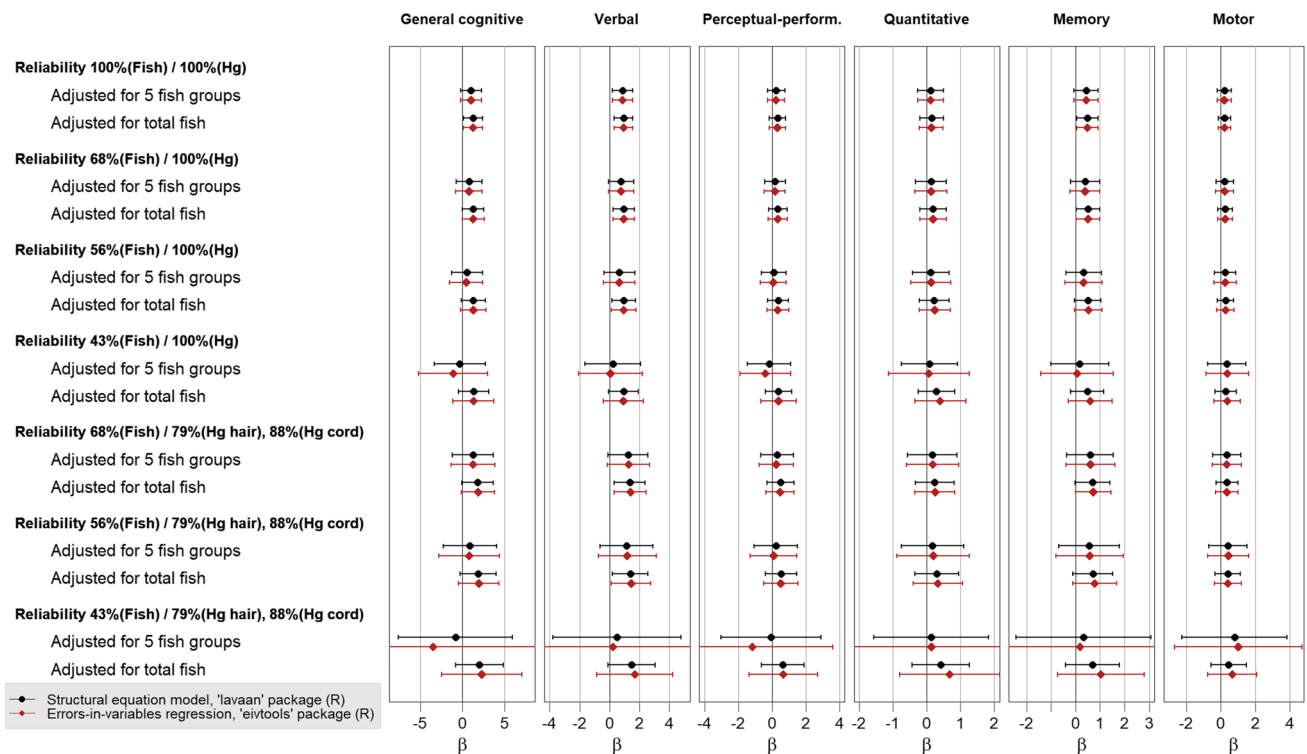
Model 3: model 2 + cord blood mercury + maternal fish consumption during pregnancy

Model 4: model 3 but replacing children’s total fish consumption by the different fish categories (lean fish, swordfish, other large oily fish, canned fish, and other fish)



**Fig. 3** Meta-analysis of the association between hair mercury concentrations at age 4 and child neuropsychological development according to cohort. Models adjusted for the same variables as in Table 3 (model 4)





**Fig. 4** Association between hair THg concentrations and child neuropsychological development assessed by the McCarthy test under different scenarios of measurement error in seafood and THg vari-

ables. Two alternative models were fitted: adjusted for children’s total fish intake versus adjusted for children’s 5 seafood groups intake. Models adjusted for the same variables as in Table 3 (model 4)

## Discussion

In this Spanish birth cohort study, we observed that Hg concentrations followed a decreasing trend from birth to age 4; however, half of the children still had Hg concentrations above the EPA recommendations and 11% above the equivalent for the PTWI proposed by the WHO at 4 years old. We observed that increased Hg levels were associated with higher scores in most of the MSCA scales, however, only the verbal scale remained statistically associated when fish intake variables were separately adjusted in the models. Moreover, these associations were additionally attenuated, or even disappeared, when we took into account theoretical scenarios of low precision in fish intake and Hg measurements.

Levels observed in this study were similar to those found in previous Spanish studies conducted on children, such as in 4-year-old children from Menorca [29] and from Granada [8], both populations with a geometric mean (GM) of 1.0  $\mu\text{g/g}$  and around 50% of the children with levels above the EPA recommendations. On comparing with international studies, levels observed in this study were much higher than those observed in other populations from North or East Europe, such as 6–11-year-old children from the Czech Republic (geometric mean = 0.098  $\mu\text{g/g}$ ) [30], Denmark

(geometric mean = 0.326  $\mu\text{g/g}$ ) [31] or Germany (geometric mean = 0.055  $\mu\text{g/g}$ ). Other European studies conducted in Mediterranean regions found Hg concentrations that were higher than in North Europe, but still lower than in our study, such as in children aged 7–9 years from Italy (mean = 0.88  $\mu\text{g/g}$ ) [32] or 11–12-year-old children from Greece (GM: 0.30–0.44  $\mu\text{g/g}$ , depending of the location) [33]. These patent differences in Hg concentrations between the Mediterranean countries and the Northern countries could be related with the amount and type of fish consumed. In the multi-centre study EPIC (European Investigation into Cancer and Nutrition), a description of the consumption of total fish and the fish sub-groups was provided by the different European countries participating in the study [34]. The lowest fish consumption was observed in Germany and the highest in Spain. The greatest intake of very fatty fish was in the coastal areas of Northern Europe (Denmark, Sweden and Norway), although the fish species that were most frequently consumed were salmon, with less Hg content than others such as swordfish and tuna, which are more frequently consumed in Southern countries. Hg concentrations were observed to be higher in those populations where fish constitute the main source of proteins, such as 6.5-year-old children from Seychelles (mean: 6.5  $\mu\text{g/g}$ ) [35] or 7-year-old children from the Faroe Islands (GM: 3.0  $\mu\text{g/g}$ ) [36].

We also assessed the relationship between postnatal exposure to Hg and child neuropsychological development. We observed that increasing hair Hg concentrations were associated with better scores on the MSCA assessed at 4–5 years of age. The coefficients for this association still remained positive and statistically significant when we included the variable ‘child total fish intake’ in the models, but were substantially attenuated when we replaced the total fish intake variable by the different categories of fish. Measurement error in confounders has been shown to affect effect estimates of exposure variables. Moreover, this bias could lead to either an over or underestimation of regression parameters depending on the direction of the effect of confounders and their correlation with exposure [22]. The FFQ is a good instrument method for assessing and classifying mothers and children according to their usual dietary intake [19, 20]; however, it might suffer from measurement error due to the general difficulties in evaluating regular dietary intake: memory bias, portion sizes, etc. Failing to control for negative confounding from seafood intake could result in the underestimation of both Hg toxicity and fish benefits [37]. In fact, we observed that the positive association observed in our study between Hg exposure and the MSCA disappeared when models were adjusted for fish groups in a scenario of 68% reliability in seafood intake estimates, irrespectively of the presence of measurement error in Hg.

We also included the variable cord blood THg concentrations and maternal fish intake during pregnancy in the models, since both of them have been associated with children’s neuropsychological development in our study population [16, 38]. However, the coefficients for the association between postnatal exposure to Hg and the MSCA scores remained virtually the same. Increasing importance has been given to taking prenatal exposure into account to identify cognitive effects from postnatal MeHg exposure [36]. The decreasing trend in Hg concentrations from the prenatal to postnatal period [39, 40, our data] and also the decreased postnatal susceptibility of the central nervous system [41] make it more difficult to disentangle the possible neurotoxic effect from just postnatal exposure.

Other factor that could be influencing our results is the parental socioeconomic characteristics. Children’s fish intake and, therefore, exposure to mercury, is directly associated with the socioeconomic status, being children from mothers who worked at the time of the assessment those who consumed more quantity of fish and had higher mercury concentrations [10, 14]. Additionally, parental socioeconomic status and maternal education was recently related with children’s neuropsychological development in one of the INMA cohorts participant in this study [42]. We have controlled by several variables related to the socio-economic status (social class, maternal and paternal working situation) in the

analysis but we cannot exclude some residual confounding mainly related to the socio-family environment.

Apart from MeHg and other toxicants, however, fish also contains several beneficial nutrients necessary for brain development [43]. We did not observe any adverse hair Hg-related effects in our population and even the coefficients for the association between Hg and the MSCA scores were positive for all the scales. A possible explanation for this unexpected association is that hair Hg concentrations could be acting as a proxy of the fish nutrients that are beneficial for child neuropsychological development. We found similar results when we evaluated the effect of prenatal exposure to Hg on child neuropsychological development [16]. In this last study, we also showed that this association was highly influenced by maternal fish consumption. High Hg concentrations in cord blood was associated with lower scores only among children whose mothers consumed fewer than three weekly servings of fish during pregnancy and among children with lower  $n-3$  PUFAs concentrations. Ralston and Raymond (2018) recently attributed this positive association between Hg and children’s neuropsychological development observed in the present and other previous studies [44, 45] to the high amount of selenium found in the ocean fish [46]. The increasing MHg exposures from maternal consumption of typical varieties of ocean fish result in neurological benefits rather than deficits in their children. MeHg is a highly selective irreversible inhibitor of selenoenzymes that normally prevent oxidative damage in the brain.

Previous studies have evaluated the possible association between postnatal exposure to Hg and child neuropsychological development but with heterogeneous results. Postnatal Hg measured in blood samples at 5 years old in Inuit children from Northern Canada was associated with higher action tremor amplitude [47] and alterations of visual evoked potentials response [48], but not with children’s behaviour [49] in models adjusted for selenium and PUFAs. In a study conducted on 66-month-old children from the Seychelles Islands, hair Hg concentrations were not associated with cognitive and language ability, reading and arithmetic achievement, visual-spatial ability or behaviour [35]. In these models the authors adjusted for prenatal exposure to Hg measured in maternal hair samples but they did not adjust for fish consumption. In another study conducted on children from the Faroe Islands, the authors mutually adjusted the models for both pre and postnatal exposure to Hg and evaluated the possible effects on child neuropsychological development at 7 years old. Prenatal Hg was inversely associated with some of the neuropsychological outcomes, but most of these associations weakened regarding the postnatal exposure to Hg [36]. In the same cohort, hair Hg concentration measured at 14 years of age was associated with prolonged latencies of brainstem evoked potential peaks III–V [40] in an analysis adjusted for prenatal exposure to Hg and

PCBs. In Spain, the association between Hg hair levels at 4 years of age and child neuropsychological development was evaluated in one of the first INMA cohorts conducted in Granada [8]. The authors found a negative association between Hg concentrations above 1 µg/g and child cognitive, verbal and memory development in models adjusted for child fish consumption. In a recent study conducted in Bangladesh, hair Hg at 10 years old did not associate with cognitive development but children in the highest tertile of hair-Hg had a lower prevalence of hyperactivity and peer relationship problems, compared to children in the lowest tertile [50]. The authors did not adjust for prenatal exposure to Hg and fish intake. Finally, in a moderate Hg exposed population in Amazonia (Brazil), hair concentrations did not associate with child cognitive development at 3–7 years old [51]. Differences in methodology (exposure assessment, neuropsychological tests used, age at assessment and adjustment for confounders) make comparability among studies more difficult and can also be a possible source of heterogeneity in the results.

There are some weaknesses in our study: first, hair Hg concentrations have been suggested as a more imprecise biomarker than blood Hg since they are dependent on the rate of hair growth [24]. In addition, 20% of the population who reached the survey at 4–5 years did not take part in this study; the main reason was the unavailability of hair samples for the Hg analysis. We evaluated the differences between the included ( $n = 1252$ ) and the excluded ( $n = 302$ ) population and we observed that there was a higher proportion of children from the Gipuzkoa cohort among the excluded population (64% from Gipuzkoa, 23% from Sabadell and 11% from Valencia,  $p$  value  $\chi^2 < 0.001$ ). We also observed statistically significant differences according to the parity; there was a higher proportion of primiparous mothers among those included (57% vs. 51%,  $p$  value  $\chi^2 = 0.046$ ). The loss of follow-up in cohort studies could represent a bias in estimating some exposure-outcome associations; however, we do not think that our results were highly influenced by this 20% drop in the study population. Despite this loss of follow-up, our study has a considerable sample size in comparison to other birth cohort studies. Another advantage in our study is the prospective design and the exhaustiveness in data collection, which made it possible to obtain detailed information concerning determinants of Hg exposure and children's neuropsychological development. This was possible because the study population was followed up from the early stages of pregnancy until the children were aged 4–5. This prospective follow-up will enable us to study the possible adverse effects of Hg exposure on cognitive development in the future.

In conclusion, in this Spanish birth cohort study we observed a decreasing trend in Hg concentrations from birth to age 4; however, a considerable proportion of children still

had Hg concentrations above the USA EPA and WHO recommendations. Swordfish was the fish specie which intake increased more Hg hair levels. Lean fish and canned fish were also substantively related with Hg levels. The association between hair Hg concentrations and the MSCA scores was positive for all the scales and statistically significant for the verbal, memory and general cognitive scales. However, only the verbal scale remained statistically significant when models were adjusted by all children's fish intake variables. Moreover, these associations were additionally attenuated, or even disappeared, when we took into account theoretical scenarios of low precision in fish intake and Hg measurements.

At present, there is insufficient evidence of the possible neurotoxic effects of postnatal Hg exposure at moderate doses; therefore, more research about this topic is needed in order to unravel these complex associations. On the other hand, some studies have found significant associations at older ages; hence, in our cohort it is advisable to continue evaluating children neuropsychologically throughout childhood.

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#### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Hospital La Fe in Valencia, the Institut Municipal d'Assistència Sanitària in Barcelona, Comitè Ètic de Investigació Clínica del Hospital Donostia, and Comitè Ètic

de Investigación Clínica del Área Sanitaria de Gipuzkoa) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.


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## Affiliations

Sabrina Llop<sup>1,2</sup>  · Mario Murcia<sup>1,2</sup> · Rubén Amorós<sup>3</sup> · Jordi Julvez<sup>4,2,5,6,7</sup> · Loreto Santa-Marina<sup>2,8,9</sup> · Raquel Soler-Blasco<sup>1</sup> · Marisa Rebagliato<sup>1,2,10</sup> · Carmen Iñiguez<sup>1,2</sup> · Xabier Aguinagalde<sup>11</sup> · Gorka Iriarte<sup>11</sup> · Maria-Jose Lopez-Espinosa<sup>1,2,12</sup> · Ainara Andiaarena<sup>9,13</sup> · Llúcia Gonzalez<sup>1,2</sup> · Jesús Vioque<sup>2,14</sup> · Jordi Sunyer<sup>2,5,6,7</sup> · Ferran Ballester<sup>1,2,12</sup>

<sup>1</sup> Epidemiology and Environmental Health Joint Research Unit, Foundation for the Promotion of Health and Biomedical Research in the Valencian Region, FISABIO-Public Health, FISABIO–Universitat Jaume I–Universitat de València, Av. Catalunya 21, 46020 Valencia, Spain

<sup>2</sup> Spanish Consortium for Research on Epidemiology and Public Health (CIBERESP), Av. Monforte de Lemos, 3-5. Pabellón 11, 28029 Madrid, Spain

<sup>3</sup> School of Mathematics, University of Edinburgh, Peter Guthrie Tait Road, Edinburgh EH9 3FD, UK

<sup>4</sup> Institut d'Investigació Sanitària Pere Virgili (IISPV), Hospital Universitari Sant Joan de Reus, Reus, Spain

<sup>5</sup> Barcelona Institute for Global Health (ISGlobal), Dr. Aiguader 88, 08003 Barcelona, Spain

<sup>6</sup> Municipal Institute of Medical Research, IMIM-Hospital del Mar, Dr. Aiguader 88, 08003 Barcelona, Spain

<sup>7</sup> Universitat Pompeu Fabra (UPF), Plaça de la Mercè 10-12, 08002 Barcelona, Spain

<sup>8</sup> Health Department of Basque Government, Sub-directorate of Public Health of Gipuzkoa, 20013 San Sebastián, Spain

<sup>9</sup> Biodonostia Health Research Institute, Group of Environmental Epidemiology and Child Development, Doctor Begiristain, s/n, 20014 San Sebastián, Spain

<sup>10</sup> Department of Medicine, Universitat Jaume I, Avenida de Vicent Sos Baynat s/n, 12071 Castellón de la Plana, Spain

<sup>11</sup> Laboratorio de Salud Pública de Alava, Santiago 11, 01002 Vitoria Gasteiz, Spain

<sup>12</sup> Nursing School, Universitat de València, C/Jaume Roig s/n, 46010 Valencia, Spain

<sup>13</sup> Faculty of Psychology, University of the Basque Country, Tolosa Hiribidea 70, 20018 San Sebastián, Spain

<sup>14</sup> Universidad Miguel Hernandez, Avenida de Alicante KM 87, 03550 Sant Joan d'Alacant, Spain