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Selenium status during pregnancy and child psychomotor development—Polish Mother and Child Cohort study

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BACKGROUND: The studies on the impact of selenium (Se) levels in different pregnancy periods on child psychomotor functions are limited. The aim of this study was to evaluate the impact of prenatal Se on child neurodevelopment.

METHODS: The study population consisted of 410 mother–child pairs from Polish Mother and Child Cohort. Se levels were measured in each trimester of pregnancy, at delivery, and in cord blood by graphite furnace atomic absorption spectrometry. Psychomotor development was assessed in children at the age of 1 and 2 y using the Bayley Scales of Infant and Toddler Development.

RESULTS: Plasma Se levels decreased through pregnancy (from 48.3 ± 10.6 µg/l in the first trimester to 38.4 ± 11.8 µg/l at delivery; $P < 0.05$). A statistically significant positive association between Se levels in the first trimester of pregnancy and motor development ($\beta = 0.2$, $P = 0.002$) at 1 y of age, and language development ($\beta = 0.2$, $P = 0.03$) at 2 y of age was observed. The positive effect of Se levels on cognitive score at 2 y of age was of borderline significance ($\beta = 0.2$, $P = 0.05$).

CONCLUSION: Prenatal selenium status was associated with child psychomotor abilities within the first years of life. Further epidemiological and preclinical studies are needed to confirm the association and elucidate the underlying mechanisms of these effects.

It is widely acknowledged that maternal nutrient status can influence development of fetal brain and consequently maturation of the child's cognitive functions, psychomotor abilities, intelligence, and behavior (1). In this framework, micronutrient supplementation that it is widely recommended during pregnancy period may have a significant impact on child neurodevelopment.

Selenium (Se) is involved in biosynthesis of several selenoproteins. It is particularly well maintained in the brain, even in the presence of a lower dietary supply (2). This suggests a relevant role of Se in the brain, as an essential component of a number of enzymes including glutathione peroxidases and

thioredoxin reductases. They act as antioxidants by catalyzing breakdown of hydrogen peroxide and organic hydroperoxides or forming reduced protein disulfide bonds (3,4). Se is also incorporated into deiodinases, which are responsible for conversion of the thyroid hormone thyroxine (T4) to its active form, triiodothyronine (T3).

On average, Se intake of 60–70 µg per day is recommended for adults, with increasing requirements for pregnant and lactating women (5). Se worldwide dietary intake is high in some countries, like Venezuela, Canada, the United States, and Japan, and much lower in Europe (2). The nationally representative dietary survey data from eight European countries has highlighted that there is a risk of low intake of essential trace elements in specific populations and age groups (6). Based on such estimates, the mean Se intake in women aged 18–60 ranged from 34 µg/d in Denmark, to 45 µg/d in France. Further analysis has indicated that from 36 to 76% of women had Se intake below the lower reference nutrient intake, namely, the intake value below which it is unlikely that normal health can be maintained over longer periods.

The existing studies evaluating the impact of food and micronutrients supplementation on children's development have produced conflicting results, mainly because of the lack of a valid indicator and assessment of the micronutrients and outcome variables (7–9). Although there is some evidence to support multi micronutrients having positive effect on child psychomotor development, the data for single nutrients is much weaker (7). In animal models, Se deficiency has been shown to affect neurological development in the offspring (3,10,11). Two recently published studies have evaluated the impact of Se on child development (12,13). The first one has indicated that both low and high levels of cord serum Se had adverse effects on an infant's neurobehavioral development (12). The second study by Skräder *et al.* (13) indicated a positive effect of maternal selenium status during pregnancy on children's development at 1.5 y of age.

The aim of this study was to evaluate the impact of Se during pregnancy period on child psychomotor development based

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on the prospective Polish Mother and Child Cohort (REPRO_PL) study (14).

RESULTS

Parental and Child Characteristics

Parental and child characteristics are summarized in [Table 1](#). About 52% of the children were girls. On average, the children were born at the 39th wk of gestation (± 1.3 wk) with the mean birth weight of 3,359 g (± 484 g). The mean maternal age was 31 (± 4.4 y) and paternal 33 (± 5.5 y). Most of the mothers (66%) and 43% of the fathers had a university degree. The majority of women were married (76%) and employed (89%). About 9% of the women indicated alcohol consumption and 11% were classified as smokers based on the cotinine level in saliva. In addition, half of the children were exposed to environmental tobacco smoke (ETS) within the first 2 y of life. Less than 17% of the women consumed multiple micronutrient capsules (with maximum 55 μ g Se content) during the first trimester of pregnancy (22% during the second and 20% during the third trimester). The mean composite scores for cognitive, language, and motor development were on an average or high average level in the assessments carried out at 1 and 2 y of age ([Table 2](#)).

Selenium Level During Pregnancy

Se levels in the blood collected in each trimester of pregnancy, at delivery and in cord blood, are presented in [Table 2](#), while correlations between microelement levels in each time period are shown in [Table 3](#). The mean Se level decreased through pregnancy period and at delivery (from 48.3 ± 10.6 μ g/l in the first trimester to 38.4 ± 11.8 μ g/l at delivery) ($P < 0.05$). A moderate correlation was observed between Se levels in blood collected in the first and the second and between the first and the third trimester of pregnancy ($r = 0.4$) as well as between the second and the third trimester of pregnancy, and between the third trimester of pregnancy and delivery ($r = 0.5$). The weakest correlation was observed between Se levels in the three trimesters of pregnancy and cord blood (the lowest between Se levels in the second trimester and cord blood $r = 0.08$). The correlation between Se level in maternal blood collected at delivery and in cord blood was 0.4.

Association Between Se Level During Pregnancy and Child Psychomotor Development

[Table 4](#) presents the association between maternal Se levels in the first trimester of pregnancy, at delivery, and in cord blood and child neurodevelopment. In the model adjusted for the examiner, a statistically significant positive association was observed between Se levels in the blood collected during the first trimester of pregnancy and child motor skills at 1 ($\beta = 0.2$, $P = 0.001$) as well as 2 ($\beta = 0.2$; $P = 0.04$) y of age, and cognitive development at 2 y of age ($\beta = 0.2$; $P = 0.03$). For language abilities at 2 y of age, the association was of borderline significance ($\beta = 0.2$, $P = 0.05$). In the same model for Se levels in the blood collected from the mothers at delivery, no statistically significant associations with any domains of child neurodevelopment were observed ($P > 0.05$), whereas for Se

levels in cord blood, a statistically significant positive association was observed in the case of language development at 2 y of age ($\beta = 0.3$, $P = 0.02$). The analysis with adjustment for a variety of confounders confirmed a statistically significant positive association between Se levels in blood collected in the first trimester of pregnancy and motor functions at 1 ($\beta = 0.2$, $P = 0.002$) and language functions at 2 y of age ($\beta = 0.2$, $P = 0.03$). For cognitive abilities at 2 y of age, the association was of borderline significance ($\beta = 0.2$, $P = 0.05$).

DISCUSSION

This prospective Polish Mother and Child Cohort indicated a positive effect of prenatal selenium status on child psychomotor abilities within the first 2 y of life. It needs to be pointed out that significant effects of Se on child development were mainly found when considering Se level in the first trimester of pregnancy; nevertheless, data concerning the effect of Se levels at delivery and in cord blood suggest a similar magnitude of the association, although not statistically significant taking into account the power limitations for that associations.

Two recently published studies have evaluated the impact of Se levels on child neurodevelopment (12,13). In the study by Skróder *et al.* (13), the Bayley Scales of Infant Development and MacArthur's Communicative Development Inventory were used for child psychomotor assessment at 1.5 y of age. In this study, similarly to our findings, increase in maternal Se concentration was associated with improvement in children's language and psychomotor development (13). The second study has indicated that both low and high levels of cord serum Se had adverse effects on neonatal neurodevelopment (12). In our assessment, maximum Se level in cord plasma was 56 μ g/l, which is much lower than observed in previous study, so the analysis for a high Se level had no point.

Our findings support the experimental evidence indicating a significant role of Se in brain and behavior development. Marked reduction of brain Se content following genetic inactivation of selenoprotein P produces movement disorders and spontaneous seizures in mice (15,16). Although the mechanisms by which Se influences neurodevelopment are still to be elucidated, animal studies reported a protective role of Se against cerebral ischemia-induced neuronal damage (17,18) and MeHg behavioral toxicity (19). In agreement, *in vitro* studies have shown that Se protects neurons from oxidative damage and inflammatory processes (20,21). In addition, the role of Se in activation of thyroid hormones reported by animal studies might also be implicated in Se effects on maturation of cognitive functions (22). Of note, Se is also able to counteract the adverse developmental effects of lead, as indicated by a recent rat study showing amelioration of lead-induced cognitive deficits in adult rats supplemented with Se (23). Thus, Se deficiency could have more impact in the presence of adverse environmental factors (including lead exposure), to which the fetus and infant could be exposed to in real scenarios.

Based on the existing data, the intake of Se varies hugely worldwide from low to even toxic concentrations with the mean values of 40 μ g per day in Europe, and 93 μ g per day in

Table 1. Children and parental characteristics (N = 410)

Characteristic	n or mean	% or SD
Gender (N = 410)		
Boys	199	48.5
Girls	211	51.5
Gestational age (weeks); mean, SD (N = 396)	39.2	1.3
Birth weight (g); mean, SD (N = 396)	3,358.7	484.3
Birth length (cm); mean, SD (N = 396)	55.1	3.5
Head circumference at birth (cm); mean, SD (N = 340)	34.3	1.6
Chest circumference at birth (cm); mean, SD (N = 338)	33.4	1.8
Breastfeeding (months) (N = 409)		
0–5	179	43.8
≥6	230	56.2
Day care attendance at 1 y olds (N = 393)		
No	367	93.4
Yes	26	6.6
Day care attendance at 2 y olds (N = 213)		
No	165	77.5
Yes	48	22.5
Age at Bayley-III test administration (months)		
For 1 y olds; mean, SD (N = 374)	12.8	1.5
For 2 y olds; mean, SD (N = 234)	24.9	2.8
Type of delivery (N = 375)		
Cesarean	138	36.8
Vaginal	237	63.2
Maternal age (years); mean, SD (N = 389)	30.8	4.4
Paternal age (years); mean, SD (N = 385)	32.7	5.5
Maternal education (N = 410)		
Primary/vocational	22	5.4
Secondary	118	28.8
Higher	270	65.9
Paternal education (N = 403)		
Primary/vocational	69	17.1
Secondary	160	39.7
Higher	174	43.2
Marital status (N = 409)		
Married	312	76.3
Unmarried	97	23.7
Maternal employment (N = 409)		
Employed	362	88.5
Unemployed	47	11.5
Socioeconomic status (N = 405)		
High	91	22.5
Medium	274	67.7
Low	40	9.9
Maternal prepregnancy BMI (kg/m ²); mean, SD (N = 406)	22.6	3.7
Multiple micronutrient supplementation during the first trimester (including Se) (N=410)		
Yes	69	16.8
No	341	83.2
Saliva cotinine level in pregnancy (N = 369)		
<10 ng/ml	327	88.6
≥10 ng/ml	42	11.4
Alcohol consumption during pregnancy (N = 358)		
No	327	91.3
Yes	31	8.7
Children's ETS exposure after birth (N= 410)		
No	200	48.8
Yes	210	51.2

ETS, environmental tobacco smoke.

the United States (2). The recently published study performed in Poland indicates the mean daily intake of Se at the level of 30 µg/d (24). Taking into account plasma Se levels below 60 µg/l as low (25,26), 92% of our studied women seemed to have inadequate Se status in early pregnancy (Se levels below 50 µg/l were observed in 76% of our pregnant women). Se levels observed in our population were lower comparing to other studies in this field (48.3 µg/l plasma Se level between 8 and 12 wk of pregnancy for REPRO_PL cohort vs. 60 µg/l median plasma Se at 14 wk of pregnancy in Bangladesh (13) or 31 µg/l Se level in cord plasma for REPRO_PL cohort vs. 125 µg/l median Se level in Iran (27), 69 µg/l median Se level in Baltimore, USA (28), 63 µg/l in Shanghai, China (12)). Plasma glutathione peroxidase activity correlates with Se in plasma and reaches plateau at plasma concentrations of 70–90 µg/l (26), which indicates that the women in our study might have a lower activity of this enzyme (only 12 women in REPRO_PL had Se level higher than 70 µg/l). It is worth noting that in Poland plasma Se levels have been decreasing in the last three decades (24,29). Cord plasma Se levels in the study performed

between 1981 and 1983 were 48 µg/l, whereas in 1997–1999, it was 33 µg/l. Further decrease was observed in our study.

The reason for variability in Se intake relates not only to the Se content of the soil, but also to the factors that determine availability of Se to the food chain, including Se speciation, soil pH, and organic-matter content, and the presence of iron that can complex with Se (30).

Correlation between Se status and maternal BMI was very low ($r = 0.05$), which indicates that Se status does not necessarily reflect the overall nutritional status. It is worth to mention that in our cohort about 20% of the women consumed multiple micronutrient capsules (with Se as one of their components) but this did not influence Se status ($r = -0.01$) or associations with child development (1-y-old children: cognitive: $P = 0.8$, language and motor: $P = 0.6$; 2-y-old children: all abilities: $P = 0.9$). A similar observation has been reported by Skróder *et al.* (13).

The prospective study design and assessment of Se levels in each trimester of pregnancy as well as in maternal (at delivery), and in cord blood constitute an important advantage of this study. Additionally, a series of detailed questionnaires (and biomarker measurements) made it possible to assess reliably the confounding variables. Restricting our study population to healthy women allowed us to eliminate additional confounding factors, though we have to consider the possibility that other unmeasured risk factors (e.g., maternal IQ, children's maternal relationship, and home environment) produced associations between the exposures of interest and child neurodevelopment. Finally, in the current analysis, we assessed multiple aspects of child neurodevelopment by a well-standardized and widely used tool for early and fairly comprehensive measures.

Limitations of the study are also worth noting. We were not able to assess dietary habits of the women to include them in the analysis, and we did not measure internal exposure to other essential and neurotoxic elements. However, in the analysis by Skróder *et al.*, the models were additionally adjusted for essential (Zn, Mn, I) and neurotoxic elements (As, Cd, Pb) and the impact of Se on child psychomotor development was still significant. This indicates that the association with Se was not just a proxy for intake of other micronutrients capable of affecting child development (13). To what extent Se may protect against toxic exposures remains to be evaluated based on REPRO_PL. Although we did not formally correct for multiple comparisons, the associations between Se levels and child development were consistent across the regression models and with the results of previous studies on the topic, thus supporting the evidence of an actual Se effect independent of the covariates.

Table 2. Characteristics of the exposure and outcome variables

Variables	Mean	SD	Min	Max
Se levels (µg/l)				
in the first trimester of pregnancy (N = 410)	48.3	10.6	16.1	91.4
in the second trimester of pregnancy (N = 151)	42.3	9.1	14.8	69.7
in the third trimester of pregnancy (N = 130)	37.3	9.8	14.2	61.7
in maternal blood at delivery (N = 310)	38.4	11.8	13.8	86.3
in cord blood (N = 311)	31.1	8.2	13.8	56.3
Composite score for one year old children N = 374				
Cognitive	106.8	10.3	80.0	145.0
Language	108.4	13.6	68.0	141.0
Motor	105.5	14.0	73.0	151.0
Composite score for two years old children N = 234				
Cognitive	112.8	16.4	80.0	145.0
Language	102.4	13.0	74.0	144.0
Motor	111.8	14.4	73.0	154.0

Table 3. Pearson correlation between the levels of selenium in each trimester of pregnancy, at delivery, and in cord blood

Se levels	Se (first trimester)	Se (second trimester)	Se (third trimester)	Se (maternal blood at delivery)	Se (cord blood)
Se (first trimester)	1				
Se (second trimester)	0.4	1			
Se (third trimester)	0.4	0.5	1		
Se (maternal blood at delivery)	0.3	0.3	0.5	1	
Se (cord blood)	0.1	0.08	0.2	0.4	1

Table 4. Selenium levels during the first trimester of pregnancy, in maternal blood collected at delivery, in cord blood and child psychomotor development

Selenium level in different pregnancy periods	1-y-old children β (95% CI)			2-y-old children β (95% CI)		
	Cognitive	Language	Motor	Cognitive	Language	Motor
Model 1						
Se (first trimester)	0.01 (-0.1 to 0.1)	0.04 (-0.07 to 0.2)	0.2 (0.1 to 0.4)**	0.2 (0.02 to 0.4)*	0.2 (-0.001 to 0.3)***	0.2 (0.003 to 0.3)*
Se (maternal blood at delivery)	-0.07 (-0.2 to 0.03)	-0.1 (-0.2 to 0.001)	0.1 (-0.1 to 0.2)	0.1 (-0.07 to 0.3)	0.1 (-0.07 to 0.3)	0.1 (-0.1 to 0.3)
Se (cord blood)	0.01 (-0.1 to 0.2)	-0.04 (-0.2 to 0.1)	0.2 (-0.02 to 0.4)	0.1 (-0.1 to 0.3)	0.3 (0.05 to 0.5)*	0.1 (-0.2 to 0.3)
Model 2						
Se (first trimester)	0.04 (-0.1 to 0.1)	0.04 (-0.1 to 0.1)	0.2 (0.1 to 0.4)*	0.2 (-0.003 to 0.4)***	0.2 (0.02 to 0.4)*	0.2 (-0.02 to 0.4)
Se (maternal blood at delivery)	-0.05 (-0.2 to 0.1)	-0.1 (-0.2 to 0.03)	0.1 (-0.1 to 0.2)	0.1 (-0.1 to 0.3)	0.1 (-0.1 to 0.3)	0.1 (-0.1 to 0.3)
Se (cord blood)	0.003 (-0.2 to 0.2)	-0.1 (-0.2 to 0.1)	0.2 (-0.02 to 0.4)	0.1 (-0.2 to 0.4)	0.2 (-0.1 to 0.4)	0.1 (-0.2 to 0.4)

Model 1 is adjusted for the examiner; for 1-y-old assessments: Se (first trimester): $N = 373$, Se (maternal blood at delivery): $N = 301$, Se (cord blood): $N = 301$; for 2-y-old assessments: Se (first trimester): $N = 231$, Se (maternal blood at delivery): $N = 231$, Se (cord blood): $N = 231$. Model 2 is adjusted for the examiner, mother age, mother education, child gender, marital status, and cotinine level; for 1-y-old assessments: Se (first trimester): $N = 368$, Se (maternal blood at delivery): $N = 278$, Se (cord blood): $N = 278$; for 2-y-old assessments: Se (first trimester): $N = 191$, Se (maternal blood at delivery): $N = 158$, Se (cord blood): $N = 157$.

β , beta coefficient; CI, confidence interval.

* $P < 0.05$; ** $P = 0.001$; *** $P = 0.05$.

Conclusion

Prenatal selenium status was associated with child psychomotor abilities within the first years of life. Further epidemiological and preclinical studies are needed to confirm the association and elucidate the mechanisms underlying these effects. Taking into account the results obtained in the current study and the existing knowledge, nutritional status of women during pregnancy must be carefully monitored to prevent nutritional unbalance and deficiency of important micronutrients.

METHODS

Study Design and Population

The mother-child pairs included in the present study constitute a part of Polish Mother and Child Cohort (REPRO_PL cohort)—a multicenter prospective cohort established in 2007 with the aim to evaluate environmental and lifestyle-related factors contributing to the pregnancy outcomes, children's health, and neurodevelopment (31–35). The detailed description of the cohort methodology has been published elsewhere (31,32). Briefly, the women were recruited into the study if they fulfilled the following criteria: single pregnancy up to 12 wk of gestation, no assisted conception, no pregnancy complications, and no chronic disease as specified in the study protocol. The study subjects were interviewed once in each trimester of pregnancy to collect and update sociodemographic data, medical, and reproductive history as well as information about environmental, occupational, and lifestyle factors. In addition, during each visit and after delivery, biological samples (including saliva, urine, blood, cord blood, and hair) were collected.

The children's health status and neurodevelopment was assessed twice, at 1 and 2 y of age.

The current analysis was restricted to 410 children from Lodz and Legnica districts. Among them, 198 children had both assessments (at 1 and 2 y of age), 176 were examined only at around the 12th mo, and 36 only at the 24th mo of age.

The study was approved by the Ethical Committee of the Nofer Institute of Occupational Medicine, Łódź, Poland, and a written consent was obtained from all the study subjects.

Sample Collection and Se Assessment

Se level was assessed in the blood collected from each woman during the first (8–12 wk of pregnancy), the second (20–24 wk of pregnancy), and the third (30–34 wk of pregnancy) trimesters of pregnancy, and

in maternal blood collected at delivery as well as in cord blood. The blood samples were collected using a venoject system free of trace elements with lithium heparin as an anticoagulant. After centrifugation, plasma was collected and frozen at -20°C until the analysis. Plasma Se concentration was determined by the use of the graphite furnace atomic absorption spectrometry according to the method of Nève *et al.* (36) using Unicam 989 QZ Solar apparatus. Accuracy of the method was checked using Se reference material (Nycomed, Oslo, Norway). The mean Se level of the reference serum was $78.0\text{ }\mu\text{g/l}$, while of that obtained in our laboratory was $77.4 \pm 5.0\text{ }\mu\text{g/l}$.

Child Neurodevelopment Assessment

The Bayley Scales of Infant and Toddler Development (the third edition—Bayley-III) was used to assess children's neurodevelopment at around the 13th (± 1.5) and 25th (± 2.8) mo of age (32,37). Details regarding child psychomotor assessment have been published elsewhere (33–35). Child psychomotor development measured by a raw score/chronologic age was yielded with each subtests, and composite scores for language, motor scales, and composite score equivalent for cognitive scale were generated based on those data.

Covariates

The evaluated covariates that were identified from the literature were as follows: parental age; parental education; marital status; socioeconomic status; child gender; major pregnancy complications, which appeared after inclusion into the study (including gestational diabetes and gestational hypertension); maternal BMI; type of delivery; gestational age and biometric indicators at birth; breastfeeding; number of siblings; day care attendance; multi micronutrient supplementation; active/passive smoking and alcohol consumption during pregnancy; and child ETS exposure after birth. Sociodemographic data as well as information about alcohol consumption during pregnancy were obtained based on questionnaires. Parental education was expressed as the highest completed formal schooling. Socioeconomic status of the family was measured during pregnancy and after the birth of the child based on the following question: "What is the financial status of your family?" The women who declared that they had sufficient money for current expenses and that it was possible for them to put a substantial sum aside were allocated into the high income category. Those who indicated sufficient money for current expenses, with possibility to put some money aside were allocated into the medium category, and those who declared insufficient money for current expenses were allocated into the low income category. During each prenatal visit scheduled within the study, the women were interviewed by a gynecologist or midwife about the use of vitamins, minerals, other

dietary supplements, and medications (the name, dose, and time period of their intake were recorded). All of them were checked for selenium content. Prenatal exposure to tobacco constituents was assessed based on the cotinine level in saliva (collected three times during pregnancy) and a child ETS exposure after birth on the cotinine level in urine (collected at the 12th and the 24th mo of age). The biomarker levels were measured using the high-performance liquid chromatography coupled with tandem mass spectrometry/positive electrospray ionisation and isotope dilution method (38). As the cotinine levels in each trimester of pregnancy were highly correlated (the first with the second trimester: $r = 0.8$; the first with the third trimester: $r = 0.7$; the second with the third trimester: $r = 0.8$, $P < 0.001$), the samples from between the 8th and the 12th wk of gestation were used as biomarkers of active and passive smoking. The cotinine levels were log transformed. The analysis included the following indicators at birth (measured by a clinical nurse after birth with the standard measurement procedures): child birth weight (in grams), birth length, head and chest circumference (in centimeters). Pregnancy duration was estimated using the date of the last menstrual period or ultrasound if it differed from the last menstrual period-based estimate by > 2 wk.

Statistical Analysis

Correlation between microelement levels in each trimester of pregnancy, at delivery, and in cord blood was examined by the Pearson linear correlation coefficient.

The linear regression was used to analyze the relationship between Se levels and child psychomotor development. First, an analysis was performed between the potential confounding variables and the Bayley test results. The following confounders (significant in the univariate model at the level of 0.1) for the multivariate model were identified: child gender ($P \leq 0.08$), parental age ($P \leq 0.03$), parental education ($P \leq 0.08$), prenatal ETS exposure ($P \leq 0.05$), child ETS exposure within the first 2 y of life ($P < 0.06$), and marital status ($P < 0.03$). As some confounders (namely: mother and father's age, mother and father's education, pre and postnatal ETS exposure), were highly correlated, the sensitivity analysis was performed, and only maternal age and education and cotinine level in pregnancy were selected in the final model. The second stage of the analysis focused on the evaluation of the impact of Se level in the first trimester of pregnancy, in maternal blood at delivery, and in cord blood on child psychomotor performance at 1 and 2 y of age. In the first model, a confounding effect of the examiner who administered the test was taken into account. The final model was conducted with adjustment for potential confounders. Taking into account the smaller number of samples collected during the second and the third trimesters of pregnancy, the analysis focused on those trimesters was not performed. The variance inflation factor was computed for any variable in each final model to verify the presence of multicollinearity among explanatory variables. When significantly different from 0, regression coefficients were reported together with 95% confidence interval.

Statistical significance was specified as $P < 0.05$ (two-sided P values). The analysis was performed using the R software.

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