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The role of fingernail selenium in the association between arsenic, lead and mercury and child development in rural Vietnam: a cross-sectional analysis

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Abstract

As, Pb and Hg are common environmental contaminants in low- and middle-income countries. We investigated the association between child toxicant exposure and growth and development and determined if this association was mitigated by Se concentration. Toxicant concentrations in fingernail samples, anthropometry and Bayley's Scales of Infant Development, 3rd edition domains were assessed in 36-month-old children whose mothers had been part of a randomised controlled trial in rural Vietnam. Multivariable regression analyses were performed to estimate the effect of toxicant exposure on clinical outcomes with adjustments for potential confounders and interaction with fingernail Se concentration. We analysed 658 children who had data for at least one physical or developmental outcome, and at least one toxicant measurement, and each of the covariates. Fingernail As concentration was negatively associated with language (estimate per 10 % increase in As: −0·19, 95 % CI: (–0·32, −0·05)). Pb was negatively associated with cognition (estimate per 10 % increase in Pb: −0·08 (–0·15, −0·02)), language (estimate per 10 % increase in Pb: −0·18 (–0·28, −0·10)) and motor skills (estimate per 10 % increase in Pb: −0·12 (–0·24, 0·00)). Hg was negatively associated with cognition (estimate per 10 % increase in Hg: −0·48, (–0·72, −0·23)) and language (estimate per 10 % increase in Hg −0·51, (–0·88, −0·13)) when Se concentration was set at zero in the model. As Se concentration increased, the negative associations between Hg and both cognition and language scores were attenuated. There was no association between toxicant concentration and growth. As, Pb and Hg concentrations in fingernails of 3-year-old children were associated with lower child development scores. The negative association between Hg and neurological development was reduced in magnitude with increasing Se concentration. Se status should be considered when assessing heavy metal toxicants in children and their impact on neurodevelopmental outcomes.

Key words: Child development: Selenium: Arsenic: Lead: Mercury: Toxicants: Vietnam

Rapid urbanisation and industrial expansion in emerging market countries with less developed regulatory frameworks can lead to persistent environmental contamination with toxicants[1]. This is compounded in some areas (e.g. Bangladesh, Vietnam) by the presence of naturally occurring As in ground water and staple food supplies[2,3]. Long-term exposure to inorganic toxicants like As, Pb and Hg has been associated with adverse health effects and may be detrimental to child development, even at low levels[4].

Children are particularly susceptible because of increased absorption capacity required to supply essential nutrients

Abbreviations: BSID, Bayley Scales of Infant and Toddler Development, 3rd edition; HAZ, height-for-age Z score; RCT, randomised controlled trial.

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needed to thrive and higher consumption of food relative to body weight[4]. Previous studies, although limited by small sample size, varied designs and data analyses, report an association between Pb and Hg exposure and decreased IQ and poor educational outcomes, and between *in utero* exposure to As and intrauterine growth restriction, preterm birth and low birth weight[4,5]. Accordingly, the United Nations' Sustainable Development Goals for 2030 aim to reduce deaths and illness from hazardous chemicals and air, water and soil pollution and contamination[6], making the elimination of environmental contamination and mitigation of adverse health effects global health priorities.

Se, while sharing many chemical properties with its fellow metalloid As, is an essential micronutrient that is only toxic to humans in excess[7]. It is one of only six elements that make up the twenty-one amino acids and is involved in a number of critical physiological processes including redox control, immune function and the endocrine system[7]. Furthermore, biochemical and animal studies have shown a high binding affinity between bioavailable Se and toxicants, suggesting Se biochemistry may be an adaptive mechanism for detoxifying and removing metal toxicants from the body[8,9]. Despite the evidence from animal experiments, research investigating the association between Se status and child development, as well as the interaction between Se and toxic metals and its consequence on child growth and development is scarce.

We aimed to investigate the potential role of Se in mitigating the adverse effects of As, Pb and Hg on physical and neurological development in 3-year-old children in Ha Nam province, Vietnam, using fingernail toxicant concentration as a proxy for exposure during the last 3 months.

Methods

Study design, setting and participants

This study is a secondary analysis of a cohort of 36-month-old children whose mothers had participated in a cluster randomised controlled trial (RCT) (ACTRN: 12610000944033) that investigated the effect of antenatal Fe supplementation on infant development[10]. In the RCT, all communes in Ha Nam province, other than those in the principal town district, were randomly assigned to one of three treatment groups. Recruitment occurred between September and November 2010, and all eligible pregnant women were invited to participate. Supplementation with Fe or multiple micronutrients was given until 3 months postpartum, with monitoring until the children reached 6 months of age[10]. At 12 months of age mother–child pairs were invited to take part in a follow-up prospective cohort study with monitoring for an two additional years[11]. Six monthly assessments were carried out at commune health stations at 12, 18, 24, 30 and 36 months of age. No nutritional supplements were given to children or to the mothers after 3 months postpartum.

In the final assessment at 36 months, children had anthropometric measurements taken and child development was assessed. Samples of fingernails, toenails and hair were collected for toxicant measurements.

Participant selection for the current study

A total of 1258 pregnant women were recruited into the original RCT, with 1168 remaining at the trial conclusion when their children reached 6 months. A total of 1063 women agreed to continue in the follow-up cohort, and 1019 remained when children were aged 36 months. Of these, 361 were excluded from the current analysis due to insufficient data: 4 did not provide anthropometric data, 37 did not complete a child development assessment, 302 did not provide biological samples to estimate toxicant exposure and 359 did not provide sufficient covariate data. Sample size retention, from recruitment into the original RCT through to the analysis sample used in this study, is shown in Fig. 1.

Outcome variables

Height was measured using a portable ShorrBoard® with footwear removed. Measurements were in triplicate, with a second researcher checking all measurements and the median used for analysis. Height-for-age Z scores (HAZ) were calculated using WHO Anthro (V.3.2.2, January 2011)[12].

Child development was assessed for cognitive, language and motor domains at 36 months of age using the Bayley Scales of Infant and Toddler Development, 3rd edition (BSID)[13], that had been adapted for Vietnam and used in previous studies[10]. Experienced teams of community-based psychologists conducted the assessment, following training from a Vietnamese expert based on the BSID III manual, and were monitored closely by the research supervisor (TH).

Domain scores were tallied from the number of successful tasks the children could achieve within each domain and then standardised into composite scores using BSID's validated scaling algorithm based on child's age in weeks[14].

Primary predictors

Child exposure levels to As, Pb, Hg and Se was measured at 36 months using fingernail samples, reflecting exposure over the previous 3–6 months. Nail samples were collected using stainless steel clippers and stored at room temperature; duplicate samples were taken from children where the initial sample was insufficient. Nails were collected in zip-locked bags then placed into mineral depleted tubes (Becton Dickson, product number 368 380- BD Hemogard/Royal Blue). The sample treatment and analysis were completed in the National Measurement Institute (NMI) laboratory, which is a National Association of Testing Authorities (NATA) accredited laboratory. An in-house method was developed by following AOAC (16th Edition) Methods 986·15 and 974·14. A pre-digestion cleaning process was included as the following: nail samples (minimum 10 mg) were transferred to 50 ml polypropylene tubes and 10 ml 0·5 % Triton X-100 surfactant was added. Samples were sonicated for 30 min, allowed to stand for several days, and then

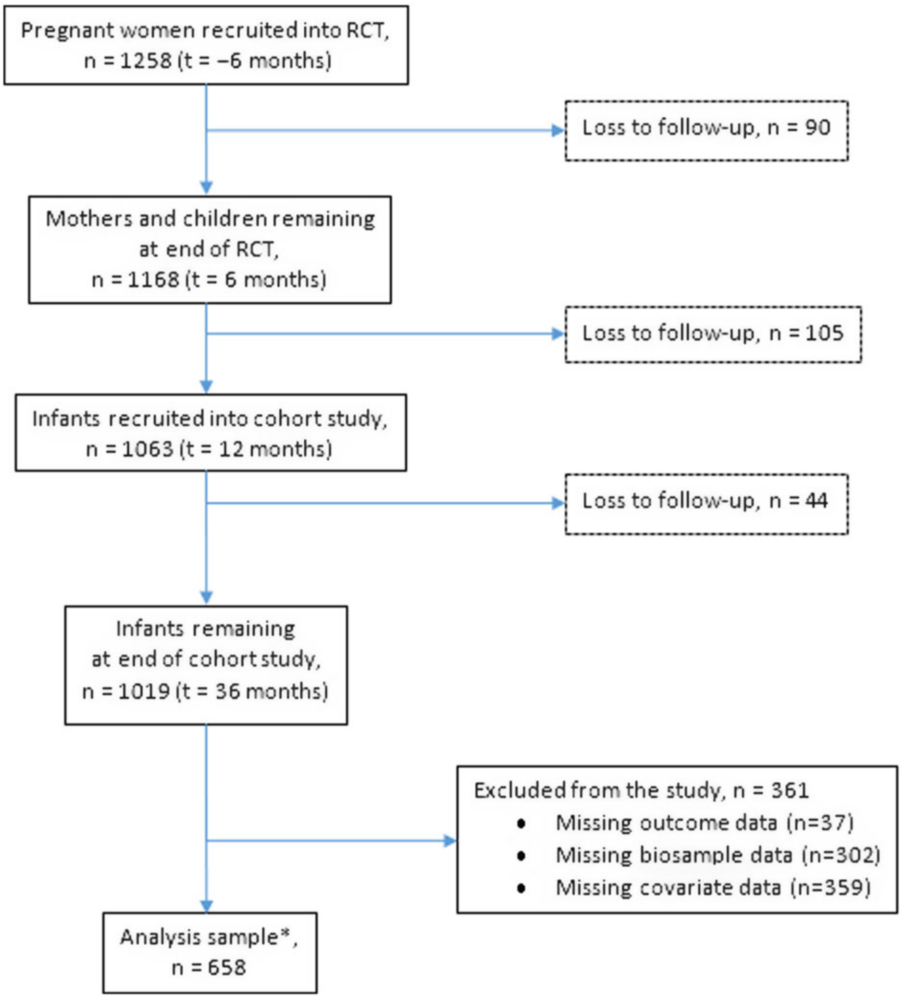

Fig. 1. Flow diagram of sample size retention spanning the original RCT and the subsequent cohort study. 't' denotes the age of the children in the cohort. *Analysis sample defined as subjects providing sufficient data for a regression model between infant development, fingernail toxicant levels and fingernail Se levels. Included subjects had data for at least one physical or one neurological development outcome, at least one measure of toxicant exposure and all of the covariates. BSID: Bayley's scales of infant and toddler development; RCT: randomised controlled trial.

sonicated again for 30 min. The nail samples were washed repeatedly with high purity water and then dried at 40° overnight. The cleaned and dried nail samples were weighed into 50 ml polypropylene tubes and digested in 1 mL nitric acid by heating for 2 h on a hot block at 95–100°C. The digested samples were diluted to 15 ml with ultrapure water, then prepared for ICP-MS analysis (Agilent 7900) after a further 1·25-fold dilution together with blanks, duplicates and matrix spikes with in-house reference material. The limit of reporting is 0·01 mg/kg for all elements; however, a minimal mass of 10 mg is required. For those samples less than 10 mg, the results are semi-quantitative.

Confounders

Potential confounders were identified from the domains of the WHO *Stunted growth and development: context, causes and consequences* framework[15]. The chosen set of confounders consisted of sex of child, maternal education level (not completing and at least completing high school), original RCT intervention arm (antenatal Fe or multi-micronutrient supplement), exclusive breastfeeding for the first 6 months and household wealth index score. Household wealth index score was derived from the Young Lives wealth index, a country-specific questionnaire of housing quality, access to services and consumer durables[16].

In addition to being a predictor for child development, the interaction between fingernail Se concentration and the toxicant (fingernail As, Pb and Hg concentration), HAZ scores and BSID domain scores was included.

Statistical methods

Linear regression analysis was performed to estimate (with two-sided 95 % CI) the association between toxicant levels, HAZ scores and BSID domain scores. The distributions of all the variables of interest in this analysis were assessed using descriptive

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statistics and histograms. Fingernail As, Pb and Hg distributions exhibited positive skew and were natural-log transformed prior to analysis; fingernail Se remained untransformed. In order to improve interpretability of regression analysis involving log-transformed predictor variables, estimates of the association between outcome and toxicant level were reported as change in outcome per 10 % increase of toxicant level. Three types of regression models were fitted: univariable linear regression between each outcome and each toxicant[17]; multivariable linear regression between each outcome and each toxicant, adjusting for the set of selected controlling variables and multivariable linear regression between each outcome and each toxicant with Se included as a potential interaction term.

Sensitivity analysis was performed on the final set of models to take into consideration the influence of outliers. Robust regression using Stata's 'rreg' package and default tuning level was applied to the final models and their estimates compared against their linear regression model counterparts[18]. As no change in the conclusions made from the linear regression models were made after applying robust regression, only the results of the linear regression models are reported.

This analysis included children at 36 months of age with data for at least one physical or one neurological development outcome, and at least one measure of toxicant exposure, and each of the covariates. In order to assess for potential biases induced by sample attrition, the distribution of the variables of interest was compared between the participants included in this study and those from the original RCT not included in this cross-sectional analysis. No sample size was pre-defined for this secondary analysis.

All statistical analyses were performed using Stata 15.0[19].

Ethics

The prospective cohort study and the original RCT (ACTRN: 12610000944033) were approved by the Melbourne Health Human Research Ethics Committee and the Ha Nam Provincial Human Research Ethics Committee. Written informed consent was obtained from all participants in the RCT and cohort study.

Results

A total of 658 children (62 % of those enrolled in the cohort study) met the eligibility criteria for this analysis (Table 1). Mean height was 91·2 cm, which translated to a HAZ score of −1·1. On BSID testing, children had a standardised mean cognition score of 96·2 and social–emotional score of 98·8. Overall, they were above the standardised mean for language and motor skills (104·5 and 109·4, respectively). Two-thirds of mothers had

Table 1. Characteristics of children who remained in the prospective cohort study at 36 months of age*
(Number and percentages)

	Followed up at 36 months (*n* 1019)		Included in analysis sample (*n* 658)		Excluded from analysis sample (*n* 361)	
	n	%	*n*	%	*n*	%
Sex of child, *n*/N (%) female	473/1017	46·5	304	46·2	169/359	47·1
Mother's highest education level, *n*/N (%)						
Less than high school	681	66·8	439	66·7	242	67·0
At least high school	338	33·2	219	33·3	119	33·0
Original RCT arm, *n*/N (%)						
Daily maternal iron	336	33·0	214	32·5	122	33·8
Twice-weekly maternal iron	355	34·8	238	36·2	117	32·4
Twice-weekly maternal multi-micronutrient	328	32·2	206	31·3	122	33·8
Exclusive breastfeeding at 6 months, *n*/N (%)	179/965	18·5	126	19·1	53/307	17·3
	Mean	SD	Mean	SD	Mean	SD
Wealth index (unitless)	0·7	0·07	0·7	0·08	0·7	0·07
Child's length (cm)	91·1	3·4	91·2	3·4	91·0	3·5
Child's HAZ score	–1·2	0·9	–1·1	0·9	–1·2	0·9
Bayley's composites						
Cognition	96·2	5·7	96·2	6·0	96·2	5·1
Language	104·7	8·6	104·5	9·0	105·1	7·9
Motor	109·7	11·1	109·4	11·6	110·4	10·1
Social–emotional	99·2	10·1	98·8	10·3	100·1	9·7
	Median	IQR	Median	IQR	Median	IQR
Fingernail As (μg/g)	0·4	0·3–0·5	0·4	0·3–0·5	0·4	0·3–0·6
Fingernail Pb (μg/g)	2·8	2·0–4·1	2·7	2·0–4·1	3·2	2·6–4·4
Fingernail Hg (μg/g)	0·2	0·2–0·3	0·2	0·2–0·3	0·2	0·2–0·3
Fingernail Se (μg/g)						
Mean	0·6		0·6		0·6	
SD	0·2		0·2		0·2	

n: number with attribute; N: sample size; RCT, randomised controlled trial; IQR: interquartile range; HAZ: height-for-age z-score.
* For any variables where the denominator differs from sample total, the denominator is explicitly written.

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Table 2. Growth and development outcomes associated with fingernail As, Pb and Hg in 36-month-old children from Ha Nam Province, Vietnam, after adjusting for mother's education, antenatal RCT arm, sex of the child, exclusive breastfeeding and wealth index
(Estimates and 95 % CI)

	Estimate*	95 % CI	*P*-value
As			
HAZ score (*n* 657)	−0·00	−0·02, 0·01	0·46
BSID: cognition (*n* 628)	−0·08	−0·17, 0·01	0·078
BSID: language (*n* 628)	−0·19	−0·32, −0·05	0·005
BSID: motor (*n* 628)	−0·09	−0·26, 0·08	0·30
BSID: social–emotional (*n* 621)	−0·07	−0·23, 0·08	0·35
Pb			
HAZ score (*n* 658)	−0·00	−0·01, 0·01	0·46
BSID: cognition (*n* 630)	−0·08	−0·15, −0·02	0·007
BSID: language (*n* 630)	−0·18	−0·28, −0·10	< 0·001
BSID: motor (*n* 630)	−0·12	−0·24, 0·00	0·057
BSID: social–emotional (*n* 622)	−0·03	−0·14, 0·08	0·49
Hg			
HAZ score (*n* 657)	0·01	−0·00, 0·02	0·18
BSID: cognition (*n* 628)	0·04	−0·03, 0·10	0·28
BSID: language (*n* 628)	0·11	0·02, 0·21	0·022
BSID: motor (*n* 628)	0·01	−0·11, 0·14	0·86
BSID: social–emotional (*n* 620)	0·02	−0·10, 0·13	0·75

RCT, randomised controlled trial; HAZ: height-for-age z-score; BSID: Bayley Scales of Infant Development.
* The models were fitted using log-transformed As, Pb and Hg concentrations and the estimate represents a 10 % increase obtained from the estimate on a log-scale multiplied by $\log_e(1{\cdot}10)$.

not achieved a secondary school level education. The mean wealth index score for the households of the cohort was 0·7, corresponding to the less poor category using the Vietnam-specific, Young Lives wealth index cut-offs[16]. No difference was observed among any of the characteristics between the analysis sample (*n* 658) and those excluded due to insufficient data for the regression models (*n* 361, Table 1).

Association between toxicant concentration, child developmental scores and growth

Associations between toxicants and physical and neurological development are described in Table 2. Fingernail As was negatively associated with BSID language score (estimate per 10 % As increase: −0·19, 95 % CI: (−0·32, −0·05), $P = 0{\cdot}005$); fingernail Pb was negatively associated with BSID cognition (estimate per 10 % Pb increase: −0·08 (−0·15, −0·02), $P = 0{\cdot}007$), BSID language (−0·18 (−0·28, −0·10), $P < 0{\cdot}001$) and BSID motor scores (−0·12 (−0·24, 0·00), $P = 0{\cdot}057$). Fingernail Hg was positively associated with BSID language (estimate per 10 % Hg increase: 0·11 (0·02, 0·21), $P = 0{\cdot}022$). There was no association between As, Pb or Hg concentrations and HAZ scores.

We found that fingernail Se was positively associated with growth (i.e. HAZ score) (0·44 (0·04, 0·83), $P = 0{\cdot}03$), but not developmental scores (online Supplementary Table S1).

Interaction effect between Se and toxicants on child development scores and growth

There was no evidence of interaction between As and Se concentration across all the developmental outcome variables, nor between any of the toxicants and Se on HAZ score when Se was included in the model as a potential interaction term (online Supplementary Table S2–S4). However, a statistically significant interaction between Se and Hg concentration on both cognition (Fig. 2(a)) and language (Fig. 2(b)) was observed. In this model, a negative association between Hg and both cognition and language was revealed. The change in BSID cognition score per 10 % increase in fingernail Hg concentration was −0·12, −0·04, 0·02 and 0·10 points, for children at the first, second, third and fourth quintiles of fingernail Se concentration, respectively; the change in language score per 10 % increase in fingernail Hg concentration was −0·06, −0·03, 0·10 and 0·20 points for children at the first, second, third and fourth quintiles of fingernail Se concentration, respectively (Fig. 2(a) and (b)). Therefore, as Se concentration increased, the negative associations between Hg and both cognition and language scores were attenuated.

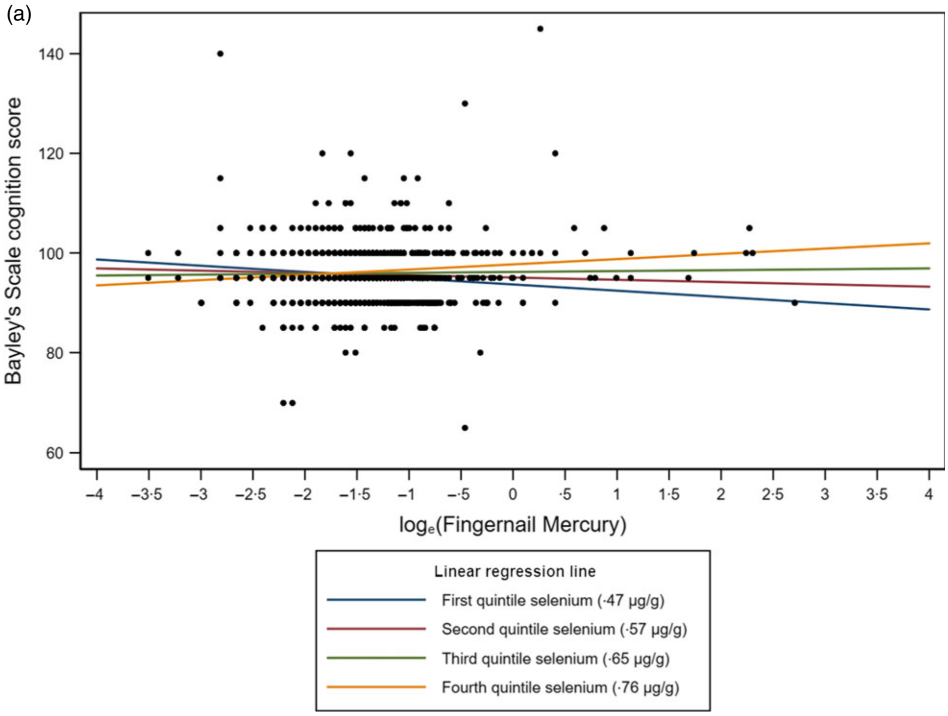
Discussion

This study investigated the association between As, Pb and Hg status, as well as their interaction with the nutrient Se, on child growth and neurological development in a semi-rural province in Vietnam. We found that fingernail concentrations of As and Pb were negatively associated with neurodevelopmental scores in 3-year-old children. When the interaction with Se was included in the analysis, a negative association between Hg and both cognition and language was also revealed. The degree of negative association of both Pb and Hg on particular BSID domains were at their highest for those in the first quintile Se level but reduced at higher quintile groups. There was no association between toxicants and HAZ.

We found no previous studies describing the association between toxicant levels and child neurodevelopment in Vietnam. However, in a study in China, Pb was negatively correlated with both cognition and language in two hundred and fifty eight 3-year-old children[20]. The level of toxicant exposure estimated in our study using fingernail samples was consistent with levels reported in cohorts of a similar age group living in environments similarly affected by a high abundance of toxicants[21]. We found that all three assessed toxicants were negatively associated with neurodevelopment at lower Se levels. Although the prenatal period seems to represent the most sensitive stage for the negative effect of toxicants on neurodevelopment, chronic exposure after birth has also been implicated in poorer cognitive performance[4].

The lack of association between toxicant exposure and HAZ was consistent with the very limited evidence of any such association in the literature. A systematic review by Rahman *et al.* (2017) found no association between As exposure during pregnancy and fetal growth and limited evidence of negative association between As exposure and growth during early childhood[22].

Se is mostly sourced through diet, with Brazil nuts, seafood, fish, meat, poultry, grains and wheat-based products being the main dietary sources. However, Se content in foods is largely dependent on the concentration of the mineral in the soil, which explains the wide range of Se intake across the globe, with one in



Estimated BSID cognition score change (and 95% CI) per 10% increase in fingernail mercury level and at selected fingernail Se concentrations.	
Se	Estimate (95% CI)
First quintile 0·47 µg/g	−0·12 (−0·21, −0·02)
Second quintile 0·57 µg/g	−0·04 (−0·11, 0·03)
Third quintile 0·65 µg/g	−0·02 (−0·05, 0·08)
Fourth quintile 0·76 µg/g	0·10 (0·03, 0·18)

Fig. 2. Interaction between fingernail Selenium (Se) and fingernail Mercury (Hg) on (a) Bayley's Scale cognition and (b) Bayley's Scale language scores in 36-month-old children from Ha Nam province, Vietnam. Interaction effects are shown in the figures.

seven people presenting with low Se intake due to low concentration in staple crops[23]. Se deficiency decreases the activity of selenoproteins and may lead to impaired cognitive development in children, as well as compromised immune and thyroid function[24]. Although, the assessment of Se in nails has the advantage of representing long-term exposure, it does not have a reference range. A previous study that assessed Se in serum in primary school children from Bac Ninh province, located near Ha Nam (around 70 km distance), showed a high prevalence of Se deficiency (a mean of < 70 µg/l in 75·6 % of the population, mean (SD) of 61 (13·6) µg/l)[25]. Thus, we assume that in our study Se status was in the low range.

Se has a high affinity for toxicants and forms biologically inert complexes, thus potentially protecting against heavy metal-induced toxicity. Furthermore, due to the antioxidant capacity of some selenoproteins, Se antagonises the pro-oxidant effect of toxicants[26]. Nearly all environmental Hg is anthropogenic, released at a steadily increasing rate in the 200 years post-industrial revolution[27]. Se has a particularly high chemical affinity to Hg, and so selenoproteins may have a secondary adaptive function as an endogenous response to a sudden environmental exposure to Hg [28]. Selenoproteins, characterised by the presence of the amino acid selenocysteine, form stable complexes with Hg preventing transit of free neurotoxic organomercury into the central nervous system[28]. Therefore, we believe that the intertwining effect of Se and Hg on neurodevelopmental outcomes is most likely driven by endogenous detoxification of Hg by Se.

Our finding that the negative association between Hg and child neurodevelopment was of a lower magnitude at higher concentrations of Se contrasts with previous research that investigated the relationship between prenatal Hg exposure and interaction with Se and cognitive performance in 456 Italian children at 40 months of age[24]. In that study, children had low Hg and Se concentrations in cord blood and concentrations in infancy and childhood were not assessed. There was no association between Hg concentration in cord blood and child cognitive scores. The highest BSID cognition score was reported for children who had low Hg and medium Se concentrations in cord blood, suggesting that either too much or too little Se had a negative impact on cognition. Our study used fingernail samples in 3-year-old children, collected at the same time as the child development assessment, thus providing information on exposure and interaction of these two elements over the previous 3–6 months.

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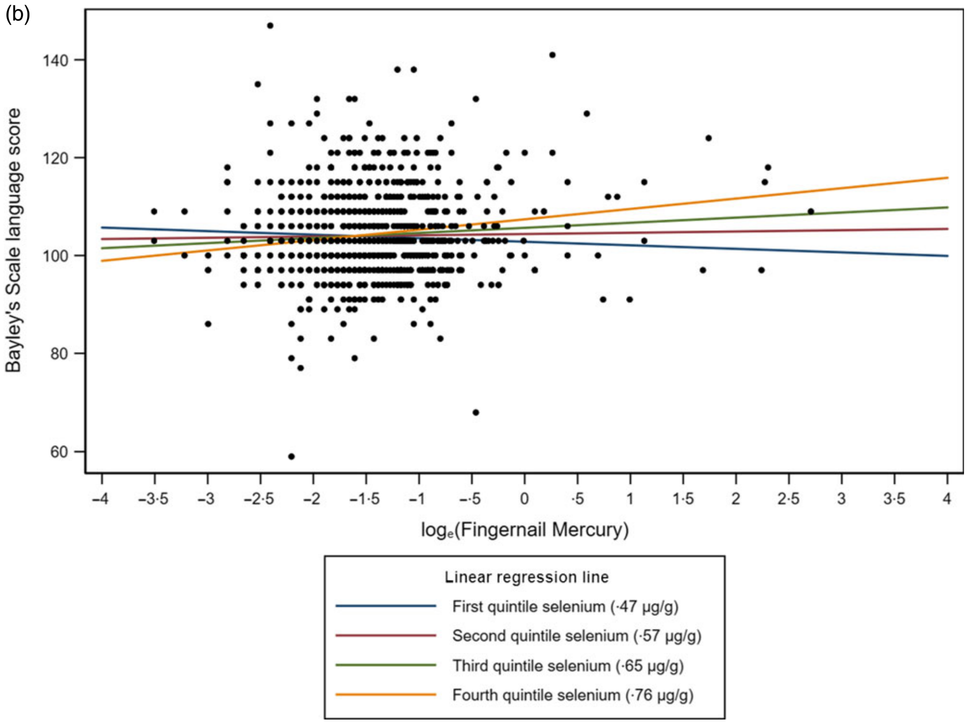

Estimated BSID language score change (and 95% CI) per 10% increase in fingernail mercury level and at selected fingernail Se concentrations.	
Se	Estimate (95% CI)
First quintile 0·47 μg/g	–0·06 (–0·21, 0·08)
Second quintile 0·57 μg/g	–0·03 (–0·08, 0·14)
Third quintile 0·65 μg/g	0·10 (0·00, 0·20)
Fourth quintile 0·76 μg/g	0.20 (0·09, 0·32)

Fig. 2. (Continued)

This research was conducted in Ha Nam province, Vietnam, located in the Red River delta. This area is typical of many semi-rural settings in South-East Asia where there is increasing industrialisation. In Ha Nam province, exposure to Hg occurs through the consumption of organic compounds (methylmercury) in large fresh water fish, a staple of the local diet(29). Pb levels in soil are increased by anthropogenic activity such as the recycling of Pb batteries(30). As groundwater contamination is a major ecological issue, with levels exceeding WHO guidelines(31), in spite of initiatives designed to decontaminate the main drinking water sources(32).

Chronic exposure to Pb during prenatal or postnatal periods has been associated with inferior neurodevelopment in children(33). The protective effect of Se on Pb toxicity has been demonstrated in different experimental studies; however, this has been poorly explored in human studies. Al-Saleh *et al.* failed to demonstrate a protective role for Se on the neurodevelopment of a small sample of Saudi-breastfed infants(34). Our findings of a reduced magnitude negative association between toxicant and BSID score at higher concentrations of Se (although did not reach significance for Pb) supports the hypothesis that adequate Se intake is fundamental for promoting adequate neurodevelopment in children living in areas with high exposure to environmental toxicants. If confirmed, this has important implications for environmental and public health policy in developing and emerging nations(33,34).

We used fingernail samples in this analysis although hair and nails are both considered stable markers that reflect long-term chronic exposure to trace elements. Nails are considered the marker of preference for As (35) and Se(36), while hair has been used for Pb and Hg(37,38). Nonetheless, a significant correlation between Pb concentration in hair and nails has been shown by Kim and Kim(38), indicating that nails are also a useful and reliable marker. The use of nails to assess long-term Hg exposure is well established as a reliable marker(39).

The strengths of this study lie in the large representative sample from a setting where children are very likely exposed to environmental contamination with toxicants. Mother/child pairs in this analysis were originally randomly selected across Ha Nam province for participation in an RCT and so the results are likely representative of many similar rapidly industrialising areas in Vietnam and South East Asia. The assessment of toxicants and Se in children's fingernails is a strength of this study, given that these elements accumulate in keratinised matrices like nails and hair. Nails are less vulnerable to external contamination and can validly measure more elements than hair due to their dense concentration of fibrous proteins(40).

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This study has some limitations. Even though this was part of a prospective cohort study with data collected over 3 years, we only assessed tissue levels of toxicants at one time point, when children were 3 years of age. Therefore, causality cannot be inferred, although it is estimated that nail clippings reflect 3–6 months of prior heavy metal exposure[40]. We did not have complete data on all 1019 children who finished the cohort study. Given the large proportion of missing data, the results of our analysis based on complete cases are hypothesis generating. Although we applied strict selection criteria that limited the sample size to 658, no differences in characteristics of included and excluded subjects were found. The effect on neurodevelopment although statistically significant was small across this population. However, our findings flag the importance of including Se assessment in studies of heavy metal toxicity and pave the way for future intervention studies in Se-deficient populations that have high exposure to heavy metals to mitigate their negative effects on child neurological development. In this cohort, we assume overall Se status was low[25]. In a Se-sufficient population, a larger effect may be observed, highlighting the need for further research.

Conclusion

In this study, we found that higher As, Pb and Hg tissue concentrations correlated with lower neurodevelopmental scores in young Vietnamese children, as assessed using the Bayley Scales of Infant Development 3rd edition, but there was no effect on growth. Se status reduced the magnitude of this negative association in the case of Hg and to a lesser extent Pb, but not As. Our findings support the hypothesis that adequate Se intake is fundamental for promoting adequate neurodevelopment in children living in areas with high exposure to environmental toxicants. The effect sizes across the study population are small and require confirmation in populations with differing levels of Se sufficiency. However, if confirmed, there are important implications for environmental and public health policy in developing and emerging nations.

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S. H., H. T., T. T., J. F. and B. B. designed and conducted the original RCT and follow-up. J. E., B. C., S. B., D. H., S. H. and B. B. designed this study. A. X. D. and A. D. coordinated the Se and toxicant analysis. J. E. and S. B. performed statistical analysis. J. E., B. R. C., B. B., S. B., A. X. D. and D. H. drafted the manuscript. All authors contributed to revising the manuscript and approved the final version.

The authors declare that they have no competing interests.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114522001374

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