Potential Role of Selenium in Modifying the Effect of Maternal Methylmercury Exposure on Child Neurodevelopment-A Review

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Potential role of selenium in modifying the effect of maternal methylmercury exposure on child neurodevelopment – A review

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ABSTRACT

Selenium (Se) is an essential trace element for normal neurodevelopment. It is incorporated into multiple selenoenzymes which have roles in the brain and neurological function, the synthesis of thyroid hormones, the antioxidant defense system, DNA synthesis, and reproduction. Fish is a source of both Se and neurotoxic methylmercury (MeHg). Selenium is known to ameliorate the effects of MeHg in experimental animals, but studies in children exposed to both Se and MeHg through prenatal fish consumption have been inconclusive. Research on Se's implications for pregnancy and child neurodevelopment is limited. The aims of this review are to summarize the literature on the biological roles of Se during pregnancy and the potential role in mitigating the effects of MeHg exposure from fish consumption on human health. This review has shown that Se concentrations among pregnant women globally appear insufficient, with the majority of pregnant women reporting Se concentrations below 70 μg/L during pregnancy. The role of Se in child development and its interactions with MeHg in children are inconclusive. Further investigation of the interaction between Se and MeHg in relation to child neurodevelopment in high fish-eating populations is required to fully elucidate effects.

1. Introduction

Selenium (Se) is an essential micronutrient which is required for the synthesis and function of numerous selenoenzymes, including glutathione peroxidases (GPx), selenoprotein P (SePP1), thioredoxin reductase (TRx) and iodothyronine deiodinases (DIOs), which are essential for the production of thyroid hormone, the antioxidant defense system, DNA synthesis, fertility, and reproduction, as well as brain and neurological functions (Mehdi et al., 2013; Solovyev, 2015). Selenium is essential in pregnancy, with Se deficiency being associated with pregnancy complications such as preeclampsia, gestational diabetes, and preterm birth (Duntas, 2020) The guidelines for Se intakes during pregnancy vary across the world (EFSA, 2014; IOM, 2000; NHMRC, 2005; Scientific Advisory Committee on Nutrition, 2013; World Health Organization, 2000) however, there are currently no recommendations for optimal Se concentrations during pregnancy.

Fish is a good source of Se (primarily in the chemical form of selenomethionine); however, it also contains methylmercury (MeHg), which in adequate dosage may be neurotoxic. Methylmercury is known to cross the placenta and accumulate in the developing fetal brain (Li et al., 2010). The mechanisms responsible for Se protective role against the toxic effects of MeHg are complex and not fully understood. However, the high affinity of Hg to Se-containing groups can result in formation of an inert Hg-Se complex reducing its toxicity (Bjørklund, 2015; Ralston and Raymond, 2018; Spiller, 2018). Furthermore, Se may protect against MeHg induced toxtcity through its antioxidant properties (Ercal et al., 2001; Ralston and Raymond, 2010). While Se and MeHg can both have significant effects on child neurodevelopment their interactions in relation to brain development are not well understood. There is currently a substantial research gap in our knowledge of Se concentrations in pregnancy across various populations, and there is inconclusive evidence on the relationship between maternal Se status and neurodevelopment of children in populations with moderate and high Se status, particularly those with high fish consumption who are also exposed to MeHg. The aim of this review is to summarize and review the available literature on the biological functions of Se in pregnancy, with a

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focus on the maternal requirements for optimum fetal neurodevelopment as well as the potential role of Se in modifying the effect of MeHg exposure through fish consumption on human health.

2. Material search strategy

A review of literature available in English was conducted in the Medline (OVID), PubMed and Google Scholar databases using the following search phrases in different combinations: ("Selenium") AND ("Pregnancy" OR "Prenatal" OR "Maternal") AND ("child" OR "infant" OR "neurodevelopment" OR "development") AND ("Mercury" OR "Methylmercury" OR "MeHg" OR "Mercury Selenium Interactions" OR "Se:Hg OR "MeHg and Se" OR "Selenium–mercury antagonism").

Selected articles were required to meet one or more of the following criteria: (1) report prenatal Se status in Se biomarkers (serum/plasma/ whole blood/ erythrocytes) at any time during a healthy pregnancy, at birth, or at multiple time points; (2) examine the relationship between maternal or cord Se status and child neurodevelopment at any age; (3) examine the relationships between maternal Se or MeHg while adjusting for Se or MeHg or examining the interaction between the two, all the while examining the role in child neurodevelopment.

The search for selenium status in healthy pregnancy yielded 423 results of which 384 did not meet our pre-specified criteria of a prenatal selenium and mercury measurement. Searching for studies with Se and Hg measurements and neurodevelopmental outcomes yielded an additional 31 results of which 6 did not fulfill the previously stated criteria. As this was a narrative review of the human literature rather than a systematic review, no risk of bias assessment was conducted, or quality control criteria applied.

2.1. Human Selenium metabolism

Selenium is predominantly absorbed in the lower part of the small intestine and, under normal physiological conditions, Se absorption ranges between 70% and 90% (Roman et al., 2014). Selenium can be absorbed in both organic (selenomethionine (SeMet) and selenocysteine (SeCys)) and inorganic forms (selenites and selenates). The chemical composition of Se influences the metabolic pathways, with the organic forms being more bioavailable for the synthesis of selenoproteins. As illustrated in Fig. 1, regardless of the chemical composition all ingested Se is transformed to hydrogen selenide (H_2Se) in the liver (Daniels, 1996). Some SeMet is incorporated into methionine-containing proteins such as albumin or hemoglobin (Qazi et al., 2019), while the remainder of organic Se is metabolized to SeCys which is further metabolized to H_2Se by transulfurization (Burk, 2015). Inorganic Se is metabolised to SeO_3 (selenite) or SeO_4 (selenate). SeO_3 is converted to selenodiglutathione (GSSeSG) which is further reduced to glutathioselenol (GSSeH) before reacting with glutathione to form H_2Se (Qazi et al., 2019). All Se must be converted to H_2Se before being transported to the liver, where it is converted to selenophosphatase (SePhp) and incorporated into selenoproteins as selenocysteine (SeCys) (Ferreira et al., 2021). Selenoprotein P is released into the bloodstream and transports Se to numerous tissues for selenoprotein synthesis (Burk and Hill, 2015). Excess Se is detoxified via sequential methylation into dimethylselenide (DMSe) and excreted through the breath or via urine in the form of selenosugars or trimethylselenide (TMSe) (Roman et al., 2014).

2.2. Biomarkers of Selenium status

Selenium status refers to the amount of biologically active nutrient in the body and represents the nutrient's intake, retention, and metabolism (Combs, 2015). Estimating the dietary Se intake from foods can be challenging owing to fluctuations of Se content in foods induced by environmental factors and errors associated with dietary assessment instruments. These challenges make the dietary measurement of Se intake generally an unreliable indicator of Se status (Navarro-Alarcon and Cabrera-Vique, 2008).

The most widely used biomarker of Se status is the Se concentration in plasma (or serum). These concentrations are mostly influenced by dietary intake and are an indicator of recent consumption. However, other factors such as age, sex, smoking habits, inflammation, and pregnancy may also have an influence on plasma Se concentrations (Faupel-Badger et al., 2007; Huang et al., 2012; Lloyd et al., 1983). Plasma Se concentrations generally indicate short-term status only, whereas measurement of whole blood Se or erythrocyte-selenium (Ery-Se) concentrations represents long-term status (Roman et al.,

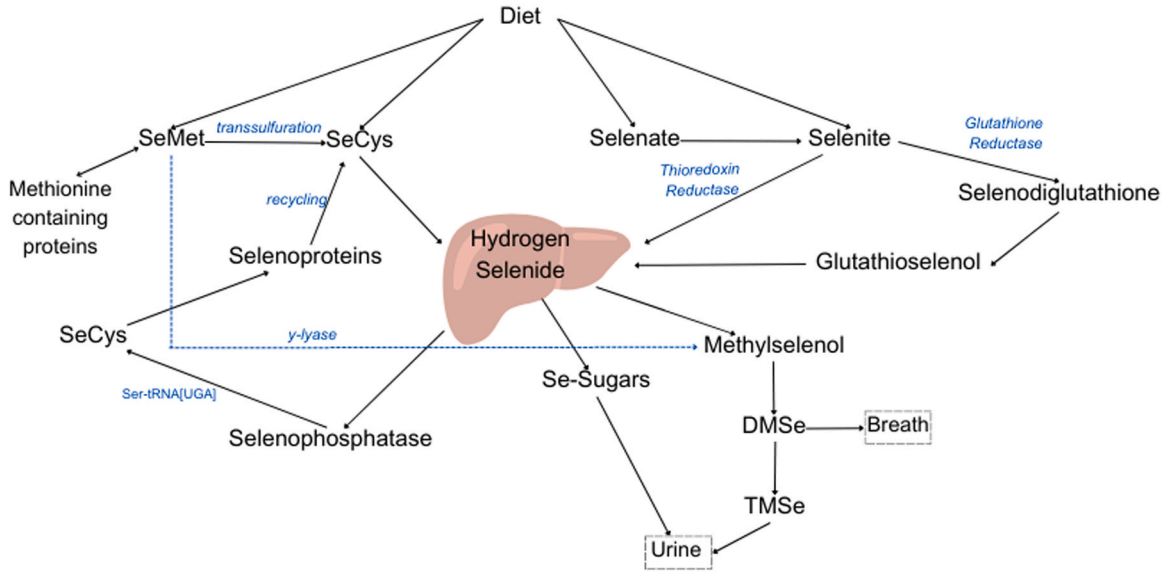

Fig. 1. Diagram demonstrating the absorption, metabolism, distribution and excretion of Se in humans. Food-derived Se is absorbed in both organic (SeMet, SeCys) and inorganic (Selenate, Selenite) forms. All forms of Se are converted to Hydrogen Selenide (H2Se) and transferred to the liver, where H_2Se is converted to SePhp, then SeCys, and finally incorporated into selenoproteins. Selenium is distributed to other organs via selenoproteins, which circulate in the bloodstream. Excess Se is excreted as DMSe in the breath and selenosugars and TMSe in the urine. Adapted from (Ferreira et al., 2021; Roman et al., 2014; EFSA, 2023). Abbreviations: DMSe, dimethylselenide; H2Se, Hydrogen Selenide; Se, Selenium; SeCys, selenocysteine; SePhp, selenophosphatase; SeMet, selenomethionine, TMSe, trimethylselenide.

2014). Urinary Se is a non-invasive short-term indicator of Se status but is only useful for determining recent dietary intake, not nutritional status, furthermore, its use as a biomarker is limited by individual variability in hydration status, physical activity, climate, diet, and genetic factors (Greiner et al., 2020; Phiri et al., 2020). Although hair and nail Se measures are non-invasive methods that can be used to assess Se status, they are not reliable biomarkers because they are dependent on a variety of factors, including the form of Se consumed, smoking habits, and exposure to external contamination through hair and nail products (Ashton et al., 2009; Combs, 2015; Filippini et al., 2017).

Whilst Se can be measured in serum, plasma, whole blood, and urine, a more accurate biomarker approach is to assess its functional status as selenoproteins. Glutathione peroxidases (GPx) is the main selenoprotein in the selenium-dependent antioxidant defense system (Chu et al., 2004). Plasma GPx3 enzyme activity has been used to estimate recommended daily Se intake (Thomson, 2004); however, lower Se intakes are needed for GPx to reach a steady state than are required for optimal SePP1 expression. Plasma contains 50–60% SePP1, which is essential for the whole-body transfer of Se from the liver to other tissues and Se homeostasis (Butler and Whanger, 1992). Additionally, SePP1 acts as an antioxidant and contributes to the trans-placental transfer of Se to the fetus (Kasik and Rice, 1995). As SePP1 is susceptible to antioxidant activity and plays a role in the transplacental transfer of Se to the fetus, SePP1 may be considered as a valuable marker of Se status and function particularly during pregnancy. SePP1 activity is regarded as a reliable indicator of Se function, since SePP1 has a longer half-life in the blood compared to other Se biomarkers, it is also indicative of long-term Se status (Brodin et al., 2020; Fairweather-Tait et al., 2011; Schomburg, 2022).

2.3. Recommended daily intakes and reference ranges

The recommendations for Se intakes vary across the globe owing to Se availability in the soil, genetic variations in Se metabolism, cultural differences in dietary patterns, and the techniques used to calculate nutrient needs (Fairweather-Tait et al., 2011). Numerous criteria can be used to develop the recommendations, such as the requirement to prevent deficiency or to optimize GPx activity or plasma SePP1 expression (Combs, 2015). There is currently no specific recommendation for reference nutrient intake (RNI) for pregnancy in the UK; however, the RNI for Se in the UK for women is 60 μg /day and 75 μg /day for men, with no adjustments during pregnancy (Scientific Advisory Committee on Nutrition, 2013). The Australian Government's National Health and Medical Research Council (NHMRC, 2005) suggests that the recommended daily intake (RDI) for Se in women is 60 μg/day, rising to 65 μg/day during pregnancy. Similar to this, in the US, the National Institutes of Health (NIH) advises a daily intake of 55 μg for women, which increases to 60 μg during pregnancy (IOM, 2000). The World Health Organization RNI is significantly lower, with greater intakes recommended for pregnant (2nd trimester - 28 g/day; 3rd trimester - 30 g/day) and breastfeeding women (0–6 months post-partum - 35 g/day; 7–12 months - 42 g/day) (World Health Organization, 2000). Based on optimizing SePP1 expression the European Food Safety Authority (EFSA) has established the adequate intake for Se for adult men, women, and pregnant women at 70 μg/day and lactating women are advised to consume 85 μg/day (EFSA, 2014).

Selenium adequacy has been suggested to be achieved at circulating Se concentrations between 70 and 100 μg/L (Combs, 2001). It has been suggested, however, that circulating Se concentrations between 90 and 140 μg/L are the optimal range for maximum SePP1 expression (Hurst et al., 2013). There is currently no optimal serum reference range for Se concentrations or SePP1 activity during pregnancy.

2.4. Selenium functions in pregnancy

Optimal maternal nutrition is crucial for the continuous physiological changes related to pregnancy and healthy fetal development (Mousa et al., 2019; Procter and Campbell, 2014). Increased oxidative stress occurs during pregnancy owing to increases in placental mitochondrial activity and production of reactive oxygen species (ROS) (Schoots et al., 2018). Selenium insufficiency, impair antioxidant defenses system and may trigger oxidative stress in the placenta. Selenium's antioxidant properties make it essential for human reproduction, with GPx, SePP1, and TrxRs playing important roles in reducing oxidative stress (Ceko et al., 2016). The balance of oxidative vs antioxidant enzymes is critical for optimal fetal development. Uncontrolled ROS generation can lead to adverse pregnancy outcomes such as gestational diabetes, gestational hypertension, and fetal growth restriction (Toboła-Wróbel et al., 2020). The majority of selenoproteins found in the placenta, including GPx and SePP1, have antioxidant characteristics whereas TRx is involved in redox regulation processes (Hogan and Perkins, 2022). Selenoproteins also play essential functions in the regulation of metabolism, endocrine function, and energy balance, all of which are critical during periods of rapid growth such as gestation (Ojeda et al., 2022).

Selenium is a key component of the thyroid hormones. The fetus is entirely dependent on maternal transmission of thyroid hormones until the fetal endocrine system begins to develop at approximately 14–16 weeks gestation (Morreale de Escobar et al., 2004). Subsequently, the fetus depends on maternal Se and iodine intake to function adequately (Velasco et al., 2018). Selenium is incorporated into the DIOs, which activate the thyroid hormone; DIO2 is an activating enzyme that converts inactive thyroxine (T4) into active triiodothyronine (T3), producing more than 80% of T3 which is crucial for the development of fetal organs (Pieczyńska and Grajeta, 2015).

2.5. Selenium status in pregnancy

Circulating Se concentrations gradually decrease during pregnancy (Pieczyńska and Grajeta, 2015). This decrease may be from hemodilution or owing to the physiological changes in pregnancy such as a greater Se requirement as there is transfer from mother to the fetus (Kantola et al., 2004; Pieczyńska and Grajeta, 2015). Selenium is also required for production of antioxidant proteins such as GPx and SePP1 which are used to counteract the increased oxidative stress which occurs during pregnancy (Ceko et al., 2016).

Adequate Se concentrations are essential for optimal fetal and infant development (Pappas et al., 2019). For the purpose of this review, we regarded circulating Se concentrations below 70 μg /L as insufficient. Those between 70 and 90 μg /L were considered suboptimal, and concentrations between 90 and 140 μg /L were considered optimal. We based these cut-offs on the blood's SePP1 expression, which is considered to be the most reliable indicator of an adequate Se supply to all tissues and a reflection of the saturation of the functional Se body pool (EFSA, 2017). Selenium insufficiency during pregnancy is prevalent in many populations, as depicted in Table 1. Selenium insufficiency has been associated with several pregnancy complications such as infertility, miscarriage, preterm birth, pregnancy-induced hypertension, and gestational diabetes, and are indicative of a crucial role for Se in human reproduction (Barman et al., 2020; Pieczyńska and Grajeta, 2015; Rayman et al., 2011; Wilson et al., 2018).

Table 1 displays the circulating Se concentrations of women throughout pregnancy. There is large variability in Se concentrations across different stages of pregnancy and between studied populations. Studies evaluating Se concentrations at multiple time-points during pregnancy have all shown a decrease from the first to third trimesters. Only two studies out of a total of 11 reported optimal concentrations of circulating Se in serum or plasma during the first trimester, while three studies reported suboptimal Se concentrations. More than 50% of the studies reviewed had an insufficient Se concentration at the beginning of pregnancy, with Se concentrations during this period ranging from 44 μg/L to 107 μg/L. In the second trimester, the range for Se

Table 1
Summary of Serum/ Plasma Selenium concentrations in healthy pregnancy.

Reference	Country	Sample size	Time of Sampling	Se status	Sample Type
				μg/L	(Analytical Method)
Erol et al. (2021)	Turkey	70	1st Trimester (n = 26)	44.59 ± 8.40	Serum (AAS)
			2nd Trimester (n = 22)	46.15 ± 8.15	
			3rd Trimester (n = 22)	36.15 ± 6.25	
Pieczyńska et al. (2019)	Poland	94	1st Trimester	44.36 ± 8.58	Serum (EAAS)
			2nd Trimester	43.16 ± 8.47	
			3rd Trimester	40.97 ± 7.5	
Varsi et al. (2017)	Norway	114	18wks gestation	76 (68, 82)	Serum (ICP-MS)
			28wks gestation	72 (64, 81)	
			36wks gestation	67 (59, 76)	
Polanska et al. (2016)	Poland	410	1st Trimester	48.3 ± 10.6	Plasma (AAS)
			2nd Trimester	42.3 ± 9.1	
			3rd Trimester	37.3 ± 9.8	
			Delivery	38.4 ± 11.8	
Nwagha et al. (2011)	Nigeria	130	1st Trimester (n = 34)	107 ± 16	Serum (AAS)
			2nd Trimester (n = 44)	83 ± 17	
			3rd Trimester (n = 52)	79 ± 14	
Veisa et al. (2021)	Latvia	129	1st Trimester	101.5 (35.6)	Serum (FAAS)
Liu et al. (2021)	China	398	1st Trimester	66.8 ± 13.3	Serum (ICP-MS)
Lozano et al. (2020)	Spain	1249	1st Trimester	79.57 ± 9.64	Serum (ICP-MS)
Jankowska et al. (2021)	Poland	340	1st Trimester	46.77 ± 10.84	Plasma (GFAAS)
Amorós et al. (2018)	Spain	650	1st Trimester	79.74 ± 7.92	Serum (ICP-MS)
Lewandowska et al. (2019)	Poland	363	10–14wks gestation	62.9	Serum (ICP-MS)
Rayman et al. (2011)	Netherlands	1129	12wks gestation	80.5 ± 10.3	Serum (ICP-MS)
Wilson et al. (2018)	Australia	1065	15 ± 1wks gestation	72 ± 12	Plasma (ICP-MS)
Mistry et al. (2015)	UK	472	15 ± 1wks gestation	79.0 (71.8, 87.4)	Plasma (ICP-MS)
Atamer et al. (2005)	Turkey	28	28–39wks gestation	87.50 ± 10.96	Serum (AAS)
Stråvik et al. (2021)	Sweden	604	29wks gestation	67 (46–93)	Plasma (ICP-MS)
Maleki et al. (2011)	Iran	40	34–39wks gestation	58.51 ± 11.85	Plasma (EAAS)
Eze et al. (2020)	Nigeria	58	34wks and over	94 ± 36	Serum (ASS)
Iqbal et al. (2020)	Pakistan	80	3rd Trimester	178 ± 86	Serum (ICP-OES)
Jiang et al. (2019)	China	1, 495	3rd Trimester	136.5 ± 48.3	Serum (ICP-MS)
da Silva et al. (2017)	Brazil	32	3rd Trimester	56.4 ± 15.3	Serum (ICP-MS)
Haque et al. (2016)	Bangladesh	118	3rd Trimester	Urban: 32.10 ± 1.50	Serum (FAAS)
				Rural: 32.29 ± 2.09	
Rezende et al. (2015)	Brazil	61	3rd Trimester	47 ± 15	Plasma (ICP-MS)
Ghaemi et al. (2013)	Iran	38	3rd Trimester	82.03 ± 15.54	Plasma (AAS)
Farzin and Sajadi (2012)	Iran	60	3rd Trimester	104 ± 27.8	Serum (GFAAS)
Röllin et al. (2021)	South Africa	650	Delivery	69.0 ± 3.7	Serum (ICP-MS)
Wibowo et al. (2019)	Indonesia	25	Delivery	76.42 ± 16.30	Serum (ICP-MS)
Kim et al. (2012)	Korea	29	Delivery	90 ± 10	Serum (INAA)
Mistry et al. (2008)	UK	27	Delivery	58.4 ± 14.9	Serum (AAS)

Se status displayed as Mean ± SD or Median (IQR). Abbreviations: AAS, Atomic absorption spectrometry; EAAS, Electrothermal atomic absorption spectrometry; FAAS, Flame atomic absorption spectroscopy; GFAAS, Graphite furnace atomic absorption spectrometry; ICP-MS, Inductively coupled plasma mass spectrometry; ICP-OES; Inductively coupled plasma atomic emission spectroscopy; IQR, Interquartile range; SD, Standard deviation; UK, United Kingdom; μg/L, micrograms per litre.

concentrations was lower, ranging from 42 μg/L to 83 μg/L, with no study reporting Se concentration within the optimal range; however, four studies reported prenatal Se concentrations within the suboptimal range. The results of studies examining Se concentrations in the third trimester demonstrated the greatest variability, with a range of 32 μg/L to 178 μg/L. Nevertheless, Se insufficiency was highly prevalent, with 50% of the studies reporting insufficient Se concentrations in the third trimester and at delivery. Only four out of 20 studies reported optimal circulating serum Se concentrations and five studies reporting suboptimal Se concentrations in the third trimester or delivery.

Most studies examined Se concentrations at one time-point only during pregnancy making comparisons between studies at different gestational time-points difficult to compare, given the change in Se concentrations observed throughout pregnancy. Furthermore, the measurement of Se status also differs according to the methodology used. Se status was found to be higher in whole blood or erythrocytes than in serum or plasma as seen in Supplementary Table 1. with Se status in whole blood ranging from 78.9 to 170.0 μg/L and in erythrocytes from 104 to 205.6 μg/L. Similarly, to the plasma/ serum Se concentrations, there is no reference ranges for Se status in whole blood or erythrocytes making it difficult to establish whether Se requirements are being met during pregnancy. It is also difficult to compare these studies as Se status has been assessed at different timepoints throughout pregnancy. Since erythrocytes absorb and store Se, whole blood and erythrocytes are long-term markers of Se status and represent current Se concentrations and Se absorption (Thomson, 2004). Various methods employed to measure Se status may potentially be responsible for variations in Se concentrations reported. Furthermore, there is considerable variation in the amount of selenium in soil (El-Ramady et al., 2015), which could be contributing to the disparities in Se status of pregnant women around the world, with regions with lower Se soil contents reporting lower Se status as a result of lower Se intakes.

2.6. Selenium and neurodevelopment

The term "neurodevelopment" refers to the process by which the brain creates neural pathways that affect multiple areas of performance or ability such as cognitive function, reading, social skills, memory, attention, and concentrating skills (Tau and Peterson, 2010). Adequate maternal nutrition is essential for supporting fetal and early postnatal brain development due to the rapid brain developmental that occurs during pregnancy. The brain is particularly susceptible to nutritional deficiencies and toxicants (Georgieff et al., 2018; Graf et al., 2013). Although the exact mechanism by which Se is metabolized in the brain is unknown, it is widely acknowledged that the brain has greater amounts of SePP1 expression than any other organ, suggesting that Se is essential

for its development and functioning (Whanger, 2001). SePP1 is believed to play a significant role in brain function and neurodevelopment and protect the brain from toxins and ROS (Naderi et al., 2021).

Maternal Se status has been associated with child neurodevelopment, albeit findings are inconclusive, and the majority of studies are in populations with insufficient Se concentrations (Table 2). In studies where maternal Se concentration is below suboptimal concentrations, significant associations between maternal Se concentrations and neurodevelopmental outcomes have been observed. Polanska et al. (2016) observed a positive relationship between first trimester maternal plasma Se concentrations and psychomotor development in 1 year old children, as well as with mental and language scores at 2 years of age in a Polish birth cohort, with plasma concentrations that were below the deficiency cut-off point of 70 μg/L. However, neither maternal Se concentrations in the second nor third trimesters of pregnancy revealed a significant association with neither of the child neurodevelopmental outcomes assessed. In a Norwegian population of healthy pregnant women, a negative association was observed between insufficient prenatal Se concentrations (< 71 μg/L) at 18 weeks gestation and infant neurodevelopment at 6 months (Varsi et al., 2017). A Greek prospective longitudinal mother-child cohort found a weak positive correlation between urinary Se concentrations at 13 weeks gestation and children's cognitive scores at age 4 years (Kippler et al., 2016).

Skröder et al. (2015) found a significant positive relationship between maternal erythrocyte selenium (Ery-Se) concentrations at 30 weeks gestation and language comprehension as well as psychomotor development in 1.5-year-old children, with girls demonstrating a stronger association with psychomotor development. A subsequent investigation in the Bangladesh cohort reported positive associations between maternal Ery-Se at 14 weeks gestation with child cognitive outcomes, particularly at 10 years (Skröder et al., 2017). Significant associations were also found in a Croatian coastal fish-eating population between maternal whole blood Se concentrations at delivery and children's cognitive development, specifically psychomotor but not motor at 18 months however, there was no association between BSID-III scores and cord blood Se concentrations (Močenić et al., 2019). On the contrary, whole blood cord Se concentrations were positively associated with language abilities at 18 months and 2 years old (Calamandrei et al., 2022; Tratnik et al., 2017), and with the emotional development in school aged children (Garí et al., 2022).

In a Spanish multicenter birth cohort with suboptimal prenatal Se concentrations, non-linear relationships have been observed in two separate investigations (Amorós et al., 2018a; Amorós et al., 2018b). Maternal Se concentrations during the initial trimester of pregnancy were found to have an inverse U-shaped association with child neurodevelopment at the age of 12 months and again at 5 years. Children whose mothers had Se concentrations higher than 86 μg/L during the first trimester showed a negative association between mental and psychomotor scores and maternal Se concentrations and suggested that the association between maternal Se and child's neurodevelopment may be affected by the INMT rs6970396 gene (Amorós et al., 2018a). The SNPs in the INMT gene have been found to play a significant role in Se excretion and detoxification (Kuehnelt et al., 2015), with individuals with the AA or AG INMT genotype (TMSe producers) being able to convert Se into TMSe which is excreted in urine, resulting in increased Se excretion and possibly reduced toxicity. Infants who carried the A genotype (TMSe producers), as compared to GG carriers, appeared to benefit more from Se up to 86 μg/L and had better scores with Se above 86 μg/L, suggesting a Se-gene interaction. It is not yet understood how SNPs in INMT impact the relationship between maternal Se and child neurodevelopment and this requires further investigation in populations with a range of Se status. Yang et al. (2013) found a similar inverted U-shaped association between cord blood Se and behavior scores in newborns at 3 days old with the inflection point at 100 μg/L. Maternal urinary Se during the third trimester of pregnancy showed a similar inverted U-shaped link with girls' mental and motor scores but not with boys' (Li et al., 2020).

Reports of adverse neurodevelopmental outcomes and an increased risk of developing attention deficit hyperactivity disorder (ADHD) have been linked to higher maternal and cord whole blood Se concentrations (Cord serum ≥63.1 μg/L; Whole blood ≥168 μg/L) during late stages of pregnancy and delivery (Fruh et al., 2021; Kobayashi et al., 2022; Lee et al., 2021; Ode et al., 2015; Rayman et al., 2015; Wang et al., 2022; Yildirim et al., 2019). However, it is challenging to compare the results of these investigations owing to the timing of maternal Se status measurement (at a later stage of pregnancy) as different biomarkers, including cord blood, whole blood, and Ery-Se have been used. Moreover, two of these studies (Lee et al., 2021; Ode et al., 2015) only examined the diagnosis of neurodevelopmental disorders such as ADHD, autism spectrum disorder (ASD), and dissociative disorders (DD), while others used neurodevelopmental research tools rather than diagnostic criteria.

It is clear that maternal Se concentrations at the beginning of pregnancy and in cord whole blood are beneficial for a child's neurodevelopment, but it is also evident that higher concentrations may have adverse effects on child development. This suggests that there may be an ideal maternal Se concentration or optimal Se-range that is associated with better neurodevelopment assessment scores, above which Se neurotoxicity may occur.

2.7. Selenium interactions with Hg

Fish serves as a source of both Se and MeHg (Se: 0.15–0.58 μg/g; MeHg: 0.02–0.55 μg/g (Barone et al., 2021)), making the interaction between Se and MeHg particularly relevant to neurodevelopment, especially in populations who regularly consume fish. Methylmercury can easily cross the placenta and accumulates in the foetus, resulting in greater amounts of MeHg in cord blood than in the mother (Ursinyova et al., 2019) and the developing central nervous system is particularly vulnerable to MeHg exposure (Grandjean and Herz, 2011). The Faroe Islands, a population that regularly consumes high amounts of fish and whale meat, have reported adverse effects of MeHg exposure through seafood consumption due to the high intakes of sea mammals (Debes et al., 2006). Nevertheless, the benefits of maternal fish consumption on a child's development have been demonstrated by a number of investigations (Hibbeln et al., 2019). Findings from the Seychelles Child Development Study (SCDS), where an average of 8.5 fish meals are consumed weekly, with no mammal meat consumed, have consistently shown no adverse effects of MeHg exposure on child developmental outcomes and suggest that the benefits of fish consumption may have a protective effect against MeHg (Strain et al., 2015, 2021). Fish in the Republic of Seychelles contain the similar concentrations of MeHg as fish in the United States but owing to the high consumption of fish in the Seychellois diet, the population is exposed to MeHg concentrations approximately 10 times that of the US. Such criteria make the Seychellois an ideal population to assess the benefits and risks of fish consumption on human development and health (Myers et al., 2007). Even though some fish species have a high Hg content, recent findings from Sabino et al. (2022) show that the Hg:Se ratio for those species is less than one, indicating a low risk of Hg toxicity.

Evidence suggests that Se may help reduce the risks of exposure to MeHg, possibly owing to the formation of inert Se-Hg precipitates and through the antioxidant properties of seleno-proteins (Gerson et al., 2020; Ralston and Raymond, 2010). Methylmercury has a strong affinity for Se and forms metabolically inert mercury-selenide (Se-Hg). The formation of inert Se-Hg precipitates can bind to the SePP1 structure and demethylates MeHg resulting in decreased MeHg accumulation in tissues (Bjørklund, 2015; Bjørklund et al., 2017; Khan and Wang, 2009). The formation of Se-Hg precipitates assists in limiting the damage of MeHg in brain tissue however it can result in inhibition of Se-dependent enzymes (Bjørklund, 2015; Bjørklund et al., 2017). When Se-dependent enzymes are inhibited, selenoprotein synthesis is hindered and

Table 2
Summary of investigations assessing the effects of selenium and interactions between selenium and methylmercury on a child's neurodevelopment.

Reference	N	Country	Time of Sampling	Se Biomarker (units)	Se Status	Hg Biomarker (units)	Hg status	Child Age at Testing	Neurodevelopment Test	Results
Polanska et al. (2016)	410	Poland	1st, 2nd, 3rd trimester, delivery	Plasma, Cord blood (μg/L)	48.3 ± 10.6 42.3 ± 9.1 37.3 ± 9.8 38.4 ± 11.8	X	X	1 yrs, 2 yrs	BSID-II	+ve Se and motor development at 1 yrs +ve Se and language development and cognitive function at 2 yrs, during the first trimester only.
Varsi et al. (2017)	114	Norway	18wks, 28wks 36wks gestation	Serum (μg/L)	76 (68, 82) 72 (64, 81) 67 (59, 76)	X	X	6mo	ASQ	+ve Se (18wks gestation) and psychomotor score at 6mo
Kipplerr et al., 2016	575	Greece	13wks gestation	Urine (μg/L)	23 ± 8.6	X	X	4 yrs	MSCA	+ve (marginally) Se and cognitive and verbal development
Skröder et al. (2015)	750	Bangledesh	30wks gestation	Erythrocyte (μg/g)	0.46	X	X	18mo	BSID-II, MSCA (specifically developed for Bangladesh)	+ve, Se and cognitive performance, especially language and psychomotor development.
Skröder et al. (2017)	1408	Bangledesh	14wks gestation	Erythrocyte (μg/g)	0.45 ± 0.11	X	X	5 yrs, 10 yrs	WPPSI-III at 5 yrs, WISC-IV at 10 yrs	+ve Se and cognitive function scores at 5 and 10 yrs.
Močenić et al. (2019)	205	Croatia	Delivery	Whole blood (μg/L)	Maternal: 92.6 ± 22.4 Cord: 98.7 ± 21.8	X	X	1.5 yrs	BSID-III	+ve maternal Se and cognitive abilities.
Garí et al. (2022)	436	Poland	Delivery	Whole blood (μg/L)	Cord 30.3 (35.4, 41.0)	Maternal hair (ug/g),	0.18 (0.31, 0.49)	7 yrs	SDQ, IDS	+ve, cord Se and emotional development
Calamandrei et al. (2020)	984; PHIME Croatia: 141 PHIME Slovenia: 212; REPRO _PL: 311	Croatia, Slovenia, Poland	Delivery	Whole blood (μg/L)	Cord PHIME Croatia 42.5 ± 9.0; PHIME Slovenia 40.3 ± 8.0; REPRO_PL 31.1 ± 8.2	Maternal hair (ng/g)	PHIME Croatia 962.2 (1231.0); PHIME Slovenia 389.8 (322.8); REPRO_PL 489.1 (752.5)	PHIME cohort: 18mo; REPRO_PL cohort: 24mo	BSID-III	+ve cord Se and language abilities
Tratnik et al. (2017)	361; PHIME Croatia: 124 PHIME Slovenia: 237	Croatia, Slovenia	Delivery	Cord Serum (μg/L)	40.1 (17–70)	Maternal hair (ng/g), Cord blood (ng/g)	Maternal: Croatia; 598 (505–708); Slovenia: 273 (244–306); Cord: Croatia:3.41 (2.96–3.94); Slovenia: 1.58 (1.42–1.74)	18mo	BSID-III	+ve association between cord Se and language score in the ε4 non-carriers, Se levels altered the relationship between Hg and neurodevelopment.
Amorós et al. (2018)a	650	Spain	1st Trimester	Serum (μg/L)	79.74 ± 7.92	Cord whole blood μg/L	9.86 ± 13.42	12mo	BSID	inverted U-shape; breaking point at 86 ug/L, no interaction between MeHg and Se was observed.
Amorós et al. (2018)b	490	Spain						5 yrs	MSCA	inverted U-shape; breaking point at 85 μg/L
Li et al. (2020) a	544	China	36–42wks gestation	Urine (μg/L)	11.47 ± 2.34	X	X	2 yrs	BSID	inverted U-shaped; between maternal urinary Se and mental and psychomotor scores in girls, but not boys.
Yang et al. (2013)	927	China	Delivery	Cord serum (μg/L)	Median: 63.1	X	X	3 days old	NBNA	inverted U-shape; breaking point at 100 μg/L
Kobayashi et al. (2022)	48,731	Japan	2nd or 3rd Trimester	Whole blood (μg/L)	Maternal: 168 (156–181) Cord:	Whole blood (ng/g)	Maternal 3.64 (2.56–5.19) Cord: 7.56 (5.22–10.7)	from 0.5 to 4 yrs	ASQ-3	maternal blood Se ≥ 168 μg/L associated with neurodevelopmental delay, independent of maternal

(*continued on next page*)

Table 2 (*continued*)

Reference	N	Country	Time of Sampling	Se Biomarker (units)	Se Status	Hg Biomarker (units)	Hg status	Child Age at Testing	Neurodevelopment Test	Results
					178 (163–194)					MeHg levels, no Se and MeHg interaction in cord blood
Wang et al. (2022)	148	China	Delivery	Plasma (μg/L)	Cord: 127.38 ± 1.24; boys: 120.85 ± 1.24; girls 133.72 ± 1.24	X	X	school age	WISC, Wechsler Intelligence Scale for Children	-ve cord Se and verbal and overall intelligence scores, in boys only
Lee et al. (2021)	1550	USA	Delivery (up to 72hrs after)	Red blood cells (μg /L)	NT (651): 286.15 ± 53.86; ASD (66): 302.49 ± 85.16; ADHD (216): 291.75 ± 59.42; DD (617): 289.61 ± 64.07	X	X	0–8 yrs	Diagnosis of neurodevelopmental disorder (ASD, ADHD, other DD)	-ve, High maternal Se and child's neurodevelopment.
Ode et al. (2015)	ADHD case:166 Control: 166	Sweden	Delivery	Cord serum (μg/L)	49 ± 12 cases, 48 ± 8.9 controls	X	X	5–17 yrs	Diagnose of ADHD	-ve, higher Se associated with increased chance of ADHD diagnosis
Castriotta et al. (2020)	470	Italy	20–22wks gestation, delivery	Whole blood (μg/L)	Maternal: 122.1 ± 26.5; Cord: 117.4 ± 27.1	Whole blood (ng/g)	Maternal: 3.4 ± 3.8 Cord: 5.6 ± 4.9	40mo	BSID-III	A higher risk of poor neurodevelopment was seen in the high MeHg and low Se groups for cord blood.
Golding et al. (2017)	4484	UK	11wks gestation	Whole Blood (μg/L)	108	Whole Blood (μg/L)	1.86	8 yrs	WISC-III Uk	Null, adjusting for maternal blood Se had no effect on the mercury and child IQ association
Oken et al. (2016)	872	USA	28wks gestation	Erythrocyte (μg/L)	206 ± 35	Erythrocyte (μg/L)	4.0 ± 3.6	7.7 yrs	KBIT-II, WRAVMA, WRAML	No associations between prenatal Se or MeHg status and child cognition.
Al-Saleh et al. (2019)	206	Saudi	Post-partum	Whole Blood (μg/L)	181.04 ± 29.63	Whole blood (μg/L)	0.47 ± 0.18	3–12 months	DDST-II, PEDS	Null, The protective role of Se in infant neurodevelopment was difficult to detect due to the high Se levels in all mothers
Tatsuta et al. (2017)	566	Japan	Delivery	Cord Plasma (μg/L)	Boys: 66.3 ± 10.2 Girls: 67.0 ± 9.6	Cord blood (ng/g) maternal hair (μg/g)	Cord blood: Boys: 16.5 (5.7–36.9); Girls: 15.0 (4.8–39.3); maternal hair: 2.5 (0.3–11.0)	18 m old	BSID-III, KSPD	controlling for Se did not alter the negative association between MeHg and BSID
Choi et al. (2008)	Cohort 1 N = 1022), Cohort 2 (N = 182)	Faroe Island	Delivery	Cord whole blood (μg/L)	111.6 (100.8–123.1)	Cord whole blood (μg/L)	22.9 (13.4–41.3)	7 yrs	NES, Finger Tapping Test and Hand–Eye Coordination Test; attention, WISC-R, Boston Naming Test	No significant interaction between Se and MeHg or effects of Se on child neurodevelopment
Saint-Amour et al. (2006)	102	Canada	Delivery	Cord blood (μmol/L)	Cord: 4.44 ± 2.08	Cord blood (μmol/L)	Cord: 119.30 ± 101.50	5–6 yrs	Visual evoked potentials	No interaction between cord blood Se and blood Hg.

ADHD, Attention deficit hyperactivity disorder; ASD, Autism spectrum disorder; ASQ, Ages and Stages Questionnaire: A Parent-Completed, Child-Monitoring System; BSID, Bayley scale of infant development; BRIEF, Behavior Rating Inventory of Executive Function; DD, Dissociative disorders; GEC, Global Executive Composite; IDS, Intelligence and Development Scales: KBIT-II, The Kaufman Brief Intelligence Test 2nd edition; MSCA, McCarthy Scales of Children's Abilities; NBNA, Neonatal Behavioural Neurological Assessment; NT; neurotypical; μg/L, micrograms per litre; SDQ, Strengths and Difficulties Questionnaire; WISC-IV, Wechsler Intelligence Scale for Children®, fourth edition WISC-R, Wechsler Intelligence Scale for Children-Revised; WRAVMA, Wide Range Assessment of Visual Motor Abilities; WRAML, Wide Range Assessment of Memory and Learning; WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence™;

Se-dependent enzyme production is decreased, thereby compromising Se bioavailability. Selenoenzymes are essential for human health and foetal development as they defend the body against oxidative damage which is particularly relevant among fish-eating populations considering Se protects against Hg-induced oxidative stress (Bjørklund et al., 2017; Ralston and Raymond, 2010, 2018). The evidence suggests that the Se protective effect against Hg toxicity is attributed to ensuring adequate Se is available to replace the Se lost in the process of Hg mitigation, enabling normal selenoprotein synthesis to continue. Therefore, Se:Hg molar ratios greater than 1 are considered to be protective against MeHg toxicity (Gerson et al., 2020; Park and Mozaffarian, 2010; Ralston and Raymond, 2010, 2018; Ralston et al., 2016; Spiller, 2018). Additionally, the Health Benefit Value of Selenium (HBVSe), which accounts for both the benefits of Se as well as its ability to protect against MeHg, has been proposed (Ralston et al., 2019). A positive HBVSe provides a good indication of seafoods that should be consumed during pregnancy for maternal and offspring health (Ralston et al., 2019).

There has been little investigation into the interaction between Se and MeHg when assessing the effects of prenatal fish consumption on child developmental outcomes. In a recent study, Castriotta et al. (2020) found no association between total Hg and Se concentrations in maternal blood at 20wks gestation and infant neurodevelopment outcomes at 40 months, nevertheless the author noted a significantly greater risk of impaired neurodevelopment in children who had low cord blood Se and high MeHg concentrations. A study of Japanese pregnant women with greater Hg and Se exposures than reported in previous research found no associations between Hg and Se concentrations in maternal and cord blood and neurodevelopmental delay in children between the ages of 0.5 and 4 years (Kobayashi et al., 2022). Earlier work from this author investigating effects of maternal mercury status during pregnancy on infant birth size and impacts of Se reported no significant associations between maternal blood Se and birth size (Kobayashi et al., 2019).

Al-Saleh et al. (2019) observed no protective effect of high maternal Se concentrations against MeHg on neurodevelopmental delay at 3–12 months of age in a study of Saudi Arabian infants. This study examined the Se:MeHg ratios in maternal blood, which were all greater than 1 and considerably higher than MeHg:Se ratios. However, in this investigation it was difficult to assess if Se had a protective effect on infant neurodevelopment, because all mothers had high Se concentrations. Authors who investigated the association between prenatal mercury exposures and child neurodevelopment in a moderate fish-eating population while correcting for Se exposure found similar null results with no differences observed when controlling for maternal Se concentrations (Golding et al., 2017; Oken et al., 2016; Tatsuta et al., 2017). Similarly, Amoros et al. (2018a) found that controlling for MeHg exposure did not affect the association between maternal Se concentrations and child development. Additionally, in Inuit and Faroe Island populations that regularly consume fish and sea mammals, there was no evidence of an association between cord blood Se and MeHg concentrations and neurodevelopmental scores (Choi et al., 2008; Saint-Amour et al., 2006).

It is challenging to reach a conclusion on the interaction of Se with MeHg and its potential role in modifying the effect on child neurodevelopment. Whilst the lack of association has been demonstrated in many of the reviewed studies, low cord Se and high MeHg concentrations were found to result in poorer neurodevelopment in infants (Castriotta et al., 2020). Selenium concentrations were mostly measured in maternal blood, erythrocytes, and cord blood; whereas prenatal serum Se or information on specific selenoprotein activities interactions with MeHg were not available. Since Se and MeHg are measured at different stages during pregnancy and in different biomarkers such as maternal blood, erythrocytes, cord blood, or child hair, there is heterogeneity between studies making it difficult to draw conclusions. Furthermore, few studies have investigated the interaction between maternal Se and MeHg on infant neurodevelopment in populations with high fish consumption and high Se and MeHg co-exposures.

3. Conclusion

Although it is clear that Se plays several vital roles in pregnancy and child neurodevelopment, it is evident that globally, women do not have a sufficient Se status during pregnancy. The range between Se deficiency and toxicity is narrow and the Se concentrations during pregnancy that are beneficial or harmful for neurodevelopment have not yet been determined. Further research is needed, in particular in high-fish eating populations to determine the optimal maternal Se concentration range for neurodevelopment and to evaluate the potential role of Se in modulating the effects of MeHg exposure on human health.

CRediT authorship contribution statement

Maria Wesolowska: Conceptualization, Methodology, Investigation, Resources, Writing – original draft. **Alison J Yeates:** Writing – review & editing. **Emeir M McSorley**: Writing – review & editing. **Edwin van Wijngaarden:** Writing – review & editing. **Conrad F. Shamlaye:** Writing – review & editing. **Gary J Myers**: Resources, Writing – review & editing. **JJ Strain:** Writing – review & editing. **Maria S Mulhern:** Supervision, Conceptualization, Methodology, Validation, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neuro.2023.08.003.

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