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Variability of plasma/serum and erythrocyte selenium in the first year of life: a systematic review

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Abstract

Selenium is particularly necessary in infants because of their rapid physical growth period in addition to being indispensable for neurodevelopment. Severe deficiency can lead to cardiomyopathy, hypothyroidism and faltering growth. However, selenium can be toxic at high doses. In the pediatric age group, plasma/serum and erythrocyte selenium levels seem to increase with age, except in the first year of life. Understanding the variability in selenium status during this period can help to identify infants at risk of deficiency and develop strategies for controlling and preventing its consequences. This review aimed to identify the extent and characteristics of the variability of selenium status during the first year of life. A search was conducted across five databases to find articles published until July 30, 2024, with no limitations on the language or date of publication. Articles were screened, data were extracted independently by two reviewers, and any disagreement was resolved by a third reviewer. A total of 22 studies comprising 1288 participants were included in this review, 21 of which assessed plasma/serum selenium and 12 assessed erythrocyte selenium. In the first four months of age, serum/plasma selenium decreased, remained stable, or increased depending on feeding, with an increase in supplemented formula-fed infants and breastfed infants of supplemented mothers. Erythrocyte selenium levels showed a declining trend, except in infants fed supplemented formula or breastfed by supplemented mothers. Variability of serum/plasma and erythrocyte selenium levels in the first year was associated with maternal selenium intake/supplementation and the selenium content of the infant's diet.

Key words: plasma selenium, erythrocyte selenium, infant, infant feeding, dietary supplementations.

Abbreviations

ESPGHAN - European Society for Paediatric Gastroenterology, Hepatology and Nutrition

FDA - Food and Drug Agency

NOS - Newcastle-Ottawa Scale

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

T3 - triiodothyronine

T4 - thyroxine

QCRI - Qatar Computing Research Institute

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Introduction

Selenium is an essential micronutrient for the immune system, thyroid metabolism, and oxidative balance. It is particularly necessary in infants because of their rapid physical growth period, in addition to being indispensable for neurodevelopment.[1–3] Severe deficiency can lead to cardiomiopathy, muscular weakness, erythrocyte macrocytosis, hypothyroidism, pseudoalbinism, faltering growth and alopecia.[4,5] However, at high doses, selenium can be toxic, causing adverse effects, or even increase the all-cause mortality.[6] Therefore, it is recommended to treat only deficiency or supplement individuals who have inadequate food ingestion according to recommendations for a specific age.[7]

Selenium status can be assessed by tissue analysis (hair, nails, and blood), residues (urine, stool and expired air) or functional tests (selenoproteins activities). Plasma or serum selenium is the most commonly used biomarker for evaluating variations in a short period of time.[8] Erythrocyte selenium is a marker for detecting chronic deficiency, as it reflects selenium ingestion within 120 days, when hemocatheresis usually occurs.[9]

In the pediatric age group, plasma/serum selenium and erythrocyte selenium seem to increase with age,[10–12] except in the first year of life. In a cohort of 166 healthy German children younger than one year, Muntau et al. observed a decrease in serum selenium concentrations from birth to 4 months of age, followed by an increase in subsequent age groups until adulthood.[10] In another sample of newborns and infants, there was also a decrease in plasma and erythrocyte selenium in healthy infants younger than one year of age.[13]

Newborns store selenium in proportion to their birth weight and gestational age,[14–16] which is used as they grow and is gradually replaced by food.[17] Preterm and small-for-gestational-age neonates are born with a low selenium body content and are at greater risk of developing deficiency; therefore, they are candidates for supplementation.[16] There are reports of selenium deficiency in infants under six months of age receiving parenteral nutrition without selenium supplementation, which evolved with growth retardation and alopecia, and reversible pseudoalbinism with supplementation.[5] Selenium deficiency has also been linked to various diseases, including retinopathy of prematurity, pulmonary bronchodysplasia, necrotizing enterocolitis, and other pulmonary diseases.[17]

In pregnancy, higher selenium intake is associated with a lower incidence of preterm birth,[18] and low serum selenium concentrations are associated with gestational diabetes

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mellitus[19] and preeclampsia.[20] However, selenium supplementation doesn't appear to improve maternal, fetal, or neonatal outcomes.[21] In addition, children of mothers deficient in selenium during pregnancy are at greater risk of developing infections, neurodevelopmental delays, attention deficit hyperactivity disorder and autism spectrum disorder.[22,23]

Understanding the variability of selenium status during the first year of life can help identify infants at risk of deficiency and develop strategies for controlling and preventing its consequences. Therefore, the aim of this study was to identify the extension and characteristics of this variability.

Methods

A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[24] as a reporting guideline. The review protocol was registered at the PROSPERO registry (CRD42023456203).

Search strategy

A search was conducted across 5 databases (Embase, PubMed, Scopus, Lilacs, and Scielo) using the key search terms 'selenium' AND 'infant' to find articles published until July 30, 2024 in peer-reviewed journals (specific terms included in the search are available in Table S1- Supplementary Material). A manual search was conducted in the bibliography of the selected articles. There were no limitations on language or date of publication.

Eligibility criteria and study selection

A PICOS sequence (Table 1) was used to identify relevant studies. The eligibility screening of titles and abstracts was carried out by 2 independent researchers (C.B.A and T.T.S.) using Rayyan QCRI® (Qatar Computing Research Institute, Qatar) software. A third reviewer (L.H.P.) was consulted when disagreements happened in this phase. Bibliographic references of included studies were also checked.

Reviews, letter to the editor, case reports, cohorts of unhealthy children, premature or children older than 1-year-old, studies that didn't answered the research question and with uncompleted data were excluded. Since breastfeeding is the gold standard [25,26] and standard formula is its first alternative, both breastfed and standard formula-fed infants were included

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in the study. Considering that the aim of the study was not to compare different formulas, other formula-fed infants were excluded if they were younger than 6 months. Specifically, soy formula-fed infants were also excluded due to the potential risk to child development and thyroid function associated with the high content of isoflavones, as well as the lack of consensus regarding their use at this age."[27–29].

Studies were included when conducted on healthy full-term birth infants younger than 1-year-old who had blood samples of plasma/serum or erythrocyte selenium collected at different ages (specific age or no more than three months of age range), and whose values were described according to age.

Data extraction and synthesis

Data and characteristics of studies and populations, feeding (breastfeeding or infant formula), laboratorial analysis methods, blood samples (plasma/serum and erythrocyte selenium) and methodological limitations were extracted independently by two authors (C.B.A. and T.T.S) and tabulated on Microsoft Office Excel®. Plasma and erythrocyte selenium in μmol/L were converted to μg/L (x 78.74) for comparison. The data was synthesized in two tables and five figures. In Figures 4 and 5, descriptive statistical analyses were conducted, with the mean concentration over time aggregated by study, depicted through extraction graphs, utilizing Stata MP 14.0 (Stata Corporation, College Station, TX).

Quality assessment

Clinical trials and observational studies, including cohort, cross-sectional and case-control, were assessed using a modified version of the Newcastle-Ottawa Scale (NOS)[30–32] (Table S2 - Supplementary Material). Since our review's focus did not involve evaluating quality of intervention in clinical trial studies, we abstained from conducting a risk of bias evaluation for the clinical trials included in the present review. Therefore, the same quality assessment NOS criteria for cohort studies was employed in the clinical trials.

Results

The initial search resulted in 6148 articles, of which 2092 were duplicated. The exclusion of articles based on titles and abstracts resulted in 96 articles for full text screening. Despite attempts to contact the authors, 5 full reports could not be retrieved, resulting in 91

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articles to the next step of screening. A total of 23 studies met the inclusion criteria. An additional article was detected in manual search, resulting in a total of 24 articles in this review (Figure 1). Three articles comprised the same population and had complementary information, therefore they were combined and considered as a single study in the subsequent analysis, resulting in a total of 22 studies.

Study characteristics

Studies included were published between 1985 and 2019. Most of them were carried out in European countries (n=10) and comprised cohorts or clinical trials (n=16). Biomarkers of selenium status assessed in papers were plasma/serum selenium (n=21), and erythrocyte selenium (n=12) which are illustrated in the Venn diagram (Figure 2).

Sixteen studies (72%) evaluated children younger than 6-month-old and six studies (27%) evaluated children up to 1-year-old. Fifteen studies (68%) assessed feeding: breastfeeding versus infant formula (n=10), breastfeeding (n=3) or infant formula alone (n=2). Six studies used infant formula supplemented with selenium. Three studies supplemented lactating mothers with selenium and evaluated selenium in breastmilk, selenium ingestion and biomarkers in infants, and (two of them) plasma/serum selenium in mothers. Characteristics of studies and biomarkers of selenium status according to age and feeding are described in Table 2 and Table 3 respectively. The results are structured into serum/plasma and erythrocyte selenium. Serum/plasma selenium comprised the following subtopics: no feeding assessment, serum/plasma selenium concentration in breastfed infants, and formula-fed infants. The concentration of selenium in breast milk has been included as a specific topic due to its potential variability based on maternal selenium status and its potential impact on the selenium status of the breastfed infant. The main findings are summarized in Figure 3. Serum/plasma selenium (no feeding assessment)

Of the 21 studies that evaluated serum/plasma selenium, 7 did not evaluate infant feeding, with a total of 543 participants, representing 32% of the population included in the review. Figure 4 shows the mean plasma/serum selenium concentrations of the 5 studies that had at least 1 month between blood samples. In two European studies, concentrations decreased during the first 4 months, and then increased.[10,42] In the Indonesian study,[55] there was a slight increase from 6 to 12 months. In the Finnish study,[35] concentrations decreased from 1 month to 11 months, and in the Italian study,[49] selenium concentrations remained stable at 1 month. In studies with a larger sample size (454 participants in total, or 84% of the

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population in the trials that did not evaluate feeding), selenium concentrations decreased during the first 4 months and increased up to 1 year.[10,42,49,55]

Serum/plasma selenium in breastfed infants

Thirteen studies with a total of 469 participants evaluated serum/plasma selenium concentrations in breastfed infants, as shown in Figure 5A. In 3 of these studies, the mothers were supplemented with selenium (sodium selenite, selenium-fortified yeast or selenomethionine).[34,39,46]

In breastfed infants of unsupplemented mothers, selenium concentrations remained stable or increased in most studies.[33,36–38,41,44,46,48,51,52] In two studies (one American and one Venezuelan), selenium decreased during the first 2 months.[39,50] In the American study,[39] selenium concentrations remained stable for up to 3 months, whereas in the Venezuelan study,[50] selenium concentrations increased from 2 to 4 months. The overlap of the mean concentrations in Kumpulainen's studies[34,36] suggests that they represent a similar sample (therefore, only one study is shown in Figure 5A). In breastfed infants of supplemented mothers, selenium concentrations increased more than those in infants of unsupplemented mothers.[34,39,46]

Serum/plasma selenium concentrations ranged from 27.6 to 140 μg/L in the first days of life – the lowest in the Australian study,[51] and the highest in the Venezuelan study.[50] During the first 4 months, concentrations remained lower in the Polish study,[46] at 30.9 μg/L, and in the Italian study,[52] at 32.3 μg/L; and higher in the Venezuelan study,[50] at 155 μg/L, and the American studies,[37–39] with variations of 80 to 100 μg/L.

Only 4 studies had a sample size of more than 50 children.[34,41,50,51] Three of these studies, with a total of 221 participants, showed stabilization of plasma/serum selenium concentrations during the first 4 months in breastfed infants of unsupplemented mothers.[34,41,50] During this period, selenium concentrations increased in infants of supplemented mothers, in a total of 74 participants.[34,39,46] From 4 months to 1 year, 3 studies, with a total of 134 participants showed increased concentrations in infants of unsupplemented mothers.[33,34,48]

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Selenium concentration in breast milk

Selenium concentration in breast milk was analyzed in 9 studies, as shown in Figure 5B. The selenium concentration in the breast milk of unsupplemented mothers varied between 6 and 27 μg/L,[34,37–39,41,44,46,51] with the lowest value in the Polish study[46] and the highest in one of the American studies.[4] The exception was the Venezuelan study,[50] which showed even higher selenium concentrations, ranging from 31 to 53 μg/L. In mother supplemented with selenium (sodium selenite, selenium-fortified yeast or selenomethionine), the selenium content of breast milk ranged from 10 to 20 μg/L.[34,39,46]

Selenium concentrations in breast milk were assessed over time in 4 studies.[34,38,39,46] In these four studies, selenium concentration in unsupplemented mothers gradually decreased during the first 6 months. In 3 of these 4 studies, selenium increased in supplemented mothers only in the first 2 months and was maintained or decreased over the following 6 months.[34,39,46]

Serum/plasma selenium in formula-fed infants

Ten studies evaluated infants fed supplemented or unsupplemented infant formula. Figure 5C shows the mean serum/plasma selenium concentrations of formula-fed infants, and Figure 5D shows the mean selenium concentration in infant formula. Again, as observed in breastfed infants, there was an overlap in mean serum/plasma selenium concentrations in the Finnish studies, suggesting a similar sample.[34,36]

In unsupplemented formula-fed infants, serum/plasma selenium concentrations decreased during the first 4 months in 6 studies,[34,36,37,40,41,44] with a total of 120 participants. In supplemented formula-fed infants, evaluated in 5 studies (75 participants), concentrations were maintained or increased.[33,37,39,48,51] The selenium content of unsupplemented infant formula ranged from 2.5 to 13 μg/L and that of supplemented formula from 15 to 34 μg/L.

Serum/plasma selenium concentrations in formula-fed infants ranged from 20.5 to 98 μg/L. The lowest values were observed in the New Zealand study,[40] and the highest in one of the American studies.[37]

In summary, serum/plasma selenium concentrations in formula-fed infants decreased when the selenium content of infant formula was less than 15 μg/L, [34,36,37,39–41,43–45,51] and were maintained or increased when it was 15 μg/L or more.[33,36,37,39,40,51]

Erythrocyte selenium

Twelve studies with a total of 426 participants evaluated erythrocyte selenium concentrations in infants younger than 4 months of age.[35,37–40,44,47,49–53,56] Eight of these twelve studies evaluated feeding (breastfed infants by supplemented and unsupplemented mothers, and supplemented or unsupplemented formula-fed infants). In most studies, erythrocyte selenium concentration remained stable or decreased, regardless of feeding. In four studies, an increase in erythrocyte selenium concentration was observed during the first months,[40,49,50,52] except in the Venezuelan study, where a decrease was observed after 2 weeks.[50]

In studies with samples smaller than 45 infants,[35,37–39,44,47,51,53] erythrocyte selenium decreased during the first 4 months. In the Italian study,[49] in which the sample size was larger (n=129), erythrocyte selenium concentrations were maintained during the first month.[50]

Discussion

In this systematic review, comprising 24 articles (22 studies) and 1288 participants, we analyzed the extent and characteristics of the variability of selenium status during the first year of life, represented by plasma/serum selenium and erythrocyte selenium. Feeding was assessed in 14 of the included studies.

Serum/plasma selenium during the first year

In studies with no feeding assessment, serum/plasma selenium concentrations tended to decrease during the first 4 months of age, followed by an increase in subsequent months. This coincides with the introduction of complementary feeding (between 4 to 6 months of age) recommended by the Committee on Nutrition of the *European Society for Paediatric Gastroenterology, Hepatology and Nutrition* (ESPGHAN).[57]

When formula-fed infants were evaluated in the first 4 months of age, plasma/serum selenium concentrations varied with the quantity of selenium in formulas, showing stabilization or increase when selenium was ≥ 15 μg/L. It is worth noting that since 2005, the *European Society of Gastroenterology, Hepatology and Nutrition* (ESPGHAN) has recommended the fortification of infant formula. However, it was not until 2015, that the

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Food and Drug Agency (FDA) published a recommendation requiring 13 to 46 µg Se/L.[17] Prior to standardization of infant formula fortification, the amount of selenium varied depending on the raw materials used in manufacturing.[58] Therefore, studies assessing infant formula fortification were conducted before the recommendations.

On the other hand, breastfeeding ensured stability of plasma/serum selenium concentrations in infants. Three to six months of maternal supplementation was associated with increased plasma/serum selenium concentrations in infants, with greater increases with the use of seleniomethionine, followed by selenium-fortified yeast and sodium selenite. In contrast, selenium concentrations remained stable in the breastfed infants of unsupplemented mothers. However, there are no currently recommendations for maternal supplementation.

Selenium concentration in breast milk and the effect of selenium supplementation on mother serum selenium concentration

When analyzing the selenium concentration in breast milk, studies showed a gradual decrease during the first 6 months, whereas maternal supplementation promoted an increase in selenium during the first 2 months, after which it remained stable or decreased until 6 months. The literature shows that colostrum has a high selenium content, however, the trend demonstrates variability, showing a decrease as lactation progresses,[14] or an initial increase from colostrum to 3 months followed by a subsequent decrease.[59] Otherwise, serum/plasma selenium remains stable or increases in infants, suggesting that this is a more physiological trend.

Selenium concentrations in mature milk vary widely, from as low as 2.6 µg/L in the Keshan region (recognized as selenium-deficient) in China, to 15 to 22 µg/L in the USA and Japan, and as high as 49 to 90 µg/L in Venezuela.[14,46] In the included studies, the selenium content of breast milk varied from 5 to 24 µg/L in unsupplemented mothers, and from 10 to 20 µg/L in supplemented mothers. Accordingly, differences in the selenium content of breast milk depend on the geographical region, as does the amount of maternal selenium intake over time and the resulting selenium status.[60]

The importance of maternal selenium intake can be illustrated in the case of Finland, where selenium intake is associated with grain consumption. In 1976, when the population only consumed grains from local producers, a low selenium intake was estimated (mean of 30 µg/day), which resulted in a decrease in the mean selenium concentration in breast milk from 10.7 to 5.8 µg/L in the first 3 months. In 1980, with the importation of grains from the USA,

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selenium consumption increased to 50 µg/day, resulting in a smaller decrease in the selenium content of breast milk (from 11.8 to 10 µg/L) within the first 3 months.[61] The following year (1981), an increase in selenium consumption of 75 µg/day was estimated due to the import of new wheat and rye, and the use of fertilisers containing sodium selenite since 1984 [62] could explain both the tendency to increase selenium concentrations in breast milk and serum of supplemented or unsupplemented mothers observed by Kumpulainen et al. in 1985.[34]

Lactation requires 8 to 15 µg of selenium daily to maintain concentrations of 10 to 20 µg/L of selenium in breast milk. The recommendation during lactation is 59 to 70 µg/day (while the recommendation for women is 45 to 55 µg/day) to meet the needs of the infant and mother during this period.[60,63] Supplementation, preferably with selenomethionine and selenium-fortified yeast, which appears to be more effective, should be considered if selenium intake is low. And especially if intake has been low since pregnancy, when selenium requirements may increase by 10 to 23 µg/day,[64] and the recommendation is 49 to 60 µg/day.[65]

In studies that evaluated maternal supplementation, mothers received 100 to 200 µg/day of selenium (higher than recommended) in the form of sodium selenite, selenium-fortified yeast, or selenomethionine. Selenium-fortified yeast and selenomethionine promoted an increase in breast milk selenium concentrations up to 2 months, followed by maintenance or decline in subsequent months,[34,39,46] whereas sodium selenite would maintain selenium concentrations at 100 µg and promote an increase of up to 4 months at 200 µg.[34,46] A gradual decline over the months would be expected in mothers with adequate or elevated serum selenium concentrations.

Two of the included studies evaluated maternal serum selenium in supplemented mothers.[34,46] Maternal selenium supplementation resulted in an increase in serum selenium concentrations during the first 4 to 6 months, followed by stabilization. From a mean baseline status of 55 µg/L, the increase ranged from 35 to 50 µg/L when supplemented with sodium selenite and from 50 to 85 µg/L with selenium-fortified yeast in the first few months.[34,46]

Erythrocyte selenium

Erythrocyte selenium decreased over time in most studies (9 of 12 studies), but because it is a long-term marker and the studies evaluated children up to 4 months of age, it

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would be necessary to know the maternal selenium status during pregnancy to predict the behavior of this marker during this period.

Maternal selenium status during pregnancy plays an important role, as there is a high demand for selenium due to increased thyroid hormone synthesis (thyroxine and triiodothyronine), which is essential for fetal and neonatal growth and brain development. Within 4-6 weeks after delivery, maternal serum thyroxine (T4) and triiodothyronine (T3) levels return to pre-gestational levels.[66,67] After birth, thyroid hormone synthesis in newborns is stimulated by placental abruption and thermal environmental changes. At 48 hours, T4 levels reach a peak that takes several weeks to normalise, while T3 production increases fourfold after birth. T4 levels do not fully inhibit TSH secretion, maintaining rising T4 and T3 levels until 1 to 2 months after birth, when the hypothalamic-pituitary-thyroid axis matures.[67] During this period, there may be a consequent high requirement for selenium, as selenium is essential for key enzymes that catalyse the activation of thyroid hormone to active T3.[68]

In addition, most studies evaluating selenium concentration were not adjusted per erythrocyte mass and, considering that haemoglobin decreases in the first few months of life,[69] the decrease in erythrocyte selenium may reflect this physiological state rather than a decrease in selenium stores themselves.

Study limitations

The studies analyzed in this review were conducted in different geographical regions with different soil concentrations and selenium consumption patterns, which makes it difficult to interpret and compare the results. Furthermore, the lack of information on maternal selenium status since pregnancy hinders the ability to predict its influence on the variability of long-term markers. This review did not use exclusion criteria for methodological quality due to the heterogeneity of the studies. Additionally, differences in control group selection criteria, which were not consistently reported, as well as differences in laboratory analysis methods and follow-up periods affected comparisons between groups.

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Conclusion

It cannot be asserted that selenium levels in serum/plasma and erythrocytes increase with age in infants under one year of age, as has been observed in older children.[12] As expected, the studies analyzed in this review indicate that the variability of these selenium biomarkers in the first year is associated with maternal selenium intake/supplementation and the selenium content of the infant's diet.

Serum/plasma selenium concentrations are generally maintained or even increased during the first few months of life in breastfed infants. These concentrations are associated with selenium intake and, in children younger than 1-year-old, with the selenium content of breast milk or infant formula until the introduction of complementary feeding. Consequently, it cannot be deduced from the available studies that there is a physiological decrease in selenium concentrations during this timeframe. Studies show a declining trend in erythrocyte selenium, except in infants fed supplemented formula or breastfed by supplemented mothers.

In addition, a more pronounced decrease in selenium concentration in breast milk may be associated with inadequate maternal intake. Therefore, maternal intake of selenium as well as other micronutrients, should be assessed and, if necessary, adjusted for exclusively breastfed infants. Maternal supplementation should be considered in cases of micronutrient depletion when low intake occurs over a prolonged period of time. Compared with breastfed infants, exclusively formula-fed infants appear to be at lower risk of selenium depletion as a result of adjustments made to the selenium content of infant formulae over the past few decades.

Given the lack of consensus on whether serum or plasma selenium concentrations decrease physiologically during the first year of life, and whether the decrease is associated with poor outcomes, population-based studies are needed in geographical regions with low and high soil selenium levels. These studies should assess biochemical selenium markers in children and their mothers, and selenium concentrations in the breast milk of healthy, exclusively breastfed children under six months. In the absence of such studies, supplementation should be considered in cases based on thorough clinical and dietary assessment.

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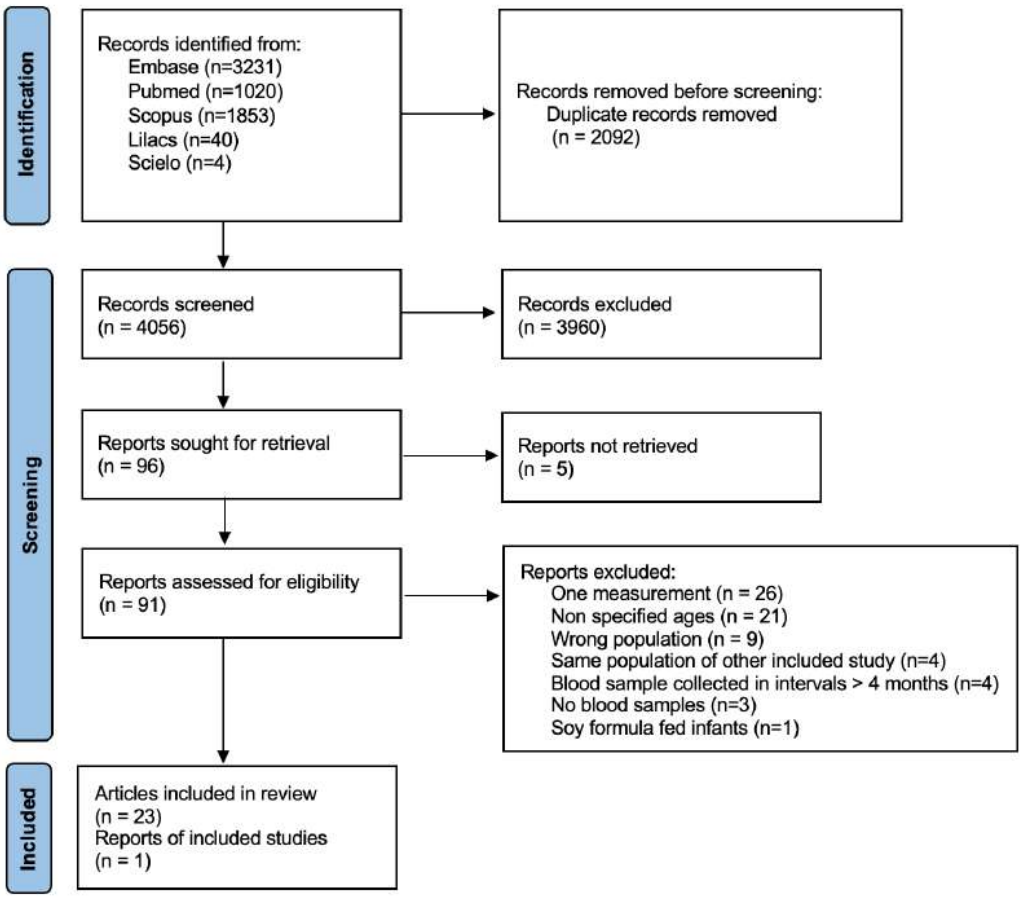

Figure 1 – Flow diagram of selected articles

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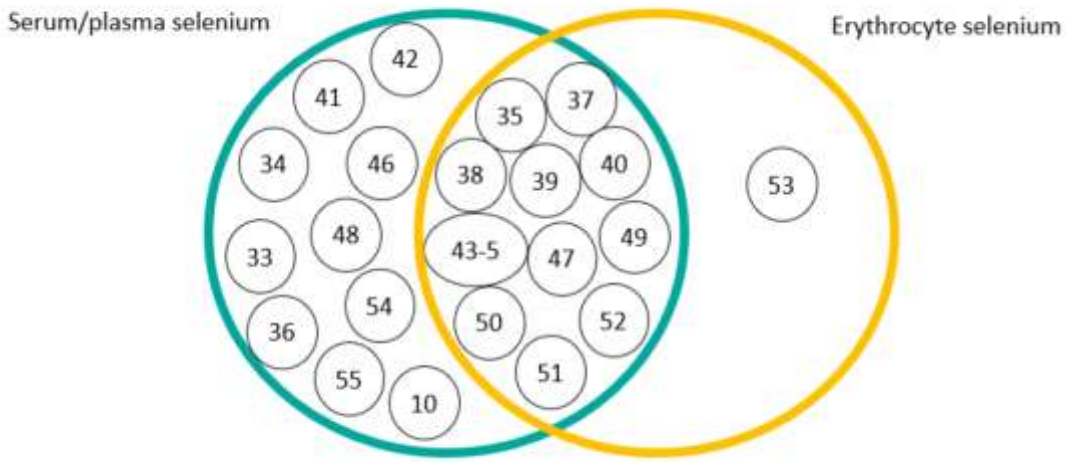

Figure 2 – Venn diagram illustrating articles that assessed serum/plasma and erythrocyte selenium

Circles with numbers inside represent referenced articles.

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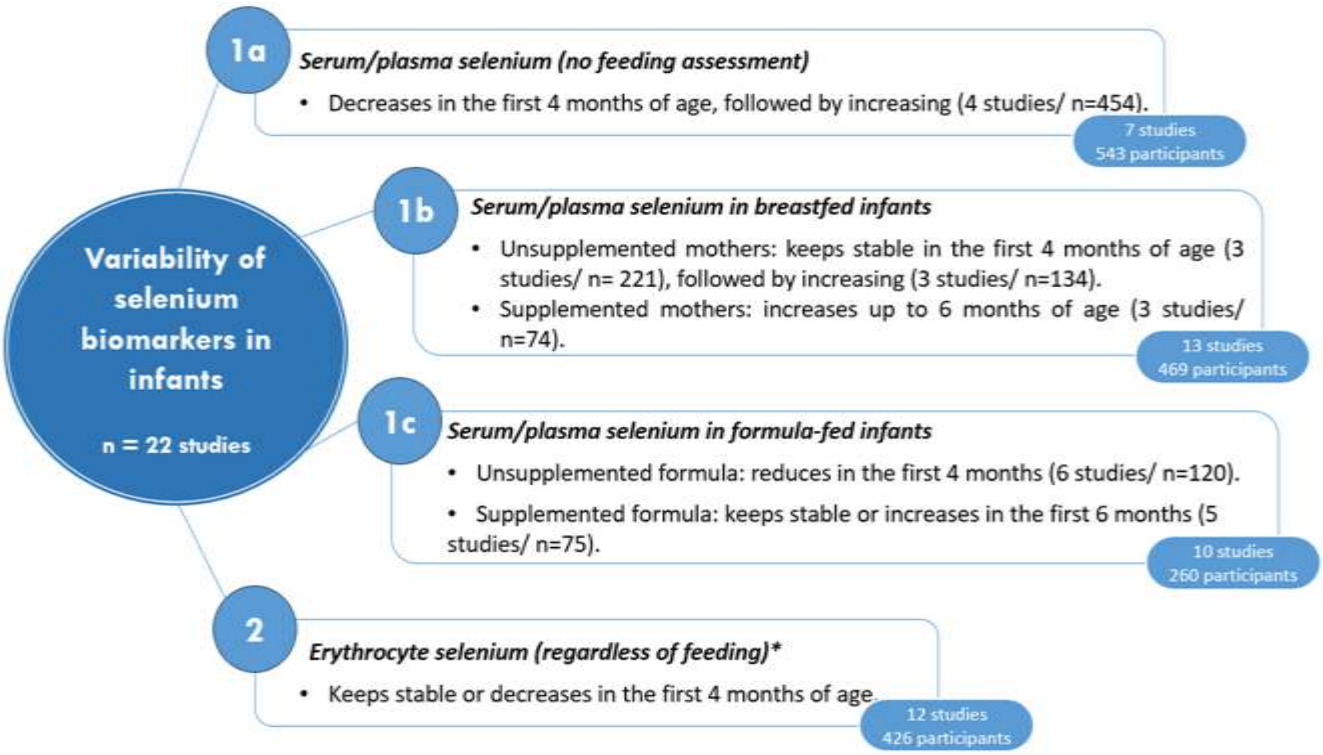

Figure 3 – Main findings of the analyzed studies

*Erythrocyte selenium probably not affected by feeding during the first 4 months of age.

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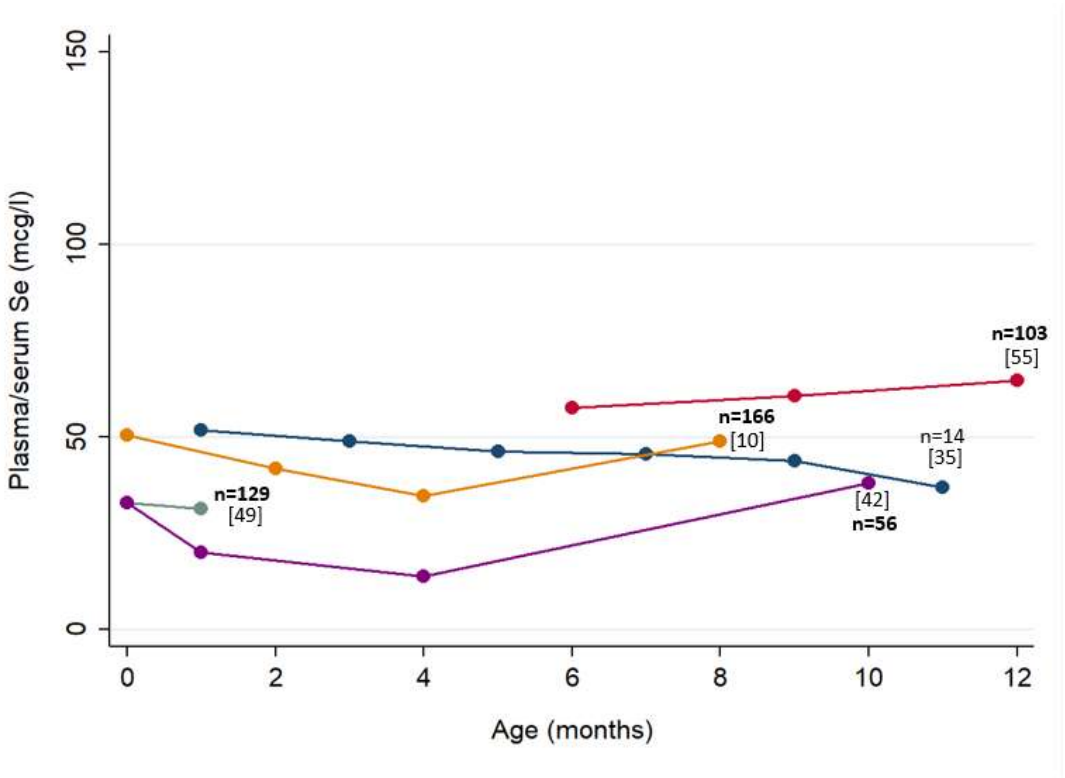

Figure 4 – Mean plasma/serum selenium concentration according to age of studies that did not evaluate infant feeding

The lines represent the mean plasma/serum selenium concentration of a specific study. Study reference numbers in brackets at the end of the line. Sample sizes > 50 subjects in bold type. Se: selenium.

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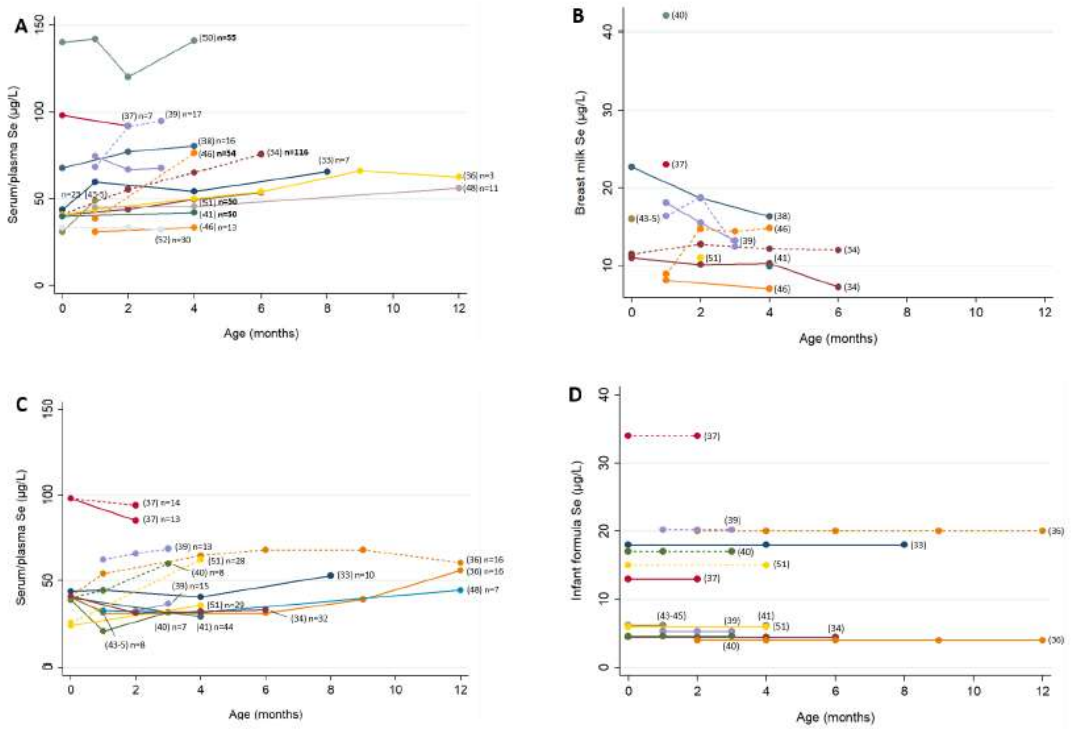

Figure 5 – A: Mean serum/plasma selenium concentration of breastfed infants according to age; B: Mean breast milk selenium variation according to infant age; C: Mean serum/plasma selenium concentration in formula-fed infants according to age; D: Mean infant formula selenium concentration. Study reference numbers in parenthesis at the end of the line. Continuous lines represent the mean serum/plasma selenium concentrations of breastfed infants from not supplemented mothers or not supplemented infant formulas. Short-dash lines represent mean concentrations of infants from supplemented mothers or fortified infant formula; or mean selenium concentration from supplemented mothers or supplemented formula. Studies are differentiated by colors. Se: selenium.

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Table 1. PICOS criteria for inclusion and exclusion of studies

Parameter	Inclusion criterion	Exclusion criterion
Population	Populations of healthy full-term birth infants younger than 1-year-old	Nonhuman studies and studies in diseased or ill children, premature (gestational age <37 weeks) infants or children > 1-year-old
Intervention	No need for intervention. In feeding assessment: breastfeeding as gold standard and infant formula.	Soy formula fed infants were excluded when < 6 months-old, as it is not routinely recommended.
Comparison	No comparison criteria were applicable	No comparison criteria were applicable
Outcome measures	Blood samples of plasma/serum or erythrocyte selenium collected at different ages	Blood samples collected at no specified ages or more than three months of age range
Study design	Cross-sectional, cohort studies, case-control studies, randomized clinical trials	Reviews, letter to the editor, case series and case reports

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Table 2. Methodological characteristics of studies included in the review.

Author/Year/Country	Study design	Feeding	Blood analysis	Laboratory method
Hatano et al. 1985 Japan [33]	Cross-sectional	IF or BF ICF: 17-52 weeks	Plasma (µg/L)	AAS
Kumpulainem et al. 1985 Finland [34]	Randomized clinical trial	BF/ BF+Selenite/ BF+SeY/ IF	Serum (µg/L)	ETAAS
Alfthan et al. 1986 Finland [35]	Cohort study	NI	Serum/plasma and erythrocyte (µg/L)	ETAAS ADF
Kumpulainen et al. 1987 Finland [36]	Randomized clinical trial	BF/ IF/ SIF	Serum (µg/L)	ETAAS
Litov et al. 1989 USA [37]	Randomized clinical trial	BF/ IF/ SIF	Plasma and erythocyte (µg/L)	ETAAS
Johnson et al. 1993 USA [38]	Clinical trial	NI	Plasma and erythocyte (µg/L)	GC-ECD
McGuire et al. 1993	Randomized clinical trial	BF/ BF +SeM/ BF +SeY/	Plasma and	GC-ECD

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USA [39]		IF/ SIF	erythocyte (µg/L)	
Darlow et al. 1995 New Zealand [40]	Randomized clinical trial	IF/ SIF	Plasma (µg/L); Erythrocyte (ηg/g Hb)	GFAAS
Jochum et al. 1995 Germany [41]	Cohort study	BF/ IF	Plasma (µg/L)	HGAAS
Rossipal et al. 1995 Austria [42]	Cross-sectional	IF	Serum (µg/L)	HGAAS
Daniels et al. 1996-97-98 Australia [43–45]	Randomized clinical trial	BF/ IF	Plasma (µg/L); Erythrocyte (ηg/g Hb)	ETAAS GFAAS
Trafikowska et al. 1998 Poland [46]	Clinical trial	BF/ BF +Selenito/ BF +SeY	Plasma (µg/L)	Fluorometric method
Daniels et al. 2000 Australia [47]	Cross-sectional	NI	Plasma (µg/L); Erythrocyte (ηg/g Hb)	ETAAS GFAAS
Sievers et al. 2001	Cohort study	BF/ IF	Plasma (µg/L)	ICP-MS

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Germany [48]		ICF: 4-6 months		
Muntau et al. 2002 Germany [10]	Cross-sectional	NI ICF: 4 months	Serum (μg/L)	ETAAS
Strambi et al. 2004 Italy [49]	Cohort study	NI	Plasma and erythrocyte (μg/L)	GFAAS
Loui et al. 2008 Venezuela [50]	Case-control study	BF	Serum (μg/L); Erythrocyte (μg/g Hb)	INAA ICP-MS
Daniels et al. 2008 Australia [51]	Randomized clinical trial	BF/ IF/ SIF	Plasma (μg/L); Erythrocyte (ηg/g Hb)	GFAAS
Nassi et al. 2009 Italy [52]	Case-control study	BF	Plasma (μg/L); Erythrocyte (ηg/g)	GFAAS
Sakamoto et al. 2012 Japan [53]	Cohort study	BF	Erythrocyte (ηg/g)	ICP-MS
Tsuzuki et al. 2013	Cohort study	NI	Serum (μg/L)	NI

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Japan [54]				
Diana et al. 2019				
Indonesia [55]	Cross-sectional	NI	Serum (μg/L)	ICP-MS

IF: Infant formula; BF: breastfeeding; ICF: introduction of complementary feeding; AAS: atomic absorption spectrometry; SeY: selenium enriched yeast; ETAAS: electrothermal atomic absorption spectrometry; NI: not informed; ADF: acid digestion fluorimetry; SIF: supplemented infant formula; GC-ECD: gas chromatography-electron capture detector; SeM: selenomethionine; GFAAS: graphite furnace atomic absorption spectrometry; HGAAS: hydride generation atomic absorption spectrometry; ICP-MS: inductively coupled plasma mass spectrometry; INAA: instrumental neutron activation analysiss.

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Table 3 – Biomarkers of selenium according to age group and feeding

Author/ Year/ Country	Time of blood collection (sample size)	Feeding (Se content in µg/L)	Mean (SD), median [IQR]	
			Serum/ Plasma (µg/L)	Erythrocyte (µg/L)[†]
Hatano, 1985/ Japan [(33)]	UCB (n=10)		43,8 (6,7)	
	1-5 weeks (n=25)	BF (20) IF (18)	59,8 (10)[a] 44,3 (7,6)[a]	
	6-16 weeks (n=27)	BF (20) IF (18)	54,2 (8)[b] 40,3 (11,6)[b]	
	17-52 weeks (n=21)	BF (20) IF (18)	65,5 (13,7)[c] 52,9 (7,6)[c]	
Kumpulainen 1985 Finland [(34)]	UCB (n=200/ BF: n=67/ IF: n=32)	BF (11 ± 2) Selenite (11,5) SeY (11,4) IF (2,5 – 6,5)	41 (6)[ab]/ 56 (4)*	
	2 months (n=167)	BF (10,1 ± 0,3)[a] Selenite (11,3 ± 0,5)[ab] SeY (14,2 ± 1)[b] IF (2,5 – 6,5)	44 (1,4)[c]/ 76,8 (2,4)*[i] 51 (1,3)[cd]/ 98,8 (2,6)*[ij] 59,7 (2,1)[d]/ 125,7 (4,9)*[j] 31 (2)[b]	
	4 months (n=140)	BF (10,3 ± 0,6) Selenite (10,8 ± 0,6) SeY (13,5 ± 1,7) IF (2,5 – 6,5)	49,5 (1,5)[e]/ 88,4 (2,3)*[k] 56,5 (1,5)[ef]/ 109,5 (3,7)*[kl] 73,8 (3,5)[f]/ 141,6 (6,3)*[l] 32 (4)	
	6 months (n=116)	BF (7,2 ± 2,5) Selenite (10,5 ±	53,6 (6)[ag]/ 93,8 (2,4)*[m]	

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		0,5) SeY (13,5 ± 1,2) IF (2,5 – 6,5)	67 (2)[gh]/ 115 (3,7)*[mn] 84,5 (3,5)[h]/ 141,4 (5,4)*[n] 33 (3)	
Alfthan 1986 Finland [35]	1 month	NI	51,7	111 (14)
	3 months		49	
	5 months		46,2	
	7 months		45,6	
	9 months		43,9	82 (8,3)
	11 months (n=14)		36,8	
Kumpulainen 1987 Finland [36]	UCB (n=200)		41 (8)[b]	
	2 months (BF n=58/ FI n=16/ FIS n=16)	BF (10) IF (3 – 5) SIF (20)	44 (1) 31 (5) 54 (9)[b]	
	4 months (BF n=51/ FI n=16/ FIS n=16)	BF (10) IF (3 – 5) SIF (20)	50 (1,5) 31 (5) 64,7 (3)	
	6 months (BF n=41/ FI n=16/ FIS n=16)	BF (8) IF (3 – 5) SIF (20)	54 (2) 31 (5)[a] 68 (12)	
	9 months (BF n=12/ FI n=16/ FIS n=16)	BF IF (3 – 5) SIF (20)	66 (3) 39 (3) 68 (12)	
	12 months (BF n=3/ FI n=16/ FIS n=16)	BF IF (3 – 5) SIF (20)	62,6 (1) 56 (2)[a] 60,5 (2)	
Litov 1989 USA [37]	At birth (PS BF n=12 /IF n= 15/ SIF n=14// Ery BF n=9 /IF n= 14/ SIF n=14)	BF (23±4) IF (13) SIF (34)	98 (14) 98 (28) 98 (28)	290 (68) 300 (67) 300 (87)
	2 months (PS BF n= 7/IF n=13 /	BF (23±4) IF (13)	92 (12) 85 (18)	250 (44) 240 (50)

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	SIF n=16; Ery BF n=6 /IF n= 12/ SIF n=13)	SIF (34)	94 (16)	260 (54)
Johnson 1993 USA [38]	2 weeks	BF (22,7±2)[a]	67,7 (3,9)	260,6 (18)[b]
	8 weeks	BF (18,7±1,2)	77,2 (3,15)	260,6 (17)
	16 weeks (n=16)	BF (16,3±0,8)[a]	80,3 (3,9)	210,2 (15,6)[b]
McGuire 1993 USA [39]	4 weeks (BM n=14/ SeM n=8/ SeY n=9/ IF n=15/ SIF n=13)	BF (18,1)	74,5 (5)[a]	197,5 (16)[de]
		SeM (16,1)	71,6 (7,4)[l]	253 (20)
		SeY (16,7)	65,2 (7,1)[m]	197 (20)
		IF (5,3)	32,5 (4,5)[ab]	213 (16)[f]
		SIF (20,2)	62,3 (4,5)[bc]	245 (16)[dg]
	8 weeks	BF (15,5)	66,8 (4,2)	182(16)
		SeM (19,9)	99,8 (7,1)[l]	253 (16)
		SeY (17,7)	83,5 (6,3)[m]	197 (16)
		IF (5,3)	32,2 (4,2)	166 (8)
		SIF (20,2)	65,8 (4,7)	197,5 (14)
	12 weeks	BF (13,2)	67,6 (4,2)	150 (8)[e]
		SeM (10,5)	99,8 (7,1)	253 (16)
		SeY (14,3)	89,8 (4,7)	213 (16)
		IF (5,3)	36,4 (3,9)	142 (12)[f]
		SIF (20,2)	68,6 (4,5)[c]	134 (12)[g]
Darlow 1995 New Zealand [40]	UCB (IF n=7/ SIF n=8)	IF (4,6)	38,7 (2,4)[a]	395 (47)
		SIF (17)	40,2 (3,2)	411 (47)
	1 month (IF n=15/ SIF n=20)	IF (4,6)	20,5 (0,8)[ab]	316 (24)[d]
		SIF (17)	44,2 (1,6)[c]	411 (24)[e]
	3 months (IF n=11/ SIF n=16)	IF (4,6)	31,6 (4)[b]	221 (24)[d]
		SIF (17)	60 (4,7)[c]	498 (16)[e]
Jochum 1995 Germany [41]	At birth (n=128)		40 (9)[a]	
	4 months (BF n=50; IF n=44)	BF (9,9 ± 0,5)	42 (8)	
		IF (6,1 ± 1,9)	29 (9)[a]	
Rossipal 1995	UCB (n=7)	NI	33 (16)	
	1 months (n=56)		20 (9)	

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Austria [42]	2 a 6 months		13,75	
	7 a 12 months		38	
Daniels 1996, 1997, 1998 Australia [43–45]	0-5 d (PS: n=46/Ery: n=43) (BF n=23/ IF n=8)	BF (16)	33 (2)	532(22)
		IF (2,9-9,5)	31 (2,5)[a]	537 (36)
			40 (4)[b]	529 (32)
	6 weeks (n=31) (BF n=23/ IF n=8)		45 (2,4)	487(27)
		BF (16)	49 (3)[ac]	504 (31)
		IF (2,9-9,5)	32 (3,8)[bc]	435 (54)
Trafikowska 1998 Poland [46]	3-5 weeks	BF (8,1 ± 2,6)	30,9 (10,7)/ 50,4-54,9*	
		Selenite (8,9 ± 2,8)[a]	39,5 (15,4)[c]/ 53,2 (14)*[k]	
		SeY (8,9 ± 2,8)[b]	37,7 (17,8)[d]/ 53,2 (14)*[l]	
	2 months ± 1 week	BF (8,1 ± 2,6)	50,4-54,9*	
		Selenite (13,6 ± 5,3)[a]	87,1 (21)*[k]	
		SeY (15,9 ± 2,8)[b]	101,2 (34)*[l]	
	3 months ± 1 week	BF (8,1 ± 2,6)	50,4-54,9*	
		Selenite (13,8 ± 3,5)	105,5 (21)*	
		SeY (15 ± 4,1)	127,2 (21)*	
	4 months ± 1 week	BF (7 ± 2,5)	33,4 (11)[e]/ 50,4-54,9*	
		Selenite (15,3 ± 3,4)	65,9 (18,4)[ce]/ 102,7 (15)*	
		SeY (14,4 ± 6,4)	86,8 (29,5)[de]/ 117,5 (29)*	
Daniels 2000 Australia [47]	UCB	NI	50 (11)[a]	597 (151)
	5d (PS n=45/ Ery n=39)		32 (10)[a]	487 (27)
Sievers 2001	1 month (n=10)	BF	45,2 [32,1-65,9]	

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Germany [48]		IF	32,4 [24-50]	
	4 months (n=13)	BF	45,6 [27,1-65,1]	
		IF	31,5 [24-47]	
	12 months (n=11)	BF	56,2 [35,4-72,6]	
		IF	44,5 [41-59]	
Muntau 2002 Germany [10]	< 1 month	NI	50,5 [15,8-79][a]	
	1 a 2 months		41,9 [14,2-101]	
	2 a 4 months		34,7 [5,5-65,6][ab]	
	4 a 12 months (n=166)		49 [5,5-100][b]	
Strambi 2004 Italy [49]	1 week	NI	32,9 (19,3)	73,6 (22,6)
	2 weeks		35,3 (17)	77,2 (24,1)
	3 weeks		38,8 (24,8)	71,5 (18)
	4 weeks (n=129)		31,3 (14)	83,8 (19,6)
Loui 2008 Venezuela [50]	1-3d	BF (42 ± 10,8)	140 (25)	2300 (900)
	2 weeks		155 (26)	3200 (1000)
	4 weeks		142 (40)	3000 (1400)
	8 weeks		120 (30)	2100 (700)
	16 weeks (n=55)		141 (39)	1200 (500)
Daniels 2008 Australia [51]	3 – 5d (PS BF n=50/ IF n=29/ SIF n=28// Ery BF n=44/ IF n=31/SIF n=28)	BF (11) IF (6) SIF (15)	27,6[a] 23,7[b] 25,3[c]	608(5)[g] 629(49)[h] 513,5(34)[i]
	16 weeks (PS BF n=50/ IF n=29/ SIF n=28// Ery BF n=44/ IF n=31/SIF n=28)	BF (11) IF (6) SIF (15)	47,4(2,4)[ade] 35,5(2,4)[bdf] 62,4(3,9)[cef]	371(1,6)[g] 332(18)[hj] 395(20)[ij]
Nassi 2009 Italy [52]	2d	BF	33,3 (3,6)	557 (69)
	50d		33,4 (3,6)	655 (58)

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	100d (n=30)		32,3 (3,9)	653 (51)
Sakamoto 2012 Japan [53]	UCB (n=16)	NI		280 [259-306][a]
	3 months (n=16)			207 [194-226][a]
Tsuzuki 2013 Japan [54]	UCB (n=30)	NI	59,4 (10)	
	5d (n=30)		52,0 (8,9)	
Diana 2019 Indonesia [55]	6 months (n=103)	NI	57,5 (1,97)	
	9 months (n=103)		60,6 (1,96)	
	12 months (n=103)		64,6 (1,97)	

Se: selenium; SD: standard deviation; IQR: interquartile range; UCB: umbilical cord blood; BF: breastfeeding; IF: infant formula; SeY: breastfeeding from mothers supplemented with selenium enriched yeast; NI: not informed; SIF: supplemented infant formula; SeM: breastfeeding from mothers supplemented with selenomethionine; d: day(s); PS: plasma/serum; Ery: erythrocyte. *Mother serum selenium concentratrion. Statistical diferences ($p<0,05$) are indicated with letters. † Except for the studies of Darlow et al. 1995 (ηg/g Hb), Daniels et al. 1996, 1997, 1998, 2000, 2008 (ηg/g Hb), Nassi et al. 2009 (ηg/g Hb), Loui et al. 2008 (µg/g Hb).

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