Micronutrients during pregnancy and child psychomotor development: opposite effects of Zinc and Selenium

Kinga Polanska[1], Wojciech Hanke[1], Anna Krol[1], Jolanta Gromadzinska[2], Renata Kuras[2], Beata Janasik[2], Wojciech Wasowicz[2], Fiorino Mirabella[3], Flavia Chiarotti[3], Gemma Calamandrei[3]

[1]Department of Environmental Epidemiology, Nofer Institute of Occupational Medicine, Lodz, Poland

[2]Department of Biological and Environmental Monitoring, Nofer Institute of Occupational Medicine, Lodz, Poland

[3] Center for Behavioral Sciences and Mental Health, National Institute of Health, Rome, Italy

Correspondence: Kinga Polanska (kinga.polanska@imp.lodz.pl)

Abstract

Studies on the impact of micronutrient levels during different pregnancy periods on child psychomotor functions are limited. The aim of this study was to evaluate the association between maternal plasma concentrations of selected micronutrients, such as: copper (Cu), zinc (Zn), selenium (Se), and child neurodevelopment. The study population consisted of 539 mother-child pairs from Polish Mother and Child Cohort (REPRO_PL). The micronutrient levels were measured in each trimester of pregnancy, at delivery and in the cord blood. Psychomotor development was assessed in children at the age of 1 and 2 years using the Bayley Scales of Infant and Toddler Development. The mean cord plasma Zn, Cu and Se concentrations were 1.1 ± 0.3 mg/l, 0.6 ± 0.3 mg/l and 31.1 ± 8.2 ug/l, respectively. There were no statistically significant associations between Cu levels and any of the analyzed

domains of child development. A positive association was observed between Se level in the 1st trimester of pregnancy and child language and motor skills (β=0.2, p=0.03 and β=0.3, p=0.005, respectively) at one year of age. Motor score among one-year-old children decreased along with increasing Zn levels in the 1st trimester of pregnancy and in the cord blood (β=-12.1, p=0.003 and β=-6.5, p=0.03, respectively). A similar pattern was observed for the association between Zn level in the 1st trimester of pregnancy and language abilities at one year of age (β=-7.4, p=0.05). Prenatal Zn and Se status was associated with lower and higher child psychomotor abilities, respectively, within the first year of life. Further epidemiological and preclinical studies are necessary to confirm the associations between micronutrient levels and child development as well as to elucidate the underlying mechanisms of their effects.

Highlights

- We assessed associations between micronutrient levels in pregnancy and child neurodevelopment.
- There were no associations between Cu levels and any domains of child development.
- A positive association was observed between Se and child language and motor skills.
- A negative association was found between Zn and child language and motor skills

Keywords: zinc, selenium, copper, prenatal period, child neurodevelopment

1. Introduction

Pregnancy is a period of increased metabolic demands mainly due to the changes in a woman's physiology and requirements of a growing fetus. Nutrients and growth factors regulate brain development during fetal and early postnatal life. The developing brain is particularly vulnerable to nutritional insults as the rapid trajectory of several neurologic

processes, including synapse formulation and myelination (Georgieff, 2007; Georgieff and Rao, 2001; Dobbing, 1990; Rao and Georgieff, 2000; Kretchmer et al., 1996; Thompson and Nelson, 2001). Thus, certain nutrients, such as: proteins, essential fatty acids, iron, zinc, copper, iodine, selenium, vitamin A, choline and folate, are especially significant for the developing brain (Nyaradi et al., 2013).

Effects of any nutrient deficiency or its excess on the brain development is a function of its requirement for a nutrient in specific metabolic pathways and structural components (Georgieff, 2007; Georgieff and Rao, 2001; Dobbing, 1990; Rao and Georgieff, 2000; Kretchmer et al., 1996; Thompson and Nelson, 2001). Zinc (Zn) is an essential element with a multitude of biological functions, which plays an important role in brain development and synaptic plasticity (Shah and Sachdev, 2006; Frederickson and Danscher, 1990). In particular, Zn is not only a component of several enzymes but it is found in synaptic vesicles in areas of the brain endowed with high plasticity such as cortex and hippocampal mossy fibers; Zn is also involved in the metabolism of thyroid hormones, hormone transportation, receptor binding as well as in the metabolism of neurotransmitters (Shah and Sachdev, 2006; Frederickson and Danscher, 1990; Nakashima and Dick, 2009; Morley et al., 1980; Golub et al., 1995). Studies have shown an association between prenatal Zn deficiency and infant psychomotor development (Yang et al., 2013; Boroujeni et al., 2009; Benton and ILSI Europe a.i.s.b.l., 2008; Cetin et al., 2010; Leung et al., 2011; Georgieff, 2007). On the other hand, there is growing evidence suggesting that excess of Zn can exert neurotoxic action, lead to cellular damage in vitro (Yang et al., 2013; Zhu et al., 2012) as well as in vivo (Kong et al., 1998) and can be associated with decreased child psychomotor development (Yang et al., 2013; Hamadani et al., 2002).

Copper (Cu) is a crucial cofactor for copper-containing enzymes that function in a number of important processes, including energy production, oxidant defense, extracellular

matrix (ECM) protein crosslinking, immune function, blood cell maturation, neuropeptide and catecholamine synthesis, myocardial contractility, iron mobilization and trafficking (Uriu-Adams et al., 2010; Turski and Thiele, 2009; Gambling et al., 2011). The existing studies indicate that balance between Cu and iron assures proper neurocognitive and neurobehavioral development (Cetin et al., 2010; Gambling et al., 2011; Gambling et al., 2008; Georgieff, 2007; Leung et al., 2011; Uriu-Adams et al., 2010; Beard et al., 2003; Penland and Prohaska, 2004; Gybina and Prohaska, 2006; Beard, 2008; Prohaska and Gybina, 2005).

The well-known biological role of selenium (Se) is mainly associated with selenoproteins, which are involved in the antioxidant defence system and thyroid hormones metabolism (Rayman, 2012; Jablonska et al. 2013; Roman et al., 2014; Holmgren and Lu, 2010). Studies indicate that both low and high levels of Se can have impact on child neurodevelopment (Yang et al., 2013; Skröder et al., 2014). In our previous analysis prenatal Se status was associated positively with child psychomotor abilities within the first two years of life (Polanska et al., 2016a).

On average, for adults, Se intake of 70 μg/day (2014), Cu intake of 1.3 mg/day (2015) and Zn (2014) intake of 7.5 mg/day is recommended by the European Food Safety Authority, with increasing requirements among pregnant and lactating women (European Food Safety Authority). The nationally representative dietary survey data from eight European countries, including Poland, has highlighted that there is a risk of low intakes of essential trace elements in specific population and age groups (Mensink et al., 2013). That analysis has indicated that 1.1% of women in Poland had Cu intakes below the lower reference nutrient intake (LRNI - intake value below which it is unlikely that normal health can be maintained over longer periods) and 13.1% below the estimated average requirement (EAR – the intake adequate for 50% of the population). These estimates for Zn were: 4.6% and 16.6%, respectively. Mean Se

contents in the daily food rations collected from various public canteens and group of students ranged from 20 to 59 μg/day (Jablonska et al., 2013).

The existing studies evaluating influence of Zn, Cu and Se levels on children's development have produced conflicting results, mainly because of the lack of a valid indicator and assessment of these micronutrients. Therefore, the aim of this study was to evaluate the impact of the micronutrients: Cu, Zn, Se, measured in the blood collected in pregnancy and in the cord blood, on psychomotor development of children enrolled in the prospective Polish Mother and Child Cohort study - REPRO_PL (REPRO_PL).

2. Methods

2.1. Study design and population

The analyses were based on the mother-child pairs from the Polish Mother and Child Cohort Study (REPRO_PL cohort) - a multicenter prospective cohort established in 2007 that examines the relationship between environmental (including heavy metals, phthalates, polycyclic aromatic hydrocarbons) as well as lifestyle/psychosocial determinants (including smoking, alcohol consumption, stress, family functioning, BMI, physical activity, microelements and vitamins) and multiple aspects of the development and health of a child (Polanska et al., 2009; Polanska et al., 2011; Polanska et al., 2016b). The detailed description of the cohort methodology has been published previously (Polanska et al., 2009; Polanska et al., 2011). Briefly, the women were invited to participate in the cohort if they fulfilled the following inclusion criteria: up to 12 weeks of single pregnancy, no assisted conception, no pregnancy complications and no chronic diseases.

Based on the study protocol, the women were interviewed once in each trimester of pregnancy to collect and update socio-demographic data, medical and reproductive history as well as information about environmental, lifestyle and occupational exposure. During each

visit and after delivery, biological samples (including saliva, urine, blood, hair and cord blood) were collected.

Child's exposure, health status and neurodevelopment were evaluated at one year of age and the assessment was repeated when the child reached the age of 24 months (Polanska et al., 2011).

The current analysis was restricted to 539 children who have been examined for their neurodevelopment. Among them 303 children had both assessments (at one and two years of age), 198 were examined only at around 12 months of age and 38 only at 24 months of age (Table 2). The following factors were responsible for losses in the follow-up: refusal, child health problems, unknown address or telephone number and unknown reasons (Polanska et al., 2016b).

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

2.2. Micronutrients assessment

Blood samples were collected from each woman during the first (8^{th} - 12^{th} week of pregnancy), second (20^{th} - 24^{th} week of pregnancy), third (30^{th} – 34^{th} week of pregnancy) trimester of pregnancy, at delivery and from the cord, using a venoject system free from trace elements with lithium heparin as an anticoagulant. After centrifugation, the plasma was collected and frozen at −20∘C until the analysis. Plasma Zn and Cu concentrations were analyzed by means of the flame atomic absorption spectrometry (FAAS) (Agarwal and Henkon, 1985). This method had been validated using the reference material (lyophilized human reference serum samples of Seronorm from Nycomed Pharma AS, Oslo, Norway) and through participation in the interlaboratory comparison trials. Measurements of plasma Se concentration were performed using the graphite furnace atomic absorption spectrometry

(GFAAS) on a Unicam Solar 989 QZ apparatus with Zeeman effect background corrector, in accordance with the modified method of Nève et al. (Neve and Molle, 1986; Neve et al., 1987). Accuracy of the method for Se determination was verified using internal quality control of the certified reference material BCR-637 (IRMM, Belgium), where reference value and measured concentration were: 81.0 μg / L (in the range 74-88 μg /L) and 82.5 ± 0.7 μg / L, respectively, and external quality control of the German External Quality Assessment Scheme (G-EQUAS) for analyses in biological materials.

2.3. Child psychomotor assessment

The Bayley Scales of Infant and Toddler Development (Bayley 3rd edition) was used to assess children's neurodevelopment at one and two years of age. Details regarding child psychomotor assessment have been published elsewhere (Polanska et al., 2016a; Polanska et al., 2011).

2.4. Covariates

The following covariates were evaluated: parental age and education; marital status; socio-economic status (SES); child gender; major pregnancy complications which appeared after inclusion into the study; type of delivery; gestational age and birth outcomes; breastfeeding; number of siblings; day care attendance; cigarette smoking and alcohol consumption during pregnancy as well as child environmental tobacco smoke (ETS) exposure within the first two years of live. Details regarding socio-demographic and birth outcome data collection as well as prenatal/postnatal ETS exposure have been described elsewhere (Polanska et al., 2016a; Stragierowicz et al., 2013). In the current analysis, the women whose cotinine level in saliva was equal to or higher than 10 ng/ml were defined as active smokers (SRNT Subcommittee on Biochemical Verification, 2002).

2.5. Statistical analysis

Levels of microelements in each trimester of pregnancy, at delivery and in cord blood and psychomotor developmental scores at 1 and 2 years of age are summarized by means, standard deviation, and minimum and maximum values in the overall group of children.

Correlation between microelement levels and psychomotor developmental scores was examined by the Pearson linear correlation coefficient. The multivariate linear regression was performed to assess the effect of Zn, Cu and Se levels measured during the 1st trimester of pregnancy and in cord blood, on child psychomotor developmental scores at 1 and 2 years of age, and on the developmental score variation between 1 and 2 years of age. Following the study protocol, data on micronutrients was theoretically available for each visit; however, as a result of organizational (i.e., the lack of samples or usage of the samples for other purposes) and financial reasons (in that case randomly selected samples were evaluated), not all the samples were analyzed for micronutrient levels. In particular, the number of samples collected during the second and the third trimester of pregnancy for which micronutrients were available was much lower, thus micronutrient levels measured at these time points were not included in the multivariate analyses. The final multivariate models were performed on 239 subjects at 12 months assessment and 168 subjects at 24 months assessment, for which there were both Zn, Cu and Se in the 1st trimester of pregnancy and in the cord blood, and the confounding variables that were known to affect child's psychomotor development: examiner, mother age, mother education, child gender and smoking status based on the cotinine level. The variance inflation factor (VIF) was computed for any variable in each model to verify the presence of multicollinearity among explanatory variables, that could be excluded in the case of VIF values all lower than 5. Regression coefficients are reported together with their standard errors. STATA software was used for the statistical analyses.

3. Results

3.1. Parental and child characteristics

Parental and child characteristics are summarized in Supplementary materials (Tables S1, S2). A high percentage of the women were married (75%), employed (85%) and had a university degree (63%). Alcohol consumption during pregnancy was indicated by 9% of the women and, based on the cotinine level in saliva, 15% were classified as smokers. About 7% of the children attended day care at one and 23% at two years of age. ETS exposure after birth was noted for 36% of the children.

The mean composite scores for cognitive, language and motor development were on an average or high average level (Table 1). A positive correlation was observed for each subscale of the Bayley test results for one year assessment ($p \leq 0.001$) and between cognitive and language as well as motor and language functions ($p \leq 0.001$) for two-year assessment (Table 3). The correlation was weaker for comparisons performed between one and two years of age.

3.2. Micronutrient concentrations during pregnancy

The micronutrients concentration in the blood collected in each trimester of pregnancy, at delivery and in the cord blood is presented in Table 1. Mean Zn concentration was higher in cord blood (1.1±0.3 mg/l) and in the 1st trimester of pregnancy (0.9±0.3 mg/l) than in the other measurement periods ($p<0.001$). Mean plasma Cu concentration was slightly lower in the 1st trimester of pregnancy (2.0±0.6 mg/l) and remained fairly constant during the two other periods of pregnancy and in the maternal blood collected at delivery (2.4±0.6 mg/l in the 2nd trimester, 2.6±0.5 mg/l in the 3rd trimester and 2.4±0.7 mg/l at delivery). Cu concentration was significantly lower in the cord blood than in pregnancy period (0.6±0.3

mg/l) ($p<0.001$). Mean Se concentrations decreased throughout pregnancy and at delivery (from 48.4±10.5 ug/l in the 1st trimester to 38.4 ±11.8 ug/l at delivery) ($p<0.001$). Correlations between different microelements as well as their concentrations in different time periods are presented in Table 2.

3.3. Association between micronutrient concentrations and child psychomotor development

Table 4 presents the association between maternal micronutrient levels and child neurodevelopment with adjustment for confounders. There were no statistically significant associations between Cu levels in the blood collected during the 1st trimester of pregnancy and in the cord blood and any of the analyzed domains of child development. A positive association was observed between Se level in the 1st trimester of pregnancy and child language and motor skills ($\beta=0.18$, $p=0.03$ and $\beta=0.25$; $p=0.005$, respectively) at one year of age. Data concerning the effect of Se levels on child psychomotor development at the age of two years are in the same direction, although, taking into account power limitations for that associations, it was not statistically significant. Interestingly, motor scores among one-year-old children decreased along with increasing Zn levels in the 1st trimester of pregnancy and in the cord blood ($\beta=-12.07$, $p=0.003$ and $\beta=-6.51$, $p=0.03$, respectively). A similar pattern was observed for the association between Zn level in the 1st trimester of pregnancy and language abilities at one year of age ($\beta=-7.37$, $p=0.05$).

An additional analysis regarding micronutrient levels during pregnancy and the change in psychomotor development scores between 1 and 2 years of age is presented in Table 5. Cu in the 1st trimester of pregnancy appears to positively affect the change in the motor developmental score, even if this effect is not fully statistically significant ($p=0.06$).

4. Discussion

Our prospective cohort study indicated a positive association between Se level in the 1st trimester of pregnancy and child language and motor skills at one year of age. In addition, motor and language scores decreased along with increasing Zn levels and there were no statistically significant associations between Cu levels and any aspects of child development. Micronutrient concentrations are different in pregnant than in non-pregnant women. Plasma Zn concentration begins to decline in early pregnancy and continues to decline until delivery, when it is about 35% below its level in non-pregnant women (Wasowicz et al. 1993, King, 2000; Cetin et al., 2010; Yang et al., 2013). Significant decrease of Zn concentration was also observed in our study (from 0.9 mg/l in the 1st trimester of pregnancy to 0.77 mg/l at delivery). This decline in Zn levels has been attributed to hemodilution and/or different Zn affinity to plasma proteins as the consequence of hormonal changes during pregnancy and it can resulted from active transportation of Zn from the mother to the fetus (Wasowicz et al., 1993, King, 200). The median level of cord plasma Zn (1.05 mg/l) in our study was similar to that reported in Arctic Canada (1.1 mg/l) and higher than that reported in China (0.73 mg/l) (Butler Walker et al., 2006; Yang et al., 2013). In earlier study performed in Poland cord plasma Zn level was 0.8 mg/l (Wasowicz et al., 1993). The other study in Poland (although not covered pregnant women) has indicated the mean intake (analytical data) of Zn of 8.9 mg/day (5.3 mg/day calculated from 24-h diet recalls), which is comparable to the mean Zn intake in Spain (7.6 mg/day) and lower than that in Germany (10.9 mg/day) (Jablonska et al., 2013; Flynn et al., 2009). Similar results have been also obtained for 18 - 60 year-old females in a nationally representative dietary survey data from eight European countries (Mensink et al., 2013).

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

United States (Rayman, 2012). The detailed discussion regarding Se levels observed in our cohort has been published previously (Polanska et al., 2016a). It is worth noting that in Poland plasma Se level was 48 µg/l in the studies performed between 1981 and 1983 and above 30 µg/l in that performed between 1997 and 1999 and between 2007 and 2009 (REPRO_PL study) (Zachara et al., 1986; Jablonska et al., 2013; Wasowicz et al., 2003; Polanska et al., 2016a).

In our study, mean plasma Cu concentration increased throughout the pregnancy period (from 2.0 mg/l in the 1st trimester of pregnancy to 2.4 ml/l in the 2nd and 2.6 mg/l in the 3rd trimester of pregnancy). This is consistent with the results reported in other studies on pregnant women (Pathak 2004). Studies have found that the increase in Cu level during pregnancy is mainly in a bound form due to an increase in the carrier proteins, ceruloplasmin in response to stimulation by maternal estrogens (Pathak et al., 2004; Martín-Lagos et al., 1998; Kalra et al., 1989; Dokumov, 1968). With regard to the mean Cu intake in Poland, based on the female population, it was 1.1 mg/day, which was similar to that observed in France (1.2 mg/day), The Netherlands (1.1 mg/day), the UK (1.1 mg/day) and lower than that reported in Germany (2.2 mg/day) (Mensink et al., 2013; Flynn et al., 2009). Jablonska et al. have indicated the mean intake of Cu to be 1.4 mg/l (based on analytical data) and 0.8mg/day (based on data calculated from 24-h diet recalls) (Jablonska et al., 2013).

Our findings support the existing evidence indicating a significant role of Se in the brain and behavior development. We observed a positive association between Se level in the 1st trimester of pregnancy and child language and motor skills at one year of age. It is important that the data concerning the effect of Se levels (also in cord blood) on child psychomotor development at the age of two years are in the same direction, although not statistically significant. In the study by Skröder et al., similarly to our observations, an increase in the maternal Se concentration has been associated with improvement in children's

language and psychomotor development (Skröder et al., 2015). What is interesting is that in the study by Yang et al. both low (<100 μg/l) and high (≥100 μg/l) levels of cord serum Se had adverse effects on neonatal neurodevelopment (Yang et al., 2013). However, in our assessment, a maximum Se level in cord plasma was 56 μg/l, which is much lower than the Se level observed by Yang et al., so performing an analysis for a high Se level had no point. More details on the impact of Se on child psychomotor development can be found in our previous publication (Polanska et al., 2016a).

The existing studies evaluating the impact of Zn supplementation during pregnancy as well as Zn level in the maternal and/or cord blood on child development are not consistent. As an example, two studies have found no effect of Zn supplementation during pregnancy on child psychomotor development (Tamura et al., 2003; Caulfield et al., 2010), while in two other studies, a negative effect of Zn supplementation on developmental outcomes has been observed (Hamadani et al., 2002; Wehby and Murray, 2008). In the study by Yang and coworkers a cord serum Zn level ≥ 0.794 mg/l had an adverse effect on neonatal neurobehavioral development (Yang et al., 2013). This is in agreement with what we observed in our study – decreasing motor and language scores with increasing Zn levels. It is important to be aware of the fact that in the present study, in about 88% of the cord blood samples Zn level was higher than the threshold determined by Yang et al. (Yang et al., 2013). To explain the negative effects of Zn on psychomotor scores at one year, it is worth mentioning that Zn may have both neuroprotective and neurotoxic properties. Specific mechanisms underlying Zn neurotoxicity have been described by linking excess Zn to oxidative stress and increased rate of cell death (Morris and Levenson, 2012; Yang et al., 2013). Furthermore, given the pivotal role of Zn in glutamate neurotransmission, it can be expected that even relatively slight changes in vesicular Zn levels during early

neurodevelopment may influence cortical/hippocampal synaptogenesis and possibly later behavioural functions (Nakashima and Dick, 2009).

We have not found statistically significant associations between Cu levels and any aspects of child neurodevelopment; however, some studies in this field indicate that such associations exist, and that balance between Cu and iron assures proper child neurocognitive and neurobehavioral development (Cetin et al., 2010; Gambling et al., 2011; Gambling et al., 2008; Georgieff, 2007, Leung et al., 2011; Uriu-Adams et al., 2010; Beard et al., 2003; Penland and Prohaska, 2004; Gybina and Prohaska, 2006; Beard, 2008; Prohaska and Gybina, 2005).

An advantage of the current analysis is the assessment of micronutrient status based on measurement of Zn, Cu and Se in the blood over pregnancy period and not just on the questionnaire data regarding diet and supplements. What is important is the fact that our analysis evaluates the impact of all the three micronutrients (included in the multivariate model) on child psychomotor development. Additionally, in comparison to the existing studies, the current analysis takes advantage on inclusion of a variety of potential confounding factors and the use of a well-standardized test evaluating neurodevelopmental effects in young children (Bayley 3rd edition).

Nevertheless, limitations of the study are also worth noting. We were not able to assess dietary habits of the women in order to include them in the analysis, and we did not measure/or include internal exposure to other essential and neurotoxic elements such as Fe, Mn, As, Cd, Pb, Hg. Additionally, although we measured micronutrient levels in different pregnancy periods (for a substantial proportion of children) the final sample, taking into account availability of the data, was limited.

5. Conclusion

In conclusion our study showed that prenatal Zn and Se status was significantly associated with child psychomotor abilities within the first years of life. It needs to be highlighted that micronutrient levels in pregnant women depends on dietary sources and they are influenced by hormonal and metabolic changes through pregnancy period. Our results support the need of assuring proper nutritional status of women to prevent detrimental nutritional unbalance (Cetin et al., 2010), and indicate that micronutrient supplementation during pregnancy should be considered with more caution especially under optimal conditions. The effects here reported, and those of Zn in particular, appear to be transient as they are no more evident at 2 years of age. However, follow-up of this population may be useful to exclude effects on neuropsychological functions at later ages. Altogether, further epidemiological and preclinical studies are needed to confirm the association and elucidate the underlying mechanisms of these effects.

Acknowledgements

This study was partly funded by the National Science Centre under the call JPI HDHL Nutrition and Cognitive Function (2015/17/Z/NZ7/04273) and partly by the National Science Centre, Poland, under the grant DEC-2014/15/B/NZ7/00998, by FP7 HEALS Grant N° 603946 and the Ministry of Science and Higher Education under grant agreement no. 3068/7.PR/2014/2 by CROME Grant N° LIFE12 ENV/GR/001040.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at

References

1. Agarwal, R.P., Henkon, R.L.,1985. A simple method for simultaneous estimation of zinc and copper in erythrocytes. Biol.Trace Elem.Res.7, 199-200.
2. Bayley 3rd edition. Retrieved from (http://www.pearsonclinical.com/childhood/products/100000123/bayley-scales-of-infant-and-toddler-development-third-edition-bayley-iii.html)

3. Beard, J., Erikson, K.M., Jones, B.C., 2003. Neonatal iron deficiency results in irreversible changes in dopamine function in rats. J Nutr.133(4), 1174-1179.
4. Beard, J.L., 2008. Why iron deficiency is important in infant development. J Nutr. 138(12), 2534-2536.
5. Benton, D., ILSI Europe a.i.s.b.l., 2008. Micronutrient status, cognition and behavioral problems in childhood. Eur J Nutr. 47(3), 38-50. doi: 10.1007/s00394-008-3004-9.
6. Boroujeni, S.T., Naghdi, N., Shahbazi, M., Farrokhi, A., Bagherzadeh, F., Kazemnejad, A., Javadian, M., 2009. The effect of severe zinc deficiency and zinc supplement on spatial learning and memory. Biol Trace Elem Res. 130, 48–61.
7. Butler Walker, J., Houseman, J., Seddon, L., McMullen, E., Tofflemire, K., Mills, C., Corriveau, A., Weber, J.P., LeBlanc, A., Walker, M., Donaldson, S.G., Van Oostdam, J., 2006. Maternal and umbilical cord blood levels of mercury, lead, cadmium, and essential trace elements in Arctic Canada. Environ Res. 100(3), 295-318.
8. Caulfield, L.E., Putnick, D.L., Zavaleta, N., Lazarte, F., Albornoz, C., Chen, P., Dipietro, J.A., Bornstein, M.H., 2010. Maternal gestational zinc supplementation does not influence multiple aspects of child development at 54 mo of age in Peru. Am J Clin Nutr. 92(1), 130-136. doi: 10.3945/ajcn.2010.29407.
9. Cetin, I., Berti, C., Calabrese, S., 2010. Role of micronutrients in the periconceptional period. Hum Reprod Update. 16(1), 80-95. doi: 10.1093/humupd/dmp025.
10. European Food Safety Authority. Retrieved from (https://www.efsa.europa.eu/en/topics/topic/drv).
11. Dobbing, J., 1990. Vulnerable periods in the developing brain. In: Dobbing J, ed. Brain, behavior and iron in the infant diet. London, United Kingdom: Springer. 1–25.
12. Dokumov, S.I., 1968. Serum copper and pregnancy. Am J Obstet Gynecol. 101(2), 217-22.
13. Flynn, A., Hirvonen, T., Mensink, G.B.M., Ocke, M.C., Serra-Majem, L., Stos, K., Szponar, L., Tetens, I., Turrini, A., Fletcher, R., Wildemann, T., 2009. Intake of selected nutrients from foods, from fortification and from supplements in various European countries. Food & Nutrition Research.1. doi: 10.3402/fnr.v53i0.2038.
14. Frederickson, C.J., Danscher, G., 1990 Zinc-containing neurons in hippocampus and related CNS structures. Prog Brain Res. 83, 71-84.
15. Gambling, L., Andersen, H.S., McArdle, H.J., 2008. Iron and copper, and their interactions during development. Biochem Soc Trans. 36(6),1258-1261. doi: 10.1042/BST0361258.

16. Gambling, L., Kennedy, C., McArdle, H.J., 2011. Iron and copper in fetal development. Semin Cell Dev Biol. 22(6), 637-644. doi: 10.1016/j.semcdb.2011.08.011.
17. Georgieff, M.K., 2007. Nutrition and the developing brain: nutrient priorities and measurement. Am J Clin Nutr. 85(2), 614-620.
18. Georgieff, M.K., Rao, R., 2001. The role of nutrition in cognitive development.In: Nelson CA, Luciana M, eds. Handbook in developmental cognitive neuroscience. Cambridge, MA: MIT Press. 491–504.
19. Golub, M.S., Keen, C.L., Gershwin, M.E., Hendrickx, A.G., 1995. Developmental zinc deficiency and behavior. J Nutr. 125(8),2263-2271.
20. Gybina, A.A., Prohaska, J.R., 2006. Variable response of selected cuproproteins in rat choroid plexus and cerebellum following perinatal copper deficiency. Genes Nutr. 1(1), 51-59. doi: 10.1007/BF02829936.
21. Hamadani, J.D., Fuchs, G.J., Osendarp, S.J., Huda, S.N., Grantham-McGregor, S.M., 2002. Zinc supplementation during pregnancy and effects on mental development and behaviour of infants: a follow-up study. Lancet. 360, 290-294. doi: 10.1016/S0140-6736(02)09551-X.
22. Holmgren, A., Lu, J., 2010. Thioredoxin and thioredoxin reductase: current research with special reference to human disease. Biochem Biophys Res Commun. 396, 120–124.
23. Jablonska, E., Gromadzinska, J., Klos, A., Bertrandt, J., Skibniewska, K., Darago, A., Wasowicz, W., 2013. Selenium, zinc and copper in the Polish diet. Journal of Food Composition and Analysis. 31(2), 259–265. doi: 10.1016/j.jfca.2013.05.016
24. Kalra, R., Kalra, V.B., Sareen, P.M., Khandelwal, R., 1989. Serum copper and ceruloplasmin in pregnancy with anaemia. Indian J Pathol Microbiol. 32(1), 28-32.
25. King, J.C., 2000. Determinants of maternal zinc status during pregnancy. Am J Clin Nutr. 71(5), 1334-1343.
26. Kong, X., Liu, L., Sheng, X., 1998. Effects of excessive zinc in fodder on brain development and abilities of learning and memory and their mechanisms in young rats. Zhonghua Yu Fang Yi Xue Za Zhi. 32, 225–228.
27. Kretchmer, N., Beard, J.L., Carlson, S., 1996. The role of nutrition in the development of normal cognition. Am J Clin Nutr. 63, 997–1001.

28. Leung, B.M.Y., Wiens, K.P., Kaplan, B.J., 2011. Does prenatal micronutrient supplementation improve children's mental development? A systematic review. BMC Pregnancy and Childbirth 11, 12. doi: 10.1186/1471-2393-11-12.
29. Martín-Lagos, F., Navarro-Alarcón, M., Terrés-Martos, C., López-García de la Serrana, H., Pérez-Valero, V., López-Martínez, M.C., 1998. Zinc and copper concentrations in serum from Spanish women during pregnancy. Biol Trace Elem Res.61(1), 61-70.
30. Mensink, G.B., Fletcher, R., Gurinovic, M., Huybrechts, I., Lafay, L., Serra-Majem, L., Szponar, L., Tetens, I., Verkaik-Kloosterman, J., Baka, A., Stephen, A.M., 2013. Mapping low intake of micronutrients across Europe. Br J Nutr. 110(4), 755-773. doi: 10.1017/S000711451200565X.
31. Morley, J.E., Gordon, J., Hershman, J.M., 1980. Zinc deficiency, chronic starvation, and hypothalamic-pituitary-thyroid function. Am J Clin Nutr. 33(8), 1767-1770.
32. Morris, D.R., Levenson, C.W., 2012. Ion channels and zinc: mechanisms of neurotoxicity and neurodegeneration. J Toxicol. 2012:785647. doi: 10.1155/2012/785647.
33. Nakashima, A.S., Dyck, R.H., 2009. Zinc and cortical plasticity. Brain Res Rev. 59(2), 347-373. doi: 10.1016/j.brainresrev.2008.10.003.
34. Neve, J., Chamart, S., Molle, L., 1987. Optimization of direct procedure for the determination of selenium in plasma and erythrocytes using Zeeman effect atomic absorption spectroscopy. Trace Elem. Anal. Chem. Med. Biol. 4, 349–358.
35. Neve, J., Molle, L., 1986. Direct determination of selenium in human serum by graphite furnace atomic absorption spectroscopy. Improvements due to oxygen ashing in graphite tube and Zeeman effect background correction. Acta Pharmacol. Toxicol., 59(7), 606-609.
36. Nyaradi, A., Li, J., Hickling, S., Foster, J., Oddy, W.H., 2013. The role of nutrition in children's neurocognitive development, from pregnancy through childhood. Front Hum Neurosci.7, 97. doi: 10.3389/fnhum.2013.00097.
37. Pathak, P., Kapil, U., Kapoor, S.K., Saxena, R., Kumar, A., Gupta, N., Dwivedi, S.N., Singh, R., Singh, P., 2004. Prevalence of multiple micronutrient deficiencies amongst pregnant women in a rural area of Haryana. Indian J Pediatr. 71(11), 1007-1014.
38. Penland, J.G., Prohaska, J.R., 2004. Abnormal motor function persists following recovery from perinatal copper deficiency in rats. J Nutr. 134(8), 1984-1988.

39. Polanska, K., Hanke, W., Gromadzinska, J., Ligocka, D., Gulczynska, E., Sobala, W., Wasowicz, W., 2009. Polish mother and child cohort study- defining the problem, the aim of the study and methodological assumption. Int J Occup Med Environ Health. 22(4), 383-391. doi: 10.2478/v10001-009-0037-0.
40. Polanska, K., Hanke, W., Jurewicz, J., Sobala, W., Madsen, C., Nafstad, P., Magnus, P., 2011. Polish mother and child cohort study (REPRO_PL)- methodology of follow-up of the children. Int J Occup Med Environ Health. 24(4), 391-398. doi: 10.2478/s13382-011-0026-y.
41. Polanska, K., Hanke, W., Krol, A., Potocka, A., Waszkowska, M., Jacukowicz, A., Gromadzinska, J., Wasowicz, W., Jerzynska, J., Stelmach, W., Stelmach, I., 2016b. Polish Mother and Child Cohort Study (REPRO_PL) - Methodology of the follow-up of the children at the age of 7. Int J Occup Med Environ Health. 29(6), 883-893. doi: 10.13075/ijomeh.1896.00811.
42. Polanska, K., Krol, A., Sobala, W., Gromadzinska, J., Brodzka, R., Calamandrei, G., Chiarotti, F., Wasowicz, W., Hanke, W., 2016a. Selenium status during pregnancy and child psychomotor development-Polish Mother and Child Cohort study. Pediatr Res. 79(6), 863-869. doi: 10.1038/pr.2016.32.
43. Polish Mother and Child Cohort study RERPO_PL. Retrieved from (www.repropl.com)
44. Prohaska, J.R., Gybina, A.A., 2005. Rat brain iron concentration is lower following perinatal copper deficiency. J Neurochem. 93, 698-705.
45. Rao, R., Georgieff, M.K., 2000. Early nutrition and brain development. In: Nelson CA, ed. The effects of early adversity on neurobehavioral development. Minnesota Symposium on Child Psychology. Hillsdale, NJ: Erlbaum Associates. 31, 1–30.
46. Rayman, M.P., 2012. Selenium and human health. Lancet.379, 1256–1268.
47. Roman, M., Jitaru, P., Barbante, C., 2014. Selenium biochemistry and its role for human health. Metallomics. 6, 25–54.
48. Shah, D., Sachdev, H.P., 2006. Zinc deficiency in pregnancy and fetal outcome. Nutr Rev. 64(1), 15-30.
49. Skröder, H.M., Hamadani, J.D., Tofail, F., Persson, L.Å., Vahter, M.E., Kippler, M.J., 2014. Selenium status in pregnancy influences children's cognitive function at 1.5 years of age. Clin Nutr. 34(5), 923-930. doi: 10.1016/j.clnu.2014.09.020.

50. Skröder, H.M., Hamadani, J.D., Tofail, F., Persson, L.Å., Vahter, M.E., Kippler, M.J., 2015. Selenium status in pregnancy influences children's cognitive function at 1.5 years of age. Clin Nutr. 34, 923–930.
51. SRNT Subcommittee on Biochemical Verification, 2002. Biochemical verification of tobacco use and cessation. *Nicotine Tob Res.* 4(2), 149-159.
52. Stragierowicz, J., Mikołajewska, K., Zawadzka-Stolarz, M., Polańska, K., Ligocka, D., 2013. Estimation of cutoff values of cotinine in urine and saliva for pregnant women in Poland. Biomed Res Int. 2013:386784. doi: 10.1155/2013/386784.
53. Tamura, T., Goldenberg, R.L., Ramey, S.L., Nelson, K.G., Chapman, V.R., 2003. Effect of zinc supplementation of pregnant women on the mental and psychomotor development of their children at 5 y of age. Am J Clin Nutr. 77(6), 1512-1516.
54. Thompson, R.A., Nelson, C.A., 2001. Developmental science and the media: early brain development. Am Psychol. 56, 5–15.
55. Turski, M.L., Thiele, D.J., 2009. New roles for copper metabolism in cell proliferation, signaling, and disease. J Biol Chem.284(2), 717-721. doi: 10.1074/jbc.R800055200
56. Uriu-Adams, J.Y., Scherr, R.E., Lanoue, L., Keen, C.L., 2010. Influence of copper on early development: prenatal and postnatal considerations. Biofactors. 36(2), 136-152. doi: 10.1002/biof.85.
57. Wasowicz, W., Wolkanin, P., Bednarski, M., Gromadzinska, J., Sklodowska, M., Grzybowska, K., 1993. Plasma trace element (Se, Zn, Cu) concentrations in maternal and umbilical cord blood in Poland. Relation with birth weight, gestational age, and parity. Biol Trace Elem Res. 38(2), 205-215.
58. Wasowicz, W., Gromadzinska, J., Rydzynski, K., Tomczak, J., 2003. Selenium status of low-selenium area residents: Polish experience. Toxicol Lett. 137, 95–101.
59. Wehby, G.L., Murray. J.C., 2008. The effects of prenatal use of folic acid and other dietary supplements on early child development. Matern Child Health J. 12(2), 180-187.
60. Yang, X., Yu. X., Fu, H., Li, L., Ren, T., 2013. Different levels of prenatal zinc and selenium had different effects on neonatal neurobehavioral development. Neurotoxicology. 37, 35-39. doi: 10.1016/j.neuro.2013.04.001.
61. Zachara, B.A., Wasowicz, W., Gromadzinska, J., Sklodowska, M., Krasomski, G., 1986. Glutathione peroxidase activity, selenium and lipid peroxides concentrations in

blood from a healthy Polish population. Maternal and cord blood. Biol. Trace Elem. Res. 10, 175-187.

62. Zhu, L., Ji, X.J., Wang, H.D., Pan, H., Chen, M., Lu, T.J., 2012. Zinc neurotoxicity to hippocampal neurons in vitro induces ubiquitin conjugation that requires p38 activation. Brain Res. 1438, 1–7.