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Association of Hair Zinc Level with Cognitive and Language Delays in Children Aged 9–24 Months Old

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Abstract

BACKGROUND: Delay in cognitive and language development caused by multifactor including chronic deficiency of zinc. There were inconsistencies in previous studies between zinc levels and development.

AIM: The study aims to prove low hair zinc level is associated with delays of cognitive and language development in children 9–24 months old**.**

METHOD: This analytical observational study with case-control design, each group consisted of 69 children. Case group with cognitive and language development delays, Cognitive adaptive test/Clinical linguistic and auditory milestone <85 meanwhile control group with normal cognitive and language development. Chi-square test was used to assess association between zinc levels and incidence of cognitive and language delays. Multivariate analysis was performed by logistic regression.

RESULTS: Univariate analysis showed no association between low zinc level and delays of cognitive and language development meanwhile logistic regression showed screen time >2 h and lack of stimulation were risk factors (adjusted odds ratio [OR] 2.78; 95% Confidence interval [CI] 1.284–6.058; p = 0.010; adjusted OR 3.96; 95% CI 1.833–8.581; p < 0.001).

CONCLUSION: There is no relationship between low hair zinc level and delays in cognitive and language development, but there is an association between screen time more than 2 h and lack of stimulation with delays in cognitive and language development in children aged 9–24 months old.

Introduction

It is estimated 12–16% children have developmental disorders in the United States [1] and 8% of them are cognitive and language disorders [2]. In Indonesia, data showed 34% of 2634 children aged 0–72 months had developmental deviation and 44% of them were language disorders [3]. In addition, 14.3% of children aged <36 months suffered delay in cognitive and language development in Denpasar [4].

Language development is indicator of children's cognitive abilities. Language development will be good if cognitive are good [5], [6]. Delay in cognitive and language development will affect various life functions, causing obstacles to work in adulthood. Therefore, Indonesia Ministry of Health recommend diagnostic instrument that has been validated and available in Indonesian, namely Capute scale-Cognitive adaptive test/Clinical linguistic and auditory milestone (CAT/CLAMS) [7], [8].

The role of nutrition in the first 1000 days of life is important for cognitive development. Adequate nutrition plays important role in rapid brain development. Nutrients that roles in brain development are macronutrients carbohydrates, proteins and fats as well as micronutrients such as zinc, choline, iodine, iron, folic acid, and vitamin A [9], [10], [11].

Zinc as micronutrient plays the most important role in neurogenesis [12], [13], [14], [15], [16]. Sufficient level of zinc is required for regulation of neurotransmitters such as glutamate, G-aminobutyric acid (GABA) and acetylcholine, so that neurotransmitter remains balanced and prevent excitotoxicity which can cause brain damage and interfere learning process [16], [17], [18], [19].

The prevalence of zinc-deficient in children in Indonesia is quite high, 36.1% since Indonesia is still developing country with low socioeconomic [20]. Meassurement of zinc level through hair tissue has advantages such as noninvasive and less expensive. Zinc concentration in hair is higher, stable, and reflect zinc concentration in tissues. This is because during the hair grow, follicle is exposed to blood supply and after passed through scalp, the zinc traps in hair matrix and will be retained because of keratinization [21]. The average human hair growth about 1 cm/month, so 2–3 cm haircut taken from base of the head can reflect what has been absorbed by hair over the past 2–3 month time period [21], [22].

The role of zinc in brain has been proven as in a study in Iran girls aged 9–13 years, significant difference was found between the average level of zinc in hair and Intelligence Quotients (IQ) test scores [23]. Therefore, researchers are interested in conducting repeat study to determine the relationship between hair zinc level and delay of cognitive and language development in children aged 9–24 months in Indonesia, especially in Bali, which has high prevalence of zinc deficiency.

This research has been approved by Committee Ethics Faculty of Medicine Udayana/ Sanglah Hospital Denpasar No.670/UN14.2.2.VII.14/ LT/2020 and permission from Sanglah Central General Hospital No: LB.02.01/XIV.2.2.1/34968/2020.

Method

This analytical observational study with case-control design was carried out in children aged 9–24 months whom visited pediatric outpatient clinic or were treated in pediatric ward of Sanglah Hospital. Inclusion criteria for case group was child with Full-Scale Developmental Quotient (FSDQ) Capute Scales (CAT/CLAMS) <85 who were newly diagnosed and had never been treated for developmental disorder before. Hence, inclusion criteria for control group was child with FSDQ Capute Scales (CAT/CLAMS) >85 who had never been treated for developmental disorders.

Exclusion criteria were child with: History of preterm, low birth weight, vegetarian diet, history of vegetarian diet during pregnancy, increased metabolism, impaired absorption or increased excretion and use of diuretic therapy for >4 weeks, acute malnutrition, genetic disorders, children with family history of language delay, history of asphyxia, history of Central nervous system (CNS) infections, CNS malformations, craniofacial malformations, hearing loss, history of exposure to teratogenic chemicals, maternal history of exposure to X-ray radiation or computed tomography-scan.

The independent variable was hair zinc content, dependent variable was delay in cognitive and language development and confounding variables were gender, nonexclusive breastfeeding, stunting, low socio-economic status, history of preterm, history of low birth weight, vegetarian diet during pregnancy, increased metabolism, impaired absorption, increased excretion, and severe acute malnutrition.

External variables were anemia, history of seizures, mother's education level, father's education level, primary caregiver, screen time, stimulation, genetic disorder, history of asphyxia, history of CNS infections, CNS malformations, craniofacial malformations, hearing loss, exposure to chemicals in the womb, radiation exposure during pregnancy.

Data were analyzed by computer program. Categorical data were expressed in frequency and percentage distributions, while continuous data are expressed in medians. Hypothesis testing was carried out in this study using chi-square test with significance limit $p < 0.05$ and 95% confidence interval (CI).

The relationship between zinc level in hair with delay of cognitive and language development is expressed as odds ratio (OR). Multivariate analysis was conducted to rule out confounding variables in this study using logistic regression test to assess the relationship between zinc level in hair with cognitive and language delays after controlling confounding variables.

Procedure

Hair material was taken in occipital area and cut with length approximately 3 cm near scalp then wrapped in opaque paper and stored in plastic clip. The materials used were informed consent form, research form, Kuesioner Praskrining Perkembangan (KPSP) form, hearing test form, Capute scales (CAT/CLAMS), measure tape with accuracy 0.1 cm, digital body scale, ICPE-9000 spectrometer, scissors, opaque paper, plastic clips, Easy Touch GCHb® personal diagnostic tool and Easy Touch® hemoglobin (Hb) stick.

Result

During study period, 185 subjects met inclusion criteria and 47 subjects were excluded (Figure 1). All subjects filled those sheets, underwent physical examination, KPSP examination, Capute scales examination, hearing test, measurement of Hb level, and hair zinc level.

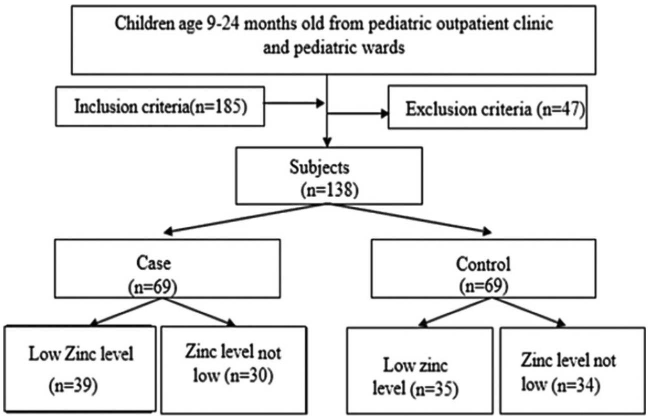

Figure 1: Flowchart of the study

The characteristics of both groups did not differ clinically, except for screen time and stimulation

(Table 1). The age of the subjects in this study was not normally distributed with median age in case group 23 (9–24) months and control group 20 (9–24) months. The distribution of zinc level in this study was not normally distributed with the lowest concentration being 0 mg/kg (<0.0001) and the highest being 1108.0 mg/kg. Hair zinc level in case group had median (minimum-maximum) 76.66 (0–838.21) mg/kg and control group had median (minimum-maximum) 132.99 (0–1108.00) mg/kg.

Table 1: Characteristics of subjects

Characteristics	Case n = 69	Control n = 69
Gender, n (%)		
male	39 (56.5)	38 (55.1)
Female	30 (43.5)	31 (44.9)
Exclusive breastfeeding		
No	44 (63.8)	38 (55.1)
Yes	25 (36.2)	31 (44.9)
Stunting		
Yes	17 (24.6)	7 (10.1)
No	52 (75.4)	62 (89.9)
Anemia		
Yes	14 (20.3)	16 (23.2)
No	55 (79.7)	53 (76.8)
History of seizure		
Yes	9 (13)	5 (7.2)
None	60 (87)	64 (92.8)
Sosioeconomy status		
Low	18 (26.1)	11 (15.9)
High	51 (73.9)	58 (84.1)
Mother's educational degree		
Low	28 (40.6)	25 (36.2)
High	41 (59.4)	44 (63.8)
Father's educational degree		
Low	31 (44.9)	27 (39.1)
High	38 (55.1)	42 (60.9)
Primary caregiver		
Others	23 (33.3)	20 (29.0)
Parents	46 (66.7)	49 (71.0)
Screen time		
> 2 h	52 (75.4)	30 (43.5)
< 2 h	17 (24.6)	39 (56.5)
Stimulation		
Lack	43 (62.3)	17 (24.6)
Enough	26 (37.7)	52 (75.4)

In this study, most children with cognitive and language delays had low zinc level (56.5%) compared to group without cognitive and language delays (50.7%). Bivariate analysis using chi-square hypothesis test and OR calculation showed that low zinc level had no relationship with cognitive and language development delays in children aged 9–24 months (Table 2).

Table 2: The association of hair zinc level with cognitive and language delay in children age 9–24 months old

Level of Zinc, n (%)	Cognitive and language delay		OR	CI 95%	p-value
	Case (n = 69)	Control (n = 69)			
Low	39 (56.5)	35 (50.7)	1.263	0.646-2.469	0.495
Not low	30 (43.5)	34 (49.3)			

Screen time >2 h and stimulation had different proportions size, which is clinically important. Multivariate analysis was conducted in low hair zinc level with both variables that thought to be associated with cognitive and language delays. It was found that low hair zinc levels did not associated with cognitive and language development delay in children aged 9–24 months; however, screen time and lack of stimulation could increase the risk of delays in cognitive and language development by 2.788 times and 3.966 times. Multivariate analysis of cognitive and language development delays in children with confounding variables is shown in Table 3.

Table 3: Multivariate analysis of low zinc level and confounding factors with cognitive and language delay in children

	Adjusted OR	CI 95%	p-value
Low level of zinc	1.404	0.665–2.967	0.373
Screen time >2 h	2.788	1.284–6.058	0.010
Lack of stimulation	3.966	1.833–8.581	0.000

Discussion

In this study, the median age of subjects in case group was 23 months, in accordance with Joint Committee on Infant Hearing which found children with speech delay were generally noticed by parents when they were 18–24 months old [24]. Most of the variables did not show any clinical important characteristic differences between case groups compared to control group. Children with partial cognitive and language development delay had screen time >2 h (75.4%) and had less stimulation (62.3%).

Screen time and simulations provided by parents seems to affect children's cognitive and language abilities. All children in this study have been introduced to screen media since the age <2 years, especially television which can affect duration time of stimulation.

Based on recommendations of American Academy of Pediatrics 2016, children under 18 months should not be introduced to screen devices other than for video calls and recommends parents whom wish to introduce smartphones to children aged 18–24 months must choose good program and provide assistance while children watching the program [25].

Canadian study found media exposure >2 h daily was experienced by 85% of children aged <3 years in Canada so this study used media exposure limit >2 h [26].

Stimulation in this study also showed clinical different of effect size in case group. As many as 62.3% children who experience delays in cognitive and language development had insufficient stimulation according to their age compared to 24.6% of children without delay. Stimulation through games and verbal interactions between mothers and their children could increase development quotient values [27].

Several confounding variables and other external variables which can bias the relationship of hair zinc levels with cognitive and language development delays did not show any clinically important differences in this study. This can be caused the minimum sample size for each of these variables weren't measured.

In this study, boys dominated in case group than control group. Based on previous studies, it is known that boys have 2.6 times greater tendency to experience delays in cognitive and language development compared to girls due to slower male physiology and effect of testosterone that slows the growth of left hemisphere neurons [28], [29]. Naturally, boys tend to be more easily distracted and have lower sense of self-control than girls [30].

This study also found that exclusive breastfeeding or nonexclusive breastfeeding did not provide clinically important difference in incidence of cognitive and language development delays. In contrast to meta-analysis showed breastfed increased children's cognitive 5.32 times (95% CI = 4.51–6.14) compared to formula-fed children [31]. Breastfeeding more than 4 months increase the value of Mental Development Index from Bayley scale at age 1 and 2 years [31]. In this study, 58.3% children with low hair zinc level did not receive exclusive breastfeeding, since zinc in formula milk could only be absorbed 20% compared to breast milk which could be absorbed 60% [32].

Case group in this study whom suffered stunting was 24.6%, bigger than control group which only 10.1% suffered stunting. The minimum sample calculation was not carried out for stunting variable, so it is possible that sample in this study was too small to cause statistic significant effect size. Chronic malnutrition/stunting conditions that occur in infancy in postnatal period up to 2 years need to be aware because these conditions will cause cognitive impairment and poor school and work performance, due to low cognitive abilities including literacy, numeracy, vocabulary, and reasoning [19], [33].

In this study, control group had more anemia (23.3%) than case group. This condition occurred because some of the samples in control group were obtained from pediatric ward suffered acute infections such as acute diarrhea, bronchiolitis and pneumonia as well as children who had febrile seizures and first seizure without fever. Anemia can be a risk factor for acute infections such as pneumonia and diarrhea, and thus anemia is found more frequent [34].

In this study, although there was no clinically significant differences in history of seizures, the case group showed bigger number than control group (13% and 7.2%). Children with epileptic seizures or non-epileptic seizures with onset age of seizure <1 year/ history of focal seizures/serial seizures within 24 h or seizures longer than 15 min were found have significant lower IQ scores than control. They also tend to have lower speed in processing memory and information index than normal children [35].

In this study, most children with cognitive and language development delays came from family with low socioeconomic status than control group (26.1% and 15.9%). Low family economic status is associated with macronutrient and micronutrient deficiency conditions which also potentially delay children's cognitive and language development [36], [37].

The proportion of children who have cognitive and language development delays was higher in those with low maternal education level, low paternal education level and non-parental primary caregivers, although these differences were not clinically different from control group. Based on previous studies, socio-economic factors role in these three variables. The primary caregivers of biological mothers who have low education level and come from low socio-economic families tend to be associated with children whom suffered cognitive and motor delays. They do not know how to provide age-appropriate stimulation and unable to provide optimum stimulation facilities to their children [37].

This study found that case group had low zinc level was 56.5%, while control subjects with low zinc level was 50.7%. OR of low zinc level for experiencing cognitive and language development delays in this study was 1.404 times, with 95% CI 0.665–2.967. These results prove that there is no relationship between low zinc levels with cognitive and language delays in children aged 9–24 months (p = 0.373).

In this study, more than 50% of the subjects had zinc deficiency despite exclusion of several factors. It can be explained through study in Indonesian healthy adolescents aged 13–18 years, with normal diet, had zinc deficiency 77.48% [38]. Zinc deficiency often occurs when children start complementary foods, especially in developing countries, which factory-made fortified complementary foods are rarely given due to economic considerations. Mothers often make homemade complementary foods with traditional recipes thus doesn't met micronutrients requirement. Socio-economic and mother's education level role in choosing the composition of complementary foods, but this study did not analyze the daily complementary foods for children so that it was not possible to determine the cause of the zinc deficiency.

In this study, case group had more hair zinc level below the cutoff point 130 mg/kg. These results resemble study in 112 term neonates with birth weight >2500 g and come from low socio-economic group. This study showed that hair zinc concentrations have low sensitivity to detect marginal zinc deficiency, but impaired cognitive development could be seen in marginal zinc deficiency [39]. Zinc is needed for optimal brain development since womb for neurogenesis, myelination, synaptogenesis, and release of neurotransmitters [40].

A clinical trial in 52 low birth weight infants compared between the groups receiving zinc supplements and those receiving placebo until the age of 5 months showed no difference in serum zinc levels at 12 months of age. This could be due to complementary foods had been given at the age of 12 months and no difference in types of complementary foods between the two groups. Differences in cognitive scores at the age of 12 months are thought to indicate differences in zinc level in brain tissue that affect cognitive and these differences cannot be evaluated through fluctuating zinc serum [41].

Another study conducted in group girls aged 9–13 years also showed children with lower IQ level; the mean zinc level was also lower than the group of children with normal IQ level [23].

Research in Lubuk Rumbai Village showed 96.5% children with zinc intake <77% recommended dietary allowance had intelligence level below average. It showed that low zinc level increase the incidence of children have low intelligence 24.5 times compared to normal zinc and low socio-economic level causes insufficient intake of nutrients that rich of zinc such as nutrients from animal origin. In this study, the zinc results was fluctuating but showed low zinc level as risk factor, in accordance with research in developing country, weak socio-economic condition risky for insufficient intake of zinc-containing nutrients and risky for suffering chronic zinc deficiency that is not visible through serum zinc analysis [42].

The effect of zinc administration appears to be beneficial when administered to older children. Previous trials in group age 6–8 years and 9–11 years, found in the age group 6–8 years, combination of zinc and iron deficiency significantly associated with lower verbal memory test results compared to those in sufficient group. There was significant increase in average verbal memory test according to Mann-Whitney test after Fe and zinc supplements were given. In age group 6–8 years, a single zinc deficiency did not significantly affect the results compared to those without deficiency. Differences appear in older age group 9–11 years, there was effect of single zinc deficiency on significant decrease in memory test results and increase in nonverbal memory test results after being given zinc supplements for 3 months [15].

Similar results were also shown in study assessed ability of verbal memory, nonverbal memory and concentration. In age group 6–8 years, verbal and nonverbal memory skills were most affected by Fe deficiency compared to zinc deficiency, although the combined deficiency had significant effect on lower score of verbal memory test [43]. Contrary to previous results, in 9–11 years old group showed zinc deficiency affected verbal memory more than iron deficiency. Umamaheswari *et al.* [15] and Chaudhary *et al.* [43] showed that zinc affect cognitive at older age compared to younger age.

Another study showed that zinc supplementation 20 mg for 6 months significantly increased intelligence test scores in children aged 6–8 years [44]. Meghrazi *et al.* conducted in group of children aged 9–13 years showed children with lower IQ level, mean zinc level lower than the group of children with normal IQ level [23].

The studies mentioned above show similarities with Castillo-Duran *et al.* [39] both studies were conducted on children below 2 years old. Contradictory with Meghrazi *et al.* [23], this can be explained that during infancy and early childhood hair zinc concentration decrease and reach its lowest value until age 2–3 years [45], [46]. The reduced zinc concentration of hair due to the usage of zinc in other tissues during accelerated growth. Zinc in blood that pass through hair follicles during this growth spurt are also reduced because has been used by other tissues such as liver, muscle, hormone glands, brain, and others [22]. Zinc level will increase again during prepubertal period when growth acceleration does not occur, this can cause hair zinc level differ based on age [22].

Research on rats found that concentration of zinc in brain after birth is quite high and increase with growth but turnover of zinc in brain is also very slow, as evidenced by zinc supplementation for 2 weeks–6 months in rats that did not increase the concentration of zinc in brain, so that in younger age population, zinc intake such as from food or supplements does not significantly affect hippocampal zinc level. Moreover zinc level affects cognitive function in hippocampus. In the study, the role of zinc supplementation in brain is to reduce copper concentration in brain, while excess copper in brain can catalyze the formation of free radicals, oxidative damage occurs and disrupts cellular metabolism, so zinc supplementation provides protection against cognitive impairment due to copper excess [47]. Although hair zinc can be used to assess tissue zinc status, hair zinc at the age below 3 years cannot be used to assess zinc level in brain tissue because mismatch between zinc in brain and in other body tissues. Assessment of zinc status using samples derived from hair should be used to evaluate zinc level when the body is not in catch-up period [47]. The results of this study did not find significant relationship between hair zinc levels and delays in cognitive and language development, but found that screen time >2 h daily increased the risk of cognitive and language development delays in children 2.78 times (95% CI 1.284–6.058; p = 0.010). In addition to screen time, insufficient stimulation also effect the occurrence of delay in cognitive and language development 3.966 times (95% CI 31.83–8.581; p = 0.000).

A study conducted in children aged under 5 years found that exposure to smartphone and television media more than 2 h daily had negative impact on children's cognitive and language development and significantly hampered the value of communication in the Ages and Stages Developmental Questionnaire [48]. Long-term exposure to smartphone may be associated with lower cognitive abilities, especially short-term memory, reading, counting, and language skills [26]. Children aged 3–5 years who have lower screen time or in accordance with the recommendations tend to have memory capacity 3.48 times higher than children who have longer screen time [49]. Screen time without interactive content, will distract children to practice other important skills such as motor and communication skills.

Screen time affect interaction time of children with parents which indirectly reduces verbal and nonverbal stimulation from parents [50]. An increase of 1 point of simulation in parenting will increase 0.57 points of child development [37]. Therefore, it is important to reduce screen time to increase interaction time of children with parents in the form of reading books together, telling story, singing songs, playing outdoor, naming objects, counting, and drawing so that these stimuli provide good learning signals which important for the development of children's cognition [37], [50].

Conclusion

This study concluded that there was no relationship between low hair zinc level and delay in cognitive and language development in children 9–24 months, but screen time more than 2 h daily and lack of stimulation were associated with delay in cognitive and language development in children aged 9–24 months.

References

1. American Academy of Pediatrics. Developmental surveillance and screening of infants and young children. Pediatrics. 2001;108(1):192-6. https://doi.org/10.1542/peds.108.1.192 PMid:11433077
2. Scheffler F, Vogel D, Astern R, Burgess J, Conneally RT, Salerno K. Screening for Communication and Cognitive Disorders in Infants and Toddlers. Pediatr Nurs. 2008;33(6):473-80. PMid:18196710
3. Soedjatmiko. Early detection of toddler developmental disorders. Sari Pediatr. 2001;3(3):175-88.
4. Windiani IG, Soetjiningsih. Assessment of CAT (cognitive adaptive test)/CLAMS (clinical linguistic and auditory milestone scale) in children at Werdhi Kumara I child care center Denpasar. Sari Pediatr. 2010;12(4):228-32.
5. Busari JO, Weggelaar NM. How to investigate and manage the child who is slow to speak sources and selection criteria. BMJ. 2004;328:272-6. https://doi.org/10.1136/bmj.328.7434.272 PMid:14751899
6. Hartanto F, Selina H, Zuhriah H, Fitra S. The influence of language development in cognitive development of children aged 1-3 years old. Sari Pediatr. 2011;12(6):386-90.
7. Health Ministry Republic of Indonesia. Regulation of the Minister of Health of the Republic of Indonesia Number 66 of 2014 concerning Monitoring of Child Growth, Development, and Developmental Disorders. Jakarta: Health Ministry Republic of Indonesia; 2014.
8. Dhamayanti M, Herlina M. Screening for cognitive and language disorders using the Capute scale (cognitive adaptive test/clinical linguistic and auditory milestone scale-cat/clams). Sari Pediatr. 2009;11(3):189-98.
9. Alves-Rodrigues A, Shao A. The science behind lutein. Toxicol Lett. 2004;150(1):57-83. https://doi.org/10.1016/j.toxlet.2003.10.031 PMid:15068825
10. Georgieff MK. Nutrition and the developing brain: Nutrient priorities and measurement. Am J Clin Nutr. 2007;85(2):614S-20S. https://doi.org/10.1093/ajcn/85.2.614S PMid:17284765
11. Lien EL, Hammond BR. Nutritional influences on visual development and function. Prog Retin Eye Res. 2011;30(3):188-203. https://doi.org/10.1016/j.preteyeres.2011.01.001 PMid:21296184
12. Bhatnagar S, Taneja S. Zinc and cognitive development. Br J Nutr. 2001;85(S2):S139-45. https://doi.org/10.1079/bjn2000306 PMid:11509102
13. Black M. The evidence linking zinc deficiency with children's cognitive and motor functioning. J Nutr. 2003;133(1):1473-6. https://doi.org/10.1093/jn/133.5.1473S PMid:12730446
14. Agustian L, Sembiring T, Ariani A. The role of zinc on children's growth. Sari Pediatr. 2009;11(4):244-9.
15. Umamaheswari K, Bhaskaran M, Krishnamurthy G, Vasudevan H, Vasudevan K. Effect of iron and zinc deficiency on short term memory in children. Indian Pediatr. 2011;48(4):289-93. https://doi.org/10.1007/s13312-011-0060-7 PMid:20972302
16. Takeda A. Significance of Zn^{2+} signaling in cognition: Insight from synaptic Zn^{2+} dyshomeostasis. J Trace Elem Med Biol. 2014;28(4):393-6. https://doi.org/10.1016/j.jtemb.2014.06.021 PMid:25049058
17. Sandstead HH. Causes of iron and zinc deficiencies and their effects on brain. J Nutr. 2000;130 Suppl 2S:347S-9S. https://doi.org/10.1093/jn/130.2.347S PMid:10721903
18. Minami A, Takeda A, Yamaide R, Oku N. Relationship between zinc and neurotransmitters released into the amygdalar extracellular space. Brain Res. 2002;936(1-2):91-4. https://doi.org/10.1016/s0006-8993(02)02499-x PMid:11988235
19. Mayneris-Perxachs J, Swann JR. Metabolic phenotyping of malnutrition during the first 1000 days of life. Eur J Nutr. 2019;58(3):909-30. https://doi.org/10.1007/s00394-018-1679-0 PMid:29644395
20. Herman S. The problem of Vitamin A deficiency (VAC) and prospects for overcoming it. Health R D Med. 2012;17(4):40-4.
21. King J., Brown KH, Gibson RS, Krebs NF, Lowe NM, Siekmann JH, *et al.* Biomarkers of nutrition for development (BOND)-zinc review. J Nutr. 2016;146(4):858S-85S. https://doi.org/10.3945/jn.115.220079 PMid:26962190
22. International Zinc Nutrition Consultative Group (IZiNCG). Technical document. Food Nutr Bull. 2004;5 Suppl 2:94-200.
23. Meghrazi K, Sabet M., Kheradmand F, Akhgar M. A research on the level of zinc and copper in the hair of students with lower IQ. Zahedan J Res Med Sci. 2017;19(12):113-32.
24. Joint Committee on Infant Hearing. Principles and guidelines for early hearing detection and intervention programs. Pediatrics. 2019;120:898-921.
25. American Academy of Pediatrics. Media and young minds. Pediatrics. 2016;138(5):1-6.
26. Canadian Pediatrics Association. Screen Time and Young Children: Promoting Health And Development in a Digital World. J Pediatr Child Health. 2017;22(8):461-8.
27. Gofin R, Adler B, Palti H. Time trends of child development

in a Jerusalem community. Paediatr Perinat Epidemiol. 1996;10(2):197-206. https://doi.org/10.1111/j.1365-3016.1996.tb00043.x

PMid:8778692

28. Hidajati Z. “Faktor Risiko Disfasia Perkembangan Pada Anak”. Semarang: University of Diponegoro; 2009.
29. Lindsay G, Strand S. Children with language impairment: Prevalence, associated difficulties and ethnic disproportionality in an English population. Front Educ. 2016;1(2):1-14.
30. Ko CH, Yen JY, Chen CC, Chen SH, Yen CF. Gender differences and related factors affecting online gaming addiction among Taiwanese adolescents. J Nerv Ment Dis. 2005;193(4):273-7. https://doi.org/10.1097/01.nmd.0000158373.85150.57

    PMid:15805824
31. Anderson JW, Johnstone BM, Remley DT. Breast-feeding and cognitive development: A meta-analysis. Am J Clin Nutr.1999;70(4):525-35. https://doi.org/10.1093/ajcn/70.4.525

    PMid:10500022
32. Morrow-Tlucak M, Haude RH, Ernhart CB. Breastfeeding and cognitive development in the first 2 years of life. Soc Sci Med. 1988;26(6):635-9. https://doi.org/10.1016/0277-9536(88)90028-7

    PMid:3363405
33. Gardner JM, Powell CA, Baker-Henningham H, Walker SP, Cole TJ, Grantham-McGregor SM. Zinc supplementation and psychosocial stimulation: Effects on the development of undernourished Jamaican children. Am J Clin Nutr. 2005;82(2):399-405. https://doi.org/10.1093/ajcn.82.2.399

    PMid:16087985
34. Viana MB. Anemia and infection: A complex relationship. Rev Bras Hematol Hemoter. 2011;33(2):90-2. https://doi.org/10.5581/1516-8484.20110024

    PMid:23284251
35. Sherman E, Brooks B, Clymont T, McAllister W. Detecting epilepsy related cognitive problems in clinically refered children with epilepsy: Is the WISC-IV A useful tool? Epilepsia. 2012;53(6):1060-6. https://doi.org/10.1111/j.1528-1167.2012.03493.x

    PMid:22554239
36. Ozkan M, Senel S, Arslan E, Karacan C. The socioeconomic and biological risk factors for developmental delay in early childhood. Eur J Pediatr. 2012;171(12):1815-21. https://doi.org/10.1007/s00431-012-1826-1

    PMid:22983025
37. Zhang J, Guo S, Li Y, Wei Q, Zhang C, Wang X, *et al.* Factors influencing developmental delay among young children in poor rural china: A latent variable approach. BMJ Open. 2018;8(8):e021628. https://doi.org/10.1136/bmjopen-2018-021628

    PMid:30173158
38. Anwar K, Hardinsyah H, Damayanthi E, Sukandar D. Probability method for analyzing the prevalence of calcium, iron, zinc, and Vitamin D deficiencies among Indonesian adolescent. J Gizi Pangan. 2018;13(2):93-102.
39. Castillo-Duran C, Perales CG, Hertrampf ED, Marin VB, Rivera FA, Icaza G. Effect of zinc supplementation on development and growth of Chilean infants. J Pediatr. 2001;138(2):229-35. https://doi.org/10.1067/mpd.2001.110530

    PMid:11174621
40. Takeda A, Hirate M, Tamano H, Oku N. Release of glutamate and GABA in the hippocampus under zinc deficiency. J Neurosci Res. 2003;72(4):537-42. https://doi.org/10.1002/jnr.10600

    PMid:12704815
41. Friel JK, Andrews WL, Matthew JD, Long DR, Cornel AM, Cox M, *et al.* Zinc supplementation in very low birth weight infants. J Pediatr Gastroenterol Nutr. 1993;17(1):97-104. https://doi.org/10.1097/00005176-199307000-00015

    PMid:8350219
42. Flora R, Fajar NA, Febry F, Yuliana I, Yuliarti Y. Zinc intake, zinc serum levels, and intelligence in school children in rural areas. Open Access Maced J Med Sci. 2021;25(9):394-7.
43. Chaudhary J, Jora R, Sharma P, Gehlot R, Sushil. A study of iron and zinc deficiency on short term memory in children and effect of their supplementation. Asian J Biomed Pharm Sci. 2015;5(42):12-5.
44. Khodashenas E, Mohammadzadeh A, Sohrabi M, Izanloo A. The effect of zinc supplementation on cognitive performance in schoolchildren. Int J Pediatr. 2015;3(23):1033-8.
45. Hambidge KM, Hambidge C, Jacobs M, Baum JD. Low levels of zinc in hair, anorexia, poor growth, and hypogeusia in children. Pediatr Res. 1972;6(12):868-74. https://doi.org/10.1203/00006450-197212000-00003

    PMid:4509185
46. Gibson RS, DeWolfe MS. The zinc, copper, manganese, vanadium, and iodine content of hair from 38 Canadian neonates. Pediatr Res. 1979;13(9):959-62. https://doi.org/10.1203/00006450-197909000-00001

    PMid:503662
47. Sandusky-Beltran LA, Manchester BL, McNay EC. Supplementation with zinc in rats enhances memory and reverses an age-dependent increase in plasma copper. Behav Brain Res. 2017;333:179-83. https://doi.org/10.1016/j.bbr.2017.07.007

    PMid:28693861
48. Duch H, Fisher EM, Ensari I, Font M, Harrington A, Taromino C, *et al.* Association of screen time use and language development in Hispanic toddlers: A cross-sectional and longitudinal study. Clin Pediatr (Phila). 2013;52(9):857-65. https://doi.org/10.1177/0009922813492881

    PMid:23820003
49. Zhang Z, Adamo K, Ogden N, Goldfield GS, Okely AD, Kuzik N, *et al.* Associations between screentime and cognitive development in preschoolers. Pediatr Child Health. 2021;41(3):351-60.
50. Madigan S, Browne D, Racine N, Mori C, Tough S. Associaton between screen time and children’s performance on a developmental screening test. JAMA Pediatr. 2019;173(3):244-50. https://doi.org/10.1001/jamapediatrics.2018.5056

    PMid:30688984