RESEARCH ARTICLE

Effect of Zinc and Iron Supplementation on Appetite, Nutritional Status and Intelligence Quotient in Young Children

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Abstract

BACKGROUND: Lack of appetite in young children leads to growing incidences of physical and mental growth disorders. Supplementation of certain micronutrients can increase appetite and improve nutritional status. This study aims to analyze the effects of zinc and iron supplementation on appetite, nutritional status and intelligence quotient (IQ) in young children.

METHODS: An experimental study with randomized control group pre/post-test design was conducted in Semarang, Indonesia. A total of 68 children were divided into four groups. The first group was the control group, which was given a placebo; the second group was given a zinc supplement at 10 mg/day; the third group was given an iron supplement at 7.5 mg/day; and the fourth group was given zinc and iron for three months. Appetite was assessed based on eating frequency and energy intake. Nutritional status was assessed by weight per age (W/A) and height per age (H/A) z score. IQ score was assessed based on Wechsler Preschool and Primary Scale of Intelligence (WPPSI).

RESULTS: Before intervention, low zinc intake was observed in 27.7% of the subjects and low iron intake was observed in 58.5% of them. After intervention, appetite in the second and fourth groups increased. W/A z score increased in the second and third groups. IQ score increased in the third group. No significant effect on H/A z score was observed in all groups.

CONCLUSION: Supplementation of zinc and iron for three months had a positive effect on appetite, body weight and IQ score but no significant effect on body height.

KEYWORDS: appetite, zinc, iron, growth

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Introduction

Toddlers (children 3-5 years old) are experiencing rapid growth and development, so they need higher intake of energy. Adequate food intake means having good quality and quantity of food in accordance with the needs of toddlers. The energy needs of toddlers 3-5 years old is 1,000-1,500 kcal/day.(1) This requirement can be met if a toddler eats regularly with a frequency of at least three main meals and two snacks a day; the meals should be frequent because the toddler's stomach capacity is not large. The problem often faced is the lack of appetite of toddlers so that the intake of food is reduced significantly. This condition prevents nutritional needs from being met, which may result in malnutrition and growth disorders.(2,3)

Low appetite may be due to factors such as disease, deficiency of nutrients, use of medication, and psychological issues. Deficiency of nutrients, especially micronutrients, is often experienced by toddlers. For example, anemia caused by iron deficiency can reduce appetite.(4) According to Health Research in 2013, prevalence of anemia in children aged 12-59 months was 28.1%.(5) This figure is quite high, so immediate intervention is needed. In addition to

iron, micronutrients that can affect appetite are necessary, including vitamin A, vitamin B (niacin, thiamin and cyanocobalamin), choline, magnesium and zinc.(6)

Zinc is needed by humans and animals to perform physiological functions such as growth, immunity and reproduction. Zinc deficiency causes anorexia, growth and taste disorders, dermatitis and hypogonadism.(7) Although animal studies have proven that zinc deficiency causes anorexia, the relationship between zinc deficiency and anorexia in humans remains unclear. Zinc is estimated to increase appetite through stimulation of the vagus nerve, which then affects the appetite center in the hypothalamus.(8) The prevalence of zinc deficiency in children under five years old in Indonesia is not yet known, but it is thought to be high considering that toddler diets in Indonesia are not in accordance with the recommended guidelines for balanced nutrition.(5) The results of a 2015 study stated that zinc intake in infants in the city of Semarang covered 30% of those who are categorized as poor.(3)

Iron and zinc are also very important in the growth and development of cognitive functions.(9) Many studies have shown that zinc and iron deficiency cause stunted growth and disorder of cognitive function.(10,11) For example, studies have been conducted on the effect of zinc supplementation (and combinations) on the growth of stunted children, and the effect of iron supplementation (and combinations) on the development of anemic children. (7,12) Cognitive development in children who received iron or zinc supplementation higher than placebo. Single supplementation with zinc significantly improved growth, and single supplementation with iron significantly improved growth and psychomotor development, but combined supplementation with iron and zinc had no significant effect on additional growth or development.(2) Supplementation with zinc-iron combination proved harmless and can be used as an alternative to overcome anemia and zinc deficiency. (13) However, a meta-analysis covering 18 studies suggests that zinc and iron fortification only affects body weight and not body height.(4)

Anorexia in young children cannot be taken lightly because it can have a negative impact on growth and development.(14) Many children who currently do not have a disease may experience anorexia, most likely because of deficiency in micronutrients.(15) Parents often try to give multivitamin supplements but this approach has failed to boost children's appetite. However, parents who are unable to buy supplements often ignore this situation because they think anorexia is not an urgent condition that must be addressed immediately.(16)

Many supplements containing vitamins and minerals are sold in the market, but the composition is not necessarily appropriate, and sometimes the price is not affordable to poor families.(10) Sometimes, fortified foods contain excessive nutrient composition, which is not required to increase the appetite and nutritional status of children. Supplements with specific micronutrients in the right dose are more effective to increase appetite and nutritional status. (4,6) Preparations containing only zinc or iron are more affordable than multivitamin supplements. Furthermore, the given dose is better adapted to the needs of children and can prevent side effects. Based on the preceding information, researchers are interested in evaluating the effects of zinc and iron on the appetite and nutritional status of children aged 2-5 years.

Methods

This experimental study was conducted from November 2016 to February 2017 in Semarang, Indonesia. A total of 68 subjects met the inclusion criteria: age of 30-59 months, not suffering chronic disease, without a history of allergy to zinc and iron, and with parents who are willing to sign the informed consent. The subjects were randomly divided into 4 groups, and each group consisted of 17 subjects. The first group (control group) was given a placebo, the second group was given a zinc supplement at 10 mg/day, and third group was given an iron supplement at 7.5 mg/day, and the fourth group was given zinc at 10 mg/day and iron at 7.5 mg/day. Intervention was conducted for three months.

Sample Size and Randomization

Major outcomes such as changes in appetite, z score weight per age (W/A), height per age (H/A), and intelligence quotient (IQ) score determined sample size with α=0.05 and a power of 80% from each group. An independent statistician, who kept the block size, planned and prepared the randomization list. Participants were randomly assigned to treatment groups by the field team according to the randomization list once eligibility have been met. Blinding the field team and participants were achieved through identical packaging with codes of 4 different supplements from the pharmaceutical company, without knowing their contents. The allocation codes for each identical packaging would be kept in safes at the administrative office of Diponegoro University, by the independent statistician, until the database ready to be revealed for analysis.

Outcomes

Major outcomes were changes in appetite, z score W/A, H/A and IQ score. Appetite was assessed based on eating frequency and total energy intake in a day. Total energy intake is total energy of the food calculated by adding together the energy provided from protein, total fat, carbohydrate and dietary fiber. Total energy intake, iron intake, zinc intake, body weight, height and eating frequency every day were measured every two weeks. IQ score was measured before and after intervention using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) method. Nutrient intake was measured using the Semi-quantitative Food Frequency Questionnaire and was analyzed by NutriSurvey 2007 (EBISpro, Willstaett, Germany). Nutritional status was determined by measured z score W/A and H/A using the World Health Organization's standard anthropometry for 2005.

Body weight was measured using a digital body weight scale with nearest 0.1 kg, and body height was measured using microtoise with nearest 0.1 cm. Zinc supplementation was given in the morning while iron was given in the evening. Supplement combination of zinc and iron must be given at different times because they have negative interaction. Wasting was determined if z score W/A <−2, and normal weight was determined if z score W/A ≥−2. Stunting was determined if z score H/A was <−2, and normal height was determined if z score H/A was ≥−2. IQ was categorized as high if the score was ≥110, normal if the score was 90–109, and under average if the score was <90.

Data were analyzed with dependence t test to measure mean differences between pre- and post-intervention in each group. ANOVA and Kruskal-Wallis tests were used to analyze the differences between the control and intervention groups. This trial was approved by the Ethics Committee of the Medical Faculty of Diponegoro University with the certificate number 1.000/EC/FK-RSDK/2016 and funded by a grant from the Ministry of Research, Technology and Higher Education of the Republic of Indonesia.

Results

This study began by screening 240 preschool children in Jomblang village. Among them, 80 children met the inclusion criteria and were divided randomly into four groups. Overall, 68 children (17 subjects in each group) completed the trial. The characteristics of subjects before intervention are reported in Table 1.

Table 1. Characteristics of subjects before intervention.

Variable	*n*	%
Sex		
Male	31	45.6
Female	37	54.4
Age (months)		
25–36	22	32.3
37–48	21	30.9
49–60	25	36.8
Eating frequency (times/day)		
<4	46	67.6
≥4	22	32.4
Nutritional status according to z score W/A		
Wasting	21	30.9
Normal	47	69.1
Nutritional status according to z score H/A		
Stunting	19	27.9
Normal	49	72.1
IQ Score		
<80	0	0
80–89	25	38.5
90–109	40	61.5
≥110	0	0
Zinc intake		
Low	17	26.2
Normal	48	73.8
Iron intake		
Low	38	58.5
Normal	27	41.5
Energy intake		
Low	37	53.8
Normal	31	46.2

Table 2 presents the comparison in each group before and after intervention. Table 3 presents the differences between groups. The analysis showed that after intervention, the eating frequency in the second and fourth groups increased significantly. In the second and third groups, the z score W/A increased significantly, whereas the increase in IQ scores were significant only in the third group. The z score H/A before and after intervention did not change significantly in all groups. When the groups are compared, the average eating frequency in the second group was significantly different (p=0.02) from that of the first group after intervention. Furthermore, the average eating frequency in the fourth group was significantly different (p=0.004) compared with group 1 intervention. The z score

Table 2. Minimum, maximum, and mean ± SD of eating frequency, z score, IQ score and energy intake pre- and post-intervention.

Variable	Group 1		Group 2		Group 3		Group 4	
	pre	post	pre	post	pre	post	pre	post
Eating frequency								
Min	2	3	3	3	2	3	2	3
Max	5	5	5	6	5	5	5	6
Mean ± SD	3.9 ± 0.85	4 ± 0.78	4.16 ± 0.76	4.8 ± 0.94	4.3 ± 1.4	4.25 ± 0.68	4.1 ± 0.85	5 ± 0.87
p	0.27		0.015		0.83		0.001	
Z score W/A								
Min	−4.28	−3.36	−3.01	−2.55	−3.77	−4.09	−3.92	−3.84
Max	2.71	2,7	−0.47	−0.42	2.88	2.88	−0.1	1.57
Mean ± SD	−0.75 ± 1,5	−0.8 ± 1.4	−1.9 ± 0.75	−1.79 ± 0.72	−0.4 ± 1.78	−0.24 ± 1.75	−2.08 ± 0.96	−1.88 ± 1.34
p	0.091		0.004		0.021		0.119	
Z score H/A								
Min	−2.33	−2.15	−3.11	−3.23	−4.37	−4.32	−4.04	−3.48
Max	1.95	1,41	0.66	0.47	2.72	2.48	−0.27	−0.5
Mean ± SD	−0.68 ± 1	−0.65 ± 0.88	−1.68 ± 0.85	−1.7 ± 0.9	−0.5 ± 1.7	−0.46 ± 1.62	−2.16 ± 1.05	−2.05 ± 0.89
p	0.36		0.85		0.36		0.241	
IQ score								
Min	85	85	85	85	85	85	85	85
Max	95	100	95	100	95	105	95	95
Mean ± SD	88.67 ± 3.5	89.64 ± 4.14	88.89 ± 3.2	90.33 ± 4.41	88.44 ± 3	90.94 ± 5,23	88.75 ± 3.88	89.64 ± 3.65
p	0.27		0.96		0.041		0.5	
Energy intake								
Min	1041	1000	973.4	975	1077	849.2	1157.5	1068
Max	2239.9	2074	2255	2393	2444.8	2264.5	2246	2702
Mean ± SD	1519.98 ± 396	1532 ± 345	1558 ± 405	1669 ± 427	1581 ± 417	1668 ± 373	1612 ± 363	1976 ± 472
p	0.992		0.09		0.321		0.001	

W/A in the second group was significantly different (p=0.03) after intervention, whereas mean z score W/A in the third group, although significantly different before and after the intervention, was not significantly different when compared with the score of group 1 (p=0.3). Also, the average IQ score in the third group, although significantly different before and after intervention, was not significantly different from the score of group 1 (p=0.4). Total energy intake after intervention in the fourth group increased significantly.

Discussion

This study was conducted in Jomblang, Candisari District in Semarang. Jomblang Village is densely populated and most of the residents have a low economic status. Numerous cases of malnutrition in children have been observed in this region every year.17 The results of this study also show malnutrition cases from the prevalence of wasting and stunting in this region, 30.9% and 27.9%, respectively. Prevalence of zinc deficiency in this region is 12.3% and iron deficiency is 35.4%. Socioeconomic status is the main risk factor that leads to a high incidence of malnutrition in the region.(17)

In this study, appetite was measured by counting the eating frequency of main meals and snacks and also from total energy intake. Children aged 2-5 years old normally have eating frequency ≥ 4x every day and total energy intake >1000 kcal per day.(1) Before the intervention, many children had low appetite (67.6%), which caused a low nutrient intake that resulted in malnutrition. Low appetite in children can be caused by illness and micronutrient deficiency.(2)

In this study, supplementation of zinc and iron proved to increase the appetite of children. Zinc supplementation improved the mean of eating frequency from 4.16 to 4.8 times per day. This result is similar to the findings of previous study, who conclude that zinc supplementation

Table 3. The mean difference of eating frequency, z score, IQ score, and energy intake between groups pre- and post-intervention.

Variable	Group 1	Group 2	Group 3	Group 4	*p*
Eating frequency (times/day)					
Pre	3.9	4.16	4.31	4.06	0.65
Post	4.00	4.80	4.25	5.00	0.006
Z score W/A					
Pre	-4.28	-3.01	-3.77	-3.92	0.065
Post	-3.36	-2.55	-4.09	-3.84	0.002
Z score H/A					
Pre	-0.68	-1.68	-0.5	-2.16	0.064
Post	-0.65	-1.70	-0.46	-2.05	0.075
IQ score					
Pre	88.67	88.89	88.44	88.75	0.98
Post	89.64	90.33	90.94	89.64	0.82
Energy intake (kcal)					
Pre	1520	1558	1581	1612	0.93
Post	1532	1669	1668	1976	0.038

can increase calorie intake because it can boost the appetite of children.(18) Zinc is one of micronutrient that has many important role for body function.(19) It regulates certain hormone gene receptors, stimulates food intake through the afferent vagus nerve with subsequent effects on hypothalamic peptides associated with food intake regulation. Zinc also stimulates taste bud growth and function, therefore affecting the appetite.(20,21)

Other than that, in this study, a combination of zinc and iron can improve the eating frequency from 4.1 to 5 times per day. This result means that supplementation combination of zinc and iron can raise the eating frequency higher than supplementation with zinc alone or iron alone. Improved appetite can also be observed through an increased in energy intake. Furthermore, appetite can be assessed by analyzing total energy intake. Among the four groups, a significant increased in energy intake occurred in the fourth group, which proves that a combination of zinc and iron supplement may improve the appetite of children. Supplementation with zinc and iron also has been shown to improve the nutritional status of children. Recent studies observed the efficacy of combined zinc and iron supplement for growth and micronutrient status compared to zinc or iron supplementation alone. The study conducted in Vietnam made conclusion that combined zinc and iron supplement had significant effects to zinc and iron status in Vietnamese infants, while in northeast Thailand also made similar statement about combined iron and zinc supplementation that was more preferably to iron or zinc supplementation alone to improved iron and zinc status.(22,23)

This study differs from previous study observing zinc supplementation to increased appetite. The growth of children who received zinc supplementation was not better than the one observed in the control group. (24,25) Study also found that through supplementation of zinc, Nepali infants and toddlers might had better eating behavior, specifically among children with iron deficiency anemia.(26) This study was in line with these previous study but made progress in comparing with combined iron and zinc supplementation.

A significant increase in the z score W/A was observed in groups after intervention. The increase in body weight can be due to an increase in appetite. It has been studied that zinc may stimulate appetite and energy intake or increase fat-free mass.(7) However, in this study, the z score H/A in all groups has not increased significantly because the period of supplementation is relatively short (only three months). The process of linear growth or height gain in children aged above 2 years is slower than that for children under 2 years, so a longer time is needed to increase the height significantly.(9) Zinc supplementation with multivitamins for 6 months can increase the height and weight of children more than the placebo can (4.9±1.3 vs 3.6±0.9 cm, $p<0.001$).(27) On the contrary, a study stated that iron and zinc supplementation improved iron and zinc status, but not physical growth, of healthy, breast-fed infants.(22) Other study found that daily iron supplementation might impair linear growth in iron-replete children despite containing the growth-promoting micronutrient zinc.(28) These results show that physical growth differs by age and might not just as simply lack of zinc but other factors, such as other micronutrient, involved for children in order to gain normal physical growth. Supplementation significantly reduced anemia, iron deficiency anemia or zinc deficiency, but overcoming these deficiencies is not sufficient to improve growth for infants with this condition.(29)

At the beginning of this study, the majority of subjects (61.5%) had normal IQ scores, 38.5% are under average, and none had high IQ scores. Low IQ scores affect the development and future achievements of a child because such scores cause difficulties in receiving lessons and solving problems.(30,31) Thus, effort to improve children's intelligence is more easily done at an early age by providing adequate nutrition and appropriate stimulation.(32,33) In this study, the increased in IQ score was only observed in

the third group. IQ score in the third group, which received iron supplement, increased by 2.5 points. Iron supplement can improve IQ scores because iron is very important for fetal brain to develop normally, myelination process, and the development and function of certain neurotransmitters. On the developing brain, iron needed due to its role in hemoproteins and part of non-heme enzymes that rely on the iron molecule for their activity. Thus, sufficient iron levels are essential for brain functioning and intelligence. A low level of iron in the blood prevents an improvement in brain functioning and therefore hinders an increase in the IQ scores of subjects.(34,35)

In the fourth group, which received a combination of zinc and iron supplement, no significant increase in IQ score was observed. The reason could be the negative interaction between zinc and iron, which can inhibit the absorption of each nutrient. The inhibition occurs primarily if the two minerals are ingested together in the absence of food, compounds with absorptive properties different from those of iron sulfate and zinc sulfate, and if iron is present as non-heme iron in a ratio with zinc of 2 : 1.(2,8) Before providing supplementation to the subject, the parents of the subjects were instructed to give both of these supplements with a time lag of at least 2 hours. This approach aims to prevent the emergence of negative interaction. However, 12 respondents were reluctant to provide the supplement simultaneously, thereby might result in a negative interaction that reduces the effect of each supplement.

Strength and Limitation of Study

This study aimed to assess the effect of iron and zinc supplementation on appetite, IQ in young children, and nutritional status through W/A and H/A. Two micronutrients that have negative interaction was used in this study but in order to minimize outcome bias, a certain time lag had been given. Nevertheless, the designed method used in this study was made to compare each supplement and combined supplement. This study provided the evidence that combined daily iron-zinc supplementation had a significant positive effect on appetite and energy intake. Small sample size and short term follow up (3 months) might affects the outcome off this study. Other non significant result, such as H/A might be different with longer follow up. Further randomized control trial study of each micronutrient alone or combined micronutrient, with sufficient size, preferably across populations with different nutritional status, is needed to make definitive conclusions as to the benefits and harm of daily supplementation in this age group.

Conclusion

Zinc supplementation alone can significantly increase the appetite and nutritional status of children according to W/A. Iron supplementation alone can significantly improve the nutritional status of children according to the W/A and IQ scores. A combination of zinc and iron supplement can significantly increase the appetite of children. In all groups, the zinc and iron supplement for three months has not been able to improve the nutritional status according to the H/A. It is recommended that supplementation needs to be continued throughout a longer period to have a significant effect on the nutritional status of children according to H/A.

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References

1. Kirsty, Hendricks CD. Manual of pediatric nutrition, 4th edition. Ontario: BC Decker; 2005.
2. Lind T, Lönnerdal B, Stenlund H, Gamayanti IL, Ismail D, Seswandhana R, *et al*. A community-based randomized controlled trial of iron and zinc supplementation in Indonesian infants: effects on growth and development. Am J Clin Nutr. 2004; 80: 729-36.
3. Dewi A. Gambaran asupan zat gizi mikro pada balita di Kota Semarang. Journal of Nutrition and Health. 2015; 3(2): n.p.
4. Eichler K, Wieser S, Rüthemann I, Brugger U. Effects of micronutrient fortified milk and cereal food for infants and children: a systematic review. BMC Public Health. 2012; 12: 506. doi: 10.1186/1471-2458-12-506.
5. Badan Penelitian dan Pengembangan Kesehatan Kementrian Kesehatan RI. Riset Kesehatan Dasar Tahun 2013. Jakarta: Kementrian Kesehatan RI; 2013.
6. Kim SH, Keen CL. Vitamin and mineral supplement use among children attending elementary schools in Korea: a survey of eating habits and dietary consequences. Nutr Res. 2002; 22: 433-48.
7. Arsenault JE, Romaña DL, Penny ME, Loan MDV, Brown KH. Additional zinc delivered in a liquid supplement, but not in a fortified porridge, increased fat-free mass accrual among young peruvian children with mild-to-moderate stunting. J Nutr. 2008; 138: 108-14.
8. Gropper SS, Smith JL. Advanced Nutrition and Human Metabolism. 6th edition. Belmont: Wadsworth; 2013.
9. Roche AF, Sun SS. Human Growth: Assessment and Interpretation. New York: Cambridge University Press; 2003.
10. Hoffbrand AV, Moss PAH. Kapita Selekta Hematologi. 6th edition. Jakarta: Penerbit Buku Kedokteran EGC; 2013.

11. Provan D, Baglin T, Dokal I, Vos JD. Oxford Handbook of Clinical Haematology. 4th edition. Oxford: Oxford University Press; 2015.
12. Hackett M, Melgar-Quiñonez H, Álvarez MC. Household food insecurity associated with stunting and underweight among preschool children in Antioquia, Colombia. Rev Panam Salud Publica. 2009; 25: 506-10.
13. Pudjiadi S. Ilmu Gizi Klinis Pada Anak. 2nd edition. Jakarta: Fakultas Kedokteran Universitas Indonesia; 1993.
14. Bryant-Waugh R, Markham L, Kreipe RE, Walsh BT. Feeding and eating disorders in childhood. Int J Eat Disord. 2010; 43: 98-111.
15. Almatsier S. Prinsip Dasar Ilmu Gizi. Jakarta: Gramedia Pustaka Utama; 2009.
16. DeSocio JE, O'Toole JK, Nemirow SJ, Lukach ME, Magee MG. Screening for childhood eating disorders in primary care. Prim Care Companion J Clin Psychiatry. 2007; 9: 16-20.
17. Anisa C. Status gizi dan gambaran hematologi balita. Journal of Nutrition and Health. 2016; 4(1): n.p.
18. Kelishadi R, Khademian M, Farhangpajouh N, Shahsanaee A, Bahreynian M, Mirshamsi M. Effects of zinc supplementation on subscales of anorexia in children: A randomized controlled trial. Pak J Med Sci. 2014; 30: 1213-7.
19. Hidayat A. Seng (zinc) : esensial bagi kesehatan. J Kedokter Trisakti. 1999; 18: 19-26.
20. Suzuki H, Asakawa A, Li JB, Tsai M, Amitani H, Ohinata K, *et al.* Zinc as an appetite stimulator - the possible role of zinc in the progression of diseases such as cachexia and sarcopenia. Recent Pat Food Nutr Agric. 2011; 3: 226-31.
21. Yagi T, Asakawa A, Ueda H, Ikeda S, Inui SMA. The role of zinc in the treatment of taste disorders. Recent Pat Food Nutr Agric. 2013; 5: 44-51.
22. Wasantwisut E, Winichagoon P, Chitchumroonchokchai C, Yamborisut U, Boonpraderm A, Pongcharoen T, *et al*. Iron and zinc supplementation improved iron and zinc status, but not physical growth, of apparently healthy, breast-fed infants in rural communities of Northeast Thailand. J Nutr. 2006; 136: 2405-11.
23. Berger J, Ninh N, Khan N, Nhien N, Lien D, Trung NQ, *et al*. Efficacy of combined iron and zinc supplementation on micronutrient status and growth in Vietnamese infants. Eur J Clin Nutr. 2006; 60: 443-54.
24. Silva APR, Vitolo MR, Zara LF, Castro CFS. Effects of zinc supplementation on 1- to 5-year old children. J Pediatr (Rio J). 2006; 82: 227-31.
25. Shakur S, Bano N, Malek MA, Kundu SK, Ahmed AU. Effect of zinc supplementation on appetite, growth & body composition in children suffering from non-specific etiology of feeding refusal with failure to thrive. Orion Med J. 2009; 32: 612-5.
26. Surkan PJ, Charles MK, Katz J, Siegel EH, Khatry SK, LeClerq SC, *et al.* The role of zinc and iron-folic acid supplementation on early child temperament and eating behaviors in rural Nepal: a randomized controlled trial. PLoS One. 2015; 10: e0114266. doi: 10.1371/journal.pone.0114266.
27. Rerksuppaphol S, Rerksuppaphol L. Effect of zinc plus multivitamin supplementation on growth in school children. Pediatr Int. 2016; 58: 1193-9.
28. Hasan MI, Hossain SJ, Braat S, Dibley MJ, Fisher J, Grantham-McGregor S, *et al*. Benefits and risks of Iron interventions in children (BRISC): protocol for a three-arm parallel-group randomised controlled field trial in Bangladesh. BMJ Open. 2017; 7: e018325. doi: 10.1136/bmjopen-2017-018325.
29. Dijkhuizen MA, Wieringa FT, West CE, Martuti S, Muhilal. Effects of iron and zinc supplementation in Indonesian infants on micronutrient status and growth. J Nutr. 2001; 131: 2860-5.
30. Moran VH, Lowe NM. Nutrition and the Developing Brain. New York: CRC Press; 2017.
31. Olney DK, Pollitt E, Kariger PK, Khalfan SS, Ali NS, Tielsch JM, *et al*. Young Zanzibari children with iron deficiency, iron deficiency anemia, stunting, or malaria have lower motor activity scores and spend less time in locomotion. J Nutr. 2007; 137: 2756-62.
32. Heller S. Get Smart: Samantha Heller's Nutrition Prescription for Boosting Brain Power and Optimizing Total Body Health. Baltimore, Maryland: Johns Hopkins University Press; 2010.
33. Low M, Farrell A, Biggs BA, Pasricha SR. Effects of daily iron supplementation in primary-school-aged children: systematic review and meta-analysis of randomized controlled trials. CMAJ 2013; 185: E791-802.
34. Cusick SE, Georgieff MK. The role of nutrition in brain development: the golden opportunity of the "first 1000 days". J Pediatr. 2016; 175: 16-21.
35. Georgieff MK. Nutrition and the developing brain: nutrient priorities and measurement. Am J Clin Nutr. 2007; 85: 614S-20S.