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Original Article

Iron status and developmental delay among children aged 24-36 months

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Abstract

Background Optimal child development is needed for adequate learning. Children, particularly toddlers, require iron for brain development, and consequently, overall development.

Objective To analyze for an association between iron status and developmental status in children aged 24-36 months.

Methods This explorative cross-sectional study was held in Kampung Melayu, Jakarta. Subjects were recruited using a total population sampling method. Data were collected through interview with parents, anthropometric examinations, and blood tests. Developmental status was determined using the *Ages and Stages Questionnaire-3* (ASQ-3) and iron status was based on ferritin, high sensitivity C-reactive protein (hs-CRP), and hemoglobin levels. Data analyses included Chi-square/Fisher's exact, Mann-Whitney, and logistic regression tests.

Results Of 80 subjects, 17.5% had developmental delay and 41.3% had deficient iron status. There was no significant association between iron status and developmental status in bivariate analysis, but the logistic regression analysis revealed that iron status (OR=6.9; 95%CI 1.328 to 35.633; P=0.022) and nutritional status (OR=11.75; 95%CI 1.551 to 88.979; P=0.017) contributed to developmental delay.

Conclusion Better iron status and nutritional status are associated with better child development of children aged 24-36 months. So efforts are needed to maintain iron status as well as nutritional status. **[Paediatr Indones. 2022;62:256-64 DOI: 10.14238/pi62.4.2022.256-64]**.

Keywords: *child development; iron status; children aged 24–36 months; ASQ-3*

The first 1000 days of life are key formative years for the nervous system. Brain development as well as neuro-behavioral also experiences rapid advancement at this time, as part of child development.[1,2] In children, development is evident with age and tends to be less prone to disruption after two years of age.[3] By this age, a developmental delay associated with gestational age can usually be detected, and neurological disorders can be identified.[4] However, the rapid development of the hippocampus can continue until the age of 3 years.[5] According to the *World Health Organization* (WHO), low-and middle-income (LAMI) countries have greater developmental difficulties in early childhood than high-income countries. This condition can lead to morbidities in children and adults.[6] Developmental delays were found in up to 25.8%[7] of children aged nine months to five years in Mongolia, and in 11.8% of preschool children in Iran.[8] The prevalence of developmental delay in Indonesia was

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estimated to be 13-18%.[9]

Developmental status assessments in early childhood could help in prevent or improve delays, so that brain development will not be impaired or long-lasting. Optimal development before entering school, can help children in their academic achievements and lifelong path to contributing to society.[6]

The third edition of the *Ages and Stages Questionnaire* (ASQ-3) is a child development screening tool, recommended by the *United Nations International Children's Emergency Fund* (UNICEF).[10] The ASQ-3 assesses five developmental areas, namely, communication, fine motor, gross motor, personal-social, and problem-solving. The assessment is done by interviews or observations. The ASQ-3 is easy to implement, low cost, involves parents,[10] and does not require special training.[3]

Child development is influenced by various factors such as age, sex, gestational age, birth weight, nutrition, maternal education, and family income.[9,11] Iron is an essential nutrient for child growth and development. In addition to the formation of red blood cells, iron plays a role in the development of nerve cells, namely for neurogenesis, myelination, and differentiation of brain cells.[12] Children with iron deficiency and anemia were found to have poor memory, less social interaction, delayed attention, and lower achievement.[13] However, studies have had inconsistent results. A study noted psychomotor development disorders in children with iron deficiency anemia,[14] but another study found that iron supplementation had no significant effect on language and motor development in children.[15] Iron is critical from the fetal stage to the age of 3 years. If iron deficiency occurs during this time, the child will be at risk for neurobehavioral disorders.[1] Persistent iron deficiency can lead to decreased hemoglobin levels or iron deficiency anemia. The WHO reported that the prevalence of anemia in children reached 42.6%, or around 273.2 million worldwide.[16] Iron deficiency anemia in children is common until the age of 3 years.[17] A previous study found the prevalence of infant iron deficiency anemia in East Jakarta to be 27.3%.[18]

Serum ferritin is used to assess iron status and the most frequently used indicator of iron deficiency.[19] In the absence of inflammation, serum ferritin concentration represents the amount of body iron reserves. For children <5 years, ferritin level of <12 g/L or < 30 g/L during infection indicates iron depletion,[20] and hemoglobin <11 g/dL indicates anemia.[21] Increased level of high-sensitivity C-reactive protein (hs-CRP) describes the body level of inflammation.[22]

Given the importance of screening for child development to support the learning process before entering preschool, and the need for adequate iron to support brain development at this age, we aimed to assess for a possible association between iron status and developmental status in children aged 24-36 months.

Methods

An cross-sectional study was conducted in Kampung Melayu, Jakarta, from September to October 2020. Due to the Covid-19 pandemic, total population sampling was a restricted to two weeks, as allowed by the local government. The study subjects were healthy children aged 24 to 36 months who came to the primary health centre of Kampung Melayu, Jakarta, and whose parents provided written informed consent. Children with congenital disorders and syndromes, cerebral palsy, epilepsy, mental disorders, fever, or respiratory infections were excluded. This study protocol was approved by the Health Research Ethics Committee Faculty of Medicine, Universitas Indonesia, Jakarta.

Data were obtained from interviews, anthropometric examinations, and blood tests. Subject characteristics consisted of age, gender, birth weight, gestational age, family income, and maternal education. Birth weight was classified into low (<2,500 grams) or normal (≥2,500 grams). Gestational age was classified into preterm (<37 weeks) or full term (≥ 37 weeks). Family income was classified into low (below the Jakarta Provincial Minimum Wage of Rp 4,276,350/mo) or high (>Rp 4,276,350/mo). Maternal education was classified into low (graduated from junior high or below), medium (some or graduated from high school), or high (some or graduated from college).

Child developmental status was assessed using the ASQ-3, which consists of 5 areas and 30 questions, by interviewing subjects' parents/caregivers. Scores varied by answer: 10 points for "yes," 5 points for "sometimes,", and 0 points for "not yet."[23] The total scores of each developmental area were compared to cut-off values. Developmental status was classified as delayed if at least one area was below the cut-off value and no delay if all areas scored above the cut-off values.

Weights and heights of subjects were measured using a *SECA* digital scale (nearest 0.1 kg) and *SECA* stadiometer (nearest 0.1 cm), respectively. Each measurement was performed twice and the averaged score was taken, according to standard procedure.[24] Nutritional status of body weight/body height was based on the 2006 WHO growth standard[25] and classified into insufficient (Z-score -2 SD) or sufficient (Z score -2 SD).

Blood iron status was based on levels of ferritin, hs-CRP, and hemoglobin. Ferritin examination was done by immunoassay method,[20] hs-CRP by immunoturbidimetric method,[22] and hemoglobin by cyanmethemoglobin method.[26] Iron status was classified as deficient for ferritin 12 g/L or ferritin 30 g/L when hs-CRP was 10 mg/L, and iron status was considered to be normal for ferritin >12 g/L or ferritin >30 g/L when hs-CRP was >10 mg/L, with hemoglobin level 11 g/dL or 11 g/dL.

Data analysis was performed using *Statistical Package for the Social Sciences (SPSS) version 20.0*. Categorical data are presented as frequencies and percentages. Data normality was tested using the Kolmogorov-Smirnov statistical test, and presented in mean ± standard deviation if the data distribution was normal ($P>0.05$) or in median (range) if the data distribution was not normal ($P<0.05$). Subjects' characteristics, nutritional status, iron status, and developmental status were analyzed by Chi-square/Fisher's exact tests for categorical variables and Mann-Whitney test for continuous variables. Multivariate analysis with logistic regression was applied to assess the contribution of other factors to child development. Results with P values <0.05 were considered to be statistically significant.

Results

The median age of the 80 subjects was 30 (24-36) months. There were 41 male subjects (51.3%). Most subjects were born full term, had normal birth weight, sufficient nutritional status, moderate maternal education, and low family income. The subjects' characteristics are shown in **Table 1**.

Of 14 subjects (17.5%) with developmental delay, two subjects each had two areas below the cut-off values. One of these subjects had a score below the cut-off value in the communication and problem-solving areas, and the other subject had scores below the cut-off value in the fine motor and problem-solving areas. Thus, in total there were 16 subjects in the areas of developmental delay, as shown in **Table 2**.

The median age of those with developmental delay was 26.5 (24-35) months. Developmental delay occurred more common in males (8/14 subjects). For the purpose of analysis, maternal education was narrowed to low and medium-high. The distribution of developmental status based on subjects' characteristics is shown in **Table 3**. There was no significant association between iron status and developmental status in bivariat analysis. Thirty-three subjects (41.3%) had deficient iron status (**Table 4**).

Table 1. Subjects' characteristics

Characteristics	(N=80)
Median age (range), months	30 (24-36)
Gender, n (%)	
Male	41 (51.3)
Female	39 (48.8)
Gestational age, n (%)	
Preterm	3 (3.8)
Full term	77 (96.3)
Birth weight, n (%)	
Low	12 (15)
Normal	68 (85)
Nutritional status, n (%)	
Insufficient	7 (8.8)
Sufficient	73 (91.3)
Maternal education, n (%)	
Low	33 (41.3)
Medium	45 (56.3)
High	2 (2.5)
Family income, n (%)	
Low	59 (73.8)
High	21 (26.3)

Table 2. Subjects' developmental status

Variables	(N=80)
Developmental status, n (%)	
Delay	14 (17.5)
No delay	66 (82.5)
Areas of developmental delay, n	(n=16)
Communication	5
Gross motor	1
Fine motor	5
Personal-social	1
Problem-solving	4

Table 3. Distribution of developmental status based on subjects' characteristics

Variables	Developmental status		OR (95%CI)	P value
	Delay (n=14)	No delay (n=66)		
Median age (range), months	26.5 (24-35)	30 (24-36)	-	0.115
Gender, n (%)				0.627
Male	8 (19.5)	33 (80.5)	1.333 (0.417 to 4.267)	
Female	6 (15.4)	33 (84.6)	1	
Gestational age, n (%)				0.443
Preterm	1 (33.3)	2 (66.7)	2.462 (0.208 to 29.201)	
Term	13 (16.9)	64 (83.1)	1	
Birth weight, n (%)				1.000
Low	2 (16.7)	10 (83.3)	0.933 (0.181 to 4.817)	
Normal	12 (17.6)	56 (82.4)	1	
Nutritional status, n (%)				0.098
Insufficient	3 (42.9)	4 (57.1)	4.227 (0.829 to 21.543)	
Sufficient	11 (15.1)	62 (84.9)	1	
Maternal education, n (%)				0.643
Low	5 (15.2)	28 (84.8)	0.754 (0.228 to 2.496)	
Medium-high	9 (19.1)	38 (80.9)	1	
Family income, n (%)				1.000
Low	10 (16.9)	49 (83.1)	0.867 (0.240 to 3.132)	
High	4 (19)	17 (81)	1	

Table 4. Subjects' iron status

Iron status	(N=80)
Deficient, n (%)	33 (41.3)
Iron deficiency	12 (15)
Iron deficiency anemia	21 (26.3)
Normal, n (%)	47 (58.8)

While developmental delay was more common in children with deficient iron status (24.2%), there was no statistical significant association (**Table 5**). Children's development is not only influenced by iron status, so a multivariate test was performed to assess for the contribution of other factors that could potentially influence developmental status. Subjects with deficient iron status had a 6.9 times higher risk of developing developmental delay (P=0.022). Subjects with insufficient nutritional status had an 11.75 times higher risk of developing developmental delay (P=0.017) (**Table 6**; **Figure 1**).

Discussion

Subjects' median age was 30 months, with comparable numbers of males and females. In addition, 3.8% of subjects were pre-term and 15% of subjects had low birth weight, both of which can affect the behavior and development of children.[27] Children with a history of low birth weight are also at risk of developing iron deficiency anemia.[28] The percentage of subjects with insufficient nutritional status (8.8%) was higher than reported for Jakarta children aged 0-59 months (6.2%).[29] This observation may have been caused by the COVID-19 pandemic which affected family purchasing power such that children's daily food intake was reduced. However, most subjects had adequate nutrition, despite moderate maternal education and low family income. Parents may have prioritized their children's food supply, regardless of the existing economic conditions. Furthermore, they may have received food assistance from the government.

In our study, 17.5% of subjects had developmental delays based on ASQ-3. This figure was higher than other studies using ASQ-3, namely in Iran (11.8%)8 and Singapore (13.6%).[30] This difference may have been due to our smaller number of subjects compared to others. In addition, most of the participating mothers in Iran or Singapore had diplomas or tertiary education, so they may have had better awareness and knowledge to support child development. However, this figure was in agreement with the prevalence of developmental delay in Indonesia, which reached 13-18%.[9]

Table 5. Analysis of iron status and developmental status

Variables	Developmental status		OR (95% CI)	P value
	Delay (n=14)	No delay (n=66)		
Iron status, n (%)				
Deficient	8 (24.2)	25 (75.8)	2.187 (0.679 to 7.042)	0.184
Normal	6 (12.8)	41 (87.2)	1	

Table 6. Multivariate analysis with logistic regression on developmental delay

Variables	OR	95%CI	P value
Median age (range), months	0.790	0.620 to 1.007	0.056
Gender			
Male	2.076	0.440 to 9.794	0.356
Gestational age			
Preterm	15.337	0.505 to 465.414	0.117
Birth weight			
Low	0.822	0.100 to 6.733	0.855
Nutritional status			
Insufficient	11.749	1.551 to 88.979	0.017*
Maternal education			
Low	0.171	0.028 to 1.034	0.054
Family income			
Low	1.756	0.267 to 11.544	0.558
Iron status			
Deficient	6.879	1.328 to 35.633	0.022*

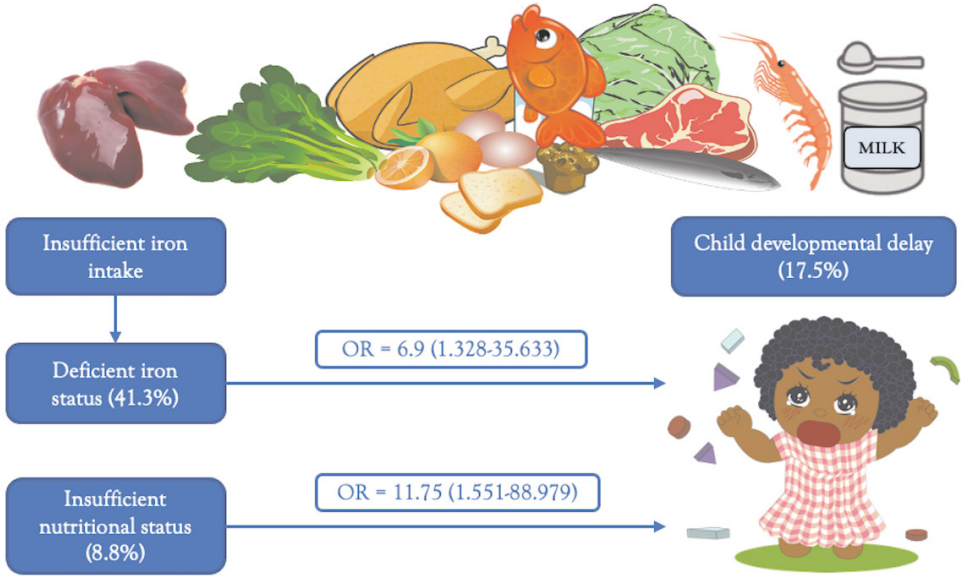

Figure 1. Association of iron status and nutritional status on child developmental delay

The median age of subjects with developmental delay was 26.5 (24-35) months, but there was no significant association between age and developmental status. Another study found a notable difference between screening results and age (P<0.000).[8] Most of their study subjects were older than ours, with age range 4-60 months old; child development stabilizes after passing the age of 2 years.[3]

In our study, more males had developmental delays than females, but there was no significant association between gender and developmental status. A similar finding was reported in South Africa, which suggests that the sex of the child can be a factor influencing child development because its interaction with other factors such as, birth weight, home circumtances, and socioeconomic.[11] Children with prematurity and low birth weight are at risk of suboptimal development.[6,31] Higher birth weight was associated with a lower incidence of developmental delay and better developmental performance.[11] Most of our subjects were born full term and had normal birth weight. There was no significant association between developmental status and gestational age or birth weight. However, a study in Rwanda found that birth weight and preterm were associated with developmental delay.[32] This finding may have been due to the high rate of developmental delay, especially among children who were born preterm or at low birth weight.[32]

Developmental delay is often found in children who have mothers with less than 12 years of education and low family income.[30] Mothers with higher education levels tended to be more responsive in interacting with children and provided more stimulating material.[33] Adequate family income can support the availability of an adequate food supply, reduce the risk of malnutrition, and, ultimately, affect cognitive and physical development.[3] However, we found no significant association between developmental status and maternal education level or family income.

In our study, 41.3% of subjects had deficient iron status; iron deficiency anemia was found in 26.3% of subjects. This figure was slightly lower than the national data for children under five years old (28.1%).[34] Iron is needed for brain activity, thus the body's iron adequacy must be considered. We found no significant association between iron status and developmental status, in contrast to an earlier study.[14] This difference may have been due to our iron status criteria, which is divide only to iron deficiency and normal iron status. In the earlier study, the iron status was divided to three criteria, iron deficiency anemia, iron deficiency, and normal. Otherwise, another study in adolescent in Sri Lanka found no significant association between iron status and smartness or educational achievement.[35] Several studies have shown mixed results. Surkan *et al.*[15] found that language and motor development scores were slightly higher in children given iron supplementation, but these scores did not differ significantly compared to non-supplemented children. In contrast, Akman *et al.*[36] showed that children with iron deficiency anemia had lower motor development score and children with iron deficiency and iron deficiency anemia had lower scores for mental development. However, after iron supplementation, the score differences were not significant. This outcome suggests that child development can be improved through iron supplementation,[36] but the benefits and consequences of iron supplementation on child development are still debatable.[37]

In our study, developmental delay was more common in subjects with deficient iron status, with a difference of more than 10% between deficient and normal iron status, suggesting that an association between iron deficiency and developmental delay is clinically crucial. Iron required for neurodevelopment, as a cofactor in myelin production, may be related to nerve conduction velocity.[12] A previous study found inferior motor function in children with iron deficiency, with and without anemia. This condition was due to changes in basal ganglia function and impaired myelination of the corticospinal tract, thus impacting motor development.[38] Iron is indispensable for dendrite formation and energy metabolism in the hippocampus, which is the center for memory, learning, and cognitive function.[5]

Apart from our small sample size, non-significant results could have been due to the influence of other factors on child development. Hence, multivariate analysis using logistic regression was performed. From the analysis, iron status and nutritional status contributed to developmental delay. Subjects with deficient iron status had a 6.9 times higher risk of developmental delay, and subjects with insufficient nutritional status had an 11.75 times higher risk of developmental delay. This result was in agreement with a study by Ahishakiye *et al.*[32] who found that children with wasting nutritional status had a 5.79 times higher risk of experiencing developmental delay compared to children with normal nutritional status.

Good nutritional status is supportive of optimal child development. Inadequate nutrition is a risk factor

for impaired neurological development, affecting children's learning abilities.[39] Behavioral problems or impaired cognitive function were found in children with acute malnutrition,[31] and developmental delay was associated with wasting.[32] However, there was no significant association between nutritional status and developmental status in our study. Brain development needs to be supported by adequate nutrition. Micronutrient deficiency and poor nutritional status are associated with developmental deficits in early and middle childhood.[40] Adequate iron storage in the body is related to the amount of iron intake.[41] Subjects with insufficient iron intake are at risk of having deficient iron status, which in turn can affect child development. Children's nutritional status was associated with cognitive development.[42] Nutrition-related biological disturbances in brain development can impact children, for example, impaired motor skills which can hinder their exploration then affects their cognitive development.[40] The conditions of wasting, stunting, and malnutrition affect the developmental attainment of children in Pakistan.[42] Children with undernutrition tend to be more unsociable and finicky, thus affecting the quality of children's interactions with caregivers and their exploration of their environment.[43] Children's smaller body size could affect the care or treatment given to them. Caregivers may provide non-age-appropriate stimulation, which could interfere with brain development.[43]

A limitation of our study was not assessing parenting style, quality, and duration of stimulation. In addition, because the study was done during the COVID-19 pandemic, selection bias may have occurred as overall parental interest in participating may have been reduced to avoid activities outside the home. As such, parents with concerns about their children's health may have been overly represented in our study. After evaluations, children with iron deficiency, inadequate nutritional status, and/or developmental delay were referred to Kampung Melayu Primary Health Center for further treatment.

In conclusion, iron status and nutritional status contribute to delayed child development. Therefore, it is necessary to monitor children's iron status and nutritional status. Regular health checks and providing adequate, healthy, nutritious, and varied food intake for children are recommended to maintain their nutritional status. Sufficient iron status can also be supported by consuming food sources of iron. In a pandemic, iron-rich food sources at affordable prices can be obtained from animal sources such as chicken liver, chicken eggs, beef liver, goldfish, tilapia, anchovies, and rebon shrimp, or vegetable sources such as spinach, sweet potato leaves, katuk leaves, red beans, tofu, and tempeh. Milk formula is also a good source of iron.

Conflict of interest

None declared.

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