

Association of Iron Deficiency with or without Anaemia and Cognitive Functions among Primary School Children in Malaysia

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ABSTRACT

Iron deficiency and anaemia affect millions of children worldwide. This study aimed to investigate the effect of iron deficiency with or without anaemia on cognitive functions, specifically with short-term memory, attention and visual-motor coordination in children. A total of 173 primary school children was enrolled. Cognitive functions were assessed using the Wechsler Intelligence Scale for Children. Three sub-tests were selected to assess processing speed (coding test), immediate auditory memory (digit span test) and visual processing and problem solving ability (maze test). The results showed significant correlation between age and coding test ($r = 0.38, p < 0.001$), digit span test ($r = 0.16, p = 0.028$), and maze test scores ($r = 0.28, p < 0.001$), and the total sub-test scores ($r = 0.43, p < 0.001$). After age adjustment of the cognitive function tests, iron deficient children without anaemia scored significantly lower than the healthy children ($p < 0.001$) on coding test, while iron deficient children with anaemia and iron deficient children without anaemia scored significantly lower ($p < 0.001$) than the healthy counterparts on maze test. No significant differences were observed on digit-span score among the groups. This study confirms the negative effect of both iron deficiency and iron deficiency anaemia on processing speed and visual-motor coordination in children.

Keywords: Anaemia, cognitive function, iron deficiency, Malaysia

INTRODUCTION

Iron deficiency anaemia is the most common form of nutritional deficiency in both developing and developed countries, affecting approximately 25 to 50% of the world's population (Saloojee and Pettifor,

2001; Khalifa *et al.*, 2009). The World Health Organization (WHO) estimates that some two billion people are anemic, and the majority due to iron deficiency (WHO, 2007). Even in developed countries such as the United States, the prevalence of iron deficiency anaemia is as high as 29% among

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low-income pregnant women (Bodnar, Cogswell & Scanlon, 2002). Among all age groups, the estimated prevalence of iron deficiency anaemia is greatest in adolescent girls and in young children during the period of brain development (Centers for Disease Control and Prevention, 2002; 2002). Without doubt, the prevalence of anaemia and iron deficiency is much greater and the challenges of combating the problem is far more complex in less developed regions, compared with the developed nations (Yip & Ramakrishnan, 2002). In a recent study conducted among aboriginal children aged 7-12 years in Malaysia, 49% were found to be anemic and 70% of the anemic children had iron deficiency (Al-Mekhlafi *et al.*, 2008). Over the last four decades, a considerable number of studies report the relationship between iron deficiency and iron deficiency anaemia with changes in cognitive function in children, but the topic still remains controversial especially in non-anemic iron deficient children (Grantham-McGregor and Ani, 2001; Sungthong, Mo-suwan & Chongsuvivatwong, 2002). Most of the studies so far have not established clearly whether the cognitive malfunction is a result of iron deficiency alone or iron deficiency with anaemia. However, iron level in the central nervous system decreases before restriction of red cell production, and thereby, the consequences in cognitive function may precede the haematological manifestation of anaemia (Yehuda & Youdim, 1989). Given the significant public health consequences of effects of iron deficiency without anaemia on cognition and behaviour, it is surprising that there is paucity of information on this topic (McGregor *et al.*, 2007; McCann and Ames, 2007; Walker *et al.*, 2007). The present study aimed to investigate the association between iron deficiency with or without anaemia on cognitive functions, specifically with short-term memory, attention and visual-motor coordination in primary school children in Malaysia.

METHODOLOGY

Study subjects

This cross-sectional study was conducted in three randomly selected rural primary schools as graded by the Ministry of Education, Malaysia. These schools were around 30 km south of Kuala Lumpur City and comprised mostly Malay ethnic students. Data collection was conducted between March through June 2001.

The subjects were selected using systematic sampling from the school registry. The total number of students was divided with the number of students required to fulfil the sample size of this study together with a 30% non-response rate. Based on this calculation, every 3rd students in the name list was included in this study. A letter explaining the research protocols and a consent form were sent to the parents of children. Only children between 9 to 11 years were recruited into the study after obtaining written informed parental consent and assent from the children. Children with chronic diseases, physical disability, hearing and learning difficulty were excluded. This study was approved by the Medical Research Ethics Committee of Universiti Kebangsaan Malaysia. Formal permission to undertake research in the selected schools was obtained from the Education Department of Selangor and the Ministry of Education, Malaysia.

Demographic and anthropometric information

Demographic data including age, gender, ethnic group, pre-school attendance, number of siblings and child position in the family were obtained from parents using a questionnaire. Socio-economic data, such as parent's education level, occupation and household income were also gathered using the questionnaire.

Body weight and height of children were measured with empty pockets and without belt, shoes and hat. Weight was measured

using a portable weighing scale (Seca, MD, USA) to the nearest 0.1 kg. Height was measured using a microtoise tape (Seca Bodymeter 208, Hamburg, Germany) to the nearest 0.1 cm. All measurements were recorded in duplicates on a standard form and calculated to obtain the average value. The mean z scores for weight-for-age and height-for-age were calculated and compared with the z-score tables of the WHO standards (2007).

Iron status determination

Capillary blood samples for the determination of haemoglobin (Hb) and serum ferritin were obtained from the middle finger using a aseptic technique. Hb was measured on site using the HemoCue B-Hemoglobin Photometer (HemoCue AB, Sweden). About 0.5mL of blood was collected into a plastic Eppendorf tube (Eppendorf, Germany) and placed in a cool box containing ice packs for serum ferritin measurement. All samples were centrifuged at 3500 rpm for 15 minutes and serum ferritin was measured within 4 hours at the Biochemistry Laboratory, University Malaya Medical Centre. Serum ferritin concentration was measured with the ACS:180 by using the ACS ferritin chemiluminometric immunoassay (Ciba Corning Diagnostics Corp., Medfield, MA). The assay was calibrated with the WHO IRP 80/602 standard (Virtanen *et al.*, 1999). The reliability of using capillary blood for serum ferritin assessment has been discussed earlier by Liappis, Mannmann & Schlebusch (1992) and Pootrakul, Skikne & Cook(1983). Iron deficiency was defined as serum ferritin less than 15 ng/mL, while anaemia was defined as Hb less than 12 g/dL (WHO, 2007). These cut-off values were used to classify subjects into three groups: healthy children with normal Hb (12 g/dL) and normal ferritin levels (≥ 15 ng/mL); iron deficient children without anaemia (ferritin < 15 ng/mL and normal Hb); and iron

deficient children with anaemia (ferritin <15 ng/mL and Hb <12 g/dL).

Cognitive function tests

The cognitive function of each subject was evaluated using three selected tests from the Wechsler Intelligence Scale for Children, third edition (WISC-III, 1991) which was translated to Bahasa Malaysia and back-translated accordingly. The translated WISC-III was pre-tested on five children. One of the authors (RA), who is a qualified child psychologist, examined the face validity. The three tests included coding, digit span and maze. The justification for the test selection was based on the application of these tests which is to assess processing speed (coding), immediate auditory memory and concentration (digit span) and visual processing and problem solving ability (maze). These WISC tests have been validated earlier as standard tests for cognitive function in older children (Chang *et al.*, 2007).

The tests were administered by the principal investigator to each subject placed in a quiet room. Instructions were given to the children according to a pre-prepared standard protocol. For the coding test the subject was instructed to complete a form that contained codes and matching numbers. This task needed to be completed within 120 seconds and the score was given for each correct answer. The digit span test is divided into digit forward and digit backward. The subject was required to repeat a series of numbers called by the researcher and the difficulty level increased after each successful answer. Each correct answer was given a score, which was summed for the final score. The maze test required the subject to draw a line from the centre towards the outside of a maze in a given time. Score was given based on the balance after deduction from a total value between 2 to 5 when an error was made. Each maze had different difficulty levels and needed to be completed in a given time.

Table 1. Anthropometric and socio-demographic characteristics among the three study groups of children

Characteristics	Healthy children (n = 143)	Iron deficiency with anemia (n = 11)	Iron deficiency without anemia (n = 19)	F-ratio	P-value ^a
Age (years)	9.4 ± 1.0	9.2 ± .86	9.5 ± .89	.22	.80
Sex: male/female (%)	46 / 54	45 / 55	37 / 63	-	.75 ^b
Birthweight (kg)	3.22 ± .45	2.96 ± .29	3.15 ± .44	1.55	.22
Weight for age	-.81 ± 1.17	-1.2 ± 1.13	-.42 ± 1.43	1.70	.35 ^c
Height for age	-.89 ± 1.09	-1.12 ± 1.09	-1.15 ± .97	.66	.60 ^c
Father's education (years)	10.9 ± 3.5	9.6 ± 4.3	10.3 ± 4.2	.77	.46
Mother's education (years)	10.0 ± 3.5	9.1 ± 3.6	9.4 ± 3.1	.64	.52
No. of siblings	5 ± 2	6 ± 3	6 ± 3	1.97	.14
Household members	7 ± 2	7 ± 2	7 ± 1	1.33	.27
Household income	1741 ± 1380	1238 ± 814	1776 ± 1407	.73	.44 ^c

The values are mean ± SD or proportion; ^aOne-way Analysis of Variance; ^bChi-square Test; ^cKruskal Wallis Test.

Scores for each test were adjusted to the age of respondents using a standard age scale table provided by the WISC-III company. Total scores were obtained by summing up the coding, digit span and maze age-adjusted score.

Statistical analysis

Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) version 17 (SPSS, Chicago, IL, USA). Distribution of data was assessed by descriptive analysis before the selection of an appropriate statistical test. The Pearson correlation coefficient test was used to determine the relationship between Hb, ferritin and cognitive test score. Partial correlation test was used to control for confounders. One-way ANOVA was used to compare baseline characteristics and cognitive function tests among the three groups: healthy children, iron-deficient children without anaemia, and iron-deficient children with anaemia. A *P*-value of <0.05 was considered statistically significant.

RESULTS

One hundred and seventy-six children were enrolled; three were excluded because they had anaemia but no iron deficiency suggesting non-iron related anaemia. Baseline characteristics of the three groups of study children (normal, children with iron deficiency and anaemia, and children with iron deficiency but no anaemia) were comparable (Table 1) and had no statistical differences in any of the characteristics. The nutritional status, as measured by weight for age *z*-scores and height for age *z*-scores indicated overall good nutritional status of the children.

On bivariate correlation tests, a statistical significant correlation was found between age and the three measures of cognitive function tests, such as coding test ($r = 0.38, p < 0.001$), digit span test ($r = 0.16, p = 0.028$), and maze test scores ($r = 0.28, p < 0.001$), and the total of the three function test scores ($r = 0.43, p < 0.001$) (Table 2). Furthermore, weight-for-age ($r = 0.15, p = 0.037$) and height-for-age ($r = 0.24, p = 0.001$)

Table 2. Correlation coefficient between age, nutritional status, haemoglobin, ferritin, and cognitive function test scores

	Weight/ Age	Height/ Age	Hb	Ferritin	Coding	Digit	Maze span	Total score
Age	.12	.10	.10	.02	.38**	.16*	.28**	.43**
Weight/Age		.55**	.15*	.06	.10	.06	.10	.12
Height/Age			.24**	.007	.09	.05	.10	.12
Hb				.30**	.15*	.02	.24*	.21*
Ferritin					.18*	.13	.27**	.27**
Coding						.31**	.23**	.91**
Digit span							.13	.46**
Maze								.59**

Weight/Age = weight-for-age; Height/Age = height-for-age; Hb = hemoglobin
 Coding = coding test; Digit span = digit span test; Maze = maze test
 Total subtests score = coding + digit span + maze test; * $P < 0.05$; ** $P \leq 0.001$.

correlated significantly with Hb (Table 2). Figure 1 shows the correlation between ferritin and age-adjusted cognitive function tests.

Table 3 shows one-way ANOVA test results of age-adjusted cognitive function tests among the three study groups: healthy children, children with iron deficiency and anaemia, and children with iron deficiency but no anaemia. All the test scores were higher among the healthy control children. Coding test scores differed significantly between healthy children and those with iron deficiency without anaemia ($p < 0.001$). Maze test scores were significantly higher in healthy children, as compared to children in the other two groups. Digit span test scores did not differ significantly among the groups. The total test scores, as expected, were significantly higher in healthy children, compared to others.

DISCUSSION

This study showed a negative effect of iron deficiency and iron deficiency anaemia on maze test, negative effect of iron deficiency without anaemia on coding test, and no effects of iron deficiency with or without anaemia on digit span test. Interestingly,

both maze and coding cognitive tests involve written tasks such as processing speed and visual-motor coordination, whereas digit span is an immediate auditory memory test. Although iron is required for both motor and brain functions (McCann & Ames, 2007), this study showed a direct relationship of iron status with children's motor function, but not their memory tests.

In our study, the mean coding score was the lowest among the children with iron deficiency without anaemia. It was 3.1 point lower among iron deficient children without anaemia than the healthy children. Anaemia is a process which shows clinical effects after iron storage has dropped to a level that affects the haematological system. Prior to development of anaemia, iron deficiency itself can affect the brain's neurochemical (Rao *et al.*, 2007) and myelination processes (Beard & Connor, 2003) that are involved in cognitive performance. It appears that the coding test could be sensitive to changes in cognitive functions as a result of iron deficiency before appearance of anaemia.

Children with iron deficiency anaemia scored the lowest in the maze test which measured visual-motor coordination. The uniqueness of the maze test is the task that

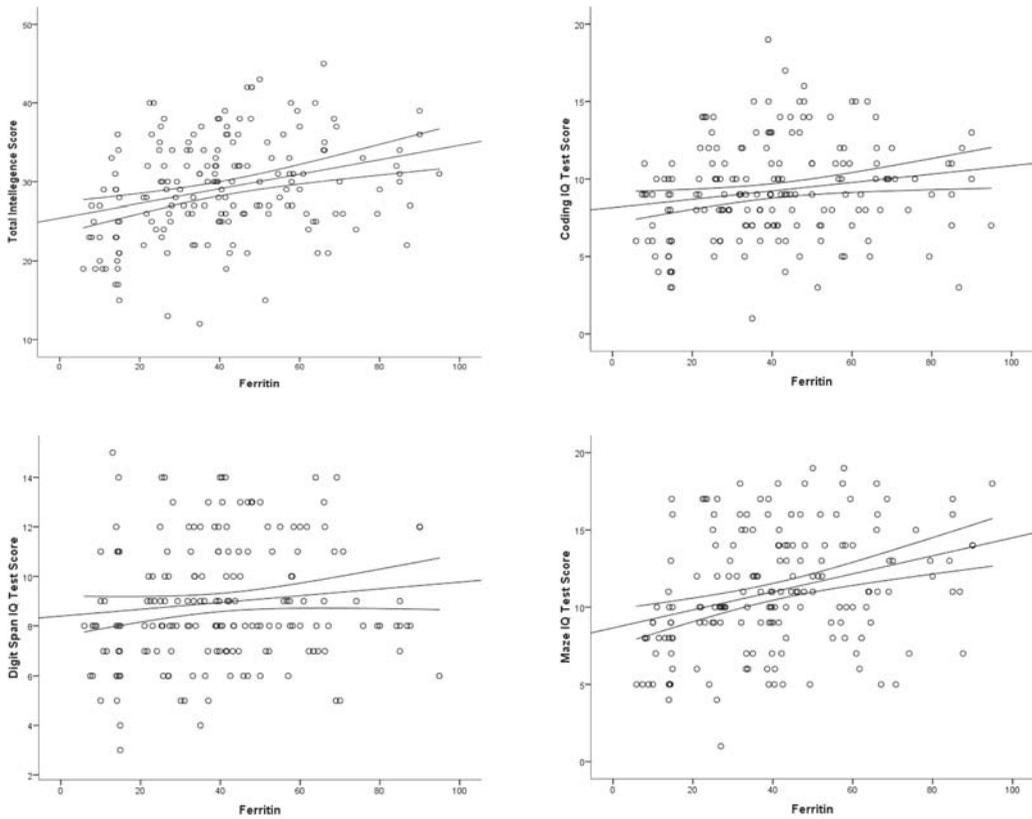


Figure 1. Correlation between ferritin (ng/mL) and age-adjusted cognitive function test scores. A linear fit model was used to draw total fit line with 95% confidence interval of mean.

Table 3. Age-adjusted cognitive function test scores among the three study groups

Characteristics	Healthy children	Iron deficiency with anemia	Iron deficiency without anemia	F-ratio	P-value ¹
Coding test	9.7 ± 3.1 ^a	7.9 ± 2.7	6.6 ± 2.3 ^b	10.10	<0.001
Digit span test	9.13 ± 2.4	7.8 ± 2.8	8.1 ± 2.8	2.71	0.07
Maze test	11.6 ± 3.8 ^c	6.4 ± 1.8 ^d	9.3 ± 3.2 ^e	13.15	<0.001
Total subtests score ²	30.2 ± 6.0 ^f	23.1 ± 5.5 ^g	24.5 ± 5.4 ^h	13.97	<0.001

The values are mean ± SD or proportion; ¹One-way Analysis of Variance; Tukey's HSD;

²Total subtests score = coding + digit span + maze

Test shows: a vs b, $p < 0.001$; c vs d, $p < 0.001$; c vs e, $p = 0.025$; d vs e, $p < 0.05$; f vs g, $p = 0.001$; f vs h, $p < 0.001$.

requires visualisation of the maze and also use of the hand to complete the maze. The whole process involves complex stimulation and signals from the eye, brain and muscles. Furthermore, as this task involves a time limit, the ability to complete each maze within the designated time makes this test more challenging. The finding on the anemic children is a clear example of the importance of iron for overall bodily function which affects cognition. A factor that has not been well studied is the role of the hand muscles used to complete the task. As iron is an important component for haemoglobin, it also has an important role in muscle function as a component of myoglobin. Study on athletes has shown lower performance in sports performance among anemic individuals (Clarkson & Haymes, 1995).

In our study, there was no significant correlation between ferritin and Hb with the digit span test, and the study groups also did not differ in digit span test scores. The digit span test requires the children to repeat a series of certain numbers and this task depends on the ability to recall numbers measuring the hearing and brain's ability. One of the explanations for this finding is related to the development of the brain. The human brain grows rapidly during the first three years of life and iron is an extreme requirement during this process (Kretschmann *et al.*, 1986). In this study, the age of the children ranged from 9 to 11 years. Hence, iron may not be the main factor for brain function at this age but may have an important role on other body functions such as the muscle performance.

Several confounders may interact in the association between iron status and children's cognitive functions. Children's cognitive growth starts from their intra-uterine environment (Cetin & Antonazzo, 2009) and continues to be influenced by household conditions (Bradley *et al.*, 2001). One important confounder of cognitive function is intrauterine growth retardation

(IUGR) (Matilainen, Heinonen & Siren Tiusanen, 2006; Many *et al.*, 2003). Children with IUGR had significantly lower cognitive functions and lower school grades compared with those with birth weights appropriate for gestational age (Tideman, Marsal & Ley, 2007). In our study the factor of IUGR was controlled by selecting children who were born full-term and had normal birth weights. For iron-related cognitive function studies, another established confounder is socio-economic status of the family (Hallberg, 1989; Bradley and Corwyn, 2002). Earlier studies in poor countries like Bangladesh (Durkin, Hasan & Hasan, 1998) and Kenya (Mung'ala-Odera *et al.*, 2006) have shown significant association between socio-economic factors and children's cognitive function. Perhaps due to the economic homogeneity of our study population, no association was found between socio-economic factors (such as parent's education and income) with cognitive function.

In this study, the WISC cognitive scores were directly correlated with age, which is an expected finding, because the ability to complete tasks depends on age. One of the strengths of this study was that we used age-adjusted cognitive function tests. Also the study results were valid for the population because the schools were selected randomly and the children were selected by systematic sampling. However, the samples were small for iron deficient groups. Another weakness of this study was the use of only ferritin as a measurement of iron deficiency. To discriminate for inflammation and infection, soluble transferring receptor should be measured, as ferritin may be increased in the above mentioned condition (Lee *et al.*, 2002). However, our children were apparently infection-free and otherwise healthy during the study period.

Several limitations should be considered when interpreting the study findings. First, the WISC cognitive function test is a western-based cognitive function

tool. Although physically, it was translated and validated for local language, the scoring format was determined using the guideline provided by the manufacturer. Furthermore, the raw score was adjusted based on the children's age which may lead to misinterpretation due to the differences in maturation between children from different regions. Finally, the low prevalence of iron deficient and anaemic children in this study may limit the strength of the findings.

CONCLUSION

Both iron deficiency without anaemia and iron deficiency with anaemia had negative effects on maze test and only iron deficiency without anaemia had negative effects on the coding test which involves processing speed, visual-motor coordination and active muscle movements, re-establishing the fact that iron is an important functional component of muscle function and attention. This study emphasises the importance of preventing not only anaemia but also iron deficiency in children in developing countries. The study results will help policy makers, public health officials, and clinicians in combating iron deficiency and reducing cognitive dysfunctions in young children.

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