RELATIONSHIP BETWEEN IRON DEFICIENCY ANAEMIA WITH COGNITIVE FUNCTION AND ACADEMIC PERFORMANCE OF THE PRIMARY SCHOOL CHILDREN IN BACHOK, KELANTAN

by

HASMIZA HALIB

Thesis submitted in fulfillment of the requirements

for the degree of

Master of Science

July 2012

ACKNOWLEDGEMENT

Alhamdulillah. Praise to ALLAH the Almighty.

First and foremost I would like to express my sincere gratitude to my supervisor Dr. Hamid Jan bin Jan Mohamed who was abundantly helpful and offered invaluable assistance, support and guidance throughout these years. Also deepest gratitude to my co-supervisor, Assoc. Prof. Pim Chau Dam for his assistance and knowledge and special thanks to Prof. Wan Manan Wan Muda for funding this project under the USM Research University research grants. Without the funding and help from these people this project would not have been accomplished. I would also like to show my gratitude to Assoc. Prof. Dr. Alvin Ng Lai Oon, lecturer and psychologist from the Universiti Kebangsaan Malaysia for his assistance, guidance and expertise regarding the Raven's cognitive test and also thank to Assoc. Prof. Dr. Ariifin Nasir, pediatrician from the HUSM for his kind in helping to examine and consult the patients with IDA.

I would also like to express my love and deepest gratitude to my beloved family especially my mother Rosnah Bahaman also to my lovely fiancé Muhammad Firdaus Adnan for their understanding, moral support and endless love during hard time of this study. I would like to thank many individuals, friends and colleagues who have not been mentioned here personally for their kind in helping me collecting data and assisting my lab work. Also, I have been grateful and blessed with a cheerful group of fellow postgraduate students. Not to be forgotten to all students, parents, principals and teachers of the schools involved are gratefully acknowledged in this study. Thanks also to the Ministry of Education and Kelantan State Department of Education for providing the permission and cooperation to the project. I would also like to extend my sincere gratitude to the Ministry of Higher Education and Universiti Sultan Zainal Abidin (UNiSZA) for providing me the scholarship to further my studies. Lastly, this thesis would not have been completed or written without the support of many people.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATION

IDA	Iron deficiency anaemia
ID	Iron deficiency
Hb	Haemoglobin
SF	Serum ferritin
LBW	Low birth weight
HAZ	Height-for-age
WAZ	Weight-for-age
NHANES III	Third National Health & Nutrition Examination Survey
RBC	Red blood cells
RCPM	Raven's coloured progressive matrices
SD	Standard deviation
WHO	World Health Organisation
MOH	Ministry of Health

PERKAITAN DI ANTARA ANEMIA KEKURANGAN FERUM DENGAN FUNGSI KOGNITIF DAN KEBOLEHAN AKADEMIK KANAK-KANAK SEKOLAH RENDAH DI BACHOK, KELANTAN

Abstrak

Anaemia kekurangan ferum merupakan salah satu masalah kekurangan mikronutrien yang paling kerap di seluruh dunia dan ia telah memberi kesan kepada jutaan kanak-kanak di dunia. Anaemia kekurangan ferum boleh membawa kepada masalah kesihatan yang lebih serius seperti menjejaskan fizikal dan juga mental kanak-kanak. Objektif utama bagi kajian ini ialah untuk mengkaji hubungkait di antara anaemia kekurangan ferum dan juga fungsi kognitif kanak-kanak sekolah. Kajian hirisan lintang telah di jalankan ke atas seramai 249 kanak-kanak Melayu sekolah rendah (122 lelaki dan 127 perempuan) berumur 7-9 tahun melalui persampelan sistematik di kawasan luar Bandar Bachok, Kelantan. Ukuran antropometri untuk berat dan tinggi diambil dan status pemakanan kanak-kanak ditentukan berdasarkan kepada *WHO 2007 growth reference.* Berat lahir direkod daripada sijil lahir. Sampel darah vena diambil bagi tujuan analisis hemoglobin dan ferritin. Kebolehan akademik kanak-kanak direkodkan berdasarkan kepada markah yang diperoleh daripada keputusan peperiksaan akhir sekolah yang merangkumi bahasa Melayu, Bahasa Inggeris, Matematik dan Sains. Fungsi kognitif diuji menggunakan *Raven's Coloured Progressive Matricess (RCPM)* yang telah diterjemahkan kepada Bahasa Melayu dan divalidasikan. Secara keseluruhan, lebih ramai kanak-kanak lelaki mengalami masalah malpemakanan berbanding kanak-kanak perempuan. Keputusan menunjukkan seramai 13.8% dan 16.3% kanak-kanak tersebut masing-masing mengalami kebantutan dan kekurangan berat badan. Berlebihan berat badan dan obesiti juga didapati di mana ia melibatkan seramai 5.6% dan 6.9% kanak-kanak. Keputusan juga mendapati seramai 12.6% kanak-kanak mengalami kekurangan ferum tanpa anemia dan 7.7% mengalami kekurangan ferum dengan anemia. Ujian korelasi pearson menunjukkan tiada korelasi yang signifikan di antara semua indikator status pemakanan seperti berat-untuk-umur, tinggi-untuk-umur serta BMI-untuk umur dengan fungsi kognitif kanak-kanak. Walaubagaimanapun, berat lahir ($r= 0.159$, $p<0.05$) dan serum ferritin ($r= 0.218$, $p<0.001$) didapati berkait secara signifikan dengan fungsi kognitif. Ujian analisis regresi berganda menunjukkan serum ferritin merupakan faktor penyumbang paling signifikan dalam penentuan keupayaan kognitif kanak-kanak ($R^2= 0.071$, $p< 0.001$). Kajian ini memberi penekanan bahawa ferum adalah komponen penting dalam menentukan fungsi kognitif kanak-kanak sekolah rendah. Oleh itu, adalah penting bagi menangani masalah malpemakanan dalam kalangan kanak-kanak terutamanya masalah anemia kekurangan ferum kerana ia memberi kesan negatif terhadap perkembangan kognitif kanak-kanak.

RELATIONSHIP BETWEEN IRON DEFICIENCY ANAEMIA WITH COGNITIVE FUNCTION AND ACADEMIC PERFORMANCE OF THE PRIMARY SCHOOL CHILDREN IN BACHOK, KELANTAN

Abstract

Iron deficiency anaemia (IDA) is the most common micronutrient deficiency in the world and it affects millions of children worldwide. IDA may leads to serious health problems such as poor cognitive and motor development As well as poor behavior in children. The main objective of the study was to investigate the relationship between IDA with cognitive function of the school children. A cross-sectional study was conducted on 249 Malay primary school children (122 males and 127 females) aged 7-9 years old by systematic sampling method in rural area of Bachok, Kelantan. Anthropometric measurement for weight and height were taken and nutritional status of the children was determined based on WHO 2007 growth reference. Birth weight was recorded from the birth certificate. Venous blood sample was drawn for haemoglobin and serum ferritin analysis. Academic performance was recorded based on marks obtained in the school final exam results in four subjects including Malay language, English, Mathemathics and science. Cognitive function was assessed using Raven's Coloured Progressive Matricess (RCPM) which has been translated to *Bahasa Malaysia* and validated accordingly. Overall, more male than female children experienced some form of malnutrition. The results showed that the prevalence of stunting and underweight were 13.8% and 16.3% respectively. Overweight (5.6%) and obesity (6.9%) was also found to be prevalent. Results revealed that the prevalence of iron deficiency without anaemia was 12.6% and 7.7% of the children was found to be iron deficient aneamia. Pearson's correlation test showed that there were no significant associations between all nutritional status indicators such as weight-for-age, height-for-age and BMI-for-age with the cognitive function of the children. However birth weight ($r= 0.159$, $p<0.05$) and serum ferritin ($r= 0.218$, $p<0.001$) correlated significantly with the cognitive function. Significant difference was also found between iron status of the children and the cognitive function ($F=20.41$, $p< 0.001$). Multiple linear regression tests showed that serum ferritin contribute the most of significant factors to the cognitive performance variance ($R^2= 0.071$, $p< 0.001$). The study emphasizes the fact that iron is an important component in determining the cognitive function of the school children. Thus it is important to overcome the problems of malnutrition especially iron deficiency anaemia among children as it affects the children's cognitive function.

CHAPTER I

INTRODUCTION

1.1 Introduction

Micronutrient deficiency and under nutrition are the most important nutritional problems worldwide (Müller & Krawinkel, 2005). Nutritional anaemia is one of the common micronutrient deficiencies and it is usually associated with deficiency of iron, folic acid and vitamin B_{12}. Among these micronutrient deficiency, iron deficiency is most commonly encountered among the population. Iron deficiency anaemia (IDA) is the most common micronutrient deficiency in developing countries (Hall *et al.*, 2001; Hashizume *et al*, 2003) including Malaysia (Tee *et al.*, 1998; Al-Mekhtafi *et al.*, 2008) as well as developed countries (Looker *et al*, 1997; Yip & Ramakrishnan, 2002). Generally, the prevalence of anemia is three to four times higher in developing countries compared to the developed countries (WHO/UNICEF/UNU 2001). It affects approximately 20-50 % of the world's population making it the most common nutritional deficiency worldwide, especially in young children and women (Saloojee & Pettifor, 2001).

In 2002, the World Health Organization (WHO) estimated anemia due to iron deficiency was one of the ten most important factors contributing to the global burden of disease which increases morbidity and mortality in children and pregnant women (WHO, 2002). WHO also estimated that about two billion people are anemic, and the majority of them are due to iron deficiency (WHO, 2007). In fact, prevalence of IDA was reported to be as high as 50% among East Asian school children and 60% among children less than 5 years of age (Stoltzfus, 2003). Even in developed countries such as the United States, iron deficiency anaemia has the highest prevalence among women and young children (Booth & Aukett, 1997; Bodnar *et al.*, 2002).

Several studies have shown a serious consequences of anaemia including impaired cognitive performance (Halterman *et al.*, 2001), behavioral disturbances (Lozoff *et al.*, 2000), lower immunity to infections leading to increased risk of mortality and morbidity (Beard, 2001) and also pregnancy complication e.g. low birth weight babies (Levy *et al.*, 2005). It also has deleterious effects on school academic performance (Liu *et al.*, 2001), decline in reproductive performance, physical performance as well as work capacity in adults (Allen, 2000; Haas & Brownlie, 2001).

According to Administrative committee on coordination/Subcommittee on Nutrition (ACC/SCN) (2000), pregnant women, pre-school children and young children aged 5-14 years were indentified to be a group of high-risk for IDA due to their high iron requirements. Among these, most affected groups are school-age children for whom there is a prevalence of 53% (ACC/SCN, 2000). Malaysia is one of the developing countries where iron deficiency has been reported to be one of the most important micronutrient deficiencies in the country (Tee *et al.*, 1998). Moreover, several studies on IDA in Malaysia also highlighted the problem of IDA among infants, children, adolescent and pregnant women (Hamid Jan *et al.*, 2010, Foo *et al.*, 2004; Siti Noor *et al.*, 2006). A study conducted in Malaysia demonstrated high prevalence of anemia and IDA among aboriginal schoolchildren aged 7-12 years with almost 49% of the children were anemic and 70% of the anemic cases are due to iron deficiency (Al-Mekhlafi *et al.*, 2008).

High prevalence of IDA among these school children suggests anaemia is a public health problem. This study is important as data on iron deficiency anaemia among school children is limited especially in Malaysia where most of the studies often focus on pregnant women and very young children. However, it is crucial to know the iron status of the school children as it is known that IDA may lead to poor mental and educational performances. In Malaysia there are not much research on IDA among school children and its association with cognitive function. Currently, some research had been done but only relating the nutritional status and/or iron deficiency with cognitive function (Anuar Zaini *et al.*, 2005; Hamid Jan *et al.*, 2011; Nasir *et al.*, 2012). However, present study has also includes the association of iron deficiency anaemia with both cognitive function as well as academic achievement. Besides, screening test for thalassemia as well as non-iron related anaemia also has been included in the method to control for other confounding factors. Lastly, school children are important assets to the country's development. Therefore, to be economically productive, these children need to be healthy and well educated. Thus there is a need to understand these problems as healthy children leads to healthier nations.

1.2 Objectives

1.2.1 General Objective

To determine the association between iron deficiency anaemia with cognitive function and academic achievement among primary school children in Bachok, Kelantan.

1.2.2 Specific objectives

i. To determine the prevalence of iron deficiency anaemia among primary school children in Bachok, Kelantan.

ii. To determine anthropometric measurements and iron status of primary school children in Bachok, Kelantan.

iii. To determine the association between iron deficiency anaemia with cognitive function and academic performance of the primary school children in Bachok, Kelantan.

CHAPTER II

LITERATURE REVIEW

2.1 Anaemia

Anaemia is a condition defined as a decrease in the number of red blood cells or decrease in the amount of haemoglobin in the red blood cells (RBCs) (Bryant, 2009). Most of the oxygen is transported to the body tissue by the RBCs, thus reduction in the red cell mass causes reduced oxygen supply to the body cells and limits the exchange of oxygen and carbon dioxide between the blood and the tissue. Anaemia may results from inadequate intake of iron, vitamin B_{12}, and folic acid. These groups of anaemia frequently called nutritional anaemias. Others may results from a variety of conditions such as haemorrhage (e.g helminth infections, blood loss in women during reproductive years), genetic abnormalities (e.g thalassemia or haemoglobinopathies), chronic disease states or drug toxicity (Kasdan, 1996).

The main cause of anaemia is inadequate intake of nutrients that required to synthesis the erythrocytes such as iron, vitamin B_{12} and folic acid. Among these, low iron intake is closely related to nutritional anaemia worldwide including developed countries (Schneider *et al.*, 2005) as well as Malaysia (Khor, 2005).

2.2 Iron deficiency and iron deficiency anaemia

Iron deficiency is a state in which there is insufficient iron to maintain normal physiological function of tissues such as the blood, brain, and muscles. Iron deficiency can exist in the absence of anaemia if it is not severe enough to cause the haemoglobin concentration to fall below the threshold for the specific sex and age group (WHO, UNICEF, UNU., 2001). Iron is a component in many proteins, including enzymes and hemoglobin that is important for the transport of oxygen to the tissues throughout the body (Lieu *et al.*, 2001). The body iron stores play an important role in regulating iron absorption according to the body's needs. It increases absorption when body's iron stores are low and decreasing it when iron storage is high. Iron deficiency occurs during the development of negative iron balance (absorption of iron is lower than loses and serum ferritin is lowered). Once the body stores of iron are used up, an individual begins to produce less hemoglobin. This is the second phase of iron deficiency. As iron deficiency develops further, it progressively leads to anaemia (Hallberg & Hulthen, 2000).

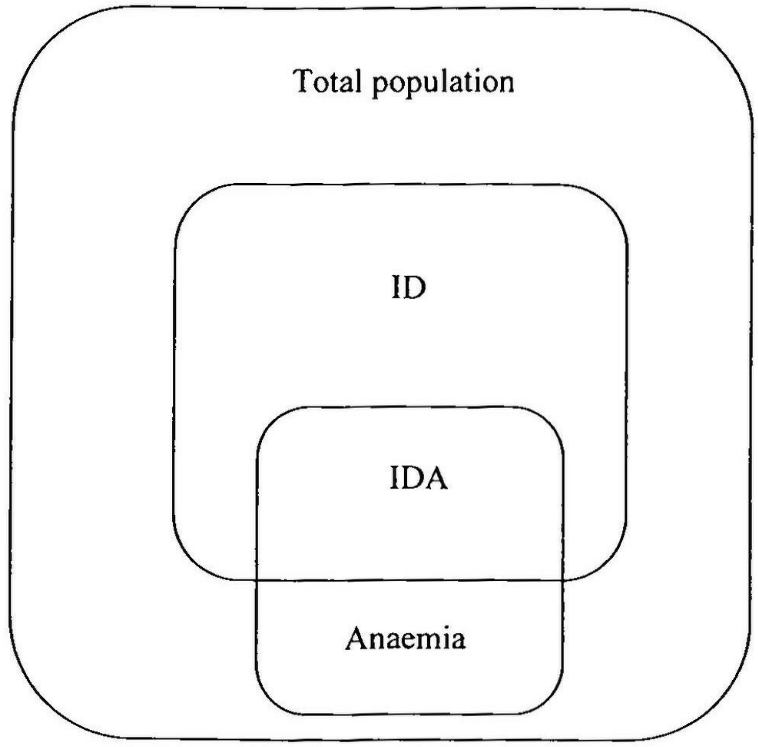

Figure 2.1 : Defination of iron status

Source : Yip (1989)

Note:

ID = Iron deficiency

IDA = Iron deficiency anaemia

Anaemia is diagnosed when an individual's hemoglobin concentration falls below a specific cutoff value for specific age and sex group as shown in Table 2.1. Iron deficiency anaemia was defined as having iron deficiency and a low haemoglobin value (WHO/UNICEF/UNU, 2001). It is a reduction in the amount of haemoglobin, which is caused by lack of iron and which eventually decreases the amount of oxygen transported to the cells around the body. In an individual with iron deficiency anaemia, red blood cells are generally smaller (microcytic) and paler than normal (hypochromic) (Stoltzfus & Dreyfuss., 1998).

Table 2.1 Normal values for haemoglobin concentration across age and gender.

Age/gender group	Haemoglobin level (g/dL)
Children 6 months to 59 months	11
Children 5-11 years	11.5
Children 12 to 14 years	12
Non-pregnant women above 15 years	12
Pregnant women	11
Men (above 15 years)	13

Source: WHO/ UNICEF/ UNU (2001)

2.3 Iron metabolism

Iron has several vital functions in the body. It serves as a carrier of oxygen to the tissues from the lungs by red blood cell haemoglobin, as a transport medium for electrons within cells, and as an integrated part of important enzyme systems in various tissues. Iron also plays important roles in cellular processes such as the synthesis of DNA, RNA and proteins; electron transport; cellular respiration; cell proliferation and differentiation; and regulation of gene expression (Hallberg *et al.*, 2000).

The body has no effective means of excreting iron. Thus, the regulation of absorption of dietary iron from the duodenum plays a critical role in iron homeostasis in the body. The human body represent 3-5 mg of iron (approximately 35 and 45 mg/kg of body weight in adult). Most of the iron in the body is distributed between red blood cell haemoglobin, the liver, muscle and macrophages of the reticuloendothelial system (Conrad *et al* ., 1999). Majority of body iron is utilized within haemoglobin in circulating red blood cells (~60-70 %). Other is distributed between the liver, muscle and macrophages of the reticuloendhothelial system (Conrad *et al.,* 1999). Approximately 20-30% of the body iron is stored within the ferritin and its degradation product hemosiderin. The remaining is primarily localized in myoglobin, cytochromes, and iron containing enzymes (Andrews, 1999). A healthy adults absorbs daily 1-2 mg of iron from the diet and this is balanced with losses of iron from desquamated skin cells, menstruation and other blood losses. The absorption of iron depends on the body's iron stores, hypoxia and rate of erythropoiesis (Ponka, 1997).

The metabolism of iron can be described as two loops, one is internal and one is external (Figure 2.2). The internal loop mainly represented by the formation and destruction of red blood cells. When red blood cells dies, which is after 120 days, it is usually taken by macrophage of the reticular-endothelial system of the body. The iron is then released and delivered to transferrin molecules in plasma and brings the iron back to red cells in different tissues that undergoing growth and developement (Hallberg, Sandstrom & Arthur., 2000).

There is thus a continous reutilization of the iron from haemoglobin in the red cells back to new red cells or other tissues. This system for internal iron transport not only controls the rate of flow of iron to different tissues but also prevents the appearance of free iron and the formation of free radicals in the circulation. The extemal loop is represented by the loss of iron from the absorption of dietary iron (Hallberg, Sandstrom & Arthur., 2000).

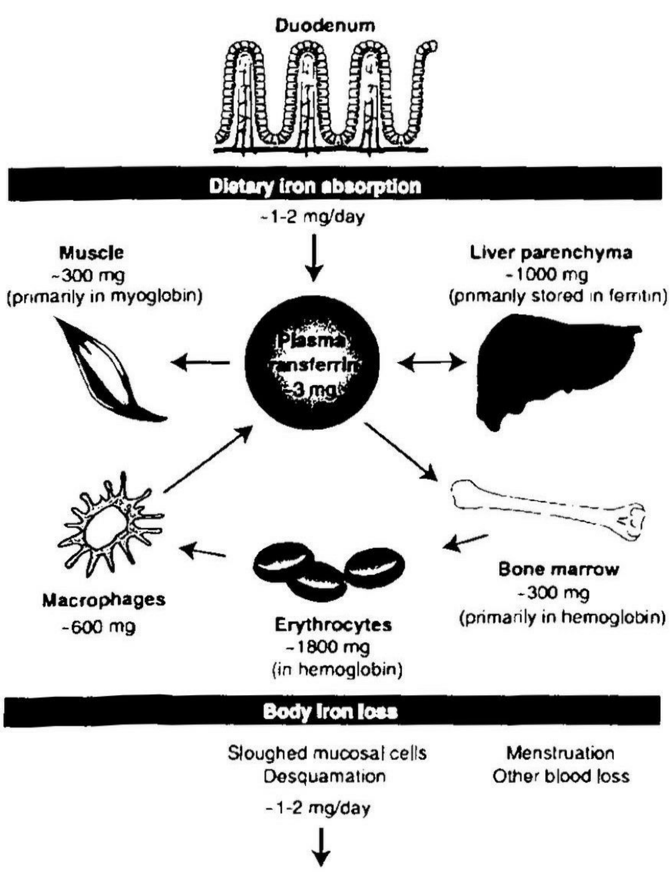

Figure 2.2 Distribution of iron
Source: Andrews (1999)

2.4 Prevalence of iron deficiency anaemia

According to WHO, anaemia is considered as a public health problem when the prevalence of low haemoglobin concentration is more than 5% in the population. WHO has suggested the following classification of countries with respect to the level of public health significance of anaemia: a prevalence of < 15% is "low", 15-40% is "medium" and > 40% is "high" (WHO/UNICEF/UNU, 2001).

2.4.1 Worldwide

The prevalence of anaemia is three to four times higher in developing countries compared to that of in the developed countries (De Maeyer & Adiels-Tegman,1985; UNICEF/UNU/WHO/MI,1999). The World Health Organization estimated that about 40% of the world's population (more than 2 billion individuals) suffers from anaemia and majority is due to iron deficiency (WHO, 2007). The population groups that are most affected are infants, school-age children, female adolescents, pregnant women and nurturing mothers (Yip, 1992). It is also estimated that 39% of children younger than 5 years, 48% of children between 5 and 14 years, 42% of all women and 52% of pregnant women in developing countries are anaemic (WHO/UNICEF/UNU, 2001). Iron deficiency (ID) is detected by low serum ferritin concentrations and estimated to be from 2 to 2.5 times the prevalence of anaemia (Aleen & Gillespie, 2001). Besides, most studies of anaemia showed that iron deficiency accounted for at least half of the cases of anaemia (DeMaeyer & Tegman, 1985; Foo *et al.*, 2004; Al-Mekhlafi *et al.*, 2008). Furthermore, a survey on the prevalence of anaemia conducted in Norway also showed the same pattern whereby at least 69% of anaemia cases was contributed by iron deficiency (Kahn *et al.*, 1990).

The problems of IDA is much greater and the challenges to combat the problems is more complex in less developed regions (Yip & Ramakrishnan, 2002). The greatest number of people affected are in Asia. In Asian countries the prevalence of IDA among adolescent was reported to be more than 40%, especially among females at the onset of menarche (Kurz, 1996). Among children, prevalence of IDA has been reported to be as high as 50% among East Asian school-aged children and almost 60% among children less than 5 years of age (Stoltzfus, 2003).

In American Continent, approximately 94 million people are believed to suffer from ID or IDA, especially in the Caribbean and in the Andes where it affects around 60% of the pregnant women (Freire, 1997). Significant iron deficiency continues to be observed even in the United States and other developed countries, especially among pregnant women, infants and young children from low-income families. Iron deficiency prevalence was estimated at 7 percent for U.S. toddlers (1-2 years old) and 5 percent for preschool aged children (3-5 years old) in 1999-2000, with higher rates for African-Americans and Latinos (Centers for Disease Control and Prevention 2002). Prevalence of IDA was also reported to be as high as 29% among low-income pregnant women in the United Sates (Bodnar, Cogswell & Scanlon, 2002). This shows that, although it is most common in less developed countries, iron deficiency and iron deficiency anemia are still a problems in some of developed countries.

2.4.2 Malaysia

Iron deficiency anaemia has been one of the most important micronutrient deficiency in the country. Various studies in the country have shown that iron deficiency anaemia remains a significant problem. A study carried out in Peninsular Malaysia reported prevalence of 22% of anemia in children aged 7-12 years of both sexes, 25% among female subjects aged 18 to under 60 years and 23% in elderly of both sexes (Tee *et al.*, 1998). Subjects studied comprised various community groups, namely fishing, rice-growing, rubber, coconut and estates around Peninsular Malaysia. Furthermore, recent study was also done among young children aged 6 to 24 months in Kelantan where the study revealed that almost 39% of the children had iron deficiency and about one third had IDA (Siti Noor *et al.*, 2006).

The prevalence of anemia among rural elderly Malays was also found to be high by Suzana *et al.*, (1999) where approximately a third of the men and women were anaemic (Hb <12 g/dl for women; <13 g/dL for men). Rural pregnant women have also shown a high prevalence of anaemia (Jamaiyah *et al.*, 2007). Study was also done among adolescents from a rural community in Sabah. It was found that 20% of the subjects were anaemic and IDA contribute largely (85.0%) to the prevalence of anaemia. The study also shows 98% of the subjects failing to meet the Malaysian RDA level and most of the female subjects (91%) had a dietary iron intake below two-third of the Malaysian RDA level (Foo *et al.*, 2004). Remote interior communities in Sarawak also showed a high prevalence of anaemia among men >40 years, adolescents, young women, as well as elderly females > 61 years old (Sagin *et al.*, 2002). Recent study done on the prevalence of IDA among young women aged 20 to 40 years involving 388 women in Kuala Lumpur revealed that the prevalence of anaemia was 20.9% while IDA was at 10.3 % (Loh & Khor, 2010).

2.5 Risk factors for iron deficiency anaemia

Iron deficiency is a precursor to iron deficiency anaemia. Factors causes iron deficiency include inadequate intake of iron or malabsorption, increased iron requirements due to growth or loss of iron from bleeding. Prolonged iron deficiency cause depleted of iron stores thus contribute to inadequate production of haemoglobin and anaemia. Other factors that affect the risk of developing IDA is the specific age and gender (DeMaeyer & Tegman, 1985).

The prevalence of IDA increases during the second years of life (between age of 12 and 18 month) and it was due to rapid growth where requirement of iron is increasing (Sheriff *et al.,* 1999; Institute of Medicine, 2001). Others is caused by the used of non-iron fortified formula in the first years of life, exclusive breast feeding for more than 6 months and early introduction of non-formula cow's milk before 1 year of age (Calvo *et al.,*1992; Moy, 2006). Study in infants aged 6 months done by Pizarro *et al* (1991) showed IDA developed at lowest frequency among infant fed with iron-fortified formula (1%) compared to 15% of breastfed infants and 20% infants fed with cow's milk or non-fortified formula.

According to a review study by Yip and Ramakrishnan (2002), diet of infants and young children in develop countries is quite adequate in iron content due to better consumption of animal foods, fortified food and complementary foods compared to those in developing countries where diet is low in iron. Besides, most infants in developing countries rely mostly on iron from breast milk. Although bioavailability of iron in breast milk is more, it may not adequately supply iron needs for older infants. Complimentary breast feeding may continue after 6 months untill 2 years as long as other foods providing iron are introduced (Wharton, 1999).

Besides infants, pregnant women, pre-school children and children aged 5-14 years also identified as high-risk group for developing IDA because of their iron requirements (ACC/SCC, 2000). Poor dietary intake was found to be the main contributing factor in the higher anaemia rates in young children from low-income households (Khor, 2005). Poor diet quality and low dietary iron bioavailability was also found to be the factors that contribute to the increased incidence of iron deficiency in Tanzania (Tatala *et al.*, 1998). The bioavailability of haem-iron, present in animal products, is high with absorption rates of 20–30%, whereas the bioavailability of non-haem iron is determined by the presence of enhancing or inhibiting factors (Hurrell *et al.*, 1991). The main enhancers of non-haem iron absorption are meat (haem iron) and vitamin C (Cook & Reddy, 2001). Inhibitors include phytate (nuts, bran and oat products, whole-wheat and brown flour), polyphenols (tea, coffee, cocoa, some spices and vegetables), calcium (milk products) and phosphorous (Reddy *et al.*, 2000). Other contributing factor is due to helmintic infection where it often reported among aboriginal children and children living in oil palm plantations as a result of poor hygiene and sanitary practices (Al-Mekhlafi *et al.*, 2008).

Besides, overweight and obesity was also found to be one of the risk factor contributed to the prevalence of IDA. Study conducted by Nead *et al* (2004) revealed that children who were overweight were 2.3 times as likely to be iron-deficient as those who were not overweight. This is because it was reported that those who try to control their weight may inadvertently limit their iron intake by limiting their food intake (Wharton, 1999). This is happened especially among adolescent girls. The risk for IDA also increased during adolescence because of a combination of accelerated growth, menstrual loss and low intake of dietary iron (Fomon *et al.*, 2003; Kurz, 1996). Furthermore, a positive iron balance is difficult to maintain during this period due to large pubertal growth spurt and maturation (Yip, 1994) and it is futher exacerbated by low iron intake especially in developing countries in which diets are relatively low in iron content and bioavailability (Yip & Ramakrishnan, 2002).

Besides, low standard of living, poor socio-economic conditions, restricted access to food and lack of knowledge for good dietary practices as well as personal hygiene contribute more to a high prevalence of ID and IDA in developing countries (Islam *et al.*, 2001; Soekarjo *et al.*, 2001). Furthermore, study also documented that intestinal parasitic infection, due to poor hygienic conditions also interferes with iron absorption, thus expanding the prevalence of iron deficiency anaemia in the developing world (Olivares *et al.*, 1999; Musaiger, 2002).

2.6 Functional and health implication of iron deficiency anaemia

Several studies have shown that iron deficiency can lead to serious consequences to health and develepoment including impairement in motor and cognitive developement, decline in mental and physical performances, decline in reproductive performance and work capacity and adverse pregnancy outcomes (Li *et al.*, 1994; Lozoff *et al.*, 2006). Studies showed that IDA has various deleterious effects and it is differed according to the stage of age. These includes defects in mental and psychomotor development of children during the first years of life (De Andrace *et al.*, 1997).

Other adverse effect of IDA include altered cognitive development and behavioural problems especially among children. Among older children it is associated with impaired school performance, learning ability and reduced physical activity (Walter 1993; Pollitt, 1997). Consistently, children reported with iron deficiency anaemia performed less well in psychomotor development compared with iron-sufficient children (De Andraca *et al.*, 1997). Most observational studies in children have found associations between iron deficiency anaemia (IDA) and poor cognitive and motor development and behavioural problems (Grantham-McGregor & Ani, 2001). Longitudinal studies consistently indicate that children who were anaemic in infancy continue to have poorer cognition, school achievement and more behaviour problems into middle childhood (Grantham-McGregor & Ani, 2001). In addition, IDA may also affect the school performance among adolescents and research done on iron supplementation showed adolescent girls whose diet was supplemented with iron felt less fatigued thus their ability to concentrate in school increased and their mood also improved (Balin *et al.*, 1992).

Iron deficiency may also negatively affect cellular immunity in children, even before the child become anaemic, and this can lead to an increase in illnesses such as diarrhoea, respiratory disease and other infections. According De silva *et al* (2003), iron deficiency anaemia increases susceptibility of the children to infection, mainly of the upper respiratory tract, which happens more often and has a longer duration in anaemic children than in healthy children. These effects can be reduced by iron supplementation or food fortification. Besides, iron deficiency may also increase the risk for chronic lead poisoning among children exposed to environmental lead (Zimmermann *et al.*, 2006).

In adults, IDA has been shown to impaire work performance. It may also caused a decreased in productivity and quality of life where it causes decrease in physical fitness and reduced work-capacity among adults (Basta *et al.*, 1980). Work performance and productivity of workers was reduced significantly as a results of defective oxidative production of cellular energy in skeletal muscle where it involves a mechanism that includes oxygen-carrying capacity and respiratory efficiency in the muscle (Beard, 2001; Haas & Brownlie, 2001)

Among pregnant women, study reported that IDA might cause low birth weight and prematurity (Allen, 1997). The impact of iron deficiency and anaemia during pregnancy on birth outcomes such as low birth weight (LBW), prematurity and infant iron status has been reported. IDA during pregnancy increases the risk of preterm labour, low birthweight, infant mortality and also causes iron deficiency in infants after 4 months of age (Schorr & Hediger, 1994; Brabin *et al.*, 2001) and according to systematic review on analysis causes of maternal death by Khan *et al* (2006), IDA may causes deaths during pregnancy and child birth in Africa and Asia.

2.7 Cognitive function

Cognition is the act of knowing and cognitive psychology is the study of all human activities related to knowledge such asthe study of how people perceive, learn, remember and think about information. These activities includes attention, creativity, memory, perception, problem solving and the use of language. "Cognition", "cognitive function" ,"cognitive performance", intelectual performance, intelligance and IQ are used interchangeable and refer to a range of cognitive domains such as attentinal capacity, memory, short-term memory, long-term memory, working memory, reasoning and executive function (Neisser, 2009). For consistency, cognitive function will be used as the term of reference throughout the text.

2.8 Iron deficiency anaemia and cognitive function

Factors influences cognitive function includes diseases, nutritional factors, metabolic and hormonal changes, ageing and drugs (Gutstein, 2001; Fried *et al.*, 2002). Among nutritional factors, micronutrient deficiencies may play a role in children's development. Micronutrient deficiencies are critical issue among children throughout the world. Iron deficiency is one of the micronutrient deficiencies, and it was considered as prevalent nutritional disorders and has a severe impact on cognitive development throughout the world (Grantham-McGregor & Ani, 2001; Walker *et al.*, 2007). Due to these problems, many research have been done in many countries and a few being done in Malaysia looking at the effect of iron deficiency and iron deficiency anaemia and its relationship with cognitive function and school achievement among school children.

In Malaysia, research has been performed by Anuar Zaini *et al* (2005) involving 1397 Malaysian primary school children in the area of Selangor aged 9-10 years old. The study found a correlation between intellectual performance and anaemia status. The intellectual performance was assessed using Raven's coloured progressive matrices (RCPM) and the results of the study showed that severe anaemic students scored lower than student with normal anemia status. Research by Kandiah and Loh (1998) at Serdang, Selangor was also conducted to study the relationship between nutritional factor and academic achievement among children in the National Type Primary School *(Tamil)*. The study indicated besides socioeconomic factor, academic achievement of the student was also affected by their level of blood haemoglobin.

Even in elderly individual, association between IDA and cognitive function was also found in some studies. Study conducted among 477 rural elderly Malays found, iron deficiency anaemia as measured by serum ferritin had been reported to be associated with poor cognitive function (Zuriati, 2003). Suzana *et al* (2005) in their study on anaemia and cognitive function among Chinese elderly in old folk's home in Klang Valley, Malaysia also found that subjects with severe cognitive impairment had a lower haemoglobin level compared to those with normal cognitive function.

Besides, several cross-sectional and case control studies overseas have also demonstrated an association between IDA and psychomotor and cognitive abnormalities as well as poor school performances among children. A review by Pollitt *et al* (1986 a) of several studies between 1976 and 1986 on iron deficiency children with and without anaemia demonstated that both anaemic and non-anaemic iron deficient children showed lower scores for mental developement and poorer problem solving skills. Another study also conducted by Pollitt *et al* (1986 b) in Thailand among school children also found consistent results. The results showed an association between iron levels and Intelligence Quotion (IQ) in 11 years old school children. Moreover, study performed in Mexico among children (6 to 12 years old) comparing iron deficient non-anaemic to normal children found a significant differences in cognitive function and brain waves between the two groups. Iron deficient children was found to have a lower scores on test of verbal, comprehension and overall IQ. Furthermore, electroencephalogram results indicated a slower brain wave activity among iron deficient children compared to that in normal children (Otero *et al.*, 1999).

Halterman *et al* (2001) performed a study on iron deficiency and cognitive achievement among school-aged children and adolescent in the United States. Results on cross-sectional analysis of NHANES III data showed that 71% of iron-deficient children had below-average math scores compared to 49% of children who had normal iron status. After adjustment for age, gender, race, poverty status, caretaker education, and lead status, iron-deficient children were 2.4 times as likely to have low math scores. Studies was also done among infants and young children regarding IDA and cognitive function. Ten years longitudinal study done by Lozoff *et al* (2000) have found that children who were anaemic in the first 2 years of life continued to function poorly in later childhood and the same children re-evaluated later at 11-14 years of age. The study revealed that children who had iron deficiency in infancy continued to have behavioural and developemental disadvantage. On top of that, iron-deficient anaemic children were also found to be more wary, hesitant and easily tired, made fewer attempts at test item, less attentive to instruction and were less playful (Lozoff *et al.,* 1998). More extensive review study concerning the effect of IDA on cognitive development done by Grantham Mc-Gregor and Ani (2001) had concluded that most of the studies on IDA and cognitive function showed a consistent evidence for poorer cognitive and motor development, poor scholastic achievement, and increased behavioural and disciplinary problems in iron deficient children.

2.9 Interventional study on iron deficiency anaemia

There were several intervention studies performed to determine the relationship between iron deficiency anaemia and cognitive function and aimed for correcting iron deficiency in population. The studies involved iron supplementation programs and the assessment of cogntive function before and after intervention. A randomised, double-blinded trial was performed to monitor the effects of iron supplementation on performance in the Bayley scales of mental and motor development among 12 to 18-month-old infants in Indonesia. The study showed that iron-deficient anaemic infants perform worse in tests of mental and motor development than do iron-sufficient infants of a comparable age. Iron deficient anaemic children score averages of 88.5 and 88.8% respective for both motor and mental skills compared to normal children. After iron intervention, developmental delays were reversed among iron-deficient anaemic infants who had received iron supplementation. It was found that scores for motor and mental skills among iron deficient anaemic children increased to 112.0 and 108.1 respectively (Idjradinata & Pollitt, 1993).

Other studies have investigated the association betwen IDA and cognitive function among pre-school and school aged children and results of the studies found a positive impacts of iron supplementation on cognitive function and educational achievements (Soemantari *et al.,* 1989). Stoltzfus *et al* (2001) had conducted a randomised trial of iron supplementation among 614 preschool children aged 6-59 months and indicated that iron supplementation significantly improved iron status and thus improved language and motor development among severely anaemic children.

Besides, a systemic review of randomised controlled trial on the effects of iron supplementation on motor and mental developement in children done by Sachdev *et al* (2004) also concluded that iron supplementation improves mental development score modestly. This effect is particularly apparent for intelligence tests above 7 years of age among anaemic or iron-deficient anaemic subjects. However, there was no convincing evidence that iron treatment has an effect on mental development in children below 27 months of age. Another systemic review and meta analysis done by Falkingham *et al* (2010) on the effects of oral iron supplementation on cognition among older children and adolescent showed that iron supplementation improved attention, concentration among adolescent and thus improved IQ among older children.This gave the idea that iron is important and deficiency of iron may causes cognitive and motor disturbance among children.

Studies were also conducted among adults to investigate the important of iron and its relation to cognitive performance. Laura and Beard (2007) performed a blinded, placebo-controlled, stratified intervention study among women aged 18-35 years old to examine the relation between iron status and cognitive ability. The women were stratified into 3 groups (Control group, ID group and IDA group) and were randomly assigned to receive iron supplement or a placebo. Cognition was assessed using 8 cognitive performance tasks from Detterman's Cognitive Abilities Test. The study found a significant improvement in serum ferritin after treatment of iron and it was associated with a 5-7 fold improvement in cognition performance.

Supplementation with iron has also been shown to cause an improvements in work productivity. According to Horton and Levin (2001), manual labourers in developing countries are more productive if they were given iron supplementation. Iron supplementation was given to rubber tappers in Indonesia and tea pickers in Sri Lanka where results from the supplementation clearly shown gain in productivity of the workers (Edgerton *et al.*, 1979). The study among Chinese female cotton mill workers by Li *et al.*, (1994) points in a similar direction. Compared with non-anaemic women, anaemic female workers in China were 15% less efficient in performing their work. However performance was increased after it was corrected by iron treatment for 4 months. Similarly, non-anaemic iron-deficient adolescent female runners significantly improved their levels of endurance and physical performance after supplementation with