INTERNATIONAL JOURNAL FOR INNOVATIVE RESEARCH IN MULTIDISCIPLINARY FIELD ISSN: 2455-0620 Volume - 7, Issue - 8, Aug – 2021
Monthly, Peer-Reviewed, Refereed, Indexed Journal with IC Value: 86.87 Impact Factor: 6.719
Received Date: 06/08/2021 Acceptance Date: 22/08/2021 Publication Date: 31/08/2021

A Systematic Review of Studies on Iron Status and Cognitive Functions in Children, Adolescents and Adults

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Abstract: *It is widely reported that iron deficiency is the most common nutritional disorder worldwide with serious implications to growth and development of affected individuals. Particularly, the cognitive effects of iron deficiency and iron supplementation among children and adolescents has received increased attention due to its impact on academic performance and ability to cope with challenges in the present day work environment . Based on detailed literature review on the role of iron in cognition, it is evident that adequate iron intake throughout life from infancy to adult years is important to realize one's cognitive potential. The results of studies conducted so far were found to implicate iron deficiency as the cause for the adverse alterations observed in specific cognitive processes such as attention, mental speed, reasoning ,visual memory and verbal learning and memory. Subsequently the effectiveness of intervention trials of iron supplements was found to demonstrate improvement in cognitive functions of especially children with some studies showing inconsistent results. Only few studies to date have investigated the cognitive effects of iron status and /or iron supplementation in adolescents and older adults. Addressing the problem of iron deficiency and examining the efficacy of iron supplementation on cognitive functions of affected individuals is imperative to improve academic performance, work productivity and efficiency. It will also help mitigate the plethora of adverse effects associated with iron deficiency .*

Key Words: *Iron deficiency, iron supplementaion , cogntive functions.*

1. INTRODUCTION:

It is well established that iron deficiency is the most prevalent nutritional deficiency worldwide (World Health Organization, 2012). In India, Kapil et al,2019 summarized that a high prevalence of iron deficiency anaemia (almost 50 percent) is found amongst all vulnerable age groups, especially mothers and children. The consequences of iron has been extensively investigated and documented. Most research studies have been consistent in reporting adverse effects of iron deficiency on physical growth and development, work capacity and productivity, pregnancy outcomes, immunity and cognition. According to Bhatnagar and Taneja (2001) cognition includes information processing skills such of perception, thinking, memory, learning and attention. The other components of cognition include reasoning, problem solving, decision-making skills, mental speed or reaction time. Several studies have also documented the potential role of iron supplementation in improving cognitive functions (Manteyet al, 2021, Chellappa and Karunanidhi, 2012, McCann and Ames 2007, Murray-Kolb and Beard, 2007, Walker et al, 2005 and Beard et al, 2005). Improving cognitive functions by improving nutritionals status of different age groups is of critical importance due to the significant association between cognitive functions and academic performance (Nesayan et al, 2019)

The relationship between iron status and impaired cognition could be traced back to a study conducted by Waite and Neilson (1919) among school children in North Queensland. Subsequently, over the past three decades many researchers found significant concurrent associations between iron status indicators and measures of cognitive function. Grantham-McGregor and Ani (2001) examined 37 published reports of case-controlled studies and preventive trials before 2001 and summarized them in an excellent review. They reported that in most of the studies, iron status was significantly associated with cognitive functions whereas a few studies yielded conflicting results. A systematic review of 43 studies on the role of brain and cognition indicated that disruption of normal iron homeostasis can result in iron accumulation in the brain which is detrimental to cognitive health (Spence et al, 2020). Studies pertaining to the effect of iron supplementation on cognitive functions were also found to yield mixed results. It must also be noted that the findings on the effect of iron status or iron supplementation on cognition emerged mostly from studies predominantly conducted among infants, preschool children and the school going population. However, more recently, similar studies have been carried out among older age groups, namely, college going population and adults.

McCann and Ames (2007) reviewed 37 studies from 1977-2006 to study the causal relation between iron deficiency, cognitive and behavioural function. They concluded that although most causal criteria are supported by at least some evidence from human or animal studies, significant gaps suggest that it would be premature to conclude that a causal connection exists between iron deficiency *per se* during development and subsequent cognitive

performance. In humans although several causal criteria have been at least partially satisfied, the specificity of both cause and effect has not been clearly established, hence necessitating the need for further research studies.

Hermoso et al, (2011) reviewed 14 randomized controlled trials that examined the effect of iron on measures of cognitive development and function of infants, children and adolescents. Iron supplementation for a period of two months was found to show an improvement on cognition and psychomotor outcomes in anaemic infants and children, though not very significant. Greig et al,(2013) systematically reviewed 10 studies on the effect of iron deficiency on cognition, mental health and fatigue in women of childbearing age. At baseline, it was found that women with iron deficiency had poorer scores on tests that assessed cognition, mental health and fatigue. Seven studies which were reviewed reported an improvement in cognitive test scores after iron supplementation.

In this paper, a systematic review of human studies relating to the effect of iron status and supplementation on specific cognitive functions such as mental speed, attention, learning and memory of verbal material, visual memory and reasoning among children adolescents and older adults is presented. Studies conducted abroad and in India are presented chronologically beginning from current findings and tracing back to earlier reports to elucidate an understanding of cognitive alterations brought about by iron status and/ or supplementation trials using iron**.**

2. LITERATURE REVIEW:

The biological basis for the cognitive effects of iron deficiency and subsequently iron supplementation has been a topic of interest over the past few years. Bryan et al, (2004) provided a review of the role of nutrition in cognitive development in children. They reported that brain tissue is overall very rich in iron. Brain iron plays an important role in several functions such oxidative metabolism, myelination, and neurotransmitter synthesis (Larsen et al, 2020). Also, it is sensitive to dietary iron depletion and repletion via homeostatic regulatory mechanisms regulated by blood brain barrier that are regulated in response to iron status (Youdim and Yehuda, 2000). Some areas of the brain that are important for cognition such as the cortex, hippocampus and striatum are most sensitive to iron deficiency than others and could perhaps affect specific cognitive functions (Beard, 2001). It is also believed that iron can affect cognitive functions as it is involved with different enzyme systems (Nyardi et al, 2013)

2.1 Iron Status and Cognitive Functions in Children

Mantey et al, (2021) studied the effect of iron status on cognitive functions of 389 primary school children from Kumasi, Ghana using Ravens Colored Progressive Matrix (RCPM) . The results revealed that anaemic children had obtained lower cognitive scores .Weak positive association was reported between cognitive scores and iron status. This study clearly shows that haemoglobin levels can be an effective predictor of cognitive performance among school children.

Sen and Kanani (2006) assessed the cognitive function of 322 underprivileged anaemic and non-anaemic school girls between 9 and 14 years of age from four Municipal schools in Vadodara. All the students were tested for their haemoglobin status and cognitive functioning. Measures of cognitive function included selected tests viz., digit span test, maze test, clerical task and visual memory from the Gujarati version of Wechsler's Intelligence Scale for Children (WISC). With regard to cognitive functions it was found that the non-anaemic girls had significantly higher scores than their anaemic counterparts in digit span and visual memory tests. However, no significant difference was observed between the anaemic and non-anaemic girls in the scores obtained in the maze test and clerical task. Based on these findings it appears that anaemia is likely to adversely affect specific cognitive functions viz., span of attention and visual memory in young adolescent girls

Metallinos-Katsaras et al, (2004) investigated the effects of iron supplementation among preschoolers with good iron status and those with iron deficiency anemia on speed of information processing, accuracy of discrimination (Continuous Performance Task), and conceptual (oddity) learning. Forty nine preschoolers between 3 and 4 years of age in Greece were selected for the study. They were divided into two groups, namely, those with anemia (n=21) and those with good iron status (n=28). In each group, the preschoolers were further divided into two groups and were assigned to either 15 mg iron treatment or placebo for a period of two months using a randomized double-blind placebo-controlled trial. At baseline, there were no significant difference between iron-treated and placebo groups either within the good iron status or anemic group on any of the cognitive measures. After supplementation, it was found that the iron supplemented anemic subjects were not only faster but made a fewer number of errors than anemic subjects who were administered the placebo. Results also showed that the iron treated iron deficient anemic subjects responded less to irrelevant stimuli than those anemic children given placebo. Interestingly, the findings also show that iron supplementation did not demonstrate beneficial effects on cognitive functions among those with good iron status. This study also demonstrates that the cognitive benefits of iron are limited to specific cognitive tasks such as attention and speed of information processing.

Bandhu et al , (2003) investigated the effect of three months of iron therapy on selected cognitive tasks among 18 anemic and 34 non -anemic control subjects with a mean age of 9.26+/-0.26 years using the Ravens Progressive

Matrices Test scores and Digit Span Attention Test Scores. Before supplementation, the anemic boys had lower hematological values and obtained lower cognitive test scores values. After three months of iron supplementation the results showed significant improvement in cognitive scores when compared to their pre-treatments values. Surprisingly the significant improvement in cognitive scores with specific reference to abstract reasoning was similar to the scores obtained by the control group . No significant difference was observed when these scores were compared with the control group. From this study it is can be noted that supplementation of iron for three months results in a marked improvement in abstract reasoning which is cognitive function assessed by Ravens Progressive Matrices Test scores

Bruner et al, (1996) conducted a double-blind placebo-controlled study to evaluate the cognitive effects of iron supplementation among adolescent girls in grade 9-12 from 4 high schools in Baltimore, U.S.A. Eighty-one non anemic iron deficient girls were identified and divided into 2 groups , namely, iron treatment and the placebo group. The findings revealed that iron treatment had no significant effect on Brief Test of Attention, Symbol Digit Modulation Test and Visual Search and Attention Test. However, verbal learning and memory test scores of the iron supplemented group was higher when compared to those in the control group. Significant improvement was observed in the supplemented group only in the total score of 3 free recall items of the Hopkins verbal learning test than the placebo group. Further, it was also observed that there were no significant differences in the delayed recall or recognition component of the test. Based on these results it could be inferred that iron supplements improve verbal learning and memory among adolescent girls.

Agarwal et al, (1989) assessed mental functions of 388 primary school children between 6 and 8 years of age in Varanasi. Malin's intelligence scale for Indian children and an arithmetic test were administered to assess intelligence, attention and concentration of the sample. The results of this study revealed no significant differences between the Intelligence Quotient scores of anaemic and non-anaemic children, except for the subtest digit span in which the performance of the non-anaemic group was better. Observations on the arithmetic test scores showed that anaemic children performed worse than their non-anaemic counterparts. These findings indicate an association between anaemia and levels of attention and concentration as assessed using the digit span test and arithmetic tests

Seshadri and Gopaldas (1989) investigated the impact of iron supplementation on cognitive functions of 94 school children between 5 and 8 years of age. Before haemoglobin level was known, the children were stratified by age and every third child was then randomly assigned to a control group. The remaining two children in each triplet were assigned to the iron treatment group which was supplemented with 20mg elemental iron and 0.1 mg folic acid per day for 60 days. No placebo was used in the study. The Indian adaptation of the Wechsler's Intelligence Scale for Children (WISC) was used for assessing cognition. Results revealed that anaemic children had significantly lower scores on the Wechsler's Intelligence Scale for Children (WISC) than non-anaemic children. After treatment, the results indicated that the group receiving iron significantly improved in verbal performance and Intelligence Quotient in all ages whereas the controls did not. Among the iron treated group, a significant improvement was seen in the anaemic children than the non-anaemic children. These findings demonstrate that cognitive gains can be achieved as a result of iron therapy in school children.

Seshadri and Gopaldas (1989) also examined the effect of iron on cognitive functions in older children between 8 and 15 years of age. Forty-eight boys were selected for the study and matched for age, hemoglobin level, and baseline scores in tests for cognitive function. They were divided into sixteen groups comprising of three in each group. By using a double-bind randomized controlled design , each triplet in the sixteen groups was further assigned into three groups viz., Group-A receiving 30 mg elemental iron, Group –B receiving 40 mg elemental iron per day and Group-C receiving placebo. The assessment tests included visual recall, digit span, maze learning (visual motor coordination), and clerical task test. Analysis of treatment effect revealed significant improvement in all cognitive tasks in the groups receiving 30 and 40 mg of iron. Further, it was observed that that the group receiving 40 mg iron had significantly higher scores in the digit span, maze, clerical task and visual recall. Also, no change in cognitive function was observed in the placebo group**.** These results indicate that iron supplementation facilitates improvement in cognitive functions.

Further, Seshadri and Gopaldas (1989) also assessed the impact of iron supplements on cognitive functioning of girls between 8 and 15 years of age . Eighty-three pairs of girls were matched for age, hemoglobin and cognition. The final data on 65 pairs of girls who completed the study were given. A double- blind randomized controlled trial was used and the matched pairs were randomized to either treatment with 60 mg elemental iron per day or placebo tablets for one year. Visual recall, digit span, maze and clerical task were used to measure cognitive skills. The study revealed that improvement in cognitive functions was more marked among anaemic girls who were supplemented with iron than the non-anaemic girls in the same group. It was found that, iron treatment significantly improved overall cognitive scores in anaemic girls in the iron treated group than the non anaemic girls. It was further reported that cognitive functions among anaemic girls who received iron treatment was significantly better than the placebo group. These findings highlight the importance of iron therapy for improving selected cognitive functions.

The cognitive responses of anemic Indian children between 5 and 8 years of age to iron- supplements were assessed by Seshadri et.al., (1982) using the Indian adaptation of the Wechsler's Intelligence Scale for Children (WISC). For this purpose, supplements comprising of 20 mg elemental iron and 0.1 mg folic acid were given daily for a period of 60 days to one group while the other group that served as controls received placebo treatment. At the end of the study, it was found that the supplemented children showed significant improvement in hemoglobin levels. It was also observed that they also showed improvement in the scores on the Indian adaptation of the Wechsler's Intelligence Scale for Children (WISC). Further, the findings revealed that the control group failed to show an improvement either in hemoglobin levels or in the scores on the Wechsler's Intelligence Scale for Children. The study shows that in addition to increasing the blood hemoglobin levels, iron-folic acid supplements may also be beneficial in improving the cognitive performance of children.

2.2 Role of Iron on Cognitive Functions of Adolescents:

The effect of iron and zinc supplementation on cognitive functions of female adolescents in Chennai was examined by Chellappa and Karunanidhi (2012). Biochemical measures included assessment of haemoglobin, serum ferritin and serum zin . Cognitive tests of mental speed, sustained attention, abstract reasoning, verbal and visual memory and verbal and visual recognition were assessed at baseline and after four months of supplementation. The results revealed that the groups supplemented with iron and combined iron and zinc showed significant improvement in their visual memory scores. Significant improvement in the test for mental speed on accuracy levels was observed with iron supplementation. No significant change was observed in the iron and combined iron and zinc treated groups in other cognitive measures such sustained attention, abstract reasoning immediate and delayed recall of verbal material and verbal and visual recognition compared with the control group. These results indicate that effectiveness iron may be limited to selected cognitive functions.

Lynn and Harland (1998) examined the effect of iron supplementation on the Intelligent Quotient (IQ) of iron deficient children between 12-16 years of age in England. Results indicated that after 16 weeks of iron supplementation there was no correlation between hemoglobin and Intelligent Quotient, ferritin and Intelligent Quotient. The group with low iron status (ferritin <12µg/L) showed a significant treatment effect on visual reasoning. The group with moderate iron status showed no benefit from treatment, whereas the group with high iron status showed significant benefits. Since the findings were inconsistent, the benefits of iron in improving cognitive functions are inconclusive and require further inquiry

The relationship between iron status and cognition was examined by Groner et al,(1986) in a group of pregnant adolescents in U.S.A Results revealed that the group receiving iron treatment for one month showed significant gains on the Digit Symbol test, arithmetic and attention sub-scales while controls reported no change. These results indicate the beneficial role of iron supplementation in short term memory, mental speed arithmetic efficiency and attention in pregnant adolescents

2.3 Role of Iron on Cognitive Functions of Adults:

Portugal-Nunes (2020) conducted a study among 162 older community-dwelling individuals in Portugal. Assessment of iron status was performed using several blood biomarkers. The results revealed that there was a positive association between iron status and memory and between iron storage and nutritional status. The study also revealed that lower iron status is associated with functional tiredness and poorer memory ability,

Kheder et al, (2008) assessed the influence of iron deficiency anaemia (IDA) and iron supplementation for 3 months on cognitive function and intelligence of 28 young adults with IDA. Results revealed that compared to controls, patients demonstrated lower scores of different cognitive tests which showed significant improvement after treatment. The study showed positive correlation between haemoglobin levels and total verbal and performance IQ scores before and after treatment. This study shows that IDA can significantly influence cognitive performance in adult population and that iron supplementation can result in modest improvements in cognitive performance

Murray-Kolb and Beard (2007) conducted a study to examine the relation between iron status and cognitive abilities in 149 young women between 18 and 35 years of age at Pennsylvania State University. Computerized cognitive performance tasks of the Detterman's Modal Modek of information processing were was used to test cognitive performance before and after iron supplementation. Baseline results showed that iron-sufficient women scored better and were faster and better on cognitive tasks than those who were deficient in iron . After treatment, the significant improvement in serum ferritin was found to be associated with the significant improvement in cognitive performance and significant improvement in haemoglobin was associated with improved speed. The findings indicate that iron status is associated and information processing in adult women of reproductive age. The study also indicates that severity of iron deficiency affects accuracy and processing speed of several cognitive function. The results also highlight that increase in iron status due to supplementation results in a remarkable increase in cognition scores on the test for attention, memory and speed of young women.

With a view to study the effect of maternal iron deficiency on cognitive functions, Beard et al,(2005) conducted a prospective, randomized, controlled, intervention trial in South Africa among 81 mothers. Results revealed a strong association between iron status and Digit symbol test scores, which is a measure of mental speed, visuomotor coordination and short-term memory and also in Ravens Progressive Matrices Test Scores, which is a measure of intelligence and abstract reasoning. No change was observed in cognitive test scores of the control group. Correlation and regression analysis revealed significant correlation between the cognitive test scores obtained and iron status variables. The findings of this study clearly suggests that iron status has a strong influence on cognitive functioning.

Kretsch et al, (1998) reported the relationship between iron status and cognitive function in 14 obese dieting women. Iron status was assessed by hemoglobin and hematological measures. Cognitive functions were assessed by tests measuring sustained attention, short-term memory, simple reaction time, motor performance and focused attention. The findings revealed that subjects with lower hemoglobin had a consistently lower ability to sustain attention than those subjects with higher hemoglobin levels. Additionally, sustained attention scores were significantly correlated and predictive of changes to hemoglobin levels. No other cognitive tests were found to significantly correlate with iron status measures. The findings indicate the potential role of iron in influencing sustained attention.

3. SUMMARY AND CONCLUSIONS:

Based on the detailed review of literature there are strong reasons to suspect that iron deficiency may compromise cognitive functioning and that iron treatment may bring about improvement in specific cognitive functions such as mental speed, attention, abstract reasoning and verbal and visual memory. Improving cognitive function is very important since several studies show a significant relationship between cognitive profile and academic performance. However, the scarcity of consistent results on the cognitive benefits of iron treatment in different age groups necessitates the need for further research.

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