Dietary Iron is Associated with Memory in Midlife: Longitudinal Cohort Study

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Abstract: This work examined associations between dietary iron and cognitive function in mid-life adults using data from the 1946 British Birth Cohort, a representative population-based sample of men and women born in England, Scotland or Wales. Linear regression was used to determine the association between dietary iron intake or a measure of available iron (calculated by adjusting iron intake for dietary modifiers that are known to inhibit or enhance iron absorption) at ages 36, 43 and 53 years and cognitive measures at ages 43 and 53 years. Cognitive measures included verbal memory, assessed by a three-trial 15-word learning task, and speed and concentration, assessed by a timed letter search task. Examining the data cross-sectionally; dietary iron at ages 43 and 53 years was positively and significantly associated with verbal memory after adjustment for potential confounders. Examining the data longitudinally; earlier dietary iron exposure was significantly associated with later verbal memory. No associations were observed between dietary iron and measures of speed and concentration when examining the data both cross-sectionally and longitudinally. The current study shows that impaired cognition, specifically memory, resulting from inadequate iron intake may extend beyond childhood and also be present in midlife. This finding, coupled with the high prevalence of people reporting iron intakes below the Lower Reference Nutrition Intake in the UK, provide reason for concern.

Keywords: National Survey of Health and Development, 1946 Birth Cohort, Cognitive Decline, Midlife Adults, Nutrition.

INTRODUCTION

The association between iron and cognitive ability in children, and the potential mechanisms to explain this association, are well documented. Specifically, iron deficiency has been shown to be causally linked to memory and concentration in children and young people [1-4]. However, due to the limited literature on the topic, the association between iron and cognitive ability in mid and later life is less clear. The few studies that do exist have focused on older people, or those with cognitive impairment or other medical conditions [5, 6] and thus their applicability to the general population is reduced. Furthermore, these studies have numerous confounding factors making it difficult to draw firm conclusions. In a cross-sectional study examining diet and cognitive function in 260 people aged 65-90 years, those who consumed more iron performed better on short screening tests of cognitive function [7]. However, a larger study examining 1451 participants of a similar age observed that both very high and very low plasma iron concentrations were related to poorer performance, in tests of long-term memory, calculation and visuomotor skills in men, and very high plasma concentrations of iron were associated with poorer short and long-term recall in women [8]. The cross-sectional nature of previous work excludes the possibility of defining the temporal nature of the observed associations. Relevant large-scale longitudinal studies in adults are clearly necessary; we therefore examined associations between dietary iron and cognitive function in midlife in the 1946 British Birth Cohort (also known as the MRC National Survey of Health and Development, NSHD), which is a large representative population-based sample born in 1946, post World War II. We hypothesised that cohort participants with low dietary iron exposure would perform less well in cognitive tests, and would show a greater decline in these measures as they aged, compared to those with higher dietary iron exposure.

METHODS

Participants were drawn from the MRC National Survey of Health and Development (NSHD), a social class stratified sample initially consisting of 5,362 single births within marriage to families of non-manual or agricultural occupation, and a random one in four sample of single births within marriage to families of manual occupation. The cohort has been followed up 21 times, most recently completed at age 53 years in

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1999, when the sample size was 3,050. At this age the cohort was shown to be fairly representative of the UK population, except that more of those who did not respond had never married, and were least advantaged in terms of cognitive ability, educational attainment, and social class [9]. Ethical approval for this research was obtained from the North Thames Multi-Centre Research Ethics Committee, and from relevant local research ethics committees in the survey areas. Written informed consent was obtained from all participants.

Diet was assessed using a 5-day estimated (unweighed) food diary at ages 36, 43 and 53 years. All food and drink consumed at and away from home were recorded with portion size estimates using household measures. Nutrient composition of the diet was calculated using McCance and Widdowson's The Composition of Foods, using an appropriate version for each time point [10, 11]. Because of the discrepancy between the amount of dietary iron consumed and the amount that is absorbed, an algorithm, developed by some of the authors, was used to adjust iron intake from each meal for dietary modifiers that are known to inhibit or enhance iron absorption, yielding a measure of *available iron* [12]. Goldberg cut-offs, which assess energy intake in relation to estimated energy expenditure by considering age, gender, body size and physical activity levels, were used to identify participants who may have under-reported their dietary intakes [13]. Supplements were not included since intake of these was not assessed at the ages of 36 and 43 years. Use of iron supplements by cohort members is likely to be minimal.

Cognitive outcomes obtained at ages 43 and 53 years were verbal memory, assessed by a three-trial 15-word learning task, and speed and concentration, assessed by a timed letter search task [14, 15]. To minimise practice effects, parallel forms were used for both tests.

Potential confounding variables were gender, along with three factors that are known to be related to diet quality and cognitive outcomes: 1. highest educational qualifications attained by age 26 years (a) no qualifications (reference category), b) vocational only, c)'O' level or equivalent, d)'A' level or equivalent, and degree or equivalent), 2. Registrar General occupational social class (a) I (reference category) or b) II, c) III d) Nonmanual, e) III Manual, f) IV or g) V), and 3. general cognitive ability, represented by the Heim AH4 group abilities test [14] at age 15 years and the National Adult Reading Test (NART) [14, 16] at age 53 years.

Data were examined for the possibility of selection bias. Participants with any missing data were excluded from the analyses; only those with full repeated measures and all covariates were included.

To determine if dietary iron was associated with cognition when examining the data cross-sectionally, data collected at age 43 were examined. Linear regression was used to examine associations between iron intake at age 43 and the memory and letter search outcomes also measured at age 43. These linear regression analyses were repeated using the measure of available iron, in place of intake data, again to examine associations with the memory and letter search outcomes. The cross-sectional analyses were then repeated using iron and cognition data measured at age 53 years.

We also examined the data longitudinally, using regression models to look first at earlier measures of available iron and the memory and letter search outcomes measured at later ages. Additionally, we examined earlier available iron and later cognitive decline. Cognitive decline was defined as the difference in cognitive scores between the ages of 43 and 53 years. To examine this association available iron, measured at ages 36 and 43 years, and decline in cognitive scores were tested using conditional models of change, where cognitive scores at age 53 years were adjusted for their corresponding scores at age 43 years [14].

Regression models initially included adjustment for social class, educational attainment, general ability at age 15 years and gender. The NART was also included as a proxy for general cognitive ability for models with cognitive outcomes at age 53 years. Iron exposure variables were divided into quartiles (separately for data collected at ages 36, 43 and 53 years) and entered into the regression models as categorical variables. The highest exposure was considered the reference category.

RESULTS

Participants with missing data for any of the cognition outcomes were on average of higher social class with slightly lower educational attainment and general ability at age 15 years. Iron intakes were slightly higher in those with complete data (mean 11.8mg/day vs. 11.2mg/day, $p<0.05$).

Table 1: Summary Data for Dietary Iron and Cognitive Measures of Subjects in NSHD at Ages 36, 43 and 53 Years

		Age 36 years		Age 43 years		Age 53 years	
		Males	Females	Males	Females	Males	Females
		Mean (standard deviation)					
Diet	**Total iron intake (mg/day)**	13 (4)	10 (4)	13 (4)	10 (4)	12 (4)	10 (3)
	Total available iron (mg/day)	2.2 (0.6)	1.8 (0.5)	2.2 (0.6)	1.8 (0.6)	2.1 (0.6)	1.9 (0.5)
Cognition	**Verbal memory score**	n/a	n/a	23 (6)	26 (6)	23 (6)	24 (6)
	Letter search speed score	n/a	n/a	324 (75)	350 (72)	270 (73)	286 (75)
	NART*	n/a	n/a	n/a	n/a	35 (10)	34 (9)

*NART – National Adult Reading Test.

Search speed and verbal memory scores were lower at age 53 years than at age 43 years, indicating declining performance with age (Table **1**). Mean iron intake was higher at age 43 years than at age 36 and 53 years. However, mean available iron was consistent over the 17 year period (around 2mg per day).

In cross-sectional analyses, the lowest quartile of total iron intake and available iron at age 43 years differed significantly from the reference category (highest exposure) in terms of its association with verbal memory, after adjustment for potential confounders, indicating a disproportionately lower memory score in those with the lowest quartile of iron availability (Table **2**). Similarly, at age 53 years the lowest two quartiles of iron intake and available iron differed significantly from the reference category (highest exposure) in their association with verbal memory (Table **2**, Figure **1**). The differences between the highest and the lowest values for iron intake and available iron at 43 years were associated with a 2.7 and 2.9 word (~6%) change in verbal memory scores respectively. Similar differences were observed at age 53 years.

Cross-sectionally, there was no association between iron intake and search speed after adjustment for general ability at age 15 years, educational achievement, social class and gender. However, when using available iron, a positive association was observed at age 43 years but not at age 53 years.

The regression models described were repeated excluding subjects who were classified as possible under-reporters of dietary intake using the Goldberg cut-offs and calculations [13]. These accounted for 402 (18%) and 324 (19%) survey members at ages 43 and 53 years, respectively. Exclusion of these survey members in cross-sectional analyses made minimal difference to the coefficients in the models and both iron intake and available iron remained significantly associated with verbal memory. All remaining analyses were carried out without exclusion of possible under-reporters.

Table 2: Linear Regression Coefficients for the Association Between Quartiles of Available Iron and Verbal Memory

			Verbal Memory							
			Age 43 years			Age 53 years				
			Coefficient	95 % CI		p	Coefficient	95 % CI		p
Available Iron	**Age 36 years**	**Q2**	0.15	-0.63	0.94	NS	0.33	-0.76	1.42	NS
		Q3	-0.34	-1.00	0.32	NS	-0.32	-1.23	0.58	NS
		Q4	-0.76	-1.45	-0.07	0.032	-1.43	-2.39	-0.46	0.004
	Age 43 years	**Q2**	0.04	-0.55	0.64	NS	0.09	-0.75	0.93	NS
		Q3	0.01	-0.59	0.62	NS	-0.39	-1.25	0.47	NS
		Q4	-0.81	-1.44	-0.18	0.012	-1.05	-1.96	-0.15	0.022
	Age 53 years	**Q2**	-	-		-	-0.40	-1.53	-0.73	NS
		Q3	-	-		-	-1.20	-2.34	-0.06	0.039
		Q4	-	-		-	-1.25	-2.43	-0.07	0.038

NS = non significant at p=0.05.
Available Iron Quartile 1 = reference category (highest intake); quartile 4 = lowest intakes.

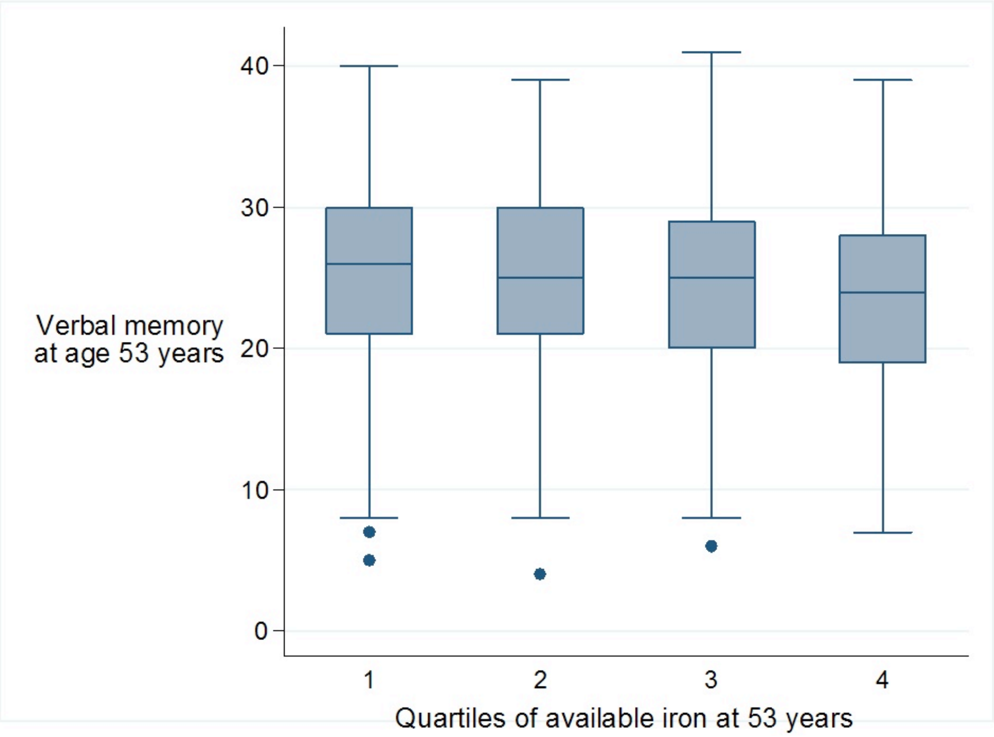

Figure 1: Box plots of verbal memory at 53 years by quartiles of available iron. Box plots showing median, IQR, normal range and outliers. Quartile 1: 2.30-6.23 mg/day. Quartile 2: 1.96-2.30 mg/day. Quartile 3: 1.64-1.96 mg/day. Quartile 4: 0.62-1.64 mg/day. Quartile 1 = reference category (highest intake); quartile 4 = lowest intakes.

In longitudinal analyses, the association between the lowest quartile of iron intake and available iron at age 36 years and verbal memory at age 43 years differed significantly from the association with the remaining quartiles (Table **2**), again indicating a disproportionately lower memory score among those in the lowest quartile of iron availability at earlier ages. The same was observed for the association between iron intake and available iron at age 43 years and verbal memory at age 53 years (Table **2**). There was no significant association between change in available iron and memory at age 43 years, as tested by adding available iron at age 43 years to a model already containing available iron at age 36 years. Longitudinally, no significant associations were found between available iron at age 36 years and search speed at age 43 years or between available iron at age 43 years and search speed at age 53 years.

Changes in verbal memory score, between 43 and 53 years, ranged from -20 points to 23 points, with 54% of individuals showing a decline. Using conditional models, available iron at 36 and 43 years was not associated with change in verbal memory between 43 and 53 years.

Mean change in search speed between 43 and 53 years was a decline of 58 points, with 82% of the population studied showing some decline. Available iron at 36 and 43 years was not associated with change in search speed.

DISCUSSION

This is the first study to examine longitudinally the relationship between available iron and cognitive ability in adults. In the 1946 British Birth Cohort iron intake and available iron at 36 and 43 years were positively associated with subsequent verbal memory at 43 and 53 years, although not with cognitive decline. This was observed for those with the lowest iron availability rather than across the full range of availability, and was independent of cognitive ability at age 15 years, educational attainment, and adult social class. These effects were not observed, however, for measures of speed and concentration.

Although extensive literature documents the causal relationship between iron and cognitive function in children, previous work in adults is sparse, with a lack of large-scale epidemiological evidence examining associations between *dietary* iron (i.e. not iron status) and cognitive function. There is some literature on iron status and cognitive function but not all cohorts have blood measures and there was a need to investigate relationships with dietary iron, particularly taking into account other dietary factors that influence its availability in the body. Consistent with the findings here, a smaller, cross-sectional study examining diet and cognitive function in 260 people aged 65-90 years observed that subjects who consumed more iron performed better on short screening tests of cognitive function [7]. Examining iron status rather than dietary iron, but nonetheless with similar findings, was a trial in 113 women aged 18-35 years. This reported that improvements in iron status, through iron supplementation, led to improvements across several domains of cognition, including attention, memory and learning [17]. The authors reported that speed was also affected by iron status, with iron-deficient anaemic individuals completing tasks less quickly. However this effect was only observed when iron-replete individuals were compared to iron-deficient anaemic individuals rather than to iron-deficient individuals without anaemia, and was not uniformly observed across all tests [17]. A cross-sectional study examining 1451 participants aged 60-98 years found that very low and very high plasma iron concentrations were related to poorer performance in tests of long-term memory, calculation and visuomotor in men, while in women an inverse linear association was observed, with very high plasma concentrations of iron being associated with poorer short and long-term recall [8]. The cross-sectional nature of the work makes it impossible to determine whether iron influenced cognition or whether cognition was a determinant of iron intake. These findings are different from those observed in the current study using dietary data and further work is needed to confirm a hemotoxic effect of high iron status. It could be postulated that the negative effects were observed only in the older cohort because of cumulative effects of high exposure. As the 1946 British Birth Cohort ages this could be examined further.

While plasma iron markers are considered to be more objective measures of iron exposure than dietary intake, these are by no means ideal, with multiple sources of bias influencing the interpretation of results. This is particularly so in ageing population-based cohorts where the effects of inflammation on serum ferritin for example, are commonplace. Iron status will not mirror iron use within certain compartments of the body, as seen in some patients with dementia in which an excess of iron deposition in the brain is frequently masked by presentation of iron deficiency when examining blood markers [18]. In the present study, associations between iron exposure and cognitive measures did not notably differ for intake and values for available iron generated by a predictive algorithm. This may be because the iron absorption enhancers and inhibitors counterbalance each other in this age group. Thus in middle age *dietary* iron exposure may have greater applicability to public health policies than intervention based on markers, where mechanisms to alter the latter at the population level rather than in the individual clinical case remain unclear. It is, however, important to establish whether this is the case in older populations and whether gender differences seen in iron markers are also of importance when examining dietary iron.

We should note potential study limitations. First, there was a disproportionate loss to follow-up of those who were relatively disadvantaged, including those with lower prior cognitive ability. However, we have no reason to believe that this would have altered the pattern of associations observed, and if anything may have resulted in an *underestimation* of the effect sizes. Second, while no significant associations were found between available iron or iron intake and cognitive decline, the relatively young age of this cohort means that we cannot be certain that such an association would not be observed in later life. Thus it would be informative to repeat these analyses when further cognitive data, measured at a later age, becomes available in the NSHD. The current study considered only iron from foods and thus ignored supplement use and so may be underestimating iron intake in some people and, as with any dietary study, is open to the problems of misreporting. Dietary iron is not consumed in isolation, other dietary factors may play a role in the observed associations and further study in this area is warranted. Against these limitations the 1946 British Birth Cohort has comprehensive prospective information on dietary iron intake, which we found to correlate highly with available iron, as well as a measure of prior cognitive ability, which helped to rule out the possibility of reverse causality, i.e. that the association between iron and cognition merely reflects higher iron intake in those with higher cognitive ability.

Iron deficiency anaemia is one of the most prevalent diseases worldwide, with a significant impact on cognitive impairment [19]. The current study shows that risk of cognitive impairment from inadequate iron intake is also present in midlife in a high-income country and, with 20% of women aged 19-64 years recently reporting iron intake below the Lower Reference Nutrition Intake (LRNI) [20], this provides reason for concern. It should be noted however, that the findings here do not support the use of iron supplements or advocate excessively high intakes of dietary iron in the absence of iron deficiency. The association with verbal memory did not alter between the highest quartiles of iron exposure suggesting that increased iron intake above a certain level does not add any further benefit in terms of cognitive function. Similarly, these findings do not exclude the possibility that high iron exposure may be positively associated with neurotoxicity in later life. This study suggests that a well balanced diet containing iron-rich foods, such as lean meat, fish and dark green vegetables, and avoidance of iron deficiency may be beneficial for cognitive function in mid-life adults.

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Competing Interests

All authors have no financial, personal or profession interests to declare.

Contributions of Authors

All authors contributed to the design, analysis and interpretation of this study and had final approval of the version to be published. APR and JJP led previous related work in this cohort on estimating iron availability.

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