The role of micronutrients in psychomotor and cognitive development

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The literature on the effects of micronutrients on cognitive, motor and behavioural development is reviewed focusing mainly on children. Iron, zinc, iodine and vitamins are discussed. The review is selective and concentrates on the more recent work and areas of controversy. There are well established associations with poor development and iron and iodine deficiency but the deficiencies usually occur in disadvantaged circumstances and establishing causal relationships is difficult.

Micronutrient deficiencies are extremely common world-wide. They are known to affect growth and health and in this paper we focus on their role in behavioural and cognitive development. We will selectively review evidence linking iron, zinc and iodine to behavioural development. We have chosen these deficiencies because they are highly prevalent and most research on the effect of micronutrients on behaviour has concerned them. A few studies have been conducted on vitamin deficiencies and we will briefly mention them. We will also focus mainly on children. It is possible that other micronutrient deficiencies affect behaviour but information on them is extremely limited.

Studying the effects of single nutrient deficiencies on behaviour presents several problems. Deficiencies generally occur in conditions of relative poverty and in developing countries they are often associated with protein energy malnutrition and other micronutrient deficiencies as well as infections. All these factors themselves may affect behavioural development; moreover, some of them may interact with each other, modifying their effect on development. Because of the many confounding factors, demonstrating a causal relationship between a deficiency and behavioural development is difficult and the only truly satisfactory way is through randomised treatment trials in deficient populations. Animal studies are also useful but care must be taken when extrapolating the findings to humans.
Iron deficiency

In 1985, anaemia was estimated to affect 46–51% of children under 5 years in developing countries and 7–12% in developed countries. There has been a recent decline in prevalence in some developed countries but, in Britain, anaemia remains common and ranges to as high as 39% in inner-city children. Iron deficiency is the commonest cause of anaemia and is usually due to inadequate dietary intake of bioavailable iron and/or excessive loss due to parasitic infections. Periods of rapid growth are the most vulnerable stages and anaemia is usually most prevalent around 6–24 months. However, some intensely infected populations of school children who are heavily infected with hookworm are at very high risk.

Iron deficiency anaemia causes reduced work capacity in children and reduced work capacity and productivity in adults. Since the late 1960s an association between altered behaviour and poor cognition and iron deficiency anaemia has been recognised and a considerable amount of research conducted since then. We will discuss the observational studies first then the treatment trials.

Observational studies

A recent review identified 18 studies showing cross-sectional associations between iron deficiency anaemia and poor cognitive function, motor development, behaviour or school achievement levels and there are other studies showing similar associations, e.g. Walker et al. However the findings are not totally consistent and several studies have failed to find associations. Small samples and the confounding effect of protein energy malnutrition may explain some of the negative findings.

Longitudinal studies have found that children who were anaemic in the first two years of life continued to function poorly in later childhood. In Costa Rica, Chile, and Israel children remained with poorer cognitive and motor function and school achievement levels. In general, the investigators controlled for many social background factors. One study found that the children had more soft neurological signs as well as lower IQs, however the study details have not been reported.

In another study by Hurtado et al., records of children who were enrolled in a US federal programme of nutritional supplementation were reviewed and the children located in grade five when they were around 10 years of age. Those children who were anaemic on enrolment between 6 and 59 months of age were more likely to be in special education classes, suggesting mild to moderate mental retardation, than non-anaemic children, even after controlling for many possible confounding variables. The evidence is, therefore, remarkably consistent that iron deficiency
anaemia in the first 2 years is a risk factor for poor development in later childhood.

Most children in these studies were given iron treatment when they were anaemic, therefore, the results raise the question as to whether the developmental deficits in anaemic young children are reversible. However, anaemic children generally come from disadvantaged backgrounds\textsuperscript{12} so the associations could be due to confounding variables and treatment trials are required to make causal inferences. We will discuss trials by young and older children because the findings tend to be different.

\textit{Treatment trials in anaemic children under 2 years of age}

Early trials in young children tended to last less than 2 months and all those which had placebo groups failed to find improvements to the children's developmental levels\textsuperscript{13}. Most children improve with test practise so, when improvements occurred and there was no control group, the results are not possible to interpret.

Five longer-term trials lasting 2–6 months were located from England\textsuperscript{14}, Costa Rica\textsuperscript{15,16}, Chile\textsuperscript{17} and Indonesia\textsuperscript{18}. Three of the studies found no significant benefit but, unfortunately, they had no placebo anaemic group but had non-anaemic controls\textsuperscript{15–17}. The longest trial ran for 6 months\textsuperscript{16} and the children's' scores on the Bayley test are shown in Figure 1. There was no hint of the treated anaemic children catching up to the non-anaemic children. However, it is possible that the development of anaemic children may progress at a different rate from that of non-anaemic children; therefore, it is difficult to interpret a negative finding.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{This diagram shows that compared with non-anaemic children, treated iron deficient anaemic children had lower mental development indices (MDI) before treatment and failed to catch up with treatment. IDA = Iron deficiency anaemia. Adapted from Lozoff et al\textsuperscript{16}.}
\end{figure}
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Fig. 2 This figure shows a significant improvement in the mental development index of treated iron deficient anaemic children compared with untreated controls. Adapted from Idjradinata and Pollitt.

The remaining two studies were randomised controlled trials with placebo groups. One was in England and failed to find benefits to the children’s development measured on the Denver test; however, this is only a screening test and unlikely to be sensitive to small differences. In the other Indonesian study, the treated anaemic children showed remarkably large gains to their developmental levels (Fig. 2).

Thus the evidence that the poor development of anaemic children improves with treatment hinges on one relatively small study. We, therefore, need more well-designed studies to establish with certainty whether anaemic children respond to treatment.

Prophylactic trials in children under 2 years of age

Preventive trials avoid perceived ethical issues concerning having placebo anaemic groups. Six preventive trials have been reported in which children were randomly assigned to iron treatment or placebo in the first few months of life before anaemia was apparent. Details of two recent studies that showed no benefit are not available. In one, non-anaemic Chilean children were treated from 6–12 months when they showed no advantage compared with the placebo group. In the other study, English children were treated from 9–18 months and showed no benefits. Two other studies which showed no significant benefits at 12 months of age are difficult to interpret. Malaria confused the results in one of them. Children who were malaria free and received iron had longer fixation times in a test of habituation, suggesting better attention ability. Investigators failed to report their results by the assigned group in the other.

In contrast, two studies showed clear benefits. In Canada, children who were treated from 1–2 months of age first showed benefits...
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Fig. 3 This diagram shows that the developmental quotients (DQs) of children who received unfortified cows’ milk declined more compared with those that received iron fortified cows’ milk. Adapted from Williams et al.3.

in psychomotor development at 9 and again at 12 months. But they were no longer significant at 15 months and their mental development was not affected. However, the loss from the study was considerable at 15 months. In the final study23, English children were assigned to cows’ milk or iron fortified formula from 7-18 months. The iron treated group showed significant benefits at 24 months (Fig. 3). One problem with interpreting the results is that the formula would have had other nutrients which could have played a role and the cows’ milk could have reduced the absorption of other nutrients.

It would appear likely that iron deficiency anaemia detrimentally affects young children’s development but the evidence is inconsistent and when all the data are available careful examination is needed to determine why some studies showed no effect. Possible explanations are the age of the child at the time of anaemia and the severity and duration of anaemia.

Treatment trials in older anaemic children

Studies of older children have been more consistent than those with younger ones. Briefly, of nine randomised controlled trials in children over 3 years of age, eight showed improvements in cognition or school achievement from iron treatment13. A study in Thailand24 failed to find improvements in school achievement. This failure may be due to the outcome measures not being sensitive to small changes in the child’s state. Two of three other trials with only non-anaemic children as controls showed improvements. Although some of these studies had small samples, or the placebo group was given other micronutrients, the evidence is reasonably consistent that iron improves anaemic school-aged children’s cognition.
Lozoff12 recently reviewed possible mechanisms linking iron deficiency to behaviour. These include direct effects of poor environments, permanent changes to neuromaturation, altered neurotransmitter function and 'functional isolation'. Iron deficiency during the brain growth spurt in the rat results in a permanent reduction in the amount of iron in the brain in spite of treatment. Iron is essential for myelination and iron deficient rats exhibit hypomyelination. There are also permanent deficits in the number of brain dopamine receptors and altered dopaminergic and serotonergic neurotransmission. These differences are thought to relate to changes in behaviour and arousal. Iron deficient rats show abnormal stress response25.

Iron deficient anaemic children show delayed auditory evoked potentials, which persist after correction of anaemia and may relate to hypomyelination. Anaemic children also show increased wariness, hesitance, unhappiness, fearfulness and tiredness. They stay closer to their mothers, interact with their environment less and are more likely to be carried. Their mothers show less pleasure in play and are less encouraging when their child is being tested12. It is likely that some of the mothers’ behaviour is in response to the child’s altered behaviour because during developmental assessments the testers also behaved differently towards anaemic children. Children with protein energy malnutrition behave very similarly and it is thought that they ‘functionally isolate’ themselves from their environment and this isolation detrimentally affects their development.

Conclusions for iron

In conclusion, iron deficient anaemic children are at high risk of concurrent and longer-term poor development and behavioural differences; however, they also come from disadvantaged backgrounds. The evidence of a benefit from iron treatment in anaemic older children is reasonably good. In children under 2 years of age, the evidence is less clear and the interpretation is hampered by the extremely few therapeutic trials using randomised controlled designs. However, it would be unusual for older children to be more vulnerable than younger children. The presence of three randomised trials (two preventive) showing benefits suggests that iron effects development in at least some children. There are several biologically plausible mechanisms linking iron deficiency to behavioural deficits.
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Zinc deficiency

It is extremely difficult to measure zinc status on a population basis so that the true prevalence of zinc deficiency is unknown; however, it is likely to be extremely common. Zinc deficiency is found in populations where the diet is low in flesh foods and high in substances which inhibit absorption such as phytates, fibre and cows' milk. The demand for zinc is higher in stages of rapid growth such as infancy, adolescence and pregnancy. In addition, excessive losses of zinc occur in diarrhoea and some parasitic infections. Although, children in developing countries are at most risk of zinc deficiency, it also occurs in developed countries.

Zinc deficiency has been associated with growth failure, impaired taste acuity and appetite, reduced immune response, diarrhoea and pregnancy complications. More recently, there has been concern that children's development may be detrimentally affected. Zinc deficiency is one of many causes of growth retardation and stunted (low height-for-age) children usually have poor development. It is possible that zinc deficiency plays a role in their poor development.

Research in animals

In a recent review of literature on zinc deficiency and behaviour in animals, Golub and colleagues found that, in rats, severe zinc deficiency in early pregnancy causes abnormal brain development and later in pregnancy causes persistent deficits in adulthood in several cognitive tasks. These differences are most apparent when response to electric shock or food bait is used as re-inforcers and the findings were attributed to altered stress response and motivation to perform the tasks. Severe zinc deficiency postnatally was also associated with poorer performance on memory tasks in several studies.

Fewer studies have looked at mild to moderate deficiency. In a cross over study with juvenile monkeys, Golub and colleagues showed that concurrent moderate zinc deficiency was associated with reduced activity levels and poorer attention and memory. The animal model most relevant to malnourished human populations is probably that used by Golub and colleagues in which monkeys were exposed to marginal zinc deficiency from conception throughout childhood. The monkeys showed transient growth retardation in infancy and adolescence and behavioural changes characterised by reduced activity and exploration. Impaired performance on cognitive tests was most marked in adolescence.
Research in children

Several trials of the effect of zinc supplementation on children’s cognitive and motor development and behaviour have recently been conducted and the details of the published studies are summarised in Table 1. There have been two randomised controlled trials in low birth weight children\textsuperscript{31,32}. In one study\textsuperscript{31}, at seven months of age, the supplemented group had significantly higher motor, but not mental, development scores. However, there was a large loss of data at most test sessions (only 25 of an initial 52 infants were tested at 12 months) and it is not clear how the loss may have affected the results. In the second study\textsuperscript{32}, babies born > 36 weeks gestation with birth weights < 10th percentile showed no overall treatment benefits. But the subgroup of children with birth weight below 2500 g showed benefits to their motor development from zinc. A third study with low birth weight, term babies in Brazil used a matched control design with the groups separated by time\textsuperscript{33}. No benefits were found to the children’s development but improvements were found in the children’s behaviour during the test.

Two randomised controlled trials in children under 2 years of age examined the effect of zinc on behaviour. Both studies showed behavioural differences with zinc supplementation. In Guatemala\textsuperscript{34}, there was no effect of zinc on the children’s motor milestones at any time or on their behaviour after three months of supplementation. After 7 months, the zinc supplemented group sat for significantly longer periods of time than the placebo group and showed a tendency to lie down less ($P = 0.1$). When controlling for many variables including time being carried, the treated group were also found to play more; however, the definition of play was confusing and the implications of these findings for children’s development are not clear. In the other Indian study\textsuperscript{35}, the zinc supplemented group was found to be significantly more active than the controls. However, there were no baseline measures of activity and the study was ‘piggy backed’ on a larger study and the loss of subjects was not reported.

Two pair-matched, randomised trials in school-aged children, in Canada\textsuperscript{36} and Guatemala\textsuperscript{37}, failed to find benefits to cognition from zinc treatment. However, an extremely limited range of cognitive functions were assessed. It is also possible that many of the Canadian children were not zinc deficient as the only response to treatment was a growth response in a subgroup of children ($n = 8$) with low hair zinc.

In two other studies of school-aged children, a computerised battery of cognitive tests was used which measured a wide range of cognitive and motor functions. In the first study in China\textsuperscript{38}, school children were randomised by classrooms ($n = 9$) to three groups, zinc alone, micronutrients alone or zinc with micronutrients for 10 weeks. The groups receiving zinc, consistently improved in most tests more than the micronutrient alone...
<table>
<thead>
<tr>
<th>Source</th>
<th>Sample and study design</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Results</th>
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<tr>
<td>Friel et al³</td>
<td>n = 52 VLBW infants, mean gestational age 29 weeks. Randomised controlled treatment trial</td>
<td>Supplemented 6 months: 11 mg/l Zn, 0.9 mg/l Cu. Unsupplemented: 6.7 mg/l Zn, 0.6 mg/l Cu. Assessed at 3, 6, 9, 12 months. All fed iron fortified formula</td>
<td>Biochemistry: blood and hair samples. Anthropometry Cognition: Griffiths developmental assessment</td>
<td>Significant difference in growth velocities and Griffiths motor subscale between supplemented and unsupplemented group No significant difference in Griffiths global score between supplemented and unsupplemented group</td>
</tr>
<tr>
<td>Bentley³</td>
<td>n = 108; 6-9 months</td>
<td>10 mg Zn or placebo; 7 months' duration</td>
<td>Behaviour observed for one 12 h day at baseline and 3 and 7 months later</td>
<td>No difference at baseline or 3 months. At 7 months supplemented group sat more. Motor milestones not different</td>
</tr>
<tr>
<td>Ashworth et al³</td>
<td>134 LBW term babies randomly assigned to placebo or 1 mg Zn. 71 matched babies given 5 mg Zn the following year</td>
<td>Zn 5 mg or placebo 8 weeks</td>
<td>Morbidity Bayley mental and motor scales. Behaviour ratings</td>
<td>5 mg Zn reduced diarrhoea No effect on Bayley scores Significantly more responsive in 5 mg Zn groups</td>
</tr>
<tr>
<td>Sazawal et al³</td>
<td>n = 93 children 12-23 months</td>
<td>10 mg elemental Zn and multivitamins given daily for 7 to 6 months to treatment group. Multivitamins given to control group</td>
<td>Behaviour observation for 2 consecutive days, 5 h/day No baseline data</td>
<td>Significantly more time in high-movement activities with Zn Significant treatment effect on children's activity rating score and energy expenditure score</td>
</tr>
<tr>
<td>Cavan et al³</td>
<td>n = 162, -81.5 months</td>
<td>Treatment: 10 mg Zn daily and micronutrients or micronutrients only, 25 week duration</td>
<td>Anthropometry Biochemistry: Functional assessments. Taste acuity, cell-mediated immunity, 3 subtests of Detroit Test of Learning Aptitude</td>
<td>Significant treatment effect for mid-arm circumference and triceps skinfold only, not significant for height and weight No significant treatment effect for functional physiological and cognitive measurements</td>
</tr>
<tr>
<td>Gibson et al³</td>
<td>60 boys aged 5–7 years</td>
<td>10 mg Zn daily, or placebo</td>
<td>Anthropometry: height, weight, weight-for-height Dietary assessment Cognition: 4 subtests of Detroit Tests of Learning Aptitude Hair Zn, serum Zn</td>
<td>No overall treatment effect on anthropometry, biochemistry ocognition Growth response seen among children who had impaired taste acuity and hair Zn &lt; 1.68 mmol/g at initial assessment</td>
</tr>
<tr>
<td>Penland et al³</td>
<td>n = 372, 6–9 years old</td>
<td>A. 20 mg Zn daily</td>
<td>Growth: knee height. Neuro-psychological functions: visual motor tracking, continuous performance, visual perception, short-term visual memory, oddity task</td>
<td>Knee height: B &gt; C &gt; A Neurological findings: significant treatment effect when A or B compared with C, tracking, continuous performance, visual memory, oddity task</td>
</tr>
</tbody>
</table>

zn = zinc treatment, Cu = copper treatment, VLBW = very low birth weight
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Conclusions for zinc

In conclusion, there are relatively few studies and most of them suffered from problems including a large loss of subjects, unreported subject loss and lack of base line data, failure to randomise to treatment, poorly defined measures or very restricted measures and inappropriate analyses. Sometimes it was not clear whether the population was actually zinc deficient. The studies covered different ages from birth to around 10 years, and used treatments of different duration and composition, including zinc with copper, zinc with mixtures of minerals and vitamins, zinc with multivitamins, and zinc alone. However, of the 7 studies published in detail, 5 found some differences in the treated groups. In young children this consisted of behavioural differences such as increased activity and more responsiveness to the environment. There is no evidence of a cognitive effect in the first 2 years but few studies examined this. One of three studies in school-aged children found an effect on cognition. Two abstract reports one of infants and one of school-aged children also found benefits. These findings, combined with persuasive evidence from animal research, suggest that zinc deficiency affects children’s behaviour; however, the evidence is inconclusive and more well designed studies are needed. Characteristics of the population likely to benefit, the precise nature of the benefits and what is the most effective type and duration of treatment need further study.

Iodine deficiency

Iodine deficiency remains a significant public health problem in many countries and is estimated to be responsible for 5.7 million cases of cretinism and 43 million cases of less severe cognitive impairment. The term ‘iodine deficiency disorders’ (IDD) has been adopted to describe the spectrum of effects of iodine deficiency which include goitre, endemic cretinism, neuromotor delays, and increased pre- and post-natal mortality.

Iodine and fetal brain development

The most robust evidence of the role of iodine in mental development has come from randomised controlled trials of iodine supplementation.
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of women of child bearing age. Pharoah and colleagues\textsuperscript{43} clearly showed in Papua New Guinea that an injection of intramuscular iodine before conception eliminated endemic cretinism in the iodine treated group. Among the non-cretins, children whose mothers received iodised oil were also found to have better cognitive and motor function 10 years later. Three other studies in Ecuador\textsuperscript{44}, Zaire\textsuperscript{45}, and Peru\textsuperscript{46} all found that children born to mothers supplemented prior to conception\textsuperscript{44,46} or in pregnancy\textsuperscript{45} had better developmental levels compared with children born to unsupplemented mothers, although the differences did not reach statistical significance in Peru\textsuperscript{46}.

It is thought that maternal thyroxin levels mediate the effect of iodine deficiency on fetal development\textsuperscript{47}. A recent study from The Netherlands\textsuperscript{48} suggests that thyroxin levels, even within the normal range in euthyroid mothers, can affect fetal brain development. The investigators found that children of mothers with thyroxin below the 5th and 10th percentiles at 12 weeks of pregnancy had significantly poorer psychomotor development at 10 months compared with children whose mothers had higher thyroxin levels\textsuperscript{48}. This is the first study to show that even in iodine sufficient areas, a maternal thyroxin level within the normal reference range may still be suboptimal for normal fetal development. Maternal thyroxin levels in pregnancy have previously been shown to correlate with children's cognitive and motor function at 14–15 years in an iodine deficient area\textsuperscript{49}.

Iodine and behavioural development in childhood

Many observational studies have compared children in iodine sufficient and iodine deficient areas and nearly all have found poorer psychomotor or cognitive development in children living in iodine deficient areas\textsuperscript{50}. However, iodine deficient areas are generally more remote, poorer, and lacking in facilities compared with iodine sufficient areas and these differences themselves could account for the children's poor development. In order to minimise these differences, a recent study from Bangladesh\textsuperscript{51} controlled for a wide range of micro-environmental and psychosocial factors as well as the presence of undernutrition and infection and a significant relationship between children's serum thyroxin levels and their cognitive function remained\textsuperscript{51}.

In an attempt to demonstrate a causal relationship others have conducted treatment trials in children. In two studies\textsuperscript{52,53}, children from an iodine deficient area were treated with iodised oil and compared with children from a control village. In Ecuador\textsuperscript{52}, only the treated girls had significantly higher intelligence than the control girls. In Spain\textsuperscript{53}, no benefits were found.
Two randomised controlled trials in iodine deficient areas were conducted in Malawi\textsuperscript{54} and Bolivia\textsuperscript{55}. In Malawi, the iodine treated children had better cognitive function than untreated children although pretreatment scores were not used. In Bolivia, no benefits were found from iodine supplementation; however, the placebo group also improved in iodine status making interpretation difficult.

A recent study from South Africa\textsuperscript{56}, showed that school children given biscuits fortified with iodine, iron, vitamin A, and β-carotene showed improvement in one out of nine tests of cognitive function. However it is difficult to attribute this effect to iodine alone.

The role of iodine deficiency in the mental development of school-aged children, therefore, remains an unanswered question. Only one iodine trial had a randomised controlled design with pre and post measures and that had problems with iodine spill over into the placebo group. The wide use of iodine fortification makes further randomised trials in children difficult.

Conclusions for iodine

There is conclusive evidence that iodine deficiency during intra-uterine life causes cretinism and impairs cognitive and motor development. The role of iodine supplementation in the cognitive development of school-aged children in iodine deficient areas is less clear although supplementing adolescent girls will ensure they are iodine sufficient before commencing child bearing.

Vitamins

Although Western diets are broadly adequate, subclinical vitamin deficiencies occur in population pockets\textsuperscript{57,58}. It is well established that severe deficiency of certain vitamins results in adverse neurological and intellectual outcomes (e.g. thiamine and beri-beri, niacin and pellagra, vitamin B\textsubscript{12} and combined degeneration of the cord)\textsuperscript{59}. It is, however, controversial as to whether vitamin supplementation of apparently healthy children and young adults would produce any extra benefit to their intellectual function.

Vitamins and cognition in healthy children

We found six clinical trials that examined the effect of multivitamin supplementation on young peoples' cognitive function. Two\textsuperscript{57,60} reported significant improvements in the intelligence of school children treated
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with multivitamins. The third reported gains only in females and the fourth found gains only in children given 100% of the RDA with no gains among those who received 50% and 200% of the RDA. However, two other studies using similar methods and vitamins showed no benefits.

The major limitation of studies linking multivitamins to improved intellectual function in children is the absence of any convincing physiological explanation for the findings. Given the inconsistent results and the lack of plausible biological mechanisms to explain the positive findings, the suggestion that vitamin supplementation improves the intellectual development of healthy children and young adults remains unproved. The existing vitamin status of the population must play a role and supplementing children who have normal levels could be potentially dangerous. It has been shown in Britain that 46% of parents whose children were taking vitamins did not know that they could be toxic.

**Vitamins and cognition in the elderly**

Many observational studies have found significant positive correlations between the cognitive functions of elderly populations and their serum levels or dietary intake of various vitamins including thiamine, pyridoxine, β-carotene, vitamins B₁₂, C, and E, and folic acid. However, some (e.g. Ravaglia et al. and Winograd et al.) found no such correlations and in one the association disappeared after controlling for age, education, and sex. So the major limitation of these cross-sectional associations is that they may be reflecting unmeasured confounding factors or deterioration in food habits of the elderly caused by cognitive decline rather than the opposite.

There are many uncontrolled trials of vitamin treatment in the elderly but they are impossible to interpret. We will briefly discuss controlled trials. Vitamin E has been shown to slow the progression of Alzheimer's disease. Clausen and co-workers found that a cocktail of antioxidants given to the elderly produced slight but significant improvement in psychological scores. Pyridoxine improved long-term memory in elderly men compared with a matched placebo group. However, one randomised trial of vitamin B₁₂ in the elderly, and a trial of antioxidants (tocopherol and deprenyl) on patients with early Parkinson's disease found no significant treatment effect.

**Mechanism**

Unlike children, there are plausible explanations for the potential benefits of vitamin B₁₂ and folic acid, and antioxidants on the mental
functions of the elderly. The first mechanism is the role of vitamin B\textsubscript{12} and folic acid in reducing homocysteine levels. Elevated homocysteine level has been linked with atherosclerosis which is a mediator of vascular dementia\textsuperscript{75}. The second mechanism is the possible role of free radicals in the pathogenesis of normal brain ageing and Alzheimer's disease\textsuperscript{69,70}. By neutralising free radicals, antioxidants can theoretically slow cognitive decline by reducing oxidative neural senescence.

Conclusions for vitamins

There is no good conceptual justification to suggest that healthy children can improve their intellectual function by taking supplementary vitamins and the evidence from treatment trials is inconsistent. However, in the elderly, it is theoretically possible that improved intake of antioxidant vitamins and vitamin B\textsubscript{12} and folic acid may prevent or reverse ageing related cognitive impairment. Although the empirical evidence for this conclusion is extremely weak, the potential benefits are theoretically plausible and the topic needs more research.

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