Vitamin B_{12} status of pregnant Indian women and cognitive function in their 9-year-old children

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Abstract

Background. *Recent research has highlighted the influence of maternal factors on the health of the offspring. Intrauterine experiences may program metabolic, cardiovascular, and psychiatric disorders. We have shown that maternal vitamin B_{12} status affects adiposity and insulin resistance in the child. Vitamin B_{12} is important for brain development and function.*

Objective. *We investigated the relationship between maternal plasma vitamin B_{12} status during pregnancy and the child's cognitive function at 9 years of age.*

Methods. *We studied children born in the Pune Maternal Nutrition Study. Two groups of children were selected on the basis of maternal plasma vitamin B_{12} concentration at 28 weeks of gestation: group 1 (n = 49) included children of mothers with low plasma vitamin B_{12} (lowest decile, < 77 pM) and group 2 (n = 59) children of mothers with high plasma vitamin B_{12} (highest decile, > 224 pM).*

Results. *Children from group 1 performed more slowly than those from group 2 on the Color Trail A test (sustained attention, 182 vs. 159 seconds; $p < .05$) and the Digit Span Backward test (short-term memory, $p < .05$), after appropriate adjustment for confounders. There were no differences between group 1 and group 2 on other tests of cognitive function (intelligence, visual agnosia).*

Conclusions. *Maternal vitamin B_{12} status in pregnancy influences cognitive function in offspring.*

Key words: Maternal vitamin B_{12} status, offspring cognitive function, short-term memory, sustained attention

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Introduction

Vitamin B_{12} is an important nutrient for brain development and function [1, 2]. The developing brain may be more sensitive to vitamin B_{12} nutrition than the mature brain. Fetal vitamin B_{12} requirements are provided by active transport across the placenta [3]. Low maternal vitamin B_{12} status reduces the amount of vitamin B_{12} transported to the fetus [4]. Vitamin B_{12} deficiency is common in Indians, largely owing to vegetarianism [5–11], but there is little information on the relationship between maternal vitamin B_{12} status and offspring brain development and cognitive function. Some studies in the Western world have shown that vitamin B_{12}–deficient infants (born to vegetarian mothers) are anemic, irritable, and anorectic and thrive poorly. These infants also have marked developmental regression and poor brain growth [12, 13].

The Pune Maternal Nutrition Study (PMNS) is a community-based prospective study designed to investigate the relationship between maternal nutrition and the risks of type 2 diabetes and cardiovascular disease in the offspring. We collected information on maternal nutrition during pregnancy and fetal growth. The children born from these pregnancies are periodically investigated for growth measurements and identification of risk factors for type 2 diabetes and cardiovascular disease. We have shown that maternal vitamin B_{12} status influences intrauterine growth and also insulin resistance in the child at 6 years of age [11]. Here we report the relationship between maternal plasma vitamin B_{12} status during pregnancy and the child's cognitive function at 9 years of age.

Subjects and methods

Details of the PMNS design and methods have been published [14, 15]. Briefly, we studied 814 pregnancies from six villages near Pune between 1993 and 1997. The mothers were on average 21 years old and had a body mass index of 18.1 kg/m^2. At 28 weeks of gestation, 65% of the mothers had low plasma vitamin B_{12} concentrations (< 150 pM), 35% had elevated plasma total homocysteine concentrations (> 10 μM), and more than 90% had high plasma methylmalonic acid concentrations (> 0.26 μM); all of these values were suggestive of vitamin B_{12} deficiency. Detailed anthropometric measurements were obtained from 770 normal, singleton babies within 72 hours after delivery. The children have been serially followed up, with repeat anthropometric measurements every 6 months. At 6 years of age (in 2002 and 2003), we assessed 653 children (97% of surviving children) for cardiovascular risk factors and measured plasma vitamin B_{12} concentrations.

When the children were 9 years of age (in 2005), we designed a study to investigate the association between maternal vitamin B_{12} status in pregnancy and cognitive function of the offspring. Two groups of children were defined on the basis of maternal plasma vitamin B_{12} concentration at 28 weeks of gestation. Group 1 consisted of children born to mothers who had low vitamin B_{12} concentrations during pregnancy (n = 57), and group 2 consisted of children born to mothers with high vitamin B_{12} concentration (n = 61). Low and high vitamin B_{12} concentrations were defined as the lowest (< 77 pM) and highest (> 224 pM) deciles of maternal plasma vitamin B_{12} concentration at 28 weeks of gestation.

Maternal erythrocyte folate concentrations were measured at the time of the original study (1993–96), taking all necessary precautions in the collection, transport, and storage of samples [16]. We measured plasma vitamin B_{12}, total homocysteine, and methylmalonic acid concentrations in freeze-stored (–80°C) samples in February 2004, as previously described [17–20]. Socioeconomic status was assessed by the Standard of Living Index designed by the National Family Health Survey-2 [16, 21]. We also collected information on the education of the head of the family, as measured by the number of years of school completed.

The KEM Hospital Research Ethics Committee approved the study. The children gave their assent and the parents gave informed written consent for the study. For illiterate subjects, consent was read aloud and their thumb impression was taken.

Psychological tests

We performed four tests of cognitive function in these children; the children's performance was scored according to Indian norms [22, 23].

Raven's Colored Progressive Matrices (CPM) is a group-administered test to measure intelligence. A series of patterns from which one piece is missing is shown to the child, who is asked to choose the correct piece from six options. The number of correct responses and the time taken to complete the tests are recorded [24].

Visual Recognition is a test of visual agnosia. The child is shown 10 pictures of different objects and asked to name them. The number of correct responses is recorded [23].

The Color Trail test (CTT) measures sustained attention and executive function. Colored circles (yellow and pink) are numbered 1 to 25, and the child is required to connect numbers serially, at two levels of complexity (A and B). CTT-A is a sustained-attention task, whereas CTT-B involves complex thinking and is a test of executive function. The time taken to complete each part of the test and the number of errors are recorded [23, 25].

The Digit Span test measures short-term or working memory. A series of numbers or digit strings of increasing length is read aloud, and the child has to repeat the numbers in a forward and backward sequence. The longest digit string recalled is considered the span [22, 26].

Statistical analysis

Differences in the performance of the two groups were tested by analysis of variance (ANOVA), with adjustment for potential confounders using three models. Model 1 was adjusted for the child's age, sex, education, Standard of Living Index, head circumference, and weight at the time of the study. Model 2 was adjusted for model 1 potential confounders plus the child's plasma vitamin B_{12} concentration at 6 years of age. Model 3 was adjusted for model 2 potential confounders plus education of the head of the family. A two-sided significance level of .05 was used. Associations between cognitive performance and body size were tested by Pearson's partial correlations, with adjustment for various confounders. Data were analyzed by the SPSS, version 11.0. Power calculations showed that our study had 75% power to detect a difference of 15% between the two groups at a 5% significance level.

Results

Maternal characteristics during pregnancy are shown in **table 1** and characteristics of the children in **table 2**. The mothers were young, with an average age of 21 years, and belonged to the lower socioeconomic class. Of the 118 children (57 born to mothers in the low-vitamin-B_{12} group and 61 to mothers in the high-vitamin-B_{12}

TABLE 1. Characteristics of mothers with low and high vitamin B_{12} status at 28 weeks of gestation

Characteristic	Low vitamin B_{12} status (< 77 pM)	High vitamin B_{12} status (> 224 pM)
Mean ± SD age at pregnancy—yr	20.3 ± 3.2	21.7 ± 3.9*
Mean ± SD pre pregnancy weight—kg	42.0 ± 4.9	41.0 ± 6.1
Mean ± SD Standard of Living Index score	28.0 ± 7.7	28.0 ± 8.1
Median (25th–75th quartile) hemoglobin—g/L	11.6 (10.2–12.2)	11.4 (10.1–12.4)
Median (25th–75th quartile) mean corpuscular volume—fL	84.4 (79.0–89.8)	82.6 (77.0–87.2)
Median (25th–75th quartile) plasma vitamin B_{12}—pM	67.0 (61.0–73.0)	278.0 (246.0–367.0)***
Median (25th–75th quartile) plasma total homocysteine—μM	10.8 (9.5–12.2)	7.3 (5.4–9.0)***
Median (25th–75th quartile) plasma methylmalonic acid—μM	0.9 (0.5–1.7)	0.3 (0.2–0.8)***
Median (25th–75th quartile) red cell folate—nM	379 (313–437)	443 (344–598)*

*$p < .05$
***$p < .001$ for the comparison between mothers with low and high vitamin B_{12} status

TABLE 2. Measurements in children

Measurement	Group 1[a] (n = 49; 19 boys)	Group 2[b] (n = 59; 31 boys)
At birth[c]		
Mean ± SD gestational age—wk	39 ± 2.2	39 ± 1.4
Cesarean delivery—no.	3	1
Mean ± SD birthweight—kg	2.5 ± 0.38	2.5 ± 0.40
Mean ± SD head circumference—cm	33.1 ± 1.4	32.9 ± 1.3
At 6 yr[c]		
Median (25th–75th quartile) plasma vitamin B_{12}—pM	215.5 (153.0–280.0)	246.5 (183.0–399.0)**
Median (25th–75th quartile) hemoglobin—g/L	11.6 (11.0–12.0)	11.6 (11.0–12.0)
Median (25th–75th quartile) mean corpuscular volume—fL	78.8 (75.0–74.0)	76.7 (80.0–79.0)
At time of study (9 yr)[c]		
Mean ± SD age—yr	9.5 ± 0.5	9.7 ± 0.5
Median (25th–75th quartile) education — yr	4 (3.0–4.0)	4 (3.0–4.0)
Mean ± SD height—cm	128.3 ± 5.5	129.1 ± 6.0
Mean ± SD weight—kg	22.7 ± 3.6	22.4 ± 3.1
Mean ± SD head circumference—cm	50.1 ± 2.4	50.3 ± 1.4

**$p < .01$ for the comparison between groups 1 and 2.
a. Mothers of group 1 children had low vitamin B_{12} status (< 77 pM) during pregnancy.
b. Mothers of group 2 children had high vitamin B_{12} status (> 224 pM) during pregnancy.
c. *P* values at birth were adjusted for gestation, parity, and sex.
d. *P* values in childhood were adjusted for age and sex.

group), 10 died during the follow-up period (8 from group 1 [3 boys and 5 girls] and 2 girls from group 2). Thus, we were able to study 49 children in group 1 (19 boys) and 59 children in group 2 (31 boys). The children were on average 9.6 years old and studying in the 4th standard at school. The two groups of children were similar in age, socioeconomic status, years of education, height, weight, and head circumference. As compared with National Center for Health Statistics (NCHS) standards [27], these children were shorter (–0.81 SD for boys and –0.72 SD for girls) and lighter (–1.30 SD for boys and –1.42 SD for girls). At 6 years of age, the children from group 1 had lower plasma vitamin B_{12} concentrations than children from group 2 (219 vs. 253 pM, $p < .01$), but blood hemoglobin concentration and erythrocyte mean corpuscular volume were similar in the two groups. The children's vitamin B_{12} concentrations at 6 years were significantly correlated with maternal vitamin B_{12} concentration during pregnancy ($r = 0.16$, $p < .001$).

As a group, these children performed satisfactorily compared with the Indian standards on the Raven's CPM, Visual Recognition, and Digit Span tests. However, 90% performed below the reference median for the CTT. There was no difference in performance between boys and girls, nor was there any association of performance with socioeconomic status. For a combined analysis of the two groups (because there was no significant difference in the head circumference of the two groups), larger head circumference both at birth and at 9 years correlated with a better performance on the Raven's CPM, Visual Recognition, and

Digit Span Forward tests (r = ~0.3, p < .01), and higher birthweight was correlated with higher scores on the Visual Recognition and Digit Span Forward tests (r = ~0.2, p < .05).

Children in group 1 performed more slowly (13% on average) on the CTT-A than children in group 2 (**table 3**). They also performed worse on the Digit Span Backward test (**table 3**, models 2 and 3). These differences were significant after adjustment for a number of possible confounders, such as age, sex, head size, education, socioeconomic status, and child's vitamin B_{12} status at 6 years. These results were also independent of the child's gestational age at birth, mode of delivery, and history of breastfeeding. There were no differences between the two groups in performance on the Raven's CPM and Visual Recognition tests. Maternal circulating concentrations of total homocysteine, methylmalonic acid, and folate were not related to children's cognitive performance.

Discussion

Our study demonstrates an association between maternal vitamin B_{12} status during pregnancy and children's cognitive functioning. Higher maternal plasma vitamin B_{12} concentration in pregnancy was an independent predictor of the child's cognitive performance on the CTT-A and Digit Span Backward tests, after controlling for a number of possible confounders, including the child's own vitamin B_{12} status at 6 years of age. For CTT-B, even though children from group 2 performed faster, the difference was not significant. Both CTT-A and CTT-B evaluate complex cognitive function, including sustained attention, visual scanning and tracking, graph motor speed, recognition of numbers, visual pursuit, vigilance, and number sequencing. These functions are governed by the frontal lobe. Part A is primarily a test of sustained visual attention involving perceptual tracking and simple sequencing, whereas part B assesses higher-order functioning of the frontal systems and is more complex than part A. The Digit Span test is a measure of short-term memory, which is governed by the temporal lobe. Thus, vitamin B_{12} status during intrauterine growth could influence different aspects of brain growth and neurocognitive development. Our prospective data collection allowed us to control for the possible influences on neurocognitive development of a number of factors, including length of gestation, mode of delivery, socioeconomic status, education, and the child's own postnatal vitamin B_{12} status.

A possible role of vitamin B_{12} in brain development and function has been demonstrated in only a few studies. Most of these are small case reports. Wighton et al. reported a case of neurologic deterioration in a child of a mother with severe megaloblastic anemia that commenced between 3 and 6 months of age and progressed to a comatose premorbid state by 9 months [28]. Lucke et al. reported neurologic symptoms in four infants of mothers consuming a vegan diet who had pernicious anemia [29]. Children from macrobiotic families in the Netherlands were reported to have impaired cognitive performance [30]. In these children, cobalamin deficiency was associated with a suboptimal performance on Raven's CPM, which measure intelligence. Vitamin B_{12}–deficient schoolchildren in Guatemala had slower reaction times on psychological tests, lower academic performance, attention problems, and delinquent behavior [31]. In elderly subjects, vitamin B_{12} deficiency was associated with neuropsychiatric disorders, even in the absence of anemia or a change in erythrocyte volume [32]. The exact mechanism of neurocognitive dysfunction in vitamin B_{12} deficiency is not clear. Severe vitamin B_{12} deficiency in pernicious anemia manifests as diffuse, though uneven, degeneration of white matter in the brain, spinal cord, and peripheral nerves [33, 34]. Reduced

TABLE 3. Children's scores on psychological tests[a]

Test	Group 1[b]	Group 2[c]	*P* value		
			Model 1	Model 2	Model 3
Raven's CPM (score)	23.5 ± 8.3	22.0 ± 8.5	NS	NS	NS
Raven's CPM (min)	16.9 ± 3.0	16.8 ± 3.0	NS	NS	NS
Visual Recognition (score)	7.7 ± 0.8	7.4 ± 1.5	NS	NS	NS
CTT-A (sec)	182.0 ± 55.2	159.0 ± 41.2	.02	.02	.02
CTT-B (sec)	289.0 ± 77.2	282.0 ± 71.4	NS	NS	NS
Digit Span Forward (no. of digits)	4.3 ± 1.1	4.4 ± 1.2	NS	NS	NS
Digit Span Backward (no. of digits)	2.6 ± 0.9	2.9 ± 1.2	.01	.02	.02

CPM, Colored Progressive Matrices; CTT, Color Trail Test; NS, not significant

a. Values are means ± SD; *p* values are for differences between group 1 and group 2. Model 1 is adjusted for child's age, sex, education, Standard of Living Index, head circumference, and weight at the time of the study. Model 2 is adjusted for model 1 measurements plus child's plasma vitamin B_{12} concentration at 6 years of age. Model 3 is adjusted for model 2 measurements plus education of the head of the family.

b. Mothers of group 1 children had low vitamin B_{12} status (< 77 pM) during pregnancy.

c. Mothers of group 2 children had high vitamin B_{12} status (> 224 pM) during pregnancy.

S-adenosylmethionine-dependent transmethylation reactions could affect myelination of neurons and also levels of neurotransmitters in specific brain areas [35]. The lack of association of cognitive performance with other indicators of maternal vitamin B_{12} deficiency (plasma total homocysteine and methylmalonic acid concentrations) and folate status raises the possibility of an as yet unknown but specific action of vitamin B_{12} on the brain.

Another important finding of our study is the association between head circumference (both at birth and at 9 years) and intelligence, visual recognition, and short-term memory. A number of studies have reported an association between head size and cognitive performance. In a study of 8-year-old English children, IQ was related to head growth in the prenatal period and during infancy [36]. In very-low-birthweight infants, subnormal head circumference at 8 months of age was associated with poor cognitive function, academic achievement, and behavior at 8 years of age [37]. In another study in Pune, low birthweight adversely affected children's intelligence and academic performance [38].

The strength of our study is its prospective design and long-term follow-up, with serial measurements of several parameters. The limitations of our study include the relatively small number of children, although we are now extending the study to include the full cohort of more than 700 children. Moreover, the children's vitamin B_{12} concentrations were measured 3 years earlier than the cognitive function tests, not concurrently with them. We think that their vitamin B_{12} status is unlikely to have changed substantially, because dietary habits in a given family are fairly stable.

Single maternal nutrient deficiencies have been associated with abnormalities in children's nervous systems: for example, maternal iodine deficiency with cretinism and folate deficiency with neural tube defects. Food fortification with these two nutrients has achieved remarkable success. Our results raise the possibility that vitamin B_{12} may be similarly involved in brain development. Given the substantial prevalence of vitamin B_{12} deficiency in India, there is a need for further studies, including studies of the effect of maternal vitamin B_{12} supplementation.

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