Child dietary intake of folate and vitamin B_{12} and their neurodevelopment at 24 and 30 months of age

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Gatica-Domínguez G, Rothenberg SJ, Torres-Sánchez L, Schnaas ML, Schmidt RJ, López-Carrillo L.
Child dietary intake of folate and vitamin B_{12} and their neurodevelopment at 24 and 30 months of age.
Salud Publica Mex. 2018;60:388-394.
https://doi.org/10.21149/8581

Abstract

Objective. To evaluate whether child dietary intake of folate and vitamin B_{12}, is associated with mental and psychomotor development in Mexican children, respectively, at 24 and 30 months of age. **Materials and methods.** Information about neurodevelopment and dietary intake of folate and vitamin B_{12} at 24 and 30 months of age among 229 children belonging to a perinatal cohort was analyzed longitudinally. Dietary information was assessed using a semi-quantitative food frequency questionnaire, and neurodevelopment by Bayley Scale of Infant Development II. **Results.** At 30 months of age, dietary folate intake was marginally associated with increased Mental Development Index (MDI) (β=8.33; 95%CI -0.48, 17.14; p=0.06). Non-significant positive associations of vitamin B_{12} with MDI were found. Psychomotor Development Index (PDI) was not associated with these nutrients. **Conclusion.** Dietary folate intake in early childhood may benefit the mental development of children.

Keywords: child development; folic acid; vitamin B_{12}; diet

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Resumen

Objetivo. Evaluar si la ingesta dietética infantil de folato y vitamina B_{12} se asocia con el desarrollo mental y psicomotor en niños mexicanos de 24 y 30 meses de edad. **Material y métodos.** La información del neurodesarrollo y la ingesta dietética de folato y B_{12} a los 24 y 30 meses de edad de 229 niños pertenecientes a una cohorte perinantal, se analizó longitudinalmente. La información dietética se obtuvo por un cuestionario de frecuencia de alimentos semicuantitativo y el neurodesarrollo mediante la Escala de Desarrollo Infantil de Bayley II. **Resultados.** A los 30 meses de edad, la ingesta dietética de folato se asoció marginalmente con un incremento del Índice de Desarrollo Infantil (IDM) (β=8.33; IC95% -0.48, 17.14; p=0.06). Se observaron asociaciones positivas no significativas entre la B_{12} y el IDM. El Índice de Desarrollo Psicomotor (IDP) no se asoció con dichos nutrientes. **Conclusión.** La ingesta dietética infantil de folato puede beneficiar el desarrollo mental.

Palabras clave: desarrollo infantil; ácido fólico; vitamina B_{12}; dieta

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Received on: March 3, 2017 • **Accepted on:** January 17, 2018
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Deficiencies of folate and vitamin B_{12}, both prenatal and early childhood, are associated respectively with slower child neurodevelopment. Brain development begins in the prenatal period and continues through puberty with rapid growth in the first two years of life.[1,2]

Folate is involved in DNA synthesis, proliferation, differentiation and apoptosis of neural stem cells.[3] Vitamin B_{12} plays an important role in the conversion of phosphatidylethanolamine to phosphatidylcholine, which comprise 14 and 11% of the myelin from the central neural system, respectively.[4]

There is consistent evidence showing a positive association of dietary intake and/or plasma concentration of folate and vitamin B_{12} from the mother during pregnancy with the mental development of children.[1] However, information about plasma concentrations and/or dietary intake of folate and vitamin B_{12} from the child in relation to their neurodevelopment is scarce. At 18 months of age, plasma concentrations of folate and vitamin B_{12} are positively associated with mental development.[5] Also, in a study with adolescents a lower cognitive function was detected among those who consumed a macrobiotic diet (cereals, pulses, and vegetables, with small additions of seaweed, fermented foods, nuts, seeds, and seasonal fruit; fish occasionally; meat and dairy products avoided) until six years of age, compared to those who consumed an omnivorous diet.[6] Additionally, in a randomized clinical trial, children from 6 to 30 months of age were supplemented for six months with folic acid (150 μg) and vitamin B_{12} (1.8 μg); an increase was observed in the gross motor development as well as in problems solution.[7]

The aim of this study was to evaluate the association of dietary intake of folate and vitamin B_{12} with mental and psychomotor development, at 24 and 30 months of age, in a cohort of Mexican children.

Materials and methods

This study is derived from a perinatal prospective cohort which was conducted in four municipalities in the state of Morelos, Mexico between 2001 and 2009. The detailed methodology has been previously described.[8,9] From a total of 442 births that occurred in that period, 229 children had information about: dietary intake and neurodevelopment assessment at 24 and/or 30 months of age, and were included in this report; 41 children were considered ineligible for presenting cerebral atrophy, prematurity (<37 weeks), neonatal death, congenital hypothyroidism, cleft lip/palate, perinatal asphyxia, birth weight <2 kg, coming from a twin birth and/or mother had ≤15 years of age; 102 were lost to follow-up; 69 were excluded for not having information of interest and one had a total energy intake ~4000 Kcal which was considered implausible. Maternal information about socio-demographic characteristics, dietary habits, gynecological and obstetric history, tobacco and alcohol consumption, breastfeeding, among others was also available.

This study was approved by the Ethics Committee of the National Public Health Institute of Mexico. Informed consents were obtained from study participants at the baseline and an informed re-consent letter was obtained for the evaluation of children.

Dietary folate and vitamin B_{12} intake

Mothers were interviewed about the dietary intake of folate and vitamin B_{12} of the child, through a semi-quantitative food frequency questionnaire at 24 and 30 months old of their child.[10] This instrument includes four dishes and 44 foods grouped in dairy, fruits, vegetables, grains, white/red/processed meat and sweets with predetermined portions. The frequency of consumption was classified according to 10 response categories, going from 'never' up to 'six times per day'.

Standardized recipes for dishes were used and the folate retention factor was considered according to the cooking method (Food Intake and Analysis System - FIAS 3.0; University of Texas, Huston, 1996). Total vitamin B_{12} and other nutrients such as dietary folate equivalent (DFE) were estimated based on the reference tables of nutritional food composition No. 20 of the United States Department of Agriculture (USDA).[11]

Child neurodevelopment

Mental and psychomotor development was evaluated with the Spanish version of the Bayley Scale of Infant Development II (BSID-II).[12] The BSID-II is a tool to assess cognitive, motor and socio-personal development. It may be applied from one up to 42 months of age and has two indexes: mental (MDI) and psychomotor (PDI). MDI includes assessment of recognition memory, habituation to visual and auditory stimuli, visual acuity and preference, the ability to resolve problems, the ability to count, generalization, classification, vocalization, language, among others. PDI assess motor development and control of gross and fine movements through rolling, crawling and creeping, sitting, standing, walking, running, jumping, prehension, adaptive use of writing instruments, as well as imitation of hand movements.

Home neurodevelopment assessments were performed at 24 and 30 months of child's age in the presence of their mother or caregiver. The test was applied by two trained psychologists with an inter-observer agreement of 0.96 for MDI and 0.98 for the PDI.[8]

Covariates of interest

Child anthropometry. In each visit, children were measured and weighed by nurses previously trained for that purpose.

Maternal intellectual capacity (IQ). Maternal IQ was measured through the reduced version of the Wechsler Adult Intelligence Scale in Spanish.[13]

Home environment. It was assessed at 6 and 30 months of age of the child by the Home Observation for Measurement Test Environment (Home Observation for Measurement of Environment, HOME). This scale evaluates the stimulation of the child through communication and interaction with household members, the type of toys available, etc.[14]

Statistical analysis

Participants were compared to non-participants according to available mother, father, child and family characteristics, through t test, Kruskal Wallis and Xi^2.

We calculated and compared the proportion of boys and girls at 24 and 30 months with low intake of folate (DFE <150 μg/d) and vitamin B_{12} (<0.9 μg/d) using the cut-off points recommended by the Institute of Medicine of the United States (IOM) for children, regardless of gender, from one to three years of age.[15] We also estimated and compared the averages of MDI and PDI.

The MDI and PDI associations with the dietary intake of folate and vitamin B_{12} (continuous variables and adjusted by the residual method)[16] were evaluated using generalized models of mixed effects. The fixed portion included folate or vitamin B_{12}. The random part of the models included the intercept of each subject and its heteroscedasticity adjusted by specifying the structure of the residual errors within groups of the lower level of the model and assuming that these effects are independent, with normal distribution, but with a different variance for each age at which the child was evaluated. In the fixed part, the absence of collinearity was confirmed through the variance inflation factor and heteroscedasticity was adjusted by the Huber-White estimator of the variance-covariance.

We considered as confounders those variables that caused a change of at least 10% in at least one coefficient of the raw models of folate/vitamin B_{12} with MDI/PDI, respectively. The Akaike (AIC) and Bayesian (BIC) information criteria were used to determine the goodness of fit of the models. Additionally, all models were graphically diagnosed and the normality of residuals was assessed using Shapiro-Wilks test.

A sensitivity analysis was performed adjusting the final models by available data of hemoglobin at 24 months in a subsample of 90 children. STATA 13.0* was used for all analyzes.

Results

The mothers of the children in the study were young (22 years old), mostly primiparous (81.2%), with an average schooling of almost 11 years, an IQ of 88.6 ± 12.7 and a normal BMI at first trimester (23.5 ± 3.9 kg/m^2). Only 7.5% reported having smoked and 24.2% were exposed to secondhand smoke during pregnancy. Most mothers (~85%) had a poor dietary intake of iron during the first and third trimester of pregnancy. Approximately 59% of children were born by cesarean section, 8.3% did not receive breastfeeding and had on average 30.8 ± 4.7 points in HOME scale (table I).

Compared with children who were excluded or lost in the postnatal follow-up (n =172), a higher percentage (69.4%) of children included in this study it received more than 12 weeks of breastfeeding and had parents with less schooling (table I).

On average, girls had higher MDI at both ages, however this difference was not statistically significant. In contrast, the PDI was significantly higher in boys than in girls, although only at 24 months old. No significant differences were observed in dietary variables under study according to gender or age at evaluation (table II). Low dietary intake of folate and vitamin B_{12} was observed in a very small percentage of boys (from 0.79 to 3.97%) and girls (from 0.97 to 1.94%) at both 24 and 30 months of age (data not included). An increase in MDI with increased dietary folate was observed at 30 months of age (p=0.06) (table III).

Discussion

The results of this study may indicate increased child neurodevelopment associated with dietary folate intake. Also, they weakly suggest that dietary vitamin B_{12} intake may have a positive association with child neurodevelopment.

Although we do not identify previous studies that would have evaluated the association between dietary folate and vitamin B_{12} intake with child neurodevelopment, our results are similar to those reported in a study of about 500 children in northern India, where

* StataCorp., College Station, TX, USA.

Table I
Parental, child and family selected characteristics among included, excluded and lost children in the study. Morelos, Mexico 2001-2009

Variables		*Included (n=229)*	*Excluded and Lost (n=172)*
Maternal			
Age (years)	mean ± SD	22.2 ± 4.3	22.4 ± 4.2
Schooling (years)	mean ± SD	10.9 ± 3.3	10.9 ± 3.1
Intellectual coefficient	mean ± SD	88.6 ± 12.7	88.5 ± 12.3
No previous pregnancy	%	81.2	81.4
BMI (Kg/m^2)*	mean ± SD	23.5 ± 3.9	23.7 ± 4.0
Salaried	%	48.5	48.5
Smoking during pregnancy (%)			
Active	%	7.5	7.8
Passive	%	24.2	22.9
Dietary iron intake (mg/day)			
At 1st trimester	median, P_{10}-P_{90}	19.6, 12.3-30.9	18.5, 11.8-27.9
< 27mg/day	%	83.3	88.3
At 3rd trimester	median, P_{10}-P_{90}	19.3, 12.0-28.4	18.6, 13.0-26.6
< 27mg/day	%	86.2	90.3
Paternal			
Age (years)	mean ± SD	24.9 ± 5.1	25.3 ± 4.8
Schooling (years)‡	mean ± SD	10.7 ± 3.3	11.5 ± 3.2
Child			
Male (%)	%	55.0	54.2
Cesarean birth (%)	%	59.4	59.3
Height at birth (cm)	mean ± SD	50.3 ± 2.3	50.4 ± 2.4
Birthweight (Kg)	mean ± SD	3.3 ± 0.5	3.2 ± 0.4
Breastfeeding (%)‡			
Never	%	8.3	5.9
≤ 12 weeks	%	22.3	34.1
>12 weeks	%	69.4	60.0
Family			
HOME scale	mean ± SD	30.8 ± 4.7	30.0 ± 4.4

* At 1st trimester of pregnancy
‡ $P<0.05$

plasma concentrations of folate and vitamin B_{12} were significantly associated with mental development at 18 months of age. Also the increment in mental development associated with folate was not observed in children with low plasma vitamin B_{12} concentrations (<25th percentile). In our study it was not possible to evaluate the association of folate through defined strata of dietary intake of vitamin B_{12} by a reduced sample size. In addition, our results show no association between child dietary intake of folate and vitamin B_{12} with psychomotor development, which also was observed in the study described previously.[5] It is possible that the lack of significance in the results of our study is explained not only by the small sample size but also by the use of the food frequency questionnaire that may have low sensitivity and specificity,[17] and it has also been

Table II

Child neurodevelopment and dietetic folate, vitamin B_{12} and total energy according to age at evaluation. Morelos, Mexico 2001-2009

Variables		*24 months*		*30 months*	
		Boys (n=126)	*Girls (n=103)*	*Boys (n=126)*	*Girls (n=103)*
Bayley scale					
Mental	mean ± SD	85.2 ± 10.0	86.1 ± 10.4	89.8 ± 8.4	90.8 ± 8.4
Psycomotor*	mean ± SD	96.7 ± 8.7	92.8 ± 8.0	93.0 ± 10.2	92.6 ± 9.4
Diet					
Energy (Kcal/day)	median (P_{10}-P_{90})	1 397.0 (1 029.1-2 026.1)	1 447.1 (980.6-1 876.8)	1 427.2 (926.5-2 046.4)	1 447.9 (956.0-1 829.8)
Folate (µg/day)‡	median (P_{10}-P_{90})	390.5 (278.0-529.6)	362.3 (252.9-518.1)	378.3 (269.1-510.0)	391.1 (269.4-556.8)
Vitamin B_{12} (µg/day)	median (P_{10}-P_{90})	5.7 (3.8-7.1)	5.5 (4.0-7.0)	5.2 (3.5-7.1)	5.5 (3.9-6.8)

* At 24 months boys vs. girls (*p*<0.001)
‡ As dietary folate equivalents

Table III

Mixed models coefficients of dietary folate* or vitamin B_{12}* with neurodevelopment according to age at evaluation. Morelos, Mexico 2001-2009

Age (months)	*Mental*				*Psychomotor*			
	Folate (mg/d)‡ (n=210)		*Vitamin B_{12} (µg/d) (n=207)*		*Folate (mg/day)‡ (n=200)*		*Vitamin B_{12} (µg/day) (n=189)*	
	b§	*95%CI*	*b*#	*95%CI*	*b*&	*95%CI*	*b*≠	*95%CI*
24	5.36	-4.89-15.61	0.25	-0.45-0.96	1.04	-8.94-11.01	-0.04	-0.79-0.71
30	8.33∞	-0.48-17.14	0.19	-0.37-0.74	11.19	-2.34-24.72	0.45	-0.68-1.59

* Energy-adjusted
‡ As dietary folate equivalents
§ Adjusted by maternal schooling, HOME, parity, child birthweight and z score of child BMI
# Adjusted by maternal schooling, IQ, HOME, paternal schooling and child birthweight
& Adjusted by maternal schooling, HOME, parity, BMI at 1st trimester of pregnancy, paternal schooling, child sex, birthweight, and z score of child BMI
≠ Adjusted by maternal schooling, maternal IQ, HOME, dietary iron intake at 3rd trimester and BMI at 1st trimester, paternal schooling, child sex, birthweight and z score of child BMI
∞ *p* value=0.06

Sample sizes are different due to missing values in one or more covariables

observed elsewhere.[18] We are aware that a limitation of this study is that due to the small sample size, other nutrients related with child neurodevelopment such as iron, zinc and ω-3 PUFAs could not be analyzed.

Not only is postnatal child dietary intake of folate and vitamin B_{12} is associated with their mental development, but so is the maternal intake of these nutrients during pregnancy.[3] Previously, in mothers of children under study it was found that vitamin B_{12} deficiency significantly reduced mental development during the first year of life (β=-1.6; 95%CI=-2.8 to -0.3). Also, dietary folate was negatively associated with mental development among offspring whose mothers were genetically susceptible (carriers of MTHFR *677TT* genotype) with a dietary folate intake <400 mg/day (β=-1.8; 95%CI=-3.6 to -0.04).[19]

Experiments have shown that folate has specific effects on the central nervous system from the embryonic period to adulthood; it is involved in neurogenesis, proliferation, migration, neuronal differentiation and synaptic plasticity.[20] Its deficiency in breast feeding alters behavior and learning ability[21] and in adulthood promotes sensory axonal regeneration.[22] Folate stimulates the Notch signaling pathway and Erk 1/2 phosphorylation, participates in the biosynthesis of neurotransmitters and epigenetic mechanisms that partially explain the above effects.[20,21,23] With folate, vitamin B_{12} is involved in the cycle of one carbon that is essential for the synthesis and integrity of the genome,[23] it contributes to the formation of myelin and the functioning of the central nervous system.[24]

It is important to note some methodological considerations for interpreting our results. Initially, it was found that participating children received breastfeeding longer and their parents had less schooling than those who were lost or excluded from the study. This reduces the generalizability of our results. It is possible that the reported associations in this study are a conservative estimate due to random measurement error inherent to the food frequency questionnaire used to estimate dietary folate and vitamin B_{12}. However, in this respect, it was found that the total daily energy intake by the study children was similar not only to that reported in children from one to four years in the National Health and Nutrition Survey of Mexico,[25] but also to the recommendations of the IOM of the United States for children from one to three years.[26] Additionally, provisions were taken to reduce the possibility of a differential error, which included blinding of the child dietary intake to the psychologists who applied the BSID-II test as well as blinding of the child neurodevelopment status to the interviewers who collect information about child dietary intake. Moreover, it is unlikely our results are explained by confounders (*i.e.*, home environment, breastfeeding, and maternal IQ) that were taken into account in the multivariate models. Also, in a subsample of the study population, adjustment by hemoglobin at 24 months of age (n=90), because anemia in preschoolers is highly prevalent (20.4% in 2012),[27] or maternal plasma folate and/or vitamin B_{12} at first trimester of pregnancy, did not change the results (n=133) (data not shown).

In conclusion, our results suggest that dietary folate intake in early childhood may benefit the mental development of children.

Acknowledgements

This study was funded by grants (41708, 31034-M, 13915) from Mexico's *Consejo Nacional de Ciencia y Tecnología* (Conacyt). Also, it was partially founded by the Fogarty International Center and National Institute of Aging of the National Institutes of Health (D43TW009315). The content is solely the responsibility of the authors and does not necessarily represent the official views of the Fogarty International Center or the National Institutes of Health.

Declaration of conflict of interests. The authors declare that they have no conflict of interests.

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