

Prenatal supplementation with DHA improves attention at 5 y of age: a randomized controlled trial¹

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ABSTRACT

Background: Docosahexanoic acid (DHA) is an important constituent of the brain. Evidence from well-designed intervention trials of the long-term benefits of increasing DHA intake during pregnancy has been sparse.

Objective: We evaluated global cognition, behavior, and attention at age 5 y in the offspring of Mexican women who participated in a randomized controlled trial of prenatal DHA supplementation.

Design: A total of 1094 women were randomly assigned to receive 400 mg of either DHA or placebo/d from 18 to 22 wk of pregnancy until delivery. We assessed cognitive development and behavioral and executive functioning, including attention, in 797 offspring at age 5 y (82% of 973 live births) with the use of the McCarthy Scales of Children's Abilities (MSCA), the parental scale of the Behavioral Assessment System for Children, Second Edition (BASC-2), and the Conners' Kiddie Continuous Performance Test (K-CPT). We compared the groups on raw scores, T-scores, and standardized scores, as appropriate. We examined heterogeneity by the quality of the home environment, maternal intelligence, and socioeconomic status.

Results: There were no group differences for MSCA scores ($P > 0.05$), but the positive effect of the home environment at 12 mo on general cognitive abilities was attenuated in the DHA group compared with in the placebo group (P -interaction < 0.05). There were no differences between groups on the BASC-2. On the K-CPT, offspring in the DHA group showed improved mean $\pm$ SD T-scores compared with those of the placebo group for omissions (DHA: 47.6 ± 10.3 ; placebo: 49.6 ± 11.2 ; $P < 0.01$) with no differences ($P > 0.05$) for the other K-CPT scores or of the proportion who were clinically at risk of attention deficit hyperactivity disorders after Bonferroni correction for multiple comparisons.

Conclusion: Prenatal exposure to DHA may contribute to improved sustained attention in preschool children. This trial was registered at clinicaltrials.gov as NCT00646360. *Am J Clin Nutr* doi: 10.3945/ajcn.114.101071.

Keywords: attention, child development, fatty acids, prenatal supplementation, omega-3 fatty acids, preschool cognitive development

INTRODUCTION

Interventions and policies to improve maternal and child nutritional status during the first 1000 d of life are effective means

to improve short- and long-term cognitive performance, schooling, and other cognitive-related outcomes (1, 2), thereby contributing to economic progress and development (3–5). Several nutrients, especially trace elements such as iron and zinc and, more recently, n–3 fatty acids are critical for the development of the human brain and neurotransmitter function. In particular, the n–3 fatty acid DHA (22:6n–3) has been identified in animal and human studies as being crucial for the development of the central nervous system. Biological evidence has supported the importance of DHA on global cognition and behavioral and executive functioning, particularly attention, through its role in frontal cortex functions (6–8). In animal models, induced n–3 deficiency has caused the activity and habituation patterns that are consistent with attention-deficit hyperactivity disorder (ADHD)⁹ (9, 10). In human-infants studies, maternal DHA status at delivery has been inversely correlated with distractibility (11). In school-age children with ADHD, supplementation with DHA improved working memory (12), and higher blood concentrations of DHA and the n–3 fatty acid EPA were associated with better attention and literacy outcomes (13). Attention is an important component of cognitive performance and helps in optimizing learning outcomes; improved attention during the first decade of life has been associated with better school performance in the long term (14).

Infant DHA stores are established early beginning in utero through the first year of life. Therefore, an adequate maternal DHA supply during both pregnancy and lactation is key to establishing adequate offspring stores (15). The main dietary sources of DHA are cold-water fish and seafood. Although the

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⁹Abbreviations used: ADHD, attention-deficit hyperactivity disorder; BASC-2, Behavioral Assessment System for Children, Second Edition; HOME, Home Observation for Measurement of the Environment; ISI, inter-stimuli interval; K-CPT, Kiddie Continuous Performance Test; POSGRAD, Prenatal Omega-3 Fatty Acid Supplementation and Child Growth and Development; RCT, randomized controlled trial.

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human body can convert the more-common α -linolenic n-3 fatty acid into DHA, dietary sources and enzymatic conversion may not be sufficient to ensure an adequate supply of preformed DHA during the first 1000 d of life, and supplementation may be required (16).

Despite all the biological and empirical evidence that supports the potential benefits of DHA supplementation during pregnancy on the cognitive and behavioral functioning of offspring, to our knowledge, no randomized controlled trials (RCTs) have adequately assessed the impact on offspring cognitive and behavioral functioning beyond infancy. Consequently, the objective of this study was to determine whether prenatal DHA supplementation improves global cognitive function, parent-reported behavioral functioning, and performance on an objective measure of attention at 5 y of age in Mexican children whose mothers participated in an RCT of the effects of prenatal supplementation with DHA on child growth and development in the POSGRAD (Prenatal Omega-3 Fatty Acid Supplementation and Child Growth and Development) study.

METHODS

We followed up with offspring who were born to women who participated in the POSGRAD study. The detailed methods of the original trial (clinicaltrials.gov; NCT00646360) have been described elsewhere (17). Briefly, between 2005 and 2007, pregnant women who were planning to deliver at the Instituto Mexicano del Seguro Social General Hospital 1 (which provides medical services to an employed, middle-income population) in Cuernavaca, Mexico, were randomly assigned ($n = 1094$) to receive either an algal DHA supplement (400 mg/d; produced by Martek Biosciences and distributed by Mead Johnson) or a corn- and soy-oil-based placebo from midgestation (18–22 wk) until delivery. Detailed information on birth outcomes was obtained, and all live births ($n = 973$) were followed prospectively (Figure 1). All study protocols were approved by the Research, Ethics and Biosecurity Commissions of the Instituto Nacional de Salud Pública, Mexico, and by the Institutional Review Board of Emory University. The study procedures were described to subjects, and written informed consent and verbal assent were obtained from the mother (or primary caregiver) and the children, respectively.

Measures of cognition

Child cognitive functioning was measured at 5 y of age with the use of the Spanish language version of the McCarthy Scales of Children's Abilities (MSCA) (18). The MSCA is a comprehensive test battery that measures a variety of cognitive and motor behaviors in children aged 2.5 through 8.5 y and includes 18 subtests that constitute the following 6 scales: Verbal, Perceptual-Performance, Quantitative, Memory, Motor, and General Cognitive. The General Cognitive scale is derived from the Verbal, Perceptual-Performance, and Quantitative scales.

Study psychologists ($n = 3$) who were trained by the lead psychologist (LS) administered the MSCA to the study children in a quiet and private setting within the hospital; the entire test battery took ~ 1 h. The administration of the MSCA was supervised through direct random observations and a review of the completed MSCA forms. The original data were entered on site.

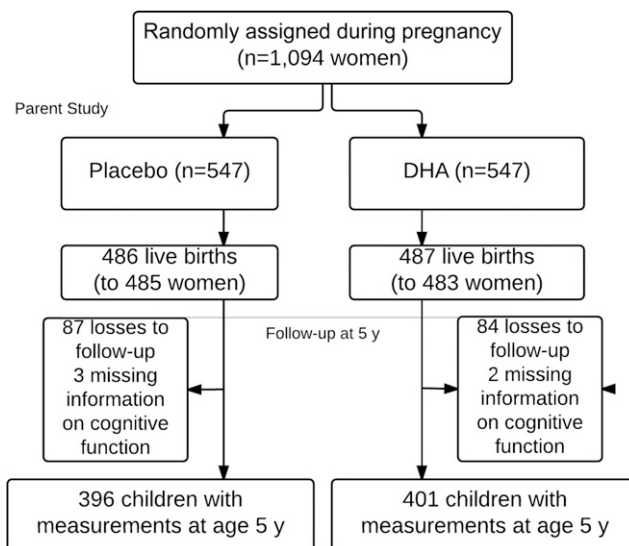


FIGURE 1 Sample flowchart for the assessment of the impact of prenatal supplementation with DHA on cognitive outcomes at 5 y of age.

Raw scores were computed for each scale and converted into scale indexes with the use of the Scale Index Equivalents of Composite Raw Scores Table, which is standardized for the child's age at the time of test administration as described in the MSCA manual (19). The Verbal, Perceptual-Performance, Quantitative, Memory, and Motor scale indexes have a mean $\pm$ SD score of 50 ± 10 . The General Cognitive scale index has a mean $\pm$ SD score of 100 ± 15 .

Measures of behavior

The parent-report version of the Behavioral Assessment System for Children, Second Edition (BASC-2), was used. This tool was developed as a "multimethod, multidimensional system to evaluate the perceived behavior of children and young adults between 2 and 25 years of age" (20, 21). The tool assesses adaptive and maladaptive behaviors. For this assessment, trained psychologists used the Spanish version of the BASC-2 Parent Rating Scale to interview caregivers about their perception of their children's behaviors. An initial clinical history was completed to better understand each child's context and was followed by a list of 134 statements with Likert-scale-type responses (i.e., never, sometimes, often, almost always). The BASC-2 scale provides scores on the following 3 broad domains: externalizing problems (hyperactivity and aggression), internalizing problems (anxiety, depression, and somatization), and adaptive skills; an overall composite of problem behaviors is given by the Behavioral Symptoms Index. Critical items include aggression, anxiety, attention problems, atypicality, conduct problems, depression, hyperactivity, somatization, and withdrawal. Optional scales include anger control, bullying, developmental and social disorders, emotional self-control, executive functioning, negative emotionality, and resiliency. Percentiles were calculated relative to the BASC-2 normative sample, which included 5892 children from different ethnicities and was designed to "resemble the U.S. population with respect to sex, socio-economic status, race/ethnicity, geographic region, and special education classification" (20, 21).

Measures of attention

We measured attention with the use of the Conners' Kiddie Continuous Performance Test (K-CPT), which is an objective measure of attention that was administered directly to the child at the follow-up visit at age 5 y. The K-CPT was developed as a tool to screen for attention disorders but is also sensitive to small changes of measures of attention along the entire spectrum of the distribution (not only in the extremes) (22–24). The test takes ~8 min, and children are asked to respond to target stimuli that appear on a screen and to refrain from responding to nontarget stimulus. The interstimuli intervals (ISIs) range between 1500–3000 ms, and the display time lasts 500 ms. The test includes 5 different blocks, each of which is divided into 2 sub-blocks of 20 trials each (one sub-block with 1500-ms ISIs, and the other subblock with 3000-ms ISIs). The information obtained overall includes the number of omissions (nonresponses to targets), commissions (responses to nontargets), Hit response time

("average speed of correct responses for the entire test"), and a hit-response SE (response speed consistency). More-specific indicators are the variability of a SE ("within respondent speed consistency in relation to his own overall standard error"), detectability ("value of the difference between signal and noise distributions"), perseverations ("any reaction that is less than 100 ms is considered a perseveration"), and hit reaction time and SE by ISI and block change (intra-stimuli time) (22).

The K-CPT was directly administered to the children with the use of a computer at the study headquarters. We compared the results to the standardization sample from the K-CPT validation study, which included 454 children aged 4 and 5 y who were selected to match the US Census on a number of key demographic variables including sex, region, race or ethnicity, and parental education. Also, 100 children in this sample had previously been diagnosed with ADHD and were included to develop a clinical norm but did not contribute to the standard nonclinical norm (22). The K-CPT software (MHS, Second Edition) generates T-scores and percentiles for each of the indicators relative to this distribution. The K-CPT indexes are presented in raw and T-score formats. The T-score approach allows for the comparison of a performance level to existing validated norms and was, for that reason, used as the outcome of interest. A T-score of 50 represents the mean for the comparison group. These T-scores have an SD of 10 and, and a T-score ≥ 1 SD is considered to be high and indicates greater risk of an attention problem (22). T-scores were used to assess inattention, impulsivity, and vigilance (22). We also compared individual child profiles to the clinical and non-clinical distributions and computed the probability of being a clinical case of an attention disorder.

TABLE 1

Selected characteristics of 797 children who were followed up at age 5 y as part of the POSGRAD study by initial treatment assignment¹

	Placebo (n = 396)	DHA (n = 401)	P
Maternal characteristics at random assignment			
Age, y	26.3 $\pm$ 4.7 ²	26.3 $\pm$ 4.9	0.94
Gestational age, wk	20.5 $\pm$ 2.1	20.5 $\pm$ 2.0	0.84
Socioeconomic status ³	0.04 $\pm$ 1.0	0.02 $\pm$ 1.0	0.73
Schooling (completed high school or more), %	60.7	55.8	0.16
Time in school, y	12.1 $\pm$ 3.6	11.8 $\pm$ 3.5	0.31
Ravens score	41.1 $\pm$ 9.3	40.4 $\pm$ 9.1	0.34
Primigravida, %	38.7	34.9	0.27
Weight, kg	63.6 $\pm$ 11.0	62.4 $\pm$ 11.6	0.12
Height, cm	155.4 $\pm$ 5.6	154.8 $\pm$ 5.7	0.10
BMI, kg/m ²	26.3 $\pm$ 4.3	26.0 $\pm$ 4.3	0.29
Offspring characteristics			
Birth weight, g	3,214 $\pm$ 467	3,216 $\pm$ 451	0.95
Birth length, cm	50.4 $\pm$ 2.6	50.3 $\pm$ 2.3	0.77
Head circumference at birth, cm	34.3 $\pm$ 1.8	34.4 $\pm$ 1.6	0.34
Low birth weight (<2500 g), %	4.6	5.5	0.54
Gestational age, wk	39.1 $\pm$ 1.7	39.0 $\pm$ 1.9	0.74
Preterm birth, ⁴ %	8.1	10.0	0.36
Sex (M), %	54.3	53.6	0.85
Intrauterine growth retardation, %	10.7	11.0	0.88
Breastfeeding at 3 mo, %	23.7	24.9	0.69
Duration of breastfeeding, mo	9.5 $\pm$ 7.6	9.4 $\pm$ 8.1	0.84
HOME score ⁵	36.8 $\pm$ 4.4	36.6 $\pm$ 4.4	0.59
More than one caregiver at age 5 y, %	61.5	57.5	0.28
Height at age 5 y, cm	108.3 $\pm$ 4.4	108.3 $\pm$ 4.4	0.88

¹Sample sizes vary slightly for individual variables because of item-specific missing values. *P* values were determined with the use of the *t* test for comparisons of means and the chi-square test for comparisons of proportions. HOME, Home Observation for Measurement of the Environment; POSGRAD, Prenatal Omega-3 Fatty Acid Supplementation and Child Growth and Development.

²Mean $\pm$ SD (all such values).

³Measured on the basis of a score considering assets and computed with the use of a principal components analysis.

⁴Defined as <37 wk of gestation

⁵Measurement of home environment at 12 mo of age.

Other variables

Maternal characteristics obtained at recruitment included obstetric history, dietary intake, anthropometric measurements, socioeconomic status, and performance on the Raven's Progressive Matrices test; offspring characteristics obtained at birth

TABLE 2

Comparison of measures of cognitive development with the use of McCarthy Scales of Children's Abilities at 5 y of age in children born to women who participated in a trial of 400 mg DHA/d during pregnancy by intervention group¹

Variable	Placebo (n = 396)	DHA (n = 401)	P
Raw McCarthy score			
Verbal	50.9 $\pm$ 11.5	50.6 $\pm$ 11.1	0.67
Perceptual-performance	46.7 $\pm$ 9.3	46.9 $\pm$ 9.3	0.73
Quantitative	20.1 $\pm$ 6.4	19.9 $\pm$ 6.3	0.60
Memory	25.3 $\pm$ 7.6	25.3 $\pm$ 7.6	0.98
Motor	37.8 $\pm$ 7.0	38.1 $\pm$ 6.8	0.53
General cognitive	117.9 $\pm$ 23.3	117.7 $\pm$ 22.0	0.94
Scale index McCarthy score			
Verbal	43.5 $\pm$ 8.7	43.3 $\pm$ 8.5	0.69
Perceptual-performance	48.7 $\pm$ 8.3	49.0 $\pm$ 8.3	0.60
Quantitative	45.3 $\pm$ 9.7	45.1 $\pm$ 9.6	0.70
Memory	42.1 $\pm$ 8.7	42.2 $\pm$ 9.0	0.92
Motor	47.9 $\pm$ 8.8	48.3 $\pm$ 8.9	0.54
General cognitive	92.9 $\pm$ 13.3	92.4 $\pm$ 13.4	0.64

¹All values are means $\pm$ SDs. *P* values were determined with the use of the *t* test for comparison of means.

included size, sex, and gestational age as described previously (17, 25). Details of feeding practices were obtained during the first year of life, and a trained study psychologist also assessed the quality of the home environment with the use of the Spanish version of the Home Observation for Measurement of the Environment (HOME) (26) during a home visit at 12 mo of age and again at 5 y of age. Similarly, at the follow-up at age 5 y, trained staff also collected details of health histories and child-care practices by interviewing the mothers or primary caregivers and obtained anthropometric measurements for all offspring.

Data analysis

We generated descriptive statistics for all variables previously described and assessed the normality of continuous outcomes. We evaluated if there were any differences by treatment group in the final analytic sample for selected maternal characteristics obtained at the time of enrollment and offspring characteristics at birth and also tested for a potential selection bias by comparing the final analytic sample to those subjects who were lost to follow-up (prenatal and postnatal). We used Student's *t* tests to compare group means for continuous variables and chi-square tests to examine differences in proportions for categorical variables. Because there were no differences by treatment group (37) for any examined baseline characteristics or age at follow-up, no further adjustments were made in the primary comparisons. We tested for heterogeneity by selected characteristics that were determined a priori by examining interaction terms between treatment and 1) maternal intelligence scores, 2) socioeconomic status, 3) sex, and 4) the HOME score at 12 and 60 mo of age. Bonferroni correction for multiple testing, in which the resulting *P* value was multiplied by the number of tests that measured similar constructs, was used whenever there were significant associations and both unadjusted and corrected *P* values were reported.

All analyses were done with SAS 9.3 software (SAS Institute Inc.), and *P* < 0.05 was considered statistically significant. The analytic sample had >95% power to detect effect sizes as small as 0.3 SD for intent-to-treat comparisons.

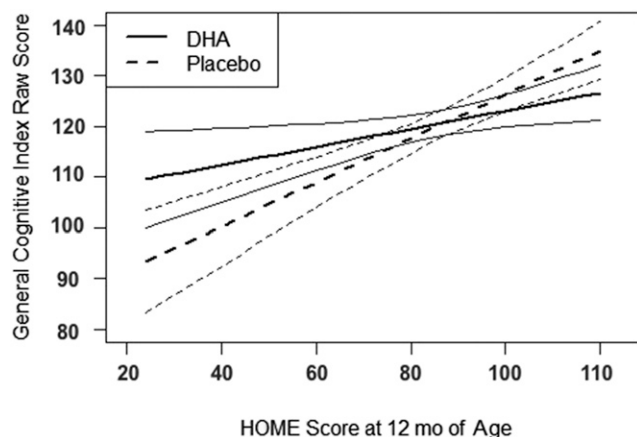


FIGURE 2 Relation between HOME score and Composite McCarthy Composite Raw Score at 5 y of age by intervention group. Lighter lines represent 95% CIs. Placebo: *n* = 396; DHA: *n* = 401. HOME, Home Observation for Measurement of the Environment.

RESULTS

We measured cognitive outcomes, behavioral functioning, and attention in 797 children (396 children in the placebo arm and 401 children in the DHA arm), who represented 82% of the birth cohort (*n* = 973) (Figure 1). There were no significant differences between intervention and control groups across a range of maternal and child characteristics (Table 1), and there were not any significant differences between children who were studied at age 5 y and those who did not attend the examination (results not shown). The main reasons for a loss to follow-up were migration and a lack of interest in continued participation in the study; these reasons did not differ by treatment group.

Effects of DHA on cognitive functioning

The intent-to-treat analysis revealed no significant differences by treatment group in the mean General Cognitive score or 6 subscales of the MSCA (Table 2). All scores were within normal ranges. However, we showed evidence of effect modification by HOME scores at 12 mo of age for the General Cognitive score on the MSCA (*P*-interaction < 0.05). The magnitude of the positive association between the quality of home stimulation during infancy and later cognitive functioning was decreased in subjects who were exposed to DHA (β = 0.71; 95% CI: 0.13, 1.29) in utero compared with in the placebo group (β = 1.71; 95% CI: 1.09, 2.33) (Figure 2). Similar relations were shown for the Verbal,

TABLE 3

Behaviors reported by parents with the use of BASC-2 of a sample of Mexican children whose mothers participated in POSGRAD results by treatment group¹

	Placebo (<i>n</i> = 396)	DHA (<i>n</i> = 401)
Externalizing problems composite, %	53.9 ± 27.4	51.4 ± 29.2
Hyperactivity	59.5 ± 25.5	57.9 ± 27.8
Aggression	48.7 ± 28.3	45.8 ± 30.0
Internalizing problems composite, %	63.0 ± 26.7	62.5 ± 26.6
Anxiety	74.3 ± 22.0	72.5 ± 22.5
Depression	51.2 ± 29.8	51.1 ± 31.0
Somatization	52.3 ± 28.9	54.4 ± 27.9
Adaptive skills composite, %	52.5 ± 27.8	54.3 ± 28.8
Withdrawal	44.8 ± 29.8	43.6 ± 30.5
Adaptability	54.8 ± 28.9	55.7 ± 29.1
Activities in daily life	58.3 ± 29.5	60.8 ± 29.7
Atypicality	54.4 ± 29.7	53.4 ± 30.1
Attention problems	48.0 ± 30.1	51.2 ± 30.8
Functional communication	42.6 ± 23.1	42.1 ± 24.3
Social skills	51.1 ± 29.5	53.3 ± 29.6
Behavioral Symptoms Index, %	51.5 ± 28.4	51.0 ± 29.8
Anger control	51.4 ± 27.5	49.6 ± 28.9
Bullying	53.9 ± 26.7	52.0 ± 29.5
Developmental and social disorders	53.6 ± 27.9	53.9 ± 27.9
Emotional self-control	56.0 ± 29.7	53.5 ± 31.9
Executive functioning	55.7 ± 29.2	54.8 ± 30.9
Negative emotionality	54.7 ± 30.2	52.0 ± 31.3
Resiliency	51.8 ± 28.6	52.1 ± 29.8

¹All values are means ± SDs. Percentiles were determined relative to the standard population. None of the comparisons were significant. BASC-2, Behavioral Assessment System for Children, Second Edition; POSGRAD, Prenatal Omega-3 Fatty Acid Supplementation and Child Growth and Development.

Perceptual-Performance, and Memory domains ($P < 0.10$). There was no significant heterogeneity by sex, maternal intelligence scores, socioeconomic status, or HOME scores at 60 mo of age.

Effects of DHA on behavior

There were no significant differences between DHA and placebo groups on any aspects of child behavioral functioning (either on the composite or individual scales of the BASC-2) as reported by the caregivers (**Table 3**). There was also no evidence of heterogeneity by sex, maternal intelligence scores, socioeconomic status, or HOME scores at 12 or 60 mo of age.

Effects of DHA on attention

Children in the DHA group had significantly fewer omissions on the K-CPT than did children in the control group with no differences between groups for commissions or Hit response times (**Table 4**). The Hit response time Block Change and Hit SE by Block Change, which are the 2 components of vigilance, were also significantly better in the DHA group, but there were no significant differences between groups on any of the impulsivity components. However, these associations were attenuated after Bonferroni correction for multiple comparisons. Compared with controls, a higher proportion of children in the DHA group had a T-score <40 for omissions, and fewer children had a T-score >60 . These differences in distribution remained significant after

Bonferroni correction for multiple testing (**Table 5**). There were no significant differences in the response style or proportion of children who were classified at clinical risk of suffering from a disorder (>70 th percentile) such as ADHD (22). There was no heterogeneity by sex, maternal intelligence scores, socioeconomic status, or HOME scores at 12 and 60 mo of age.

DISCUSSION

Prenatal supplementation with DHA had no overall effect on global measures of cognitive functioning at age 5 y, but the effect of the quality of the home environment during infancy on later cognition was significantly reduced in offspring who were exposed in utero to DHA than in the control group who received a placebo. These findings are similar and consistent with our earlier findings in this cohort whereby we showed evidence of selective effects on measures of motor development at 18 mo of age (28). This interaction can be interpreted 2 ways. On one side, it is possible that DHA supplementation was a substitute of early stimulation for children with less-stimulating home environments; if this was the case, DHA could be particularly important for cognitive functioning for kids with less-stimulating environments. In contrast, it is less likely but also possible that prenatal DHA decreases the effect of early stimulation on development in which case better targeted interventions would be necessary to prevent this unintended consequence.

TABLE 4

K-CPT main-component scores by intervention group in Mexican children whose mothers participated in the POSGRAD study¹

	Placebo ($n = 396$)	DHA ($n = 401$)	P	P after Bonferroni correction
Overall				
Omissions	49.5 $\pm$ 11.2	47.6 $\pm$ 10.3*	0.01	0.11
Commissions	51.1 $\pm$ 10.2	51.2 $\pm$ 11.0	0.86	—
Hit response time	56.1 $\pm$ 10.6	55.5 $\pm$ 10.5	0.36	—
Inattention				
Omissions ²	49.5 $\pm$ 11.2	47.6 $\pm$ 10.3*	0.01	0.11
Commissions ²	51.1 $\pm$ 10.2	51.2 $\pm$ 11.0	0.86	—
Hit response time ²	56.1 $\pm$ 10.6	55.5 $\pm$ 10.5	0.36	—
Hit response time, SE	51.7 $\pm$ 9.6	51.2 $\pm$ 9.5	0.42	—
Variability	50.7 $\pm$ 8.8	50.2 $\pm$ 8.3	0.40	—
Detectability	50.1 $\pm$ 10.7	49.9 $\pm$ 10.3	0.72	—
Hit response time ISI change	49.9 $\pm$ 13.4	50.6 $\pm$ 12.7	0.47	—
Hit SE ISI change	49.2 $\pm$ 9.8	50.1 $\pm$ 10.0	0.90	—
Impulsivity				
Commissions ³	51.1 $\pm$ 10.2	51.2 $\pm$ 11.0	0.86	—
Hit response time ³	56.1 $\pm$ 10.6	55.5 $\pm$ 10.5	0.36	—
Perseverations	44.8 $\pm$ 7.1	45.6 $\pm$ 9.1	0.13	—
Vigilance				
Hit response time block change	52.0 $\pm$ 12.5	50.1 $\pm$ 12.2*	0.04	0.44
Hit SE by block change	49.9 $\pm$ 9.4	48.2 $\pm$ 10.0*	0.01	0.11

¹All values are means $\pm$ SDs. T-scores were determined relative to the standard population (higher values represent poorer performance). For Bonferroni correction, P values were multiplied by the 11 different outcomes measured in the test. Adjusted P values are only reported for significant ($P < 0.05$) results. * $P < 0.05$ for difference between treatment groups before Bonferroni correction for multiple testing. ISI, interstimuli interval; K-CPT, Kiddie Continuous Performance Test; POSGRAD, Prenatal Omega-3 Fatty Acid Supplementation and Child Growth and Development.

²Same variable as previously reported in the overall category. The variable was repeated to show it is as a component of inattention.

³Same variable as previously reported in the overall category. The variable was repeated to show it is as a component of impulsivity.

TABLE 5Distribution of K-CPT scores relative to the standard sample by intervention group in POSGRAD¹

	Placebo (<i>n</i> = 396)	DHA (<i>n</i> = 401)	<i>P</i>	<i>P</i> after Bonferroni correction
Omissions score, % of children				
<40	14.4	25.7	<0.0001	<0.0001
40–60	69.4	64.6	—	—
>60	16.2	9.7	—	—
Commissions score, % of children				
<40	12.1	16.2	0.08	—
40–60	67.2	59.9	—	—
>60	20.7	23.9	—	—
Hit response time score, % of children				
<40	3.3	6.7	0.08	—
40–60	64.9	61.9	—	—
>60	31.8	31.4	—	—
Response style (β) score, % of children				
<40	9.6	12.5	0.35	—
40–60	68.4	68.1	—	—
>60	22.0	19.5	—	—
Overall score, % of children				
>70	8.1	7.2	0.62	—

¹Values were determined for children of the POSGRAD group within the specified T-score relative to the standard population. For Bonferroni correction, *P* values were multiplied by the 11 different outcomes measured in the test. Adjusted *P* values are only reported for significant (*P* < 0.05) results. K-CPT, Kiddie Continuous Performance Test; POSGRAD, Prenatal Omega-3 Fatty Acid Supplementation and Child Growth and Development.

More importantly, we present evidence of a beneficial effect of prenatal supplementation with DHA on objective measures of attention and executive function at preschool age. Children whose mothers received DHA during pregnancy committed fewer omissions than those in the placebo group. These results are consistent with evidence from animal models and biological evidence linking DHA to functions of the prefrontal cortex such as responsiveness and sustained attention. Similar clinical trials that have assessed the effect of DHA supplementation on measures of attention during childhood have yielded mixed results. The DHA for Maternal and Infant Outcomes trial, which provided 800 mg DHA and 100 mg EPA/d during the last 2 trimesters of pregnancy to Australian women showed no effect of the intervention on offspring attention, working memory, and inhibitory control at 2 y of age. The only difference reported by the authors was that children in the intervention group, compared with the controls, were able to look away from target toys fewer times when distracted by other toys (29). However, Jensen et al. (30) reported improvements in the attention of offspring at age 5 y in an RCT of postnatal supplementation in which lactating women received 200 mg of either DHA or placebo/d. Consistent with our findings, the only effect of the intervention was on the Sustained Attention Scale of the Leiter International Performance Scale.

We showed no group differences of any parent-reported behaviors on the BASC-2, including attention problems, in contrast with the objective results obtained from the K-CPT. The more-subjective nature of the BASC-2 could have accounted for these differences. Also, our results for the K-CPT show no differences in the clinical range (in the number of children with clinical problems) but only significant differences within the normal population. Hence, it is possible that the BASC-2, which is designed to detect attention problems, missed these more subtle differences.

This trial has important characteristics that distinguish it from previous studies. First, supplementation was done exclusively with

DHA that was obtained from an algal source that was provided only during pregnancy as opposed to a combination of n–3 fatty acids. Second, the study population was from an urban area in Mexico, which is a setting that is representative of many low- to middle-income countries that have experienced the nutrition transition with very low intakes of n–3 fatty acids, especially of preformed DHA, and high intakes of n–6 fatty acids primarily from vegetable oils (31). Third, and most importantly, we used the MSCA and K-CPT, which provided objective measures of cognitive functioning and attention, in combination with the parent-reported BASC-2, which facilitated a comprehensive assessment of the effect of prenatal supplementation with DHA on cognitive and behavioral functioning during the preschool years; moreover, all of these measures were previously used in Mexican children (32). Other strengths of the study include the low attrition rate through age 5 y, the large sample size, the availability of data on potential determinants of cognitive and behavioral outcomes including the quality of the home environment during early life and caregiver characteristics, and that the cohort remained balanced for several maternal and child characteristics.

Potential limitations of the study include the lack of measures of DHA status and details of the quality of the child's learning environment, especially of the school quality at the time of follow-up. Other factors that potentially affected sustained attention at 5 y of age included maternal first- or second-hand smoking and alcohol consumption during pregnancy (33), exposure to environmental pollutants prenatally and across the life span (34, 35), sleep patterns (36), and the presence of an illness or distress at the time that the test was administered. Children were not tested if they were unwell in the current study, and none of the women smoked during pregnancy. We do not have data for these other variables. However, the randomized design allowed us to expect that both observed and unobserved characteristics were balanced across treatment groups, and although we could not confirm it, we expect

that random assignment minimized potential biases that are related to these other factors. Similarly, we did not observe systematic differences in baseline characteristics by attrition status.

An important consideration is the clinical significance of the observed differences in measures of attention shown in this study (fewer omissions). Children in the study were generally healthy, and the prevalence of clinical cases was low (7.6%; $n = 61$). Fewer than 10% of children in the DHA group had a T-score that was >60 for omissions (>1 SD from the mean), which could be interpreted as a “high mean” or even “elevated” risk of developing a clinical condition (22), compared with $>16\%$ of controls. Conversely, $>25\%$ of the children in the DHA group had a T-score <40 [which is interpreted as having “lower than average” risk (22)] compared with 14% of controls. Razza et al. (37) showed a longitudinal association between attentional performance at 5 y of age (measured with the use of the Leiter International Performance Scale) and academic achievement at 9 y of age in a sample of >2500 low-income children from 20 cities across the United States. Follow-up of the children in the current study will be important to assess if differences measured by the K-CPT at 5 y of age translate into better academic performance or other functional outcomes during the school years.

In conclusion, our results show the potential of DHA supplementation in the second half of pregnancy to improve the sustained attention of offspring beyond infancy. No differences were shown regarding parent-reported measures of attention problems, which are less-objective measures. The current study confirms the observed differences between treatment groups in the interaction between prenatal DHA and the quality of the home environment in early life on cognitive abilities seen previously in our cohort (27), suggesting that these effects may persist through early childhood. There is evidence that the benefits of improving nutrition during the first 1000 d of life on cognitive outcomes may not become evident until children start school and are more challenged by the environment (38, 39). The long-term significance of our current findings and impact of the POSGRAD intervention on cognitive and behavioral functioning during the school years remains to be determined.

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