Effects of periconceptional folate on cognition in children of women with epilepsy

NEAD study

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Abstract

Objective

Emerging evidence suggests potential positive neuropsychological effects of periconceptional folate in both healthy children and children exposed in utero to antiseizure medications (ASMs). In this report, we test the hypothesis that periconceptional folate improves neurodevelopment in children of women with epilepsy by re-examining data from the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study.

Methods

The NEAD study was an NIH-funded, prospective, observational, multicenter investigation of pregnancy outcomes in 311 children of 305 women with epilepsy treated with ASM monotherapy. Missing data points were imputed with Markov chain Monte Carlo methods. Multivariate analyses adjusted for multiple factors (e.g., maternal IQ, ASM type, standardized ASM dose, and gestational birth age) were performed to assess the effects of periconceptional folate on cognitive outcomes (i.e., Full Scale Intelligence Quotient [FSIQ], Verbal and Nonverbal indexes, and Expressive and Receptive Language indexes at 3 and 6 years of age, and executive function and memory function at 6 years of age).

Results

Periconceptional folate was associated with higher FSIQ at both 3 and 6 years of age. Significant effects for other measures included Nonverbal Index, Expressive Language Index, and Developmental Neuropsychological Assessment Executive Function at 6 years of age, and Verbal Index and Receptive Language Index at 3 years of age. Nonsignificant effects included Verbal Index, Receptive Index, Behavior Rating Inventory of Executive Function–Parent Questionnaire Executive Function, and General Memory Index at 6 years of age, and Nonverbal Index and Expressive Index at 3 years of age.

Conclusions

Use of periconceptional folate in pregnant women with epilepsy taking ASMs is associated with better cognitive development.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The NEAD Investigator Group is listed in Appendix 2.

Glossary

ASM = antiseizure medication; **CI** = confidence interval; **DAS** = Differential Ability Scales; **DTVMI-5** = Developmental Test of Visual-Motor Integration–5th Edition; **FSIQ** = Full Scale Intelligence Quotient; **ITT** = intent-to-treat; **MTHFR** = methyl tetrahydrofolate dihydrofolate reductase; **NEAD** = Neurodevelopmental Effects of Antiepileptic Drugs; **NEPSY** = Developmental Neuropsychological Assessment; **PLS-4** = Preschool Language Scale–4th Edition; **PPVT-4** = Peabody Picture Vocabulary Test–4th Edition.

In the general population, folate supplementation is recommended for all women of childbearing potential to prevent birth defects (i.e., spina bifida)¹ and may improve cognitive and behavioral neurodevelopmental outcomes.^{2–9} Antiseizure medications (ASMs) can produce both anatomic and neurodevelopmental deficits, although the risks vary across ASMs.¹⁰ Two large studies have not found evidence that periconceptional folic acid supplementation can reduce ASM-associated malformations,^{11,12} but 2 recent publications from the Norwegian Mother and Child Cohort study suggest that periconceptional folate may have a protective effect against fetal ASM-induced language delay and autistic traits on the basis of validated maternal surveys with fetal ASM exposure.^{13,14} However, some prior studies have not found an effect of periconceptional folate in children of women who took ASMs during pregnancy.^{15,16}

We previously reported from our Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study based on blinded objective neuropsychological testing that periconceptional folate in children with fetal ASM exposure was associated with increased Full Scale Intelligence Quotient (FSIQ) at 3 and 6 years of age, increased Verbal Index score at 3 years of age, reduced Behavior Assessment System for Children parent ratings of somatization and atypicality, and reduced Behavior Assessment System for Children teacher ratings of anxiety.^{17–20} However, given that our prior publications were focused on differential ASM effects, many aspects of the neuropsychological battery in regard to folate were not published. In this present report, we extend our investigation to explore the relationship of periconceptional folate exposure to cognitive development across the multiple measures from the detailed formal neuropsychological evaluations in children with fetal ASM exposure from the NEAD study.

Methods

Design

The NEAD study was a prospective observational investigation with blinded cognitive assessment. Pregnant women with epilepsy on ASM monotherapies (i.e., carbamazepine, lamotrigine, phenytoin, or valproate) were enrolled (October 1999–February 2004) across 25 epilepsy centers in the United States and United Kingdom (Appendix 2 provides a list of individual centers). No other ASMs were used in adequate numbers to assess. A nonexposed control group was not

included because the NIH review panel unanimously recommended deletion from our original design.

Standard protocol approvals, registrations, and patient consents

The study is registered at clinicaltrials.gov as NCT00021866. The Institutional Review Board at each site approved the study. Written informed consent was obtained according to the Declaration of Helsinki. An NIH-appointed Data Safety Monitoring Board monitored study conduct.

Participants

Women with an IQ < 70 were excluded to avoid floor effects because maternal IQ is the major predictor of child IQ.²¹ Other exclusions included positive syphilis or HIV serology, progressive cerebral disease, other major disease (e.g., diabetes mellitus), exposure to known teratogenic agents other than ASMs, poor ASM compliance, drug abuse in the prior year, or drug abuse sequelae.

Procedures

Potentially confounding variables were assessed (e.g., maternal IQ, age, education, employment, race/ethnicity, seizure/epilepsy types and frequency, ASM doses, compliance, medical history, socioeconomic status, UK/US site, concomitant medications, alcohol, tobacco, or other drugs during pregnancy, unwanted pregnancy, abnormalities/complications in present or prior pregnancies, enrollment and birth gestational ages, birth weight, breastfeeding, and childhood medical diseases). Abnormalities/complications in prior and present pregnancies included miscarriages, malformations, and obstetrical complications such as caesarian sections or hemorrhage. Adherence for periconceptional folate and other medications before enrollment was collected retrospectively by mother report (the average gestational age at enrollment was 18 weeks, 95% confidence interval [CI] = 17–19). Adherence for all medicines and vitamins, including folate after enrollment, was collected prospectively by mother report. Periconception folate and pregnancy folate were collected as potentially confounding variables in the NEAD study, but periconceptional folate is the primary issue in the present analyses. Periconceptional folate exposure was determined retrospectively at the time of enrollment by report of the mother. She was classified as taking periconceptional folate if she reported taking folate ≥ 1 month before conception. The folate dose at conception was used for analyses. Periconceptional folate was categorized as to daily dose of 0, >0.0 to 0.4, >0.4 to 1.0, >1.0 to 4.0, and >4.0 mg. Except for maternal

IQ variables were collected from the mothers, their seizure/medication diary, or medical record review. Compliance for ASMs was assessed by interviewing all mothers and reviewing diaries and ASM levels (75% of mothers, $n = 229$). Blinded neuropsychological assessors evaluated cognitive outcomes. Neuropsychological examiners were trained and monitored to ensure quality. Annual workshops were conducted, and assessors were asked to identify errors and corrections for videotaped test sessions containing administration/scoring errors. In addition, the neuropsychology core director reviewed and approved videotapes of assessor practice test sessions and record forms. If failed, assessors were required to submit additional videotaped practice assessments.

Further details of the neuropsychological tests are offered elsewhere.^{17–19} Evaluations of cognitive outcomes included the Differential Ability Scales (DAS)²² at 3, 4.5, and 6 years of age. At 3 years of age, testing also included the Preschool Language Scale–4th Edition (PLS-4),²³ the Peabody Picture Vocabulary Test–4th Edition (PPVT-4),²⁴ and the Developmental Test of Visual-Motor Integration–5th Edition (DTVMI-5).²⁵ Testing at 6 years of age also included the core battery of the Children’s Memory Scale,²⁶ the Behavior Rating Inventory of Executive Function–Parent Questionnaire (BRIEF),²⁷ selected subtests from the Developmental Neuropsychological Assessment (NEPSY),²⁸ the Expressive One-Word Picture Vocabulary Test,²⁹ and the DTVMI-5.²⁵

From the NEAD neuropsychological batteries, the primary a priori dependent variables included the General Conceptual Ability score from the DAS at 6 years of age, which is similar to the FSIQ score from the Wechsler Full Scale Intelligence Scales. In addition, we constructed Verbal and Nonverbal indexes and subcomponents of language using Expressive and Receptive Language indexes from both the 3- and 6-year assessments to examine components of language and other cognitive functions. Other dependent variables at 6 years of age included the Children’s Memory Scale General Memory Score, the NEPSY Executive Function Score, and the BRIEF Global Executive Composite Score.

The Verbal Index score from the 3-year assessment was created by averaging the Expressive Communication and the Auditory Comprehension subtest scores of the PLS-4,²³ the Naming Vocabulary and the Verbal Comprehension subtest scores of the DAS,²² and the score from the PPVT-4.²⁴ The Nonverbal Index score was the average of the scores from the Block Building subtest of the DAS²² and the DTVMI-5.²⁵

The Verbal Index score from the 6-year assessment was created by averaging the scores from the Word Definitions and Verbal Similarities subtests from the DAS,²² the Expressive One-Word Picture Vocabulary Test,²⁹ and the Phonological Processing, Comprehension of Instructions, and Sentence Repetition subtests from the NEPSY-2.²⁸ The Nonverbal Index was the average of the scores from Pattern

Table 1 Demographics of women enrolled in NEAD study

Mothers/children, n^a	305/311
Maternal IQ^b	98 (96–100)
Mean maternal age, y	30 (29–30)
Gestational age at enrollment, wk	18 (17–19)
Gestational age at birth, wk	39 (39–39)
Years maternal education	14 (14–14)
Enrolled UK site, n (%)	105 (34)
Periconceptional folate, n (%)	174 (57)
Alcohol use, n (%)^c	24 (8)
Epilepsy type, n (%)^d	
Focal	184 (60)
Generalized	97 (32)
GTCS	24 (8)
Convulsions, n (%)^e	
0	225 (81)
>5	8 (3)
Race/ethnicity, n (%)	
White	245 (80)
Black	14 (5)
Hispanic	31 (10)
Other	15 (5)
Study status, n (%)	
Completed study	222 (73)
Lost to follow-up	34 (11)
Voluntary withdrawal by participant	33 (11)
Other/missing	6 (2)
Noncompliance/protocol violation	4 (1)
Medical event to child or mother	3 (1)
Withdrawal by investigator	3 (1)

Abbreviations: GTCS = generalized tonic-clonic seizures; NEAD = Neurodevelopmental Effects of Antiepileptic Drugs.

Data are value (95% confidence intervals) or number (percent).

^a Three hundred five mothers enrolled (311 children enrolled).

^b Data were available for IQ in 304 mothers; outcomes at age 6 years were available in 225 children (72%); cognitive outcomes were available for at least 1 test age (i.e., 2, 3, 4.5, or 6 years) in 279 children (90% of total enrolled sample).

^c Any alcohol use during pregnancy (yes vs no).

^d Epilepsy types were focal, generalized (includes absence, juvenile myoclonic, genetic, and other idiopathic generalized not otherwise classified), and GTCS (unknown if generalized or secondary generalized).

^e Number (percent) of mothers without convulsions or >5 convulsions during pregnancy; seizure frequency during pregnancy was not reported for 14 mothers.

Construction, Matrices, and Recall of Designs recall subtests of the DAS,²² the Arrows subtest from the NEPSY-2,²⁸ and the DTVMI-5.²⁵

Table 2 Model summary for age 6 outcomes: intent-to-treat analysis

Age 6 outcomes	All ASMs (n = 311)		Without valproate (n = 249)	
	Coefficient ± SD	p Value	Coefficient ± SD	p Value
FSIQ				
ASM group (4 levels)		<0.001		0.254
Periconception folate use	5.9 ± 1.76	0.001	6.0 ± 1.85	0.002
Maternal IQ	0.3 ± 0.05	<0.001	0.4 ± 0.05	<0.001
Standardized ASM dose	−0.1 ± 0.04	0.008	−0.1 ± 0.05	0.195
Gestational age	0.9 ± 0.39	0.028	0.8 ± 0.40	0.042
Verbal Index				
ASM group (4 levels, p value only)		<0.001		0.783
Preconception folate use	2.9 ± 1.54	0.064	2.7 ± 1.59	0.092
Maternal IQ	0.2 ± 0.05	<0.001	0.3 ± 0.05	<0.001
Standardized ASM dose	−0.1 ± 0.04	0.034	0.0 ± 0.04	0.318
Socioeconomic status	1.7 ± 0.35	<0.001	2.0 ± 0.37	<0.001
Nonverbal Index				
ASM group (4 levels)		<0.001		0.056
Preconception folate use	3.1 ± 1.40	0.028	3.0 ± 1.49	0.046
Maternal IQ	0.1 ± 0.04	0.004	0.2 ± 0.04	<0.001
Standardized ASM dose	−0.1 ± 0.04	0.009	−0.1 ± 0.04	0.169
Gestational age	0.9 ± 0.33	0.010	0.9 ± 0.34	0.010
Expressive Index				
ASM group (4 levels)		0.003		0.215
Preconception folate use	3.3 ± 1.66	0.049	2.8 ± 1.76	0.115
Maternal IQ	0.1 ± 0.05	0.010	0.2 ± 0.06	0.005
Standardized ASM dose	−0.1 ± 0.04	0.011	−0.1 ± 0.04	0.163
Education	1.3 ± 0.31	<0.001	1.4 ± 0.33	<0.001
Maternal age	0.5 ± 0.14	<0.001	0.6 ± 0.15	<0.001
Receptive Index				
ASM group (4 levels)		<0.001		0.886
Preconception folate use	2.1 ± 1.67	0.216	1.7 ± 1.78	0.346
Maternal IQ	0.2 ± 0.05	<0.001	0.3 ± 0.05	<0.001
Standardized ASM dose	−0.1 ± 0.04	0.044	0.0 ± 0.04	0.398
Socioeconomic status	1.7 ± 0.38	<0.001	2.1 ± 0.41	<0.001
NEPSY Executive Function				
ASM group (4 levels)		<0.001		0.179
Preconception folate use	3.9 ± 1.61	0.018	3.3 ± 1.71	0.053
Maternal IQ	0.1 ± 0.05	0.079	0.1 ± 0.05	0.016
Standardized ASM dose	−0.1 ± 0.04	0.011	−0.1 ± 0.04	0.090
Gestational age	1.1 ± 0.32	0.001	1.0 ± 0.35	0.003

Continued

Table 2 Model summary for age 6 outcomes: intent-to-treat analysis (*continued*)

Age 6 outcomes	All ASMs (n = 311)		Without valproate (n = 249)	
	Coefficient ± SD	p Value	Coefficient ± SD	p Value
BRIEF Global Executive Composite				
ASM group (4 levels)		0.285		0.758
Preconception folate use	−2.3 ± 1.90	0.235	−3.6 ± 2.07	0.086
Maternal IQ	0.0 ± 0.05	0.531	0.0 ± 0.06	0.555
Standardized ASM dose	0.1 ± 0.05	0.015	0.1 ± 0.05	0.062
General Memory Index				
ASM group (4 levels)		<0.001		0.243
Preconception folate use	1.6 ± 2.72	0.562	−0.4 ± 2.93	0.881
Maternal IQ	0.3 ± 0.07	0.001	0.3 ± 0.08	<0.001
Standardized ASM dose	−0.1 ± 0.06	0.022	−0.1 ± 0.07	0.139
Maternal age	0.5 ± 0.23	0.022	0.7 ± 0.26	0.010

Abbreviations: ASM = antiseizure medication; BRIEF = Behavior Rating Inventory of Executive Function; FSIQ = Full Scale Intelligence Quotient; NEPSY = Developmental Neuropsychological Assessment.

At age 3, the Expressive Language Index comprised the Expressive Communication score from the PLS-4²³ and the Naming Vocabulary subtest from the DAS.²² The Receptive Language Index comprised the Auditory Comprehension score from the PLS-4,²³ the PPVT-4,²⁴ and the Verbal Comprehension score from the DAS.²² At age 6, the Expressive Language Index was made up of the Word Definitions and Similarities scores from the DAS,²² the Expressive One Word Picture Vocabulary Test,²⁹ and the Verbal Fluency from the NEPSY.²⁸ The Receptive Language Index comprised the Comprehension of Instructions, Sentence Repetition, and Phonological Processing subtest scores from the NEPSY.²⁸

Statistical analysis

Sample sizes were determined for 80% power to detect a 0.5-SD IQ difference, a clinically meaningful difference observed in prior studies.¹⁰ The approach to analyses was similar to our prior publications on the NEAD study.^{17–19} The primary analysis used linear regression models with ASM and periconceptual folate as the main predictors of interest. All models were also adjusted for maternal IQ and standard dose (same as previous analyses). Additional covariates examined were maternal age, gestation age at birth, race/ethnicity, maternal education, epilepsy/seizure types, employment, socioeconomic status, US/UK site, alcohol/tobacco use, and unwanted pregnancy. Because specific ASM, ASM dose, and maternal IQ are important covariates, they were included as predictors in all linear models, along with periconceptual folate as the main predictor of interest and child cognitive measures as outcomes. Other covariates were selected into the model with a forward selection algorithm. Starting with a model including ASM, dose, maternal IQ, and folate, each additional covariate was

individually assessed, and the covariate with the largest *F* statistic, provided that *p* < 0.5, was selected into the model. This process continued until no additional covariates were significant (*p* < 0.5) when added to the model. The forward selection algorithm was applied to the total enrolled analysis dataset, and the same covariates selected for that model were used for the completers analysis. Diagnostic plots were inspected to ensure that distributional assumptions of the models were met. For the total enrolled analysis, Markov chain Monte Carlo methods^{30,31} were used to impute missing age 6 or age 6 outcomes from available age 2, 3, and 4.5 IQs, baseline variables related to outcome, likelihood of missing data, and other additional covariates assessed for inclusion in the final models. As detailed previously,¹⁹ the number of completers at each age was 187 at 2 years, 230 at 3 years, 209 at 4.5 years, and 225 at 6 years. The imputation procedure generated 50 imputed datasets and fitted regression models to each. Regression parameter estimates were combined across imputations with standard errors that incorporated imputation uncertainty. Mothers of children with missing age 6 outcomes differed on maternal age and US/UK site (imputation model included these variables). Standard errors and CIs of parameter estimates incorporated imputation uncertainty. Intent-to-treat (ITT) analyses for age 6 were considered the primary analyses here. Secondary analyses for age 3 ITT and for age 3 and 6 completers without imputations for missing data were conducted. Analyses were performed at the NEAD Data and Statistical Center with SAS 9.4 and R statistical software. A major goal of the present study was to conduct exploratory comparisons across a variety of cognitive domains. In this context, we felt it was more important to avoid type 2 errors, so we did not correct for multiple comparisons.

Data availability

All data included in these analyses will be shared as anonymized data via request from any qualified investigator.

Results

The NEAD study enrolled 305 women with epilepsy who had 311 live births. Demographics are depicted in table 1. Results of the ITT analyses at 6 years of age are the primary analyses and are depicted in table 2. As previously reported,¹⁹ FSIQ at 6 years of age was significantly related to ASM group, periconceptional folate use, maternal IQ, standardized dose, and gestational age. Periconceptional folate effects were also seen for Nonverbal Index, Expressive Language, and NEPSY Executive Function but not for Verbal Index, Receptive Index, BRIEF Executive Composite, and General Memory Index. Means (95% CIs) for individual cognitive measures as a function of folate vs no folate exposure at 6 years of age are presented in table 3. Means (95% CIs) for Verbal Index and Nonverbal Index for each ASM by folate exposure are depicted in figures 1 and 2. These differences for FSIQ was depicted in a prior publication.¹⁹

Similar to 6 years of age, FSIQ at 3 years of age was significantly related to ASM group, periconceptional folate use,

Table 3 Age 6 and 3 regression least squares means (95% CI) for intent-to-treat analysis

Measure	LS means (95% CI)	
	No folate	Folate
Age 6 y		
FSIQ	101 (98–104)	107 (105–109)
Verbal Index	100 (98–103)	103 (101–105)
Nonverbal Index	103 (101–105)	106 (104–108)
Expressive Index	100 (9–103)	104 (102–106)
Receptive Index	101 (99–104)	103 (101–105)
NEPSY Executive Function	101 (99–104)	105 (103–107)
BRIEF Global Executive Composite	103 (100–106)	101 (99–103)
General Memory Index	99 (95–103)	101 (97–104)
Age 3 y		
FSIQ	95 (92–98)	100 (97–102)
Verbal Index	95 (92–98)	99 (96–101)
Nonverbal Index	101 (98–104)	104 (102–106)
Expressive Index	97 (94–100)	100 (97–103)
Receptive Index	94 (91–96)	98 (96–100)

Abbreviations: BRIEF = Behavior Rating Inventory of Executive Function–Parent Questionnaire; CI = confidence interval; FSIQ = Full Scale Intelligence Quotient; LS = least squares; NEPSY = Developmental Neuropsychological Assessment.

maternal IQ, standardized dose, and gestational age but also to maternal age (table 4). Periconceptional folate effects were also seen for Verbal Index and Receptive Index but not for Nonverbal Index and Expressive Language. Means (95% CIs) for individual cognitive measures as a function of folate vs no folate exposure at 3 years of age are presented in table 3.

None of the ASM group by periconceptional folate interactions were significant, suggesting that the folate effects were similar across ASMs. Furthermore, similar effects were seen when children exposed to valproate were excluded (tables 2 and 4), but not as many factors were significant with the smaller sample sizes despite the fact the folate/nonfolate differences appeared less for valproate than other ASMs (figures 1 and 2). The numbers (percent) of mothers and children with nonmissing FSIQ at age 6 years exposed to different levels of folate are given in table 5. As previously published,¹⁹ an effect for periconceptional folate was seen for FSIQ at age 6 ($F = 2.5$, $p = 0.045$) with doses >0.04 mg/d showing significantly higher IQ than the no folate group.

Discussion

The NEAD study found positive associations of periconceptional folate exposure to better neurodevelopmental scores across a variety of cognitive variables in children of women with epilepsy taking ASMs. At 6 years of age, periconceptional folate was associated with higher FSIQ, Nonverbal Index, Expressive Language Index, and NEPSY Executive Function. However, significant effects were absent at 6 years of age for Verbal Index, Receptive Index, BRIEF Executive Function, and General Memory Index. Although the overall pattern at 3 years of age was similar, differences existed. At 3 years of age, positive associations were present for FSIQ, Verbal Index, Receptive Language Index, but nonsignificant effects were present for Nonverbal Index and Expressive Index. The pattern of findings was similar across all ASMs (see figures 1 and 2 for Verbal and Nonverbal indexes and a prior publication¹⁹ for FSIQ).

The findings from our analyses of the objective measures from the detailed neuropsychological battery of the NEAD study are consistent with the findings from the Norwegian Mother and Child Cohort study in regard to the association of periconceptional folate with improved neurodevelopmental outcomes in children of women with epilepsy taking ASMs. In addition, the NEAD findings suggest that periconceptional folate effects involve multiple areas of neuropsychological function, including global, language, nonverbal, and executive functions, extending into the school-aged years, which are more predictive of adult cognitive abilities. Furthermore, the findings likely have implications beyond women with epilepsy because ASMs are among the most common teratogenic drugs prescribed to women of childbearing age, and fewer than half of ASM prescriptions are for epilepsy, the remainder being prescribed for pain and psychiatric disorders.³²

Figure 1 Means and 95% confidence intervals for age 6 Verbal Index by antiseizure medication

Strengths of this study are our prospective design, use of assessor-blind objective cognitive assessment battery with standardized measures, and detailed monitoring of multiple potential confounding factors. Limitations are its relatively small non-population-based sample, loss to follow-up, nonrandomization, no pharmacokinetic measures, and no unexposed controls. We did not directly assess diagnoses of autism spectrum disorder. Periconceptional folate was assessed retrospectively at the time of enrollment (mean 18 weeks), and no folate levels were obtained early in pregnancy. Thus, we cannot confirm adherence to folate dosing, which is similar to the large majority of the literature on periconceptional folate.³³ However, any misclassification due to errors in recollection about folate use would not be expected to be associated with the outcome measures because the information on folate collection was completed before the children were born. Ideally, a prospective study

assessing folate intake and levels for folate or homocysteine before and during early pregnancy is needed to determine the effects on ultimate cognitive outcomes. In the absence of such data, we have to depend on observational studies with retrospective assessment of periconceptional folate intake. Randomized pregnancy trials of antiepileptic drugs are not possible, and observational studies might be confounded by differences in baseline characteristics (e.g., maternal IQ, ASM dose). Our analyses controlled for baseline group differences, but some residual confounding effects are possible. In addition, the present study extends assessment of periconceptional effects to several additional objective cognitive domains. Note that 7 of the 13 comparisons across 3 and 6 years of age were significant, with 1 additional measure exhibiting a statistical trend. We consider these clinically significant given that the effect of folate is seen across multiple domains.

Figure 2 Means and 95% confidence intervals for age 6 Nonverbal Index by antiseizure medication

Table 4 Model summary for age 3 outcomes: Intent-to-treat analysis

Age 3 outcomes	All ASMs		Without valproate	
	Coefficient $\pm$ SD	<i>p</i> Value	Coefficient $\pm$ SD	<i>p</i> Value
FSIQ				
ASM group (4 levels)		0.018		0.769
Periconception folate use	4.6 $\pm$ 2.23	0.040	4.2 $\pm$ 2.42	0.085
Maternal IQ	0.3 $\pm$ 0.06	<0.001	0.3 $\pm$ 0.07	<0.001
Standardized ASM dose	−0.1 $\pm$ 0.05	0.037	−0.1 $\pm$ 0.06	0.351
Gestational age	1.2 $\pm$ 0.48	0.015	1.1 $\pm$ 0.51	0.030
Maternal age	0.6 $\pm$ 0.19	0.001	0.7 $\pm$ 0.22	0.003
Verbal Index				
ASM group (4 levels)		<0.001		0.907
Preconception folate use	3.8 $\pm$ 1.94	0.050	2.7 $\pm$ 2.12	0.208
Maternal IQ	0.2 $\pm$ 0.06	0.002	0.2 $\pm$ 0.06	0.001
Standardized ASM dose	−0.1 $\pm$ 0.05	0.003	−0.1 $\pm$ 0.05	0.066
Maternal age	0.5 $\pm$ 0.18	0.014	0.5 $\pm$ 0.20	0.017
Socioeconomic status	1.1 $\pm$ 0.46	0.020	1.3 $\pm$ 0.50	0.010
Race: Hispanic ^a	−3.3 $\pm$ 3.12	0.289	−3.8 $\pm$ 3.32	0.257
Race: black ^a	−5.5 $\pm$ 4.70	0.241	−3.5 $\pm$ 4.84	0.472
Race: other ^a	−12.5 $\pm$ 3.88	0.001	−7.6 $\pm$ 4.36	0.083
Nonverbal Index				
ASM group (4 levels)		0.033		0.338
Preconception folate use	3.1 $\pm$ 1.93	0.107	4.0 $\pm$ 2.06	0.051
Maternal IQ	0.2 $\pm$ 0.06	0.001	0.2 $\pm$ 0.06	0.001
Standardized ASM dose	−0.1 $\pm$ 0.05	0.018	−0.1 $\pm$ 0.05	0.126
Gestational age	0.9 $\pm$ 0.41	0.024	1.0 $\pm$ 0.43	0.021
Expressive Index				
ASM group (4 levels)		<0.001		0.976
Preconception folate use	3.2 $\pm$ 2.21	0.151	1.3 $\pm$ 2.44	0.593
Maternal IQ	0.2 $\pm$ 0.07	0.010	0.2 $\pm$ 0.07	0.003
Standardized ASM dose	−0.1 $\pm$ 0.05	0.006	−0.1 $\pm$ 0.06	0.084
Maternal age	0.5 $\pm$ 0.19	0.007	0.6 $\pm$ 0.22	0.009
Race: Hispanic ^a	−5.3 $\pm$ 3.65	0.147	−6.0 $\pm$ 3.89	0.123
Race: black ^a	−5.4 $\pm$ 5.27	0.304	−3.7 $\pm$ 5.48	0.499
Race: other ^a	−14.0 $\pm$ 4.45	0.002	−11.1 $\pm$ 4.97	0.026
Maternal post-high school education	5.8 $\pm$ 2.66	0.031	6.8 $\pm$ 2.99	0.025
Receptive Index				
ASM group (4 levels)		0.001		0.668
Preconception folate use	4.6 $\pm$ 1.92	0.019	3.8 $\pm$ 2.09	0.068
Maternal IQ	0.2 $\pm$ 0.06	0.001	0.2 $\pm$ 0.06	0.001

Continued

Table 4 Model summary for age 3 outcomes: Intent-to-treat analysis (*continued*)

Age 3 outcomes	All ASMs		Without valproate	
	Coefficient ± SD	p Value	Coefficient ± SD	p Value
Standardized ASM dose	−0.1 ± 0.05	0.006	−0.1 ± 0.05	0.083
Maternal age	0.4 ± 0.18	0.017	0.4 ± 0.20	0.030
Socioeconomic status	1.0 ± 0.46	0.024	1.4 ± 0.50	0.007
Race: Hispanic ^a	−1.4 ± 3.11	0.653	−1.8 ± 3.29	0.581
Race: black ^a	−6.1 ± 4.68	0.193	−3.9 ± 4.79	0.413
Race: other ^a	−11.2 ± 3.87	0.004	−5.0 ± 4.34	0.254

Abbreviations: ASM = antiepileptic medication; FSIQ = Full Scale Intelligence Quotient.

^a Four categories for race (black, Hispanic, other, white).

The present study further highlights the importance of periconceptional folate to optimize outcomes in offspring from pregnancies of women taking ASMs. Note that these other studies were conducted in different cohorts and had their own strengths and limitations. The presence of a positive signal across different studies adds to the confidence in that signal.

Periconceptional folate is known to reduce the risk of spina bifida³⁴ and may improve cognitive and behavioral neurodevelopment^{2–9} in pregnancies of the general population. The results of the Norwegian Mother and Child Cohort study and the NEAD study suggest that periconceptional folate may be even more important for the children of women taking ASMs. Fewer than half of the pregnancies in the general population are planned, and the situation may be worse for women with epilepsy.³⁵ About 25% of women in the Norwegian Mother and Child Cohort study and ≈43% in the NEAD study were not taking periconceptional folate.^{13,19} These issues emphasize the importance of informing women of childbearing age and encouraging folate supplementation, especially if they are taking ASMs.

The most appropriate dose of periconceptional folate is not clear. In the NEAD study, all dose groups >0.4 mg/d differed from the no folate group.¹⁹ The low-dose group (>0–0.4 mg/d) had an intermediate IQ between those of the no folate group and >0.4 mg/d groups, but it did not differ statistically from other groups. However, only 6 children were in the low-dose group (>0–0.4 mg), which limited exploring dose-dependent effects. Furthermore, the sample sizes in the higher-dose groups, although larger, are still rather small. Low folate levels as reflected by elevated maternal homocysteine at pre-conception are inversely associated with cognitive performance in children at 6 years after birth.³⁶ However, concerns have been raised that higher doses of folate supplementation might be injurious and increase the risk of autism.³⁷ Because some ASMs interfere with folate levels or mechanisms (e.g., enzyme-inducing ASMs and lamotrigine), the dose for women taking ASMs might differ from that for the general population. Higher doses could be considered for women taking ASMs that interfere with folate or women with personal or family history of neural tube defects in pregnancies, but the safety of doses >4 to 5 mg/d has been questioned.³⁷ In addition, folic acid does not have the same metabolic pathway as folate. Folic acid requires hepatic conversion via methyl tetrahydrofolate dihydrofolate reductase (MTHFR) to be utilized, and the activity of hepatic dihydrofolate reductase varies greatly among individuals. Our study did not measure genetic variability such as the *MTHFR* gene. Clearly, additional studies are required to determine both the most effective and safe dose of folic acid and the timing of folate in both healthy women and women taking ASMs to achieve optimal neurodevelopment in humans. In the absence of definitive data, we recommend that folate supplementation in women of childbearing potential should be at least 0.4 to 1.0 mg/d.

The results of the Norwegian Mother and Child Cohort study suggest that the critical period for folate exposure occurs in first trimester on the basis of time of supplementation; furthermore, plasma folate levels later in the pregnancy were not associated with cognitive outcomes, although they were

Table 5 Periconceptional folate dose categories for mothers and children with nonmissing FSIQ at age 6 years

Folate dose categories	Mothers, n (%)	Children, n (%)
Folate not taken	91 (41.2)	91 (40.4)
≤0.4 mg	6 (2.7)	6 (2.7)
>0.4–1 mg	27 (12.2)	29 (12.9)
>1–<4 mg	41 (18.6)	42 (18.7)
≥4 mg	53 (24.0)	54 (24.0)
Unknown	3 (1.4)	3 (1.3)
All	221 (100.0)	225 (100.0)

Abbreviation: FSIQ = Full Scale Intelligence Quotient.

inversely associated with autistic traits.^{13,14} In contrast, although the risk for congenital malformations occurs in the first trimester, the main adverse effects of ASMs on neuropsychological function might be due primarily to third trimester exposure.^{38,39} Fetal alcohol syndrome appears to be primarily from alcohol exposure of the immature brain in the third trimester, resulting in neuronal apoptosis and altered synaptogenesis.⁴⁰ Similarly, some ASMs produce the same effect on the immature brain.^{38,39}

The underlying mechanisms of both folate and ASMs on the immature brain and their potential interaction are poorly understood, and the precise clinical neuropsychological risks to children for most fetal ASMs exposures, including their combinations, remain unknown.⁴¹ A combination of basic and clinical research is critical to fully delineate the effects of folate and ASMs on the developing fetus to maximize the care of pregnant women who require ASMs.

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David W. Loring, PhD	Departments of Neurology and Pediatrics, Emory University, Atlanta, GA	Author	Major role in the study design, acquisition of data; revised the manuscript for intellectual content
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NEAD Investigator Group	See Appendix	Coinvestigators	Major role in the acquisition of data

Appendix 2 NEAD Sites and Study Group

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Georgia Health Sciences University, Augusta, Georgia

Georgetown University, Washington, DC

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Harvard - Massachusetts General, Boston, Massachusetts

Henry Ford Hospital, Detroit, Michigan

Medical College of Cornell University, New York City, New York

Minnesota Epilepsy Group, St. Paul, Minnesota

Ohio State University, Columbus, Ohio

Riddle Health Care, Media, Pennsylvania

Rush University Medical Center, Chicago, Illinois

St. Mary's Hospital, Manchester, England

The Comprehensive Epilepsy Care Center for Children and Adults, St. Louis, Missouri

University of Alabama, Birmingham, Alabama

University of Cincinnati, Cincinnati, Ohio

University of Kansas School of Medicine - Wichita, Wichita, Kansas

University of Liverpool, Liverpool, England

University of Manchester, Manchester, England

University of Miami, Miami, Florida

University of Southern California, Los Angeles, California

University of Utah, Salt Lake City, Utah

University of Washington, Seattle, Washington

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