

Maternal Plasma Folate Levels in Pregnancy and Early Childhood Cognitive and Language Development

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The Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) Study
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Background

*Fetal central nervous system (CNS) development is reliant on the adequacy of the maternal micronutrient folate levels. Folate is a water-soluble vitamin which is involved with cell proliferation, CNS repair, and gene expression.

*Folic acid supplementation during pregnancy has been shown to prevent certain neurologic defects. Public Health agencies recommend supplementation with folic acid before & during pregnancy and many countries fortify the food supply.

*Researchers have recently published that maternal folic acid supplementation may be associated with lower risk of severe language delay & autism spectrum disorder.

Maternal folic acid supplementation in early pregnancy has been found to be associated with a reduced risk of severe language delay at three years (Roth, et al; *JAMA*, 2011; from a large population-based sample of nearly 39,000 children in the Norwegian Mother and Child Cohort Study) and reduced risk of autism spectrum disorders (Suren, et al; 85,000 children including 270 with autism from the same Norwegian sample; *JAMA*, 2013).

Schmidt et al, published that folic acid intake (as measured by diet records and supplement use) was lower in the first month of pregnancy for mothers of children with autism spectrum disorders (*American Journal of Clinical Nutrition*, 2011). This association was strongest for mothers and children with certain variant genotypes for inefficient folate metabolism.

Purpose

*To determine if maternal plasma folate (MPF) levels during pregnancy are related to cognitive and language outcomes at 2 years old.

Methods

*The Conditions Affecting Neurocognitive Development and Learning in Early childhood (CANDLE) Study is a prospective, longitudinal, community-based study of 1503 mother-infant dyads from mid-gestation into early childhood. The sample is representative of the population of Memphis, Shelby County, TN. Mothers were recruited during the 16-28th weeks of a single, low medical risk pregnancy.

Genetic, environmental, social, nutritional and health measures were obtained. The retention rate 77% for the 2 year old child visit, and children are followed to older ages (around 4 years old in 2014).

*Child cognitive and language development was measured by the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley) at 2 years in 1090 children. The Bayley includes norm-referenced, age-standardized index scores. Subtest scaled scores were assessed in Expressive and Receptive Language.

*Maternal plasma folate (MPF) was measured in the second and third trimesters of 935 and 925 mothers, respectively. Most mothers had both MPF measures.

*Multiple linear regression was used to examine the relationship between MPF and childhood developmental outcomes in the presence of child's gender; mother's age, race, education, IQ, marital status, insurance, depression screen; parent-child interaction and any breastfeeding in first year of life.

Demographics & Variables

Sample size 1090

Child sex: Male 50.5%, Female 49.5%

Maternal race: Black 64.5%, White 33%, Other 2.5%

Maternal marital status: Married/Living with partner 58.4%, Single 41.6%

Maternal Education: Less/Equal High School 55.7%, More 44.3%

Maternal Insurance: Medicaid 55%, Other/None 45%

Maternal age at delivery

Maternal IQ (*Wechsler Abbreviated Scale of Intelligence, WASI*)

Maternal depressive symptoms, prenatal or at 2 yrs (*Brief Symptom Inventory, BSI*)

Parent-Child interaction, at 2 years (*Parent Child Interaction Teaching Scale, NCAST*)

Any breastfeeding in 1st year (*Nutrition Data System for Research, NDSR*)

Results

Correlations were computed in **bivariate analyses** to examine the relationship between each outcome (Cognitive and Language Composite Scores) and the independent variables.

General linear models were used to determine significant predictors of Cognitive and Language Composite Scores.

-Based on the bivariate analyses, maternal depressive symptoms (BSI at the prenatal or 2 year clinic visit) were not included in the final regression model; other predictors were statistically significant and therefore were included in the final model.

Bivariate Analyses Results

Bayley Cognitive and Language Composite scores (and Receptive and Expressive Scaled scores) were correlated with Maternal plasma folate during the 2nd and 3rd trimesters.

•This correlation was significant ($p < .0001$) but not strong ($r < 0.25$).

Linear Models Results

Maternal plasma folate in the 2nd trimester (though *not* the 3rd) was a statistically significant predictor for Bayley Cognitive Composite scores ($p = 0.120$). Maternal plasma folate measures were *not* significant predictors of Language Composite scores (or Receptive or Expressive Scaled scores).

In addition to the association with folate, other predictors of Cognitive score included child's gender; mother's race, IQ, and parent child interaction ($R^2 = 0.26$); predictors of Language score included these plus maternal insurance and report of any breastfeeding in the first year of life ($R^2 = 0.27$).

Predictors of Cognition at 2 years old	p-value
Maternal Race	<.0001
Maternal IQ	<.0001
Parent Child Interaction	<.0001
Child's sex	.0006
Maternal plasma folate 2 nd trimester	.0120

Predictors of Language at 2 years old	p-value
Maternal Race	<.0001
Maternal IQ	.0194
Parent Child Interaction	<.0001
Child's sex	<.0001
Insurance type	.0008
Ever breastfed during 1 st year	.0041

Conclusion & Discussion

*Maternal plasma folate levels were positively associated with cognitive, but not language outcomes, in 2-year-old children.

*Maternal plasma folate levels were not significant predictors of any of the language measures at two years of age in this study after controlling for known confounding variables. .

*While this study benefits from a relatively large sample size and multiple measures for both mother and child at various time points, certainly it remains difficult to ascertain precise effects from an array of potentially important variables. Many of these important variables were included in the analysis for this study and several were found to also be significant predictors of cognitive and language outcomes (as shown in tables).

*Since mild language deficits and/or those seen in Autism Spectrum Disorders may not be evident until after 2 years of age, research is ongoing to evaluate developmental outcomes at older ages as language skills advance. We also hope to evaluate for additional features of Autism Spectrum Disorder.

*Further research to explore potential implications on periconceptual pregnancy planning and prenatal care is warranted.

References

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Acknowledgements

Special thanks to the CANDLE participants (parents and children) and the many clinicians and researchers involved in this very collaborative study.

The CANDLE Study
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