Choline concentrations in human maternal and cord blood and intelligence at 5 y of age[1–3]

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ABSTRACT

Background: Animal studies indicate that maternal prenatal choline supplementation leads to permanent enhancement of attention and spatial memory abilities in offspring, whereas dietary choline restriction during pregnancy impairs cognitive function in offspring. The association between gestational choline concentrations and neurodevelopmental outcome in humans has not been studied.

Objective: Our objective was to assess the relation between maternal and cord blood choline concentrations and child intelligence quotient (IQ) scores at 5 y of age.

Design: With data and samples from a prospective study (n = 404 maternal-child pairs), serum concentrations of free and total choline were measured in maternal serum at 4 gestational age intervals (16–18 wk, 24–26 wk, 30–32 wk, and 36–38 wk) and in cord blood. Child IQ at 5 y of age was assessed with the Wechsler Preschool and Primary Scale of Intelligence-Revised. Multiple regression techniques were used to estimate the relation between choline concentrations and Full Scale IQ, Verbal and Performance IQ, and subscales that assess spatial relation and memory ability while adjusting for other factors that affect IQ.

Results: There was no effect at gestational ages 16–18 wk, 24–26 wk, 30–32 wk, and 36–38 wk or in cord blood of serum concentrations of free or total choline on Full Scale child IQ or on selected scales related to visuospatial processing and memory.

Conclusion: Gestational and newborn choline concentrations in the physiologic range showed no correlation with childhood intelligence. *Am J Clin Nutr* 2008;87:896–902.

INTRODUCTION

An impressive array of animal studies show that perinatal choline supplementation enhances cognitive ability and that choline restriction can impair brain development (1). The role of perinatal choline on brain function has never been studied in humans despite the widely recognized importance of choline in development (2).

Choline is an essential nutrient involved in numerous metabolic pathways, some of which are particularly important during the rapid cellular growth that occurs during fetal development. Choline is required for the synthesis of phospholipids, the major component of cellular membranes (3, 4). In addition, choline is an important methyl donor and is thereby crucial for DNA regulation and repair, protein function, and intermediary metabolism (5–8). The neurotransmitter, acetylcholine, is produced directly from free choline in cholinergic neurons (9–11).

Choline is provided primarily through the diet, although de novo synthesis of phosphatidylcholine takes place in the liver and kidney and is up-regulated during pregnancy to meet the burden of increased fetal requirements. Choline concentrations in newborn humans and other mammals are markedly higher than maternal choline concentrations, which are depleted by fetal demand (4, 12). Evidence from animal studies indicates that perinatal choline supplementation or restriction fundamentally alters the course of brain development, particularly in the hippocampus, and that resulting enhancements or deficits in attention and spatial memory persist through adulthood (13–16).

In humans, the hippocampus is a critical brain region for the formation and consolidation of declarative memory and, therefore, the learning of new information (17). Memory, along with attention, reasoning, language, perception, and construction, is a crucial component of human intelligence (18). Animal data raise the possibility that prenatal choline exposure could affect hippocampal development and memory capabilities (14, 19–24) and thus affect intelligence in humans.

There have not been any human studies of choline concentrations and intelligence. We therefore conducted a historical cohort study to estimate the relation between maternal choline status during pregnancy and at delivery and the intelligence quotient (IQ) score of the child at 5 y of age. We hypothesized that higher choline concentrations measured over 4 time intervals in the second and third trimesters of pregnancy and at birth are related to a higher Full Scale IQ score at 5 y of age. We further hypothesized that a choline effect would be particularly evident in scores on IQ subtests more specifically related to visuospatial cognition and memory.

SUBJECTS AND METHODS

Study sample

The blood samples and outcome data for this investigation were collected as part of the Infant Growth Project (IGP), a

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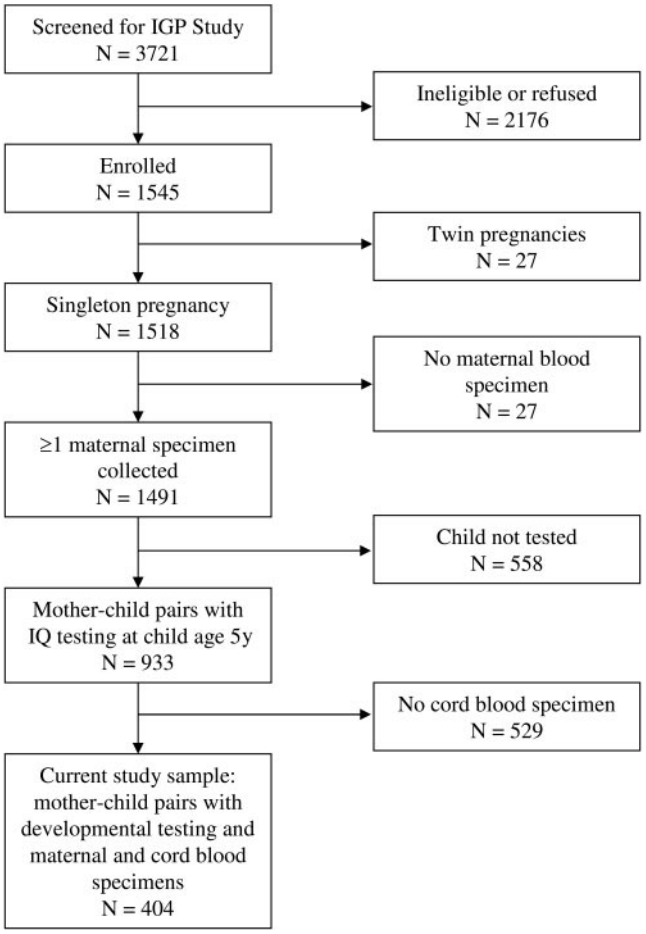

FIGURE 1. Flow diagram for study sample selection. IGP, Infant Growth Project; IQ, intelligence quotient.

prospective study of the effect of intrauterine growth restriction on child cognitive function conducted by the National Institute of Child Health and Human Development and the University of Alabama at Birmingham. Subject recruitment was described previously (25). Briefly, between 1985 and 1988, study participants with 1 or 2 previous births were recruited from an indigent, primarily black population of women receiving prenatal care in an Alabama county health department, 95% of whom had identifiable risk factors for growth restriction (25).

Of 3721 women screened, 1545 were enrolled in the IGP study (**Figure 1**). For our analysis, twin pregnancies ($n = 27$) were excluded, leaving 1518 women with singleton pregnancies; 1491 of these women contributed ≥1 antenatal serum specimen for storage in the study repository. Maternal blood was collected from women at 4 intervals during pregnancy (16–18 wk, 24–26 wk, 30–32 wk, and 36–38 wk). Of the 933 mother-child pairs who returned for IQ and other testing at age 5 y, 404 had contributed a cord blood specimen and ≥1 antenatal maternal serum specimen for long-term storage. Maternal specimens were centrifuged, and aliquots were frozen within 20–60 min of collection. Cord blood specimens were refrigerated at 4 °C within 60 min of collection, then centrifuged, divided into aliquots, and frozen within 24 h. Both maternal and cord blood specimens were stored at −80 °C since processing. We were able to locate a total of 1776 serum specimens in the repository; 1752 were successfully analyzed. The Office of Human Subjects Research at the National Institutes of Health granted an exemption from institutional review board approval because data and specimens could not be linked to identifiable women.

Laboratory methods

Serum concentrations of free and total choline were measured with a modification of the liquid chromatography–tandem mass spectrometry method described by Holm et al (26). For free and total choline at population median concentrations, the within- and between-day CVs are 3% and 4%, respectively. A pilot test of 40 randomly selected samples from the IGP collection was conducted before the current study. Results indicated that the storage conditions had adequately preserved the analytes of interest, because their concentrations were within the range expected for fresh samples (data not shown).

Demographic and developmental assessments

Demographic data were collected by maternal interview. Birth outcome data were obtained from the hospital record.

The child's IQ was measured at mean (±SD) age of 5.5 ± 0.5 y, based on the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R). The WPPSI-R test measures cognitive function in children aged 2 y 11 mo to 7 y 3 mo. The computed Full Scale IQ is the most reliable score on the test, with internal consistency coefficient of 0.96 and test-retest reliability of 0.91 (26, 27). Verbal and Performance IQ scores were recorded, as were scaled scores for the 10 WPPSI-R subtests. The WPPSI-R test and other neuropsychological tests were performed in a single 3-h session by extensively trained evaluators who had no knowledge of the results of the children's serum analyses (28).

Maternal cognitive ability and the quality of the home environment are important predictors of children's IQ scores (29). Therefore, maternal receptive language was measured with the use of the Peabody Picture Vocabulary Test-Revised (PPVT-R; 1981), and the quality of the child's home environment was assessed with the Home Screening Questionnaire (HSQ). Small for gestational age (SGA) was defined as a birth weight < 10th percentile for gestational age on the basis of the standard of Brenner et al (30). Gestational age was based on last menstrual period and was always confirmed by ultrasound scanning, which was performed at ≤20 wk gestation in most cases. If the sonographic estimate of gestational age differed by >2 wk from the last menstrual period, the sonographic dating was used (25).

Statistical methods

Wilcoxon's signed rank test was used to compare both free and total choline values between different gestational age windows. Correlation of choline between different gestational age windows was assessed with the use of Spearman's rank correlation coefficients.

To assess an overall trend, a repeated-measures model was fit with gestational age as a linear term. Correlation between choline measures from the same woman was incorporated by using an autoregressive order 1 correlation model that allows for a decreasing correlation pattern as the time difference increases.

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TABLE 1
Characteristics of the study population ($n = 400$)[1]

Maternal age (y)	24.2 ± 4.3[2]
Race [*n* (%)]	
White	114 (28.5)
Black	286 (71.5)
Parity [*n* (%)]	
1	265 (66.3)
2	135 (33.8)
Highest grade completed [*n* (%)][3]	
≤8	15 (3.9)
9–11	120 (31.1)
12	136 (35.2)
13–15	108 (28.0)
≥16	9 (2.3)
Household income below 1986 poverty level [*n* (%)][4]	243 (70.0)
Maternal raw PPVT-R score	129 ± 15
Home Screening Questionnaire score	36.5 ± 6.4
Infant characteristics	
Gestational age (wk)	38.2 ± 2.6
Birth weight (g)	3028 ± 643
Male [*n* (%)]	211 (52.8)
SGA [*n* (%)]	40 (10)
Head circumference (cm)	33.5 ± 2.1
Child WPPSI-R scores	
Full Scale IQ	82.4 ± 12.1 (45–118)[5]
Verbal IQ	84.0 ± 11.9 (27–116)
Performance IQ	84.4 ± 13.3 (49–130)
Information subscale	6.6 ± 2.7 (1–16)
Block Design subscale	6.8 ± 2.5 (1–15)

[1] PPVT-R, Peabody Picture Vocabulary Test–Revised; SGA, small for gestational age; WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence–Revised; IQ, intelligence quotient.
[2] $\bar{x}$ ± SD (all such values).
[3] $n = 386$.
[4] $n = 347$.
[5] $\bar{x}$ ± SD; range in parentheses (all such values).

Serum free and total choline values were normalized within each gestational age window (including cord values from delivery). The normalization was carried out by successive log-transformations until either the skewness or kurtosis did not decrease in absolute value. Once a normalizing transformation was determined, the sample mean and SD were used to create *z* scores for each measure at each gestational window.

For each choline measure, 3 multivariate models were fit to estimate the association between choline and Full Scale IQ score. Potential confounders initially included in all models were maternal raw score on the PPVT-R, quality of home environment as measured by the HSQ, gross family income above or below the poverty level, gestational age, maternal alcohol use during pregnancy, maternal race, maternal tobacco use during pregnancy, infant sex, maternal age, and highest grade of maternal education. Choline *z* score was forced to be retained in all models. The first model started with the factors listed above, along with choline *z* score, and used backward elimination until all remaining terms were significant at $P < 0.05$. The factors reported in the literature to be associated with IQ (the first 5 in the list), along with choline *z* score, were forced to be retained in the final model. A second model was obtained through the same process used to obtain the first model except that the initial list of factors included factors that might be intermediary variables for choline and IQ (birth weight, SGA status, infant head circumference, child head circumference), and birth weight and SGA status were also forced to be retained in the final model. A third model was obtained through the same process used to obtain the first model except that only choline *z* score was forced to be retained in the final model.

Statistical significance was defined at the 0.05 level, and all analyses were conducted with the use of SAS v9.0 (SAS Institute, Cary, NC). No previous data correlating maternal or cord blood choline with childhood IQ were available for use in estimation of statistical power. Assuming a 0.05 significance level, this study had 80% power to detect a minimum correlation of 0.12 between free choline and IQ.

RESULTS

Characteristics of the study population are presented in **Table 1**. The socioeconomic profile for the study participants is consistent with a disadvantaged inner-city population. Thirty-five percent of subjects had not finished high school, and a large majority reported a gross family income under the 1986 federal poverty level for a family of 4 (<$11 000/y) (31). Mean PPVT-R raw scores, a measure of maternal receptive language, were well below the national mean (25). Scores on the HSQ also indicate that, on average, the developmental environments of the children's homes were below the national average (25). Similarly, mean child IQ scores were lower than national norms.

Free choline and total choline concentrations (median, interquartile range) in maternal serum at 4 gestational age windows and in cord blood serum are shown in **Table 2**. There was no significant change in maternal free choline across the gestational ages analyzed (P for trend = 0.62). In contrast, serum concentrations of total choline increased significantly through gestation (P for trend < 0.0001). Newborn concentrations of free choline were significantly higher than maternal concentrations at 36–38 wk gestation (36.40 μmol/L compared with 10.10 μmol/L; $P < 0.0001$). Conversely, maternal concentrations of total choline at 36–38 wk were significantly higher than concentrations in the newborn (2.75 compared with 1.40 mmol/L; $P < 0.0001$).

TABLE 2
Free and total choline concentrations in maternal blood at different gestational age windows and in cord blood[1]

	16–18 wk	24–26 wk	30–32 wk	36–38 wk	Cord
Free choline (μmol/L)	9.34 (7.69–11.50) [355]	9.39 (7.76–11.00) [371]	9.14 (7.85–10.80) [348]	10.10 (8.46–12.00) [298]	36.40 (27.80–49.25) [364]
Total choline (mmol/L)	2.57 (2.33–2.80) [356]	2.62 (2.43–2.90) [374]	2.69 (2.49–2.95) [349]	2.75 (2.48–2.99) [298]	1.40 (1.24–1.56) [330]

[1] All values are median; interquartile range in parentheses; *n* in brackets.

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TABLE 3
Relation between free choline concentrations and selected intelligence quotient (IQ) and subscale scores on the Wechsler Preschool and Primary Scale of Intelligence–Revised at age 5, adjusted[1]

	Full Scale IQ		Verbal IQ		Performance IQ		Block Design subtest		Information subtest	
	Parameter estimate	*P*	Parameter estimate	*P*	Parameter estimate	*P*	Parameter estimate	*P*	Parameter estimate	*P*
16–18 wk gestation (n = 322)										
Free choline (z score)	−0.12	0.85	−0.42	0.50	0.42	0.54	0.19	0.17	−0.16	0.25
Maternal PPVT-R score	0.16	0.0005	0.15	0.001	0.16	0.002	0.02	0.01	0.03	0.003
HSQ score	0.25	0.01	0.16	0.11	0.21	0.07	0.02	0.32	0.07	0.004
Maternal education	0.89	0.03	0.76	0.07	0.98	0.03	0.14	0.12	0.21	0.02
Female (child)	4.37	0.0005	5.20	<0.0001	2.36	0.09	0.44	0.10	1.21	<0.0001
Black	−5.64	0.001	−6.08	0.0005	−4.09	0.04	−0.05	0.89	−1.14	0.003
24–26 wk gestation										
Free choline (z score)	−0.27	0.66	−0.30	0.62	0.18	0.79	0.20	0.15	−0.15	0.26
Maternal PPVT-R score	0.19	<0.0001	0.18	<0.0001	0.19	0.0001	0.03	0.006	0.04	<0.0001
HSQ score	0.27	0.007	0.17	0.08	0.26	0.03	0.03	0.11	0.06	0.004
Female (child)	3.38	0.006	4.61	0.0001	1.09	0.43	0.16	0.55	1.14	<0.0001
Black	−4.08	0.006	−4.39	0.002	−2.62	0.12	0.13	0.69	−0.72	0.02
30–32 wk gestation										
Free choline (z score)	−0.37	0.56	−0.68	0.28	0.15	0.84	0.05	0.74	−0.16	0.28
Maternal PPVT-R score	0.20	<0.0001	0.18	<0.0001	0.17	0.001	0.02	0.01	0.04	<0.0001
Maternal education	0.90	0.02	0.65	0.10	0.03	0.03	0.14	0.10	0.20	0.03
Female (child)	3.44	0.005	4.73	0.0001	1.50	0.29	0.22	0.42	1.14	<0.0001
Black	−6.00	0.0002	−5.62	0.0005	−5.36	0.004	−0.33	0.36	−1.16	0.002
36–38 wk gestation										
Free choline (z score)	−0.24	0.68	−0.55	0.36	0.25	0.72	0.03	0.77	−0.11	0.41
Maternal PPVT-R score	0.20	<0.0001	0.19	<0.0001	0.17	0.001	0.02	0.01	0.04	<0.0001
Maternal education	0.90	0.02	0.65	0.10	1.04	0.02	0.14	0.10	0.20	0.03
Female (child)	3.44	0.005	4.73	0.0001	1.49	0.29	0.22	0.42	1.14	<0.0001
Black	−6.00	0.0002	−5.62	0.0005	−5.36	0.004	−0.32	0.36	−1.16	0.002
Cord blood (n = 332)										
Free choline (z score)	−0.09	0.68	−0.20	0.36	0.09	0.72	0.01	0.77	−0.04	0.41
Maternal PPVT-R score	0.20	<0.0001	0.18	<0.0001	0.05	0.001	0.02	0.01	0.04	<0.0001
Maternal education	0.90	0.02	0.64	0.10	1.03	0.02	0.14	0.10	0.20	0.03
Female (child)	3.44	0.005	4.73	0.0001	1.49	0.29	.21	0.42	1.14	<0.0001
Black	−6.00	0.0002	−5.62	0.0005	−5.36	0.004	−0.32	0.36	−1.16	0.002

[1] PPVT-R, Peabody Picture Vocabulary Test–Revised; HSQ, Home Screening Questionnaire. For Full Scale IQ, analysis was by multivariate regression with backward elimination, forcing free choline to be retained in the model. All models initially included free choline, maternal PPVT-R raw score, HSQ score, poverty status, maternal race, education level, smoking, alcohol use, gestational age at delivery, and child sex. For subscale measures, covariates from the final model for Full Scale IQ were included.

For both free and total choline, there were statistically significant positive correlations between choline concentrations collected from individual mothers at the different gestational age windows; these were stronger for total choline (r = 0.41–0.65, $P < 0.0001$) than for free choline (r = 0.16–0.28, $P < 0.003$). At each gestational age window, maternal serum free choline was correlated with maternal total choline (r = 0.09–0.15, P = 0.01–0.06). In cord blood, there was no correlation between concentrations of free and total choline (r = −0.07, P = 0.23). Maternal concentrations of free choline at 16–18 wk and 24–26 wk were not correlated with cord blood free choline, but third trimester (30–32 wk and 36–38 wk) maternal concentrations of free choline were positively correlated with free choline concentrations in cord blood (r = 0.13–0.16, $P < 0.04$). There were no correlations between any maternal concentrations of total choline and cord blood total choline (data not shown).

Because animal studies have shown beneficial effects of choline exposure at times that may correspond to all trimesters of human pregnancy, we examined the relation between serum choline concentration and child Full Scale IQ score at all 4 available gestational intervals and in cord blood. Results of multiple linear regression analyses adjusted for covariates are presented in **Tables 3** and **4**. The known predictive factors, including maternal PPVT-R raw score, maternal education, race, and quality of the home environment, were strongly related to child Full Scale IQ score. There was no association between free or total choline concentration in either the maternal or fetal circulation and Full Scale IQ score at 5 y of age at any of the time points studied.

Modeling that forced risk factors reported in the literature to be in the final model also found no significant association between choline concentration and child IQ (final models not shown). We also tested additional models that included birth weight, SGA status, infant head circumference, and child head circumference as possible confounders. Again, no effect of maternal or cord blood concentration of choline on child IQ was detected (final models not shown).

Full Scale IQ is a measure of general intelligence (27) and may be too broad a measure of cognition to reflect an effect of choline.

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TABLE 4
Relation between total choline and selected intelligence quotient (IQ) and subscale scores on the Wechsler Preschool and Primary Scale of Intelligence-Revised at age 5 y, adjusted[1]

	Full Scale IQ		Verbal IQ		Performance IQ		Block Design subtest		Information subtest	
	Parameter estimate	*P*	Parameter estimate	*P*	Parameter estimate	*P*	Parameter estimate	*P*	Parameter estimate	*P*
16–18 wk gestation										
Total choline (*z* score)	0.49	0.44	0.003	1.0	0.77	0.28	0.20	0.14	−0.02	0.90
Maternal PPVT-R score	0.15	0.0006	0.14	0.001	0.15	0.002	0.02	0.02	0.03	0.002
HSQ score	0.25	0.01	0.18	0.08	0.20	0.08	0.02	0.38	0.07	0.002
Maternal education	0.88	0.03	0.73	0.08	1.02	0.03	0.15	0.09	0.21	0.02
Female (child)	4.36	0.0005	5.43	<0.0001	2.09	0.13	0.38	0.15	1.27	<0.0001
Black	−5.46	0.002	−5.78	0.0008	−4.14	0.03	−1.13	0.72	−1.03	0.006
24–26 wk gestation										
Total choline (*z* score)	0.53	0.41	0.11	0.86	0.68	0.35	0.12	0.40	−0.03	0.84
Maternal PPVT-R score	0.18	<0.0001	0.17	<0.0001	0.18	0.0002	0.03	0.006	0.04	<0.0001
HSQ score	0.27	0.006	0.19	0.05	0.25	0.03	0.03	0.15	0.07	0.002
Female (child)	3.21	0.009	4.41	0.0002	0.89	0.52	0.14	0.60	1.09	<0.0001
Black	−4.03	0.006	−4.36	0.002	−2.58	.012	0.11	0.73	−0.70	0.02
30–32 wk gestation										
Total choline (*z* score)	0.44	0.49	0.12	0.84	0.64	0.39	0.09	0.51	−0.04	0.76
Maternal PPVT-R score	0.20	<0.0001	0.19	<0.0001	0.17	0.001	0.02	0.01	0.04	<0.0001
Maternal education	0.93	0.02	0.72	0.07	1.02	0.03	0.15	0.10	0.22	0.02
Female (child)	3.38	0.006	4.70	0.0001	1.41	0.32	0.21	0.44	1.14	<0.0001
Black	−5.58	0.0007	−5.41	0.0009	−4.82	0.01	−0.23	0.54	−1.15	0.002
36–38 wk gestation										
Total choline (*z* score)	0.51	0.47	0.19	0.79	0.77	0.36	0.08	0.60	0.02	0.89
Maternal PPVT-R score	0.24	<0.0001	0.23	<0.0001	0.18	0.0008	0.02	0.02	0.05	<0.0001
HSQ score	0.26	0.03	0.18	0.10	0.32	0.01	0.04	0.15	0.06	0.02
Female (child)	3.28	0.02	4.56	0.0008	1.47	0.36	0.17	0.58	1.16	0.0001
Cord blood (n = 301)										
Total choline (*z* score)	0.61	0.36	−0.06	0.92	0.90	0.25	0.18	0.22	−0.01	0.92
Maternal PPVT-R score	0.14	0.003	0.15	0.002	0.15	0.01	0.02	0.07	0.03	0.001
HSQ score	0.27	0.01	0.15	0.14	0.25	0.05	0.03	0.18	0.06	0.01
Maternal education	1.00	0.02	0.97	0.02	1.04	0.04	0.13	0.16	0.22	0.02
Female (child)	3.57	0.007	4.42	0.0005	1.49	0.34	0.21	0.47	1.01	0.0004
Black	−6.24	0.0007	−6.26	0.0003	−5.02	0.02	−0.15	0.71	−1.27	0.001

[1] PPVT-R, Peabody Picture Vocabulary Test–Revised; HSQ, Home Screening Questionnaire. For Full Scale IQ, analysis was by multivariate regression with backward elimination, forcing free choline to be retained in the model. All models initially included free choline, maternal PPVT-R raw score, HSQ score, poverty status, maternal race, education level, smoking, alcohol use, gestational age at delivery, and child sex. For subscale measures, covariates from the final model for Full Scale IQ were included.

Animal data indicate a specific hippocampal effect of choline on visuospatial attention, memory, and performance. Tests of human memory that correlate highly with the specific component of memory of interest in rodents were not conducted in the IGP study and were not available for this analysis. Thus, with the use of the same covariates in the final models for Full Scale IQ detailed above, corresponding models were fit to estimate the association between choline concentrations and each of the following WPPSI-R scores: the Verbal and Performance IQ scores, as indicators of relative verbal ability and visual-nonverbal skills; the Block Design subtest scaled score, in which abilities in spatial visualization, spatial reasoning, and reproduction of models are assessed; and the Information subtest scaled score, which in part assesses long-term memory and recall (27). These scores were selected for analysis because of their more targeted focus on abilities of interest and to avoid the unwanted consequences of multiple testing of all available WPPSI-R subscales. Results of multiple linear regression analyses adjusted for covariates are presented in Tables 3 and 4. There was no association between free or total choline concentration in either the maternal or fetal circulation and any of these more specific measures of visuospatial ability and memory at 5 y of age at any of the time points studied.

DISCUSSION

Animal data showing a strong relation between choline status and cognition raised the important questions: is choline related to intelligence in humans, and, if so, could choline supplementation increase intelligence? The relation between gestational choline status and child IQ score has not been addressed previously, possibly because of, in part, the difficulty of collecting samples to measure choline exposure during pregnancy and then following the offspring long enough to get a valid and reliable measure of intelligence.

Our results show no relation between physiologic free and total choline concentrations during pregnancy and children's Full Scale IQ, Verbal and Performance scales, and 2 subscales more specifically related to visuospatial cognition and memory, areas specifically affected by choline in rodents. We were able to

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analyze multiple samples over the course of pregnancy as well as cord blood. Moreover, data on other influences on child IQ such as maternal scores on the PPVT-R and developmental quality of the home environment were collected to address potential confounding. By measuring maternal choline concentrations at multiple points during pregnancy, we were able to assess choline nutriture at points in human gestation that correspond to times in animal development when choline was shown to affect cognition (13–16, 32). We found no correlation between choline concentrations and WPPSI-R IQ scores at any points. Thus, circulating choline over a range of physiologic concentrations in human pregnancy is not an important determinant of child IQ score in this population and does not appear to influence scores on IQ subscales related to visuospatial ability and memory.

Choline plays an important role in brain development (4, 8). Offspring of rat dams whose diet was supplemented with choline at embryonic days 12–17 (of a 22-d gestation period) show abilities in spatial memory and learning 3 d sooner than offspring of dams fed a control diet (14, 33). Prenatal choline supplementation also improves memory capacity, precision (34), and retention (33) among exposed rats. Similar enhancements in memory are seen when rats are supplemented with choline on postnatal days 16–30 (8). Conversely, offspring of rats who receive a choline-restricted diet in late pregnancy show hippocampal apoptosis and impaired memory (1).

Rat and human brain development proceed at different rates, and the human gestational correlates of specific pre- and postnatal exposure windows in the rat are not known with precision. Nevertheless, in a model of neurodevelopment across species, Clancy et al (32) have reported that embryonic days 12–17 in the rat correspond to human gestational days 38–81 (first trimester). Similarly, rat postnatal days 16–30 correspond to human gestational days 169 and beyond, or >24 wk gestation. We were able to measure serum free and total choline in human samples broadly corresponding to the perinatal exposure windows in the rat models.

Choline circulates in a free form or bound to phospholipids (primarily as phosphatidylcholine). Concentrations of free and phospholipid bound (total) choline in the current study were similar to those reported previously (12, 35–37). There are conflicting data about changes over time of gestational concentrations of free and total choline in maternal serum. As in a previous report (38), we found that maternal free choline remained stable throughout gestation, although others have reported increasing free choline with gestational age (37). We observed an increase in maternal concentrations of total choline with gestational age, in contrast to an earlier report (36). In previous studies (12, 35, 36), as in ours, free choline was higher and total choline was lower in cord blood than in maternal blood.

Women in the current study consumed their usual diets. They were not eating choline-enriched diets and were not receiving choline supplementation. Therefore, our results indicate that choline concentrations in a physiologic range observed among women consuming a regular diet during pregnancy are not related to IQ in their offspring. We cannot rule out the possibility that choline supplementation could have an IQ effect.

In rodents, choline supplementation affects hippocampal development and improves spatial memory. We examined the relation of choline concentrations with Full Scale IQ and with selected subscores on the WPPSI-R test that depend more specifically on memory and visuospatial abilities and found no choline effect. Nevertheless, it is possible that choline may affect scores on an assessment tool that more directly measures specific components of memory and hippocampal function.

Serum concentrations of free and total choline may be influenced by recent intake of choline-containing foods. However, women who had relatively high or relatively low concentrations of choline early in pregnancy tended to remain relatively high or relatively low as pregnancy progressed, based on the significant correlation between choline concentrations over the course of pregnancy. Certainly, our longitudinal study provides more information on choline status during gestation than cross-sectional studies.

Note that the subjects in this study were from an inner-city population with substantial socioeconomic disadvantages, as evidenced by the high poverty rate, high prevalence of resource-poor environments, and scores on developmental tests well below national norms among both mothers and their children. It is possible that an effect of choline on intelligence was overshadowed by the relatively greater influence of these social and economic factors. However, multiple regression analyses were adjusted for these factors, and our results were strongly negative. Although the study population characteristics are comparable to other low-income, urban, minority populations, our results may not apply to other socioeconomic groups.

Our study has a number of strengths. Our sample size was sufficient to detect small differences in child IQ. Individual serum free and total choline values well above and below previously reported means (12, 35–37) were present in our sample. This wide range of choline concentrations should have made it possible to identify a choline effect on IQ had there been one. We were able to examine choline concentrations at multiple time points in pregnancy, allowing us to account for uncertainty in the correlation of developmental time courses between rats and humans. The original study from which this secondary analysis arose was specifically designed to assess relations between gestational exposures and child neurodevelopmental outcomes. As a result, extensive data on factors that may affect child IQ were collected and were included in our multivariate analyses. Child IQ was measured with a reliable and valid instrument.

In conclusion, although animal data strongly suggest that higher choline concentrations are correlated with improved cognitive performance in choline-supplemented rodents, this first human study found no relation between maternal choline concentrations at multiple time points during gestation or cord blood choline on IQ scores at 5 y of age. It is possible that pharmacologic doses of choline could affect intelligence in humans. In the physiologic range of concentrations derived from diet and de novo synthesis, however, choline was not correlated with intelligence in our population.

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The authors' responsibilities were as follows—CS and JT: had full access to all of the data and took responsibility for the integrity of the data; CS, JT, and JLM: conceived and designed the study; PMU: conducted the biochemical assays; CS, PMU, JT, and JLM analyzed and interpreted the data and critically analyzed the manuscript for important intellectual content; CS: drafted the manuscript; JT: conducted the statistical analysis; all authors contributed substantially to the manuscript. None of the authors had a personal or financial conflict of interest.

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