Maternal Prepregnancy BMI and Child Cognition: A Longitudinal Cohort Study
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Maternal Prepregnancy BMI and Child Cognition: A Longitudinal Cohort Study

WHAT'S KNOWN ON THIS SUBJECT: Maternal obesity is an increasingly important public health concern and may adversely affect central nervous system development in offspring. However, few studies have explored the relationship between maternal prepregnancy BMI and neurodevelopmental outcomes in children, with conflicting results.

WHAT THIS STUDY ADDS: Using data from a large and contemporary UK birth cohort, we found that maternal prepregnancy BMI is negatively associated with children’s cognitive performance. The relationship appears to become stronger as children get older, although the overall effect size is modest.

abstract

OBJECTIVE: To examine the association between maternal prepregnancy BMI and cognitive performance in children at 5 and 7 years of age.

METHODS: This is a secondary analysis of data from the Millennium Cohort Study, a prospective population based cohort of 19,517 children in the United Kingdom. Standardized cognitive assessments of children, involving components of the British Ability Scales, second edition and a number skills test, were performed at 5 and 7 years of age. Principal components analysis was used to identify a general cognitive ability factor (g) from individual test scores. Maternal prepregnancy BMI was retrospectively self-reported when children were 9 months old. Mixed-effects linear regression models were fitted, controlling for multiple socio-demographic factors, child’s birth weight, child’s BMI, maternal smoking, and maternal diabetes. Complete data were available for 11,025 children at 5 years, and 9,882 children at 7 years.

RESULTS: Maternal prepregnancy BMI was negatively associated with children’s cognitive performance (g) at age 5 (P = .0069) and age 7 (P < .0001). The overall effect size was modest: a 10-point increase in maternal BMI was associated with a decrease in cognitive performance of ~1/10th of an SD at age 7.

CONCLUSIONS: Maternal prepregnancy BMI is negatively associated with children’s cognitive performance, even after adjusting for multiple socio-demographic confounders and children’s BMI. The relationship appears to become stronger as children get older, although the overall effect size is modest. In utero fetal programming or residual confounding may explain these findings. Pediatrics 2013;131:56–63

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KEY WORDS
obesity, BMI, pregnancy, cognition, Millennium Cohort Study

ABBREVIATIONS
BAS-II—British Ability Scales, second edition
CNS—central nervous system
g—general cognitive ability factor
g5—general cognitive ability factor at age 5 years
g7—general cognitive ability factor at age 7 years
GCSE—General Certificate of Secondary Education
MCS—Millennium Cohort Study
NFER—National Foundation for Educational Research
PCA—principal components analysis

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Maternal obesity is an increasingly important public health concern in developed countries and the developing world. In the United Kingdom, ~20% of women of childbearing age are obese, and maternal obesity is associated with adverse outcomes for both the mother and child. These include an increased risk of gestational diabetes, preeclampsia, caesarean delivery, and miscarriage. Neonates born to obese mothers are at increased risk of congenital anomalies, fetal macrosomia, and newborn unit admission. Long-term consequences for offspring include an increased risk of obesity and features of the metabolic syndrome in childhood. It has been proposed that these persisting effects on offspring metabolism are the result of in utero fetal programming caused by a suboptimal intrauterine environment.

Animal studies have suggested that maternal obesity may adversely affect central nervous system (CNS) development in offspring. In humans, an association has been reported between maternal obesity and emotional problems and core symptoms of attention-deficit hyperactivity disorder in school-aged children. However, the literature investigating the relationship between maternal BMI and children’s cognitive outcomes is limited and inconsistent. Néggers et al. reported an association between maternal obesity and lower IQ and nonverbal ability scores in 5-year-old African-American children. However, their cohort was a highly selected, small (\( n = 555 \)), and disadvantaged population whose mothers were initially recruited on the basis of low plasma zinc levels for participation in a randomized clinical trial of zinc supplementation during pregnancy. A Finnish study revealed that maternal prepregnancy obesity was a predictor of intellectual disability (IQ < 70) in children aged 11 years in a cohort born in 1986 but not in a separate cohort born in 1966. The authors do not explain the discrepancy in findings between the cohorts. Brion et al. did not show any significant relationship between maternal prepregnancy BMI status and children’s verbal and nonverbal skills at 2 to 3 years of age, using data from 2 European cohorts. However, children born to overweight and obese mothers did exhibit lower IQ at the age of 8 years than offspring of normal weight mothers. A recent study using the National Longitudinal Survey of Youth in the United States revealed that maternal prepregnancy obesity was associated with reduced reading and mathematics test performance in offspring, in a cohort of 3421 children aged 5 to 7 years.

A recent systematic review highlighted the need for further study into the relationship between maternal obesity and neurodevelopmental outcomes in children, given the limitations of existing data. We investigated the relationship between maternal prepregnancy BMI and cognitive outcomes in children at 5 and 7 years of age by using data from the UK Millennium Cohort Study (MCS).

**METHODS**

**Millennium Cohort Study**

The MCS is a nationally representative prospective cohort study of 19,244 families across the United Kingdom. A random 2-stage sample of all infants born in 2000–2002 and residing in the United Kingdom at 9 months of age was drawn from the Department of Social Security child benefit registers. Infants who died within the first 9 to 10 months after birth are not included. Ethnically diverse and socioeconomically disadvantaged areas were oversampled to ensure adequate representation for subgroup analyses including the most vulnerable families. To exclude confounding from known risks of multiple births, we limited our analyses to singletons.

**Maternal BMI**

Mothers reported their prepregnancy weight and height in a structured interview conducted when their child was 9 months old. These were used to calculate BMI. Reported prepregnancy BMI of below 16 was considered to most likely be erroneous, given the difficulty of conceiving at this degree of underweight, and these cases were excluded from further analysis (\( n = 113 \)).

**Cognitive Assessments**

Cognitive assessments of the children at 5 and 7 years of age were performed by trained researchers. At age 5, this involved 3 subscales of the British Ability Scales, second edition (BAS-II); naming vocabulary, picture similarities, and pattern construction. These tests assess expressive language, nonverbal reasoning, and spatial visualization, respectively. BAS-II is a nationally standardized cognitive assessment battery for children. At age 7, assessment involved 2 subscales of BAS-II (word reading and pattern construction, assessing verbal ability, and spatial visualization, respectively) and a number skills test adapted from the National Foundation for Educational Research (NFER) Progress in Math tests. Inter-rater reliability statistics for the relevant subscales of BAS-II vary between 0.63 and 0.89 at age 5, and 0.88 and 0.98 at age 7.

To get a better understanding of the children’s general cognitive ability, and to simplify results, the 3 separate assessment scales at each age were combined into a single index by using principal components analysis (PCA). PCA is a method of data reduction, which is used to understand the underlying structure of a set of correlated variables, and to reduce a data set to a more manageable size while retaining as much of the original information as possible. The Centre for Longitudinal Studies uses this technique to analyze
cognitive outcomes within the MCS.\textsuperscript{20,21} PCA confirmed the presence of a general underlying factor (g) for the assessments at both 5 (g5) and 7 (g7) years of age. g5 accounted for 57% of the total variance among the 3 tests at age 5. The loading of each test on the underlying factor was as follows: naming vocabulary, 0.57; picture similarities, 0.57; and pattern construction, 0.59. g7 accounted for 63% of the total variance among the 3 tests at age 7. The loading of each test on the underlying factor was as follows: word reading, 0.60; pattern construction, 0.57; and number skills, 0.74. g scores were standardized to a mean of 100 and an SD of 15.

**Covariates**

A number of variables were identified as potential confounders before statistical analysis: child’s gender; child’s birth weight; child’s ethnicity (6 categories using UK Census classification); maternal age; maternal highest academic qualification (7 categories: none, General Certificate of Secondary Education [GCSE] grades D–G, O level/GCSE grades A–C, A/AS/S level, diploma in higher education, first degree, higher degree); father’s highest academic qualification (as for mothers with the addition of a “no father” category for lone parent families); family socioeconomic class (higher of mother or father using 8-class UK national statistics socioeconomic classification); Organization for Economic Cooperation and Development equivalized (OECD) family income; current maternal smoking status (yes/no); maternal diabetes during pregnancy (yes/no); and child’s standardized BMI at 5 and 7 years (age-specific z scores, calculated from measured height and weight by using the least mean square method and UK reference standards\textsuperscript{22–24}). Information regarding all confounding factors was obtained at the time of recruitment to the study when children were 9 months old, with the exception of children’s BMI, measured at 5 and 7 years of age.

**Cohort Size**

In total, 18,981 singleton children were eligible for follow-up at 5 and 7 years of age; 15,043 singletons participated in follow-up at age 5 (79.3%), of whom 11,025 provided complete data for cognitive assessments, maternal BMI, and all covariates (58.1% of those eligible for follow-up); and 13,681 singletons participated in follow-up at age 7 (72.1%), of whom 9,882 provided complete data (52.1%).

**Statistical Analysis**

Associations of maternal prepregnancy BMI status with the covariates and children’s cognitive scores (unadjusted for confounders) were explored by using 2-tailed t tests and z tests, with Bonferroni correction for multiple comparisons. Regression models were fitted to explore the relationship between maternal prepregnancy BMI (as a continuous variable) and children’s cognitive scores, controlling for all covariates described above. The MCS data are geographically clustered, coming from a total of 398 geographical areas known as “superwards,” and this was taken into account by fitting a random effect in all models (following guidance from the Centre for Longitudinal Studies).\textsuperscript{16} The mixed-effects regression models were fitted in R 2.11.1 by using the lme procedure.\textsuperscript{25} Several potential models were fitted: linear, quadratic, and cubic. Models were compared by using Akaike information criterion (AIC) penalized log likelihood.\textsuperscript{26} Separate models were fitted with the underlying general cognitive factors (g) and the individual cognitive test scores as the outcome. Two approaches to missing data were adopted: (1) complete cases analysis (listwise deletion) and (2) multiple imputation\textsuperscript{27} by using the Amelia II imputation package for R.\textsuperscript{28} All of the outcome variables and covariates were included in the multiple imputation procedure. Analyses using multiply imputed data are presented in this article. Analyses using complete cases are included in supplementary figures. Models are presented graphically with a separate effect for 16 narrow bands of maternal BMI (“narrow bands model”). To investigate predictors for participant attrition, a logistic regression model was fitted to identify factors associated with loss to follow-up between ages 5 and 7.

**RESULTS**

Descriptive characteristics of the study population are shown in Table 1. Mean maternal prepregnancy BMI was 23.7. Children born to obese mothers (BMI $\geq 30$) were, on average, born with a higher birth weight than children born to normal weight mothers (BMI 18.5–24.9), and exhibited a higher BMI at ages 5 and 7. Both obese and underweight (BMI 16–18.5) mothers had on average lower educational attainment, lower family socioeconomic group, and lower family income when compared with normal weight mothers. Children born to overweight (BMI 25–29.9), obese, and underweight mothers had lower mean cognitive performance scores than children of normal weight mothers (before adjusting for potential confounders) at 5 and 7 years of age.

Linear regression models provided the best fit to the data (as determined by the AIC penalized log likelihood). Parameter values and P values for all covariates in the models of children’s g at 5 and 7 years are given in Supplemental Table 2. Figure 1 shows the results of the final linear models, controlling for all of the covariates described above. At both age 5 ($\beta = -0.075, P = .0069$) and age 7 ($\beta = -0.17, P < .0001$), a significant
negative relationship was observed between maternal prepregnancy BMI and $g$. A 10-point increase in maternal prepregnancy BMI corresponds to a decrease in $g$7 of 1.5 ($\sim$1/10th of an SD).

The results of the analyses using complete case data (Supplemental Table 2) were similar to those using multiply imputed data (Fig 1), although the relationship between maternal prepregnancy BMI and $g$ did not reach statistical significance at age 5 ($\beta = -0.055, P = .066$).

Regression models of the individual cognitive test scores gave similar results to those of the $g$. At age 5, a significant negative relationship was observed between maternal prepregnancy BMI and children's spatial visualization; however, no relationship was seen between maternal BMI and children's expressive language and nonverbal reasoning (Fig 2). At age 7, a significant negative relationship was observed between maternal prepregnancy BMI and performance in each of the 3 separate cognitive assessments (verbal ability, spatial visualization, and number skills; Fig 3).

A number of factors were found to be significantly ($P < .05$) associated with loss to follow-up between ages 5 and 7; male gender, nonwhite ethnicity, lower cognitive scores at age 5 ($g_5$), lower family income, younger maternal age, lower maternal academic qualification, and maternal smoking. Most of these factors are associated with reduced cognitive performance at age 7 (Supplemental Table 2). Maternal BMI was not associated with loss to follow-up between ages 5 and 7.

**DISCUSSION**

**Summary of Findings**

By using data from the UK MCS, we found that maternal prepregnancy BMI is negatively associated with cognitive...
performance in children at 5 and 7 years of age. At age 5, this association is seen for children’s spatial visualization, but not for verbal expression and nonverbal reasoning. At age 7, the association is consistent across all cognitive assessments (verbal ability, spatial visualization, and number skills). These associations remain significant after adjusting for various socio-demographic confounders and for children’s BMI. Although the associations are statistically significant, the overall effect size is modest: a 10-point increase in maternal prepregnancy BMI is associated with a decrease in children’s general cognitive performance of \( \sim 1/10 \text{th of an SD at age 7} \).

**Comparison With Other Studies**

Few published studies investigate the relationship between maternal BMI and cognitive performance in children.\(^{11-14}\) Direct comparison with the studies by Neggers et al.\(^{11}\) and Heikura et al.\(^{12}\) is difficult because of differences in cognitive measures assessed and in the sample population of children. However, both studies suggest that there may be a negative relationship between maternal prepregnancy BMI and children’s cognitive outcomes.

A more direct comparison is possible with the studies by Brion et al.\(^{13}\) and Tanda et al.\(^{14}\) Tanda et al.\(^{14}\) report similar findings to our study, with lower performance in reading and mathematics (assessed by using Peabody Individual Achievement Tests) seen in 5- to 7-year-old children born to mothers with prepregnancy obesity, when compared with offspring of normal weight mothers.\(^{14}\) These associations remained significant after controlling for multiple socio-demographic factors, as well as maternal cognitive ability. The magnitude of the effect is comparable with our findings; maternal obesity was associated with a reduction in reading scores of 0.23 of an SD and in mathematics scores of 0.16 of an SD.

Brion et al.\(^{13}\) reported that maternal prepregnancy overweight/obesity (BMI \( \geq 25 \)) was associated with lower IQ scores in 8-year-old children but was not associated with cognitive performance at 2 to 3 years of age, after controlling for various socio-demographic factors. One possible explanation for these findings is that maternal obesity causes subtle effects on children’s cognitive development, which may become more apparent as children reach a certain developmental age. In our study, we found a stronger relationship between maternal BMI and children’s cognitive outcomes at 7 years of age than at 5 years of age. However, it is important to note that different cognitive assessment subscales were used at age 5 and 7 in the MCS, and this may contribute to the differences in strength of the associations we observed. Brion et al.\(^{13}\) handled maternal BMI as a categorical variable for analysis, and combined overweight and obese categories. They did not
analyze children of obese mothers (BMI $\geq 30$) as a separate group, and this may have prevented them from identifying significant differences in cognitive performance in these children. Furthermore, their cognitive assessments at 2 to 3 years of age relied upon parental reports via questionnaires, as opposed to direct assessment of the children. This may have resulted in parental response bias. A further limitation of Brion et al's study is significant loss to follow-up, resulting in considerably smaller sample sizes (between 2046 and 4873 for the various cognitive assessments) than in our study.

**Potential Mechanisms**

Obesity is recognized to be a risk factor for cognitive decline and dementia in older age. It is thought that altered metabolic and adipokine signaling in obesity may have direct adverse effects on the CNS, and studies have identified triglycerides, free fatty acids, and leptin as possible mediators of obesity-related CNS dysfunction. There is evidence that maternal obesity affects offspring metabolic function via intrauterine effects. Bio-active agents (including cytokines, peptides, and hormones) are transferred from mother to fetus via the placenta, and in vivo studies suggest that some of these mediators can influence fetal CNS development. Therefore, it is plausible that the suboptimal intrauterine environment in obesity may have direct effects on the developing fetal brain.

Recent animal studies support this hypothesis. Various physiologic changes were demonstrated in the hippocampus of offspring by using a diet-induced maternal obesity model in rodents. These include increased markers of oxidative stress, differences in neuronal proliferation and differentiation, increased susceptibility to inflammation, and reduced brain-derived neurotrophic factor production. Brain-derived neurotrophic factor has been shown to support neuronal growth and differentiation, and plays an important role in hippocampus dependent cognitive functions including long-term memory. Furthermore, the study offspring exhibited differences in performance in maze tests, which assess spatial learning, compared with controls.

**Strengths and Limitations**

Our study has a number of key strengths. We use data from a large and contemporary population-based UK cohort, with sufficient sample size to investigate the relationship between maternal BMI and children's cognitive performance. Data are available for a variety of important potential confounding factors, including socio-demographic factors, children's BMI, children's birth weight, maternal smoking, and diabetes. In contrast with previous studies, all of the cognitive assessments involve direct administration of standardized tests by trained interviewers.

Study limitations include a significant loss to follow-up and missing data for some covariates. However, the overall results are similar when analyses are performed by using listwise deletion and multiple imputation, suggesting that missing data are not significantly influencing our findings. Direct measurement of maternal prepregnancy BMI is not available in the MCS, with maternal prepregnancy weight retrospectively reported when the children were aged 9 months. This introduces a potential for inaccuracy.

In common with other studies, we are unable to control for a number of potentially relevant confounding factors. There is no direct assessment of parental cognitive ability in the MCS; therefore, we are unable to directly control for parental IQ. Maternal nutrition and exercise during pregnancy could potentially confound the relationship between maternal obesity and children's cognition. Obesity is likely to be linked with poor nutrition, and there is evidence that nutritional status influences cognitive development. Physical exercise has been associated with cognitive function in children and adults, and recent animal studies suggest that maternal exercise during pregnancy may have effects on the CNS in offspring. However, detailed data...
Regarding nutrition and exercise during pregnancy were not collected in the MCS. Although we adjusted for family socioeconomic class and family income in our analyses, it remains possible that residual confounding by socioeconomic status may be present.

**Conclusions**

By using data from a large, contemporary national birth cohort, we found that maternal prepregnancy BMI is negatively associated with children's cognitive performance, even after adjusting for various socio-demographic confounders and children's BMI. The relationship appears to become stronger as the children get older. Although our study design does not permit any inferences of causation, a suboptimal intrauterine environment in obesity may have direct effects on the developing fetal brain. Our study supports current guidance from the National Institute for Health and Clinical Excellence advising women to achieve a healthy weight before conception. Further studies are required to investigate whether these findings persist into later childhood, and explore possible biological mechanisms by which maternal obesity may influence fetal brain development.

**References**


FRESH FROM THE RANCH: Recently, I had dinner with my daughter at a local restaurant. Of my four children, she has by far and away the most interesting diet. She had difficulty deciding between the snails and mussels, but eventually settled on the snails. As we munched on the tasty mollusks, she wondered out loud where the restaurant had gotten the snails. After all, we have snails in the garden and we do not eat them (and consider them pests). According to an article in The New York Times (Dining & Wine: October 16, 2012), raising snails is quite the specialized profession. The most famous US snail rancher lives just north of Bakersfield, CA. Prized by top chefs around the US, she raises garden snails (Helix aspersa) that have a fresh flavor, a hint of basil, and no grit. How she manages to produce such delicious and savory snails is a bit mysterious. She reports that it took years—if not decades—to fully understand how to cultivate the animal. For example, snails can escape from screen-secured hutches by banding together and pushing the screen. Too many snails together in a small space leads to massive die offs. They seem to prefer eating fresh lettuce and watermelon and are quite noisy eaters. They also have a lot of sex. Snails are hermaphrodites, meaning they have both male and female sex organs. Snails become sexually mature by one year of life (terrestrial snails live five to seven years). Once mature, they engage in a mating ritual that lasts two to 12 hours, involves shooting each other with a love dart, and culminates with each snail impregnating the other. Snails lay eggs which can be eaten as caviar (although at this time few people do this). So while I regaled my daughter with stories of snail ranching and ideas for a side business, I finally had to confess that the snails were most likely the canned variety from France. Still, slathered in butter and garlic, they were quite delicious.

Noted by WVR, MD
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