Intrauterine Effects of Maternal Prepregnancy Overweight on Child Cognition and Behavior in 2 Cohorts

WHAT'S KNOWN ON THIS SUBJECT: Maternal prepregnancy overweight may be associated with child behavioral problems, such as inattention-hyperactivity, and lower intellectual function in offspring. However, few studies have explored this issue, and it is unclear whether associations, if replicated, reflect biological intrauterine mechanisms.

WHAT THIS STUDY ADDS: In this study, maternal prepregnancy overweight was not consistently associated with child behavioral problems or measures of cognitive abilities. We found no strong evidence of biological intrauterine mechanisms for these associations.

abstract

FREE

OBJECTIVE: Greater maternal prepregnancy adiposity has been associated with behavioral problems, such as attention-deficit/hyperactivity disorder, and lower intellectual function in offspring. However, few studies of humans have explored this, and it is unclear if intrauterine mechanisms or confounding factors drive these associations.

PATIENTS AND METHODS: Parental adiposity and offspring verbal skills, nonverbal skills, and behavioral problems were assessed in the British Avon Longitudinal Study of Parents and Children ($N = \sim 5000$) and Dutch Generation R ($N = \sim 2500$) cohorts. We aimed to determine the plausibility of intrauterine effects by (1) adjusting for multiple confounders, (2) comparing associations between maternal and paternal overweight with offspring cognition/behaviors, and (3) searching for cross-cohort consistency.

RESULTS: Maternal prepregnancy overweight was associated with reduced child verbal skills (unadjusted). However, after adjusting for confounders, this result was not consistently observed in both cohorts. Maternal overweight was also associated with child total behavior problems and externalizing problems even after adjusting for confounders. However, this was observed in Generation R only and was not replicated in the British Avon Longitudinal Study of Parents and Children. No associations of maternal overweight with child attention problems, emotional/internalizing problems, or nonverbal skills were observed in either cohort. Paternal overweight was not associated with any of the child outcomes but was also less strongly related to potential confounding factors than was maternal overweight.

CONCLUSIONS: Overall, we found little consistent evidence of intrauterine effects of maternal prepregnancy overweight on child cognition and behavior. Some associations initially observed were not consistently replicated across cohorts or robust to adjustment for confounding factors and, thus, are likely to reflect confounding by socioeconomic or postnatal factors. *Pediatrics* 2011;127:e202–e211

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KEY WORDS

ALSPAC, behavioral problems, cognitive function, cohort, Generation R, intrauterine exposure, obesity, pregnancy

ABBREVIATIONS

ADHD—attention-deficit/hyperactivity disorder
ALSPAC—Avon Longitudinal Study of Parents and Children
SDQ—Strengths and Difficulties Questionnaire
CBCL—Child Behavior Checklist
PARCA—Parent Report of Children's Abilities
OR—odds ratio
CI—confidence interval

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FINANCIAL DISCLOSURE: *Dr Verhulst is a director at the Department of Child and Adolescent Psychiatry, Erasmus University Medical Center-Sophia Children's Hospital, which publishes the Dutch translations of the Achenbach System of Empirically Based Assessment and from which he receives remuneration; the other authors have indicated they have no financial relationships relevant to this article to disclose.*

There is some evidence from human and animal studies that maternal overweight and obesity prepregnancy is associated with reduced offspring cognitive abilities and greater risk of behavioral problems. A recent study of ~12 000 children from 3 Nordic cohorts found an association between maternal prepregnancy overweight or obesity and core symptoms of attention-deficit/hyperactivity disorder (ADHD) in school-aged children.[1] This association was replicated and extended in a follow-up study of ~1700 5-year-old Finnish children that revealed associations with child attention and emotional problems.[2] For cognitive development, in 2 Finnish cohorts initiated in 1966 and 1986 and studied concurrently, maternal prepregnancy obesity was associated with increased risk of mild intellectual disability in offspring. However, this was only found in the latter, more contemporary cohort,[3] which suggests that an association may only be apparent in more contemporary cohorts who are experiencing the obesity epidemic. There is also evidence from animal studies that maternal diet-induced obesity prepregnancy results in alterations in offspring brain development.[4]

Few replication studies exist in which these reported associations of maternal prepregnancy overweight with child cognitive function and behavioral problems are explored. In addition, it is not clear if associations involve intrauterine mechanisms or reflect confounding by familial socioeconomic position or other postnatal risk factors. The aim of this study was to investigate maternal prepregnancy overweight and offspring cognition and behavior in 2 pregnancy cohorts: the Avon Longitudinal Study of Parents and Children (ALSPAC), based in Britain, and the Generation R cohort, based in the Netherlands. We aimed to determine the plausibility of intrauterine effects by adjustment for multiple indicators of socioeconomic position, by comparing associations between maternal and paternal BMI with offspring cognition and behaviors and by searching for cross-cohort consistency. The rationale for comparing maternal to paternal associations is based on the assumption that maternal exposures in pregnancy that directly affect fetal development will produce a considerably stronger association than paternal exposures at the same time, which would not generally be expected to affect fetal development.[5] Associations driven by shared familial, social, genetic, and environmental factors will be likely to produce similar maternal-paternal associations. This approach is validated by markedly discordant associations of maternal and paternal smoking in pregnancy with offspring birth weight, which is known to be directly affected by maternal prenatal smoking.[5]

METHODS

Participants

ALSPAC

ALSPAC is a geographically based prospective cohort study in which the health and development of children are investigated.[6] Pregnant women who resided in 3 health districts in the southwest of England with an expected date of delivery between April 1, 1991, and December 31, 1992, were eligible to enroll. There were 14 541 pregnant women recruited, and 13 678 had a live-born, singleton child. For this study, we excluded parents and children of multiple births. Data on both maternal and paternal BMI are available for 7641 mother-partner pairs. Data on nonverbal skills at 8 years are available in 6353 children. Data on verbal skills were assessed in 9731 (sentence length) and 9901 (word production) children at 38 months, and on behavioral problems in 9314 children at 47 months. Analyses of nonverbal skills, sentence length, word production, and behavioral problems were conducted on 3221, 4658, 4712, and 4873 children, respectively, with complete data on both maternal and paternal BMI, all confounders and child outcomes. Ethical approval of the study was obtained from the ALSPAC Law and Ethics Committee (IRB00003312) and 3 local research ethics committees.

Generation R

The Generation R study is a population-based pregnancy cohort.[7,8] Pregnant women who resided in the city of Rotterdam, Netherlands, with delivery dates of April 2002 to January 2006 were approached by their midwives to participate. The parents of a total of 7295 children gave consent for the postnatal period. Data on maternal and paternal BMI are available in 4142 mother-partner pairs. Data on nonverbal skills at 30 months are available for 4339 children, on verbal skills (word production, sentence length) at 30 months in 4674 children, and on behavioral problems at 36 months in 3922 children. Analyses of nonverbal skills, sentence length, word production, and behavioral problems were conducted on 2258, 2398, 2385, and 2046 children, respectively, with complete data on both maternal and paternal BMI, all confounders and child outcomes. The cohort study protocol was approved by the Medical Ethical Review Board of the Erasmus Medical Center, Rotterdam. All parents of participating children gave written informed consent.

Maternal and Paternal Overweight

ALSPAC

At initial enrollment, mothers provided their height and prepregnancy weight, from which prepregnancy BMI was calculated (kg/m^2). Paternal BMI was derived from self-reported height and weight from a questionnaire sent to partners at 12weeks' gestation. Mater-

nal weight was also measured at the first antenatal clinic visit (median gestational age: 10 completed weeks [interquartile range: 8–14]). Because measured gestational weight and self-reported prepregnancy weight were highly correlated ($r = 0.97$; $P < .0001$), self-reported prepregnancy weight was used because of the higher numbers available. Maternal and paternal BMI were grouped according to the World Health Organization categories for underweight (<18.50), normal (18.50–24.99), overweight (≥25.00), and obese (≥30.00). These were used to generate 2 binary variables: overweight/obese versus normal BMI, and obese versus normal BMI.

Generation R

Maternal prepregnancy weight, analyzed in this study, was obtained from a patient-completed questionnaire at enrollment. In addition, weight (kg) and height (cm) were measured at enrollment, while the patients were wearing light clothing and no shoes, and were used to calculate maternal BMI (kg/m2). In this study sample, 47% and 71% of all women were enrolled before a gestational age of 14 and 18 weeks, respectively. Correlation of prepregnancy weight obtained from a patient-completed questionnaire and weight measured at enrollment was 0.96 ($P < .001$). Paternal BMI was derived from self-reported height and weight from a questionnaire sent to partners at 12 weeks' gestation. Maternal and paternal BMI were grouped into overweight, obese, and normal BMI categories as described above for ALSPAC.

Child Cognition and Behavior

ALSPAC

Vocabulary and word combination levels were assessed by using questions adapted from the MacArthur Toddler Communication questionnaire.[9] These were included in maternal questionnaires sent at 38 months postnatal. Vocabulary scores were based on 123 items and word combination scores were derived from a list of 2- and 3-word phrases. Nonverbal skills were assessed by using the faces subtest of the Diagnostic Analysis of Nonverbal Accuracy test (DANVA),[10] which measures recognition of emotion, administered at the 8-year clinic. Child behavioral problems were assessed at 4 years by maternal report by using the Strengths and Difficulties Questionnaire (SDQ).[11] The SDQ comprises 25 questions that generate scores for inattention-hyperactivity, emotional symptoms, peer problems, conduct problems, and prosocial behavior, as well as total behavioral problems. Scores analyzed and used for comparison with Generation R's Child Behavior Checklist (CBCL) measures are based on those previously compared by Goodman[12] (SDQ inattention-hyperactivity versus CBCL attention problems; SDQ emotional problems versus CBCL internalizing problems; SDQ conduct problems versus CBCL externalizing problems; total behavioral problems from both instruments). Psychologist-assessed general intelligence also was explored on the basis of a short form (using alternate items) of the Wechsler Intelligence Scale for Children II (United Kingdom[13]) at 8 years. Teacher-rated behavioral problems at 8 years also were assessed by using the SDQ.

Generation R

Verbal skills at 30 months was assessed by using parent report on a Dutch translation of the Language Development Survey.[14] The survey contains a 310-word vocabulary checklist and also asks the parent to write down 5 of their child's best sentences. Nonverbal skills were assessed by using the Dutch version of the Parent Report of Children's Abilities (PARCA)[15] at 30 months. PARCA comprises parent-administered subtests for (1) matching-to-sample, (2) block building, and (3) imitation, and parental report of quantitative skills, spatial abilities, symbolic play, planning and organizing, adaptive behaviors, and memory. An overall PARCA score was derived from the sum of the parent-administered and parent-reported sections.

Maternal-reported child behavioral problems were assessed by using the CBCL for toddlers (1.5-5 [18 months to 5 years of age])[16] at 36 months. The CBCL contains 99 items, each of which is scored on a 3-point scale (0: not true; 1: somewhat or sometimes true; 2: very true or often true) on the basis of the child's behavior during the preceding 2 months. These result in a total problems score, plus various subscales of behavior, of which attention, internalizing problems and externalizing problems are analyzed in this study.

Confounders and Mediators

ALSPAC

In a questionnaire sent at 32 weeks' gestation, mothers recorded their own and their partner's highest education level. Mothers also recorded their occupation and their partner's occupation, which were used to allocate them to social categories according to the 1991 Office and Populations Censuses and Surveys standard.[17] A single variable (head of household) was derived from the highest social class of either parent. Family income per week was assessed at 47 months after delivery. Maternal smoking in each of the 3 trimesters was recorded from questionnaires sent at 18 and 32 weeks' gestation. Smoking at any time during pregnancy was recorded in this study. Breastfeeding was assessed repeatedly during infancy and was categorized as never breastfed, partially breastfed, and exclusively breastfed, as reported at 2 months of age. Infant

size was calculated by converting weight and height, from health visitor records (at median age 3.7 years), into age-specific weight-for-height *z* scores.

Generation R

Postal questionnaires were used to obtain information on educational level and family income. Maternal smoking during pregnancy was assessed by using 3 prenatal questionnaires. Maternal smoking in the present study was defined as smoking during any stage of pregnancy. Breastfeeding (yes/no) at 2 months of age was assessed by postal questionnaire at 2 and 6 months of age. Infant size at 30 and 36 months was assessed by using data from child health care centers, and variables for weight-for-height *z* scores were created.

Statistical Analysis

Confounder associations of maternal overweight, paternal overweight, and child outcomes with indicators of socioeconomic position were explored by using logistic regression (for parental overweight) and ordinal logistic regression (quintiles for child outcomes), with dichotomized indicators of socioeconomic position. Associations of maternal and paternal overweight with child verbal skills, nonverbal skills, and behavioral problems were explored with child outcome scores divided into quintiles and analyzed by using ordinal logistic regression with the following statistical models: (1) maternal and paternal overweight individual models unadjusted for confounders; (2) maternal and paternal overweight individual models adjusted for confounders; (3) maternal and paternal overweight mutually adjusted without confounders; and (4) maternal and paternal overweight mutually adjusted and with confounder-adjustment. When persisting associations were observed, an additional fifth model was used to adjust for potential mediators (infant size, breastfeeding). Complete case analyses were conducted for all models; however, to address the missing-data issues, multivariate multiple imputation was conducted (see Supplemental Table 8, Supplemental Table 9, and Supplemental Table 10). All analyses were performed by using Stata 10 (Stata Corp, College Station, TX).

RESULTS

Sample characteristics for each cohort are displayed in Table 1. Associations of socioeconomic position with parental overweight and offspring outcomes are displayed in Tables 2 and 3. Lower maternal and paternal education, income, and social class were associated with greater odds of maternal and paternal prepregnancy overweight and obesity. Maternal overweight was more strongly associated with socioeconomic factors than was paternal overweight. Lower socioeconomic position was associated with reduced sentence length scores and total behavioral problems, but was not associated with nonverbal skills or word production scores.

In unadjusted models, maternal prepregnancy overweight was consistently (in both cohorts) associated with sentence formation (Table 4). However, after confounders were adjusted for, there was little persisting evidence in Generation R; in ALSPAC, although the association persisted, it was substantially attenuated compared with the unadjusted association. The persisting ALSPAC association between maternal prepregnancy overweight and offspring sentence length was not altered by additional adjustment for infant size (odds ratio [OR]: 0.84 [95% confidence interval (CI): 0.72–0.98]; $P = .02$, adjusted for weight-for-height age-specific infant *z* score, paternal overweight, and confounders), but was partially accounted for by breastfeeding (OR: 0.90 [95% CI: 0.79–1.03]; $P = .1$). There were no associations (unadjusted or adjusted) observed with nonverbal skills or word production in either cohort.

Maternal overweight was associated with increased child total behavioral problems in Generation R, both unadjusted and adjusted for confounders (Table 5). However, no such associations were observed in ALSPAC in either model. For the behavioral subscales in Generation R (attention, internalizing, externalizing), associations persisted with child externalizing problems when confounders were adjusted for, but with no strong evidence of associations with child attention or internalizing problems. No associations were observed with the equivalent behavioral subscales in ALSPAC. The observed association in Generation R with child total behavioral problems was not substantially altered by additional adjustment for infant size (OR: 1.21 [95% CI: 0.97–1.50]; $P = .09$). The confounder-adjusted association also persisted after additional adjustment for breastfeeding (OR: 1.22 [95% CI: 0.97–1.50]; $P = .05$).

Maternal overweight and obesity were strongly associated with greater psychologist-assessed child general intelligence (IQ), even after adjusting for confounders (Table 6). For teacher-reported behavioral problems, results were not materially different to those based on maternal-report, although with slightly stronger effect sizes for unadjusted associations (Table 7). None of the associations were substantially altered after adjustment for child BMI (data not shown).

Paternal overweight was not associated with any of the child outcomes in most models. Maternal and paternal overweight associations with child outcomes were similar to one another, ex-

TABLE 1 Sample Characteristics in the ALSPAC and Generation R Cohorts

Characteristic	*n*	Median	Interquartile Range	Category	*n*	%
Child characteristics						
ALSPAC						
Child nonverbal score (DANVA)	3221	4	3–6	—	—	—
Child sentence length (MacArthur)	4658	24	21–26	—	—	—
Child word production (MacArthur)	4712	241	229–246	—	—	—
Child behavioral problems (SDQ)						
Total	4873	8	5–11	—	—	—
Hyperactivity	4873	4	2–5	—	—	—
Emotional	4873	1	0–2	—	—	—
Conduct problems	4873	2	1–3	—	—	—
Generation R						
Child nonverbal score (PARCA)	3187	47.5	43.8–51.0	—	—	—
Child sentence length (LDS)	2398	4.6	2.6–6.2	—	—	—
Child word production (LDS)	2385	259	222–283	—	—	—
Child behavioral problems (CBCL)						
Total problems	2046	16	9–26	—	—	—
Attention problems	2483	1	0–2	—	—	—
Internalizing	2046	3	1–6	—	—	—
Externalizing	2045	7	3–12	—	—	—
Parental characteristics						
ALSPAC						
Maternal overweight/obesity	4886	—	—	Yes	1040	21.3
				No	3846	78.7
Paternal overweight/obesity	4886	—	—	Yes	2300	47.1
				No	2586	52.9
Maternal education[a]	4886	—	—	CSE/none	573	11.7
				Vocational	401	8.2
				O level	1746	35.7
				A level	1283	26.3
				Degree	883	18.1
Paternal education[a]	4886	—	—	CSE/none	796	16.3
				Vocational	373	7.6
				O level	1102	22.6
				A level	1451	29.7
				Degree	1164	23.8
Family weekly income (net)	4886	—	—	<£100	204	4.2
				£100–199	576	11.8
				£200–299	1286	26.3
				£300–399	1185	24.3
				>£400	1635	33.5
Family social class[b]	4886	—	—	IV/V	174	3.6
				IIIM	453	9.3
				IIINM	1195	24.5
				II	2221	45.5
				I	843	17.3
Maternal prenatal smoking	4886	—	—	Yes	850	17.4
				No	4036	82.6
Breastfeeding	4792	—	—	Yes	689	14.4
				No	4103	85.6
Generation R						
Maternal overweight/obesity	3187	—	—	Yes	704	22.1
				No	2483	77.9
Paternal overweight/obesity	3187	—	—	Yes	1543	48.4
				No	1644	51.6
Maternal education[c]	3187	—	—	Primary/none	128	4.0
				Secondary 1	287	9.0
				Secondary 2	856	26.9
				Higher 1	814	25.5
				Higher 2	1102	34.6

TABLE 1 Continued

Characteristic	*n*	Median	Interquartile Range	Category	*n*	%
Paternal education[c]	3187	—	—	Primary/none	176	5.5
				Secondary 1	374	11.7
				Secondary 2	789	24.8
				Higher 1	653	20.5
				Higher 2	1195	37.5
Family monthly income (net)	3187	—	—	€900 or less	149	4.7
				€900–1400	230	7.2
				€1400–1800	211	6.6
				€1800–2200	349	10.9
				>€2200	2248	70.5
Maternal prenatal smoking (any)	3187	—	—	Yes	704	22.1
				No	2483	77.9
Breastfeeding	2967	—	—	Yes	2054	69.2
				No	913	30.8

DANVA indicates Diagnostic Analysis of Nonverbal Accuracy test; LDS, Language Development Survey; CSE, Certificate of Secondary Education.

[a] 0 level, national school exams at 16 years; A level, national school exams at 18 years.

[b] IV/V, partly skilled occupations/unskilled occupations; IIIM, manual, skilled occupations; IIINM, nonmanual, skilled occupations; II, managerial and technical occupations; I, professional occupations.

[c] Secondary 1, lower vocational, intermediate general school, or 3 years general secondary school; Secondary 2, >3 years general school, secondary school, intermediate vocational, or first year higher vocational; Higher 1, higher vocational or bachelor's degree; Higher 2, higher academic education or PhD.

TABLE 2 Associations of Indicators of Potential Confounders and Mediators With Maternal and Paternal Prepregnancy Overweight

	Maternal Overweight/Obesity			Paternal Overweight/Obesity		
	OR	95% CI	*P*	OR	95% CI	*P*
ALSPAC[a]						
Maternal education nondegree (vs degree)	1.98	1.61–2.44	<.001	1.41	1.21–1.63	<.001
Paternal education nondegree (vs degree)	1.77	1.48–2.12	<.001	1.43	1.26–1.64	<.001
Income lowest quartile (vs higher)	1.47	1.23–1.75	<.001	0.92	0.79–1.08	.3
Social class manual (vs nonmanual)	1.74	1.45–2.10	<.001	1.12	0.95–1.33	.2
Maternal smoking yes (vs no)	1.22	1.02–1.45	.03	0.93	0.80–1.08	.4
Breastfeeding yes (vs no)	0.65	0.54–0.78	<.001	0.73	0.63–0.86	<.001
Generation R[b]						
Maternal education nondegree (vs degree)	1.87	1.55–2.26	<.001	1.21	1.05–1.40	.01
Paternal education nondegree (vs degree)	1.81	1.50–2.17	<.001	1.31	1.13–1.51	<.001
Income lower quartile (vs higher)	1.64	1.33–2.04	<.001	0.96	0.79–1.16	.7
Maternal smoking yes (vs no)	1.22	1.00–1.49	.04	1.03	0.87–1.22	.7
Breastfeeding yes (vs no)	0.58	0.49–0.70	<.001	0.82	0.70–0.96	.01

[a] $n = 4886$ with data on parental size and all indicators socioeconomic position.

[b] $n = 3187$ with data on parental size and all indicators of socioeconomic position.

cept for stronger maternal associations observed with child sentence length (ALSPAC), behavior problems (Generation R), and psychologist-administered IQ (ALSPAC). Additional adjustment of maternal overweight associations for paternal overweight did not materially alter observed associations.

Results of the main analyses were repeated by using imputed data sets for missing data and are provided in Supplemental Table 8, Supplemental Table 9, and Supplemental Table 10 (Generation R, $N = 5420$; ALSPAC, $N = 10\,874$). These results were similar to those presented here by using samples that excludes participants with any missing data. Specifically, results for ALSPAC were essentially the same, although effect sizes in fully adjusted analyses in Generation R were somewhat weaker than those presented here, meaning that they were more consistent with the overall null findings in ALSPAC.

DISCUSSION

On the basis of 2 European pregnancy cohorts, ALSPAC (United Kingdom) and Generation R (Netherlands), we find little consistent evidence of intrauterine effects of maternal prepregnancy overweight on offspring cognitive development and behavioral problems. Of a wide range of measures explored (nonverbal skills, verbal skills, total behavioral problems, attention-hyperactivity problems, emotional-internalizing problems, and conduct-externalizing problems), there were no associations with maternal overweight that persisted for both cohorts after adjustment for confounders.

In Generation R, maternal overweight was associated with greater child total

TABLE 3 Associations of Potential Confounders and Mediators With Child Cognition and Behavior: Ordinal OR for Being in a Higher Quintile

	Nonverbal Skills			Sentence Length			Word Production			Behavioral Problems		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
ALSPAC[a]												
Maternal education nondegree (vs degree)	1.08	0.93–1.25	.3	0.51	0.44–0.58	<.001	0.90	0.79–1.03	.1	1.50	1.31–1.71	<.001
Paternal education nondegree (vs degree)	1.11	0.97–1.28	.1	0.52	0.46–0.59	<.001	0.85	0.76–0.96	.007	1.46	1.30–1.64	<.001
Income lowest quartile (vs rest)	1.03	0.86–1.24	.7	0.65	0.57–0.75	<.001	0.94	0.81–1.08	.4	1.88	1.64–2.16	<.001
Social class manual (vs nonmanual)	1.21	0.99–1.47	.06	0.51	0.43–0.59	<.001	0.92	0.78–1.07	.3	1.59	1.37–1.84	<.001
Maternal smoking yes (vs no)	0.96	0.81–1.15	.7	0.84	0.73–0.96	.01	0.88	0.77–1.01	.07	1.61	1.41–1.84	<.001
Breastfeeding yes (vs no)	0.81	0.67–0.97	.02	1.70	1.47–1.97	<.001	1.25	1.08–1.45	.003	0.72	0.62–0.83	<.001
Generation R[b]												
Maternal education nondegree (vs degree)	1.07	0.92–1.24	.4	0.67	0.57–0.77	<.001	0.91	0.79–1.05	.2	1.29	1.10–1.51	.001
Paternal education nondegree (vs degree)	1.04	0.90–1.21	.6	0.73	0.64–0.85	<.001	0.83	0.72–0.96	.01	1.29	1.10–1.51	.001
Income lowest quartile (vs rest)	1.12	0.90–1.41	.3	0.43	0.35–0.54	<.001	0.65	0.51–0.82	<.001	2.05	1.60–2.62	<.001
Maternal smoking yes (vs no)	1.09	0.90–1.31	.4	0.74	0.62–0.88	.001	0.90	0.75–1.08	.3	1.33	1.10–1.61	.003
Breastfeeding yes (vs no)	1.11	0.94–1.32	.2	1.44	1.23–1.69	<.001	1.32	1.12–1.55	.001	0.81	0.68–0.96	.02

[a] *n* = 3221, nonverbal; 4658, sentence length; 4712, word production; 4873, behavioral problems.
[b] *n* = 2258, nonverbal; 2398, sentence length; 2385, word production; 2046, behavioral problems.

TABLE 4 Associations of Parental Prepregnancy Overweight and Ordinal OR for Offspring Cognition: Ordinal OR for Being in a Higher Quintile

	Individual Maternal-Paternal Models						Mutually Adjusted Maternal-Paternal Models					
	Model 1[a]			Model 2[b]			Model 1[a]			Model 2[b]		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Nonverbal skills												
ALSPAC[c]												
Maternal overweight	0.99	0.85–1.16	.9	0.97	0.83–1.14	.7	1.00	0.85–1.16	.97	0.98	0.84–1.14	.8
Paternal overweight	0.98	0.87–1.11	.7	0.96	0.85–1.09	.6	0.98	0.87–1.11	.7	0.97	0.85–1.09	.6
Generation R[d]												
Maternal overweight	1.08	0.91–1.30	.4	1.08	0.90–1.30	.4	1.08	0.90–1.30	.4	1.08	0.90–1.30	.4
Paternal overweight	1.02	0.88–1.18	.8	1.02	0.88–1.18	.8	1.01	0.87–1.17	0.9	1.01	0.87–1.17	.9
Language—sentence length												
ALSPAC[c]												
Maternal overweight	0.77	0.68–0.87	<.001	0.88	0.78–1.00	.06	0.76	0.67–0.87	<0.001	0.88	0.77–1.00	.05
Paternal overweight	0.99	0.89–1.09	.8	1.04	0.94–1.16	.4	1.01	0.91–1.12	0.9	1.05	0.95–1.17	.3
Generation R[d]												
Maternal overweight	0.79	0.67–0.94	.007	0.88	0.74–1.05	.2	0.81	0.68–0.96	0.02	0.90	0.75–1.07	.2
Paternal overweight	0.85	0.74–0.98	.02	0.88	0.76–1.02	.09	0.87	0.75–1.00	0.05	0.90	0.77–1.03	.1
Language—word production												
ALSPAC[c]												
Maternal overweight	0.91	0.81–1.04	.2	0.95	0.84–1.08	.5	0.91	0.80–1.03	0.1	0.94	0.83–1.07	.4
Paternal overweight	1.07	0.97–1.19	.2	1.09	0.98–1.21	.1	1.08	0.98–1.20	0.1	1.09	0.99–1.21	.09
Generation R[d]												
Maternal overweight	0.87	0.73–1.03	.1	0.91	0.76–1.08	.3	0.87	0.73–1.04	0.1	0.91	0.76–1.09	.3
Paternal overweight	0.97	0.84–1.12	.7	0.99	0.85–1.14	.9	0.99	0.85–1.14	0.8	1.00	0.86–1.15	.97

Maternal/paternal overweight or obese versus normal BMI.
[a] Unadjusted.
[b] Adjusted for maternal education, paternal education, family income, social class (ALSPAC only), and maternal smoking.
[c] Diagnostic Analysis of Nonverbal Accuracy test at 8 years (*n* = 3221), MacArthur at 38 months (sentence length, *n* = 4658; word production, *n* = 4712).
[d] PARCA at 30 months (*n* = 2258), Language Development Survey at 30 months (sentence length, *n* = 2398; word production, *n* = 2385).

behavioral problems and externalizing behavior. However, statistical evidence for these associations was modest after socioeconomic factors were adjusted for (*P* = .05 for both), replication was not observed in ALSPAC, and these associations attenuated to the null in analyses using imputed data sets for missing data. Thus, it is unlikely that the observed associations are because of intrauterine mechanisms and are likely to reflect residual

TABLE 5 Associations of Parental Prepregnancy Overweight and Ordinal OR for Offspring Behavioral Problems: Ordinal OR for Being in a Higher Quintile

	Individual Maternal-Paternal Models						Mutually Adjusted Maternal-Paternal Models					
	Model 1[a]			Model 2[b]			Model 1[a]			Model 2[b]		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Total behavioral problems, quintiles												
ALSPAC[c]												
Maternal overweight	1.11	0.98–1.25	.1	1.01	0.89–1.14	.9	1.11	0.99–1.26	.08	1.01	0.90–1.15	.8
Paternal overweight	0.96	0.87–1.07	.5	0.94	0.85–1.04	.3	0.96	0.86–1.06	.4	0.94	0.85–1.04	.3
Generation R[d]												
Maternal overweight	1.29	1.07–1.56	.008	1.21	1.00–1.47	.05	1.29	1.07–1.57	.008	1.21	1.00–1.47	.05
Paternal overweight	1.01	0.86–1.17	.9	1.01	0.86–1.18	.9	0.98	0.84–1.14	.8	0.99	0.85–1.16	.9
Attention/hyperactivity problems, quintiles												
ALSPAC[c]												
Maternal overweight	1.04	0.92–1.18	.5	0.92	0.82–1.05	.2	1.04	0.92–1.17	.6	0.93	0.82–1.05	.2
Paternal overweight	1.02	0.92–1.13	.7	0.98	0.88–1.08	.6	1.02	0.92–1.13	.7	0.98	0.89–1.09	.7
Generation R[d]												
Maternal overweight	1.14	0.96–1.35	.1	1.04	0.88–1.25	.6	1.15	0.97–1.37	.1	1.06	0.89–1.27	.5
Paternal overweight	0.95	0.82–1.10	.5	0.92	0.80–1.06	.3	0.94	0.81–1.08	.4	0.92	0.79–1.06	.2
Emotional/internalizing problems, quintiles												
ALSPAC[c]												
Maternal overweight	1.00	0.89–1.13	.96	0.99	0.88–1.12	.9	1.01	0.90–1.15	.8	1.00	0.88–1.13	.99
Paternal overweight	0.93	0.84–1.03	.2	0.93	0.84–1.03	.2	0.93	0.84–1.03	.1	0.93	0.84–1.03	.2
Generation R[d]												
Maternal overweight	1.15	0.96–1.39	.1	1.12	0.92–1.35	.3	1.16	0.96–1.41	.1	1.12	0.93–1.36	.2
Paternal overweight	0.97	0.83–1.13	.7	0.98	0.84–1.14	.8	0.95	0.81–1.11	.5	0.97	0.83–1.13	.7
Conduct/externalizing problems, quintiles												
ALSPAC[c]												
Maternal overweight	1.04	0.92–1.18	.5	1.00	0.88–1.13	.9	1.05	0.93–1.19	.5	1.00	0.88–1.13	.98
Paternal overweight	0.97	0.88–1.07	.5	0.97	0.88–1.07	.6	0.96	0.87–1.07	.5	0.97	0.88–1.08	.6
Generation R[d]												
Maternal overweight	1.24	1.02–1.50	.03	1.21	1.00–1.46	.06	1.24	1.03–1.51	.02	1.21	1.00–1.47	.05
Paternal overweight	0.99	0.85–1.15	.9	0.99	0.85–1.15	.9	0.97	0.83–1.13	.7	0.97	0.83–1.13	.7

Maternal/paternal overweight or obese versus normal BMI.

[a] Unadjusted.

[b] Adjusted for maternal education, paternal education, family income, social class (ALSPAC only), and maternal smoking.

[c] SDQ total problems at 47 months, emotional, conduct, and attention problems ($n = 4873$).

[d] CBCL total problems at 36 months, internalizing, externalizing ($n = 2046$); attention ($n = 2483$).

TABLE 6 Psychologist-Administered Child IQ at 8 Years and Maternal Prepregnancy Overweight in ALSPAC: Ordinal OR of Higher Child IQ Quintile

	Mutually Adjusted Maternal-Paternal Models					
	Unadjusted[a]			Confounder-Adjusted[b]		
	OR	95% CI	*P*	OR	95% CI	*P*
Maternal overweight/obese[c]	0.68	0.59–0.79	<.001	0.84	0.73–0.98	.03
Paternal overweight/obese[c]	0.87	0.77–0.98	.02	0.96	0.85–1.08	.5

Maternal and paternal obesity mutually adjusted for one another in all models.

[a] Unadjusted for confounders.

[b] Adjusted for maternal and paternal education, family income, social class, and maternal smoking.

[c] Versus normal BMI; $n = 3480$.

confounding by factors not completely controlled for by the variables included in the analysis. As mentioned in the introduction, maternal prepregnancy overweight has been found to be associated with child attention problems in 3 Nordic cohorts. However, this was not supported by the present study; no association was observed with child attention/hyperactivity problems in either ALSPAC or Generation R. Because the previous study was based on teacher-rated behavior and maternal report was used in the present study, it is possible that maternal reporting bias may be diluting an association. Indeed, a recent study revealed that robust associations with teacher-rated child behavior problems (inattention and emotionality) were weak or null when maternal-rated behavior was analyzed.[2] However, analyses repeated in ALSPAC by using teacher-rated behavioral problems were not materially different to those based on maternal report. Thus, it is possible that the findings from the previous studies reflect residual confounding. This might occur, for example, if being overweight led to more adverse behavioral ratings by teachers. However, in the present study teacher-rated associations were not substantially altered by adjustment for child BMI.

TABLE 7 Teacher-Rated Behavioral Problems at 8 Years and Maternal Prepregnancy Overweight in ALSPAC: Ordinal OR for Being in a Higher Quintile

	Individual Maternal-Paternal Models						Mutually Adjusted Maternal-Paternal Models					
	Model 1[a]			Model 2[b]			Model 1[a]			Model 2[b]		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Total behavioral problems, quintiles												
Maternal overweight	1.19	1.00–1.42	.05	1.19	1.00–1.42	.05	1.18	0.98–1.41	.07	1.10	0.92–1.32	.3
Paternal overweight	1.14	0.99–1.32	.07	1.14	0.99–1.32	.08	1.13	0.98–1.30	.1	1.13	0.98–1.31	.09
Attention problems—quintiles												
Maternal overweight	1.18	0.99–1.41	.07	1.07	0.89–1.28	.5	1.16	0.97–1.39	.1	1.06	0.89–1.27	.5
Paternal overweight	1.15	0.99–1.33	.06	1.12	0.97–1.30	.1	1.14	0.98–1.32	.08	1.12	0.96–1.30	.1
Emotional problems, quintiles												
Maternal overweight	1.16	0.97–1.40	.1	1.13	0.94–1.36	.2	1.15	0.95–1.38	.1	1.12	0.92–1.35	.3
Paternal overweight	1.13	0.97–1.31	.1	1.14	0.98–1.33	.09	1.12	0.96–1.30	.2	1.13	0.97–1.32	.1
Conduct problems, quintiles												
Maternal overweight	1.03	0.83–1.29	.8	0.95	0.76–1.19	.7	1.03	0.83–1.28	.8	0.95	0.76–1.19	.7
Paternal overweight	1.04	0.87–1.24	.7	1.01	0.84–1.21	.9	1.03	0.86–1.24	.7	1.01	0.84–1.22	.9

$n = 2325$ (total problems), 2349 (attention), 2358 (emotional problems), 2355 (conduct).

[a] Unadjusted.

[b] Adjusted for maternal education, paternal education, family income, social class, and maternal smoking.

Key strengths of this study are the inclusion of 2 similar pregnancy cohorts, the incorporation of a means of cross-population replication, and the exploration of paternal prepregnancy overweight together with multiple indicators of socioeconomic position as measures of residual confounding. A limitation, as mentioned above, is the reliance on maternal report for the behavioral and cognitive measures, which may have resulted in maternal response bias. Although repeated analyses in ALSPAC by using psychologist-administered and teacher-rated assessments suggest that this is unlikely for the behavioral outcomes, it is possible that maternal response bias may have affected the analyses of infant verbal skills. In addition, we aimed to compare the same measures across the cohorts; however, different instruments were applied in each cohort for the cognitive and behavioral measures. Despite this, the fact that consistent results were observed even when different instruments were used is particularly reassuring. In addition, for the behavioral measures, the SDQ (implemented in ALSPAC) and the CBCL (implemented in Generation R) have been compared with one another previously.[12] Equivalent validity has been observed between the 2 instruments, with scores from the SDQ and CBCL being both highly correlated and equivalent at detecting inattention and hyperactivity, internalizing problems, and externalizing problems.[12]

Although the maternal-paternal comparisons were conducted to explore the likelihood of intrauterine mechanisms, in this particular context these comparisons and the additional adjustment for paternal overweight may not capture shared confounding factors as well as in previous analyses (eg, maternal and paternal smoking).[5] In this case, maternal overweight seems much more strongly associated with socioeconomic factors than does paternal overweight; hence, some of the stronger maternal (versus paternal) associations are likely to reflect residual confounding rather than intrauterine effects.

CONCLUSIONS

On the basis of the findings of 2 European pregnancy cohorts, we find little consistent evidence for intrauterine effects of maternal prepregnancy overweight on child verbal skills, nonverbal skills, and behavioral problems. Previously reported findings of associations with child ADHD and intellectual function are not supported by the present study. Although some associations were observed in this study with respect to child verbal skills, total behavioral problems, and externalizing problems, these were inconsistent between cohorts and generally did not persist in analyses using imputed data. Studies with designs that can further address the issue of confounding by using alternative methods may be particularly useful. This could be conducted, for example, by using genetic variants that are reliably associated with adiposity as instrumental variables for its causal intrauterine effect (ie, mendelian randomization studies).[5,18,19]

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