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Maternal pre-pregnancy obesity and neuropsychological development in pre-school children: a prospective cohort study

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BACKGROUND: Maternal pre-pregnancy obesity may impair infant neuropsychological development, but it is unclear whether intrauterine or confounding factors drive this association.

METHODS: We assessed whether maternal pre-pregnancy obesity was associated with neuropsychological development in 1,827 Spanish children. At 5 years, cognitive and psychomotor development was assessed using McCarthy Scales of Children's Abilities, attention deficit hyperactivity disorder (ADHD) symptoms using the Criteria of Diagnostic and Statistical Manual of Mental Disorders, and autism spectrum disorder symptoms using the Childhood Asperger Syndrome Test. Models were adjusted for sociodemographic factors and maternal intelligence quotient. We used paternal obesity as negative control exposure as it involves the same source of confounding than maternal obesity.

RESULTS: The percentage of obese mothers and fathers was 8% and 12%, respectively. In unadjusted models, children of obese mothers had lower scores than children of normal weight mothers in all McCarthy subscales. After adjustment, only the verbal subscale remained statistically significantly reduced (β: −2.8; 95% confidence interval: −5.3, −0.2). No associations were observed among obese fathers. Maternal and paternal obesity were associated with an increase in ADHD-related symptoms. Parental obesity was not associated with autism symptoms.

CONCLUSION: Maternal pre-pregnancy obesity was associated with a reduction in offspring verbal scores at pre-school age.

The prevalence of overweight and obesity is rapidly increasing worldwide, and over 30% of women of childbearing age are obese, an important risk factor for a range of pregnancy and child health outcomes (1). Chronic low-grade inflammation during pregnancy, an important characteristic of obesity, can affect brain development and function and cause neuropsychological disabilities, including cognitive and behavioral alterations, in the offspring (2,3). Animal studies have shown that maternal diet-induced obesity is associated with alterations in maze performance (4) and hyperactivity in the offspring (2), and with elevations in inflammatory markers in the brain and morphological changes in hippocampal neurons with shorter and decreased number of neurons (5). Besides inflammation, other biological mechanisms through which maternal obesity can influence child neurodevelopment include leptin, a hormone produced by the adipose tissue, and which has been involved in mood disturbances, thyroid dysfunction, nutrient deficits such as vitamin D or folic acid, and neurotoxins present in the adipose tissue (i.e., mercury, persistent organic pollutants) (6).

The majority of epidemiological studies suggest that the offspring of women who are overweight or obese before pregnancy are at increased risk for cognitive deficits and behavioral problems in childhood and adolescence (6–28). Regarding cognitive deficits, in the UK Millennium Cohort Study, for example, a 10-point increase in maternal pre-pregnancy body mass index (BMI) was associated with a decrease of 1.5 points of children's general cognitive ability at 7 years ($n = 10{,}000$ children) (13). In a recent study in the Rhea cohort in Greece, maternal obesity (BMI $\geq 30\ kg/m^2$) was associated with a reduction of 4 points of general cognitive ability at 4 years ($n = 772$) (28). Regarding behavioral problems, a study in the Raine Australian cohort showed that maternal pre-pregnancy overweight and obesity were associated with higher odds of affective problems between the ages of 5 and 17 years (odd ratio (OR): 1.72, 95% confidence interval (CI): 1.11, 2.67) ($n = 2{,}868$) (20). Another study in US observed that very obese women (BMI $\geq 35\ kg/m^2$) had increased odds of psychosocial problems including attention-deficit/hyperactivity disorder diagnosis (4.55, 95% CI: 1.80, 11.46) and autism or developmental delay diagnosis (3.13, 95% CI: 1.10, 8.94) ($n = 1{,}311$) (24).

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Most of these studies, however, have not been able to disentangle whether the observed associations were because of a causal intrauterine mechanism or residual confounding due to shared family and socioeconomic contexts. If this association is causal, this will represent a serious public health concern, given the high impact that both obesity and neuropsychological disabilities have globally.

Causal inference can be strengthened by using approaches that minimize problems of residual confounding collecting data on parents and other family members. The paternal-comparison approach, for example, uses the father as negative control: a maternal intrauterine effect would produce stronger associations than the paternal effect. The sibling-comparison approach compares siblings whose mother were obese and non-obese before pregnancy, and assumes that familial background will generally be similar between them (29). Few studies so far have used these approaches. Among the studies that used the maternal–paternal comparison approach (9,15–17,20,28), only three found that the association between BMI and mental development was stronger than the paternal one (15,20,28). Similarly, only one of the two studies that used the sibling approach (18,19) showed that maternal obesity was associated with lower child intelligence quotient (IQ) after sibling-comparison, (19) Given the inconsistency of results between studies, more research is needed to understand whether intrauterine mechanisms or confounding factors drive this association.

In this study, we assessed whether maternal pre-pregnancy overweight and obesity were associated with cognitive, psychomotor, and behavioral development of pre-school children from the Spanish INMA birth cohort. We used paternal BMI as a negative control exposure because it involves the same source of confounding than maternal obesity, but not the hypothesized causal intrauterine mechanisms.

METHODS

Study Participants

The population-based birth cohort INMA (INfancia y Medio Ambiente—Environment and Childhood) recruited pregnant women of general population in different Spanish regions (Asturias, Gipuzkoa, Sabadell, and Valencia) between 2003 and 2008 following a common protocol (30). Inclusion criteria were as follows: age ≥ 16 years, singleton pregnancy, no assisted conception, intention to deliver at the reference hospital, and no communication problems (30). Women included were similar to the Spanish general population in terms of maternal age at delivery, maternal education, and maternal country of birth (data not shown). The study was approved by the Ethical Committees of the centers involved in the study and participants provided written informed consent.

Among the 2,644 pregnant women initially recruited, 89 did not have data on maternal or paternal BMI and were excluded from the analysis (**Supplementary Figure S1 online**). Women who underwent induced or spontaneous abortions or fetal deaths ($n = 96$), children whose parents did not give written informed consent for the 5 years visit ($n = 332$), and those who participated in that visit but did not conduct any of the neuropsychological tests ($n = 300$) were also excluded. Therefore, a total of 1,827 children undertook at least one neuropsychological development test at around 5 years of age (mean: 4.8 years, standard deviation (SD): 0.6) and were included in the current analysis. This corresponds to a retention rate of 69%.

Maternal and Paternal Overweight and Obesity

Maternal height was measured, and maternal pre-pregnancy weight was reported by the mother during the first prenatal visit (mean: 13.9 weeks of gestation, SD: 2.8). Mothers also reported paternal weight and height. Parental pre-pregnancy BMI (kg/m^2) was classified into underweight (< 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30.0 kg/m^2) according to the World Health Organization classification.

Children's Neuropsychological Development

Cognitive and motor development was assessed using the McCarthy Scales of Children's Abilities (MSCA) adapted to the Spanish population (31). The global cognitive index and five subscales (verbal, performance, quantitative, memory, and motor) were examined. Raw MSCA scores were standardized having a mean of 100 and a SD of 15. Tests were performed at the primary health center, in the presence of the mother, by trained psychologists. To avoid inter-observer variability, a strict protocol was applied including inter-observer trainings (inter-observer variability < 5%). Also, children who during the test performance presented less than optimal cooperation, had behavioral problems, or were under influential conditions were excluded ($n = 18$). We assessed the internal consistency of MSCA subscales by using the Cronbach's alpha coefficient obtaining values ranging from 0.64 (motor) to 0.90 (global cognitive index) (**Supplementary Table S1**).

Inattention and hyperactivity/impulsivity symptomatology was assessed using the attention deficit hyperactivity disorder (ADHD)—Criteria of Diagnostic and Statistical Manual of Mental Disorders-4th Edition (ADHD-DSM-IV) form (32). The ADHD-DSM-IV comprises 18 items categorized in inattention (9 symptoms) and hyperactivity (9 symptoms). Each ADHD symptom is rated on a 4-point scale (0 = never or rarely, 1 = sometimes, 2 = often, or 3 = very often). Autism spectrum disorder symptoms were assessed using the Childhood Asperger Syndrome Test (CAST) (33). This questionnaire consists of 37 items; each question can be scored with 0 or 1 points, except for 6 questions that do not score. The ADHD-DSM-IV form was completed by teachers, whereas the CAST test was completed by trained psychologist after observing the child and interviewing the parents. It is important to note that the 18 children who were excluded from the MSCA tests because of less than optimal cooperation were not *a priori* excluded from the ADHD-DSM-IV and CAST analyses. Internal consistency of ADHD-DSM-IV was 0.92 (inattention) and 0.90 (hyperactivity) and that of CAST was 0.64 (**Supplementary Table S1**).

Covariates

Information on covariates was obtained by questionnaires completed by the mothers and by face-to-face interviews conducted by trained interviewers during the first and third trimesters of pregnancy (parental age, education, and social class, maternal country of birth, smoking, parity, marital status, and employment status), at 1 year of the child (breastfeeding duration, maternal employment status, daycare attendance, and main child minder), and at 5 years of the child (maternal employment status, number of people living with the child, physical activity, and hours of television viewing of the child). Parental social class was coded according to the International Standard Classification of Occupations-88 system. Five categories of occupational class (I being the highest and V the lowest) were considered: I, managers of companies with 10 or more employees, senior technical staff, and higher level professionals; II, managers of companies with < 10 employees, and intermediate level professionals; III, financial management, administrative and other support staff, other self-employed professionals, supervisors of manual workers, and skilled non-manual workers; IV, skilled and partly skilled manual workers; and V, unskilled manual workers. We grouped the five levels into three: semi-skilled/unskilled (IV and V),

skilled manual/non-manual (III), and professionals and managers q (I–III). Maternal weight throughout pregnancy was extracted from the prenatal visit records, and used to estimate gestational weight gain (first weight measured at around 12 gestational weeks and last weight measured at 39 gestational weeks). Weight gain was then classified as low, recommended, and high based on the U.S. Institute of Medicine guidelines. Sex of the child, birth weight, and gestational age were also obtained from clinical records. An indicator of maternal verbal IQ and maternal mental health was assessed using the Similarities subtest of the Weschler Adult Intelligence-Third Edition (WAIS-III) (34), and the global severity index was assessed by Symptom Checklist 90 Revised (SCL-90-R) (35), at 5 years of age of the child. Weight and height of the child were measured at 5 years, and BMI was used to estimate age- and sex-specific *z*-scores. Children with BMI ≥ 85th percentile were classified as overweight.

Statistical Analysis

We performed multiple imputation for missing values using chained equations, where a total of 50 completed data sets were generated, separately for each INMA cohort (**Supplementary Table S2**). Distributions in imputed data sets were similar to those observed (**Supplementary Table S3**). Analyses were performed in both complete case and imputed data sets.

Multivariable linear regression models were used to assess the association between maternal pre-pregnancy overweight and obesity and MSCA scores, and negative binomial regression models were used to assess the association with ADHD-DSM-IV and CAST scales. First, models were adjusted for age and sex of the child (model 1). Second, a set of socioeconomic variables were included: maternal and paternal education and social class (model 2). Third, covariates associated with maternal and paternal BMI and at least one neuropsychological test (McCarthy global cognitive index, ADHD, and CAST) ($P < 0.05$) were included in the model: maternal age, parity, maternal employment status during pregnancy, and maternal IQ. To minimize the residuals of the model, we also included covariates that were only associated with the outcome: maternal employment status at 5 years, breastfeeding duration, daycare attendance, and child physical activity (model 3). Finally, a fourth model included paternal BMI categories (model 4), as previously suggested (29). Models 1–3 were repeated using maternal BMI as a continuous variable. We also repeated all these models using paternal rather than maternal overweight and obesity as an independent variable.

Standardized effect size (Cohen's *d*) was calculated dividing the β coefficients by one SD (magnitude of effect size: 0.20 = small, 0.50 = moderate, and 0.80 = large). Further, effect modification by gestational weight-gain categories was assessed through inclusion of the interaction terms in model 3 (statistically significant effect modification, if $P < 0.05$) and stratified analyses. For the majority of women ($n = 1{,}563$), we had available weight measured during the first prenatal visit (≤12 pregnancy weeks), and we therefore repeated model 3 using measured instead of self-reported maternal weight to see whether this influenced our results. We also repeated model 3 excluding mothers who did not live with the father to evaluate the validity of maternal report of paternal BMI. There is a growing evidence of a possible association between overweight children and poor cognitive function (36); we, hence, excluded children classified as overweight at 5 years of age to see whether being overweight at the time of outcome assessment could influence the associations observed with maternal pre-pregnancy obesity. All statistical analyses were conducted with the Stata 14.0 statistical software (Stata, College Station, TX).

RESULTS

Overall, 19% and 8% of mothers, and 44% and 12% of fathers were overweight and obese, respectively (**Table 1**). A total of 4% and 1% of mothers and fathers were underweight, respectively. Compared with normal-weight mothers, overweight and obese mothers were more likely to have a lower education, social class, and IQ, and to be smokers, multiparae, and non-employed (**Table 1**). Children from obese and overweight mothers were more likely to be breastfed shorter and to not attend daycare during the first year of life. Paternal obesity was more prevalent in higher educational and social classes, but overweight was relatively evenly distributed (**Table 1**). Cognitive and behavioral outcomes were generally worse among lower social and educational classes, non-working mothers, smokers, and children who breastfed less (**Supplementary Table S4**). Cohort participants included in the analysis were older and had higher education and social class levels than excluded participants (**Supplementary Table S5**).

Children of obese mothers had lower scores in all the MSCA subscales compared with children of normal weight mothers in the unadjusted model 1, although not all associations reached statistical significance (e.g., verbal: −5.18 points, 95% CI: −7.82, −2.54; motor: −2.62, 95% CI: −5.29, 0.06) (**Table 2**). After adjustment for socioeconomic and other covariates, only the reduction in the verbal subscale remained statistically significant (−2.76, 95% CI: −5.33, −0.19) (model 3, **Table 2**). This association corresponded to a Cohen's *d* of −0.18 (95% CI: −0.36, −0.01), indicating a small effect size. Adjusting for paternal BMI had very small effects (Model 4, **Table 2**). We also observed a reduction in MSCA scores with increasing continuous BMI, but none of these associations remained statistically significant after adjusting for socioeconomic and other covariates (**Table 2**). No associations were observed among underweight or overweight mothers (**Table 2**). A reduction in MSCA scores was also observed among children of obese fathers, but associations were no longer significant after adjusting for socioeconomic variables (**Table 3**). We also did not observe any association between underweight or overweight fathers and child MSCA subscales (**Table 2**). Complete case analyses yielded similar results for both maternal and paternal models (**Supplementary Tables S6 and S7**).

Obese and underweight mothers had children with higher inattention and hyperactivity symptoms, respectively, than normal weight mothers (**Table 4**). Similarly, children of underweight and obese fathers had higher attention deficit hyperactivity disorder (ADHD)-related symptoms than children of normal weight fathers. None of these associations, however, reached statistical significance. Adjustment for socioeconomic and other covariates did not change the effect estimates (**Table 4**). Neither maternal nor paternal BMI was associated with autism-related symptoms (**Table 4**). Complete case analyses yielded similar results for both maternal and paternal models, but associations were statistically significant (**Supplementary Table S8**). In the complete case analysis, we also observed higher autism-related symptoms among children of overweight fathers (**Supplementary Table S8**).

No evidence for interaction was shown between gestational weight gain and maternal obesity on verbal scores (P interaction = 0.39). When we considered measured

Table 1. Parent and child characteristics by parental weight status ($n = 1.827$)

Characteristics	Mothers				Fathers			
	Underweight 75 (4%)	Normal 1,266 (69%)	Overweight 343 (19%)	Obese 143 (8%)	Underweight 6 (1%)	Normal 745 (43%)	Overweight 811 (44%)	Obese 225 (12%)
Maternal characteristics								
Age at delivery								
<25 years	4 (6.4)	41 (65.1)	11 (17.5)	7 (11.1)	1 (1.6)	42 (66.7)	16 (25.4)	4 (6.4)
25–29 years	32 (7)	319 (69.8)	69 (15.1)	37 (8.1)	1 (0.2)	204 (44.6)	196 (42.9)	56 (12.3)
30–34 years	21 (2.5)	605 (70.8)	164 (19.2)	65 (7.6)	3 (0.4)	361 (42.2)	391 (45.7)	100 (11.7)
≥35 years	18 (4)	298 (66.4)	99 (22.1)	34 (7.6)	1 (0.2)	177 (39.4)	206 (45.9)	65 (14.5)
Missing data, *n*	0	3	0	0	0	1	2	0
Social class								
Semi-skilled/unskilled	43 (4.9)	577 (65.1)	180 (20.3)	86 (9.7)	5 (0.6)	348 (39.3)	391 (44.1)	142 (16)
Skilled manual/non-manual	17 (3.4)	361 (71.9)	89 (17.7)	35 (7)	1 (0.2)	217 (43.2)	229 (45.6)	55 (11)
Professionals and managers	15 (3.4)	327 (74.7)	74 (16.9)	22 (5)	0 (0)	220 (50.2)	190 (43.4)	28 (6.4)
Missing data, *n*	0	1	0	0	0	0	1	0
Education								
Primary or less	16 (4.3)	223 (59.3)	87 (23.1)	50 (13.3)	1 (0.3)	157 (41.8)	157 (41.8)	61 (16.2)
Secondary	36 (4.7)	513 (66.7)	158 (20.6)	62 (8.1)	3 (0.4)	312 (40.6)	344 (44.7)	110 (14.3)
University degree	23 (3.4)	527 (77.6)	98 (14.4)	31 (4.6)	2 (0.3)	315 (46.4)	308 (45.4)	54 (8)
Missing data, *n*	0	3	0	0	0	1	2	0
Smoking								
Never smoke	29 (3.5)	577 (68.9)	161 (19.2)	70 (8.4)	2 (0.2)	344 (41.1)	380 (45.4)	111 (13.3)
Quit early pregnancy	27 (4)	494 (72.8)	111 (16.4)	47 (6.9)	3 (0.4)	310 (45.7)	298 (43.9)	68 (10)
During pregnancy	19 (7)	167 (61.2)	62 (22.7)	25 (9.2)	1 (0.4)	112 (41)	116 (42.5)	44 (16.1)
Missing data, *n*	0	28	9	1	0	19	17	2
Parity								
Primiparae	44 (4.2)	756 (72.2)	173 (16.5)	74 (7.1)	3 (0.3)	482 (46)	458 (43.7)	104 (9.9)
Multiparae	30 (3.9)	509 (65.4)	170 (21.9)	69 (8.9)	3 (0.4)	303 (39)	351 (45.1)	121 (15.6)
Missing data, *n*	1	1	0	0	0	0	2	0
Employment status during pregnancy								
No	14 (5.1)	170 (61.8)	58 (21.1)	33 (12)	0 (0)	99 (36)	121 (44)	55 (20)
Yes	60 (4)	1,069 (70.7)	274 (18.1)	109 (7.2)	6 (0.4)	668 (44.2)	672 (44.4)	166 (11)
Missing data, *n*	1	27	11	1	0	18	18	4
Employment status at 5 years								
No	26 (5.3)	318 (64.9)	101 (20.6)	45 (9.2)	0 (0)	189 (38.6)	231 (47.1)	70 (14.3)
Yes	46 (3.7)	893 (70.8)	232 (18.4)	90 (7.1)	5 (0.4)	559 (44.3)	549 (43.5)	148 (11.7)
Missing data, *n*	3	55	10	8	1	37	31	7
Intelligence quotient	9.2 (2.3)	9.7 (2.4)	9.6 (2.4)	9 (2.6)	10.2 (3.5)	9.6 (2.4)	9.7 (2.4)	9.1 (2.4)
Missing data, *n*	7	109	16	6	0	64	62	12
Paternal characteristics								
Age at child's birth								
<25 years	1 (3.5)	19 (65.5)	6 (20.7)	3 (10.3)	1 (3.5)	23 (79.3)	5 (17.2)	0 (0)
25–29 years	19 (6.6)	194 (67.1)	54 (18.7)	22 (7.6)	3 (1)	129 (44.6)	121 (41.9)	36 (12.5)
30–34 years	30 (3.9)	551 (72.1)	124 (16.2)	59 (7.7)	1 (0.1)	332 (43.5)	329 (43.1)	102 (13.4)
≥35 years	24 (3.3)	498 (67.5)	158 (21.4)	58 (7.9)	1 (0.1)	297 (40.2)	353 (47.8)	87 (11.8)
Missing data, *n*	1	4	1	1	0	4	3	0
Social class								
Semi-skilled/unskilled	44 (4.1)	729 (67.1)	217 (20)	96 (8.8)	4 (0.4)	454 (41.8)	471 (43.4)	157 (14.5)
Skilled manual/non-manual	13 (4)	226 (70)	61 (18.9)	23 (7.1)	1 (0.3)	137 (42.4)	149 (46.1)	36 (11.2)

Table 1 Continued

Characteristics	Mothers				Fathers			
	Underweight 75 (4%)	Normal 1,266 (69%)	Overweight 343 (19%)	Obese 143 (8%)	Underweight 6 (1%)	Normal 745 (43%)	Overweight 811 (44%)	Obese 225 (12%)
Professionals and managers	15 (3.9)	290 (76.1)	55 (14.4)	21 (5.5)	0 (0)	181 (47.5)	176 (46.2)	24 (6.3)
Others	0	1 (100)	0	0	0	1 (100)	0	0
Missing data, *n*	3	20	10	2	1	12	13	7
Education								
Primary or less	26 (4.3)	384 (62.9)	131 (21.4)	70 (11.5)	2 (0.3)	230 (37.6)	256 (41.9)	123 (20.1)
Secondary	34 (4.2)	584 (72)	142 (17.5)	51 (6.3)	4 (0.5)	356 (43.9)	372 (45.9)	79 (9.7)
University degree	15 (3.7)	294 (73.3)	70 (17.5)	22 (5.5)	0 (0)	198 (49.4)	180 (44.9)	23 (5.7)
Missing data, *n*	0	4	0	0	0	1	3	0
Child characteristics								
Sex								
Female	35 (3.9)	633 (71)	167 (18.7)	56 (6.3)	4 (0.5)	382 (42.9)	406 (45.6)	99 (11.1)
Male	40 (4.3)	633 (67.6)	176 (18.8)	87 (9.3)	2 (0.2)	403 (43.1)	405 (43.3)	126 (13.5)
Missing data, *n*		0	0	0	0	0	0	0
Birth weight	3,091 (386)	3,245 (465)	3,324 (440)	3,383 (517)	3,048 (674)	3,237 (452)	3,279 (462)	3,317 (504)
Missing data, *n*	1	7	0	2	0	3	6	1
Gestational age	39.5 (1.7)	39.6 (1.5)	39.7 (1.5)	39.7 (1.5)	39.9 (1.7)	39.6 (1.5)	39.7 (1.5)	39.5 (1.6)
Missing data, *n*	0	0	0	0	0	0	0	0
Breastfeeding duration								
< 16 weeks	26 (3.8)	441 (64.5)	138 (20.2)	79 (11.6)	1 (0.2)	271 (39.6)	319 (46.6)	93 (13.6)
≥ 16 weeks	45 (4.1)	792 (72.3)	198 (18.1)	61 (5.6)	5 (0.5)	494 (45.1)	471 (43)	126 (11.5)
Missing data, *n*	4	33	7	3	0	20	21	6
Daycare attendance at 1 year								
No	49 (4.4)	740 (66.4)	226 (20.3)	99 (9)	4 (0.4)	451 (40.5)	513 (46.1)	146 (13.1)
Yes	22 (3.4)	476 (74.3)	104 (16.2)	39 (6.1)	1 (0.2)	306 (47.7)	265 (41.3)	69 (10.8)
Missing data, *n*	4	50	13	5	1	28	33	10
Physical activity at 5 years								
Moderately active	28 (4.1)	473 (69.1)	138 (20.2)	46 (6.7)	0 (0)	306 (44.7)	294 (42.9)	85 (12.4)
Active	34 (4.1)	583 (70)	149 (17.9)	67 (8)	3 (0.4)	350 (42)	382 (45.9)	98 (11.8)
Very active	13 (5.1)	167 (65.2)	52 (20.3)	24 (9.4)	2 (0.8)	107 (41.8)	112 (43.8)	35 (13.7)
Missing data, *n*	0	43	4	6	1	22	23	7

SD, standard deviation.
Values are percentages for categorical variables and means (SD) for continuous variables. Row percentages.

maternal weight instead of self-reported ($n = 1,563$), results of maternal obesity with verbal cognitive scores were attenuated (self-reported: −2.73 (−5.51, 0.05); measured: −0.66 (−3.36, 2.04)). This is because of women who had a BMI close to 30 and were initially classified as overweight, but then classified as obese when measured weight was considered. However, results of BMI in continuous did not change (self-reported: −0.17 (−0.34, 0.01); measured: −0.16 (−0.33, 0.01)). Only one obese mother was not living with the father at the moment of recruitment, and therefore the coefficient did not change after excluding this woman (not shown). Fifteen percent of the children were overweight at 5 years of age, and after excluding them from the analysis, the coefficient for the verbal score did not change (not shown).

DISCUSSION

In this study, we found an association between maternal pre-pregnancy obesity and reduced child's verbal cognitive scores at pre-school age. Reductions observed in other cognitive domains in the offspring of obese mothers appeared to be largely explained by socioeconomic confounding. Paternal BMI did not influence the maternal BMI associations with cognitive scores, and was not associated with cognitive scores after adjustment for socioeconomic variables. Maternal and paternal underweight and obesity were associated with an increase in ADHD-related symptoms at pre-school age, but associations did not reach statistical significance. Neither maternal nor paternal BMI was associated with autism symptoms.

Table 2. Association of maternal pre-pregnancy weight status with cognitive and psychomotor scores at pre-school age

Test	Maternal BMI	*N*	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
			β (95% CI)	*β* (95% CI)	*β* (95% CI)	*β* (95% CI)
Global cognitive index						
	Underweight	75	−0.02 (−3.44, 3.40)	0.92 (−2.34, 4.18)	1.28 (−1.94, 4.50)	1.36 (−1.87, 4.59)
	Normal	1,266	Ref	Ref	Ref	Ref
	Overweight	343	−0.33 (−2.11, 1.45)	0.84 (−0.87, 2.56)	1.06 (−0.64, 2.76)	1.00 (−0.71, 2.71)
	Obese	143	−4.40 (−7.00, −1.80)**	−2.09 (−4.59, 0.42)	−1.51 (−4.00, 0.98)	−1.65 (−4.19, 0.89)
	Continuous	1,827	−0.24 (−0.40, −0.08)**	−0.05 (−0.20, 0.11)	−0.02 (−0.18, 0.13)	−0.02 (−0.18, 0.14)
Verbal						
	Underweight	75	−0.33 (−3.80, 3.14)	0.42 (−2.94, 3.78)	0.81 (−2.51, 4.13)	0.97 (−2.35, 4.29)
	Normal	1,266	Ref	Ref	Ref	Ref
	Overweight	343	−0.48 (−2.29, 1.33)	0.50 (−1.27, 2.27)	0.69 (−1.07, 2.44)	0.63 (−1.13, 2.39)
	Obese	143	−5.18 (−7.82, −2.54)**	−3.22 (−5.81, −0.63)*	−2.76 (−5.33, −0.19)*	−2.92 (−5.53, −0.30)*
	Continuous	1,827	−0.29 (−0.46, −0.13)**	−0.13 (−0.29, 0.03)	−0.12 (−0.27, 0.04)	−0.12 (−0.29, 0.04)
Performance						
	Underweight	75	0.32 (−3.09, 3.73)	1.03 (−2.31, 4.36)	1.22 (−2.10, 4.53)	1.22 (−2.10, 4.54)
	Normal	1,266	Ref	Ref	Ref	Ref
	Overweight	343	−0.40 (−2.17, 1.36)	0.48 (−1.25, 2.22)	0.64 (−1.09, 2.37)	0.63 (−1.11, 2.38)
	Obese	143	−1.29 (−3.90, 1.32)	0.44 (−2.13, 3.02)	0.86 (−1.72, 3.43)	0.84 (−1.79, 3.46)
	Continuous	1,827	−0.06 (−0.22, 0.10)	0.08 (−0.08, 0.24)	0.10 (−0.06, 0.26)	0.11 (−0.05, 0.28)
Quantitative						
	Underweight	75	−0.20 (−3.66, 3.25)	0.64 (−2.70, 3.97)	0.92 (−2.40, 4.24)	0.88 (−2.44, 4.20)
	Normal	1,266	Ref	Ref	Ref	Ref
	Overweight	343	0.22 (−1.58, 2.02)	1.20 (−0.55, 2.96)	1.38 (−0.37, 3.13)	1.34 (−0.42, 3.10)
	Obese	143	−3.72 (−6.35, −1.09)**	−1.85 (−4.42, 0.72)	−1.23 (−3.79, 1.33)	−1.35 (−3.97, 1.26)
	Continuous	1,827	−0.20 (−0.37, −0.04)*	−0.04 (−0.20, 0.12)	−0.01 (−0.17, 0.14)	−0.02 (−0.18, 0.14)
Memory						
	Underweight	75	−0.37 (−3.86, 3.11)	0.39 (−3.00, 3.78)	0.72 (−2.64, 4.08)	0.74 (−2.62, 4.11)
	Normal	1,266	Ref	Ref	Ref	Ref
	Overweight	343	0.39 (−1.43, 2.20)	1.33 (−0.45, 3.11)	1.50 (−0.27, 3.27)	1.35 (−0.43, 3.13)
	Obese	143	−3.75 (−6.38, −1.11)**	−1.90 (−4.49, 0.69)	−1.39 (−3.97, 1.19)	−1.80 (−4.43, 0.83)
	Continuous	1,827	−0.16 (−0.32, 0.00)	−0.00 (−0.17, 0.16)	0.02 (−0.15, 0.18)	−0.00 (−0.17, 0.16)
Motor						
	Underweight	75	0.38 (−3.12, 3.87)	0.76 (−2.72, 4.24)	0.70 (−2.79, 4.18)	0.69 (−2.80, 4.18)
	Normal	1,266	Ref	Ref	Ref	Ref
	Overweight	343	−0.05 (−1.87, 1.76)	0.46 (−1.37, 2.28)	0.42 (−1.42, 2.25)	0.51 (−1.33, 2.36)
	Obese	143	−2.62 (−5.29, 0.06)	−1.61 (−4.31, 1.08)	−1.62 (−4.33, 1.09)	−1.35 (−4.10, 1.41)
	Continuous	1,827	−0.11 (−0.28, 0.05)	−0.03 (−0.20, 0.13)	−0.03 (−0.20, 0.14)	−0.02 (−0.19, 0.16)

BMI, body mass index; CI, confidence intervals; MSCA, McCarthy Scales of Children's Abilities.
*P-value <0.05; **P-value <0.01.
[a]Model 1: adjusted for age and sex of the child.
[b]Model 2: model 1 plus maternal and paternal education, and social class.
[c]Model 3: model 2 plus maternal age, parity, maternal employment status during pregnancy, and at 5 years, maternal IQ, breastfeeding duration, daycare attendance, and child physical activity.
[d]Model 4: model 3 plus paternal BMI.

Table 3. Association of paternal pre-pregnancy weight status with cognitive and psychomotor scores at pre-school age

Tests	Paternal BMI	*N*	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
			β (95% CI)	*β* (95% CI)	*β* (95% CI)	*β* (95% CI)
Global cognitive index						
	Underweight	6	0.32 (−11.48, 12.12)	2.73 (−8.52, 13.98)	2.36 (−8.79, 13.51)	2.78 (−8.40, 13.97)
	Normal	785	Ref	Ref	Ref	Ref
	Overweight	811	0.05 (−1.41, 1.51)	0.36 (−1.03, 1.76)	0.65 (−0.73, 2.04)	0.71 (−0.68, 2.10)
	Obese	225	− 2.78 (−4.99, − 0.56)*	− 0.34 (−2.50, 1.81)	0.32 (−1.82, 2.46)	0.51 (−1.68, 2.69)
	Continuous	1,827	− 0.27 (−0.47, − 0.07)**	− 0.07 (−0.26, 0.12)	− 0.01 (−0.20, 0.18)	− 0.00 (−0.20, 0.19)
Verbal						
	Underweight	6	5.10 (−6.86, 17.06)	6.90 (−4.69, 18.50)	6.52 (−4.94, 17.99)	7.39 (−4.10, 18.88)
	Normal	785	Ref	Ref	Ref	Ref
	Overweight	811	0.90 (−0.59, 2.38)	1.12 (−0.32, 2.57)	1.33 (−0.10, 2.76)	1.43 (−0.00, 2.87)
	Obese	225	− 2.77 (−5.02, − 0.51)*	− 0.81 (−3.04, 1.41)	− 0.11 (−2.32, 2.10)	0.29 (−1.96, 2.54)
	Continuous	1,827	− 0.21 (−0.41, − 0.01)*	− 0.05 (−0.25, 0.15)	0.01 (−0.19, 0.21)	0.04 (−0.16, 0.25)
Performance						
	Underweight	6	− 3.93 (−15.69, 7.82)	− 2.27 (−13.75, 9.22)	− 2.22 (−13.69, 9.24)	− 2.53 (−14.04, 8.99)
	Normal	785	Ref	Ref	Ref	Ref
	Overweight	811	− 0.35 (−1.80, 1.11)	− 0.13 (−1.55, 1.29)	0.14 (−1.28, 1.56)	0.12 (−1.30, 1.55)
	Obese	225	− 1.69 (−3.90, 0.51)	0.08 (−2.12, 2.27)	0.42 (−1.78, 2.62)	0.27 (−1.98, 2.51)
	Continuous	1,827	− 0.21 (−0.41, − 0.02)*	− 0.07 (−0.27, 0.12)	− 0.03 (−0.23, 0.16)	− 0.06 (−0.26, 0.14)
Quantitative						
	Underweight	6	− 6.17 (−18.07, 5.74)	− 3.72 (−15.25, 7.80)	− 4.53 (−16.01, 6.95)	− 4.29 (−15.81, 7.22)
	Normal	785	Ref	Ref	Ref	Ref
	Overweight	811	− 0.98 (−2.46, 0.50)	− 0.66 (−2.09, 0.77)	− 0.38 (−1.81, 1.05)	− 0.35 (−1.79, 1.08)
	Obese	225	− 2.04 (−4.26, 0.19)	0.20 (−1.99, 2.40)	0.78 (−1.42, 2.97)	0.87 (−1.37, 3.12)
	Continuous	1,827	− 0.22 (−0.42, − 0.02)*	− 0.04 (−0.23, 0.16)	0.02 (−0.18, 0.22)	0.03 (−0.18, 0.23)
Memory						
	Underweight	6	3.04 (−8.98, 15.07)	4.94 (−6.76, 16.64)	4.27 (−7.37, 15.91)	4.63 (−7.04, 16.31)
	Normal	785	Ref	Ref	Ref	Ref
	Overweight	811	− 0.50 (−2.00, 1.00)	− 0.19 (−1.65, 1.27)	0.06 (−1.40, 1.52)	0.10 (−1.36, 1.57)
	Obese	225	− 1.12 (−3.38, 1.13)	0.94 (−1.30, 3.18)	1.51 (−0.73, 3.74)	1.67 (−0.62, 3.95)
	Continuous	1,827	− 0.13 (−0.33, 0.08)	0.05 (−0.15, 0.25)	0.10 (−0.10, 0.30)	0.10 (−0.10, 0.31)
Motor						
	Underweight	6	− 5.32 (−17.36, 6.72)	− 4.67 (−16.67, 7.33)	− 5.80 (−17.84, 6.25)	− 5.42 (−17.51, 6.67)
	Normal	785	Ref	Ref	Ref	Ref
	Overweight	811	− 0.16 (−1.66, 1.33)	− 0.05 (−1.54, 1.44)	0.01 (−1.50, 1.51)	0.05 (−1.46, 1.56)
	Obese	225	− 2.04 (−4.33, 0.24)	− 1.09 (−3.41, 1.23)	− 1.13 (−3.47, 1.21)	− 0.96 (−3.35, 1.42)
	Continuous	1,827	− 0.18 (−0.38, 0.03)	− 0.10 (−0.30, 0.11)	− 0.09 (−0.30, 0.12)	−0.09 (−0.30, 0.13)

BMI, body mass index; CI, confidence intervals; MSCA, McCarthy Scales of Children's Abilities.
*P-value <0.05; **P-value <0.01.
[a]Model 1: adjusted for age and sex of the child.
[b]Model 2: model 1 plus maternal and paternal education, and social class.
[c]Model 3: model 2 plus maternal age, parity, maternal employment status during pregnancy, and at 5 years, maternal IQ, breastfeeding duration, daycare attendance, and child physical activity.
[d]Model 4: model 3 plus maternal BMI.

Table 4. Association of maternal and paternal pre-pregnancy weight status with behavioral outcomes at pre-school age

Test	Parental BMI	*N*	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
			IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
ADHD-DSM-IV						
Inattention						
	Mother					
	Underweight	75	0.92 (0.07, 12.94)	1.05 (0.11, 10.07)	1.07 (0.18, 6.30)	1.12 (0.22. 5.53)
	Normal	1,266	Ref	Ref	Ref	Ref
	Overweight	343	1.01 (0.18, 5.53)	1.08 (0.42, 2.77)	1.11 (0.57, 2.14)	1.05 (0.55, 1.99)
	Obese	143	1.55 (0.17, 13.74)	1.99 (0.41, 9.78)	1.97 (0.55, 6.96)	1.40 (0.44, 4.53)
	Continuous	1,827	1.04 (0.90, 1.21)	1.04 (0.97, 1.13)	1.04 (0.98, 1.11)	1.03 (0.97, 1.09)
	Father					
	Underweight	6	3.32 (0.44, 25.03)	3.25 (0.64, 16.61)	3.63 (0.79, 16.44)	3.46 (0.77, 15.49)
	Normal	785	Ref	Ref	Ref	Ref
	Overweight	811	1.03 (0.13, 8.25)	1.08 (0.42, 2.77)	1.07 (0.57, 2.03)	1.06 (0.59, 1.92)
	Obese	225	2.39 (0.29, 19.89)	2.64 (0.68, 10.18)	2.36 (0.80, 6.89)	2.12 (0.73, 6.17)
	Continuous	1,827	1.07 (0.89, 1.31)	1.07 (0.96, 1.19)	1.06 (0.98, 1.15)	1.05 (0.97, 1.14)
Hyperactivity						
	Mother					
	Underweight	75	1.38 (0.21, 9.30)	1.32 (0.25, 7.17)	1.23 (0.30, 5.16)	1.23 (0.31, 4.81)
	Normal	1,266	Ref	Ref	Ref	Ref
	Overweight	343	1.03 (0.76, 1.38)	1.01 (0.79, 1.30)	1.03 (0.84, 1.26)	1.00 (0.82, 1.23)
	Obese	143	1.17 (0.59, 2.34)	1.14 (0.67, 1.95)	1.13 (0.79, 1.62)	1.03 (0.70, 1.52)
	Continuous	1,827	1.00 (0.94, 1.06)	1.00 (0.97, 1.03)	1.00 (0.98, 1.03)	1.00 (0.97, 1.02)
	Father					
	Underweight	6	1.25 (0.34, 4.57)	1.31 (0.38, 4.53)	1.36 (0.39, 4.71)	1.38 (0.39, 4.76)
	Normal	785	Ref	Ref	Ref	Ref
	Overweight	811	1.03 (0.63, 1.70)	1.05 (0.82, 1.34)	1.07 (0.86, 1.34)	1.08 (0.90, 1.30)
	Obese	225	1.42 (0.54, 3.71)	1.40 (0.73, 2.66)	1.39 (0.94, 2.08)	1.38 (0.96, 1.99)
	Continuous	1,827	1.02 (0.94, 1.12)	1.02 (0.97, 1.08)	1.02 (0.98, 1.06)	1.02 (0.98, 1.06)
CAST						
	Mother					
	Underweight	75	1.02 (0.81, 1.28)	1.01 (0.85, 1.20)	1.00 (0.84, 1.19)	1.01 (0.85, 1.19)
	Normal	1,266	Ref	Ref	Ref	Ref
	Overweight	343	1.01 (0.84, 1.22)	1.01 (0.91, 1.12)	1.02 (0.93, 1.12)	1.02 (0.93, 1.11)
	Obese	143	1.12 (0.86, 1.45)	1.08 (0.90, 1.31)	1.06 (0.92, 1.23)	1.06 (0.91, 1.23)
	Continuous	1,827	1.00 (0.99, 1.02)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
	Father					
	Underweight	6	0.90 (0.52, 1.54)	0.83 (0.49, 1.42)	0.88 (0.51, 1.49)	0.85 (0.50, 1.46)
	Normal	785	Ref	Ref	Ref	Ref
	Overweight	811	1.11 (0.89, 1.39)	1.08 (0.96, 1.22)	1.08 (0.97, 1.21)	1.08 (0.97, 1.20)
	Obese	225	1.07 (0.95, 1.20)	1.02 (0.92, 1.13)	1.02 (0.93, 1.13)	1.01 (0.91, 1.13)
	Continuous	1,827	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)	1.00 (0.99, 1.02)

ADHD-DSM-IV, Attention Deficit Hyperactivity Disorder-Criteria of Diagnostic and Statistical Manual of Mental Disorders-4th Edition; BMI, body mass index; CAST, Childhood Asperger Syndrome Test; CI, confidence intervals; IRR, incidence rate ratio.
*P-value <0.05; **P-value <0.01.
[a]Model 1: adjusted for age and sex of the child.
[b]Model 2: model 1 plus maternal and paternal education, and social class.
[c]Model 3: model 2 plus maternal age, parity, maternal employment status during pregnancy, and at 5 years, maternal IQ, breastfeeding duration, daycare attendance, and child physical activity.
[d]Model 4: model 3 plus paternal or maternal BMI.

Up to now, 15 studies have examined cognitive and psychomotor outcomes in relation to maternal weight status before pregnancy (7,9–15,17,19,22,23,26–28). The majority of previous studies suggest an association between maternal obesity, but not maternal overweight, and reduced offspring cognitive ability; psychomotor development is generally not affected (7,10–15,19,23). This is in agreement with our results showing a reduction in verbal cognitive and not psychomotor scores in obese women only. These studies, however, differ in terms of how maternal BMI was treated (in continuous or overweight/obesity separated or combined) and reported (prospective or retrospective), the neuropsychological development instruments used, evaluators, and age at assessment, and the confounders considered. Further, most of them could not examine whether these associations were because of intrauterine biological mechanisms or residual confounding. Huang *et al.* (19) using a sibling-comparison design could conclude that maternal obesity had a major role on child's IQ, particularly on verbal IQ scale, than familial and genetic factors that siblings share. In a recent study in the Rhea Greek cohort, with higher obesity rates than in INMA, a reduction in multiple MSCA scales was observed in children of obese mothers; no associations were observed with paternal obesity (28). They observed a reduction in performance, quantitative, and global cognitive index scores of higher magnitude than in INMA. It is important to note that although the reduction of 2 points in the verbal MSCA scores observed in our study might not be relevant at the individual level, the public health impact of this reduction is of concern both in terms for the clinical relevance, as more children will be below the normal range, and for the resulting economic costs.

Results of the present study are similar to those observed in the same cohort at 1 year of age (15). At 1 year, we observed a reduction in cognitive scores of the Bayley Scales of Infant Development (BSID) of similar magnitude as the reduction in the MSCA verbal scores reported here (model 3: 1 year cognitive score: −2.69, 95% CI: −5.27, −0.11; 5 years verbal score: −2.76, 95% CI: −5.33, −0.19). This reduction was also observed after controlling for socioeconomic factors. The BSID cognitive subscale score comprises performance abilities, memory, and first verbal learning. In our cohort, the 1-year BSID cognitive score was only modestly correlated with the 4-year MSCA subscales (e.g., Pearson's verbal subscale $r=0.23$; $P<0.001$). Previous studies have also reported low predictive validity of the BSID test (37), suggesting that children who had poor BSID cognitive scores at 1 year will not necessarily have poor MSCA scores at age 4. Cognitive development continues until early adulthood, and its evaluation at early ages might reflect an intermediate stage of development when measurements might have more variability. Children develop more cognitive abilities over the years, and these abilities can be assessed with more specific instruments at older ages. Studies at older ages are therefore needed to confirm whether the reduction in cognitive scores observed in the present study persists and which are the domains mostly affected.

Only three other previous studies assessed neuropsychological development in different follow-up periods during childhood and adolescence (9,23,27). One of these observed poorer cognitive outcomes at each age (23), whereas another one observed higher cognitive scores associated with maternal obesity only in the first follow-up (27). These studies, however, did not use parental- or sibling-comparison approaches. Only one study (9) used the paternal approach but did not find any evidence of reduction in cognitive ability at different ages throughout childhood. In the current study, we used the paternal comparison approach and confirmed a reduction in cognitive scores associated with maternal BMI at two different ages during childhood. It is important to note that socioeconomic factors were associated with both maternal and paternal obesity, suggesting that father's BMI was a good negative control. Indeed, we observed a stronger effect of maternal than paternal obesity on child cognitive development, suggesting that a maternal mechanism is more likely to explain this association. This mechanism could be direct, reflecting an intrauterine biological mechanism, or indirect, reflecting the greater role of mother in childhood caregiver and nutrition. Although we considered some of these postnatal factors such as daycare attendance or maternal employment status during childhood, we cannot rule out residual confounding.

Thirteen studies have assessed whether maternal pre-pregnancy obesity is associated with increased behavioral and developmental problems in the offspring (6,8,9,14,16, 18,20–22,24–26,28), and most of them found that maternal obesity was associated with an increase in ADHD- and autism-related symptoms during childhood (6,8,14,20–22,24,25,28). However, most of them did not use familial comparison approaches, and this may lead to an overestimation of the risk associated with maternal obesity. Among studies using the familial comparison approaches, two studies did not find any associations (9,18), whereas three others observed an increase in behavioral problems associated with obesity of the mother (20,21,28) or the father (16). In the present study, we found that offspring of underweight and obese mothers and fathers had an increase in ADHD-related symptoms. Associations of mothers and fathers were of similar magnitude and even stronger for the father. The paternal associations may indicate residual confounding due to shared familial factors such as attachment or playing behavior that can influence behavioral problems in the offspring, and they have not been considered in our analysis.

Physiological mechanisms underlying obesity-related neuropsychological disabilities in the offspring are still unknown, but there is an increasing evidence for a role of inflammatory processes (3). Obesity is associated with elevated inflammatory markers derived from the increased adipose tissue and the instauration of a low-grade endotoxemia due to the increased permeability of the intestinal wall (3). These inflammatory markers can be transferred to the offspring brain and induce a neuroinflammatory process activating microglia and impairing neuroendocrine activity,

neurotransmitter function, and neurocircuitry. These brain alterations can disrupt the normal fetal brain development trajectory, and produce long-term consequences and predict neurobehavioral disorders and cognitive impairment of the offspring (2,3). Other potential mechanisms involve thyroid dysfunction, nutritional deficiencies such as vitamin D or folic acid, reduced birth weight, child overweight/obesity, or lipophilic environmental neurotoxicants (38). Hormone levels (e.g., insulin and leptin) and epigenetic alterations could also have a role (38). Given the complex physiology linked to obesity status during pregnancy, it is possible that one or more of these potential mechanisms underlie the infant verbal cognitive impairment observed in the present study.

The main strength of our study is the use of maternal–paternal comparison design and the similarity of results observed at earlier ages in the same cohort. Another strength is the use of validated psychologist-, teacher-, and parent-reported neuropsychological tools. An additional strength is the inclusion of a large set of potential confounders. However, some methodological aspects need to be addressed. First, our study has a small sample size including only 143 obese women; this may have hindered the observation of statistically significant associations in the other cognitive domains. Another limitation is related to the assessment of maternal obesity as BMI might not represent an optimal proxy for obesity-related physiological conditions. Inflammatory markers in obesity, for example, correlate better with measures of central adiposity, such as waist circumference and waist-to-hip ratio, rather than with the general measure of BMI (39). Third, paternal BMI was reported by the mother. All but one of the obese mothers lived with the baby's father, somewhat reducing the likelihood of erroneous reporting. Further, we assume that the maternal and paternal BMI misclassification is likely to be non-differential and would thus bias the associations toward the null. Fourth, in our population lower education and social class, and shorter duration of breastfeeding are linked to being obese before pregnancy and to lower cognitive scores; thus, the most susceptible mother–child pairs could have been excluded from the analysis. Finally, given the multiple comparisons involved performed, we cannot rule out the possibility of chance finding. To avoid errors due to false-positive statistically significant associations (type I errors), we emphasized those results that persisted after considering all potential confounders and interpreted the consistency of results with other studies (19,28). We did not apply statistical correction for multiple comparisons because this would increase type II errors, false-negative findings, arguably more serious in public health research, (40) and it also assumes variability in all results to be random, (40) which may not be the case as maternal and paternal weight statuses are related, as are the different neuropsychological tests.

Although the majority of studies, including the present one, have reported an association of maternal obesity on cognitive development outcomes in children, a definitive causal association still needs to be proven. As each study design has unique biases that, alone, cannot be sufficient for strong inference, the combination of different study designs might be needed to prove causation. This might include Mendelian randomization studies or cross-cohort comparisons where confounding structures for obesity or child cognition differ systematically across populations.

CONCLUSION

In this study, we found little evidence of an association between maternal pre-pregnancy obesity and neuropsychological development at pre-school age. Maternal pre-pregnancy obesity may be associated with a small reduction in offspring verbal cognitive scores. Associations for ADHD symptoms are likely to be attributable to residual confounding.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/pr

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REFERENCES

1. Poston L, Harthoorn LF, Van Der Beek EM. Obesity in pregnancy: implications for the mother and lifelong health of the child. A consensus statement. Pediatr Res 2011;69:175–80.
2. Fernandes C, Grayton H, Poston L, et al. Prenatal exposure to maternal obesity leads to hyperactivity in offspring. Mol Psychiatry 2012;17:1159–60.
3. Castanon N, Lasselin J, Capuron L. Neuropsychiatric comorbidity in obesity: role of inflammatory processes. Front Endocrinol 2014;5:74.
4. Bilbo SD, Tsang V. Enduring consequences of maternal obesity for brain inflammation and behavior of offspring. FASEB J 2010;24:2104–15.
5. Tozuka Y, Kumon M, Wada E, Onodera M, Mochizuki H, Wada K. Maternal obesity impairs hippocampal BDNF production and spatial

learning performance in young mouse offspring. Neurochem Int 2010;57:235–47.
6. Rodriguez A, Miettunen J, Henriksen TB, et al. Maternal adiposity prior to pregnancy is associated with ADHD symptoms in offspring: evidence from three prospective pregnancy cohorts. Int J Obes 2008;32:550–7.
7. Neggers YH, Goldenberg RL, Ramey SL, Cliver SP. Maternal prepregnancy body mass index and psychomotor development in children. Acta Obes 2003;82:235–40.
8. Rodriguez A. Maternal pre-pregnancy obesity and risk for inattention and negative emotionality in children. J Child Psychol Psychiatry 2010;51:134–43.
9. Brion MJ, Zeegers M, Jaddoe V, et al. Intrauterine effects of maternal prepregnancy overweight on child cognition and behavior in 2 cohorts. Pediatrics 2011;127:e202–11.
10. Heikura U, Taanila A, Hartikainen AL, et al. Variations in prenatal sociodemographic factors associated with intellectual disability: a study of the 20-year interval between two birth cohorts in northern Finland. Am J Epidemiol 2008;167:169–77.
11. Hinkle SN, Schieve LA, Stein AD, Swan DW, Ramakrishnan U, Sharma AJ. Associations between maternal prepregnancy body mass index and child neurodevelopment at 2 years of age. Int J Obes 2012;36:1312–9.
12. Tanda R, Salsberry PJ, Reagan PB, Fang MZ. The impact of prepregnancy obesity on children's cognitive test scores. Matern Child Health J 2012;17:222–9.
13. Basatemur E, Gardiner J, Williams C, Melhuish E, Barnes J, Sutcliffe A. Maternal prepregnancy BMI and child cognition: a longitudinal cohort study. Pediatrics 2012;131:56–63.
14. Buss C, Entringer S, Davis EP, et al. Impaired executive function mediates the association between maternal pre-pregnancy body mass index and child ADHD symptoms. PLoS ONE 2012;7:e37758.
15. Casas M, Chatzi L, Carsin AE, et al. Maternal pre-pregnancy overweight and obesity, and child neuropsychological development: two Southern European birth cohort studies. Int J Epidemiol 2013;42:506–17.
16. Suren P, Gunnes N, Roth C, et al. Parental obesity and risk of autism spectrum disorder. Pediatrics 2014;133:e1128–38.
17. Bliddal M, Olsen J, Stovring H, et al. Maternal pre-pregnancy BMI and intelligence quotient (IQ) in 5-year-old children: a cohort based study. PLoS ONE 2014;9:e94498.
18. Chen Q, Sjolander A, Langstrom N, et al. Maternal pre-pregnancy body mass index and offspring attention deficit hyperactivity disorder: a population-based cohort study using a sibling-comparison design. Int J Epidemiol 2014;43:83–90.
19. Huang L, Yu X, Keim S, Li L, Zhang L, Zhang J. Maternal prepregnancy obesity and child neurodevelopment in the Collaborative Perinatal Project. Int J Epidemiol 2014;43:783–92.
20. Robinson M, Zubrick SR, Pennell CE, et al. Pre-pregnancy maternal overweight and obesity increase the risk for affective disorders in offspring. J Dev Orig Health Dis 2013;4:42–8.
21. Van Lieshout RJ, Schmidt LA, Robinson M, Niccols A, Boyle MH. Maternal pre-pregnancy body mass index and offspring temperament and behavior at 1 and 2 years of age. Child Psychiatry Hum Dev 2013;44:382–90.
22. Krakowiak P, Walker CK, Bremer AA, et al. Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. Pediatrics 2012;129:e1121–8.
23. Craig WY, Palomaki GE, Neveux LM, Haddow JE. Maternal body mass index during pregnancy and offspring neurocognitive development. Obstet Med 2013;6:20–5.
24. Jo H, Schieve LA, Sharma AJ, Hinkle SN, Li R, Lind JN. Maternal prepregnancy body mass index and child psychosocial development at 6 years of age. Pediatrics 2015;135:e1198–209.
25. Li M, Fallin MD, Riley A, et al. The association of maternal obesity and diabetes with autism and other developmental disabilities. Pediatrics 2016;137:e20152206.
26. Pugh SJ, Richardson GA, Hutcheon JA, et al. Maternal obesity and excessive gestational weight gain are associated with components of child cognition. J Nutr 2015;145:2562–9.
27. Torres-Espinola FJ, Berglund SK, Garcia-Valdes LM, et al. Maternal obesity, overweight and gestational diabetes affect the offspring neurodevelopment at 6 and 18 months of age—a follow up from the PREOBE cohort. PLoS ONE 2015;10:e0133010.
28. Daraki V, Roumeliotaki T, Koutra K, et al. Effect of parental obesity and gestational diabetes on child neuropsychological and behavioral development at 4 years of age: the Rhea mother–child cohort, Crete, Greece. Eur Child Adolesc Psychiatry 2017 (doi:10.1007/s00787-016-0934-2).
29. Smith GD. Assessing intrauterine influences on offspring health outcomes: can epidemiological studies yield robust findings? Basic Clin Pharmacol Toxicol 2008;102:245–56.
30. Guxens M, Ballester F, Espada M, et al. Cohort profile: the INMA—INfancia y Medio Ambiente—(Environment and Childhood) Project. Int J Epidemiol 2012;41:930–40.
31. McCarthy D MSCA, Escalas McCarthy de Aptitudes y Psicomotricidad para Niños. Madrid: TEA Ediciones, 2009.
32. Association AP. Manual Diagnóstico y Estadístico de los Trastornos Mentales. Barcelona: Masson, 2002.
33. Scott FJ, Baron-Cohen S, Bolton P, Brayne C. The CAST (childhood Asperger syndrome test): preliminary development of a UK screen for mainstream primary-school-age children. Autism 2002;6:9–31.
34. Weschler D. Weschler Adult Intelligence Scale-III (Escala de inteligencia de Wechsler para adultos-III) (WAIS-III). Madrid; TEA Ediciones, 2001.
35. Martinez-Azumendi O, Fernandez-Gomez C, Beitia-Fernandez M. Factorial variance of the SCL-90- R in a Spanish out-patient psychiatric sample. Actas Esp Psiquiatr 2001;29:95–102.
36. Li Y, Dai Q, Jackson JC, Zhang J. Overweight is associated with decreased cognitive functioning among school-age children and adolescents. Obesity 2008;16:1809–5.
37. Lung FW, Shu BC, Chiang TL, Chen PF, Lin LL. Predictive validity of Bayley scale in language development of children at 6–36 months. Pediatr Int 2009;51:666–9.
38. Van Lieshout RJ. Role of maternal adiposity prior to and during pregnancy in cognitive and psychiatric problems in offspring. NutrRev 2013;71:S95–101.
39. Hermsdorff HH, Zulet MA, Puchau B, Martinez JA. Central adiposity rather than total adiposity measurements are specifically involved in the inflammatory status from healthy young adults. Inflammation 2011;34:161–70.
40. Rothman KJ. No adjustments are needed for multiple comparisons. Epidemiology 1990;1:43–6.