International Journal of Epidemiology, 2017, 1653–1666
doi: 10.1093/ije/dyx122
Advance Access Publication Date: 13 July 2017
Original article

Neurocognitive Development

Association between pre-pregnancy overweight and obesity and children's neurocognitive development: a systematic review and meta-analysis of observational studies

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Editorial decision 8 June 2017; Accepted 14 June 2017

Abstract

Background: Obesity and overweight during pregnancy have been negatively associated with fetal and offspring neurodevelopment. The aim of this systematic review and meta-analysis was to assess the effect of the relationship between pre-pregnancy overweight and obesity with children's neurocognitive development.

Methods: We systematically searched MEDLINE, EMBASE, the Cochrane Library and the Web of Science databases from their inception through February 2017 for follow-up studies comparing the relationship between pre-pregnancy weight status and children's cognition. The Mantel-Haenszel fixed-effects method was used to calculate pooled effect size (ES) values and their corresponding 95% confidence intervals (CIs) comparing children's neurocognitive development between pre-pregnancy normal weight, as reference, with overweight and obesity categories.

Results: Fifteen articles were included in the systematic review, and nine of them in the meta-analysis. The pooled ES values for overweight and obese mothers were −0.02 (95% CI: −0.05 to 0.02) and −0.06 (95% CI: −0.09 to −0.03), respectively. The pooled ES for the relationship between pre-gestational excess weight (overweight and obesity) and children's neurocognitive development was −0.04 (95% CI: −0.06 to −0.02).

Conclusions: Pre-pregnancy obesity might have negative consequences on the neurocognitive development of offspring.

Key words: Pregnancy, obesity, children, cognition, cognitive function, neurocognitive development

Key Messages

- This systematic review identified 15 articles that investigated the relationship between pre-pregnancy weight status and children's neurocognitive development.
- This meta-analysis showed that pre-pregnancy obesity, but not overweight, was negatively related with children's neurocognitive development.
- Future studies are needed to better define the mechanisms underlying the associations between pre-pregnancy obesity and children's neurocognitive development.

Introduction

Overweight and obesity prevalence have greatly increased in recent years, becoming one of the most important public health problems in most countries. Worldwide, the proportion of adults with excess weight has been estimated at approximately 37% for men and 38% for women.[1] Around 60% of women at reproductive age from the USA and Australia are classified as overweight or obese.[2] Specifically, in 2011–12, the prevalence of obesity among women of reproductive age in the USA was 31.8%, half of whom classified as obesity class I, and the other half as obesity classes II and III. This prevalence has not stopped growing since the 1970s (less than 10%).[1,3] In adults, overweight and obesity have been associated with several cardiometabolic diseases, cancer and reproductive disorders, among others.[4]

Maternal overweight and obesity could result in negative outcomes for both mother and fetus, and could also influence fertility, as well as the duration and outcomes of pregnancy.[5] During pregnancy, overweight mothers are at risk of gestational diabetes, thromboembolism, preterm delivery, caesarean section and preeclampsia; the fetus also has an increased risk of death, congenital anomalies and macrosomia.[6] Furthermore, obesity during pregnancy could affect the mother's and child's health later in life. Women could be at increased risk of heart disease, diabetes and hypertension, and children could be at increased risk of developing future obesity and heart disease.[7] Strategies to combat excess weight, such as physical activity interventions, have shown some effectiveness in mitigating this negative influence.[8–10]

Obesity and overweight during pregnancy have been negatively associated with fetal and offspring neurodevelopment. Maternal obesity produces an inflammatory uterine environment that could negatively influence brain development during gestation[11,12] and, as a consequence might result in neurodevelopmental impairment in offspring.[13]

The physiological mechanisms behind these long-term negative consequences in offspring are unclear. The fetal programming hypothesis suggests that the exposure of the fetus to an adverse intrauterine environment would be sufficient to produce permanent programming changes in tissue function and, as a result, long-term adverse effects on offspring neurodevelopment.[14,15] Other factors might also influence this relationship, such as pregravid obesity which has been associated with a high risk of vitamin D deficiency that could have a direct impact on the nutritional status of the neonate.[16] Moreover, some psychological conditions such as personality characteristics, increased stress levels or stress sensitivity in obese mothers also have been proposed as possible mediators of this association.[17]

Three previous systematic reviews[17–19] have examined the role of pre-pregnancy weight status in children's neurodevelopment. All of them reported a negative relationship between pre-pregnancy excess weight, especially obesity, and children's neurodevelopment, and stated that children from pre-pregnancy overweight/obese women could be at increased risk of some disorders in childhood and adolescence, such as attention deficit hyperactivity disorder, eating and psychotic disorders or motor development disorders. These systematic reviews are valuable in understanding the evidence regarding the effects of pre-pregnancy weight status on children's cognitive skills, but they did not quantify these effects. Because of the steadily rising of women's obesity prevalence worldwide, it seems necessary to ascertain the effect of this problem on children's cognitive development. The aim of our systematic review and meta-analysis was to assess the effect of pre-pregnancy overweight and obesity on children's neurocognitive development.

Methods

This meta-analysis has been registered in PROSPERO (Registration Number: CRD42016042101), and was guided by the MOOSE (Meta-analysis of Observational Studies in Epidemiology) Statement[20] and the Cochrane Collaboration Handbook.[21]

Search strategy

A literature search was performed in MEDLINE (via PubMed), EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic

Reviews and Web of Science databases from their inception through February 2017. The search strategy combined the following relevant terms: 'pregnancy', 'maternal', 'gestational', 'weight status', 'obesity', 'adiposity', 'weight gain', 'body mass index', 'cognition', 'neurodevelopment', 'intellectual', 'intelligence', 'cognitive function' and 'academic' (Table S1, available as Supplementary data at *IJE* online, for MEDLINE database search strategy). The references lists of the retrieved articles were also reviewed for any additional relevant studies. The systematic review was independently performed by two reviewers (C.A.B. and I.C.R.) and disagreements were resolved by consensus meetings. The overall percentage of agreement was calculated to evaluate inter-rater agreement for inclusion of eligible articles.

Selection criteria

Studies concerning the relationship between pre-pregnancy weight status and children's cognition were included. Inclusion criteria were as follows: (i) participants: pregnant women and their offspring; (ii) study design: follow-up studies; (iii) exposure: calculated pre-pregnancy weight status; and (iv) outcome: children's cognition assessed by standardized test scores or curricular-based grades related to specific subject areas. Studies were excluded when they were not written in English or Spanish, and also when they included pregnant women younger than 15 years. Studies were likewise excluded when the target population was specifically: (i) mothers with intellectual disabilities; (ii) children not born at full term; and (iii) children with mental disorders that could limit generalizability [attention-deficit/hyperactivity disorder (ADHD), conduct or neuropsychiatric disorders including schizophrenia, or any detected delay in communication, adaptive, cognition or socio-emotional domains].

Data extraction

Two researchers (C.A.B. and I.C.R.) independently collected the following data from original studies: (i) country; (ii) mothers' age at birth; (iii) weight status criteria used for the classification of the mothers' body mass index (BMI); (iv) cohort year of birth; (v) age of the children at evaluation; (vi) number of children in each cohort; and (vii) tool and/or scale used for the children's neurocognitive development assessment and domains evaluated. Also, estimates regarding the association between pre-pregnancy weight status and children's neurocognitive development were extracted as originally reported by the studies. Disagreements in data collection were resolved by discussion. The overall percentage of agreement was calculated to evaluate inter-rater agreement for inclusion in the data extraction process. Corresponding authors of studies were contacted to obtain missing data.

Quality assessment

After concealment of information about authors, affiliations, date and source of each manuscript, two investigators (C.A.B. and I.C.R.) independently assessed its methodological quality. A standardized checklist for reporting observational longitudinal research was used.[22] This checklist includes two categories of criteria: (i) aspects that could influence effect estimates (such as the description of the validity and reliability of the measurement methods); and (ii) descriptive and contextual issues (such as the definition of the study population, eligibility criteria and method used for data collection). The rating list consists of 33 criteria, and each criterion was assessed as 'yes' (=1), 'no' (=0) or 'not applicable' (=?); thus, the quality score for each study ranged from 0 to 33. Disagreements were resolved by consensus with a third investigator (V.M.V.).

Data synthesis and statistical analysis

Effect size (ES) was the principal outcome; this statistic provides a measure of change in the outcome variable in terms of standard deviation units. A standardized mean difference score was calculated for each pre-pregnancy weight status category as an estimate of ES.[23] When studies provided a linear regression β coefficient, it was used to calculate a standardized mean difference score.[23,24] When studies provided odds ratio (OR) estimates, the ES was calculated using the natural log OR.[23,25] A pooled estimate for each weight status category based on the World Health Organization (WHO) weight status classification[26] was calculated when the studies presented estimates for BMI values. Other weight status criteria, such as the Centers for Disease Control and Prevention (CDC) criteria, were considered similar to those of WHO; thus, their estimates for the relationship between excess weight categories and children's neurocognitive development were jointly considered with those from WHO when we calculated the pooled ES estimates.

Some concerns regarding repeated measurements in the same sample should be considered in this meta-analysis as follows.

i. When a study included two cohorts, their data were analysed as independent samples;
ii. When cognitive development was measured within the same cohort using different tests, a main pooled estimate considering the values for all the tests was

performed (if a test provided a total score value, this was the only one considered for the pooled estimate);

iii. When in the same cohort, the association estimates were calculated more than once with the same test, in order to avoid overrepresentation bias, only the latter estimate was considered for the meta-analysis. However, the effect sizes are shown in tables summarizing the original study results in order to provide information regarding whether the effect differed depending on the age of the children;

iv. When several estimates were reported within the same study, the most adjusted model was used for the pooled ES estimate.

v. Finally, only studies reporting separate data for pre-pregnancy overweight and obesity were included in the meta-analysis.

The Mantel-Haenszel fixed-effects method[27] was used to compute pooled ES estimates and their respective 95% confidence intervals (95% CIs), which were used to examine the effect of overweight and obesity categories on children's cognition, using normal weight as the reference category. Additionally, a pooled ES of excess weight (overweight and obesity) was conducted and compared with normal weight (reference category). Since general intelligence/full-scales scores are considered a representative construct of all mental performance, we also calculated a pooled general intelligence/composite cognitive scores ES estimate. The heterogeneity of the results across studies was evaluated using the I^2 statistical parameter. I^2 values of <25%, 25–50% and >50% usually correspond to small, medium and large heterogeneity, respectively;[28] the corresponding *P*-values were also considered.

Sensitivity analysis was conducted by removing studies one by one in order to assess the robustness of the summary estimates, and to detect whether any particular study accounted for a large proportion of heterogeneity. Random-effects meta-regression was used to evaluate whether effect estimates differed according to children's age, since this could be considered a source of heterogeneity. For this meta-regression analysis, each included study was individually considered, in order to reflect the reported measurements at different ages.

Finally, publication bias was evaluated using Egger's regression asymmetry test for assessment of 'small studies effects'.[29] Statistical analyses were performed using StataSE software, version 14 (StataCorp).

Results

The search retrieved a total of 3823 articles. Of these, 836 were removed as duplicates and 2987 were screened based on the title and abstract. Finally, 15 articles met the inclusion criteria[30–44] (Figure 1). The mean inter-rater agreement for inclusion of eligible articles was 85%.

Table 1 summarizes the main characteristics of the included studies. The included samples ranged from 215 to 11 025, belonging to 13 cohorts born between 1959 and 2012. Five cohorts were from the USA;[35–38,40–42] two each from The Netherlands,[32,44] the UK,[30,32] Spain[33,43] and Greece;[33,34] and one each from Denmark[31] and Poland.[39] The mothers' age at birth ranged from 15 to over 40 years, and children's neurocognitive development was assessed when they were aged between 6 months and 14 years. Three studies[30,39,43] provided data at two follow-up times. All studies but two[38,42] used the WHO criteria for establishing mothers' pre-pregnancy weight status. Studies used several different scales for measuring cognition-related aspects, such as general intelligence/total scores,[31–35,37–39,40,43,44] language-related skills,[30–32,34,36–39,41–43] mathematics-related skills,[41,42] executive functions-related measurements (spatial visualization, performance, sequential processing and simultaneous processing),[30,31,34,37,40,44] nonverbal skills[30,32,38] and academic achievement.[36] The mean inter-rater agreement for extraction data of included studies was 87%.

Tables 2 to 5 summarize the association between maternal pre-pregnancy weight status and children's cognitive development total score as retrieved from the original articles. Among all articles, one provided data regarding the intensity of this relationship using OR estimates from logistic regression models[32] (Table 2). Another article provided data as means obtained in a cognition test[43] (Table 3). The remaining 13 articles showed estimates of β coefficients from multiple logistic regression models using normal weight as reference (Tables 4 and 5).

The data extracted from the included studies were adjusted for several family and child covariates (Table S2, available as Supplementary data at *IJE* online). All except five articles provided data by weight status categories.[30–32,39,43] Within these articles, the estimates of the relationship between children's neurocognitive development and mothers' weight status were reported in a continuous scale,[30,31,43] or as an excess weight category that combined overweight and obese individuals.[32,39] Only one cohort[32] found a small but negative association between maternal pre-pregnancy excess weight (including both overweight and obesity groups) and offspring general intelligence (OR = 0.84; 95% CI = 0.73 to 0.98).

Study quality

Studies met 57.58%[38] to 84.84%[41] of the quality criteria, as assessed by the Quality of Reporting of Observational Longitudinal Research[22] instrument (Table S3, available as

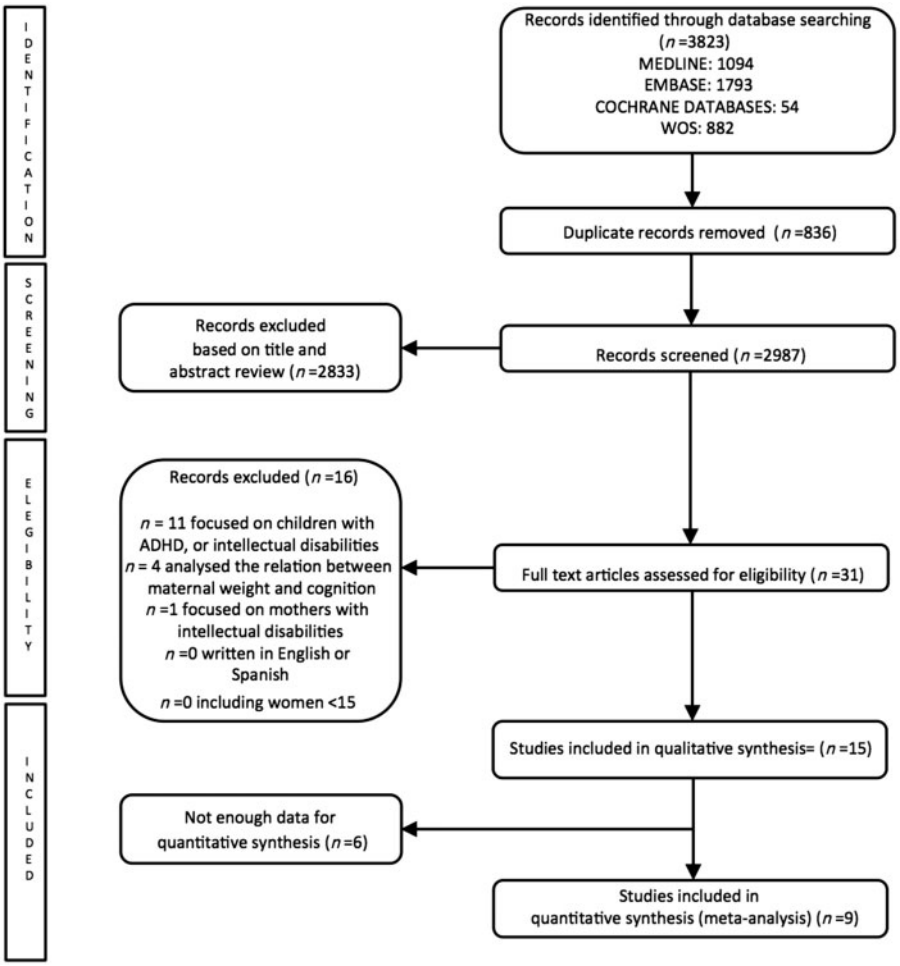

Figure 1. Literature search PRISMA consort diagram.

Supplementary data at *IJE* online). Only one study[41] included information regarding the reasons for refusing to participate in the study, and no studies included the justification for the number of participants. Furthermore, only one study[41] discussed the qualitative or quantitative impact of potential biases. Only four studies[30,34,41,42] informed about the reliability and validity of the tool used to measure neurocognitive development.

Meta-analyses

For the calculation of the pooled ES of overweight and obesity categories, only the studies providing separate data for these pre-pregnancy weight status categories were included.[33–38,40–43]

ES for the relationship between weight status and children's neurocognitive development were −0.02 (95% CI: −0.05 to 0.02) and −0.06 (95% CI: −0.09 to −0.03) for pre-pregnancy overweight and obesity, respectively. Heterogeneity estimates were $I^2 = 0.0\%$ ($P = 0.98$) and $I^2 = 0.0\%$ ($P = 0.680$) for pre-pregnancy overweight and obesity analyses, respectively (Figure 2). The pooled effect for the excess weight category was −0.04 (95% CI: −0.06 to −0.02). The heterogeneity estimate was $I^2 = 0.0\%$ ($P = 0.83$).

Additionally, the pooled ES estimate for weight status and children's general intelligence, or full-scales scores,[33–35,37,38,40] were −0.02 (95% CI: −0.06 to 0.02) and −0.05 (95% CI: −0.10 to 0.00) for pre-pregnancy overweight and obesity analyses, respectively. Heterogeneity estimates were $I^2 = 0.0\%$ ($P = 0.89$), and $I^2 = 0.0\%$ ($P = 0.60$) for pre-pregnancy overweight and obesity analyses, respectively (Figure 3). The pooled effect for the excess weight category was −0.03 (95% CI: −0.06 to 0.00). The heterogeneity estimate was $I^2 = 0.0\%$ ($P = 0.85$).

Sensitivity analyses

Sensitivity analyses suggested that the pooled ES or heterogeneity were not modified either in the overweight or in the obesity analyses by removing the included cohorts one

Table 1. Characteristics of the included studies

Author	Country	Mothers' age[1]	Mothers' BMI reference values[2]	Cohorts' year of birth	Age of child at evaluation (years)[3]	*n*	Neurodevelopment assessment of children and dimensions
Basatemur *et al.* 2012[30]	UK	24.7–29.0	WHO	2000–02	5.0	11025	British Ability Scale (BAS-II): ✓ Expressive language ✓ Nonverbal reasoning ✓ Spatial visualization
					7.0	9882	British Ability Scale (BAS-II): ✓ Verbal ability ✓ Spatial visualization
							National Foundation for Educational Research (NFER)
Bliddal *et al.* 2014[31]	Denmark	21.0–40.0	WHO	1996–2002	5.0–5.3	1783	Wechsler Primary and Preschool Scales of Intelligence (WPPSI): ✓ Verbal ✓ Performance ✓ IQ
Brion *et al.* 2010[32]	The Netherlands	NA	WHO	2002–06	2.5	2398/2385*	Language Development Survey: ✓ Verbal skills (sentence length and word production)
						2258	Dutch Version of the Parent Report of Children's Abilities (PARCA) ✓ Nonverbal skills
	England	NA	WHO	1991–92	3.2	4658/4712**	MacArthur Toddler and Communication Questionnaire: ✓ Vocabulary and word combination
					8.0	3221	Diagnostic Analysis of Nonverbal Accuracy test: ✓ Nonverbal skills Wechsler Intelligence Scale for Children II: ✓ IQ
Casas *et al.* 2013[33]	Spain	25.0–35.0	WHO	2004–08	1.2	1869	Bayley Scales of Infant Development (BSID): ✓ Cognitive development scores.
	Greece	25.0–35.0	WHO	2007–09	1.5	397	Bayley Scales of Infant Development (BSID): ✓ Cognitive development scores
Daraki *et al.* 2017[34]	Greece	29.5 (4.8)–30.2 (5.4)	WHO	2007–09	4.3 (0.2)	772	McCarthy Scales of Children's Abilities (MCSA): ✓ Verbal scale ✓ Perceptual-performance scale ✓ Quantitative scale ✓ Memory scale
Hinkle *et al.* 2012[35 a]	USA	15.0–50.0	WHO	2001	1.5–3.1	6850	Bayley Short Form-Research Edition (BSF-R): ✓ Mental development index.
Hinkle *et al.* 2013[36 a]	USA	15.0–50.0	WHO	2001	5–6	5100	Standardized test: ✓ Reading ✓ Mathematics

(Continued)

Table 1. Continued

Author	Country	Mothers' age[1]	Mothers' BMI reference values[2]	Cohorts' year of birth	Age of child at evaluation (years)[3]	*n*	Neurodevelopment assessment of children and dimensions
Huang *et al.* 2014[37]	USA	20.0–40.0	WHO	1959–65	7.1 (0.8)	8059	Wechsler Intelligence Scale for Children (WISC): ✓ Verbal scale ✓ Performance scale ✓ Full- scale IQ
Neggers *et al.* 2003[38]	USA	21.6 (7.3)	Normal: 19.8–26.0 Overweight: 26.1–29.0 Obese: >29.0	NA	5.3 (0.3)	355	Differential Ability Scales (DAS): ✓ Verbal ability ✓ Nonverbal ability ✓ IQ Peabody Picture Vocabulary Test (PPVT) ✓ Receptive language skills
Polanska *et al.* 2015[39]	Poland	30.5 (4.5)	WHO	2007	1.0 (0.1)	437	Bayley Scales of Infant Toddler Development: ✓ Cognitive skills ✓ Composite language
					2.0 (0.2)	279	Bayley Scales of Infant Toddler Development: ✓ Cognitive skills ✓ Composite language
Pugh *et al.* 2015[40]	USA	NA	WHO	1983–86	10.0	530	Stanford-Binet Intelligence Scale: ✓ IQ Wisconsin Card Sorting test: ✓ Perseverative errors Trail making test part B: ✓ Executive function
Pugh *et al.*2016[41]	USA	NA	WHO	1983–86	6, 10 and 14	574	Wide Range Achievement Test-Revised (WART-R) and Wechsler Individual Achievement test (WAIT): ✓ Mathematics ✓ Reading ✓ Spelling
Tanda *et al.* 2012[42]	USA	25.4 (0.5)	CDC	1979–94	6.0 (0.6)	3412	Peabody Individual Achievement Test (PIAT): ✓ Mathematics ✓ Reading recognition
Torres-Espinola *et al.* 2015[43]	Spain	31.0 (3.8)	WHO	2007–12	0.5	215	Bayley Scales of Infant Development (BSID-III): ✓ Cognitive skills ✓ Receptive language ✓ Expressive language ✓ Composite language
					1.5	197	Bayley Scales of Infant Development (BSID-III): ✓ Cognitive skills ✓ Receptive language ✓ Expressive language ✓ Composite language

(Continued)

Table 1. Continued

Author	Country	Mothers' age[1]	Mothers' BMI reference values[2]	Cohorts' year of birth	Age of child at evaluation (years)[3]	*n*	Neurodevelopment assessment of children and dimensions
Veldwijk *et al.* 2011[44]	The Netherlands	29.9 (4.2)	WHO	1990–94	7.3 (0.3)	274	Kaufman Assessment Battery for Children (K-ABC): ✓ Sequential processing scale ✓ Simultaneous processing scale ✓ Mental processing scale

[1]Range or mean (SD) of maternal age as reported by the original studies.
[2]Range or mean (SD) of children at measurement point as reported by the original studies.
[3]BMI (body mass index) reference values; WHO (World Health Organization): normal (18.5 to 24.9); overweight (25.0 to 29.9); and obese (30 to 39.9); CDC (Centers for Disease Control and Prevention): normal (18.5 to 24.9); overweight (25.0 to 29.9); and obese (30 or higher).
*$n = 2398$ for sentence length and $n = 2385$ for word production.
**$n = 4658$ for sentence length and $n = 4712$ for word production.
[a]Hinkle *et al.* 2012 and 2013 are based on the same sample population, thus only Hinkle *et al.* 2012 was considered for the meta-analysis due to the use of the Bayley Short Form-Research Edition (BSF-R) validated scale.
[b]Pugh *et al.* 2015 and 2016 are based on the same population; both were included in the meta-analysis by pooling scores from for Stanford-Binet Intelligence Scale (Pugh *et al.* 2015) and Wide Range Achievement Test-Revised (WART-R) and Wechsler Individual Achievement test (WAIT) (Pugh *et al.* 2016).
NA, not available.

by one (Table S4, available as Supplementary data at *IJE* online).

Random-effects meta-regression model

The random-effects meta-regression model showed that the effect of prepregnancy overweight ($P = 0.48$) or obesity ($P = 0.32$) on children's neurocognitive development was not related with children's age. This model showed that children's age was also not related with the heterogeneity observed across the studies. (Figure S1A-B, available as Supplementary data at *IJE* online)

Publication bias

Funnel plots did not display evidence of publication bias for any of the pooled subgroup analyses (overweight $P = 0.29$ and obesity $P = 0.23$) [25] (Table S5, available as Supplementary data at *IJE* online).

Discussion

The association between pre-pregnancy weight status and neurocognitive development among healthy offspring has not yet been elucidated. This meta-analysis aimed to assess the effect of pre-pregnancy mothers' overweight and obesity on offspring's neurocognitive development. Overall, this study showed that mothers who are obese before pregnancy, but not overweight, have a negative influence on the offspring's neurocognitive development (ES = −0.06; 95% CI: −0.09 to −0.03). Furthermore, pre-pregnancy obesity could have a small negative, though not statistically significant, effect on children's general intelligence (ES = −0.05; 95% CI: −0.10 to 0.00).

The results of this meta-analysis are in line with previous reviews that have suggested a negative relationship between pre-pregnancy obesity and children's neurocognitive development.[17–19] Even though a mild, or even negligible, influence of pre-pregnancy obesity on children's neurodevelopment or general intelligence, this finding should be cautiously taken into consideration due to the worldwide increasing number of women of childbearing age, and considering that gestation and childhood are critical periods in neurocognitive development. Furthermore, additional experimental research on the relationship between pre-pregnancy obesity and children's neurodevelopment, including longer follow-up periods, is needed.

The model proposed by van der Burg *et al.*[45] suggests that mother's obesity produces a chronic systemic inflammation ambience with negative consequences for fetal development. This obesity-related inflammatory process increases insulin concentrations, leptin levels and other

Table 2. Odds ratio (95% CI) for excess of weight (overweight/obesity) as predictor of children's cognition (normal weight as reference category)

Author	Tool for children's cognition assessment and dimensions	Children's age[a]	OR (95% CI)
Brion *et al.* 2010[32]	Diagnostic Analysis of Nonverbal Accuracy test		
	✓ ALSPAC. Nonverbal skills	2.5	0.97 (0.83 to 1.14)
	MacArthur Toddler and Communication Questionnaire		
	✓ ALSPAC. Sentence length	2.5	0.88 (0.78 to 1.00)
	✓ ALSPAC. Word production	2.5	0.95 (0.84 to 1.08)
	Dutch Version of the Parent Report of Children's Abilities (PARCA)		
	✓ Generation R. Nonverbal skills	3.2	1.08 (0.90 to 1.30)
	Language Development Survey		
	✓ Generation R. Sentence length	3.2	0.88 (0.74 to 1.05)
	✓ Generation R. Word production	3.2	0.91 (0.76 to 1.08)
	Wechsler Intelligence Scale for Children II		
	✓ ALSPAC. IQ	8	0.84 (0.73 to 0.98)

[a]Range or mean (SD) of children at measurement point as reported by the original studies.

Table 3. Chidren's cognition mean scores (±SD) by excess of weight category

Author	Tool for children's cognition assessment and dimensions	Children's age[a]	Overweight ± SD	Effect size[b]	Obesity ± SD	Effect size[b]
Torres-Espinola *et al.* 2015[43]	Bayley Scales of Infant Development (BSID-III):					
	✓ Composite cognitive	0.5	109.1 ± 8.0	0.20	112.8 ± 7.1	0.69
	✓ Expressive language	0.5	10.7 ± 2.0	0.36	11.1 ± 1.8	0.59
	✓ Receptive language	0.5	12.2 ± 2.2	0.27	12.6 ± 2.3	0.45
	✓ Composite language	0.5	109.0 ± 9.8	0.41	111.0 ± 8.9	0.62
	✓ Composite cognitive	1.5	123.4 ± 11.3	0.27	121.6 ± 9.6	0.12
	✓ Expressive language	1.5	10.4 ± 2.0	−0.15	10.4 ± 2.1	−0.16
	✓ Receptive language	1.5	11.9 ± 1.1	0.00	11.4 ± 1.3	−0.30
	✓ Composite language	1.5	106.2 ± 8.2	−0.19	105.5 ± 8.8	−0.26

[a]Range or mean (SD) of children at measurement point in years as reported by the original studies.
[b]Normal weight as category of comparison.

low-grade inflammatory markers that could produce errors in brain maturation.[46] Other physiological obesity-related changes such as oxidative stress and endothelial dysfunction might also negatively influence children's brain maturity.[47]

Besides this hypothesis, new explanations have been suggested to clarify this relationship. The epigenetic hypothesis proposes that the fetus receives a set of information related to environmental factors from the mother, which is capable of producing changes in gene expression responsible not only for metabolic diseases but also for psychiatric disorders across the life span.[48] Previous research has described that these effects might be the consequence of interaction between genes and increased levels of fatty acids, glucose, leptin and inflammatory markers[49] that might have an influence on plasticity and cognitive function.[50] Children from obese mothers are at greater risk of developing insulin resistance and cardiometabolic diseases and also of having excess overall and central adiposity.[51–53] Additionally, obesity has been associated with cognitive deficits, not only in children but also in adolescents and adults, regardless of socioeconomic factors. A bidirectionality in causal pathways has been suggested, in such a way that lower scores on tests for executive function have been related with the development of obesity across the life span.[54]

In addition to obesity during pregnancy, pre-pregnancy obesity has been associated with neurocognitive developmental deficits such as cognitive deficits and also with autism spectrum[55] and psychotic[56] disorders in offspring. Our meta-analysis confirms that pre-pregnancy obesity, but not overweight, could be associated with worse neurocognitive development scores in children. Current evidence has elucidated that neural circuits and brain structure growth are

Table 4. Body mass index as predictor (β coefficients) of cognition in multiple linear regression models

Author	Tool for children's cognition assessment and dimensions	Children's age (SD)[a]	β coefficients
Basatemur *et al.* 2012[30]	British Ability Scale (BAS-II):		
	✓ British Ability scale: g	5.0	−0.08 ($P < 0.0001$)
	✓ British Ability scale: g	7.0	−0.17 ($P = 0.0069$)
Bliddal *et al.* 2014[31]	Wechsler Primary and Preschool Scales of Intelligence:		
	✓ IQ	5.0–5.3	−0.27 (−0.50 to −0.03)
Polanska *et al.* 2015[39]	Bayley Scales of Infant Toddler Development:		
	✓ Composite language	1	1.6 (−1.2 to 4.5)
	✓ Composite cognitive	1	2.8 (−0.04 to 5.7)
	✓ Composite language	2	1.4 (−2.1 to 4.9)
	✓ Composite cognitive	2	2.2 (−1.4 to 5.7)
Veldwijk *et al.* 2011[44]	Kaufman Assessment Battery for Children (K-ABC):		
	✓ Sequential processing scale	7.3 (0.3)	−0.66 (−1.08 to −0.25)
	✓ Simultaneous processing scale	7.3 (0.3)	−0.66 (−1.11 to −0.22)
	✓ Mental processing scale	7.3 (0.3)	−0.55 (−0.95 to −0.14)

[a]Range or mean (SD) of children in years at measurement point as reported by the original studies.

continuous procedures from conception to adulthood, and therefore related to executive functions and cognition acquisition.[46] In that way, offspring from obese mothers might be at higher risk of suffering from deficits in their brain maturation and neurocognitive development, regardless of the age at which they are evaluated.

Additional pathways that could potentially explain worse neurocognitive development in offspring from obese mothers could include some gestational complications, which are more common among obese mothers, such as congenital abnormalities, preeclampsia, gestational diabetes mellitus, iatrogenic preterm delivery or increased rates of labour induction and caesarean deliveries.[57] In particular, research has related gestational diabetes and hypertension during pregnancy with delay in brain maturity and induction of neurobehavioural abnormalities in offspring, affecting intellectual function, although the causal influence remains unclear.[33,58,59]

Previous studies[31,33,45] have suggested that the relationship between a mother's excess weight and neurocognitive development could be confounded by other pre- and postnatal factors such as home conditions, family income or maternal and paternal educational or intelligence levels.[60] Our findings suggest that the relationship between pre-pregnancy obesity and children's neurocognitive development scores could be independent of those confounders, as all the included studies considered family sociodemographic variables in their analyses. Conversely, we cannot ignore the possible residual confounding effect that could result from incomplete or unreliable measurements of sociodemographic variables. Furthermore, the relationships between mothers' pre-pregnancy weight status and children's cognitive function were softened after controlling for some covariates such as maternal age and/or education, family income or children's age. Additional research is needed for examining how these effects could be confounded by other important mother's (general intelligence, maternal depression, gestational diabetes or maternal glucose intolerance) and child's (birthweight or cardiorespiratory fitness) covariates, and by more accurate socioeconomic variables measurements.

The limitations of this study are those common to meta-analyses: publication bias, selection bias, potential ecological fallacy and limited information from study reports. In particular, we should detail the following constraints that may affect the robustness of our pooled estimates.

i. Although we did not find evidence for significant publication bias in our study, it is perfectly conceivable that studies with poor results were unlikely to be published.
ii. We should consider that the meta-analyses were not conducted using the original data as provided by the studies (β and OR values), but by using ES estimates and their corresponding 95% CIs from the published data; thus bias cannot be ruled out.
iii. Only seven studies scored positively in at least two-thirds of the quality assessment scale items, which could threaten the internal validity of these studies. Studies should be required to include more complete information regarding sampling criteria such as the sample size rationale, number of population meeting and not meeting the eligibility criteria, reasons for refusing participation, and comparisons between those who agree to participate and those who not. Also, more accurate information regarding the impact of bias and statistical analysis is needed.
iv. Although included studies have children's neurocognitive development as a main outcome variable, there is

Table 5. β coefficient for linear regression models using cognition variables as dependent variables (normal weight as reference category)

Author	Tool for children's cognition assessment and dimensions	Children's age (SD)[1]	Overweight (95% CI)	Effect size[2]	Obesity (95% CI)		Effect size[2]	
Casas *et al.* 2013[33]	Bayley Scales of Infant Development: INMA	1.2	−0.88 (−2.64 to 0.88)	−0.02	−2.72 (−5.35 to −0.10)		−0.05	
	Bayley Scales of Infant Development: RHEA	1.5	1.41 (−2.26 to 5.08)	0.04	−3.71 (−8.45 to 1.02)		−0.09	
Daraki *et al.* 2017[34]	McCarthy Scales of Children's Abilities (MCSA):							
	✓ Verbal scale	4.3 (0.2)	−0.88 (−3.34 to 1.58)	−0.03	−2.24 (−5.32 to 0.84)		−0.06	
	✓ Perceptual-p scale	4.3 (0.2)	−2.90 (−5.40 to −0.40)	−0.09	−4.60 (−7.74 to −1.47)		−0.12	
	✓ Quantitative scale	4.3 (0.2)	−0.82 (−3.42 to 1.77)	−0.02	−4.43 (−7.68 to −1.18)		−0.11	
	✓ General cognitive	4.3 (0.2)	−1.84 (−4.28 to 0.60)	−0.06	−4.03 (−7.08 to −0.97)		−0.10	
	✓ Memory scale	4.3 (0.2)	−0.28 (−2.82 to 2.25)	−0.01	−2.83 (−6.00 to 0.34)		−0.07	
	✓ Executive function	4.3 (0.2)	−2.47 (−4.97 to 0.04)	−0.07	−4.92 (−8.06 to −1.78)		−0.12	
Hinkle *et al.* 2012[35]	Bayley Short Form-Research Edition (BSF-R):							
	✓ Mental development index	1.5–3.1	−0.21 (−0.88 to 0.46)	−0.01	−0.57 (−1.63 to 0.48)[a]	−2.13 (−3.32, −0.93)[b]	−0.02[a]	−0.05[b]
Hinkle *et al.* 2013[36]	Standardized test:							
	✓ Reading	NA	−0.11 (−0.19 to −0.03)	−0.04	−0.14 (−0.27 to 0.00)[a]	−0.14 (−0.29, 0.02)[b]	−0.03[a]	−0.03[b]
	✓ Mathematics	NA	−0.06 (−0.13 to 0.02)	−0.02	−0.06 (−0.16 to 0.04)[a]	−0.14 (−0.29, 0.01)[b]	−0.02[a]	−0.03[b]
Huang *et al.* 2014[37]	Wechsler Intelligence Scale for Children:							
	✓ Verbal scale	7.1 (0.8)	−0.50 (−1.3 to 0.4)	−0.02	−2.50 (−4.0 to −1.0)		−0.03	
	✓ Performance scale	7.1 (0.8)	−0.20 (−1.1 to 0.8)	−0.01	−1.00 (−2.7 to 0.7)		−0.01	
	✓ Full-scale IQ	7.1 (0.8)	−0.30 (−1.10 to 0.50)	−0.01	−2.00 (−3.50 to −0.50)		−0.03	
Neggers *et al.* 2003[38]	Differential Ability Scales (DAS):							
	✓ IQ	5.3 (0.3)	−1.10 (SE: 2.00)	−0.04	−4.70 (SE: 1.40)		−0.20	
	✓ Nonverbal score	5.3 (0.3)	−0.47 (SE: 2.6)	−0.01	−5.6 (SE: 1.8)		−0.19	
Pugh *et al.* 2015[40]	Stanford-Binet Intelligence Scale:							
	✓ IQ	10.0	−0.88 (−1.46 to −0.30)	−0.15	−2.45 (−3.53 to −1.36)		−0.23	
Pugh *et al.* 2016[41]	Wide Range Achievement Test-Revised (WART-R) and Wechsler Individual Achievement test (WAIT):							
	✓ Mathematics	6-10-14	−1.10 (−1.83 to −0.40)	−0.15	−2.85 (−4.27 to 1.44)		−0.10	
	✓ Reading	6-10-14	−0.79 (−1.31 to −0.26)	−0.15	−2.38 (−3.91 to −0.86)		−0.16	
	✓ Spelling	6-10-14	−1.04 (−1.72 to −0.35)	−0.15	−2.75 (−4.23 to −1.27)		−0.19	
Tanda *et al.* 2012[42]	Peabody Individual Achievement Test (PIAT)							
	✓ Reading recognition	6.0 (0.6)	−0.81 (SE: 0.59)	−0.02	−3.14 (SE: 0.80)		−0.08	
	✓ Mathematics	6.0 (0.6)	−0.81 (SE: 0.57)	−0.03	−2.37 (SE: 0.83)		−0.06	

SE, standard error.

[a]Obesity class I.

[b]Obesity class II and III.

[1]Range or mean (SD) of children at measurement point in years as reported by the original studies.

[2]Normal weight as category for comparison.

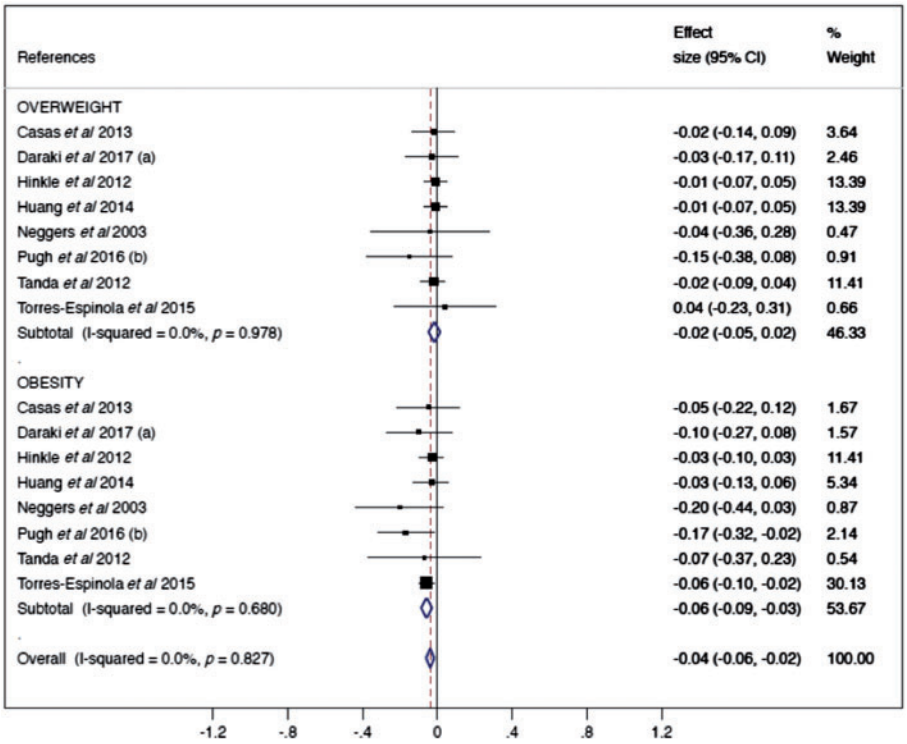

Figure 2. Pooled estimated effect size for children's neurodevelopment. a) This cohort represents the pooled effect size estimation for REAH sample of children's scores obtained on Bayley Scales of Infant Development (BSID) and McCarthy Scales of Children's Abilities (MCSA), extracted from Casas et al 2013 and Daraki et al 2017, respectively. b) This cohort represents the pooled effect size estimation for Pugh et al sample of children's scores obtained on Stanford-Binet Intelligence Scale and Wide Range Achievement Test-Revised (WART-R) and Wechsler Individual Achievement test (WAIT), extracted from Pugh et al 2015 and Pugh et al 2016, respectively. CI: Confidence Interval.

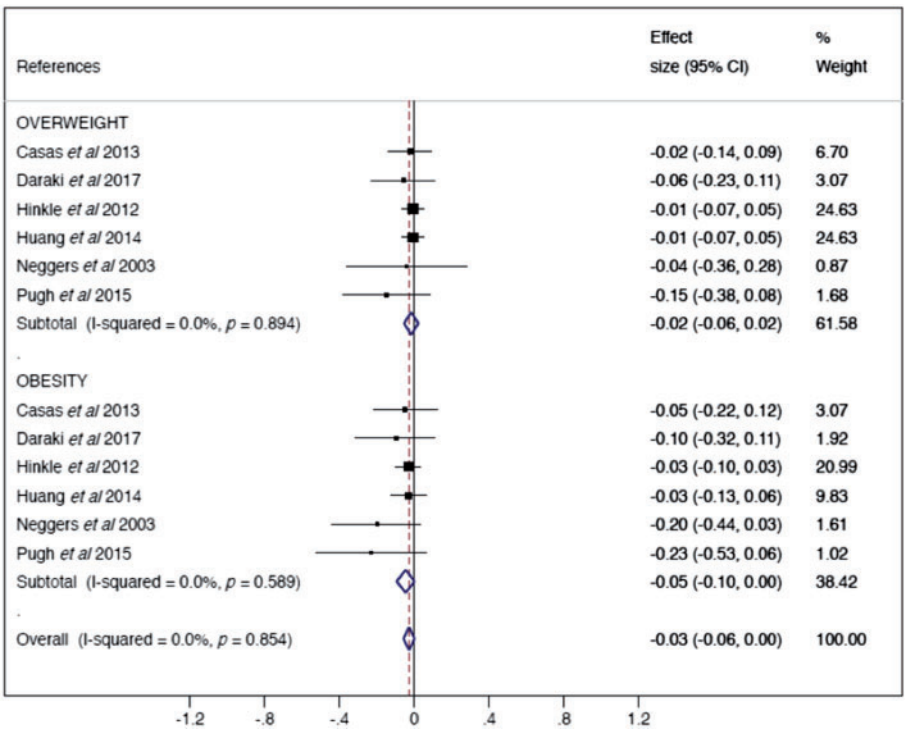

Figure 3. Pooled estimated effect size for children's general intelligence/composite cognitive scores. CI: Confidence Interval.

not a single universally accepted scale for the measurement of this construct, and only two scales have been used in more than one study: the Wechsler Intelligence Scale (in two studies) and the Bayley Scales of Infant Development (in three studies). Moreover, when limiting the analysis to general intelligence or composite scores, ES were similar.

v. Though meta-regression analyses did not find any statistically significant differences across children's age at evaluation, due to the reduced number of studies included in the meta-regression analysis, this finding should be taken cautiously.

vi. Because most studies lack rationale for the sample size estimates, the prevalence of excess weight in the samples could influence our pooled ES estimates. However, subgroup analyses including only studies from the USA, where the obesity prevalence is one of the highest in the world, showed similar pooled ES to when all studies were included: −0.02 (95% CI: −0.10 to 0.07) for overweight and −0.06 (95% CI: −0.12 to −0.01) for obesity. Therefore, we thought that the inclusion of cohorts from North America and Europe could actually be considered as an external validity indicator for our findings. Additionally, sensitivity analyses reinforced the results of this study, showing no ES changes when removing studies one by one.

Our meta-analysis provides supporting evidence that pre-pregnancy obesity may have negative consequences on offspring's neurocognitive development. Therefore, in order to mitigate the risk of future health cognition problems in childhood, it may advisable to implement interventions aimed at preventing overweight and obesity in all women of childbearing age, and particularly those who are planning a pregnancy. Further research is needed to elucidate the specific cognition functions more negatively affected by this relationship and to determine the effects of some variables that could act as moderators or mediators in this relationship.

Supplementary Data

Supplementary data are available at *IJE* online.

Funding

C.A.B. is supported by a grant from the Spanish Ministry of Education, Culture and Sport (FPU13/03137). I.C.R. is supported by a grant from the University of Castilla-La Mancha (FPU13/01582).

Conflict of interest: None declared.

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