OXFORD UNIVERSITY PRESS | International Journal of Epidemiology

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| Journal: | *International Journal of Epidemiology* |
| Manuscript ID | Draft |
| Manuscript Type: | Original Article |
| Date Submitted by the Author: | n/a |
| Complete List of Authors: | Álvarez-Bueno, Celia; Universidad de Castilla-La Mancha, Health and Social Research Center<br>Cavero-Redondo, Iván; Universidad de Castilla-La Mancha, Health and Social Research Center<br>Lucas-de la Cruz, Lidia; Universidad de Castilla-La Mancha, Health and Social Research Center<br>Notario-Pacheco, Blanca; Universidad de Castilla-La Mancha, Health and Social Research Center<br>Martínez-Vizcaíno, Vicente; Universidad de Castilla-La Mancha, Health and Social Research Center; Universidad Autónoma de Chile, Facultad de Ciencias de la Salud |
| Key Words: | pregnancy, obesity, children, cognition, cognitive function, neurocognitive development |
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# Association between pre-pregnancy BMI and children's neurocognitive development: a systematic review and meta-analysis of observational studies.

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**Word count Main Document:** 3113

**Word count Abstract:** 204

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## ABSTRACT

**Background:** Obesity and overweight during pregnancy have been negatively associated with foetal 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 May 16, 2016, for follow-up studies comparing the relationship between pre-pregnancy weight status and children's cognition. Random-effects models by the DerSimonian and Laird method were 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:** Ten studies were included in the systematic review, and seven of them in this meta-analysis. The pooled ES values for overweight and obese mothers were, -0.03 (95% CI: -0.09 to 0.02), and -0.23 (95% CI: -0.35 to -0.11), respectively. The pooled ES for the relationship between pre-gestational excess of weight (overweight and obesity) and children's neurocognitive development was -0.12 (95% CI: -0.19 to -0.06).

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


**Keywords:** pregnancy, obesity, children, cognition, cognitive function, neurocognitive development.

**KEY MESSAGES:**

- This systematic review identified ten 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 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 of weight has been estimated at approximately 37% for men and 38% for women [1]. In adults, overweight and obesity have been associated with several cardiometabolic diseases, cancer and reproductive disorders, among others. [2]

Maternal overweight and obesity could result in negative outcomes for both mother and foetus, and could also influence fertility, as well as the duration and outcomes of pregnancy. [3] During pregnancy overweight mothers are at risk of gestational diabetes, thromboembolism, preterm delivery, caesarean section and preeclampsia; the foetus has also an increased risk of death, congenital anomalies and macrosomia. [4] 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. [5] Strategies to combat excess weight, such as physical activity interventions, have shown some effectiveness on mitigate this negative influence. [6-8]

Obesity and overweight during pregnancy have been negatively associated with foetal and offspring neurodevelopment. Maternal obesity produces an inflammatory uterine environment that could negatively influence the brain development during gestation [9,10] and, as a consequence might result in neurodevelopmental impairment in offspring. [11]

The physiological mechanisms behind these long-term negative consequences in offspring are unclear. The foetal programming hypothesis suggests that the exposure of the foetus 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. [12, 13] Other factors might also influence this relationship, such as pregravid obesity, which has been associated with a high risk of vitamin D deficit that could have a direct impact on the nutritional status of the neonate. [14] Moreover, some psychological conditions such as personality characteristics, increased stress levels or stress sensitivity in obese mothers have been also proposed as possible mediators of this association. [15]

As far as we know, no study has reported separately a pooled estimate of the effect of pre-pregnant overweight and obesity on offspring neurocognitive development, while it was true that a recent systematic review [15] reported that offspring from mothers with obesity may be at increased risk of neurocognitive impairment, this review did not separately examine the influence of pre-pregnancy and pregnant obesity, and included jointly children's neurocognitive impairment with psychiatric and psychological

disorders as outcomes. 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 had been registered in PROSPERO (Registration Number: CRD42016042101), and was guided by the MOOSE (Meta-analysis of Observational Studies in Epidemiology) Statement [16] and the Cochrane Collaboration Handbook [17].

### 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 to May 16, 2016. 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 for MEDLINE database search strategy). The references' list of the retrieved articles was also reviewed looking for any additional relevant study. The systematic review was independently performed by two reviewers (CA and IC) 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 body mass index (BMI) 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 BMI; and (iv) outcome: children's cognition assessed by standardised 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 included: (i) pregnant women younger than 16 years old; (ii) children with any mental disorders that could limit the generalisation of data such as attention-deficit/hyperactivity disorder (ADHA), antisocial personality disorder, neuropsychiatric disorder including schizophrenia, or any detected delay in communication, adaptive, cognition or socio-emotional domains; and (iii) children not born at full term.

**Data extraction**

Two researchers (CA and IC) independently collected the following data from original studies: (1) country, (2) mothers' age at birth, (3) cohorts' year of birth, (4) age of children at evaluation, (5) number of children in each cohort, (6) weight status criteria used for the classification of the mothers' BMI, and (7) tool and/or scale used for the children's neurodevelopment assessment. Also, estimates regarding the association between pre-gestational BMI 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 (CA and IC) independently assessed its methodological quality. A standardised checklist for reporting of observational longitudinal research

was used [18]. This checklist includes two categories of criteria: i) aspects that could influence effect estimates, and ii) descriptive and contextual issues. 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 (VM).

**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 standardised mean difference score was calculated for each pre-pregnancy weight status category as an estimate of ES [19]. When studies provided a linear regression β coefficient, it was used to calculate a standardised mean difference score [19,20]. When studies provided odds ratio (OR) estimates, the ES was calculated using log OR divided by 1.81 [19,21]. A pooled estimate for each weight status category based on World Health Organization (WHO) cut-off points [22] was calculated when the studies presented estimates for BMI levels. When a study included two cohorts, their data were analysed as independent samples. In cohorts where the association estimates were calculated more than once during the follow-up period, only the latter estimate was considered for the meta-analysis.

The DerSimonian and Laird method [23] 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 a reference category. Additionally, a pooled ES of excess of weight (overweight and obesity) was conducted and compared with normal weight (reference category). 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 [24]; 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 separately evaluate whether cognitive test assessment data were different depending on children´s age.

Finally, publication bias was evaluated using Egger's regression asymmetry test for assessment of 'small studies effects' [25].

Statistical analyses were performed using StataSE software, version 14 (StataCorp).

**RESULTS**

The search retrieved a total of 3677 articles. Of these, 818 were removed as duplicates and 2859 were screened based on the title and the abstract. Ten studies met the inclusion criteria [26–35] (Figure 1). The mean of inter-rater agreement for inclusion of eligible articles was 95%.

Table 1 summarises the main characteristics of the included studies. The total sample included 63,115 children belonging to 12 cohorts born between 1956 and 2012. Five cohorts were from the United States of America [30–34], two from Spain [29,35], two from the United Kingdom [26,28], and one each from Denmark [27], Netherlands [28] and Greece [29]. The mothers' age at birth ranged from 16 to over 40 years, and children's neurocognitive development was assessed when they were aged between 14 months and 10 years. Two studies [26,35] provided data at two follow-up times. All

studies but two [32,34] 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 [26,27,34], vocabulary and word combination [28–31], working memory [33] and academic achievement [35]. The mean inter-rater agreement for extraction data of included studies was 92%.

Table 2 summarises the association between maternal pre-pregnancy weight status and children's cognitive development total score as originally retrieved. All except three articles provided data by weight status categories [26–28]. In these three articles, the estimates of the relationship between children's neurocognitive development and mother's BMI were reported in a continuous scale [26,27] or as an excess of weight category combining overweight and obese individuals [28]. The two articles that provided data from three cohorts estimated the intensity of this relationship using OR estimate from logistic regression models [28,35]. Only one cohort [28] found a small but negative association between pre-pregnancy mother's obesity and offspring's neurocognitive development (OR= 0.91; 95% CI= 0.84 to 0.99). Eight studies, using multiple linear regression models, provided data from nine cohort samples showing an inverse association between pre-pregnancy weight status category (normal weight as reference) and children's neurocognitive test scores. Only one study found a direct, but not significant, association between pre-pregnancy overweight and children's neurocognitive test scores (β: 0.64; 95% CI: -2.97 to 4.25) [29].

**Study quality**

Studies met from 57.58% [32] to 75.76% [31,34] of the quality criteria, as assessed by the Quality of Reporting of Observational Longitudinal Research [18] instrument (Table S2). Only one study [27] included information regarding differences between

participants and non-participant individuals, and no studies included the reasons for refusing participation. Furthermore, no study discussed the qualitative or quantitative impact of potential biases.

Only two studies [26,34] informed about the reliability and validity of the tool used to measure neurocognitive development. Additionally, only two studies [31,34] mentioned the number of subjects that met and did not meet eligibility criteria, and the reasons for not eligibility of the remaining sample.

**Meta-analyses**

For the calculation of the pooled ES of overweight and obesity categories, only the seven studies providing separated data for these pre-pregnancy weight status categories were included [30–34]. Those studies included eight mothers' samples for each weight status categories (overweight and obesity).

ES for the relationship between weight status and children's neurocognitive development were -0.03 (95% CI: -0.09 to 0.02) and -0.23 (95% CI: -0.35 to -0.11) for overweight and obesity pre-pregnancy mothers, respectively. Heterogeneity estimates were $I^2 = 51.1\%$ ($p = 0.046$), and $I^2 = 84.0\%$ ($p < 0.001$), for the overweight and obesity pre-pregnancy mothers analyses, respectively (Figure 2). The pooled effect for the excess of weight category was -0.12 (95%CI: -0.19 to -0.06). Heterogeneity estimate was $I^2 = 81.5\%$ ($p< 0.001$).

**Sensitivity analyses**

Sensitivity analyses suggested that the pooled ES was modified neither in the overweight nor in the obesity analyses by removing one by one the included cohorts. On the other hand, sensitivity analyses revealed that heterogeneity decreased in the pre-

pregnancy mother's overweight estimate when cohorts were removed one by one from the studies by Pugh *et al.* ($I^2 = 0.0$; p = 0.52) and Torres-Espinola *et al.* ($I^2 = 45.4\%$; p = 0.09). A decrease of heterogeneity was also observed in pre-pregnancy mother's obesity estimate by removing Tanda *et al.* cohort ($I^2 = 61.6\%$; p = 0.02) (Table S3).

**Random-effects meta-regression model**

The random-effects meta-regression model showed that the effect of pre-pregnancy overweight (p = 0.14) or obesity (p = 0.31) 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)

**Publication bias**

Funnel plots did not display evidence of publication bias for any of the pooled subgroup analyses (overweight p = 0.57 and obesity p = 0.27) [25] (Table S4).

**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 prior to pregnancy, but not overweight, have a negative influence on the offspring's neurocognitive development (ES = -0.23; 95% CI = -0.35 to -0.11).

The model proposed by van der Burg *et al.* [36] suggests that mother's obesity produces a chronic systemic inflammation ambient with negative consequences for foetal development. This obesity-related inflammatory process increases insulin concentrations, leptin levels and other low-grade inflammatory markers that could

produce errors in brain maturation [37]. Other physiological obesity-related changes such as oxidative stress and endothelial dysfunction might also negatively influence children's brain maturity [38].

Besides this hypothesis, new explanations have been suggested to clarify this relationship. The epigenetic hypothesis proposes that the foetus 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 life span [39]. Children from obese mothers are at greater risk of developing insulin resistance, cardiometabolic diseases and also of having excess overall and central adiposity [40-42]. 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. [43]

In addition to obesity during pregnancy, pre-pregnancy obesity has been associated with neurodevelopmental deficits such as cognitive deficits and also with autism spectrum [44] and psychotic [45] 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 continuous procedures from conception to adulthood, and therefore related to executive functions and cognition acquisition. [37] It should be borne in mind that offspring from obese mothers might be involved in a vicious cycle where they could be at higher risk of suffering deficits in their brain maturation and neurocognitive development, independently of the age at which they are evaluated.

Additional pathways that could potentially explain the worsening in neurocognitive development of 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 [46].

Previous studies [27,29,36] have suggested that the relationship between a mother's excess weight and neurocognitive development could be confounded by other pre- and post-natal factors such as home conditions, family income, or maternal and paternal educational or intelligence levels [47]. Our findings suggest that the relationship between pre-pregnancy obesity and children's neurocognitive development scores is independent of those confounders, as all the included studies considered familiar socio-demographic variables in their analyses.

The sensitivity analyses showed that the ES was not changed by removing any study. The heterogeneity among studies was only substantially modified by removing three cohorts. By removing Pugh *et al.* cohort from the overweight pooled estimation the heterogeneity of the analysis decreased to 0.0%; this could be explained because it included mothers who were light users of marijuana and alcohol in their first trimester, but who did not have substance abuse diagnoses. Removing Torres-Espinola *et al.* from the pre-pregnancy overweight mothers did not change the heterogeneity but it became statistically non-significant, probably because this study included the smallest sample, and also was the only one that found that children from obese mothers are not at risk of developing worse neurocognitive scores than their peers. By removing the Tanda *et al.* cohort from the obese pre-pregnancy mothers, heterogeneity among studies decreased; it is noted that this was the only study that used mathematics and reading test scores to measure children's cognitive development.

The limitations of this study are those common to meta-analyses: publication bias, selection bias, potential ecological fallacy and limited information from study reports. Particularly 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 the ES estimates and their corresponding 95% CIs from the published data, thus bias cannot be ruled out; iii) only three studies scored positively in at least two-thirds of the quality assessment scale items, which could limit the generalisation of conclusions; iv) although the included studies have children's neurocognitive development as a main outcome variable, there is 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); v) children's age at which the tests were performed could influence our estimations, though meta-regression analyses did not find any statistically significant differences among children's age at evaluation; and vi) the countries where the samples came from might constitute another important source of bias. However, the subgroup analyses including studies developed in the USA alone showed similar values to those retrieved in the total analyses: 0.05 (95% CI: -0.11 to 0.01) for overweight and -0.25 (95% CI: -0.40 to -0.09) 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 analysis reinforced the results of this study, showing no ES changes by removing studies one by one.

Our meta-analysis provides supporting evidence that obesity may have negative health consequences not only on women who intend to become pregnant, but also on their 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.

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**Table 1.** Characteristics of included studies.

| Author | Country | n | Mothers' age | Cohorts' year of birth | Age of child at evaluation (years) | BMI reference values | Neurodevelopment assessment of children |
|---|---|---|---|---|---|---|---|
| Basatemur et al. 2012 [26] | United Kingdom | 11025 | 24.7-29.0 | 2000-02 | 5.0 and 7.0 | WHO | British Ability Scale |
| Bliddal et al. 2014 [27] | Denmark | 1783 | <21.0->40.0 | 1996-2002 | 2.0-7.0 | WHO | WISC |
| Brion et al. 2010 [28] | England | 4712 | NA | 1991-92 | 3.2 | WHO | MacArthur Toddler and Communication |
| | Netherlands | 2398 | NA | 2002-06 | 2.5 | WHO | Questionnaire Language Development Survey |
| Casas et al. 2013 [29] | Spain | 1967 | >16.0- | 2004-08 | 1.2 | WHO | BSID |
| | Greece | 412 | >35.0 | 2007-09 | 1.5 | WHO | |
| Hinkle et al. 2012 [30] | USA | 6050 | 15.0-50.0 | 2001 | 1.5-3.1 | WHO | BSID |
| Huang et al. 2014 [31] | USA | 30212 | >16.0->40.0 | 1959-65 | 7.0 | WHO | WISC |
| Neggers et al 2003 [32] | USA | 355 | 21.6 | NA | 5.0 | Normal: 19.8-26.0 Overweight: 26.1-29.0 Obese: >29.0 | Differential Ability Scales |
| Pugh et al. 2015 [33] | USA | 574 | NA | 1983-86 | 10.0 | WHO | Stanford-Binet Intelligence Scale |
| Tanda et al. 2013 [34] | USA | 3412 | 25.4 | 1979-94 | 6.0 | CDC | PIAT mathematics and reading scores |
| Torres-Espinola et al. 2015 [35] | Spain | 215 | 31.0-34.0 | 2007-12 | 0.5 and 1.5 | WHO | BSID |

NA: Not Available; WISC: Wechsler Intelligence Scale; BSID: Bayley Scales of Infant Development; WHO: World Health Organization; CDC: Center fro Disease Control and Prevention.

**Table 2.** Association between maternal pre-pregnancy BMI and cognitive development expressed as β or Odds Ratio values.

| Author | Cognitive development total score | |
|---|---|---|
| Basatemur et al. 2012 [26] | -0.17 (-0.23, -0.10)[1]<br>-0.08 (-0.13, -0.02)[2] | |
| Bliddal et al. 2014 [27] | -0.27 (-0.50, -0.03) | |
| Brion et al. 2010 [28] | 0.91 (0.84, 0.99)*<br>0.85 (0.79, 1.01)* | |
| | **Overweight** | **Obesity** |
| Casas et al. 2013 [29] | -0.95 (-2.69, 0.79)<br>0.64 (-2.97, 4.25) | -2.93 (-5.49, -0.36)<br>-4.20 (-8.88, 0.49) |
| Hinkle et al. 2012 [30] | -0.21 (-0.88, 0.46) | -0.57 (-1.63, 0.48)[a] -2.13 (-3.32, -0.93)[b] |
| Huang et al. 2014 [31] | -0.30 (-1.10, 0.50) | -2.00 (-3.50, -0.50) |
| Neggers et al. 2003 [32] | -1.10 (SE: 2.00) | -4.70 (SE: 1.40) |
| Pugh et al. 2015 [33] | -0.59 (-0.92, -0.25) | -2.10 (-3.18, -1.02) |
| Tanda et al. 2013 [34] | -0.70 (-1.51, 0.10) | -1.69 (-2.80, -0.57) |
| Torres-Espinosa et al. 2015 [35] | 2.46 (0.91, 6.61)*[1]<br>1.54 (0.63, 3.79)*[2] | 0.98 (0.24, 3.96)*[1]<br>2.92 (1.26, 6.79)*[2] |

[1] : first measurement; [2] : second measurement; * Odds Ratio values; [a]: obesity class I; [b]: obesity class II and III; Obesity ; SE: Standard Error.

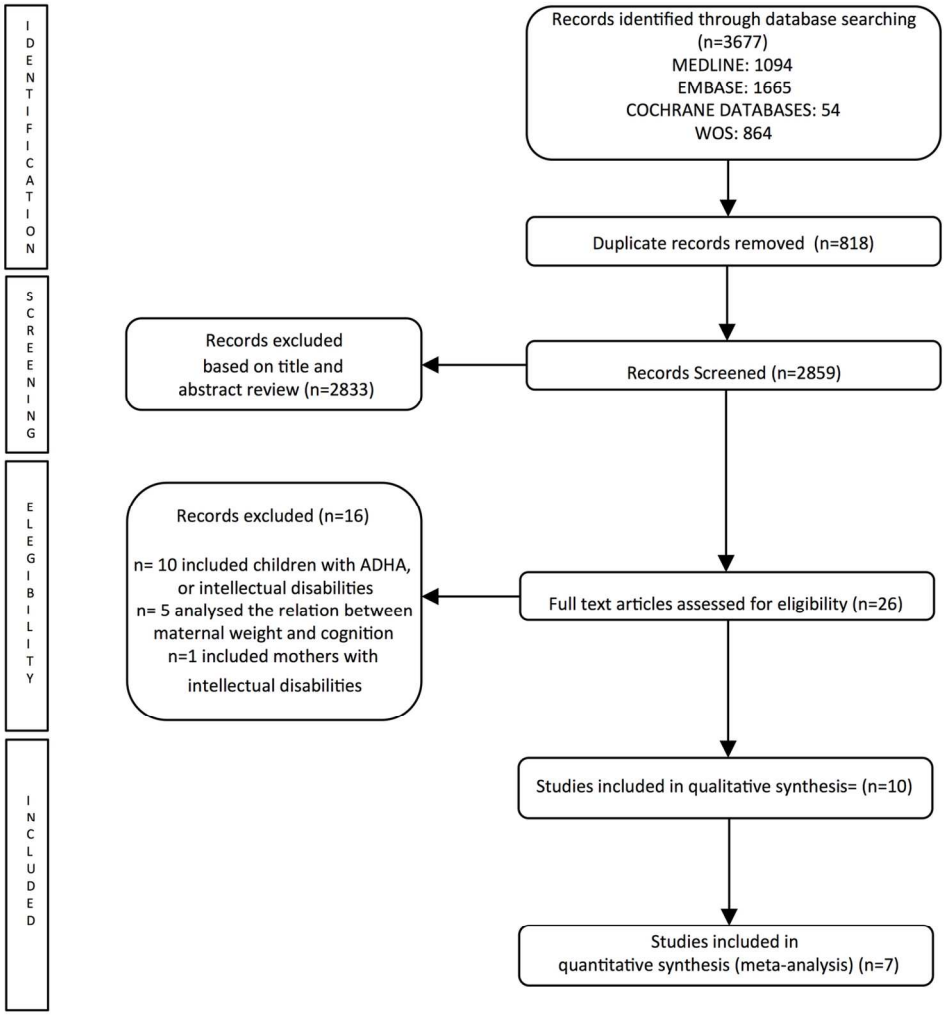


Figure 1. Literature search PRISMA consort diagram

129x135mm (300 x 300 DPI)

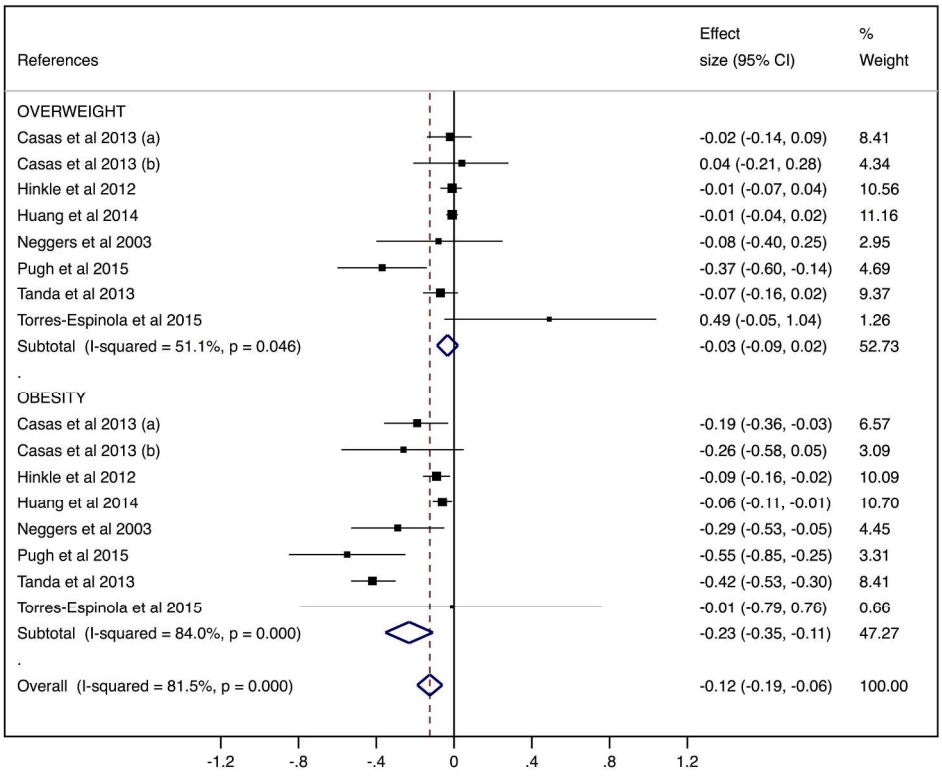


Figure 2. Pooled stimated effect size for overweight and obesity categories/ CI: Confidence Interval; a and b: cohorts`samples from Casas el at study.

239x203mm (300 x 300 DPI)