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Review Article

The independent and joint associations of maternal pre-pregnancy body mass index and gestational weight gain with macrosomia: systematic review and meta-analysis

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Abstract: Objective: The aim of this study was to assess and quantify the independent and joint associations of maternal body mass index (BMI) and gestational weight gain (GWG) with macrosomia. Methods: PubMed, ELSEVIER Science Direct and Springer Link (up to May. 2015) were searched, and the reference list of retrieved articles was reviewed. Four authors independently extracted the data. Rev Man 5.2 and Stata 11.0 were used to perform all statistical analyses. Fixed-effects or random-effects model was used to pool the results of individual studies (expressed as odds ratios [ORs] accompanying 95% confidence intervals [CIs]). Results: The systematic review and meta-analysis included 31 studies. The independent effects of maternal pre-pregnant overweight (the pooling OR was 1.62 [1.47, 1.78], reference by normal weight), obese (2.31 [2.05, 2.59]) and excessive GWG in overall (2.12 [1.92, 2.34], reference by adequate GWG) were at significantly odds of giving birth to a macrosomia. The joint effects of maternal excessive GWG in four classes (2.85 [2.36, 3.45], 2.07 [1.94, 2.22], 2.10 [1.93, 2.27] and 1.90 [1.62, 2.22], respectively, according to order of increasing BMI, reference by adequate GWG within the class) were at significantly odds of giving birth to a macrosomia. Conclusion: The results of our study showed that increasing maternal BMI and GWG were independently associating with an increasing risk of macrosomia and jointly associating significantly with macrosomia, but the association between maternal excessive GWG and macrosomia tend to be decreased with the increasing of pre-pregnant BMI.

Keywords: Body mass index, gestational weight gain, macrosomia, obese, systematic review, meta-analysis

Introduction

Fetal macrosomia has been defined in several different ways, such as birth weighing at least 4000/4500 g (8 lb 13 oz/9 lb 15 oz) or greater than 90% for gestational age after correcting for neonatal sex and ethnicity [1, 2]. According to an published article in 2008, the prevalence of macrosomia, newborns weighing more than 4000 g, in developed countries was between 5% and 20% [1] in 1995-2005. While the prevalence of macrosomia in 23 developing countries ranged from 0.5% in India to 14.9% in Algeria, collecting data in Africa and Latin America in 2004-2005, and in Asia in 2007-2008 [2]. Especially in China, with almost a subquintuple people of the world, it had increased from 6.9% in 2007-2008 [2] to 7.3% in 2011 [3] in total, and ranging from 4.1% to 13.4% among provinces in 2011 [3]. And the upward trend remained continuing.

Macrosomia is a risk factor for adverse delivery outcomes to both the fetus and the maternal, which is not only associating with increased rates and risks in adverse obstetric outcomes, such as caesarean delivery, perineal trauma, brachial plexus injury, clavicular fracture, meconium aspiration and prenatal asphyxia compared to infants with normal birth weight [4-8], but also going to have many effects on later life, such as overweight or obesity, type 2 diabetes, asthma, persistent plexus injuries, cancer, metabolic syndrome, and insulin resistance during childhood and adulthood [8-20].

Due to a large number of risks that macrosomia pose to both the fetus and the maternal, it is

Table 1. IOM gestational weight gain recommendation: 1990 versus 2009 guidelines

Classes of BMI	1990 Recommendations			2009 Recommendations for Total		
	Prepregnancy BMI (kg/m^2)	Total Weight Gain		Prepregnancy BMI (kg/m^2)	Total Weight Gain	
		Range (kg)	Range (lbs)		Range (kg)	Range (lbs)
Underweight	<19.8	12.5-18	28-40	<18.5	12.5-18	28-40
Normal-weight	19.8-26	11.5-16	25-35	18.5-24.9	11.5-16	25-35
Overweight	26.1-29	7-11.5	15-25	25-29.9	7-11.5	15-25
Obese	>29	≥7	≥15	≥30.0	5-9	11-20

2009 Recommendations: Calculations assume a 0.5-2 kg (1.1-4.4 lbs) weight gain in the first trimester.

necessary and important to determine risk factors for macrosomia. According to the American College of Obstetricians and Gynecologists Practice Bulletin No. 22 in 2000, the risk factors (excluding preexisting diabetes mellitus) for fetal macrosomia, in decreasing order of importance, are as follows: a history of macrosomia, maternal pre-pregnancy weight, gestational weight gain, multiparity, male fetus, gestational age more than 40 weeks, ethnicity, maternal birth weight, maternal height, maternal age younger than 17 years and a positive 50-g glucose screen with a negative result on the three-hour glucose tolerance test [21].

The weight before and during pregnancy are important indicators of monitoring and evaluating a woman's nutritional status. Furthermore, among such many risk factors of macrosomia, pre-pregnant BMI and GWG are mainly controllable, which could be changed by women of reproductive age.

Recent studies have suggested that pre-pregnant overweight or obesity and excessive GWG were likely contributors to the increased incidence of macrosomia, but the findings have been discordance. In order to assess and quantify the independent and joint associations of maternal BMI and GWG with macrosomia, we conducted the systematic review and meta-analysis, using the currently published observational studies.

Materials and methods

Data sources and search

The search strategy was "(Macrosomia OR macrosomic OR (giant baby) OR (giant infant) AND (pregnancy OR pregnant OR gestation OR prenatal OR gestational OR fertile period) AND (BMI OR (body mass index) OR (gestational weight gain)". Three electronic bibliographic databases (Pub med, ELSEVIER Science Direct (SDOS) and Springer Link) were searched systematically from January 2006 to May 2015. The reference lists of relevant studies were also searched for additional eligible studies.

Study selection

Observational studies were included irrespective of publication status, sample size, follow-up duration. As shown in **Table 1**, studies classified pre-pregnancy BMI and gestational weight gain according to the recommendations of the Institute Of Medicine (IOM) in 1990 or in 2009. The IOM issued the 2009 GWG guidelines updating the 1990 guidelines in response to an increase in pre-pregnancy BMI and GWG among all population subgroups, and changing demographics of the maternal population including age and race/ethnicity [22].

Study determined macrosomia as birth weight greater than 4000 g or 4500 g. Potentially eligible articles were identified according to the following inclusion criteria: (1) they were original epidemiologic studies; (2) participants were pregnant women, and (3) the outcome was macrosomia. exclusion criteria: (1) participants are special sample, such as diabetic or gestational diabetic patient; (2) pre-pregnancy BMI and gestational weight gain categories didn't match with the recommendations of the Institute Of Medicine in 1990 or 2009. Studies included in the meta-analysis were: (1) reported pre-pregnant BMI category in the standard format (kg/m^2); (2) reported odds ratios (ORs) accompanying 95% confidence intervals (CIs) or had sufficient raw data to calculate; and (3) had a reference group of normal-weight or adequate gestational weight gain, no inclusion of underweight in the reference category. In the case of multiple publications resulting from the same data, either the study containing the most comprehensive information or the most recent study was selected. Disagreements regarding criteria fulfillment were resolved by discussion among the researchers.

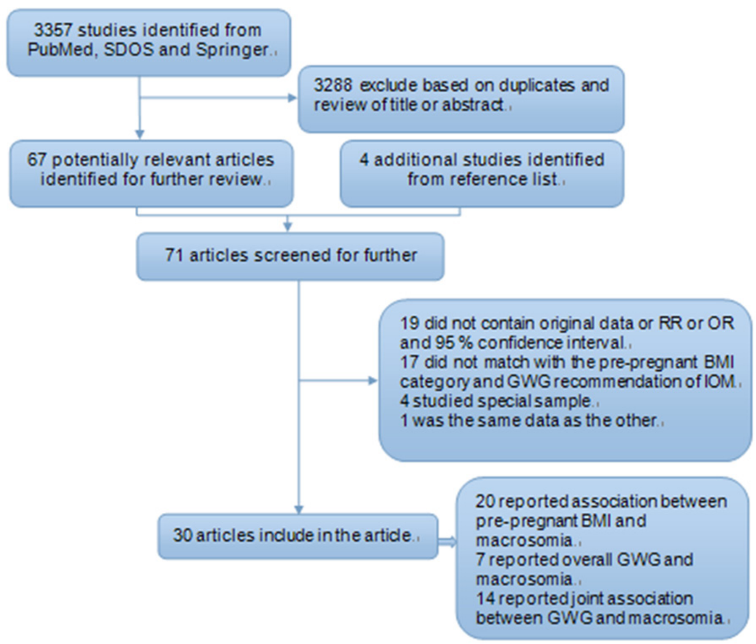


Figure 1. Flow diagram for retrieving studies from searches.

Data-extraction form

Information extracted from each article included: first-author, publication year, study design, study size, source of study population, strategy of pre-pregnancy BMI, macrosomia defined, raw data, ORs accompanying 95% CI. Raw data for every class of pre-pregnancy BMI or GWG, rates of macrosomia in exposed and unexposed groups were obtained if possible.

Data extraction and outcomes

Two reviewers first screened studies by title/abstract and made exclusions based on the original eligibility criteria. Studies meeting the inclusion criteria were independently reviewed by four authors using a piloted data extraction form. The retrieved information including study characteristics (i.e. first author, publication year, study period, location, study design); sources and categorizations of maternal BMI and GWG; sources and ascertainment of cases; ORs and 95% CIs; definition on macrosomia. Discrepancies among the four reviewers were resolved by discussion.

Statistical analysis

Different thresholds for categorizing maternal BMI and GWG have been respectively pooled in groups classified as in 1990 or as in 2009. Maternal GWG with 12.5-18 kg (BMI ≤18.5 kg/m^2), 11.5-16 kg (BMI 18.5-24.9 kg/m^2), 7-11.5 kg (BMI 25.0-29.9 kg/m^2), and 5-9 kg (BMI ≥30 kg/m^2) were defined as adequate GWG (respectively, reference group in every class) according to the IOM in 2009, and in the same way as in 1990.

The meta-analysis was conducted and reported according to the Statement of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [23]. We extracted data from each study and analyzed with Stata11.0. The crude and adjusted ORs estimated in original studies were mostly similar, and we used adjusted estimates better than crude ones in the meta-analysis. Therefore, the sufficient raw data from several of the original studies analyzed with Rev Man 5.2 (Cochrane Review Manager; Cochrane Collaboration, Oxford, United Kingdom) to get the crude ORs accompanying 95% confidence intervals (CIs).

Heterogeneity was estimated using the chi-square test (considered to be an evidence of significant heterogeneity if P<0.1) and the Cochrane Q test (quantified with the I^2 metric, describing the total variation in OR attributable to heterogeneity) [24]. $I^2 = 0$ indicates no heterogeneity and the larger value indicates the greater heterogeneity. As is typical in meta-analyses, I^2 also was used to select the most appropriate pooling method [25]: fixed-effects models were used for $I^2 \leq 50\%$ and random-effects models were used for $I^2 > 50\%$. Z-test was applied for testing the overall effect and P<0.05 was considered statistically significant. Forest plots were constructed to graphically present study-specific pooled ORs and 95% CIs. The presence of publication bias was tested using a combination of Egger's regression asymmetry test and Begg's rank correlation test (using Stata11.0).

Results

Study selection

As shown in **Figure 1**, the primary search of Pub Med, SDOS and Springer Link identified 3357 articles, 3288 of which were excluded based

Table 2. Characteristics of studies included in the systematic review and meta-analysis

Study, year	Location (period)	Types of cases	The sample size (style)	Measure of maternal BMI	Definition of BMI (kg/m^2)	Definition of macrosomia (g)	Data pooling adjusted or not
Monique M. Hedderson, et al. 2006* [26]	In California (1996-1998)	Not specified	45,245 women in a cohort	Pre-pregnant weight and height (by self-report)	Underweight: <19.8 Normal weight: 19.8-26 Overweight: 26-29 Obese: >29	>4500	Adjusted
Haim A. Abenhaim, et al. 2007* [27]	In Montreal, Canada (1987-1997)	Not specified	18643 women in a cohort study	Pre-pregnant weight and height (by self-report)	Underweight: <19.9 Normal weight: 20-24.9 Overweght: 25-29.9 Obese I: 30-39.9 Obese II: ≥40 Overweight or Obese: >25	>4500	Adjusted
Sohinee Bhattacharya, et al. 2007* [28]	In Aberdeen (1976-2005)	≥24 weeks of gestation, singleton babies	24,241 women in a retrospective cohort study	Atantenatal booking visit (by record)	Underweight: <19.9 Normal weight: 20-24.9 Overweght: 25-29.9 Obese I: 30-34.9 Obese II: ≥35	>4000	Adjusted
C. Kabali, et al. 2007* [29]	In Canada and United States (1996-2002)	A gestational age of 180-310 days	815 women in a multicenter case control study	Pre-pregnant weight and height (by self-report)	Underweight: <19.8 Normal weight: 19.8-26 Overweight or Obese: >26	≥4000	Adjusted
Line Rode, et al. 2007* [30]	In Denmark (1996-1998)	A gestational age of ≥37 weeks, singleton birth	2,248 women in a cohort	Pre-pregnant weight and height (by self-report)	Underweight: <19.8 Normal weight: 19.8-26 Overweight: 26-29 Obese: >29	≥4000	Adjusted
Meenakshi T. Sahu, et al. 2007* [31]	In North India (2005-2006)	Singleton gestations	380 women in a cohort study	At first prenatal visit early in the second trimester (by record)	Normal weight: 19.8-24.9 Obese: ≥30	>4000	Not adjusted
L. Driul, et al. 2008 [32]	In Italy (2006)	Singleton gestations	916 women in a retrospective cohort study	Pre-pregnant weight and height (by record)	Underweight: <18.5 Normalweight: 18.5-24.9 Overweght: 25-29.9 Obese: ≥30	>4000	Not adjusted
Ihunnaya O. Frederick, et al. 2008* [33]	In Swedish Medical Center or Tacoma General Hospital (1996-2004)	A singleton birth	2,670 women in a cohort	Pre-pregnant weight and height (by self-report)	Underweight: <19.8 Normalweight: 19.8-26 Overweight: 26-29 Obese: >29	≥4000	Not adjusted
Patricia M. Dietz, et al. 2009* [34]	in US (2000-2005)	A gestational weeks ≥37, singleton birth	104,980 women in a population-based cohort study	Pre-pregnant weight and height (by self-report)	Underweight: <19.8 Normalweight: 19.8-26 Overweight: 26-29 Obese: >29	≥4500	Adjusted
SUZANNE M. GILBOA, et al. 2008 [35]	In the United States (1981-1989)	Singleton live-born	3,226 in a population-based case-control study	Pre-pregnant height and weight (by self-report)	Underweight: <18.5 Normal weight: 18.5-24.9 Overweght: 25-29.9 Obese: ≥30	>4500	Not adjusted
A. S. Khashan, et al. 2009 [36]	In Manchester, UK (2004-2006)	Singleton	99403 women in a population register-based cohort study	During the first antenatal visit	Underweight: <18.5 Normal weight: 18.5-24.9 Overweght: 25-29.9 Obese I: 30-40 Obese II: ≥40	>4500	Adjusted

Zhenyu Chen, et al. 2010 [37]	In Shenyang province, China (2009)	Not specified	2586 women in a retrospective cohort study	Pre-pregnant weight and height (by self-report)	Underweight: <18.5 Normal weight: 18.5-23.9 Overweght: 24-27.9 Obese: ≥28	>4000	Adjusted
Aisha Langford, et al. 2011* [38]	In Missouri, US (1990-2004)	A gestational age of ≥37 weeks, singleton birth	34,143 women in a population-based cohort study	Pre-pregnant weight and height (by retrospective self-report)	Underweight: <19.8 Normal weight: 19.8-26 Overweight: 26-29 Obese: >29	>4000	Adjusted
Per Ovesen, et al. 2011 [39]	In Kongeriget Danmark (2004-2010)	Singleton	403,092 women in a population-based cohort	Pre-pregnant weight and height (by self-report)	Underweight: <18.5 Normal weight: 18.5-24.9 Overweght: 25-29.9 Obese I: 30-34.9 Obese II: ≥35	>4500	Not adjusted
Kimberly K. Vesco, et al. 2011 [40]	In northwestern Oregon and southwestern Washington (2000-2005)	A gestational age of ≥37 weeks, singleton live birth	2,080 obese women In a retrospective cohort study	At beginning of pregnancy (by record)	Underweight: <18.5 Normal weight: 18.5-24.9 Overweght: 25-29.9 Obese: ≥30	>4500	Adjusted
Shouyong Gu, et al. 2012 [41]	In Jiangsu Province, China	Singleton term born	21315 women in a nested case-control study	At the first prenatal care visit	Underweight: <18.5 Normal weight: 18.5-23.9 Overweght: 24-27.9 Obese: ≥28	≥4000	Not adjusted
Yuanyuan Liu, et al. 2012 [42]	In Hebei, Jiangsu and Zhejiang Provinces. China (1993-2005)	37-42 weeks of gestation live-born, singletons	292568 women in a cohort	During the first trimester (by record)	Underweight: <18.5 Normal weight: 18.5-24.9 Overweight:25-29.9 Obese: ≥30	≥4000	Adjusted
SEBASTIAN MANZANARES GALAN, et al. 2012 [43]	In Granada, Spain (2007-2009)	Not specified	3016women in a case-control study	During first ten weeks of pregnancy (by record)	Underweight: <18.5 Normal weight: 20-24.9 Obese: ≥35	>4000	Adjusted
Inmaculada Bautista-Castan˜o, et al. 2013 [44]	In Gran Canaria, Spain (2008)	Not specified	6558 pregnant women in a population-based retrospective cohort study	Pre-pregnant weight and height (by record)	Underweight: <18.5 Normal weight: 18.5-24.9 Overweght: 25-29.9 Obese: ≥30	>4000	Adjusted
Chukwuemeka A Iyoke, et al. 2013 [45]	In South-East Nigeria (2010-2011)	Singleton babies	6,651 women in a retrospective cohort study	In the first trimester (by record)	Underweight: <18.5 Normal weight: 18.5-24.9 Overweght: 25-29.9 Obese: ≥30	Not specified	Not adjusted
Nan Li, et al. 2013 [46]	In Tianjin, China (2009-2011)	Singleton live birth	33,973 pregnant women in the cohort	Within the first 12 weeks of pregnancy (by clinical record)	Underweight: <18.5 Normal weight: 18.5-23.9 Overweight: 24.0-27.9 Obese: ≥28	≥4000	Adjusted
Se Li, et al. 2013 [47]	In US (1995-2003)	Gestational age >37 weeks, singleton birth	6687 mother-infant pairs in the cohort	Pre-pregnant weight and height (by retrospective self-report)	Underweight: <18.5 Normal weight: 18.5-24.9 Overweight: 25-29.9 Obese: ≥30	≥4000	Adjusted
Eugene Oteng-Ntim, et al. 2013 [48]	In UK (2004-2008)	≥24 weeks of gestation, singleton deliveries	23,668 women in a retrospective cohort study	At first antenatal visit (by record)	Underweight: <18.5 Normal weight: 18.5-24.9 Overweght: 25-29.9 Obese I: 30-34.9 Obese II: ≥35	>4000	Adjusted

R Scott-Pillai, et al. 2013 [49]	In UK (2004-2011)	≥24 weeks of gestation, singleton pregnancies	30,298 in retrospective cohrt study	Before 16 weeks of gestation	Underweight: <18.5 Normal weight: 18.5-24.9 Overweght: 25-29.9 Obese I: 30-34.9 Obese II: 35-39.9 Obese III: ≥40	>4000	Adjusted
Salvatore Alberico, et al. 2014 [50]	In North-Eastern Italy	a gestational age of ≥37 weeks, singleton birth	14109 women in a cohort	Pre-pregnant weight and height (by retrospective self-report)	Underweight: <18.5 Normal weight: 18.5-24.9 Overweight: 25-29.9 Obese: ≥30	>4000	Adjusted
Izumi Chihara, et al. 2014 [51]	In Hawaii (2003-2005)	20-44 weeks of gestation, singleton live births	19,130 mother-infant pairs in the cohort	Pre-pregnant weight and height (by a prenatal WIC record)	Underweight: <18.5 Normal weight: 18.5-24.9 Overweight: 25-29.9 Obese: ≥30	≥4000	Adjusted
Margaretha Haugen, et al. 2014# [52]	In Norway (1999-2008)	37-42 gestational weeks, singleton live birth	56,101 pregnant women in the prospective Cohort Study	Pre-pregnant weight and height (by questionnaire)	Normal weight: 18.5-24.9 Overweight: 25-29.9 Obese: ≥30	>4500	Adjusted
Peng Shi, et al. 2014 [53]	In Kunshan, China (2006-2010)	37-41 weeks of gestation, singleton birth	27,322 women in a retrospective cohort study	Between the 8th and 20th week of gestation (by the first prenatal visit record)	Underweight: <18.5 Normal weight: 18.5-24.9 Overweight: 25-29.9 Obese: ≥30	≥4000	Adjusted
Aimin Chen, et al. 2015 [54]	In Ohio (2006-2012)	22-44 weeks of gestation, singleton live births	869,531 women in the cohort	Pre-pregnant weight and height (by retrospective self-report)	Underweight: 15.0-18.4 Normal weight: 18.5-24.9 Overweight: 25.0-29.9 Obese: 30.0-50.0	>4000	Adjusted
Shaoping Yang, et al. 2015 [55]	Wuhan, China (2011-2013)	≥28 gestational weeks, a singleton, and live birth	85,765 mothers in the cohort	Pre-pregnant weight and height (by retrospective self-report)	Undeweight: <18.5 Normal weight: 18.5-24.9 Overweight or Obese: ≥25	>4000	Adjusted

#this article contains 2 studies. *these articles classified pregnant BMI and GWG according to IOM in 1990.

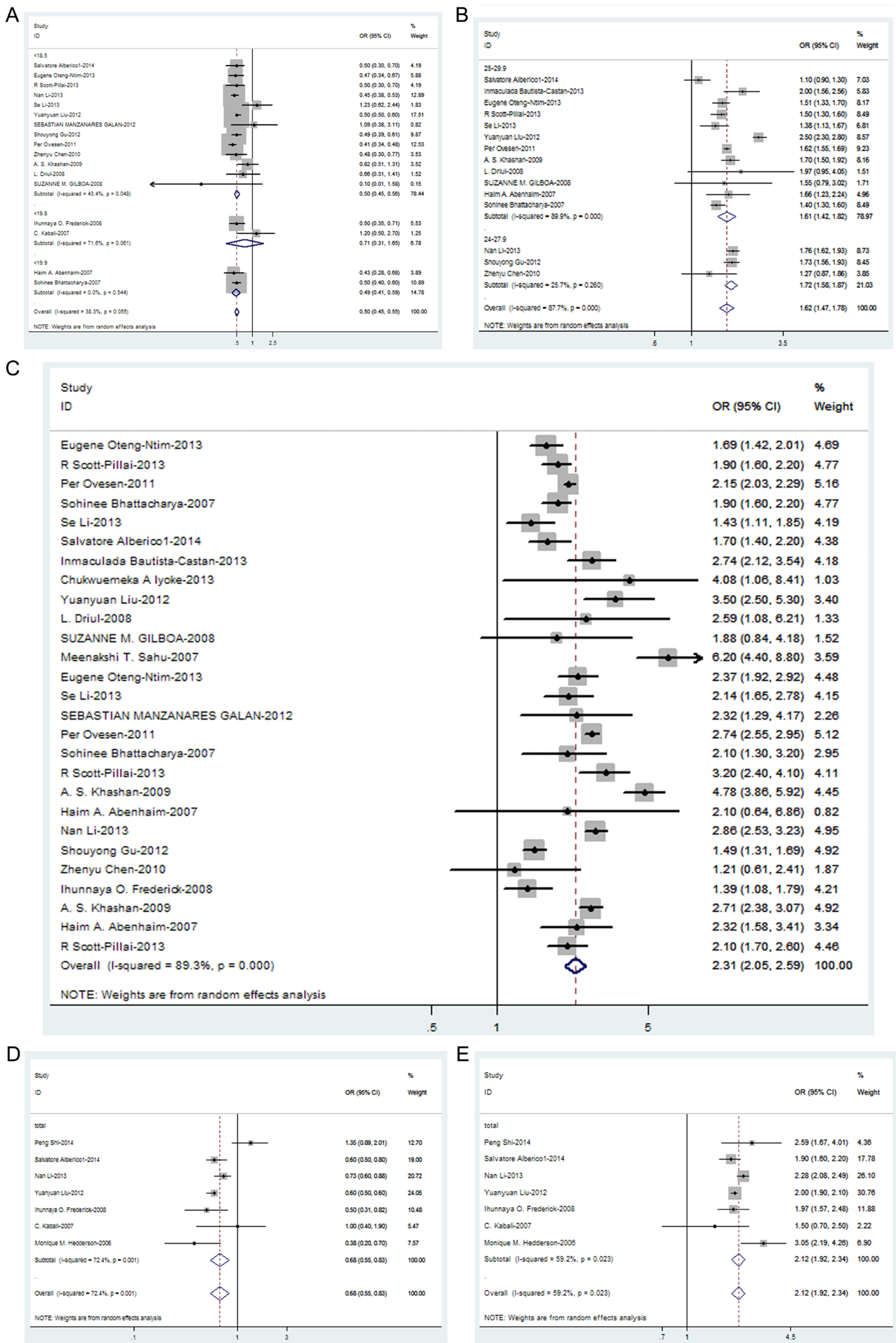
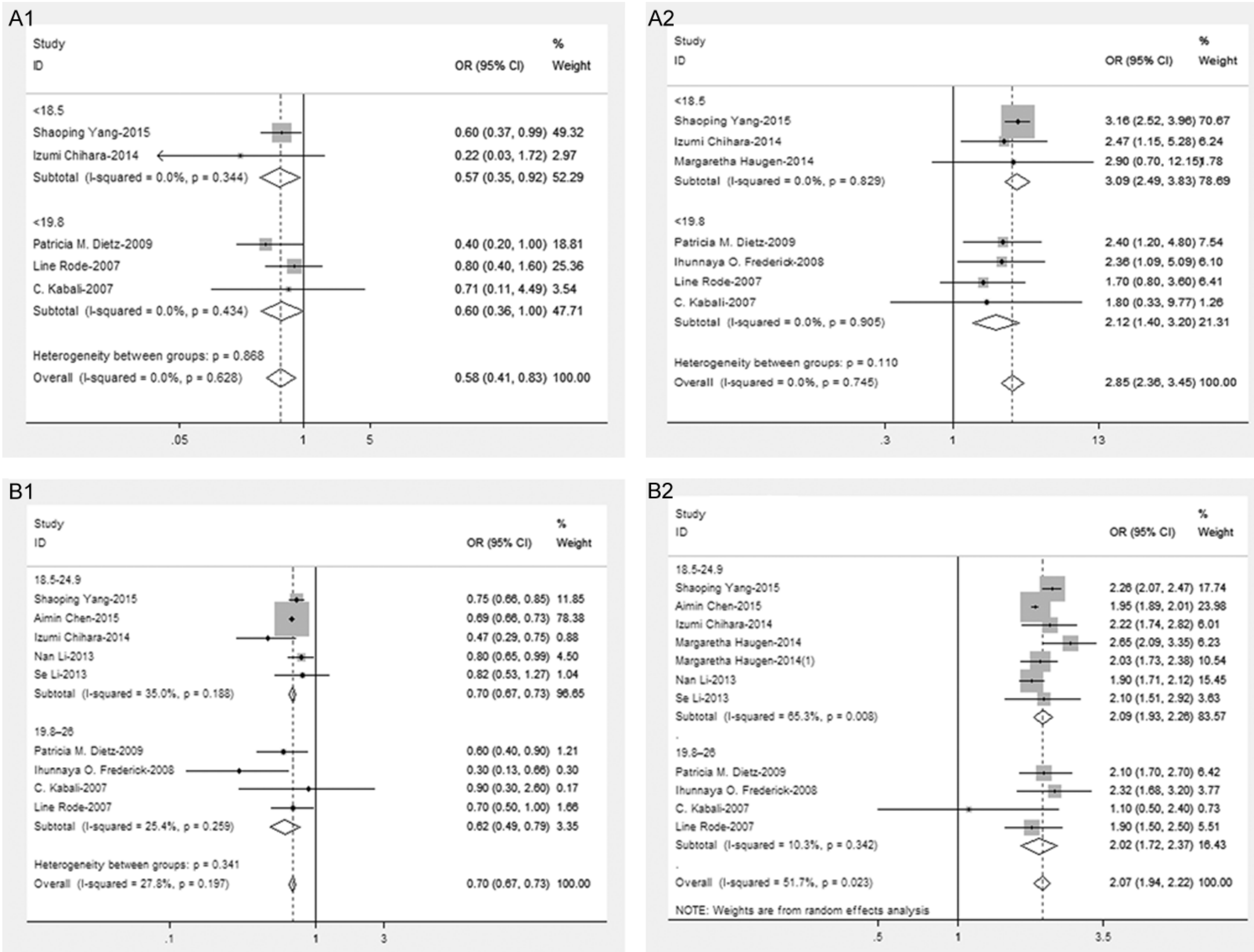


Figure 2. Forest Plot for independent associations. A: Associations between underweight and macrosomia; B: Associations between overweight and macrosomia; C: Associations between obese and macrosomia; D: Associations between inadequate GWG and macrosomia; E: Associations between excessive GWG and macrosomia.


A1
Study
ID
OR (95% CI)
%
Weight
<18.5
Shaoping Yang-2015 0.60 (0.37, 0.99) 49.32
Izumi Chihara-2014 0.22 (0.03, 1.72) 2.97
Subtotal (I-squared = 0.0%, p = 0.344) 0.57 (0.35, 0.92) 52.29
<19.8
Patricia M. Dietz-2009 0.40 (0.20, 1.00) 18.81
Line Rode-2007 0.80 (0.40, 1.60) 25.36
C. Kabali-2007 0.71 (0.11, 4.49) 3.54
Subtotal (I-squared = 0.0%, p = 0.434) 0.60 (0.36, 1.00) 47.71
Heterogeneity between groups: p = 0.868
Overall (I-squared = 0.0%, p = 0.628) 0.58 (0.41, 0.83) 100.00
.05
1
5
A2
Study
ID
OR (95% CI)
%
Weight
<18.5
Shaoping Yang-2015 3.16 (2.52, 3.96) 70.67
Izumi Chihara-2014 2.47 (1.15, 5.28) 6.24
Margaretha Haugen-2014 2.90 (0.70, 12.15) 1.78
Subtotal (I-squared = 0.0%, p = 0.829) 3.09 (2.49, 3.83) 78.69
<19.8
Patricia M. Dietz-2009 2.40 (1.20, 4.80) 7.54
Ihunnaya O. Frederick-2008 2.36 (1.09, 5.09) 6.10
Line Rode-2007 1.70 (0.80, 3.60) 6.41
C. Kabali-2007 1.80 (0.33, 9.77) 1.26
Subtotal (I-squared = 0.0%, p = 0.905) 2.12 (1.40, 3.20) 21.31
Heterogeneity between groups: p = 0.110
Overall (I-squared = 0.0%, p = 0.745) 2.85 (2.36, 3.45) 100.00
.3
1
13
B1
Study
ID
OR (95% CI)
%
Weight
18.5-24.9
Shaoping Yang-2015 0.75 (0.66, 0.85) 11.85
Aimin Chen-2015 0.69 (0.66, 0.73) 78.38
Izumi Chihara-2014 0.47 (0.29, 0.75) 0.88
Nan Li-2013 0.80 (0.65, 0.99) 4.50
Se Li-2013 0.82 (0.53, 1.27) 1.04
Subtotal (I-squared = 35.0%, p = 0.188) 0.70 (0.67, 0.73) 96.65
19.8–26
Patricia M. Dietz-2009 0.60 (0.40, 0.90) 1.21
Ihunnaya O. Frederick-2008 0.30 (0.13, 0.66) 0.30
C. Kabali-2007 0.90 (0.30, 2.60) 0.17
Line Rode-2007 0.70 (0.50, 1.00) 1.66
Subtotal (I-squared = 25.4%, p = 0.259) 0.62 (0.49, 0.79) 3.35
Heterogeneity between groups: p = 0.341
Overall (I-squared = 27.8%, p = 0.197) 0.70 (0.67, 0.73) 100.00
.1
1
3
B2
Study
ID
OR (95% CI)
%
Weight
18.5-24.9
Shaoping Yang-2015 2.26 (2.07, 2.47) 17.74
Aimin Chen-2015 1.95 (1.89, 2.01) 23.98
Izumi Chihara-2014 2.22 (1.74, 2.82) 6.01
Margaretha Haugen-2014 2.65 (2.09, 3.35) 6.23
Margaretha Haugen-2014(1) 2.03 (1.73, 2.38) 10.54
Nan Li-2013 1.90 (1.71, 2.12) 15.45
Se Li-2013 2.10 (1.51, 2.92) 3.63
Subtotal (I-squared = 65.3%, p = 0.008) 2.09 (1.93, 2.26) 83.57
19.8–26
Patricia M. Dietz-2009 2.10 (1.70, 2.70) 6.42
Ihunnaya O. Frederick-2008 2.32 (1.68, 3.20) 3.77
C. Kabali-2007 1.10 (0.50, 2.40) 0.73
Line Rode-2007 1.90 (1.50, 2.50) 5.51
Subtotal (I-squared = 10.3%, p = 0.342) 2.02 (1.72, 2.37) 16.43
Overall (I-squared = 51.7%, p = 0.023) 2.07 (1.94, 2.22) 100.00
NOTE: Weights are from random effects analysis
.5
1
3.5

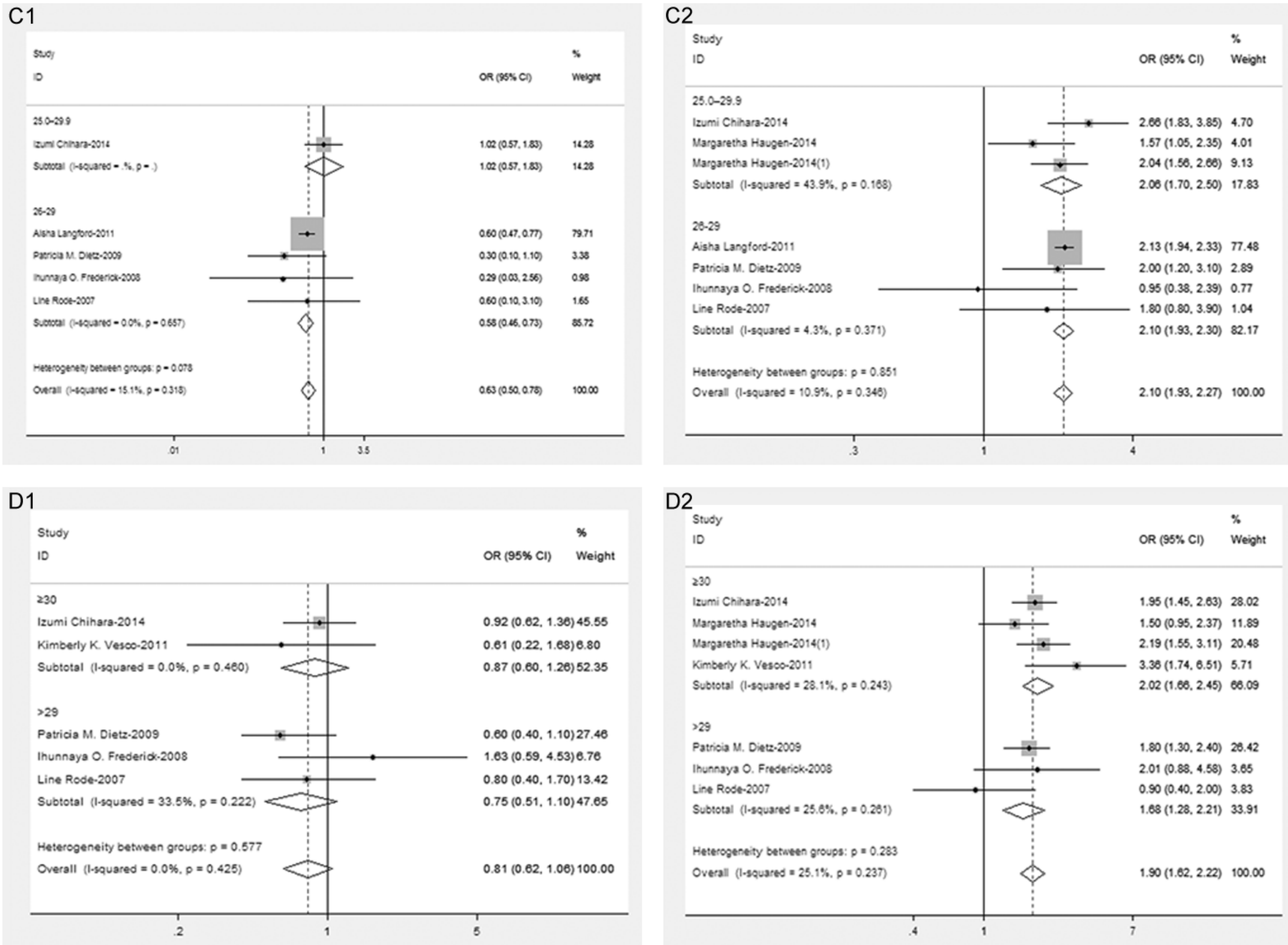


Figure 3 Forest Plot for joint associations. A1-D1: associations between inadequate GWG in four BMI classes and macrosomia; A2-D2: associations between excessive GWG in four BMI classes and macrosomia.

Table 3. Summary estimates of the meta-analysis

Maternal weight indexes and macrosomia	Studies (NO.)	Pooling OR, 95% CI	*P* value	I² (*P* value)	Method	Change pooling method	
						Pooled OR, 95% CI	*P* value
Pre-BMI							
Under weight	17	0.50 (0.45, 0.55)	0.000	38.3% (0.055)	Random	0.49 (0.46, 0.52)	0.000
Normal weight	Reference						
Overweight	15	1.62 (1.47, 1.78)	0.000	87.7% (0.000)	Random	1.65 (1.61, 1.70)	0.000
Obese	27	2.31 (2.05, 2.59)	0.000	89.3% (0.000)	Random	2.29 (2.22, 2.37)	0.000
Overall of GWG							
Inadequate	7	0.68 (0.55, 0.83)	0.000	72.4% (0.001)	Random	0.63 (0.59, 0.68)	0.000
Adequate	Reference						
Excessive	7	2.12 (1.92, 2.34)	0.000	59.2% (0.023)	Random	2.06 (1.98, 2.15)	0.000
Subgroup of GWG by pre-BMI							
Inadequate in Under weight	5	0.58 (0.41, 0.83)	0.003	0.0% (0.628)	Fixed	0.58 (0.41, 0.83)	0.003
Adequate in Under weight	Reference						
Excessive in Under weight	7	2.85 (2.36, 3.45)	0.000	0.0% (0.905)	Fixed	2.85 (2.36, 3.45)	0.000
Inadequate in Normal weight	9	0.70 (0.67, 0.73)	0.000	27.8% (0.197)	Fixed	0.70 (0.64, 0.77)	0.000
Adequate in Normal weight	Reference						
Excessive in Normal weight	11	2.07 (1.94, 2.22)	0.000	51.7% (0.023)	Random	1.99 (1.94, 2.04)	0.000
Inadequate in Overweight	5	0.63 (0.50, 0.78)	0.000	15.1% (0.318)	Fixed	0.64 (0.46, 0.88)	0.007
Adequate in Overweight	Reference						
Excessive in Overweight	7	2.10 (1.93, 2.27)	0.000	10.9% (0.346)	Fixed	2.07 (1.85, 2.32)	0.007
Inadequate in Obese	5	0.81 (0.62, 1.06)	0.123	0.0% (0.425)	Fixed	0.81 (0.62, 1.06)	0.123
Adequate in Obese	Reference						
Excessive in Obese	7	1.90 (1.62, 2.22)	0.000	25.1% (0.237)	Fixed	1.89 (1.56, 2.30)	0.000

on the review of the title/abstract; further reviewing the reference lists of the 67 articles identified another 4 studies for possible inclusion. By reviewing the whole 71 articles according to the pre-specified inclusion criteria, 41 were excluded. Therefore, 30 articles [26-55] (containing 31 eligible studies) were screened for final inclusion in the systematic review.

Study characteristics

As **Table 2** shows, among the 31 studies, 27 (87.1%) were cohort studies (3 samples were less than 1000) and 4 (12.9%) were case control studies; 19 (61.3%) were reported pre-pregnant weight and height by self-report or by clinical record, and 12 (38.7%) were reported weight and height in the first trimester by clinical record replacing the pregnant weight and height, in that the weight in the first trimester was similar to the pre-pregnant weight; 21 (67.7%) were define macrosomia as at least 4000, and 9 (29%) were define macrosomia as at least 4500 g, the other one was unknown; 20 (64.5%) reported association between pre-pregnant BMI and macrosomia, 7 (22.6%) reported association between gestational weight gain in total and macrosomia, 14 (45.2%) reported association between gestational weight gain in subgroup by pre-pregnant BMI and macrosomia.

Meta analysis results

The quantitative findings are presented in **Figures 2**, **3** and **Table 3**.

The independent effects of maternal pre-pregnant overweight (the pooling OR was 1.62 [1.47, 1.78], reference by normal weight), obese (2.31 [2.05, 2.59]) and excessive GWG in overall (2.12 [1.92, 2.34], reference by adequate GWG) were at significantly odds of giving birth to a macrosomia. But maternal pre-pregnant underweight (0.50 [0.45, 0.55]) and inadequate GWG in total (0.68 [0.55, 0.83]) associating with macrosomia were negative, which seemed to be good for preventing macrosomia.

The joint effects of maternal excessive GWG in four pre-pregnant BMI classes (2.85 [2.36, 3.45], 2.07 [1.94, 2.22], 2.10 [1.93, 2.27] and 1.90 [1.62, 2.22], respectively, according to order of increasing BMI, reference by adequate GWG within the class) were at significantly odds of giving birth to a macrosomia. The estimates of maternal inadequate GWG in underweight, normal-weight and overweight (0.58 [0.41,

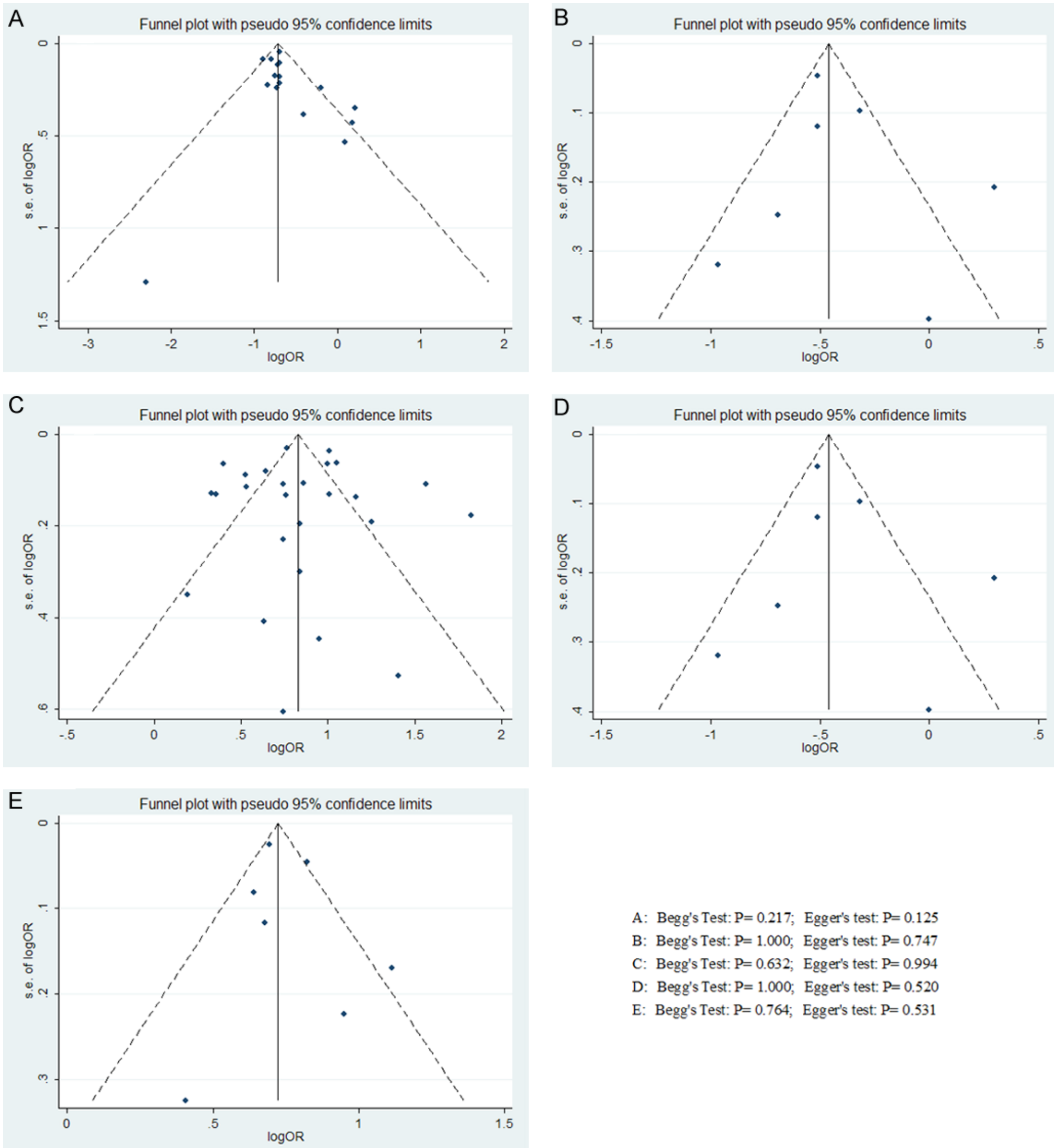


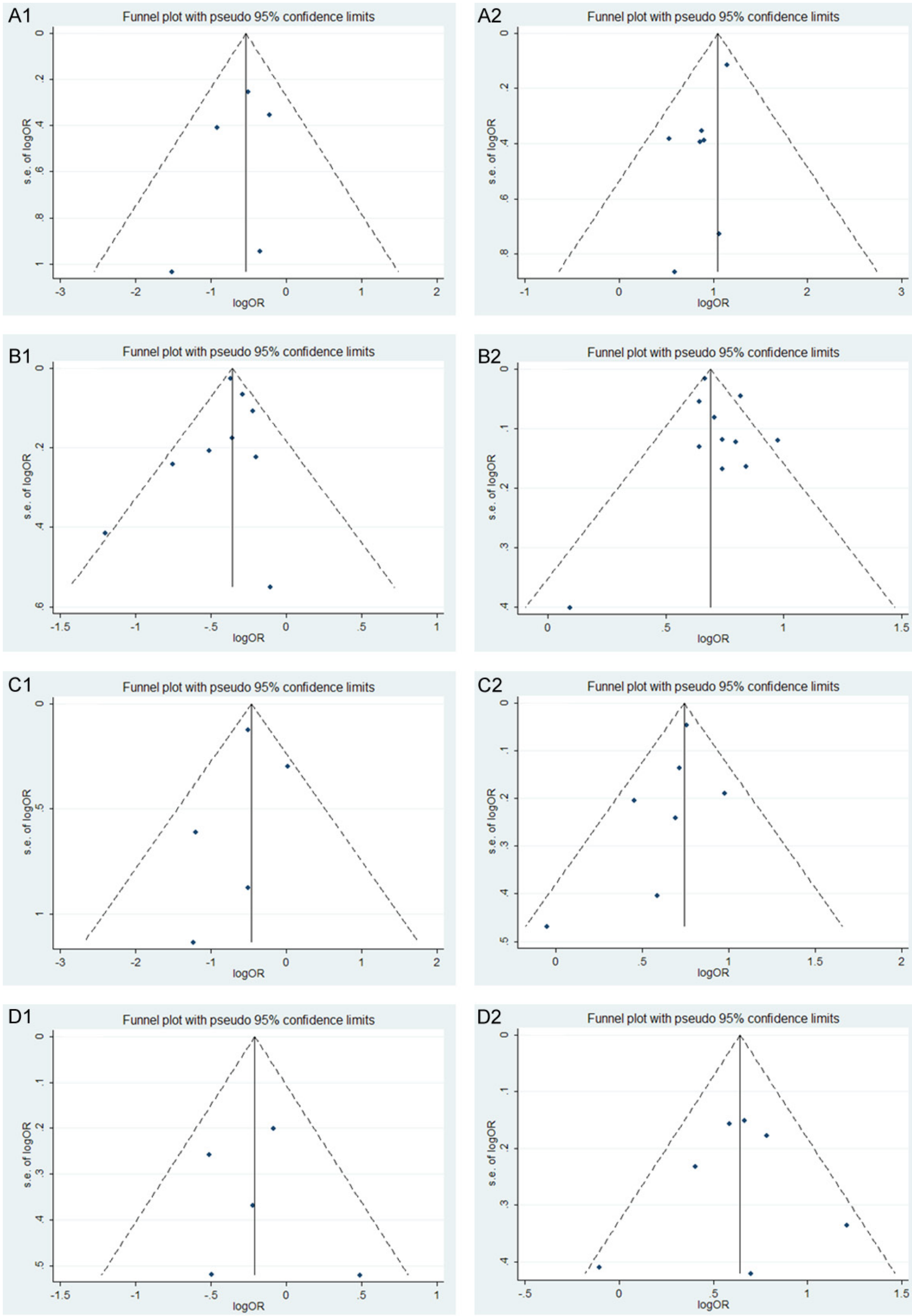
Figure 4. Funnel Plot and quantitative analysis of publication bias for independent associations. A: Bias for association between underweight and macrosomia; B: Bias for associations between overweight and macrosomia; C: Bias for associations between obese and macrosomia; D: Bias for associations between inadequate GWG and macrosomia; E: Bias for associations between excessive GWG and macrosomia.

0.83], 0.70 [0.67, 0.73], 0.63 [0.50, 0.78]) with macrosomia were significantly below 1, which were protective factor for preventing macrosomia. But in the obese group, the estimate (0.81 [0.62, 1.06]) was not so significant, which may need more studies to make the association clear.

We analyzed the data in subgroups according to the difference of BMI in IOM recommendations in 1990 and 2009, and the results of comparing the two subgroups in the same class of BMI were similar on confirming the associations between the maternal and the offspring.

Publication bias

We used Egger's test and Begg's test to create a funnel chart and found that the plots were essentially symmetric with *P* values greater



A1: Begg's Test: P= 0.806; Egger's test: P= 0.488
B1: Begg's Test: P= 0.348; Egger's test: P= 0.661
C1: Begg's Test: P= 1.000; Egger's test: P= 0.736
D1: Begg's Test: P= 0.806; Egger's test: P= 0.834

A2: Begg's Test: P= 0.764; Egger's test: P= 0.040
B2: Begg's Test: P= 1.000; Egger's test: P= 0.269
C2: Begg's Test: P= 0.133; Egger's test: P= 0.257
D2: Begg's Test: P= 0.764; Egger's test: P= 0.765

Figure 5 Funnel Plot and quantitative analysis of publication bias for joint associations. A1-D1: bias for associations between inadequate GWG in four BMI classes (in order of underweight, normal-weight, overweight and obese) and macrosomia;. A2-D2: bias for associations between excessive GWG in four BMI classes (in order of underweight, normal-weight, overweight and obese) and macrosomia.

than 0.05, suggesting that there was no obvious publication bias (**Figures 4** and **5**).

Sensitivity Analysis

As shown in **Table 3**, changing pooling models did not significantly modify the pooled ORs for macrosomia.

Comments

Main findings

This systematic review aimed at exploring the associations of pre-pregnant BMI and GWG with macrosomia. The meta-analysis demonstrated that the higher pre-pregnant weight status or gestational weight gain had associated with fetal higher birth weight. The difference among underweight group, normal-weight or overweight group and obese group were statistically significant, which presented dose-response relationship, considering adequate GWG as a reference. The mechanisms remained to be studied. The women whose pre-pregnant BMI are out of the range of normal-weight might have paid more attention to the effect of their own weight and weight gain to the health of both generations through the whole pregnancy, which might conduce to limitation of the GWG. As we all have seen that the adequate GWG of IOM recommendation in 1990 or in 2009 decreased with increasing BMI, therefore, GWG modified the association between Pre-pregnant BMI and macrosomia to a certain extent.

Maternal underweight and inadequate gestational weight gain seemed to be good for preventing macrosomia, which were reported increasing risk of giving birth to babies with low birth weight (LBW) [56, 57]. LBW is a consequence of reduced length of gestation and/or restricted fetal growth in utero [58]. Both prematurity and growth restriction make important contributions to morbidity and mortality during infancy, and in the long term these conditions may put adults at risk for a wide range of adverse health outcomes [59-61]. So appropriate maternal pre-pregnant BMI and GWG are very important to birth weight of offspring and the health during childhood and adulthood.

Strength and limitation

Strength: Our meta-analysis focused on the maternal weight status during the whole stage of pregnancy, include before and during pregnancy, impacting on delivering macrosomia, so we analyzed the independent and joint associations. Although searching for eligible article, we found three systematic reviews [56, 57, 62] relating on macrosomia, which were similar to our study, they studied parts of the whole stage of pregnancy.

In the meantime, study articles in our meta-analysis were published from January 2006 to May 2015, and the IOM issued the 2009 GWG guidelines updating the 1990 guidelines, so we split the including studies in two subgroups and respectively probed the associations of pre-pregnant BMI and GWG with macrosomia, then the subgroup results had been compared. Though the difference of IOM recommendations on total gestational weight gain was not so great, the lower limit of normal weight was decreased and the upper limit of overweight was increased, so the rang of normal-weight and overweight as a whole was expanded, therefore we analyzed the data in subgroups. And the difference between subgroup results of the associations were not statistically significant.

limitation: According to our exclusion criteria, that participants were special sample were not eligible, such as diabetic or gestational diabetic patient. As maternal pre-pregnant BMI, gestational weight gain, and diabetic were tightly linked [63-65], obesity and excessive gestational weight gain would exaggerate diabetic and diabetic could worsen macrosomia [66].We also excluded special sample studies on pregnant age like maternal age ≤18 years [67, 68], considering that it was not only a health problem, but also a public challenge. So we didn't take the interference of above factors into account in the process of analyzing the associations of pre-pregnant BMI and GWG with macrosomia.

Conclusion

Increasing maternal BMI and GWG were independently associating with an increasing risk of macrosomia and jointly associating significantly with macrosomia. With identifying macrosomia difficultly before delivery [21, 69], and the increasing trend in diabetes and obesity in women of childbearing age [70, 71], in that diabetes has synergistic effect with obese on bearing macrosomia, macrosomia should be considered as a public health problem that could be worse in the future [2]. At the earlier period of life, the birth weight of macrosomia is above the normal range, which could be a risk factor to chronic diseases in later life, so reducing the birth rate of macrosomia may improve the health level of adult life, and decrease the morbidity of chronic diseases. So it is imminent to strengthen the intervention to women of reproductive age. Based on the above consideration, the results of this study could provide reference to minimize the rate of macrosomia and implement early intervention against risk factors of chronic diseases.

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Disclosure of conflict of interest

None.

Authors' contribution

Weiqiang Zhou had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. No compensation was received for such contributions. Written permission had been obtained from all persons named in the acknowledgment section. Study concept and design: Weiqiang Zhou, Qian Hong. Acquisition of data: Weiqiang Zhou, Xing-xing Sun, Yu Hao, Shuxinyi Yang. Analysis and interpretation of data: Weiqiang Zhou, Qian Hong, Xing-xing Sun, Yu Hao, Shuxinyi Yang. Drafting of the manuscript: Weiqiang Zhou. Critical revision of the manuscript for important intellectual content: Weiqiang Zhou, Qian Hong. Statistical analysis: Weiqiang Zhou. Study supervision: Weiqiang Zhou, Qian Hong.

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