Meta-Analysis

The association of maternal gestational weight gain with cardiometabolic risk factors in offspring: a systematic review and meta-analysis

Jiaxing Wen [1,2], Axing Lv[3], Sumiya Aihemaitijiang[1,2], Hongtian Li[1,2], Yubo Zhou[1,2,*], and Jianmeng Liu[1,2]

[1]Institute of Reproductive and Child Health, Ministry of Health Key Laboratory of Reproductive Health, Peking University Health Science Center, Beijing, China
[2]Department of Epidemiology and Biostatistics, Peking University Health Science Center, Beijing, China
[3]School of Public Health, Peking University Health Science Center, Beijing, China
*Correspondence: *Y. Zhou*, Institute of Reproductive and Child Health, Ministry of Health Key Laboratory of Reproductive Health, Peking University Health Science Center, Beijing 100191, China. E-mail: zhouyubo@bjmu.edu.cn.

Context: *Gestational weight gain (GWG) is known to be a risk factor for offspring obesity, a precursor of cardiometabolic diseases. Accumulating studies have investigated the association of GWG with offspring cardiometabolic risk factors (CRFs), leading to inconsistent results.* ***Objective:*** *This study synthesized available data from cohort studies to examine the effects of GWG on offspring CRFs.* ***Data Source:*** *Four electronic databases, including PubMed, Web of Science, Scopus, and Embase, were searched through May 2023.* ***Data Extraction:*** *Cohort studies evaluating the association between GWG and CRFs (fat mass [FM], body fat percentage [BF%], waist circumference [WC], systolic blood pressure [SBP] and diastolic blood pressure, high-density-lipoprotein cholesterol [HDL-C] and low-density-lipoprotein cholesterol, triglyceride [TG], total cholesterol, fasting blood glucose, and fasting insulin levels) were included. Regression coefficients, means or mean differences with 95% confidence intervals [CIs], or standard deviations were extracted.* ***Data Analysis:*** *Thirty-three cohort studies were included in the meta-analysis. Higher GWG (per increase of 1 kg) was associated with greater offspring FM (0.041 kg; 95% CI, 0.016 to 0.067), BF% (0.145%; 95% CI, 0.116 to 0.174), WC (0.154 cm; 95% CI, 0.036 to 0.272), SBP (0.040 mmHg; 95% CI, 0.010 to 0.070), and TG (0.004 mmol/L; 95% CI, 0.001 to 0.007), and with lower HDL-C (–0.002 mmol/L; 95% CI, –0.004 to 0.000). Consistently, excessive GWG was associated with higher offspring FM, BF%, WC, and insulin, and inadequate GWG was associated with lower BF%, low-density lipoprotein cholesterol, total cholesterol, and TG, compared with adequate GWG. Most associations went non-significant or attenuated with adjustment for offspring body mass index or FM.* ***Conclusions:*** *Higher maternal GWG is associated with increased offspring adiposity, SBP, TG, and insulin and decreased HDL-C in offspring, warranting a need to control GWG and to screen for cardiometabolic abnormalities of offspring born to mothers with excessive GWG.*

Systematic Review Registration: *PROSPERO registration no. CRD42023412098.*

Key words: *cardiometabolic risk factor, gestational weight gain, meta-analysis, offspring health.*

https://doi.org/10.1093/nutrit/nuae027

INTRODUCTION

Maternal obesity is prevalent globally, with excessive gestational weight gain (GWG) as a substantial driver.[1,2] According to the guidelines of the National Academy of Medicine (NAM; formerly the Institute of Medicine [IOM]) (*see* Table S1 *in the Supporting Information online*) released in 2009, the prevalence of excessive GWG has reached 39% worldwide.[2] The corresponding figure was 50% in North America[2], as high as 58% in China[3], and kept increasing across nations.[4,5]

The highly prevalent excessive GWG not only posed a threat to maternal health but also jeopardized short- and long-term health for their offspring.[6,7] Previous studies have reported that excessive GWG may increase the risk of offspring obesity,[8] a well-known precursor of cardiometabolic diseases.[9] Accumulating epidemiological studies have investigated the impact of GWG and offspring cardiometabolic risk factors (CRFs). However, the results remain inconsistent,[10] with some reporting significant associations,[11–13] and some not reporting these associations.[14,15] Until now, there were 2 previous meta-analyses focusing on only offspring blood pressure and insulin, which reported significant results,[16,17] but none focusing on other offspring CRFs. A comprehensive picture of the impact of GWG on a spectrum of CRF outcomes is essential for preventing cardiometabolic disease, particularly given its rising burden on morbidity and mortality in populations.[18]

The objective of this meta-analysis was to examine the associations of maternal GWG with a spectrum of CRF outcomes in offspring, and to examine the mediating effects of offspring anthropometry on the associations.

METHODS

Search strategy and study selection

Our meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (*see* Table S2 *in the Supporting Information online*). The research protocol was prospectively registered at PROSPERO (http://www.crd.york.ac.uk/Prospero; no. CRD42023412098). Four electronic databases, including PubMed, Web of Science, Scopus, and Embase, were searched through May 2023. A systematic search strategy was developed to identify published reports concerning the association of GWG with offspring CRFs (eg, measures of body fatness, blood pressure, blood lipids, and glycemia). Index terms, subject subheadings, and some word truncations related to the exposure and outcome measures, according to each database, were also used to map all possible key words (*see* Table S3 *in the Supporting Information online*).

The selection of studies was conducted by 2 independent evaluators (J.W. and A.L.) to screen the titles and abstracts of all articles initially identified according to the eligibility criteria. The full texts of the potentially relevant articles were retrieved for further screening to confirm their eligibility. The reference lists of the selected articles on the topic were manually screened to identify additional publications.

The articles were eligible if they met the following PICOS (Population, Intervention, Comparison, Outcomes, and Study design) criteria (Table 1): (1) focused on healthy singleton pregnant women; (2) examined the effects of GWG; (3) assessed at least 1 of the outcomes, including fat mass (FM), body fat percentage (BF%), waist circumference (WC), systolic or diastolic blood pressure (SBP or DBP), high- or low-density-lipoprotein cholesterol (HDL-C or LDL-C), total cholesterol (TC), triglyceride (TG), fasting blood glucose (FBG) or insulin; and (4) were cohort studies published in English or Chinese. Articles were excluded if they were literature reviews, case reports, and animal or cell studies. For articles from the same cohort, the article with the most complete information was included. Disagreements were resolved by discussion or by consultation with an adjudicator (Y.Z.).

Data extraction and quality assessment

Data extraction was conducted by 2 independent reviewers (J.W. and A.L.) using a standard form, including study characteristics (first author, publication year, country, study design, sample size, offspring age at measurement), maternal GWG exposure (continuous total GWG, categorized total GWG, or others), outcomes, effect estimates (regression coefficient, mean or mean difference [MD], risk ratio [RR] or odds ratio [OR], with standard deviation [SD] or 95% confidence

Table 1 **PICOS criteria for inclusion of studies**

Parameter	Criterion
Population	Healthy singleton pregnant women
Intervention	Continuous GWG; excessive and inadequate GWG
Comparator	Adequate GWG
Outcome	At least 1 of the outcomes including FM, BF%, WC, SBP, DBP, HDL-C, LDL-C, TC, TG, FBG, or insulin
Study design	Cohort studies

Abbreviations: BF%, body fat percentage; DBP, diastolic blood pressure; FBG, fasting blood glucose; FM, fat mass; GWG, gestational weight gain; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol; SBP, systolic blood pressure; WC, waist circumference; TC, total cholesterol; TG, triglyceride.

interval [CI]), and confounders. Adjusted effect estimates were extracted, where possible; otherwise, crude estimates were extracted. If several multivariate-adjusted estimates were available, the most fully adjusted one was extracted. If a study reported both estimates adjusted without and with offspring anthropometry, which has been reported as a critical mediator,[11,16] both estimates were extracted for potential sensitivity analysis. If a study reported more than 1 estimate within the same cohort, the estimates with the longest follow-up were extracted. If a study reported several estimates from mutually exclusive cohorts, all estimates were extracted.

The methodological quality of the included cohort studies was assessed using the Newcastle-Ottawa Scale.[19] Studies were scored according to population selection (up to 4 points), outcome assessment (up to 3 points), and group comparability (up to 2 points). The total score ranged from 0 to 9, and 0–5 was defined as low quality, 6–7 as moderate quality, and 8–9 as high quality. Disagreements regarding data items or quality assessment were resolved by discussion with an adjudicator (Y.Z.), when necessary.

Statistical analysis

Effects of GWG on offspring CRFs were expressed as unstandardized regression coefficients (B) or MD with 95% CIs. For studies that reported standardized regression coefficients (β), the β was converted into B if the corresponding SD was available.[17] For studies that reported medians with 25th and 75th percentiles, the mean and SD were estimated from the median and the percentiles.[20] The most completely adjusted effect estimates were used for syntheses, where possible; otherwise, crude estimates were used. For studies that extracted both estimates adjusted without or with offspring anthropometry, the former estimates were used in the main analysis.

Heterogeneity in study results was quantified using the I^2 statistic. A fixed-effects model was applied to pool the results when $I^2 \leq 50\%$, and a random-effects model was used when $I^2 > 50\%$.[21] If 6 or more cohort studies were available, then potential sources of heterogeneity were explored using subgroup analyses and meta-regression. Publication bias was visually inspected with a funnel plot, and further quantitatively assessed using the Egger's test. The influence of potential publication bias on pooled results was assessed using the trim-and-fill method. In sensitivity analysis, we pooled and compared the estimates adjusted without and with offspring anthropometry from the same studies to explore the mediating role of offspring anthropometry. The statistical analyses were performed using Review Manager (version 5.4; Cochrane) and R package "meta" (R version 4.2.2; R Foundation for Statistical Computing). All tests were 2-sided, and $P < 0.05$ was regarded as statistically significant.

RESULTS

Study selection and characteristics

Of 8848 records identified by the initial search, 115 were selected for full-text review; 38 studies met the eligibility criteria for systematic review (Fig. 1). The characteristics of the 38 studies are shown in Table 2.[11–15,22–54] There were 10 studies performed in the United States, 5 in Brazil, 15 in Europe, 4 in Australia, and 4 in Asia. Gestational weight gain was treated differently across studies: 25 studies categorized total GWG according to the IOM recommendation (excessive, adequate, or inadequate)[12,13,15,23,24,26,28,29,31,33,35,36,38,42,43,45,46,48–52,54] or GWG tertiles[27,53]; 16 studies used continuous total GWG[11,12,14,22,23,25,29,30,33,34,36,37,39,41,44,54]; 4 studies used GWG rate[15,37,39,40]; and 6 studies used trimester-specific GWG.[24,33,36,37,39,40] The age of offspring at measurement varied between studies: 12 studies measured offspring in the infancy period (0–1 y), 23 in childhood (1—18 y), and 6 in adulthood periods (>18 y). The methodologic quality of the studies was overall acceptable, with 25 studies assessed as high quality and 13 as moderate quality (*see* Table S4 *in the Supporting Information online*).

Of the 38 studies, 5 studies were excluded from meta-analysis as they did not report SDs or 95% CIs[25,44] or reported categorical outcomes[29,31,45] that are not sufficient for statistical synthesis (*see* Table S5 *in the Supporting Information online*). Finally, 33 studies involving 90 968 mother–child pairs were included in the meta-analysis (Fig. 1).

Meta-analysis

Gestational weight gain and measures of body fatness. Twelve studies assessed the relationship of GWG with FM of offspring, 18 studies with BF%, and 13 studies with WC. Meta-analysis showed that continuous GWG was positively correlated with FM (B, 0.041; 95% CI, 0.016 to 0.067 kg per kg; $P = 0.001$; $I^2 = 89\%$) (Table 3, Fig. 2A), BF% (B, 0.145; 0.116 to 0.174 % per kg; $P < 0.001$; $I^2 = 0\%$) (Table 3), and WC of offspring (B, 0.154; 0.036 to 0.272 cm per kg; $P = 0.011$; $I^2 = 83\%$) (Table 3). As compared with adequate GWG, excessive GWG was significantly associated with greater FM (MD, 0.114; 0.042 to 0.185 kg; $P = 0.002$; $I^2 = 97\%$) (Table 4), BF% (MD, 1.359; 95% CI, 0.505 to 2.212 %; $P = 0.002$; $I^2 = 94\%$) (Table 4), and WC (MD, 1.775; 0.735 to 2.816 cm; $P < 0.001$; $I^2 = 73\%$) (Table 4);

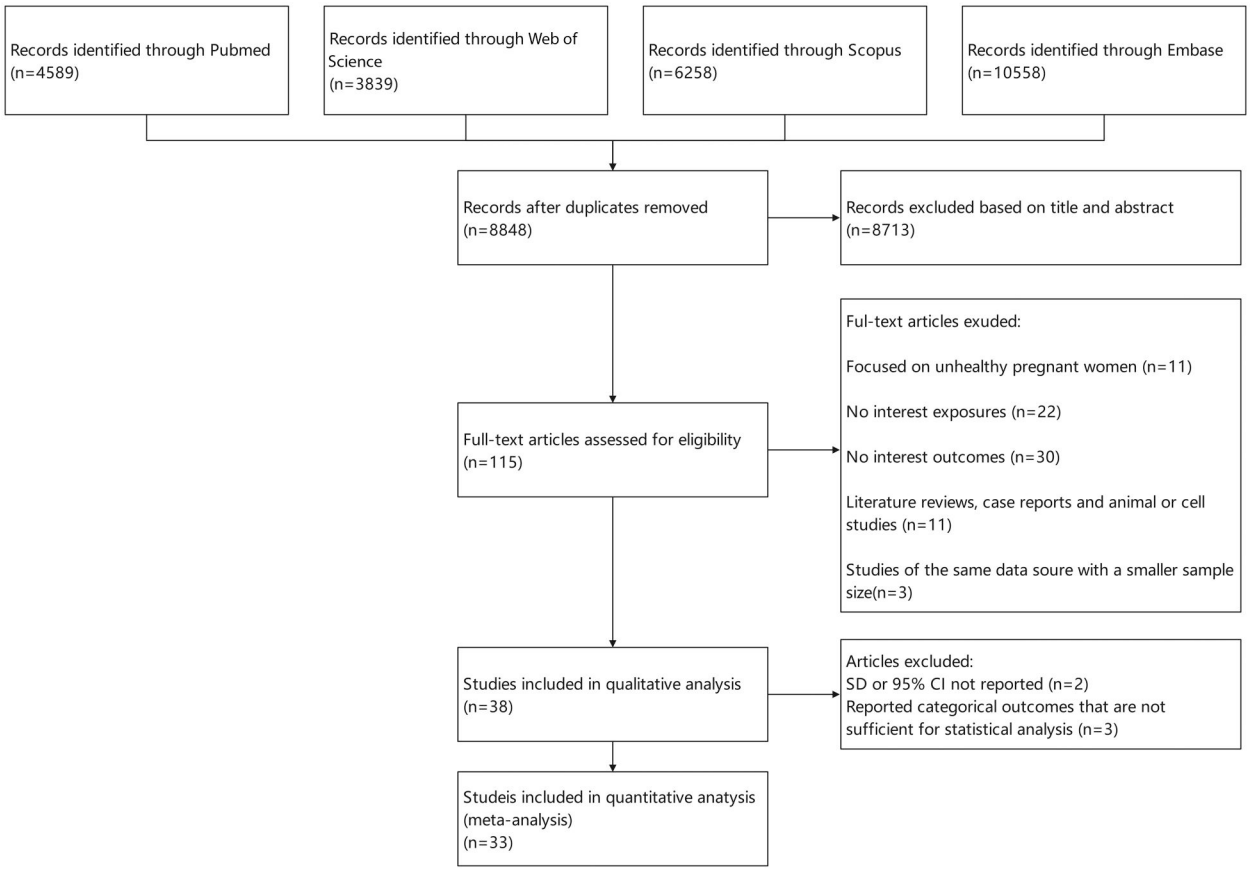

Figure 1 **Flow diagram of the literature search process**. *Abbreviations:* CI, confidence interval; SD, standard deviation

inadequate GWG was associated with lower BF% (MD, −0.960; −1.276 to −0.644 %; $P < 0.001$; $I^2 = 15\%$) (Table 4), but not with FM (MD, −0.098; −0.198 to 0.002 kg; $P = 0.056$; $I^2 = 67\%$) (Table 4) or WC (MD, 0.055; −0.213 to 0.322; cm; $P = 0.688$; $I^2 = 14\%$) (Table 4).

Gestational weight gain and blood pressure. Seventeen studies assessed the association of GWG with offspring SBP, and 15 studies with DBP. In meta-analysis, continuous GWG was positively correlated with SBP (B, 0.040; 95% CI, 0.010 to 0.070 mmHg per kg; $P = 0.009$; $I^2 = 46\%$) (Table 3, Fig. 2B), but not with DBP (B, 0.021; −0.010 to 0.052 mmHg per kg; $P = 0.179$; $I^2 = 49\%$) (Table 3). As compared with adequate GWG, excessive or inadequate GWG was not associated with SBP (excessive GWG: MD, 0.150; −0.251 to 0.552 mmHg; $P = 0.463$; $I^2 = 55\%$ [Table 4]; inadequate GWG: MD, 0.172; −0.033 to 0.377 mmHg; $P = 0.100$; $I^2 = 0\%$ [Table 4]) or DBP (excessive GWG: MD, 0.557; −0.040 to 1.154 mmHg; $P = 0.067$; $I^2 = 71\%$ [Table 4]; inadequate GWG: MD, 0.076; −0.244 to 0.396 mmHg; $P = 0.641$; $I^2 = 0\%$ [Table 4]).

Gestational weight gain and dyslipidemia. Eleven studies assessed the association of GWG with offspring HDL-C, 8 studies with LDL-C, 9 studies with TC, and 10 studies with TG. Meta-analysis showed that continuous GWG was correlated with increased TG (B, 0.004; 95% CI, 0.001 to 0.007 mmol/L per kg; $P = 0.012$; $I^2 = 0\%$) (Table 3), but not with LDL-C (B, 0.002; −0.003 to 0.007 mmol/L per kg; $P = 0.436$; $I^2 = 0\%$) (Table 3) or TC (B, −0.043; −0.202 to 0.117 mmol/L per kg; $P = 0.600$; $I^2 = 0\%$) (Table 3), and mildly associated with decreased HDL-C (B, −0.002; −0.004 to 0.000 mmol/L per kg; $P = 0.049$; $I^2 = 0\%$) (Table 3, Fig. 2C). As compared with adequate GWG, excessive GWG was not associated with LDL-C (MD, −0.030; −0.069 to 0.009 mmol/L; $P = 0.099$; $I^2 = 95\%$) (Table 4), TC (MD, −0.033; −0.088 to 0.023 mmol/L; $P = 0.246$; $I^2 = 65\%$) (Table 4), TG (MD, −0.002; −0.014 to 0.010 mmol/L; $P = 0.781$; $I^2 = 63\%$) (Table 4), or HDL-C (MD, −0.015; −0.039 to 0.010 mmol/L; $P = 0.253$; $I^2 = 59\%$) (Table 4); inadequate GWG was associated with lower LDL-C (MD, −0.050; −0.088 to −0.012 mmol/L; $P = 0.002$; $I^2 = 0\%$) (Table 4), TC (MD, −0.069; −0.119 to −0.029 mmol/L; $P = 0.007$; $I^2 = 11\%$) (Table 4), and TG (MD, −0.019; −0.033 to −0.005 mmol/L; $P = 0.006$; $I^2 = 0\%$) (Table 4),

Table 2 **Characteristics of the included studies**

Reference	Country	Study design	Sample size, n	Offspring age at measurement, y	Study quality[a]	Maternal GWG[d]			Outcomes[e]										
						Categorized	Continuous	Other[b]	FM	BF%	WC	SBP	DBP	HDL-C	LDL-C	TC	TG	FBG	Insulin
Oken et al (2007)[22]	USA	PCS	435	3	H		●					○							
Mamun et al (2009)[15]	Australia	RCS	2432	21	H	●		●				○	○						
Crozier et al (2010)[23]	UK	PCS	1695	6	H	●	●		○										
Fraser et al (2010)[24]	UK	RCS	5154	9	H	●		●	○		○	○	○	○			○		
Reynolds et al (2010)[25], c	UK	RCS	276	30	M		●			○	○								
Hull et al (2011)[13]	USA	RCS	306	0	M	●		●	○	○									
Wen et al (2011)[26]	USA	RCS	30 461	7	M	●						○							
Hochner et al (2012)[11]	Israel	RCS	1400	32	H		●				○	○	○	○	○		○	○	○
Dello Russo et al (2013)[27]	Eight European countries	RCS	12 775	9	M	●		●			○	○	○	○	○	○	○		○
Josefson et al (2013)[28]	USA	RCS	38	0	H	●			○	○								○	
Ensenauer et al (2013)[29], c	Germany	RCS	6837	6	M	●	●				○								
Carlsen et al (2014)[30]	Denmark	RCS	231	0	H		●		○	○									
Badon et al (2014)[31], c	USA	RCS	2260	0	H	●				○									
Perng et al (2014)[32]	Australian	PCS	1090	10	H					○	○	○					○		
Castillo et al (2015)[12]	Brazil	PCS	3089	7	M	●	●		○	○									
Gaillard et al (2015)[33]	Netherlands	PCS	5908	6	H	●	●			○		○	○	○	○	○	○		○
Hrolfsdottir et al (2015)[34]	Iceland	RCS	308	20	M		●	●				○	○	○	○	○	○		○
Henriksson et al (2015)[35]	Sweden	RCS	312	0	H	●			○	○									
Scheers Andersson et al (2015)[14]	Sweden	PCS	4908	18	H		●					○	○						
Starling et al (2015)[36]	USA	PCS	826	0	H	●	●		○	○									
Karachaliou et al (2015)[37]	Greece	RCS	977	4	H		●	●			○	○	○	○			○		
Brittos et al (2016)[38]	Brazil	RCS	246	1	M	●								○	○	○	○		
Gaillard et al (2016)[39]	Australia	PCS	1392	17	H		●	●			○	○	○	○	○	○	○	○	○
Hivert et al (2016)[40]	USA	RCS	979	7	M			●		○	○								
Michaliszyn et al (2017)[41]	USA	PCS	40	1	H		●	●			○								
Tam et al (2018)[42]	China	RCS	905	7	H	●					○	○	○					○	○
Carreras-Badosa et al (2018)[43]	Spain	RCS	66	6	H	●			○	○		○	○			○	○	○	○
Breij et al (2018)[44], c	Netherlands	RCS	300	0.5	H		●		○										
Torres et al (2020)[45], c	Brazil	RCS	181	6	M	●		●				○	○						
Nehab et al (2020)[46]	Brazil	RCS	124	0.3	M	●			○	○							○		
Heard-Lipsmeyer et al (2020)[47]	USA	RCS	224	2	H			●		○									
Chiavaroli et al (2021)[48]	New Zealand	RCS	57	7	H	●				○		○	○	○		○	○	○	○
Elwan et al (2021)[49]	Italy	RCS	82	0.6	M	●													○
Hunt et al (2021)[50]	USA	RCS	2802	6.8	H	●			○	○	○								
Chen Y et al (2022)[51]	China	RCS	1333	3 to 7	H	●				○									
Chen F et al (2022)[52]	China	ACS	3329	3	M	●				○									
Guixeres-Esteve et al (2023)[53]	Spain	PCS	83	1	H	●						○	○	○	○	○	○		
de Oliveira Nascimento Freitas et al (2023)[54]	Brazil	RCS	124	27	H	●	●			○	○	○	○	○	○	○		○	

[a]Study quality was assessed using the Newcastle-Ottawa Scale, with a maximum score of 9.
[b]GWG was treated as GWG rate or trimester-specific GWG.
[c]These 5 studies were not included in the meta-analysis.
[d]● represents the measurement of maternal GWG in this study (categorized, continuous or other).
[e]○ represents the outcomes measured in this study.

Abbreviations: ACS, ambispective cohort study; BF%, body fat percentage; DBP, diastolic blood pressure; FBG, fasting blood glucose; FM, fat mass; GWG, gestational weight gain; H, high quality (quality score: 8–9); HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol; M, medium quality (quality score: 6–7); PCS, prospective cohort study; RCS, retrospective cohort study; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

but not with HDL-C (MD, 0.009; −0.012 to 0.029 mmol/L; $P = 0.413$; $I^2 = 0\%$) (Table 4).

Gestational weight gain and blood glucose. Eight studies assessed the association of GWG with offspring FBG, and 9 studies with fasting insulin. In meta-analysis, continuous GWG was not associated with offspring FBG (B, 0.000; 95% CI, −0.003 to 0.003 mmol/L per kg; $P = 0.872$; $I^2 = 0\%$) (Table 3) or insulin (B, 0.003; −0.003 to 0.008 mmol/L per kg; $P = 0.394$; $I^2 = 0\%$) (Table 3). As compared with adequate GWG, excessive or inadequate GWG was not associated with offspring FBG (excessive GWG: MD, −0.028; −0.076 to 0.019 mmol/L; $P = 0.241$; $I^2 = 6\%$; inadequate GWG: MD, −0.015; −0.081 to 0.052 mmol/L; $P = 0.670$; $I^2 = 39\%$) (Table 4). As compared with adequate GWG, excessive GWG was associated with greater offspring insulin (MD, 1.774; 0.941 to 2.607 mmol/L; $P < 0.001$; $I^2 = 0\%$) (Table 4; Fig. 2D), while no significant association was found for inadequate GWG (MD, −0.055; −2.225 to 2.114 mmol/L; $P = 0.960$; $I^2 = 74\%$) (Table 4).

Table 3 **Results of meta-analysis for continuous gestational weight gain (per kg) and cardiometabolic risk factors in offspring**

Outcomes	No. of studies	B	95% CI	P[a]
FM, kg	7	0.041	(0.016, 0.067)	**0.001**
BF%, %	6	0.145	(0.116, 0.174)	**<0.001**
WC, cm	4	0.154	(0.036, 0.272)	**0.011**
SBP, mmHg	7	0.040	(0.010, 0.070)	**0.009**
DBP, mmHg	5	0.021	(−0.010, 0.052)	0.179
HDL-C, mmol/L	3	−0.002	(−0.004, 0.000)	**0.049**
LDL-C, mmol/L	2	0.002	(−0.003, 0.007)	0.436
TC, mmol/L	2	−0.043	(−0.202, 0.117)	0.600
TG, mmol/L	3	0.004	(0.001, 0.007)	**0.012**
FBG, mmol/L	3	0.000	(−0.003, 0.003)	0.872
Insulin, mmol/L	3	0.003	(−0.003, 0.008)	0.394

[a]*P* values for statistically significant associations (at $P < 0.05$) are shown in bold.

Abbreviations: B, unstandardized regression coefficient; BF%, body fat percentage; CI, confidence interval; DBP, diastolic blood pressure; FBG, fasting blood glucose; FM, fat mass; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

Mediating effect of offspring anthropometry

To explore the mediating role of offspring anthropometry, we conducted sensitivity analysis using 12 studies (11 adjusted for offspring body mass index [BMI], 1 for offspring FM), which simultaneously reported the estimates adjusted without and with this potential mediator (Table 5). After adjustment for offspring anthropometry, the pooled results turned to non-significant for TG (B: 0.005 [0.001, 0.008] mmol/L per kg; $P = 0.014$; $I^2 = 0\%$ vs 0.001 [−0.003, 0.005] mmol/L per kg; $P = 0.558$; $I^2 = 0\%$) (Table 5) and SBP (MD [excessive GWG]: 0.652 [0.259, 1.045] mmHg; $P = 0.001$; $I^2 = 0\%$ vs 0.617 [−0.375, 1.609] mmHg; $P = 0.223$; $I^2 = 67\%$) (Table 5). The results for WC (B: 0.126 [−0.042, 0.295] cm per kg; $P = 0.143$; $I^2 = 86\%$ vs 0.009 [−0.084, 0.102] cm per kg; $P = 0.849$; $I^2 = 67\%$) (Table 5) and SBP (B: 0.030 [−0.002, 0.063] mmHg per kg; $P = 0.068$; $I^2 = 49\%$ vs 0.002 [−0.037, 0.042] mmHg per kg; $P = 0.901$; $I^2 = 37\%$) (Table 5) seemed to be attenuated, although they were all non-significant.

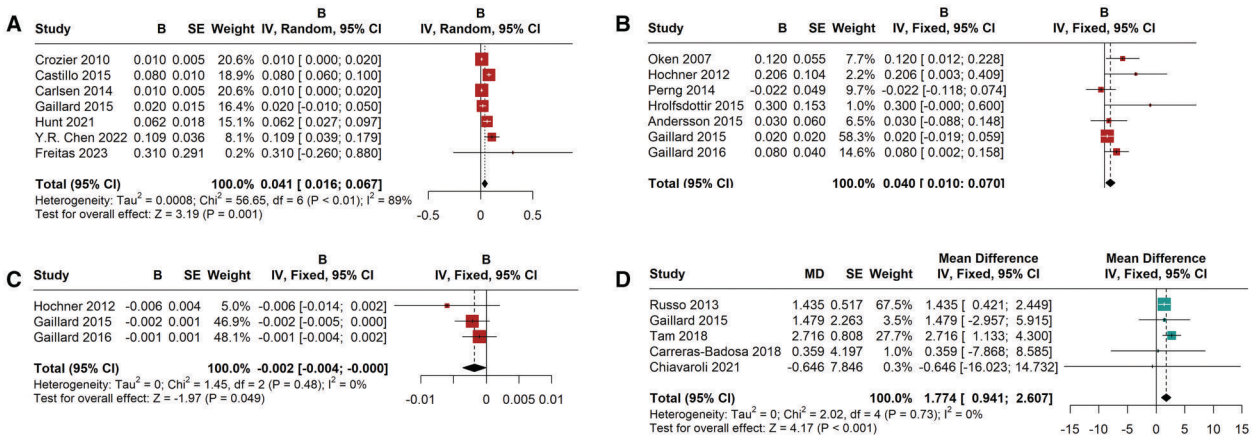

Figure 2 **Forest plots of maternal GWG and selected cardiometabolic risk factor outcomes of offspring**. (A) B-regression coefficients of the association between continuous GWG and offspring FM. (B) B-regression coefficients of the association between continuous GWG and offspring SBP. (C) B-regression coefficients of the association between continuous GWG and offspring HDL-C. (D) Mean difference in offspring insulin between excessive and adequate GWG. Squares represent effect estimates within each study, with 95% CIs represented by horizontal lines. Square size is proportional to the weight of each study. Diamonds represent the synthesized effect size. *Abbreviations*: CI, confidence interval; FM, fat mass; GWG, gestational weight gain; HDL-C, high-density-lipoprotein cholesterol; IV, inverse variance; MD, mean difference; SBP, systolic blood pressure; SE, standard error

Table 4 **Results of meta-analysis for categorized gestational weight gain and cardiometabolic risk factors in offspring**

Outcomes	No. of studies	MD	95% CI	P^a
Excessive GWG vs adequate GWG				
FM, kg	10	0.114	(0.042, 0.185)	**0.002**
BF%	12	1.359	(0.505, 2.212)	**0.002**
WC, cm	3	1.775	(0.735, 2.816)	**<0.001**
SBP, mmHg	6	0.150	(−0.251, 0.552)	0.463
DBP, mmHg	7	0.557	(−0.040, 1.154)	0.067
HDL-C, mmol/L	5	−0.015	(−0.039, 0.010)	0.253
LDL-C, mmol/L	5	−0.030	(−0.069, 0.009)	0.099
TC, mmol/L	5	−0.033	(−0.088, 0.023)	0.246
TG, mmol/L	5	−0.002	(−0.014, 0.010)	0.781
FBG, mmol/L	4	−0.028	(−0.076, 0.019)	0.241
Insulin, mmol/L	5	1.774	(0.941, 2.607)	**<0.001**
Inadequate GWG vs adequate GWG				
FM, kg	7	−0.098	(−0.198, 0.002)	0.056
BF%	5	−0.960	(−1.276, −0.644)	**<0.001**
WC, cm	3	0.055	(−0.213, 0.322)	0.688
SBP, mmHg	5	0.172	(−0.033, 0.377)	0.100
DBP, mmHg	6	0.076	(−0.244, 0.396)	0.641
HDL-C, mmol/L	3	0.009	(−0.012, 0.029)	0.413
LDL-C, mmol/L	3	−0.050	(−0.088, −0.012)	**0.002**
TC, mmol/L	2	−0.069	(−0.119, −0.029)	**0.007**
TG, mmol/L	3	−0.019	(−0.033, −0.005)	**0.006**
FBG, mmol/L	2	−0.015	(−0.081, 0.052)	0.670
Insulin, mmol/L	3	−0.055	(−2.225, 2.114)	0.960

[a]*P* values for statistically significant associations (at $P < 0.05$) are shown in bold.

Abbreviations: BF%, body fat percentage; CI, confidence interval; DBP, diastolic blood pressure; FBG, fasting blood glucose; FM, fat mass; GWG, gestational weight gain; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol; MD, mean difference; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

Table 5 **Synthesized effect size adjusted without and with offspring anthropometry[a]**

Outcomes		Unadjusted			Adjusted		
	No. of studies	TE[b]	95% CI	P^c	TE[b]	95% CI	P^c
Continuous GWG							
WC, cm	3	0.126	(−0.042, 0.295)	0.143	0.009	(−0.084, 0.102)	0.849
SBP, mmHg	4	0.030	(−0.002, 0.063)	0.068	0.002	(−0.037, 0.042)	0.901
DBP, mmHg	2	0.073	(−0.054, 0.200)	0.257	0.042	(−0.014, 0.099)	0.144
HDL-C, mmol/L	2	− 0.002	(−0.004, 0.001)	0.232	0.000	(−0.003, 0.003)	0.975
TG, mmol/L	2	0.005	(0.001, 0.008)	**0.014**	0.001	(−0.003, 0.005)	0.558
FBG, mmol/L	2	0.000	(−0.003, 0.004)	0.865	0.000	(−0.009, 0.009)	0.937
Excessive GWG vs adequate GWG							
SBP, mmHg	3	0.652	(0.259, 1.045)	**0.001**	0.617	(−0.375, 1.609)	0.223
Inadequate GWG vs adequate GWG							
FM, kg	2	− 0.185	(−1.057, 0.687)	0.678	− 0.016	(−0.545, 0.513)	0.952
SBP, mmHg	3	0.023	(−0.307, 0.353)	0.892	− 0.043	(−0.408, 0.322)	0.817
DBP, mmHg	2	0.013	(−0.296, 0.322)	0.933	− 0.034	(−0.343, 0.275)	0.831

[a]Synthesized effect size: an estimate measuring the magnitude and direction of the overall effect combining the results from individual studies.

[b]Total effect size, including unstandardized regression coefficients for continuous GWG, mean difference for excessive and inadequate GWG.

[c]*P* values for statistically significant associations (at $P < 0.05$) are shown in bold.

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; FBG, fasting blood glucose; FM, fat mass; GWG, gestational weight gain; HDL-C, high-density-lipoprotein cholesterol; SBP, systolic blood pressure; TE, total effect size; TG, triglyceride; WC, waist circumference.

Effects of maternal prepregnancy BMI and pregnancy trimesters

The effects of GWG may be modified by maternal prepregnancy BMI and pregnancy trimesters. Three studies tried to explore the interaction between maternal prepregnancy BMI and GWG on offspring body fatness. Two studies found that the effects of GWG seemed greater in women with higher prepregnancy BMI,[13,40] although 1 study reported an non-significant interaction effect between maternal prepregnancy BMI and GWG.[36] Six studies explored the effects of GWG in different trimesters of pregnancy on offspring outcomes. One study found that GWG in all 3 trimesters was

associated with adiposity[36] and another found that GWG before 36 gestational weeks but not thereafter was associated with offspring CRFs.[24] The remaining 4 studies consistently reported that GWG in early pregnancy, but less likely in mid- or late pregnancy, had significant associations with offspring CRFs.[33,37,39,40]

Heterogeneity and publication bias

Subgroup analysis and meta-regression were performed to assess the source of large heterogeneity for the associations of excessive GWG with FM ($I^2 = 97\%$), BF% ($I^2 = 94\%$), SBP ($I^2 = 55\%$), and DBP ($I^2 = 71\%$); inadequate GWG with FM ($I^2 = 67\%$); and continuous GWG with FM ($I^2 = 89\%$). According to subgroup analyses, the heterogeneity of these associations could not be explained by any of the examined characteristics, including sample size (<1000, 1000–10 000, >10 000), study quality (high, medium, or low), geographic region (Europe, Asia, America, Brazil, or Australia), adjustment of critical confounders of maternal prepregnancy BMI (adjusted or unadjusted), or offspring's age (infancy [0–1 y], childhood [1–18 y], or adulthood [>18 y]). According to meta-regression, sample size, quality score, and offspring's age seemed to partly explain the potential source of the heterogeneity (*see* Table S6 *in the Supporting Information online*).

The funnel plot for the association of excessive GWG with FM showed some asymmetry (*see* Fig. S12 *in the Supporting Information online*), with a statistically significant Egger's test ($P = 0.035$). The trim-and-fill analysis showed that the association was non-significant (MD, 0.007; −0.070, 0.083 kg; $P = 0.866$; $I^2 = 97\%$), indicating that the pooled result was likely affected by potential publication bias. No significant publication bias was found for other outcomes (*see* Figs. S13–S20 *in the Supporting Information online*).

DISCUSSION

In this meta-analysis of cohort studies, maternal GWG was associated with a range of offspring CRFs. When analyzed as a continuous variable, GWG was positively correlated with offspring FM, BF%, WC, SBP, and TG, and negatively with HDL-C. When analyzed as a categorical variable, excessive GWG was associated with greater offspring FM, BF%, WC, and insulin, and inadequate GWG was associated with lower BF%, LDL-C, TC, and TG, as compared with adequate GWG. Most of these associations went non-significant or attenuated after adjustment of offspring anthropometry, indicating that the associations of maternal GWG with offspring CRFs seem to be partly driven by offspring body weight. No significant association was observed for DBP or FBG of offspring.

To our knowledge, this is the first review that has systematically examined the association of maternal GWG with a range of offspring CRFs, integrating all available evidence from cohort studies. A previous systematic review qualitatively, but not quantitatively, summarized the effects of GWG on offspring adiposity indices such as FM and BF%.[55] Our meta-analysis showed that each increase of 1 kg in GWG was associated with 0.04-kg greater FM, 0.15% greater BF%, and 0.15-cm greater WC of offspring; consistently, offspring born from excessive GWG mothers were likely to have 0.11-kg higher FM, 1.36% higher BF%, and 1.78-cm greater WC, as compared with those from adequate GWG mothers. These findings not only supported that excessive GWG increased the risk of offspring obesity defined using BMI[56] but also enriched the evidence about the effects of maternal GWG on offspring adiposity measures. A previous meta-analysis showed that GWG was positively correlated with offspring SBP (0.05 mmHg per kg) but not with DBP.[16] We extended this meta-analysis to more recently published studies, and consistently found similar results that GWG was positively associated with offspring SBP (0.04 mmHg per kg) rather than DBP. Additionally, our meta-analysis extends previous work on other CRF outcomes. For example, we have clarified that each increase of 1 kg in GWG was associated with 0.004-mmol/L higher TG and 0.002-mmol/L lower HDL-C, excessive versus adequate GWG was associated with 1.77-mmol/L greater insulin, and inadequate GWG was associated with 0.05-mmol/L and 0.07-mmol/L lower LDL-C and TC, respectively. These associations seem to be stronger in women with higher prepregnancy BMI,[13,40] and for GWG in early pregnancy but not in later pregnancy.[33,37,39,40] Whether modifying roles of maternal BMI and periods of pregnancy exist still needs to be explored in future studies.

A web of biological factors, which are not mutually exclusive, could be the mechanisms underlying these associations. First, offspring obesity might be a critical mediator in the associations between GWG and offspring CRFs,[16,23,57] as shown in our sensitivity analysis. Mothers with excessive GWG were more likely to have genetic susceptibility to adiposity, unhealthy diet patterns, or less physical activity, all of which could be inherited in their offspring,[58] leading to greater adiposity risk and then cardiometabolic abnormalities in their offspring.[59] Second, mothers with excessive GWG could deliver greater glucose, amino acids, and free fatty acids to the fetus in utero, perturbing the fetal development or metabolism via an epigenetic process,[60] hormone secretion,[61] or appetite-regulation changes,[62] and predisposing the offspring to greater cardiometabolic risks.[63]

Our systematic review and meta-analysis had limitations. First, studies included in the meta-analysis treated GWG differently, restricted to various

outcomes, and reported different effect measures, which resulted in a limited number of available studies and difficulty in synthesizing the findings. Second, the limited number of studies restricted us to perform subgroup analysis by prepregnancy BMI and periods of pregnancy, which have been suggested to be potential modifiers. Third, high heterogeneity was observed in some outcomes, which could be partly explained by sample size, quality score, or offspring's age according to our meta-regression.

CONCLUSION

Our systematic review and meta-analysis of cohort studies showed that higher maternal GWG may predispose offspring to higher cardiometabolic risk, which could be partly driven by offspring anthropometry. Our findings support the recommendation that excessive GWG should be avoided for the health of offspring, given that children born to excessive GWG mothers may have greater cardiometabolic risk. Further studies are warranted to explore the roles of maternal prepregnancy BMI and periods of pregnancy on these associations.

Acknowledgments

Author contributions. Y.Z., H.L., and J.L. conceived and designed the study and provided overall guidance. J.W. and A.L. conducted the literature search and meta-analysis. J.W. drafted the manuscript. J.W., S.A., and Y. Z. interpreted the data. All authors reviewed and revised the manuscript, and Y.Z., H.L., and J.L. critically revised the manuscript. All authors read and approved the final manuscript.

Funding. This work was supported by Clinical Medicine Plus X—Young Scholars Project, Peking University, the Fundamental Research Funds for the Central Universities.

Declaration of interest. The authors have no relevant interests to declare.

Data availability. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Table S1 **2009 IOM pregnancy weight-gain recommendations**

Table S2 **PRISMA 2020 checklist**

Table S3 **Search strategy**

Table S4 **Quality assessment**

Table S5 **The studies excluded for meta-analysis**

Table S6 **Meta-regression**

Figure S1–S11 **Forest plots of maternal gestational weight gain and cardiometabolic risk factors**

Figure S12–S20 **Funnel plots of publication bias**

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Nutrition Reviews, 2024, 00, 1–10
https://doi.org/10.1093/nutrit/nuae027
Meta-Analysis