Journal of Developmental Origins of Health and Disease

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Review

Cite this article: Bennett CJ, Walker RE, Blumfield ML, Ma J, Wang F, Wan Y, Gwini SM, Truby H. (2019) Attenuation of maternal weight gain impacts infant birthweight: systematic review and meta-analysis. *Journal of Developmental Origins of Health and Disease* **10**: 387–405. doi: 10.1017/S2040174418000879

Received: 22 January 2018
Revised: 25 September 2018
Accepted: 3 October 2018
First published online: 9 November 2018

Key words:
birthweight; gestational weight gain; macrosomia and large for gestational age; pregnancy

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Attenuation of maternal weight gain impacts infant birthweight: systematic review and meta-analysis

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Abstract

Despite many interventions aiming to reduce excessive gestational weight gain (GWG), it is currently unclear the impact on infant anthropometric outcomes. The aim of this review was to evaluate offspring anthropometric outcomes in studies designed to reduce GWG. A systematic search of seven international databases, one clinical trial registry and three Chinese databases was conducted without date limits. Studies were categorised by intervention type: diet, physical activity (PA), lifestyle (diet + PA), other, gestational diabetes mellitus (GDM) (diet, PA, lifestyle, metformin and other). Meta-analyses were reported as weighted mean difference (WMD) for birthweight and birth length, and risk ratio (RR) for small for gestational age (SGA), large for gestational age (LGA), macrosomia and low birth weight (LBW). Collectively, interventions reduced birthweight, risk of macrosomia and LGA by 71 g (WMD: −70.67, 95% CI −101.90 to −39.43, $P < 0.001$), 16% (RR: 0.84, 95% CI 0.73–0.98, $P = 0.026$) and 19% (RR: 0.81, 95% CI 0.69–0.96, $P = 0.015$), respectively. Diet interventions decreased birthweight and LGA by 99 g (WMD −98.80, 95% CI −178.85 to −18.76, $P = 0.016$) and 65% (RR: 0.35, 95% CI 0.17–0.72, $P = 0.004$). PA interventions reduced the risk of macrosomia by 51% (RR: 0.49, 95% CI 0.26–0.92, $P = 0.036$). In women with GDM, diet and lifestyle interventions reduced birthweight by 211 and 296 g, respectively (WMD: −210.93, 95% CI −374.77 to −46.71, $P = 0.012$ and WMD: − 295.93, 95% CI −501.76 to −90.10, $P = 0.005$, respectively). Interventions designed to reduce excessive GWG lead to a small reduction in infant birthweight and risk of macrosomia and LGA, without influencing the risk of adverse outcomes including LBW and SGA.

Introduction

Gestational weight gain (GWG) can be an indicative factor of both maternal and infant complications during pregnancy.[1,2] The Institute of Medicine (IoM) stipulates guidelines in which weight gain during pregnancy can be classified as adequate, inadequate or excessive.[3] In an attempt to reduce pregnancy complications, the IoM reformed the GWG guidelines in 2009 to include stratification by pre-conception body mass index (BMI).[3] The higher the pre-conception BMI, the less weight a woman is recommended to gain during pregnancy. While inadequate GWG is still a problem in many developing nations, excessive GWG is experienced by almost half the pregnant population in developed nations.[1,4] Excessive GWG increases the risk of pregnancy complications such as gestational diabetes mellitus (GDM), pre-eclampsia and caesarean section delivery.[3] In the long term, women who gain excessive weight during pregnancy are also at higher risk of postnatal weight retention and therefore obesity and related diseases later in life.[5]

GWG has a significant impact on the developing fetus *in utero*. Excessive GWG is associated with an increased risk of large for gestational age (LGA) infants (>90% percentile) and macrosomia (birthweight >4000 g).[6] However, the complications of excessive GWG are not limited to the size of the infant at birth. In the short term, children born to mothers who gained excessive GWG are more likely to acquire infection,[7] have lower 5 min activity, pulse, grimace, appearance and respiration (APGAR) scores,[7] suffer from meconium aspiration syndrome,[7] hypoglycaemia[7] and are more likely to have increased length of hospital stay at birth.[7,8] In the long term, children who are born to mothers that experienced excessive weight gain during pregnancy are also more likely to have higher BMI *z*-scores as children[9] and suffer from obesity, diabetes and high blood pressure later in life.[10] In contrast, inadequate GWG

impairs fetal growth, increasing the risk of small for gestational age (SGA) infants, lower lean body mass, fat mass and head circumference.[11] In the long term, children of mothers who gain inadequate weight during pregnancy may be at higher risk of obesity,[12] cardiovascular disease,[13] breast cancer[12] and glucose intolerance[12] in later life. This suggests that interventions designed to reduce GWG may have a significant influence on both the mother and the health of the next generation.[14]

Many reviews have considered the effect of diet, physical activity (PA) and lifestyle interventions on GWG.[15–17] Of the reviews that have considered infant outcomes, two have shown no difference in any measures reported[15,16] and one reported a significant reduction in birthweight in PA interventions.[17] It remains unclear whether these interventions also impact infant anthropometry and thus impact offspring health in the longer term.[18] Due to the severity of consequences related to undesirable fetal growth for both mother and baby, there is an urgent need to address this gap in the literature.[18] Previous reviews in this area have been significantly limited in the translation of results due to two reasons: (i) either a small samples of studies included (⩽4 studies) and/or (ii) excluding papers published in languages other than English, reducing global translatability and possibly biasing overall effect.[19–21] Therefore, the aim of this systematic review was to evaluate differences in infant anthropometric outcomes (birthweight, birth length, macrosomia, LGA, SGA and low birthweight (LBW)) in studies designed to reduce excessive GWG.

Methods

Protocol and registration

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews (PRISMA) and the protocol has been registered with PROSPERO (CRD: 42016035907). This manuscript reports on the secondary outcomes of this protocol. The primary outcomes have been reported elsewhere.[22]

Eligibility criteria

The details of the inclusion exclusion criteria have been previously outlined.[22] Briefly, studies were eligible if they were randomized controlled trials, conducted in humans with a primary or secondary aim to reduce excessive GWG. Studies that aimed to encourage GWG were excluded. This review also required studies to report on birthweight, birth length, SGA (<10th centile), LGA (>90th centile),

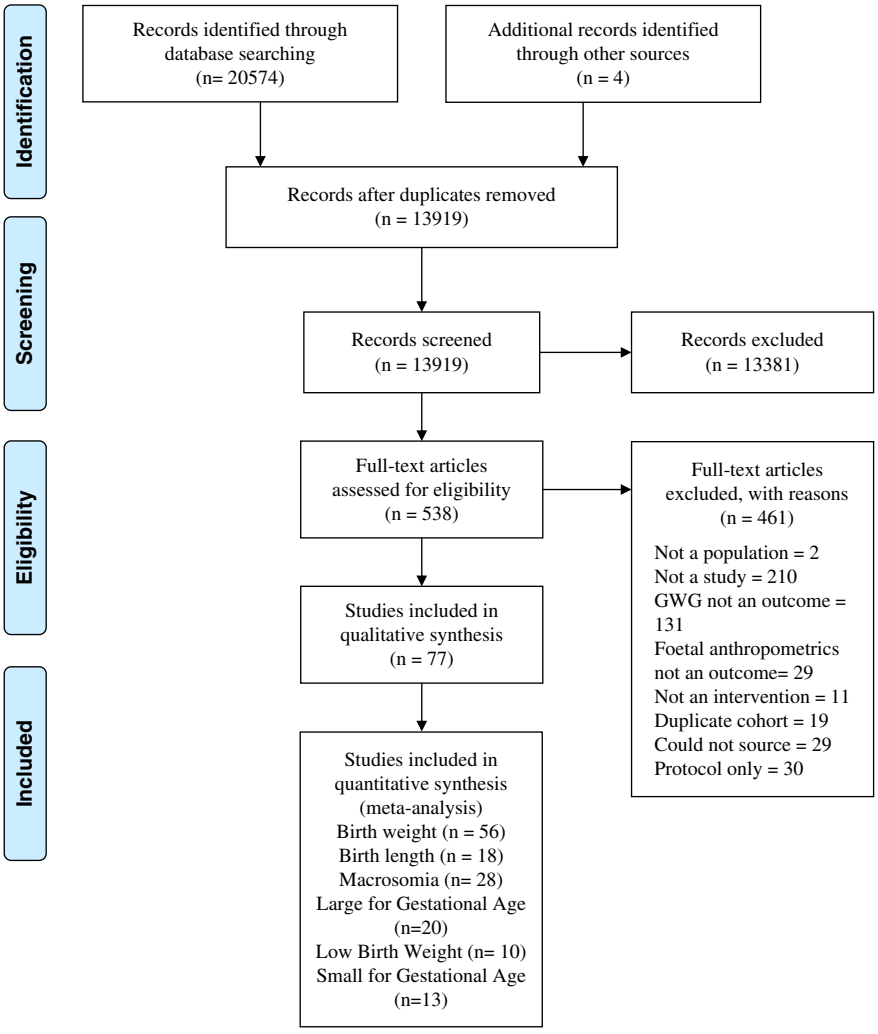

Fig. 1. PRISMA diagram of included studies.

https://doi.org/10.1017/S2040174418000879 Published online by Cambridge University Press

Table 1. Infant anthropometric outcomes in studies with a dietary intervention

First author	Setting and date	Birthweight (g) (mean (s.d.) unless otherwise specified)	Birth length (cm) (mean (s.d.) unless otherwise specified)	Macrosomia (%) (>4000 g)	Large for gestational age (%) (>90th percentile)	Small for gestational age (%) (<10th percentile)	Low birth weight (%) (<2500 g)	Overall risk of bias
Bonomo[51]	Milan, Italy 1997–2002	3365 (436), 3436.6 (462), $P = NS$	50.2 (1.7), 50.1 (2.0), $P = NS$	5.3, 10.7, $P = NS$	6, 14, $P = 0.046$	8.7, 6.0, $P = NS$	–	Unclear
Deveer[52]	Turkey Published 2013	3310 (342.4), 3587 (460.2), $P = 0.001$	–	2, 20, $P = 0.004$	4, 22, $P = 0.007$	10, 6, $P = 0.461$	–	High
Di Carlo[53]	Naples, Italy Jun 2010–Jun 2011	BW: 3078.2 (372.3), 3121.5 (430), $P = 0.6$	–	–	–	–	–	Unclear
Ilmonen[29]	Finland Apr 2002–Nov 2005	Diet + probiotic: 3489 (431), diet + placebo: 3602 (439), control: 3600 (515), $P = 0.209$	Diet + probiotic: 50.7 (1.8), diet + placebo: 51.3 (1.7), control: 51.0 (2.2), $P = 0.197$	–	–	–	–	Unclear
Korpi-Hyovalti[54]	Finland Published 2012	BW: 3871 (567), 3491 (573), $P = 0.047$	–	–	–	–	–	Unclear
Liao[55]	Wuzhou, China Mar 2010–Mar 2012	BW: 3100.1 (304.74), 3216.6 (547.52), $P = 0.037$	–	–	–	–	–	High
Markovic[39]	Camper down, Australia Jan 2011–Oct 2012	Low GI: 3450 (410), high fibre: 3430 (510), $P = 0.845$	–	Low GI: 9.7, high fibre: 14.9, $P = 0.349$	Low GI: 5.6, high fibre: 6.0, $P = 0.916$	Low GI: 5.6, high fibre: 7.5, $P = 0.648$	–	Unclear
Moses[35]	Australia Feb 2010–Sep 2012	Healthy eating: 3443 (485), low GI: 3465 (430), $P = 0.57$	Healthy eating: 50.3 (3.3), low GI: 50.3 (1.7), $P = 0.96$	Healthy eating: 13.9, low GI: 10.5, $P = 0.25$	–	–	–	Unclear
Rhodes[40]	Boston, USA Jan 2007–Jun 2009	Low-GI: 3507 (412), low-fat: 3133 (671), $P = 0.03$	–	Low-GI: 8, low-fat: 5, $P = 1.0$	Low GI: 8, low-fat 14, $P = 0.65$	–	–	Unclear
Thornton[45]	New York, USA Jun 1998–May 2005	3526 (608.4), 3586 (560.8), $P = 0.4$	–	(>4500 g): 7.8, 3.4, $P = 0.153$	–	–	–	Unclear
Walsh[57]	Dublin, Ireland Jan 2007–Jan 2011	4034 (510), 4006 (497), $P = 0.449$	52.9 (2.7), 52.6 (2.1), $P = 0.189$	51, 51, $P = 0.88$	–	–	–	Unclear

Table 1. (*Continued*)

First author	Setting and date	Birthweight (g) (mean (s.d.) unless otherwise specified)	Birth length (cm) (mean (s.d.) unless otherwise specified)	Macrosomia (%) (>4000 g)	Large for gestational age (%) (>90th percentile)	Small for gestational age (%) (<10th percentile)	Low birth weight (%) (<2500 g)	Overall risk of bias
Wolff[58]	Copenhagen, Denmark Published 2008	3575 (617), 3895 (485), P = NR	52 (3), 53 (2), P = NR	-	-	-	-	Unclear
Ye[56]	Guangzhou, China May 2012–May 2013	3390 (240), 3510 (310), P = 0.019	-	-	-	-	-	High
Zhang[37]	Ningbo, China Jan 2011–Dec 2011	3326 (292), 3556 (369), P < 0.05	-	-	-	-	-	High

NR, not reported; NS, not significant; GI, glycaemic index; '-', data not available.
Results presented: intervention, control.

LBW (<2500 g) or macrosomia (>4000 g). To limit bias, there was no limit on the age of women, the length of intervention, the content of the intervention, publication language or date.

Search strategy and selection process

A systematic search was conducted using the following electronic databases: Cochrane Library, MEDLINE, EMBASE, PsycINFO, CINAHL, Scopus, LILACS and Clinical Trials.gov was also searched at the same time. The search strategy and keywords used are outlined in Supplementary Table 1. Two native Mandarin speakers (J.M. and F.W.) also independently conducted the systematic search in: China National Knowledge Infrastructure, WangFang and VIP databases. The search was conducted in April 2016. Duplicates were removed via an electronic automated title and author search. Following the removal of duplicates, all title and abstracts were independently screened by two reviewers. Any conflicts were resolved by an independent third reviewer (H.T.). Full texts were retrieved and reviewed via the same process. Corresponding authors were contacted if full texts were unable to be retrieved or further information was required. Systematic reviews identified through the search process were subject to a manual hand searching of reference lists for possible included trials. Multiple publications from the same dataset were reviewed and the publication with the largest sample size was included.

Data extraction and quality assessment

Data extraction was completed by J.M., F.W. and Y.W. for studies published in Chinese, and by R.E.W. and C.J.B. for studies published languages other than Chinese. Data were extracted using a template adapted from the 'Cochrane data extraction template for randomized controlled trials'.[23] All data were independently extracted and reviewed by at least two reviewers (C.J.B. and R.E.W. for studies published in languages other than Chinese and J.M., F.W. and Y.W. for studies published in Chinese).

Assessment of methodological quality was completed using the Cochrane risk of bias for randomized controlled trials.[24] The overall risk of bias was determined via the following domains: random allocation sequence, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other bias. Bias was then allocated to 'high', 'unclear' or 'low' for each of the domains. If domains were all 'low' the study was considered low risk of bias overall. If studies had one or more 'unclear' domains but no 'high' domains, the study was considered an unclear risk of bias overall. If a study had one or more domains that were 'high' the overall study was considered a high risk of bias. All manuscripts were independently assessed by two reviewers for risk of bias. If reviewers disagreed on any domain of the bias tool, resolutions were made between two primary reviewers (R.E.W., C.J.B. or J.M. and F.W.). If no resolution could be made, a blinded reviewer would make a third decision, with the binding decision formed by the domain with the majority of reviewer's decisions. This was in accordance with the Cochrane handbook.[25]

Statistical analysis

The main outcome measures were birthweight, birth length, macrosomia, LBW, SGA and LGA. Studies were pooled into intervention categories for analysis. Eight categories emerged from the resultant literature: diet alone, PA alone, lifestyle (diet and PA), other, GDM diet, GDM lifestyle, GDM metformin and

https://doi.org/10.1017/S2040174418000879 Published online by Cambridge University Press

Table 2. Infant anthropometric outcomes in studies with a physical activity intervention

First author	Setting and date	Birthweight (g) (mean (s.d.) unless otherwise specified)	Birth length (cm) (mean (s.d.) unless otherwise specified)	Macrosomia (%) (>4000 g)	Large for gestational age (%) (>90th percentile)	Small for gestational age (%) (<10th percentile)	Low birth weight (%) (<2500 g)	Risk of bias
Barakat 2013[62]	Madrid, Spain Sep 2007–Jan 2011	3201 (446), 3257 (496), $P = 0.208$	–	1, 10, $P = 0.002$	–	–	–	High
Barakat 2011[63]	Madrid, Spain	3250 (493), 3402 (328), $P > 0.05$	–	5, 10, $P > 0.05$	–	–	–	Unclear
Barakat 2012[59]	Madrid, Spain	3404 (465), 3465 (411), $P > 0.05$	50.07 (2.4), 49.95 (1.9), $P > 0.05$	–	–	–	–	Unclear
Barakat 2009[60]	Madrid, Spain Jan 2000–Mar 2002	3165 (411), 3307 (477), $P > 0.1$	49.5 (1.8), 49.7 (1.8), $P > 0.1$	1.4, 10, $P > 0.1$	–	–	–	High
Barakat 2016[61]	Madrid, Spain Dec 2011–Jan 2015	3252 (438), 3218 (453), $P = 0.29$	50.0 (2.2), 49.8 (2.1), $P = 0.11$	1.8, 4.7, $P = 0.03$	–	–	4.2, 6.5, $P = 0.15$	Unclear
Barakat 2014[64]	Madrid, Spain	3203 (461), 3232 (488), $P = 0.56$	49.5 (2.07), 49.7 (2.06), $P = 0.98$	–	–	–	–	High
Bisson[65]	Quebec, Canada Oct 2011–Nov 2013	3575 (425), 3455 (368), $P =$ NR	–	–	17, 13, $P =$ NR	0, 8, $P =$ NR	–	Unclear
Cavalcante[66]	Sao Paulo, Brazil Mar 2002–Nov 2004	3222.2 (562.7), 3312.7 (656.1), $P = 0.54$	–	–	–	–	10, 5, $P = 0.54$	High
Chen[67]	Chendou, China	3172.1 (312.59), 3364.6 (368.07), $P =$ NR	–	–	–	–	–	High
Clapp 2000[32]	Ohio, USA	3660 (800), 3430 (900), $P = 0.05$[a]	51.8 (1.4), 50.6 (1.5), $P = 0.05$	–	–	–	–	Unclear
Clapp 2002[33]	Ohio, USA	Lo-Hi[b]: 3340 (357), Mod-Mod[c]: 3440 (392), Hi-Lo[d]: 3900 (350), $P < 0.0001$	Lo-Hi: 51.1 (1.5), Mod-Mod[c]: 51.2 (1.5), Hi-Lo[d]: 52.6 (1.0), $P =$ NR	–	–	–	–	Unclear
Dekker-Nikert[68]	Brisbane, Australia	3548 (459), 3597 (304), $P =$ NR	50.6 (2.2), 50.5 (1.8), $P =$ NR	–	–	–	–	High
Garshasbi[69]	Tehran, Iran Apr 2003–Jan 2004	3426 (675), 3500 (431), $P = 0.82$	–	–	–	–	–	High
Kong[70]	Iowa, USA	Overweight: 3760 (440), 3590 (460), $P =$ NR Obese: 3540 (510), 3940 (480), $P =$ NR	–	Overweight: 33, 11, $P =$ NR Obese: 22, 50, $P =$ NR	–	–	Overweight: 0, 0, $P =$ NR Obese: 0, 0, $P =$ NR	Unclear

Table 2. (*Continued*)

First author	Setting and date	Birthweight (g) (mean (s.d.) unless otherwise specified)	Birth length (cm) (mean (s.d.) unless otherwise specified)	Macrosomia (%) (>4000 g)	Large for gestational age (%) (>90th percentile)	Small for gestational age (%) (<10th percentile)	Low birth weight (%) (<2500 g)	Risk of bias
Nascimento[71]	Sao Paulo, Brazil	3267.4 (700.4), 3228.4 (591.3), $P = 0.790$ Aug 2008–Mar 2010	–	–	24.2, 24.2, $P = 1$	6.1, 3.0, $P = 1$	–	Unclear
Oostdam[44]	Amsterdam, Netherlands Jan 2007–Jan 2011	3524 (591), 3352 (591), $P = 0.14$	–	–	12.8, 1, $P =$ NR[e]	–	–	Unclear
Perales[72]	Madrid, Spain Oct 2009–Jan 2013	3347 (307.04), 3346 (307.04), $P = 0.99$	–	–	–	–		Unclear
Ruiz[73]	Madrid, Spain Sep 2007–Jan 2011	3234 (453), 3239 (433), $P =$ NR	–	2.1, 5.0, $P =$ NR	–	–	5.0, 4.8, $P =$ NR	Unclear

NR, not reported; NS, not significant; '-' = data not available.
Results presented: intervention, control.
[a]Reported as mean ± s.e.m.
[b]Lo-Hi: 20 min 5 days a week through week 20, gradually increasing to 60 min 5 days a week by week 24 and maintaining that regimen until delivery.
[c]Mod-Mod: 40 min 5 days a week from week 8 until delivery.
[d]Hi-Lo: 60 min 5 days a week through week 20, gradually decreasing to 20 min 5 days a week by week 24 and maintaining that regimen until delivery.
[e]Reported >97th percentile.

GDM 'other'. Studies categorized as 'other' did not have interventions that satisfied the other categories listed. Where studies reported results of subgroups but not overall results (such as by maternal BMI category), the groups were combined using the Cochrane formula for combining groups.[25] For studies with more than one arm, only the most intensive arm was chosen for the meta-analysis as not to duplicate representation from control groups.[26–31] However, an exception to this rule was a study conducted by Ainuddin *et al.*[30] compared metformin alone, metformin and insulin and insulin alone. For this study only the metformin and insulin alone arms were included in the meta-analysis to ensure appropriate comparison to other studies included. Further, comparator groups were defined as standard care following antenatal care guidelines as appropriate. Studies that reported standard error of the mean (s.e.m.) were converted to standard deviation (s.d.).[32–38] Studies were excluded from the meta-analysis for the following reasons: (i) no true control ($n = 6$),[33–35,39–41] (ii) inadequate statistical reporting,[42,43] (iii) studies did not have standard criteria for LGA,[26,44] SGA[26] or macrosomia,[45] (iv) studies that were too heterogeneous to compare (other and GDM other category) [36,46–49] and (v) data were reported as mean ± s.e.m. but when converted to s.d. data were biologically implausible.[32]

Actual mean difference meta-analyses were conducted on birthweight and birth length to enable ease of interpretation.[50] Risk ratio meta-analyses were conducted for dichotomous data which includes the prevalence of LGA, SGA, macrosomia and LBW. The I^2 statistic was used as an assessment of heterogeneity, with an I^2 statistic of >50% regarded as substantial heterogeneity.[25] Funnel plots were used to visually analyze if large studies were influencing the results of the meta-analyses. Sensitivity analyses were conducted removing one study at a time, to assess the bias of one study. Meta-regression used 'high' risk of bias as a covariate to explain heterogeneity and explore the relationship with effect size of studies with a 'high' risk of bias. Statistical analyses were conducted using Stata/SE 13.1. *P*-values <0.05 were considered statistically significant.

Results

Of the 20,578 records screened, 77 studies were included in this review (Fig. 1). Information regarding the intervention and demographic information are available in Supplementary Tables 2–6. Briefly, all interventions included singleton pregnancies with mean maternal age ranging from 24 to 36 years, baseline BMI ranging from 20.2 to 38.6 and percentage of preterm births ranging from 0.8 to 19%. Further, the included studies represent results from 19,806 infants from 20 countries including: America, Australia, New Zealand, Brazil, Canada, China, Denmark, Finland, Iran, Ireland, Italy, Germany, Spain, United Kingdom, Pakistan, Norway, Belgium, Turkey, Sweden and The Netherlands.

Interventions were categorized into the following groups; diet ($n = 14$),[29,35,37,39,40,45,51–58] PA ($n = 18$),[32,33,44,59–74] lifestyle (diet and PA) ($n = 21$),[26–28,31,43,74–89] diet alone for women with GDM ($n = 6$),[33,34,38,42,90–92] metformin compared with standard care of insulin for women with GDM ($n = 5$),[30,93–96] metformin compared with glyburide for women with GDM ($n = 1$),[41] lifestyle for women with GDM ($n = 5$),[67,97–101] PA for women with GDM ($n = 1$),[102] 'other' in women without GDM ($n = 5$)[36,46–49] and

https://doi.org/10.1017/S2040174418000879 Published online by Cambridge University Press

Table 3. Infant anthropometric outcomes in studies with a lifestyle intervention

First author	Setting and date	Birthweight (g) (mean (s.d.) unless otherwise specified)	Birth length (cm) (mean (s.d.) unless otherwise specified)	Macrosomia (%) (>4000 g)	Large for gestational age (%) (>90th percentile)	Small for gestational age (%) (<10th percentile)	Low birth weight (%) (<2500 g)	Overall risk of bias
Althuizen[75]	Netherlands Feb 2005–May 2006	3550 (466), 3431 (456), $P = NR$	–	19, 14, $P = NR$	–	–	–	High
Asci[76]	Istanbul, Turkey Jun 2011–Jul 2012	3268 (380), 3298 (423), $P = 0.76$	50.04 (1.78), 50.40 (1.90), $P = 0.29$	–	–	–	–	Unclear
Bogaerts[31]	Flanders, Belgium Mar 2008–Apr 2011	Brochure: 3386 (682), lifestyle: 3444 (503), control: 3504 (583), $P = 0.54$	–	–	–	–	–	Unclear
Dodd[77]	Adelaide, Australia Jun 2008–Dec 2011	–	–	15, 19, $P = 0.04$	19, 21, $P = 0.24$	–	–	Unclear
Guelinckx[27]	Leuven, Belgium Mar 2006–Jan 2008	Passive: 3585 (398), active: 3492 (468), control: 3419 (425), $P = 0.106$	Passive 51.0 (2.1), active: 50.6 (2.0), control: 50.0 (1.8), $P = 0.182$	Passive: 13.5, active: 11.9, control: 7.0, $P = 0.312$	–	–	–	Unclear
Hawkins[78]	Massachusetts, USA Apr 2010–Aug 2011	3338.8 (640.7), 3429.8 (532.6), $P = 0.64$	–	–	–	–	–	Unclear
Hui 2012[79]	Manitoba, Canada Jul 2004–Feb 2010	3490 (509), 3516 (530), $P = 0.73$	–	–	11.8, 17.0, $P = 0.41$	–	–	Unclear
Hui 2014[80]	Manitoba, Canada May 2009–Dec 2011	Healthy weight: 3356 (474), 3633 (555), $P = 0.047$ Overweight/obese: 3665 (506), 3650 (481), $P = 0.26$	–	–	Healthy weight: 7, 11, $P = 0.902$ Overweight/obese: 15, 3, $P = 0.13$	–	–	Unclear
Liang[81]	Bingzhou, China Jul 2005–Nov 2008	3313.1 (385.7), 3331.5 (393.7), $P > 0.05$	–	–	–	–	–	High
Luoto[82]	Pirkanmaa, Finland Oct 2007–Dec 2008	3313.1 (385.7), 3331.5 (393.7), $P = 0.035$	–	17.2, 20.8, $P = 0.31$	12.1, 19.7, $P = 0.043$	4.7, 2.9, $P = 0.53$	–	Unclear
Petrella[74]	Modena, Italy April–Oct 2011	3498 (342), 3010 (715), $P = 0.001$	–	–	–	–	–	Unclear
Phelan[83]	Rhode Island, USA 2006–2008	Healthy weight: 3367 (459), 3271 (467), $P = NR$ Overweight/obese: 3430 (650), 3442 (629), $P = NR$	–	Healthy weight 7, 3, $P = NR$ Overweight/obese: 17, 16, $P = NR$	–	–	Healthy weight 4, 3, $P = NR$ Overweight/obese: 6, 5, $P = NR$	Unclear

Table 3. (*Continued*)

First author	Setting and date	Birthweight (g) (mean (s.d.) unless otherwise specified)	Birth length (cm) (mean (s.d.) unless otherwise specified)	Macrosomia (%) (>4000 g)	Large for gestational age (%) (>90th percentile)	Small for gestational age (%) (<10th percentile)	Low birth weight (%) (<2500 g)	Overall risk of bias
Polley[43]	Pittsburgh, USA	Health weight: 3133, 3226.4, P = NR Overweight: 3282.8, 3349.0, P = NR	–	Health weight: 3, 0, P = NR Overweight: 0, 0, P = NR	–	–	Health weight: 13, 10, P = NR Overweight: 4, 9, P = NR	Unclear
Poston[84]	United Kingdom	3420 (580), 3450 (580), P = 0.37	–	14, 14, P = 0.93	13, 11, P = 0.35	7, 5, P = 0.12	4, 5, P = 0.93	Unclear
Rauh[85]	Munich, Germany Feb 2010–Aug 2011	3406 (406), 3414 (445), P = 0.890	51.4 (2.4), 51.7 (2.4), P = 0.351	–	6.4, 8.9, P = 0.495	3.8, 3.8, P = 0.985	–	Unclear
Ruchat[28]	Ontario, Canada	Low[a]: 3559 (391), 3550 (378), P = NR Mod[b]: 3452 (453) Control[c]: 3550 (378), P = NR	Low[a]: 51.0 (2.0) Mod[b]: 51.1 (2.7) Control[c]: 51.1 (2.5), P = NR	Low[a]: 9 Mod[b]: 12 Control[c]: 7, P = NR	–	–	Low[a]: 0	Unclear
Renault[26]	Copenhagen, Denmark Mar 2009–Mar 2012	Median (IQR), PA + D: 3605 (1945–5450), PA: 3695 (805–4910), control: 3641 (1223–5280)	–	PA + D: 22%, PA: 30%, control: 25% P = NS	PA + D: 6.9%, PA: 6.4%, control: 6.7% P = NS[d]	PA + D: 5.4%, PA: 3.2%, control: 1.5% P = NS[e]	–	Unclear
Sagedal[86]	Norway Sep 2009–Feb 2013	3411 (485), 3450 (538), P = 0.361	50.0 (2.1), 49.9 (2.7), P = 0.867	11.8, 14.0, P = 0.451	2.4, 3.7, P = 0.351	10.5, 9.2, P = 0.679	–	Low
Skouteris[87]	Melbourne, Australia Aug 2011–Aug 2013	3517.56 (507.89), 3523.46 (531.35), P = NR	–	–	–	–	–	Unclear
Vesco[88]	Oregon and Washington, USA Oct 2009–July 2011	3484 (583), 3678 (583), P = NR	–	11, 22, P = NR	9, 26, P = NR	5, 7, P = NR	–	High
Vinter[89]	Denmark Oct 2007–2010	Median (IQR) 3742 (3464–4070), 3593 (3335–3930), P = 0.039	–	32, 25.3, P = 0.07	15.4, 11.7, P = 0.340	–	–	Unclear

IQR, interquartile range; NR, not reported; NS, not significant; PA, physical activity; D, diet symbols; '–', data not available.
Results presented: intervention, control.
[a]Low = low intensity physical activity + diet intervention.
[b]Mod = moderate intensity physical activity + diet intervention.
[c]Control = dietary advice.
[d]124% of relative birthweight.
[e]76% or less of relative birthweight.

Table 4. Infant anthropometric outcomes in studies in women with gestational diabetes mellitus

First author	Setting and date	Birthweight (g)	Birth length (cm)	Macrosomia (%) (>4000 g)	Large for gestational age (%) (>90th percentile)	Small for gestational age (%) (<10th percentile)	Low birth weight (%) (<2500 g)	Overall risk of bias
Diet								
Garner[90]	Ottawa, Canada Sep 1991–May 1994	3437 (575), 3544 (601), $P=0.118$	–	16.1, 18.7, $P=0.666$	–	–	–	Unclear
Grant[38]	Toronto, Canada Apr 2006–Jan 2007	3124 (526), 3330 (984), $P=$NS	–	–	–	–	–	Unclear
Louie[34]	Camperdown, Australia	LGI: 3300 (686), HF: 3300 (671), $P=0.619$	LGI: 49.7 (2.1), HF: 49.7 (2.0), $P=0.995$	LGI: 2.1, HF:6.7, $P=0.286$	LGI: 12.8, HF: 4.4, $P=0.157$	LGI: 10.6, HF: 8.9, $P=0.787$	–	Unclear
Moreno-Castilla[91]	Catalonia, Spain Nov 2008–Jul 2011	–	–	1.4, 6.7, $P=0.21$	4.1, 8, $P=0.49$	10.8, 16.0, $P=0.47$	–	Unclear
Rae[42]	Perth, Australia Feb 1992–Jun 1995	3461 (NR), 3267 (731), $P=0.105$	–	16.7, 10.7, $P=$NR	28.8, 24.6, $P=$NR	–	–	Unclear
Zhang 2011[92]	Shandong, China Feb 2009–Jul 2009	3279.5 (447.9), 3590.7 (457.8), $P<0.05$	–	–	–	–	–	High
Metformin								
Ainuddin[30]	Karachi, Pakistan Dec 2008–Dec 2010	M: 3400 (400), M + I: 3300 (500), I: 3700 (500), M and M + I: $P=0.546$, M + I and I: $P=0.001$, M and I: $P=0.002$	–	–	M: 23.3, M + I 28.1, I: 37.3, M and M + I: $P=0.632$, M and I: $P=0.115$, I and M + I: $P=0.359$	M: 11.6, M + I: 15.6, I: 6.6, M and M + I: $P=0.432$, M and I: $P=0.273$, I and M + I: $P=0.138$	–	High
Niromanesh[93]	Tehran, Iran Dec 2010–Jan 2012	3300 (400), 3400 (400), $P=0.005$	50.4 (2.0), 51.1 (2.3), $P=0.033$	3.8, 10.0, $P=0.118$	17.5, 35.0, $P=0.12$	3.8, 2.5, $P=1$	–	Unclear
Rowan[94]	Australia and New Zealand Oct 2002–Nov 2006	3372 (572), 3413 (569), $P=0.33$	50.3 (2.8), 50.3 (2.4), $P=0.91$	–	19.3, 18.6, $P=0.83$	7.2, 9.7, $P=0.21$	–	Unclear
Silva[41]	Brazil Jul 2008–Oct 2009	G: 3463 (535.6) M: 3360 (509.5), $P=0.36$	–	G: 15, M: 6.2, $P=0.24$	G: 22.5, M: 9.4, $P=0.14$	–	–	Unclear

Table 4. (*Continued*)

First author	Setting and date	Birthweight (g)	Birth length (cm)	Macrosomia (%) (>4000 g)	Large for gestational age (%) (>90th percentile)	Small for gestational age (%) (<10th percentile)	Low birth weight (%) (<2500 g)	Overall risk of bias
Spaulonci[95]	Sao Paulo, Brazil Nov 2007–Jan 2010	3143.7 (446.6), 3237.6 (586.8), $P = 0.390$	–	0, 6.5, $P = 0.242$	–	–	–	Unclear
Tertti[96]	Turku, Finland Jun 2006–Dec 2010	3604 (488), 3589 (448), $P =$ NR	–	20, 15, $P = 0.38$	14.5, 15.9, $P = 0.8$	–	–	Unclear
Lifestyle								
Chen[101]	Foshan, China Oct 2001–Oct 2005	3210 (750), 3790 (690), $P < 0.05$	–	–	–	–	–	High
Sun[97]	Guangzhou, China May 2012–Dec 2012	3220 (1320), 3350 (2160), $P < 0.05$	–	–	–	–	–	High
Xie[98]	Wuzhou, China Oct 2006–Oct 2010	3074 (770), 37920 (690), $P =$ NR	–	–	–	–	–	High
Yang[99]	Tianjin, China Dec 2010–Oct 2012	3371 (530), 3469 (570), $P = 0.021$	50.1 (1.8), 50.2 (1.9), $P = 0.248$	11.2, 17.5, $P = 0.019$	–	–	4.1, 3.9, $P = 0.865$	Unclear
Zhang 2012[100]	Shenzhen, China Jul 2009–Jan 2011	3403.3 (326.5), 3601.1 (409.9), $P < 0.05$	–	–		–	–	High
Physical Activity								
Halse[102]	Perth, Australia	3176 (526), 3319 (478), $P > 0.05$	49.8 (2.5), 49.9 (2.9), $P > 0.05$	–	–	–	–	Unclear
Other								
Jie[103]	Guangdong, China Sep 2012–Sep 2014	–	–	8, 27, $P = 0.000$	–	–	–	High

M, metformin; I, insulin; G, glyburide; LGI, low glycaemic index; HF, high fibre; NS, not significant; NR, not reported; '–', data not available.
Results presented: intervention, control.

Table 5. Infant anthropometric outcomes in studies with an intervention categorized as 'other'

First author	Setting and date	Birthweight (g) (mean (s.d.) unless otherwise specified)	Birth length (cm) (mean (s.d.) unless otherwise specified)	Macrosomia (%) (>4000 g)	Large for gestational age (%) (>90th percentile)	Small for gestational age (%) (<10th percentile)	Low birth weight (%) (<2500 g)	Overall risk of bias
Brownfoot[47]	Melbourne, Australia Jan 2010–Nov 2012	3404.7 (561.3), 3364.9 (623.8), $P=0.36$	–	–	7.3, 7.1, $P=0.97$	9.2, 12.6, $P=0.16$	–	Unclear
Herring[49]	Philadelphia, USA 2013–2014	3147, 3361, $P=$ NR	–	–	8, 7, $P=1.0$	4, 0, $P=0.48$	–	Unclear
Jeffries[48]	Melbourne, Australia Jul 2007–May 2008	3416 (452.4), 3421 (504.7), $P=0.95$	–	–	6.5, 9.9, $P=0.47$	7.3, 10.8, $P=0.37$	–	Unclear
Quinlivan[36]	Melbourne, Australia	3500 (556), 3400 (781), $P=0.162$	–	–	–	–	–	Unclear
Syngelaki[46]	London, United Kingdom Oct 2010–Jun 2013	–	–	–	16.8, 15.4, $P=0.79$	–	–	Unclear

NS, not significant; NR, not reported; '–', data not available.
Results presented: intervention, control.

'other' for women with GDM ($n=1$).[103] Study characteristics and methodological quality have been reported previously.[22] For individual results reported in this review, see Tables 1–5.

Overall

Regardless of intervention type, studies designed to reduce excessive GWG reduced offspring birthweight by 71 g (WMD: −70.67, 95% CI −101.90 to −39.43, $P<0.001$, $I^2=67.2\%$) ($n=56$ studies, Fig. 2) and reduced the risk of macrosomia by 16% (RR: 0.84, 95% CI 0.73–0.98, $P=0.026$, $I^2=46.9\%$) ($n=28$ studies, Fig. 3). Studies that reported LGA incidence ($n=20$ studies) reduced the prevalence of LGA by 19% (RR: 0.81, 95% CI 0.68–0.96, $P=0.015$, $I^2=45.4\%$) (Fig. 4). No intervention type significantly influenced the birth length (Fig. 5), risk of LBW (Fig. 6) or SGA (Fig. 7).

Women who started interventions without GDM

Diet interventions reduced infant birthweight by 99 g (WMD: −98.8, 95% CI −178.85 to −18.76, $P=0.016$, $I^2=79.3\%$). Lifestyle and PA interventions did not result in a difference in birthweight (Fig. 2). PA interventions reduced the risk of macrosomia by 59% (RR: 0.41, 95% CI 0.25–0.68, $P<0.001$, $I^2=16.3\%$) (Fig. 3). No significant differences in risk of macrosomia were found for any other intervention type. The risk of LGA was reduced 65% by diet interventions (RR: 0.35, 95% CI 0.17–0.72, $P=0.004$, $I^2=6.6\%$) (Fig. 5). No other intervention type had significant results for birthweight, birth length, macrosomia, LBW, SGA and LGA.

Women with GDM

Diet and lifestyle interventions in women with GDM decreased infant birthweight by 211 and 296 g, respectively (WMD: −210.74, 95% CI −374.77 to −46.71, $P=0.012$, $I^2=58.87\%$ and WMD: −295.93, 95% CI −501.76 to −91.10, $P=0.005$, $I^2=73.6\%$, respectively). Furthermore, interventions that used metformin did not significantly reduce or increase birth weight compared with insulin (Fig. 2). No other intervention type had significant results for birthweight, birth length, macrosomia, LBW, SGA and LGA.

Risk of bias

Overall risk of bias is available in Tables 1–5 and further details available in Supplementary Tables 2–6. Twenty-one studies received an overall 'high risk' of bias. Of the studies that received a 'high risk' of bias half did not clearly state the blinding protocol of participants or personnel. Furthermore, almost half did not adequately explain the randomization procedure ($n=9$) or method of allocation concealment ($n=8$). Fifty-five studies received an overall 'unclear risk' of bias. Of the studies that received an overall 'unclear risk', $n=44$ did not state the blinding of personnel and $n=43$ did not state the blinding of participants. Regardless of the overall risk of bias, $n=52$ studies received an 'unclear' for selective outcome reporting due to an inability to check reported outcomes with planned outcomes due to studies not having a published protocol. Visual, subjective assessment of funnel plots suggest a low to medium level of publication bias (Appendices 1–6).

Sensitivity analyses

When single studies were removed to examine sensitivity of estimates, the WMD and RR did not alter considerably, indicating that no single study introduced a high degree of bias.

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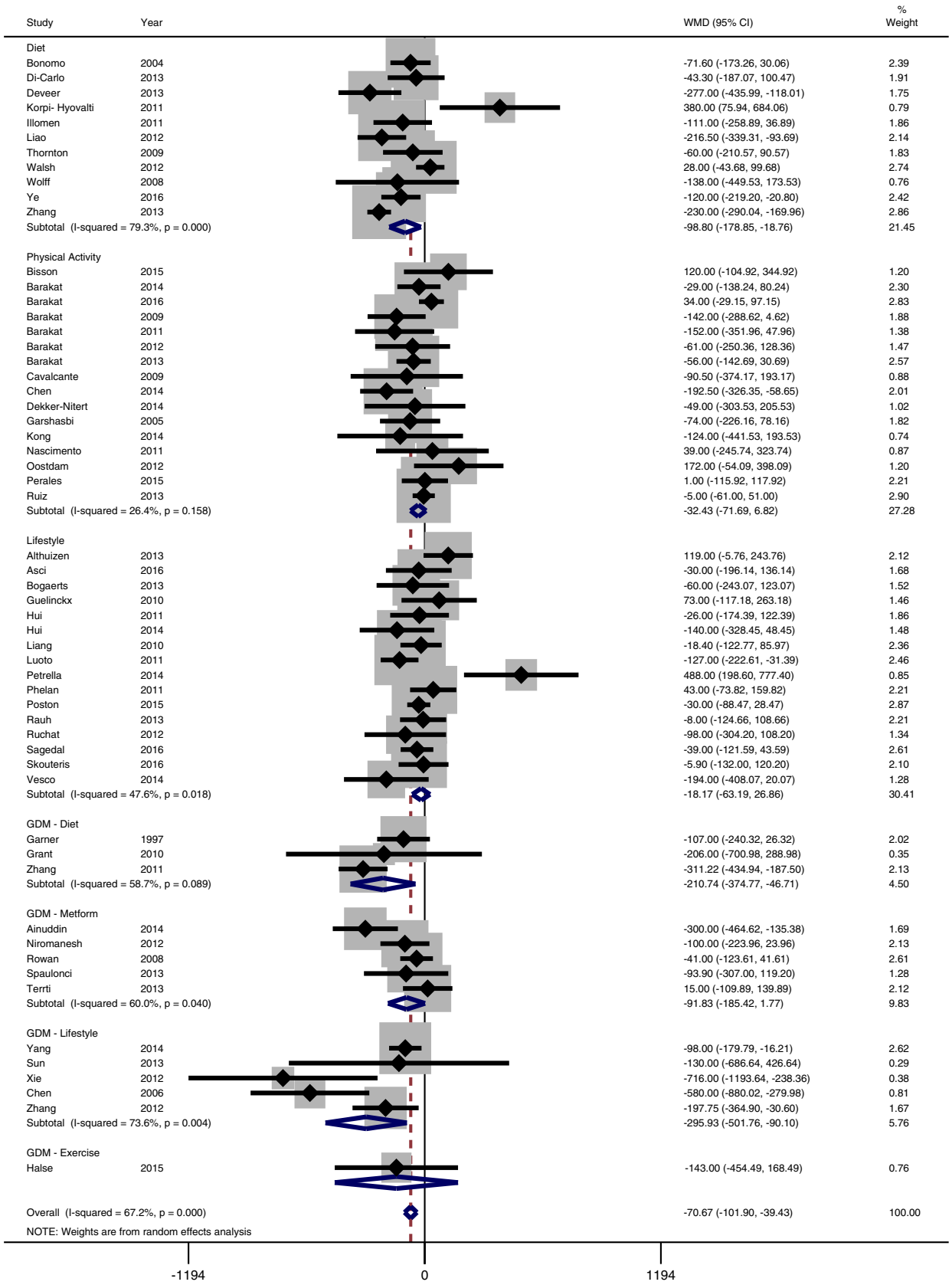

Fig. 2. Infant birthweight weighted mean difference meta-analysis of randomized controlled trials designed to reduce excessive gestational weight gain.

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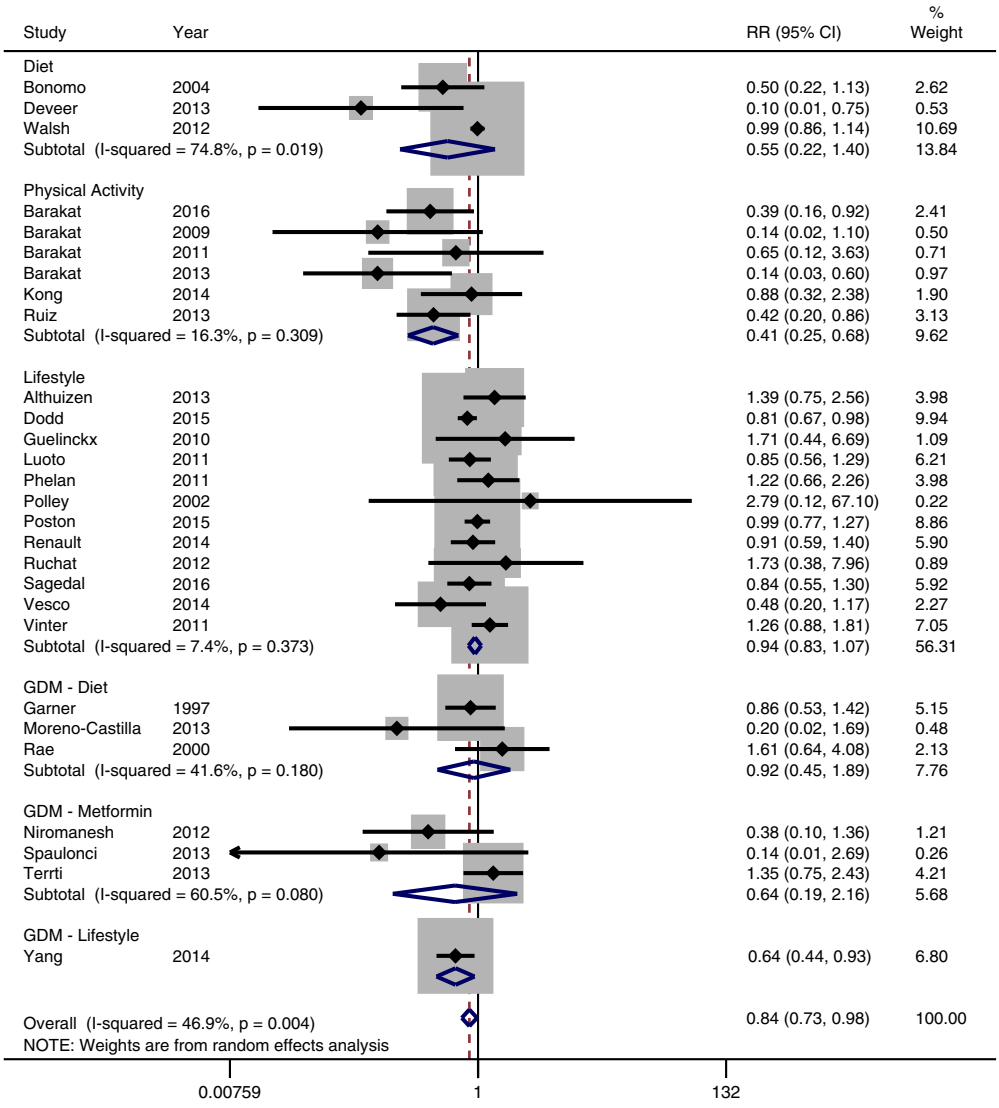

Fig. 3. Macrosomia relative risk meta-analysis of randomized controlled trials designed to reduce excessive gestational weight gain.

Meta-regression quality assessment

'High risk' of bias used a covariate had a significant negative effect on the birthweight analysis ($b = -106.82$, 95% CI −171.71 to −41.94, $P = 0.002$). No other meta-analysis effect size was significantly impacted by risk of bias.

Discussion

This review found that interventions designed to prevent excessive GWG during pregnancy had a significant impact on infant anthropometric outcomes including birthweight, macrosomia and LGA. In women without GDM, diet interventions were effective in reducing birthweight, while PA interventions reduced the risk of macrosomia. In women with GDM, both diet and 'lifestyle' interventions reduced offspring birthweight.

Results indicate that interventions delivered to the mother during the antenatal period can reduce birthweight and the risk of macrosomia and LGA. Previous research has suggested that a reduction of only 1–2 kg during pregnancy is not enough to reduce adverse pregnancy outcomes, especially in the overweight and obese population, and hence interventions are not worthwhile.[104] However, this theory is not supported by the findings of this systematic review. The primary outcomes of this review showed that interventions designed to reduce GWG, were modestly successful, but only reduced GWG by 1–2 kg on average,[22] which is consistent with previous systematic reviews.[16,17,21] In juxtaposition, the infant anthropometric results of this review are contrary to some previous reviews, which suggest that there was no significant difference between infant birth weight and risk of macrosomia, when intervention and control groups were compared.[15,17] The current review builds on the previous review as it has a more diverse sample and is tightly controlled for bias. Furthermore, results suggests that regardless of the IOM classifications of excessive GWG, interventions can reduce the risk of adverse infant anthropometric outcomes associated with excessive GWG.

Maternal diet has been shown to influence infant body composition.[105] Multiple methods of dietary interventions that lead to macronutrient distribution manipulation were included in this review. The success of diet interventions observed in this review are supported by findings from animal and human studies which

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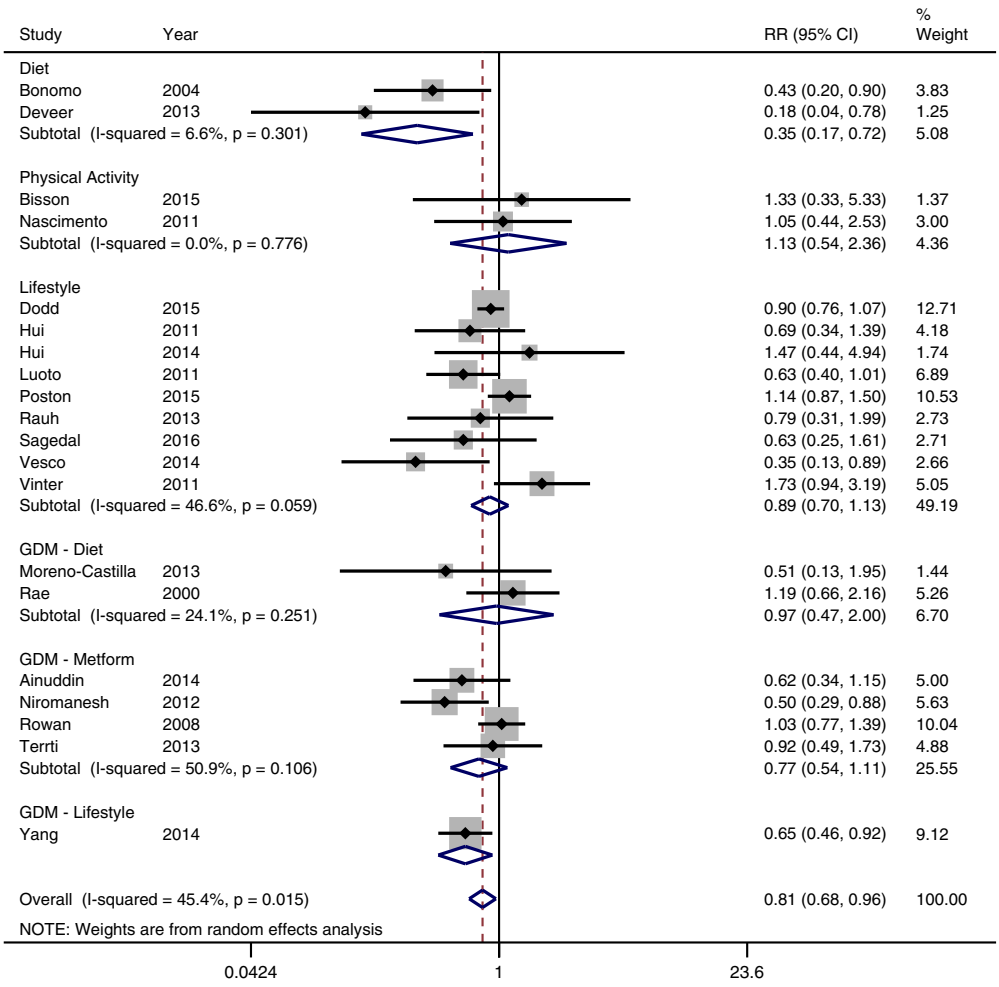

Fig. 4. Large for gestational age relative risk meta-analysis of randomized controlled trials designed to reduce excessive gestational weight gain.

suggested that manipulating the macronutrient distribution to provide a low protein diet could increase fat deposition,[106] predominantly centrally deposited,[107] which in turn can also affect an infant's body composition.[105,108] More specifically, maternal low protein and low ratio of protein:carbohydrate diets are associated with abdominal fat deposition.[105] Further, maternal high polyunsaturated fat diets are associated with healthful upper thigh fat deposition.[105] Therefore, the results of this review support existing literature and suggest offspring of women who are at high risk of excessive GWG may benefit from maternal dietary counselling in pregnancy.

The influence of interventions on infant anthropometric outcomes in women with GDM was the most profound. Women with GDM are three times as likely to have a high birthweight infant compared with normoglycaemic mothers, due to increased insulin resistance in the mother.[109] The modified Penderson's hypothesis purports that the size of the infant is not directly fuel mediated, but indirectly through fetal hyperinsulinemia response which increases fat deposition.[110] This hypothesis suggests that maternal glycaemic control is imperative to the health of the fetus and therefore the decreased risk of macrosomia and LGA may be partially explained by improved glycaemic control in the intervention groups compared with controls. The results of this study highlights the importance of maternal glycaemic and GWG control in GDM for the health of both mother and child, supporting currently primary care guidelines. Furthermore, interventions that reduce infant birthweight and risk of macrosomia and LGA, without increasing adverse outcomes such as SGA and LBW may have long term positive outcomes for the infants. Infants born macrosomic are more likely need an caesarean section delivery, suffer from birth trauma and have an increased risk of severe neonatal morbidity.[111]

Strengths and limitations

A strength and novel aspect of this systematic review was the international sample of studies included. This is the first systematic review considering the infant anthropometrics of studies designed to prevent GWG that has included studies from China, largely inaccessible to those outside of China. The Chinese population contribute almost 20% of the world's population.[112,113] Furthermore, globalization is increasing and therefore, healthcare settings and recommendations need to be applicable to a wider variety of ethnicities. A limitation of this review was the inclusion of only a small number of studies that addressed the outcomes SGA and LBW. For future studies considering the role of intervention in preventing or reducing GWG, it is recommended to report infant outcomes such as SGA and LBW. Further, the majority of studies defined macrosomia to be >4000 g. However, it has been suggested that a cut off of >4500 g may be more indicative of complications in some ethnic groups.[114] Therefore, future studies should endeavour to use appropriate cut

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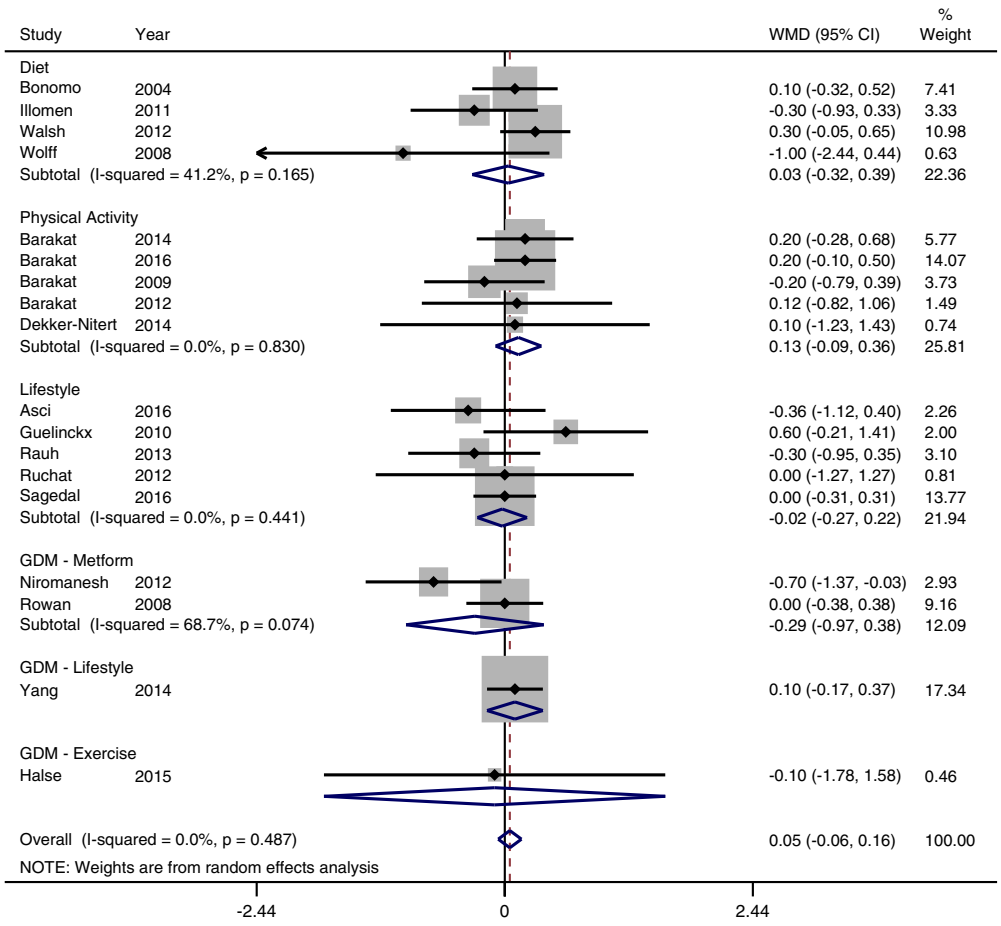

Fig. 5. Infant birth length weighted mean difference meta-analysis of randomized controlled trials designed to reduce excessive gestational weight gain.

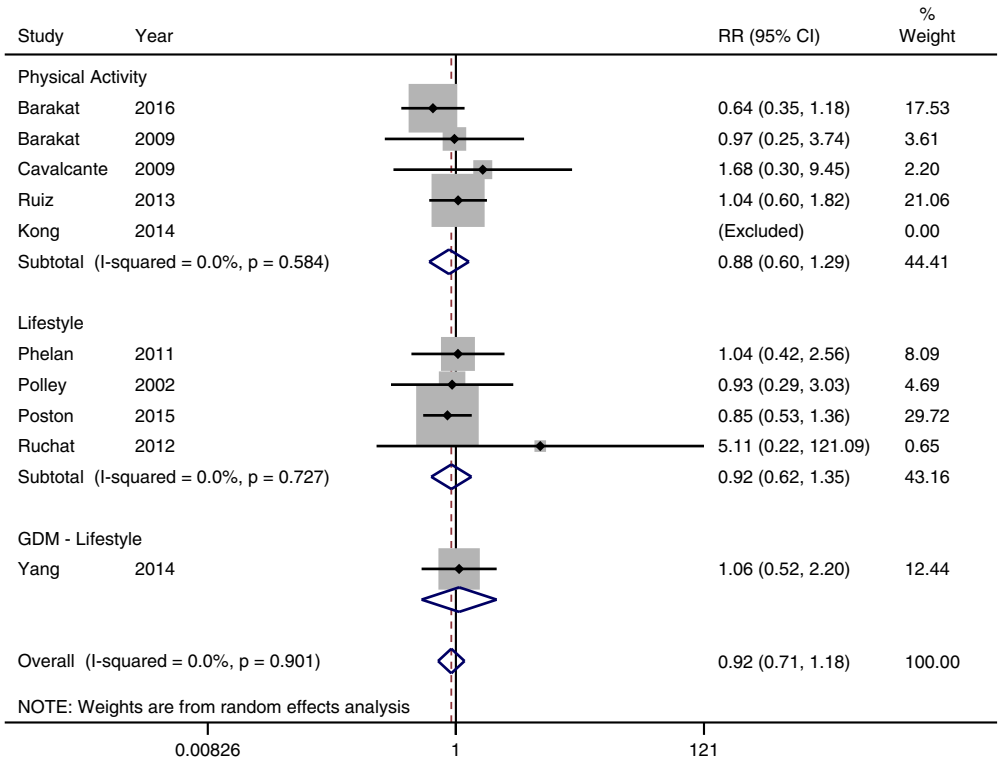

Fig. 6. Low birth weight relative risk meta-analysis of randomized controlled trials designed to reduce excessive gestational weight gain.

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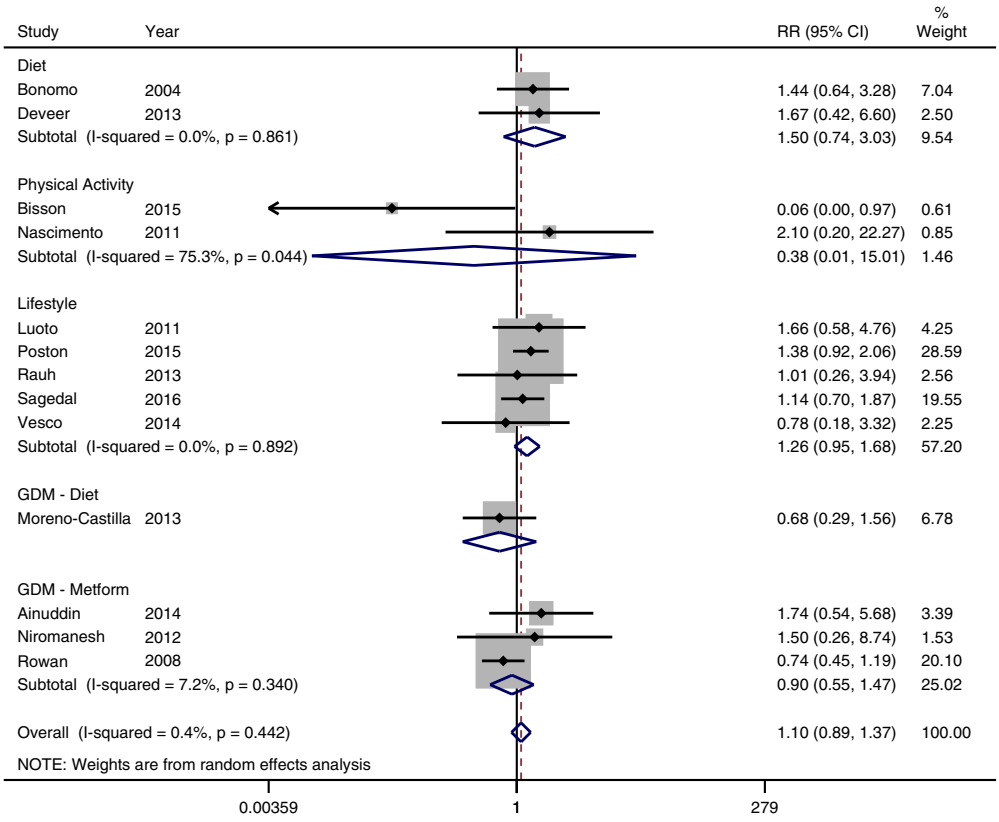

Fig. 7. Small for gestational age relative risk meta-analysis of randomized controlled trials designed to reduce excessive gestational weight gain.

offs for the ethnic population represented.[115] Another limitation of this review is that $n = 28$ studies included in this review were considered to be 'high' risk of bias. To ensure these studies were not significantly influencing results a meta-regression was conducted with 'high-risk' as a covariate. This showed that birthweight, but no other outcome was significantly influenced. Therefore, the weighted mean difference of birthweight should be interpreted with caution. However, this highlights that research in this area need to improve reporting clarity and transparency. Not including studies with a high risk of bias would have significantly reduced the translatability of results to a global sample, as studies published in languages other than English had a higher prevalence of high risk of bias. Further, the meta-analyses show high statistical heterogeneity. However, steps were taken to account or examine the effects of this issue, for example, use of random effects model and conducting sensitivity analyses. It is recognized by the authors of this review that to blind participants in a diet, exercise or lifestyle intervention is extremely difficult. However, future studies in this area should clearly report the blinding procedure of both participants and personnel. As with any systematic review, the results of this review contain the available evidence and therefore is limited by the selection bias of the studies included.

Conclusion

Interventions designed to reduce excessive GWG produce a small reduction in infant birthweight and risk of macrosomia and LGA, without influencing birth length or risk of adverse outcomes such as LBW and SGA. Regardless of the intervention type (diet, PA or lifestyle (diet + PA)), these interventions have the potential to significantly reduce the life-long consequences of high birthweight in offspring born to women at high risk of excessive GWG and GDM. Interventions designed to reduce excessive GWG are confirmed to be an important strategy available to improve the health of the next generation.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S2040174418000879

Acknowledgment. This systematic review was conducted as part of a PhD funded by the Australian Government Research Training Scheme (RTS).

Financial Support. This article received no other financial support.

Conflicts of interest. The authors have nothing to declare.

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https://doi.org/10.1017/S2040174418000879 Published online by Cambridge University Press